VENCLEXTA™ TABLET

PRODUCT NAME

Venetoclax

Trade Names

VENCLEXTA™

INDICATIONS

Chronic Lymphocytic Leukemia

VENCLEXTA is indicated, in combination with rituximab or as monotherapy, for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

VENCLEXTA is indicated, in combination with obinutuzumab, for the treatment of patients with previously untreated CLL.

Acute Myeloid Leukemia

VENCLEXTA is indicated, in combination with a hypomethylating agent or in combination with low-dose cytarabine, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy [see **CLINICAL STUDIES/USE IN SPECIFIC POPULATIONS]**.

DOSAGE AND ADMINISTRATION

Recommended Dosage Regimen

Instruct patients to take VENCLEXTA tablets with a meal and water at approximately the same time each day. VENCLEXTA tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

The 10, 50, and 100 mg strengths are interchangeable at equivalent doses (e.g., patients can take 2 x 50 mg tablets or 10 x 10 mg tablets instead of 1 x 100 mg VENCLEXTA tablet as needed) [see **Pharmacokinetics**].

Chronic Lymphocytic Leukemia

VENCLEXTA Dose Ramp-Up Schedule

The starting dose of VENCLEXTA is 20 mg once daily for 7 days. The VENCLEXTA dose must be administered according to a weekly ramp-up schedule to the daily dose of 400 mg over a

period of 5 weeks as shown in Table 1. The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of tumor lysis syndrome (TLS).

Table 1. Dosing Schedule for Ramp-Up Phase in Patients with CLL

Week	Venetoclax Daily Dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5	400 mg

VENCLEXTA in Combination with Obinutuzumab

VENCLEXTA should be given for a total of 12 cycles: 6 cycles in combination with obinutuzumab, followed by 6 cycles of VENCLEXTA as a single agent.

On Cycle 1 Day 1, start obinutuzumab administration at 100 mg, followed by 900 mg, which may be administered on Day 1 or Day 2. Administer 1000 mg on Days 8 and 15 of Cycle 1, and on Day 1 of five subsequent cycles (total of 6 cycles, 28 days each).

On Cycle 1 Day 22, start VENCLEXTA according to the ramp-up schedule (see Table 1), continuing through Cycle 2 Day 28. After completing the ramp-up schedule, patients should continue VENCLEXTA 400 mg once daily from Cycle 3 Day 1 of obinutuzumab to the end of Cycle 12.

VENCLEXTA in Combination with Rituximab

Start rituximab administration after the patient has completed the ramp-up schedule with VENCLEXTA (see Table 1) and has received the 400 mg dose of VENCLEXTA for 7 days. Administer rituximab on Day 1 of each 28-day cycle for 6 cycles, with rituximab dosed at 375 mg/m^2 intravenously for Cycle 1 and 500 mg/m^2 intravenously for Cycles 2-6.

Patients should continue VENCLEXTA 400 mg once daily for 24 months from Cycle 1 Day 1 of rituximab.

VENCLEXTA as Monotherapy

The recommended dose of VENCLEXTA is 400 mg once daily after the patient has completed the ramp-up schedule. VENCLEXTA should be taken orally once daily until disease progression or unacceptable toxicity is observed.

<u>Acute Myeloid Leukemia</u>

The dose of VENCLEXTA depends upon the combination agent.

The VENCLEXTA dosing schedule (including ramp up) is shown in Table 2.

Table 2. Dosing Schedule for Ramp-Up Phase in Patients with AML

Day	**VENCLEXTA Daily Dose**	
1	100 mg	
2	200 mg	
3	400 mg	
4 and beyond	400 mg when dosing in combination with a hypomethylating agent	600 mg when dosing in combination with low-dose cytarabine

Initiate the hypomethylating agent or low-dose cytarabine on Cycle 1 Day 1.

Azacitidine should be administered at 75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1.

Decitabine should be administered at 20 mg/m^2 intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1 Day 1.

Cytarabine should be administered at a dose of 20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1.

Interrupt VENCLEXTA dosing as needed for management of hematologic toxicities and blood count recovery [see **DOSE MODIFICATIONS BASED ON TOXICITIES**]. Refer to the azacitidine, decitabine, or low-dose cytarabine prescribing information for additional information.

VENCLEXTA, in combination with a hypomethylating agent or low-dose cytarabine, should be continued until disease progression or unacceptable toxicity is observed.

Missed Dose

If the patient misses a dose of VENCLEXTA within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal daily dosing schedule. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the next day.

If the patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time.

Risk Assessment and Prophylaxis for Tumor Lysis Syndrome

Patients treated with VENCLEXTA may develop TLS. Refer to the appropriate section below for specific details on management. Assess patient-specific factors for level of risk of TLS and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose of VENCLEXTA to reduce risk of TLS.

Chronic Lymphocytic Leukemia

VENCLEXTA can cause rapid reduction in tumor, and thus poses a risk for TLS in the initial 5-week ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including comorbidities, particularly reduced renal function (creatinine clearance [CrCl] <80mL/min), and tumor burden. Splenomegaly may contribute to the overall TLS risk. The risk may decrease as tumor burden decreases with VENCLEXTA treatment [see **WARNINGS AND PRECAUTIONS**].

Perform tumor burden assessments, including radiographic evaluation (e.g., CT scan). Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA.

Prophylaxis for Tumor Lysis Syndrome

Chronic Lymphocytic Leukemia

Table 3 below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumor burden determination from clinical trial data. In addition, consider all patient comorbidities for risk-appropriate prophylaxis and monitoring, either outpatient or in hospital.

Table 3. Recommended TLS Prophylaxis Based on Tumor Burden in Patients with CLL

Tumor Burden		**Prophylaxis**		**Blood Chemistry Monitoring[c,d]**
		Hydration[a]	**Anti-hyperuricemics[b]**	**Setting and Frequency of Assessments**
Low	All LN <5 cm AND ALC <25 x 10^9/L	Oral (1.5-2 L)	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours

				• For subsequent ramp-up doses: Pre-dose
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x 10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalization for patients with CrCl <80mL/min; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x 10^9/L AND any LN ≥5 cm	Oral (1.5-2 L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12, and 24 hours Outpatient • For subsequent ramp-up doses: Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; CrCl = creatinine clearance; LN = lymph node.
[a]Instruct patients to drink water daily starting 2 days before and throughout the dose ramp-up phase, specifically prior to and on the days of dosing at initiation and each subsequent dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.
[b]Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLEXTA.
[c]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[d]For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

Acute Myeloid Leukemia

The VENCLEXTA daily dose ramp-up is 3 days with azacitidine or decitabine, or 4 days with low-dose cytarabine (see Table 2).

Follow prophylaxis measures listed below:

- All patients should have white blood cell count $<25 \times 10^9$/L prior to initiation of VENCLEXTA, and cytoreduction prior to treatment may be required.
- All patients should be adequately hydrated and receive anti-hyperuricemic agents prior to initiation of first dose of VENCLEXTA and during ramp-up phase.
- Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA.
    - Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during ramp-up, and 24 hours after reaching final dose.
- For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukemia involvement in bone marrow, elevated pretreatment lactate dehydrogenase [LDH] levels, or reduced renal function), additional measures should be considered, including increased laboratory monitoring and reduced VENCLEXTA starting dose.

Dose Modifications Based on Toxicities

Chronic Lymphocytic Leukemia

Dosing interruption and/or dose reduction for toxicities may be required. See Table 4 and Table 5 for recommended dose modifications for toxicities related to VENCLEXTA. For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 2 weeks after completing the ramp-up phase, reassess for risk of TLS to determine if reinitiation with a reduced dose is necessary (e.g., all or some levels of dose ramp-up schedule) [see **DOSAGE AND ADMINISTRATION**].

Table 4. Recommended VENCLEXTA Dose Modifications for Toxicities[a] in CLL

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 5) [see **DOSAGE AND ADMINISTRATION**].
		For any events of clinical TLS,[b] resume at a reduced dose following resolution (see Table 5) [see **DOSAGE AND ADMINISTRATION**].
Non-Hematologic Toxicities		

Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt VENCLEXTA. Once the toxicity has resolved to grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt VENCLEXTA. Follow dose reduction guidelines in Table 5 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
Hematologic Toxicities		
Grade 3 neutropenia with infection or fever; or grade 4 hematologic toxicities (except lymphopenia) [see **DOSAGE AND ADMINISTRATION**]	1st occurrence	Interrupt VENCLEXTA. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with VENCLEXTA if clinically indicated. Once the toxicity has resolved to grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose.
	2nd and subsequent occurrences	Interrupt VENCLEXTA. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 5 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
Consider discontinuing VENCLEXTA for patients who require dose reductions to less than 100 mg for more than 2 weeks. [a]Adverse reactions were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. [b]Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures [see **ADVERSE REACTIONS**].		

Table 5. Dose Reduction for Toxicity During VENCLEXTA Treatment of CLL

Dose at Interruption, mg	Restart Dose, mg[a]
400	300
300	200
200	100
100	50
50	20
20	10
[a]Continue the reduced dose for 1 week before increasing the dose.	

Acute Myeloid Leukemia

Dose modification for other toxicities

Monitor blood counts frequently through resolution of cytopenias. Dose modification and interruptions for cytopenias are dependent on remission status. Dose modifications of VENCLEXTA for adverse reactions are provided in Table 6 [see **WARNINGS AND PRECAUTIONS**].

Table 6. Recommended Dose Modifications for Toxicities[a] During VENCLEXTA Treatment of AML

<table>
<tr><th colspan="3">Hematologic Toxicities[a] Lasting >1 Week of Grade 4 Neutropenia With or Without Fever or Infection, or Grade 4 Thrombocytopenia</th></tr>
<tr><th>Before Remission[b] is Achieved</th><th colspan="2">After Remission[b] is Achieved</th></tr>
<tr><td rowspan="3">Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated.

In most instances, VENCLEXTA and azacitidine, decitabine, or low-dose cytarabine cycles should not be interrupted due to cytopenias prior to achieving remission.</td><td colspan="2">Delay subsequent treatment cycle of VENCLEXTA and azacitidine, decitabine, or low-dose cytarabine and monitor blood counts.

Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia.</td></tr>
<tr><th>For first occurrence</th><th>For subsequent occurrences</th></tr>
<tr><td>Once the toxicity has resolved to grade 1 or 2, resume VENCLEXTA therapy at the same dose in combination with azacitidine, decitabine, or low-dose cytarabine.</td><td>Once the toxicity has resolved to grade 1 or 2, resume VENCLEXTA therapy at the same dose in combination with azacitidine, decitabine, or low-dose cytarabine and reduce duration of VENCLEXTA administration by 7 days during each of the subsequent cycles, i.e., 21 days instead of 28 days.</td></tr>
<tr><td colspan="3">[a]Adverse reactions were graded using NCI CTCAE version 4.0.
[b]Bone marrow confirmation of <5% blasts with cytopenia.</td></tr>
</table>

Dose Modifications for Use with CYP3A Inhibitors

Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors increases venetoclax exposure (i.e., C_{max} and AUC) and may increase the risk for TLS at initiation and during ramp-up phase.

In patients with CLL, concomitant use of VENCLEXTA with strong CYP3A inhibitors is contraindicated at initiation and during ramp-up phase [see **CONTRAINDICATIONS**].

In all patients, if a CYP3A inhibitor must be used, follow the recommendations for managing drug-drug interactions summarized in Table 7. Monitor patients more closely for signs of toxicities [see **DOSAGE AND ADMINISTRATION**].

Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor [see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**].

Table 7. Management of Potential VENCLEXTA Interactions with CYP3A Inhibitors

<table>
<tr><th>Inhibitors</th><th colspan="2">Initiation and Ramp-Up Phase</th><th>Steady Daily Dose (After Ramp-Up Phase)[a]</th></tr>
<tr><td rowspan="2">Strong CYP3A inhibitor</td><td>CLL</td><td>Contraindicated</td><td rowspan="2">Reduce the VENCLEXTA dose to 100 mg or less.</td></tr>
<tr><td>AML</td><td>Day 1 – 10 mg
Day 2 – 20 mg
Day 3 – 50 mg
Day 4 – 100 mg or less</td></tr>
<tr><td>Moderate CYP3A inhibitor</td><td colspan="3">Reduce the VENCLEXTA dose by at least 50%</td></tr>
<tr><td colspan="4">[a]In patients with CLL, avoid concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors. Consider alternative medications or reduce the VENCLEXTA dose as described in Table 5.</td></tr>
</table>

CONTRAINDICATIONS

In patients with CLL, concomitant use of VENCLEXTA with strong CYP3A inhibitors is contraindicated at initiation and during ramp-up phase [see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**].

WARNINGS AND PRECAUTIONS

Tumor Lysis Syndrome

Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients treated with VENCLEXTA [see **ADVERSE REACTIONS**].

VENCLEXTA can cause rapid reduction in tumor, and thus poses a risk for TLS at initiation and during the ramp-up phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6-8 hours following the first dose of VENCLEXTA and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including comorbidities (particularly reduced renal function), tumor burden, and splenomegaly in CLL [see **DOSAGE AND ADMINISTRATION**].

All patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases. Interrupt dosing if needed; when restarting VENCLEXTA, follow dose modification guidance [see **DOSAGE AND ADMINISTRATION**].

Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during ramp-up phase [see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**]. Also, inhibitors of P-gp may increase venetoclax exposure [see **DRUG INTERACTIONS**].

Neutropenia

In patients with CLL, grade 3 or 4 neutropenia has occurred in patients treated with VENCLEXTA in combination studies and monotherapy studies [see **ADVERSE REACTIONS**].

In patients with AML, grade 3 or 4 neutropenia is common before starting treatment. The neutrophil counts can worsen with VENCLEXTA in combination with a hypomethylating agent or low-dose cytarabine. Neutropenia can recur with subsequent cycles of therapy.

Monitor complete blood counts throughout the treatment period. Dose interruptions or dose reductions are recommended for severe neutropenia. Consider supportive measures including antimicrobials for any signs of infection and prophylactic use of growth factors (e.g., G-CSF) [see **DOSAGE AND ADMINISTRATION**].

Serious Infection

Serious infections, including events of sepsis and events with fatal outcome, have been reported in patients treated with VENCLEXTA [see ADVERSE REACTIONS]. Monitor patients for fever and any symptoms of infection and treat promptly. Interrupt dosing as appropriate.

Immunization

The safety and efficacy of immunization with live attenuated vaccines during or following VENCLEXTA therapy have not been studied. Live vaccines should not be administrated during treatment with VENCLEXTA and thereafter until B-cell recovery.

Increased Mortality in Patients with Multiple Myeloma when VENCLEXTA is Added to Bortezomib and Dexamethasone

In a randomized trial (BELLINI; NCT02755597) in patients with relapsed or refractory multiple myeloma, the addition of VENCLEXTA to bortezomib plus dexamethasone, a use for which VENCLEXTA is not indicated, resulted in increased mortality. Treatment of patients with

multiple myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

ADVERSE REACTIONS

Clinical Trial Experience in CLL

CLL14

The safety of VENCLEXTA in combination with obinutuzumab versus obinutuzumab and chlorambucil was evaluated in an open-label randomized (1:1) phase 3 study in patients with previously untreated CLL and coexisting medical conditions. Details of the study treatment are described in the Clinical Studies section [see **CLINICAL STUDIES**].

At the time of data analysis, the median duration of exposure to VENCLEXTA was 10.5 months (range: 1 to 13.5 months) and to obinutuzumab and chlorambucil for 6 and 12 cycles, respectively.

In the VENCLEXTA + obinutuzumab arm, adverse events led to discontinuation in 16% of patients, dose reductions in 21% of patients, and dose interruptions in 74% of patients. The most common adverse reaction that led to dose interruption of VENCLEXTA was neutropenia.

Table 8 provides the adverse reactions reported in CLL14. Adverse reactions are listed by MedDRA body system organ class, rate, and, frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing rate.

Table 8. Summary of Adverse Reactions Reported with Incidence of ≥10% and ≥5% Higher for all Grades or ≥2% Higher for Grade 3 or 4 in Patients Treated with VENCLEXTA Plus Obinutuzumab Compared with Obinutuzumab Plus Chlorambucil

Adverse Reaction by Body System	VENCLEXTA + Obinutuzumab (N=212)		Obinutuzumab + Chlorambucil (N=214)	
	All Grades % (Frequency)	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Blood & lymphatic system disorders				
Neutropenia[a]	60 (Very common)	56	62	52
Gastrointestinal disorders				
Diarrhea	28 (Very common)	4	15	<1
[a]Includes neutropenia and neutrophil count decreased.				

Other adverse reactions reported in the VENCLEXTA + obinutuzumab arm are presented below:

Blood & lymphatic system disorders: anemia (17%), febrile neutropenia (6%), lymphopenia (1%)

Gastrointestinal disorders: nausea (19%), constipation (13%), vomiting (10%)

General disorders and administration site conditions: fatigue (15%)

Infection and infestation disorder: pneumonia (8%), upper respiratory tract infection (8%), urinary tract infection (5%), sepsis[a] (4%)

Investigations: blood creatinine increased (3%)

Metabolism and nutrition disorder: hyperuricemia (4%), hyperkalemia (2%), hyperphosphatemia (2%), hypocalcemia (1%), tumor lysis syndrome (1%)

[a]Includes the following terms: sepsis, septic shock, and urosepsis.

MURANO (GO28667)

The safety of VENCLEXTA in combination with rituximab versus bendamustine in combination with rituximab was evaluated in an open-label randomized phase 3 study in patients with CLL who had received at least one prior therapy. Details of the study treatment are described in Clinical Studies section [see **CLINICAL STUDIES]**. At the time of data analysis, the median duration of exposure was 22 months in the VENCLEXTA + rituximab arm compared with 6 months in the bendamustine + rituximab arm.

Discontinuations due to adverse events occurred in 16% of patients treated with VENCLEXTA + rituximab. Dose reductions due to adverse events occurred in 15% of patients treated with VENCLEXTA + rituximab. Dose interruptions due to adverse events occurred in 71% of patients treated with VENCLEXTA + rituximab. The most common adverse reaction that led to dose interruption of VENCLEXTA was neutropenia.

Table 9 provides the adverse reactions reported in MURANO.

