Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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The IDMC reviewed unblinded safety data at regular intervals, and the efficacy and safety at the pre-planned interim analysis. An independent review committee (IRC) consisting of radiologists who reviewed the scans, and oncologists who reviewed radiologists' assessment as well as relevant clinical data to evaluate the patient for response and progression/non-progression, were blinded to treatment arms. There was no overlap or relationship in terms of membership between the IDMC and IRC.

SUPPLEMENTARY METHODS

ELIGIBILITY CRITERIA

Key exclusion criteria included transformation of chronic lymphocytic leukemia (CLL) to aggressive or central nervous system involvement by CLL, previous allogeneic or autologous stem-cell transplant, major organ dysfunction, active infection, other active malignancy, current pregnancy or breastfeeding, and receipt of warfarin (during venetoclax dose ramp-up) or strong CYP3A4 inhibitors/inducers.

RESPONSIVENESS TO PRIOR THERAPY

High-risk CLL status was defined as having ANY of the following features: 17p deletion, no response to front-line chemotherapy-containing regimen, or relapsed disease within 12 months after chemotherapy alone or within 24 months after chemoimmunotherapy. All others were considered to be of low-risk status.

PROTOCOL AMENDMENT TO VENETOCLAX DOSE RAMP-UP

A global amendment was submitted to and approved by the ethics committees of the study centers concerning the venetoclax ramp-up period. The amendment was completed on June 10, 2014, and made a change to the duration of the venetoclax titration schedule to accommodate alteration to the starting dosage duration from 20 mg for 1 day to 20 mg daily for 1 week. Thus, patients randomized to the venetoclax arm had a more gradual 5-step dose ramp-up of 20, 50, 100, and 200 mg/day over a 5-week period to reach the target dose of 400 mg/day.

The number of patients who received the test starting dose of venetoclax, 20 mg <1 week as per the former TLS prophylaxis and management guidelines versus current guidelines, which recommend 20 mg for 1 week, are below:

- 179 patients 20 mg days 1–7, then 50 mg
- 10 patients 20 mg for 1 day, then 50 mg on day 2
- 2 patients 20 mg for 2 days, then 50 mg on day 3

- 2 patients 20 mg for 6 days, then 50 mg on day 7
- 1 patient started on 100 mg in error

TREATMENT STRATEGY IN THE EXPERIMENTAL ARM

Rituximab was started after venetoclax ramp-up as this approach was safe and efficacious in an earlier Phase 1b trial.[1] It was also hypothesized that the potential risk for tumor lysis syndrome is further mitigated by administering one drug before the other given that both venetoclax and rituximab have potential to induce tumor lysis syndrome.

Continuation of monotherapy treatment beyond the 6 months of combination therapy to 2 years (from cycle 1 day 1) was considered optimal to maximize the number and depth of responses, based on observations of improved responses over time with venetoclax as monotherapy[2] and in combination with rituximab in earlier studies that had serial response assessments.[1] Two years were considered adequate to maintain and potentially further improve the depth and duration of response induced in the first 6 months of combination treatment while minimizing toxicities and patient inconvenience.

CENTRAL LABORATORY ASSESSMENTS

Central laboratory assessments included CLL biological prognostic factors, genomic aberrations using fluorescence *in situ* hybridization, mutational analysis of the immunoglobulin heavy-chain variable region gene (IGHV), and immunophenotyping of circulating lymphocytes.[3,4] *TP53* mutation status was assessed by targeted next-generation sequencing spanning exons 2–11 (entire coding region of *TP53*). The cutoff was ≥5% allele frequencies. Silent mutations in nonreference alleles were removed and mutations in nonreference alleles that showed up in >1% of the population were removed.
del(17p) status was assessed centrally by the Vysis CLL FISH probe kit, FDA approved for treatment of patients with venetoclax and uses a cutoff value of 7% to define abnormality.

DURATION OF NEUTROPENIA

The duration of neutropenia with a highest grade of 3 or 4 was calculated based on the duration of all neutropenia AEs with the highest grade of 3 or 4 (i.e. starts with onset of any grade of neutropenia as long as the highest grade is grade 3 or 4, until the time of AE resolution, or death date, study discontinuation, onset of the next neutropenia, or the clinical cut-off data, whichever occurred earlier, if not resolved.

STATISTICAL ANALYSES

Three sensitivity analyses of investigator-assessed progression-free survival (PFS) and IRC-assessed PFS were conducted to test for the potential impact of differences in modeling or censoring approaches:

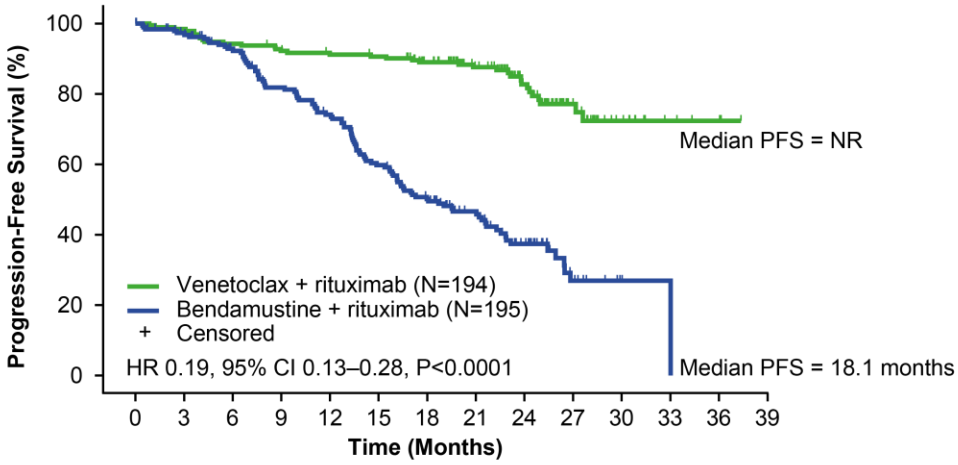
1. An unstratified log-rank test
2. PFS analyses with censoring at initiation of nonprotocol−specified anti-CLL therapy before meeting disease progression criteria to assess potential confounding of treatment effect estimates by subsequent therapy
3. PFS analyses with censoring of death or disease progression after more than one missed response assessment at the date of last adequate response assessment.

To adjust for multiple testing, the prespecified hierarchical testing of three key secondary efficacy endpoints was used in the following order: IRC-assessed complete response (CR)/CR with incomplete hematologic recovery (CRi); IRC-assessed overall response rate; and overall survival (OS). Because the study met its primary endpoint, a formal statistical test of IRC-assessed CR/CRi rate between the two arms was performed at the two-sided significance level of 0.05 using a stratified Cochran–Mantel–Haenszel test. As this endpoint was not statistically significant, P-values for the subsequent hierarchically tested endpoints could only be considered descriptive.

Distributions of time-to-event endpoints, including PFS, OS, EFS and TTNT were estimated by the Kaplan–Meier method. All randomized patients were included in the efficacy analyses (intention-to-treat population). All randomized patients who received at least one dose of study drug were included in the safety analyses.

