oncology exchange
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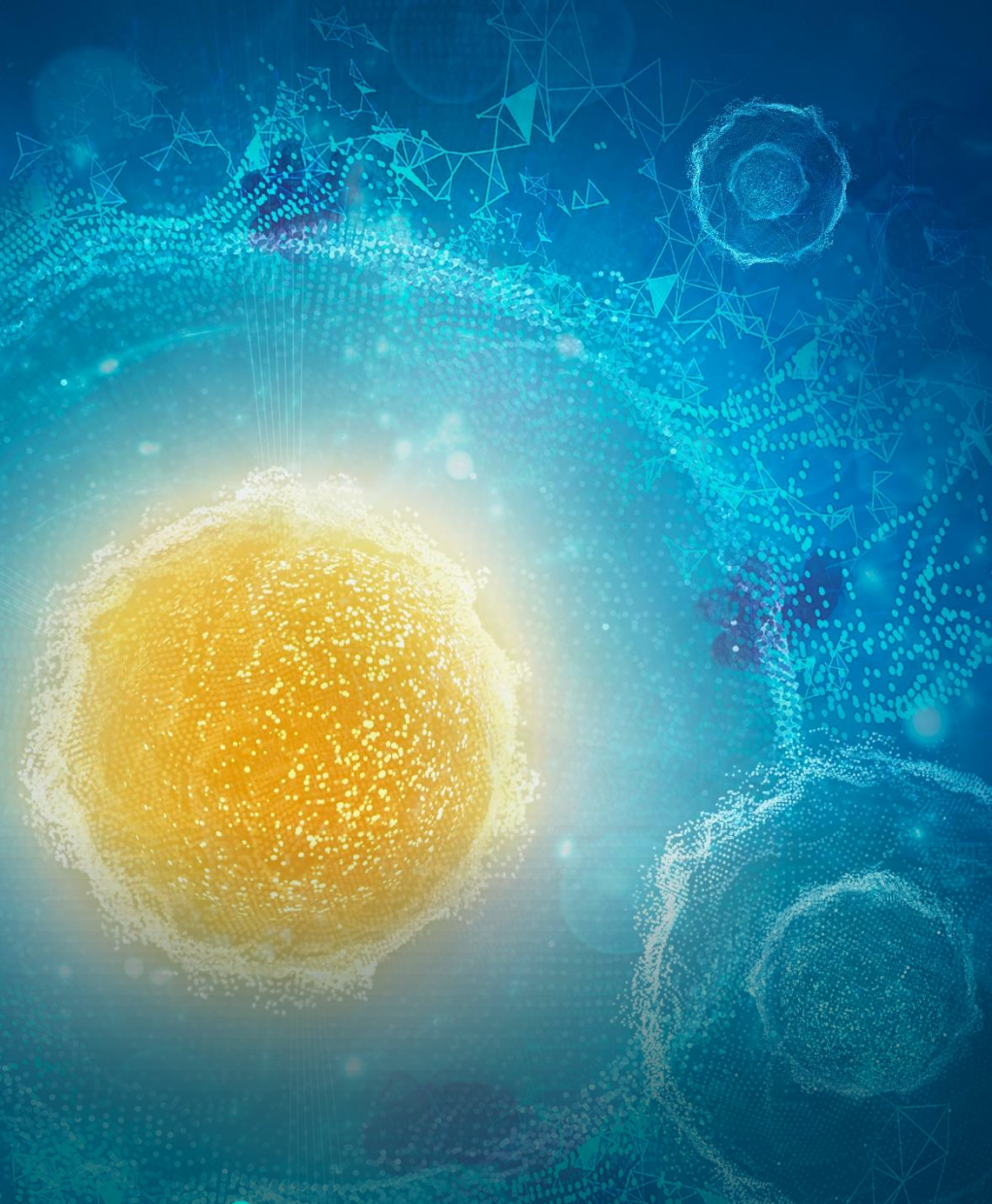
Dr. Ralph Boccia

The Center for Cancer and Blood Disorders
Bethesda, Maryland

cencora

EXPLORING TIME OFF TREATMENT WITH A BCL-2 INHIBITOR*†

A review of VENCLEXTA-based regimens for patients with CLL/SLL



***VEN+G regimen:** Designed to be completed after 12 months (twelve 28-day treatment cycles): GAZYVA® (obinutuzumab) is administered in Cycles 1-6, and VENCLEXTA is taken orally 400 mg/day from Cycle 3, Day 1, after the first two cycles of GAZYVA and the 5-week VENCLEXTA dose ramp-up.[1]
†VEN+R regimen: Designed to be completed after 24 months (twenty-four 28-day treatment cycles after the 5-week VENCLEXTA dose ramp-up): rituximab is administered in Cycles 1-6; VENCLEXTA is taken orally 400 mg/day from Cycle 1, Day 1 of rituximab through Cycle 24.[1]

GAZYVA® is a registered trademark of Genentech, Inc.
BCL-2=B-cell lymphoma-2; CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma; VEN+G=VENCLEXTA + GAZYVA; VEN+R=VENCLEXTA + rituximab.

1. VENCLEXTA Prescribing Information.

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venetoclax tablets 10mg, 50mg, 100mg

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AbbVie Disclaimer

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Today’s Objectives

Exploring Chemo-Free, **Fixed-Duration** Treatment With VENCLEXTA Regimens:

Review clinical outcomes of VENCLEXTA regimens for CLL

Discuss how to dose and administer VENCLEXTA for patients with CLL

Consider what a chance for time off treatment could mean for your patients with CLL

What is your level of familiarity and/or clinical experience with VENCLEXTA?

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VENCLEXTA® (venetoclax tablets)

Indication

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

Select Important Safety Information

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

IV=intravenous; P-gp=P-glycoprotein.

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What Does Time Off Treatment Mean for Your Patients?

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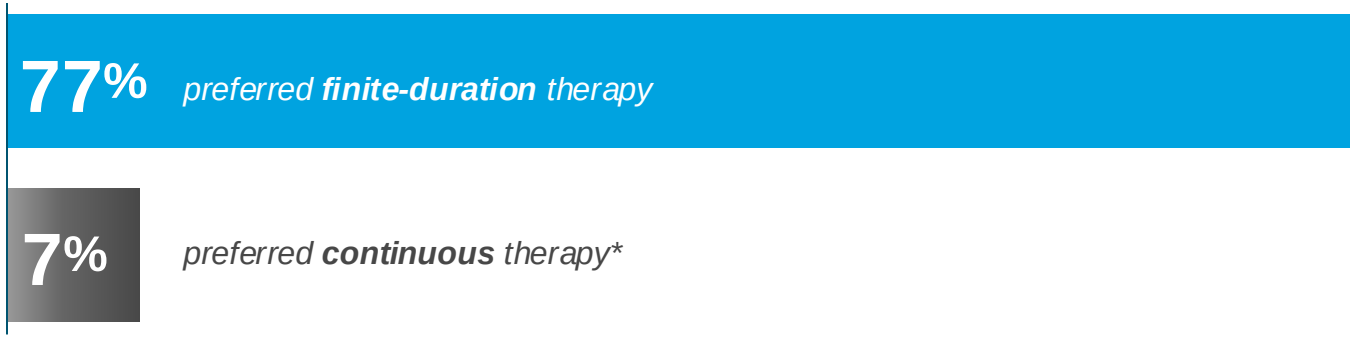
Over 3 out of 4 Respondents Preferred Finite-Duration Therapy

CLL Society Patient Preference Survey (2021)[1,2]

The survey was not designed to measure preference for venetoclax fixed-duration regimens.

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



Survey question results:

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

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

How does this align with what you see among your patients’ preferences?

*Until disease progression or intolerance.

uMRD=undetectable minimal residual disease.

1. Koffman B, et al. Poster presented at: 63rd ASH Annual Meeting and Exposition; December 11-14, 2021. 2. Koffman B, et al. *Blood*. 2021;138(suppl 1):1927-1929.

VENCLEXTA Regimens Offer Patients Chemo-Free, Fixed-Duration Treatment Options in CLL[1*†]

VENCLEXTA + GAZYVA® (obinutuzumab) in previously untreated CLL

1 YEAR
FIXED DURATION

→ **TREATMENT-FREE PERIOD** →

VENCLEXTA + rituximab in R/R CLL

~2 YEARS
FIXED DURATION‡

→ **TREATMENT-FREE PERIOD** →

Treat-to-progression regimens

CONTINUOUS TREATMENT UNTIL PROGRESSION OR UNACCEPTABLE TOXICITY

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

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

*__CLL14 trial design and primary endpoint:__ In a randomized clinical trial of 432 patients (VEN+G: N=216; GCIb: N=216) with previously untreated CLL and with a median follow-up of 28 months (range: 0-36 months), VEN+G reduced the risk of progression or death by 67% vs GCIb (HR=0.33; 95% CI: 0.22-0.51 [*P*<0.0001]). Median PFS was not reached in either arm.