Table 9. Summary of Adverse Reactions Reported with Incidence of ≥10% and ≥5% Higher for all Grades or ≥2% Higher for Grade 3 or 4 in Patients Treated with VENCLEXTA Plus Rituximab Compared with Bendamustine Plus Rituximab

	VENCLEXTA + Rituximab (N=194)		Bendamustine + Rituximab (N=188)	
Adverse Reaction by Body System	**All Grades % (Frequency)**	**Grade 3 or 4 %**	**All Grades %**	**Grade 3 or 4 %**
Blood & lymphatic system disorders				
Neutropenia	61 (Very common)	58	44	39
Gastrointestinal disorders				
Diarrhea	40 (Very common)	3	17	1
Infections & infestations				
Upper respiratory tract infection	22 (Very common)	2	15	1
Metabolism and nutrition disorders				
Tumor lysis syndrome	3 (Common)	3	1	1

Based on the existing safety profile of VENCLEXTA, other adverse drug reactions (all grades) reported in the VENCLEXTA + rituximab arm of MURANO include:

Blood & lymphatic system disorders: anemia (16%), febrile neutropenia (4%), lymphopenia (0%; considered an adverse reaction based on the mechanism of action)

Gastrointestinal disorders: nausea (21%), constipation (14%), vomiting (8%)

General disorders and administration site conditions: fatigue (18%)

Infections & infestations: pneumonia (9%), urinary tract infections (6%), sepsis (1%)

Investigations: blood creatinine increase (3%)

Metabolism and nutrition disorders: hyperkalemia (6%), hyperphosphatemia (5%), hyperuricemia (4%), hypocalcemia (2%)

During treatment with single agent VENCLEXTA after completion of VENCLEXTA + rituximab combination treatment, the most common all-grade adverse reactions (≥10% patients) reported were diarrhea (19%), neutropenia (14%), and upper respiratory tract infection (12%); the most common grade 3 or 4 adverse reaction (≥2% patients) was neutropenia (11%).

Monotherapy Studies (M13-982, M14-032, and M12-175)

The safety of VENCLEXTA is based on pooled data of 352 patients treated with VENCLEXTA in two phase 2 trials (M13-982 and M14-032) and one phase 1 trial (M12-175). The trials enrolled patients with previously treated CLL, including 212 patients with 17p deletion and 148 patients who had failed an inhibitor of the B-cell receptor pathway. Patients were treated with VENCLEXTA 400 mg monotherapy once daily following a dose ramp-up schedule.

The most frequently reported serious adverse reactions (≥2%) unrelated to disease progression were pneumonia and febrile neutropenia.

Discontinuations due to adverse events not related to disease progression occurred in 9% of patients.

Dosage reductions due to adverse events occurred in 13% of patients. Dose interruptions due to adverse events occurred in 36% of patients. Of the most frequent adverse events (≥4%) leading to dose reductions or interruptions, the one identified as adverse reaction was neutropenia (5% and 4%, respectively).

Adverse reactions identified in 3 trials of patients with previously treated CLL using VENCLEXTA monotherapy are presented in Table 10.

Table 10. Adverse Reactions Identified in Patients with CLL Treated with VENCLEXTA Monotherapy

Adverse Reaction by Body System	**All Grades Frequency N=352**	**All Grades % N=352**	**Grade 3 or 4 % N=352**
Blood and lymphatic system disorders			
Neutropenia[a]	Very common	50	45
Anemia[b]	Very common	33	18
Lymphopenia[c]	Very common	11	7
Febrile neutropenia	Common	6	6
Gastrointestinal disorders			
Diarrhea	Very common	43	3
Nausea	Very common	42	1
Vomiting	Very common	16	1
Constipation	Very common	16	<1
General disorders and administration site conditions			
Fatigue	Very common	30	3
Infections and infestations			
Upper respiratory tract infection	Very common	26	1
Pneumonia	Very common	12	7
Urinary tract infection	Common	9	1
Sepsis[d]	Common	5	3

Investigations			
Blood creatinine increased	Common	8	<1
Metabolism and nutrition disorders[e]			
	N=168	**N=168 All Grades**	**N=168 Grade ≥3**
Tumor lysis syndrome[f]	Common	2	2
Hyperkalemia[g]	Very common	17	1
Hyperphosphatemia[h]	Very common	14	2
Hyperuricemia[i]	Common	10	<1
Hypocalcemia[j]	Very common	16	2

[a]Includes neutropenia and neutrophil count decreased.
[b]Includes anemia and hemoglobin decreased.
[c]Includes lymphopenia and lymphocyte count decreased.
[d]Includes escherichia sepsis, sepsis, septic shock, urosepsis, corynebacterium bacteraemia, corynebacterium sepsis, klebsiella bacteraemia, klebsiella sepsis, pulmonary sepsis, staphylococcal bacteraemia, and staphylococcal sepsis.
[e]Adverse reactions for this body system are reported for patients who followed the 5-week ramp-up dosing schedule and TLS prophylaxis and monitoring measures described in Dosage and Administration section.
[f]Reported as TLS events.
[g]Includes hyperkalemia and blood potassium increased.
[h]Includes hyperphosphatemia and blood phosphorus increased
[i]Includes hyperuricemia and blood uric acid increased.
[j]Includes hypocalcemia and blood calcium decreased.

Clinical Trial Experience in AML

VIALE-A

The safety of VENCLEXTA in combination with azacitidine (N=283) versus placebo with azacitidine (N=144) was evaluated in a double-blind randomized study in patients with newly diagnosed AML. Details of the study treatment are described in **CLINICAL STUDIES** [see **CLINICAL STUDIES**].

The median duration of treatment was 7.6 months (range: <0.1 to 30.7 months) in the VENCLEXTA in combination with azacitidine arm and 4.3 months (range: 0.1 to 24.0 months) in the placebo with azacitidine arm.

The median number of cycles of azacitidine was 7 (range: 1 to 30) in the VENCLEXTA in combination with azacitidine arm and 4.5 (range: 1 to 26) in the placebo with azacitidine arm.

In the VENCLEXTA in combination with azacitidine arm, serious adverse reactions were reported in 83% of patients, with most frequent (≥5%) being febrile neutropenia (30%),

pneumonia (23%), and sepsis (16%). In the placebo with azacitidine arm, serious adverse reactions were reported in 73% of patients.

In the VENCLEXTA in combination with azacitidine arm, adverse reactions led to VENCLEXTA treatment discontinuations in 24% of patients, VENCLEXTA dose reductions in 2%, and VENCLEXTA dose interruptions in 72%.

In the placebo with azacitidine arm, adverse reactions led to placebo treatment discontinuations in 20% of patients, placebo dose reductions in 4%, and placebo dose interruptions in 57%.

In the VENCLEXTA in combination with azacitidine arm, no event led to venetoclax discontinuation in ≥5% of patients.

The most frequent adverse reactions (≥5%) leading to VENCLEXTA dose interruptions in the VENCLEXTA in combination with azacitidine arm were febrile neutropenia (20%), neutropenia (20%), pneumonia (14%), thrombocytopenia (10%), and sepsis (8%). In the placebo with azacitidine arm, the most frequent adverse reaction (≥5%) leading to placebo dose interruption were pneumonia (14%), neutropenia (10%), and sepsis (6%). Among patients who achieved bone marrow clearance of leukemia, 53% underwent VENCLEXTA dose interruptions for ANC <500/microliter.

The 30-day and 60-day mortality rates observed with VENCLEXTA in combination with azacitidine were 7% (21/283) and 15% (43/283), respectively.

Table 11 provides the adverse reactions reported in VIALE-A.

Adverse reactions are listed by MedDRA body system organ class, rate, and frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing rate.

Table 11. Common (≥10%) Adverse Reactions Reported with ≥5% Higher (All-Grade) or ≥2% Higher (Grade ≥3) Incidence in Patients Treated with VENCLEXTA + Azacitidine Compared with Placebo + Azacitidine

Adverse Reaction by Body System	All Grades Frequency	VENCLEXTA + Azacitidine (N=283)		Placebo + Azacitidine (N=144)	
		All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Blood and lymphatic system disorders					
Thrombocytopenia[a]	Very common	51	48	41	38
Neutropenia[b]	Very common	45	45	30	28
Febrile neutropenia	Very common	42	42	19	19

Anemia[c]	Very common	28	26	21	20
Gastrointestinal disorders					
Nausea	Very common	44	2	35	<1
Diarrhea	Very common	41	5	33	3
Vomiting	Very common	30	2	23	<1
Stomatitis	Very common	12	<1	6	0
General disorders and administration site conditions					
Fatigue	Very common	21	3	17	1
Asthenia	Very common	16	4	8	<1
Infections and infestations					
Sepsis[d]	Very common	18	18	14	14
Metabolism and nutrition disorders					
Decreased appetite	Very common	25	4	17	<1
Musculoskeletal and connective tissue disorders					
Arthralgia	Very common	12	<1	5	0
Nervous system disorder					
Dizziness/syncope[e]	Very common	19	4	8	1
Respiratory, thoracic, and mediastinal disorders					
Dyspnea	Very common	13	3	8	2
Vascular disorder					
Hemorrhage[f]	Very common	38	10	37	6
Hypotension	Very common	10	5	6	3

[a]Includes thrombocytopenia and platelet count decreased.
[b]Includes neutropenia and neutrophil count decreased.
[c]Includes anemia and hemoglobin decreased.
[d]Includes sepsis, escherichia sepsis, septic shock, bacteraemia, staphylococcal sepsis, klebsiella sepsis, pseudomonal sepsis, urosepsis, bacterial sepsis, candida sepsis, clostridial sepsis, enterococcal sepsis, fungal sepsis, neutropenic sepsis, and streptococcal sepsis.
[e]Includes vertigo, dizziness, syncope, and presyncope.
[f]Includes multiple terms; epistaxis, petechiae, and haematoma occurred in ≥5% of patients.

Other adverse reactions (all grades) reported in the VENCLEXTA + azacitidine arm are presented below:

Gastrointestinal disorders: abdominal pain (11%)

Hepatobiliary disorders: cholecystitis/cholelithiasis[a] (4%)

Infections and infestations: pneumonia[b] (34%), urinary tract infection (9%)

Investigations: blood bilirubin increased (7%), weight decreased (13%)

Metabolism and nutrition disorders: hypokalemia (29%), tumor lysis syndrome (1%)

Nervous system disorders: headache (11%).

[a]Includes following terms: cholecystitis acute, cholelithiasis, cholecystitis, and cholecystitis chronic.

[b]Includes following terms: pneumonia, lung infection, bronchopulmonary aspergillosis, pneumonia fungal, pneumonia klebsiella, atypical pneumonia, pneumonia viral, infectious pleural effusion, pneumonia haemophilus, pneumonia pneumococcal, pneumonia respiratory syncytial viral, pulmonary mycosis, pulmonary nocardiosis, and tuberculosis.

M14-358

The safety of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) was evaluated in a non-randomized study in patients with newly diagnosed AML.

VENCLEXTA in Combination with Azacitidine

The most common adverse reactions (≥30%) of any grade were nausea (64%), diarrhea (61%), thrombocytopenia/platelet count decreased (54%), neutropenia/neutrophil count decreased (46%), hypokalemia (35%), febrile neutropenia (39%), vomiting (38%), fatigue (36%), and pneumonia[a] (38%).

Serious adverse events were reported in 77% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia and pneumonia.

Discontinuations of VENCLEXTA due to adverse events occurred in 25% of patients. The most frequent adverse reactions leading to drug discontinuation (≥2%) were febrile neutropenia and pneumonia.

Dosage interruptions of VENCLEXTA due to adverse events occurred in 68% of patients. The most frequent adverse reactions leading to dose interruption (≥5%) were febrile neutropenia, neutropenia/neutrophil count decreased, and pneumonia.

Dosage reductions of VENCLEXTA due to adverse reactions occurred in 1% of patients. Dose reduction occurred in 1 patient, due to neutrophil count decreased.

The 30-day and 60-day mortality rates observed with VENCLEXTA in combination with azacitidine were 2.4% (2/84) and 8.3% (7/84), respectively.

[a]Includes the following terms: pneumonia, lung consolidation, and pneumonia fungal.

VENCLEXTA in Combination with Decitabine

The most common adverse reactions (≥30%) of any grade were thrombocytopenia/platelet count decreased (71%), febrile neutropenia (65%), nausea (65%), fatigue (45%), pneumonia[a] (45%),

diarrhea (45%), hypokalemia (35%), hypotension (35%), decreased appetite (32%), dizziness (39% for single term), vomiting (39%), neutropenia/neutrophil count decreased (35%), and headache (32%).

Serious adverse events were reported in 81% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia, pneumonia, bacteremia, and sepsis.

Discontinuations of VENCLEXTA due to adverse events occurred in 26% of patients. The most frequent adverse reaction leading to drug discontinuation (≥5%) was pneumonia.

Dosage interruptions of VENCLEXTA due to adverse events occurred in 65% of patients. The most frequent adverse reactions leading to dose interruption (≥5%) were febrile neutropenia, neutropenia/neutrophil count decreased, pneumonia, and platelet count decreased.

Dosage reductions of VENCLEXTA due to adverse events occurred in 6% of patients. No events were reported for more than one patient.

The 30-day and 60-day mortality rates observed with VENCLEXTA in combination with decitabine were 6% (2/31) and 10% (3/31), respectively.

[a]Includes following terms: pneumonia, pneumonia fungal, and lung infection.

VIALE-C

The safety of VENCLEXTA (600-mg daily dose) in combination with low-dose cytarabine (N=142) versus placebo with low-dose cytarabine (N=68) was evaluated in a double-blind randomized study **(**based on 6-month follow-up data cutoff of 15 August 2019) in patients with newly diagnosed AML [see **CLINICAL STUDIES].**

The median duration of treatment was 4.1 months (range: <0.1 to 23.5 months) in the VENCLEXTA in combination with low-dose cytarabine arm and 1.7 months (range: 0.1 to 20.2 months) in the placebo with low-dose cytarabine arm.

The median number of cycles of low-dose cytarabine was 4 (range: 1 to 22) in the VENCLEXTA in combination with low-dose cytarabine arm and 2 (range: 1 to 22) (28 days per cycle) in the placebo with low-dose cytarabine arm.

Serious adverse reactions were reported in 67% of patients in VENCLEXTA in combination with low-dose cytarabine arm, with the most frequent (≥10%) being pneumonia (20%), febrile neutropenia (17%), and sepsis (13%). In the placebo with low-dose cytarabine arm, serious adverse reactions were reported in 62% of patients. The most frequent were febrile neutropenia (18%), sepsis (18%), and pneumonia (16%).

In the VENCLEXTA in combination with low-dose cytarabine arm, adverse reactions led to treatment discontinuations in 26% of patients, venetoclax dose reductions in 10%, and venetoclax dose interruptions in 63%.

In the placebo with low-dose cytarabine arm, adverse reactions led to placebo treatment discontinuations in 24% of patients, placebo dose reductions in 7%, and placebo dose interruptions in 51%.

The most frequent adverse reaction leading to venetoclax discontinuation in the VENCLEXTA in combination with low-dose cytarabine arm was pneumonia (7%); sepsis (4%) was the most frequent adverse reaction leading to discontinuation in the placebo with low-dose cytarabine arm.

The most frequent adverse reactions (≥2%) leading to dose reductions in the VENCLEXTA in combination with low-dose cytarabine arm was thrombocytopenia (2%). The most frequent adverse reactions (≥5%) leading to dose interruption in the VENCLEXTA in combination with low-dose cytarabine arm were neutropenia (23%), thrombocytopenia (15%), pneumonia (8%), febrile neutropenia (8%), and anemia (6%), and in the placebo with low-dose cytarabine arm were pneumonia (12%), thrombocytopenia (9%), febrile neutropenia (7%), neutropenia (6%), and sepsis (6%). Among patients who achieved bone marrow clearance of leukemia, 37% underwent VENCLEXTA dose interruptions for ANC <500/microliter.

The 30-day and 60-day mortality rates observed with VENCLEXTA in combination with low-dose cytarabine were 13% (18/142) and 20% (29/142), respectively.

Table 12 presents adverse reactions identified in the VIALE-C trial data based on 6-month follow-up with cutoff date of 15 August 2019.

Table 12. Common (≥10%) Adverse Reactions Reported with ≥5% Higher (All-Grade) or ≥2% Higher (Grade ≥3) Incidence in Patients Treated with VENCLEXTA + Low-Dose Cytarabine Compared with Placebo + Low-Dose Cytarabine

Adverse Reaction by Body System	All Grades Frequency	VENCLEXTA + Low-Dose Cytarabine (N=142)		Placebo + Low-Dose Cytarabine (N=68)	
		All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Blood & lymphatic system disorders					
Thrombocytopenia[a]	Very common	50	50	46	44
Neutropenia[b]	Very common	53	53	22	21
Febrile neutropenia	Very common	32	32	29	29
Anemia	Very common	29	27	22	22
Gastrointestinal disorders					
Nausea	Very common	43	1	31	0
Diarrhea	Very common	33	3	18	0
Vomiting	Very common	29	<1	15	0
Abdominal pain	Very common	12	0	4	1

Infections and infestations					
Pneumonia[c]	Very common	30	25	22	22
Investigations					
Blood bilirubin increased	Very common	11	2	1	0
Metabolism and nutrition disorders					
Hypokalemia	Very common	31	12	25	16
Nervous System Disorders					
Headache	Very common	14	0	4	0
Dizziness/syncope[d]	Very common	14	2	6	0
Vascular Disorders					
Hemorrhage[e]	Very common	42	11	31	7

[a]Includes thrombocytopenia and platelet count decreased.
[b]Includes neutropenia and neutrophil count decreased.
[c]Includes pneumonia, lung infection, pneumonia fungal, pulmonary mycosis, bronchopulmonary aspergillosis, pneumocystis jirovecii pneumonia, pneumonia cytomegaloviral, pneumonia pseudomonal.
[d]Includes vertigo, dizziness, syncope, and presyncope.
[e]Includes multiple terms; no events occurred in ≥5% of patients.

Other adverse drug reactions reported in the VENCLEXTA + low-dose cytarabine arm are presented below:

Gastrointestinal disorder: stomatitis (10%)

General disorders and administration site conditions: fatigue (16%), asthenia (12%)

Hepatobiliary disorders: cholecystitis/cholelithiasis[a] (2%)

Infections and infestations: sepsis[b] (15%), urinary tract infection (7%)

Investigations: weight decreased (10%)

Metabolism and nutrition disorders: decreased appetite (22%), tumor lysis syndrome (6%)

Musculoskeletal and connective tissue disorders: arthralgia (8%)

Respiratory, thoracic, and mediastinal disorders: dyspnea (8%)

Vascular disorders: hypotension (10%).

[a]Includes following terms: cholecystitis acute, cholecystitis, and cholecystitis chronic.

[b]Includes following terms: sepsis, septic shock, bacteraemia, neutropenic sepsis, bacterial sepsis, and staphylococcal sepsis.

M14-387

VENCLEXTA in Combination with Low-Dose Cytarabine

The most common adverse reactions (≥30%) of any grade were nausea (70%), thrombocytopenia/platelet count decreased (61%), diarrhea (50%), hypokalemia (49%), neutropenia/neutrophil count decreased (46%), febrile neutropenia (44%), fatigue (43%), decreased appetite (37%), anemia/hemoglobin decreased (32%), and vomiting (30%).

Serious adverse events were reported in 91% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia, pneumonia, and sepsis.

Discontinuations of VENCLEXTA due to adverse events occurred in 33% of patients. The most frequent adverse reactions leading to VENCLEXTA discontinuation (≥2%) were thrombocytopenia, sepsis, and haemorrhage intracranial.

