

Supplemental Appendix

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

Supplement to: Andrew D. Zelenetz, Gilles Salles, Kylie D. Mason, et al. Venetoclax plus R- or G-CHOP in non-Hodgkin lymphoma: results from the CAVALLI phase 1b trial

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Preclinical analyses of venetoclax with rituximab and obinutuzumab, with and without CHOP, in non-Hodgkin lymphoma models

Methods

In-vitro studies primarily utilized fluorescence-activated cell sorting to measure direct cell death induction/apoptosis by Annexin V/propidium iodide (PI) staining of human lymphoid cell lines (WSU-DLCL2, SU-DHL4, and Z138). Z138 cells (obtained from Martin Dyer, University of Leicester) and WSU-DLCL-2 cells (Ref: ACC 575; DSMZ Deutsche Sammlung für Mikroorganismen und Zellkulturen) were cultured in RPMI1640 (Invitrogen) + 10% FCS + 1% GlutaMAX™ (Invitrogen), and SU-DHL4 cells (Ref: ACC 495; DSMZ) were cultured in DMEM (Invitrogen) + 10% FCS + 1% GlutaMAX. Briefly, 1×10^5 target cells/well were incubated with 10 µg/mL of obinutuzumab or rituximab in combination with venetoclax (dose range, 25 nM to 25 µM) for 20–24 h (untreated samples were used as a negative control). Cells were washed with Annexin V binding buffer (10 mM HEPES/NaOH pH 7.4, 140 mM NaCl, 2.5 mM CaCl_2), stained with Annexin V FITC (Roche) for 15 min, washed again, and re-suspended in Annexin V binding buffer containing PI. Samples were analyzed immediately on a BD FACSCanto™ II.

Additionally, the impact of BCL2 inhibition on antibody-dependent cellular cytotoxicity (ADCC) induction was evaluated. Peripheral blood mononuclear cells (PBMCs) were isolated from the blood of healthy donors and pre-incubated alone for 20 h at 37°C (5% CO_2) in the presence or absence of 2500 nM or 250 nM venetoclax, before using them as effector cells in a 4-h ADCC assay. The respective antibody dilutions were added to SUDHL4 target cells and incubated for 10 min before addition of PBMCs (4 h ADCC: E:T 20:1). Effector (E) and target (T) cells were then incubated for 4 h at 37°C (triplicates for all samples). The final volume of all wells was 200 µL/well. Lactate dehydrogenase (LDH) release was measured using the LDH Cytotoxicity Detection Kit (Roche Applied Science #11644793001).

Spontaneous release (corresponding to target cells incubated with effector cells without antibody or inhibitor) was defined as 0% cytotoxicity; maximal release (corresponding to target cells lysed with 2% Triton X-100) was defined as 100% cytotoxicity. The average percentage of ADCC and standard deviations of the triplicates of each experiment were

calculated. Statistical analysis for drug-treated versus untreated cells was based on Student's *t*-test two-sided paired analysis.

In-vivo efficacy of venetoclax monotherapy or venetoclax in combination with the anti-CD20 antibodies, rituximab or obinutuzumab, was evaluated in WSU-DLCL2 and SU-DHL4 subcutaneous xenograft models. Briefly, 5×10^6 cells were injected subcutaneously into CB-17 SCID/beige mice (Charles River Laboratories). When a tumor volume of 100–300 mm³ was reached, animals were distributed into treatment groups (n=8 to 10 animals/group). Venetoclax (100 mg/kg) was administered once daily (QD) by oral gavage (PO) for 21 days; anti-CD20 antibodies (3–30 mg/kg) were delivered intravenously (IV) once during the treatment period. CHOP combination treatment was administered as follows: cyclophosphamide 30 mg/kg, IV, once; doxorubicin 2.475 mg/kg, IV, once; vincristine 0.375 mg/kg, IV, once; prednisone 0.15 mg/kg, PO QD for 5 days. Fitted tumor volumes were determined by curve fitting applied to Log₂-transformed individual tumor volume data using a linear mixed-effects model. Animal body weights during the treatment period were assessed to measure drug tolerability twice weekly.

Results

The combination of venetoclax with the anti-CD20 antibodies, rituximab and obinutuzumab, was evaluated *in vitro* using NHL cell lines that were previously reported to be resistant to venetoclax despite expressing relatively high levels of BCL2.¹ Treatment of DLBCL (Su-DHL-4 and WSU-DLCL2) and MCL (Z138) cells with venetoclax (2500 nM) resulted in 90–100% cell death (supplemental Figure 1 A–F). At lower concentrations of venetoclax (250 nM), combination treatment with either rituximab or obinutuzumab increased the rate of apoptosis compared with venetoclax treatment alone (supplemental Figure 1).

Given that the combination of venetoclax with anti-CD20 antibodies led to greater cell death, we evaluated the efficacy of these drugs *in vivo* using the SU-DHL-4 and WSU-DLCL2 DLBCL xenograft models. In the SU-DHL-4 xenograft model, venetoclax enhanced the efficacy of rituximab based on increased tumor regressions and growth delay (supplemental Figure 2A). The latter results are consistent with previously reported data in the DoHH2 NHL model.¹ In the WSU-DLCL2 xenograft model, which is less sensitive to rituximab, venetoclax

plus rituximab increased tumor growth inhibition when compared with monotherapies (supplemental Figure 2B). Greater efficacy was achieved in this model when venetoclax was combined with R-CHOP versus R-CHOP alone or venetoclax plus rituximab (supplemental Figure 2C). The combination of venetoclax plus obinutuzumab also led to tumor regressions with an increased duration of sustained antitumor response, which was durable in the Su-DHL-4 xenograft model (supplemental Figure 2D). In the WSU-DLCL2 xenograft model, which is also less sensitive to obinutuzumab alone, the combination of venetoclax with obinutuzumab increased tumor growth inhibition compared with monotherapies (supplemental Figure 2E). However, given that the WSU-DLCL2 model is very sensitive to G-CHOP, the addition of venetoclax to this regimen did not result in greater efficacy when compared with G-CHOP alone (supplemental Figure 2F). Venetoclax with anti-CD20 antibodies, or in combination with CHOP, was well tolerated *in vivo* based on minimal changes in animal body weights (data not shown). Venetoclax did not antagonize natural killer cell-mediated ADCC or B-cell depletion induced by rituximab or obinutuzumab treatment *ex vivo* (supplemental Figure 1 G–H). Thus, combining rituximab or obinutuzumab with venetoclax led to superior efficacy in DLBCL xenograft models.

Additional methods

Full list of inclusion and exclusion criteria

Inclusion criteria

- Signed informed consent form(s)
- Age ≥ 18 years
- Histologically confirmed B-cell non-Hodgkin lymphoma (NHL)
 - Any relapsed/refractory patients who are enrolled during the dose escalation should have received only a single previous treatment regimen (excluding R-CHOP)
- At least one bi-dimensionally measurable lesion on CT scan defined as >1.5 cm in its longest dimension
- Ability and willingness to comply with the study protocol procedures
- Confirmed availability of archival or freshly biopsied tumor tissue meeting protocol defined specifications prior to study enrollment
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
- Adequate hematologic function (unless caused by underlying disease, as established by extensive bone marrow involvement or as a result of hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator), defined as follows:
 - Hemoglobin ≥ 9 g/dL
 - Absolute neutrophil count $\geq 1.5 \times 10^9/L$
 - Platelet count $\geq 75 \times 10^9/L$
- For women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined non-hormonal contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 12 months after the last dose of rituximab, or 18 months after the last dose of obinutuzumab
 - Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation,

symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception

- Non-vasectomized male patients must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 12 months after completing therapy with rituximab or 18 months after completing therapy with obinutuzumab
 - A partner who is surgically sterile or postmenopausal (for at least 1 year) or who is taking hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) for at least 3 months prior to study drug administration
 - Total abstinence from sexual intercourse; double barrier method (condom plus diaphragm or cervical cup with spermicidal, contraceptive sponge, jellies, or cream)
 - Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Males must agree to abstain from sperm donation for at least 12 months after the last dose of rituximab or 18 months after the last obinutuzumab dose

Exclusion criteria

- Patients with mantle cell lymphoma or small lymphocytic lymphoma
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies, or known sensitivity or allergy to murine products
- Contraindication to receive any of the individual components of CHOP, rituximab, or obinutuzumab
- Prior anthracycline therapy
- Ongoing corticosteroid use >30 mg/day of prednisone or equivalent. Patients who received corticosteroid treatment with ≤30 mg/day of prednisone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration prior to cycle 1 day 1. Patients may have received a brief (<7 days) course of systemic

steroids (≤ 100 mg prednisone equivalent per day) prior to initiation of study therapy for control of lymphoma related symptoms

- CNS lymphoma
- Vaccination with live vaccines within 28 days prior to treatment
- Chemotherapy or other investigational therapy within 28 days prior to the start of cycle 1
- History of other malignancy that could affect compliance with the protocol or interpretation of results
 - Patients with a history of curatively treated basal or squamous cell carcinoma, or stage 1 melanoma of the skin or in situ carcinoma of the cervix are eligible
 - Patients with a malignancy that has been treated with surgery alone with curative intent will also be excluded, unless the malignancy has been in documented remission without treatment for ≥ 5 years prior to enrollment
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results or that could increase risk to the patient, including renal disease that would preclude chemotherapy administration or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Significant cardiovascular disease (such as New York Heart Association class III or IV cardiac disease, congestive heart failure, myocardial infarction within the past 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Left ventricular ejection fraction $< 50\%$ as defined by MUGA. Echocardiogram may be used if MUGA is not available
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to cycle 1 day 1
- Received the following agents within 7 days prior to the first dose of venetoclax:

