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Venetoclax (Ven), an orally administered, potent BCL-2 inhibitor, has demonstrated efficacy in chronic lymphocytic leukaemia (CLL) in combination with rituximab (R) or obinutuzumab (G). Our aim was to investigate the addition of bendamustine (B) to these Ven-containing regimens in relapsed/refractory (R/R) or first-line (1L) CLL. This multi-arm, non-randomized, open-label, phase 1b study was designed to evaluate the maximum tolerated dose (MTD) and safety/tolerability of Ven with BR/BG, with 3+3 dose-escalation followed by safety expansion. Patients received Ven (schedule A) or BR/BG first (schedule B) to compare safety and determine dose/schedule for expansion. Six Ven-BR/-BG cycles were to be administered, then Ven monotherapy until disease progression (R/R) or fixed-duration 1-year treatment (1L). Overall, 33 R/R and 50 1L patients were enrolled. No dose-limiting toxicities were observed (doses 100–400-mg), and the MTD was not reached. Safety was similar between schedules; no tumour lysis syndrome (TLS) occurred during dose-finding. Schedule B and Ven 400-mg were chosen for expansion. The most frequent grade 3–4 toxicity was neutropenia: R/R 64%, 1L Ven-BR 85%, 1L Ven-BG 55%. Grade 3–4 infection rate was: R/R 27%, 1L Ven-BR 0%, 1L Ven-BG 27%. During expansion, one clinical and two laboratory TLS cases occurred. Fewer than half the patients completed six combination therapy cycles with all study drugs; rates of bendamustine discontinuation were high. Overall response rate was 91% in R/R and 100% in 1L patients (16/49 1L patients received Ven for >1 year). In conclusion, addition of bendamustine to Ven-R/-G increased toxicity without apparent efficacy benefit.

Clinical trial: NCT01671904

Introduction

Treatment of chronic lymphocytic leukaemia (CLL) has evolved in recent years, resulting in improved survival,[1] with chemo-immunotherapy being the standard-of-care over the past decade.[2] However, agents targeting pathways involved in CLL cell proliferation and survival, such as B-cell receptor signaling[3,4] and B-cell lymphoma-2,[5] are now standard treatment options.[6–14]

Combination of the selective B-cell lymphoma-2 (BCL-2) inhibitor venetoclax (Ven) with type II anti-CD20 antibody obinutuzumab (G; GA101) in a single-arm, phase 1b trial conferred high response rates with deep remission among patients with previously untreated (1L) or relapsed/refractory (R/R) CLL.[13] Recently, Ven with rituximab (R) or G demonstrated impressive efficacy in phase 3 CLL trials,[6–8] leading to approval of Ven-R and Ven-G in the R/R and 1L treatment settings, respectively.[15,16] Bendamustine is an established chemotherapy agent in CLL that has shown clinical activity in combination with anti-CD20 antibodies.[17–20] Whether the addition of a chemotherapy agent such as bendamustine to Ven-R or Ven-G could further improve outcomes in CLL has not yet been elucidated. The combination of Ven with bendamustine plus R (BR) produced greater growth inhibition in non-Hodgkin lymphoma (NHL) xenograft models than either Ven-R or BR alone,[21] suggesting potential for increased clinical activity in B-cell malignancies. In addition, BCL-2 overexpression may be involved in resistance to the pro-apoptotic effects of chemoimmunotherapy, so the addition of Ven could overcome this and act as a chemosensitizer.[22] We therefore evaluated a triplet combination of Ven with bendamustine and an anti-CD20 antibody (R or G) in 1L and R/R CLL.

Methods

Study design and treatment

This phase 1b, multi-arm, non-randomized, open-label study (NCT01671904) was conducted at 11 sites across USA and Europe. Review boards at all institutions approved the protocol. Patients provided written informed consent. The study comprised two phases: dose-finding and safety-expansion. Dose-finding, employing standard 3+3 dose-escalation (Supplementary Table S1), was designed to include Ven doses from 100–600 mg daily with standard-dose BR/BG (Figure 1; bendamustine: 90 mg/m^2 (1L) or 70 mg/m^2 (R/R) Days (D)1–2 Cycle (C)1–6; R: 375 mg/m^2 D1 C1 then 500 mg/m^2 D1 C2–6; G: 100 mg D1, 900 mg D2, 1000 mg D8 and D15 C1 then 1000 mg D1 C2–6). To

mitigate tumour lysis syndrome (TLS) risk, Ven was initiated using a weekly ramp-up to target dose (Figure 1). TLS prophylaxis included hydration, a uric acid reducer, and hospitalization (Supplementary Table S2).

Dose-finding compared two administration schedules for TLS risk mitigation during cycle 1 (Figure 1): schedule A (Ven ramp-up, followed by BR/BG) and schedule B (Ven introduced after 21-day BR/BG loading period). After each stage, an internal monitoring committee (IMC) and scientific overview committee (SOC) reviewed the data and provided dose/schedule recommendations for subsequent dose-finding stages and safety expansion (Supplementary Figure S1).

Patients received six 28-day cycles of Ven-BR/-BG. R/R patients continued single-agent Ven until disease progression (PD), death, or unacceptable toxicity; 1L patients received 6 months of single-agent Ven for a total of 1-year treatment duration. Ven could be extended in 1L patients with detectable minimal residual disease (MRD) in bone marrow (BM) and/or partial response after 1 year of treatment. See Supplementary Methods for further details of study treatments and procedures.

Objectives

Primary objectives were to identify the maximum tolerated dose (MTD) of Ven combined with BR, and evaluate safety/tolerability of Ven-BR in R/R and 1L CLL. Secondary objectives included efficacy evaluation of Ven-BR (including complete response [CR], overall response rate [ORR], duration of response, and progression-free survival [PFS]). Exploratory objectives were to determine the MTD of Ven with BG, safety and efficacy of Ven-BG, and the undetectable MRD (uMRD) rate with Ven-BR/-BG.

Patients

Patients ≥18 years with a diagnosis of CLL according to International Workshop on CLL (iwCLL) 2008 guidelines,[23] in need of therapy, with an Eastern Cooperative Oncology Group performance status of 0–1 and adequate hematologic function (platelet count ≥75,000/mm^3 or ≥30,000/mm^3 if due to marrow involvement of CLL, and/or disease related immune thrombocytopenia; absolute neutrophil count ≥1,000/mm^3; hemoglobin ≥9 g/dl) were eligible (Supplementary Table S3). Patients with R/R CLL must have received 1–3 prior lines of therapy.

Assessments

Baseline molecular characteristics were assessed centrally (Supplementary Methods). Safety and tolerability were assessed by incidence and type of DLTs (Supplementary Table S4), AEs (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.0[24]), and serious AEs, laboratory variables, and vital signs. TLS was classified according to Howard criteria.[25] Efficacy was assessed by investigators according to iwCLL 2008 guidelines.[23]

Central MRD assessment was performed at Ohio State University, USA using five-colour flow cytometry according to the European Research Initiative on CLL principle.[26]

Statistical analyses

Safety and efficacy analyses included all patients receiving ≥1 dose of any study drug. Peripheral blood (PB) MRD analyses reported landmark MRD rates after treatment completion in the 1L population and after antibody completion in the R/R population, given the difference in duration of treatment in these two populations. MRD analysis populations included all patients reaching the specified landmark time-point, plus those discontinuing the study earlier for AEs, PD, or death. Given the long recruitment time, some patients had not reached the specific timepoint, therefore the intention-to-treat approach was not used. At each landmark assessment, the first evaluable PB MRD sample after the specified time-point was used. For BM MRD, due to limited sampling, best MRD response was reported, calculated in the efficacy population. Time-to-event analyses employed Kaplan–Meier methodology.[27]

Results

Patients

Thirty-three R/R and 50 1L patients were enrolled between January 2014 and June 2017 (Supplementary Figure S2). All R/R patients were enrolled in Ven-BR cohorts; 1L patients were enrolled in Ven-BR (n=27) or Ven-BG (n=23) cohorts. All 33 R/R patients were included in safety and efficacy analyses. One 1L patient enrolled in the Ven-BG cohort did not receive study drug, therefore 49 patients (27 Ven-BR, 22 Ven-BG) were included in analyses. Data cut-off was 17 August 2018; no further follow-up will be available.

In R/R patients, median number of prior CLL therapies was 1 (range, 1–3); 79% had received fludarabine-based combinations and 6% Bruton's tyrosine kinase inhibitors; none had received phosphoinositide-3-kinase inhibitors (Table 1). Among patients with available baseline samples for central testing, del(17p) and/or *TP53* mutation was present in 42% of R/R and 13% of 1L patients; 67% of R/R and 60% of 1L patients had unmutated immunoglobulin heavy-chain variable region (IGHV) (Table 1).

Treatment exposure

In total, 79% (26/33) of R/R, 96% (26/27) of 1L Ven-BR, and 95% (21/22) of 1L Ven-BG patients received Ven 400 mg. Fewer than half completed six cycles of the planned triple-drug combination (Supplementary Table S5). Overall, 16 R/R, 11 1L Ven-BR, and nine 1L Ven-BG patients completed six bendamustine cycles. R/R patients received a median of five (range, 1–6) bendamustine cycles and six (range, 1–6) cycles of R. 1L patients received a median of five (range, 1–6) bendamustine cycles; the median number of cycles of R or G received was six (range, 1–6).

Median Ven treatment duration was 676 days (range, 48–1649) in R/R, 371 days (range, 4–1150) in 1L Ven-BR, and 336 days (range, 11–620) in 1L Ven-BG patients. Sixteen 1L patients, eight per arm, received Ven beyond 1 year (range, 381–1150 days). Median relative dose intensity of Ven was 100% (range, 41–100) in R/R (n=30/33), 87% (range, 37–100) in 1L Ven-BR (n=26/27), and 100% (range, 33–100) in 1L Ven-BG (n=21/22) patients (Supplementary Methods).

Safety

During dose-finding, R/R patients were enrolled to 100-mg (schedule A), 200-mg (schedule A), or 400-mg (schedule A or B) Ven cohorts; all 1L patients were included in the 400-mg (schedule A or B) Ven cohorts (Supplementary Table S6). The 600-mg Ven dose was not explored after review of the present study and program-wide data, including phase 1b studies in CLL with Ven-R and Ven-G, where the recommended phase 2 dose of Ven was 400 mg.[13,28] Eighteen patients received C1 treatment according to schedule A, and 21 patients according to schedule B (Supplementary Table S6). No DLTs were observed with either treatment schedule or combination and the MTD was not reached in the doses explored. Ven 400 mg was selected as the recommended dose for expansion. There were no safety differences between schedules A and B and no TLS events were reported. After reviewing

safety data from the dose-finding phase and program-wide data, including from phase 1b studies with Ven-G[13] and Ven-R in CLL,[28] the IMC and SOC recommended schedule B (debulking with BR or BG followed by Ven), presuming increased practicality with mitigating risk of TLS and a reduced number of high-risk TLS patients.

All safety-evaluable patients reported ≥1 AE. All-grade infusion-related reaction events occurred in 12% of R/R and 45% of 1L patients (Table 2); all were grade 1–2 excepting for two grade 3 events with Ven-BG. Serious AEs were reported in 52% of R/R and 53% of 1L patients (Supplementary Table S7); grade 3–4 AEs occurred in 82% of R/R and 92% of 1L patients (Table 2). The most frequent grade 3–4 AEs were neutropenia and thrombocytopenia (Table 2). Infections were mainly low grade and driven by upper respiratory tract and urinary tract infections (Table 2). Grade 3–4 infections occurred in 27% of R/R, 0% of 1L Ven-BR, and 27% of 1L Ven-BG patients. The frequency of grade 3–4 neutropenia was evenly distributed between patients who received 1–4 or 5–6 bendamustine cycles (Supplementary Table S8). More grade 3–4 AEs occurred during combination therapy versus monotherapy (Supplementary Table S9), with grade 3–4 neutropenia being reported in 65% of patients during combination therapy and 39% during monotherapy. Overall, 64%, 85%, and 59% of patients in the R/R, 1L Ven-BR, and 1L Ven-BG arms, respectively, received growth factors as prophylaxis and/or treatment (Supplementary Table S10); further details of growth factor treatment and response are not available.

Three TLS cases were reported during safety-expansion, all in patients receiving schedule B: one laboratory and one clinical TLS occurred in two R/R patients, whereas the other laboratory TLS occurred in a 1L Ven-BG patient (Supplementary Table S11). Both laboratory TLS events occurred prior to initiation of Ven. The clinical TLS event occurred on day 29 after administration of Ven 50 mg (D1 of the second BR cycle); it was diagnosed due to clinical symptoms of hypotension and dyspnoea with hyperkalaemia (potassium: 7.6 mmol/L) and elevated phosphorus levels (2.97 mmol/L). Electrocardiogram data were not provided by the centre. BR was permanently discontinued and single-agent Ven was re-introduced on study day 61 without further incidence of TLS. All TLS events resolved with standard-of-care measures; the two laboratory events did not lead to permanent discontinuation of any study drug.