SUPPLEMENTARY FIGURES

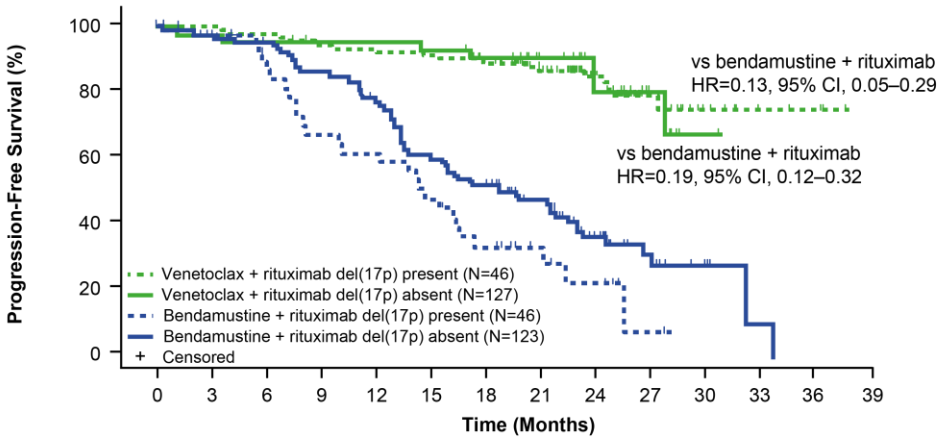
Figure S1. Kaplan–Meier estimates of independent review committee-assessed progression-free survival for venetoclax plus rituximab compared with bendamustine plus rituximab (intention-to-treat population)



No. of patients at risk

Venetoclax + rituximab	194	190	182	177	173	171	157	116	75	34	14	5	3
Bendamustine + rituximab	195	178	162	138	124	100	82	56	34	11	2	1	

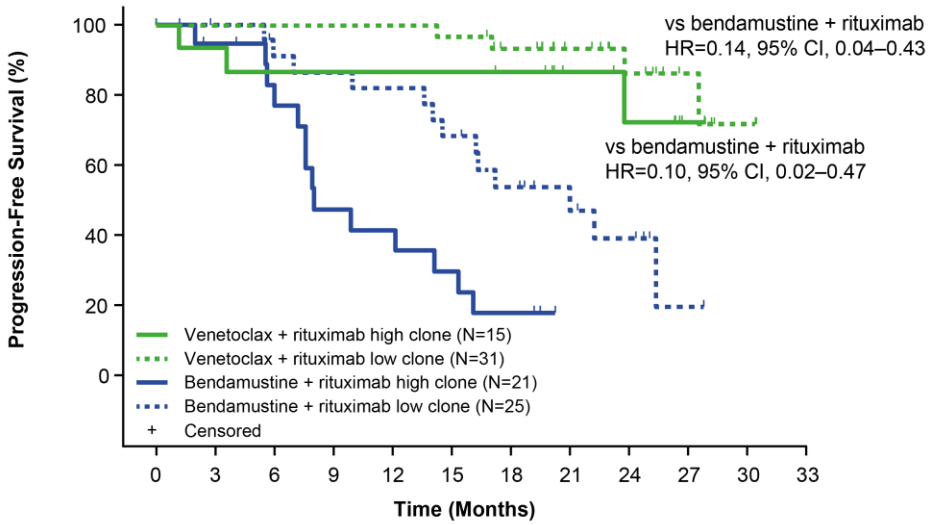
Figure S2. Kaplan–Meier estimates of investigator-assessed progression-free survival by del(17p) status as centrally assessed (Vysis CLL FISH probe kit) using a 7% cutoff value



No. of patients at risk

Venetoclax + rituximab del(17p) present	46	44	43	43	43	42	36	25	17	7	2		
Venetoclax + rituximab del(17p) absent	127	127	124	118	116	114	105	76	48	20	10	4	3
Bendamustine + rituximab del(17p) present	46	40	34	27	25	20	14	8	5	1			
Bendamustine + rituximab del(17p) absent	123	114	108	99	88	70	60	44	26	10	3	1	

Figure S3. Kaplan–Meier estimates of INV-assessed progression-free survival for venetoclax plus rituximab compared with bendamustine plus rituximab in patients with del(17p) with low and high clone sizes (intention-to-treat population).

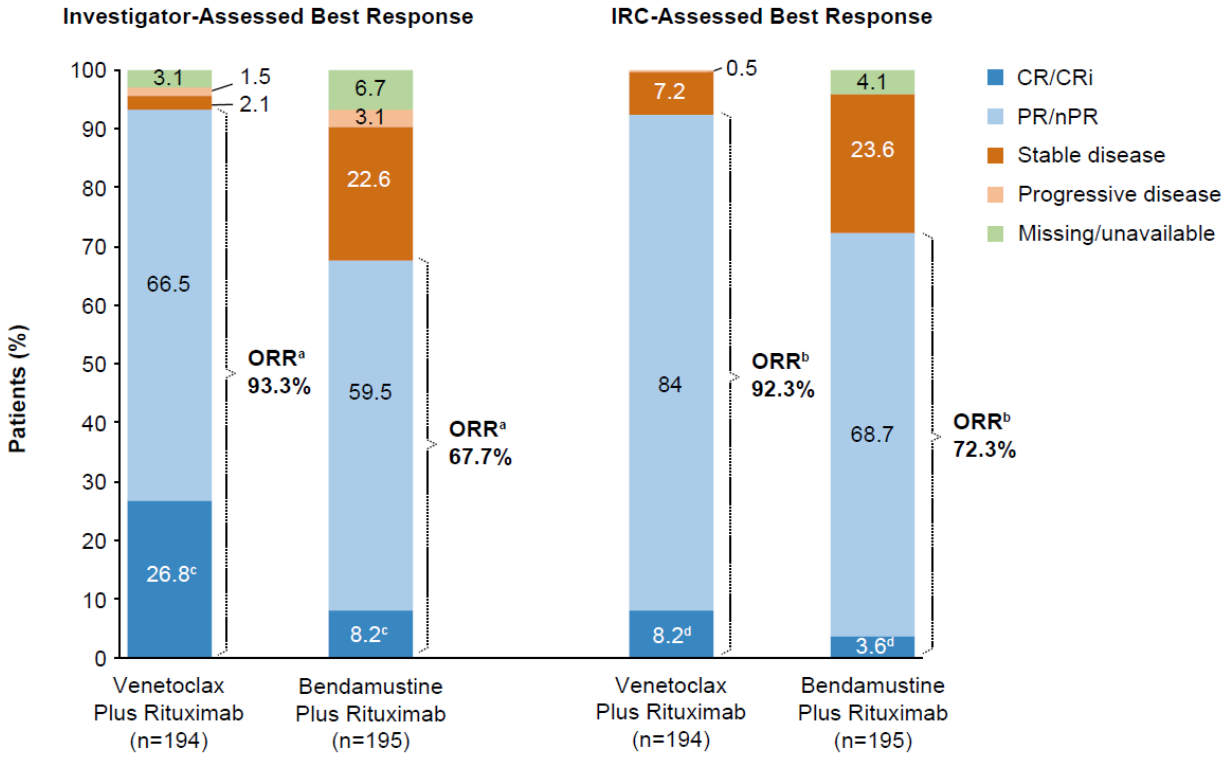


No. of patients at risk

Venetoclax + rituximab high clone	15	14	13	13	13	13	12	8	5	1	
Venetoclax + rituximab low clone	31	30	30	30	30	29	24	17	12	6	2
Bendamustine + rituximab high clone	21	17	14	8	7	5	3				
Bendamustine + rituximab low clone	25	23	20	19	18	15	11	8	5	1	