Dosage reductions of VENCLEXTA due to adverse events occurred in 7% of patients. The most frequent adverse reaction leading to dose reduction (≥2%) was thrombocytopenia.

Dosage interruptions of VENCLEXTA due to adverse events occurred in 59% of patients. The most frequent adverse reactions leading to VENCLEXTA interruption (≥5%) were thrombocytopenia and neutropenia.

Important Adverse Reactions

Tumor Lysis Syndrome

Tumor lysis syndrome is an important identified risk when initiating VENCLEXTA.

Chronic Lymphocytic Leukemia

Monotherapy Studies (M13-982 and M14-032)

In the initial phase 1 dose-finding trials, which had shorter (2 to 3 week) ramp-up phase and higher starting dose, the incidence of TLS was 13% (10/77; 5 laboratory TLS, 5 clinical TLS), including 2 fatal events and 3 events of acute renal failure, 1 requiring dialysis.

The risk of TLS was reduced after revision of the dosing regimen and modification to prophylaxis and monitoring measures [see **DOSAGE AND ADMINISTRATION**]. In venetoclax clinical trials, patients with any measurable lymph node ≥10 cm or those with both an ALC ≥25 x 10^9/L and any measurable lymph node ≥5 cm were hospitalized to enable more intensive hydration and monitoring for the first day of dosing at 20 mg and 50 mg during the ramp-up phase.

In 168 patients with CLL starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg in studies M13-982 and M14-032, the rate of TLS was 2%. All events were laboratory TLS (laboratory abnormalities that met ≥2 of the following criteria within 24 hours of each other: potassium >6 mmol/L, uric acid >476 µmol/L, calcium <1.75 mmol/L, or phosphorus >1.5 mmol/L); or were reported as TLS events and occurred in patients who had a lymph node(s) ≥5 cm and/or ALC ≥25 x 10^9/L. All events resolved within 5 days. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias or sudden death and/or seizures was observed in these patients. All patients had CrCl ≥50 mL/min.

MURANO

In the open-label, randomized phase 3 study (MURANO), the incidence of TLS was 3% (6/194) in patients treated with venetoclax + rituximab. After 77/389 patients were enrolled in the study, the protocol was amended to include the TLS prophylaxis and monitoring measures described in Dosage and Administration section [see **DOSAGE AND ADMINISTRATION**]. All events of TLS occurred during the VENCLEXTA ramp-up phase and resolved within two days. All 6 patients completed the ramp-up and reached the recommended daily dose of 400 mg of VENCLEXTA. No clinical TLS was observed in patients who followed the current 5-week ramp-up dosing schedule and TLS prophylaxis and monitoring measures described in Dosage and Administration section [see **DOSAGE AND ADMINISTRATION**]. The rates of grade ≥3 laboratory abnormalities relevant to TLS were hyperkalemia 1%, hyperphosphatemia 1%, and hyperuricemia 1%.

CLL14

In the open-label, randomized phase 3 study (CLL14), the incidence of TLS was 1% (3/212) in patients treated with venetoclax + obinutuzumab [see **WARNINGS AND PRECAUTIONS**]. All three events of TLS resolved and did not lead to withdrawal from the study. Obinutuzumab administration was delayed in two cases in response to the TLS events.

Acute Myeloid Leukemia

VIALE-A and VIALE-C

In the randomized, phase 3 study (VIALE-A) with venetoclax in combination with azacitidine, the incidence of TLS was 1.1% (3/283, 1 clinical TLS) and in phase 3 study (VIALE-C) the incidence of TLS was 5.6% (8/142, 4 clinical TLS, 2 of which were fatal). The studies required reduction of white blood cell count to <25 x 10^9/L prior to venetoclax initiation and a dose ramp-up schedule in addition to standard prophylaxis and monitoring measures [see **DOSAGE AND ADMINISTRATION**]. All cases of TLS occurred during dose ramp-up.

VENCLEXTA in Combination with Decitabine (M14-358)

There were no reported events of laboratory or clinical TLS reported with VENCLEXTA in combination with decitabine.

<u>Neutropenia</u>

Neutropenia is an identified risk with VENCLEXTA treatment.

Chronic Lymphocytic Leukemia

MURANO

In the MURANO study, neutropenia (all grades) was reported in 61% of patients in the venetoclax + rituximab arm. Forty-three percent of patients treated with venetoclax + rituximab experienced dose interruption, and 3% of patients discontinued venetoclax due to neutropenia. Grade 3 neutropenia was reported in 32% of patients and grade 4 neutropenia in 26% of patients. The median duration of grade 3 or 4 neutropenia was 8 days (range: 1-712 days). Clinical complications of neutropenia, including febrile neutropenia, grade ≥3 and serious infections occurred at a lower rate in patients treated with venetoclax + rituximab arm compared with the rates reported in patients treated with bendamustine + rituximab: febrile neutropenia 4% versus 10%, grade ≥3 infections 18% versus 23%, and serious infections 21% versus 24%.

CLL14

In the CLL14 study, neutropenia (all grades) was reported in 58% of patients in the venetoclax + obinutuzumab arm. Forty-one percent experienced dose interruption, 13% had dose reduction and 2% discontinued venetoclax due to neutropenia. Grade 3 neutropenia was reported in 25% of patients and grade 4 neutropenia in 28% of patients. The median duration of grade 3 or 4 neutropenia was 22 days (range: 2 to 363 days). The following complications of neutropenia were reported in the venetoclax + obinutuzumab arm versus the obinutuzumab + chlorambucil arm, respectively: febrile neutropenia 6% versus 4%, grade ≥3 infections 19% versus 16%, and serious infections 19% versus 14%.

Acute Myeloid Leukemia

VIALE-A
In the VIALE-A study, grade ≥3 neutropenia was reported in 45% of patients. The following were reported in the VENCLEXTA + azacitidine arm versus the placebo + azacitidine arm, respectively: febrile neutropenia 42% versus 19%, grade ≥3 infections 64% versus 51%, and serious infections 57% versus 44%.

M14-358
In the M14-358 study, neutropenia was reported in 35% (all grades) and 35% (grade 3 or 4) of patients treated with VENCLEXTA + decitabine.

VIALE-C
In the VIALE-C study, grade ≥3 neutropenia was reported in 53% of patients. The following were reported in the VENCLEXTA + low-dose cytarabine arm versus the placebo + low-dose cytarabine arm, respectively: febrile neutropenia 32% versus 29%, grade ≥3 infections 43% versus 50%, and serious infections 37% versus 37%.

DRUG INTERACTIONS

Effect of Other Drugs on VENCLEXTA

Venetoclax is predominantly metabolized by CYP3A4.

CYP3A Inhibitors

Co-administration of ketoconazole increased venetoclax C_{max} by 130% and AUC_{∞} by 540%.

Co-administration of ritonavir increased venetoclax C_{max} by 140% and AUC by 690%.

Compared with venetoclax 400 mg administered alone, co-administration of posaconazole with venetoclax 50 mg and 100 mg resulted in 61% and 86% higher venetoclax C_{max}, respectively. The venetoclax AUC_{24} was 90% and 144% higher, respectively [see **PHARMACOLOGIC PROPERTIES**].

For patients requiring concomitant use of VENCLEXTA with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, dronedarone, fluconazole, verapamil) administer VENCLEXTA dose according to Table 7.

Monitor patients more closely for signs of VENCLEXTA toxicities [see **DOSAGE AND ADMINISTRATION**].

Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor [see **DOSAGE AND ADMINISTRATION**].

Avoid grapefruit products, Seville oranges, and starfruit during treatment with VENCLEXTA, as they contain inhibitors of CYP3A.

OATP1B1/1B3 and P-gp Inhibitors

Co-administration of a single dose of rifampin, an OATP1B1/1B3 and P-gp inhibitor, increased venetoclax C_{max} by 106% and AUC_{∞} by 78% [see **PHARMACOLOGIC PROPERTIES**]. Avoid concomitant use of venetoclax with P-gp inhibitors (e.g., amiodarone, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor) at initiation and during the ramp-up phase; if a P-gp inhibitor must be used, monitor closely for signs of toxicities.

CYP3A Inducers

Co-administration of once-daily rifampin, a strong CYP3A inducer, decreased venetoclax C_{max} by 42% and AUC_{∞} by 71%. Avoid concomitant use of VENCLEXTA with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort) or moderate CYP3A

inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin). Consider alternative treatments with less CYP3A induction [see **PHARMACOLOGIC PROPERTIES**].

Azithromycin

Co-administration of venetoclax with azithromycin decreased venetoclax C_{max} by 25% and AUC_{∞} by 35%. No dose adjustment is needed when venetoclax is co-administered with azithromycin [see **PHARMACOLOGIC PROPERTIES]**.

Effects of VENCLEXTA on Other Drugs

Warfarin

In a drug-drug interaction study in healthy volunteers, administration of a single dose of venetoclax with warfarin resulted in an 18% to 28% increase in C_{max} and AUC_{∞} of R-warfarin and S-warfarin. Because venetoclax was not dosed to steady state, it is recommended that the international normalized ratio (INR) be monitored closely in patients receiving warfarin [see **PHARMACOLOGIC PROPERTIES]**.

P-gp substrates

Administration of a single 100-mg dose of venetoclax with digoxin resulted in a 35% increase in digoxin C_{max} and a 9% increase in digoxin AUC_{∞}. Therefore, co-administration of narrow therapeutic index P-gp substrates (e.g., digoxin, everolimus, and sirolimus) with VENCLEXTA should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before VENCLEXTA [see **PHARMACOLOGIC PROPERTIES]**.

USE IN SPECIFIC POPULATIONS

Reproduction, Pregnancy, and Lactation

Studies in animals have shown embryo-fetal toxicity.

Animal Data

In embryo-fetal development studies, VENCLEXTA was administered to pregnant mice and rabbits to evaluate potential effects after implantation and subsequent embryo-fetal development during the respective periods of organogenesis. In mice, VENCLEXTA was associated with increased post-implantation loss and decreased fetal body weight at 150 mg/kg/day (maternal exposures approximately 1.2 times the human AUC exposure at a 400-mg dose). In rabbits, VENCLEXTA at 300 mg/kg/day produced maternal toxicity, but no fetal toxicity (maternal exposures approximately 0.2 times the human AUC exposure at a 400-mg dose). No teratogenicity was observed in either the mouse or the rabbit. Additionally, M27 administered at the maximum feasible dose of 250 mg/kg/day in a mouse embryo-fetal development study did not produce embryo-fetal toxicity or teratogenesis. The M27 dose of 250 mg/kg/day resulted in

maternal exposures that were approximately 9 times the human M27 AUC exposure at a dose of 400 mg/day of venetoclax.

Reproduction

Pregnancy test

Females of reproductive potential should undergo pregnancy testing before initiation of VENCLEXTA.

Contraception

Females of reproductive potential should use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last VENCLEXTA dose.

Fertility

Based on findings in animals, male fertility may be compromised by treatment with VENCLEXTA [see **PRE-CLINICAL SAFETY DATA**].

Pregnancy

VENCLEXTA should not be used during pregnancy.

There are no adequate and well-controlled data from the use of VENCLEXTA in pregnant women. Studies in animals have shown embryo-fetal toxicity.

Lactation

It is not known whether venetoclax or its metabolites are excreted in human milk. Available data in animals have shown excretion of venetoclax/metabolites in milk [see **PRE-CLINICAL SAFETY DATA**].

A risk to the newborns/infants cannot be excluded.

Breastfeeding should be discontinued during treatment with VENCLEXTA.

Pediatric Use

The safety and efficacy of VENCLEXTA in children and adolescents younger than 18 years have not been established.

Geriatric Use

No specific dose adjustment is required for elderly patients (aged ≥65 years). No clinically meaningful differences in safety or efficacy were observed between patients <65 years of age and those ≥65 years of age in combination and monotherapy studies.

The efficacy for combination of VENCLEXTA in combination with Azacitadine therapy for treatment of newly-diagnosed acute myeloid leukemia (AML) in adults was observed mainly in subjects aged 75 years or older.

Renal Impairment

No specific clinical trials have been conducted in subjects with renal impairment. No dose adjustment is needed for patients with mild or moderate renal impairment (CrCl ≥30 mL/min) [see **PHARMACOLOGIC PROPERTIES**]. While severe renal impairment (CrCl ≥15 mL/min and <30 mL/min) did not affect venetoclax pharmacokinetics in 6 patients with AML, clinical experience is limited, and a recommended dose has not been determined for patients with severe renal impairment (CrCl <30 mL/min) or patients on dialysis.

Patients with reduced renal function (CrCl <80 mL/min) may require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with VENCLEXTA [see **DOSAGE AND ADMINISTRATION**].

Hepatic Impairment

No dose adjustment is recommended in patients with mild or moderate hepatic impairment [see **PHARMACOLOGIC PROPERTIES**].

A 50% dose reduction throughout treatment is recommended for patients with severe hepatic impairment; monitor these patients more closely for signs of toxicity [see **PHARMACOLOGIC PROPERTIES**].

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of VENCLEXTA on the ability to drive and use machines have been performed. VENCLEXTA has no or negligible influence on the ability to drive and use machines.

DRUG ABUSE AND DEPENDENCE

No data are available regarding VENCLEXTA and drug abuse/drug dependency.

OVERDOSAGE

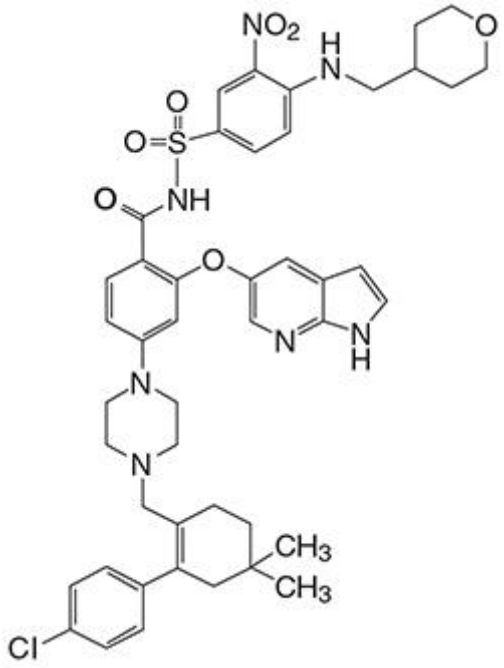
Daily doses of up to 1200 mg of VENCLEXTA have been evaluated in clinical trials. There has been no experience with overdose in clinical trials. If an overdose is suspected, treatment should consist of general supportive measures.

PRODUCT DESCRIPTION

VENCLEXTA tablets for oral administration are supplied as pale yellow or beige tablets that contain 10, 50, or 100 mg venetoclax as the active ingredient. Each tablet also contains the following inactive ingredients: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic. In addition, the 10 mg and 100 mg coated tablets include the following: iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide. The 50 mg coated tablets include the following: iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide. Each tablet is debossed with "V" on one side and "10", "50", or "100" corresponding to the tablet strength on the other side.

Venetoclax is a light-yellow-to-dark-yellow solid with the empirical formula $C_{45}H_{50}ClN_7O_7S$ and a molecular weight of 868.44. Venetoclax has very low aqueous solubility.

Venetoclax is described chemically as 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide) and has the following chemical structure:



PHARMACOLOGIC PROPERTIES

Mechanism of Action

Venetoclax is a potent, selective, and orally bioavailable small-molecule inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in various hematologic and solid tumor malignancies and has been implicated as a resistance factor for certain therapeutic agents. Venetoclax binds directly to the BH3-binding groove of

BCL-2, displacing BH3 motif-containing pro-apoptotic proteins like BIM, to initiate mitochondrial outer membrane permeabilization (MOMP), caspase activation, and programmed cell death. In nonclinical studies, venetoclax has demonstrated cytotoxic activity in a variety of B-cell and other hematologic malignancies.

Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of VENCLEXTA up to 1200 mg once daily on the QTc interval was evaluated in an open-label, single-arm study in 176 patients with previously treated CLL or Non-Hodgkin lymphoma (NHL). VENCLEXTA had no effect on QTc interval, and there was no relationship between venetoclax exposure and change in QTc interval.

Pharmacokinetics

Absorption

Following multiple oral administrations, maximum plasma concentration of venetoclax was reached 5-8 hours after dose. Venetoclax steady state AUC increased proportionally over the dose range of 150-800 mg. Under low-fat meal conditions, venetoclax mean (± standard deviation) steady state C_{max} was 2.1 ± 1.1 μg/mL and AUC_{24} was 32.8 ± 16.9 μg•h/mL at the 400 mg once-daily dose.

Under low-fat meal conditions, two 50 mg venetoclax tablets are bioequivalent to one 100 mg venetoclax tablet, ten 10 mg venetoclax tablets are bioequivalent to two 50 mg venetoclax tablets, and ten 10 mg venetoclax tablets are bioequivalent to one 100 mg venetoclax tablet. The three strengths are interchangeable at equivalent doses.

Food Effect

Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold, and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared with fasting conditions. Venetoclax should be administered with a meal [see **DOSAGE AND ADMINISTRATION]**.

Distribution

Venetoclax is highly bound to human plasma protein with unbound fraction in plasma <0.01 across a concentration range of 1-30 μM (0.87-26 μg/mL). The mean blood-to-plasma ratio was 0.57. The population estimate for apparent volume of distribution (Vd_{ss}/F) of venetoclax ranged from 256-321 L in patients.

Metabolism

In vitro studies demonstrated that venetoclax is predominantly metabolized by CYP3A4. M27 was identified as a major metabolite in plasma, with an inhibitory activity against BCL-2 that is at least 58-fold lower than venetoclax *in vitro*.

Elimination

The population estimate for the terminal phase elimination half-life of venetoclax was approximately 26 hours. After a single oral administration of 200 mg radiolabeled [^{14}C]-venetoclax to healthy subjects, >99.9% of the dose was recovered in feces, and <0.1% of the dose was excreted in urine within 9 days. Unchanged venetoclax accounted for 20.8% of the administered radioactive dose excreted in feces. The pharmacokinetics of venetoclax does not change over time.

Specific Populations

Age, Race, Sex, and Weight

Based on population pharmacokinetic analyses, age, race, sex, and weight do not have an effect on venetoclax clearance.

Pediatric Use

Pharmacokinetics of venetoclax has not been evaluated in patients <18 years of age [see **USE IN SPECIFIC POPULATIONS**].

Renal Impairment

Based on a population pharmacokinetic analysis that included 321 subjects with mild renal impairment (CrCl ≥60 and <90 mL/min), 219 subjects with moderate renal impairment (CrCl ≥30 and <60 mL/min), 6 subjects with severe renal impairment (CrCl ≥15 and <30 mL/min) and 224 subjects with normal renal function (CrCl ≥90 mL/min), venetoclax exposures in subjects with mild, moderate, or severe renal impairment are similar to those with normal renal function. The pharmacokinetics of venetoclax has not been studied in subjects with CrCl <15 mL/min or subjects on dialysis [see **USE IN SPECIFIC POPULATIONS**].