†__MURANO trial design and primary endpoint:__ In a randomized clinical trial of 389 patients (VEN+R: N=194; BR: N=195) with previously treated CLL and with a median follow-up of 23.4 months (range: 0-37.4+ months), VEN+R reduced the risk of progression or death by 81% vs BR (HR=0.19; 95% CI: 0.13-0.28 [*P*<0.0001]). Median PFS not reached in VEN+R vs 18.1 months in BR (95% CI: 15.8-22.3).

‡From Day 1, Cycle 1 of rituximab.

R/R=relapsed/refractory; TTP=treat-to-progression; GCIb=GAZYVA in combination with chlorambucil; HR=hazard ratio; CI=confidence interval; PFS=progression-free survival; BR=bendamustine + rituximab.

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Venetoclax Helps Restore the Process of Apoptosis[1]

The ability to evade apoptosis is an important hallmark of cancer.[2]

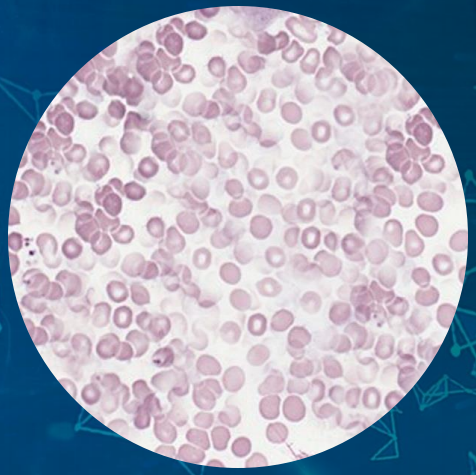
BCL-2 is an antiapoptotic protein[3-5]

A healthy cell with **normal expression** of BCL-2 has **balanced cell survival and cell death**

A CLL cell with **overexpressed** BCL-2 is able to **evade apoptosis**

Restoration of apoptosis is not limited to leukemic cells

Venetoclax selectively binds to BCL-2, triggering events that lead to apoptosis[1]



Based on preclinical studies.

1. VENCLEXTA Prescribing Information. 2. Souers AJ, et al. *Nat Med*. 2013;19(2):202-208. 3. Plati J, et al. *Integr Biol (Camb)*. 2011;3(4):279-296.
4. Hanahan D, et al. *Cell*. 2000;100(1):57-70. 5. Lagadinou ED, et al. *Cell Stem Cell*. 2013;12(3):329-341.

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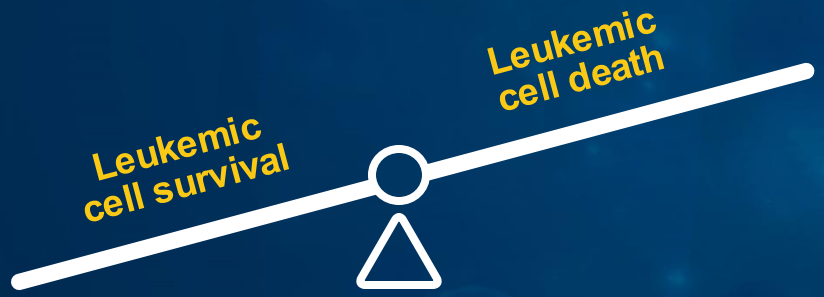

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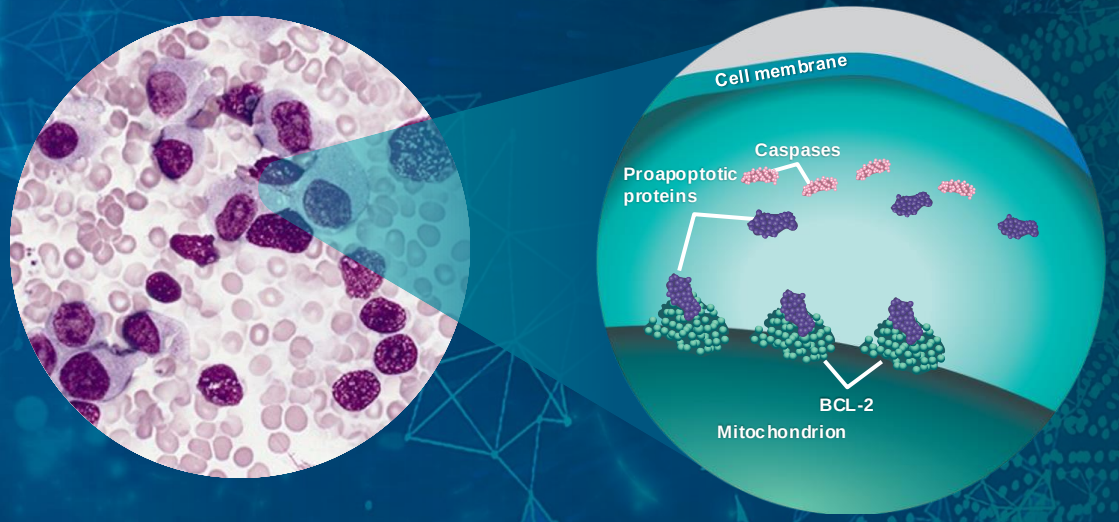

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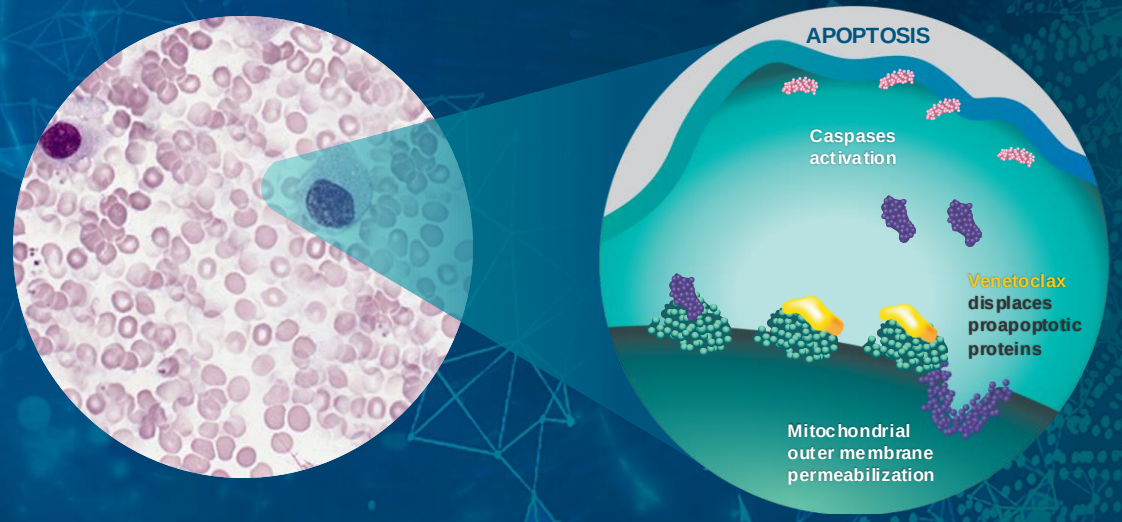

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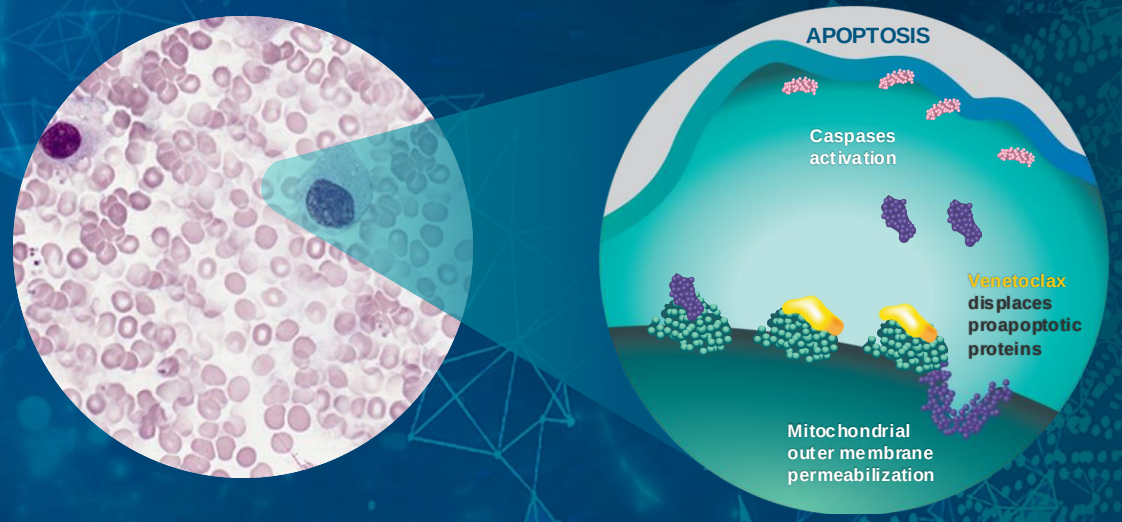

