Poster #: 1406

XXI IWCLL International Workshop on CLL

Efficacy and toxicity of venetoclax and obinutuzumab in the first-line CLL patients with comorbidities: analysis of real-world data from the Polish Adult Leukemia Group (PALG) centers

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OBJECTIVES

- to analyze the efficacy and toxicity of Ven-Obi in a real-world population of comorbid patients treated outside clinical trials.

CONCLUSIONS

- The combination of Ven-Obi in de novo CLL is an effective and generally well-tolerated first-line therapy in CLL patients with significant comorbidities under real-world conditions.
- *TP53* aberrations did not affect early treatment outcomes.
- Longer follow-up is mandatory.

INTRODUCTION

- Venetoclax combined with obinutuzumab (Ven-Obi) is considered the standard of care for patients with treatment-naïve (TN) chronic lymphocytic leukemia (CLL) and comorbid conditions based on the results of CLL14 phase 3 clinical trial.
- in all clinical trials, the inclusion and exclusion criteria could be a source of selection bias, which is particularly important when interpreting the results in an older and burdened patient population. Therefore, there is a need for the results of this study to be confirmed by analysis of real-life data.

METHODS

- This was a retrospective analysis of adult patients with TN CLL and comorbid conditions in routine medical practice in Poland between November 2021 and August 2024.
- Eligibility criteria:
  - the diagnosis of CLL with indications to start treatment according to the iwCLL guidelines;
  - ECOG performance status ≤ 2;
  - the presence of comorbidities defined as a CIRS total score of > 6 and/or creatinine clearance (CrCl) > 30 mL/min and < 70 mL/min.
- The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Bioethics Committee (Approval ID: AKBE/66/2025).
- A log-rank test was used for group comparison. Fisher exact test and chi-square test were used for the univariate analysis. Due to small number of events, multivariate analysis was not performed.

RESULTS

Table 1. Baseline patients characteristic.

		All	With TP53 aberration
N		220	19
Age, median (range), years		70 (45-86)	72 (50-85)
Age ≥ 75 years, n (%)		56 (25.5%)	6 (31.6%)
ECOG, median, (range)		1 (0-3)	1 (0-2)
Sex, Male, n (%)		134 (60.9%)	7 (36.8%)
Binet stage, n (%)	A	30 (14.8%)	2 (10.5%)
	B	71 (35%)	3 (15.8%)
	C	102 (50%)	14 (73.7%)
	Missing	17	-
Rai stage, n (%)	Low	8 (3.7%)	0
	Intermediate	98 (45%)	5 (26.3%)
	High	112 (51.4%)	14 (73.7%)
	Missing	2	-
TLS risk category, n (%)	Low	35 (16.1%)	2 (10.5%)
	Intermediate	112 (51.6%)	11 (57.9%)
	High	70 (32.3%)	6 (31.6%)
	Missing	3	-
CIRS score > 6, n (%)		185 (84.1%)	12 (63.2%)
CIRS score, median (range)		8 (0-30)	7 (0-13)
Calculated CrCL < 70 ml/min, n(%)		106 (48.2%)	18 (%)
Bulky disease (> 5 cm), n (%)		49 (22.3%)	4 (21.1%)
Cytogenetic subgroup, n (%)	Del(17p)	18 (9.5%)	18 (94.8%)
	Not evaluated	30	1
	Del(11q)	28 (21.2%)	7 (36.8%)
	Not evaluated	88	12
	Tri(12)	11 (12.8%)	1/8 (12.5%)
	Not evaluated	134	11
	Del(13q)	43 (43.4%)	5/11 (45.5%)
	Not evaluated	121	8
TP53 mutational status, n (%)	Mutated	2 (2%)	2
	Unmutated	99 (98%)	1
	Not evaluated	119	-
IgHV mutational status	Mutated	37 (72.5%)	0
	Unmutated	14 (27.5%)	2 (100%)
	Not evaluated	169	17
Median follow-up time, (95% CI), months		25.9 (24.5-27.9)	26.2 (22.9-31)

Figure 1. A The estimated two-year overall survival (OS) and progression-free survival (PFS) of patients (n=220). B Overall response rate (ORR) after treatment completion in evaluable patients was 97.4% (n=199).

