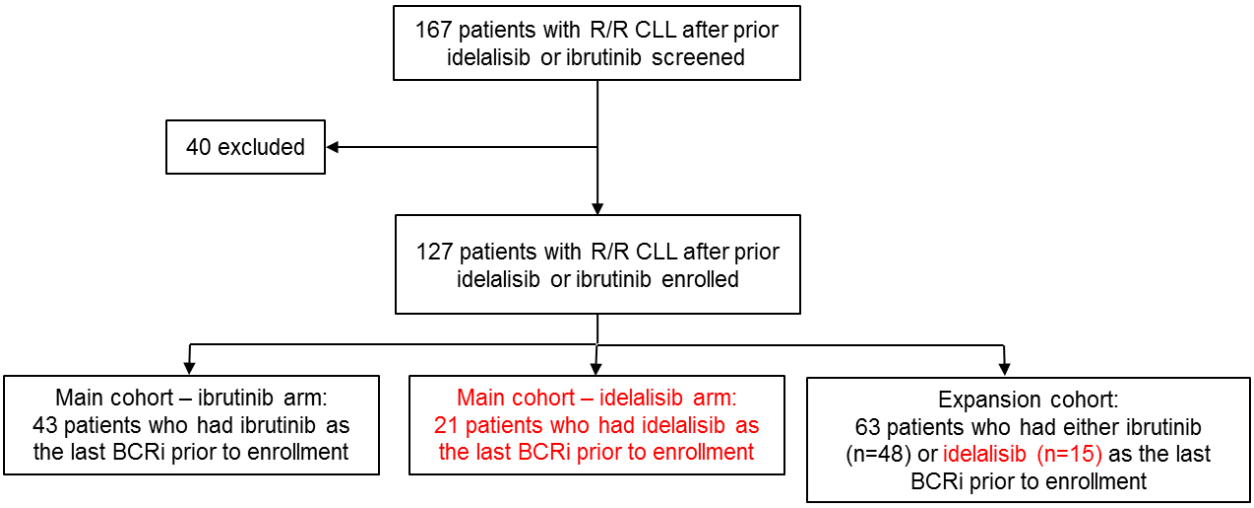
SUPPLEMENTARY APPENDIX

Supplement to: Coutre et al. Venetoclax for Patients with Chronic Lymphocytic Leukemia Who Progressed During or After Idelalisib Therapy

CONTENTS

SUPPLEMENTARY METHODS

Figure S1. M14-032 Trial Enrollment Scheme



Data reported in this publication are from the patients shown in red, who had received idelalisib as the last BCRi prior to enrollment (21 from the main cohort and 15 from the expansion cohort). Patients who received ibrutinib as their last BCRi prior to enrollment are reported in a separate publication.

Complete Inclusion and Exclusion Criteria

Inclusion Criteria

1. Patient must voluntarily sign and date an informed consent form, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study specific procedures.
2. Patient must be ≥ 18 years of age.
3. Patient must have a diagnosis of chronic lymphocytic leukemia (CLL) that meets published 2008 International Workshop on CLL (IWCLL) National Cancer Institute Working Group (NCI-WG) criteria.
4. Patient has relapsed/refractory disease with an indication for treatment according to the 2008 IWCLL NCI-WG criteria.
5. Patient who has refractory disease or developed recurrence after therapy with either ibrutinib or idelalisib and meets one of the following criteria:
    a. Treatment failure with either of the above agents;
    b. Progression during treatment or after discontinuation of either of the above agents.
6. Patient has an Eastern Cooperative Oncology Group (ECOG) performance score of ≤2.
7. Patient must have adequate bone marrow function at screening, defined as follows:
    a. Absolute neutrophil count (ANC) ≥1000/μL. An exception exists for patients with an ANC <1000/μL at screening: when bone marrow is heavily infiltrated with underlying disease (approximately 80% or more), granulocyte colony-stimulating factor (G-CSF) may be administered at the discretion of the investigator, after screening and prior to the first dose of venetoclax to achieve the ANC eligibility criteria (≥1000/μL).
    b. Platelet count ≥30,000/mm^3 (without transfusion support, evidence of mucosal bleeding, known history of bleeding episode within 3 months of screening and history of bleeding disorder).
    c. Hemoglobin level ≥8.0 g/dL. For patients with autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP), hemoglobin level of <8 g/dL, and platelet count of <30,000/mm^3 without corticosteroid therapy, a discussion between the investigator and the AbbVie medical monitor must occur.