Bendamustine was permanently discontinued due to AEs in 33% of R/R and 37% of 1L patients (Supplementary Table S12). The most common AE leading to permanent bendamustine withdrawal was neutropenia. Ven was interrupted and/or reduced due to AEs in 67% of R/R and 82% of 1L patients, most frequently due to neutropenia

(R/R, 36% of patients; 1L Ven-BR, 63%; 1L Ven-BG, 46%) (Supplementary Table S12). Ven was permanently discontinued due to AEs in 27% of R/R and 29% of 1L patients (Supplementary Tables S12 and S13).

Two deaths were reported: one due to stage 4, high-grade malignant haemangioendothelioma in a R/R patient, resulting in multiple organ failure on study day 144, and one due to haemorrhagic transformation of stroke on study day 83 in a 1L Ven-BR patient with history of hypertension and concomitant grade 3 treatment-related thrombocytopenia (platelet levels were normal at screening).

Efficacy

Overall response rate was 91% (30/33) in R/R patients (including 42% [14/33] with CR/complete response with incomplete haematologic recovery [CRi]). All 1L patients responded (overall response rate 100%; including 44% [12/27] CR/CRi for Ven-BR, and 68% [15/22] CR/CRi for Ven-BG). Responses were similar regardless of cytogenetic status, IGHV status or whether patients received 1–4 or 5–6 bendamustine cycles (Table 3).

Landmark PB uMRD rates were 58% (18/31) ≥12 months after last R dose in R/R patients, and 71% (15/21) and 89% (16/18) ≥3 months after last Ven dose with 1L Ven-BR and Ven-BG, respectively (Figure 2). These rates were observed regardless of whether patients received 1–4 or 5–6 bendamustine cycles and were maintained over time (Figure 2).

In the R/R population, after a median follow-up of 26 months (range, 24–31) from the last R dose, among patients who reached ≥24 months after the last R dose plus those who discontinued earlier, the PB uMRD rate was sustained at 37% (10/27). For the 1L population, ≥12 months after completion of all treatment (last Ven dose; median follow-up 14 months [range, 12–18]), the PB uMRD rate was sustained at 67% (12/18) for Ven-BR and 90% (9/10) for Ven-BG. 41–49% of patients had missing samples for BM MRD analysis. Among patients with samples available, the rate of uMRD as best MRD response in the BM was 53% (9/17), 69% (11/16), and 92% (11/12) in the R/R, 1L Ven-BR, and 1L Ven-BG arms, respectively. Among patients with PB and BM post-baseline paired samples from the same day, concordance between a patient's MRD status determined from PB and BM was high and similar across the arms (Supplementary Table S14).

MRD kinetics in individual patients are shown in Figure 3. Among 24 R/R patients who achieved PB uMRD in ≥1 assessment and had subsequent PB MRD assessment(s), nine converted to MRD positivity (low or high levels) in two consecutive assessments, of whom three experienced PD as of the current follow-up. In 42 1L patients who

achieved PB uMRD in ≥1 assessment and had subsequent PB MRD assessment(s), five converted to MRD positivity, only one of whom experienced PD. Median time to first MRD conversion (from the first PB uMRD result) was 360 days (range, 42–848) and 224 days (range, 77–600) in the R/R and 1L Ven-BR arms, respectively. For the patient in the 1L Ven-BG arm who experienced MRD conversion, time from first PB uMRD result to conversion was 324 days.

PFS is shown in Figure 4. After a median observation time of 36.5 months (range, 1–54) and 21.6 months (range, 1–43) in the R/R and 1L populations, respectively, estimated 24-month PFS was 87% (95% confidence interval, 74–99) for R/R, 96% (95% confidence interval, 89–100) for 1L Ven-BR, and 100% (95% confidence interval, 100–100) for 1L Ven-BG patients. Seven PDs, including two cases of Richter's transformation to diffuse large B-cell lymphoma, were reported in the R/R population. Only one PD was observed with 1L Ven-BR. No PDs were reported with 1L Ven-BG. Among the eight patients who progressed, four (all R/R) had baseline del(17p) and/or *TP53* mutation.

Discussion

In this phase 1b study, 400 mg Ven daily was selected, in combination with standard doses of BR/BG, for safety expansion in R/R and 1L CLL patients. While no MTD was reached during dose escalation up to 400 mg, both triplet combination regimens with bendamustine in the expansion phase showed increased toxicity versus Ven-R and Ven-G alone,[6–8] leading to low tolerability, as seen with high rates of bendamustine discontinuation. The fact that fewer than half of all patients were able to complete the full six cycles of bendamustine may at least partially explain the apparent lack of efficacy seen here in comparison with the efficacy of backbone Ven-R or Ven-G, despite the preclinical rationale.

Neutropenia was the most important toxicity in triplet combinations in both 1L and R/R CLL populations. Rates of grade 3–4 neutropenia, however, were generally consistent with those observed with Ven-R in R/R CLL in the MURANO trial (58% [112/194]),[7] with Ven-G in 1L CLL in CLL14 (53% [112/212]),[8] and with ibrutinib plus BR in R/R CLL in the HELIOS study (54% [154/287]).[11,14] The small sample size in the 1L Ven-BR arm could have contributed to the numerically high rates of grade 3–4 neutropenia in this arm and limits the ability to make comparisons. Despite high rate of neutropenia, infections were mainly low grade and driven by upper respiratory tract and urinary tract infections. In 1L populations, grade 3–4 infections appeared to be higher with Ven-BG (27%

[6/22]) than Ven-BR (0% [0/27]), which is probably a reflection of the non-randomized nature of the study and the small numbers involved. However, a high rate of infections has been seen with BG combinations in CLL (21.4% grade ≥3 in the GREEN phase 3b study[29]), and in the randomized phase 3 GALLIUM study of BG versus BR in follicular lymphoma, grade 3–5 infection rates were also higher with BG than BR (26% vs. 20%).[30] Grade 3–4 infection rates were higher in the present study than those seen in the CLL14 trial with Ven-G (17.5%)[8] and in the CLL2-BAG trial during induction with G and Ven (19% [6/31]).[31] The grade 3–4 infection rate in the R/R population was higher than that seen with Ven-R in MURANO (18% [34/194]),[7] but similar to the rate of grade ≥3 infection reported with ibrutinib plus BR in HELIOS (29% [83/287]).[11] Direct between-study comparisons are difficult to interpret given differences in sample sizes, baseline characteristics, treatment duration, and follow-up. However, addition of bendamustine to Ven-R or Ven-G in the current study led to significantly increased infection rates and reduced the tolerability of these combinations. Increased toxicity with bendamustine-containing combinations with Ven is also seen in NHL,[32,33] limiting the use of these combinations with Ven in future CLL treatment strategies.

The higher CR rates observed with 1L Ven-BG than Ven-BR were consistent with previous demonstration of superior efficacy of G compared with R when used in combination with chemotherapy.[34] Similarly, landmark (≥3 and ≥9 months after treatment) PB uMRD rates were higher in 1L Ven-BG than 1L and R/R Ven-BR patients. Around half of patients in all arms did not provide BM samples for MRD assessment (an exploratory study endpoint), which affects the interpretability of BM uMRD rates. However, there was a high concordance between BM and PB results in paired samples. This was consistent with the concordance between PB and BM MRD determination seen with Ven treatment in the MURANO (86%) and CLL14 (87%) studies,[6,35] suggesting that PB MRD status reflects BM MRD status in Ven-treated patients. High PB uMRD rates observed were consistent with those seen in phase 2 and 3 trials with Ven-R,[6] Ven-G,[8,35] and Ven plus ibrutinib[36] and higher than reported previously with BG[20] or BR alone in 1L patients,[37] highlighting the efficacy of Ven-R and Ven-G alone, independent of the addition of bendamustine. However, cross-trial comparisons with this phase 1b study must be made with caution, and previous analyses were performed in the respective intention-to-treat populations, as opposed to the subgroup of evaluable patients we had to use, and overall sample sizes were much larger. Re-emergence of MRD in PB, which was observed in a minority of patients, mainly in the R/R population, did not appear to be associated with immediate development of PD. Larger trials are needed to identify patients most likely

to convert to MRD positivity, the impact and time from the MRD conversion on the appearance of clinical progression, and the feasibility of time-limited therapy in CLL.

The 2-year PFS rate reported here in the R/R group with Ven-BR is similar to that seen with Ven-R in MURANO (85%),[7] suggesting no benefit from the addition of bendamustine overall. In contrast, 2-year PFS in 1L patients was higher than that reported with Ven-G in CLL14 (88%);[8] however, the two studies are very different and it should be noted that the CLL14 study recruited patients with co-existing conditions, whereas the population of the present study was relatively young, with a good performance status, and numbers were small. Also, 16/49 1L patients continued Ven beyond 1 year.

A limitation of this study was the small sample size in each arm and non-randomized allocation to verify significant safety and efficacy differences across triplet combinations and across the number of bendamustine cycles received. In addition, most patients were <65 years old with creatinine clearance ≥70 mL/min, with a good performance status, which may have affected some of the study outcomes.

400 mg daily Ven given with standard-dose BR or BG increased toxicity compared with published data for Ven-R and Ven-G, without an apparent efficacy benefit for the addition of bendamustine. The question remains whether there is an optimal number of bendamustine cycles that would be beneficial for all or for a particular subgroup of CLL patients, or whether the addition of bendamustine (with a different dose/schedule) to Ven-R or Ven-G could improve clinical outcomes without impaired tolerability. However, considering the extent of the toxicity reported here, exploration of lower bendamustine doses is expected to have a limited role. Indeed, in the era of novel targeted agents replacing the standard chemo-immunotherapy regimens and demonstrating improved safety and efficacy profiles, there seems to be minimal need to add standard chemotherapy to novel regimens.

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Data-sharing statement Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). 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).

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YJ, HH, DSP, WS, KH, MM, and GS analyzed the data and were involved in the writing process; SS, FM, C-MW, GC, MH, BE, MFK, TG, GL, YJ, HH, DSP, WS, KH, MM, and GS interpreted the data, participated in manuscript development, and gave final approval.

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TABLES AND FIGURES

Table 1: Baseline characteristics

Characteristic	R/R Ven-BR (*n*=33)*	1L Ven-BR (*n*=27)	1L Ven-BG (*n*=22)
Median age, years (range)	62 (38–77)	65 (27–73)	64 (38–74)
Age ≤65 years, *n* (%)	22 (67)	15 (56)	12 (55)
Male, *n* (%)	20 (61)	14 (52)	15 (68)
ECOG PS 0–1, *n* (%)	32 (97)	27 (100)	22 (100)
Rai stage, *n* (%)			
I	5 (15)	2 (7)	4 (18)
II	2 (6)	4 (15)	6 (27)
III	7 (21)	8 (30)	4 (18)
IV	15 (46)	5 (19)	0
Unknown	4 (12)	8 (30)	8 (36)
Creatinine clearance <70 mL/min, *n* (%)	8 (24)	11 (41)	5 (23)
Pre-treatment TLS risk, *n* (%)			
Low	7 (21)	2 (7)	7 (32)
Medium	16 (49)	19 (70)	10 (46)
High	10 (30)	6 (22)	5 (23)
Cytogenetics, *n* (%)†			
del(17p) and/or *TP53* mut‡	13 (42)	2 (10)	3 (17)
del(11q)	6 (19)	2 (10)	3 (17)
Trisomy 12	4 (13)	3 (14)	2 (11)
No abnormalities	2 (7)	1 (5)	1 (6)
del(13q)	6 (19)	13 (62)	9 (50)
IGHV unmutated, *n*/*N* (%)§	20/30 (67)	10/20 (50)	15/21 (71)
Serum β-2 microglobulin, *n*/*N* (%) ≥3.5 mg/mL	8/16 (50)	5/8 (63)	5/8 (63)
Prior therapies received, *n* (%)			
Fludarabine-based treatment	26 (79)	0	0

Bendamustine or BR	4 (12)	0	0
BTKis	2 (6)	0	0
PI3Ki	0	0	0

*The Ven-BG cohort did not open in R/R patients.

†FISH cut-offs for positivity: del(17p) >7%; del(11q) >6%; del(13q) >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%.

