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

VENCLEXTA **FIXED-DURATION REGIMENS** FOR CLL MAY OFFER BENEFITS ACROSS:

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 at least 30 days after the last dose.

Please see additional Important Safety Information at the bottom of each page or click the Full ISI button below.
Please see accompanying full Prescribing Information at the PI link on the left of each page.

PI

REFS

FULL ISI +

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.

FOR HEALTHCARE PROFESSIONALS

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VENCLEXTA **FIXED-DURATION REGIMENS** FOR CLL MAY OFFER BENEFITS ACROSS:

CLINICAL OUTCOMES[1]

1L efficacy | 1L safety

R/R efficacy | R/R safety

PATIENT EXPERIENCE[1]

Potential benefits of a fixed-duration therapy

FIXED TREATMENT, FIXED COST[1]

No additional VENCLEXTA regimen patient out-of-pocket (OOP) costs after completing treatment per the recommended dosing*

The National Comprehensive Cancer Network® (NCCN®) recommends venetoclax (VENCLEXTA®) + obinutuzumab (GAZYVA®) as a preferred 1L regimen for patients with previously untreated CLL/SLL (category 1 for patients with significant comorbidities [creatinine clearance [CrCl] <70 mL/min]) and venetoclax (VENCLEXTA®) + rituximab as a preferred regimen (category 1) for second-line and subsequent therapy in patients with previously treated CLL/SLL[2†]

- The VENCLEXTA + GAZYVA regimen (VEN+G) is designed to be completed after 12 months (twelve 28-day treatment cycles): GAZYVA 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]
- The VENCLEXTA + rituximab regimen (VEN+R) is designed to be completed after 24 months (twenty-four 28-day treatment cycles after the 5-week VENCLEXTA dose ramp-up): rituximab is administered at 375 mg/m^2 on Day 1, Cycle 1 and 500 mg/m^2 on Day 1, Cycles 2–6; VENCLEXTA is taken 400 mg/day orally from Cycle 1, Day 1 of rituximab through Cycle 24[1]

*Drug cost refers to the Wholesale Acquisition Cost. 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.

†See NCCN Guidelines® for the NCCN definitions of Categories of Preference and Categories of Evidence and Consensus.

CLL=chronic lymphocytic leukemia; 1L=first-line; R/R=relapsed/refractory; MOA=mechanism of action.

PI

REFS

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- 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.

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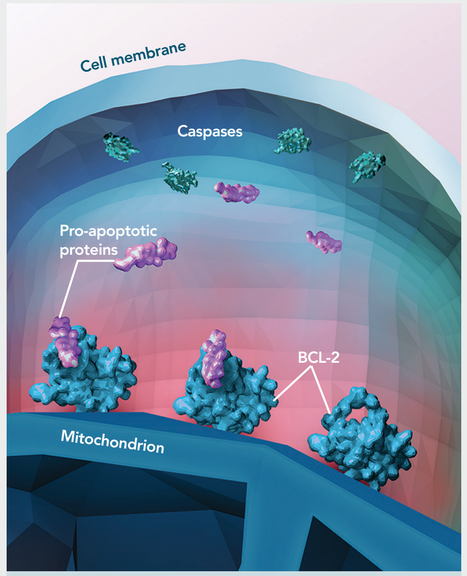
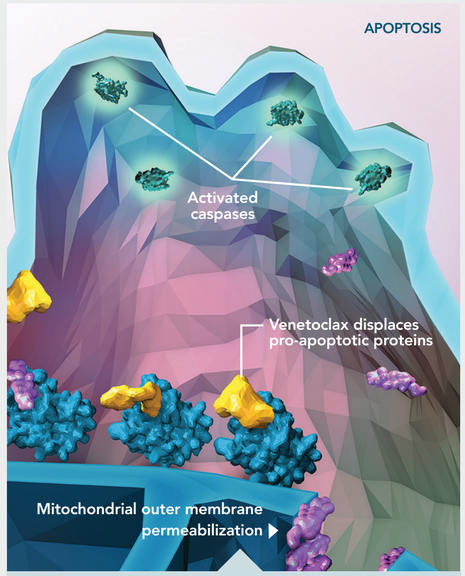
VENCLEXTA combination regimens for CLL work through 2 distinct mechanisms of action[1,3,4]

Venetoclax is a first-in-class treatment that targets BCL-2 to help restore the process of apoptosis[1,5]

- The ability to evade apoptosis is an important hallmark of cancer. Overexpression of BCL-2 has been demonstrated in CLL cells and has been associated with resistance to chemotherapy



Overexpressed BCL-2 allows hematologic cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1]



Venetoclax selectively binds to BCL-2, displacing pro-apoptotic proteins and triggering events that lead to apoptosis.[1]

BCL-2=B-cell lymphoma 2.

Based on preclinical studies.

Obinutuzumab and rituximab are monoclonal antibodies that target the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes[3,4]

- Upon binding to CD20, the antibodies mediate B-cell lysis
- Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC)

PI

REFS

FULL ISI +

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Important Safety Information

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.
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Venetoclax is treatment tha BCL-2 to help process of ap

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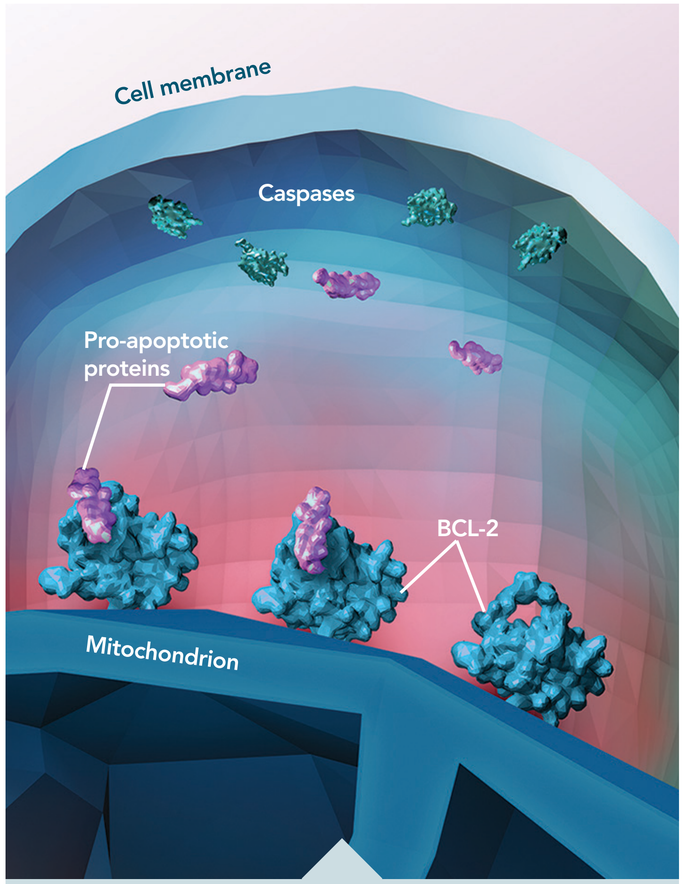
BCL-2=B-cell lymph

Venetoclax mechanism of action[1]



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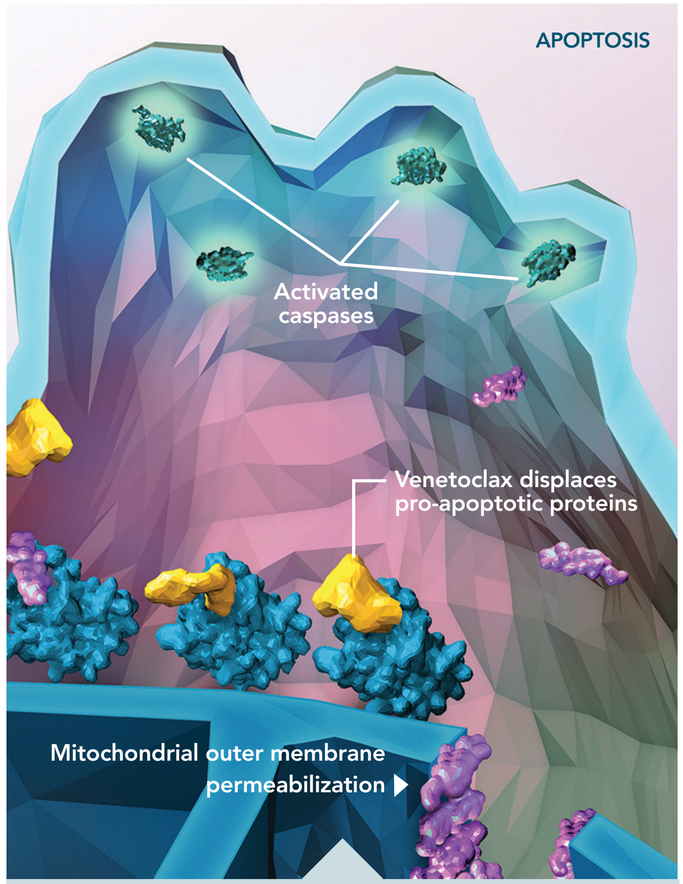

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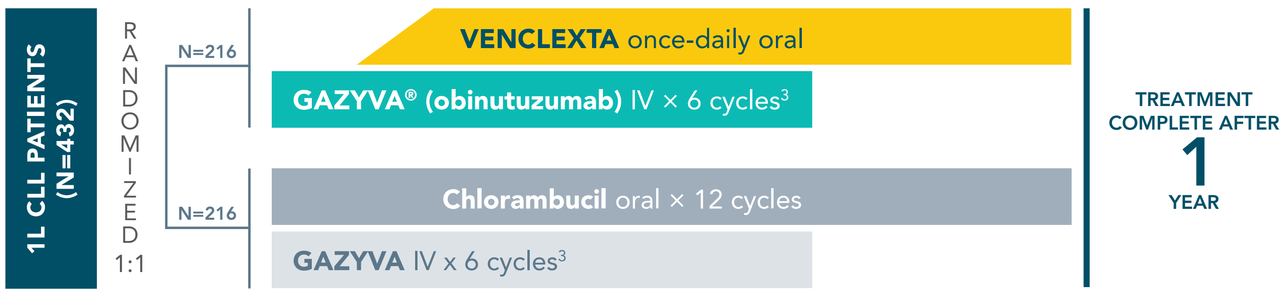
Designed for patients to complete treatment in 1 year[1]

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



Graphic not to scale.

Select inclusion criteria

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

Select clinical endpoints

- **Primary endpoint:** PFS (IRC-assessed PFS was the basis for FDA approval of VEN+G)[1]
- **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)[6,7]

- CLL14 was a multicenter, open-label, actively controlled phase 3 trial (randomized 1:1)[1,7]
- 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 Day 1 (the first dose could be split as 100 mg and 900 mg on Days 1 and 2, respectively), and on Days 8 and 15 of Cycle 1. For all subsequent 28-day cycles, GAZYVA 1000 mg was administered on Day 1 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]

PFS=progression-free survival; IV=intravenous; CIRS=Cumulative Illness Rating Scale; CLcr=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; GClb=GAZYVA + chlorambucil; uMRD=undetectable minimal residual disease.

Study design | Baseline characteristics | PFS | Subgroup PFS analysis | Post hoc PFS analysis | Response rates | uMRD | PFS by MRD

PI

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FULL ISI +

Indication

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

Important Safety Information

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.

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VEN+G was studied in patients whose age and disease characteristics were representative of the broad CLL patient population[8]

Baseline demographics and disease characteristics[8]*		
Characteristic	**VEN+G (N=216)**	**GClb (N=216)**
Age, years; median (range)	72 (43–89)	71 (41–89)
Age ≥70, %	62	59
Male, %	68	66
Binet stage, %		
Binet stage A	21	20
Binet stage B	36	37
Binet stage C	43	43
Median CIRS score (range)	9 (0–23)	8 (1–28)
CLcr <70 mL/min, %	60	55
CLL subsets, %		
17p deletion	9	7
TP53 mutation	9	6
11q deletion	18	20
IgVH unmutated	56	57
IgVH mutated	35	38

Baseline demographics and disease characteristics[8]* (continued)		
Characteristic	**VEN+G (N=216)**	**GClb (N=216)**
High TLS risk category, %†	22	20
Lymph nodes ≥10 cm	5	5
Lymph nodes ≥5 cm to <10 cm and ALC ≥25 × 10^9/L	14	12
Medium TLS risk, %	64	68
Low TLS risk, %	13	12
ECOG performance status, %		
0	41	48
1	46	40
2	13	12
Baseline ALC (× 10^9/L); median	56	58

*Patients with missing results not included.