Hepatic Impairment

Based on a population pharmacokinetic analysis that included 69 subjects with mild hepatic impairment, 7 subjects with moderate hepatic impairment, and 429 subjects with normal hepatic function, venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic function. Mild hepatic impairment was defined as normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin >1.0 to 1.5 times ULN, moderate hepatic impairment as total bilirubin >1.5 to 3.0 times ULN, and severe hepatic impairment as total bilirubin >3.0 ULN.

In a dedicated hepatic impairment study, venetoclax C_{max} and AUC in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment were similar to subjects with normal hepatic function. In subjects with severe (Child-Pugh C) hepatic impairment, the mean venetoclax C_{max} was similar to subjects with normal hepatic function, but venetoclax AUC was 2.3- to 2.7-fold higher than subjects with normal hepatic function [see **USE IN SPECIFIC POPULATIONS**].

Drug Interactions

CYP3A Inhibitors

Co-administration of 400 mg once-daily ketoconazole, a strong CYP3A, P-gp, and BCRP inhibitor, for 7 days in 11 previously treated patients with NHL increased venetoclax C_{max} by 130% and AUC_{∞} by 540%.

Co-administration of 50 mg once-daily ritonavir, a strong CYP3A, P-gp, and OATP1B1/B3 inhibitor, for 14 days in 6 healthy subjects increased venetoclax C_{max} by 140% and AUC by 690%.

Compared with venetoclax 400 mg administered alone, co-administration of 300 mg posaconazole, a strong CYP3A and P-gp inhibitor, with venetoclax 50 mg and 100 mg for 7 days in 12 newly diagnosed patients with AML resulted in 61% and 86% higher venetoclax C_{max}, respectively. The venetoclax AUC_{24} was 90% and 144% higher, respectively.

CYP3A Inducers

Co-administration of 600 mg once-daily rifampin, a strong CYP3A inducer, for 13 days in 10 healthy subjects decreased venetoclax C_{max} by 42% and AUC_{∞} by 71%.

OATP1B1/1B3 and P-gp Inhibitors

Co-administration of a 600-mg single dose of rifampin, an OATP1B1/1B3 and P-gp inhibitor, in 11 healthy subjects increased venetoclax C_{max} by 106% and AUC_{∞} by 78%.

Azithromycin

Co-administration of 500 mg of azithromycin on the first day followed by 250 mg of azithromycin for 4 days in 12 healthy subjects decreased venetoclax C_{max} by 25% and AUC_{∞} by 35%.

Gastric Acid-Reducing Agents

Based on population pharmacokinetic analysis, gastric acid-reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) do not affect venetoclax bioavailability.

Warfarin

In a drug-drug interaction study in three healthy volunteers, administration of a single 400-mg dose of venetoclax with 5 mg warfarin resulted in 18% to 28% increase in C_{max} and AUC_{∞} of R-warfarin and S-warfarin.

Digoxin

In a drug-drug interaction study in 10 healthy subjects, administration of a single 100-mg dose of venetoclax with 0.5 mg digoxin, a P-gp substrate, resulted in a 35% increase in digoxin C_{max} and a 9% increase in digoxin AUC_{∞}.

In vitro Studies

In vitro studies indicated that venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at clinically relevant concentrations. Venetoclax is a weak inhibitor of UGT1A1 *in vitro*, but it is not predicted to cause clinically relevant inhibition of UGT1A1. Venetoclax is not an inhibitor of UGT1A4, UGT1A6, UGT1A9, and UGT2B7.

Venetoclax is a P-gp and BCRP substrate as well as a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor *in vitro*. Venetoclax is not expected to inhibit OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K at clinically relevant concentrations.

PRE-CLINICAL SAFETY DATA

Carcinogenesis

Venetoclax and the M27 major human metabolite were not carcinogenic in a 6-month transgenic (Tg.rasH2) mouse carcinogenicity study at oral doses up to 400 mg/kg/day of venetoclax, and at a single dose level of 250 mg/kg/day of M27. Exposure margins (AUC), relative to the clinical AUC at 400 mg/day, were approximately 2-fold for venetoclax and 5.8-fold for M27.

Mutagenesis

Venetoclax was not mutagenic in an *in vitro* bacterial mutagenicity (Ames) assay, did not induce numerical or structural aberrations in an *in vitro* chromosome aberration assay using human peripheral blood lymphocytes, and was not clastogenic in an *in vivo* mouse bone marrow micronucleus assay at doses up to 835 mg/kg. The M27 metabolite was negative for genotoxic activity in *in vitro* Ames and chromosome aberration assays.

Impairment of Fertility

Fertility and early embryonic development studies with venetoclax were conducted in male and female mice. These studies evaluated mating, fertilization, and embryonic development through implantation. There were no effects of venetoclax on estrous cycles, mating, fertility, corpora lutea, uterine implants, or live embryos per litter at dosages up to 600 mg/kg/day (in male and

female mice, approximately 2.8 and 3.2 times the human AUC exposure at 400-mg dose, respectively). However, a risk to human male fertility exists based on testicular toxicity (germ cell loss) observed in dogs at all dose levels examined (exposures of 0.5 to 18 times the human AUC exposure at 400mg dose). Reversibility of this finding has not been demonstrated.

Animal Pharmacology and/or Toxicology

In addition to testicular germ cell loss, other toxicities observed in animal studies with venetoclax included dose-dependent reductions in lymphocytes and red blood cell mass. Both effects were reversible after cessation of dosing with venetoclax, with recovery of lymphocytes occurring by 18 weeks post treatment. Both B- and T-cells were affected, but the most significant decreases occurred with B-cells. Decreases in lymphocytes were not associated with opportunistic infections. The M27 metabolite orally administered to mice had effects similar to those with venetoclax (decreased lymphocytes and red blood cell mass) but of lesser magnitude, consistent with its low *in vitro* pharmacologic potency.

Venetoclax also caused single-cell necrosis in various tissues, including the gallbladder and exocrine pancreas, with no evidence of disruption of tissue integrity or organ dysfunction; these findings were minimal to mild in magnitude. Following a 4-week dosing period and subsequent 4-week recovery period, minimal single-cell necrosis was still present in some tissues and reversibility has not been assessed following longer periods of dosing or recovery.

Furthermore, after approximately 3 months of daily dosing in dogs, venetoclax caused progressive white discoloration of the hair coat, due to loss of melanin pigment in the hair. No changes in the quality of the hair coat or skin were observed, nor in other pigmented tissues examined (e.g., the iris and the ocular fundus of the eye). Reversibility of the hair coat changes has not been assessed in dogs.

In pregnant rats, maternal systemic exposures (AUC) to venetoclax were approximately 14-times higher than the exposure in humans at a 400-mg dose. Measurable levels of radioactivity in fetal tissues (liver, GI tract) were >15-fold lower than maternal levels in the same tissues. Venetoclax-derived radioactivity was not detected in fetal blood, brain, eye, heart, kidney, lung, muscle, or spinal cord.

Venetoclax was administered (single dose; 150 mg/kg oral) to lactating rats 8-10 days parturition. Venetoclax in milk was 1.6 times lower than in plasma. Parent drug (venetoclax) represented the majority of the total drug-related material in milk, with trace levels of three metabolites.

In a juvenile toxicology study, mice were administered VENCLEXTA at 10, 30, or 100 mg/kg/day by oral gavage from 7 to 60 days of age. Clinical signs of toxicity included decreased activity, dehydration, skin pallor, and hunched posture at ≥30 mg/kg/day. In addition, mortality and body weight effects occurred at 100 mg/kg/day. Other venetoclax-related effects were reversible decreases in lymphocytes at ≥10 mg/kg/day, which were consistent with adult mice, and considered non-adverse.

The VENCLEXTA No Observed Adverse Effect Level (NOAEL) of 10 mg/kg/day in mice is approximately 0.06 times a clinical dose of 400 mg on a mg/m^2 basis for a 20-kg child.

CLINICAL STUDIES

Chronic Lymphocytic Leukemia

CLL14

CLL14 was a randomized (1:1), multicenter, open label phase 3 study that evaluated the efficacy and safety of VENCLEXTA in combination with obinutuzumab versus obinutuzumab in combination with chlorambucil for previously untreated CLL in patients with coexisting medical conditions (total Cumulative Illness Rating Scale [CIRS] score >6 or creatinine clearance <70 Ml/min). Patients in the study were assessed for risk of TLS and received prophylaxis accordingly prior to obinutuzumab administration. All patients received obinutuzumab at 1000 mg on Cycle 1 Day 1 (the first dose could be split as 100 mg and 900 mg on Days 1 and 2), and 1000-mg doses on Days 8 and 15 of Cycle 1, and on Day 1 of each subsequent cycle, for a total of 6 cycles. On Day 22 of Cycle 1, patients in the VENCLEXTA + obinutuzumab arm began the 5-week VENCLEXTA ramp-up schedule [see **DOSAGE AND ADMINISTRATION**]. After completing the ramp-up schedule on Cycle 2 Day 28, patients received VENCLEXTA 400 mg once daily from Cycle 3 Day 1 until the last day of Cycle 12. Patients randomized to the obinutuzumab + chlorambucil arm received 0.5 mg/kg oral chlorambucil on Day 1 and Day 15 of Cycles 1 to 12, in the absence of disease progression or unacceptable toxicity. Each cycle was 28 days. Following completion of 12 cycles of VENCLEXTA, patients continued to be followed for disease progression and overall survival.

Baseline demographic and disease characteristics were similar between the study arms (Table 13).

Table 13. Demographics and Baseline Characteristics in CLL14

Characteristic	VENCLEXTA + Obinutuzumab (N=216)	Obinutuzumab + Chlorambucil (N=216)
Age, years; median (range)	72 (43-89)	71 (41-89)
White, %	89	90
Male, %	68	66
ECOG performance status, %		
0	41	48
1	46	41
2	13	12
CIRS score, median (range)	9 (0-23)	8 (1-28)
Creatinine clearance <70 Ml/min, %	60	56
Binet Stage at screening, %		
A	21	20

B	36	37
C	43	43

At baseline, the median lymphocyte count was 55 x 10^9 cells/L in both study arms. On Cycle 1 Day 15, the median count decreased to 1.03 x 10^9 cells/L (range: 0.2 to 43.4 x 10^9 cells/L) in the obinutuzumab + chlorambucil arm compared with 1.27 x 10^9 cells/L (range: 0.2-83.7 x 10^9 cells/L) in the VENCLEXTA + obinutuzumab arm.

The median follow-up at the time of analysis was 28 months (range: 0 to 36 months).

The primary endpoint was progression-free survival (PFS) as assessed by investigators using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

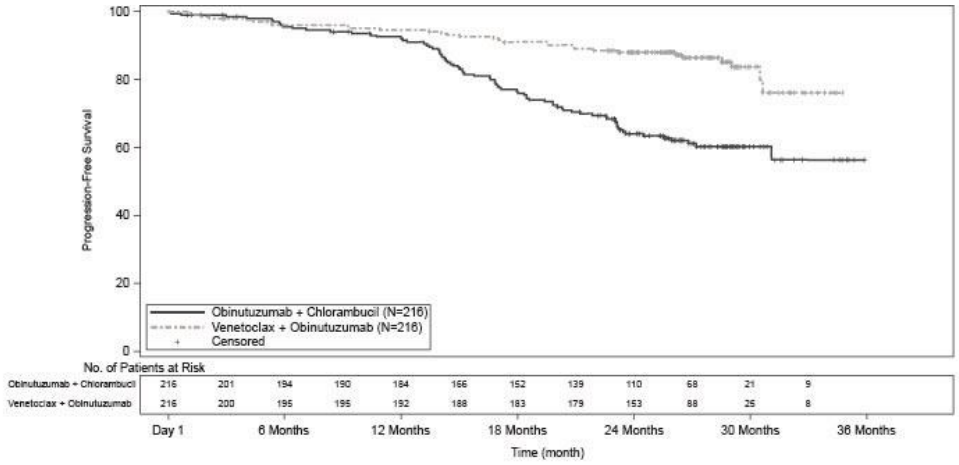
Efficacy results for CLL14 are shown in Table 14. The Kaplan-Meier curve for PFS is shown in Figure 1.

Table 14. Efficacy Results for CLL14

	VENCLEXTA + Obinutuzumab (N=216)	**Obinutuzumab + Chlorambucil (N=216)**
Progression-free survival, investigator-assessed		
Number of events (%)	30 (14)	77 (36)
Median, months	Not Reached	Not Reached
HR (95% CI)	0.35 (0.23, 0.53)	
p-value	<0.0001	
12-month estimate, % (95% CI)	95 (91.5, 97.7)	92 (88.4, 95.8)
24-month estimate, % (95% CI)	88 (83.7, 92.6)	64 (57.4, 70.8)
Progression-free survival, IRC-assessed		
Number of events (%)	29 (13)	79 (37)
Median, months	Not Reached	Not Reached
HR (95% CI)	0.33 (0.22, 0.51)	
p-value	<0.0001	
12-month estimate, % (95% CI)	95 (91.5, 97.7)	91 (87.3, 95.1)
24-month estimate, % (95% CI)	89 (84.2, 93)	64 (57, 70.4)
Response rate		
ORR, % (95% CI)	85 (79.2, 89.2)	71 (64.8, 77.2)
CR+Cri, %	50	23
PR, %	35	48
Time to next anti-leukemic therapy		
Number of events (%)	27 (13)	45 (21)

Median, months	Not reached	Not reached
HR (95% CI)	0.6 (0.37, 0.97)	
CI = confidence interval; CR = complete response; Cri = complete response with incomplete marrow recovery; HR = hazard ratio; IRC = independent review committee; ORR = overall response rate (CR + Cri + Npr + PR); PR = partial response.		

Figure 1. Kaplan-Meier Curve of Investigator-Assessed Progression-Free Survival (ITT Population) in CLL14



Minimal residual disease (MRD) was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The cutoff for a negative status was <1 CLL cell per 10^4 leukocytes. Rates of MRD negativity regardless of response and in patients with CR/Cri are shown in Table 15.

Table 15. Minimal Residual Disease Negativity Rates Three Months After the Completion of Treatment in CLL14

	VENCLEXTA + Obinutuzumab (N=216)	Obinutuzumab + Chlorambucil (N=216)
Peripheral Blood		
MRD negativity rate, n (%)	163 (76)	76 (35)
[95% CI]	[69.17, 81.05]	[28.83, 41.95]
p-value	<0.0001	
MRD negativity rate in patients with CR/Cri, n (%)	91 (42)	31 (14)
[95% CI]	[35.46, 49.02]	[9.96, 19.75]
p-value	<0.0001	
Bone Marrow		
MRD negativity rate, n (%)	123 (57)	37 (17)
[95% CI]	[50.05, 63.64]	[12.36, 22.83]
p-value	<0.0001	
MRD negativity rate in patients with CR/Cri, n (%)	73 (34)	23 (11)
[95% CI]	[27.52, 40.53]	[6.87, 15.55]
p-value	<0.0001	
CI = confidence interval; CR = complete response; Cri = complete response with incomplete marrow recovery; MRD = minimal residual disease.		

In paired samples, the concordance of MRD negativity between peripheral blood and bone marrow samples at end of treatment was 91% in the VENCLEXTA + obinutuzumab arm and 58% in the obinutuzumab + chlorambucil arm.

Health-Related Quality of Life (HRQoL) was evaluated using the M. D. Anderson Symptom Inventory (MDASI)-CLL and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Patients receiving VENCLEXTA + obinutuzumab and obinutuzumab + chlorambucil reported no impairment from baseline in physical functioning, role functioning, and global health status/quality of life during treatment and follow-up per the EORTC QLQ-C30, and no increase in symptom burden and interference per the MDASI-CLL. The HRQoL was maintained in both arms with no increase in symptom burden or worsening observed in any quality-of-life domains.

65-month follow-up

Efficacy was assessed after a median follow-up of 65 months (Table 16).

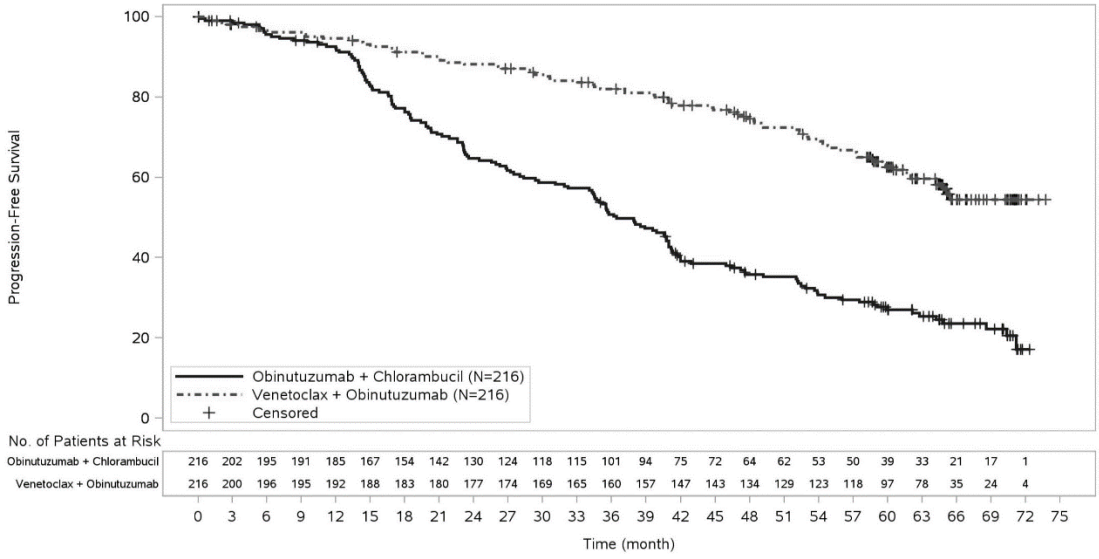
Table 16. Investigator-Assessed Efficacy Results in CLL14 (65–Month Follow-up)

Endpoint	VENCLEXTA + Obinutuzumab N = 216	Obinutuzumab + Chlorambucil N = 216
Progression-free survival		
Number of events (%)	80 (37)	150 (69)

Median, months (95% CI)	NR (64.8, NE)	36.4 (34.1, 41.0)
HR, stratified (95% CI)	0.35 (0.26, 0.46)	
Overall survival		
Number of events (%)	40 (19)	57 (26)
Median, months (95% CI)	NR	NR
HR, stratified (95% CI)	0.72 (0.48, 1.09)	
Time to next anti-leukaemic treatment		
Number of events (%)	62 (29)	125 (58)
Median, months (95% CI)	NR	52.9 (44.9, 59.0)
HR, stratified (95% CI)	0.42 (0.31, 0.57)	
Del(17p) and/or *TP53* mutation	N = 25	N = 24
Number of events (%)	13 (52)	19 (79)
Median, months (95% CI)	57.3 (32.3, NE)	29.0 (17.5, 43.3)
IgVH mutation		
Mutated	N = 76	N = 83
Number of events (%)	14 (18)	26 (31)
Median, months (95% CI)	NR	NR (71.4, NE)
Unmutated	N = 121	N = 123
Number of events (%)	42 (35)	91 (74)
Median, months (95% CI)	NR (69.5, NE)	40.6 (34.1, 44.9)
CI= confidence interval; HR: hazard ratio; NE = not evaluable; NR = not reached		

The Kaplan-Meier curve for investigator-assessed PFS is shown in Figure 2.

