Supplementary Appendix

Supplement to: Comprehensive Safety Analysis of Venetoclax Monotherapy in Relapsed/Refractory Chronic Lymphocytic Leukemia

Matthew S. Davids, Michael Hallek, William G. Wierda, Andrew W. Roberts, Stephan Stilgenbauer, Jeffrey Jones, John Gerecitano, Su Young Kim, Jalaja Potluri, Todd Busman, Andrea Best, Maria Verdugo, Rod A. Humerickhouse, Elisa Cerri, Monali Desai, Peter Hillmen, John F. Seymour

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1. Supplementary Methods

Additional Study Information

Arm A of the M12-175 study enrolled patients with relapsed/refractory CLL.[1] Patients were assigned sequentially to dose-escalation groups and received maximum cohort doses of 150, 200, 300, 400, 600, 800, 1200mg daily venetoclax until disease progression or unacceptable toxicity. Only patients who were assigned to receive 400mg venetoclax on this study were included in this analysis, including an expansion cohort treated at 400mg daily. All patients included from M13-982 and M14-032 received the recommended 400mg daily dose.[2,3]

Key Enrollment Criteria

Patients had to have an Eastern Cooperative Oncology Group performance score ≤1 for enrollment in M12-175 (first in human study) and ≤2 for M13-982 (del[17p]) and M14-032 (BCRi failure). Patients were required to have an absolute neutrophil count (ANC) ≥1000/μL (granulocyte-colony stimulating factor [G-CSF] support was allowed to meet eligibility), hemoglobin ≥8g/dL, platelet count ≥30,000/mm^3 (M13-982 main cohort: ≥40,000/mm^3), and CrCl ≥50mL/min. Exclusion criteria were Richter's transformation, active and uncontrolled autoimmune cytopenias, or any significant history of renal, pulmonary, neurologic, psychiatric, endocrinologic, metabolic, immunologic, cardiovascular, or hepatic disease that in the opinion of the investigator would have adversely effected patient participation in the studies.

Drug Interactions with Venetoclax

Per pharmacokinetic data, concomitant use of venetoclax with strong or moderate CYP3A inducers is not recommended. Concomitant use of venetoclax with strong CYP3A inhibitors is contraindicated during initial dose ramp-up and venetoclax dosing should be reduced (from the recommended 400 mg daily dose) when concomitant CYP3A inhibitors are taken during maintenance of daily venetoclax. Concomitant use of venetoclax with moderate CYP3A inhibitors or P-gp inhibitors is not recommended; venetoclax dosing should be reduced if concomitant medications in these classes are needed.[4]

Table S1. Management of Drug Interactions with Venetoclax[4]

	Venetoclax dose ramp-up	**Maintenance of daily dose following 5-week ramp-up**
Strong CYP3A inhibitors	Contraindicated	Avoid use or reduce dose
Moderate CYP3A inhibitors	Avoid use or reduce dose	
P-gp inhibitors	Avoid use or reduce dose	

Venetoclax Dose Adjustments

Dose adjustments were recommended for patients with grade 3/4 adverse events (AEs).[4] At the time of the first event, venetoclax could be interrupted and dosing resumed at the target dose following resolution of the AE. If subsequent AEs required dose interruptions, dosing could resume at a lower dose following resolution of the AE (see supplemental methods). For neutropenia, G-CSF could be administered concurrently with venetoclax as needed and was strongly recommended for patients with grade 4 events (ANC <500/μL). If the patient developed febrile neutropenia or grade 4 neutropenia persisting for more than one week despite G-CSF support, then venetoclax dosing was interrupted until recovery of ANC >500/μL. Following dose interruption, venetoclax could then be re-initiated at a lower dose. For blood chemistry changes or symptoms suggestive of TLS, dosing on the next day was withheld unless there was resolution of changes/symptoms within 24–48 hours of the last dose; subsequently dosing resumed at the same dose. If changes or symptoms resolved more than 48 hours after the last dose, dosing was resumed at a lower dose.

