A chance to

BREAK FREE

VENCLYXTO® + rituximab offers patients with R/R CLL a chance for longer progression-free survival with a 24-month fixed treatment duration[1]

In the primary analysis of the MURANO trial, VENCLYXTO + rituximab significantly reduced the risk of progression or death by 83% vs bendamustine + rituximab (HR: 0.17; 95% CI: 0.11-0.25, *P*<0.0001); mPFS was not reached with VENCLYXTO + rituximab vs 17 months (95% CI: 15.5-21.6) with bendamustine + rituximab. In an updated efficacy analysis with all patients off treatment, the 36-month PFS estimate for VEN+R was 71.4% (95% CI: 64.8-78.1) vs 15.2% (95% CI: 9.1-21) in the BR arm.[1]

EXPANDED INDICATION IN R/R CLL:

VENCLYXTO in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

VENCLYXTO monotherapy is indicated for the treatment of CLL:

- In the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or
- In the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

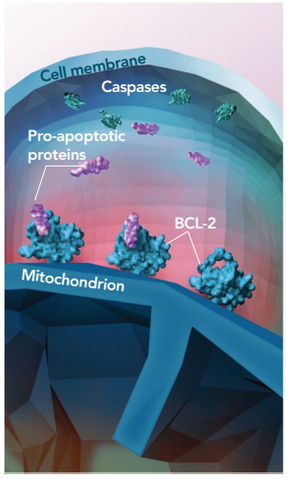
BR=bendamustine + rituximab; CI=confidence interval; HR=hazard ratio; mPFS=median progression-free survival; R/R=relapsed/refractory; TP53=tumour protein 53.

DRAFT material based on July 2018 DRAFT SMPC.

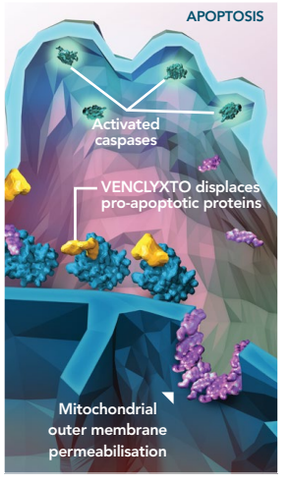
VENCLYXTO®
venetoclax tablets

VENCLYXTO® + rituximab (VEN+R): A regimen that targets BCL-2 and CD20

VENCLYXTO ADDRESSES THE OVEREXPRESSION OF BCL-2, AN IMPORTANT DEFECT OF CLL, BY RESTORING THE ABILITY OF B CELLS TO UNDERGO APOPTOSIS[1,2]



Overexpressed BCL-2 allows CLL cells to evade apoptosis by sequestering pro-apoptotic proteins.[3]



VENCLYXTO selectively binds to BCL-2, displacing pro-apoptotic proteins, and triggering events that lead to apoptosis.

Based on preclinical studies.

Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes[4]

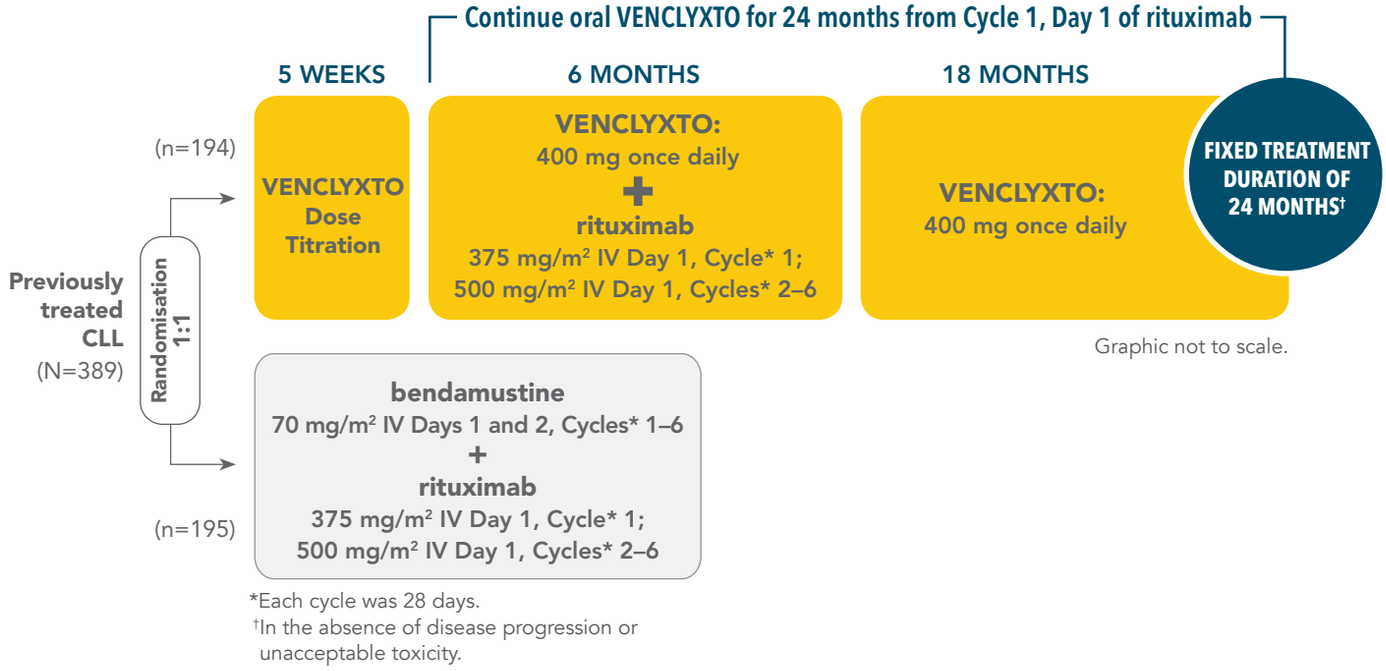
- Upon binding to CD20, rituximab mediates B-cell lysis
- Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC)

BCL-2=B-cell lymphoma 2; CD20=cluster of differentiation 20; CLL=chronic lymphocytic leukaemia.