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VENCLEXTA

VEN+G
for PREVIOUSLY UNTREATED CLL

VEN+R
for R/R CLL

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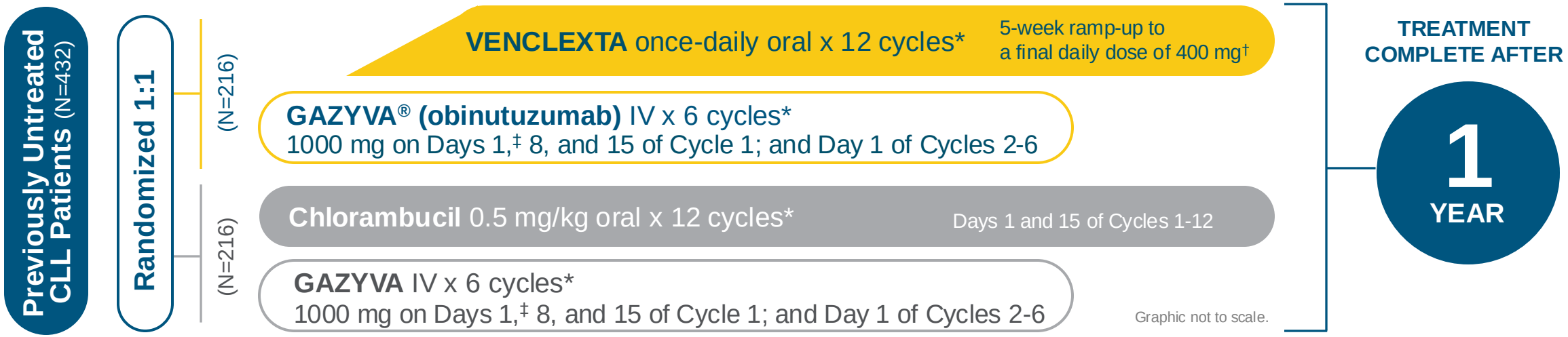
Designed for Patients to Complete Treatment in 1 Year[1]

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

CLL14 was a multicenter, open-label, actively controlled, phase 3 trial that evaluated the efficacy and safety of VENCLEXTA in combination with GAZYVA (VEN+G) in patients with previously untreated CLL and coexisting medical conditions (total CIRS >6 or CrCl <70 mL/min). The primary endpoint was PFS (IRC-assessed PFS was the basis for FDA approval of VEN+G).



98% MEDIAN ALC REDUCTION

After the first treatment cycle of GAZYVA and before the VENCLEXTA dose ramp-up, median ALC was reduced by 98%[2]

- Per the trial protocol, tumor burden was assessed based on ALC and lymph node size[1]; the effect of the first GAZYVA treatment cycle on lymph node size was not evaluated[2]
- The trial started with an initial cycle of GAZYVA followed by the 5-week VENCLEXTA dose ramp-up; median lymphocyte count was reduced in the safety evaluable population (N=212) from 55 x 10^9 cells/L at baseline to 1.27 x 10^9 cells/L at Day 15; median lymphocyte counts are descriptive in nature and were not powered for any type of comparison; changes in TLS risk status based on ALC reduction were at the discretion of the trial investigators

*Each cycle=28 days. †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. ‡The first GAZYVA dose could be split as 100 mg and 900 mg on Days 1 and 2, respectively.

CIRS=Cumulative Illness Rating Scale; CrCl=creatinine clearance; IRC=independent review committee; ALC=absolute lymphocyte count.

1. VENCLEXTA Prescribing Information. 2. Data on file, AbbVie Inc. ABVRRTI69608.

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VEN+G Demonstrated Durable PFS Without Long-Term Treatment[1]

IRC-assessed PFS (primary endpoint)

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

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

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

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

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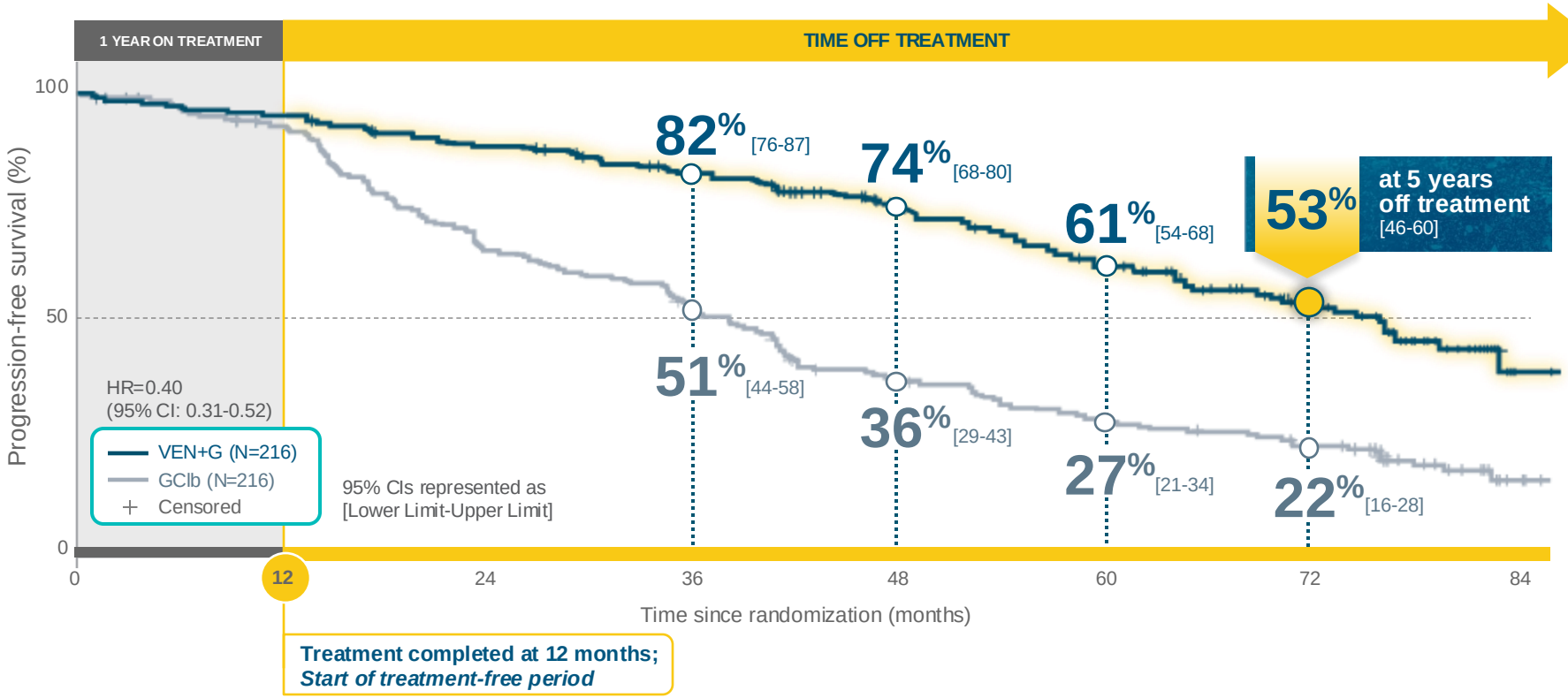
6-Year Follow-Up Analysis of PFS[1,2]*

INV-assessed PFS (overall follow-up of 86.5 months)



Number of patients at risk

VEN+G	216	193	177	160	139	112	79	3
GClb	216	185	130	101	67	50	36	3

The PFS follow-up analysis was not tested for statistical significance

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

*Based on data as of clinical data cutoff date of November 14, 2022; time of analysis was not pre-specified.

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

INV=investigator.

1. Al-Sawaf O, Robrecht S, Zhang C, et al. Abstract presented at the European Hematology Association Congress 2023; June 8-11, 2023.
2. Data on file, AbbVie Inc. 6-year data ABVRRTI76226.

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6-Year Follow-Up Analysis of TTNT[1,2]*

TIME TO NEXT TREATMENT†

At the time of the 6-year analysis*:

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

64%
(139/216)

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

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

Not tested for statistical significance.

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

1. Al-Sawaf O, Robrecht S, Zhang C, et al. Abstract presented at the European Hematology Association Congress 2023; June 8-11, 2023.
2. Data on file, AbbVie Inc. 6-year data ABVRRTI76226.

