FIXED-DURATION VENETOCLAX PLUS OBINUTUZUMAB IMPROVES PROGRESSION-FREE SURVIVAL AND MINIMAL RESIDUAL DISEASE NEGATIVITY IN PATIENTS WITH PREVIOUSLY UNTREATED CLL AND COMORBIDITIES

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Background

The multinational, open-label, phase 3 CLL14 trial (NCT02242942) compared fixed-duration targeted venetoclax plus obinutuzumab (VenG) treatment with chlorambucil-obinutuzumab (ClbG) treatment in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities.

Aims

We present endpoint analyses with particular emphasis on progression-free survival (PFS) and minimal residual disease (MRD)-negativity.

Methods

Pts with a CIRS score >6 and/or an estimated creatinine clearance <70 mL/min were randomized 1:1 to receive equal duration treatment with 12 cycles of standard Clb or Ven 400 mg daily in combination with G for the first 6 cycles. The primary endpoint was PFS. MRD-negativity in peripheral blood (PB) or bone marrow (BM) 3 months after treatment completion was a key secondary endpoint. MRD was analyzed serially from Cycle 4 every 3 months by an allele-specific oligonucleotide polymerase chain reaction assay (ASO-PCR; cut-off, 10^{-4}) and by next generation sequencing (NGS; cut-offs, 10^{-4}, 10^{-5}, 10^{-6}).

Results

In total, 432 pts were enrolled; 216 in each treatment group (intent-to-treat population). Median age, total CIRS score, and CrCl at baseline were 72 years, 8, and 66.4 ml/min respectively. After 29 months median follow-up, superior PFS was observed with VenG vs ClbG (Figure 1a). Median PFS was not reached in either group: at Month 24, PFS rates were 88% with VenG and 64% with ClbG (hazard ratio [HR] 0.35; 95% confidence interval [CI] 0.23–0.53; P<0.0001). MRD-negativity by ASO-PCR was significantly higher with VenG vs ClbG in both PB (76% vs 35% [P<0.0001]) and BM (57% vs 17% [P<0.0001]) 3 months after treatment completion. Overall, 75% of VenG MRD-negative pts in PB were also MRD-negative in BM vs 49% in the ClbG group. Landmark analysis for this timepoint by PB MRD status showed that MRD-negativity was associated with longer PFS. MRD-negativity rates were

more sustainable with VenG: 81% (VenG) vs 27% (ClbG) of pts were MRD-negative 12 months after treatment completion; HR for MRD conversion 0.19; 95% CI 0.12–0.30 (median time off-treatment: 19 months) (Figure 1b). MRD-negativity rates by NGS confirmed these results; 78% (VenG) vs 34% (ClbG) of pts had MRD-negative status at $<10^{-4}$, 35% vs 15% at $\geq 10^{-6}$–$<10^{-5}$ and 31% vs 4% at $<10^{-6}$, respectively.

Figure 1a: Investigator-assessed progression-free survival

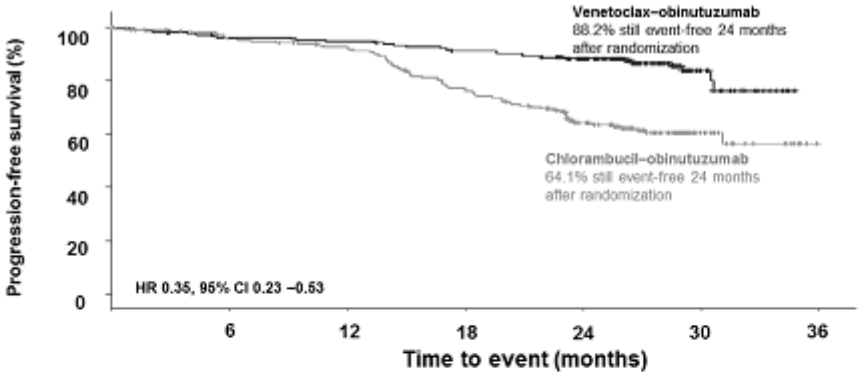
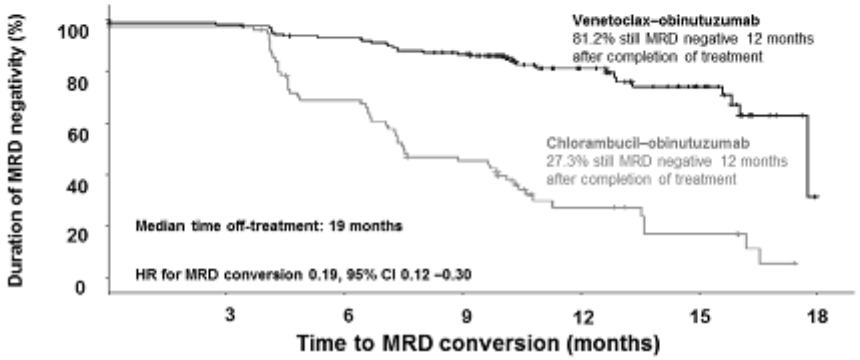


Figure 1b: Duration of MRD negativity after treatment completion



Conclusion

Fixed-duration VenG induced deep, high ($<10^{-4}$ in 3/4 of pts and $<10^{-6}$ in 1/3 of pts), and long lasting MRD-negativity rates (with a low rate of conversion to MRD-positive status 1 year after treatment) in previously untreated pts with CLL and comorbidities, translating into improved PFS.