†TLS risk category was chosen based on investigator discretion, lymph node size, and ALC.[1,6]

TP53=tumor protein 53; *IgVH*=immunoglobulin heavy-chain variable gene; TLS=tumor lysis syndrome; ALC=absolute lymphocyte count; ECOG=Eastern Cooperative Oncology Group.

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

IRC-assessed PFS (primary endpoint)[1]

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)[1]:

- 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.[1]
HR=hazard ratio; CI=confidence interval.

PI

REFS

FULL ISI +

Indication

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

Important Safety Information

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.
- **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.

IRC-assessed PFS (primary endpoint)[1]

67%

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

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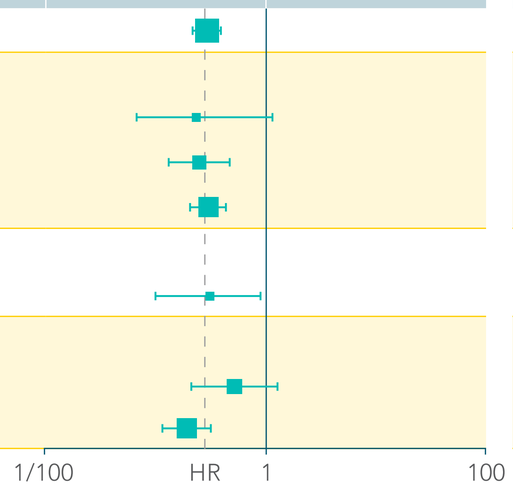
Descriptive subgroup analyses were performed to evaluate consistency with the primary PFS endpoint[1,8]

- The subgroup analyses were not powered or tested to demonstrate a statistically significant difference in PFS treatment effect for any subgroup examined
- Subgroups represent a small sample of the ITT population and differences in subgroup demographics or disease characteristics limit the ability to interpret the data

IRC-assessed PFS subgroup analysis*					Progression or death events (%)			
Select demographic subgroups	Hazard ratio	95% CI	Favors VEN+G	Favors GClb	VEN+G (n)	Events (%)	GClb (n)	Events (%)
All patients (ITT population)	0.33	0.22–0.51			216	29 (13)	216	79 (37)
Age (years)								
40-59	0.26	0.05–1.27			18	2 (11)	16	6 (38)
60-69	0.27	0.12–0.63			64	7 (11)	73	26 (36)
≥70	0.35	0.21–0.60			134	20 (15)	127	47 (37)
Cytogenetic hierarchical type								
17p deletion	0.35	0.13–0.94			17	7 (41)	14	10 (71)
***IgVH* mutational status**								
Mutated	0.57	0.25–1.27			76	9 (12)	83	17 (20)
Unmutated	0.21	0.12–0.37			121	16 (13)	123	57 (46)



*HR value was stratified for the ITT population.[1]
All other subgroup HR values were unstratified.[8]
ITT=intent to treat.

Study design | Baseline characteristics | PFS | Subgroup PFS analysis | Post hoc PFS analysis | Response rates | uMRD | PFS by MRD

PI
REFS

FULL ISI +

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Important Safety Information

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.

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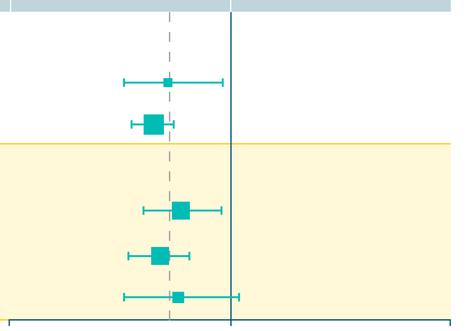
Select demographic subgroups	Hazard ratio	95% CI	Favors VEN+G	Favors GClb	VEN+G (n)	Events (%)	GClb (n)	Events (%)
***TP53* mutational status**								
Mutated	0.31	0.11–0.88			19	6 (32)	13	10 (77)
Unmutated	0.22	0.12–0.40			152	14 (9)	144	52 (36)
ECOG performance status at baseline								
0	0.38	0.19–0.76			89	11 (12)	103	28 (27)
1	0.25	0.14–0.47			99	14 (14)	87	43 (49)
2	0.36	0.09–1.38			27	3 (11)	25	7 (28)



All subgroup HR values were unstratified.

Study design | Baseline characteristics | PFS | Subgroup PFS analysis | Post hoc PFS analysis | Response rates | uMRD | PFS by MRD

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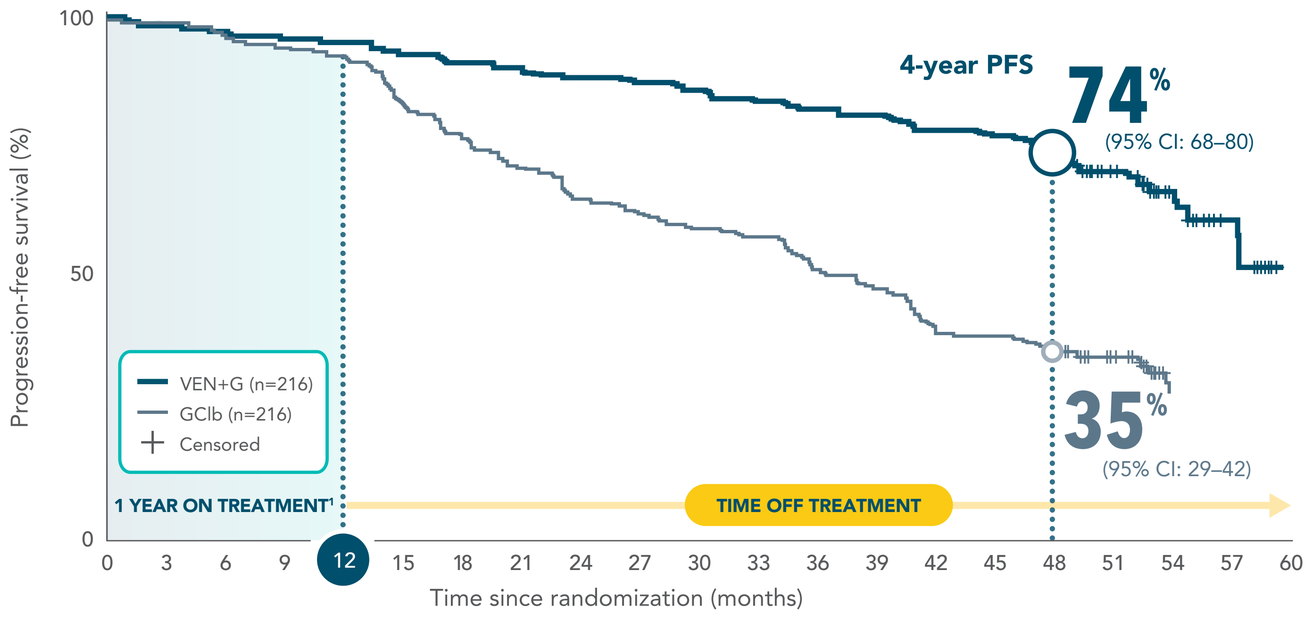
4-year post hoc analysis of INV-assessed PFS[9]*



Number of patients at risk

VEN+G	216	200	196	195	192	188	183	180	177	174	168	164	159	156	136	131	90	57	24	13
GClb	216	202	195	191	185	167	154	142	130	124	118	115	101	94	74	70	47	38	13	7

- **The rates shown for PFS are estimates and can be unreliable due to a large number of patients censored at the tail end of the curve**

These post hoc analyses were not tested for statistical significance

- With a median follow-up of 52.4 months (range: 0–61.1 months), median PFS was not reached for the VEN+G arm (95% CI: 57.3–NE) and was estimated to be 36.4 months (95% CI: 34.1–41.0) in the GClb arm (HR=0.33; 95% CI: 0.25–0.45)
- Of the 61 events in the VEN+G arm, 26 were deaths without disease progression and 35 were disease progression. Of the 138 events in the GClb arm, 16 were deaths without disease progression and 122 were disease progression†

A post hoc survival analysis was performed at the 4-year follow-up*

- OS data remained immature and the median OS had not been reached in either arm
- There were 34 events in the VEN+G arm and 41 in the GClb arm
  - Rates of death were 16% in the VEN+G arm and 19% in the GClb arm (HR=0.85; 95% CI: 0.54–1.35)

*Based on data as of clinical data cutoff date of September 11, 2020.
†Number of events based on earliest event of disease progression or deaths without disease progression due to any cause.

Study design | Baseline characteristics | PFS | Subgroup PFS analysis | Post hoc PFS analysis | Response rates | uMRD | PFS by MRD

PI

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Indication

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

Important Safety Information

Lactation

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

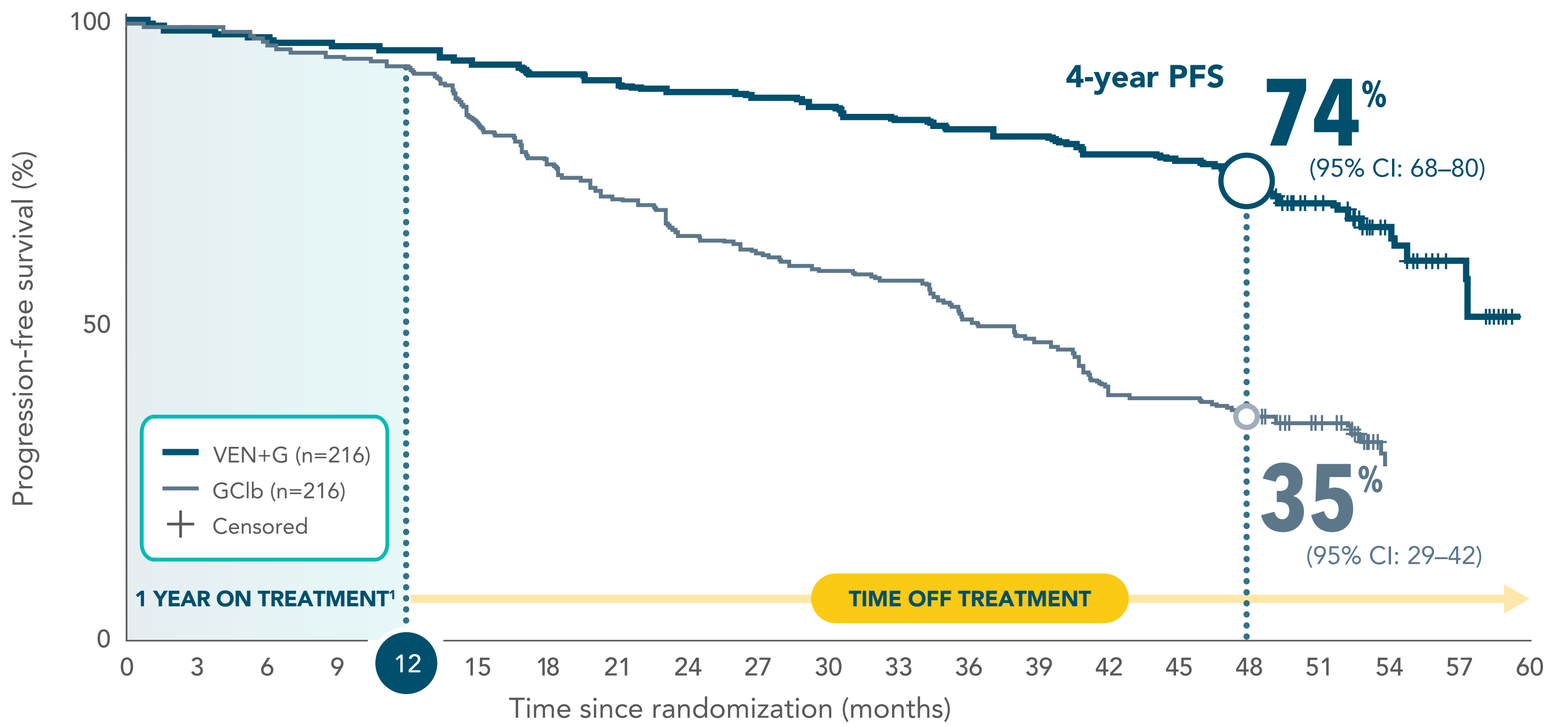
Females and Males of Reproductive Potential

- Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 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.