VENCLYXTO® venetoclax tablets

VENCLYXTO® + rituximab: A combination regimen compared with a standard CIT (BR) in patients who received at least one prior therapy[1]

MURANO: A RANDOMISED, MULTICENTRE, PHASE 3 TRIAL



Graphic not to scale.

*Each cycle was 28 days.
†In the absence of disease progression or unacceptable toxicity.

Primary endpoint[1,5]:	Secondary endpoints included[5]:
INV-assessed PFS‡	IRC-assessed PFS; INV- and IRC-assessed ORR, PR, CR, and CRi; OS; rates of clearance of minimal residual disease§‖

‡Assessed using the International Workshop for Chronic Lymphocytic Leukemia (iwCLL) updated National Cancer Institute–sponsored Working Group (NCI-WG) guidelines (2008).
§ORR defined as CR + CRi + nPR + PR.
‖Minimal residual disease was evaluated in the peripheral blood and/or bone marrow using ASO-PCR and/or flow cytometry. The cutoff for a negative status was <1 CLL cell per 10^4 leukocytes per iwCLL guidelines.[1,6]

- Select inclusion criteria:
  - Previously treated with at least one prior therapy (including at least 1 chemotherapy-containing regimen)[5]
  - Patients treated with prior bendamustine provided the duration of response was ≥24 months[5]

ASO-PCR=allele-specific oligonucleotide polymerase chain reaction; BR=bendamustine + rituximab; CIT=chemoimmunotherapy; CLL=chronic lymphocytic leukaemia; CR=complete remission; CRi=complete remission with incomplete marrow recovery; INV=investigator; IRC=independent review committee; IV=intravenous; nPR=nodular partial remission; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial remission.

MURANO patient demographics and baseline disease characteristics[1]

MURANO DEMOGRAPHICS AND BASELINE PATIENT CHARACTERISTICS

Median age; years (range)		65 (22-85)
White (Caucasian); %		97
Male; %		74
Median time since diagnosis; years (range)		6.7 (0.3-29.5)
Tumour burden; %	ALC ≥25 x 10^9/L One or more nodes ≥5 cm	68 47
Chromosomal aberrations; %	Del(17p) *TP53* mutations Del(11q) Unmutated *IgVH*	27 26 37 68
Median follow-up time at the time of analysis; months (range)		23.8 (0.0-37.4)

PRIOR LINES OF THERAPY IN MURANO TRIAL

Median prior lines of therapy (range)		1 (1-5)
Prior therapy; %	Alkylating agents Purine analogues* Anti-CD20 antibodies B-cell receptor pathway inhibitors	94 81 77 2

*Including 55% FCR.

ALC=absolute lymphocyte count; CD20=cluster of differentiation 20; Del(17p)=17p deletion; Del(11q)=11q deletion; FCR=fludarabine + cyclophosphamide + rituximab; IgVH=immunoglobulin variable-region heavy-chain gene; TP53=tumour protein 53.

VENCLYXTO® venetoclax tablets

VEN+R demonstrated superior PFS[1]

Median follow-up was 23.8 months (range: 0.0-37.4) in the primary analysis of the MURANO trial

INV-ASSESSED PFS (ITT POPULATION) IN PATIENTS WITH R/R CLL

	VEN+R (n=194)	BR (n=195)
Number of events (%)	32 (16.5)	114 (58.5)
Disease progression	21	98
Death events	11	16
Median, months (95% CI)	NR	17.0 (15.5-21.6)
Hazard ratio (95% CI)	0.17 (0.11-0.25)	
P-value*	<0.0001	

Data cutoff date, 8 May 2017.
*Stratified *P*-value.

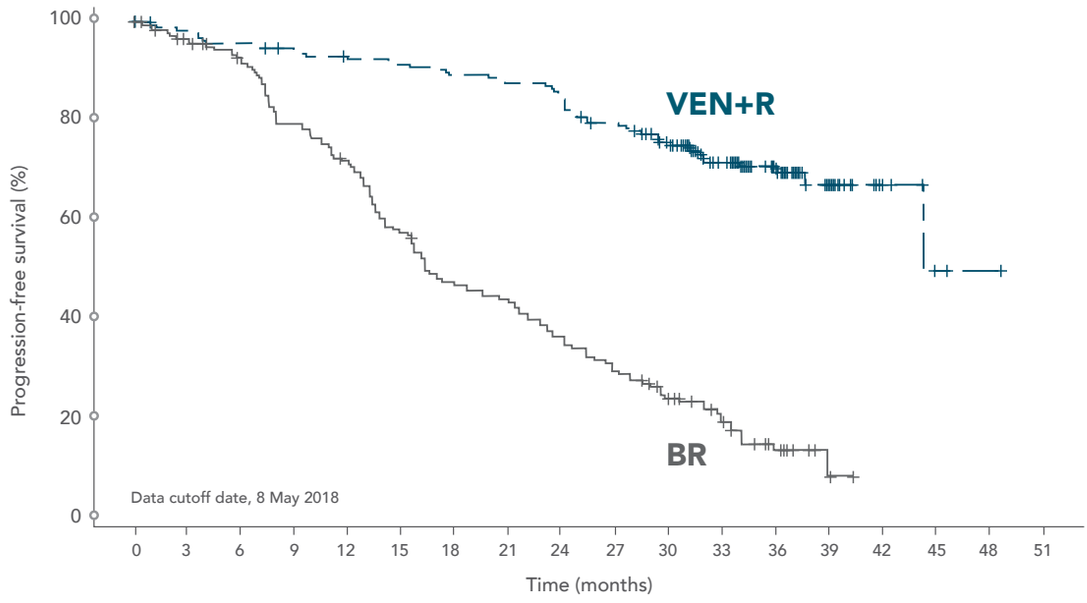
83%
reduction in the risk of progression or death vs BR
HR=0.17
(95% CI: 0.11-0.25)
P<0.0001*