R/R relapsed/refractory, Ven venetoclax, B bendamustine, R rituximab, 1L first-line, G obinutuzumab, ECOG PS Eastern Cooperative Oncology Group performance status, TLS tumour lysis syndrome, mut mutated, IGHV immunoglobulin heavy-chain variable region, BTKi Bruton's tyrosine kinase inhibitor, PI3Ki phosphoinositide 3-kinase inhibitor, FISH fluorescence *in situ* hybridization, NGS next-generation sequencing.

***Table 2*: Treatment-emergent AEs**

AE	R/R Ven-BR (*n*=33)*		1L Ven-BR (*n*=27)		1L Ven-BG (*n*=22)	
	All grades	**Grade 3–4**	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**
Any AE, *n* (%)	33 (100)	27 (82)	27 (100)	25 (93)	22 (100)	20 (91)
AEs occurring in ≥20% of patients, *n* (%)*						
Infections and infestations	28 (85)	9 (27)	20 (74)	0	16 (73)	6 (27)
Neutropenia	21 (64)	21 (64)	24 (89)	23 (85)	12 (55)	12 (55)
Nausea	18 (55)	0	18 (67)	2 (7)	16 (73)	0
Thrombocytopenia	16 (49)	8 (24)	16 (59)	10 (37)	15 (68)	11 (50)
Diarrhea	15 (46)	6 (18)	13 (48)	1 (4)	11 (50)	2 (9)
Anaemia	13 (39)	4 (12)	13 (48)	3 (11)	8 (36)	2 (9)
Leukopenia	12 (36)	7 (21)	5 (19)	3 (11)	2 (9)	2 (9)
Asthenia	12 (36)	1 (3)	8 (30)	1 (4)	9 (41)	0

Pyrexia	11 (33)	0	13 (48)	0	8 (36)	1 (5)
Fatigue	10 (30)	3 (9)	8 (30)	0	5 (23)	1 (5)
Hypertension	7 (21)	4 (12)	1 (4)	0	3 (14)	1 (5)
Cough	7 (21)	0	6 (22)	0	3 (14)	0
Decreased appetite	7 (21)	0	3 (11)	0	7 (32)	0
Dizziness	7 (21)	0	2 (7)	0	0	0
Vomiting	6 (18)	0	7 (26)	1 (4)	4 (18)	1 (5)
Rash	6 (18)	0	7 (26)	0	5 (23)	0
Headache	5 (15)	0	8 (30)	0	7 (32)	0
Constipation	5 (15)	0	8 (30)	0	4 (18)	0
Infusion-related reaction	4 (12)	0	8 (30)	0	14 (64)	2 (9)
Hyperuricemia	2 (6)	1 (3)	4 (15)	2 (7)	5 (23)	1 (5)
Arthralgia	2 (6)	0	3 (11)	0	5 (23)	1 (5)

Infection AEs occurring in >5% of patients, *n* (%)*

Bronchitis	10 (30)	1 (3)	3 (11)	0	2 (9)	0
Urinary tract infection	8 (24)	2 (6)	4 (15)	0	4 (18)	3 (14)
Nasopharyngitis	7 (21)	0	6 (22)	0	4 (18)	0
Erysipelas	4 (12)	1 (3)	0	0	0	0
Influenza	4 (12)	0	1 (4)	0	1 (5)	0
Gastroenteritis	4 (12)	1 (3)	0	0	1 (5)	0
Pneumonia	3 (9)	2 (6)	1 (4)	0	0	0
Upper RTI	3 (9)	0	3 (11)	0	5 (23)	0
Oral herpes	3 (9)	0	2 (7)	0	2 (9)	0
Sinusitis	3 (9)	0	1 (4)	0	2 (9)	0
Herpes zoster	3 (9)	0	1 (4)	0	0	0
Conjunctivitis	2 (6)	0	2 (7)	0	0	0
Herpes virus infection	1 (3)	1 (3)	2 (7)	0	0	0

Pharyngitis	1 (3)	0	3 (11)	0	1 (5)	0
Lung infection	0	0	2 (7)	0	0	0
Cytomegalovirus	0	0	0	0	2 (9)†	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.

*Any-grade AEs in any population or treatment arm.

†Details of the diagnosis of these events were not reported, so it is not known whether they were symptomatic or detected via screening.

AE adverse event, R/R relapsed/refractory, Ven venetoclax, B bendamustine, R rituximab, 1L first-line, G obinutuzumab, RTI respiratory tract infection, MedDRA Medical Dictionary for Regulatory Activities, PT preferred term, SOC scientific overview committee.

***Table 3*: Response according to 2008 International Workshop on CLL guidelines in the R/R and 1L populations**

Patients	Entire cohort	Responses per cytogenetic status*					Responses per IGHV status		Responses per number of cycles of bendamustine received	
		del(17p) and/or *TP53* mut	del(11q)	Trisomy 12	None	del(13q)	Mutated	Unmutated	1–4	5–6
R/R patients, *n* (%)										
Ven-BR, *n*†	33	12	6	4	2	6	3	19	13	20
ORR	30 (91)	11 (85)	6 (100)	4 (100)	2 (100)	6 (100)	3 (100)	19 (100)	11 (85)	19 (95)
CR/CRi	14 (42)	3 (23)	4 (67)	3 (75)	2 (100)	2 (33)	3 (100)	7 (37)	5 (39)	9 (45)
PR	16 (49)	8 (62)	2 (33)	1 (25)	0	4 (67)	0	12 (63)	6 (46)	10 (50)
1L patients, *n* (%)										
Ven-BR, *n*	27	2	2	3	1	13	8	10	9	18
ORR	27 (100)	2 (100)	2 (100)	3 (100)	1 (100)	13 (100)	8 (100)	10 (100)	9 (100)	18 (100)
CR/CRi	12 (44)	2 (100)	2 (100)	1 (33)	0	5 (39)	5 (63)	5 (50)	3 (33)	9 (50)

PR	15 (56)	0	0	2 (67)	1 (100)	8 (62)	3 (38)	5 (50)	6 (67)	9 (50)
Ven-BG, *n*	22	3	3	2	1	9	3	15	6	16
ORR	22 (100)	3 (100)	3 (100)	2 (100)	1 (100)	9 (100)	3 (100)	15 (100)	6 (100)	16 (100)
CR/CRi	15 (68)	2 (67)	3 (100)	1 (50)	1 (100)	6 (67)	2 (67)	11 (73)	6 (67)	11 (69)
PR	7 (32)	1 (33)	0	1 (50)	0	3 (33)	1 (33)	4 (27)	2 (33)	5 (31)

*Responses by cytogenetic abnormalities according to the modified hierarchical model in patients with samples available for cytogenetic assessment.

†The Ven-BG cohort was not explored in R/R patients.

CLL chronic lymphocytic leukaemia, R/R relapsed/refractory, 1L first-line, mut mutated, Ven venetoclax, B bendamustine, R rituximab, ORR overall response rate, CR complete response, CRi complete response with incomplete haematologic recovery, PR partial response, G obinutuzumab.

Figure legends

Figure 1: **Treatment and dosing schedules.** Schedule A: venetoclax followed by BR/BG. Schedule B: BR/BG followed by venetoclax. Schedule A with Ven-BR was explored in R/R patients before schedule B in the R/R and 1L populations. Data from schedule A provided safety guidance for subsequent dose-finding for patients in schedule B after a data review by the IMC and SOC. 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; the treatment plan consisted of venetoclax plus BR or BG (6 x 28-day cycles) in combination with venetoclax, then single-agent venetoclax; each cohort continued treatment until PD, death, or unacceptable toxicity in R/R patients, or for a total of 1 year treatment duration in 1L patients (with potential for extension if BM was positive for MRD or patient had PR). Venetoclax ramp-up and maximum cohort dose are indicated by the blue arrows. BR/BG dosing schedule: bendamustine: 90 mg/m^2 (1L) or 70 mg/m2 (R/R) D1–2 per cycle for six cycles; R: 375 mg/m^2 (C1) then 500 mg/m^2 (C2–6) D1 per cycle; G: 100 mg D1, 900 mg D2, 1000 mg D8 and D15 C1 then 1000 mg D1 (C2–6). Ven venetoclax, B bendamustine, R rituximab, D day, C cycle, G obinutuzumab, W week, R/R relapsed/refractory, 1L first-line, IMC internal monitoring committee, SOC scientific overview committee, PD disease progression, BM bone marrow, MRD minimal residual disease, PR partial response.

Figure 2: **MRD status by flow in PB and BM in (a) R/R population and (b) 1L population.** Discontinued includes patients who discontinued study due to PD, death, or AE (if applicable) before achieving the specified landmark time-point; missing includes patients who reached the time-point but had no sample available for MRD analysis; undetermined includes patients with MRD level $<10^{-4}$, but <200 000 leukocytes analyzed. uMRD: <1 CLL cell per 10^4 mononuclear cells; low-level MRD: ≥1 CLL cell per 10^4 mononuclear cells to <1 CLL cell per 10^2 mononuclear cells; high-level MRD: ≥1 CLL cell per 10^2 mononuclear cells. MRD minimal residual disease, PB peripheral blood, BM bone marrow, R/R relapsed/refractory, 1L first-line, R rituximab, B bendamustine, Ven venetoclax, G obinutuzumab, PD disease progression, AE adverse event, uMRD undetectable MRD, CLL chronic lymphocytic leukaemia.

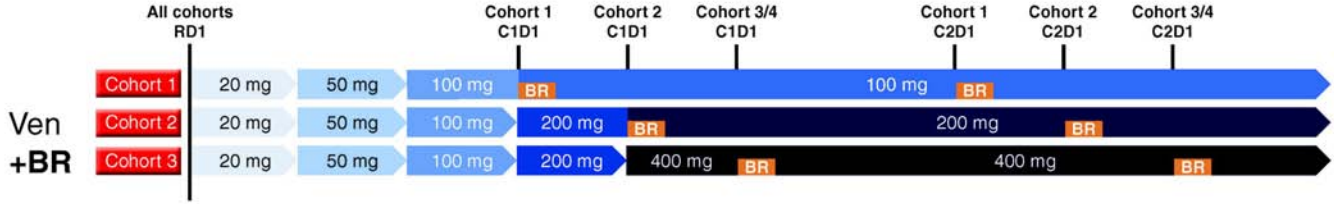
Figure 3: **MRD kinetics in individual patients in (a) R/R population and (b) 1L population.** uMRD was defined as <1 CLL cell per 10^4 mononuclear cells in samples with a minimum of 200 000 leukocytes ($<10^{-4}$). Low-level MRD was defined as between 1 CLL cell per 10^4 and 1 cell per 10^2 mononuclear cells ($\geq10^{-4}$–$<10^{-2}$). High-level MRD was defined as ≥1 CLL cell per 10^2 mononuclear cells ($\geq10^{-2}$). MRD minimal residual disease, R/R relapsed/refractory, 1L first-line, Ven venetoclax, B bendamustine, R rituximab, PB peripheral blood, BM

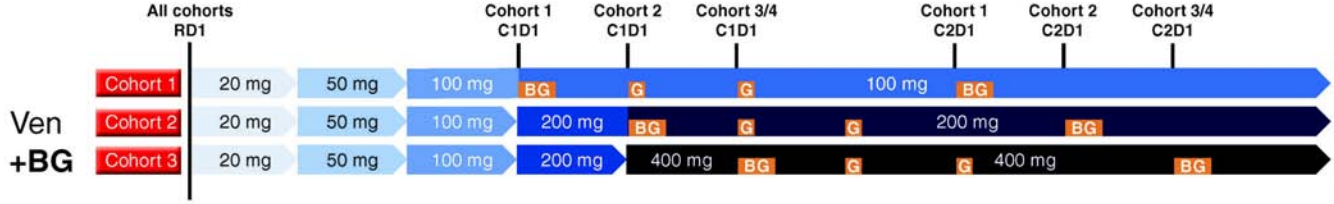
bone marrow, IGHV immunoglobulin heavy-chain variable region, Tx treatment, PD disease progression, G obinutuzumab, uMRD undetectable MRD, CLL chronic lymphocytic leukaemia.

Figure 4: **Progression-free survival.** 1L first-line, Ven venetoclax, B bendamustine, R rituximab, G obinutuzumab, R/R relapsed/refractory.