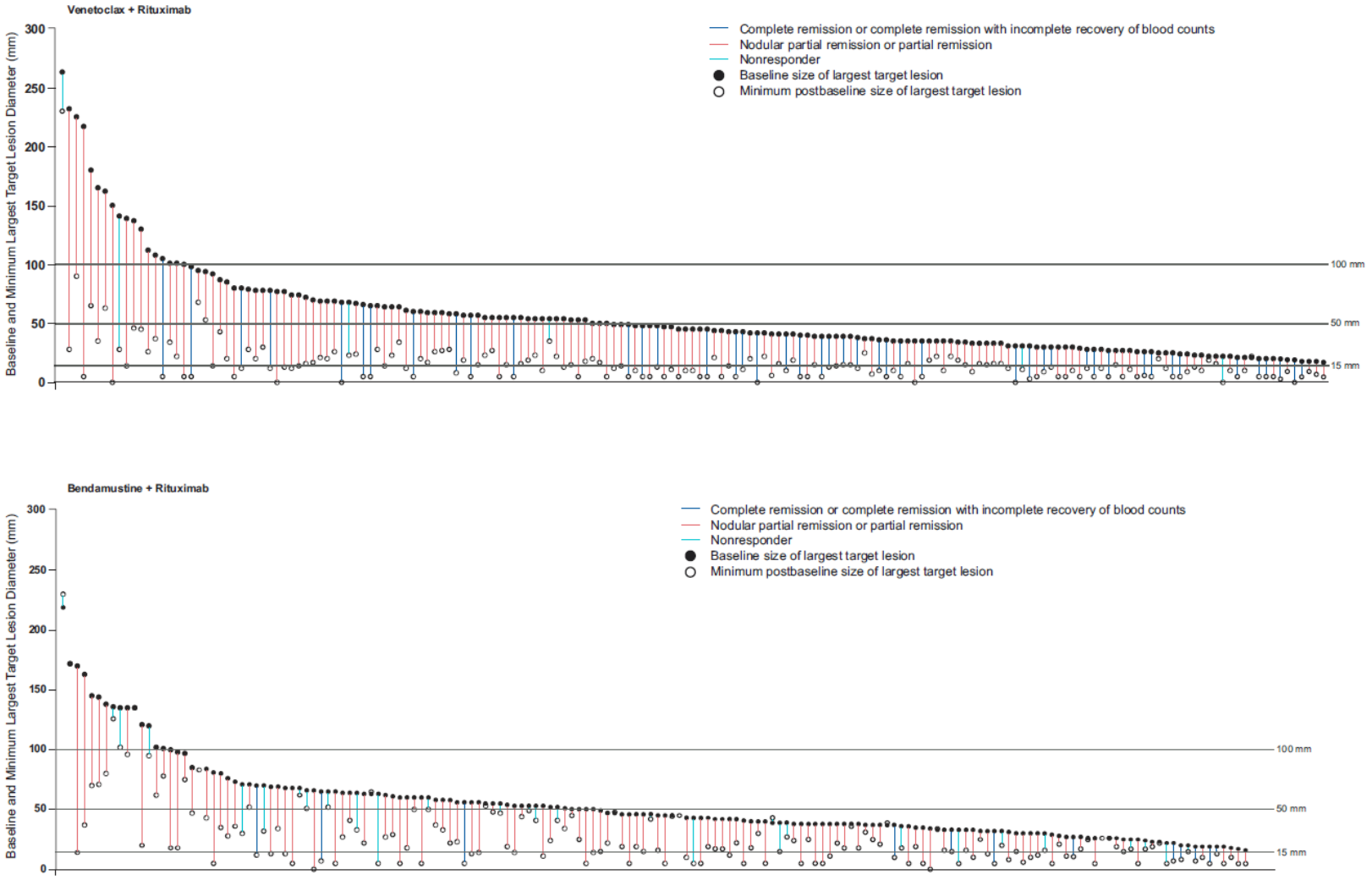
Low clone size, 7% to 20% del(17p) nuclei; high clone size, >20% del(17p) nuclei as determined by Vysis CLL FISH probe kit.
The number of patients in the venetoclax arm with small and large clone sizes was 31 and 15, and in the bendamustine arm, 25 and 21.

Figure S4. Best response rates (ITT population)



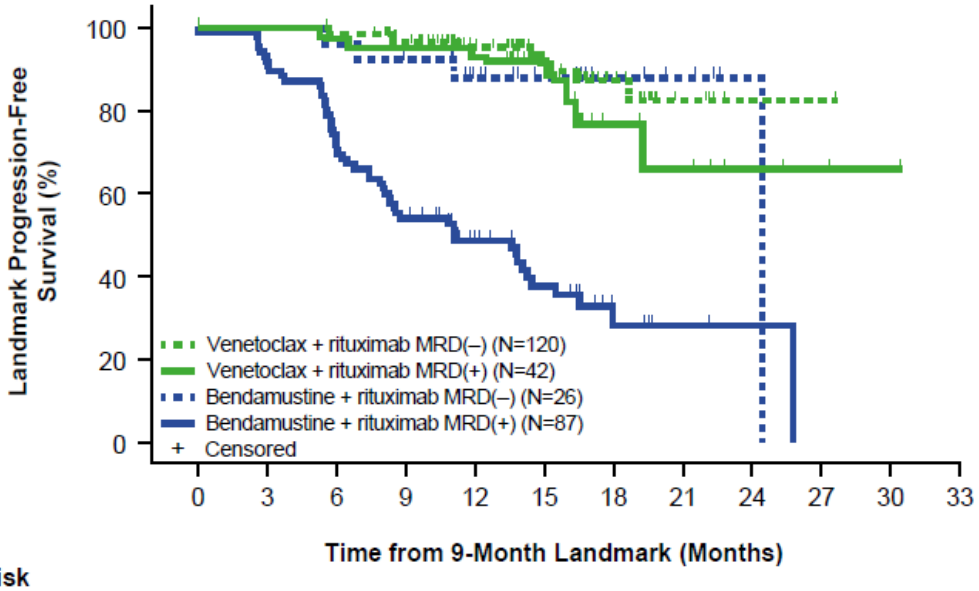
[a] Difference (95% CI) between arms, 25.6% (17.9 to 33.3).
[b] Difference (95% CI) between arms, 20.0% (12.4 to 27.6).
[c] Difference (95% CI) between arms, 18.6%.
[d] Difference (95% CI) between arms, 4.7% (–0.3 to 9.6); P=0.0814.
CR, complete response; CRi, complete response with incomplete hematological recovery; ORR, overall response rate; nPR, nodular partial response; PR, partial response.

Figure S5. Response rates for venetoclax plus rituximab compared with bendamustine plus rituximab: baseline and minimum post-baseline longest diameter from the same largest target lesion at end of combination treatment.



A ≥90% reduction in lymph nodes from baseline was observed in 12.4% (22/177) in the venetoclax arm versus 6.6% (11/166) in the bendamustine arm.

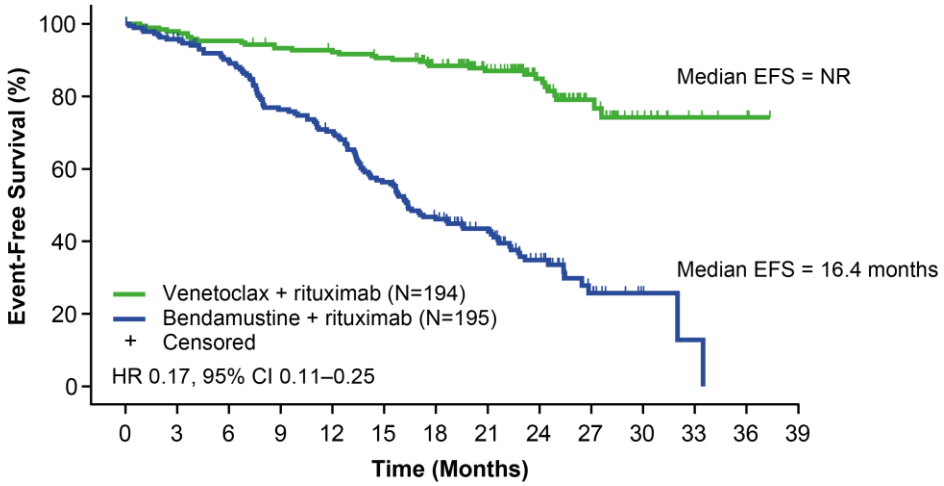
Figure S6. Investigator-assessed progression-free survival by minimal residual disease (MRD) response status in peripheral blood at the end of combination treatment in patients with known MRD status