8. Patient must have adequate coagulation profile, renal function, and hepatic function, per laboratory reference range at screening, as follows:
    a. Activated partial thromboplastin time (aPTT) and prothrombin time (PT) not to exceed 1.5× the upper limit of normal (ULN).
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level ≤1.5× ULN of institution's normal range.
    c. Bilirubin level ≤1.5× ULN. Patients with AIHA and Gilbert's syndrome may have a bilirubin level >1.5× ULN, per discussion between the investigator and the AbbVie medical monitor.
    d. Creatinine clearance (CrCl) ≥50 mL/min determined by using 24-hour measured glomerular filtration rate (GFR) or estimated by using the modified Cockcroft-Gault equation. For patients who have a body mass index (BMI) of >30 kg/m^2, 24-hour measured CrCl is required.
    CrCl (mL/min) = [(140 − age in years) × (weight in kg) × (0.85 if the patient is female)][72 × (serum creatinine in mg/dL)]

Or, if serum creatinine is reported in μmol/L: CrCl (mL/min) = [(140 − age in years) × (weight in kg) × (0.85 if the patient is female)][0.815 × (serum creatinine in mmol/L)]

9. For high-risk patients, a pre-approval by the AbbVie medical monitor is required prior to enrollment.
10. Female patients of childbearing potential and non-sterile male patients must practice at least one of the following methods of birth control with their partner(s) beginning with initial study drug administration and continuing to 30 days after the last dose of study drug:
    a. Total abstinence from sexual intercourse as the preferred lifestyle of the patient; periodic abstinence is not acceptable;
    b. Intrauterine device (IUD);
    c. Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or cream AND a condom);
    d. Hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior to study drug administration;
    e. Surgically sterile partner(s); acceptable sterility surgeries are vasectomy, bilateral tubal ligation 3 months prior to screening, bilateral oophorectomy, or hysterectomy.

11. If hormonal contraceptives are used, the specific contraceptive must have been used for at least 3 months prior to study drug administration. If the patient is currently using a hormonal contraceptive, she should also use a barrier method during this study from initial study drug administration to 30 days after the last dose of study drug. Any contraception method must be continued for 30 days after the last dose of study drug.Females of childbearing potential (i.e., postmenopausal for at least 1 year with no alternative medical reason or surgically sterile) must have negative results for pregnancy test performed:
    a. At screening with a serum sample obtained within 14 days prior to the first study drug administration, and
    b. Prior to dosing with urine sample obtained on week 1 day 1, if it has been >7 days since obtaining the serum pregnancy test results.
12. Male patients must agree to refrain from sperm donation, from initial study drug administration until 90 days after the last dose of study drug.

Exclusion Criteria

1. Patient has previously received venetoclax.
2. Patient has undergone allogeneic stem cell transplantation within the past 1 year.
3. Patient has developed Richter's transformation confirmed by biopsy.
4. Patient has active and uncontrolled autoimmune cytopenias (for 2 weeks prior to screening), including AIHA and ITP despite low-dose corticosteroids.
5. Patient has tested positive for HIV (due to potential drug-drug interactions between anti-retroviral medications and venetoclax, as well as anticipated venetoclax mechanism–based lymphopenia that may potentially increase the risk of opportunistic infections).
6. Patient has chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection requiring treatment. Patients with serologic evidence of prior vaccination for HBV (i.e., HBs Ag−, anti-HBs+ and anti-HBc−) and positive anti-HBc from intravenous immunoglobulin (IVIG) may participate.
7. Patient has received any of the following within 30 days prior to the first dose of study drug with the exception of a B-cell receptor pathway inhibitor (BCR PI):
    a. Any anti-cancer therapy including chemotherapy, immunotherapy, or radiotherapy;

b. Investigational therapy, including targeted small molecule agents (with the exception of ibrutinib and idelalisib).