FIGURE 1

Schedule A





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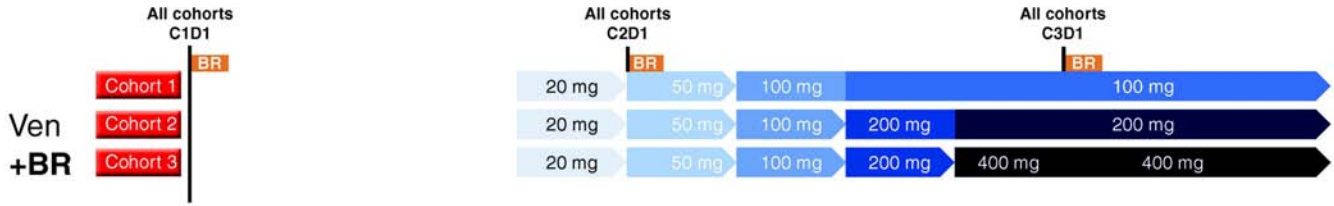
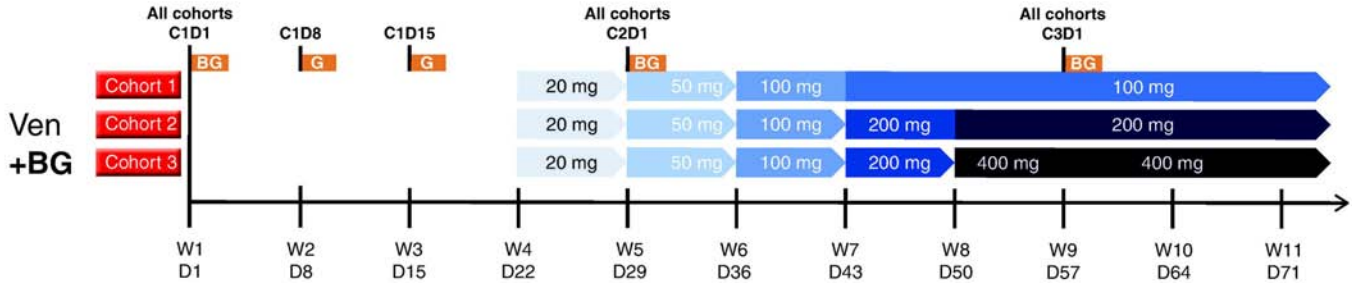
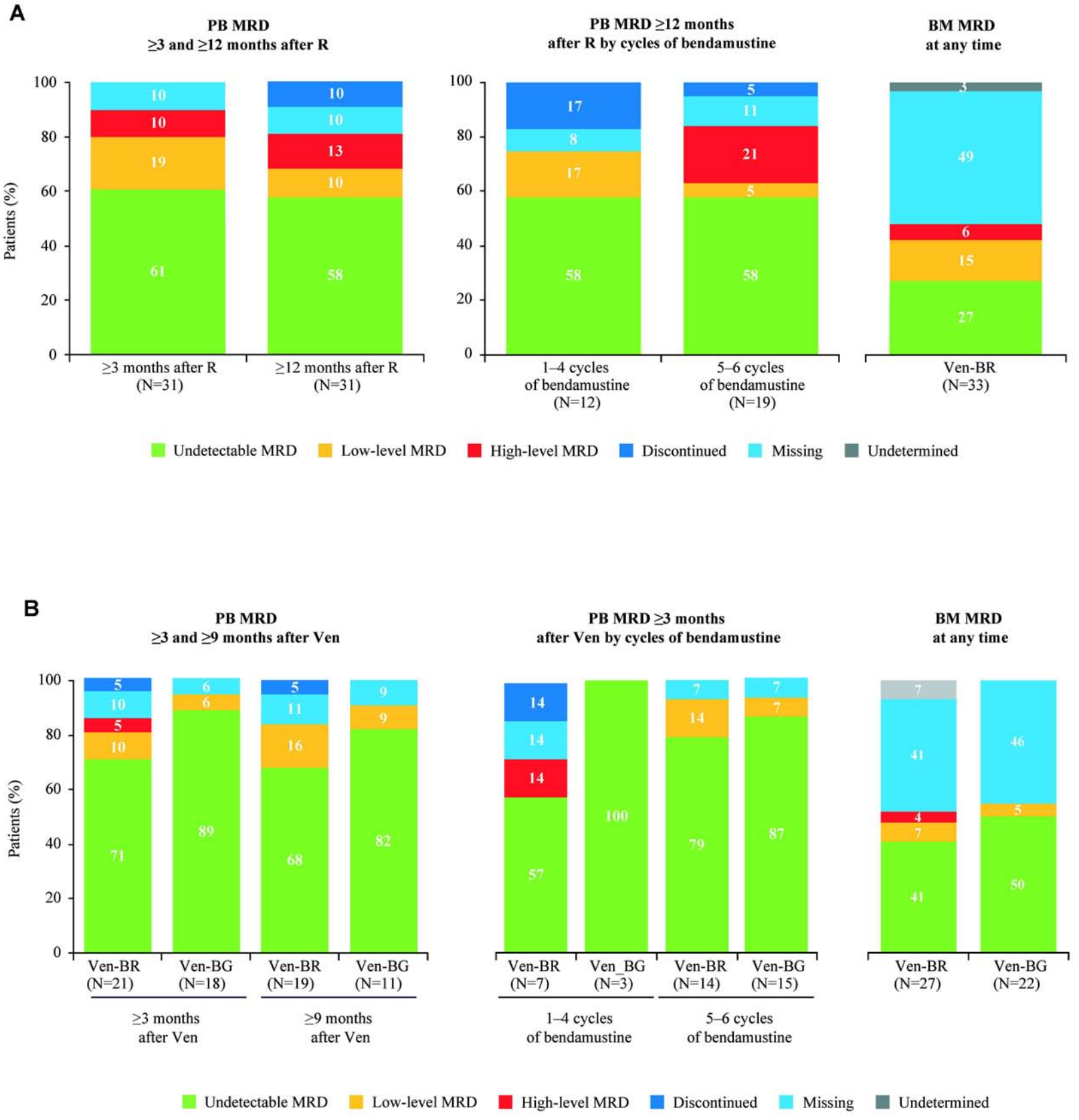
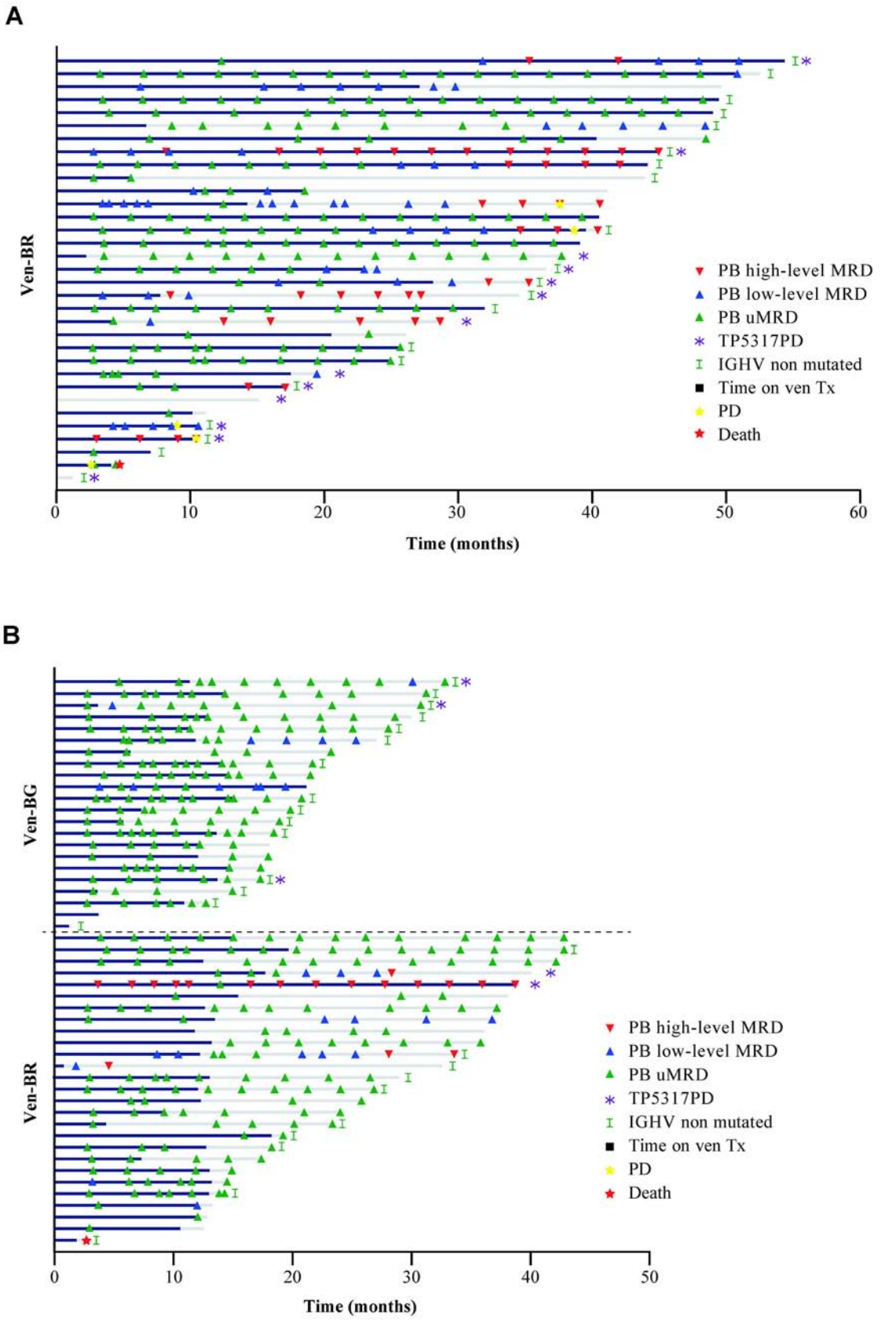
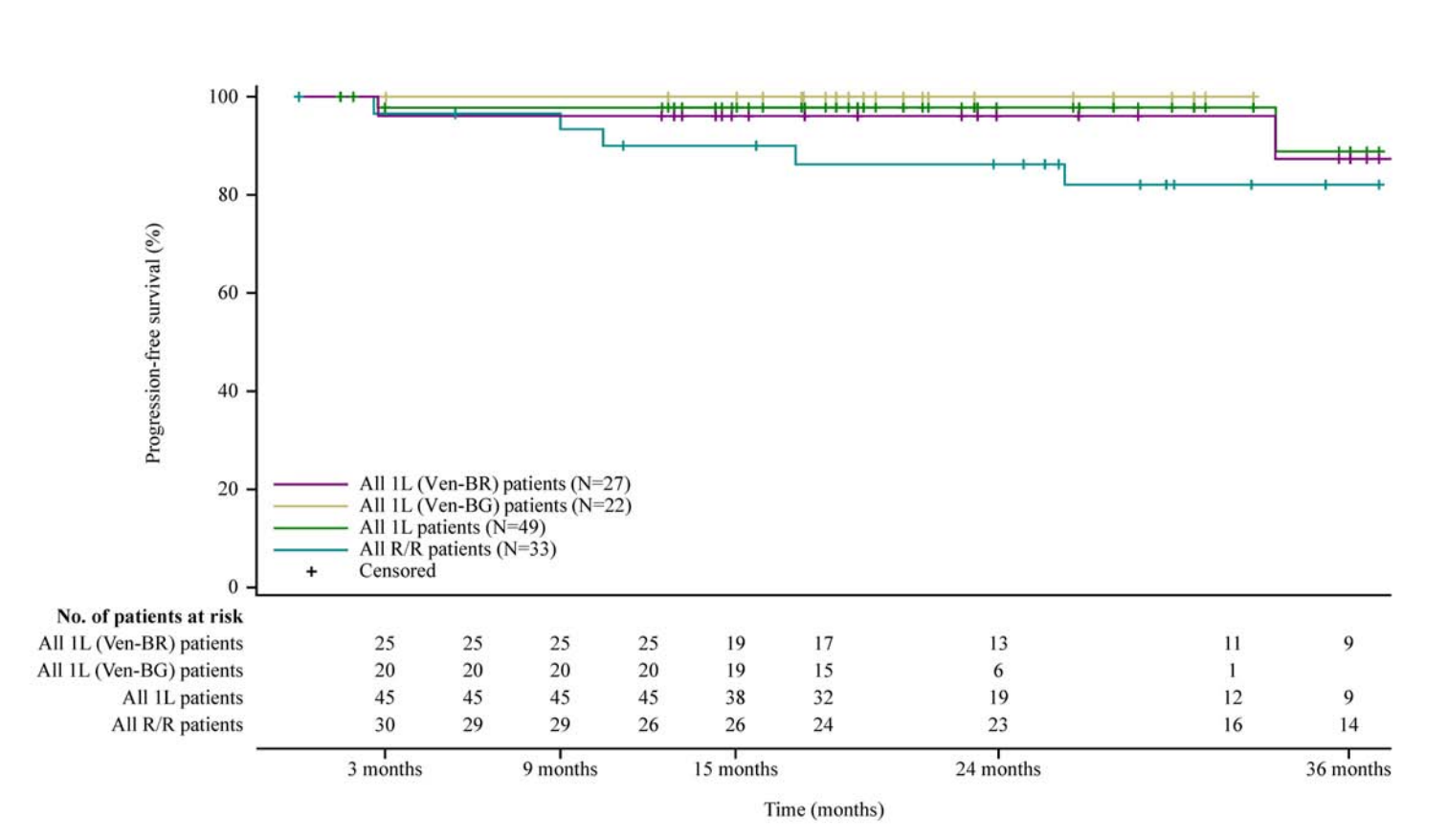