Table S2. Recommended Restart Dose Following Interruption of Venetoclax Treatment[4]

Dose at interruption, mg	Restart dose, mg
400	300
300	200
200	100
100	50
50	20
20	10

Early Review of Venetoclax Dosing Schedule and TLS Prophylaxis and Monitoring

Venetoclax dosing has been established following continual review and analysis of emerging data. Early in its development, venetoclax was found to induce tumor lysis syndrome (TLS) in patients with bulky relapsed/refractory CLL. In the first-in-human study, the first 3 patients experienced laboratory changes consistent with TLS after a single venetoclax dose of either 100 or 200mg.[1] Despite reducing the starting dose to 50mg and using a 3-week dose ramp-up to a maximum dose of 1200mg, laboratory TLS based on criteria established by Howard et al,[5] was observed in 4 additional patients, and clinical TLS in 3 patients, including 1 fatality after escalation to 1200mg, with a second fatality in the setting of TLS reported in a later phase Ib combination study after an initial dose of 50mg.[6]

Comprehensive review of all available data was conducted and a multivariate analysis identified bulky lymph nodes ≥5cm in largest diameter on CT scanning and elevated screening absolute lymphocyte count (ALC) $\geq 38.9 \times 10^9$/L as risk factors for TLS following administration of venetoclax. Screening creatinine clearance (CrCl) < 80 mL/min was also identified as a contributing factor. These TLS risk factors were not unique to venetoclax and have been previously identified in the literature.[7-9] Thus, TLS risk groups based on lymph node bulk and degree of lymphocytosis (eg, high risk identified as having any lymph node ≥10 cm; or both lymph node ≥5 cm and absolute lymphocyte count [ALC] $\geq 25 \times 10^9$/L) were introduced.[10] The first analysis to determine TLS risk factors considered ALC $>39 \times 10^9$/L at screening as high risk, though further medical review led to expansion of this threshold to $\geq 25 \times 10^9$/L.[11] Specific TLS prophylaxis and vigilant laboratory monitoring were instituted with intensity commensurate with the patient's TLS risk group. Population pharmacokinetic modeling based on exposure data indicated that at a 20mg starting dose 98% patients would achieve exposures similar to that observed in the patients without TLS (C_{max} below 0.23 µg/mL). This led to further modification of the dosing regimen by starting with a 20mg daily dose and more gradual ramp-up over 5 weeks to a target daily dose of 400mg allowing for a more gradual tumor reduction. For example, data from the M12-175 study showed a more gradual reduction in circulating absolute lymphocyte count for patients in the expansion cohort who initiated venetoclax at 20mg and over 5 weeks versus patients in the dose-escalation cohorts who started dosing at 50mg and had a more compressed ramp-up over 3 weeks.[1]

Rasburicase Prophylaxis

Rasburicase was administered per regional standards or institutional dosing guidelines for patients with elevated uric acid level at baseline (above the upper limit of the normal range) prior to the initial dose of venetoclax at 20mg and 50mg.

Definition of Serious Adverse Events (SAEs)

Events were considered SAEs if they met any of the following criteria: death of the patient, AE that was considered life-threatening per the investigator, required hospitalization, AE leading to congenital anomaly, or an AE that resulted in a condition that substantially interfered with activities of daily living. TLS laboratory assessments were required only during the dose ramp-up period.

Multivariate Predictive Modeling Analysis

Neutropenia

To explore potential baseline factors that may predict higher rates of grade 3 or 4 neutropenia, we performed a multivariate predictive modeling analysis using the integrated safety data from the three clinical studies. We explored different predictive models, including Classification and Regression Trees, Sequential BATTing, Additive Index model, LASSO, and the optimal combinations of diagnostic tests based on AUC (optAUC).[12-17] The best model was chosen based on the cross-validation performance assessment.[15-17] The best predictive model was derived from the optimal combinations of diagnostic tests based on AUC (optAUC).[12] Baseline characteristics used as factors in the model included Binet staging[18] at screening, prior fludarabine treatment, prior bendamustine treatment, prior granulocyte-colony stimulating factor use, screening absolute neutrophil count (ANC) $\geq 1x10^9$/L, screening ANC by grade (normal, grade 1, 2, 3, or 4), extent of bone marrow infiltrate by trephine/biopsy, age >65 years, gender (male or female), Eastern Cooperative Oncology Group performance status (0, 1, or 2), number of prior therapies, baseline platelet counts, 17p deletion status, whether the patient had failed prior B-cell receptor signaling pathway inhibitor therapy, and TLS risk categories (low, medium, or high).