VEN+G Offers a Well-Studied Safety Profile With Exposure Limited to 1 Year[1]

VEN+G Safety From the CLL14 Trial

- The median duration of exposure to VENCLEXTA was 10.5 months (range: 0-13.5 months); the median number of cycles was 6 for GAZYVA® (obinutuzumab)
- In the VEN+G arm, fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients, most often from infection, compared with 1% (3/214) of patients in the GClb arm[1,2]
- Serious adverse reactions were reported in 49% of patients in the VEN+G arm, most often due to febrile neutropenia and pneumonia (5% each)
- TLS is an important identified risk when initiating VENCLEXTA
- TLS prophylaxis and monitoring protocols can reduce the risk of TLS
- The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS
- There were no new safety signals detected at the 6-year follow-up[3]

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%

1. VENCLEXTA Prescribing Information. 2. Data on file, AbbVie Inc. ABVRRTI69608. 3. Al-Sawaf O, et al. Abstract presented at European Hematology Association Congress 2023; June 8-11, 2023.

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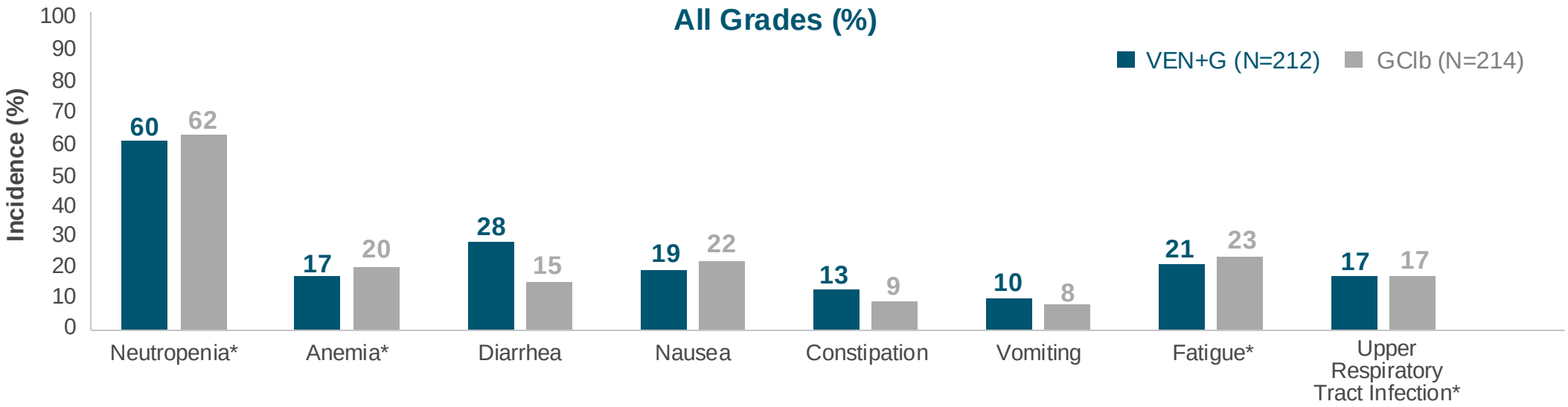
VEN+G Offers a Well-Studied Safety Profile With Exposure Limited to 1 Year[1]

Adverse Reactions (≥10%) in Patients Treated With VEN+G



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

Granulocyte colony-stimulating factor (G-CSF) was used to treat neutropenia in 44% of patients in the VEN+G arm and 46% of patients in the GClb arm.[2]

*Includes multiple adverse reaction terms.

1. VENCLEXTA Prescribing Information. 2. Fischer K, et al. *N Engl J Med*. 2019;380(23):2225-2236.

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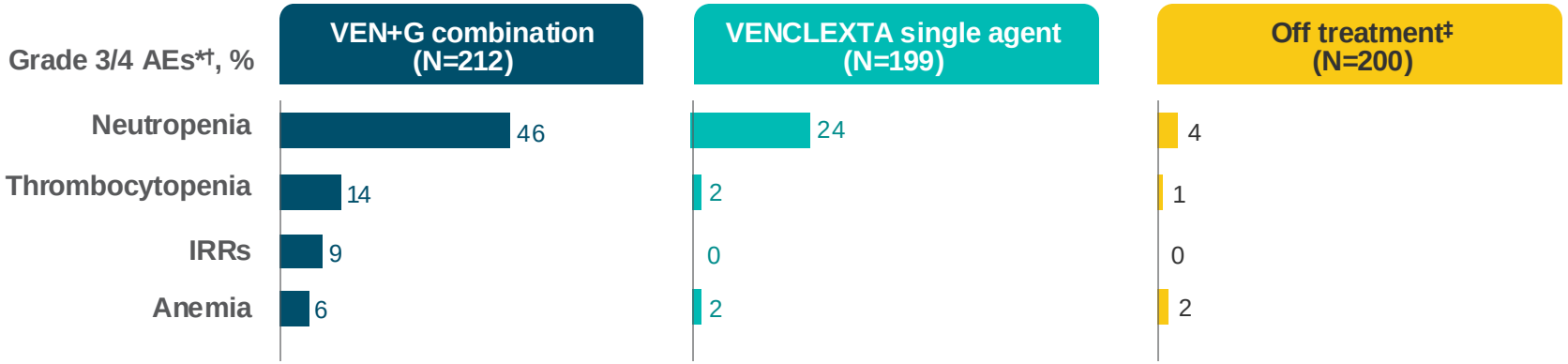
Limit Patients' VEN+G Exposure and Potential Side Effects After Completing Treatment[1]



There were no new safety signals detected at the 6-year follow-up.[2]

- **Other important Grade 3/4 AEs**
  - **Febrile neutropenia: 4%** during combination-therapy period, **0%** during single-agent period, **1%** during off-treatment period
  - **Pneumonia: 3%** during combination-therapy period, **1%** during single-agent period, **3%** during off-treatment period
  - **TLS: 1%** during combination-therapy period, **0%** during single-agent period, **0%** during off-treatment period
- **VEN+G combination-therapy period (6 cycles):** Includes Grade 3 and 4 treatment-emergent AEs occurring on or before last exposure date of GAZYVA + 29 days
- **VENCLEXTA single-agent period (6 cycles):** Includes Grade 3 and 4 AEs occurring after the start of the VENCLEXTA monotherapy period to last date of VENCLEXTA + 29 days

‡**Off treatment:** Includes Grade 3 and 4 AEs occurring after 29 days and up to 6 months after treatment completion.

- Multiple occurrences of the same AE in an individual during the same treatment period are counted only once for that treatment period

ADDITIONAL SAFETY INFORMATION >

*Based on data as of clinical cutoff date of November 14, 2022.[1]

†The chart reflects Grade 3/4 AEs with incidence ≥5%.[1]

AEs=adverse events; IRRs=infusion-related reactions.

1. Data on file, AbbVie Inc. 6-year data ABVRRTI76226. 2. Al-Sawaf O, et al. Abstract presented at the European Hematology Association Congress 2023; June 8-11, 2023.

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Additional Safety Information From the CLL14 Trial[1]

Cardiovascular adverse events in patients treated with VEN+G*†

	VEN+G (N=212)		GClb (N=214)	
Adverse Reaction by Body System	**Any Grade (%)**	**Grade ≥3 (%)†**	**Any Grade (%)**	**Grade ≥3 (%)†**
Cardiac disorders				
Atrial fibrillation	3	2	2	1
Myocardial infarction‡	2	2	1	1
Cardiac failure	2	2	<1	0
Vascular disorders				
Hypertension	7	3	5	<1
Hypotension	5	1	4	2

The analysis was not powered to demonstrate a statistically significant difference between VEN+G and GClb adverse events.

BACK

*Based on data as of clinical data cutoff date of August 23, 2019.
†Shown are Grade 3, 4, and 5 events with frequency 1% or higher and their corresponding Any Grade rates.
‡Includes multiple adverse reaction terms.
1. Al-Sawaf O, et al. *Lancet Oncol*. 2020;21(9):1188-1200.