No. of patients at risk

Venetoclax + rituximab MRD(–)	120	120	118	104	69	45	20	6	1	1	
Venetoclax + rituximab MRD(+)	42	41	40	39	30	20	8	6	3	2	1
Bentamustine + rituximab MRD(–)	26	26	25	23	16	11	6	4	1		
Bendamustine + rituximab MRD(+)	87	79	61	45	32	18	6	2	1		

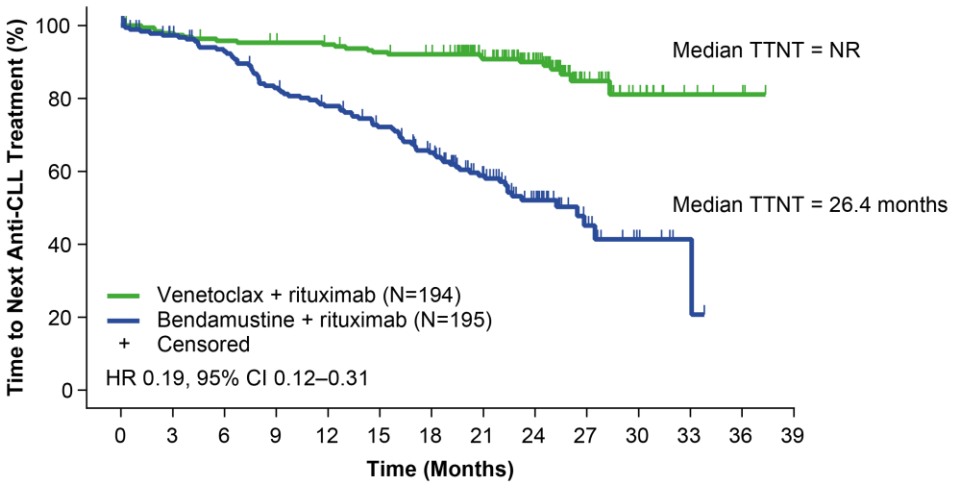
Figure S7. Event-free survival (EFS) for venetoclax plus rituximab compared with bendamustine plus rituximab



No. of patients at risk													
Venetoclax + rituximab	194	189	184	178	175	171	155	113	75	33	14	5	3
Bendamustine + rituximab	195	177	162	138	126	101	80	56	34	11	3	1	

CI, confidence interval; HR, hazard ratio; NR, not reached.

Figure S8. Time to next anti-CLL treatment for venetoclax plus rituximab compared with bendamustine plus rituximab



No. of patients at risk													
Venetoclax + rituximab	194	189	184	182	179	174	171	137	98	34	14	5	3
Bendamustine + rituximab	195	179	168	149	138	125	106	73	44	15	6	2	

CI, confidence interval; HR, hazard ratio; NR, not reached; TTNT, time to next treatment.

SUPPLEMENTARY TABLES

Table S1. Summary of tumor lysis syndrome (TLS) prophylaxis and monitoring measures following protocol amendment

TLS risk category[a]	Day 1 of dose level	Prophylactic medication	Hospitalization	Hydration[b]	Laboratory assessments[c,d]
Low risk	20, 50, 100, 200, 400 mg	Oral uric acid reducer (eg, allopurinol 300 mg/day) beginning ≥72 hours prior to dose and continued until first week of venetoclax plus rituximab combination therapy is completed.	No	Oral hydration of 1.5−2 L/day beginning ≥48 hours prior to dose and continuing for ≥24 hours after dose.	Chemistry and hematology within 72 hours prior to dose, before dosing (defined as ≤4 hours before venetoclax dose), and 8 and 24 hours after dosing time points. 8-hour chemistry results reviewed before patient leaves outpatient clinic. Investigator reviews 24-hour laboratory results prior to next-day dosing.
Medium risk	20 and 50 mg		No[e,f]	Oral hydration of 1.5−2 L/day beginning ≥48 hours prior to dose and continuing for ≥24 hours after dose. In addition to oral hydration, IV hydration (1.5−2 L) given in outpatient setting during clinic stay.	
	100, 200, 400 mg	Continue oral uric acid reducer as above.		Oral hydration of 1.5−2 L/day beginning ≥48 hours prior to dose and continuing for ≥24 hours after dose.	
High risk	20 and 50 mg	Oral uric acid reducer (eg, allopurinol 300 mg/day) beginning ≥72 hours prior to dose and continued until first week of venetoclax plus rituximab combination therapy is completed. Rasburicase administered per regional standards/institutional guidelines as prophylaxis prior to first venetoclax dose for high-risk patients with high uric acid levels at predose (above local laboratory ULN or Cairo-Bishop threshold of 476 µmol/L). For patients with	Yes[f]	Oral hydration of 1.5−2 L/day beginning ≥48 hours prior to dose and continuing for ≥24 hours after dose.	Chemistry and hematology within 72 hours prior to dose, before dosing (defined as ≤4 hours before venetoclax dose), and 4 (serum chemistry only), 8, 12 (serum chemistry only), and 24 hours after dosing time points. Samples sent immediately to laboratory, and results reviewed promptly by investigator. 24-hour after dosing, laboratory results reviewed by investigator before patient leaves hospital or receives any additional study drug.

		contraindication to rasburicase (ie, glucose 6 phosphate dehydrogenase deficiency), TLS risk-mitigation plan reviewed with Medical Monitor.			
	100, 200, 400 mg	Continue oral uric acid reducer as above.	No[e,f]	Oral hydration of 1.5−2 L/day beginning ≥48 hours prior to dose and continuing for ≥24 hours after dose. In addition to oral hydration, IV hydration (1.5−2 L) given in outpatient setting during clinic stay.	Chemistry and hematology within 72 hours prior to dose, before dosing (defined as up to 4 hours before venetoclax dose), and 8 and 24 hours after dosing time points. 8-hour chemistry results reviewed before patient leaves outpatient clinic. Investigator reviews 24-hour laboratory results prior to next-day dosing.

[a] *Low risk*: all measurable lymph nodes with largest diameter <5 cm by radiographic assessment AND absolute lymphocyte counts <25×10^9/L; *medium risk*: largest diameter of measurable lymph nodes ≥5 cm and <10 cm by radiologic assessment OR absolute lymphocyte count ≥25×10^9/L; *high risk*: presence of any lymph node with largest diameter ≥10 cm by radiologic assessment OR presence of BOTH absolute lymphocyte count ≥25×10^9/L AND measurable lymph node with largest diameter ≥5 cm by radiologic assessment.

[b] For patients unable to maintain oral hydration at 1.5−2 L/day starting ≥48 hours prior to start of treatment, IV hydration in outpatient setting on day of dosing during clinic stay recommended (unless being hospitalized) to assure full amount of hydration achieved. For patients for whom volume overload is considered a significant risk, hospitalization is considered.

[c] Results from predose laboratory values not required to be available prior to initiating venetoclax treatment, provided laboratory values obtained within 24 hours before dosing are within normal limits. For laboratory samples drawn on days on study treatment, "before dosing" laboratory samples drawn within 0−4 hours before dose. Other laboratory samples occurring on same day obtained within a ±15-minute window of any exact scheduled time. Any laboratory tests occurring at time intervals ≥24 hours after dose obtained within ±2 hour window of scheduled time.

[d] Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have subsequent venetoclax dose withheld until electrolyte abnormalities resolve. Patients who developed electrolyte abnormalities undergo aggressive management and further monitoring. If active correction of electrolytes performed, first or subsequent venetoclax dose only given when electrolytes stable without any more treatment for ≥24 hours. Any time during ramp-up period, if venetoclax withheld for ≤7 days, patient resumes venetoclax at same dose level or at one dose level lower, as determined by investigator based on risk assessment (including tumor burden status). Dose resumed at one dose level lower if dose was withheld ≥7 days with exception of initial dose level of 20 mg (400 mg → 200 mg, 200mg → 100 mg, 100 mg → 50 mg, 50 mg → 20 mg).

[e] Patients with creatinine clearance <80 mL/min and/or who have higher tumor burden (defined per investigator discretion) handled as TLS high-risk patients.