- Steroid therapy for anti-neoplastic intent within 7 days prior to the first dose of study drug
- Strong and moderate CYP3A inhibitors
- Strong and moderate CYP3A inducers
- Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of venetoclax
- Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- Presence of positive test results for hepatitis B (HBsAg) or hepatitis C (hepatitis C virus [HCV] antibody)
 - Patients who are positive for HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation
 - Patients with occult or prior HBV infection (defined as positive total HBcAb and negative HBsAg) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly DNA testing
- Known infection with HIV or human T-cell leukemia virus 1 (HTLV 1)
- Women who are pregnant or lactating
- Recent major surgery (within 6 weeks prior to the start of cycle 1 day 1), other than for diagnosis
- Any of the following abnormal laboratory values:
 - Calculated creatinine clearance <50 mL/min with the use of the 24-hour creatinine clearance or modified Cockcroft Gault equation (with the use of ideal body mass [IBM] instead of mass):

$$eCCR = \frac{(140 - \text{age}) \times \text{IBM (kg)} \times [0.85 \text{ if female}]}{72 \cdot \text{serum creatinine (mg/dL)}}$$

Or, if serum creatinine is in $\mu\text{mol/L}$:

$$e\text{CCR} = \frac{(140 - \text{age}) \times \text{IBM (kg)} \times [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum creatinine } (\mu\text{mol/L})}$$

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × upper limit of normal (ULN)
- Total bilirubin ≥1.5 × ULN (or >3 × ULN for patients with documented Gilbert syndrome)
- International normalized ratio (INR) >1.5 × ULN for patients not receiving therapeutic anticoagulation
- Partial thromboplastin time (PTT) or activated PTT (aPTT) >1.5 × ULN

Summary of tumor lysis syndrome (Howard criteria)² prophylaxis and monitoring measures

Tumor lysis syndrome (TLS) is a risk for patients with NHL who are treated with high cell killing agents. Risk is highest for those with bulky disease, elevated pretreatment LDH levels, elevated leukocyte count, and dehydration.³ Patients with bulky disease, defined as any lymph node ≥ 8 –10 cm on the screening CT scan (depending on protocol version) and/or lymphocytosis due to circulating lymphoma cells, were considered at higher risk of TLS and were required to be hospitalized for more intensive monitoring during the initial dose of venetoclax. Patients who did not present with bulky disease and/or lymphocytosis were not considered at higher risk for TLS and did not require hospitalization but may have been hospitalized per discussion with the investigator and Medical Monitor.

The risk of TLS in the setting of R-CHOP or G-CHOP was assessed by the investigator, and prophylaxis and management undertaken per protocol and institutional standard.

All patients received prophylaxis for TLS prior to the initiation of the first dose of venetoclax. Prophylaxis included the following:

- Appropriate hydration, consisting of a fluid intake of approximately 2–3 L/day starting 24–48 h days before the start of venetoclax treatment and continued for ≥ 24 h after the first dose (for patients for whom volume overload was considered a significant risk, hospitalization was considered).
- Administration of an agent to reduce uric acid, such as allopurinol 300 mg/day PO, beginning 72 h prior to the first venetoclax dose. Rasburicase IV was administered (unless medically contraindicated) for those patients with elevated uric acid levels prior to treatment, defined as a value above the local laboratory ULN or 476 $\mu\text{mol/L}$. Agents were given until normalization of serum uric acid and other laboratory evidence of TLS (e.g., elevated serum LDH levels).
- Laboratory results were reviewed and electrolyte values should not have demonstrated any clinically significant abnormalities within 24 h before, and at 8 and 24 h after, the first dose of venetoclax; or the patient should have received additional prophylactic treatment (including management of electrolytes) and hydration prior to the initiation of dosing.
- Patients at higher risk of TLS were hospitalized for the initial venetoclax dose.

- For patients at particularly high risk for TLS, as judged by the investigator, consideration was given to starting at a lower dose of venetoclax and increasing venetoclax dose in a stepwise fashion in discussion with the Medical Monitor.

On the day of the initial visit with administration of venetoclax, serial vital sign assessments were performed, and serum chemistry and hematology samples drawn prior to the dose of venetoclax and at 8 and 24 h following the dose. The serum chemistry and hematology samples were sent immediately to the laboratory and the investigator or designee reviewed the results promptly. Laboratory results from predose samples were reviewed prior to venetoclax administration unless laboratory results from within the prior 24 h had already been reviewed. Laboratory values obtained prior to the dose of venetoclax were used to determine whether a patient developed a change related to TLS. Laboratory results from the 24-h postdose assessments (and 8-h postdose assessment for inpatients) were reviewed prior to receiving the dose of venetoclax for that day. Patients who developed electrolyte changes suggestive of TLS underwent aggressive management and further monitoring.

Pharmacokinetics

Plasma concentrations of venetoclax for pharmacokinetic assessments were collected predose and at 2, 4, 6, and 8 hours postdose on day 4 of cycle 1; at predose and 8 hours postdose on day 8 of cycle 1; and predose on day 10 of cycle 2. Plasma venetoclax concentrations were measured using a validated liquid chromatography tandem mass spectrometry assay. The maximum plasma venetoclax concentration (C_{max}) and time to C_{max} (T_{max}) were the observed values. Total systemic exposure to venetoclax was estimated by calculating the area under the plasma venetoclax concentration–time curve (AUC) using the linear trapezoidal method.

Exploratory endpoints

Biomarker assessments were performed at central laboratories. BCL2 and MYC expression were assessed by immunohistochemistry in tumor tissue using Ventana Bcl-2 (124) and c-MYC (Y69) assays. The cutoff value for BCL2 positivity was $\geq 50\%$ of tumor cells showing moderate to strong staining; for MYC positivity, the cutoff value was $\geq 40\%$ of tumor cells showing nuclear staining of any intensity. Chromosomal rearrangements in BCL2 and MYC gene loci were measured by fluorescence in situ hybridization (FISH) on lymph node tissue using Vysis LSI BCL2 (Abbott Molecular, Abbott Park, IL) and MYC Dual Color Break Apart Probes (ZytoVision GmbH, Bremerhaven, Germany). BCL2 and MYC translocations were considered to be positive if signals were observed in $\geq 50\%$ of nuclei. Genes associated with the ABC or GCB cell-of-origin (COO) DLBCL subtypes were evaluated by NanoString.

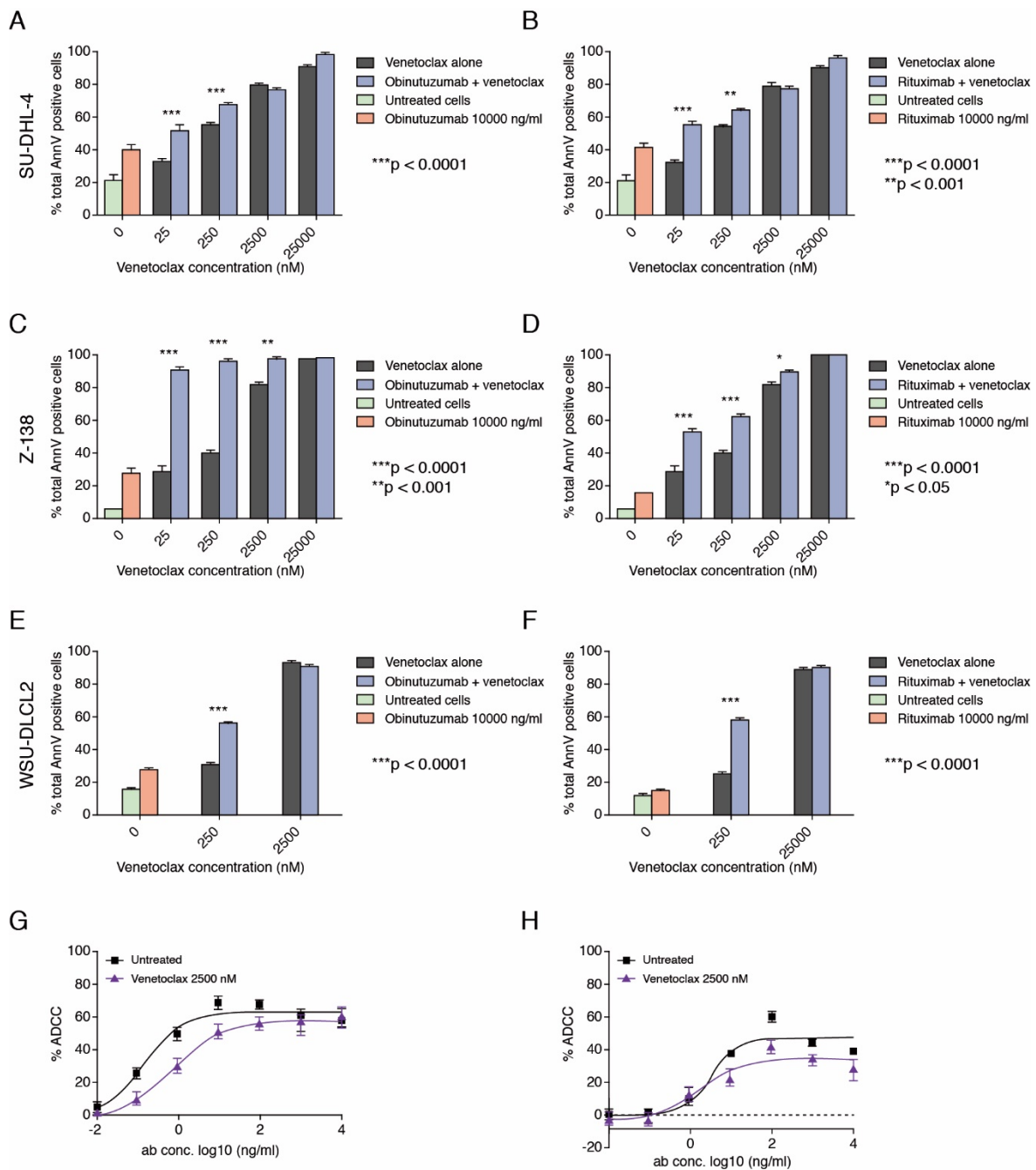
Additional results

Treatment modifications

Adverse events (AEs) led to venetoclax discontinuation by 3 patients in cohort 1 of each arm. Across cohorts 2-4 combined, no patients discontinued from arm A and 10 discontinued from arm B.

Thirteen patients (6 in arm A, 7 in arm B) had dose delays of >7 days due to AEs. One patient received 5 cycles of G-CHOP in arm B cohort 2, before switching to receive a sixth cycle of R-CHOP off study. Nine patients received pre-phase steroids (dose not recorded) for 4-8 days.

