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Final 7-year Follow Up and Retreatment Substudy Analysis of MURANO: Venetoclax-Rituximab-Treated Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia

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Summary

The MURANO study (NCT02005471) showed superior progression-free survival (PFS) and overall survival (OS) with fixed-duration venetoclax-rituximab (VenR) vs bendamustine-rituximab (BR) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)

We report the final analyses of MURANO, with 7 years median follow up

Retreatment with VenR is a viable option for pretreated patients, based on best overall response rate (ORR) and undetectable(u) minimal residual disease (MRD) findings

In this final long-term analysis of the MURANO trial, PFS and OS benefits for 2-year fixed treatment with VenR over BR were sustained

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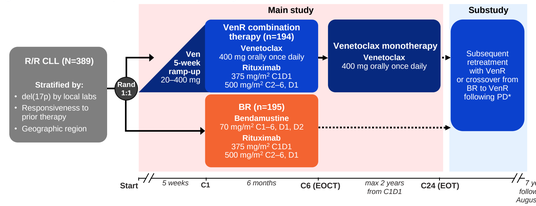
Background

- The Phase 3 MURANO trial reported superior PFS and OS with fixed-duration VenR vs BR in patients with R/R CLL[1]
  - At the 5-year update, the median PFS was 53.6 vs 17.0 months (P<0.0001), and 5-year OS rates were 82.1% vs 62.2% (P<0.0001) in patients treated with VenR vs BR, respectively[2]
  - At 48 months of follow up, deep responses with uMRD were associated with favorable PFS.[3]
- We report efficacy of VenR vs BR from the final analyses of MURANO, with a data cut off of 3 August 2022 and ~7 years median follow up.

Methods

- MURANO is a global, phase 3, open-label, randomized study (**Figure 1**).
- Peripheral blood MRD was measured centrally by allele-specific oligonucleotide-polymerase chain reaction (PCR) and/or flow cytometry ($<10^{-4}$ threshold for uMRD).
- All adverse events (AE) were reported until 28 days after the last dose of Ven or 90 days after last dose of R, whichever was longer. After this, only deaths, serious AEs, or AEs of concern that were believed to be Ven-related were reported.

Figure 1. MURANO (NCT02005471) study design



*Investigator-assessed progressive disease according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria. C, cycle; D, day; del(17p), deletion 17p; EOCT, end of combination treatment; EOT, end of treatment; max, maximum; PD, progressive disease; Rand, randomization.

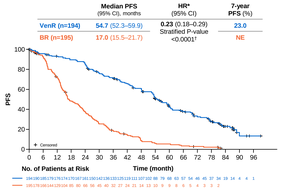
Results: MURANO main study

Efficacy outcomes

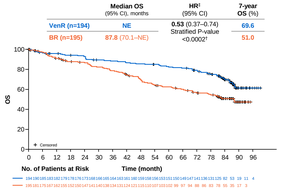
- Median (range) follow up for efficacy was 86.8 months (0.3–99.2) for VenR and 84.4 months (0.0–95.0) for BR.
- PFS and OS benefits with VenR over BR were sustained at 7 years (**Figure 2**).

Figure 2. PFS and OS of VenR vs BR

	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	54.7 (52.3–59.9)	0.23 (0.18–0.29) Stratified P-value <0.0001†	23.0
BR (n=195)	17.0 (15.5–21.7)		NE



	Median OS (95% CI), months	HR‡ (95% CI)	7-year OS (%)
VenR (n=194)	NE	0.53 (0.37–0.74) Stratified P-value <0.0002‡	69.6
BR (n=195)	87.8 (70.1–NE)		51.0



*Stratified HR is presented, unstratified HR=0.25. †P-values are descriptive only. ‡Stratified HR is presented, unstratified HR=0.54. CI, confidence interval; HR, hazard ratio; NE, not estimable.

Subsequent anti-leukemic treatment

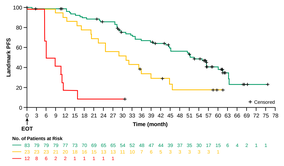
- Time to next anti-leukemic treatment (TTNT) (95% CI) was longer for VenR at 63.0 months (56.1–73.6) vs 24.0 months (20.7–29.5) for BR (HR 0.30).
- Overall, 95 (49.0%) VenR-treated patients and 131 (67.2%) BR-treated patients received subsequent anti-leukemic treatment.