[f] Nephrology (or acute dialysis service) consultation considered on admission (per institutional standards or based on investigator discretion) for hospitalized patients to ensure emergency dialysis available and appropriate staff aware and prepared to handle any necessary intervention for TLS. Telemetry considered.

IV, intravenous; ULN, upper limit of normal,

Table S2. Definition of study endpoints and timing of assessments

Endpoint	Definition and analysis method
Investigator-assessed progression-free survival (PFS)[a]	Investigator-assessed PFS, the primary endpoint, was defined as the time from randomization to the first occurrence of progression or relapse using iwCLL guidelines,[5] or death from any cause, whichever occurred first. All patients who discontinued due to AEs or any reasons other than progression were followed until they withdrew their consent, or death, and were included in the primary PFS analysis. All patients followed for OS regardless of progression status. Disease status was evaluated by CT scanning of target lesions, blood counts, and physical examination of indicator lesions in up to six of the largest dominant nodes or tumor masses as well as six extra-nodal lesions. A similar procedure was conducted for nontarget lesions. CT scanning was performed at screening, the interim response assessment (within 14 days of day 1 of cycle 4), and 2−3 months after completion of the 6 cycles of combination therapy (or 4 weeks after day 1 of the last cycle for early termination). At each follow-up visit, patients were assessed for response/progression by clinical assessment only. In addition, at any time during the study when clinical or laboratory findings suggested that the response may have improved from stable disease (SD) to PR, or from PR to CR, a CT scan was performed to confirm the response. Patients who had not progressed, relapsed, or died at the time of analysis were censored on the date of the last adequate disease assessment. If no adequate disease assessments were performed after the baseline visit, PFS was censored at the time of randomization. Continued CT imaging was not required after radiographic progression was confirmed. A two-sided, stratified, log-rank test was used to compare distributions of investigator-assessed PFS between the treatment groups (venetoclax plus rituximab compared with bendamustine plus rituximab) stratified by the presence or absence of the 17p deletion, risk status (high or low), and geographic region.
Independent review committee-assessed PFS	Disease progression was evaluated every 3 months by an independent review committee review using the 2008 criteria of the International Workshop on CLL.[5] A two-sided, stratified, log-rank test was used to compare results between treatment groups.
Investigator- and independent review committee–assessed PFS in patients with del(17p)	PFS was assessed as stated above in patients with the 17p deletion identified by fluorescence *in situ* hybridization testing performed at a central laboratory. A two-sided, unstratified, log-rank test was used to compare results between treatment groups.
Protocol-defined investigator- and independent review committee–assessed overall response rate	All patients had clinical response assessments (including targeted physical examination and laboratory examinations) at screening, Day 1 of every cycle during the combination therapy, at interim response assessment (within 14 days of Cycle 4 Day 1), after combination therapy (defined as 4 weeks after Day 1 of Cycle 6 or 4 weeks after Day 1 of the last cycle for early termination), and at 2−3 months after Day 1 of the last cycle of combination therapy. At each follow-up visit, patients were assessed for response/progression by clinical assessment only. However, if at any time when clinical or laboratory findings suggested that the response may have improved from stable disease (SD) to PR, or from PR to CR, a CT scan was performed to confirm the response. Using the 2008 iwCLL guidelines,[5] investigators and the independent

	review committee categorized patients as having a complete response, complete response with incomplete marrow recovery (CRi), nodular partial response, or partial response. CT scans were mandated at baseline, cycle 4 and the end of combination treatment visit (12 weeks after day 1 of the last cycle of combination therapy; ~9 month time point). CT scans after the 9 month visit were to be performed to confirm a suspected change in response status, that is, SD to PR or PR to CR/CRi. Response rates in the treatment groups were compared using stratified Cochran−Mantel−Haenszel tests. Stratification factors are identical to those used for the primary endpoint.
Minimum residual disease (MRD)	MRD negativity was defined as blood or marrow with less than one CLL cell per 10,000 leukocytes (10^{-4}).[5] MRD was assessed in peripheral blood by iwCLL recommended methods[5], ASO-PCR and flow cytometry, in all patients and in bone marrow by flow cytometry (due to sample limitation). For both ASO-PCR and flow cytometry, only samples that had a limit of detection (LOD) below 10^{-4} were considered for MRD determination. MRD negativity rates are reported separately in blood and bone marrow. A bone marrow aspirate was obtained at baseline and at the end of combination treatment response visit to assess MRD in all responders. In addition, peripheral blood samples for MRD testing were collected at baseline, within 14 days of day 1 of cycle 4 (interim assessment), completion of combination therapy/early treatment termination visit (if applicable), the end of combination treatment response visit, and every 3 months during the follow-up or at any visit during the follow-up until progression. For MRD in peripheral blood, results from ASO-PCR and flow cytometry were combined in order to minimize missing data caused by sample loss and technical failure of individual methodologies. Given the overall high concordance rate between ASO-PCR and flow cytometry (85.4% from 1291 pairs of peripheral blood samples), a conservative hierarchical algorithm of combining MRD results from two assays was established to determine MRD status for each patient at each time point: Step 1. MRD positive by either ASO-PCR or flow = MRD positive. Step 2. If a sample was not MRD positive by Step 1, and MRD negative by ASO-PCR and/or flow = MRD negative. Step 3. If MRD undetermined by both ASO-PCR and flow = MRD positive. In addition, patients for whom no post-baseline MRD assessment was available at a specific time point were considered “MRD positive” for that particular time point. These measures ensured a conservative approach for reporting MRD results in this study.

	Peripheral blood MRD negativity rates from the two treatment arms at the end of combination treatment response visit were compared using the Chi-square test. Analysis was based on intent-to-treat population, whereby patients missing an MRD result were considered MRD positive.
Duration of response	Duration of response was defined for patients with a best overall response as the time from first occurrence of a documented complete response or partial response to disease progression/relapse, as assessed by the investigator, or death from any cause. For patients achieving a response who did not manifest disease progression or relapse, or die at the time of analysis, duration of response was censored on the date of last adequate response assessment. Patients who never achieved disease responses were not included in this analysis. Time-to-event analysis of duration of response incorporated data only from the subset of patients in both treatment arms that achieved an overall disease response. As this was a nonrandomized comparison, a formal statistical test was not conducted, and the results were only summarized by the treatment arm estimates and confidence intervals.
Overall survival (OS)	OS was defined as the time from the date of randomization to the date of death from any cause. Patients who were not reported as having died at the time of the analysis were censored at the date when they were last known to be alive, as documented by the investigator. A two-sided, stratified, log-rank test was used to compare results between treatment groups.
Event-free survival (EFS)	EFS was defined as the time between date of randomization and the date of disease progression/relapse, death, or start of a new anti-CLL treatment. If the specified event (disease progression/relapse, death, start of a new anti-CLL treatment) did not occur, patients were censored at the date of last adequate tumor assessment. For patients without an event who did not have postbaseline tumor assessments, EFS was censored at the time of randomization. A two-sided, stratified, log-rank test was used to compare results between treatment groups.
Time to next anti-CLL treatment	Time to next anti-CLL treatment was defined as the time from randomization to start of new, nonprotocol, anti-CLL therapy or death from any cause. For patients who did not receive the next anti-CLL treatment or died at the time of analysis, time to next anti-CLL treatment was censored at the date when the patient was last known to be alive without having received additional antilymphoma treatment. A two-sided, stratified, log-rank test was used to compare results between treatment groups.

[a] Primary endpoint.