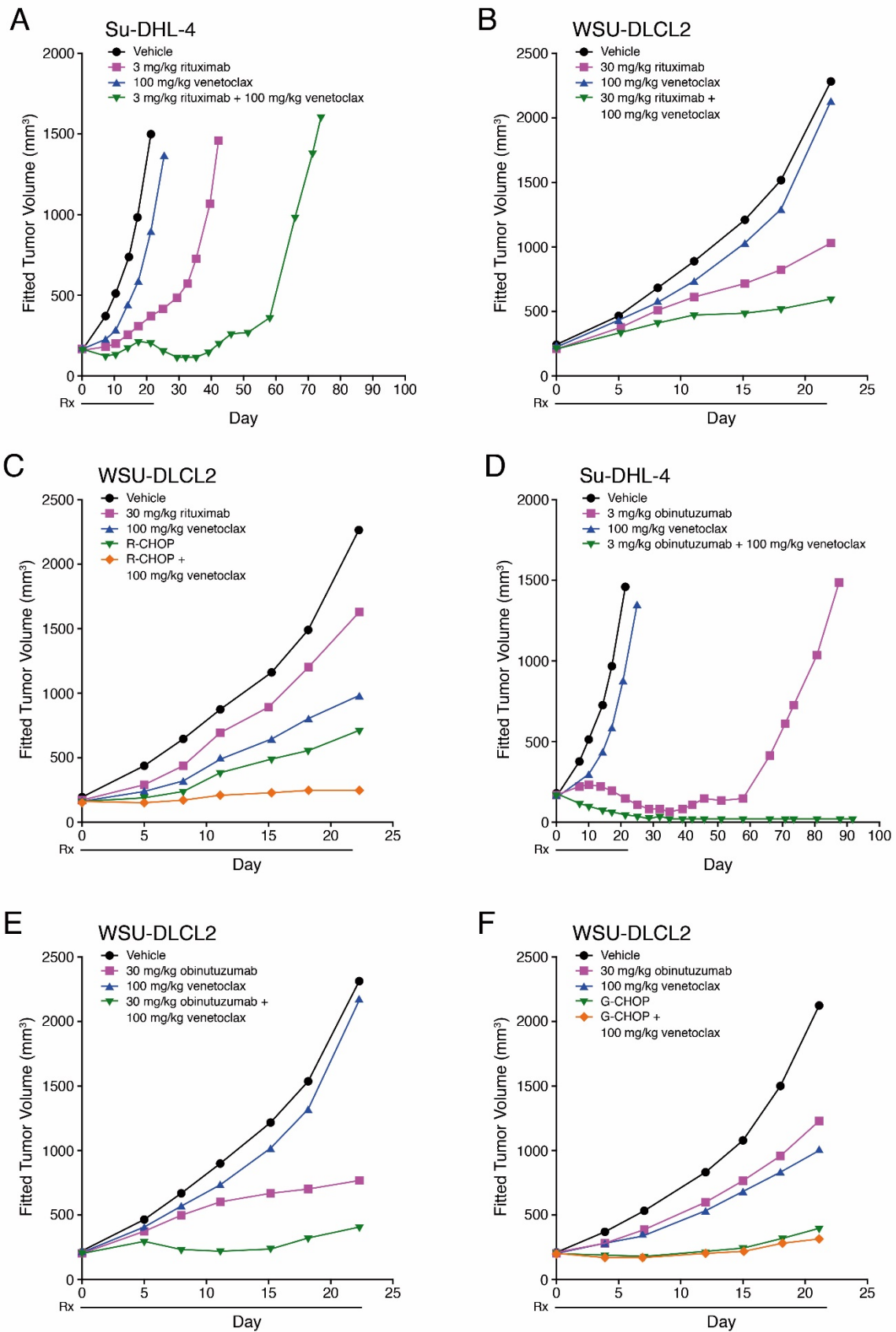
Supplemental Figure 1. Direct cell death and antibody-dependent cellular cytotoxicity induction of rituximab/obinutuzumab in combination with venetoclax.



A–F: Direct cell death induction. Tumor targets (A, B: SU-DHL-4, C, D Z-138, E, F WSU DLCL2) were incubated for 20–24 h with 10,000 ng/mL obinutuzumab (A, C, E) or rituximab (B, D, F) in the absence or presence of different concentrations of venetoclax (25 nM–25 μM). Induction of cell death was determined by flow cytometry determining the percentages of Annexin V-positive cells. **G–H: Assessment of antibody-dependent cellular cytotoxicity (ADCC).** Healthy donor-derived peripheral blood mononuclear cells (PBMCs) were pre-incubated for 20 h in the presence or absence of 2500 nM or 250 nM venetoclax before being used as effector

cells in an ADCC assay. The PBMCs were incubated with SU-DHL-4 as target cells (E:T 20:1) in the presence of either obinutuzumab (G) or rituximab (H) titrations. Tumor cell killing was determined by lactate dehydrogenase release after 4 h.

Supplemental Figure 2. In-vivo efficacy of venetoclax in combination with anti-CD20 and CHOP therapies in diffuse large B-cell lymphoma xenograft models.



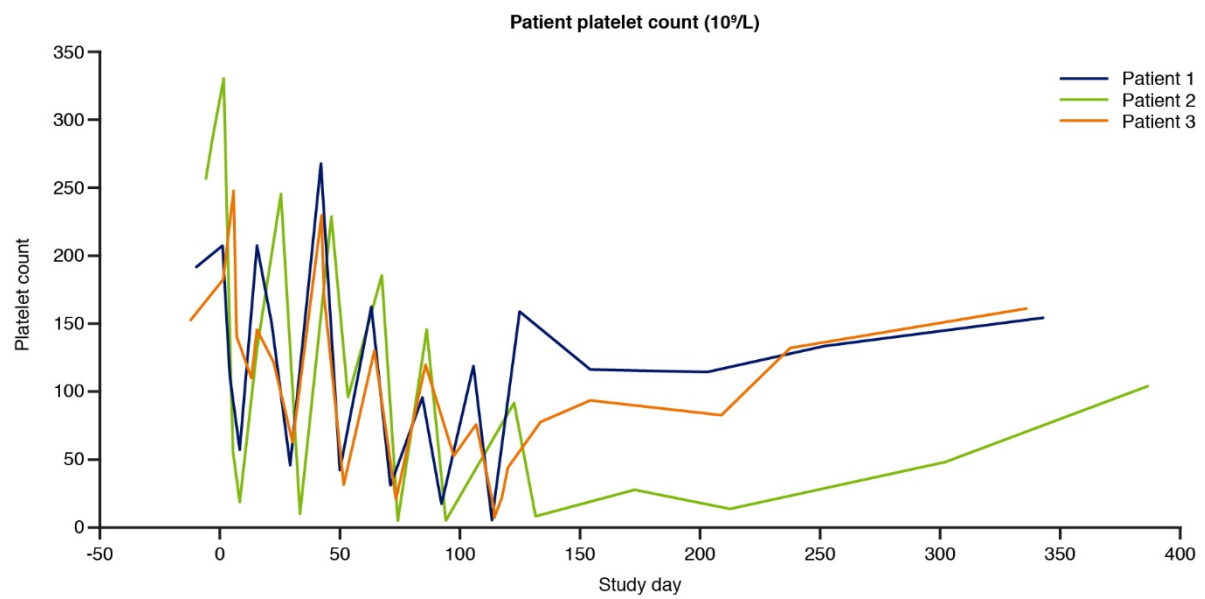
A–C: In-vivo efficacy of venetoclax in combination with rituximab (A and B) or R-CHOP (C) in Su-DHL-4 (A) and WSU-DLCL2 (B, C) DLBCL xenograft models. **D–F:** In-vivo efficacy of venetoclax in combination with obinutuzumab (D, E) or G-CHOP (F) in Su-DHL-4 (D) and WSU-DLCL2 (E, F) DLBCL xenograft models. Rituximab and obinutuzumab were administered once, intravenously, while venetoclax was dosed orally and daily for 21 days at the doses indicated. R- and G-CHOP were administered once during the treatment period. Solid lines below the x-axis denote the treatment period for in-vivo efficacy studies. For CHOP combination treatment: cyclophosphamide 30 mg/kg, IV, once; doxorubicin 2.475 mg/kg, IV, once; vincristine 0.375 mg/kg, IV, once; prednisone 0.15 mg/kg, PO QD × 5 days.

All in-vivo studies were approved by Genentech's Institutional Animal Care and Use Committee and adhere to the NIH Guidelines for the Care and Use of Laboratory Animals.

CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL, diffuse large B-cell lymphoma; G-CHOP, obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; IV, intravenously; PO, orally; QD, once daily; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; and Rx, treatment.