4-year post hoc analysis of INV-assessed PFS[9]*



Number of patients at risk

VEN+G	216	200	196	195	192	188	183	180	177	174	168	164	159	156	136	131	90	57	24	13
GClb	216	202	195	191	185	167	154	142	130	124	118	115	101	94	74	70	47	38	13	7

- **The post hoc analysis was not tested for statistical significance**
- **The rates shown for PFS are estimates and can be unreliable due to a large number of patients censored at the tail end of the curve**

*Based on data as of clinical data cutoff date of September 11, 2020.

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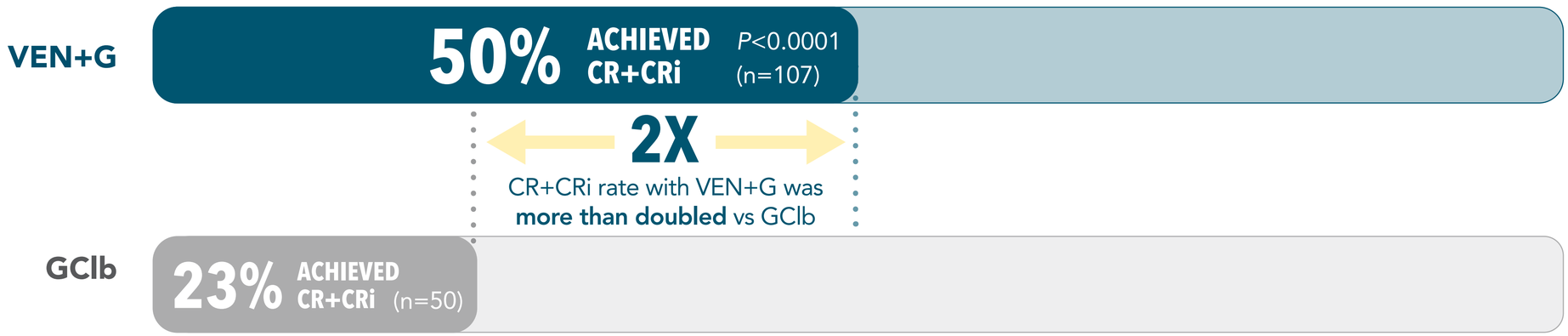
VEN+G demonstrated impressive rates of complete remission with 1 year of treatment[1]

INV-assessed response*† rates for VEN+G (N=216) vs GClb (N=216), respectively (secondary endpoint)[1,6,7]



- **CR:** 46% (n=100) with VEN+G vs 22% (n=47) with GClb[1]
- **ORR:** 85% (n=183; 95% CI: 79–89) with VEN+G vs 71% (n=154; 95% CI: 65–77) with GClb; *P*=0.0007[1]
- **PR:** 35% (n=76) with VEN+G vs 48% (n=104) with GClb[1]

*Per the 2008 iwCLL guidelines.
†Assessed 3 months after treatment completion.[7]
PR=partial remission; iwCLL=International Workshop on Chronic Lymphocytic Leukemia.

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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.

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uMRD rates with VEN+G

MRD was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) 3 months after treatment ended. Undetectable MRD was defined as having achieved <1 CLL cell per 10,000 leukocytes.[1]

While undetectable MRD and response rates are both measures of disease, it is possible for a patient with a PR to be MRD negative, and for a patient with a CR to be MRD positive.[10]

The FDA considers MRD as not yet an established surrogate for clinical outcomes in patients with CLL.[11]

In the ITT population (secondary endpoint)[7]

76% **uMRD** in peripheral blood in the ITT population

- The rate of undetectable MRD in peripheral blood (ITT population) was 76% (163/216) in VEN+G patients (95% CI: 69–81), compared with 35% (76/216) in GClb patients (95% CI: 29–42); *P*<0.0001[1]
  - **In patients with a CR,** the rate of undetectable MRD in peripheral blood was 87% (87/100) for VEN+G (95% CI: 79–93) and 62% (29/47) for GClb (95% CI: 46–75); *P*=0.0005[1]
  - VEN+G undetectable MRD in bone marrow was 57% in the ITT population (n=123/216; 95% CI: 50–64)[1]
  - **91% concordance:** Of the 134 patients with undetectable MRD in peripheral blood who had matching bone marrow specimens, 122 patients had undetectable MRD in the bone marrow[1]

Indication

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

Important Safety Information

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.

uMRD rates

MRD was evaluated usi
as having achieved <1 (

While undetectable MR
to be MRD positive.[10]

The FDA considers MRD

In the ITT population

76%

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atient with a CR

) in VEN+G
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7/100) for VEN+G

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In the ITT population (secondary endpoint)[7]

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

Important Safety Information
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Rates of uMRD and PFS in patients with evaluable MRD status

Rates of undetectable MRD* in peripheral blood in evaluable patients in the VEN+G arm[8]:

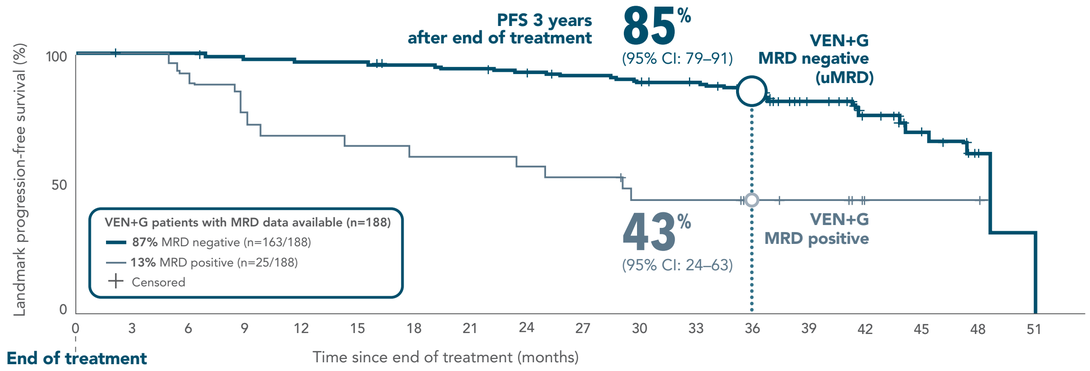
87% achieved **undetectable MRD** (163/187)

- Of evaluable GClb patients, 42% achieved undetectable MRD (76/182)

The population with evaluable results (n=369) excludes results missing due to progressive disease (PD), withdrawal (including withdrawal due to toxicity), deaths without disease progression, MRD status unknown, and other missing samples or assessments. Not prespecified or tested for statistical significance.[8]

*Assessed 3 months after treatment completion.[7]

In evaluable VEN+G patients, PFS was assessed in an exploratory post hoc analysis[9]



Number of patients at risk

VEN+G MRD neg (uMRD)	163	162	161	157	156	155	151	149	145	142	127	123	90	58	35	19	4	1
VEN+G MRD pos	25	25	23	19	17	16	15	15	14	13	10	10	6	5	1	1	1	

- **Not tested for statistical significance**
- **The PFS estimates can be unreliable due to the small number of patients at risk at the tail end of the MRD positive curve**
- From the 4-year post hoc analysis of INV-assessed PFS at the clinical data cutoff date of September 11, 2020

Study design | Baseline characteristics | PFS | Subgroup PFS analysis | Post hoc PFS analysis | Response rates | uMRD | PFS by MRD

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Indication

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Important Safety Information

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.

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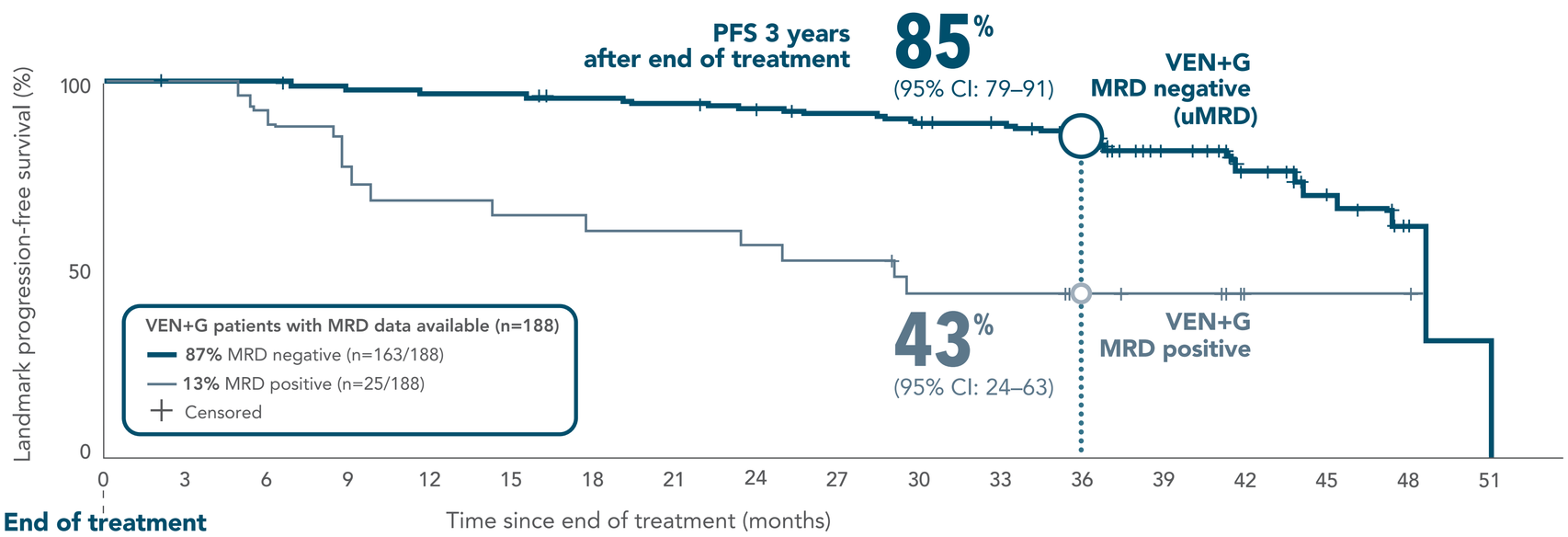

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VEN+G offers a well-studied safety profile with exposure limited to 1 year[1]

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 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[8]
- 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 is an important identified risk when initiating VENCLEXTA
- The incidence of TLS was 1% (3/212) in patients treated with VEN+G. All 3 events of TLS resolved and did not lead to withdrawal from the trial. Obinutuzumab administration was delayed in 2 cases in response to the TLS events

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%
- Neutropenia led to discontinuation of VENCLEXTA in 2% of patients, reduction in 13%, and dose interruption in 41%

Safety overview | Adverse reactions

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Indication

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

Important Safety Information

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 at least 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.

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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.

Safety overview | Adverse reactions

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FULL ISI +

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Important Safety Information

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.
- **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.

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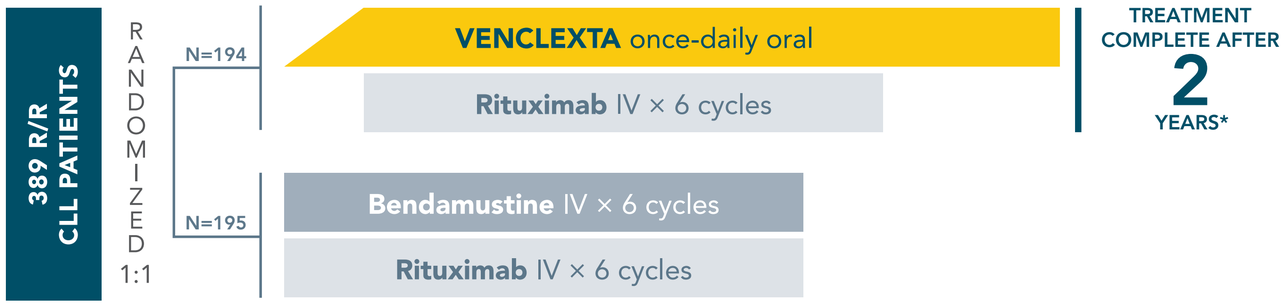
Designed for patients to complete treatment at 2 years[1]*

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



Graphic not to scale.