Serious Infections

To explore potential baseline factors that may predict for serious infections on venetoclax, we performed a multivariate predictive modeling analysis using the integrated safety data from the three clinical studies. We explored different predictive models, including Classification and Regression Trees, Sequential BATTing, Additive Index model, LASSO, and the optimal combinations of diagnostic tests based on AUC (optAUC).[12-17] The best model was chosen based on the cross-validation performance assessment.[15-17] The best predictive model was derived from the optimal combinations of diagnostic tests based on AUC (optAUC).[12] Baseline characteristics used as factors in the model included age >65 years, gender (male or female), time from CLL diagnosis to first dose of venetoclax, Binet staging[18] at screening, number of prior therapies, prior fludarabine treatment, whether the patient had failed prior B-cell receptor signaling pathway inhibitor therapy, screening absolute neutrophil count (ANC) $\geq 1x10^9$/L, screening serum creatinine level, screening lymphocyte count, and Eastern Cooperative Oncology Group performance status (0, 1, or 2).

2. Supplementary Results

Table S3. Summary of Adverse Events While on Venetoclax by Grade				
	All Patients N=350			
Event, n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Common any grade AEs (≥10% of all patients)				
Diarrhea	91 (26)	45 (13)	9 (3)	0
Neutropenia	4 (1)	9 (3)	56 (16)	72 (21)
Nausea	97 (28)	37 (11)	3 (1)	0
Anemia	26 (7)	23 (7)	58 (17)	2 (0.5)
Fatigue	55 (16)	35 (10)	8 (2)	1 (0.3)
Upper respiratory tract infection	22 (6)	60 (17)	2 (0.5)	2 (0.5)
Thrombocytopenia	15 (4)	10 (3)	17 (5)	32 (9)
Cough	38 (11)	25 (7)	0	0
Headache	42 (12)	18 (5)	2 (0.5)	0
Pyrexia	39 (11)	19 (5)	2 (0.5)	0
Constipation	42 (12)	13 (4)	1 (0.3)	0
Vomiting	34 (10)	17 (5)	4 (1)	0
Hyperkalemia	22 (6)	6 (2)	21 (6)	1 (0.3)
Hyperphosphatemia	22 (6)	22 (6)	4 (1)	0
Peripheral edema	27 (8)	17 (5)	3 (1)	0
Hypocalcemia	17 (5)	17 (5)	5 (1)	2 (0.5)
Pneumonia	4 (1)	12 (3)	22 (6)	2 (0.5)
Back pain	15 (4)	22 (6)	2 (0.5)	0
Abdominal pain	17 (5)	13 (4)	7 (2)	0
Dizziness	32 (9)	5 (1)	0	0
Dyspnea	25 (7)	7 (2)	5 (1)	0
No grade 5 AEs were reported among these common events. Patients with more than one occurrence of the same AE were summarized by the worst grade of the events reported.				

Table S4. First Onset and Prevalence of Adverse Events Over Time on Venetoclax					
	Days on Venetoclax Monotherapy				
N	Ramp-up n=350	Ramp-up – 91 days n=334	92 – 183 days n=319	184 – 365 days n=285	>365 days n=202
Any grade AE					
First onset	323	15	4	1	0
Prevalence	323	305	286	266	187
Serious AE					
First onset	77	35	11	24	35
Prevalence	77	62	38	58	63
AE leading to dose reduction					
First onset	8	14	9	10	4*
Prevalence	8	18	19	21	17
AE leading to dose interruption					
First onset	46	29	11	17	18[†]
Prevalence	46	43	35	45	37

Reported is the number of patients with events during each time interval. During the dose ramp-up period, patients started at 20mg daily with weekly increases over 5 weeks to the target dose of 400mg daily venetoclax. Some patients took longer than 5 weeks to ramp-up but AEs are included in the dose ramp-up interval. Patients received 400mg daily venetoclax during subsequent time intervals. The number of patients per time interval reduced with time on venetoclax due to discontinuations or disease progression. Thus, those included after one year (n=202) were patients who were able to tolerate venetoclax long term. Analysis of first onset over time counted an event for a patient only for the time interval for the onset of first occurrence. If a patient experienced more than one event of the same preferred AE term, then only the first occurrence was included. Analysis of prevalence over time counted a patient in every time interval for which an AE was present. If a patient had a recurrence of the same preferred AE term, the recurrent event was also counted in every time interval for which the AE was present.