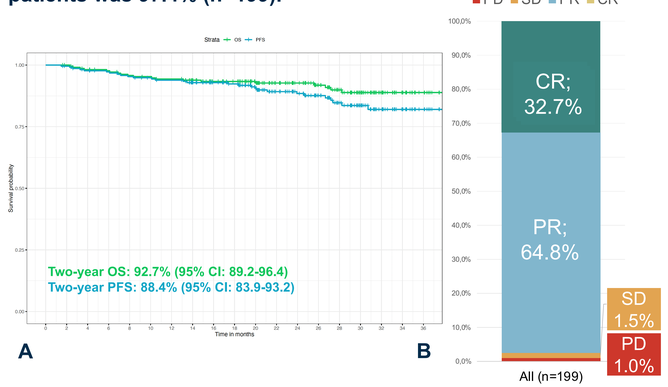

Figure 2. Two-year PFS (A) and OS (B) with patients with CIRS>6 (blue curve) vs CIRS≤6 (yellow curve)

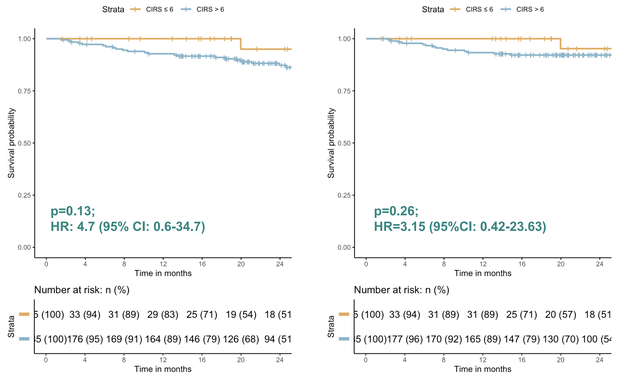

Figure 3. Two-year PFS (A) and OS (B) with patients without TP53 gene aberrations (yellow curve) vs with (blue curve).

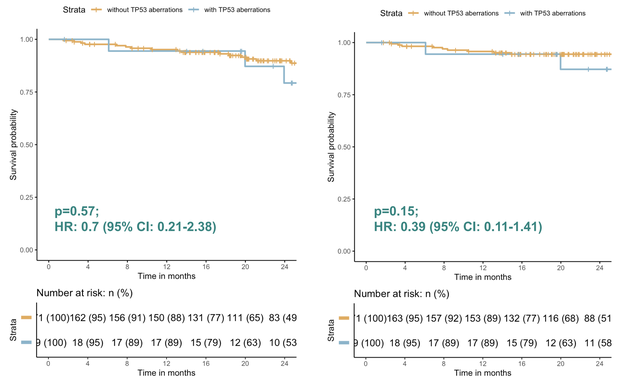

Table 2. The results of univariate analysis of potential influence of baseline prognostic factors on the PFS and OS.

		PFS			OS		
		HR	95% CI	p	HR	95% CI	p
Binet	A			0.84	-	-	0.54
	B	1.07	0.35-3.29	0.91	1.57	0.48-5.1	0.45
	C	0.79	0.33-1.92	0.61	0.75	0.3-2.22	0.6
Rai stage at diagnosis 3-4 vs 0-2		1.02	0.49-2.14	0.96	1.1	0.49-2.72	0.8
Male sex vs female		2.08	0.88-4.88	0.1	1.89	0.68-5.25	0.22
Age (as a continuous variable)		1.00	0.99-1.02	0.68	1	0.98-1.03	0.7
TP53 aberrations vs without		0.70	0.21-2.38	0.57	0.39	0.11-1.41	0.15
CIRS > 6 vs ≤ 6		4.71	0.64-34.7	0.19	3.15	0.42-23.63	0.26
ECOG	0	-		0.44	-	-	0.29
	1	1.13	-	0.82	2.09	0.45-9.65	0.35
	2	2.12	0.4-3.2	0.18	4.15	0.86-19.97	0.08
	3	0.00	0.71-6.33	0.99	0.00	0.00-nr	0.99
Lymph nodes >5 cm vs ≤5		0.84	0.32-2.21	0.73	1.03	0.34-3.1	0.96
PLT count <30 x 10 ^{9}/L vs ≥ 30 x 10 ^{9}/L		1.08	0.15-7.94	0.94	0.05	0.03-11.62	0.59
Hb concentration <9 g/dL vs >9 g/dL		1.01	0.41-2.49	0.99	0.95	0.32-2.87	0.93
CrCl <70 ml/min vs ≥70 ml/min		1.36	0.65-2.85	0.42	1.99	0.78-5.05	0.15
Presence of del(11) vs without		1.84	0.42-8.11	0.42	2.97	0.38-23.03	0.3
Presence of tri(12) vs without		1.39	0.18-10.8	0.75	24.2	0.00-132895.05	0.47
Presence of del(13) vs without		1.1	0.38-3.16	0.87	0.98	0.30-3.22	0.98

Table 3. Reported adverse events during Ven-Obi therapy.