8. Patient has received the following within 7 days prior to the first dose of study drug:
    a. Steroid therapy with anti-neoplastic intent;
    b. Strong and moderate cytochrome P450 (CYP)3A inhibitors.
9. Patient has consumed the following within 3 days prior to the first dose of study drug:
    a. BCR PI (ibrutinib or idelalisib);
    b. Grapefruit or grapefruit products;
    c. Seville oranges (including marmalade containing Seville oranges);
    d. Star fruit.
10. Patient has known contraindication or allergy to both xanthine oxidase inhibitors and rasburicase.
11. Patient has malabsorption syndrome or other condition that precludes enteral route of administration.
12. Patient has a cardiovascular disability status of New York Heart Association Class ≥2. Class 2 is defined as cardiac disease in which patients are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnea, or angina pectoris.
13. Patient has a significant history of cardiovascular, pulmonary, renal, hepatic, neurologic, psychiatric, endocrinologic, metabolic, or immunologic disease that in the opinion of the investigator would adversely affect his/her participation in this study or interpretation of study results. For patients who have required an intervention for any above diseases within the past 6 months, a discussion between the investigator and the AbbVie medical monitor must occur.
14. Patient has unresolved toxicities from prior anti-cancer therapy defined as any grade 2 or higher clinically significant non-hematologic toxicity (excluding alopecia).
15. Patient exhibits evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
    a. Uncontrolled systemic infection (viral, bacterial, or fungal);
    b. Febrile neutropenia.
16. Patient has a history of active malignancy other than CLL within the past 2 years prior to study entry, with the exception of:

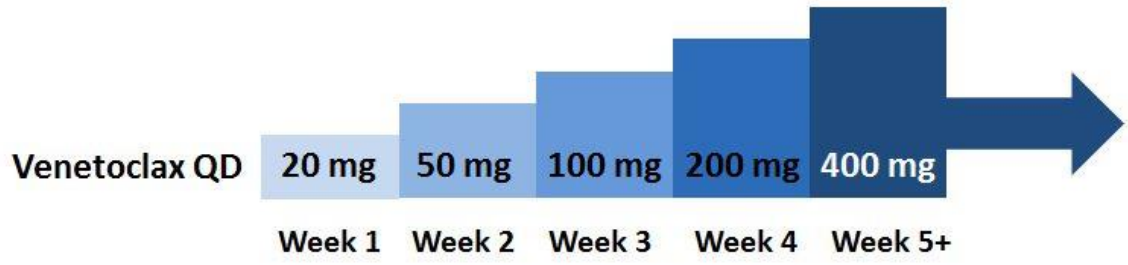
a. Adequately treated in situ carcinoma of the cervix uteri;
b. Adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin;
c. Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.

17. A female patient is pregnant or breast-feeding.

Venetoclax Treatment

All patients received an initial 20 mg dose of venetoclax on Week 1 Day 1 during the ramp-up period (**Figure S2**). If one of more changes from the pre-dose value in electrolytes suggestive of tumor lysis syndrome (TLS) occurred within 24 hours of the initial 20 mg dose, no additional doses were administered until they resolved. If correction of electrolytes was needed, the subsequent venetoclax dose was given only when electrolytes were stable without any further treatment for at least 24 hours. When laboratory abnormalities were resolved, the patient remained on the 20 mg dose through Week 1. Patients who had drug interruptions could then escalate to the 50 mg dose at Week 2 after they had received the 20 mg dose for 7 days. After 1 week at 50 mg, dose increments were implemented so that the patient received 100 mg at week 3, 200 mg at week 4, and the target dose of 400 mg at week 5 (or additional steps to the designated 400 mg dose), as tolerated.