Table S3. International Working Group on Chronic Lymphoid Leukemia response definitions[5]

Parameter	Complete response[a]	Partial response[b]	Progressive disease[c]
Group A (tumor load)			
Lymphadenopathy[d]	None >1.5 cm	Decrease ≥50%	Increase ≥50%
Hepatomegaly	None	Decrease ≥50%	Increase ≥50%
Splenomegaly	None	Decrease ≥50%	Increase ≥50%
Blood lymphocytes	<4000/µL	Decrease ≥50% over baseline	Increase ≥50% over baseline
Marrow[e]	Normocellular, <30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines complete response with incomplete marrow recovery	50% reduction in marrow infiltrate or B-lymphoid nodules	
Group B (function of hematopoietic system, or marrow)			
Platelet count	>100,000/µL	>100,000/µL or increase ≥50% over baseline	Decrease ≥50% over baseline secondary to CLL
Hemoglobin	>11.0 g/dL	>11.0 g/dL or increase ≥50% over baseline	Decrease >2 g/dL over baseline secondary to CLL
Neutrophils[e]	>1500/µL	>1500/µL or >50% improvement over baseline	

[a] All of the criteria have to be met, and patients have to lack disease-related constitutional symptoms.
[b] At least two of the criteria of group A plus one of the criteria of group B have to be met; stable disease is absence of progressive disease and failure to achieve at least a partial response.
[c] At least one of the above criteria of group A or group B has to be met.
[d] Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).
[e] These parameters are irrelevant for some response categories.

Table S4. Demographic and baseline disease characteristics

Characteristic	Venetoclax plus rituximab n=194	Bendamustine plus rituximab n=195
Sex, n (%)		
Male	136 (70.1)	151 (77.4)
Female	58 (29.9)	44 (22.6)
Age, years		
Median	64.5	66.0
Min–Max	28–83	22–85
ECOG score, n (%)		
N	194	194
0	111 (57.2)	108 (55.7)
1	82 (42.3)	84 (43.3)
2	1 (0.5)	2 (1.0)
Rai staging at diagnosis[a], n (%)		
N	130	140
Stage 0–II	88 (67.7)	103 (73.6)
Stage III–IV	30 (23.1)	18 (12.9)
Fludarabine refractory[b], n (%)		
N	191	194
Yes	27 (14.1)	30 (15.5)
No	164 (85.9)	164 (84.5)
Creatinine clearance[c], n (%)		
N	194	195
<50 mL/min	6 (3.1)	10 (5.1)
≥50 mL/min	188 (96.9)	185 (94.9)
Baseline tumor lysis syndrome risk, n (%)		
N	194	195
High	54 (27.8)	55 (28.2)
Medium	106 (54.6)	104 (53.3)
Low	34 (17.5)	36 (18.5)
Absolute lymphocyte count, × 10^9/L		
<25	65 (33.5)	61 (31.3)
Platelets, × 10^9/L		
Median (min–max)	113.0 (13.0–419.0)	123.5 (11.0–457.0)
<100 × 10^9/L, %	42.8	33.5
Hemoglobin, g/dL		
Median (min–max)	11.4 (5.5–16.7)	12.0 (6.8–16.1)
<10 g/dL, %	31.4	19. 1
del(17p) status, n (%)		
N	173	169
Absent	127 (73.4)	123 (72.8)
Present	46 (26.6)	46 (27.2)
***TP53* mutation status, n (%)**		

N	192	184
Mutated	48 (25.0)	51 (27.7)
Unmutated	144 (75.0)	133 (72.3)
del(17p) vs. *TP53* mutation status, n/N (%)	171	158
Only del(17p)	24 (14.0)	18 (11.4)
TP53 mutation only	19 (11.1)	23 (14.6)
del(17p) and *TP53* mutated	22 (12.9)	22 (13.9)
IGHV mutational status[d], n (%)		
N	180	180
Mutated	53 (29.4)	51 (28.3)
Unmutated	123 (68.3)	123 (68.3)
Stratification factor: risk status (derived), n (%)[e]		
N	194	195
High	109 (56.2)	118 (60.5)
Low	84 (43.3)	75 (38.5)
Number of prior CLL therapies, n (%)		
N	194	195
1	111 (57.2)	117 (60.0)
2	57 (29.4)	43 (22.1)
3	22 (11.3)	34 (17.4)
>3	4 (2.1)	1 (0.5)
Type of prior CLL therapies, n (%)		
Alkylating agent	182 (93.3)	185 (95.4)
Purine analog	157 (80.5)	158 (81.4)
Anti-CD20 antibody	153 (78.5)	148 (76.3)
B-cell receptor inhibitors	5 (2.6)	3 (1.5)

[a] Unknown Rai stage at diagnosis: 12 (9.2%) patients in the venetoclax plus rituximab arm and 19 (13.6%) patients in the bendamustine plus rituximab arm.

[b] Per investigator assessment. Indicating not fludarabine refractory did not mean patients were exposed to fludarabine.

[c] Based on Cockcroft–Gault formula.

[d] Unknown IGHV mutational status: 4 (2.2%) patients in the venetoclax plus rituximab arm and 6 (3.3%) patients in the bendamustine plus rituximab arm.

[e] High-risk status was defined as having ANY of the following features: 17p deletion, or no response to front-line chemotherapy-containing regimen, or relapsed disease within 12 months after chemotherapy alone or within 24 months after chemoimmunotherapy. All others were considered to be of low-risk status. One patient in the venetoclax plus rituximab arm and two patients in the bendamustine plus rituximab arm had an unknown or missing risk status.

ECOG, Eastern Cooperative Oncology Group; Max, maximum; Min, minimum.

Table S5. Adverse events (AEs) (any grade) leading to dose modification

	Venetoclax + rituximab arm n=194		Bendamustine + rituximab arm n=188	
	Venetoclax	**Rituximab**	**Bendamustine**	**Rituximab**
Dose interruption				
Patients with ≥1 AE leading to dose interruption, n (%)	135 (69.6)	39 (20.1)	53 (28.2)	69 (36.7)
AE leading to dose interruption of any treatment in ≥5 patients in either arm, n (%)				
Neutropenia	84 (43.3)	25 (12.9)	22 (11.7)	23 (12.2)
Neutrophil count decreased	5 (2.6)	0	4 (2.1)	4 (2.1)
Thrombocytopenia	9 (4.9)	1 (0.5)	8 (4.3)	6 (3.2)
Pneumonia	8 (4.1)	1 (0.5)	3 (1.6)	3 (1.6)
Upper respiratory tract infection	7 (3.6)	1 (0.5)	4 (2.1)	4 (2.1)
Bronchitis	5 (2.6)	3 (1.6)	2 (1.1)	1 (0.5)
Infusion-related reaction	0	6 (3.1)	2 (1.1)	23 (12.6)
Diarrhea	9 (4.6)	0	0	0
Nausea	7 (3.6)	0	1 (0.5)	1 (0.5)
Dose reduction				
Patients with ≥1 AE leading to dose reduction, n (%)	27 (13.9)	2 (1.0)	26 (13.8)	2 (1.1)
AE leading to dose reduction of any treatment in ≥2 patients in either arm, n (%)				
Neutropenia	16 (8.2)	1 (0.5)	14 (7.4)	0
Febrile neutropenia	2 (1.0)	0	3 (1.6)	0
Thrombocytopenia	0	0	3 (1.6)	0
Anemia	1 (0.5)	0	2 (1.1)	0
Treatment discontinuation				
Patients with ≥1 AE leading to treatment discontinuation, n (%)	25 (12.9)	10 (5.2)	17 (9.0)	13 (6.9)
AE leading to discontinuation of any treatment in in either arm, n (%)				
Neutropenia	5 (2.6)	2 (1.0)	3 (1.6)	3 (1.6)
Thrombocytopenia	5 (2.6)	0	2 (1.1)	1 (0.5)
Autoimmune hemolytic anemia	2 (1.0)	0	0	0
Pneumonia	2 (1.0)	0	3 (1.6)	3 (1.6)
Anemia	1 (0.5)	0	1 (0.5)	1 (0.5)