- MURANO was a phase 3, multicenter, open-label, actively controlled trial (randomized 1:1)[1,10]
- 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

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

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[12]

Select clinical endpoints

- **Primary endpoint:** PFS (IRC-assessed PFS was the basis for approval of VEN+R)[12,13]
- **Select secondary endpoints:** IRC-assessed CR/CRi, IRC-assessed ORR, OS, INV-assessed PFS, uMRD
  - 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[13]

Study design | Baseline characteristics | PFS | Subgroup PFS analysis | Post hoc PFS analysis | OS: 5-year analysis | Response rates | uMRD | PFS by MRD

PI

REFS

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Contraindication

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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.

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Baseline patient characteristics were generally well balanced between study arms[1,13-15]

MURANO demographics and baseline characteristics[13,14]*		
Characteristic	**VEN+R** (N=194)	**BR** (N=195)
Age, years; median (range)	65 (28–83)	66 (22–85)
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
1 or more nodes ≥5 cm	46	48
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)

*Patients with missing results not included.

The majority of patients in the study had 1 prior therapy. Chemotherapy with or without anti-CD20 was the most common prior therapy[1,13-15]

MURANO prior therapies		
Number of prior lines of therapy, %	**VEN+R** (N=194)	**BR** (N=195)
Median number (range)	1 (1–5)	
1	57	60
2	30	22
≥3	13	18
Previous CLL regimens		
Median number (range)	1 (1–5)	
Alkylating agents, %	95	93
Purine analogs, %	81	81
CD20 antibodies, %	76	79
B-cell receptor pathway inhibitors, %	2	3
FCR, %	54	55
BR, %	2	3

FCR=fludarabine + cyclophosphamide + rituximab.

Indication

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Important Safety Information

Tumor Lysis Syndrome (cont'd)

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- 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.
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VEN+R demonstrated durable PFS without long-term treatment*

IRC-assessed PFS (primary endpoint)[1]

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)[1]:

- 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.[1]
†Number of events based on earliest event of disease progression or deaths without disease progression due to any cause.[1]

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- 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.

IRC-assessed PFS (primary endpoint)[1]

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)[1]:

- 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

[†]Number of events based on earliest event of disease progression or deaths without disease progression due to any cause.[1]

Indication

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

Important Safety Information

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.

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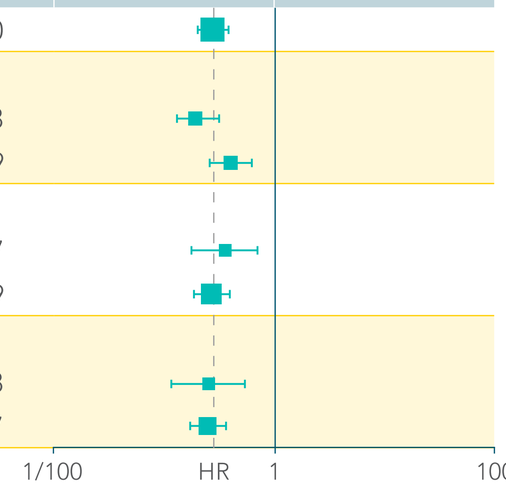
Descriptive subgroup analyses were performed to evaluate consistency with the primary PFS endpoint[14]

- The subgroup analyses were not powered or tested to demonstrate a statistically significant difference in PFS treatment effect for any subgroup examined
- Subgroups represent a small sample of the ITT population and differences in subgroup demographics or disease characteristics limit the ability to interpret the data

IRC-assessed PFS subgroup analysis*

Select demographic subgroups	VEN+R (n)	BR (n)	Hazard ratio	95% CI
All patients (ITT population)	194	195	0.20	0.14–0.30
Age (years)				
<65	97	89	0.12	0.07–0.23
≥65	97	106	0.30	0.18–0.49
Cytogenetic hierarchical type				
17p deletion, abnormal	36	40	0.26	0.11–0.57
17p deletion, normal	158	155	0.19	0.12–0.29
***IgVH* mutational status**				
Mutated	53	51	0.18	0.07–0.48
Unmutated	123	123	0.17	0.10–0.27



*HR value was stratified for the ITT population.
All other subgroup HR values were unstratified.

Study design | Baseline characteristics | PFS | Subgroup PFS analysis | Post hoc PFS analysis | OS: 5-year analysis | Response rates | uMRD | PFS by MRD

PI

REFS

FULL ISI +

Indication

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

Important Safety Information

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 at least 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.

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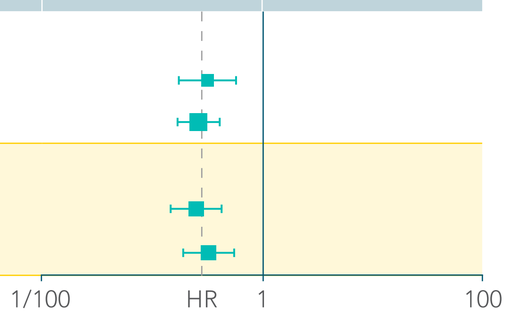
- The subgroup analyses were not powered or tested to demonstrate a statistically significant difference in PFS treatment effect for any subgroup examined
- Subgroups represent a small sample of the ITT population and differences in subgroup demographics or disease characteristics limit the ability to interpret the data

IRC-assessed PFS subgroup analysis

Select demographic subgroups	VEN+R (n)	BR (n)	Hazard ratio	95% CI
***TP53* mutational status**				
Mutated	48	51	0.23	0.12–0.45
Unmutated	144	133	0.18	0.11–0.29
Presence of bulky disease				
<5 cm	100	97	0.17	0.09–0.30
≥5 cm	84	88	0.25	0.15–0.42



All subgroup HR values were unstratified.

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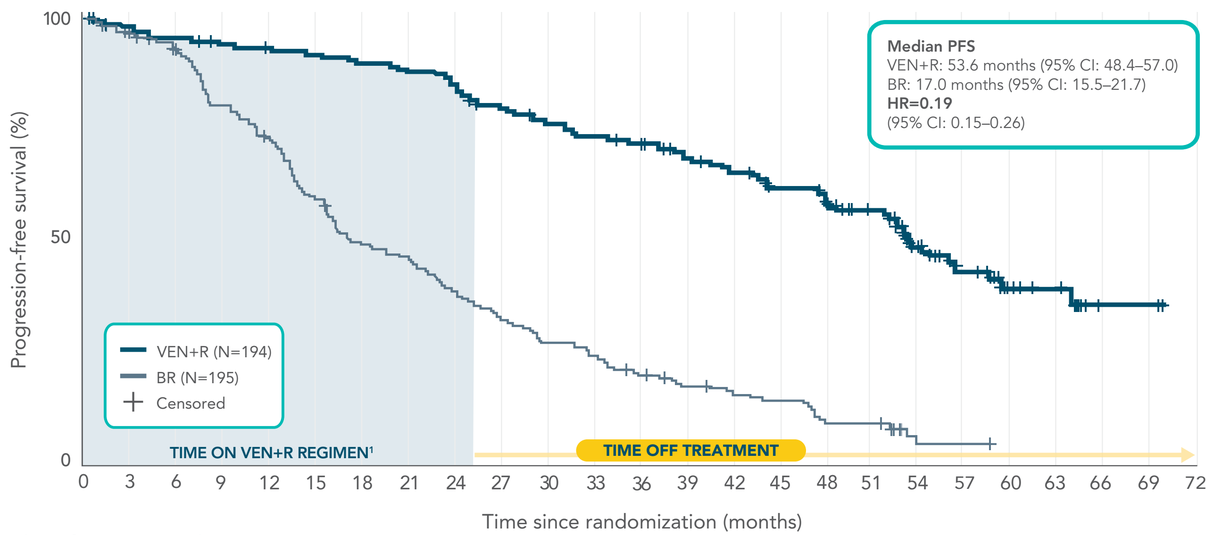
5-year post hoc analysis of INV-assessed PFS[16]*



Number of patients at risk

VEN+R	194	190	185	179	176	174	170	167	161	150	142	136	132	123	116	104	99	87	57	33	15	10	3	3	2
BR	195	178	165	143	128	103	84	79	65	55	44	39	31	24	21	18	11	10	2	1					

The post hoc analysis was not tested for statistical significance

- After a median follow-up of 59.2 months (range: 0–71.5 months)†:
  - There were 101 events in the VEN+R arm (87 progressions and 14 deaths without disease progression)
  - There were 167 events in the BR arm (148 progressions and 19 deaths without disease progression)
- **These data are currently under evaluation by the FDA**

*Clinical cutoff date of May 8, 2020.
†Calculation based on reverse Kaplan-Meier method (where patients who were censored in the OS analysis were treated as events and all deaths were censored).

- **The PFS are estimates and can be unreliable due to a large number of patients censored at the tail end of the curve in the VEN+R arm**

Study design | Baseline characteristics | PFS | Subgroup PFS analysis | Post hoc PFS analysis | OS: 5-year analysis | Response rates | uMRD | PFS by MRD

PI
REFS

FULL ISI +

Indication

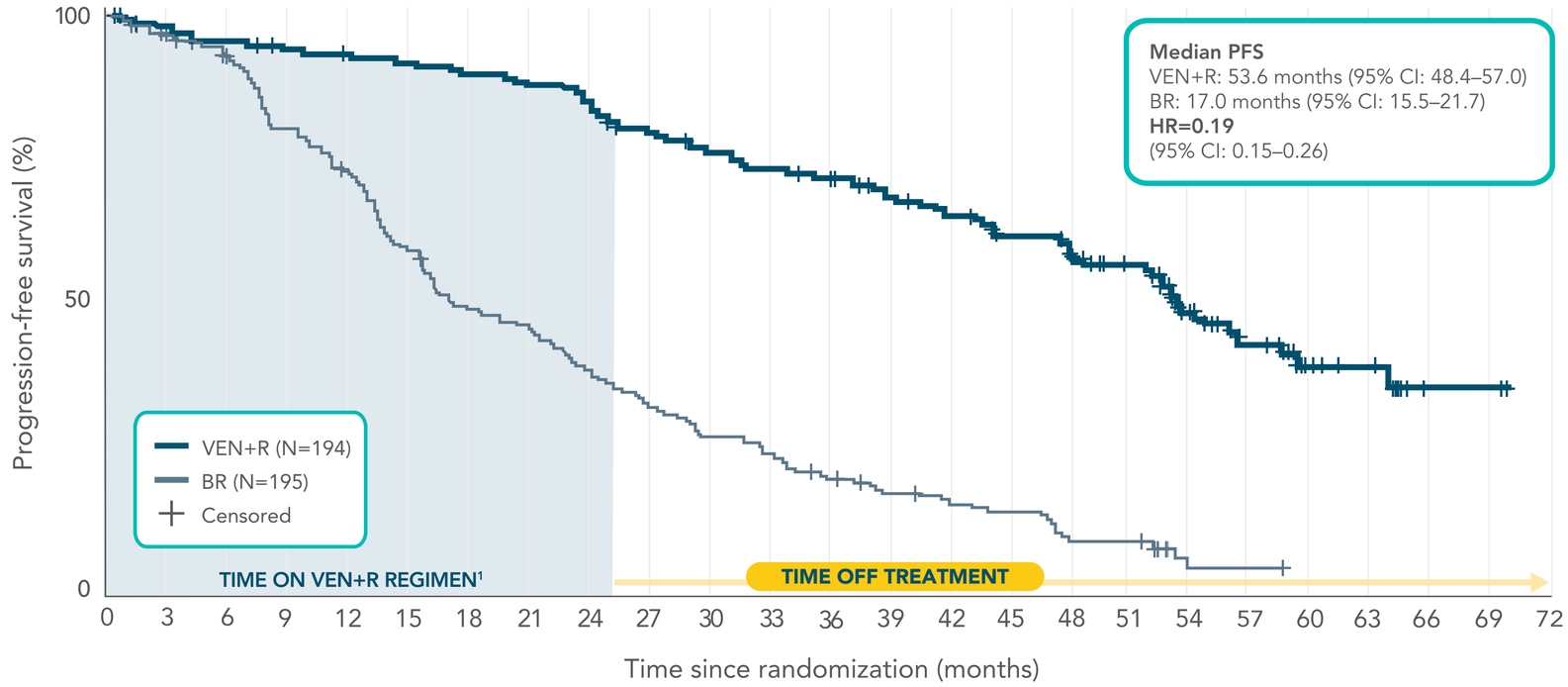
- VENCLEXTA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Important Safety Information

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.
- **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.