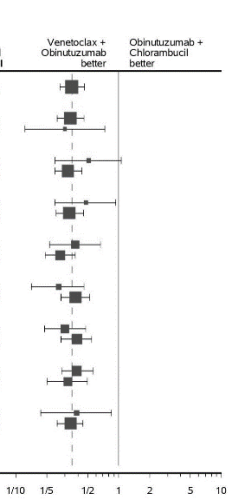
Figure 2. Kaplan-Meier Curve of Investigator-Assessed Progression-Free Survival (ITT Population) in CLL14 (65-Month Follow-up)



The PFS benefit with VENCLEXTA + obinutuzumab versus obinutuzumab + chlorambucil treatment was consistently observed across all subgroups of patients evaluated, including: 17p deletion, *TP53* mutation status, *TP53* mutation and/or 17p deletion status, *IgVH* mutational status, chromosome 11q deletion, age, estimated creatinine clearance, and CIRS score (Figure 3).

Figure 3. Forest Plot of Investigator-Assessed PFS in Subgroups From CLL14 (65-Month Follow-up)

Subgroups	Total n	Obinutuzumab + Chlorambucil (N=216) n	Events	Median (Months)	Venetoclax + Obinutuzumab (N=216) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	432	216	150	36.4	216	80	NE	0.35	(0.27, 0.46)
17p Deletion									
Normal	387	194	129	38.9	193	66	NE	0.34	(0.25, 0.46)
Abnormal	31	14	13	15.2	17	13	47.0	0.30	(0.12, 0.74)
TP53 Mutation Status									
Mutated	42	19	15	19.8	23	14	49.0	0.51	(0.24, 1.06)
Unmutated	382	194	132	38.9	188	64	NE	0.32	(0.24, 0.44)
p53 Mutation and/or 17p Deletion									
Mutated	49	24	20	20.8	25	15	49.0	0.48	(0.24, 0.94)
Unmutated	368	184	122	38.9	184	63	NE	0.33	(0.25, 0.45)
IGVH Mutational Status									
Mutated	159	83	40	59.9	76	17	NE	0.38	(0.21, 0.66)
Unmutated	244	123	100	26.9	121	55	64.2	0.27	(0.19, 0.38)
Chromosome 11Q Deletion									
Mutated	77	38	31	18.0	39	19	61.8	0.26	(0.14, 0.46)
Unmutated	339	168	110	40.5	171	60	NE	0.38	(0.28, 0.52)
Age Group 70 (yr)									
<70	171	89	61	39.6	82	26	NE	0.30	(0.19, 0.48)
>=70	261	127	89	36.4	134	54	NE	0.39	(0.28, 0.55)
Estimated Creatinine Clearance									
< 70 mL/min	248	119	83	40.8	129	52	NE	0.39	(0.28, 0.56)
>= 70 mL/min	180	94	64	35.5	86	28	NE	0.32	(0.20, 0.50)
Cumulative Illness Rating Scale (category)									
<= 6	69	39	26	52.9	30	8	NE	0.39	(0.17, 0.85)
> 6	363	177	124	35.5	186	72	NE	0.34	(0.25, 0.45)



Unstratified hazard ratio is displayed.
CI = confidence interval
NE = not evaluable

At a median follow-up of 65 months, HRQoL measures were consistent with the primary analysis.

GP28331

A multicenter, open-label, non-randomized study of VENCLEXTA administered in combination with obinutuzumab included 32 patients with previously untreated CLL. The median follow-up in the study was 27 months (range: 16 to 39 months). Twenty-two patients had a baseline creatinine clearance ≥70 mL/min and a baseline ECOG of 0 or 1 and were therefore eligible to receive chemo-immunotherapy (e.g., fludarabine, cyclophosphamide, rituximab [FCR] or bendamustine and rituximab [BR]) as treatment. For these 22 patients, the median age was 62 years (range: 47 to 68 years), 68% were male, and 50% had ECOG score of 1. Key efficacy results were consistent with those observed in CLL14. The overall response rate was 100%, with 73% (16/22) of patients achieving a CR/CRi (investigator-assessed). Median duration of response was not reached (range: 10 to 33 months). The 12-month PFS rate was 100% (95%CI: 100.0 to 100.0) and the 24-month PFS rate was 86% (95%CI: 72.02 to 100.00). After ≥3 months from the last venetoclax dose, 68% (15/22) of patients were MRD negative ($<10^{-4}$) in peripheral blood, assessed using flow cytometry.

MURANO

MURANO was a randomized (1:1), multicenter, open label phase 3 study that evaluated the efficacy and safety of VENCLEXTA in combination with rituximab versus bendamustine in combination with rituximab in patients with CLL who had received at least one line of prior therapy. Patients in the VENCLEXTA + rituximab arm completed the 5-week ramp-up schedule [see **DOSAGE AND ADMINISTRATION**] and received 400 mg VENCLEXTA daily for 2 years from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity. Rituximab was initiated after the 5-week dose ramp-up at 375 mg/m^2 for Cycle 1 and 500 mg/m^2 for Cycles 2-6. Each cycle was 28 days. Patients randomized to bendamustine + rituximab received bendamustine at 70 mg/m^2 on Days 1 and 2 for 6 cycles and rituximab at the

above-described dose and schedule. Following completion of 24 months of venetoclax + rituximab regimen, patients continued to be followed for disease progression and overall survival.

A total of 389 patients were randomized: 194 to the venetoclax + rituximab arm and 195 to the bendamustine + rituximab arm. Baseline demographic and disease characteristics were similar between the venetoclax + rituximab and bendamustine + rituximab arms (Table 17).

Table 17. Demographics and Baseline Characteristics in MURANO

Characteristic	VENCLEXTA + Rituximab (N=194)	Bendamustine + Rituximab (N=195)
Age, years; median (range)	65 (28-83)	66 (22-85)
White, %	97	97
Male, %	70	77
ECOG performance status, %		
0	57	56
1	42	43
2	1	1
Tumor burden, %		
Absolute lymphocyte count ≥25 x 10^9/L	66	69
One or more nodes ≥5 cm	46	48
Number of prior lines of therapy		
Median number (range)	1 (1-5)	1 (1-4)
1, %	57	60
2, %	29	22
≥3, %	13	18
Previous CLL regimens		
Median number (range)	1 (1-5)	1 (1-4)
Prior alkylating agents, %	95	93
Prior purine analogs, %	81	81
Prior anti-CD20 antibodies, %	76	78
Prior B-cell receptor pathway inhibitors, %	2	3
FCR, %	54	55
Fludarabine refractory, %	14	15
CLL subsets, %		
17p deletion	27	27
11q deletion	35	38
TP53 mutation	25	28
IgVH unmutated	68	68
Time since diagnosis, years; median (range)	6.44 (0.5-28.4)	7.11 (0.3-29.5)

FCR = fludarabine, cyclophosphamide, rituximab.

The median follow-up at the time of analysis was 23.8 months (range: 0.0 to 37.4 months).

The primary endpoint was progression-free survival (PFS) as assessed by investigators using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

Efficacy results for MURANO are shown in Table 18. The Kaplan-Meier curves for PFS is shown in Figure 4.

Table 18. Efficacy Results for MURANO

	INV Assessed		**IRC Assessed**	
	VENCLEXTA + Rituximab (N=194)	**Bendamustine + Rituximab (N=195)**	**VENCLEXTA + Rituximab (N=194)**	**Bendamustine + Rituximab (N=195)**
Progression-free survival				
Number of events (%)	32 (16)	114 (58)	35 (18)	106 (54)
Disease progression	21	98	26	91
Death events	11	16	9	15
Median, months (95% CI)	Not reached	17.0 (15.5, 21.6)	Not reached	18.1 (15.8, 22.3)
HR (95% CI)	0.17 (0.11, 0.25)		0.19 (0.13, 0.28)	
p-value[a]	$p < 0.0001$		$p < 0.0001$	
12-month estimate, % (95% CI)	93 (89.1, 96.4)	73 (65.9, 79.1)	91 (87.2, 95.2)	74 (67.6, 80.7)
24-month estimate, % (95% CI)	85 (79.1, 90.6)	36 (28.5, 44.0)	83 (76.6, 88.9)	37 (29.4, 45.4)
Response rate				
ORR, % (95% CI)	93 (88.8, 96.4)	68 (60.6, 74.2)	92 (87.6, 95.6)	72 (65.5, 78.5)
CR+CRi, (%)	27	8	8[b]	4[b]
nPR, (%)	3	6	2	1
PR, (%)	63	53	82	68
Overall survival				
Number of deaths (%)	15 (8)	27 (14)	NA	NA
HR (95% CI)	0.48 (0.25, 0.90)		NA	
Time to next anti-leukemic therapy				
Number of events (%)	23 (12)	83 (43)	NA	NA
Median, months	Not reached	26.4	NA	NA
HR (95% CI)	0.19 (0.12, 0.31)		NA	
Event-free survival				

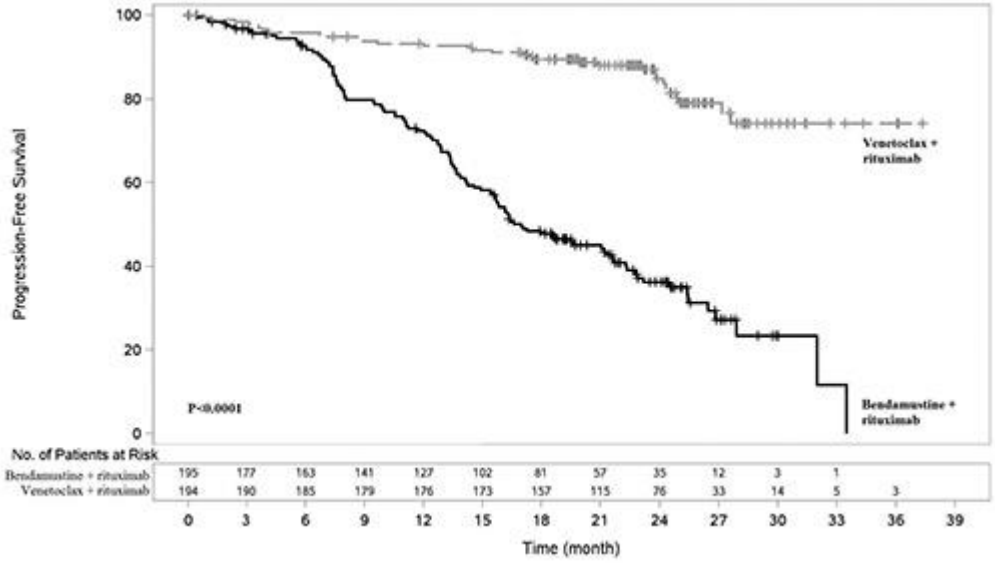
Number of events (%)	33 (17)	118 (61)	NA	NA
Median, months	Not reached	16.4	NA	NA
HR (95% CI)	0.17 (0.11, 0.25)		NA	

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; HR = hazard ratio; INV = investigator; IRC = independent review committee; NA = not available; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.

[a]Stratified log-rank test.

[b]The discrepancy between IRC- and INV-assessed CR rate was primarily due to interpretation of residual adenopathy on CT scans. Eighteen patients in the VENCLEXTA + rituximab arm and 3 patients in the bendamustine + rituximab arm had negative bone marrow and lymph nodes <2 cm.

Figure 4. Kaplan-Meier Curve of Investigator-Assessed Progression-Free Survival (ITT Population) in MURANO



At the time of primary analysis (data cutoff date 8 May 2017), 65 patients completed the 24-month venetoclax + rituximab treatment regimen without progression and 78 patients were still receiving venetoclax (+18 months of treatment). Of the 65 patients who remained progression free at 24 months, only 2 patients progressed after treatment completion. Twelve patients had a 3-month follow-up visit and remained progression free. Of the 12 patients, 5 were also assessed at 6-month follow-up and remained progression free.

Minimal residual disease was evaluated using ASO-PCR and flow cytometry. The cutoff for a negative status was one CLL cell per 10^4 leukocytes. Minimal residual disease data were available in peripheral blood in nearly all patients (187/194 in the venetoclax + rituximab arm versus 179/195 in the bendamustine + rituximab arm) and in a subset of patients for bone marrow (74/194 in the venetoclax + rituximab arm versus 41/195 in the bendamustine + rituximab arm). Peripheral blood MRD negativity rates, assessed at any time during the study, were observed in 84% (162/194) of patients in the venetoclax + rituximab arm versus 23%

(45/195) of patients in the bendamustine + rituximab arm. Bone marrow MRD negativity rates were 27% (53/194 patients) in the venetoclax + rituximab arm versus 2% (3/195 patients) in the bendamustine + rituximab arm. At the 9-month response assessment, MRD negativity in the peripheral blood was 62% in the venetoclax + rituximab arm versus 13% in the bendamustine + rituximab arm and this rate was maintained in the venetoclax + rituximab arm for at least an additional 9 months (60% in venetoclax + rituximab versus 5% in bendamustine + rituximab), the last visit for which complete data were available prior to the clinical cutoff date.

HRQoL was evaluated using the MDASI, EORTC QLQ-C30, and the EORTC QLQ-CLL16. A protocol error in the Schedule of Assessments resulting in missed assessments during Day 1 of initiation in the venetoclax + rituximab arm significantly limited the size of the PRO-evaluable population. To assess the generalisabiliy of the limited PRO-evaluable population for the venetoclax + rituximab arm, a summary of baseline characteristics for the PRO-evaluable and ITT populations was used to confirm that the disease- and treatment-related symptoms were similar at baseline for both groups. Patients in both arms maintained their HRQoL scores from all three questionnaires at the end of the treatment cycle and during follow-up, however these data should be interpreted with caution due to the limited PRO-evaluable population.

59-month follow-up

Efficacy was assessed after a median follow-up of 59.2 months (data cut-off date 8 May 2020). Efficacy results for the MURANO 59-month follow-up are presented in Table 19.

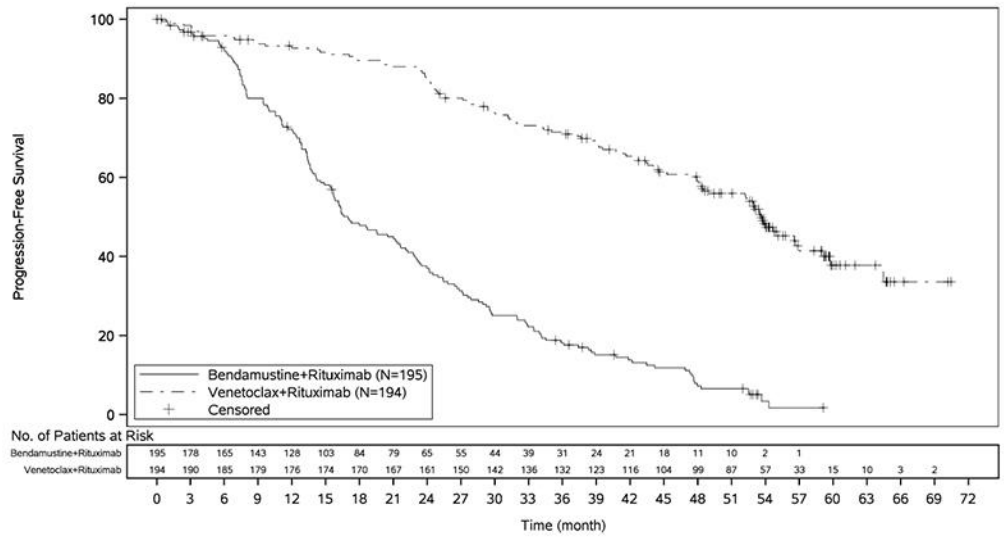
Table 19. Investigator-Assessed Efficacy Results in MURANO (59-Month Follow-up)

Endpoint	**VENCLEXTA + Rituximab N = 194**	**Bendamustine + Rituximab N = 195**
Progression-free survival		
Number of events (%)[a]	101 (52)	167 (86)
Median, months (95% CI)	54 (48.4, 57.0)	17 (15.5, 21.7)
HR, stratified (95% CI)	0.19 (0.15, 0.26)	
Overall survival		
Number of events (%)	32 (16)	64 (33)
HR (95% CI)	0.40 (0.26, 0.62)	
60-month estimate (95% CI)	82 (76.4, 87.8)	62 (54.8, 69.6)
Time to next anti-leukemic treatment		
Number of events (%)[b]	89 (46)	149 (76)
Median, months (95% CI)	58 (55.1, NE)	24 (20.7, 29.5)
HR, stratified (95% CI)	0.26 (0.20, 0.35)	
MRD negativity[c]		
Rate in peripheral blood at end of treatment (%)[d]	83 (64)	NA[f]
3-year PFS estimate from end of treatment (95% CI)[e]	61 (47.3, 75.2)	NA[f]
3-year OS estimate from end of treatment (95% CI)[e]	95 (90.0, 100.0)	NA[f]
CI = confidence interval; MRD = minimal residual disease; NE = not evaluable; OS = overall survival; PFS = progression-free survival; NA = not applicable.		

[a] In the venetoclax + rituximab arm, 87 and 14 events were due to disease progression and death, compared with 148 and 19 events in the bendamustine + rituximab arm, respectively.
[b] In the venetoclax + rituximab arm, 68 and 21 events were due to patients starting a new anti-leukemic treatment and death, compared with 123 and 26 events in the bendamustine + rituximab arm, respectively.
[c] Minimal residual disease was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and/or flow cytometry. The cut-off for a negative status was one CLL cell per 10^4 leukocytes.
[d] In patients that completed venetoclax treatment without progression (130 patients).
[e] In patients that completed venetoclax treatment without progression and were MRD negative (83 patients).
[f] No equivalent to end of treatment visit in bendamustine + rituximab arm.