Febrile neutropenia	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Immune thrombocytopenic purpura	1 (0.5)	0	0	0
Appendicitis	1 (0.5)	1 (0.5)	0	0
Lung infection	1 (0.5)	0	0	0
Peritoneal tuberculosis	1 (0.5)	0	0	0
Crohn's disease	1 (0.5)	0	0	0
Diarrhea	1 (0.5)	0	0	0
Pyrexia	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Sudden cardiac death	1 (0.5)	0	0	0
Colorectal cancer	1 (0.5)	1 (0.5)	0	0
Pancreatic carcinoma	1 (0.5)	0	0	0
Vertigo	1 (0.5)	0	0	0
Alanine aminotransferase increased	1 (0.5)	0	0	0
Status epilepticus	1 (0.5)	1 (0.5)	0	0
Acute respiratory failure	1 (0.5)	1 (0.5)	0	0
Infusion-related reaction	0	0	2 (1.1)	3 (1.6)
Aplasia pure red cell	0	0	1 (0.5)	1 (0.5)
Neutropenic sepsis	0	0	1 (0.5)	1 (0.5)
Sepsis	0	0	1 (0.5)	1 (0.5)
Septic shock	0	0	1 (0.5)	0
Rash	0	0	1 (0.5)	1 (0.5)
Rash maculo−papular	0	0	1 (0.5)	0
Atrial fibrillation	0	0	1 (0.5)	0
Platelet count decreased	0	0	1 (0.5)	0
Hypotension	0	0	1 (0.5)	0
Abscess limb	0	1 (0.5)	0	0
Peritoneal tuberculosis	0	1 (0.5)	0	0
Memory impairment	0	1 (0.5)	0	0
Small intestinal obstruction	0	1 (0.5)	0	0
Tenosynovitis	0	1 (0.5)	0	0

Adverse event reporting period: Prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention were reported (e.g. serious adverse events related to invasive procedures, such as biopsies). After initiation of study drug, all adverse events, regardless of relationship to study drug, were reported until 28 days after the last dose of study drug (maximum 2 years for venetoclax), or 90 days after last dose of rituximab, whichever was

longer. After this period, investigators were to report any deaths, serious adverse events, or other adverse events of concern believed to be related to prior study drug treatment.

Table S6. Sensitivity analyses for progression-free survival (PFS) by investigator and IRC assessments

	Investigator-assessed PFS		IRC-assessed PFS	
Analysis	**Venetoclax plus rituximab N=194**	**Bendamustine plus rituximab N=195**	**Venetoclax plus rituximab N=194**	**Bendamustine plus rituximab N=195**
Unstratified log-rank test (ITT)				
Patients with event, n	32	114	35	106
Median PFS (95% CI), months	NR	17.0 (15.5, 21.6)	NR	18.1 (15.8, 22.3)
HR (versus B+R) (95% CI)	0.17 (0.12, 0.26)		0.20 (0.14, 0.30)	
P-value (log-rank test)	<0.0001		<0.0001	
Censoring for non-protocol therapy prior to disease progression[a] (ITT)				
Patients with event, n	31	110	34	101
Median PFS (95% CI), months	NR	17.1 (15.7, 21.6)	NR	19.0 (16.2, 22.5)
HR (versus B+R) (95% CI)	0.17 (0.11, 0.25)		0.19 (0.13, 0.29)	
P-value (log-rank test)	<0.0001		<0.0001	
2-year rate, %	85.8	36.6	83.7	38.5
Censoring for missing PFS assessments[b] (ITT)				
Patient with event, n	30	106	35	96
Median PFS (95% CI), months	NR	18.0 (15.7, 22.3)	NR	19.6 (16.2, 22.8)
HR (versus B+R) (95% CI)	0.16 (0.11, 0.25)		0.20 (0.13, 0.30)	
P-value (log-rank test)	<0.0001		<0.0001	
2-year rate, %	85.2	37.4	82.8	39.4
Stratified log-rank test (As Treated)				
Patient with event, n	32	114	N/A	
Median PFS (95% CI), months	NR	17.0 (15.5, 21.6)		
HR (versus B+R) (95% CI)	0.17 (0.11, 0.25)			
P-value (log-rank test)	<0.0001			
2-year rate, %	84.9	36.3		

[a] Patients who started nonprotocol–specified anti-CLL treatment before the occurrence of a PFS event were censored at the time of the new treatment initiation. Two of the 194 patients (1.0%) in the venetoclax plus rituximab arm and 8/195 patients (4.1%) in the bendamustine plus rituximab arm received new antileukemic treatments before progression.

[b] Patients with progressive disease or death reported after missing more than one visit consecutively were censored at their last adequate response assessment date before the missed visits.

AT, as-treated population; B, bendamustine; CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee; ITT, intent to treat population; NR, not reached; R, rituximab.

Table S7. Reasons for the lower independent review committee CR/CRi rate relative to the investigator-assessed CR/CRi rate

Reason for discrepancy	Venetoclax plus rituximab n=42	Bendamustine plus rituximab n=9
CT scan (all reasons)	33	7
Lesions 16–20 mm	18	3
Lesions 21–30 mm	10	2
Lesions >30 mm	1	2
Anatomy missing	3	0
Spleen enlarged	1	0
Bone marrow, elements missing	4	2
Growth factor use	2	0
Spleen size /ALC fluctuation	2	0
Adverse event – secondary malignancy[a]	1	0

The IRC-adjudicated reduction in CR/CRi rates was proportional in the two treatment arms.

[a] Omental and peritoneal nodules likely related to metastatic lung cancer rather than CLL. No biopsy available.

ALC, absolute lymphocyte count; CR, complete response; CRi, complete response with incomplete hematologic recovery; PR, partial response.

Table S8. Minimal residual disease (MRD) response rate in bone marrow

	Best MRD negativity rate on study	
ITT population	**Venetoclax + rituximab (N=194)**	**Bendamustine + rituximab (N=195)**
MRD in bone marrow[a]		
Negative, n (%)	53 (27)	3 (2)
Non-negative, n (%)	141 (73)	192 (99)
Assay positive	17 (9)	36 (19)
Assay failure	4 (2)	2 (1)
PD/death/withdrew	N/A	N/A
Sample missing	120 (62)	154 (79)
Difference of MRD negativity (95% CI)	25.8% (19.0, 32.6)	
P-value[b]	<0.0001	

[a] Combining ASO-PCR and flow cytometry.

[b] Descriptive P-values.

ASO-PCR, allele-specific oligonucleotide polymerase chain reaction; ITT, intent to treat.

Concordance between MRD status in peripheral blood and bone marrow was 84.3% based on 108 pairs of post-baseline samples across both arms, 82.5% for the venetoclax arm and 85.3% for the bendamustine arm; 48 of 60 (80%) patients with peripheral blood MRD negativity also measured MRD negative in bone marrow samples, while 48 out of 53 (91%) patients that measured MRD negative in bone marrow also measured MRD negative in blood. These data suggest that peripheral blood MRD negativity data may be a good surrogate for bone marrow MRD negativity in this study.

Table S9. Follow-up anticancer therapy use (intent-to-treat population).

Treatment, n (%)	Venetoclax plus rituximab N=194	Bendamustine plus rituximab N=195
Patients with ≥ 1 treatment	8 (4.1)	54 (27.7)
Total number of treatments	14	95
Selected therapies of interest		
Ibrutinib monotherapy	1 (0.5)	33 (16.9)
BTK inhibitor BGB 3111	0	2 (1.0)
R-CHOP	1 (0.5)	4 (2.1)
Venetoclax monotherapy	1 (0.5)	3 (1.5)
Allogenic stem cell Transplantation	0	3 (1.5)
CHOP	0	3 (1.5)
Idelalisib and rituximab	1 (0.5)	2 (1.0)

BTK, Bruton's tyrosine kinase; R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab.

