Effect of fixed-duration venetoclax plus obinutuzumab (VenG) on progression-free survival (PFS), and rates and duration of minimal residual disease negativity (MRD–) in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities.

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Background:
The multinational, open-label, phase 3 CLL14 trial compared fixed-duration targeted VenG treatment with chlorambucil-obinutuzumab (ClbG) in previously untreated pts with CLL and comorbidities. Here we present endpoint analyses with particular emphasis on MRD− and PFS.

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 (C) of standard Clb or Ven 400 mg daily in combination with G for first 6 C. Primary endpoint was PFS. MRD− in peripheral blood (PB) or bone marrow (BM) 3 months (mo) after treatment completion was a key secondary endpoint. MRD was analyzed serially from C4 every 3 mo 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:

432 pts were enrolled; 216 in each treatment group (intent-to-treat population). After 29 mo median follow-up, superior PFS was observed with VenG vs ClbG (HR 0.35; 95% CI 0.23–0.53; P<0.0001). MRD− 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 mo 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− was associated with longer PFS. Higher MRD− rates were achieved early and were more sustainable with VenG: 81% (VenG) vs 27% (ClbG) of pts were MRD-negative 12 mo after treatment completion; HR for MRD conversion 0.19; 95% CI 0.12–0.30 (median time off-treatment: 19 mo). MRD− rates by NGS confirmed these results; 78% (VenG) vs 34% (ClbG) of MRD− at $<10^{-4}$, 31% vs 4% at $<10^{-6}$ and 35% vs 15% at $\geq 10^{-6}$–$<10^{-5}$, respectively.

Conclusions:

Fixed-duration VenG induced deep ($<10^{-6}$ in 1/3 of pts), high, and long lasting MRD− rates (with a low rate of conversion to MRD+ status 1 year after treatment) in previously untreated pts with CLL and comorbidities, translating into improved PFS. Clinical trial information: NCT02242942