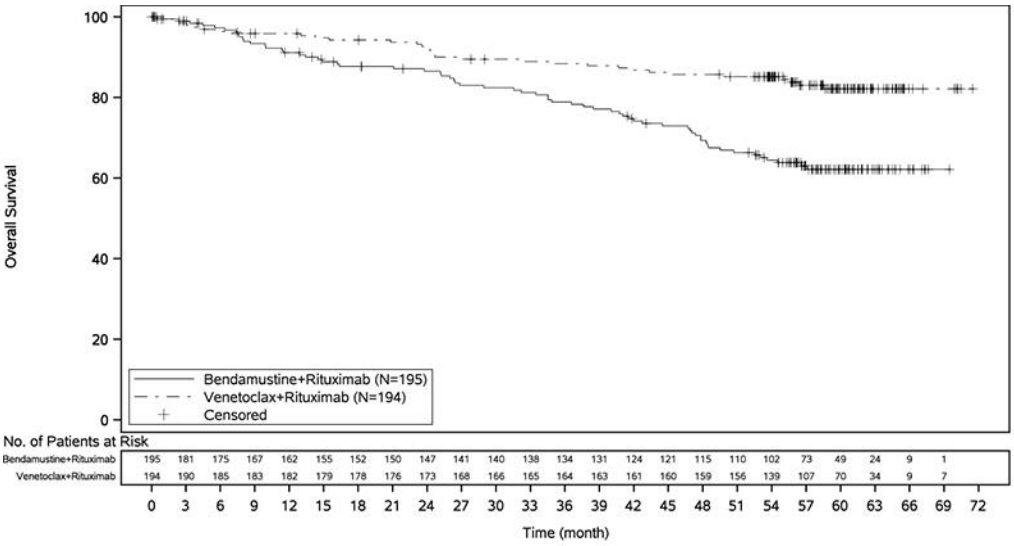
In total, 130 patients in the VENCLEXTA + rituximab arm completed 2 years of VENCLEXTA treatment without progression. For these patients, the 3-year PFS estimate post-treatment was 51% [95 % CI: 40.2, 61.9]. The Kaplan-Meier curve for investigator-assessed PFS is shown in Figure 5.

Figure 5. Kaplan-Meier Curve of Investigator-Assessed Progression-Free Survival (ITT Population) in MURANO (59-Month Follow-up)



The Kaplan-Meier curve for overall survival is shown in Figure 6.

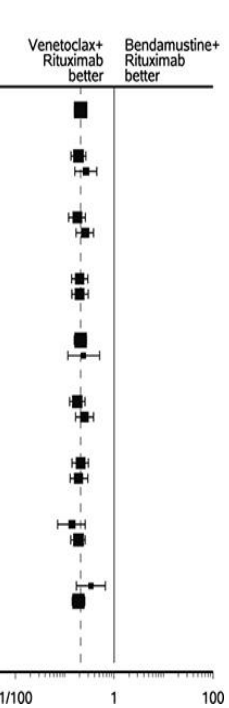
Figure 6. Kaplan-Meier Curve of Overall Survival (ITT Population) in MURANO (59-Month Follow-up)



The observed PFS benefit of VENCLEXTA + rituximab compared with bendamustine + rituximab was consistently observed across all subgroups of patients evaluated, including high-risk patients with deletion 17p/TP53 mutation and/or unmutated *IgVH* (Figure 7).

Figure 7. Forest Plot of Investigator-Assessed PFS in Subgroups From MURANO (59-Month Follow-up)

Subgroups	Total n	Bendamustine+ Rituximab (N=195) n	Median (Months)	Venetoclax+ Rituximab (N=194) n	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	389	195	17.0	194	53.6	0.21	(0.16, 0.27)
Chromosome 17p Deletion (central)							
Normal	250	123	21.6	127	55.1	0.19	(0.13, 0.27)
Abnormal	92	46	14.6	46	47.9	0.27	(0.16, 0.45)
p53 Mutation and/or 17p Deletion (central)							
Unmutated	201	95	22.9	106	56.6	0.18	(0.12, 0.26)
Mutated	147	75	14.2	72	45.3	0.26	(0.17, 0.38)
Age Group 65 (yr)							
< 65	186	89	15.4	97	49.0	0.20	(0.14, 0.29)
>= 65	203	106	21.7	97	57.0	0.20	(0.14, 0.30)
Age Group 75 (yr)							
< 75	336	171	16.4	165	53.5	0.21	(0.16, 0.28)
>= 75	53	24	20.0	29	64.5	0.24	(0.12, 0.51)
Number of Prior Regimens							
1	228	117	16.4	111	54.0	0.18	(0.13, 0.26)
> 1	161	78	18.6	83	53.1	0.25	(0.17, 0.38)
Bulky Disease (Lymph Nodes with the Largest Diameter)							
< 5 cm	197	97	16.6	100	53.8	0.21	(0.14, 0.30)
>= 5 cm	172	88	15.8	84	48.4	0.19	(0.13, 0.29)
Baseline IgVH Mutation Status							
Mutated	104	51	24.2	53	NE	0.14	(0.07, 0.26)
Unmutated	246	123	15.7	123	52.2	0.19	(0.13, 0.26)
Refractory vs. Relapse to Most Recent Prior Therapy							
Refractory	59	29	13.6	30	31.9	0.34	(0.17, 0.66)
Relapse	330	166	18.6	164	53.8	0.19	(0.14, 0.25)



17p deletion status was determined based on central laboratory test results.
Unstratified hazard ratio is displayed on the X-axis with logarithmic scale.
NE = not evaluable.

Patients with CLL harbouring 17p deletion or TP53 mutation

The safety and efficacy of VENCLEXTA in 107 patients with previously treated CLL with 17p deletion were evaluated in a single arm, open-label, multi-center study (M13-982). Patients followed a 4- to 5-week ramp-up schedule starting at 20 mg and increasing to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Patients continued to receive VENCLEXTA 400 mg once daily until disease progression or unacceptable toxicity was observed. The median age was 67 years (range: 37 to 85 years); 65% were male, and 97% were white. The median time since diagnosis was 6.8 years (range: 0.1 to 32 years; N=106). The median number of prior anti-CLL treatments was 2 (range: 1 to 10 treatments); 49.5% with a prior nucleoside analogue, 38% with prior rituximab, and 94% with a prior alkylator (including 33% with prior bendamustine). At baseline, 53% of patients had one or more nodes ≥5 cm, and 51% had ALC ≥25 x 10^9 /L. Of the patients, 37% (34/91) were fludarabine refractory, 81% (30/37) harboured the unmutated I*gVH* gene, and 72% (60/83) had *TP53* mutation. The median time on treatment at the time of evaluation was 12 months (range: 0 to 22 months).

The primary efficacy endpoint was overall response rate (ORR) as assessed by an IRC using the IWCLL updated NCI-WG guidelines (2008). Efficacy results are shown in Table 20. Efficacy data are presented for 107 patients with data cut-off date 30 April 2015. An additional 51 patients were enrolled in a safety expansion cohort. Investigator-assessed efficacy are presented for 158 patients with a later data cut-off date 10 June 2016. The median time on treatment for 158 patients was 17 months (range: 0 to 34 months).

Table 20: Overall response rate and duration of response (DOR) in patients with previously treated CLL with 17p deletion (Study M13-982)

Endpoint	**IRC assessment (N=107)[a]**	**Investigator assessment (N=158)[b]**
Data cut-off date	30 April 2015	10 June 2016
ORR, % (95% CI)	79 (70.5, 86.6)	77 (69.9, 83.5)
CR + CRi, %	7	18
nPR, %	3	6
PR, %	69	53
DOR, months, median (95% CI)	NR	27.5 (26.5, NR)
PFS, % (95% CI) 12-month estimate 24-month estimate	 72 (61.8, 79.8) NA	 77 (69.1, 82.6) 52 (43, 61)
PFS, months, median (95% CI)	NR	27.2 (21.9, NR)
TTR, months, median (range)	0.8 (0.1-8.1)	1.0 (0.5-4.4)

[a]One patient did not harbor the 17p deletion.
[b]Includes 51 additional patients from the safety expansion cohort.
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DOR = duration of response; IRC = independent review committee; nPR = nodular partial remission; NA = not available; NR = not reached;

ORR = overall response rate (CR + CRi + nPR + PR); PFS = progression-free survival; PR = partial remission; TTR = time to first response.

Minimal residual disease was evaluated using flow cytometry in 93 of 158 patients who achieved complete remission (CR), complete remission with incomplete marrow recovery (CRi), or partial remission (PR) with limited remaining disease with VENCLEXTA treatment. MRD negativity was defined as a result below 0.0001 (<1 CLL cell per 10^4 leukocytes in the sample). Twenty-seven percent (41/158) of patients were MRD negative in the peripheral blood, including 15 patients who were also MRD negative in the bone marrow.

Patients with CLL who have failed a B-cell receptor pathway inhibitor

The efficacy and safety of VENCLEXTA in patients with CLL who had been previously treated with and progressed on or after ibrutinib (Arm A) or idelalisib (Arm B) therapy were evaluated in an open-label, multi-center, non-randomised, phase 2 study (M14-032). Patients received a daily dose of VENCLEXTA following the ramp-up schedule. Patients continued to receive VENCLEXTA 400 mg once daily until disease progression or unacceptable toxicity was observed.

Efficacy was evaluated by investigators and an IRC according to IWCLL updated NCI WG guidelines (2008). Response assessments were performed at 8 weeks, 24 weeks, and every 12 weeks thereafter for the 64 patients in the main cohort, while the patients enrolled in the expansion had disease assessment at weeks 12 and 36.

A total of 127 patients were enrolled in the study, which included 64 patients in the main cohort (43 with prior ibrutinib, 21 with prior idelalisib) and 63 patients in an expansion cohort (48 with prior ibrutinib, 15 with prior idelalisib). The median age was 66 years (range: 28 to 85 years), 70% were male, and 92% were white. The median time since diagnosis was 8.3 years (range: 0.3to 18.5 years; N=96). The median number of prior anti-CLL treatments was 4 (range: 1to 15 treatments). At baseline, 41% of patients had one or more nodes ≥5 cm, and 31% of patients had ALC ≥25 x 10^9/L.

Efficacy data are presented with data cutoff date of 31 January 2017. Investigator-assessed efficacy (N=108) included all 64 patients in the main cohort with more than 24 weeks of assessment, 37 patients in the expansion cohort with 36week assessment, and 7 patients who had progressed prior to the 36-week assessment. Efficacy results by IRC (N=97) included 64 patients from the main cohort and 33 patients from the expansion cohort.

Efficacy results for 108 patients assessed by investigator and 97 patients assessed by IRC are shown in Table 21.

Table 21: Efficacy results in Study M14-032

	IRC Assessment N=97	**Investigator Assessment N=108**

ORR, % (95% CI)	73 (63.2, 81.7)	66 (56.0, 74.6)
CR + Cri, %	1	9
nPR, %	0	2
PR, %	72	55
DOR, % (95% CI) 6-month estimate 12-month estimate	N=71 97 (87.6, 99.2) NA	N=71 96 (86.8, 98.5) 85 (72.0, 92.4)
Time to first response, median, months (range)	2.5 (1.0-8.9)	2.5 (1.6, 14.9)
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DOR = duration of response; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.		

The median duration of treatment with VENCLEXTA for 127 patients with investigator assessment was 10.2 months (range: 0.1 to 25.6 months). The median duration of treatment with VENCLEXTA for 97 patients with IRC assessment was 12.3 months (range: 0.1 to 25.6 months).

The MRD negativity rate in peripheral blood for all 127 patients was 23% (29/127), including 5 patients who achieved MRD negativity in bone marrow.

Elderly patients

Of the 107 patients who were evaluated for efficacy from M13-982 study, 57% were 65 years or older. Of the 108 patients who were evaluated for efficacy from M14-032 study, 57% were 65 years or older.

Of the 352 patients evaluated for safety from 3 open-label trials of VENCLEXTA monotherapy, 57% were 65 years or older.

There were no overall differences in safety or efficacy observed between older and younger patients.

Acute Myeloid Leukemia

VIALE-A

VIALE-A was a randomized (2:1), double-blind, placebo-controlled, multicenter phase 3 study that evaluated the efficacy and safety of VENCLEXTA in combination with azacitidine versus placebo in combination with azacitidine in patients with newly diagnosed AML who were ineligible for intensive chemotherapy.

Patients in VIALE-A completed the 3-day ramp-up schedule to a final 400-mg once-daily dose during the first 28-day cycle of treatment [see **DOSAGE AND ADMINISTRATION**] and received VENCLEXTA 400 mg orally once daily thereafter in subsequent cycles. Azacitidine at 75 mg/m^2 was administered either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. Placebo orally once daily was administered on Day 1-28 plus azacitidine at 75 mg/m^2 on Day 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA or placebo was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50 × 10^3/microliter. For patients with resistant disease at the end of Cycle 1, a bone marrow assessment was performed after Cycle 2 or 3 and as clinically indicated.

Azacitidine was resumed on the same day as VENCLEXTA or placebo following interruption [see **DOSAGE AND ADMINISTRATION**]. Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity.

A total of 431 patients were randomized: 286 to the VENCLEXTA + azacitidine arm and 145 to the placebo + azacitidine arm. The baseline demographic and disease characteristic are shown in Table 22.

Table 22. Baseline Demographic and Disease Characteristics in Patients with AML in VIALE-A

Characteristic	**VENCLEXTA + Azacitidine N=286**	**Placebo + Azacitidine N=145**
Age, years; median (range)	76 (49, 91)	76 (60, 90)
Race		
White; %	76	75
Black or African American; %	1.0	1.4
Asian; %	23	23
Males; %	60	60
ECOG performance status; %		
0-1	55	56
2	40	41
3	5.6	3.4
Bone marrow blast; %		
<30%	30	28
≥30% to <50%	21	23
≥50%	49	49
Disease history; %		
De novo AML	75	76
Secondary AML	25	24
Cytogenetic risk detected[a] %		

Intermediate	64	61
Poor	36	39
Mutation analyses detected; n/N[b] (%)		
IDH1 or IDH2 [c,d]	61/245 (25)	28/127 (22)
IDH1[c]	23/245 (9.4)	11/127 (8.7)
IDH2[d]	40/245 (16)	18/127 (14)
FLT3[e]	29/206 (14)	22/108 (20)
NPM1[f]	27/163 (17)	17/86 (20)
TP53[f]	38/163 (23)	14/86 (16)

[a]Per the 2016 National Comprehensive Cancer Network (NCCN) Guidelines.
[b]Number of evaluable BMA specimens received at baseline.
[c]Detected by Abbott RealTi*me* IDH1 assay.
[d]Detected by Abbott RealTi*me* IDH2 assay.
[e]Detected by LeukoStrat® CDx FLT3 mutation assay.
[f]Detected by MyAML® assay.

The dual primary endpoints of the study were overall survival (OS) measured from the date of randomization to death from any cause and composite complete remission rate (complete remission + complete remission with incomplete blood count recovery; CR+CRi). The overall median follow-up at the time of analysis was approximately 20.5 months (range: <0.1 to 30.7 months).

VENCLEXTA + azacitidine demonstrated 34% reduction in the risk of death compared with placebo + azacitidine (p <0.001). The efficacy results are presented in Table 23 and Table 24.

Table 23. Efficacy Results in VIALE-A

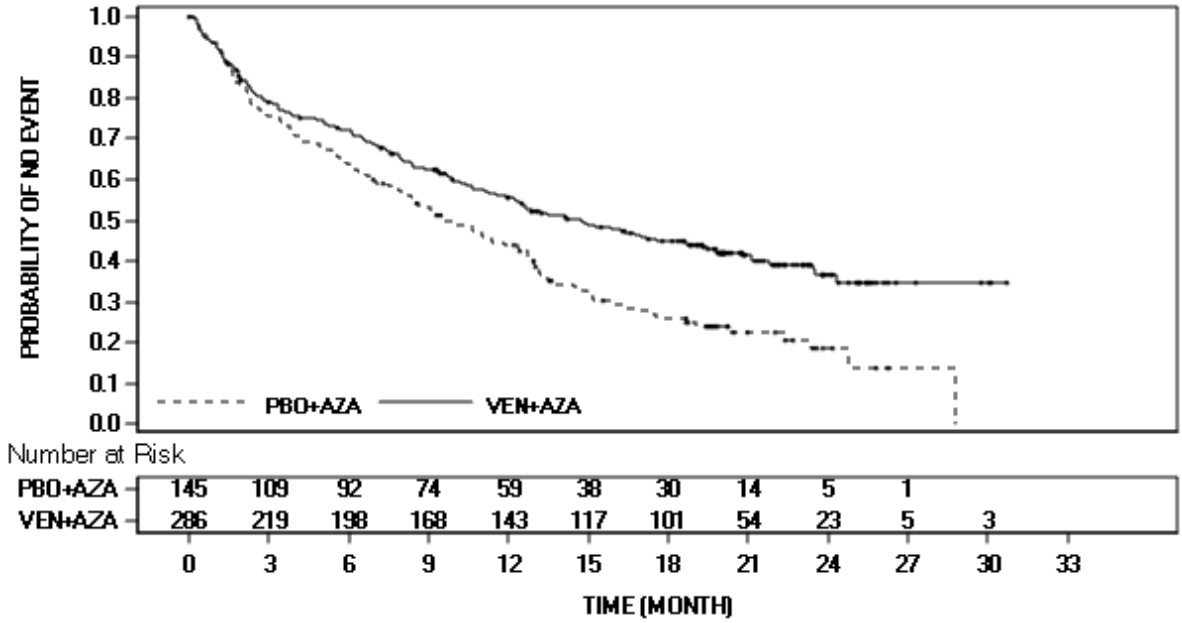
Endpoint	**VENCLEXTA + Azacitidine**	**Placebo + Azacitidine**
Overall survival	**(N=286)**	**(N=145)**
Number of deaths, n (%) Median[a] survival, months (95% CI)	161 (56) 14.7 (11.9, 18.7)	109 (75) 9.6 (7.4, 12.7)
Hazard ratio[b] (95% CI)	0.66 (0.52, 0.85)	
p-value[b]	<0.001	
CR + CRi[c]	**(N=147)**	**(N=79)**
n (%) (95% CI)	96 (65) (57, 73)	20 (25) (16, 36)
p-value[d]	<0.001	

CI = confidence interval.
CR (complete remission) was defined as absolute neutrophil count >1,000/microliter, platelets >100,000/microliter, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; CRi = complete remission with incomplete blood count recovery.
[a]Kaplan-Meier estimate at the second interim analysis (data cut-off date 4 January 2020).

[b]Hazard ratio estimate (venetoclax + azacitidine vs placebo + azacitidine) is based on Cox-proportional hazards model stratified by cytogenetics (intermediate risk, poor risk) and age (18 to <75 years, ≥75years) as assigned at randomization; p-value based on log-rank test stratified by the same factors.
[c]The CRi+CRi rate is from a planned interim analysis of first 226 patients randomized with 6 months of follow-up at the first interim analysis (data cut-off date 1 October 2018).
[d]P-value is from Cochran-Mantel-Haenszel test stratified by cytogenetics (intermediate risk, poor risk) and age (18 to <75 years, ≥75 years).

The Kaplan-Meier curve for OS is shown in Figure 8

Figure 8. Kaplan-Meier Curve for Overall Survival in VIALE-A



Key secondary efficacy endpoints are presented in Table 24.

