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MRD-Driven Venetoclax and Rituximab Combination in Previously Untreated Chronic Lymphocytic Leukemia: Results of the Prospective, Multicenter, Phase II Trial of the Polish Adult Leukemia Group (VERITA PALG-CLL5)

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OBJECTIVES

- To evaluate the efficacy and safety of MRD-guided venetoclax plus rituximab (VR) in treatment-naive CLL patients in a multicenter, prospective phase II trial.

CONCLUSIONS

- MRD-driven venetoclax + rituximab therapy is highly effective in patients with previously untreated CLL.
- Extending treatment beyond 12 cycles in patients with suboptimal response was found to be safe and led to the achievement of complete response with undetectable MRD in a significant proportion of patients.

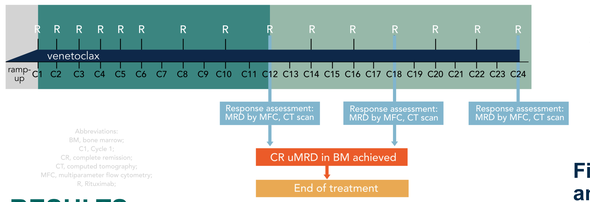
INTRODUCTION

- Fixed-duration regimens combining venetoclax with anti-CD20 antibodies (rituximab or obinutuzumab) are a mainstay of the current therapy for chronic lymphocytic leukemia (CLL).
- Achieving undetectable measurable residual disease (uMRD) with venetoclax-based regimens is associated with improved long-term outcomes. In the Phase III MURANO trial, patients achieving uMRD after VR had superior OS compared with MRD+ patients (95.3% vs. 72.9% at 3 years post-EOT).
- The optimal duration of VR therapy remains uncertain.
- It can be hypothesized that adjusting the duration of therapy to MRD status may provide an optimal balance between treatment activity and toxicity

METHODS

- The study design is shown in Fig.1
- Following the standard venetoclax ramp-up phase, venetoclax 400 mg PO daily was administered combined with rituximab 375 mg/m2 during the first infusion then 500 mg/m2 IV every 4 weeks during Cycles 1-6, and then every 8 weeks thereafter.
- The duration of VR treatment was 12, 18 or 24 cycles depending on the depth of response. MRD measurements in the peripheral blood and the bone marrow were performed at Cycle 12, 18 and 24 using flow cytometry
- Patients who achieved a complete remission (CR) with bone marrow MRD<10-4 (uMRD) at Cycle 12 or Cycle 18 discontinued the therapy. All other patients discontinued therapy at Cycle 24.
- The primary objective of the study was to demonstrate that this strategy leads to a 35% rate of CR with uMRD

Figure 1. Study design.



RESULTS

- Enrollment: 103 patients recruited (Feb 2022 – May 2023) in 10 Polish Adult Leukemia Group (PALG) centers. Baseline patient characteristics are shown in Table 1.
- Follow-up at this analysis: Median 27.3 months (range 1.2–37.1).
- Response was assessed in 101/103 pts because 2 pts were withdrawn early during ramp-up and Cycle 1 due to complications (prolonged COVID-19; AIHA with sepsis). These 2 pts and were followed only for survival.
- Primary objective achieved – 60/103 patients (58%) reached CR with BM uMRD at this analysis. Three patients remain on treatment.
- Response at Cycle 12 (n=101 evaluable):
  - Overall response rate (ORR): 98%
  - CR MRD$^-$: 45 (44%)
  - CR MRD$^+$: 4 (4%)
  - PR MRD$^-$: 39 (39%)
  - PR MRD$^+$: 11 (11%)
  - SD: 1 (1%), PD: 1 (1%)
- After C12 additional CR with uMRD were achieved by 9/51 (17.6%) pts continuing treatment until Cycle 18 and by 6/37 (16.2%) pts continuing therapy until Cycle 24 (Fig. 2)
- Outcomes during follow-up:
  - Disease progression: 3 patients.
  - Deaths: 4 patients, all in sustained CR MRD$^-$ (causes: stroke, other primary malignancy, suicide, unknown).
  - Estimated 24-month PFS: 95.9% (95% CI 92.1–99.9%).
  - Estimated 24-month OS: 98.0% (95% CI 95.3–100.0%).