Figure S2. Venetoclax Dosing Schedule



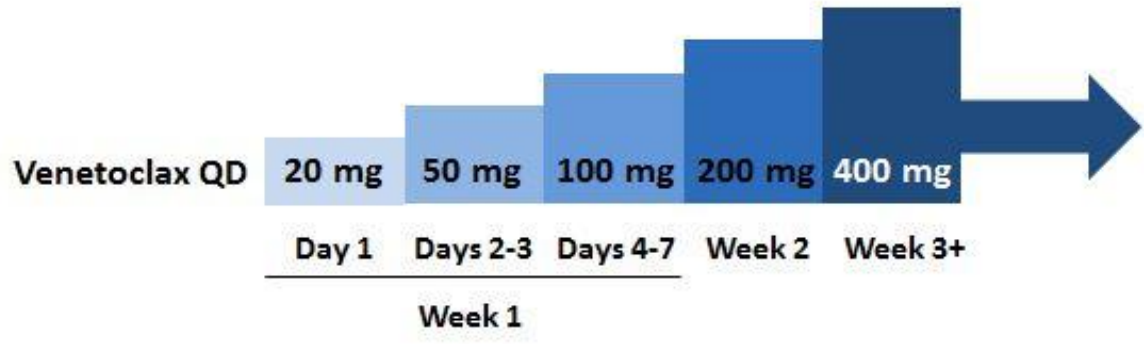
For patients in the expansion cohort, a modified lead-in period could be implemented if a high-risk patient had clinical signs of progression during screening, which allowed for ramp up to 400 mg by Week 3 Day 1 (**Figure S3**). These patients were hospitalized and began the ramp-up period with an initial 20 mg dose of venetoclax on Week 1 Day 1. If no significant findings suggestive of clinical or laboratory TLS occurred within 24 hours, the dose was increased to 50 mg on Week 1 Day 2. If no significant findings suggestive of clinical or laboratory TLS occurred within 24 hours, the same dose was administered for 2 days prior to the next dose level. The dose of venetoclax was further increased to 100 mg on Week 1 Day 4 and was continued through Week 1 Day 7. If there were no significant findings suggestive of clinical or laboratory TLS that occurred within 24 hours at this dose level, then the dose of venetoclax was increased to 200 mg

on Week 2 Day 1. Patients remained in the hospital for at least 24 hours after reaching the 200-mg dose. If no significant findings suggestive of clinical or laboratory TLS occurred within 24 hours, then the patient continued at the 200 mg dose through Week 2 Day 7. Patients were hospitalized the night before dosing 400 mg venetoclax on Week 3 Day 1 and remained in the hospital until the investigator reviewed laboratory results from 24 hours after dosing and the results raised no concerns for TLS-related electrolyte changes.

Patients enrolled in the expansion cohort with bulky disease at study entry who were non-responders or who had signs of clinical progression after completing the ramp up to 400 mg either by clinical disease assessment or by computed tomography/magnetic resonance imaging between Week 6 and Week 12 could escalate to a 600 mg dose of venetoclax.

Prior to dose escalation, laboratory values had to be reviewed in real time by the investigator and before the patient's next dose to ensure appropriate management. Depending on laboratory values, the patient may have continued dosing, dose may have been withheld until resolution, the patient may have required hospitalization for further monitoring, or additional post-dose laboratory checks may have been performed.

Figure S3. Venetoclax Dosing Schedule: Modified for Selected High-Risk Patients



Prophylaxis and Management of Tumor Lysis Syndrome

The on-target effects of venetoclax can cause rapid reduction in tumor size, which may pose a risk of TLS during initial dosing. Thus, prophylaxis and monitoring procedures were implemented to mitigate the risk of TLS with venetoclax. For prophylaxis, tumor burden was categorized for all enrolled patients before venetoclax was administered. Tumor burden was assessed on the basis of nodal disease and absolute lymphocyte count at screening (**Table S1**).

Table S1. Tumor Burden Categories for Prophylaxis of Tumor Lysis Syndrome

Category	Definition
Low	All measurable lymph nodes with largest diameter <5 cm AND ALC <25× 10^9/L
Medium*	Any measurable lymph node with largest diameter ≥5 and <10 cm OR ALC ≥25× 10^9/L
High	Any measurable lymph node with largest diameter ≥10 cm OR ALC ≥25× 10^9/L AND any measurable lymph node with largest diameter ≥5 but <10 cm
ALC, absolute lymphocyte count. *Patients with a medium tumor burden who had a creatinine clearance of <80 mL/min may have been treated by following procedures for a high tumor burden, at the investigator's discretion.	

TLS prophylaxis was initiated in all patients prior to the first 20 mg and 50 mg doses of venetoclax. An oral uric acid reducing agent (eg, allopurinol) was initiated at least 72 hours prior to venetoclax dosing. Rasburicase was administered or considered per regional standards or institutional guidelines for patients with high tumor burden and those with rapidly rising uric acid levels. Treatment may have been continued for up to 5 weeks based on the ongoing risk of TLS development. Patients allergic to allopurinol must have used another uric acid reducer. Oral hydration with fluids intake of 1.5 – 2 L/day was initiated at least 48 hours prior to the start of treatment for all patients, as well as at all subsequent dose increment steps during the ramp-up period and was continued for at least 24 hours after dosing until all of the chemistry laboratory values remained within the upper limit of the normal range. Oral hydration was recommended beyond 24 hours post-dose for patients who demonstrated any laboratory changes.