Supplemental Figure 3. Individual patient platelet counts for 3 patients in arm B cohort

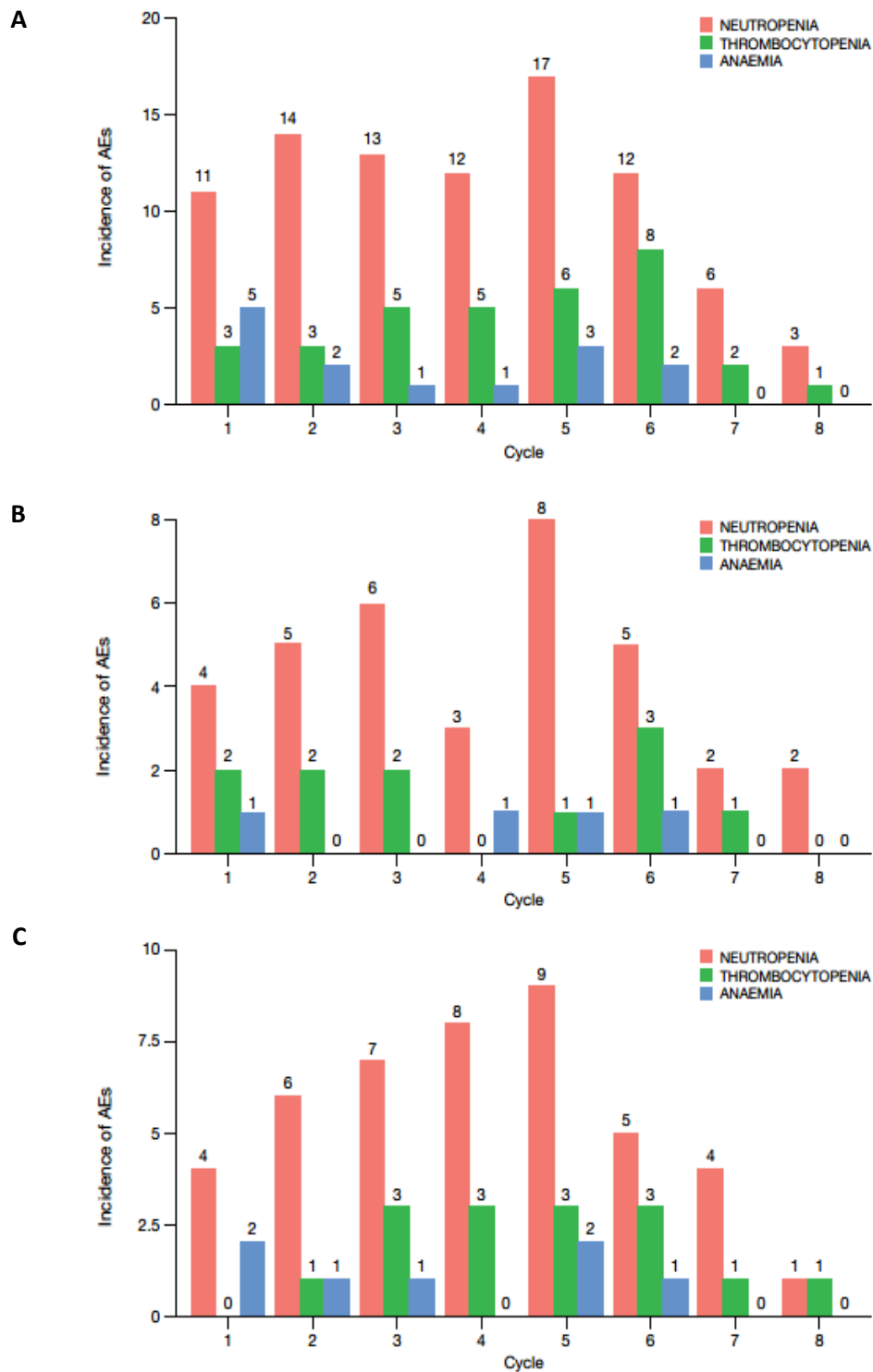
4A.



Patients received obinutuzumab (1000 mg IV) on days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-8 plus CHOP (21-day cycles). Venetoclax (800 mg) was given on days 4-10 of cycle 1, and days 1-10 of cycles 2-8. The platelet count nadir occurred mid-cycle, but thrombocyte numbers increased before the next cycle.

CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone; and IV, intravenously.

Supplemental Figure 4. Incidence of cytopenias per cycle in all phase 1b patients (A), diffuse large B-cell lymphoma patients (B), and follicular lymphoma patients (C).

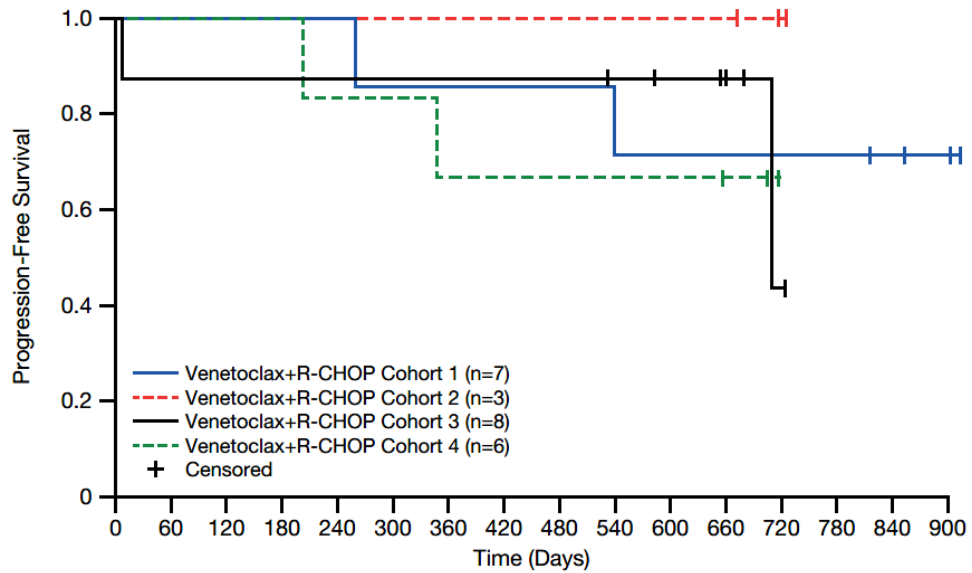


Data shown represent patient numbers.

AEs indicates adverse events.

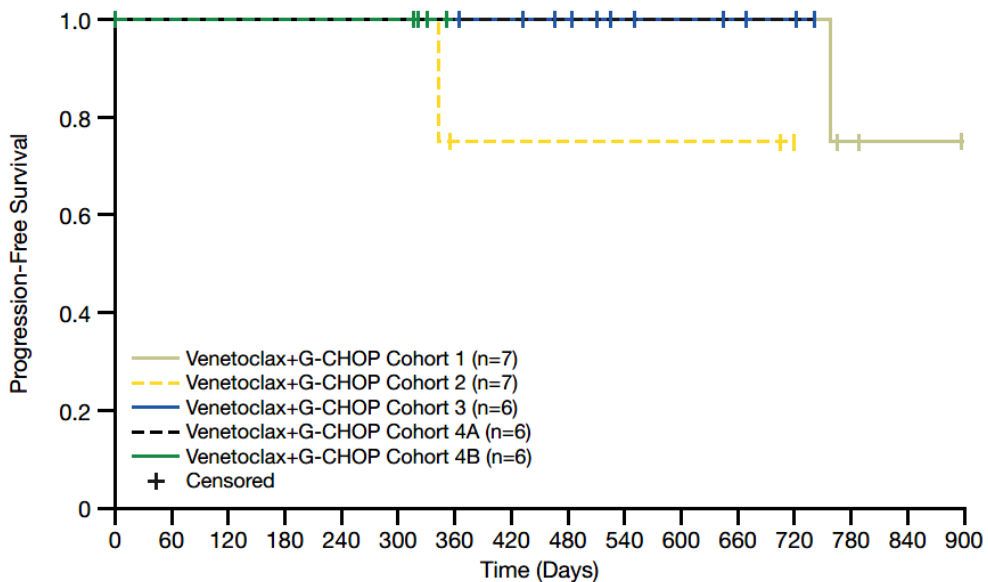
Supplemental Figure 5. Kaplan-Meier curves for progression-free survival for patients in arm A (A) and arm B (B).

A



No. of Patients at risk		0	60	120	180	240	300	360	420	480	540	600	660	720	780	840	900
Venetoclax+R-CHOP Cohort 1	7	7	7	7	7	7	6	6	6	6	6	5	5	5	5	3	2
Venetoclax+R-CHOP Cohort 2	3	3	3	3	3	3	3	3	3	3	3	3	3	2			
Venetoclax+R-CHOP Cohort 3	8	7	7	7	7	7	7	7	7	6	5	4	1				
Venetoclax+R-CHOP Cohort 4	6	6	6	6	6	5	5	4	4	4	3	3	2				

B

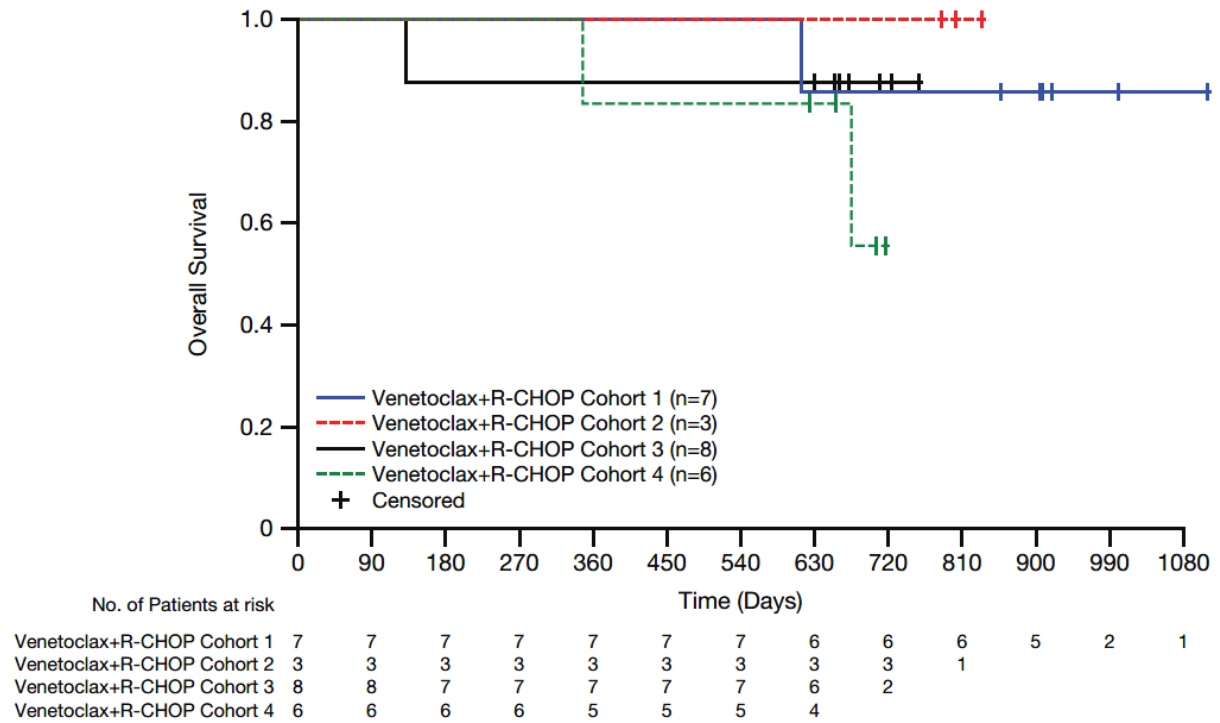


No. of Patients at risk		0	60	120	180	240	300	360	420	480	540	600	660	720	780	840	900
Venetoclax+G-CHOP Cohort 1	7	5	5	5	5	5	5	5	5	5	5	5	5	5	2	1	
Venetoclax+G-CHOP Cohort 2	7	7	6	6	6	6	6	2	2	2	2	2	2	1			
Venetoclax+G-CHOP Cohort 3	6	6	6	6	6	6	6	6	5	4	4	4	3	2			
Venetoclax+G-CHOP Cohort 4A	6	6	6	6	6	6	6	6	5	2	1	1					
Venetoclax+G-CHOP Cohort 4B	6	6	6	6	6	6	5	1									