5-year post hoc analysis of INV-assessed PFS[16]*



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BR	195	178	165	143	128	103	84	79	65	55	44	39	31	24	21	18	11	10	2	1					

- **The post hoc analysis was not tested for statistical significance**
- **The PFS are estimates and can be unreliable due to a large number of patients censored at the tail end of the curve in the VEN+R arm**
- **These data are currently under evaluation by the FDA**

*Clinical cutoff date of May 8, 2020.

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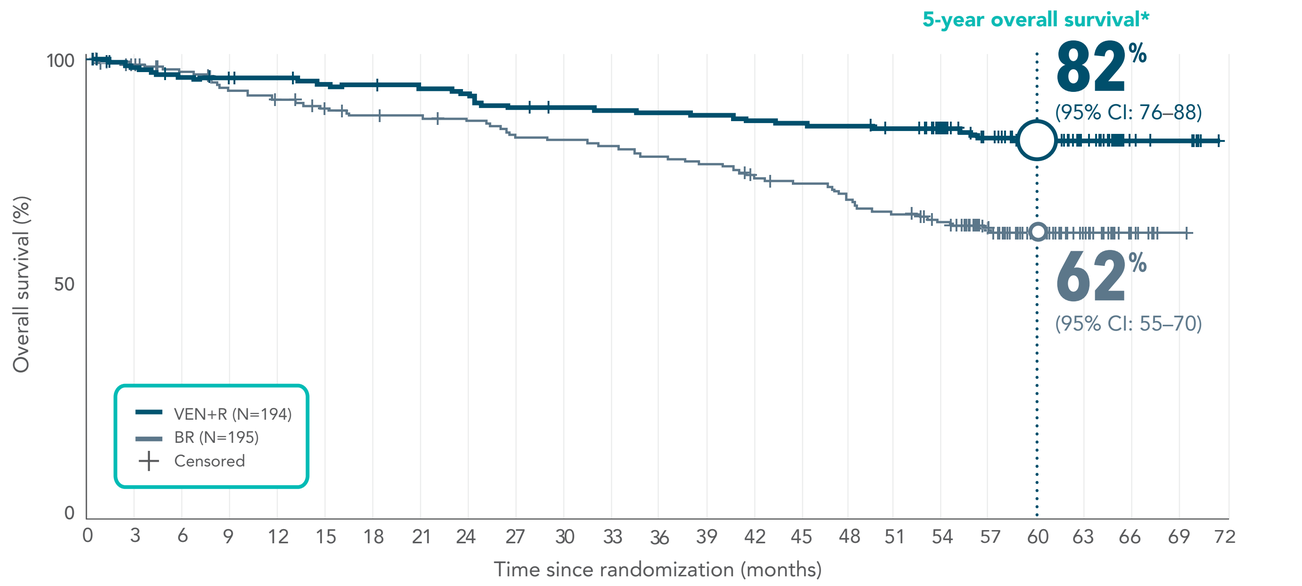
5-year post hoc analysis of overall survival[16]



Number of patients at risk

VEN+R	194	190	185	183	182	179	178	176	173	168	166	165	164	163	161	160	159	156	139	107	70	34	9	7
BR	195	181	175	167	162	155	152	150	147	141	140	138	134	131	124	121	115	110	102	73	49	24	9	1

- **The post hoc analysis was not tested for statistical significance**
- **The rates shown for 5-year overall survival are estimates and can be unreliable due to the large number of patients censored at the tail portion of the curve**

*Clinical cutoff date of May 8, 2020.

A survival analysis was performed at the 5-year follow-up

- Median OS was not reached in either arm
- The rates of death were 16% (n=32) in the VEN+R arm and 33% (n=64) in the BR arm
  - HR=0.40; 95% CI: 0.26-0.62
- **These data are currently under evaluation by the FDA**

Treatment after VEN+R at the 4-year follow-up:

- In a 4-year follow-up analysis of the VEN+R patient cohort, 42 (22%) of 194 patients received subsequent therapy with modalities that included: BTK inhibitor (n=12), BCL-2 inhibitor (n=14), PI3K inhibitor (n=1), CIT (n=14), and other (n=1)[17]
  - Among the 12 patients treated with a BTK inhibitor, 10 patients achieved a response and 2 patients were not evaluable

Study design | Baseline characteristics | PFS | Subgroup PFS analysis | Post hoc PFS analysis | OS: 5-year analysis | Response rates | uMRD | PFS by MRD

PI

REFS

FULL ISI +

Indication

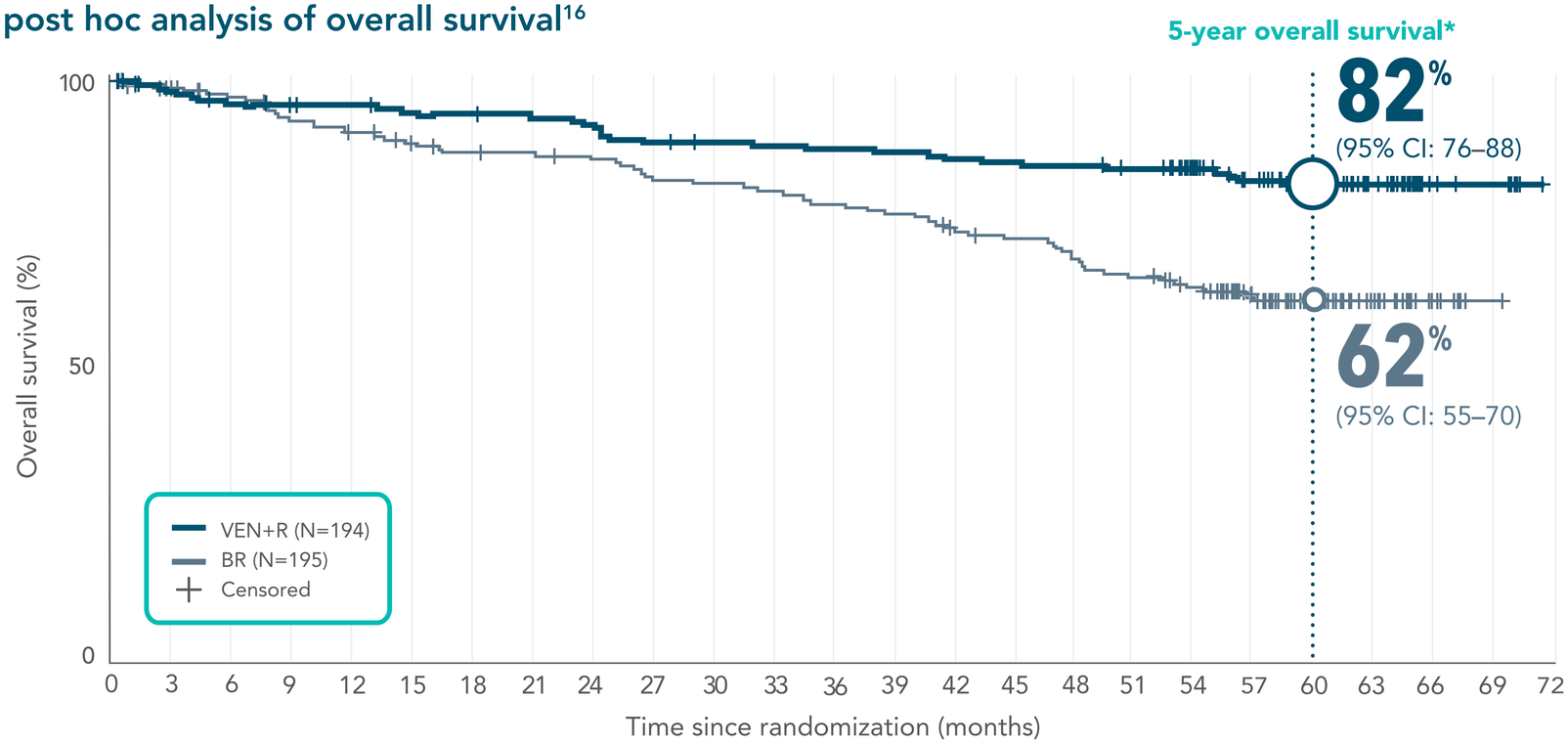
- VENCLEXTA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Important Safety Information

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.

5-year post hoc analysis of overall survival[16]



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BR	195	181	175	167	162	155	152	150	147	141	140	138	134	131	124	121	115	110	102	73	49	24	9	1

- **The post hoc analysis was not tested for statistical significance**
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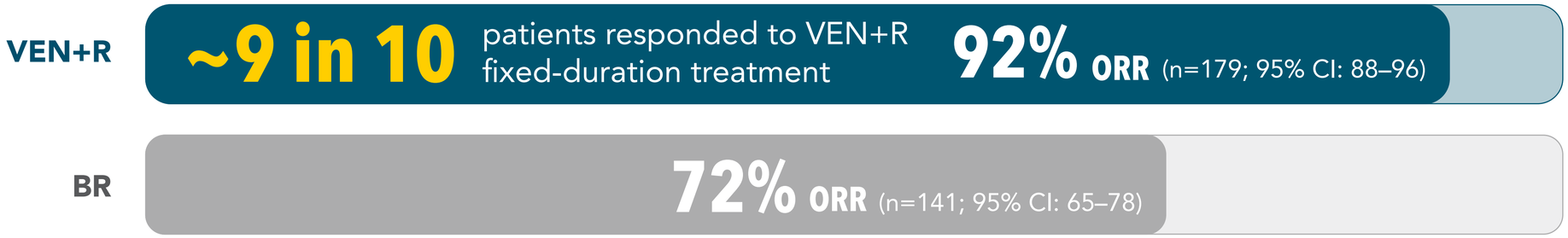
VEN+R demonstrated impressive rates of response with 2 years* of treatment[1]

IRC-assessed response rates for VEN+R (N=194) vs BR (N=195), respectively (secondary endpoint)



- **CR+CRi:** 8% (n=16) vs 4% (n=7)
- **PR:** 82% (n=160) vs 68% (n=133)
- **nPR:** 2% (n=3) vs 1% (n=1)
- Response rates were assessed per 2008 iwCLL guidelines

- INV-assessed ORR for VEN+R was 93% (n=181; 95% CI: 89–96) compared with 68% (n=132; 95% CI: 61–74) in the BR arm[14]
- INV-assessed CR/CRi for VEN+R was 27% (n=52) compared with 8% (n=16) in the BR arm[14]
- INV-assessed vs IRC-assessed CR/CRi discordance was primarily due to interpretation of residual adenopathy on CT scans; specifically, 33 out of 51 patients across both arms with discordance had lesions ≤3 cm despite bone marrow clearance[12,13]

Key secondary endpoints were ranked for hierarchical testing as: (1) IRC-assessed CR/CRi rate, and (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**.[12,13]

*From Cycle 1, Day 1 of rituximab in the absence of disease progression or unacceptable toxicity.[1]
nPR=nodular partial remission.

Study design | Baseline characteristics | PFS | Subgroup PFS analysis | Post hoc PFS analysis | OS: 5-year analysis | Response rates | uMRD | PFS by MRD

PI
REFS

FULL ISI +

Indication

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

Important Safety Information

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 at least 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.