MRD status

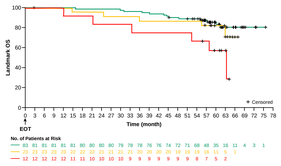
- Achievement of uMRD was associated with prolonged PFS in VenR-treated patients (**Figure 3**).
- Most patients who received the full 2 years of VenR treatment had uMRD at EOT; generally, MRD conversion with subsequent PD did not occur until ~4 years post EOT (**Figure 4**).

Figure 3. Median PFS and OS at EOT for patients who completed 2 years of Ven without PD

Patients who completed 2 years of Ven without PD*	Median PFS since EOT (95% CI), months	HR (95% CI); P-value†
uMRD (n=83)	52.5 (44.5–61.5)	
Low MRD+ (n=23)	29.3 (20.2–37.5)	vs uMRD: 3.46 (1.75–6.86); <0.0001
High MRD+ (n=12)	4.6 (2.8–8.3)	vs uMRD: 17.22 (5.70–52.00); <0.0001

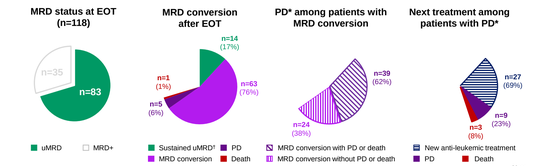


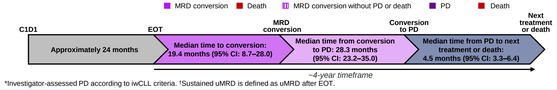
Patients who completed 2 years of Ven without PD*	Median OS since EOT (95% CI), months	HR (95% CI); P-value†
uMRD (n=83)	NE (NE–NE)	
Low MRD+ (n=23)	NE (92.7–NE)	vs uMRD: 1.07 (0.34–3.35); NS
High MRD+ (n=12)	63.1 (51.5–NE)	vs uMRD: 2.39 (0.73–7.80); NS



Low MRD+ is defined as ≥1 CLL cell/10,000 leukocytes to <1 CLL cell/100 leukocytes, high MRD+ is defined as ≥1 CLL cell/100 leukocytes. Stratified HR (95% CI) for Low MRD+ vs High MRD+: PFS, 3.22 (1.04–9.97), P=0.0350; OS, 2.27 (0.44–11.69), P=NS. *Investigator-assessed PD according to iwCLL criteria. †Stratified HRs and P-values are presented, P-values are descriptive only; NS, not significant.

Figure 4. Disease status of patients at and beyond EOT





*Investigator-assessed PD according to iwCLL criteria. †Sustained uMRD is defined as uMRD after EOT.

- Favorable baseline characteristics were over-represented among patients with enduring uMRD (**Table 1**).

Table 1. Summary of baseline mutations in the VenR-treated patients by uMRD status

VenR-treated patients, n (%)	*TP53** (n=192)†		IGHV§ (n=176)†		GC¶ (n=154)	
	wild-type‡ (n=144)	mutated (n=48)	mutated‡ (n=53)	unmutated (n=123)	no GC‡ (n=106)	GC present (n=48)
Patients with sustained uMRD (n=14)	13/144 (9.0)	1/48 (2.1)	7/53 (13.2)	6/123 (4.9)	6/106 (5.7)	4/48 (8.3)
Patients without sustained uMRD (n=180)	131/144 (91.0)	47/48 (97.9)	46/53 (86.8)	117/123 (95.1)	100/106 (94.3)	44/48 (91.7)

GC was defined as ≥3 copy number alterations. *Assessed by NGS. †Biomarker evaluable population. ‡Favorable characteristic. §Assessed by PCR. ¶Assessed by aCGH. aCGH, array comparative genomic hybridization; GC, genomic complexity; IGHV, immunoglobin heavy chain variable region genes; NGS, next generation sequencing; *TP53*, tumour protein 53.

MRD status (cont.)

- Among the 14 patients with sustained uMRD after EOT, median number of prior therapies was 1 (range 1–3).
- Among the small group of patients with favorable disease biology (*IGHV* mutated, no *TP53* aberrancy and no GC), a portion (7/43 [16.3%]) had very long term enduring uMRD following 2 years of VenR.