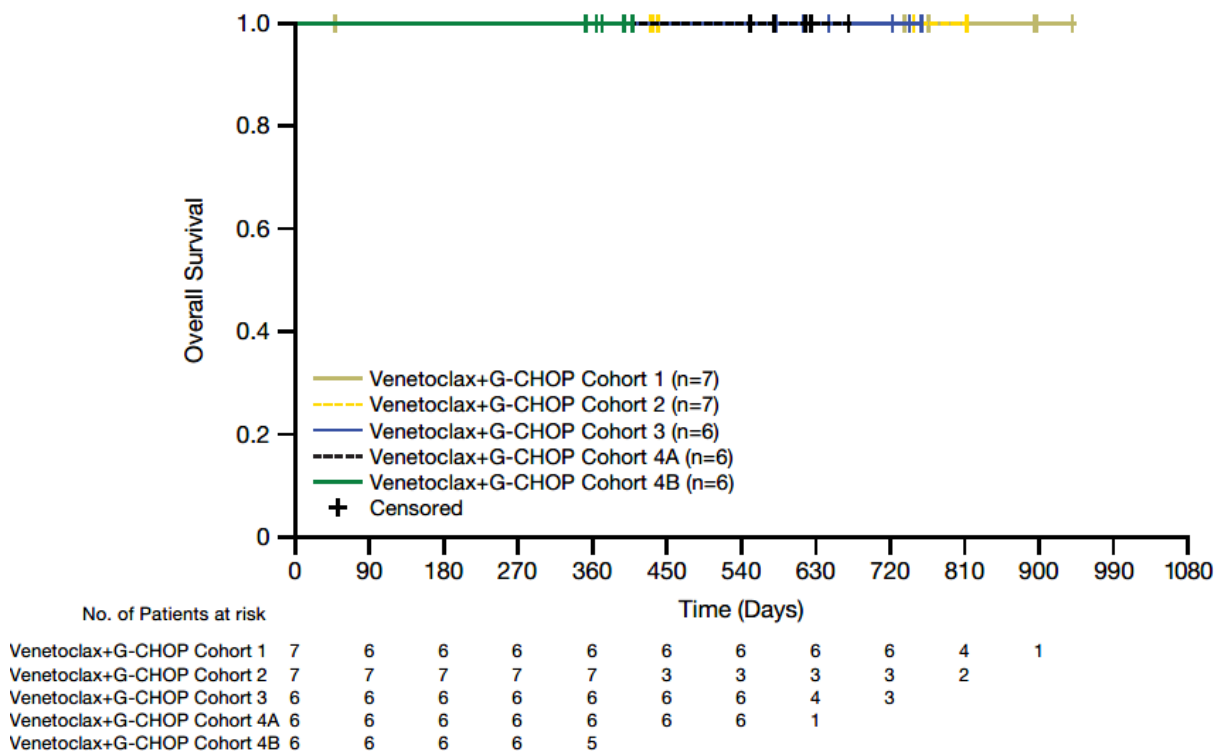
G-CHOP indicates obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; and R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Supplemental Figure 6. Kaplan-Meier curves for overall survival for patients in arm A (A) and arm B (B).

A



B



G-CHOP indicates obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; and R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Supplemental Table 1. Guidelines for dose delay or modification of venetoclax, rituximab, or obinutuzumab and CHOP chemotherapy.

Event(s)	Dose delay or modification
Grade 3/4 neutropenia on cycle day 1 with or without infection or fever *	<ul style="list-style-type: none"> • Delay doses of all study treatment. • Administer growth factors (e.g., G-CSF for neutropenia as indicated and for all subsequent cycles).
First delay	<ul style="list-style-type: none"> • If ANC recovers to $>1 \times 10^9/L$ by day 7 of the scheduled date for the next cycle, administer full dose of study treatment. • If ANC recovers to $>1 \times 10^9/L$ on or after day 8 of the scheduled date for the next cycle, reduce the dose of venetoclax to the previously tested (lower) dose level (dose will be reduced by $\geq 25\%$). • If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of venetoclax. Decisions must be made in consultation with and with approval of the Medical Monitor.
Recurrent grade 3 neutropenia on cycle day 1	<ul style="list-style-type: none"> • Delay doses of all study treatment. • If ANC recovers to $>1 \times 10^9/L$ by day 7 of the scheduled date for the next cycle, administer full dose of study treatment. • If ANC recovers to $>1 \times 10^9/L$ on or after day 8 of the scheduled date for the next cycle, then: <ul style="list-style-type: none"> ○ If no prior dose reduction of venetoclax: reduce the dose of venetoclax to the previously tested (lower) dose level (dose will be reduced by $\geq 25\%$). ○ If there was a prior reduction of venetoclax: the venetoclax dose reduction should be maintained, and the doses of cyclophosphamide and doxorubicin should be reduced to 75% of the original dose. ○ For subsequent episodes, further dose reduction of venetoclax or doxorubicin and cyclophosphamide may be considered. • If grade 3 neutropenia persists despite growth factor support and following venetoclax, cyclophosphamide, and doxorubicin dose reductions, in the absence of fever, patient may continue with study treatment. • If patient develops grade 3 febrile neutropenia or infection despite growth factor support and following venetoclax, cyclophosphamide, and doxorubicin dose reductions, discontinue all study treatment permanently.
Recurrent grade 4 neutropenia on cycle day 1	<ul style="list-style-type: none"> • If patient develops persistent grade 4 neutropenia requiring dose delay despite growth factor support and following venetoclax, cyclophosphamide, and doxorubicin dose reductions, discontinue all study treatment permanently.
Febrile neutropenia or neutropenia with infection during cycle 1	<ul style="list-style-type: none"> • Hold obinutuzumab dose until it resolves. • If cycle 1 day 8 is delayed to within 2 days of day 15, then omit the day 8 dose and administer the day 15 dose as previously scheduled (if infection or neutropenic fever has resolved). • If cycle 1 day 15 is delayed to within 2 days of cycle 2, then omit the day 15 dose and administer the cycle 2 day 1 dose of obinutuzumab + CHOP as scheduled (if infection or neutropenic fever has resolved). <ul style="list-style-type: none"> ○ <i>Note:</i> obinutuzumab should not be held for asymptomatic neutropenia.

Grade 4 thrombocytopenia, first episode	<ul style="list-style-type: none"> • Modify venetoclax dose by reducing to next dose level or decrease dosing schedule to 7 days.
Recurrent grade 3 thrombocytopenia in consecutive cycles	<ul style="list-style-type: none"> • Modify venetoclax dose by reducing to next dose level or decrease dosing schedule to 7 days.
Grade 3 thrombocytopenia on cycle day 1, first episode	<ul style="list-style-type: none"> • Delay doses of all study treatment. • If platelet count recovers to $50 \times 10^9/L$ by day 7 of the scheduled date of the next cycle, administer full dose of study treatment. • If platelet count recovers to $50 \times 10^9/L$ on/after day 8 of the scheduled date of the next cycle, reduce the dose of venetoclax to the previously tested (lower) dose level (dose will be reduced by $\geq 25\%$) or decrease dosing schedule to 7 days. Full dose of R-CHOP or G-CHOP may be given. • If the patient had baseline thrombocytopenia and the primary cause of thrombocytopenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of cyclophosphamide and doxorubicin.
Recurrent grade 3/4 thrombocytopenia on cycle day 1	<ul style="list-style-type: none"> • Delay doses of all study treatment. • Reduce the dose of venetoclax to the previously tested (lower) dose level (dose will be reduced by $\geq 25\%$) or decrease dosing schedule to 7 days. • If recurrent grade 3/4 thrombocytopenia on cycle day 1 after venetoclax dose reduction: <ul style="list-style-type: none"> ○ The venetoclax dose reduction should be maintained, and the doses of cyclophosphamide and doxorubicin should be reduced to 75% of the original dose. ○ For subsequent episodes, further dose reduction of venetoclax or doxorubicin and cyclophosphamide may be considered. • If patient develops grade 4 thrombocytopenia following venetoclax, cyclophosphamide, and doxorubicin dose reductions, discontinue all study treatment permanently.
Severe thrombocytopenia (platelets $<10,000/\mu L$) and/or symptomatic bleeding in patients who are not receiving concomitant anticoagulants or platelet inhibitors during cycle 1	<ul style="list-style-type: none"> • Hold obinutuzumab in case of severe thrombocytopenia (platelets $<10 \times 10^9/L$) or symptomatic bleeding (irrespective of platelet count) until it resolves. • If the cycle 1 day 8 dose is delayed, then omit the day 8 dose and administer the day 15 dose as previously scheduled (if symptomatic bleeding has resolved). • If the cycle 1 day 15 dose is delayed, then omit the day 15 dose and administer the cycle 2 day 1 dose of obinutuzumab + CHOP as scheduled (if symptomatic bleeding has resolved).