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TLS Is an Important Identified Risk When Initiating VENCLEXTA[1]

TLS Incidence in the CLL14 Trial

1%
Laboratory TLS

0%
Clinical TLS

- **The incidence of laboratory TLS was 1%** (3/212) in patients treated with VEN+G; all 3 events of TLS occurred during treatment with GAZYVA, before treatment initiation with VENCLEXTA; all 3 events of TLS resolved and did not lead to withdrawal from the trial; GAZYVA administration was delayed in 2 cases in response to the TLS events[1,2]
- **The incidence of clinical TLS was 0%[2]**

Managing TLS

- VENCLEXTA can cause rapid reductions 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 prophylaxis and monitoring protocols can reduce the risk of TLS**
- **The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS**

1. VENCLEXTA Prescribing Information. 2. Data on file, AbbVie Inc. ABVRRTI69608.

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VENCLEXTA

VEN+G
for PREVIOUSLY UNTREATED CLL

VEN+R
for R/R CLL

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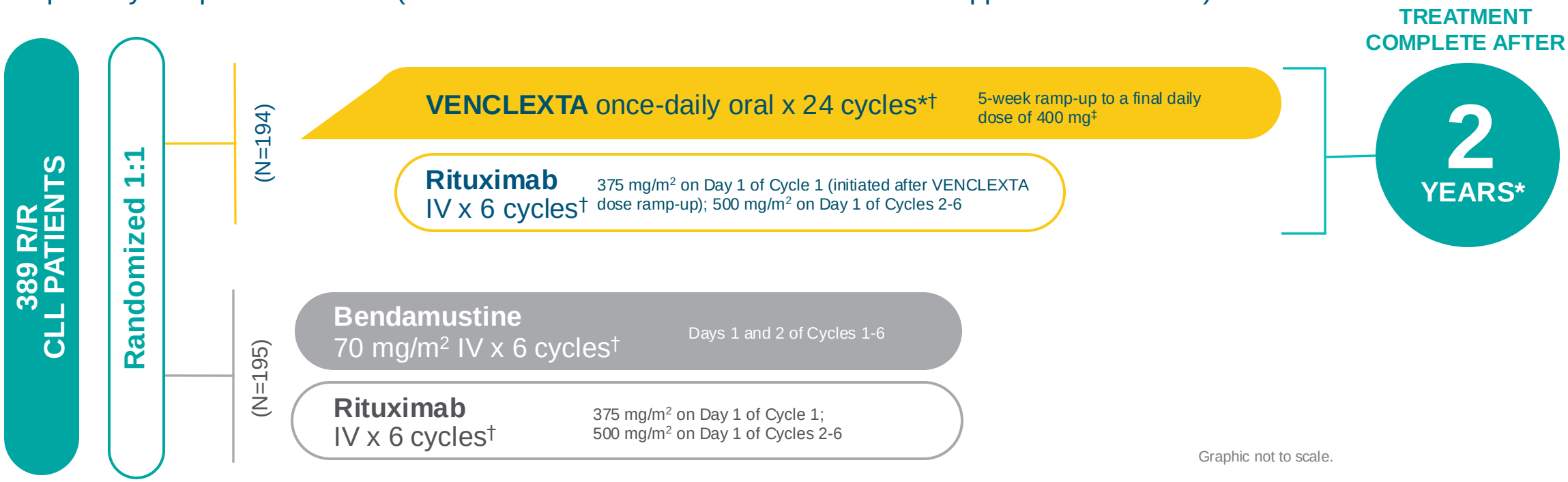
Designed for Patients to Complete Treatment in 2 Years[1]*

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

MURANO was a phase 3 multicenter, open-label, actively controlled trial that evaluated the efficacy and safety of VENCLEXTA in combination with rituximab (VEN+R) in patients with CLL who had received at least one prior therapy.[1,2]
The primary endpoint was PFS (IRC-assessed PFS was the basis for FDA approval of VEN+R).



Graphic not to scale.

*From Cycle 1, Day 1 of rituximab, in the absence of disease progression or unacceptable toxicity. †Each cycle=28 days. ‡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.

1. VENCLEXTA Prescribing Information. 2. Seymour JF, et al. *N Engl J Med*. 2018;378(12):1107-1120.

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VEN+R Demonstrated Durable PFS Without Long-Term Treatment[1]*

IRC-assessed PFS (primary endpoint)

reduction in risk of progression or death vs BR

HR=0.19; 95% CI: 0.13-0.28 (*P*<0.0001)

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

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

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

1. VENCLEXTA Prescribing Information.

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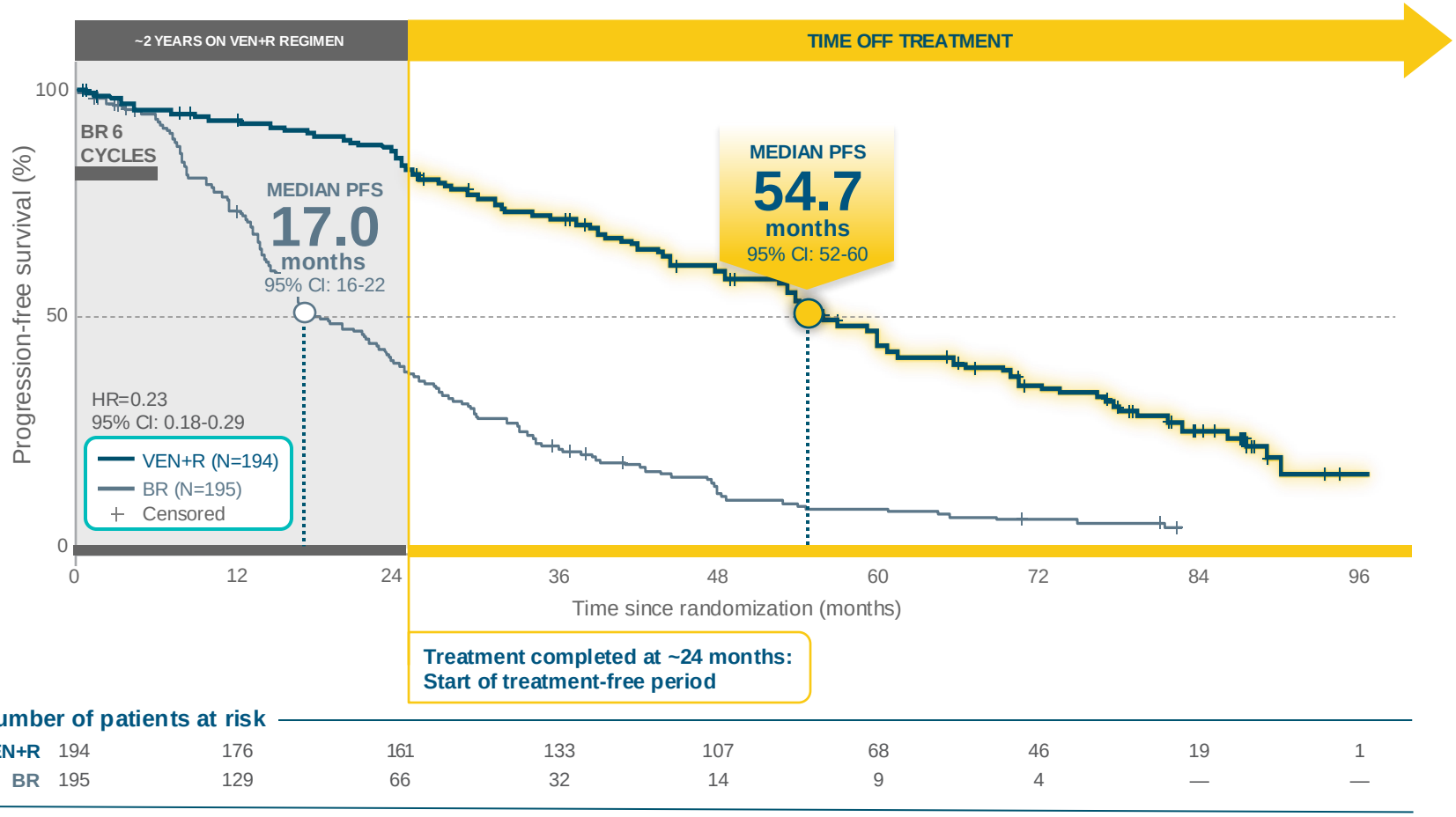
7-Year Follow-Up Analysis of PFS[1,2]*

INV-assessed PFS (overall follow-up of 99.2 months)



Number of patients at risk

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

The PFS follow-up analysis was not tested for statistical significance

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

*Based on data as of clinical data cutoff date of August 3, 2022; time of analysis was not pre-specified.

1. Kater AP, Harrup R, Kipps TJ, et al. Abstract presented at the European Hematology Association Congress 2023; June 8-11, 2023.
2. Data on file, AbbVie Inc. 7-year MURANO ABVRRTI76236.

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7-Year Follow-Up Analysis of TTNT[1,2]*

TIME TO NEXT TREATMENT†

At the time of the 7-year analysis*:

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

38%
(73/194)

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

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

Not tested for statistical significance.

*Based on data as of clinical data cutoff date of August 3, 2022; time of analysis was not pre-specified.
†TTNT was defined as the time from randomization to start of a new CLL therapy or death.
1. Kater AP, Harrup R, Kipps TJ, et al. Abstract presented at the European Hematology Association Congress 2023; June 8-11, 2023. 2. Data on file, AbbVie Inc. 7-year MURANO ABVRRTI76236.