A
PB MRD
≥3 and ≥12 months after R
PB MRD ≥12 months
after R by cycles of bendamustine
BM MRD
at any time
Patients (%)
100
80
60
40
20
0
10
10
19
61
10
10
13
10
58
17
8
17
58
5
11
21
5
58
3
49
6
15
27
≥3 months after R
(N=31)
≥12 months after R
(N=31)
1–4 cycles
of bendamustine
(N=12)
5–6 cycles
of bendamustine
(N=19)
Ven-BR
(N=33)
Undetectable MRD
Low-level MRD
High-level MRD
Discontinued
Missing
Undetermined
B
PB MRD
≥3 and ≥9 months after Ven
PB MRD ≥3 months
after Ven by cycles of bendamustine
BM MRD
at any time
Patients (%)
100
80
60
40
20
0
5
10
5
10
71
6
6
89
5
11
16
68
9
9
82
14
14
14
57
100
7
14
79
7
7
87
7
41
4
7
41
46
5
50
Ven-BR
(N=21)
Ven-BG
(N=18)
Ven-BR
(N=19)
Ven-BG
(N=11)
Ven-BR
(N=7)
Ven_BG
(N=3)
Ven-BR
(N=14)
Ven-BG
(N=15)
Ven-BR
(N=27)
Ven-BG
(N=22)
≥3 months
after Ven
≥9 months
after Ven
1–4 cycles
of bendamustine
5–6 cycles
of bendamustine
Undetectable MRD
Low-level MRD
High-level MRD
Discontinued
Missing
Undetermined


A
Ven-BR
PB high-level MRD
PB low-level MRD
PB uMRD
TP5317PD
IGHV non mutated
Time on ven Tx
PD
Death
0
10
20
30
40
50
60
Time (months)
B
Ven-BG
Ven-BR
PB high-level MRD
PB low-level MRD
PB uMRD
TP5317PD
IGHV non mutated
Time on ven Tx
PD
Death
0
10
20
30
40
50
Time (months)


Progression-free survival (%)
100
80
60
40
20
0
All 1L (Ven-BR) patients (N=27)
All 1L (Ven-BG) patients (N=22)
All 1L patients (N=49)
All R/R patients (N=33)
+ Censored
No. of patients at risk
All 1L (Ven-BR) patients 25 25 25 25 19 17 13 11 9
All 1L (Ven-BG) patients 20 20 20 20 19 15 6 1
All 1L patients 45 45 45 45 38 32 19 12 9
All R/R patients 30 29 29 26 26 24 23 16 14
3 months
9 months
15 months
24 months
36 months
Time (months)

SUPPLEMENTARY INFORMATION

Stilgenbauer et al.

Venetoclax and bendamustine plus rituximab or obinutuzumab in CLL: Final results of a phase 1b study (GO28440)

Supplementary methods

Prophylaxis

Granulocyte colony-stimulating factor was permitted as primary prophylaxis for neutropenia in each treatment cycle per the American Society of Clinical Oncology guidelines,[1] or according to site institutional standards.

Dose modification and drug discontinuation

No rituximab or obinutuzumab dose modifications were permitted; however, bendamustine dose could be reduced to 70 or 50 mg/m^2 due to toxicity. Patients permanently discontinued bendamustine and/or rituximab or obinutuzumab for grade ≥3 toxicity unresolved after 3 weeks that had a reasonable possibility of being related to their administration, or recurrent grade ≥3 neutropenia with infection despite granulocyte colony-stimulating factor support. Venetoclax discontinuation was recommended according to the same criteria if the toxicity was believed to be venetoclax-related. Venetoclax could be continued following discontinuation of bendamustine and/or rituximab or obinutuzumab. All study treatment was discontinued in the case of disease progression.

Assessments

Baseline characteristics assessed centrally included cytogenetic aberrations, mutational analysis of immunoglobulin heavy-chain variable region and *TP53* genes, and serum β2-microglobulin expression. Measurable lymph-node size assessments by computed tomography/magnetic resonance imaging were mandatory pre-treatment to assess tumor lysis syndrome (TLS) risk (Supplementary Table S2) and subsequently to confirm response.

Bone marrow (BM) biopsy was required whenever there was a clinical indication of response, starting from the end of Cycle (C) 2.

Peripheral blood (PB) minimal residual disease (MRD) samples were taken at baseline, C4, any time complete response (CR) was determined, every 2–3 months after the last rituximab/obinutuzumab dose (relapsed/refractory and previously untreated [1L]), and (1L) every 3 months after the last venetoclax dose. BM MRD samples were required at CR confirmation and 3 months after 1 year of treatment. Undetectable (u)MRD was defined as <1 CLL cell/10^4 mononuclear cells; low-level MRD

as 1 CLL cell per 10^4–10^2 mononuclear cells (≥10^{-4}–<10^{-2}), and high-level MRD as ≥1 CLL cell per 10^2 mononuclear cells (≥10^{-2}).

Sample size

Planned enrollment was approximately 100 patients, assuming 3–6 for each dose-finding cohort and at least 14 additional patients for each expansion cohort. The sample size of approximately 20 patients for the selected dose level was chosen to provide a reasonable likelihood of detecting adverse events.

Dose intensity calculation

Dose intensity for venetoclax was calculated as the total dose received by patients divided by the expected total target dose, starting from the first day that the target venetoclax dose for a cohort was given until the last day of venetoclax treatment or clinical cut-off date (whichever occurred first). Dose reductions were incorporated into the numerator. The target dose for cohort 1 was 100 mg; thus, the first day a patient in this cohort received 100 mg was counted as the first day in the dose intensity calculations, and the expected target dose remained at 100 mg until the patient discontinued venetoclax or increased the dose (e.g. after the initiation of the safety-expansion phase of the study). During the expansion phase, the target dose for all cohorts was 400 mg, counted from the first day a patient began dose escalation from his/her dose-finding target dose, until the patient discontinued venetoclax or clinical cut-off date. If a patient did not reach the intended dose during dose ramp-up, either in the dose-escalation or safety-expansion cohorts, then that patient was excluded from the dose intensity calculations.

Supplementary Table S1 Dose escalation rules

Standard 3+3 dose escalation rules apply

- If no DLT is observed in any of three patients in the current cohort, the next cohort may begin enrollment without further expansion of the current cohort. Expansion beyond three patients in this instance is still possible without any DLTs with the approval of the IMC and SOC
- If a DLT is observed in one of three patients at a given dose level during the DLT observation period prior to dose escalation, additional patients will be enrolled at that dose level for a total of at least six patients (unless a second DLT is observed prior to enrolling six patients) to evaluate fully that dose level
  - If no additional patients (one of six or <33%) experience a DLT during the DLT observation period prior to dose escalation, then the next dose cohort regimen may be evaluated, after consultation with the study investigators
  - If DLTs are observed in two or more patients during the DLT observation period prior to dose escalation (or in one-third or more of patients if the cohort includes more than six patients), further enrollment at that dose level and dose escalation will be halted and that dose will be considered as exceeding the MTD
- The MTD can only be established with a minimum of six patients per cohort. If the highest planned cohort enrolls three patients with no DLTs, three additional patients must be enrolled into that cohort before that dose can be qualified as the MTD. All six (or more) patients may be enrolled at once if no further dose finding is planned (i.e. if the dose is intended to be the study MTD, even if toxicities do not limit dose finding beyond that dose). If ≥33% of patients experience a DLT in a cohort with six or more evaluable patients, the previous cohort (if performed) can only be considered as the MTD if six patients were enrolled in the cohort and there were fewer than two DLTs

The highest (or most dose intensive) dosing regimen resulting in DLTs in less than one-third of a minimum of six patients will be considered the study MTD for that unique combination of patient population and schedule. One study MTD per schedule will be considered for further study in the safety-expansion stage for each patient population

DLT dose-limiting toxicity, IMC internal monitoring committee, SOC scientific overview committee, MTD maximum tolerated dose.

Supplementary Table S2 Risk categorization and prophylaxis measures for TLS

TLS risk categorization	**Low risk:** Presence of all measurable lymph nodes with the largest diameter <5 cm by radiographic assessment AND absolute lymphocyte counts <25 X 10^9/l	**Medium risk:** An absolute lymphocyte count ≥25 X 10^9/l OR The presence of any measurable lymph nodes with the largest diameter ≥5 cm and <10 cm by radiologic assessment	**High risk:** The presence of BOTH an absolute lymphocyte count ≥25 X 10^9/l AND a measurable lymph node with the largest diameter ≥5 cm but <10 cm by radiologic assessment OR The presence of any measurable lymph node with the largest diameter ≥10 cm by radiologic assessment
Prophylaxis measures			
All patients had to receive the following TLS prophylaxis measures prior to the initiation of the first dose of venetoclax			
Oral uric acid reducer	Oral uric acid reducer, such as allopurinol 300 mg/day, beginning ≥72h prior to dose and continued until the first week of combination therapy with venetoclax and rituximab/obinutuzumab was completed. Rasburicase was administered per regional standards/institutional guidelines as prophylaxis prior to the first dose of venetoclax for all patients with high uric acid levels (above the local laboratory ULN or threshold of 476 µmol/l). For patients with a contraindication to rasburicase (i.e. glucose-6 phosphate dehydrogenase deficiency), the TLS risk-mitigation plan was reviewed with the Medical Monitor. Uric acid levels following treatment with rasburicase were analyzed using specific guidelines: • On days of study drug administration, pre-dose laboratory samples should be drawn within 0–4h before the start of infusion, unless otherwise specified • Unless otherwise indicated, other laboratory tests occurring on the same day should be obtained within a ±15-min window of any scheduled time • Laboratory tests occurring at time intervals ≥24h post-dose should be obtained within a ±2-h window of the scheduled time • Instruction manuals and supply kits were to be provided for all central laboratory assessments.		
Oral hydration*	Oral hydration of 1.5–2 l/day beginning ≥48h prior to the venetoclax dose and continuing for ≥24h post-venetoclax dose.		

Hospitalization	All patients had to be hospitalized for the first venetoclax dose. Hospitalization began the evening prior to dosing and continued for 24h after dosing. Upon admission, the following was done:	
	Serum chemistry and hematology†‡	Hematology, chemistry, and vital signs (pre-dose where applicable) at 8h and 24h post-dose Chemistry within 72h prior to dose: pre-dose; and at 4h, 6h, 8h, 10h, 12h, and 24h post-dose Vital signs at any hematology and/or chemistry laboratory assessment
	Rasburicase	Rasburicase was administered per regional standards/institutional guidelines as prophylaxis prior to the first dose of venetoclax for all patients with high uric acid levels (above the local laboratory ULN or threshold of 476 µmol/l). For patients with a contraindication to rasburicase (i.e. glucose-6 phosphate dehydrogenase deficiency), the TLS risk-mitigation plan was reviewed with the Medical Monitor. Uric acid levels following treatment with rasburicase were analyzed using specific guidelines: • On days of study drug administration, pre-dose laboratory samples should be drawn within 0–4h before the start of infusion, unless otherwise specified • Unless otherwise indicated, other laboratory tests occurring on the same day should be obtained within a ±15-min window of any scheduled time • Laboratory tests occurring at time intervals ≥24h post-dose should be obtained within a ±2-h window of the scheduled time • Instruction manuals and supply kits were to be provided for all central laboratory assessments
	IV hydration*	Upon hospital admission, IV hydration was started with a target of approximately 2–3 l/day or as clinically appropriate.
During ramp-up period	Serial vital signs were performed. Chemistry and hematology laboratory sample draws were taken. The frequency of these monitoring parameters varied depending on the TLS risk category, along with whether or not hospitalization was required after the initiation of a dose level for the patient. Any patient could be hospitalized at subsequent dose finding if deemed necessary at the investigator's discretion. For subsequent dose increases during the venetoclax ramp-up period: 100, 200, and 400 mg: all patients, irrespective of their risk category, continued administration of an oral uric acid reducer as indicated above. Additional TLS prophylaxis and monitoring procedures were tailored to the individual TLS risk category as follows: • Low-risk patients o Received oral hydration and the subsequent venetoclax dose increases (100, 200, 400 mg) as outpatients	