Thrombocytopenia with platelets <20,000/ μ L and/or symptomatic bleeding in patients who are receiving concomitant anticoagulants or platelet inhibitors during cycle 1 ^{†,‡}	<ul style="list-style-type: none"> • Hold obinutuzumab in case of platelets <20 \times 10⁹/L or symptomatic bleeding (irrespective of platelet count) until it resolves. • If the cycle 1 day 8 dose is delayed, then omit the day 8 dose and administer the day 15 dose as previously scheduled (if symptomatic bleeding has resolved). • If the cycle 1 day 15 dose is delayed, then omit the day 15 dose and administer the cycle 2 day 1 dose of obinutuzumab + CHOP as scheduled (if symptomatic bleeding has resolved). • For patients who are receiving concomitant anticoagulant when thrombocytopenia with platelets <20 \times 10⁹/L develops, adjust the dose or hold the drug per investigator discretion. • For patients who are on platelet inhibitors when thrombocytopenia with platelets <20 \times 10⁹/L develops, consider temporarily holding their use.[‡]
Grade 1/2 neutropenia and/or thrombocytopenia	<ul style="list-style-type: none"> • No dose reduction or delay.
Grade 3/4 infection, with/without neutropenia	<ul style="list-style-type: none"> • Hold rituximab or obinutuzumab.
Hemorrhagic cystitis	<ul style="list-style-type: none"> • Patients should be adequately hydrated before and after cyclophosphamide administration, and should be instructed to void frequently. If gross hematuria develops, cyclophosphamide should be withheld until resolution of cystitis. A dose reduction of 50% for cyclophosphamide may be considered at the next cycle. Re-escalation of cyclophosphamide to the initial full dose is recommended if symptoms do not recur.
Grade 1–4 heart failure or grade 3/4 LVSD	<ul style="list-style-type: none"> • Discontinue R-CHOP chemotherapy permanently.
Bilirubin >3.0 mg/dL	<ul style="list-style-type: none"> • Delay treatment with R-CHOP until resolution to grade \leq1 within 14 days. Evaluate for causality.
Bilirubin between 1.5 and 3.0 mg/dL	<ul style="list-style-type: none"> • Reduce doxorubicin and vincristine dose by 25% of baseline. With subsequent courses of treatment, if bilirubin has returned to \leq1 mg/dL, full doses may be given. Give full dose of rituximab or obinutuzumab and continue current dose of cyclophosphamide and prednisone or prednisolone. Evaluate for causality.
Grade 4 neurotoxicity	<ul style="list-style-type: none"> • Discontinue R-CHOP or G-CHOP chemotherapy permanently.
Grade 2/3 neurotoxicity	<ul style="list-style-type: none"> • Hold R-CHOP or G-CHOP chemotherapy. • If recovered to grade \leq1 value within 14 days, administer full dose rituximab and continue current dose of cyclophosphamide and prednisone or prednisolone. Reduce vincristine dose by 50% for current cycle and all subsequent cycles.
Grade 3/4 tumor lysis syndrome	<ul style="list-style-type: none"> • Hold all study treatment (venetoclax and R-CHOP). The patient's next dose may be delayed for up to 14 days. Following complete resolution of tumor lysis syndrome, obinutuzumab or rituximab may be re-administered at the full dose during next scheduled infusion, in conjunction with prophylactic therapy and CHOP chemotherapy. • Venetoclax dosing may be reinitiated at target or reduced dose following discussion with the Medical Monitor, in conjunction with prophylactic therapy.
Anaphylaxis	<ul style="list-style-type: none"> • Discontinue rituximab or obinutuzumab permanently. CHOP and venetoclax may be continued when recovered if not attributable to CHOP or venetoclax.

Grade 4 IRR	<ul style="list-style-type: none"> Discontinue rituximab or obinutuzumab permanently. CHOP and venetoclax may be continued when recovered.
Grade 3 IRR, second episode	<ul style="list-style-type: none"> Discontinue rituximab or obinutuzumab permanently. CHOP and venetoclax may be continued when recovered.
Grade 1 neurotoxicity (peripheral neuropathy)	<ul style="list-style-type: none"> Continue treatment at full dose; vincristine may be decreased at the discretion of the investigator.
Grade 3/4 non-hematologic toxicity not specifically described above (excluding alopecia, nausea, and vomiting)	<ul style="list-style-type: none"> Delay R-CHOP or G-CHOP for a maximum of 2 weeks. If improved to grade ≤ 1 or baseline, continue study therapy at full dose, or reduce dose at the discretion of the investigator per site's standard procedures after discussion with the Medical Monitor.
Grade 1 non-hematologic toxicity	<ul style="list-style-type: none"> No dose reduction or delay.

*All based on laboratory results obtained within the time frame listed in the schedule of assessments prior to infusion of day 1 of that cycle of R-CHOP.

†If the clinical condition of the patient required the use of concomitant anticoagulants, the patient was at increased risk of bleeding when thrombocytopenia with platelets $<20,000/\mu\text{L}$ developed. When possible, prior therapy with vitamin K antagonists was replaced with low-molecular-weight heparin before cycle 1 day 1.

‡Clinical decision making adjusted depending on the patient-specific assessment of benefit and risk.

ANC indicates absolute neutrophil count; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; G-CHOP, obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; G-CSF, granulocyte colony-stimulating factor; IRR, infusion-related reaction; LVSD, left ventricular systolic dysfunction; and R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Supplemental Table 2. Summary of dose-limiting toxicities in arms A and B.

	Cohort	DLT	Outcome
Arm A			
	1 (200 mg VEN)	Gr 3 neutropenia	11-day delay in start of next R-CHOP
	3 (600 mg VEN)	Gr 4 sepsis	Discontinuation of all study treatment in cycle 1
	3 (600 mg VEN)	Gr 4 laboratory TLS	No clinical sequelae
Arm B			
	1 (200 mg VEN)	Gr 3 acute coronary syndrome and gr 3 infection	
	1 (200 mg VEN)	Gr 3 pneumonia	
	2 (400 mg VEN)	Gr 4 febrile neutropenia	Planned therapy completed without dose reduction
	3 (600 mg VEN)	Gr 4 sepsis	Discontinuation of all study treatment in cycle 1

DLT indicates dose-limiting toxicity; Gr, grade; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; TLS, tumor lysis syndrome; and VEN, venetoclax.

Supplemental Table 3. All-grade adverse events occurring in $\geq 20\%$ of patients in any cohort in either arm.*

Arm A: VEN + R-CHOP, n (%)	VEN 200 mg Cohort 1 (n = 7)	VEN 400 mg Cohort 2 (n = 3)	VEN 600 mg Cohort 3 (n = 8)	VEN 800 mg Cohort 4 (n = 6)	Total (N = 24)
Neutropenia	4 (57.1)	2 (66.7)	5 (62.5)	2 (33.3)	13 (54.2)
Nausea	3 (42.9)	2 (66.7)	1 (12.5)	5 (83.3)	11 (45.8)
Diarrhea	3 (42.9)	2 (66.7)	2 (25.0)	3 (50.0)	10 (41.7)
Fatigue	5 (71.4)	0	3 (37.5)	2 (33.3)	10 (41.7)
Neuropathy peripheral	2 (28.6)	1 (33.3)	3 (37.5)	3 (50.0)	9 (37.5)
Constipation	1 (14.3)	2 (66.7)	3 (37.5)	2 (33.3)	8 (33.3)
Peripheral sensory neuropathy	3 (42.9)	1 (33.3)	2 (25.0)	2 (33.3)	8 (33.3)
Anemia	4 (57.1)	1 (33.3)	1 (12.5)	2 (33.3)	8 (33.3)
Febrile neutropenia	3 (42.9)	0	2 (25.0)	3 (50.0)	8 (33.3)
Thrombocytopenia	4 (57.1)	1 (33.3)	2 (25.0)	0	7 (29.2)
Cough	2 (28.6)	0	3 (37.5)	1 (16.7)	6 (25.0)
Infusion-related reaction	1 (14.3)	2 (66.7)	1 (12.5)	2 (33.3)	6 (25.0)
Stomatitis	2 (28.6)	1 (33.3)	1 (12.5)	2 (33.3)	6 (25.0)
Asthenia	2 (28.6)	1 (33.3)	3 (37.5)	0	6 (25.0)
Hypokalemia	3 (42.9)	1 (33.3)	2 (25.0)	0	6 (25.0)
Dyspnea	3 (42.9)	1 (33.3)	0	1 (16.7)	5 (20.8)
Headache	1 (14.3)	0	3 (37.5)	1 (16.7)	5 (20.8)
Vomiting	0	2 (66.7)	1 (12.5)	2 (33.3)	5 (20.8)
Edema peripheral	2 (28.6)	0	2 (25.0)	0	4 (16.7)
Alopecia	1 (14.3)	0	0	3 (50.0)	4 (16.7)
Gastroesophageal reflux disease	1 (14.3)	0	1 (12.5)	2 (33.3)	4 (16.7)
Dizziness	1 (14.3)	0	2 (25.0)	1 (16.7)	4 (16.7)
Mucosal inflammation	1 (14.3)	0	2 (25.0)	1 (16.7)	4 (16.7)
Decreased appetite	1 (14.3)	1 (33.3)	1 (12.5)	1 (16.7)	4 (16.7)
Paresthesia	2 (28.6)	0	0	1 (16.7)	3 (12.5)
Dyspnea exertional	0	1 (33.3)	1 (12.5)	1 (16.7)	3 (12.5)
Nasal congestion	1 (14.3)	0	1 (12.5)	1 (16.7)	3 (12.5)
Pyrexia	0	0	1 (12.5)	2 (33.3)	3 (12.5)
Dysgeusia	0	1 (33.3)	1 (12.5)	1 (16.7)	3 (12.5)
Dyspepsia	1 (14.3)	1 (33.3)	0	1 (16.7)	3 (12.5)
Back pain	0	0	1 (12.5)	2 (33.3)	3 (12.5)
Arthralgia	2 (28.6)	0	0	1 (16.7)	3 (12.5)
Muscular weakness	2 (28.6)	0	0	1 (16.7)	3 (12.5)
Weight decreased	2 (28.6)	0	0	1 (16.7)	3 (12.5)
Insomnia	0	0	2 (25.0)	1 (16.7)	3 (12.5)