Safety

- No new safety signals were identified since the 5-year data cut,[2] with all patients outside of the AE reporting window.

Results: MURANO retreatment/crossover substudy

Substudy population

- Of the 34 patients with PD who entered the substudy, 25 were retreated with VenR:
  - Median time (range) from the final study drug dose in the main study to VenR retreatment in the substudy was 2.3 years (1.2–3.1)
  - Median follow up (range) was 33.4 months (2.7–44.0).
- Most patients who received VenR retreatment were classified as high risk (**Table 2**).

Table 2. Baseline characteristics of substudy patients

Patient characteristic at substudy baseline	Patients retreated with VenR (n=25)
Median age, years (range)	66 (49–82)
No. of prior therapies*, n (%)	
2	20 (80.0)
3	4 (16.0)
≥4	1 (4.0)
del(17p)‡ and/or *TP53* mutation‡, n (%)	
yes	8 (32.0)
no	5 (20.0)
unknown/not assessed	12 (48.0)
del(17p)‡, n (%)	
deleted	7 (28.0)
not deleted	8 (32.0)
unknown/not assessed	10 (40.0)

Patient characteristic at substudy baseline	Patients retreated with VenR (n=25)
TP53§, n (%)	
mutated	5 (20.0)
unmutated	17 (68.0)
unknown/not assessed	3 (12.0)
IGHV§, n (%)	
mutated	1 (4.0)
unmutated	22 (88.0)
unknown/not assessed	2 (8.0)
GC‖, n (%)	
0–2	9 (36.0)
3–4	3 (12.0)
≥5	8 (32.0)
unknown/not assessed	5 (20.0)

*Including the VenR treatment they received in the main study. ‡Assessed by aCGH. §Assessed by NGS. ‖Assessed by PCR.

Efficacy outcomes and MRD status amongst VenR-retreated patients

- Among the VenR-retreated patients, median PFS (95% CI) was 23.3 months (15.6–24.3), best ORR was 72.0%, complete response rate was 24%; median OS was not reached.
- Overall, 44% of patients in the substudy never achieved uMRD in the main study.
- Eight VenR-retreated patients achieved uMRD at the retreatment EOCT, all of whom responded: CR/CR with incomplete count recovery, n=4; nodular partial remission (PR)/PR, n=3; stable disease, n=1
  - No patients retained their uMRD status at the retreatment EOT.

Conclusions

- In this final long-term analysis of the MURANO trial, PFS and OS benefits for 2-year fixed treatment with VenR over BR were sustained, and longer TTNT with VenR was observed vs BR.
- Achievement of uMRD was associated with prolonged PFS in VenR-treated patients.
- In patients retreated with VenR in the substudy, best ORR was 72.0% and uMRD was still attainable in this high-risk population.
- Retreatment with VenR is a viable option for pretreated patients, based on ORR and uMRD findings.
- Overall, these data continue to support the use of fixed-duration VenR in R/R CLL.

Presented at the Biennial International Workshop on Chronic Lymphocytic Leukemia™ (iwCLL 2023) | October 6–9, 2023

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Acknowledgments

These data have previously been presented at the European Hematology Association Annual Meeting 2023. The authors thank the patients and their families and all MURANO study team members and investigators. Special thanks are offered to Anne-Marie Kevie-Kersemaekers for her contribution. Venetoclax is being developed in a collaboration between Genentech and AbbVie. Genentech and AbbVie provided financial support for the study and participated in the design, study conduct, analysis, and interpretation of data, as well as the writing, review, and approval of the presentation Third-party medical writing assistance, under the direction of the authors, was provided by Kiyanah Coghiel-Fox, BSc, Rachel Dobb, PhD, and Tayna Carlisle, MSc, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