- PFS was also assessed by an Independent Review Committee (IRC) demonstrating a statistically significant 81% reduction in the risk of progression or death for patients treated with VEN+R compared with BR (HR: 0.19; 95% CI: 0.13-0.28, *P*<0.0001)

VEN+R: Many patients continued to be progression-free post-treatment

- In an updated efficacy analysis (median follow-up of 36 months) with all patients off treatment, the 36-month PFS estimate for VEN+R was 71.4% (95% CI: 64.8-78.1) vs 15.2% (95% CI: 9.1-21) in the BR arm

INV-ASSESSED PFS (ITT POPULATION)



No. of patients at risk																	
VEN+R	194	190	185	179	176	174	170	167	161	150	135	99	61	21	6	2	1
BR	195	178	164	142	128	103	84	79	65	55	41	26	10	2			

PFS rates were evaluated 6 months after completion of the 24-month fixed treatment regimen

- Of the 130 patients taking VEN+R who completed 24 months of treatment without progression, 92 patients completed the 6-month post-treatment follow-up visit
- Of the 92 patients, the estimated PFS rate at 6 months post-treatment was 92%

BR=bendamustine + rituximab; CI=confidence interval; CLL=chronic lymphocytic leukaemia; HR=hazard ratio; INV=investigator; ITT=intent to treat; PFS=progression-free survival; R/R=relapsed/refractory.

Results of subgroup analyses: VEN+R demonstrated a consistent observed PFS benefit across all evaluated subgroups in the primary analysis[1]

PFS benefit was observed across subgroups regardless of number of prior regimens, relapsed vs refractory to most recent therapy, or genetic abnormalities

INV-ASSESSED PFS SUBGROUP ANALYSIS IN THE MURANO TRIAL

Subgroups	VEN+R n	BR n	Hazard ratio (95% CI)*
All patients	194	195	0.17 (0.12-0.26)
Number of Prior Regimens			
1	111	117	0.14 (0.08-0.24)
>1	83	78	0.24 (0.13-0.42)
Relapsed vs Refractory to Most Recent Therapy			
Refractory	30	29	0.32 (0.15-0.70)
Relapsed	164	166	0.14 (0.09-0.23)
Chromosome 17p Deletion (Central)			
Normal	127	123	0.19 (0.12-0.32)
Abnormal	46	46	0.13 (0.05-0.29)
Baseline *IgVH* Mutation Status			
Mutated	53	51	0.11 (0.04-0.31)
Unmutated	123	123	0.16 (0.10-0.26)
***TP53* Mutation**			
Unmutated	144	133	0.15 (0.09-0.25)
Mutated	48	51	0.19 (0.10-0.36)
Bulky Disease (Lymph Nodes With the Largest Diametre)			
<5 cm	1 00	97	0.13 (0.07-0.24)
≥5 cm	84	88	0.24 (0.14-0.40)
Age Group 65 (yr)			
<65 yr	97	89	0.11 (0.06-0.21)
≥65 yr	97	106	0.24 (0.14-0.41)
Age Group 75 (yr)			
<75 yr	165	171	0.17 (0.11-0.26)
≥75 yr	29	24	0.23 (0.08-0.64)

Data cutoff date, 8 May 2017.

*Unstratified hazard ratio is displayed on the x-axis with logarithmic scale. The size of each square is proportional to the amount of data available.

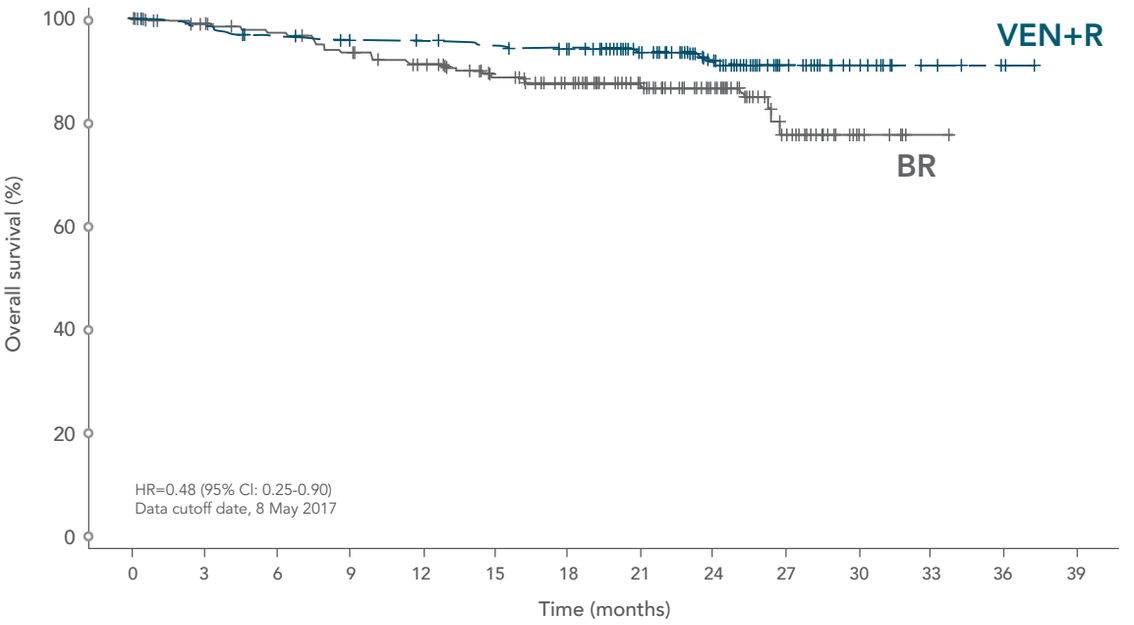
The INV-assessed PFS subgroup analysis was not designed to show treatment effect or powered to show statistical significance in subpopulations.