	o Oral hydration consisting of fluid intake of approximately 1.5–2 l/day starting ≥48h prior to dosing. For patients who were hospitalized, IV hydration was encouraged at these dose increases for patients unable to maintain such oral hydration. Also in those patients, IV hydration in the outpatient setting on the day of dosing during the clinic stay was recommended in order to ensure adequate hydration was achieved. For patients in whom volume overload was considered a significant risk, hospitalization was considered. o Hematology upon hospital admission prior to D1 of dose: pre-dose; and at 8h, 24h, 48h, and 72h post-dose o Chemistry upon hospital admission prior to D1 of dose: pre-dose; and at 4h, 6h, 8h, 10h, 12h, 24h, 48h, and 72h post-dose o Vital signs at hematology and/or chemistry laboratory assessment • Medium-risk patients with a creatinine clearance ≥80 ml/min received their subsequent dose increases as an outpatient o Patients treated as an outpatient received the following: oral hydration consisting of fluid intake of approximately 1.5–2 l/day starting ≥48h prior to dosing. For patients who were not hospitalized, IV hydration was encouraged at subsequent dose increases for patients unable to maintain such oral hydration. Also in those patients, IV hydration in the outpatient setting on the day of dosing during the clinic stay was recommended in order to ensure adequate hydration was achieved. For patients in whom volume overload was considered a significant risk, hospitalization was considered • Medium-risk patients with creatinine clearance <80 ml/min and/or who had high tumor burden (defined per the discretion of the investigator) could continue being hospitalized at dose increases above 50 mg/day of venetoclax o Hospitalized patients received the following: oral hydration consisting of fluid intake of approximately 1.5–2 l/day ≥48h prior to dosing. When hospitalized, IV hydration was started with a target of approximately 2–3 l per day or as clinically appropriate. Serum chemistry samples were drawn upon admission, prior to dosing (defined as up to 4h before venetoclax dose), and at 4h, 8h, 12h, and 24h post-dose o Patients were treated with a uric acid reducer, such as allopurinol or rasburicase, as per label or local guidance. Treatment with allopurinol started 3 days prior to D1 of C1. Due to a potential interaction between allopurinol and bendamustine, which may lead to severe skin reactions, allopurinol was paused during the days of bendamustine administration and re-started from the day after the second bendamustine administration. If rasburicase was available, it was considered, especially in patients with elevated pre-treatment urate levels despite allopurinol, as it is more efficacious than allopurinol o For patients with a contraindication to rasburicase, i.e. glucose-6 phosphate dehydrogenase deficiency, the TLS risk-mitigation plan had to be reviewed with the Medical Monitor. Uric acid levels following treatment with rasburicase were analyzed using specific guidelines as described above for the low-risk category o Hematology upon hospital admission prior to D1 of dose: pre-dose; and at 8h, 24h, 48h, and 72h post-dose o Chemistry upon hospital admission prior to D1 of dose: pre-dose; and at 4h, 6h, 8h, 10h, 12h, 24h, 48h, and 72h post-dose o Vital signs at any hematology and/or chemistry laboratory assessment

	• High-risk patients§ o All high-risk patients were hospitalized for monitoring at subsequent dose increases above 50 mg/day of venetoclax. Hospitalization began the evening prior to the dose of venetoclax and continued for 24h after. o Oral hydration consisting of fluid intake of approximately 1.5–2 l/day starting ≥48h prior to dosing. When hospitalized, IV hydration was started with a target of approximately 2–3 l per day or as clinically appropriate. o For patients with a contraindication to rasburicase, i.e. glucose-6 phosphate dehydrogenase deficiency, the TLS risk-mitigation plan had to be reviewed with the Medical Monitor. Uric acid levels following treatment with rasburicase were analyzed using specific guidelines as described above for the low-risk category: o Drug administration, pre-dose laboratory samples should be drawn within 0–4h before the start of infusion, unless otherwise specified o Unless otherwise indicated, other laboratory tests occurring on the same day should be obtained within a ±15-min window of any scheduled time o Laboratory tests occurring at time intervals ≥24h post-dose should be obtained within a ±2-h window of the scheduled time o Hematology upon hospital admission prior to D1 of dose: pre-dose; and at 8h, 24h, 48h, and 72h post-dose o Chemistry upon hospital admission prior to D1 of dose: pre-dose; and at 4h, 6h, 8h, 10h, 12h, 24h, 48h, and 72h post-dose o Vital signs at any hematology and/or chemistry laboratory assessment
	First dose of bendamustine + obinutuzumab (applicable on days on which the patient is not taking venetoclax) o Patients should be treated with a uric acid reducer as per label or local guidance. Treatment with allopurinol should start 3 days prior to D1 of C1. Due to a potential interaction between allopurinol and bendamustine, which may lead to severe skin reactions, allopurinol should be paused during the days of bendamustine administration and re-started from the day after the second bendamustine administration. If rasburicase is available, it should be considered, especially in patients with elevated pre-treatment urate levels despite allopurinol, as it is proven to be more efficacious than allopurinol o Patients should receive oral hydration (approximately 3 l/day recommended) starting 3 days before the first dose of obinutuzumab and should receive IV hydration on D1 and D2 of C1 (approximately 3 l/day recommended). Oral hydration should restart on D3 and continue until and including D8 (approximately 3 l/day recommended). o Hematology, chemistry, and vital signs (pre-dose where applicable) on C1D1, C1D2, C1D3, C1D5, and C1D8.‖

*For patients unable to maintain oral hydration at 1.5–2 l/day starting at least 48h prior to the start of treatment, IV hydration in the outpatient setting on the day of dosing during the clinic stay was recommended (unless being hospitalized) to assure that this full amount of hydration was achieved. For patients for whom volume overload was considered a significant risk, hospitalization was considered.
†Results from pre-dose laboratory values were not required to be available prior to initiating venetoclax treatment, provided that laboratory values obtained within 24h before dosing were within normal limits. For laboratory samples drawn on days on study treatment, “before dosing” laboratory samples were drawn within 0–4h before the dose.
‡Any patient who, at any dose, developed clinically significant electrolyte abnormalities must have subsequent venetoclax dose held until the electrolyte abnormalities resolve. Patients who developed electrolyte abnormalities underwent aggressive management and further monitoring. At any time during the ramp-up period, if venetoclax was held for 7 days or less, the patient may resume venetoclax at the same dose level or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status). Dose was resumed at one lower dose level if dose held more than 7 days with the exception of initial dose level of 20 mg (400 mg → 200 mg, 200 mg → 100 mg, 100 mg → 50 mg, 50 mg→ 20 mg).
§Nephrology (or acute dialysis service) consultation was considered on admission (per institutional standards or based on investigator discretion) for hospitalized patients to ensure emergency dialysis was available and the appropriate staff were aware and prepared to handle any necessary intervention for TLS. Telemetry was also considered.
||Laboratory tests could be required at these time-points for venetoclax. If laboratory tests/vital signs were requested for the same time-point, one set was sufficient per time-point.

TLS tumor lysis syndrome, ULN upper limit of normal, IV intravenous, D day, C cycle.

Supplementary Table S3 Inclusion/exclusion criteria

Inclusion criteria
• Signed informed consent form • Age ≥18 years • Diagnosis of CLL, as defined by iwCLL guidelines.[2] Patients with prolymphocytic leukemia, defined as ≥55% prolymphocytes in the peripheral blood, or Richter's transformation were excluded • Patients with relapsed or refractory CLL must have met the following requirements: – Received at least one prior chemotherapy-containing treatment regimen but not more than three prior treatment lines: ▪ For patients with 17p deletion and/or *TP53* mutation: previously treated with at least one but not more than three lines of therapy, including at least one prior standard chemotherapy-containing regimen according to current guidelines OR at least one prior alemtuzumab-containing therapy OR at least one prior treatment with a B-cell receptor inhibitor, either ibrutinib or idelalisib – Requires treatment in the opinion of the investigator – Patients with relapsed disease must have developed progressive disease following a response to the prior treatment regimen – Patients with refractory disease must have failed to respond or relapsed within 6 months of the last prior regimen • Patients with previously untreated CLL must meet the following requirements: – Received no prior systemic therapy for CLL. Patients with a history of emergency, loco-regional radiotherapy, e.g. for relief of compressive signs or symptoms, or corticosteroids are eligible • Requires treatment according to one or more criteria based on iwCLL guidelines[2] • ECOG performance status of 0–1 • Hematology values within the following limits independent of growth factor support or transfusion, unless cytopenia is caused by the underlying disease, i.e. no evidence of additional bone marrow dysfunction such as myelodysplastic syndrome, hypoplastic bone marrow: – Platelet count ≥75 000/mm^3, unless thrombocytopenia clearly due to marrow involvement of CLL, and/or disease-related immune thrombocytopenia, in which case platelet count ≥30 000/mm^3 – Absolute neutrophil count ≥1000/mm^3, without growth factor support, unless neutropenia is definitely due to marrow involvement of CLL – Total hemoglobin ≥9 g/dl, without transfusion support, unless anemia is clearly due to marrow involvement of CLL • Adequate coagulation, renal, and hepatic function, per laboratory reference range at screening as follows: – Activated partial thromboplastin time/partial thromboplastin time and prothrombin time not to exceed 1.2 × ULN, unless in presence of known lupus allowed anticoagulant – Calculated creatinine clearance ≥30 ml/min using 24-h creatinine clearance or modified Cockcroft–Gault equation (using ABM):

$$eCCr = \frac{(140 - age) \bullet ABM\ (kg) \bullet [0.85\ if\ female]}{72 \bullet serum\ creatinine\ (mg/dl)}$$

Or, if serum creatinine is in μmol/l:

$$eCCr = \frac{(140 - age) \bullet ABM\ (kg) \bullet [1.23\ if\ male,\ 1.04\ if\ female]}{serum\ creatinine\ (\mu mol/l)}$$

IBM should be used instead of ABM when the patient's BMI is ≥30 kg/m^2:

BMI = ABM (kg)/(height in cm/100)^2
IBM (kg) = [(height in cm − 154) × 0.9] + (50 if male, 45.5 if female)

- Enzymes AST, alanine transaminase, ALT ≤3.0 × ULN of institution's normal range
- Bilirubin ≤1.5 × ULN
  - Patients with Gilbert's syndrome could have a bilirubin >1.5 × ULN, per discussion between the investigator and the Medical Monitor

- Female patients must have been surgically sterile, postmenopausal (for at least 1 year), or have negative results for a pregnancy test performed as follows:
  - At screening, on a serum sample obtained within 14 days prior to the first study drug administration, and
  - Prior to dosing, on a urine sample obtained on the first day of the dose-escalation or expansion stage if it has been >7 days since obtaining the serum pregnancy test result
- All female patients not surgically sterile or postmenopausal (for at least 1 year) must have been practicing at least one of the following methods of birth control during study participation and for 30 days after the last dose of venetoclax, 12 months after the last dose of BR, or 18 months after the last dose of BG, whichever is later
- Non-vasectomized male patients must have been practicing at least one of the following methods of birth control during study participation and for 90 days after the last dose of venetoclax or 18 months after the last dose of BR or BG, whichever is later. They must also have refrained from donating sperm during study participation and for 90 days after the last dose of venetoclax or 18 months after the last dose of BR or BG
  - Total abstinence from sexual intercourse (minimum one complete menstrual cycle)
  - A vasectomized male partner
  - Hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) that started ≥3 months prior to study drug administration
  - Double-barrier method (condom + diaphragm or vaginal cup with spermicidal contraceptive sponge, jellies, or cream)

Exclusion criteria

- Previous allogeneic stem cell transplant
- Known human immunodeficiency virus positivity
- Uncontrolled autoimmune hemolytic anemia or thrombocytopenia
- Positive test results for chronic HBV infection, defined as:
  - Seropositivity for HBsAg or HBcAb
  - Patients positive for HBcAbs following administration of IVIg could be eligible only if PCR is negative for HBV. Patients with positive HBV core antibody must have been willing to

undergo monthly HBV DNA testing for at least 1 year after the last anti-CD20 infusion. Eligibility of patients thought to have passive transfer of HBV core antibodies or HBV surface antibodies from IVIg administration must have been discussed with the Medical Monitor