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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[2]
  - 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[3]
  - Patients needed to receive at least 90% of the target dose to be counted as receiving a full cycle[2]
- TLS is an important identified risk when initiating VENCLEXTA
- TLS prophylaxis and monitoring protocols can reduce the risk of TLS
- The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS
- There were no new safety signals detected at the 7-year follow-up[4]

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]

1. VENCLEXTA Prescribing Information. 2. Data on file, AbbVie Inc. ABVRRTI69609. 3. Seymour JF, et al. *N Engl J Med*. 2018;378(12):1107-1120.
4. Kater AP, et al. Abstract presented at the European Hematology Association Congress 2023; June 8-11, 2023.

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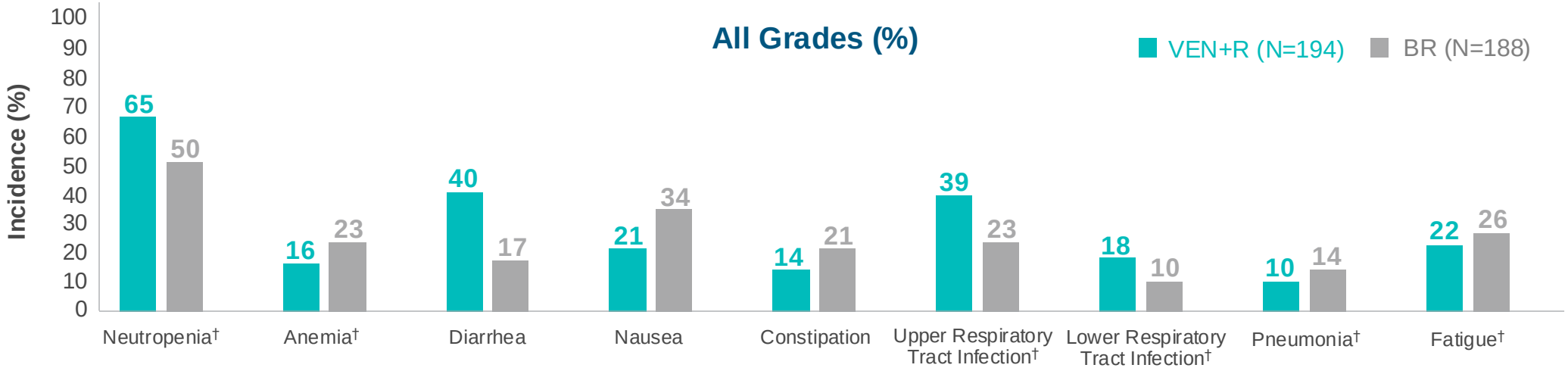
VEN+R Offers a Well-Studied Safety Profile With Exposure Limited to 2 Years[1]*

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



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

*From Cycle 1, Day 1 of rituximab. †Includes multiple adverse reaction terms.

1. VENCLEXTA Prescribing Information.

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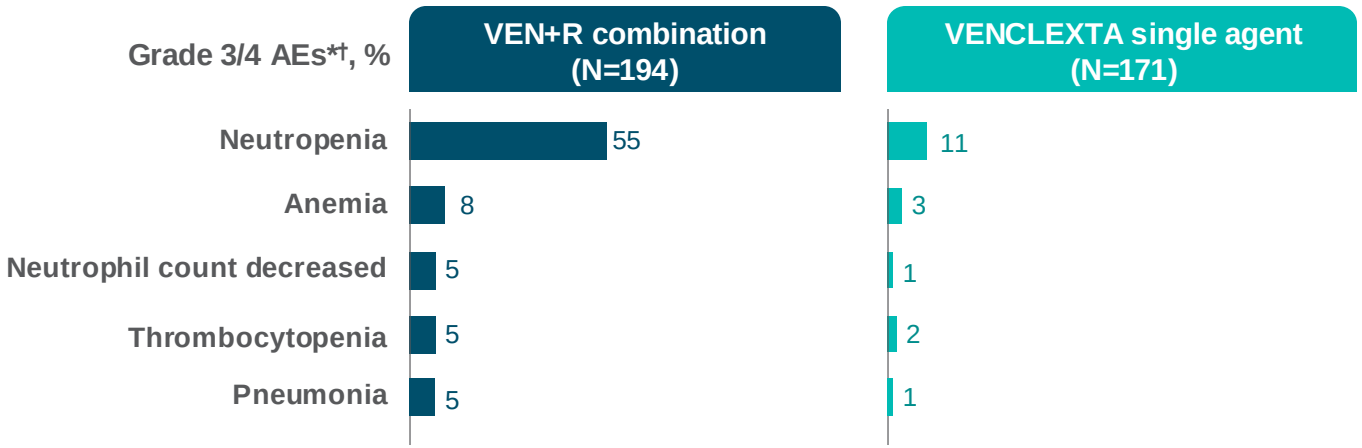
New Incidence of Grade 3 and 4 Adverse Events (AEs) Decreased During the VENCLEXTA Single-Agent Period[1]



There were no new safety signals detected at the 7-year follow-up.[2]

- **Other important Grade 3/4 AEs**
  - **Febrile neutropenia: 4%** during combination-therapy period, **0%** during single-agent period
  - **TLS: 3%** during combination-therapy period, **0%** during single-agent period
- **VEN+R combination-therapy period (6 cycles):** includes treatment-emergent AEs with an onset date from initiation of the VENCLEXTA dose ramp-up to within 90 days after last rituximab dose[3]
- **VENCLEXTA single-agent period (18 cycles):** includes patients who had at least 1 VENCLEXTA dose more than 90 days after last rituximab dose and treatment-emergent AEs with an onset date more than 90 days after last rituximab dose[3]
- Multiple occurrences of the same adverse event in an individual during the same treatment period are counted only once for that treatment period[3]

*Based on data as of clinical cutoff date of August 3, 2022.[1]
†The chart reflects Grade 3/4 AEs with incidence ≥5%.
1. Data on file, AbbVie Inc. 7-year MURANO ABVRRTI76236. 2. Kater AP, et al. Abstract presented at the European Hematology Association Congress 2023; June 8-11, 2023. 3. Data on file, AbbVie Inc. ABVRRTI69609.

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TLS Is an Important Identified Risk When Initiating VENCLEXTA[1]

TLS Incidence in the MURANO Trial

3%	0%
Overall TLS	**Clinical TLS***

- **The incidence of TLS was 3% overall** (6/194) in patients treated with VEN+R; after 77/389 patients were enrolled in the trial, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures
- All events of TLS occurred during the VENCLEXTA ramp-up period and were resolved within two days; all six patients completed the ramp-up and reached the recommended daily dose of 400 mg of VENCLEXTA

*__The incidence of clinical TLS was 0%__ in patients who followed the current 5-week ramp-up schedule and TLS prophylaxis and monitoring measures.

Managing TLS

- VENCLEXTA can cause rapid reductions 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 prophylaxis and monitoring protocols can reduce the risk of TLS**
- **The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS**

1. VENCLEXTA Prescribing Information.

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VENCLEXTA Dosing Recommendations

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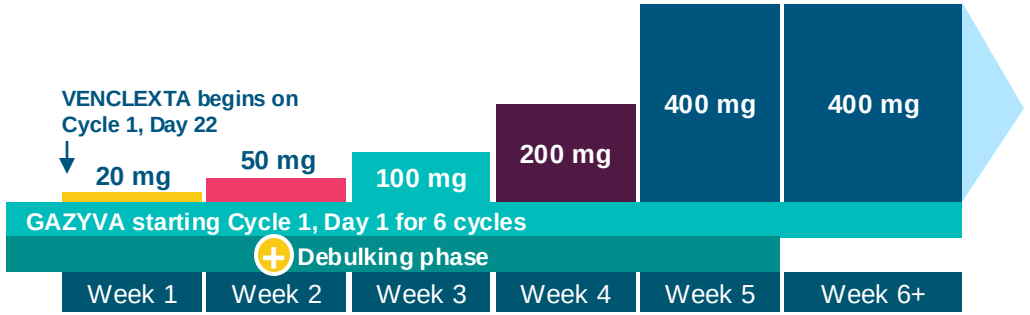
VENCLEXTA Dosing for CLL Includes a Gradual 5-Week Ramp-Up[1]

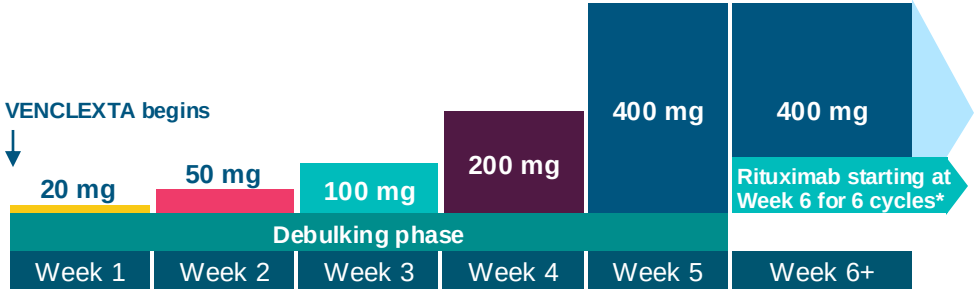
The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS

VEN+G for Previously Untreated CLL



Patients should continue VENCLEXTA 400 mg once daily from Cycle 3, Day 1 until the last day of **Cycle 12**

VEN+R for R/R CLL



Patients should continue VENCLEXTA 400 mg once daily for **24 cycles** from Cycle 1, Day 1 of rituximab

The first 4 weeks of VENCLEXTA are provided in 4 weekly wallet blister packs.