Atrial fibrillation	1 (14.3)	1 (33.3)	1 (12.5)	0	3 (12.5)	
Pruritus	1 (14.3)	1 (33.3)	0	0	2 (8.3)	
Bone pain	0	1 (33.3)	0	1 (16.7)	2 (8.3)	
Maculo-papular rash	1 (14.3)	0	0	1 (16.7)	2 (8.3)	
Lacrimation increased	2 (28.6)	0	0	0	2 (8.3)	
Dysuria	0	1 (33.3)	0	1 (16.7)	2 (8.3)	
Upper respiratory tract infection	1 (14.3)	0	0	1 (16.7)	2 (8.3)	
Abdominal distention	2 (28.6)	0	0	0	2 (8.3)	
Abdominal pain upper	0	1 (33.3)	1 (12.5)	0	2 (8.3)	
Abdominal pain	0	0	1 (12.5)	1 (16.7)	2 (8.3)	
Malaise	2 (28.6)	0	0	0	2 (8.3)	
Oral candidiasis	2 (28.6)	0	0	0	2 (8.3)	
Tachycardia	0	0	1 (12.5)	0	1 (4.2)	
Dry skin	0	1 (33.3)	0	0	1 (4.2)	
Cardiomyopathy	0	1 (33.3)	0	0	1 (4.2)	
Pain	0	0	0	0	0	
Arm B: VEN + G-CHOP, n (%)	VEN 200 mg Cohort 1 (n = 7)	VEN 400 mg Cohort 2 (n = 7)	VEN 600 mg Cohort 3 (n = 6)	VEN 800 mg Cohort 4A (n = 6)	VEN 800 mg Cohort 4B (n = 6)	Total (N = 32)
Neutropenia	2 (28.6)	4 (57.1)	5 (83.3)	6 (100.0)	2 (33.3)	19 (59.4)
Nausea	3 (42.9)	4 (57.1)	3 (50.0)	5 (83.3)	4 (66.7)	19 (59.4)
Constipation	6 (85.7)	3 (42.9)	2 (33.3)	2 (33.3)	1 (16.7)	14 (43.8)
Vomiting	5 (71.4)	4 (57.1)	0	4 (66.7)	1 (16.7)	14 (43.8)
Diarrhea	5 (71.4)	3 (42.9)	2 (33.3)	2 (33.3)	1 (16.7)	13 (40.6)
Fatigue	5 (71.4)	2 (28.6)	2 (33.3)	3 (50.0)	1 (16.7)	13 (40.6)
Thrombocytopenia	2 (28.6)	3 (42.9)	2 (33.3)	4 (66.7)	2 (33.3)	13 (40.6)
Infusion-related reaction	4 (57.1)	1 (14.3)	2 (33.3)	2 (33.3)	3 (50.0)	12 (37.5)
Anemia	1 (14.3)	1 (14.3)	1 (16.7)	5 (83.3)	4 (66.7)	12 (37.5)
Cough	3 (42.9)	3 (42.9)	0	3 (50.0)	2 (33.3)	11 (34.4)
Pyrexia	1 (14.3)	5 (71.4)	2 (33.3)	1 (16.7)	2 (33.3)	11 (34.4)
Dysgeusia	1 (14.3)	3 (42.9)	1 (16.7)	2 (33.3)	4 (66.7)	11 (34.4)
Abdominal pain upper	1 (14.3)	1 (14.3)	0	1 (16.7)	0	3 (9.4)
Dyspepsia	1 (14.3)	1 (14.3)	1 (16.7)	0	0	3 (9.4)
Muscular weakness	0	1 (14.3)	0	1 (16.7)	1 (16.7)	3 (9.4)
Febrile neutropenia	2 (28.6)	4 (57.1)	0	1 (16.7)	1 (16.7)	8 (25.0)
Decreased appetite	2 (28.6)	2 (28.6)	1 (16.7)	2 (33.3)	1 (16.7)	8 (25.0)
Headache	3 (42.9)	3 (42.9)	1 (16.7)	0	0	7 (21.9)
Nasal congestion	2 (28.6)	1 (14.3)	0	2 (33.3)	1 (16.7)	6 (18.8)
Bone pain	2 (28.6)	1 (14.3)	2 (33.3)	0	1 (16.7)	6 (18.8)

Abdominal pain	0	1 (14.3)	1 (16.7)	3 (50.0)	1 (16.7)	6 (18.8)
Hypokalemia	1 (14.3)	2 (28.6)	0	1 (16.7)	1 (16.7)	5 (15.6)
Edema peripheral	0	1 (14.3)	0	3 (50.0)	1 (16.7)	5 (15.6)
Pain	1 (14.3)	1 (14.3)	0	1 (16.7)	2 (33.3)	5 (15.6)
Mucosal inflammation	1 (14.3)	3 (42.9)	0	1 (16.7)	0	5 (15.6)
Insomnia	2 (28.6)	2 (28.6)	0	0	1 (16.7)	5 (15.6)
Upper respiratory tract infection	2 (28.6)	0	1 (16.7)	1 (16.7)	1 (16.7)	5 (15.6)
Neuropathy peripheral	0	2 (28.6)	1 (16.7)	1 (16.7)	2 (33.3)	6 (18.8)
Asthenia	2 (28.6)	0	1 (16.7)	1 (16.7)	0	4 (12.5)
Weight decreased	0	1 (14.3)	0	2 (33.3)	1 (16.7)	4 (12.5)
Dizziness	1 (14.3)	1 (14.3)	0	0	2 (33.3)	4 (12.5)
Arthralgia	1 (14.3)	2 (28.6)	1 (16.7)	0	0	4 (12.5)
Back pain	0	2 (28.6)	1 (16.7)	0	1 (16.7)	4 (12.5)
Peripheral sensory neuropathy	0	1 (14.3)	1 (16.7)	1 (16.7)	1 (16.7)	4 (12.5)
Maculo-papular rash	1 (14.3)	0	2 (33.3)	0	0	3 (9.4)
Dyspnea	0	1 (14.3)	0	1 (16.7)	1 (16.7)	3 (9.4)
Oral candidiasis	0	0	1 (16.7)	1 (16.7)	1 (16.7)	3 (9.4)
Muscular weakness	0	1 (14.3)	0	1 (16.7)	1 (16.7)	3 (9.4)
Dry skin	0	2 (28.6)	0	0	0	2 (6.3)
Tachycardia	0	0	0	0	2 (33.3)	2 (6.3)
Stomatitis	0	0	1 (16.7)	0	1 (16.7)	2 (6.3)
Abdominal distention	0	1 (14.3)	0	1 (16.7)	0	2 (6.3)
Atrial fibrillation	1 (14.3)	0	0	0	1 (16.7)	2 (6.3)
Pruritus	0	0	1 (16.7)	1 (16.7)	0	2 (6.3)
Alopecia	0	0	1 (16.7)	0	0	1 (3.1)
Gastroesophageal reflux disease	0	0	0	1 (16.7)	0	1 (3.1)
Malaise	1 (14.3)	0	0	0	0	1 (3.1)
Paresthesia	0	1 (14.3)	0	0	0	1 (3.1)
Lacrimation increased	0	0	1 (16.7)	0	0	1 (3.1)
Cardiomyopathy	0	0	0	0	0	0
Dyspnea exertional	0	0	0	0	0	0
Dysuria	0	0	0	0	0	0

*Percentages represent the incidence of that specific AE per cohort in each arm.

Adverse events (AEs) were coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). The protocol-specified safety reporting window was 30 days after the last dose of VEN or CHOP, or 90 days after the last dose of rituximab or obinutuzumab. After this period, only serious AEs, AEs of special interest, and AEs that were deemed by the investigator to be related to study drug were reported.

G-CHOP indicates obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; and VEN, venetoclax.

Supplemental Table 4. Serious adverse events.

Arm A: VEN + R-CHOP, n (%)	VEN 200 mg Cohort 1 (n = 7)	VEN 400 mg Cohort 2 (n = 3)	VEN 600 mg Cohort 3 (n = 8)	VEN 800 mg Cohort 4 (n = 6)	Total (N = 24)	
Patients with ≥1 SAE	5 (71.4)	2 (66.7)	3 (37.5)	3 (50.0)	13 (45.8)	
Arm B: VEN + G-CHOP, n (%)	VEN 200 mg Cohort 1 (n = 7)	VEN 400 mg Cohort 2 (n = 7)	VEN 600 mg Cohort 3 (n = 6)	VEN 800 mg Cohort 4A (n = 6)	VEN 800 mg Cohort 4B (n = 6)	Total (N = 32)
Patients with ≥1 SAE	5 (71.4)	4 (57.1)	3 (50.0)	5 (83.3)	5 (83.3)	22 (68.8)

AE indicates adverse event; G-CHOP, obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SAE, serious adverse event; and VEN, venetoclax.

Supplemental Table 5. Grade 3/4 thrombocytopenia.

Arm A: VEN + R-CHOP, n (%)	VEN 200 mg Cohort 1 (n = 7)	VEN 400 mg Cohort 2 (n = 3)	VEN 600 mg Cohort 3 (n = 8)	VEN 800 mg Cohort 4 (n = 6)	Total (N = 24)	
Grade 3	1 (14.3)	0	0	0	1 (4.2)	
Grade 4	2 (28.6)	0	1 (12.5)	0	3 (12.5)	
Arm B: VEN + G-CHOP, n (%)	VEN 200 mg Cohort 1 (n = 7)	VEN 400 mg Cohort 2 (n = 7)	VEN 600 mg Cohort 3 (n = 6)	VEN 800 mg Cohort 4A (n = 6)	VEN 800 mg Cohort 4B (n = 6)	Total (N = 32)
Grade 3	1 (14.3)	2 (28.6)	1 (16.7)	2 (33.3)	2 (33.3)	8 (25.0)
Grade 4	1 (14.3)	0	1 (16.7)	2 (33.3)	0	4 (12.5)

G-CHOP indicates obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; and VEN, venetoclax.