- Positive test results for HCV
  - Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA
- History of severe, defined as grade 4 and/or requiring permanent discontinuation of prior antibody therapy, allergic or anaphylactic reactions to human, humanized, chimeric, or murine mAbs
- History of intolerance to prior bendamustine treatment, defined as toxicity requiring permanent discontinuation of bendamustine, or other contraindication to bendamustine treatment
- History of bendamustine-refractory disease, defined as no response to treatment or relapse/progression within 6 months of previous bendamustine-containing regimen
- History of progressive multifocal leukoencephalopathy
- Received a biologic agent (e.g. a mAb) within 8 weeks prior to the first dose of study drug
- Received a live viral vaccination within 6 months prior to the first dose of study drug
- Received any of the following agents within 28 days prior to the first dose of study drug, or has not recovered to less than grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:
  - Any anti-cancer therapy including chemotherapy or radiotherapy (except local radiation therapy for palliation), steroid therapy for anti-neoplastic intent, and investigational therapy, including targeted small molecule agents
- Received the following agents within 7 days prior to the first dose of venetoclax:
  - Strong and moderate CYP3A inhibitors such as fluconazole, ketoconazole, and clarithromycin
  - Strong and moderate CYP3A inducers such as rifampin and carbamazepine
  - Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit within 3 days prior to the first dose of venetoclax
- History of a prior significant toxicity, other than thrombocytopenia, from another BCL-2 family protein inhibitor
- A cardiovascular disability status of New York Heart Association Class $\geq$2. Class 2 was defined as cardiac disease in which patients are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain
- A significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, cardiovascular, hepatic disease, or other condition that, in the opinion of the investigator, would adversely affect the patient's participation in this study or interpretation of study outcomes
- A female patient who was pregnant or breast-feeding
- History of other active malignancies other than CLL within the past 3 years prior to study entry, with the exception of:
  - Adequately treated in situ carcinoma of the cervix uteri
  - Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin
  - Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent
- Malabsorption syndrome or other condition that precludes enteral route of administration
- Known allergy to both xanthine oxidase inhibitors and rasburicase

- Evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
  - Uncontrolled systemic infection (viral, bacterial, or fungal)
  - Diagnosis of fever and neutropenia within 1 week prior to study drug administration

CLL chronic lymphocytic leukemia, iwCLL International Workshop on CLL, ECOG Eastern Cooperative Oncology Group, ULN upper limit of normal, ABM actual body mass, eCCR estimated creatinine clearance, IBM ideal body mass, BMI body mass index, AST aspartate aminotransferase, ALT alanine aminotransferase, B bendamustine, R rituximab, G obinutuzumab, HBV hepatitis B virus, HBsAg hepatitis B surface antigen, HBcAb hepatitis B core antibody, IVIg intravenous immunoglobulin, PCR polymerase chain reaction, HCV hepatitis C virus, mAb monoclonal antibody, CYP3A cytochrome P450, family 3, subfamily A, BCL-2 B-cell lymphoma 2.

Supplementary Table S4 Assessment of DLTs

DLTs in this study are defined as specific AEs (as defined below) occurring during the DLT observation window

Any of the following AEs (including clinically significant abnormal laboratory values) that are attributed as having a reasonable possibility of being related to the administration of venetoclax and/or BR and/or BG, and that cannot be attributed by the investigator to a clearly identifiable cause such as tumor progression, concurrent illness, or concomitant medication, will be considered a DLT:

- Grade 4 neutropenia (that was not present at screening) not responsive to G-CSF lasting more than 14 days
- Grade 3 or 4 febrile neutropenia with fever lasting longer than 4 days
- Grade 4 thrombocytopenia (or reduction of >50% for those patients with thrombocytopenia at baseline) resulting in bleeding, or that does not improve to grade ≤2 (or to ≥80% of the baseline value, whichever is lower) within 3 weeks
- Clinical TLS
- Grade 4 IRRs secondary to rituximab or obinutuzumab despite appropriate premedication and administration rate (defined as an infusion-related toxicity occurring during or within 24h after completing an infusion of rituximab or obinutuzumab). A grade 3 IRR that is reversible with treatment and does not require a dose delay of >24h was not considered a DLT
- All other grade 3, 4, or 5 AEs attributable to venetoclax were considered a DLT if they persisted for more than 2 weeks with or without treatment, with the following exceptions:
  - Grade 3 neutropenia without fever that does not resolve within 4 weeks
  - Grade 3 thrombocytopenia that does not result in bleeding and does not resolve within 4 weeks
  - Grade 3 or 4 lymphopenia and/or leukopenia
  - Grade 3 anemia that does not resolve within 4 weeks
  - Grade 3 TLS other than clinical TLS that resolves within 72h.
  - Grade ≥3 hyperuricemia or hypocalcemia or grade 3 hyperkalemia, if transient (lasting <72h) and without manifestations of clinical TLS
  - Grade 3 hyperphosphatemia with hospitalization primarily for monitoring/prophylaxis
  - Grade 3 or 4 elevations in bilirubin associated with hemolysis resolving within 14 days
  - Grade 3 nausea, vomiting, and/or diarrhea unless unresponsive to treatment

Any AE that met the definition of a DLT as described above, but was observed outside the DLT observation window, was not be considered a DLT because of combination therapy. During dose-finding, patients who experienced an AE meeting the definition of a DLT before the DLT observation window (before combination treatment) did not receive combination treatment and were considered not evaluable for combination DLT assessment. In this scenario, all drugs were to be held, and consultation with the Medical Monitor was to occur to discuss continued study participation. Enrolling an additional patient to meet DLT observation requirements originally fulfilled by the discontinued patient may be necessary.

DLT dose-limiting toxicity, AE adverse event, B bendamustine, R rituximab, G obinutuzumab, G-CSF granulocyte-colony stimulating factor, TLS tumor lysis syndrome, IRR infusion-related reaction.

Supplementary Table S5 Treatment cycles received

Patients, *n* (%)	R/R Ven-BR (*n* = 33)	1L Ven-BR (*n* = 27)	1L Ven-BG (*n* = 22)
All therapy components			
Patients completing 6 cycles, *n* (%)	16 (49)	11 (41)	8 (36)
Bendamustine			
Median no. of cycles (range)	5 (1–6)	5 (1–6)	5 (1–6)
Patients completing, *n* (%)			
Exactly 1 cycle	4 (12)	1 (4)	4 (18)
Exactly 2 cycles	2 (6)	2 (7)	0
Exactly 3 cycles	3 (9)	4 (15)	0
Exactly 4 cycles	4 (12)	2 (7)	2 (9)
Exactly 5 cycles	4 (12)	7 (26)	7 (32)
Exactly 6 cycles	16 (49)	11 (41)	9 (41)
Rituximab			
Median no. of cycles (range)	6 (1–6)	6 (1–6)	–
Patients completing 6 cycles, *n* (%)	13 (39)	10 (37)	–
Obinutuzumab			
Median no. of cycles (range)	–	–	6 (1–6)
Patients completing 6 cycles, *n* (%)	–	–	11 (50)

Supplementary Table S6 Venetoclax dose levels evaluated

Patients, *n*	R/R Ven-BR (*n* = 33)		1L Ven-BR (*n* = 27)		1L Ven-BG (*n* = 22)
Dose-finding	Schedule A	Schedule B	Schedule A	Schedule B	Schedule B
100 mg	3	–	–	–	–
200 mg	3	–	–	–	–
400 mg	6	6	6	7	8
Safety-expansion	Schedule B				
400 mg	15		14		14

R/R relapsed/refractory, Ven venetoclax, B bendamustine, R rituximab, 1L first-line, G obinutuzumab.

Supplementary Table S7 Summary of SAEs

Patients, *n* (%)	R/R Ven-BR (*n* = 33)	1L Ven-BR (*n* = 27)	1L Ven-BG (*n* = 22)
Patients with ≥1 SAE	17 (52)	14 (52)	12 (55)
Overall total number of events	35	27	30
SAEs occurring in ≥5% of patients in any arm			
Infections	7 (21)	2 (7)	4 (18)
Febrile neutropenia	2 (6)	2 (7)	0
Acute kidney injury	1 (3)	1 (4)	1 (5)
Thrombocytopenia	0	0	3 (14)
Diarrhea	0	0	1 (5)
Enteritis	0	0	1 (5)
Gastritis	0	0	1 (5)
Renal failure	0	1 (4)	2 (9)
Seizure	0	0	1 (5)
Infusion-related reaction	0	0	1 (5)
Blood creatinine increased	0	0	2 (9)
Toxic skin eruption	0	0	1 (5)
Arthralgia	0	0	1 (5)
Acute cholecystitis	0	0	1 (5)
Lung disorder	0	0	1 (5)
Pulmonary edema	0	0	1 (5)

Treatment-emergent AEs only.

SAE serious adverse event, R/R relapsed/refractory, Ven venetoclax, B bendamustine, R rituximab, 1L first-line, G obinutuzumab, AE adverse event.

Supplementary Table S8 Grade 3–4 AEs* by number of cycles of bendamustine

Patients, *n* (%)	R/R Ven-BR (*n* = 33)		1L Ven-BR (*n* = 27)		1L Ven-BG (*n* = 22)	
No. of cycles of bendamustine	1–4 (*n* = 13)	5–6 (*n* = 20)	1–4 (*n* = 9)	5–6 (*n* = 18)	1–4 (*n* = 6)	5–6 (*n* = 16)
Any grade 3–4 AE	12 (92)	15 (75)	8 (89)	17 (94)	6 (100)	14 (88)
Neutropenia	8 (62)	13 (65)	7 (78)	16 (89)	3 (50)	9 (56)
Thrombocytopenia	6 (46)	2 (10)	5 (56)	5 (28)	6 (100)	5 (31)
Infection	5 (39)	4 (20)	0	0	3 (50)	3 (19)
Leukopenia	4 (31)	3 (15)	0	3 (17)	1 (17)	1 (6)
Febrile neutropenia	3 (23)	0	1 (11)	1 (6)	0	0
Diarrhea	3 (23)	3 (15)	1 (11)	0	0	2 (13)
Anemia	3 (23)	1 (5)	0	3 (17)	2 (33)	0
Hypertension	3 (23)	1 (5)	0	0	0	1 (6)
Lymphopenia/ lymphocyte count decreased	2 (15)	1 (5)	3 (33)	3 (17)	0	0
Fatigue	1 (8)	2 (10)	0	0	1 (17)	0
Nausea	0	0	2 (22)	0	0	0
Renal failure	0	0	0	1 (6)	0	2 (13)
Infusion-related reaction	0	0	0	0	0	2 (13)

Treatment-emergent AEs only.

*Grade 3–4 AEs occurring in at least two patients in at least one treatment arm.

AE adverse event, R/R relapsed/refractory, Ven venetoclax, B bendamustine, R rituximab, 1L first-line, G obinutuzumab.

Supplementary Table S9 Summary of grade 3–4 AEs, occurring in ≥5% of patients in any treatment arm, during the combination therapy and monotherapy periods

Patients, *n* (%)	Combination therapy period (*n* = 82)			Ven monotherapy period (*n* = 64)		
	R/R Ven-BR (*n* = 33)	1L Ven-BR (*n* = 27)	1L Ven-BG (*n* = 22)	R/R Ven-BR (*n* = 25)	1L Ven-BR (*n* = 23)	1L Ven-BG (*n* = 16)
Total number of events	112	113	111	57	40	34
Patients with ≥1 grade 3–4 AE	26 (79)	24 (89)	20 (91)	16 (64)	14 (61)	8 (50)
Neutropenia	20 (61)	22 (82)	11 (50)	8 (32)	12 (52)	5 (31)
Thrombocytopenia	8 (24)	8 (30)	11 (50)	0	2 (9)	0
Leukopenia	5 (15)	3 (11)	2 (9)	2 (8)	0	0
Diarrhea	4 (12)	1 (4)	2 (9)	2 (8)	0	0
Anemia	4 (12)	3 (11)	2 (9)	0	1 (4)	0
Lymphocyte count decreased	3 (9)	2 (7)	0	2 (8)	1 (4)	0
Hypertension	2 (6)	0	1 (5)	1 (4)	0	0
TLS	2 (6)	0	1 (5)	0	0	0
Fatigue	2 (6)	0	1 (5)	0	0	0
Hyperuricemia	1 (3)	2 (7)	1 (5)	0	1 (4)	0
Febrile neutropenia	1 (3)	2 (7)	0	1 (4)	0	0

Hypocalcemia	1 (3)	0	2 (9)	0	0	0
Hypophosphatemia	1 (3)	0	1 (5)	0	1 (4)	0
Hyperglycemia	1 (3)	0	1 (5)	0	0	0
Hypokalemia	1 (3)	0	1 (5)	0	0	0
AST increased	1 (3)	0	1 (5)	0	0	0
Vomiting	0	1 (4)	1 (5)	0	0	0
Nausea	0	2 (7)	0	0	0	0
Renal failure	0	1 (4)	2 (9)	0	0	0
Urinary tract infection	0	0	3 (14)	0	0	0
Infusion-related reaction	0	0	2 (9)	0	0	0
Enteritis	0	0	1 (5)	0	0	0
Immune thrombocytopenic purpura	0	0	1 (5)	0	0	0
Leukocytosis	0	0	1 (5)	0	0	0
Pseudomonas infection	0	0	1 (5)	0	0	0
Sepsis	0	0	1 (5)	0	0	0
ALT increased	0	0	1 (5)	0	0	0
Pulmonary edema	0	0	1 (5)	0	0	0
Toxic skin eruption	0	0	1 (5)	0	0	0

Drug intolerance	0	0	1 (5)	0	0	0
Acute pyelonephritis	0	0	0	0	0	1 (6)
Gastritis	0	0	0	0	0	1 (6)
Pyrexia	0	0	0	0	0	1 (6)
Seizure	0	0	0	0	0	1 (6)

Treatment-emergent AEs only.

