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Venetoclax–obinutuzumab for previously untreated chronic lymphocytic leukemia: 5-year results of the randomized CLL14 study

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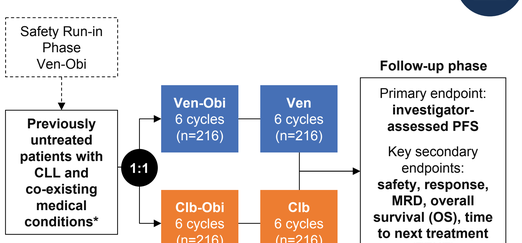
BACKGROUND

The CLL14 trial (NCT02242942) showed **significant improvement in progression-free survival** (PFS) with **fixed-duration venetoclax-obinutuzumab** (Ven-Obi) compared with chlorambucil (Clb)-Obi chemoimmunotherapy in patients with previously untreated chronic lymphocytic leukemia (CLL) and co-existing conditions.[1]

High rates of undetectable minimal residual disease (uMRD) suggested deep remissions; thus, long-term efficacy data including patients with high-risk disease are of particular interest.[2]

We report updated efficacy and safety data from the ongoing follow-up of the CLL14 open-label trial, with all patients now having been off study treatment for at least 4 years.

METHODS



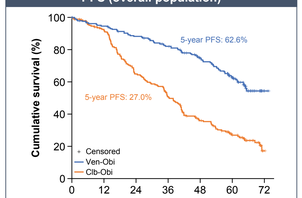
- Median follow-up for this analysis was 65.4 months (IQR 52.6–69.4). Follow-up is ongoing, all patients are off study treatment.
- MRD response was measured in the peripheral blood by next generation sequencing every 3–6 months, up to 9 months after the last patient was enrolled.

*Patients had a cumulative illness rating scale >6 and/or creatinine clearance <70mL/min.
IQR, interquartile range.

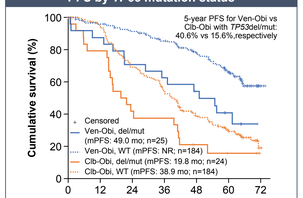
5-YEAR PFS AND OS

- PFS continued to be superior for Ven-Obi vs Clb-Obi, (median NR vs 36.4 months, respectively; HR 0.35 [95% CI 0.26–0.46], p<0.0001), and was observed across biological risk groups.
  - A multivariable analysis indicated 17p deletion and high disease burden as independent prognostic factors for PFS in patients treated with Ven-Obi.

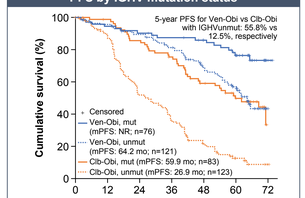
PFS (overall population)



PFS by *TP53* mutation status



PFS by IGHV mutation status



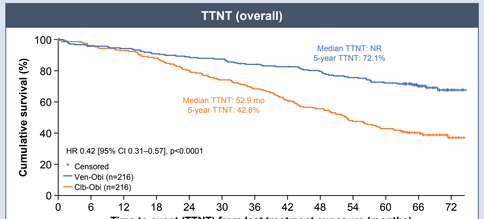
- At the 5-year update, OS rate was 81.9% for patients in the Ven-Obi arm and 77.0% for patients in the Clb-Obi arm (HR 0.72 [95% CI 0.48–1.09], p=0.12); median OS was NR in both arms.

CI, confidence interval; del, deletion; HR, hazard ratio; IGHV, immunoglobulin-like heavy chain gene; mo, months; mPFS, median PFS; mut, mutated; NR, not reached; unmut, unmutated; WT, wild-type.

TTNT

- TTNT was longer with Ven-Obi vs Clb-Obi regardless of biological risk factor (5-year TTNT, respectively, for patients with: *TP53*del/mut, 48.0% vs 20.8%; IGHVunmut, 66.2% vs 25.1%).
- Most patients received targeted agents as 2L therapy after PD: the majority received BTKi monotherapy (Ven-Obi: 58.1%; Clb-Obi: 54.3%); 25.8% (Ven-Obi) and 30.9% (Clb-Obi) received 2L CIT.

TTNT (overall)

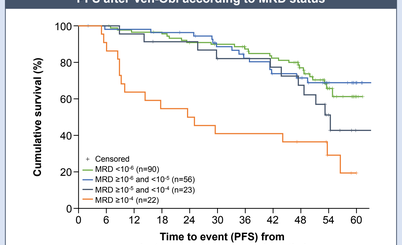


2L, second-line; BTKi, Bruton's tyrosine kinase inhibitor; CIT, chemo/chemoimmunotherapy; NLT, next anti-leukemic therapy; PD, progressive disease.

