WITH >6 YEARS OF FOLLOW-UP IN PREVIOUSLY UNTREATED CLL, AND >7 YEARS OF FOLLOW-UP IN R/R CLL

VENCLEXTA®
venetoclax tablets 10mg, 50mg, 100mg

THE POWER TO OFFER TIME OFF TREATMENT

With fixed-duration VENCLEXTA regimens, offer your patients the chance for **durable PFS without continuous treatment**

- **VEN+G regimen:** Designed to be completed after 12 months (twelve 28-day treatment cycles): GAZYVA® (obinutuzumab) is administered in Cycles 1–6, and VENCLEXTA is taken orally 400 mg/day from Cycle 3, Day 1, after the first two cycles of GAZYVA and the 5-week VENCLEXTA dose ramp-up[1]
- **CLL14 trial design and primary endpoint:** In a randomized clinical trial of 432 patients (VEN+G: N=216; GClb: N=216) with previously untreated CLL and with a median follow-up of 28 months (range: 0–36 months), VEN+G reduced the risk of progression or death by 67% vs GClb (HR=0.33; 95% CI: 0.22–0.51 [*P*<0.0001]). Median PFS was not reached in either arm[1]
- **VEN+R regimen:** Designed to be completed after 24 months (after the 5-week VENCLEXTA dose ramp-up): rituximab is administered in Cycles 1–6; VENCLEXTA is taken orally 400 mg/day for 24 months from Cycle 1, Day 1 of rituximab[1]
- **MURANO trial design and primary endpoint:** In a randomized clinical trial of 389 patients (VEN+R: N=194; BR: N=195) with previously treated CLL and with a median follow-up of 23.4 months (range: 0–37.4+ months), VEN+R reduced the risk of progression or death by 81% vs BR (HR=0.19; 95% CI: 0.13–0.28 [*P*<0.0001]). Median PFS was not reached in VEN+R vs 18.1 months in BR (95% CI: 15.8–22.3)[1]

CLL=chronic lymphocytic leukemia; R/R=relapsed/refractory; PFS=progression-free survival; VEN+G=VENCLEXTA + GAZYVA; GClb=GAZYVA + chlorambucil; HR=hazard ratio; CI=confidence interval; VEN+R=VENCLEXTA + rituximab; BR=bendamustine + rituximab.

Indication

VENCLEXTA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Important Safety Information

Contraindication

- Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome (TLS).

Tumor Lysis Syndrome

- Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients treated with VENCLEXTA.
- VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase in all patients, and during reinitiation after dosage interruption in patients with CLL/SLL. 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. TLS, including fatal cases, has been reported after a single 20 mg dose.

Please see additional Important Safety Information on pages 12–13 and throughout the piece.
Please see full Prescribing Information at www.rxabbvie.com/pdf/venclexta.pdf.

Are you offering your CLL patients the chance for time off treatment?

VENCLEXTA + GAZYVA® (obinutuzumab) in previously untreated CLL[1]

1 YEAR
FIXED DURATION → **TREATMENT-FREE PERIOD**

VENCLEXTA + rituximab in R/R CLL[1]

~2 YEARS
FIXED DURATION* → **TREATMENT-FREE PERIOD**

Treat-to-progression regimens

CONTINUOUS TREATMENT UNTIL PROGRESSION OR UNACCEPTABLE TOXICITY

Treatment duration and treatment-free period are not to scale and may vary by patient. Not representative of all patients.

No comparative safety or efficacy conclusions regarding VENCLEXTA regimens and TTP regimens can be drawn from the visual. Presentation of this information is not to imply that VENCLEXTA regimens and TTP regimens are interchangeable or therapeutically equivalent.

For more information about dosing with VENCLEXTA, please see the full Prescribing Information.

*From Day 1, Cycle 1 of rituximab.[1]
TTP=treat-to-progression.

Important Safety Information (cont'd)

Tumor Lysis Syndrome (cont'd)

- In patients with CLL/SLL who followed the current (5 week) dose ramp-up and the TLS prophylaxis and monitoring measures, the rate of TLS was 2% in the VENCLEXTA CLL/SLL monotherapy trials. The rate of TLS remained consistent with VENCLEXTA in combination with obinutuzumab or rituximab. With a 2- to 3-week dose ramp-up and higher starting dose in patients with CLL/SLL, the TLS rate was 13% and included deaths and renal failure.
- The risk of TLS is a continuum based on multiple factors, particularly reduced renal function, tumor burden, and type of malignancy. Splenomegaly may also increase the risk of TLS in patients with CLL/SLL.
- Assess all patients for risk and provide appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases. Interrupt dosing if needed; when restarting VENCLEXTA follow dose modification guidance in the Prescribing Information.
- Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during the ramp-up phase, and requires VENCLEXTA dose reduction.

Please see additional Important Safety Information on pages 12–13 and throughout the piece.
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CLL Society Patient Preference Survey (2021)[2,3]

The survey was conducted to assess patients' understanding, awareness, and preference related to finite therapies and MRD testing, and was not designed to measure preference for any specific CLL treatment.