Disclosures

A.P.K. – current employment: Amsterdam University Medical Centers, University of Amsterdam; leadership: HOVON (president of executive board, chairman of the CLL working group), Amsterdam UMC (Chairman Good Research Practice committee), EHA (Chairman Scientific Working group on CLL), ERIC (member executive board); consulting or advisory role, and research funding: AbbVie, AstraZeneca, BMS, Janssen, Gemmab, LAVA, Roche/Genentech; speaker's bureau: AbbVie, Janssen; travel, accommodation, expenses: AbbVie, AstraZeneca, Janssen, Roche/Genentech. **R.H. –** consulting or advisory role: AstraZeneca (20 July 2021). **T.J.K. –** research funding and/or advisory role: Ascerta/AstraZeneca, Celgene, Genentech/Roche, Gilead, Janssen, Loxo Oncology, TG Therapeutics, Verastem, Pharmacyclics/AbbVie, Breast Cancer Research Foundation, MD Anderson Cancer Center, Oncternal Therapeutics, Inc., Specialized Center of Research [SCOR] - The Leukemia and Lymphoma Society [LLS], California Institute for Regenerative Medicine [CIRM], National Cancer Institute/NIH, Velosbio, Inc. – Research Agreement; travel/honoraria: Pharmacyclics/AbbVie, Genentech/Roche, Janssen, Gilead, National Cancer Institute/NIH, Velosbio, Inc. – Research Agreement; travel/honoraria: Pharmacyclics/AbbVie, Genentech/Roche, Janssen, Gilead, National Cancer Institute/NIH, Celgene, European Research Initiative on CLL [ERIC], Dava Oncology, Breast Cancer Research Foundation, IwNHL, NCCN CLL/SLL Early Leukemia Panel Meeting, OncLive; patents, royalties or other intellectual property: Cirmtuzumab was developed by TJK in the TJK laboratory and licensed by the University of California to Oncternal Therapeutics, Inc., which provided stock options and research funding to the TJK laboratory. **B.E. –** current employment: University Hospital Cologne, Faculty of Medicine; ended employment in the past 24 months: University Hospital Cologne, Faculty of Medicine; leadership: Director Prof. Michael Hallek; honoraria: Roche, AbbVie, BeiGene, AstraZeneca, MSD; consulting or advisory role: Janssen, AbbVie, Gilead, AstraZeneca, BeiGene, MSD; Lilly; speaker's bureau: Roche, AbbVie, BeiGene, AstraZeneca; travel, accommodation, expenses: BeiGene. **C.J.O. –** honoraria: AbbVie, AstraZeneca, BeiGene, Janssen, Merck, Incyte, Novartis, Seattle Genetics, Roche. **S.A. –** honoraria, and consulting or advisory role: AbbVie, Roche, AstraZeneca, BMS, Paladin, Novartis, Pfizer, Janssen; research funding: Novartis. **N.L. –** consulting or advisory role: AbbVie, AstraZeneca, BeiGene, Eli Lilly/Loxo, Genentech, Janssen, Pharmacyclics; research funding to institution: AbbVie, AstraZeneca, BeiGene, Eli Lilly/Loxo, Genentech, MingSight, Octapharma, Oncternal, TG Therapeutics. **T.R. –** current employment: Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; honoraria and research funding: AbbVie, Janssen, AstraZeneca, BeiGene, Regeneron, Octapharma; consulting or advisory role: AstraZeneca, BeiGene; travel, accommodation, expenses: Janssen, AstraZeneca. **J.d.L.S. –** no conflicts of interest to declare. **U.J. –** honoraria Roche. **G.C. –** honoraria: Gilead Sciences, Janssen, Celgene, Roche, AbbVie, Novartis; consulting or advisory role: Roche, Celgene, Mabq, MedCell; travel, accommodation, expenses: Roche. **M.M. –** current employment: Consultant in Hematology; honoraria: AbbVie, Janssen. **C.M. –** current employment: Cytogenetici, Human Genetics, AUMC Amsterdam; research funding: financing for array-analysis MURANO sample. **B.C. –** current employment and stock ownership: AbbVie. **M.T-M. and M.L. –** current employment and stock ownership: Roche/Genentech. **R.M. –** current employment: Roche; ended employment in the past 24 months and honoraria: Hubrecht Institute; research funding: Oncode Institute. **M.B. –** current employment, stock ownership, and honoraria: Roche. **J.F.S. –** honoraria: AbbVie, AstraZeneca, BeiGene, BMS, Gilead, Janssen, Roche; consulting or advisory role: AbbVie, AstraZeneca, BeiGene, BMS, Genor Biu, Gilead, Janssen, Roche, TG Therapeutics; speaker's bureau and travel, accommodation or expenses: AbbVie, AstraZeneca, Roche; research funding: AbbVie, BMS, Janssen, Roche; patents, royalties, other intellectual property: AbbVie; expert testimony: BMS, TG Therapeutics.