Table 1. Basic characteristic of study population

Main cohort (VERITA PALG-CLL5)	
Enrolled, n	103
Median age, years (range)	66 (38-85)
Female sex, %	45.6
ECOG (0 | 1 | 2 | 3), %	30.1 | 68.0 | 1.9
RAI staging system at diagnosis (0 | 1 | 2 | 3 | 4 | unk), %	1.1 | 29.1 | 25.2 | 8.7 | 18.4 | 17.5
TLS risk assessment (low | medium | high), %	10.68 | 51.46 | 37.86
Presence of *TP53* aberration, %	13.7
IGHV mutational status (unmutated | mutated), %	56.6 | 44.4

Figure 2. Alluvial diagram of response evolution in patients at C12, C18 and C24 assessments.

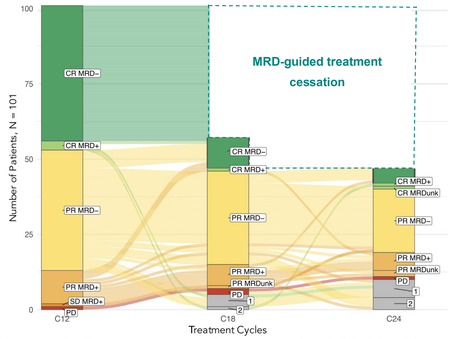


Figure 3. Progression-free survival (PFS; A) and overall survival (OS) of 103 patients included in the study.

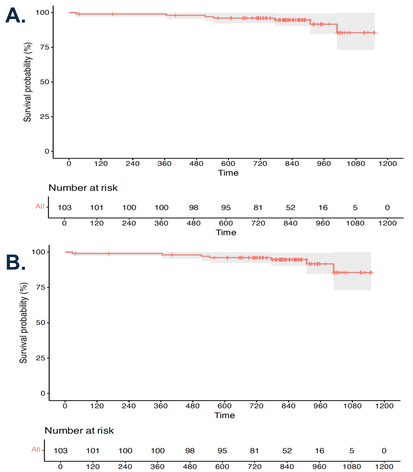


Figure 4. Progression-free survival (PFS; A) and overall survival (OS) stratified according to IGHV mutational status.

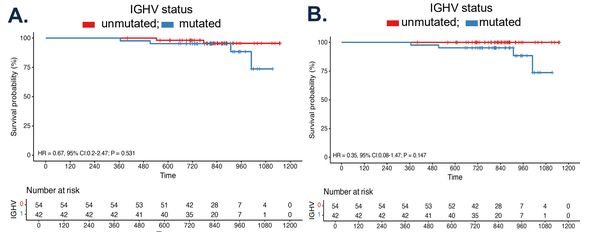


Figure 5. Progression-free survival (PFS; A) and overall survival (OS) stratified according to presence of *TP53* aberration.

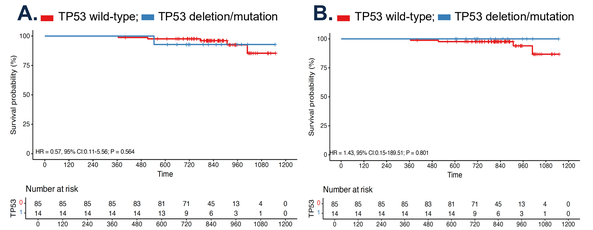


Table 2. Summary of adverse events (grade 3–5).

Adverse Event grade 3-5 (n=103)	Number of patients, (%)
Neutropenia	65 (63.1%)
Infections	8 (7.7%)
Pneumonia	3 (2.9%)
Upper respiratory tract infections	2 (1.9%)
Anemia	6 (5.8%)
Thrombocytopenia	5 (4.9%)
Febrile neutropenia	3 (2.9%)
Diarrhea	3 (2.9%)
Laboratory TLS	2 (1.9%)
Hemolytic anemia	2 (1.9%)
Suicide	1 (1%)
Merkel cell carcinoma	1 (1%)
Aspartate aminotransferase activity increased	1 (1%)
Blood urea nitrogen concentration increased	1 (1%)
Serum creatinine concentration increased	1 (1%)
Hyperphosphatemia	1 (1%)
Hyperphosphatemia and hyperuricemia	1 (1%)
Hypertension	1 (1%)
Lower limb pain	1 (1%)
Fracture	1 (1%)
Vitreous hemorrhage of the right eye	1 (1%)
Hypocalcemia	1 (1%)
Vomiting	1 (1%)
Immune thrombocytopenia	1 (1%)