Week 5 and onward are provided in a bottle containing 100-mg VENCLEXTA tablets.

The recommended dosage of VENCLEXTA may be delivered using any of the approved tablet strengths (eg, patients can take 2 x 50-mg tablets or 10 x 10-mg tablets instead of 1 x 100-mg tablet as needed). VENCLEXTA may also be given as monotherapy until disease progression or unacceptable toxicity.

GAZYVA® is a registered trademark of Genentech, Inc.
*Start rituximab after patient has received the 400-mg dose of VENCLEXTA for 7 days.
1. VENCLEXTA Prescribing Information.

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VENCLEXTA Dosing for CLL Includes a Gradual 5-Week Ramp-Up[1]

98%
MEDIAN ALC REDUCTION

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

- Per the trial protocol, tumor burden was assessed based on ALC and lymph node size[2]; the effect of the first GAZYVA treatment cycle on lymph node size was not evaluated[1]
- The trial started with an initial cycle of GAZYVA followed by the 5-week VENCLEXTA dose ramp-up; median lymphocyte count was reduced in the safety evaluable population (N=212) from 55 × 10^9 cells/L at baseline to 1.27 × 10^9 cells/L at Day 15
- Median lymphocyte counts are descriptive in nature and were not powered for any type of comparison
- Changes in TLS risk status based on ALC reduction were at the discretion of the trial investigators

1. Data on file, AbbVie Inc. ABVRRTI69608. 2. VENCLEXTA Prescribing Information.

GAZYVA® is a registered trademark of Genentech, Inc.
*Start rituximab after patient has received the 400-mg dose of VENCLEXTA for 7 days.
1. VENCLEXTA Prescribing Information.

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VENCLEXTA Drug Interactions and Severe Hepatic Impairment[1]

Dose modifications for managing potential drug interactions

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		
Strong or moderate CYP3A inducer	Avoid concomitant use of VENCLEXTA with strong or moderate CYP3A inducers	
Warfarin	Monitor international normalized ratio (INR) more frequently in patients using warfarin concomitantly with VENCLEXTA	
P-gp substrates	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	

*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**

Dosage modifications for use in 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

CYP3A=cytochrome P450 3A.

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TLS Prophylaxis and Monitoring Protocols Can Reduce the Risk of TLS[1]

VENCLEXTA can cause rapid reduction in tumor burden and thus poses a risk for TLS in the initial 5-week ramp-up phase. TLS can also occur upon resumption of VENCLEXTA following a dosage interruption. Assess patient-specific factors for level of risk of TLS and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose of VENCLEXTA to reduce risk of TLS. 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 the ramp-up. Institute prophylaxis and monitoring as needed.

Perform tumor burden assessments, including radiographic evaluation (eg, CT scan), prior to initiation of treatment with VENCLEXTA

Assess blood chemistry in all patients and correct preexisting abnormalities prior to initiation of treatment with VENCLEXTA

The risk of TLS is a continuum based on multiple factors, particularly reduced renal function (CrCl <80 mL/min) and tumor burden; splenomegaly may also increase the risk of TLS

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 may decrease as tumor burden decreases; appropriate prophylaxis can help lower the risk of TLS

Blood chemistry monitoring to be reviewed in real time:

- Potassium
- Calcium
- Creatinine
- Phosphorus
- Uric acid

Refer to the Prescribing Information for detailed information on recommended TLS prophylaxis, monitoring, and treatment setting during dose ramp-up.

CT=computerized tomography.

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Dose Modifications or Interruptions Can Help Manage Select Adverse Reactions[1]

VENCLEXTA dose modifications are recommended if any of the following adverse reactions* occur:

- Grade 3 or 4 nonhematologic adverse reactions
- Grade 3 neutropenia with infection or fever
- Grade 4 hematologic adverse reactions (except lymphopenia)
- Blood chemistry changes or symptoms suggestive of TLS

Interrupt dosing or reduce dose for adverse reactions. Consider discontinuing VENCLEXTA for patients who require dose reductions to less than 100 mg for more than 2 weeks.

- 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)

Refer to the Prescribing Information for detailed information on dosage modifications for adverse reactions.

Your patient experiences a first occurrence of Grade 3 neutropenia with fever.

How do you proceed?

*Adverse reactions were graded using NCI CTCAE version 4.0.
NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.
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What Can Fixed-Duration Treatment Mean for Patients With CLL?

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How May Fixed-Duration Treatment Benefit Your Patients With CLL?

Time Off Treatment

- **Set a target stop date** that can encourage compliance and optimize clinical outcomes, followed by a **treatment-free period**[1,2]
- Offer your patients the chance for **time off treatment**, and a return to life **without a daily reminder** of their treatment and disease[3]

No Ongoing Treatment Exposure

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

No Ongoing Out-of-Pocket Costs

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

How are you educating patients about treatment options and engaging them in treatment selection?
What do you see as the potential benefits of a fixed treatment duration for your appropriate patient?

*In CLL14, all adverse events were reported until 28 days after the last dose of study treatment (venetoclax, chlorambucil, or obinutuzumab). Grade 3-4 adverse events were reported for 6 months and Grade 3-4 infections were reported for 2 years after the last dose of study treatment, irrespective of causality, unless the patient received next leukemic treatment.[4,5] In MURANO, all adverse events were reported until 28 days after the last dose of study drug, or 90 days after the last dose of rituximab, whichever was longer. After this period, investigators reported any deaths, serious adverse events, or other adverse events of concern that were believed to be related to prior study drug treatment.[6] †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.

1. Greer JA, et al. *Oncologist*. 2016;21(3):354-376. 2. Ruddy K, et al. *CA Cancer J Clin*. 2009;59(1):56-66. 3. VENCLEXTA Prescribing Information. 4. Al-Sawaf O, et al. *Lancet Oncol*. 2020;21(9):1188-1200. 5. Al-Sawaf O, et al. *Lancet Oncol*. 2020;21(9)(suppl):1188-1200. 6. Seymour JF, et al. *N Engl J Med*. 2018;378(12):1107-1120.

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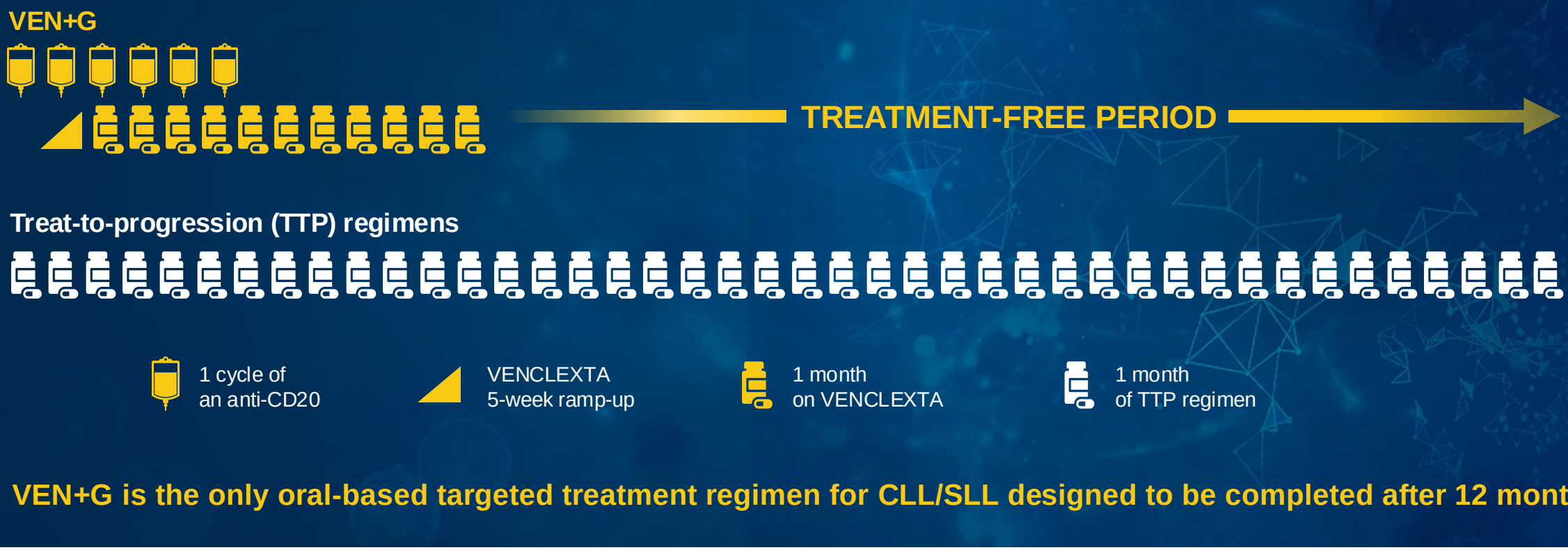
No Additional VENCLEXTA Regimen Exposure After Completing Treatment[1]



VEN+G is the only oral-based targeted treatment regimen for CLL/SLL designed to be completed after 12 months.