*Among 4 patients who required dose reductions after 365 days on therapy, the AEs resulting in dose reduction were neutropenia, thrombocytopenia, acute myocardial infarction, cardiogenic shock, fatigue, herpes zoster, upper respiratory tract infection (n=1 each). Patients could have reduced their dose for more than one reason during this time interval.

[†]Among 18 patients who required dose interruptions after 365 days on therapy, the AEs resulting in dose interruption were neutropenia (n=3), diarrhea (n=3), pneumonia (n=3), autoimmune hemolytic anemia (n=1), thrombocytopenia (n=1), acute myocardial infarction (n=1), cardiogenic shock (n=1), myocardial ischemia (n=1), abdominal discomfort (n=1), nausea (n=1), pyrexia (n=1), chronic cholecystitis (n=1), cholelithiasis (n=1), bronchopulmonary aspergillus (n=1), disseminated varicella zoster vaccine virus infection (n=1), gastrointestinal infection (n=1), infection (n=1), influenza (n=1), parotitis (n=1), urinary tract infection (n=1), injury (n=1), increased prostatic specific antigen (n=1), hyponatremia (n=1), colon adenocarcinoma (n=1), breast cancer (n=1), disease progression (n=1), salivary gland cancer (n=1), cerebrovascular accident (n=1), dizziness (n=1), and peripheral sensory neuropathy (n=1). Patients could have interrupted their dosing for more than one reason during this time interval.

Dose Adjustments

New AEs requiring dose adjustments decreased with longer time on therapy (Table S4). During the first three months on venetoclax, dose reduction for new AEs occurred in 22/350 (6%) patients and interruptions in 75/350 (21%), compared to 4/202 (2%) reductions and 18/202 interruptions (13%) after one year on therapy. Median time to first dose reduction was 3.5 months (0.1–36) and 25 patients patients had their dose reduced (9 to 300mg, 10 to 200mg, and 6 to ≤150mg). Twenty patients were able to resume 400mg dosing. Median time to first dose interruption was 1.5 months (0.07–34) and median duration of interruption was 6 days (1–141). Fifteen (4.3%) patients interrupted venetoclax more than once due to the same AE (the most common recurrent AEs were neutropenia, n=4; thrombocytopenia, n=2; diarrhea, n=2).

Table S5. Adverse Events Leading to Venetoclax Dose Adjustments or Discontinuation	
n (%)	**All Patients, N=350**
Dose reduction	45 (13)
AEs leading to dose reductions (in ≥0.5% of patients)	
Neutropenia	17 (5)
Febrile neutropenia	4 (1)
Fatigue	3 (1)
Pneumonia	3 (1)
Thrombocytopenia	3 (1)
Diarrhea	3 (1)
Autoimmune hemolytic anemia	2 (.6)
Cytopenia	2 (.6)
Vomiting	2 (.6)
Asthenia	2 (.6)
Herpes zoster	2 (.6)
Increased aspartate aminotransferase	2 (.6)
Dose interruption	120 (34)*
AEs leading to dose interruption† (in ≥1% of patients)	
Neutropenia	14 (4)
Pneumonia	11 (3)
Febrile neutropenia	9 (3)
Diarrhea	9 (3)
Nausea	9 (3)
Hyperphosphatemia	8 (2)
Thrombocytopenia	8 (2)
Vomiting	7 (2)
Pyrexia	6 (2)
Tumor lysis syndrome	6 (2)
Increased blood creatinine	5 (2)
Autoimmune hemolytic anemia	4 (1)
Immune thrombocytic purpura	4 (1)
Increased aspartate aminotransferase	3 (1)
Hyperkalemia	3 (1)
All discontinuations due to AEs	35 (10)*
AEs leading to discontinuation (in ≥0.5% of patients)	
Autoimmune hemolytic anemia	2 (.6)
Thrombocytopenia	2 (.6)
Multi organ dysfunction	2 (.6)
Myelodysplastic syndrome	2 (.6)

*Excludes those due to disease progression.