Table S10. Incidence of adverse events (all grades)

	Venetoclax plus rituximab N=194	**Bendamustine plus rituximab N=188**
Patients with ≥1 adverse event, n (%)	194 (100.0)	185 (98.4)
Total number of adverse events	978	907
Adverse events occurring in >10% of patients in either arm, n (%)		
Neutropenia	118 (60.8)	83 (44.1)
Diarrhea	77 (39.7)	31 (16.5)
Nausea	41 (21.1)	64 (34)
Anemia	30 (15.5)	43 (22.9)
Fatigue	34 (17.5)	39 (20.7)
Upper respiratory tract infection	43 (22.2)	29 (15.4)
Thrombocytopenia	26 (13.4)	42 (22.3)
Pyrexia	29 (14.9)	38 (20.2)
Cough	35 (18)	31 (16.5)
Constipation	27 (13.9)	39 (20.7)
Infusion-related reaction	16 (8.2)	45 (23.9)
Pneumonia	18 (9.3)	22 (11.7)
Headache	21 (10.8)	19 (10.1)
Vomiting	16 (8.2)	23 (12.2)
Rash	14 (7.2)	24 (12.8)
Bronchitis	20 (10.3)	13 (6.9)
Insomnia	21 (10.8)	12 (6.4)
Nasopharyngitis	22 (11.3)	10 (5.3)
Febrile neutropenia	7 (3.6)	19 (10.1)

Adverse event reporting period: Prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention were reported (e.g. serious adverse events related to invasive procedures, such as biopsies). After initiation of study drug, all adverse events, regardless of relationship to study drug, were reported until 28 days after the last dose of study drug (maximum 2 years for venetoclax), or 90 days after last dose of rituximab, whichever was longer. After this period, investigators were to report any deaths, serious adverse events, or other adverse events of concern believed to be related to prior study drug treatment.

Table S11. Protocol-defined adverse events (AEs) of special interest

	Venetoclax plus rituximab N=194	Bendamustine plus rituximab N=188
Patients with ≥1 AE, n (%)	12 (6.2)	22 (11.7)
Adverse event, n (%)		
Richter transformation	6 (3.1)	5 (2.7)
Alanine aminotransferase increase	0	2 (1.1)
Grade ≥3 adverse event, n (%)		
Tumor lysis syndrome	6 (3.1)[a]	2 (1.1)
Infusion-related reaction	6 (3.1)	18 (9.6)

[a] 8 events in 6 patients.

Adverse event reporting period: Prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention were reported (e.g. serious adverse events related to invasive procedures, such as biopsies). After initiation of study drug, all adverse events, regardless of relationship to study drug, were reported until 28 days after the last dose of study drug (maximum 2 years for venetoclax), or 90 days after last dose of rituximab, whichever was longer. After this period, investigators were to report any deaths, serious adverse events, or other adverse events of concern believed to be related to prior study drug treatment.

Table S12. Highest postbaseline plasma electrolyte and metabolite levels in patients with tumor lysis syndrome

Case	Assigned treatment	Phosphorous (mmol/L)	Uric acid (µmol/L)	Calcium (mmol/L)	Potassium (mmol/L)	Creatinine (µmol/L)	Cycle/day/hour/ venetoclax dose
		Howard criteria threshold[6]					
		>1.5 mmol/L	476 µmol/L	<1.75 mmol/L	>6.0 mmol/L	>1.5 times ULN (80 µmol/L)	
1[a]	Bendamustine plus rituximab	1.53	588[c] 1270	2.13	4.9	100[c] 220	Cycle 1 day 8
2[b]	Bendamustine plus rituximab	5.59	1802	2.15	7.2	297	Cycle 1 day 8
3	Venetoclax plus rituximab	1.55	170	2.07	6.5	68	Day 1/6-h post 20-mg dose
4	Venetoclax plus rituximab	1.99	350	1.90	6.1	112	Day 1/12-h post 20-mg dose
5	Venetoclax plus rituximab	2.34	20	2.44	6.2	75	Day 2/4-h post 50-mg dose
6	Venetoclax plus rituximab	1.63	623	1.92	4.1	116	Day 2/prior to dose – Day 1 dose 100 mg[d]
7	Venetoclax plus rituximab	1.53 2.36	130 610	2.23 2.16	6.9 4.2	115 113	Day 8/post 50-mg dose Day 22/8-h post 200-mg dose
8[e]	Venetoclax plus rituximab	1.54	12	2.42	4.8	122	Day 2/post 50-mg dose

[a] Patient also had elevated creatinine levels of 100 and 220 µmol/L on the same day.
[b] Patient had renal failure.
[c] Same day labs.
[d] Patient started on venetoclax 100 mg in error.
[e] Patient was deemed to have grade ≥3 tumor lysis syndrome on day 2 after receiving 50 mg of venetoclax because of transient increases in creatinine; however, Howard criteria for laboratory tumor lysis syndrome were not met.[6]

Table S13. Adverse events with fatal outcome

Adverse events	Venetoclax plus rituximab N=194	Bendamustine plus rituximab N=188
Fatal adverse events, n (%)	10 (5.2)	11 (5.9)
Sepsis	1 (0.5)	2 (1.1)
Pneumonia	3 (1.5)[b]	0
Lung neoplasm malignant	0	2 (1.1)
Sudden death	0	1 (0.5)
Listeria sepsis	0	1 (0.5)
Scedosporium infection	0	1 (0.5)
Acute myeloid leukemia	0	1 (0.5)
Lymphoma	0	1 (0.5)
Hemorrhagic stroke	0	1 (0.5)
Pulmonary embolism	0	1 (0.5)
Thrombocytopenia[a]	1 (0.5)	0
Cardiac failure	1 (0.5)	0
Myocardial infarction	1 (0.5)	0
Sudden cardiac death	1 (0.5)	0
Colorectal cancer	1 (0.5)	0
Status epilepticus	1 (0.5)	0
Acute respiratory failure	1 (0.5)	0

[a] Death was due specifically to pneumonia with ongoing thrombocytopenia with no bleeding.
[b] Two cases were in the setting of progression/Richter transformation.

Table S14. Incidence of secondary neoplasms[a]

Secondary neoplasm	Venetoclax plus rituximab N=194	Bendamustine plus rituximab N=188
Any, n (%)	21 (10.8)	13 (6.9)
Second primary malignancy	21 (10.8)	13 (6.9)
Excluding non-melanoma skin cancers	9 (4.6)	8 (4.2)
Type, n (%)		
Squamous cell carcinoma	5 (2.6)	2 (1.1)
Squamous cell carcinoma of skin	5 (2.6)	2 (1.1)
Basal cell carcinoma	4 (2.1)	2 (1.1)
Myelodysplastic syndrome	3 (1.5)	0
Colorectal cancer	2 (1.0)	0
Lung neoplasm malignant	0	2 (1.1)
Acute myeloid leukemia	0	1 (0.5)
Adenocarcinoma gastric	1 (0.5)	0
Adenocarcinoma of colon	0	1 (0.5)
Colon cancer	1 (0.5)	0
Lymphoma	0	1 (0.5)
Malignant melanoma	1 (0.5)	0
Medullary thyroid cancer	0	1 (0.5)
Metastatic malignant melanoma	1 (0.5)	0
Pancreatic carcinoma	1 (0.5)	0
Prostate cancer	0	1 (0.5)
Skin cancer (non-melanoma)	1 (0.5)	0
Transitional cell carcinoma	0	1 (0.5)

[a] Some patients had more than one event.

REFERENCES

1. Seymour JF, Ma S, Brander DM, et al. Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b study. Lancet Oncology 2017;18:230-40.
2. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. New England Journal of Medicine 2016;374:311-22.
3. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. New England Journal of Medicine 2000;343:1910-6.
4. Krober A, Seiler T, Benner A, et al. V(H) mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. Blood 2002;100:1410-6.
5. 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;111:5446-56.
6. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med 2011;364:1844-54.