AE adverse event, Ven venetoclax, R/R relapsed/refractory, B bendamustine, R rituximab, 1L first-line, G obinutuzumab, TLS tumor lysis syndrome, AST aspartate aminotransferase, ALT alanine aminotransferase.

Supplementary Table S10 Patients who received at least one dose of growth factor in the combination therapy period versus the monotherapy period

	Combination therapy period (*n* = 82)			Ven monotherapy period (*n* = 64)		
	R/R Ven-BR (*n* = 33)	1L Ven-BR (*n* = 27)	1L Ven-BG (*n* = 22)	R/R Ven-BR (*n* = 25)	1L Ven-BR (*n* = 23)	1L Ven-BG (*n* = 16)
Patients, *n* (%)	17 (52)	22 (82)	13 (59)	11 (44)	7 (30)	6 (38)

Ven venetoclax, R/R relapsed/refractory, B bendamustine, R rituximab, 1L first-line, G obinutuzumab.

Supplementary Table S11 Summary of treatment-emergent TLS events

Patient	TLS risk category	Abnormal laboratory parameters within 24h*		Study day (venetoclax dose at onset)	Study drug relatedness
Patient 1: 1L Laboratory TLS event (schedule B) Safety-expansion phase	High	Phosphorus 1.90 mmol/l	Uric acid 589 µmol/l	Day 2 (before any venetoclax given)	Bendamustine and obinutuzumab
Patient 2: R/R Laboratory TLS event (schedule B) Safety-expansion phase	Medium	Phosphorus 1.53 mmol/l	Uric acid 551 µmol/l	Day 3 (before any venetoclax given)	Bendamustine and rituximab
Patient 3: R/R Clinical TLS event† (schedule B) Safety-expansion phase	Medium	Phosphorus 2.97 mmol/l	Uric acid 553 µmol/l Potassium 7.6 mmol/l	Day 29 (50 mg)	Venetoclax

*Treatment-emergent abnormalities in two or more of the following laboratory values within a 24-h period: uric acid >476 µmol/l, potassium >6 mmol/l, phosphorus >1.5 mmol/l, or calcium <1.75 mmol/l.

†Clinical TLS due to clinical symptoms reported as hypotension and dyspnea. Uric acid peaked at 93 mg/l on Day 29 (63 mg/l at screening), creatinine peaked at 15 mg/l on Day 30 (9 mg/l at screening). Patient did not have bulky disease (lymph nodes ≥5 cm) and was classified as medium risk based on absolute lymphocyte count at screening (241 x 10^9/l).

TLS tumor lysis syndrome, 1L first-line, R/R relapsed/refractory.

Supplementary Table S12 Study drug dose interruptions and withdrawals

Patients, *n* (%)	R/R Ven-BR (*n* = 33)*	1L Ven-BR (*n* = 27)	1L Ven-BG (*n* = 22)
AE leading to Ven dose reduction and/or interruption	22 (67)	22 (82)	18 (82)
Neutropenia leading to Ven dose reduction and/or interruption	12 (36)	17 (63)	10 (46)
AE leading to Ven dose reduction	12 (36)	6 (22)	6 (27)
AE leading to Ven dose interruption	19 (58)	21 (78)	18 (82)
AE leading to withdrawal from Ven	9 (27)	8 (30)	6 (27)
AE leading to withdrawal from bendamustine	11 (33)	9 (33)	9 (41)
AE leading to withdrawal from R or G	10 (30)	7 (26)	5 (23)

*The Ven-BG cohort did not open in R/R patients.

R/R relapsed/refractory, Ven venetoclax, B bendamustine, R rituximab, 1L first line, G obinutuzumab, AE adverse event.

Supplementary Table S13 Venetoclax discontinuations due to AEs

AEs	Grade	Study day of treatment discontinuation
AEs leading to venetoclax discontinuation		
R/R population (Ven-BR)		
ALT increased	3	434
Gastroenteritis norovirus	3	205
Pneumonia	4	532
Neutropenia	4	309
Myelodysplastic syndrome	4	697
Squamous cell carcinoma of skin	3	856
Diarrhea	3	172
Thrombocytopenia	3	70
Neutropenia	4	236
1L population (Ven-BR)		
Sarcomatoid carcinoma	3	555
Neutropenia	3	359
Neutropenia	4	131
Urticaria	2	25
Colitis	2	279
Infected neoplasm	3	322
Asthenia	3	223
Diarrhea	3	60
1L population (Ven-BG)		
Thrombocytopenia	3	114
Thrombocytopenia	3	113
Cholecystitis acute	3	195
Abdominal pain	2	331
Diarrhea	2	224
Neutropenia	3	175

AE adverse event, R/R relapsed/refractory, Ven venetoclax, B bendamustine, R rituximab, ALT alanine aminotransferase, 1L first line, G obinutuzumab.

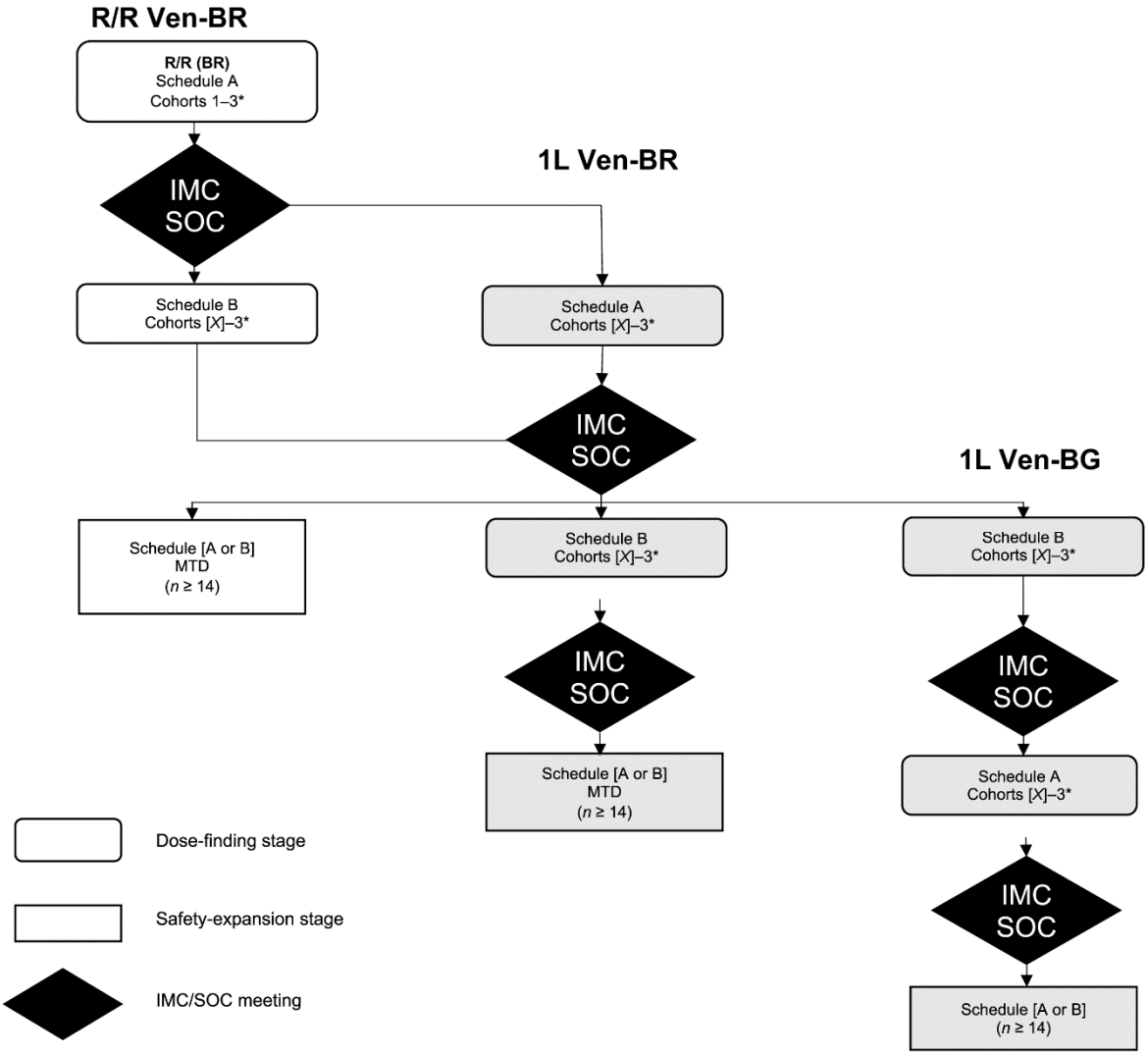
Supplementary Table S14 Concordance between MRD status determined from PB and BM

Patients, *n* (%)	R/R Ven-BR (*n* = 17)	1L Ven-BR (*n* = 8)	1L Ven-BG (*n* = 11)
Concordance between MRD status determined from PB and BM	12 (71)	8 (100)	11 (100)

Analysis performed in patients with PB and BM post-baseline paired samples from the same day.

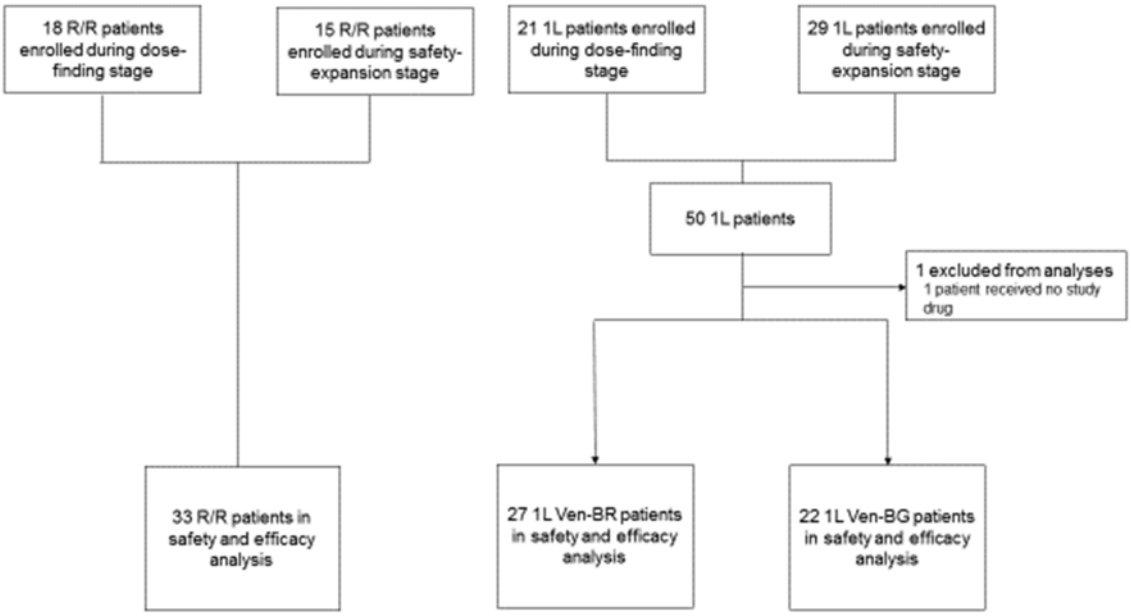
MRD minimal residual disease, PB peripheral blood, BM bone marrow, R/R relapsed/refractory, Ven venetoclax, B bendamustine, R rituximab, 1L first line, G obinutuzumab.

Supplementary Fig. S1 Study design schema.



X: starting cohort will be determined based on IMC/SOC recommendation. *More than three cohorts may be investigated but the IMC/SOC may occur prior to exploring them, unless they are the only cohorts being explored. R/R relapsed/refractory, Ven venetoclax, B bendamustine, R rituximab, IMC internal monitoring committee, SOC scientific overview committee, 1L first-line, G obinutuzumab, MTD maximum tolerated dose.

Supplementary Fig. S2 Patient flow.



R/R relapsed/refractory, 1L first-line, Ven venetoclax, B bendamustine, R rituximab, G obinutuzumab.

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