For patients with low/medium tumor burden, venetoclax doses were administered in an outpatient setting with monitoring of laboratory values within 72 hours prior to the first dose at each step of the ramp up, and at 0, 8, and 24 hours post dose. For patients with high tumor

burden or those with creatinine clearance <80 ml/min (per investigator discretion), patients were hospitalized for the initial 20 mg and 50 mg doses and more extensive laboratory monitoring was done (0, 4, 8, 12, and 24 hours); subsequent ramp up doses may have be given outpatient. For patients who demonstrated any clinically significant laboratory abnormalities, additional prophylactic treatment was administered prior to dosing. If correction of electrolytes was needed, the next dose of venetoclax was only given when electrolytes were stable for at least 24 hours without any further treatment.

Table S2. Definitions of Laboratory and Clinical Tumor Lysis Syndrome

Metabolic Abnormality	Criteria	
	Laboratory*	**Clinical**
Hyperuricemia	Uric acid >8 mg/dL (475.8 μmol/L) for adults	
Hyperphosphatemia	Phosphorus >4.5 mg/dL (1.5 mmol/L) in adults	
Hyperkalemia	Potassium >6 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7 mg/dL (1.75 mmol/L) or ionized calcium <1.12 (0.3 mmol/L)†	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury‡	Not applicable	Increase in serum creatinine level of 0.3 mg/dl (26.5 μmol/L) (or a single value >1.5 times upper limit of normal of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output <0.5 ml/kg/hour for 6 hours

Protocol definitions of TLS were based on Howard criteria.[1]

*In laboratory TLS, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 afterward. Clinical TLS requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

†The corrected calcium level in mg/dL=measured calcium level in mg/dL + 0.8 × (4-albumin in g/dL).

‡Acute kidney injury is defined as an increase in creatinine level of at least 0.3 mg/dL (26.5 μmol/L) or a period of oliguia lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical TLS. Data about acute kidney injury from Levin at al.[2]

Table S3. Modified 2008 IWCLL NCI-WG Criteria for Tumor Response

Parameter	Complete Remission (CR)	Partial Remission (PR)	Progressive Disease (PD)	Stable Disease (SD)
Note	All criteria must be met[*]	≥2 criteria from Group A AND ≥1 criterion from Group B must be met	at least 1 criterion from Group A OR from Group B must be met[†]	All criteria must be met
Group A				
Lymphadenopathy	None >1.5 cm	Decrease ≥50%[‡]	Increase ≥50%[§] or any new lymph node >1.5 cm	Change of -49% to +49%[‖]
Blood lymphocytes	<4000/μL	Decrease ≥50% from baseline	Increase ≥50% over baseline (≥5000/μL	Change of -49% to +49%
Hepatomegaly[¶]	None	Decrease ≥50%	Increase ≥50%[#]	Change of -49% to +49%
Splenomegaly[¶]	None	Decrease ≥50%	Increase ≥50%[#]	Change of -49% to +49%
Marrow	Normocellular, <30% lymphocytes, no B lymphoid nodules; hypocellular marrow defines CRi	NA	NA	NA
Group B				
Platelet count	>100,000/μL[**]	>100,000/μL or increase ≥50% over baseline[h]	Decrease of ≥50% from baseline secondary to CLL	Change of -49% to +49%
Hemoglobin	>11 g/dL[**]	>11 g/dL or increase ≥50% over baseline[h]	Decrease of >2 g/dL from baseline secondary to CLL	Increase to ≤11 g/dL over baseline or decrease <2 g/dL
Neutrophils	>1500/μL[**]	>1500/μL or increase ≥50% over baseline[h]	Decrease of ≥50% from baseline secondary to CLL	NA

Other considerations				
New lesions	None	None	Appearance of new palpable lymph nodes (>1.5 cm in longest diameter) or any new extra nodal lesion (regardless of size) or transformation to a more aggressive histology, eg, Richter Syndrome[d]	None
Non-target lesions	Nodes must be normal size as visually estimated; extra nodal and other assessable disease should be absent	No change/decreased	Unequivocal progression	No change or decrease or non-substantial increase
Target extranodal disease	Absence of any extranodal disease by physical examination (palpable, visualized extranodal) and CT scan	≥ 50% decrease in the sum of the products of diameters	≥50% increase in the longest diameter of any extra nodal lesion	Not CR, CRi, PR, or SD

To be assigned a status of PR, changes in tumor measurements were confirmed by repeat assessments performed at least 8 weeks after the clinical criteria for response are first met.