When 608 patients and 22 caregivers were asked about preference for duration of CLL therapy, if effectiveness and side effects were assumed similar:

Over 3 of 4 respondents preferred finite-duration therapy

77% *preferred **finite-duration** therapy**

7% *preferred **continuous** therapy*[†]

***Survey question results:**

- **77%** preferred finite-duration therapy, which includes:
  - **63%** who responded "Limited duration therapy that is stopped after reaching uMRD or preplanned period of time if uMRD is not reached"
  - **14%** who responded "Limited duration therapy that is stopped after preplanned period of time"
- **10%** No preference for the duration of therapy
- **7%** Therapy that is taken indefinitely
- **6%** Don't know/not sure

Limitations include the opt-in sample where the survey results may not be reflective of the general CLL population and their caregivers.

[†]Until disease progression or intolerance.

MRD=minimal residual disease; uMRD=undetectable minimal residual disease.

Are you offering your CLL patients the benefits of time off treatment?

With fixed-duration VENCLEXTA regimens, give your patients the chance for:

TIME OFF TREATMENT

- **Set a target stop date** that can encourage compliance and optimize clinical outcomes, followed by a **treatment-free period**[4,5]
- Offer your patients the chance for **time off treatment**, and a return to life **without a daily reminder** of their treatment and disease[1]

NO ONGOING TREATMENT EXPOSURE

- **Limit your patients' additional exposure to the regimen and potential side effects**, after completing treatment*

NO ONGOING OUT-OF-POCKET COSTS

- **Limit financial impact on your patients**, with no additional VENCLEXTA regimen patient out-of-pocket costs after completing treatment per the recommended dosing†

*In CLL14, all adverse events were reported until 28 days after the last dose of study treatment (venetoclax, chlorambucil, or obinutuzumab). Grade 3-4 adverse events were reported for 6 months and Grade 3-4 infections were reported for 2 years after the last dose of study treatment, irrespective of causality, unless the patient received next leukemic treatment.[6,7] In MURANO, all adverse events were reported until 28 days after the last dose of study drug, or 90 days after the last dose of rituximab, whichever was longer. After this period, investigators reported any deaths, serious adverse events, or other adverse events of concern that were believed to be related to prior study drug treatment.[8]

†Coverage and patient out-of-pocket costs for VEN+G and VEN+R vary by health plan. Patients may still incur out-of-pocket costs for other treatments or tests as directed by their healthcare providers.

Important Safety Information (cont'd)

Neutropenia

- In patients with CLL, Grade 3 or 4 neutropenia developed in 63% to 64% of patients and Grade 4 neutropenia developed in 31% to 33% of patients when treated with VENCLEXTA in combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients.
- Monitor complete blood counts. Interrupt dosing for severe neutropenia and resume at same or reduced dose. Consider supportive measures including antimicrobials and growth factors (e.g., G-CSF).

Infections

- Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with VENCLEXTA. Monitor patients for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution and resume at same or reduced dose.

Immunization

- Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. Advise patients that vaccinations may be less effective.

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See why John chose VEN+G

"It really appealed to me that with VENCLEXTA there is an end date to this treatment. I went from this place of being concerned to being hopeful."

—John: Husband, dog trainer and kennel owner, loves the outdoors, CLL patient

As of March 2023, John was still **off-treatment and progression-free** >3 years after completing 1L treatment with VEN+G.

Individual results may vary.

See more of John's story, and why he and his doctor chose VEN+G

1L=first line.

Important Safety Information (cont'd)

Embryo-Fetal Toxicity

- VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for 30 days after the last dose.

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

- **In patients with CLL receiving combination therapy with obinutuzumab,** serious adverse reactions were most often due to febrile neutropenia and pneumonia (5% each). The most common adverse reactions (≥20%) of any grade were neutropenia (60%), diarrhea (28%), and fatigue (21%). Fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients, most often from infection.

Please see additional Important Safety Information on pages 12–13 and throughout the piece.
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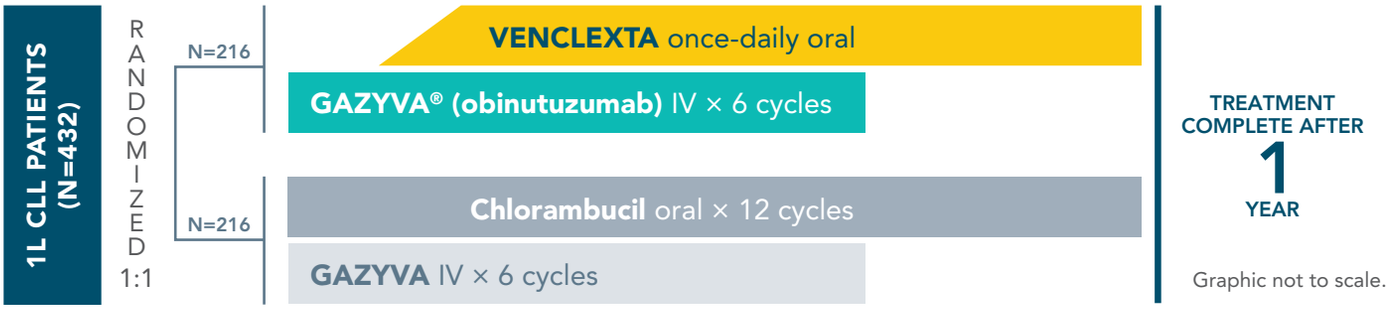
Designed for patients to complete treatment in 1 year[1]