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uMRD rates with VEN+R

MRD was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) 3 months after the last dose of rituximab. Undetectable MRD was defined as having achieved <1 CLL cell per 10,000 leukocytes.[13]

While undetectable MRD and response rates are both measures of disease, it is possible for a patient with a PR to be MRD negative, and for a patient with a CR to be MRD positive.[10]

FDA considers MRD as not yet an established surrogate for clinical outcomes in patients with CLL.[11]

In the ITT population (secondary endpoint)[13]

53%

uMRD
in peripheral blood in the ITT population

- Undetectable MRD in the ITT population that achieved PR or better: 53% (103/194) for VEN+R vs 12% (23/195) for BR. Not tested for statistical significance[1]
  - **For patients with a CR+CRi,** the rate of undetectable MRD in peripheral blood was 3% (6/194) for VEN+R and 2% (3/195) for BR[1]

Study design | Baseline characteristics | PFS | Subgroup PFS analysis | Post hoc PFS analysis | OS: 5-year analysis | Response rates | uMRD | PFS by MRD

PI
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FULL ISI +

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Rates of uMRD and PFS in patients with evaluable MRD status

Rates of undetectable MRD* in peripheral blood in evaluable patients in the VEN+R arm[16]:

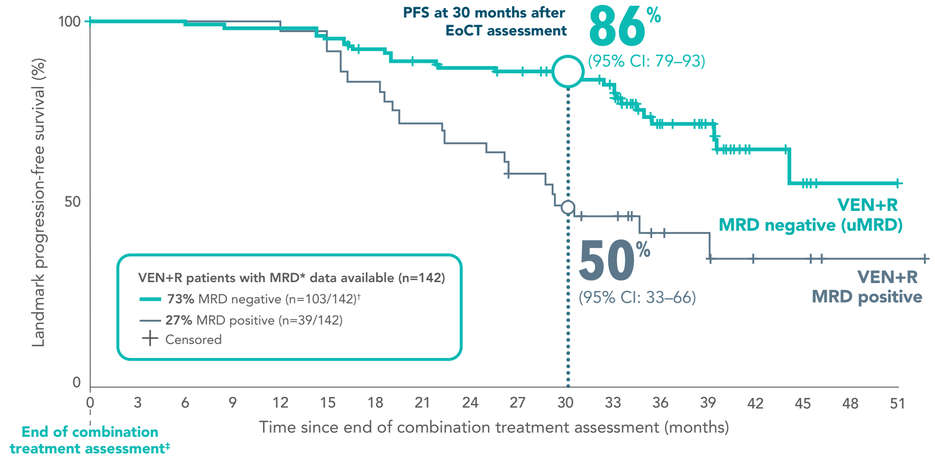
73% achieved **undetectable MRD** (103/142)

- Of evaluable BR patients, 25% achieved undetectable MRD (23/91), and 75% were MRD positive (68/91)

The population with evaluable results (n=233) excludes results missing due to PD, withdrawal (including withdrawal due to toxicity), deaths, MRD status unknown, and other missing samples or assessments. Not prespecified or tested for statistical significance.[16]

*Assessed 3 months after end of combination treatment.[1]

In evaluable VEN+R patients, PFS was assessed in an exploratory post hoc analysis[16]



Number of patients at risk

VEN+R MRD neg (uMRD)	103	103	103	101	101	98	92	88	85	83	76	68	36	22	8	6	1	
VEN+R MRD pos	39	36	36	36	36	35	30	26	24	20	17	15	8	6	3	3	1	1

- **Not tested for statistical significance**
- **The rates shown for PFS are estimates and can be unreliable due to a large number of patients censored at the tail end of the curve**
- From the 4-year post hoc analysis of INV-assessed PFS at the clinical data cutoff date of May 8, 2019[16]

†The number of patients in the VEN+R arm with undetectable MRD is based on the EoCT MRD status at the clinical cutoff date of May 8, 2017, where 1 patient wasn't categorized as negative due to missing EoCT response visit.[16]

‡The end of combination treatment assessment occurred 3 months after the end of combination treatment.[1]

EoCT=end of combination treatment.

Study design | Baseline characteristics | PFS | Subgroup PFS analysis | Post hoc PFS analysis | OS: 5-year analysis | Response rates | uMRD | PFS by MRD

PI
REFS

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Indication

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Important Safety Information

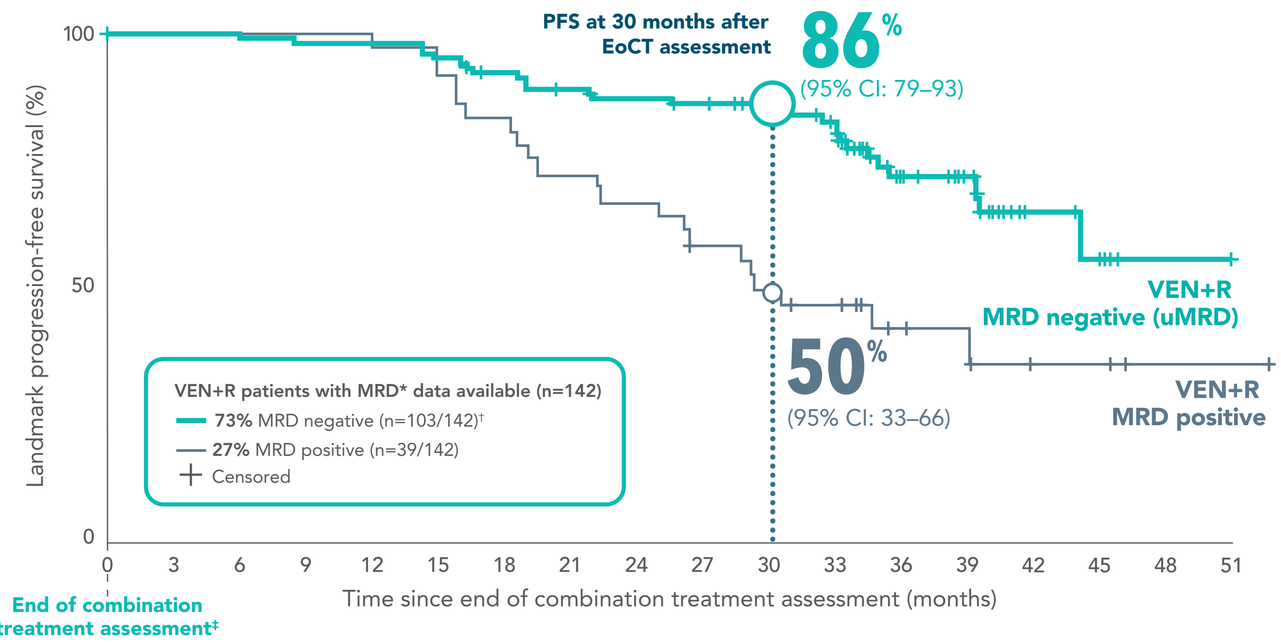
Contraindication

- 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 evaluable VEN+R patients, PFS was assessed in an exploratory post hoc analysis[16]



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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[14]
  - 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[12]
  - Patients needed to receive at least 90% of the target dose to be counted as receiving a full cycle[14]
- Tumor lysis syndrome is an important identified risk when initiating VENCLEXTA
- The incidence of TLS was 3% (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 6 patients completed 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 schedule and TLS prophylaxis and monitoring measures

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]

Safety overview | Adverse reactions

PI
REFS

FULL ISI +

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

Important Safety Information
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.

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

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.

Safety overview | Adverse reactions

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REFS

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Important Safety Information

Tumor Lysis Syndrome (cont'd)

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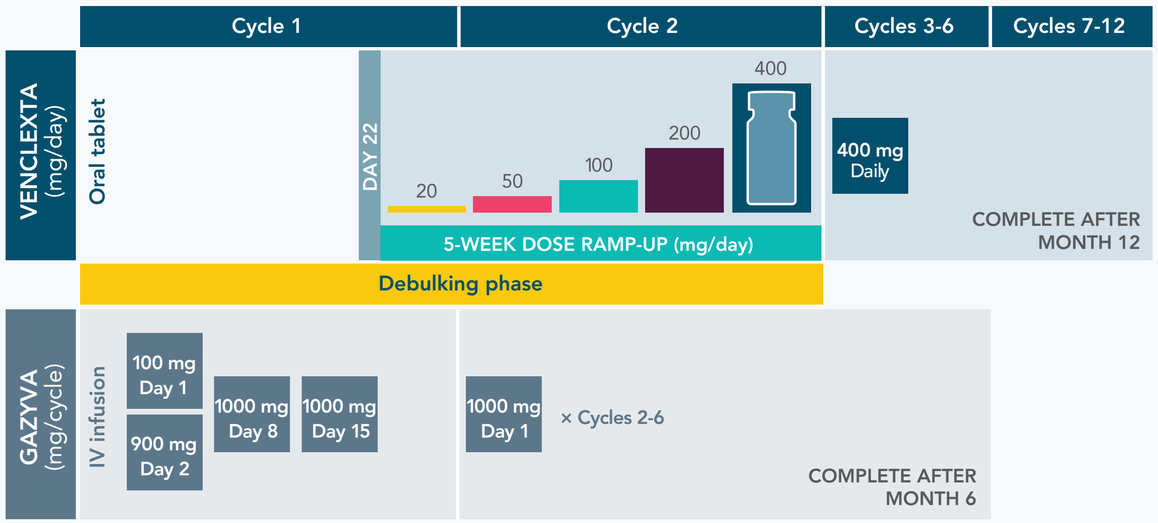
The only chemo-free regimen designed to stop treatment at 1 year in previously untreated CLL and 2 years* in R/R CLL[1]

The 5-week ramp-up is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS

1L | R/R | STARTER PACK

VEN+G in 1L CLL



Graphic not to scale. Each cycle is 28 days.

GAZYVA® (obinutuzumab)

- On Cycle 1, Days 1 and 2, administer GAZYVA 100 mg and 900 mg, respectively
- Administer GAZYVA 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle, for a total of 6 cycles
- Refer to the GAZYVA Prescribing Information for more information about recommended dosing and administration

VENCLEXTA

- Tumor burden assessments, including radiographic evaluation and blood chemistry assessment, are recommended prior to VENCLEXTA initiation to assess the risk for TLS
- On Cycle 1, Day 22, start VENCLEXTA according to the dose ramp-up schedule
- The VENCLEXTA starting dose is 20 mg once daily for 7 days, ramping up weekly to 50 mg, 100 mg, 200 mg, and finally 400 mg once daily
- After completing the ramp-up schedule on Cycle 2, Day 28, patients should continue VENCLEXTA 400 mg once daily from Cycle 3, Day 1 until the last day of Cycle 12

Note: VENCLEXTA may also be given as monotherapy until disease progression or unacceptable toxicity. Please see the full Prescribing Information for more information.
*From Cycle 1, Day 1 of rituximab.

Dosing schedules | Considerations for initiation | Starting VENCLEXTA | How VENCLEXTA is taken | Dose modifications | Dose reductions | Managing DDIs

PI

REFS

FULL ISI +

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.

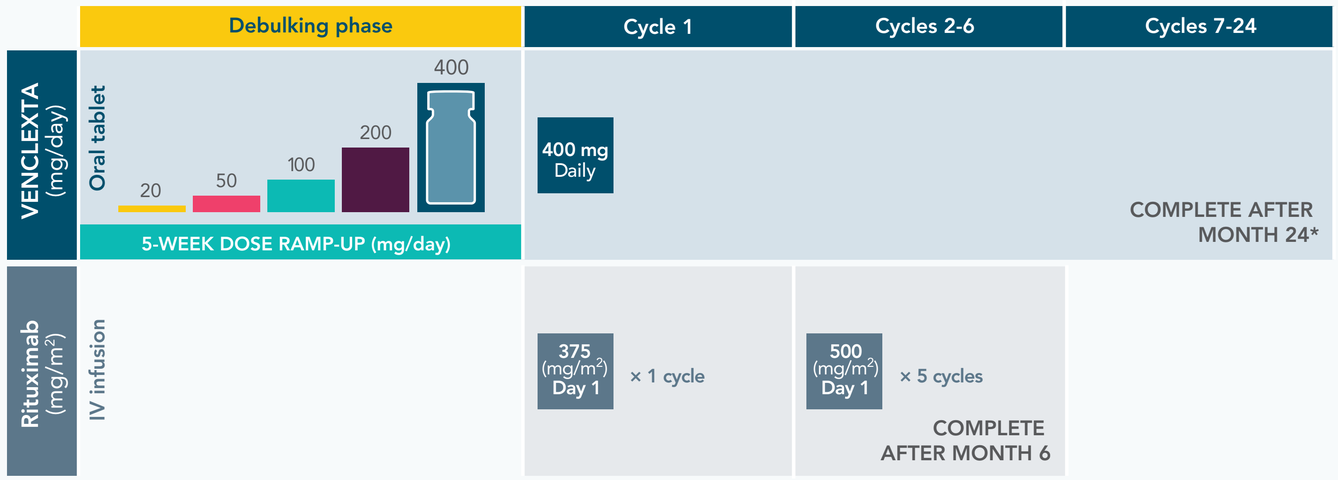
VENCLEXTA®
venetoclax tablets 10mg, 50mg, 100mg

The only chemo-free regimen designed to stop treatment at 1 year in previously untreated CLL and 2 years* in R/R CLL[1]

The 5-week ramp-up is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS

1L | R/R | STARTER PACK

VEN+R in R/R CLL



Graphic not to scale. Each cycle is 28 days.