[*]CR also required lack of disease-related constitutional symptoms.

[†]Transformation to a more aggressive histology (eg, Richter Syndrome) would also qualify as a PD.

[‡]Sum of the products of multiple lymph nodes (as evaluated by CT scans). Note in eCRF if by physical examination only.

[§]Increase in sum of the products of diameters of multiple nodes, or in greatest diameter of any previous site, or appearance of any new lymphadenopathy or organomegaly. Degree of change in lymph node or lymphocyte counts should be measured from nadir (lowest post-treatment) values.

[‖]Sum products of up to 6 lymph nodes or lymph node masses (target lesions), with no increase in a lymph node or new enlarged lymph node. Increase of <25% in lymph nodes <2 cm not significant. Decreases were measured compared to baseline (pre-treatment) values.

[¶]If enlarged before therapy.

[#]An increase in previously noted enlargement of the liver or spleen by ≥50% or de novo appearance of hepatomegaly/splenomegaly.

[**]Without the need for exogenous growth factors or transfusions.

Definition of Residual CLL Cells for MRD Assessments

Residual CLL cells were defined by cell surface expression phenotypes based on CD19/CD5/CD20 with CD3/CD38/CD79b and CD81/CD22/CD43; the level of MRD reported is the average of these two independent assays. The percentage of CLL cells identified was calculated by the number of CLL cells divided by the total number of cells measured (a minimum of 500,000 cells were measured per assay).

Key Secondary Efficacy Endpoints

PFS was defined as the number of days from the date of first dose to the date of earliest PD or death. Data for analysis were censored at the time of last tumor assessment for patients without an event or at the time of data cutoff if that assessment was performed after the cutoff. OS was defined as number of days from the date of first dose to the date of death for all dosed patients. For patients who did not die, their data were censored at the date of last study visit or the last known date to be alive, whichever is later. Secondary efficacy endpoints were analyzed by Kaplan-Meier methodology using data for all enrolled patients. Median time to event was calculated along with the corresponding 95% confidence interval.

Sample Size Justification

The M14-032 (NCT02141282) study is a phase 2, open-label, nonrandomized, multicenter trial designed to determine the efficacy and safety of venetoclax monotherapy in patients with CLL relapsed/refractory to treatment with B-cell receptor signaling pathway inhibitors. The study was designed to enroll a total of approximately 120 patients who had CLL that was refractory to treatment with idelalisib and/or ibrutinib, who had CLL that relapsed during treatment, or who experienced progression after discontinuing either of these agents. Target enrollment was approximately 20 patients with idelalisib-resistant or refractory CLL and approximately 60 patients with either idelalisib- or ibrutinib-resistant relapsed/refractory CLL. Patients who received both agents and any additional interim therapy were enrolled into the corresponding study arm based on their most recent treatment (patients who had ibrutinib-resistant or refractory CLL are not reported here).

There was no planned hypotheses testing on the primary endpoint overall response rate (ORR). ORR is presented by a point estimate and corresponding 95% confidence interval. A sample size of 20 patients ensured that the distance of true rate was within 23% of the observed rate, with 95% confidence. A sample size of 40 patients would ensure that the distance of true rate was within 17% of the observed rate, with 95% confidence.

Protocol Amendments

Four amendments and one administrative change were made to the original protocol, which was dated 21-Feb-2014. Key amendment changes are listed in **Table S4**.