BR=bendamustine + rituximab; CI=confidence interval; IgVH=immunoglobulin variable-region heavy-chain gene; INV=investigator; PFS=progression-free survival; TP53=tumour protein 53.

VENCLYXTO® venetoclax tablets

VEN+R:
Overall survival in the primary analysis of the MURANO trial[1]

OVERALL SURVIVAL (ITT POPULATION)*†



No. of patients at risk													
VEN+R	194	190	185	183	181	178	175	142	102	36	15	5	3
BR	195	181	175	166	158	146	134	102	66	29	8	2	

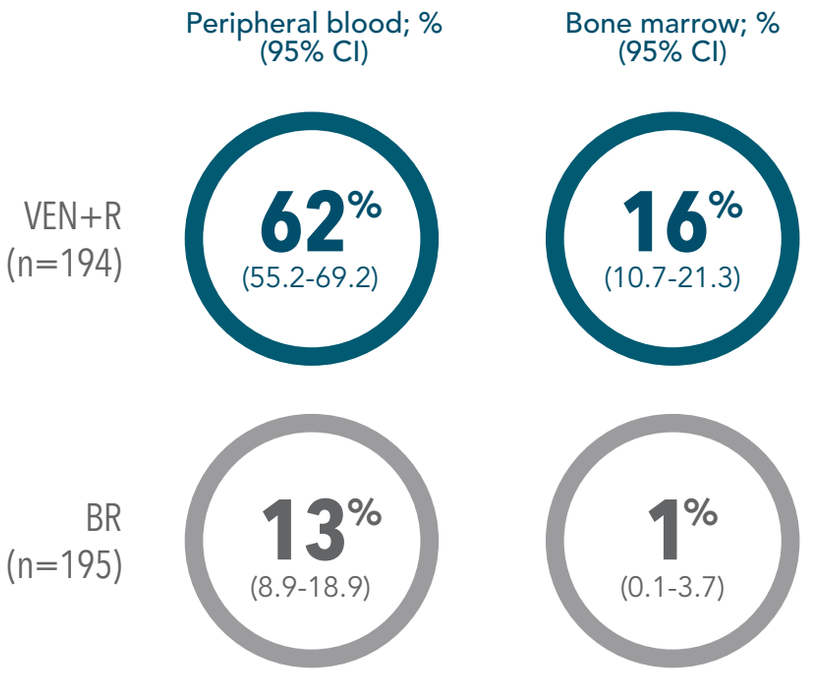
*Median follow-up was 23.8 months (range: 0.0-37.4 months).

†OS are not yet mature; descriptive endpoint, not tested for statistical significance.

BR=bendamustine + rituximab; ITT=intent to treat; OS=overall survival.

VEN+R achieved deep responses as shown by MRD negativity rates in both the peripheral blood and bone marrow[1,6*]

MRD NEGATIVITY RATES AT END OF COMBINATION TREATMENT[†‡]



Primary efficacy analysis: Data cutoff date, 8 May 2017.

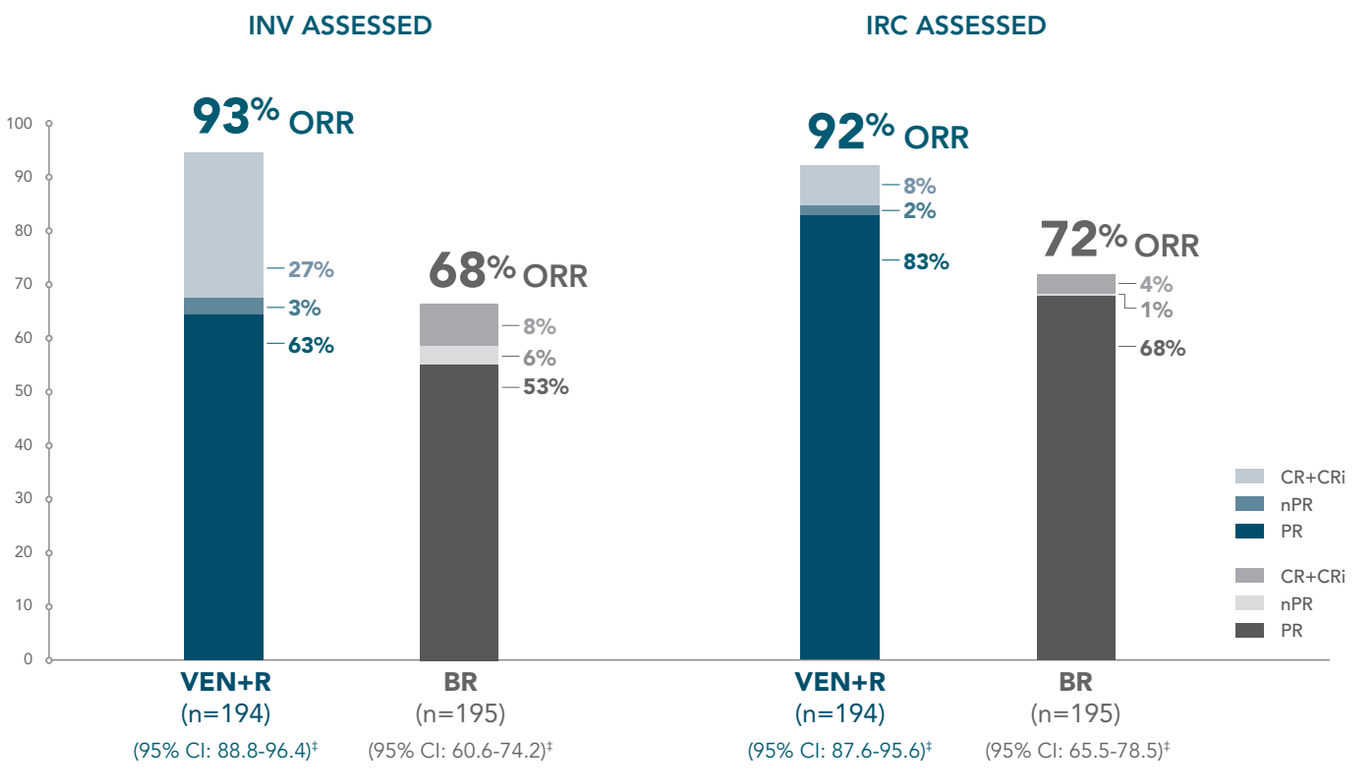
*Clinical trials aimed at maximizing the depth of remission should include at least one test to assess for MRD.[6]
[†]MRD results are descriptive; statistical significance not tested.
[‡]Minimal residual disease was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and/or flow cytometry. The cutoff for a negative status was <1 CLL cell per 10^4 leukocytes, per iwCLL guidelines.[1,6]