†Fifteen patients interrupted venetoclax more than once due to the same AE (neutropenia, n=4; thrombocytopenia, n=2; diarrhea, n=2; back spasms, n=1; vomiting, n=1, cardiac ischemia, n=1; elevated creatinine, n=1; AIHA, n=1, febrile neutropenia, n=1; infection of unknown origin, n=1; pneumonia, n=1; lymphadenopathy, n=1; pyrexia, n=1; squamous cell carcinoma, n=1).

Incidence of TLS with Venetoclax

Five patients were reported by investigators as having TLS, with 1 of these 5 patients experiencing 2 events (Table S6). However, none met clinical TLS criteria, and only two (1.7%) met Howard criteria[5] for laboratory TLS. All tumor lysis-related events occurred during dose ramp-up. Two occurred on the first day of 200mg dosing and one on day 3 of 200mg dosing, while 3 were identified during scheduled assessments for the next dose ramp-up (one at 20mg and two at 200mg). With respect the two patients whose events met Howard criteria for laboratory TLS, one presented on day 3 of dosing with clinical symptoms of fever, chills, nausea and laboratory assessments showed chemistry abnormalities of decreased calcium and increased phosphate levels. The second patient who met Howard criteria for laboratory TLS did not receive an oral uric acid reducing agent and had increased phosphate and uric acid (both grade 1) on day 1 at 200mg dosing. This patient was treated with rasburicase and no dose interruptions were needed. Venetoclax dosing was interrupted for the other 4 patients for 1–5 days. All successfully resumed venetoclax and reached the target 400mg dose.

Table S6. Incidence of TLS With Venetoclax Monotherapy

Patient	TLS Risk*	Dose/day at dose level for AE of TLS onset	Clinical chemistry (Baseline → Abnormality), mmol/L	Management
1†	High	200mg/3 days	Calcium: 2.38→1.56 Phosphate: 1.13→1.77	Hospitalized Dose interruption (3 days) Treated with calcium carbonate, calcium gluconate, IV fluids
2‡	High	200mg/6 days	Potassium: 3.9→5.3	Hospitalized Dose interruption (5 days) Treated with sodium polystyrene sulfonate, calcium gluconate, sevelamer, IV fluids
3‡	Medium	200mg/1 day	Phosphate: 1.28→1.56	Hospitalized Dose interruption (4 days) Treated with rasburicase, IV fluids
4‡	High	20mg/7 days	Potassium: 4.4→5.9 Phosphate: 1.42→2.16	Outpatient Dose interruption (2 days) Treated with sodium polystyrene sulfonate, furosemide, IV fluids Continued receiving sevelamer
		200mg/7 days	Potassium: 4.4→4.7 Phosphate: 1.1→1.23	Outpatient Treated with furosemide, dextrose, insulin, IV fluids
5†	High	200 mg/1 day	Phosphate: 1.45 → 1.74 Uric acid: 404 → 488	Outpatient Treated with rasburicase

Only patient 1 presented with clinical symptoms of fever, chills, and nausea; this patient was then identified as having clinical chemistry abnormalities meeting Howard criteria for laboratory TLS. All other patients were asymptomatic and AEs of TLS per investigator assessment were based on clinical chemistry abnormalities that were identified all during pre-defined time points for laboratory assessments during the dose ramp-up phase.

*Moderate risk, any lymph node ≥5cm to <10 cm or ALC ≥25x10^9/L; High risk, any lymph node ≥10cm or lymph node ≥5cm to <10 cm and ALC ≥25x10^9/L.

†Met Howard criteria for laboratory TLS.[5]

‡Changes in clinical chemistry levels were outside of the local laboratory reference range without meeting Howard criteria for TLS.