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DISCLOSURES

KJ: GSK, Janssen: Consultancy; BeiGene, Amgen, Roche, GSK, Takeda, Janssen, AbbVie: Honoraria; Amgen, Janssen, AbbVie: Research Funding. EIJ: Abbvie, AstraZeneca, BeiGene, Roche, Sandoz, Janssen: Consultancy, Honoraria, Research Funding, Speakers Bureau. TR: Cilag, AstraZeneca, BeiGene, Johnson&Johnson, Janssen, AbbVie: Consultancy; GSK, Regeneron, OctoPharma, AstraZeneca, BeiGene, Janssen, AbbVie: Honoraria; Roche, Lilly, Cilag, AstraZeneca, BeiGene, Takeda, Janssen, AbbVie: Research Funding; AstraZeneca, Johnson&Johnson: Travel funding. SG: Astra Zeneca, Kite/Gilead, Sobi Roche, Abbvie, Beigene: Honoraria; Astra Zeneca, Kite/Gilead, Sobi, Roche, Abbvie, Beigene: Speakers Bureau; Kite/Gilead, Sobi, Roche, Abbvie: Consultancy; Sobi: Travel funding. KW: AbbVie, BeiGene, AstraZeneca, Amgen, Gilead and Janssen: Honoraria; AbbVie, BeiGene: Travel funding. JDS: Takeda, SOBI, Novartis, Swixx, BMS, Janssen-Cilag, Sanofi, AstraZeneca, Roche, AbbVie: Honoraria; Janssen-Cilag, AstraZeneca, BeiGene, Roche, AbbVie: Consultancy; Swixx, Sanofi, AstraZeneca, AbbVie: Travel grant. JR: Abbvie, Astra Zeneca, Sanofi, Roche, Angelini, Novartis, Amgen, Swixx, Johnson and Johnson, BMS, Beigene: Consultancy, Honoraria, Speakers Bureau. AM: Roche, Abbvie, Novartis, Takeda, AstraZeneca, Novo Nordisk, Sobi; Amgen: Consultancy, Speakers Bureau. PS: Janssen, Astra-Zeneca, Roche, Abbvie: Consultancy, Honoraria, Speakers Bureau. TW: Janssen, Abbvie, BeiGene, AstraZeneca, Gilead, Janssen, Roche, Takeda: Consultancy, Honoraria, Speakers Bureau. LG: BMS, Gilead, Abbvie: Consultancy, Honoraria; Gilead, Abbvie, Roche, Novartis, Pfizer, Servier, Janssen, BMS, Takeda: Consultancy, Speakers Bureau. JR: AstraZeneca, Gilead, Roche, Janssen, Celgene, Sanofi, Takeda: Honoraria, Speakers Bureau; Gilead, Roche, Takeda: Support for attending meetings and/or travel; Swixx: Participation on a Data Safety Monitoring Board or advisory board. KG: Pfizer, TG Therapeutics, Abbvie, Amgen, Astra-Zeneca, Bei-Gene, Janssen, Sanofi-Genzyme, Novartis, Takeda, Roche, GSK, Gilead: Honoraria; Sandoz, Pfizer, TG Therapeutics, Abbvie, Amgen, Astra-Zeneca, Bei-Gene, Janssen, Sanofi-Genzyme, Novartis, Takeda, Roche, GSK, Gilead: Research Funding. TS: AstraZeneca, Janssen: Consultancy, Honoraria, Research Funding. BP: Abbvie, Roche, and Sandoz: Consultancy; Abbvie, Janssen: Research Funding; Abbvie, AstraZeneca, BeiGene Amgen, Gilead, Celgene, and Janssen: Honoraria.

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