BR=bendamustine + rituximab; CI=confidence interval; CLL=chronic lymphocytic leukaemia; iwCLL=International Workshop on Chronic Lymphocytic Leukemia; MRD=minimal residual disease.

VENCLYXTO® venetoclax tablets

ORR* exceeded 90% in the VEN+R arm in both INV and IRC assessments[1]

OVERALL RESPONSE RATE (INV AND IRC ASSESSED)*†



Primary analysis: Data cutoff date, 8 May 2017.

*ORR = CR + CRi + nPR + PR.
†IRC- and INV-assessed ORR, nPR, and PR, and INV-assessed CR + CRi results are descriptive; statistical significance not tested.
‡95% CI for ORR.

- Discrepancies between IRC- and INV-assessed CR rates were potentially due to interpretation of residual adenopathy on CT scans

BR=bendamustine + rituximab; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete marrow recovery; CT=computed tomography; INV=investigator; IRC=independent review committee; nPR=nodular partial remission; ORR=overall response rate; PR=partial response.

VEN+R demonstrated a manageable safety profile in the MURANO trial[1]

OVERALL SAFETY PROFILE OF VENCLYXTO® IN COMBINATION WITH RITUXIMAB OR AS MONOTHERAPY (N=490)

SYSTEM CLASS	FREQUENCY (ALL GRADES)*	ADVERSE REACTIONS	GRADE ≥3*
Infections and infestations	Very common	Upper respiratory tract infection	
	Common	Sepsis Pneumonia Urinary tract infection	Sepsis Pneumonia Urinary tract infection Upper respiratory tract infection
Blood and lymphatic system disorders	Very common	Neutropaenia Anaemia	Neutropaenia Anaemia
	Common	Febrile neutropaenia Lymphopaenia	Febrile neutropaenia Lymphopaenia
Metabolism and nutrition disorders	Very common	Hyperphosphataemia	
	Common	Tumour lysis syndrome Hyperkalaemia Hyperuricaemia Hypocalcaemia	Tumour lysis syndrome Hyperkalaemia Hyperphosphataemia Hypocalcaemia
	Uncommon		Hyperuricaemia
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Nausea Constipation	Diarrhoea Vomiting Nausea
	Uncommon		Constipation
General disorders and administration site conditions	Very common	Fatigue	
	Common		Fatigue
Investigations	Common	Blood creatinine increased	
	Uncommon		Blood creatinine increased

Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), and uncommon (≥1/1,000 to <1/100).

*Only the highest frequency observed in the trials is reported (based on studies MURANO, M13-982, M14-032, and M12-175).

Adverse reactions in patients with CLL treated with VENCLYXTO

VEN+R most commonly occurring adverse reactions (≥20%) of any grade:

- neutropaenia
- diarrhoea
- upper respiratory tract infection

VEN monotherapy most commonly occurring adverse reactions:

- neutropaenia/neutrophil count decreased
- diarrhoea
- nausea
- anaemia
- fatigue
- upper respiratory tract infection

VEN monotherapy most frequently reported serious adverse reactions (≥2%):

- pneumonia
- febrile neutropaenia
- TLS

This is not a complete summary of all safety information. See VENCLYXTO full Summary of Product Characteristics (SmPC) at http://www.ema.europa.eu. Globally, prescribing information varies; refer to the individual country product label for complete information.

CLL=chronic lymphocytic leukaemia; TLS=tumour lysis syndrome.

Safety topics of interest[1]

DISCONTINUATIONS, DOSE REDUCTIONS, AND DOSE INTERRUPTIONS DUE TO ADVERSE REACTIONS IN THE MURANO TRIAL

	VEN+R (n=194)
Discontinuations due to adverse reactions	16%
Dose reductions due to adverse reactions	15%
Dose interruptions due to adverse reactions	71%

- **The most common adverse reaction that led to dose modification of VENCLYXTO® in the MURANO trial was neutropaenia**
- Serious infections including events of sepsis with fatal outcome have been reported

Neutropaenia in the MURANO trial

Neutropaenia is an identified risk with VENCLYXTO treatment and occurred in 61% (all grades) of patients receiving VEN+R in the MURANO trial:

- Grade 3 neutropaenia was reported in 32% of patients
- Grade 4 neutropaenia was reported in 26% of patients
- The median duration of grade 3 or 4 neutropaenia was 8 days (range: 1-712 days)
- 43% of patients treated experienced dose interruption due to neutropaenia
- **Only 3% of patients discontinued VENCLYXTO due to neutropaenia**

CLINICAL COMPLICATIONS OF NEUTROPAENIA

	VEN+R (n=194)
Febrile neutropaenia	4%
Grade ≥3 infections	18%
Serious infections	21%

Safety topics of interest[1] (continued)

Tumour lysis syndrome (TLS)

TLS, including fatal events, has occurred in patients with previously treated CLL with high tumour burden when treated with venetoclax. TLS was reduced in the phase 1 VENCLYXTO® monotherapy dose-finding studies through implementation of a 5-week dose-titration schedule with a well-defined prophylactic and monitoring protocol approved for use with VENCLYXTO monotherapy.

