Venetoclax plus bendamustine-rituximab or bendamustine-obinutuzumab in chronic lymphocytic leukemia: final results of a phase Ib study (GO28440)

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SUPPLEMENTARY INFORMATION

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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.

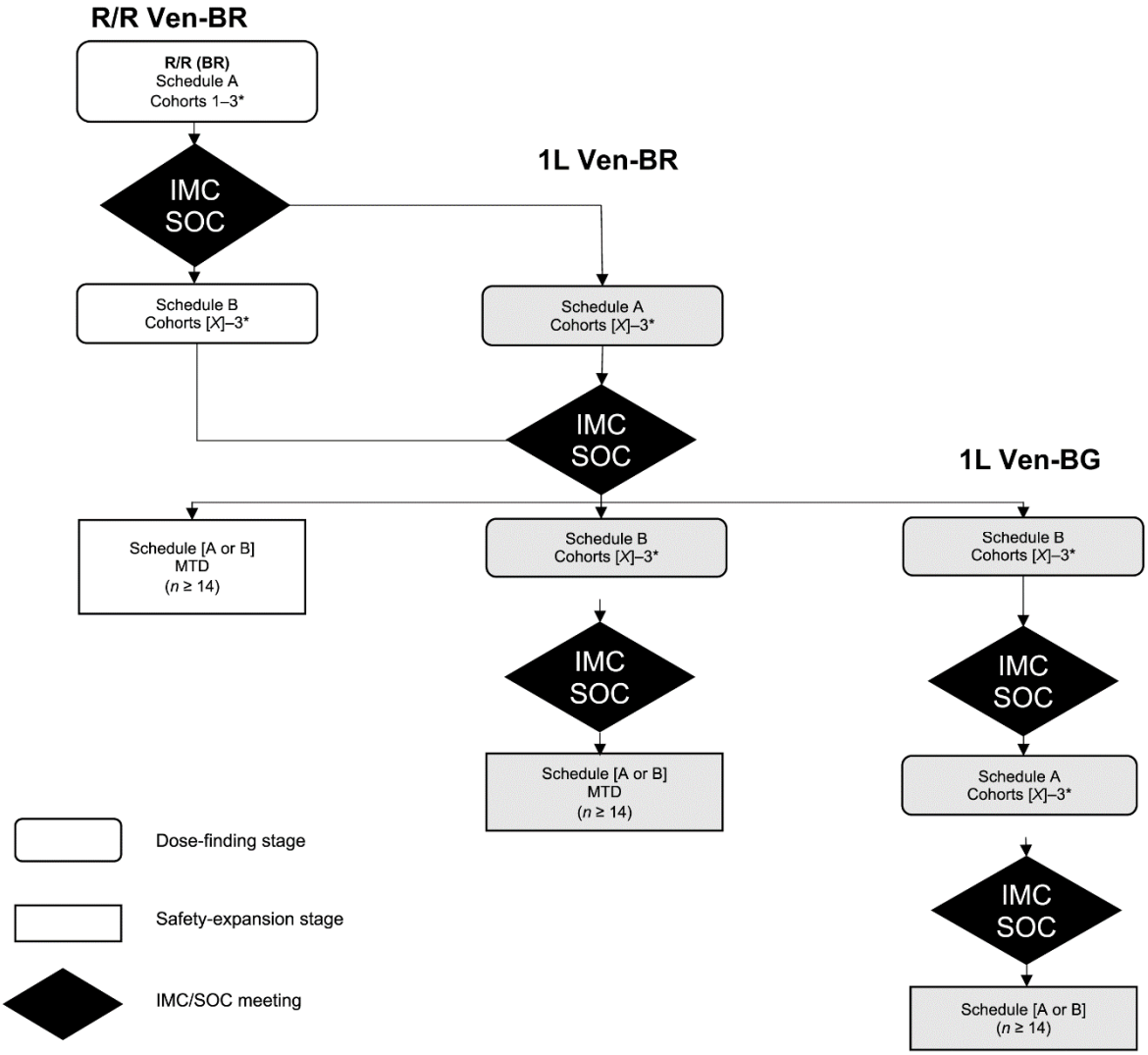
Supplementary Table S14 Concordance between MRD status determined from PB and BM

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.

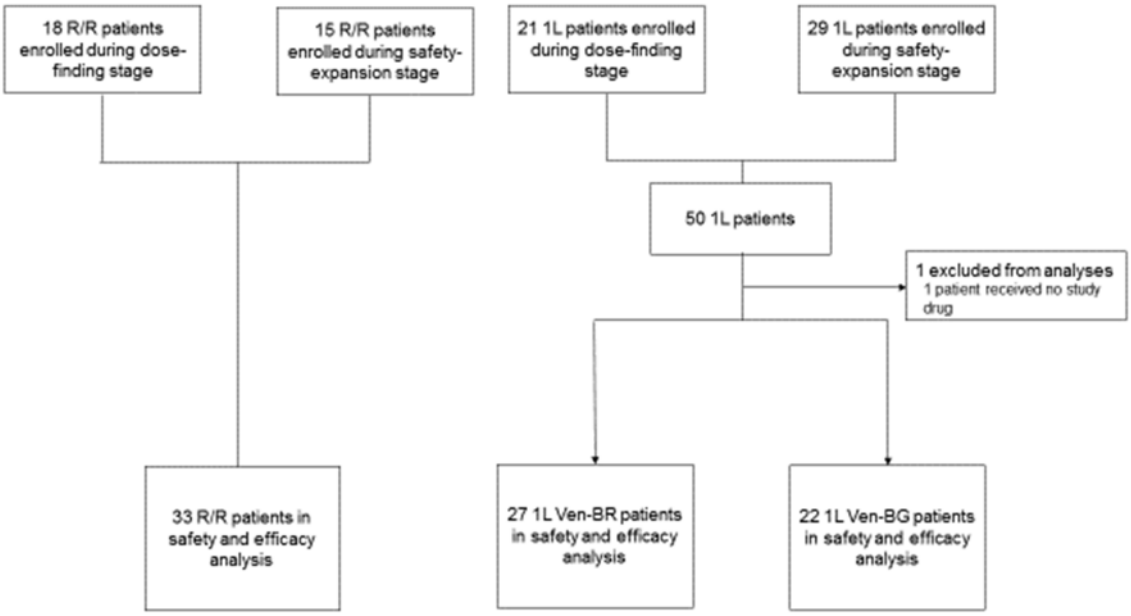
MRD minimal residual disease, PB peripheral blood, BM bone marrow, R/R relapsed/refractory, Ven venetoclax, B bendamustine, R rituximab, 1L first line, G obinutuzumab.

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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