VENCLEXTA

- Tumor burden assessments, including radiographic evaluation and blood chemistry assessment, are recommended prior to VENCLEXTA initiation to assess the risk for TLS
- The VENCLEXTA starting dose is 20 mg once daily for 7 days, ramping up weekly to 50 mg, 100 mg, 200 mg, and finally 400 mg once daily
- After ramp-up, VENCLEXTA should be taken at the recommended daily dose for 24 months

Rituximab

- Start rituximab 375 mg/m^2 after the patient has received the 400-mg dose of VENCLEXTA for 7 days
- Administer rituximab 500 mg/m^2 on Day 1 of each subsequent cycle, for a total of 6 cycles
- Refer to the rituximab Prescribing Information for more information about recommended dosing and administration

Note: VENCLEXTA may also be given as monotherapy until disease progression or unacceptable toxicity. Please see the full Prescribing Information for more information.
*From Cycle 1, Day 1 of rituximab.

Dosing schedules | Considerations for initiation | Starting VENCLEXTA | How VENCLEXTA is taken | Dose modifications | Dose reductions | Managing DDIs

PI

REFS

FULL ISI +

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venetoclax tablets 10mg, 50mg, 100mg

The only chemo-free regimen designed to stop treatment at 1 year in previously untreated CLL and 2 years* in R/R CLL[1]

The 5-week ramp-up is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS

1L | R/R | STARTER PACK

The first 4 weeks of VENCLEXTA are provided in 4 weekly wallet blister packs, found in the **VENCLEXTA starter pack**.

Doses for week 5 and onward are available in bottles containing 100-mg tablets.

Note: VENCLEXTA may also be given as monotherapy until disease progression or unacceptable toxicity. Please see the full Prescribing Information for more information.
*From Cycle 1, Day 1 of rituximab.

Dosing schedules | Considerations for initiation | Starting VENCLEXTA | How VENCLEXTA is taken | Dose modifications | Dose reductions | Managing DDIs

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REFS

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Considerations for initiation[1]

Assess blood chemistry and correct pre-existing abnormalities prior to initiation of treatment:

- Potassium
- Uric acid
- Phosphorus
- Calcium
- Creatinine

Considerations for TLS 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 (see the Dose modifications tab below)
- 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, particularly reduced renal function (CLcr <80 mL/min) and tumor burden; splenomegaly may also increase the risk
- Consider all patient comorbidities before final determination of prophylaxis and monitoring schedule
- The risk of TLS may decrease as tumor burden decreases
- Reassess the risk of TLS when reinitiating VENCLEXTA after a dosage interruption lasting more than 1 week during the ramp-up phase, or more than 2 weeks after completion of ramp-up. Institute prophylaxis and monitoring as needed

Appropriate prophylaxis can help lower the risk of TLS.

Dosing schedules | Considerations for initiation | Starting VENCLEXTA | How VENCLEXTA is taken | Dose modifications | Dose reductions | Managing DDIs

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Important Safety Information

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.
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Starting VENCLEXTA[1]

3 STEPS: ASSESS, PREPARE, INITIATE

STEP 1: ASSESS
Prior to initiation

All lymph nodes (LN)
<5 cm

AND

Absolute lymphocyte count (ALC)
<25 × 10⁹/L

STEP 2: PREPARE
At least 2 days prior to first dose

Oral hydration*:
1.5–2 L

Allopurinol†

STEP 3: INITIATE
And monitor blood chemistry‡§ for first dose of each ramp-up week

Tumor burden:

	LOW	MEDIUM	HIGH
	OUTPATIENT		
Day 1, Week:	1	2	3	4	5
Dosage	20 mg	50 mg	100 mg	200 mg	400 mg
Blood chemistry labs: Pre-Dose	☐	☐	☐	☐	☐
Blood chemistry labs: 6-8 Hours	☐	☐	—	—	—
Blood chemistry labs: 24 Hours	☐	☐	—	—	—

For more information on prophylaxis when starting VENCLEXTA, please see the full Prescribing Information.

*1.5–2 L of water (~56 ounces) should be consumed every day starting at least 2 days before the first dose and throughout the ramp-up phase, especially the first day of each dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.
†Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLEXTA.
‡Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
§For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent dose ramp-up.

Dosing schedules | Considerations for initiation | Starting VENCLEXTA | How VENCLEXTA is taken | Dose modifications | Dose reductions | Managing DDIs

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Starting VENCLEXTA[1]

3 STEPS: ASSESS, PREPARE, INITIATE

STEP 1: ASSESS
Prior to initiation

Any LN
5 cm to <10 cm

OR

ALC ≥25 × 10^9/L

STEP 2: PREPARE
At least 2 days prior to first dose

Oral hydration*:
1.5–2 L

IV hydration:
Consider for patients with medium tumor burden, occurring during outpatient stay

Allopurinol†

STEP 3: INITIATE
And monitor blood chemistry‡§ for first dose of each ramp-up week

Tumor burden:

	LOW	MEDIUM	HIGH
OUTPATIENT			
Day 1, Week:	1	2	3	4	5
Dosage	20 mg	50 mg	100 mg	200 mg	400 mg
Blood chemistry labs: Pre-Dose	☐	☐	☐	☐	☐
Blood chemistry labs: 6-8 Hours	☐	☐	—	—	—
Blood chemistry labs: 24 Hours	☐	☐	—	—	—

For the first doses of 20 mg and 50 mg, consider hospitalization for patients with medium tumor burden and CLcr <80 mL/min; for these patients, see table under "High" tumor burden for monitoring in hospital.

For more information on prophylaxis when starting VENCLEXTA, please see the full Prescribing Information.

*1.5–2 L of water (~56 ounces) should be consumed every day starting at least 2 days before the first dose and throughout the ramp-up phase, especially the first day of each dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.
†Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLEXTA.
‡Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
§For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent dose ramp-up.

Dosing schedules | Considerations for initiation | Starting VENCLEXTA | How VENCLEXTA is taken | Dose modifications | Dose reductions | Managing DDIs

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Starting VENCLEXTA[1]

3 STEPS: ASSESS, PREPARE, INITIATE

Tumor burden:

	LOW	MEDIUM	HIGH

STEP 1: **ASSESS**
Prior to initiation

Any LN
≥10 cm

OR

Any LN ≥5 cm
and ALC ≥25 × 10^9/L

STEP 2: **PREPARE**
At least 2 days prior to first dose

Oral hydration*:
1.5–2 L
+
IV hydration:
150–200 mL/h as tolerated
prior to first dose

Allopurinol†

Rasburicase[6]:
Consider for elevated
uric acid (>8 mg/dL)

STEP 3: **INITIATE**
And monitor blood chemistry‡§ for first dose of each ramp-up week

		HOSPITAL		OUTPATIENT		
Day 1, Week:		1	2	3	4	5
Dosage		20 mg	50 mg	100 mg	200 mg	400 mg
Blood chemistry labs	Pre-Dose	☐	☐	☐	☐	☐
	4 Hours	☐	☐	—	—	—
	8 Hours	☐	☐	☐	☐	☐
	12 Hours	☐	☐	—	—	—
	24 Hours	☐	☐	☐	☐	☐

For more information on prophylaxis when starting VENCLEXTA, please see the full Prescribing Information.

*1.5–2 L of water (~56 ounces) should be consumed every day starting at least 2 days before the first dose and throughout the ramp-up phase, especially the first day of each dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.
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Dosing schedules | Considerations for initiation | Starting VENCLEXTA | How VENCLEXTA is taken | Dose modifications | Dose reductions | Managing DDIs

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FULL ISI +

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Important Safety Information
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VENCLEXTA®
venetoclax tablets 10mg, 50mg, 100mg

How VENCLEXTA is taken[1]

Advise patients to:

- ✔ Take VENCLEXTA tablets exactly as they are prescribed and not to change or interrupt their dose unless they are told to do so by their doctor.
- ✔ Take VENCLEXTA orally once daily, at approximately the same time each day, according to their HCP's instructions, and that the tablets should be swallowed whole with a meal and water without being chewed, crushed, or broken.
- ✔ Be adequately hydrated every day they take VENCLEXTA to reduce the risk of TLS. The recommended volume is 6-8 glasses (~56 ounces) of water every day starting 2 days before the first dose and throughout the ramp-up phase, especially the first day of each dose increase.
- ✔ Attend every scheduled appointment for blood work or other laboratory tests.

Advise patients NOT to:

- ✖ Crush, chew, or break their VENCLEXTA tablets.
- ✖ Remove their VENCLEXTA tablets from the original packaging during the first 4 weeks of treatment, and not to transfer them to a different container.
- ✖ Take an additional dose if vomiting occurs after taking VENCLEXTA. They should take the next dose at the usual time the following day.
- ✖ Consume grapefruit products, Seville oranges, or starfruit during treatment with VENCLEXTA.

If a patient misses a dose:

Within 8 hours of the time it is usually taken, the patient should take the missed dose right away and take the next dose as usual.

By more than 8 hours, the patient should not take the missed dose and should take the next dose at the usual time.

Dosing schedules | Considerations for initiation | Starting VENCLEXTA | How VENCLEXTA is taken | Dose modifications | Dose reductions | Managing DDIs

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FULL ISI +

Indication

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

Important Safety Information

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.

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

Dose modifications or interruptions can help manage select adverse reactions[1]

- For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of the ramp-up phase or greater than 2 weeks after completing the ramp-up phase, reassess the risk of TLS to determine if reinitiation with a reduced dose is necessary (eg, all or some levels of the ramp-up schedule)

Recommended VENCLEXTA dose modifications for adverse reactions*		
TLS	**Nonhematologic adverse reactions**	**Hematologic adverse reactions**
Any occurrence: Blood chemistry changes or symptoms suggestive of TLS	Withhold the next day's dose. If resolved within 24–48 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. **Click here** to see the dose-reduction guidelines.	
	For any events of clinical TLS,† resume at a reduced dose following resolution. **Click here** to see the dose-reduction guidelines.	

*Adverse reactions were graded using NCI CTCAE version 4.0.
†Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures.

- Consider discontinuing VENCLEXTA for patients who require dose reductions to less than 100 mg for more than 2 weeks

Dose modifications for severe hepatic impairment

- Reduce the VENCLEXTA once-daily dose by 50% for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for adverse reactions

NCI=National Cancer Institute; CTCAE=Common Terminology Criteria for Adverse Events.

Dosing schedules | Considerations for initiation | Starting VENCLEXTA | How VENCLEXTA is taken | Dose modifications | Dose reductions | Managing DDIs

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FULL ISI +

Indication

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

Important Safety Information

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 at least 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.

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

Dose modifications or interruptions can help manage select adverse reactions[1]

- For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of the ramp-up phase or greater than 2 weeks after completing the ramp-up phase, reassess the risk of TLS to determine if reinitiation with a reduced dose is necessary (eg, all or some levels of the ramp-up schedule)

Recommended VENCLEXTA dose modifications for adverse reactions*		
TLS	**Nonhematologic adverse reactions**	**Hematologic adverse reactions**
1st occurrence: Grade 3 or 4 nonhematologic toxicities	Interrupt VENCLEXTA. Once the toxicity has resolved to Grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose.	
2nd and subsequent occurrences: Grade 3 or 4 nonhematologic toxicities	Interrupt VENCLEXTA. Follow dose-reduction guidelines **here** when resuming VENCLEXTA treatment after resolution. A larger dose reduction may occur at the discretion of the physician.	

*Adverse reactions were graded using NCI CTCAE version 4.0.

- Consider discontinuing VENCLEXTA for patients who require dose reductions to less than 100 mg for more than 2 weeks

Dose modifications for severe hepatic impairment

- Reduce the VENCLEXTA once-daily dose by 50% for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for adverse reactions

Dosing schedules | Considerations for initiation | Starting VENCLEXTA | How VENCLEXTA is taken | Dose modifications | Dose reductions | Managing DDIs

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Indication

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

Important Safety Information

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.
- **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.