- After 77 patients were enrolled in the VEN+R or BR treatment arms of the MURANO study, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures (5-week dose-titration schedule)
- In the MURANO study, the incidence of TLS was 3% (6/194) in patients treated with VEN+R; all events of TLS occurred during the dose-titration phase

  - All TLS events resolved within 2 days
  - All 6 patients completed the dose-titration schedule and reached the recommended daily dose of 400 mg of VENCLYXTO
- No clinical TLS was observed in patients who followed the current TLS dose-titration schedule and prophylaxis and monitoring measures
- Grade >3 laboratory abnormalities relevant to TLS were hyperkalaemia (1%), hyperphosphataemia (1%), and hyperuricaemia (1%)

BR=bendamustine + rituximab; CLL=chronic lymphocytic leukaemia.

Established protocol for prophylaxis and management of TLS[1,7]

- The risk of tumour lysis syndrome (TLS) is a continuum based on multiple factors, including tumour burden and other comorbidities. Reduced renal function (creatinine clearance [CrCl] <80 mL/min) further increases the risk
- Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose and each dose increase

STEP 1: **ASSESS** LARGE TUMOURS PRESENT GREATER RISK	STEP 2: **PREPARE** 2-3 DAYS PRIOR TO FIRST DOSE		STEP 3: **INITIATE** FIRST 5 WEEKS OF TREATMENT
Tumour burden assessment	**Anti-hyperuricaemics***	**Hydration†**	**Blood chemistry monitoring‡**
LOW TUMOUR BURDEN All LN <5 cm **AND** ALC <25 x 10^9/L	**Allopurinol**	Oral (1.5-2 L)	**Outpatient** • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent titration doses: Pre-dose§
MEDIUM TUMOUR BURDEN Any LN 5 cm to <10 cm **OR** ALC ≥25 x 10^9/L For patients with CrCl <80 mL/min and medium tumour burden, consider management as high risk for TLS	**Allopurinol**	Oral (1.5-2 L) Consider additional IV	**Outpatient** • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent titration doses: Pre-dose§ • For first dose of 20 mg and 50 mg: Consider hospitalisation for patients with CrCl <80 mL/min; see below for monitoring in hospital
HIGH TUMOUR BURDEN Any LN ≥10 cm **OR** Any LN ≥5 cm **AND** ALC ≥25 x 10^9/L	**Allopurinol or febuxostat** Consider rasburicase if baseline uric acid is elevated	Oral (1.5-2 L) and IV (150-200 mL/h as tolerated)	**In hospital** • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12, and 24 hours **Outpatient** • For subsequent titration doses: Pre-dose, 6 to 8 hours, 24 hours§

The risk of TLS may decrease as tumour burden decreases

*Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLYXTO®.
†1.5-2 L of water (6-8 glasses) should be consumed every day starting 2 days before the first dose and throughout the dose titration phase, especially the first day of each dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.
‡Blood Chemistry Monitoring: Potassium, calcium, creatinine, phosphorus, uric acid (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 titration.

- No patient is typical. Please refer to the full VENCLYXTO Summary of Product Characteristics (SmPC) when making treatment decisions

ALC=absolute lymphocyte count; IV=intravenous; LN=lymph node.

VENCLYXTO® venetoclax tablets

VEN+R:
The only R/R CLL chemo-free regimen with a 24-month fixed treatment duration[1]

The initial 5-week dose-titration schedule was designed to gradually reduce tumour burden and decrease the risk of TLS

- Patients should be adequately hydrated during the dose-titration phase to reduce the risk of TLS

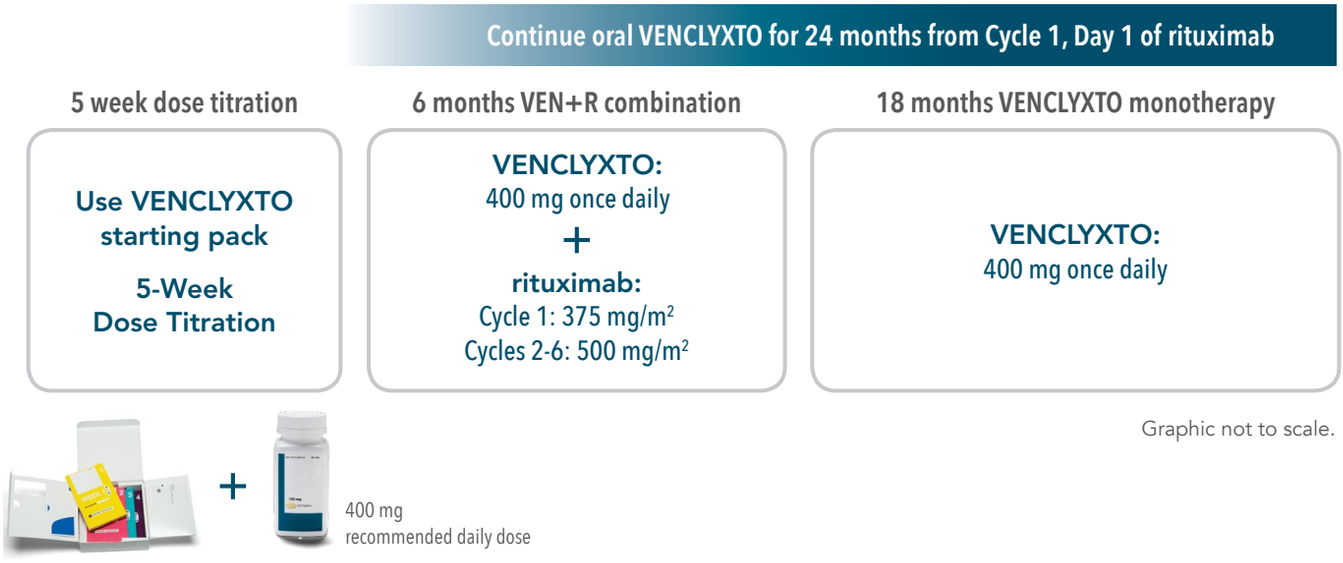
Week	VENCLYXTO® daily dose (mg)
1	20
2	50
3	100
4	200
5	400