Treatment duration and treatment-free period are not to scale and are not representative of all patients and therapeutic options. Not intended to convey comparative safety or efficacy. Not intended to imply that VENCLEXTA regimens and TTP regimens are interchangeable or equivalent. Please see the full Prescribing Information for VENCLEXTA dosing information.

CD20=cluster of differentiation 20.

1. VENCLEXTA Prescribing Information.

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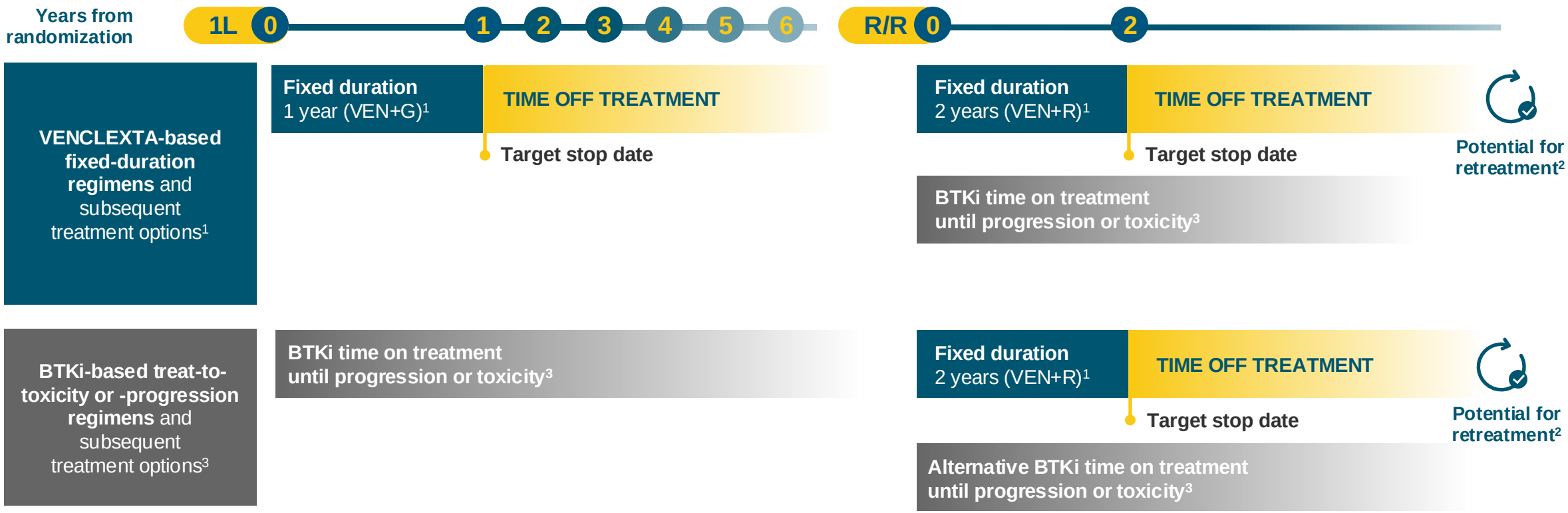
Time Off Treatment Matters for Patients With CLL: Starting Treatment With VENCLEXTA May Help Maximize Time Off Oral-Targeted Treatments



Treatment duration and treatment-free period are not to scale and are not representative of all patients and therapeutic options.
Not intended to convey comparative safety or efficacy. Not intended to imply that VENCLEXTA regimens and TTP regimens are interchangeable or equivalent. Please see the full Prescribing Information for VENCLEXTA dosing information.

1L=first line; BTKi=Bruton tyrosine kinase inhibitor.

1. VENCLEXTA Prescribing Information. 2. Kater AP, Harrup R, Kipps TJ, et al. Abstract presented at the European Hematology Association Congress 2023; June 8-11, 2023. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V.1.2024. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed November 8, 2023. To view the most recent and complete version of the guidelines, go online to NCCN.org.

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VENCLEXTA: 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.

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VENCLEXTA: Important Safety Information (cont.)

Neutropenia

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

Infections

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

Immunization

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

Embryo-Fetal Toxicity

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

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

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

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VENCLEXTA: Important Safety Information (cont.)

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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VENCLEXTA: Important Safety Information (cont.)

Drug Interactions

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

Lactation

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

Females and Males of Reproductive Potential

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

Hepatic Impairment

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

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

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NCCN PREFERRED

The National Comprehensive Cancer Network® (NCCN®) recommends certain venetoclax (VENCLEXTA®) combination regimens as *category 1 preferred* treatment options for CLL/SLL[1]*

For first-line therapy, in patients without del(17p)/*TP53* mutation

Venetoclax + obinutuzumab (GAZYVA®)
Category 1 preferred

For second-line or third-line therapy

Venetoclax + rituximab
Category 1 preferred

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*See NCCN Guidelines® for the NCCN definitions of Categories of Preference and Categories of Evidence and Consensus.
TP53=tumor protein p53.
1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V.1.2024. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed November 8, 2023. To view the most recent and complete version of the guidelines, go online to NCCN.org.
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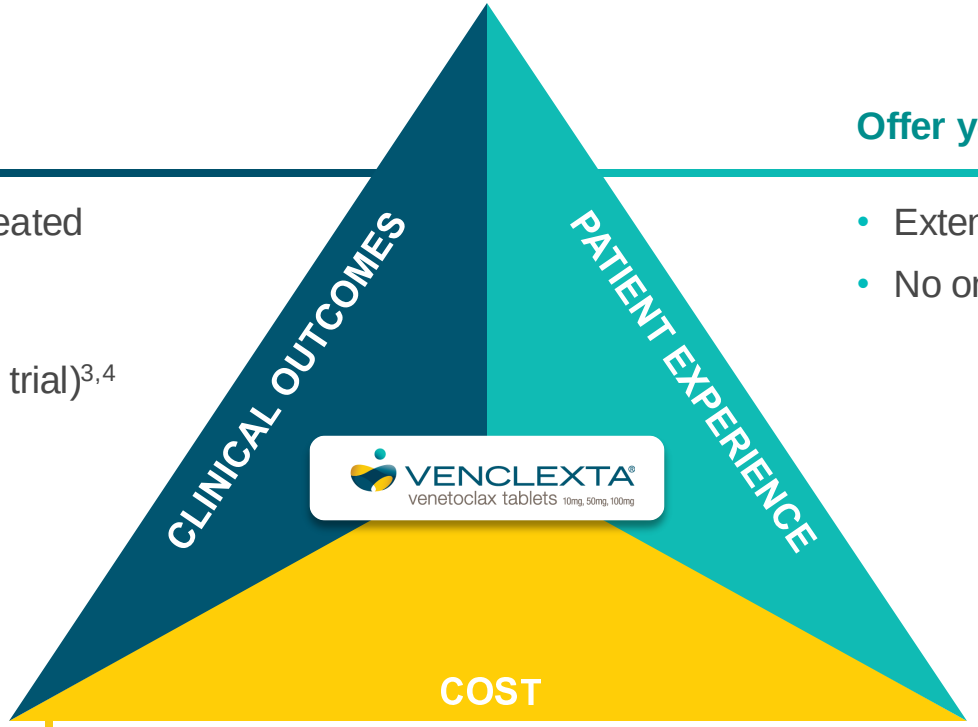
Start With VENCLEXTA, and Offer Your Patients the Chance for Durable PFS Without Continuous Treatment

Proven efficacy and well-studied safety profile

- VEN+G for previously untreated (CLL14 trial)[1,2]
  - >6 years of follow-up
- VEN+R for R/R (MURANO trial)[3,4]
  - >7 years of follow-up



Offer your patients the chance for:

- Extended time off treatment
- No ongoing treatment exposure

No ongoing out-of-pocket costs

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

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

1. Al-Sawaf O, et al. Abstract presented at the European Hematology Association Congress 2023; June 8-11, 2023. 2. Data on file, AbbVie Inc. 6-year data ABVRRTI76226. 3. Kater AP, et al. Abstract presented at the European Hematology Association Congress 2023; June 8-11, 2023. 4. Data on file, AbbVie Inc. 7-year MURANO ABVRRTI76236.

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oncology exchange

fall 2024

Clinical Session