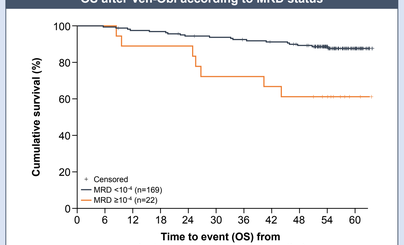
MRD ASSESSMENT

- Depth of remission beyond 10^{-4} correlates with long-term PFS, indicating the value of ultra-sensitive MRD assessments.
- Patients with MRD ≥10^{-4} after Ven-Obi have a shorter OS than patients with MRD <10^{-4}, highlighting the need for dedicated MRD-guided approaches.
- 4 years after treatment, 39 (18.1%) and 4 (1.9%) patients had sustained MRD <10^{-4} in the Ven-Obi and Clb-Obi arms, respectively.

PFS after Ven-Obi according to MRD status



OS after Ven-Obi according to MRD status



SAFETY ANALYSES

- No new safety signals were observed.
- Second primary malignancies were reported in 44 (20.8%) patients on Ven-Obi vs 32 (15.0%) on Clb-Obi.

Most frequent Grade ≥3 adverse events

	Ven-Obi (n=212)		Clb-Obi (n=214)	
	During treatment	After treatment	During treatment	After treatment
Neutropenia	51.9%	4.0%	47.2%	1.9%
Thrombo-cytopenia	14.2%	0.5%	15.0%	0.0%
Anemia	7.5%	2.0%	6.1%	0.5%
Febrile neutropenia	4.2%	1.0%	3.3%	0.5%
Leukopenia	2.4%	0.0%	4.7%	0.0%
Pneumonia	3.8%	3.0%	3.3%	1.4%
IRR	9.0%	0.0%	9.8%	0.5%
TLS	1.4%	0.0%	3.3%	0.0%

IRR, infusion-related reactions; TLS, tumor lysis syndrome.

CONCLUSIONS

- 63% of patients treated with fixed-duration Ven-Obi remain without a PFS event 4 years after treatment cessation
- The benefit with Ven-Obi was observed across all subgroups, including *TP53*del/mut and IGHVunmut
- uMRD remissions were considerably deeper and more sustained after Ven-Obi than Clb-Obi
- There were no new safety signals observed and no significant difference in frequency of secondary malignancies

REFERENCES

1. Fischer K, et al. *N Engl J Med* 2019;380(23):2225–36.
2. Al-Sawaf O, et al. *Hematol Oncol* 2021;39(2_suppl):S146.

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DISCLOSURES

OA-S: honoraria (Janssen-Cilag, Roche, Gilead Sciences, AbbVie, AstraZeneca, Adaptive Biotechnologies, BeiGene), consulting or advisory role (Roche, Janssen-Cilag, Gilead Sciences, AbbVie); research funding – granted to institution (BeiGene, Roche, AbbVie, Janssen/Pharmacyclics); travel, accommodations, expenses (Roche, AbbVie, Gilead Sciences, Janssen-Cilag). **CZ, SR, CS:** nothing to disclose. **AK, NC:** employment, may hold stocks or shares (Roche). **A-MF:** research funding – granted to institution (Celgene/Bristol Myers Squibb, AstraZeneca); travel, accommodations, expenses (AbbVie). **ET:** consulting or advisory role (Roche, AbbVie); speakers' bureau (Roche, AbbVie, Janssen-Cilag); travel, accommodations, expenses (AbbVie). **MR:** honoraria (Roche, Janssen Oncology, AstraZeneca, AbbVie, MSD); consulting or advisory role (AbbVie, Roche, AstraZeneca); research funding – granted to institution (Roche, AbbVie); patents, royalties, other intellectual property (partial patent holder, intellectual property only); travel, accommodations, expenses (AstraZeneca, Takeda). **K-AK:** honoraria, consulting or advisory role, speakers' bureau, research funding – granted to institution, expert testimony, and travel, accommodations, expenses (Roche, AbbVie). **BC:** employment, may hold stocks or shares (AbbVie). **BE:** honoraria (Roche, AbbVie, Gilead Sciences, Janssen, Novartis, Hexal, AstraZeneca, Adaptive Biotechnologies, Oxford Biomedica, Miltenyi Biotec); consulting or advisory role (Gilead Sciences, Janssen-Cilag, Roche, AbbVie, Novartis, Celgene, AstraZeneca, ArQule); speakers' bureau (Roche/Genentech, Janssen-Cilag, Gilead Sciences, Celgene, AbbVie, Novartis); research funding (Roche, AbbVie, Gilead Sciences, Janssen, Beijing Genomics Institute); travel, accommodations, expenses (Roche, AbbVie, Gilead Sciences, Janssen). **SS:** honoraria, consulting or advisory role, speakers' bureau, research funding, and travel, accommodations, expenses (AbbVie, AstraZeneca, Celgene, Gilead Sciences, GlaxoSmithKline, Roche, Janssen). **YJ:** employment, may hold stocks or (Genentech). **MH:** honoraria (Roche, Janssen, AbbVie, Gilead Sciences, AstraZeneca); consulting or advisory role and speakers' bureau (Janssen, AbbVie, Gilead Sciences, Roche/Genentech, AstraZeneca); research funding – granted to institution (Roche, AbbVie, Janssen, Gilead Sciences, AstraZeneca); travel, accommodations, expenses (Roche, Janssen). **KF:** honoraria and consulting or advisory role (AbbVie, Roche); travel, accommodations, expenses (Roche).

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