2017 - Venetoclax–obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized CLL14 study

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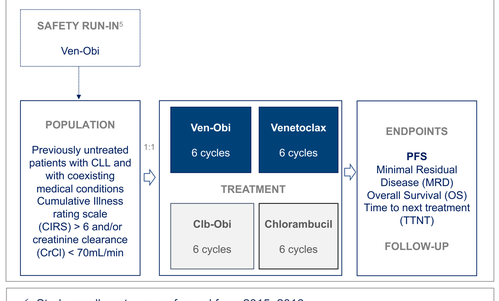
BACKGROUND

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 coexisting 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. We therefore continue to follow-up with these patients. [2, 3, 4]

Here 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 5 years.

METHODS

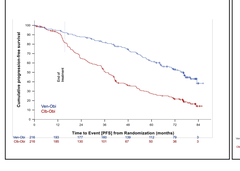


- ✓ Study enrollment was performed from 2015–2016.
- ✓ All patients are off study treatment, follow-up is ongoing.
- ✓ During follow-up, MRD response was measured in the peripheral blood by next generation sequencing (NGS) every 3–6 months up to month 18 and then every 6 months until 9 years after the last patient was enrolled.
- **Median follow-up** for this analysis was **76.4 months**.

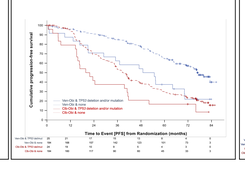
6-YEAR PFS AND OS

- PFS continued to be superior for Ven-Obi vs Clb-Obi, (median 76.2 vs 36.4 months, respectively; hazard ratio (HR) 0.40 [95% confidence interval {CI} 0.31–0.52], p<0.0001) and was observed across biological risk groups.
- The 6-year-OS rate was 78.7% in the Ven-Obi and 69.2% in the Clb-Obi arm (HR 0.69 [95% CI 0.48–1.01], p=0.052).
- A multivariable analysis indicated *TP53* deletion/mutation (HR 2.26 [95% CI 1.24–4.12]), unmutated immunoglobulin heavy chain (IGHV; HR 2.26 [95% CI 1.27–4.02]) and maximum lymph node size ≥5 cm (HR 1.92 [95% CI 1.19–3.09]) as independent prognostic factors for PFS in patients treated with Ven-Obi.

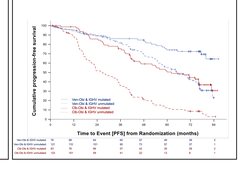
Progression-free survival
Investigator-assessed PFS



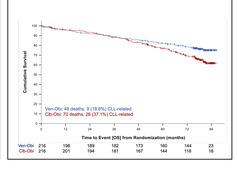
Progression-free survival – *TP53* status



Progression-free survival – IGHV status

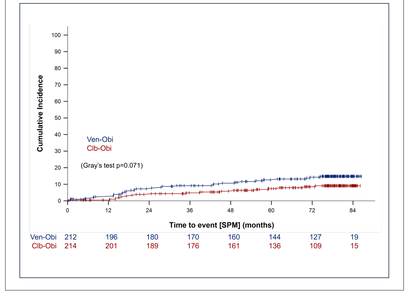


Overall Survival



SAFETY

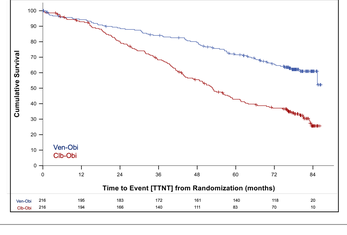
- No new safety signals.
- The secondary primary malignancy (SPM) incidence rate per 1000 patient-months was **2.3% in the Ven-Obi arm** and **1.4% in the Clb-Obi arm**.



TTNT

- TTNT was longer with Ven-Obi vs Clb-Obi (median not reached vs 52.9 months, respectively; HR 0.44 [95% CI 0.33–0.58], p<0.0001).
- Most patients received targeted agents as second-line therapy: the majority received Bruton tyrosine kinase inhibitors (BTKi; Ven-Obi: 59%; Clb-Obi: 53.4%); 17.9% (Ven-Obi) and 14.6% (Clb-Obi) received second-line Ven; 23.1% (Ven-Obi) and 30.1% (Clb-Obi) received second-line chemo/chemoimmunotherapy.

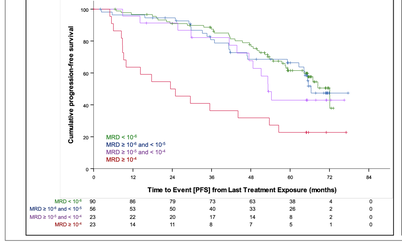
Time To Next Treatment
Defined as time to death or next-antileukemic treatment



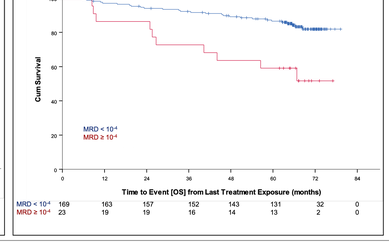
MRD ASSESSMENT

- Depth of remission of patients after Ven-Obi beyond 10^{-4} correlates with long-term PFS indicating the prognostic value of the end-of-treatment MRD status.
- Patients with MRD ≥10^{-4} after Ven-Obi have a shorter OS than patients with MRD <10^{-4}.
- 5 years after treatment, 17 (7.9%) 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
End-of-treatment MRD status in peripheral blood, by NGS



OS after VEN-Obi according to MRD status
End-of-treatment MRD status in peripheral blood, by NGS



CONCLUSIONS

53.1% of patients treated with **fixed-duration Ven-Obi** remain **without PFS event** five years after treatment cessation.

The benefit was observed across **all subgroups of patients** treated with Ven-Obi, including *TP53*del/mut and IGHVunmut.

Over **60% of patients treated with Ven-Obi** have not required a second-line treatment.

End-of-treatment MRD status after Ven-Obi significantly correlates with PFS and OS.

No new safety signals and **no significant difference in the incidence rate of secondary malignancies** observed.

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