Table S7. Relevant Laboratory Abnormalities			
n (%)	**Low TLS risk n=61**	**Moderate TLS risk n=59**	**High TLS risk n=46**
Potassium >6 mmol/L			
20 mg	0	1 (2)	3 (7)
50 mg	0	1 (2)	2 (4)
100 mg	0	0	0
200 mg	0	0	0
400 mg	0	0	0
Phosphorus >1.5 mmol/L			
20 mg	2 (3)	4 (7)	14 (30)
50 mg	2 (3)	5 (8)	6 (13)
100 mg	4 (7)	6 (10)	9 (20)
200 mg	4 (7)	5 (8)	8 (17)
400 mg	0	2 (3)	7 (15)
Uric acid >476 mmol/L			
20 mg	0	1 (2)	0
50 mg	1 (2)	0	1 (2)
100 mg	0	1 (2)	0
200 mg	1 (2)	0	3 (7)
400 mg	0	0	1 (2)
Calcium <1.75 mmol/L*			
20 mg	0	1 (2)	1 (2)
50 mg	0	3 (5)	1 (2)
100 mg	0	0	0
200 mg	0	0	1 (2)
400 mg	0	0	0

Reported are the laboratory abnormalities, with or without intervention, per tumor lysis syndrome (TLS) risk category occurring post-dose at each dose ramp-up level (20, 50, 100, 200, and 400 mg) that were consistent with Howard criteria.[5]

Risk categories were defined as: Low, all lymph nodes ≤5cm and absolute lymphocyte count [ALC] <25x10^9/L; Medium, any lymph node ≥5cm to <10cm or ALC ≥25x10^9/L; High, any lymph node ≥10cm or lymph node ≥5cm and ALC ≥25x10^9/L.

*Includes values corrected and uncorrected for albumin concentration.

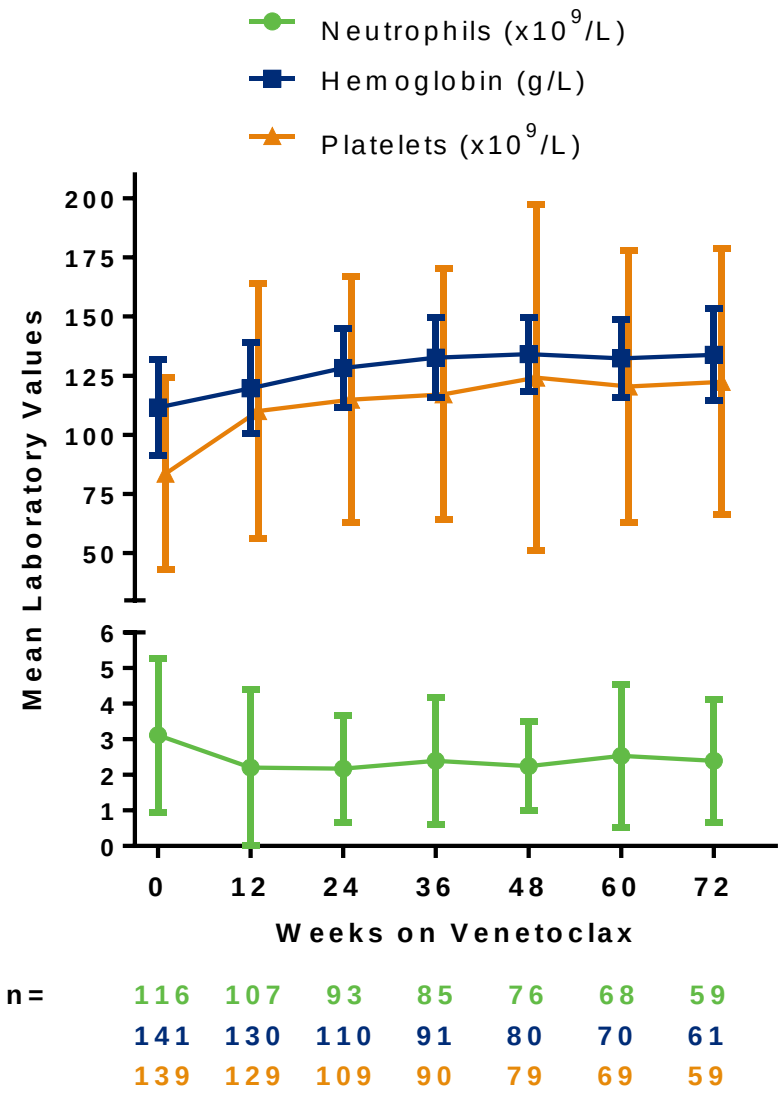
Cytopenias by Binet Staging

Of 86 patients with grade 4 neutropenia or decreased neutrophil count, 56 (65%) had Binet C at screening (151 patients in total were identified as Binet C at screening; 37% incidence of grade 4 neutropenia) and median time to grade 4 event for these patients was 22 days (range: 2–491). Grade 4 neutropenia was seen less frequently in patients with Binet A or B at screening (16% [8/49] for Binet A; 15% [22/149] for Binet B). The mean ANC for all patients was stable over time on therapy and remained above $1.5x10^9$/L.