Table S4. Summary of Protocol Amendments

Date	Summary of Change
16-May-2014	Modified to describe the three tumor burden categories for TLS that determine prophylaxis and monitoring procedures for initiation of venetoclax. Further description of the prophylaxis and monitoring measures for each tumor burden category are also provided.
	Updated to state that survival information (ie, the date and cause of death, post-treatment cancer therapies, etc.) will be collected via telephone calls and/or clinical visits at 3-month intervals after the last study visit for a period of 3 years (not 5 years as stated in original protocol) after the last patient has enrolled on the study.
14-Jan-2015	Updated to state that approximately 60, not 40 as stated in the original protocol, patients were to be enrolled in the main study arms (presented in this publication).
	Modified to describe that minimal residual disease levels would be analyzed for patients with a confirmed response of CR, CRi, or PR (not just CR as stated in the original protocol).
	The following statement was added regarding TLS management, "Subjects in the Medium Risk category who have creatinine clearance of <80 mL/min and/or higher tumor burden (i.e., ALC >100 × 10^9/L or multiple bulky nodes) may be handled as high risk subjects per investigator discretion for the first dose of ABT-199 at 20 mg and 50 mg."
22-Sept-2015	Update to the protocol to reflect the addition of the expansion cohort, which is designed to enroll approximately 60 patients with relapsed or refractory CLL after either ibrutinib or idelalisib treatments.
13-Sept-2016	Update to the protocol to clarify the survival information to be collected for patients and also additional clarification for the expansion cohort of the study.

SUPPLEMENTARY RESULTS

Table S5. Reasons for Screening Failures

Reason	Patients n=13
Failure to meet inclusion criteria[*]	
Criterion 7	2
Criterion 8	3
Met exclusion criteria[*]	
Criterion 3	1
Criterion 16	1
Withdrawal of consent	4
Other	2[†]
[*]Enumerated under Complete Inclusion and Exclusion Criteria. [†]Extensive cytopenias (n=1) and congestive heart failure (n=1).	

Disposition of Patients During Treatment

Of 14 patients who discontinued the study, no patients discontinued during the 5-week ramp up period. Of 11 patients who discontinued because of disease progression, two had Richter's transformation. One patient with Richter's transformation was diagnosed with 17p deletion/*TP53* mutation CLL 20 years ago, and was treated with five prior lines of therapy including chemoimmunotherapy, ibrutinib and idelalisib. This patient achieved PR with minimal residual splenomegaly and marrow clearance of CLL developed large cell transformation in bone marrow at week 71. The second patient with Richter's transformation was diagnosed with CLL 18 years ago, and was treated with six prior lines of therapy including chemoimmunotherapy, ibrutinib, and idelalisib. This patient achieved CR at week 60 and then development Richter's transformation at week 72.

Table S6. Reasons for Study Discontinuation and Adverse Events Leading to Dose Adjustments or Reductions

N	Patients who received idelalisib as the last prior BCRi	
	Main cohort n=21	**Expansion cohort n=15**
Study discontinuation		
Progressive disease	7*	4*
Stem cell transplantation	1	0
Patient non-compliance	0	1
Other	1[†]	0
Dose interruption (in ≥2 patients across arms)		
Diarrhea	4	1
Fatigue	2	2
Neutropenia[‡]	2	2
Thrombocytopenia[§]	1	2
Nausea	2	1
Anemia	0	2
Bronchitis	1	1
Cough	1	1
Headache	1	1
Hypertension	1	1
Dose reductions (in ≥2 patients across arms)		
Neutropenia[‡]	5	1
Thrombocytopenia[§]	4	1
Fatigue	2	3
Anemia	3	1
Edema	3	0
Bronchitis	1	1
Constipation	2	0
Cough	1	1
Diarrhea	2	0
Dyspnea	2	0
Headache	1	1
Hyperglycemia	2	0
Hypertension	1	1

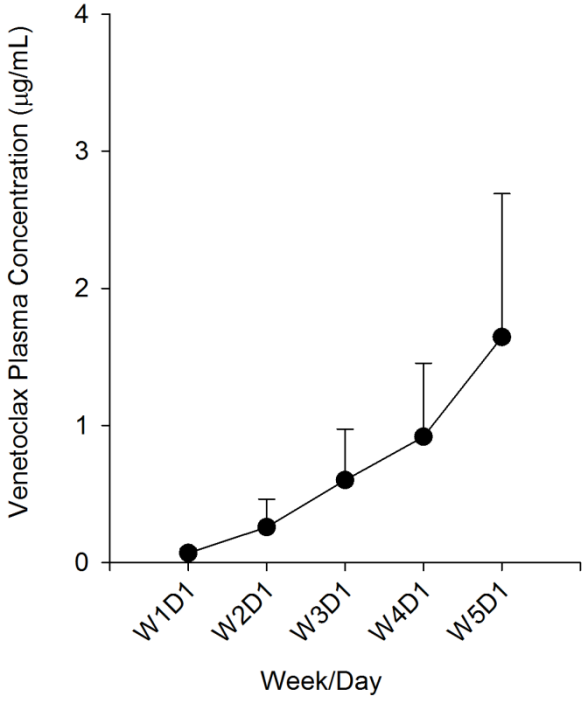
*One patient had Richter's transformation.
[†]Patient with well-controlled pre-existing immune thrombocytopenia became refractory to intervention while on study.
[‡]Neutropenia reported includes the adverse event preferred terms of neutropenia and decreased neutrophil count.
[§]Thrombocytopenia reported includes the adverse event preferred terms of thrombocytopenia and decreased platelet count.