Table 24. Additional Efficacy Endpoints in VIALE-A

Endpoint	**VENCLEXTA + Azacitidine (N=286)**	**Placebo + Azacitidine (N=145)**
CR, n (%) (95% CI)	105 (37) (31, 43)	26 (18) (12, 25)
p-value[a]	<0.001	
Median DOR[b] (months)	17.5	13.3
(95% CI)	(15.3, NR)	(8.5, 17.6)
CR+CRh, n (%) (95% CI)	185 (65) (59, 70)	33 (23) (16, 31)
p-value[a]	<0.001	
Median DOR[b] (months)	17.8	13.9
(95% CI)	(15.3, NR)	(10.4, 15.7)

CR+CRi, n (%) (95% CI) Median DOR[b] (months) (95% CI)	190 (66) (61, 72) 17.5 (13.6, NR)	41 (28) (21, 36) 13.4 (5.8, 15.5)
CR+CRh rate by initiation of Cycle 2, n (%) (95% CI)	114 (40) (34, 46)	8 (6) (2, 11)
p-value[a]	<0.001	
CR+CRi rate by initiation of Cycle 2, n (%) (95% CI)	124 (43) (38, 49)	11 (8) (4, 13)
p-value[a]	<0.001	
CR+CRh rate in *FLT3* subgroup, n/N (%) (95% CI)	19/29 (66) (46, 82)	4/22 (18) (5, 40)
p-value[c]	0.001	
CR+CRi rate in *FLT3* subgroup, n/N (%) (95% CI)	21/29 (72) (53, 87)	8/22 (36) (17, 59)
p-value[c]	0.021	
CR+CRh rate in *IDH1/2* subgroup, n/N (%) (95% CI)	44/61 (72) (59, 83)	2/28 (7) (1, 24)
p-value[c]	<0.001	
CR+CRi rate in *IDH1/2* subgroup, n/N (%) (95% CI)	46/61 (75) (63, 86)	3/28 (11) (2, 28)
p-value[c]	<0.001	
OS in *IDH1/IDH2* subgroup Number of deaths, n/N (%) Median OS[f], months (95%CI)	29/61 (48) NR (12.2, NR)	24/28 (86) 6.2 (2.3, 12.7)
Hazard ratio[g] (95% CI)	0.34 (0.20, 0.60)	
p-value[g]	<0.0001	
Transfusion independence rate, platelets, n (%) (95% CI)	196 (69) (63, 74)	72 (50) (41, 58)
p-value[a]	<0.001	
Transfusion independence rate, red blood cells, n (%) (95% CI)	171(60) (54, 66)	51 (35) (27, 44)
p-value[a]	<0.001	

CR+CRi MRD response rate[e] n (%) (95% CI)	 67 (23) (19, 29)	 11 (8) (4, 13)
p-value[a]	<0.001	
Event-free survival (EFS) Number of EFS events, n (%) Median EFS[f], (months) (95% CI)	 191 (67) 9.8 (8.4, 11.8)	 122 (84) 7.0 (5.6, 9.5)
Hazard ratio[d] (95% CI)	0.63 (0.50, 0.80)	
p-value[d]	<0.001	

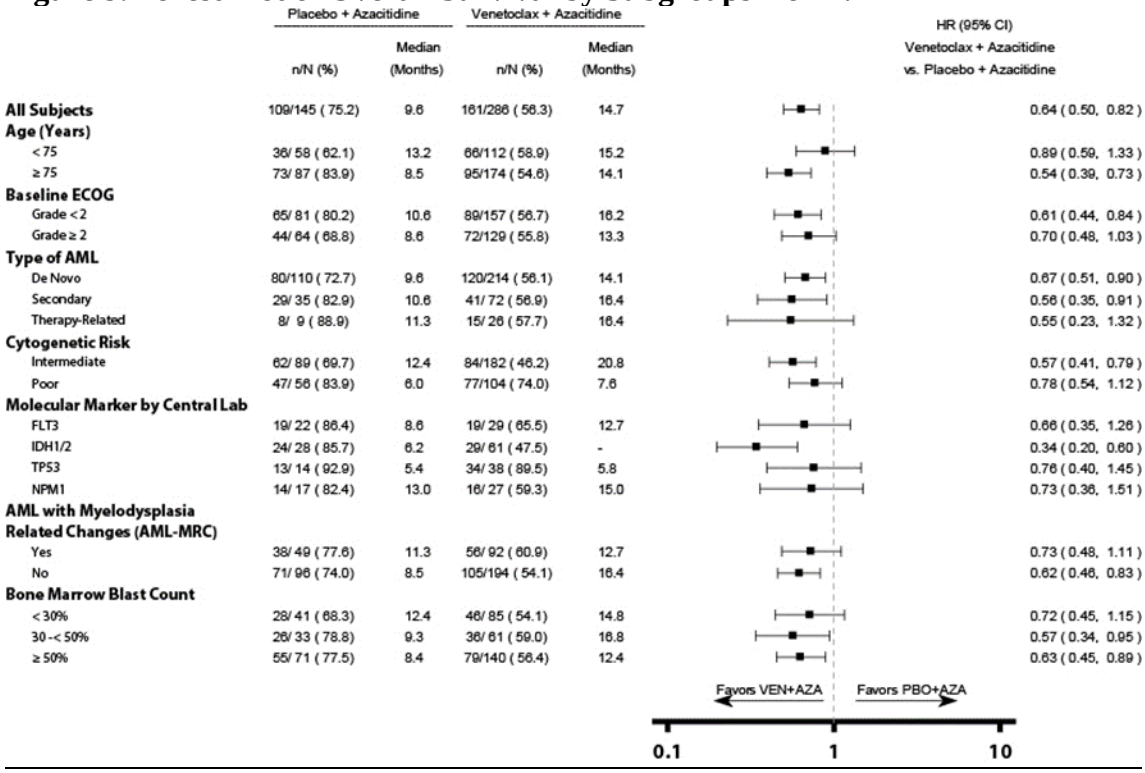
CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete blood count recovery.
CR + CRi = complete remission + complete remission with incomplete blood count recovery; DOR = duration of response; FLT = FMS-like tyrosine kinase; IDH = isocitrate dehydrogenase; MRD = minimal/measurable residual disease, NR = not reached.
CR (complete remission) was defined as absolute neutrophil count >1,000/microliter, platelets >100,000/microliter, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRh (complete remission with partial hematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).
Transfusion independence is defined as a period of at least 56 consecutive days (≥56 days) with no transfusion after the first dose of study drug and on or before the last dose of the study drug +30 days, or before relapse or disease progression or before the initiation of post-treatment therapy, whichever is earlier.
[a]P-value is from Cochran-Mantel-Haenszel test stratified by age (18 to <75 years, ≥75 years) and cytogenetic (intermediate risk, poor risk).
[b]DOR (duration of response) was defined as time from first response of CR for DoR of CR, from first response of CR or CRi for DOR of CR+CRi, or from first response of CR or CRh for DOR of CR+CRh, to the first date of confirmed morphologic relapse, confirmed progressive disease or death due to disease progression, whichever occurred earlier. Median DOR from Kaplan-Meier estimate.
[c]P-value is from Fisher's exact test.
[d]Hazard ratio estimate (venetoclax + azacitidine vs placebo + azacitidine) based on Cox-proportional hazards model stratified by age (18 to <75 years, ≥75) and cytogenetics (intermediate risk, poor risk) as assigned at randomization; p-value based on log-rank test stratified by the same factors.
[e]CR+CRi MRD response rate is defined as the % of patients achieving a CR or CRi and demonstrated an MRD response of $<10^{-3}$ blasts in bone marrow as determined by a standardized, central multicolor flow cytometry assay.
[f]Kaplan-Meier estimate.
[g]Hazard ratio estimate (venetoclax + azacitidine vs placebo + azacitidine) based on unstratified Cox-proportional hazards model. P-value from unstratified log-rank test.

Of the patients who were RBC transfusion dependent at baseline and treated with VENCLEXTA + azacitidine, 49% (71/144) became transfusion independent. Of the patients who were platelet transfusion dependent at baseline and treated with VENCLEXTA + azacitidine, 50% (34/68) became transfusion independent.

The median time to first response of CR or CRi was 1.3 month (range: 0.6 to 9.9 months) with venetoclax + azacitidine treatment. The median time to best response of CR or CRi was 2.3 month (range: 0.6 to 24.5 months).

The forest plot of OS by subgroups from VIALE-A is shown in Figure 9.

Figure 9. Forest Plot of Overall Survival by Subgroups from VIALE-A



Unstratified hazard ratio (HR) is displayed on the X-axis with logarithmic scale.
"-" = Not reached

Median OS in patients < 75 years treated with VENCLEXTA + azacitidine was 15.2 months and 13.2 months in patients treated with placebo + azacitidine (hazard ratio (HR) = 0.89, 95% CI = (0.59, 1.33)).

Median overall survival in patients ≥ 75 years treated with VENCLEXTA + azacitidine was 14.1 months and 8.5 months in patients treated with placebo + azacitidine (hazard ratio (HR) = 0.54, 95% CI = (0.39, 0.73)).

Fatigue was assessed by the Patient Reported Outcomes Measurement Information System (PROMIS), Cancer Fatigue Short Form (SF 7a), and health-related quality of life (HRQoL) was

assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) global health status/ quality of life (GHS/QoL). Patients receiving VENCLEXTA + azacitidine showed no clinically meaningful differences in the mean change from baseline fatigue score as assessed using the PROMIS-SF 7a than patients treated with placebo + azacitidine (-3.036 vs -0.796, -2.263 vs -1.976, -3.377 vs -0.990, -2.209 vs -1.745, and -1.644 vs -1.453 at Cycles 5, 7, 9, 11 and 13, respectively).

Patients treated with VENCLEXTA + azacitidine observed a longer time to deterioration defined as the first event of worsening of at least 10 in the EORTC-QLQ-C30 Global Health Status score (16.5 months; 95% CI: 9.76, not estimable) than patients treated with placebo + azacitidine (9.3 months; 95% CI: 4.67, 16.60; p=0.066). Patients receiving VENCLEXTA + azacitidine did not experience meaningful additional fatigue or decrement in HRQoL compared to patients receiving placebo + azacitidine.

M14-358

The efficacy of VENCLEXTA was established in a non-randomized clinical trial of VENCLEXTA in combination with azacitidine (n=84) or decitabine (n=31) in newly diagnosed patients with AML who were ineligible for intensive chemotherapy. Only subjects older than 60 years were recruited.

Patients received VENCLEXTA via a daily ramp-up to a final 400 mg once-daily dose. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring.

Azacitidine at 75 mg/m^2 was administered either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. Decitabine at 20 mg/m^2 was administered intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1 Day 1. Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA was interrupted up to 14 days or until ANC $\geq$500/microliter and platelet count $\geq 50 \times 10^3$/microliter.

Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity (see azacitidine full prescribing information). Dose reductions for decitabine were not implemented in the clinical trial.

Table 25 summarizes the baseline demographic and disease characteristics of the study population.

Table 25. Baseline Patient Characteristics for Patients with AML Treated with VENCLEXTA in Combination with a Hypomethylating Agent (M14-358)

Characteristic	VENCLEXTA + Azacitidine N=84	VENCLEXTA + Decitabine N=31
Age, years; median (range)	74.5 (61-90)	72 (65-86)
White; %	91	87

Male; %	61	48
ECOG performance status; % 0-1 2 3	 69 29 2	 87 13 0
Bone marrow blast; % <30% ≥30% - <50% ≥50%	 29 35 37	 23 45 32
History of antecedent hematologic disorder; %	20	16
Mutation analyses; % (identified/tested)		
TP53	22 (16/74)	27 (6/22)
IDH1 or *IDH2*	27 (20/74)	23 (5/22)
FLT- 3	15 (11/74)	14 (3/22)
NPM1	19 (14/74)	18 (4/22)
Cytogenetic risk[a,b]; %		
Intermediate	60	52
Poor	39	48
[a]As defined by the National Comprehensive Cancer Network (NCCN) risk categorization v2014. [b]No mitosis in 1 patient (excluded favorable risk by fluorescence in situ hybridization [FISH] analysis).		

The median follow-up was 28.9 months (range: 0.4 to 42.0 months) for VENCLEXTA in combination with azacitidine and 40.4 months (range: 0.7 to 42.7 months) for VENCLEXTA in combination with decitabine.

The efficacy results are shown in Tables 26 and 27 and were similar for both combinations.

Table 26. Efficacy Results for Newly Diagnosed Patients with AML Treated with VENCLEXTA in Combination with a Hypomethylating Agent (M14-358)

Endpoint	VENCLEXTA + Azacitidine N=84	VENCLEXTA + Decitabine N=31
CR, n (%) (95% CI) Median DOR[a] (months) (95% CI)	37 (44) (33, 55) 23.5 (15.1, 30.2)	17 (55) (36, 73) 21.3 (6.9, NR)
CRi, n (%) (95% CI) Median DOR[a] (months) (95% CI)	23 (27) (18, 38) 10.6 (5.6, NR)	6 (19) (8, 38) 6.1 (3.0, 16.5)
CR+CRi, n (%) (95% CI)	60 (71) (61, 81)	23 (74) (55, 88)

Median DOR[a] (months) (95% CI)	21.9 (15.1, 30.2)	15.0 (7.2, 30.0)
CRh, n (%) (95% CI) Median DOR[a] (months) (95% CI)	17 (20) (12, 30) 7.9 (5.8, NR)	5 (16) (6, 34) 7.2 (2.4, 15.3)
CR+CRh, n (%) (95% CI) Median DOR[a] (months) (95% CI)	54 (64) (53, 74) 21.7 (14.6, 30.3)	22 (71) (52, 86) 15.3 (7.2, 30.2)
Transfusion independence rate, n/N (%) Red blood cells[b] Platelets[c]	 26/51 (51) 16/27 (59)	 13/23 (57) 3/5 (60)

CI = confidence interval; NR = not reached.
CR (complete remission) was defined as absolute neutrophil count ≥1,000/microliter, platelets ≥100,000/microliter, red blood cell transfusion independence, and bone marrow with <5% blasts.
Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRh (complete remission with partial hematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).
CRi (complete remission with incomplete blood count recovery) was defined the same as all of the criteria for CR except for residual neutropenia <1,000/microliter or thrombocytopenia <100,000/microliter.
[a]DOR (duration of response) was defined as time from first response of CR for DOR of CR, or from first response of CRi for DOR of CRi, or from first response of CR or CRi for DOR of CR+CRi, or from first response of CRh for DOR of CRh, or from first response of CR+CRh for DOR of CR+CRh, to the first date of relapse, clinical disease progression, or death due to disease progression, whichever occurred earlier. Median DOR from Kaplan-Meier estimate.
[b]Evaluated for patients who were dependent at baseline for red blood cell transfusion.
[c]Evaluated for patients who were dependent at baseline for platelet transfusion.

Table 27. Time to Response in Patients with AML Treated with VENCLEXTA in Combination with a Hypomethylating Agent (M14-358)

Endpoint	VENCLEXTA in Combination with Azacitidine N=84	VENCLEXTA in Combination with Decitabine N=31
Median time to BEST response of CR (months) Range (months)	2.1 (0.7 – 10.9)	3.6 (1.2 – 17.6)
Median time to FIRST response of CR+CRh (months) Range (months)	1.0 (0.7 – 8.9)	1.8 (0.8 – 13.8)

Median time to FIRST response of CR+CRi (months) Range (months)	1.2 (0.7 – 7.7)	1.9 (0.9 – 5.4)

VENCLEXTA in Combination with Azacitidine

Efficacy results are shown in Tables 26 and 27.

Median overall survival for patients treated with VENCLEXTA in combination with azacitidine was 16.4 months (95% CI: 11.3, 24.5).

Remissions (CR or CRh) were observed across subgroups with different baseline characteristics. For patients with poor or intermediate risk cytogenetics, similar remissions rates were observed; the rates were 58% or 70%, respectively. For patients with the following identified mutations, the remissions were as follows: *TP53*: 56% (9/16), *IDH1 / 2*: 75% (15/20), *FLT-3*: 64% (7/11), and *NPM1*: 71% (10/14).

Remissions (CR or CRi) were observed across subgroups with different baseline characteristics.

For patients with poor or intermediate risk cytogenetics similar remissions rates were observed; the rates were 67% or 76%, respectively.

For patients with the following identified mutations, the remissions were as follows: *TP53*: 56% (9/16), *IDH1 / 2*: 90% (18/20), *FLT-3*: 64% (7/11), and *NPM1*: 79% (11/14).

Minimal residual disease was evaluated from bone marrow aspirate specimens for patients who achieved CR or CRh following treatment with VENCLEXTA in combination with azacitidine. Of those patients, 52% (28/54) achieved MRD less than one AML cell per 10^3 leukocytes in the bone marrow.

Minimal residual disease was evaluated from bone marrow aspirate specimens for patients who achieved CR or CRi following treatment with VENCLEXTA in combination with azacitidine. Of those patients, 48% (29/60) achieved MRD less than one AML cell per 10^3 leukocytes in the bone marrow.

Of patients treated with VENCLEXTA in combination with azacitidine, 18% (15/84) achieved a CR/CRi and subsequently received stem cell transplant.

VENCLEXTA in Combination with Decitabine

Efficacy results are shown in Table 26 and 27.

Median overall survival for patients treated with VENCLEXTA in combination with decitabine was 16.2 months (95% CI: 9.1, 27.8).

Remissions (CR or CRh) were observed across subgroups with different baseline characteristics. For patients with poor or intermediate risk cytogenetics, similar remissions rates were observed; the rates were 73% or 69%, respectively. For patients with the following identified mutations, the remissions were as follows: *TP53*: 4/6, *IDH1 / 2*: 5/5, *FLT-3*: 1/3 and *NPM1*: 4/4.

Remissions (CR or CRi) were observed across subgroups with different baseline characteristics. For patients with poor or intermediate risk cytogenetics, similar remissions rates were observed; the rates were 66% (21/32: all venetoclax + decitabine doses) or 78% (32/41: all venetoclax + decitabine doses), respectively. For patients with the following identified mutations, the remissions were as follows for all venetoclax + decitabine doses: *TP53:* 6/11*; IDH1/2:* 9/9*; FLT-3:* 3/6*; NPM1:* 7/7.

Minimal residual disease was evaluated from bone marrow aspirate specimens for patients who achieved CR or CRh following treatment with VENCLEXTA in combination with decitabine. Of those patients, 36% (8/22) achieved MRD less than one AML cell per 10^3 leukocytes in the bone marrow.

Minimal residual disease was evaluated from bone marrow aspirate specimens for patients who achieved CR or CRi following treatment with VENCLEXTA in combination with decitabine. Of those patients, 39% (9/23) achieved MRD less than one AML cell per 10^3 leukocytes in the bone marrow.

Of patients treated with VENCLEXTA in combination with decitabine, 13% (4/31) achieved a CR/CRi and subsequently received stem cell transplant.

VIALE-C

Clinical benefit was based on the rate of complete responses (CR) and duration of CR, with supportive evidence of rate of CR + CRi (complete remission with incomplete blood count recovery), duration of CR + CRi and the rate of conversion from transfusion dependence to transfusion independence.

VIALE-C was a randomized (2:1), double-blind, placebo controlled, multicenter, phase 3 study (M16-043) that evaluated the efficacy and safety of VENCLEXTA in combination with low-dose cytarabine versus placebo in combination with low-dose cytarabine in patients with newly diagnosed AML who were ineligible for intensive chemotherapy.

