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## VENETOCLAX-OBINUTUZUMAB FOR PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA: 4-YEAR FOLLOW-UP ANALYSIS OF THE RANDOMIZED CLL14 STUDY

Topic: 06. Chronic lymphocytic leukemia and related disorders - Clinical

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### Background:

The CLL14 study showed significant improvement of progression-free survival (PFS) with venetoclax-obinutuzumab (Ven-Obi) as compared to chlorambucil-obinutuzumab (Clb-Obi) in patients (pts) with previously untreated chronic lymphocytic leukemia (CLL) and coexisting conditions. High rates of undetectable minimal residual disease (uMRD) have been observed after one year fixed-duration treatment with Ven-Obi, suggesting deep remissions and feasibility of the fixed-duration concept with targeted agents for CLL.

### Aims:

The aim of this report is to provide updated efficacy and safety data from the ongoing follow-up of the CLL14 study with now all pts being off study treatment for at least 3 years.

### Methods:

Pts with previously untreated CLL and coexisting conditions were randomized 1:1 to receive 12 cycles of venetoclax with 6 cycles of obinutuzumab or 12 cycles of chlorambucil with 6 cycles of obinutuzumab. Primary endpoint was investigator-assessed PFS. Key secondary endpoints were safety, response rates, rates of minimal residual disease (MRD)(measured every 3-6 months up to 5 years after last patient enrolment) and overall survival. Follow-up is ongoing, but all pts are off study treatment. This trial was registered with ClinicalTrials.gov, number NCT02242942.

### Results:

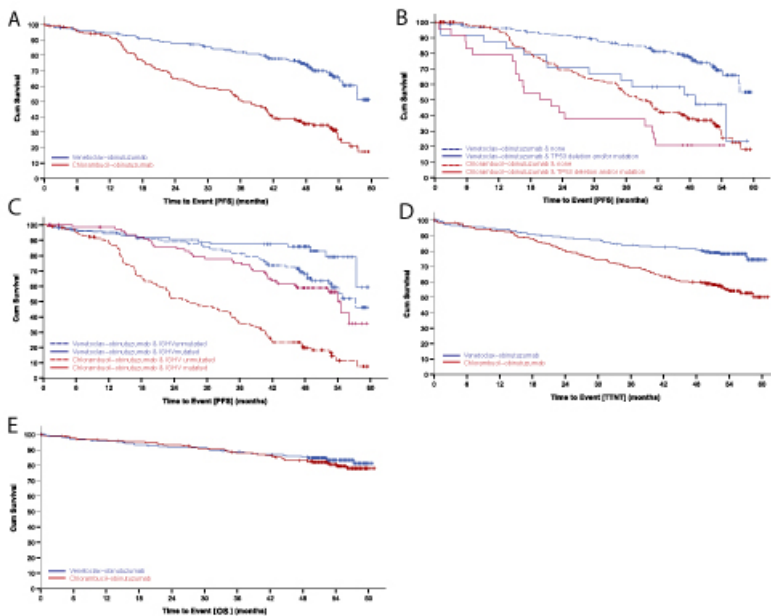
Of the 432 enrolled pts, 216 were randomly assigned to receive Ven-Obi and 216 to receive Clb-Obi. After a median follow-up of 52.4 months (interquartile range 49.5-56.2), PFS continued to be superior for Ven-Obi as compared to Clb-Obi (median not reached (nr) vs. 36.4 months; hazard ratio [HR] 0.33 [95% CI 0.25-0.45],  $p < 0.0001$ )(Fig A). At 4 years after randomization, the estimated PFS rate was 74.0% in the Ven-Obi arm and 35.4% in the Clb-Obi arm. This improvement was observed across all clinical and biological risk groups, including pts with TP53 mutation/deletion (4-year PFS 53.0% vs 20.8%) and unmutated IGHV status (4-year PFS 68.0% vs 19.8%)(Fig B,C). Overall, 35 disease progressions in the Ven-Obi arm have been observed, compared to 122 in the Clb-Obi arm. Time to next treatment was significantly longer in the Ven-Obi arm (4-year TTNT 81.1% vs 59.9%; HR 0.46, 95% CI [0.32-0.65],  $p < 0.0001$ ) (Fig D). The majority of pts received and responded to BTK inhibitor monotherapy as a second-line treatment after

progressive disease in both arms (57.1% in Ven-Obi arm, 55.6% in Clb-Obi arm).

Assessment of MRD by next-generation sequencing in peripheral blood 30 months after the end of treatment (EoT) showed that 26.9% of pts in the Ven-Obi arm still had uMRD ( $<10^{-4}$ ), 21.8% had low (L)-MRD ( $\geq 10^{-4}$  and  $<10^{-2}$ ) and 13.4% high (H)-MRD ( $\geq 10^{-2}$ ), compared to 3.2% uMRD, 8.8% L-MRD, 28.2% H-MRD in the Clb-Obi arm.

No difference in overall survival has been observed between the Ven-Obi and Clb-Obi arm; at 4 years 85.4% pts were alive in the Ven-Obi arm and 83.1% in the Clb-Obi arm (HR 0.85 [0.54-1.35],  $p=0.49$ )(Fig E). Second primary malignancies were reported in 40 (18.9%) pts in the Ven-Obi arm and 30 (14.0%) in the Clb-Obi arm. No new safety signals were observed.

### Image:



### Summary/Conclusion:

The four-year follow-up confirms the superior efficacy with longer PFS and deep remissions after fixed-duration Ven-Obi compared to Clb-Obi. The majority of pts remains without relapse three years after completing Ven-Obi treatment. Although adverse features such as TP53 mutation/deletion were not fully mitigated, fixed-duration Ven-Obi continues to be an effective treatment for all pts with CLL and with coexisting conditions.

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