Post-titration dose schedule: VEN+R combination

- VENCLYXTO and rituximab are administered in combination for 6 months after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg of VENCLYXTO for 7 days

Post VEN+R combination dose schedule: VENCLYXTO monotherapy

- Continue VENCLYXTO for 18 months or until disease progression or no longer tolerated by the patient



VENCLYXTO tablets are for daily oral use

- VENCLYXTO should be taken with a meal and water in the morning at approximately the same time each day
- Tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing
- If a patient misses a dose within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible on the same day. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the following day
- If a patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day

CLL=chronic lymphocytic leukaemia; R/R=relapsed/refractory; TLS=tumour lysis syndrome.

Dose modifications and interruptions[1]

<table>
<tr><th colspan="4">TLS</th></tr>
<tr><td rowspan="2">Blood chemistry changes suggestive of TLS</td><td rowspan="2">Withhold the following day's VENCLYXTO® dose until resolved</td><td>If resolved within 24–48 hours of last dose</td><td>Resume at same dose</td></tr>
<tr><td>If events of clinical TLS occur or blood chemistry requires more than 48 hours to resolve</td><td>Resume at reduced dose according to dose reduction guidelines</td></tr>
<tr><th colspan="4">Other toxicities</th></tr>
<tr><td>Grade 3 or 4 non-haematologic toxicities</td><td rowspan="3">Withhold VENCLYXTO treatment</td><td rowspan="2">First occurrence</td><td rowspan="2">Once the toxicity has resolved to grade 1 or baseline level, resume VENCLYXTO at the same dose</td></tr>
<tr><td>Grade 3 or 4 neutropaenia with infection or fever</td></tr>
<tr><td>Grade 4 haematologic toxicities (except lymphopaenia)</td><td>Second and subsequent occurrences</td><td>Resume at reduced dose according to dose reduction guidelines. A larger reduction may occur at the discretion of the physician</td></tr>
<tr><th colspan="4">When a dose interruption or reduction is required</th></tr>
<tr><td>Dosing interruptions lasting longer than 1 week during the first 5 weeks of dose titration</td><td colspan="3" rowspan="2">Reassess for risk of TLS to determine if restarting at reduced dose (repeating some/all levels of dose-titration phase) is required</td></tr>
<tr><td>Dosing interruptions lasting longer than 2 weeks after completing the dose titration phase</td></tr>
</table>

DOSE REDUCTION GUIDELINES

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

- Consider discontinuing VENCLYXTO for patients who require dose reductions to less than 100 mg for more than 2 weeks
- The modified dose should be continued for 1 week before increasing the dose

TLS=tumour lysis syndrome.

VENCLYXTO® venetoclax tablets

Select safety information[1]

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Concomitant use of strong CYP3A inhibitors at initiation and during the dose-titration phase
- Concomitant use of preparations containing St. John's wort

Renal impairment

- Safety in patients with severe renal impairment (CrCl <30 mL/min) or on dialysis has not been established, and a recommended dose for these patients has not been determined. VENCLYXTO should be administered to patients with severe renal impairment only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity due to increased risk of TLS

Select drug interactions: CYP3A inhibitors

- Concomitant use of VENCLYXTO with strong CYP3A inhibitors at initiation and during the dose-titration phase is contraindicated
- Concomitant use of VENCLYXTO with strong or moderate CYP3A inhibitors increases VENCLYXTO exposure and may increase the risk for TLS at initiation and during the dose-titration phase and for other toxicities. Consider alternative treatments
- Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax as they contain inhibitors of CYP3A

MANAGEMENT OF POTENTIAL VENCLYXTO INTERACTIONS WITH CYP3A INHIBITORS

INHIBITORS	INITIATION AND DOSE-TITRATION PHASE	STEADY DAILY DOSE (AFTER DOSE-TITRATION PHASE)
Strong CYP3A inhibitor	Contraindicated	Avoid inhibitor use or reduce VENCLYXTO dose by at least 75%
Moderate CYP3A inhibitor	Avoid inhibitor use or reduce the VENCLYXTO dose by at least 50%	

- Patients should be monitored closely for signs of toxicities and the dose may need to be further adjusted
- Resume the VENCLYXTO dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor

Please refer to VENCLYXTO SmPC for additional information on drug interactions including P-gp and BCRP inhibitors, CYP3A inducers, and bile acid sequestrants.

CrCl=creatinine clearance; CYP3A=cytochrome P4503A; P-gp=p-glycoprotein; SmPC=summary of product characteristics; TLS=tumour lysis syndrome.