Pharmacokinetic Results

The mean and standard deviation (shown as error bars) post-dose (8 hour) venetoclax plasma concentrations during the ramp-up period are provided in **Figure S4**. The mean 8 hour post-dose concentration increased gradually during the dose ramp-up period to reach 1.65 μg/mL on Week 5 Day 1 at the 400 mg dose.

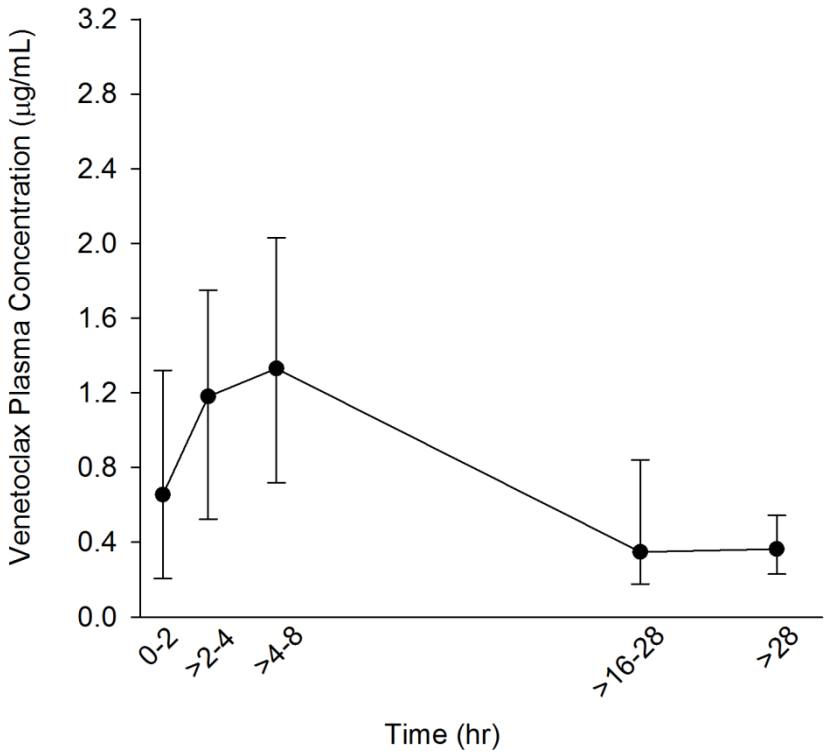
The mean pre-dose concentration ranged between 0.49 and 0.76 μg/mL across the visits between Week 8 and Week 24. The median and inter-quartile range (25th to 75th percentile) of venetoclax concentrations binned by time after the previous venetoclax dose and combined across all visits are shown in **Figure S5**. Venetoclax exposure observed in this study was consistent with that observed in the venetoclax first-in-human study in patients with CLL and non-Hodgkin's lymphoma.[3]

Figure S4. Mean 8-Hour Post-Dose Venetoclax Plasma Concentrations During the Ramp-Up Period



Abbreviations: W, week; D, day.
Error bars indicate the standard deviation.

Figure S5. Median Plasma Venetoclax Concentrations Binned by Time Relative to the Previous Dose



Error bars indicate the interquartile range.

ADDITIONAL REFERENCES

1. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. The New England journal of medicine 2011;364:1844-54.
2. Levin A, Warnock DG, Mehta RL, et al. Improving outcomes from acute kidney injury: report of an initiative. American journal of kidney diseases : the official journal of the National Kidney Foundation 2007;50:1-4.
3. Salem AH, Agarwal SK, Dunbar M, Enschede SL, Humerickhouse RA, Wong SL. Pharmacokinetics of Venetoclax, a Novel BCL-2 Inhibitor, in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Non-Hodgkin's Lymphoma. Journal of clinical pharmacology 2016;doi: 10.1002/jcph.821.