Two patients had grade 4 anemia, both with Binet C disease at screening, and the events occurred at days 9 and 40 on venetoclax. Across all patients, the mean hemoglobin level was above 12g/dL by 3 months on venetoclax.

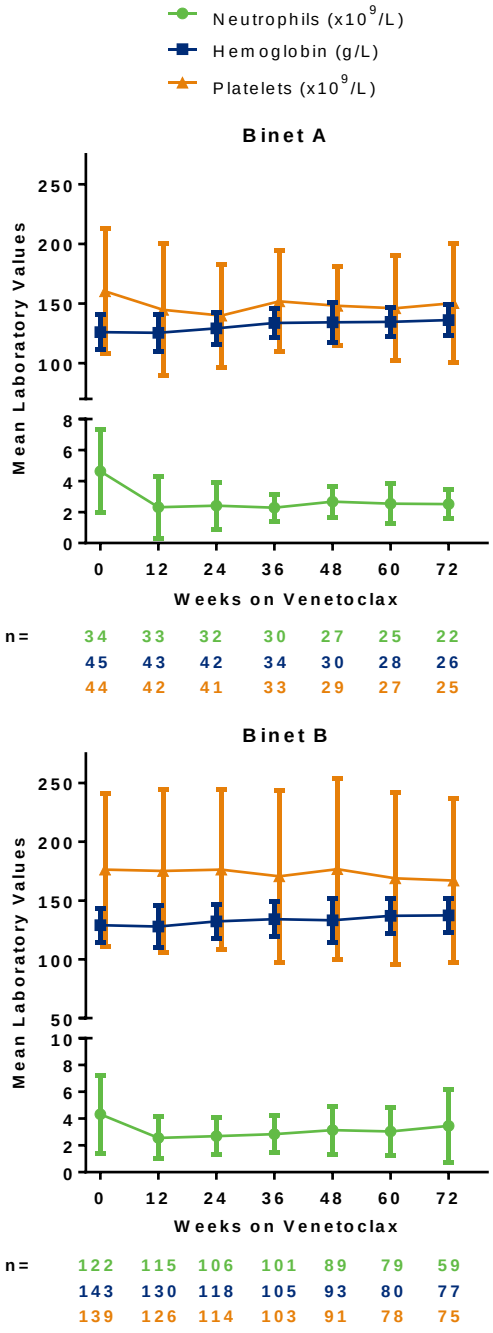
Of 44 patients with grade 4 thrombocytopenia or decreased platelet count, 32 (21%) had Binet C disease at screening (151 patients in total were identified as Binet C at screening) and no difference was seen in the median time to event for these patients versus all patients with grade 4 events. Grade 4 events were not reported as frequently for patients with Binet A or B at screening (2% [1/49] for Binet A; 7% [11/149] for Binet B). For patients with Binet A or B at screening, platelet counts remained stable from screening and over time on study. For patients with Binet C at screening, the mean platelet count started at $84x10^9$/L and was between $120x10^9$/L – 134 $x10^9$/L during time on venetoclax.

Figure S1. Mean Laboratory Values Over Time on Venetoclax for Patients with Binet C at Screening



Presented are the mean (error bars show standard deviation) for neutrophils counts, hemoglobin, and platelet counts over time on venetoclax for those patients who had Binet C staging at screening for the clinical studies. Patients were evaluable if they had both a screening value and value for the given visit. Fewer patients had values for neutrophils at screening than other parameters, which resulted in fewer evaluable patients at each subsequent visit.

Figure S2. Mean Laboratory Values Over Time on Venetoclax for Patients with Binet A or B at Screening



Presented are the mean (error bars show standard deviation) for neutrophils counts, hemoglobin, and platelet counts over time on venetoclax for those patients who had Binet A or B staging at screening for the clinical studies. Patients were evaluable if they had both a screening value and value for the given visit. Fewer patients had values for neutrophils at screening than other parameters, which resulted in fewer evaluable patients at each subsequent visit.