References

1. VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH @ Co. KG.
2. 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.
3. Anderson MA, Huang D, Roberts A. Targeting BCL2 for the treatment of lymphoid malignancies. *Semin Hematol*. 2014;51(3):219-227.
4. Rituximab Summary of Product Characteristics. Grenzach-Wyhlen, Germany: Roche Pharma AG.
5. 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.
6. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-2760.
7. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.5.2018. National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed March 27, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network.

Give your R/R CLL patients a chance to

BREAK FREE

WITH LONGER PROGRESSION-FREE SURVIVAL

VEN+R DEMONSTRATED SUPERIOR PFS VS BR: 83% REDUCTION IN RISK OF PROGRESSION[1]

- VEN+R significantly prolonged PFS (HR: 0.17; 95% CI: 0.11-0.25, *P*<0.0001). Median PFS was not reached with VEN+R vs 17 months (95% CI: 15.5-21.6) with BR
- PFS benefit demonstrated across all evaluated subgroups

VEN+R ACHIEVED DEEP RESPONSES AS SHOWN BY MRD NEGATIVITY RATES IN BOTH THE PERIPHERAL BLOOD AND BONE MARROW[1,6]

- VEN+R: 62% (95% CI: 55.2-69.2) vs BR: 13% (95% CI: 8.9-18.9) in peripheral blood
- VEN+R: 16% (95% CI: 10.7-21.3) vs BR: 1% (95% CI: 0.1-3.7) in bone marrow

VEN+R OFFERS FIXED TREATMENT DURATION AND THE OPPORTUNITY TO STOP TREATMENT[1]

- 24-month VENCLYXTO® treatment following 5-week dose titration schedule
- Of the 130 patients taking VEN+R who completed 24 months of treatment without progression, 92 patients completed the 6-month post-treatment follow-up visit; for the 92 patients, the estimated PFS rate at 6 months post-treatment was 92%*

VENCLYXTO HAS A MANAGEABLE SAFETY PROFILE[1]

- The most commonly occurring adverse reactions (≥20%) of any grade in patients receiving VEN+R were neutropaenia, diarrhoea, and upper respiratory tract infection
- The most frequently reported serious adverse reactions (≥2%) in patients receiving VENCLYXTO were pneumonia, febrile neutropaenia, and TLS
- 43% of patients treated experienced dose interruption due to neutropaenia; only 3% of patients discontinued VENCLYXTO due to neutropaenia
- Tumour lysis syndrome, including fatal events, has occurred in patients with previously treated CLL with high tumour burden when treated with VENCLYXTO. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricaemics

*Updated efficacy analysis: Data cutoff date, 8 May 2018.

BR=bendamustine + rituximab; CI=confidence interval; CLL=chronic lymphocytic leukaemia; HR=hazard ratio; PFS=progression-free survival; R/R=relapsed/refractory; SmPC=summary of product characteristics; TLS=tumour lysis syndrome.

Please see SmPC for full safety information.

abbvie

ALL-VNCLY-180101

August 2018

VENCLYXTO®
venetoclax tablets

DRAFT material based on July 2018 DRAFT SMPC.

Give your R/R CLL patients a chance to

BREAK FREE

WITH LONGER PROGRESSION-FREE SURVIVAL

VEN+R DEMONSTRATED SUPERIOR PFS VS BR: 83% REDUCTION IN RISK OF PROGRESSION[1]

- VEN+R significantly prolonged PFS (HR: 0.17; 95% CI: 0.11-0.25, *P*<0.0001). Median PFS was not reached with VEN+R vs 17 months (95% CI: 15.5-21.6) with BR
- PFS benefit demonstrated across all evaluated subgroups

VEN+R ACHIEVED DEEP RESPONSES AS SHOWN BY MRD NEGATIVITY RATES IN BOTH THE PERIPHERAL BLOOD AND BONE MARROW[1,6]

- VEN+R: 62% (95% CI: 55.2-69.2) vs BR: 13% (95% CI: 8.9-18.9) in peripheral blood
- VEN+R: 16% (95% CI: 10.7-21.3) vs BR: 1% (95% CI: 0.1-3.7) in bone marrow

VEN+R OFFERS FIXED TREATMENT DURATION AND THE OPPORTUNITY TO STOP TREATMENT[1]

- 24-month VENCLYXTO® treatment following 5-week dose titration schedule
- Of the 130 patients taking VEN+R who completed 24 months of treatment without progression, 92 patients completed the 6-month post-treatment follow-up visit; for the 92 patients, the estimated PFS rate at 6 months post-treatment was 92%*

VENCLYXTO HAS A MANAGEABLE SAFETY PROFILE[1]

- The most commonly occurring adverse reactions (≥20%) of any grade in patients receiving VEN+R were neutropaenia, diarrhoea, and upper respiratory tract infection
- The most frequently reported serious adverse reactions (≥2%) in patients receiving VENCLYXTO were pneumonia, febrile neutropaenia, and TLS
- 43% of patients treated experienced dose interruption due to neutropaenia; only 3% of patients discontinued VENCLYXTO due to neutropaenia
- Tumour lysis syndrome, including fatal events, has occurred in patients with previously treated CLL with high tumour burden when treated with VENCLYXTO. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricaemics

*Updated efficacy analysis: Data cutoff date, 8 May 2018.

BR=bendamustine + rituximab; CI=confidence interval; CLL=chronic lymphocytic leukaemia; HR=hazard ratio; PFS=progression-free survival; R/R=relapsed/refractory; SmPC=summary of product characteristics; TLS=tumour lysis syndrome.

Please see SmPC for full safety information.

abbvie

ALL-VNCLY-180101

August 2018

VENCLYXTO®
venetoclax tablets

DRAFT material based on July 2018 DRAFT SMPC.