The CLL14 trial evaluated PFS with VEN+G, a fixed-duration treatment regimen



- CLL14 was a multicenter, open-label, actively controlled phase 3 trial (randomized 1:1)[1,9]
- In CLL14, the VEN+G regimen was designed to be completed after 12 months (twelve 28-day treatment cycles):
  - GAZYVA IV infusion was administered at 1000 mg on Days 1 (the first dose could be split as 100 mg and 900 mg on Days 1 and 2, respectively), 8 and 15 of Cycle 1, and on Day 1 of each subsequent cycle for a total of 6 cycles[1]
  - VENCLEXTA oral tablets were administered according to the 5-week dose ramp-up schedule: 20 mg daily during Cycle 1, Days 22–28; 50 mg daily during Cycle 2, Days 1–7; 100 mg daily during Cycle 2, Days 8–14; 200 mg daily during Cycle 2, Days 15–21; 400 mg daily during Cycle 2, Days 22–28 and on Days 1–28 of all subsequent cycles until the end of Cycle 12[1]
  - In the GClb arm of CLL14, GAZYVA was administered in Cycles 1–6; chlorambucil was administered at 0.5 mg/kg orally on Day 1 and Day 15 of Cycles 1 to 12[1]

Select inclusion criteria[1]

- Previously untreated CLL with coexisting medical conditions (total CIRS >6 or CrCl <70 mL/min)

Select clinical endpoints[1,9,10]

- **Primary endpoint:** PFS (IRC-assessed PFS was the basis for FDA approval of VEN+G)
- **Select secondary endpoints:** MRD in bone marrow, CR/CRi (INV-assessed), MRD in peripheral blood, MRD in CR/CRi in bone marrow, MRD in CR/CRi in peripheral blood, ORR (INV-assessed), OS, TTNT (unranked)

After the first treatment cycle of GAZYVA and before the VENCLEXTA dose ramp-up, median ALC was reduced by 98%[1,11]

- Per the trial protocol, tumor burden was assessed based on ALC and lymph node size. The effect of the first GAZYVA treatment cycle on lymph node size was not evaluated. The trial started with an initial cycle of GAZYVA followed by the 5-week VENCLEXTA dose ramp-up; median lymphocyte count was reduced in the safety evaluable population (N=212) from 55 × 10^9 cells/L at baseline to 1.27 × 10^9 cells/L at Day 15. Median lymphocyte counts are descriptive in nature and were not powered for any type of comparison. Changes in TLS risk status based on ALC reduction were at the discretion of the trial investigators

IV=intravenous; CIRS=Cumulative Illness Rating Scale; CrCl=creatinine clearance; IRC=independent review committee; FDA=US Food and Drug Administration; MRD=minimal residual disease; CR=complete remission; CRi=complete remission with incomplete bone marrow recovery; INV=investigator; ORR=overall response rate; OS=overall survival; TTNT=time to next treatment; ALC=absolute lymphocyte count; TLS=tumor lysis syndrome.

Important Safety Information (cont'd)

Adverse Reactions (cont'd)

- **In patients with CLL receiving combination therapy with rituximab,** the most frequent serious adverse reaction (≥5%) was pneumonia (9%). The most common adverse reactions (≥20%) of any grade were neutropenia (65%), diarrhea (40%), upper respiratory tract infection (39%), fatigue (22%), and nausea (21%). Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of the last VENCLEXTA treatment and/or 90 days of the last rituximab were reported in 2% (4/194) of patients.
- **In patients with CLL/SLL receiving monotherapy,** the most frequent serious adverse reactions (≥5%) were pneumonia (9%), febrile neutropenia (5%), and sepsis (5%). The most common adverse reactions (≥20%) of any grade were neutropenia (50%), diarrhea (43%), nausea (42%), upper respiratory tract infection (36%), anemia (33%), fatigue (32%), thrombocytopenia (29%), musculoskeletal pain (29%), edema (22%), and cough (22%). Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of venetoclax treatment were reported in 2% of patients in the VENCLEXTA monotherapy studies, most often (2 patients) from septic shock.

Drug Interactions

- Concomitant use with a P-gp inhibitor or a strong or moderate CYP3A inhibitor increases VENCLEXTA exposure, which may increase VENCLEXTA toxicities, including the risk of TLS. Consider alternative medications or adjust VENCLEXTA dosage and monitor more frequently for adverse reactions. Resume the VENCLEXTA dosage that was used prior to concomitant use of a P-gp inhibitor or a strong or moderate CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

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VEN+G demonstrated durable PFS without long-term treatment[1]

IRC-assessed PFS (primary endpoint)