Fatal Infections

There were five fatal events of infections, with all occurring in patients with prior history of infection and or neutropenia, heavily pretreated (median of 5 prior therapies [range: 1 – 6]). This is not unexpected in patients with advanced CLL. One event occurred after venetoclax discontinuation due to disease progression. Four of the five events occurred within approximately 3 months from treatment initiation (day 17, 23, 45, 94 respectively) while one event occurred at approximately 8 months from treatment initiation. All five events were considered to be related to the pre-existing events of neutropenia and infection and not related to study drug.

Serious Infections

Overall, 79 (23%) patients experienced a serious infection when on venetoclax. Events were considered serious if they met any of the following criteria: death of the patient, AE that was considered life-threatening per the investigator, required hospitalization, AE leading to congenital anomaly, or an AE that resulted in a condition that substantially interfered with activities of daily living. In general, first onset and prevalence of serious infections decreased over time within the first year on therapy (Figure S3). Of note, the interval of time after one year on therapy ranged from 366 to 1694 days. No trend was observed with the number of serious infections reported at this time frame.

Figure S3. First Onset and Prevalence of Serious Infections

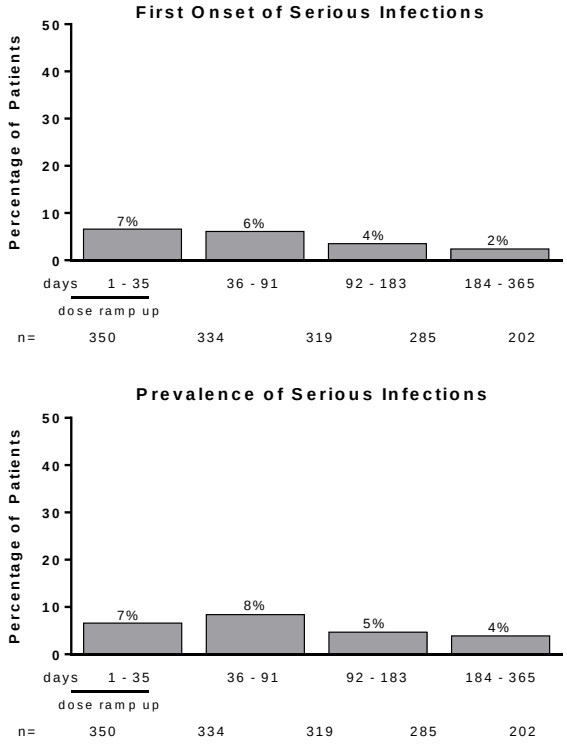


Table S8. Tumor Burden Categories and TLS Mitigation Recommendations[4]		
Tumor Burden	**Prophylaxis**	**Monitoring**[*,†]
Low All lymph nodes <5 cm and ALC <$25x10^9$/L	• Oral hydration (1.5–2 L) • Allopurinol[‡]	• Outpatient • Monitoring at pre-dose, 6–8, and 24 hours at first dose of 20mg and 50mg • Pre-dose at subsequent ramp-up doses
Medium Any lymph node 5 cm to <10 cm or ALC ≥$25x10^9$/L	• Oral hydration (1.5–2 L); consider additional intravenous • Allopurinol	• Outpatient • Monitoring at pre-dose, 6–8, and 24 hours at first dose of 20mg and 50mg • Pre-dose at subsequent ramp-up doses • Consider hospitalization for patients with creatinine clearance <80 mL/min at first dose of 20mg and 50mg; see high tumor burden for monitoring in hospital
High Any lymph nodes ≥10 cm Or Any lymph node ≥5 cm and ALC ≥$25x10^9$/L	• Oral (1.5 – 2 L) and intravenous (150–200 mL/hour as tolerated) hydration • Allopurinol; consider rasburicase if baseline uric acid level is elevated	• In hospital at first dose of 20mg and 50mg • Monitoring at pre-dose, 4, 8, 12, and 24 hours • Outpatient at subsequent ramp-up doses with monitoring at pre-dose, 6–8, and 24 hours

ALC, absolute lymphocyte count.
Administer intravenous hydration for any patient who cannot tolerate oral.
*Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[†]For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.
[‡]Start allopurinol or xanthase oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.

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