Patients in VIALE-C completed the 4-day ramp-up schedule to a final 600-mg once-daily dose during the first 28-day cycle of treatment [see **DOSAGE AND ADMINISTRATION]** and received VENCLEXTA 600 mg orally once daily thereafter in subsequent cycles. Low-dose cytarabine 20 mg/m^2 was administered subcutaneously (SC) once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1**.** Placebo orally once daily was administered on Days 1-28 plus low-dose cytarabine 20 mg/m^2 SC once daily on Days 1-10. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring.

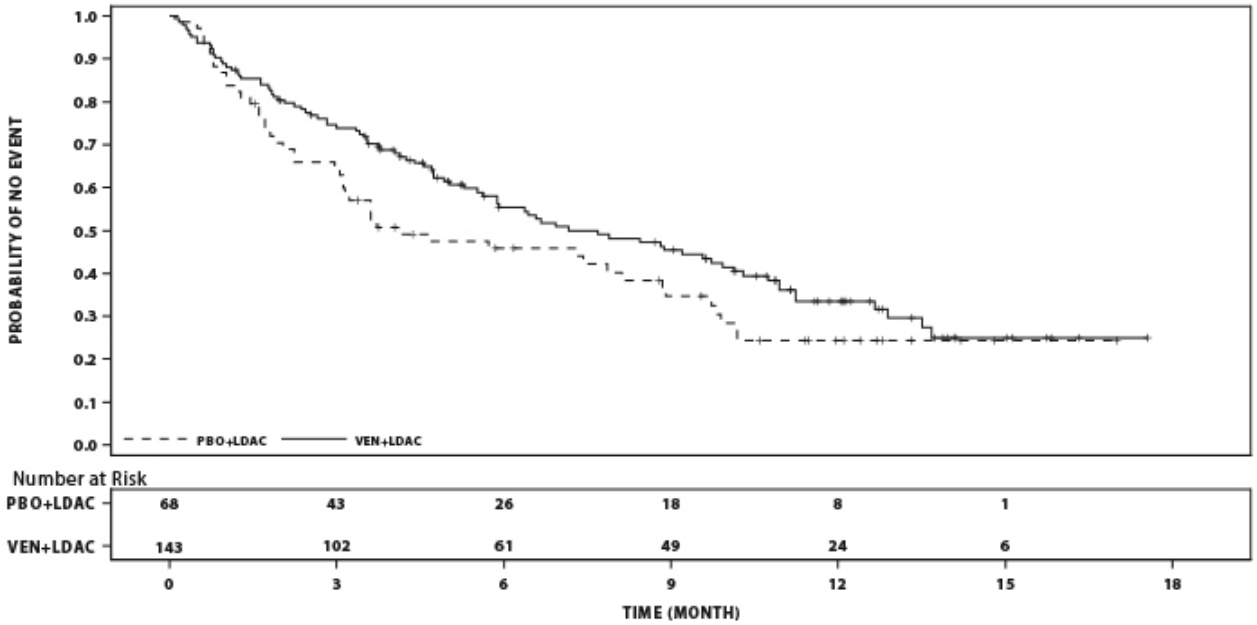
Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA or placebo was interrupted up to 14 days or until ANC ≥500/microliter and platelet count $\geq 25 \times 10^3$/microliter. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial.

Baseline demographic and disease characteristics were similar between the VENCLEXTA + low-dose cytarabine and placebo + low-dose cytarabine arms. The median age was 76 years (range: 36 to 93 years); 55% were male, and 71% were white, and ECOG performance status at baseline was 0 or 1 for 51% of patients and 2 for 42% of patients. There were 62% of patients with *de novo* AML and 38% with secondary AML. At baseline, 27% of patients had bone marrow blast count ≥30% – <50%, and 44% had ≥ 50%. Intermediate or poor cytogenetic risk was present in 63% and 32% patients, respectively. The following mutations were detected among 164 patients with samples: 19% (31) with *TP53*, 20% (33) with *IDH1* or *IDH2*, 18% (29) with *FLT3* and 15% (25) with *NPM1*.

At the time of the primary analysis for OS, patients had a median follow-up of 12 months (range: 0.1 to 17.6 months). The median OS in the VENCLEXTA + low-dose cytarabine arm was 7.2 months (95% CI: 5.6, 10.1) and in the placebo with low-dose cytarabine arm was 4.1 months (95% CI: 3.1, 8.8). The hazard ratio was 0.75 (95% CI: 0.52, 1.07; p=0.114) representing a 25% reduction in the risk of death for patients treated with VENCLEXTA + low-dose cytarabine.

The Kaplan-Meier curve for OS is shown in Figure 10.

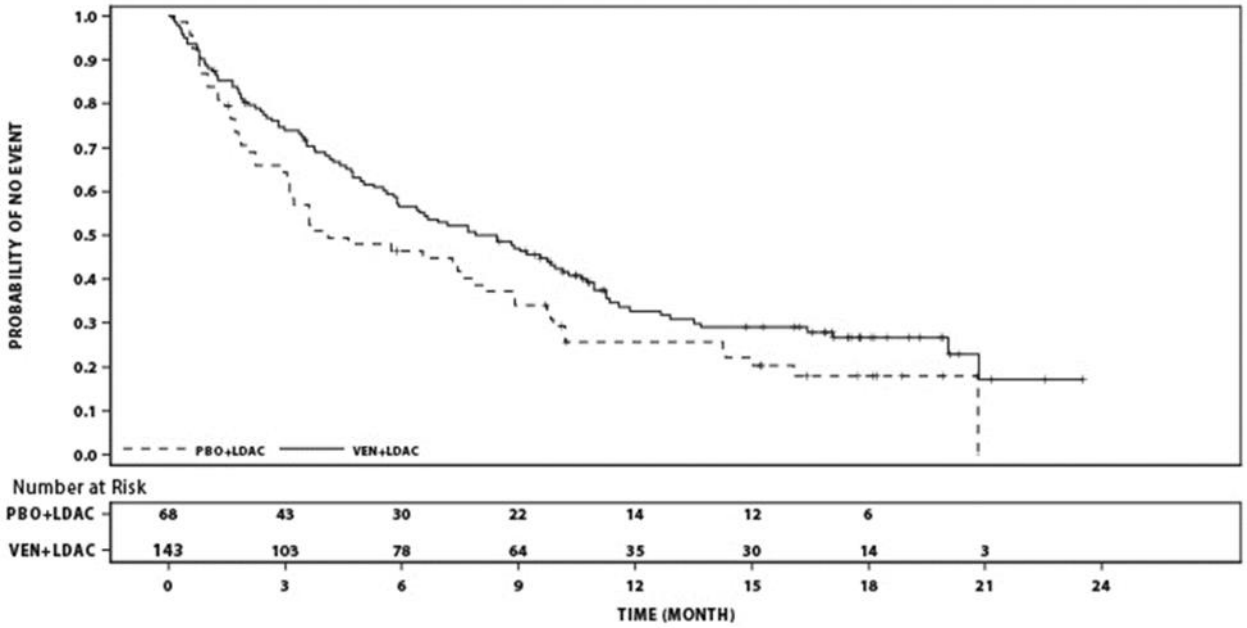
Figure 10. Kaplan-Meier Curves of Overall Survival (Primary Analysis) in VIALE-C



At the time of an additional analysis for OS, patients had a median follow-up of 17.5 months (range: 0.1 to 23.5 months). The median OS in the VENCLEXTA + low-dose cytarabine arm was 8.4 months (95% CI: 5.9, 10.1) and in the placebo + low-dose cytarabine arm was 4.1 months (95% CI: 3.1, 8.1). The hazard ratio was 0.70 (95% CI: 0.50, 0.99, nominal p=0.040)

representing a 30% reduction in the risk of death for patients treated with VENCLEXTA + low-dose cytarabine. The Kaplan-Meier curve for OS with 6 additional months of follow-up is shown in Figure 11.

Figure 11. Kaplan-Meier Curves of Overall Survival (6-month Follow-up Analysis) in VIALE-C



Efficacy results for secondary endpoints from the primary analysis are shown in Table 28 and below the table.

Table 28. Efficacy Results for Secondary Endpoints from the Primary Analysis of VIALE-C

Endpoint	**VENCLEXTA + low-dose cytarabine N=143**	**Placebo + low-dose cytarabine N=68**
CR, n (%) (95% CI) Median DOR[a] (months) (95% CI)	39 (27) (20, 35) 11.1 (5.9, NR)	5 (7) (2, 16) 8.3 (3.1, 8.3)
CR+CRi, n (%) (95% CI) Median DOR[a] (months) (95% CI)	68 (48) (39, 56) 10.8 (5.9, NR)	9 (13) (6, 24) 6.2 (1.1, NR)
CR+CRh, n (%) (95% CI) Median DOR[a] (months) (95% CI)	67 (47) (39, 55) 11.1 (5.5, NR)	10 (15) (7, 25) 6.2 (1.1, NR)

Transfusion independence[b] rate, n (%)		
Platelets	68 (48)	22 (32)
(95% CI)	(39, 56)	(22, 45)
Red blood cells, n (%)	58 (41)	12 (18)
(95% CI)	(32, 49)	(10, 29)

CI = confidence interval; CR+CRi = complete remission + complete remission with incomplete blood count recovery; CR+CRh = complete remission + complete remission with partial hematological recovery; DOR = duration of response; NR= not reached.
[a]DOR (duration of response) was defined as time from first response of CR for DOR of CR, or from first response of CR or CRi for DOR of CR+CRi, or from first response of CR or CRh for DOR of CR+CRh, to the first date of confirmed morphologic relapse, or death due to disease progression, whichever occurred earlier. Median DOR from Kaplan-Meier estimate.
[b]Transfusion independence was defined as a period of at least 56 consecutive days (≥56 days) with no transfusion after the first dose of study drug and on or before the last dose of the study drug + 30 days or before relapse or disease progression or before the initiation of post-treatment therapy whichever is earlier.

The CR+CRi rate by initiation of Cycle 2 for VENCLEXTA + low-dose cytarabine was 34% (95% CI: 27, 43) and for placebo + low-dose cytarabine was 3% (95% CI: 0.4, 10). The median time to first response of CR+CRi was 1.1 month (range: 0.8 to 4.7 months) with VENCLEXTA + low-dose cytarabine treatment. The median time to best response of CR+CRi was 1.2 month (range: 0.8 to 5.9 months).

Minimal residual disease response was defined as less than one AML cell per 10^3 leukocytes in the bone marrow. For the patients who had MRD assessment (113 patients in VENCLEXTA + low-dose cytarabine arm and 44 in placebo + low-dose cytarabine arm), the median MRD value (%) was lower in the VENCLEXTA arm when compared to the placebo arm (0.42 and 7.45, respectively). A higher number of patients had achieved CR+CRi and MRD response on VENCLEXTA arm compared to placebo arm: 8 patients (6%) (95% CI: 2, 11) vs 1 patient (1%) (95% CI: 0, 8), respectively.

Patient-reported fatigue was assessed by the Patient Reported Outcomes Measurement Information System (PROMIS), Cancer Fatigue Short Form (SF 7a) and health-related quality of life (HRQoL) was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) global health status/quality of life (GHS/QoL). Patients receiving VENCLEXTA + low-dose cytarabine did not experience meaningful decrement in fatigue or HRQoL than placebo + low-dose cytarabine, and observed reduction in PROMIS Cancer Fatigue and improvement in QHS/QoL. Relative to placebo + low-dose cytarabine, patients receiving VENCLEXTA + low-dose cytarabine observed reduction in PROMIS Cancer Fatigue that achieved a minimum important difference (MID) between two arms of 3 points by Day 1 of Cycles 3 and 5 (-2.940 vs 1.567, -5.259 versus -0.336, respectively, with lower score indicating improvement in fatigue symptom). Patients receiving VENCLEXTA + low-dose cytarabine observed improvement in GHS/QoL that achieved MID of 5 points on Day 1 of Cycles 5, 7 and 9 vs placebo + low-dose cytarabine (16.015 vs 2.627, 10.599 vs 3.481, and 13.299 vs 6.918, respectively, with higher score indicating improvement in quality of life).

The median EFS for VENCLEXTA + low-dose cytarabine was 4.7 months (95% CI, 3.7, 6.4) compared with 2.0 months (95% CI, 1.6, 3.1) for placebo + low-dose cytarabine with HR (95% CI) of 0.58 (0.42, 0.82).

M14-387

The efficacy of VENCLEXTA was established in a non-randomized clinical trial of VENCLEXTA in combination with low-dose cytarabine (N=82) in newly diagnosed patients with AML who were ineligible for intensive chemotherapy, including patients with previous exposure to a hypomethylating agent for an antecedent hematologic disorder.

Patients initiated VENCLEXTA via daily ramp-up to a final 600-mg once-daily dose. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m^2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA was interrupted up to 14 days or until ANC ≥500/microliter and platelet count $\geq 50 \times 10^3$/microliter.

Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trials.

Table 29 summarizes the baseline demographic and disease characteristics of the study population.

Table 29. Baseline Patient Characteristics for Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine in M14-387

Characteristic	VENCLEXTA in Combination with Low-Dose Cytarabine N=82
Age, years; median (range)	74 (63-90)
White; %	95
Male; %	65
ECOG performance status; % 0-1 2 3	 71 28 1
Bone marrow blast; % <30% ≥30% - <50% ≥50%	 33 22 44
History of antecedent hematologic disorder; %	48
Mutation analyses; % (identified/tested)	
TP53	14 (10/70)

IDH1 or *IDH2*	26 (18/70)
FLT-3	21 (15/70)
NPM1	13 (9/70)
Cytogenetic risk [a]; %	
Intermediate	60
Poor	32
No mitoses	9
[a]As defined by the National Comprehensive Cancer Network (NCCN) risk categorization v2014	

The median follow-up was 41.7 months (range: 0.3 to 54.0 months). Efficacy results are shown in Tables 30 and 31.

Table 30. Efficacy Results for Newly Diagnosed Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine (M14-387)

Endpoint	**VENCLEXTA in Combination with Low-Dose Cytarabine N=82**
CR, n (%) (95% CI) Median DOR[a] (months) (95% CI)	21 (26) (17 - 36) 14.8 (7.2, NR)
CRi, n (%) (95% CI) Median DOR[a] (months) (95% CI)	23 (28) (19, 39) 4.7 (2.6, 5.6)
CR+CRi, n (%) (95% CI) Median DOR (months) (95% CI)	44 (54) (42, 65) 9.8 (5.3, 14.9)
CRh, n (%) (95% CI) Median DOR[a] (months) (95% CI)	17 (21) (13, 31) 6.6 (2.8, 11.0)
CR+CRh, n (%) (95% CI) Median DOR[a] (months) (95% CI)	38 (46) (35, 58) 11.0 (6.1,28.2)
Transfusion independence rate, n/N (%) Red blood cell[b] Platelet[c]	 24/53 (45) 14/23 (61)
CI = confidence interval; NR = not reached. CR (complete remission) was defined as absolute neutrophil count ≥1,000/microliter, platelets ≥100,000/microliter, red blood cell transfusion independence, and bone marrow with <5%	

blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRh (complete remission with partial hematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).
CRi (complete remission with incomplete blood count recovery) was defined as same as all of the criteria for CR except for residual neutropenia <1,000/microliter or thrombocytopenia <100,000/microliter.
[a]DOR (duration of response) was defined as time from first response of CR for DOR of CR, or from first response of CRi for DOR of CRi, or from first response of CR or CRi for DOR of CR+CRi, or from first response of CRh for DOR of CRh, or from first response of CR or CRh for DOR of CR+CRh, to the first date of relapse, clinical disease progression, or death due to disease progression, whichever occurred earlier. Median DOR from Kaplan-Meier estimate.
[b]Evaluated for patients who were dependent at baseline for red blood cell transfusion.
[c]Evaluated for patients who were dependent at baseline for platelet transfusion.

Table 31. Time to Response in Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine (M14-387)

Endpoint	VENCLEXTA in Combination with Low-Dose Cytarabine N=82
Median time to BEST response of CR (months) Range (months)	3.0 (0.9 – 22.4)
Median time to FIRST response of CR+CRh (months) Range (months)	1.0 (0.8 – 9.4)
Median time to FIRST response of CR+CRi (months) Range (months)	1.4 (0.8 – 14.9)

Median overall survival for patients on VENCLEXTA in combination with low-dose cytarabine was 9.7 months (95% CI: 5.7, 14.0).

Remissions (CR or CRh) were observed across subgroups with different baseline characteristics. For patients with poor or intermediate risk cytogenetics, similar remissions rates were observed; the rates were 35% or 57%, respectively. For patients with the following identified mutations, the remissions were as follows: *TP53*: 20% (2/10), *IDH1/2*: 67% (12/18), *FLT-3*: 33% (5/15) and *NPM1*: 89% (8/9).

Remissions (CR or CRi) were observed across subgroups with different baseline characteristics. For patients with poor or intermediate risk cytogenetics, similar remissions rates were observed; the rates were 42% or 63%, respectively. For patients with the following identified mutations, the remissions were as follows: *TP53*: 30% (3/10), *IDH1/2*: 72% (13/18), *FLT-3*: 40% (6/15) and *NPM1*: 89% (8/9).

Minimal residual disease was evaluated in bone marrow for patients who achieved CR or CRh following treatment with VENCLEXTA in combination with low-dose cytarabine. Of those

patients, 34% (13/38) achieved MRD less than one AML cell per 10^3 leukocytes in the bone marrow.

Minimal residual disease was evaluated in bone marrow for patients who achieved CR or CRi following treatment with VENCLEXTA in combination with low-dose cytarabine. Of those patients, 32% (14/44) achieved MRD less than one AML cell per 10^3 leukocytes in the bone marrow.

Of patients treated with VENCLEXTA in combination with low-dose cytarabine, 1% (1/82) achieved a CR/CRi and subsequently received stem cell transplant.

STORAGE

Store at or below 30°C.

HOW SUPPLIED

Tablet Strength	Description of Tablet
10 mg	Round, biconvex shaped, pale yellow film-coated tablet debossed with “V” on one side and “10” on the other side
50 mg	Oblong, biconvex shaped, beige film-coated tablet debossed with “V” on one side and “50” on the other side
100 mg	Oblong, biconvex shaped, pale yellow film-coated tablet debossed with “V” on one side and “100” on the other side

VENCLEXTA is dispensed as follows:

10 mg tablets supplied as a carton containing a weekly wallet blister pack. Each pack contains 14 tablets.

50 mg tablets supplied as a carton containing a weekly wallet blister pack. Each pack contains 7 tablets.

100 mg tablets supplied as:

- a carton containing a weekly wallet blister pack. Each pack contains 7 or 14 tablets
- a bottle containing 120 tablets

Not all presentations may be available locally.

Manufactured by:
AbbVie Ireland NL B.V.
Sligo, Ireland

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Date of issue: DD MMM YYYY