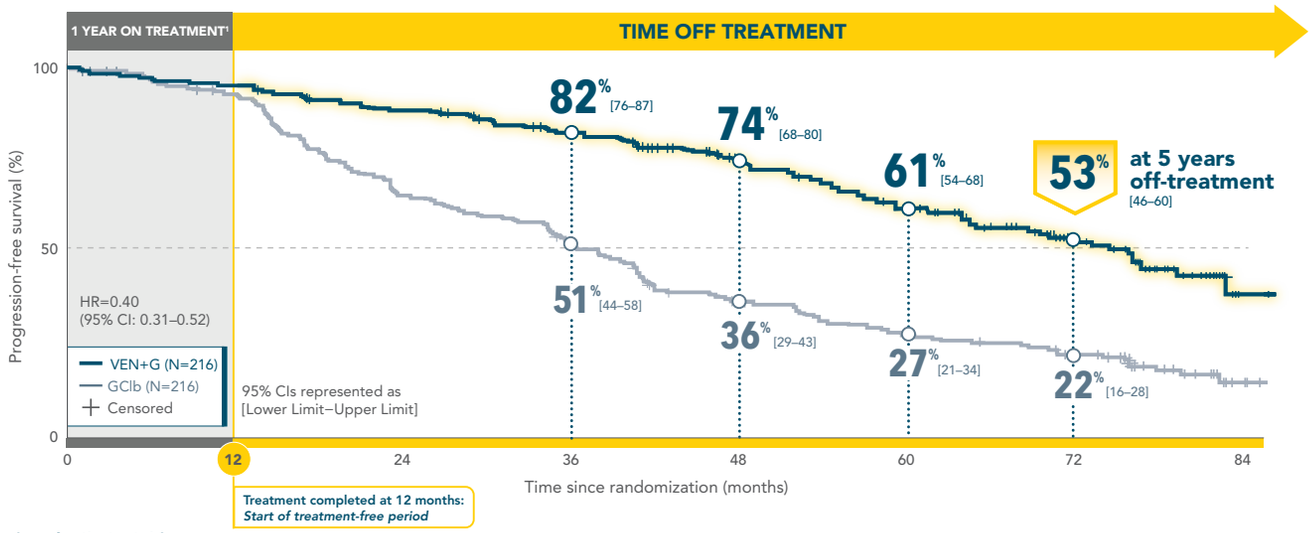
67% **reduction in risk of progression or death vs GClb** (HR=0.33; 95% CI: 0.22–0.51 [*P*<0.0001])

After a median follow-up of 28 months (range: 0–36 months):

- There were 29 events in the VEN+G arm (14 progressions and 15 deaths without disease progression) compared with 79 events in the GClb arm (71 progressions and 8 deaths without disease progression)*
- Median PFS was not reached in either arm

*Number of events based on earliest event of disease progression or deaths without disease progression due to any cause.

6-year follow-up analysis of INV-assessed PFS (overall follow-up of 86.5 months)[12,13†]



Number of patients at risk								
VEN+G	216	193	177	160	139	112	79	3
GClb	216	185	130	101	67	50	36	3

- **PFS estimates may be unreliable at the tail end of the curve due to smaller number of patients at risk**

The PFS and TTNT follow-up analyses were not tested for statistical significance[12,13]

- With a median follow-up of 76.4 months (range: 0–86.5 months), **median PFS was estimated to be 76.2 months** (95% CI: 65.1–83.3) for the VEN+G arm and 36.4 months (95% CI: 34.1–41.0) in the GClb arm (HR=0.40; 95% CI: 0.31–0.52)
- Of the 101 events in the VEN+G arm, 67 were disease progression, and 34 were deaths without disease progression. Of the 161 events in the GClb arm, 141 were disease progression, and 20 were deaths without disease progression

TIME TO NEXT TREATMENT[12,13‡]

At the time of the 6-year analysis*:

Over 6 out of 10 patients in the VEN+G arm had not received subsequent treatment

64% (139/216)

vs 35% of patients in the GClb arm (76/216)

- The decision to initiate next therapy was made by the treating physician and patient, which can be a limitation to this analysis
- Rates do not account for censoring

†Based on data as of clinical data cutoff date of November 14, 2022; time of analysis was not pre-specified.[12,13]
‡TTNT was defined as the time from randomization to start of a new CLL therapy or death.

Important Safety Information (cont'd)

Drug Interactions (cont'd)

- Patients should avoid grapefruit products, Seville oranges, and starfruit during treatment as they contain inhibitors of CYP3A.
- Avoid concomitant use of strong or moderate CYP3A inducers.
- Monitor international normalized ratio (INR) more frequently in patients receiving warfarin.

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VEN+G offers a well-studied safety profile with exposure limited to 1 year[1]

VEN+G safety from the CLL14 trial

- The median duration of exposure to VENCLEXTA was 10.5 months (range: 0–13.5 months). The median number of cycles was 6 for GAZYVA® (obinutuzumab)
- In the VEN+G arm, fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients, most often from infection, compared with 1% (3/214) of patients in the GClb arm[1,11]
- Serious adverse reactions were reported in 49% of patients in the VEN+G arm, most often due to febrile neutropenia and pneumonia (5% each)
- **Tumor lysis syndrome (TLS) is an important identified risk when initiating VENCLEXTA**
- **TLS prophylaxis and monitoring protocols can reduce the risk of TLS**
- **The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS**
- **The incidence of laboratory TLS was 1%** (3/212) in patients treated with VEN+G. All three events of TLS occurred during treatment with GAZYVA, before treatment initiation with VENCLEXTA. All 3 events of TLS resolved and did not lead to withdrawal from the trial. GAZYVA administration was delayed in 2 cases in response to the TLS events
- **The incidence of clinical TLS was 0%**[1]
- There were no new safety signals detected at the 6-year follow-up[12]

Rates of discontinuation, dose reduction, and dose interruption

- In the VEN+G arm, adverse reactions led to treatment discontinuation in 16% of patients, dose reduction in 21%, and dose interruption in 74%[1]
- Neutropenia led to discontinuation of VENCLEXTA in 2% of patients, reduction in 13%, and dose interruption in 41%