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Dose modifications or interruptions can help manage select adverse reactions[1]

- For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of the ramp-up phase or greater than 2 weeks after completing the ramp-up phase, reassess the risk of TLS to determine if reinitiation with a reduced dose is necessary (eg, all or some levels of the ramp-up schedule)

Recommended VENCLEXTA dose modifications for adverse reactions*		
TLS	**Nonhematologic adverse reactions**	**Hematologic adverse reactions**
1st occurrence: Grade 3 neutropenia with infection or fever, or Grade 4 hematologic toxicities (except lymphopenia)	Interrupt VENCLEXTA. Once the toxicity has resolved to Grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose.	
2nd and subsequent occurrences: Grade 3 neutropenia with infection or fever, or Grade 4 hematologic toxicities (except lymphopenia)	Interrupt VENCLEXTA. Follow dose-reduction guidelines **here** when resuming VENCLEXTA treatment after resolution. A larger dose reduction may occur at the discretion of the physician.	

*Adverse reactions were graded using NCI CTCAE version 4.0.

- Consider discontinuing VENCLEXTA for patients who require dose reductions to less than 100 mg for more than 2 weeks

Dose modifications for severe hepatic impairment

- Reduce the VENCLEXTA once-daily dose by 50% for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for adverse reactions

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Indication

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

Important Safety Information

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.

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Dose reduction for adverse reactions during VENCLEXTA treatment[1]

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

*During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.
†If a dosage interruption lasts more than 1 week during the ramp-up phase or more than 2 weeks after completion of ramp-up, reassess the risk of TLS and determine if reinitiation at a reduced dosage is necessary.

Dosing schedules | Considerations for initiation | Starting VENCLEXTA | How VENCLEXTA is taken | Dose modifications | Dose reductions | Managing DDIs

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Indication

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

Important Safety Information

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 at least 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.

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Dosage modifications for concomitant use with strong or moderate CYP3A inhibitors or P-gp inhibitors[1]

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

Coadministered drug	Initiation and ramp-up phase	Steady daily dose* (after ramp-up phase)
Posaconazole	Contraindicated	Reduce VENCLEXTA dose to 70 mg
Other strong CYP3A inhibitor	Contraindicated	Reduce VENCLEXTA dose to 100 mg
Moderate CYP3A inhibitor	Reduce VENCLEXTA dose by at least 50%	
P-gp inhibitor		

*Consider alternative medications or reduce the VENCLEXTA dose as described in this table.

Resume the VENCLEXTA dose that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor

CYP3A=cytochrome P450 3A; P-gp=P-glycoprotein; SLL=small lymphocytic lymphoma.

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.

VENCLEXTA®
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How may fixed-duration treatment benefit your patients with CLL?

Break free from chemotherapy and continuous oral treatment in CLL with VENCLEXTA, the only chemo-free regimen with a fixed-duration treatment of 1 year in previously untreated CLL with VEN+G and 2 years* in R/R CLL with VEN+R[1]

TREATMENT-FREE PERIOD

Fixed duration offers patients:

- a return to life without a daily reminder of their treatment and disease
- a defined end to treatment that encourages compliance and optimizes clinical outcomes[18,19]

LIMITED TREATMENT EXPOSURE

No additional VENCLEXTA regimen exposure after completing treatment

FIXED TREATMENT, FIXED COST

No additional VENCLEXTA regimen patient out-of-pocket costs after completing treatment per the recommended dosing†

*From Cycle 1, Day 1 of rituximab after the 5-week VENCLEXTA dose ramp-up.

†Drug cost refers to the Wholesale Acquisition Cost. 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.

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Indication

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

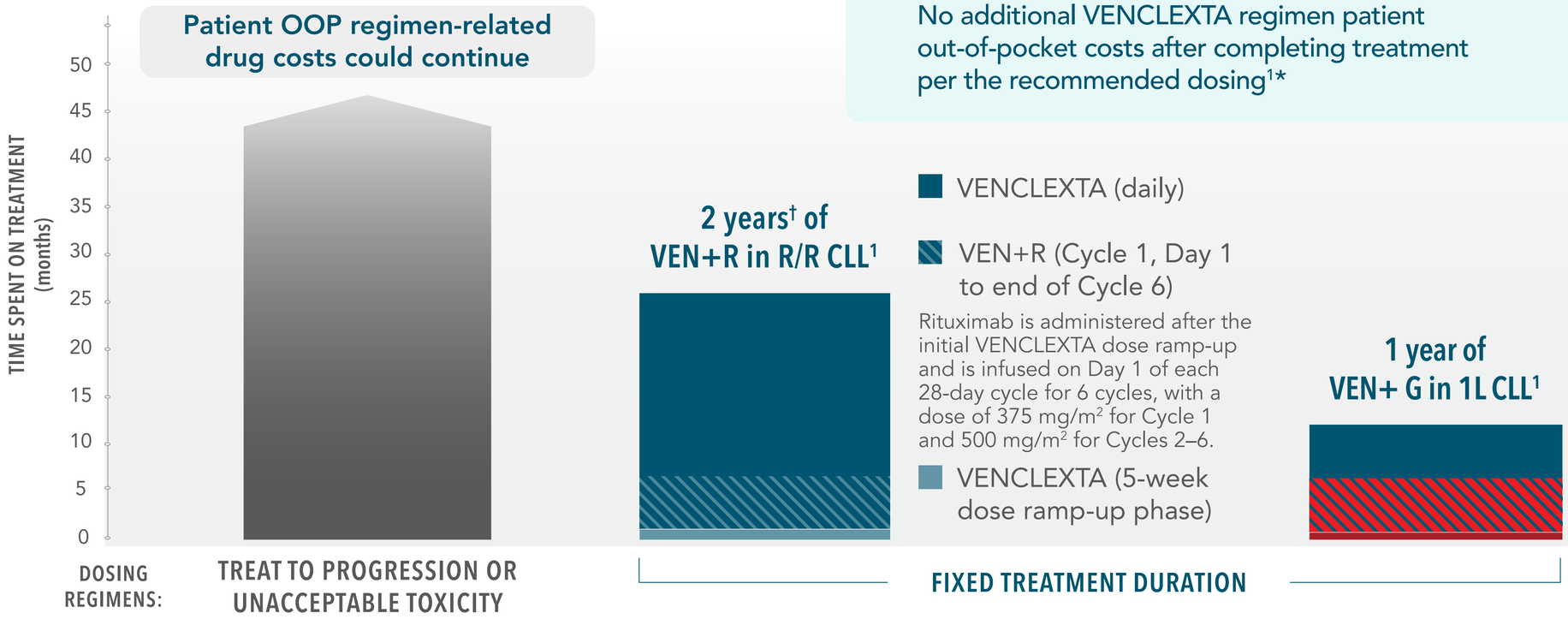
Important Safety Information

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.

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

VENCLEXTA offers patients a fixed-duration, fixed-cost treatment option in CLL[1]



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

*Drug cost refers to the Wholesale Acquisition Cost. Coverage and patient out-of-pocket costs for VEN+G and VEN+R vary by health plan, and are not represented in the graph above. Patients may still incur out-of-pocket costs for other treatments or tests as directed by their healthcare providers.

†From Day 1, Cycle 1 of rituximab.[1]

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

TTP=treat-to-progression.

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Indication

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

Important Safety Information

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.

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

Connect patients with helpful resources after VENCLEXTA has been prescribed

Patient support programs

Serious illnesses can come with many challenges. Getting VENCLEXTA shouldn't be one of them. We believe every person should get the VENCLEXTA they have been prescribed, and we offer programs to make this happen.

If your patients:

Need help understanding their insurance coverage and related financial responsibilities, **VENCLEXTA Access Solutions** is here to help.
Call (888) 249-4918 for more information.

Do not have insurance coverage or have financial concerns and meet certain eligibility criteria, the **Genentech Patient Foundation*** may be able to provide free medicine.

Have insurance and need help paying for their medicine, **Affordability Options** may be available:

- The Genentech Oncology Co-pay Assistance Program†
- Referrals to independent co-pay assistance foundations‡

The Genentech Patient Resource Center can help answer questions and connect you to the right VENCLEXTA patient support program. Call (877) 436-3683 to get started.

*To be eligible for free VENCLEXTA from the Genentech Patient Foundation, insured patients who have coverage for their medicine should try to pursue other forms of financial assistance, if available, and meet certain income requirements. Uninsured patients and insured patients without coverage for their medicine must meet a different set of income requirements.

†Eligibility criteria apply. Not valid for patients using federal or state government programs to pay for their medications and or administration of their Genentech medication. Patient must be taking the Genentech medication for an FDA-approved indication. See full Terms and Conditions at CopayAssistanceNow.com.

‡Genentech and AbbVie do not influence or control the operations or eligibility criteria of any independent co-pay assistance foundation and cannot guarantee co-pay assistance after a referral from VENCLEXTA Access Solutions. The foundations to which we refer patients are not exhaustive or indicative of Genentech's or AbbVie's endorsement or financial support. There may be other foundations to support the patient's disease state.

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Important Safety Information

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 at least 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.

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Connect patients with helpful resources for their VENCLEXTA treatment journey

VENCOMPASS®

Providing product-related support for patients taking VENCLEXTA
This program is intended to provide product-related education and support to your patients taking VENCLEXTA for an approved use during the ramp-up phase and throughout their therapy. VENCOMPASS Nurses do not provide medical advice and are trained to direct patients to speak with their healthcare professional about any treatment-related questions. Information provided is based on the full Prescribing Information and Medication Guide for VENCLEXTA.

VENCOMPASS offers resources to help VENCLEXTA patients **follow their prescribed treatment plan.***
Our resources include VENCOMPASS Nurses,† who have an extensive oncology nursing background and knowledge about VENCLEXTA, and are experienced in educating patients. They can:

- Answer product-specific questions about VENCLEXTA
- Help your patients build a routine that includes taking VENCLEXTA as prescribed
- Suggest tips on how to stay hydrated every day
- Educate patients to help them prepare for upcoming office visits, including logistical tips for telehealth appointments

For more information, call VENCOMPASS at (844) 9-COMPASS/ (844) 926-6727 or visit www.VENCLEXTA.com.

*For approved use only.
†VENCOMPASS Nurses do not provide medical advice and are trained to direct patients to speak with their healthcare professional about any treatment-related questions, including further referrals.

Patient support programs | **VENCOMPASS®**

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References

1. VENCLEXTA Prescribing Information. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V.4.2021. National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 7, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **3.** GAZYVA Prescribing Information, January 2021. **4.** RITUXAN Prescribing Information, August 2020. **5.** Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nat Med.* 2013;19(2):202-208. **6.** 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 appendix). **7.** 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. **8.** Data on file, AbbVie Inc. ABVRRTI69608. **9.** Data on file, AbbVie Inc. ABVRRTI72219. **10.** Thompson PA, Wierda WG. Eliminating minimal residual disease as a therapeutic end point: working toward cure for patients with CLL. *Blood*. 2016;127(3):279-286. **11.** US Food and Drug Administration. Hematologic malignancies: regulatory considerations for use of minimal residual disease in development of drug and biological products for treatment. Guidance for industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/hematologic-malignancies-regulatory-considerations-use-minimal-residual-disease-development-drug-and. January 2020. Accessed February 28, 2020. **12.** 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. **13.** 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 appendix). **14.** Data on file, AbbVie Inc. ABVRRTI69609. **15.** Seymour JF, Kipps TJ, Eichhorst B, et al. MURANO trial establishes feasibility of time-limited venetoclax–rituximab combination therapy in relapsed/refractory chronic lymphocytic leukemia. Presented at: 60th American Society of Hematology Annual Meeting and Exposition; December 1-4, 2018; San Diego, CA. **16.** Data on file, AbbVie Inc. ABVRRTI71322. **17.** Seymour JF, Kipps TJ, Eichhorst B, et al. Four-year analysis of MURANO study confirms sustained benefit of time-limited venetoclax–rituximab (VenR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). Presented at: 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL. **18.** Greer JA, Amoyal N, Nisotel L, et al. A systematic review of adherence to oral antineoplastic therapies. *Oncologist*. 2016;21(3):354-376. **19.** Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA Cancer J Clin*. 2009;59(1):56-66.

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Indication

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Important Safety Information

Adverse Reactions

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- **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.

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 at least 30 days after the last dose.

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Adverse Reactions

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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 at least 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.

Please see accompanying full Prescribing Information at the PI link on the left of each page.

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