Adverse events		Any	Grade 3 or 4
Blood and lymphoid system disorders, n(%)	Neutropenia	183 (83.2%)	118 (53.6%)
	Thrombocytopenia	126 (57.3%)	48 (21.8%)
	Anemia	120 (54.5%)	31 (14.1%)
	Febrile neutropenia	22 (10%)	Nd
Infections, n (%)			
Upper respiratory tract infections		17 (7.7%)	0
Pneumonia (other than COVID-19)		18 (8.6%)	8 (3.6%)
COVID-19 hospitalization		26 (11.8%) 11/26 (42.3%)	Nd
SARS-CoV-2 pneumonia		14 (6.4%)	Nd
TLS, n (%)	Biochemical	43 (19.5%)	Nd
	Clinical	8 (3.6%)	
AIHA, n (%)		9 (4.1%)	-
ITP, n (%)		6 (2.7%)	-
Diarrhea, n (%)		15 (6.8%)	8 (3.6%)
Liver toxicity, n (%)		4 (1.8%)	3 (1.4%)
Increased enzyme activity, n (%)	ALT	14 (6.4%)	5 (2.3%)
	AST	16 (7.3%)	2 (0.9%)
	ALP	9 (4.1%)	1 (0.5%)
	GGTP	5 (2.3%)	1 (0.5%)
Cardiac disorders, n (%)	Atrial fibrillation	3 (1.4%)	-
	Acute coronary syndrome	1 (0.5%)	1 (0.5%)
Increased bilirubin concentration, n (%)		5 (2.3%)	0
Cutaneous toxicity, n (%)		6 (2.7%)	Nd
Obinutuzumab IRR, n (%)		21 (9.5%)	5 (2.3%)
Secondary malignancy, n (%)		5 (2.3%)	5 (2.3%)
Fever, n (%)		5 (2.3%)	Nd
Peripheral oedema, n (%)		3 (1.4%)	Nd
Central nervous system disorder, n (%)		2 (0.9%)	Nd

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ACKNOWLEDGMENTS

The authors would like to thank the patients who participated in the study and their caregivers.

DISCLOSURES

JDS: honoraria from AbbVie, Roche, Janssen, AstraZeneca, SOBI, Takeda, BMS, Novartis, and Swixx; advisory board meetings organized by Janssen-Cilag, Sanofi, AstraZeneca, Roche, and BeiGene; and travel grants from Sanofi-Aventis, Swixx, AbbVie, and AstraZeneca. KPM: travel grant from AbbVie. BP: a consultant for Abbvie, Roche, and Sandoz; honoraria and research funding from Abbvie, AstraZeneca, BeiGene, Amgen, Gilead, Celgene, and Janssen. MW: honoraria from AbbVie, Roche, Janssen, AstraZeneca and Takeda; advisory board: Janssen; travel grants from AbbVie and Takeda. Asz: honoraria from AbbVie, Roche, Janssen-Cilag, AstraZeneca, Novartis, Amgen; travel grants from Gilead, Janssens-Cilag, Novartis, AstraZeneca. KW: honoraria and travel grants from AbbVie, Janssen, Takeda, Beigene, Accord. ELI: a consultant for Abbvie and AstraZeneca; honoraria and research funding from Abbvie, AstraZeneca, BeiGene, Roche, Sandoz and Johnson&Johnson. IH: honoraria Abbvie, Astra Zeneca, Beigene, BMS, Janssen, Pfizer, Roche; Advisory Boards: Abbvie, BMS, Beigen, Roche; and travel grants: Astra Zeneca, Gilead, Roche. TW: honoraria AbbVie, BeiGene, Roche, Janssen, AstraZeneca, Takeda, BMS, Novartis, and Pfizer; advisory board meetings organized by Janssen-Cilag, Sanofi, AstraZeneca, Roche, and BeiGene; and travel grants from AbbVie, Servier. KJ: consultant/advisory boards meetings AbbVie, Jannsen, AstraZeneca, BeiGene, Roche; research funding from AbbVie, Jannsen, AstraZeneca. KZ, BI, KW, WS, EK, PJB, AB, TB, ES, JH, MW, MH, KG, EC, PH, AK, ASzS, AWW, JK: no conflicts of interest.