Adverse reactions (≥10%) in patients treated with VEN+G[1]

	VEN+G (N=212)		GClb (N=214)	
Adverse Reaction by Body System	**Any Grade (%)**	**Grade ≥3 (%)**	**Any Grade (%)**	**Grade ≥3 (%)**
Blood and lymphatic system disorders				
Neutropenia*	60	56	62	52
Anemia*	17	8	20	7
Gastrointestinal disorders				
Diarrhea	28	4	15	1
Nausea	19	0	22	1
Constipation	13	0	9	0
Vomiting	10	1	8	1
General disorders and administration site conditions				
Fatigue*	21	2	23	1
Infections and infestations				
Upper respiratory tract infection*	17	1	17	1

*Includes multiple adverse reaction terms.

For laboratory abnormalities data, please see Table 10 in the VENCLEXTA full Prescribing Information.

Granulocyte colony-stimulating factor (G-CSF) was used to treat neutropenia in 44% of patients in the VEN+G arm and 46% of patients in the GClb arm.[9]

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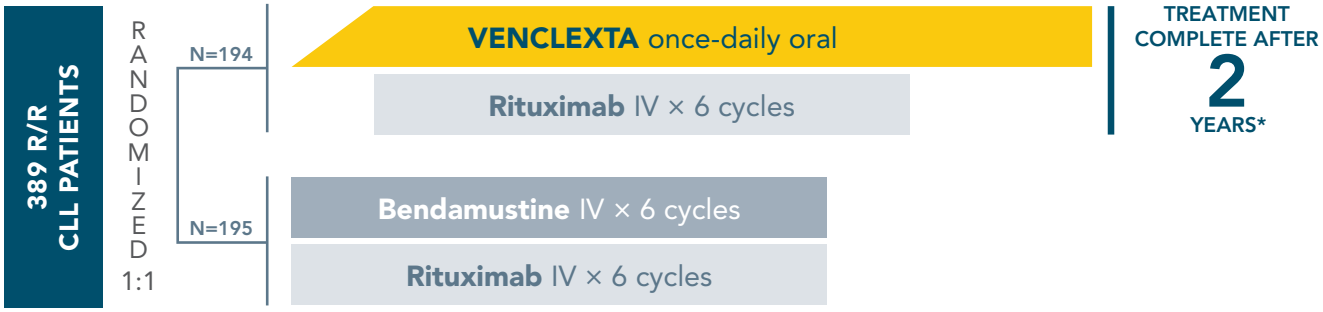
Designed for patients to complete treatment at 2 years[1]*

The MURANO trial evaluated PFS with VEN+R, a fixed-duration treatment regimen



Graphic not to scale.

- MURANO was a phase 3, multicenter, open-label, actively controlled trial (randomized 1:1)[1,8]
- The 5-week VENCLEXTA dose ramp-up was designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS
- VENCLEXTA oral tablets were administered according to the 5-week dose ramp-up schedule: 20 mg daily in Week 1, 50 mg daily in Week 2, 100 mg daily in Week 3, 200 mg daily in Week 4, and 400 mg daily from Week 5 through all subsequent weeks for 24 months from Cycle 1, Day 1 of rituximab
- Rituximab was administered after the initial VENCLEXTA dose ramp-up and was infused on Day 1 of each 28-day cycle for 6 cycles, with a dose of 375 mg/m^2 for Cycle 1 and 500 mg/m^2 for Cycles 2–6
- Patients randomized to bendamustine + rituximab received bendamustine intravenously at 70 mg/m^2 on Days 1 and 2 for 6 cycles (28-day cycle) and rituximab at the above-described dose and schedule

Select inclusion criteria

- 1–3 prior lines of therapy, including at least 1 chemo-containing regimen; and prior bendamustine only if duration of response (DoR) ≥24 months[8]

Select clinical endpoints

- **Primary endpoint:** PFS (IRC-assessed PFS was the basis for approval of VEN+R)
- **Select secondary endpoints:** IRC-assessed CR/CRi, IRC-assessed ORR, OS, TTNT (unranked), uMRD (unranked)[8,14]
  - Key secondary endpoints were ranked for hierarchical testing as: (1) IRC-assessed CR/CRi rate, (2) IRC-assessed ORR, and (3) OS. Because the study did not reach significance at the first key secondary endpoint (IRC-assessed CR/CRi rate), the remaining key secondary endpoints could not be tested for statistical significance[14]

*From Cycle 1, Day 1 of rituximab, in the absence of disease progression or unacceptable toxicity.[1]

Important Safety Information (cont'd)

Drug Interactions (cont'd)

- Avoid concomitant use of VENCLEXTA with a P-gp substrate. If concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.

Lactation

- Advise women not to breastfeed during treatment with VENCLEXTA and for 1 week after the last dose.

Females and Males of Reproductive Potential

- Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for 30 days after the last dose.