Supplemental Table 6. Patients receiving ≥90% (overall) dose intensity.*

Arm A: VEN + R-CHOP, n (%)	VEN 200 mg Cohort 1 (n = 7)	VEN 400 mg Cohort 2 (n = 3)	VEN 600 mg Cohort 3 (n = 8)	VEN 800 mg Cohort 4 (n = 6)	Total (N = 24)	
VEN	2 (28.6)	3 (100)	5 (62.5)	6 (100)	16 (66.7)	
Rituximab	5 (71.4)	3 (100)	8 (100)	5 (83.3)	21 (87.5)	
Cyclophosphamide	5 (71.4)	3 (100)	8 (100)	6 (100)	22 (91.7)	
Doxorubicin	4 (57.1)	3 (100)	8 (100)	6 (100)	21 (87.5)	
Vincristine	5 (71.4)	3 (100)	6 (75.0)	6 (100)	20 (83.3)	
Prednisone	5 (71.4)	3 (100)	8 (100)	6 (100)	22 (91.7)	
Arm B: VEN + G-CHOP, n (%)	VEN 200 mg Cohort 1 (n = 7)	VEN 400 mg Cohort 2 (n = 7)	VEN 600 mg Cohort 3 (n = 6)	VEN 800 mg Cohort 4A (n = 6)	VEN 800 mg Cohort 4B (n = 6)	Total (N = 32)
VEN	0	5 (71.4)	2 (33.3)	0	0	7 (21.9)
Obinutuzumab	4 (57.1)	6 (85.7)	5 (83.3)	4 (66.7)	4 (66.7)	23 (71.9)
Cyclophosphamide	4 (57.1)	6 (85.7)	5 (83.3)	4 (80.0)	5 (83.3)	24 (77.4)
Doxorubicin	4 (57.1)	6 (85.7)	5 (83.3)	4 (80.0)	5 (83.3)	24 (77.4)
Vincristine	4 (57.1)	6 (85.7)	5 (83.3)	6 (100)	4 (66.7)	25 (78.1)
Prednisone	4 (57.1)	6 (85.7)	5 (83.3)	6 (100)	5 (83.3)	26 (81.3)

*The total amount administered for a given drug expressed as a percentage of the theoretical cumulative dose. The relative dose intensity equation utilized in this study accounted for dose interruptions, dose reductions, and adverse event-related treatment discontinuations, and was calculated as: total actual dose to actual end of treatment/number of actual days to actual end of treatment/total planned dose to planned end of treatment/total number of days to planned end of treatment.

G-CHOP indicates obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; and VEN, venetoclax.

Supplemental Table 7. Adverse events leading to venetoclax discontinuation.*

Arm A: VEN + R-CHOP	Total: 3 patients
VEN 200mg Cohort 1	3 patients (1 patient with diarrhea; 1 patient with thrombocytopenia; and 1 patient with thrombocytopenia/neutropenia)
Arm B: VEN + G-CHOP	Total: 13 patients
VEN 200mg Cohort 1	3 patients (1 patient with esophageal stenosis; 1 patient with ACS/ infection; and 1 patient with AST/ALT increased)
VEN 400mg Cohort 2	2 patients (1 patient each with organizing pneumonia and neutropenia)
VEN 600 mg Cohort 3	2 patients (1 patient each with sepsis and thrombocytopenia)
VEN 800 mg (10 days) Cohort 4A	3 patients (all with thrombocytopenia)
VEN 800 mg (5 days) Cohort 4B	3 patients (1 patient each with <i>Pneumocystis jirovecii</i> pneumonia, cardiac arrest, and febrile neutropenia)

*VEN discontinuations due to thrombocytopenia occurred in 2 patients in arm A (cohort 1) and 4 patients in arm B (3 patients in cohort 4 and 1 in cohort 3). In arm A (cohort 1), discontinuations occurred on or after cycle 3. In arm B, discontinuations occurred on or after cycle 2 (cohort 4) and on cycle 4 (cohort 3). Although the thrombocytopenia did not result in clinically significant bleeding (grade 1 hematuria in 1 patient), 5 patients in arm B (cohort 4) who were treated with 800 mg VEN received platelet transfusions. Subsequently, additional dose finding was conducted to further define the dose and dosing regimen of VEN that could be tolerated in combination with G-CHOP (cohort 4B).

ACS indicates acute coronary syndrome; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; G-CHOP, obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PD, progressive disease; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; and VEN, venetoclax.

Supplemental Table 8. Rate of dose modification (reduction and/or delay) due to adverse events for each study drug.

Rate of dose modification	n/N (%)
Arm A: VEN + R-CHOP	
Rituximab	3/24 (12.5)
Arm B: VEN + G-CHOP	
Obinutuzumab	9/32 (28.1)
Arm A: VEN + R-CHOP and Arm B: VEN + G-CHOP*	
Cyclophosphamide	3/56 (5.4)
Doxorubicin	4/56 (7.1)
Vincristine	4/56 (7.1)
Prednisone	2/56 (3.6)

*Five patients discontinued CHOP prior to 6 cycles in cohort 1 (3 in arm B; 2 in arm A) and only 3 patients in other cohorts.

G-CHOP indicates obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; and VEN, venetoclax.

Supplemental Table 9. One-year progression-free survival.

a. By cohort

Arm A: VEN + R-CHOP					
	VEN 200 mg Cohort 1 (n = 7)	VEN 400 mg Cohort 2 (n = 3)	VEN 600 mg Cohort 3 (n = 8)	VEN 800 mg Cohort 4 (n = 6)	
Patients at risk	6	3	7	4	
1-year PFS (%)	85.7	100.0	87.5	66.7	
Missing patients	1 patient missing EOT		1 patient missing EOT	1 patient PD during treatment and 1 patient died during follow-up (encephalitis – unrelated to lymphoma)	
Arm B: VEN + G-CHOP					
	VEN 200 mg Cohort 1 (n = 7)	VEN 400 mg Cohort 2 (n = 7)	VEN 600 mg Cohort 3 (n = 6)	VEN 800 mg (10 days) Cohort 4A (n = 6)	VEN 800 mg (5 days) Cohort 4B (n = 6)
Patients at risk	5	2	6	6	1
1-year PFS (%)	100	75.0	100	100	100
Missing patients	2 patients missing EOT	4 additional patients added later in the study and have not had 24-week f/u assessment at time of data cut			1 patient missing EOT (switched from G to R on cycle 6); 4 additional patients added later in the study and had not had 24-week f/u assessment at time of data cut

b. By histology

	DLBCL	FL	Other*
Arm A: VEN + R-CHOP			
N	10	10	4
Patients at risk, n	7	10	3
1-year PFS (%)	70	100	75
Arm B: VEN + G-CHOP			
N	8	14	10
Patients at risk, n	5	9	6
1-year PFS (%)	100	90	100
Arms A + B			
N	18	24	14
Patients at risk, n	12	19	9
1-year PFS (%)	80	95	90

*Transformed lymphoma, marginal zone lymphoma, composite lymphoma, and Waldenstrom macroglobulinemia.

DLBCL indicates diffuse large B-cell lymphoma; EOT, end of treatment; FL, follicular lymphoma; f/u, follow-up; G, obinutuzumab; G-CHOP, obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PD, progressive disease; PFS, progression-free survival; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; and VEN, venetoclax.

Supplemental Table 10. Diffuse large B-cell lymphoma biomarker expression.

a. Incidence (n/N) of BCL2 and MYC subtypes

	BCL2 positive by IHC*	MYC positive by IHC*	Double expressor by IHC	BCL2 positive by FISH†	MYC positive by FISH†
DLBCL	9/14	12/14	8/14	1/15	5/15‡

*The cutoff value for BCL2 positivity was $\geq 50\%$ of tumor cells showing moderate to strong staining; for MYC positivity, the cutoff value was $\geq 40\%$ of tumor cells showing nuclear staining.

†BCL2 and MYC translocations were considered to be positive if positive signals were observed in $\geq 50\%$ nuclei.

‡Of the 5 patients who were MYC positive by FISH, 4 patients had CR and 1 patient had PD.

*b. Disease response at end of treatment by PET/CT by immunohistochemistry-derived subtype (arm A and arm B combined for diffuse large B-cell lymphoma patients)**

Patients, n (%)	Double expressor (n = 8)	BCL2-/MYC+ (n = 4)	BCL2+/MYC- (n = 1)	BCL2-/MYC- (n=1)	Data unavailable (n = 4)	Total (N = 18)
CR	7	3	1	1	4	16 (89)
PR	0	0	0	0	0	0
PD	1	1†	0	0	0	2 (11)

*If no PET-CT was performed at end of treatment, available CT results were included instead.

†Patient had PD in cycle 1 and only received 1 dose of VEN.

ABC indicates activated B cell; CR, complete response; FISH, fluorescence in situ hybridization; GCB, germinal center B cell; IHC, immunohistochemistry; PD, progressive disease; PET-CT, positron emission tomography-computed tomography; PR, partial response; and VEN, venetoclax.

Supplemental Table 11. Pharmacokinetic parameters of venetoclax following administration of a single dose of venetoclax on cycle 1 day 4 after either R-CHOP or G-CHOP.

Treatment arm/ VEN dose	N	T _{max} (h)	C _{max} (µg/mL)	AUC _{0-8h} (h·µg/mL)
Arm A: VEN + R-CHOP				
200 mg	7	4.0 (4.0–8.0)	0.723 (123%)	3.02 (102%)
400 mg	3	8.0 (4.0–8.0)	0.975 (79%)	4.10 (66%)
600 mg	8	6.0 (4.0–8.0)	1.16 (85.0%)	5.31 (91%)
800 mg	5	6.0 (4.0–8.0)	1.43 (57.8%)	6.82 (61.7%)
Arm B: VEN + G-CHOP				
200 mg	6	6.0 (4.0–8.0)	0.497 (45%)	2.25 (43%)
400 mg	6	6.0 (6.0–8.0)	1.39 (48%)	5.63 (56%)
600 mg	6	6.0 (4.0–8.0)	1.47 (66%)	6.77 (60%)
800 mg	8	8.0 (4.0–8.0)	1.98 (43%)	6.85 (29%)

T_{max} is median (range).

AUC indicates area under the concentration–time curve; C_{max}, maximum concentration observed in serum or plasma; G-CHOP, obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; T_{max}, time to C_{max}; and VEN, venetoclax.

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