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VEN+R demonstrated durable PFS without long-term treatment[1]*

IRC-assessed PFS (primary endpoint)

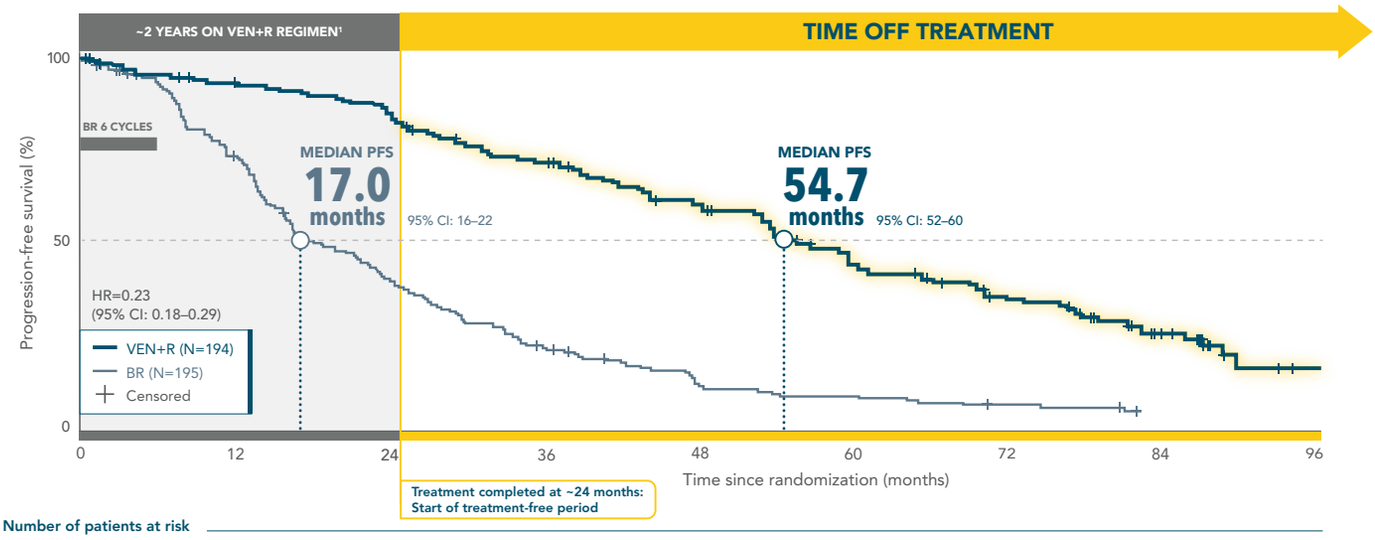
81% **reduction in risk of progression or death vs BR** (HR=0.19; 95% CI: 0.13–0.28 [*P*<0.0001])

After a median follow-up of 23.4 months (range: 0–37.4+ months):

- There were 35 events in the VEN+R arm (26 progressions and 9 deaths without disease progression) compared with 106 events in the BR arm (91 progressions and 15 deaths without disease progression)†
- The median PFS was not reached with VEN+R vs 18.1 months (95% CI: 15.8–22.3) with BR

*VEN+R is designed to be completed in 24 months from Cycle 1, Day 1 of rituximab, in the absence of disease progression or unacceptable toxicity.
†Number of events based on earliest event of disease progression or deaths without disease progression due to any cause.

7-year follow-up analysis of INV-assessed PFS (overall follow-up of 99.2 months)[15,16‡]



Number of patients at risk

VEN+R	194	176	161	133	107	68	46	19	1
BR	195	129	66	32	14	9	4	–	–

The PFS and TTNT follow-up analyses were not tested for statistical significance[15,16]

- With a median follow-up of 85.7 months (range: 0.0-99.2 months):
  - There were 136 events in the VEN+R arm (117 progressions and 19 deaths without disease progression)
  - There were 173 events in the BR arm (154 progressions and 19 deaths without disease progression)

TIME TO NEXT TREATMENT[15,16§]

At the time of the 7-year analysis‡:

Nearly 4 out of 10 patients in the VEN+R arm had not received subsequent treatment

38% (73/194)

vs 18% (36/195) of patients in the BR arm

- The decision to initiate next therapy was made by the treating physician and patient, which can be a limitation to this analysis
- Rates do not account for censoring

‡Based on data as of clinical data cutoff date of August 3, 2022; time of analysis was not pre-specified.
§TTNT was defined as the time from randomization to start of a new CLL therapy or death.

Important Safety Information (cont'd)

Females and Males of Reproductive Potential (cont'd)

- Based on findings in animals, VENCLEXTA may impair male fertility.

Hepatic Impairment

- Reduce the dose of VENCLEXTA for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more frequently for adverse reactions. No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

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VEN+R offers a well-studied safety profile with exposure limited to 2 years[1]*

VEN+R safety from MURANO trial

- At the time of data analysis, the median duration of exposure was 22 months in the VEN+R arm compared with 6 months in the BR arm
- In the VEN+R arm, fatal adverse reactions that occurred in the absence of disease progression and within 30 days of the last VENCLEXTA treatment and/or 90 days of last rituximab treatment were reported in 2% (4/194) of patients. Serious adverse reactions were reported in 46% of patients in the VEN+R arm, with the most frequent (≥5%) being pneumonia (9%)
- 93% (173/187) of patients in the VEN+R arm and 68% (127/188) of patients in the BR arm completed 6 combination treatment cycles[17]
  - 7 patients in each arm did not receive combination therapy: In the VEN+R arm, 7 patients did not receive rituximab, and in the BR arm, 7 patients did not receive either bendamustine or rituximab[8]
  - Patients needed to receive at least 90% of the target dose to be counted as receiving a full cycle[17]
- **Tumor lysis syndrome is an important identified risk when initiating VENCLEXTA**
- **TLS prophylaxis and monitoring protocols can reduce the risk of TLS**
- **The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS**
- **The incidence of TLS was 3% overall** (6/194) in patients treated with VEN+R. After 77/389 patients were enrolled in the trial, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures
- All events of TLS occurred during the VENCLEXTA ramp-up period and were resolved within two days. All six patients completed the ramp-up and reached the recommended daily dose of 400 mg of VENCLEXTA
- **The incidence of clinical TLS was 0%** in patients who followed the current 5-week ramp-up schedule and TLS prophylaxis and monitoring measures
- There were no new safety signals detected at the 7-year follow-up[15]

Rates of discontinuation, dose reduction, and dose interruption

- In the VEN+R arm, adverse reactions led to treatment discontinuation in 16% of patients, dose reduction in 15%, and dose interruption in 71%
- Neutropenia led to discontinuation of VENCLEXTA in 3% of patients and dose interruption in 46%. Thrombocytopenia led to discontinuation in 3% of patients

*From Cycle 1, Day 1 of rituximab.[1]

Adverse reactions (≥10%) in patients treated with VEN+R[1]

	VEN+R (N=194)		BR (N=188)	
Adverse Reaction by Body System	**Any Grade (%)**	**Grade ≥3 (%)**	**Any Grade (%)**	**Grade ≥3 (%)**
Blood and lymphatic system disorders				
Neutropenia†	65	62	50	44
Anemia†	16	11	23	14
Gastrointestinal disorders				
Diarrhea	40	3	17	1
Nausea	21	1	34	1
Constipation	14	<1	21	0
Infections and infestations				
Upper respiratory tract infection†	39	2	23	2
Lower respiratory tract infection†	18	2	10	2
Pneumonia†	10	7	14	10
General disorders and administration site conditions				
Fatigue†	22	2	26	<1

†Includes multiple adverse reaction terms.

For laboratory abnormalities data, please see Table 12 in the VENCLEXTA full Prescribing Information.

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Important Safety Information

Contraindication

- Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome (TLS).

Tumor Lysis Syndrome

- Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients treated with VENCLEXTA.
- VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase in all patients, and during reinitiation after dosage interruption in patients with CLL/SLL. 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. TLS, including fatal cases, has been reported after a single 20 mg dose.
- In patients with CLL/SLL who followed the current (5 week) dose ramp-up and the TLS prophylaxis and monitoring measures, the rate of TLS was 2% in the VENCLEXTA CLL/SLL monotherapy trials. The rate of TLS remained consistent with VENCLEXTA in combination with obinutuzumab or rituximab. With a 2- to 3-week dose ramp-up and higher starting dose in patients with CLL/SLL, the TLS rate was 13% and included deaths and renal failure.
- The risk of TLS is a continuum based on multiple factors, particularly reduced renal function, tumor burden, and type of malignancy. Splenomegaly may also increase the risk of TLS in patients with CLL/SLL.
- Assess all patients for risk and provide appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases. Interrupt dosing if needed; when restarting VENCLEXTA follow dose modification guidance in the Prescribing Information.
- Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during the ramp-up phase, and requires VENCLEXTA dose reduction.

Neutropenia

- In patients with CLL, Grade 3 or 4 neutropenia developed in 63% to 64% of patients and Grade 4 neutropenia developed in 31% to 33% of patients when treated with VENCLEXTA in combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients.
- Monitor complete blood counts. Interrupt dosing for severe neutropenia and resume at same or reduced dose. Consider supportive measures including antimicrobials and growth factors (e.g., G-CSF).

Infections

- Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with VENCLEXTA. Monitor patients for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution and resume at same or reduced dose.

Immunization

- Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. Advise patients that vaccinations may be less effective.

Embryo-Fetal Toxicity

- VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for 30 days after the last dose.

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

- **In patients with CLL receiving combination therapy with obinutuzumab,** serious adverse reactions were most often due to febrile neutropenia and pneumonia (5% each). The most common adverse reactions (≥20%) of any grade were neutropenia (60%), diarrhea (28%), and fatigue (21%). Fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients, most often from infection.

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Important Safety Information (cont'd)

Adverse Reactions (cont'd)

- **In patients with CLL receiving combination therapy with rituximab,** the most frequent serious adverse reaction (≥5%) was pneumonia (9%). The most common adverse reactions (≥20%) of any grade were neutropenia (65%), diarrhea (40%), upper respiratory tract infection (39%), fatigue (22%), and nausea (21%). Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of the last VENCLEXTA treatment and/or 90 days of the last rituximab were reported in 2% (4/194) of patients.
- **In patients with CLL/SLL receiving monotherapy,** the most frequent serious adverse reactions (≥5%) were pneumonia (9%), febrile neutropenia (5%), and sepsis (5%). The most common adverse reactions (≥20%) of any grade were neutropenia (50%), diarrhea (43%), nausea (42%), upper respiratory tract infection (36%), anemia (33%), fatigue (32%), thrombocytopenia (29%), musculoskeletal pain (29%), edema (22%), and cough (22%). Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of venetoclax treatment were reported in 2% of patients in the VENCLEXTA monotherapy studies, most often (2 patients) from septic shock.

Drug Interactions

- Concomitant use with a P-gp inhibitor or a strong or moderate CYP3A inhibitor increases VENCLEXTA exposure, which may increase VENCLEXTA toxicities, including the risk of TLS. Consider alternative medications or adjust VENCLEXTA dosage and monitor more frequently for adverse reactions. Resume the VENCLEXTA dosage that was used prior to concomitant use of a P-gp inhibitor or a strong or moderate CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.
- Patients should avoid grapefruit products, Seville oranges, and starfruit during treatment as they contain inhibitors of CYP3A.
- Avoid concomitant use of strong or moderate CYP3A inducers.
- Monitor international normalized ratio (INR) more frequently in patients receiving warfarin.
- Avoid concomitant use of VENCLEXTA with a P-gp substrate. If concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.

Lactation

- Advise women not to breastfeed during treatment with VENCLEXTA and for 1 week after the last dose.

Females and Males of Reproductive Potential

- Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for 30 days after the last dose.
- Based on findings in animals, VENCLEXTA may impair male fertility.

Hepatic Impairment

- Reduce the dose of VENCLEXTA for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more frequently for adverse reactions. No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

References: 1. VENCLEXTA Prescribing Information. **2.** Koffman B, Stewart C, Avruch L, et al. Awareness, knowledge, and preferences of United States (US) patients with chronic lymphocytic leukemia (CLL) and their caregivers related to finite duration (FD) therapy and minimal (measurable) residual disease (MRD). *Blood.* 2021;138(suppl):1927-1929. **3.** Koffman B, Stewart C, Avruch L, et al. Awareness, knowledge, and preferences of United States (US) patients with chronic lymphocytic leukemia (CLL) and their caregivers related to finite duration (FD) therapy and minimal (measurable) residual disease (MRD). Poster presented at: 63rd ASH Annual Meeting and Exposition; December 11-14, 2021. **4.** Greer JA, Amoyal N, Nisotel L, et al. A systematic review of adherence to oral antineoplastic therapies. *Oncologist.* 2016;21(3):354-376. **5.** Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA Cancer J Clin.* 2009;59(1):56-66. **6.** Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomized, phase 3 trial. *Lancet Oncol.* 2020;21(9):1188-1200. **7.** Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomized, phase 3 trial. *Lancet Oncol.* 2020;21(9)(suppl):1188-1200. **8.** Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2018;378(12):1107-1120. **9.** Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med.* 2019;380(23):2225-2236. **10.** Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med.* 2019;380(23)(suppl):2225-2236. **11.** Data on file, AbbVie Inc. ABVRRTI69608. **12.** Al-Sawaf O, Robrecht S, Zhang C, et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase 3 CLL14 study. *Blood.* 2024;144(18):1924-1935. **13.** Data on file, AbbVie Inc. 6-year data ABVRRTI76226. **14.** Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2018;378(12)(suppl):1107-1120. **15.** Kater AP, Harrup R, Kipps TJ, et al. Final 7-year (yr) follow up and retreatment substudy analysis of MURANO: venetoclax-rituximab (VENR)-treated patients with relapsed/refractory chronic lymphocytic leukemia (R/R CLL). Abstract presented at the European Hematology Association Congress 2023; June 8-11, 2023. **16.** Data on file, AbbVie Inc. 7-year MURANO ABVRRTI76236. **17.** Data on file, AbbVie Inc. ABVRRTI69609.

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Start with VENCLEXTA, and offer your patients the chance for durable PFS without continuous treatment[1]

Proven efficacy and well-studied safety profile

- VEN+G for 1L (CLL14 trial)[12,13]
  - >6 years of follow-up
- VEN+R for R/R (MURANO trial)[15,16]
  - >7 years of follow-up

Offer your patients the chance for:

- Extended time off treatment
- No ongoing treatment exposure

No ongoing out-of-pocket costs

- Limit financial impact on your patients, with no additional VENCLEXTA regimen patient out-of-pocket costs after completing treatment per the recommended dosing*

*Coverage and patient out-of-pocket costs for VEN+G and VEN+R vary by health plan. Patients may still incur out-of-pocket costs for other treatments or tests as directed by their healthcare providers.

1L=first line.

Scan to visit **venclextahcp.com** to learn more about fixed-duration treatment for patients with previously untreated and R/R CLL

Scan the code at right to contact a VENCLEXTA rep to learn more about VENCLEXTA

Indication

VENCLEXTA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Select Important Safety Information

- Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during ramp-up is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome (TLS).
- Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients treated with VENCLEXTA. The risk of TLS is a continuum based on multiple factors, particularly reduced renal function, tumor burden, and type of malignancy. Assess all patients for risk and provide appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases. Interrupt dosing if needed; when restarting VENCLEXTA follow dose modification guidance in the Prescribing Information.
- Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during the ramp-up phase, and requires VENCLEXTA dose reduction.
- Grade 3 or 4 neutropenia occurred in patients treated with VENCLEXTA. Monitor complete blood counts and for signs of infection; manage as medically appropriate.
- Fatal and serious infections such as pneumonia and sepsis have occurred in patients with VENCLEXTA. Monitor patients for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution.
- Do not administer live attenuated vaccines prior to, during, or after treatment until B-cell recovery occurs.
- VENCLEXTA may cause embryo-fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 30 days after the last dose.

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