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S145 VENETOCLAX-OBINUTUZUMAB FOR PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA: 6-YEAR RESULTS OF THE RANDOMIZED CLL14 STUDY

Topic: CLL clinical

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Background:

One-year fixed-duration venetoclax-obinutuzumab (Ven-Obi) is a standard-of-care for patients with previously untreated chronic lymphocytic leukemia (CLL). The CLL14 study previously demonstrated high efficacy and good tolerability of Ven-Obi in patients with CLL and coexisting conditions. Due to its ongoing follow-up, the CLL14 study provides unique insights into the long-term outcomes of patients after Ven-Obi treatment completion.

Aims:

The aim of this report is to provide updated efficacy and safety data from the ongoing follow-up of the CLL14 study, all patients being off study treatment for ≥ 5 years.

Methods:

Patients with previously untreated CLL and coexisting conditions were randomized 1:1 to 12 cycles of venetoclax with 6 cycles of obinutuzumab, or 12 cycles of chlorambucil with 6 cycles of obinutuzumab (Clb-Obi). The primary endpoint was investigator-assessed progression-free survival (PFS). Secondary endpoints included safety, rates of minimal residual disease (MRD), time to next treatment (TTNT) and overall survival (OS). Follow-up is ongoing.

Results:

Of the 432 enrolled patients, 216 were randomly assigned to receive Ven-Obi and 216 to receive Clb-Obi. At a median follow-up of 76.4 months (interquartile range 52.5-80.5), PFS remained superior for Ven-Obi compared to Clb-Obi (median 76.2 vs 36.4 months; hazard ratio [HR] 0.40 [95% CI 0.31-0.52], p<0.0001). At 6 years after randomization, the estimated investigator-assessed PFS rate was 53.1% after Ven-Obi, and 21.7% after Clb-Obi.

Progressive disease (PD) occurred in 67 cases in the Ven-Obi arm with 39 second-line treatment initiations, and in 141 cases in the Clb-Obi arm (with 103 second-line treatments). TTNT was significantly longer after Ven-Obi (6-year TTNT 65.2% vs 37.1%; HR 0.44, 95% CI 0.33-0.58, p<0.0001).

In both arms, the most frequent second-line treatments were BTK inhibitors (61.5% in the Ven-Obi arm, 55.4% in the Clb-Obi arm).

The PFS and TTNT difference between the two arms was maintained across all risk groups, including patients with

TP53 mutation/deletion (median PFS 51.9 vs 20.8 months; median TTNT 57.3 vs 29.0 months) and unmutated IGHV status (median PFS 64.8 vs 26.9 months; median TTNT 85.4 vs 40.6 months). Multivariate analysis identified *TP53* deletion/mutation, unmutated IGHV and lymph node size ≥5 cm as independent negative prognostic factors for PFS in patients treated with Ven-Obi.

Five years after treatment completion, 17 (7.9% of the intention-to-treat population) patients in the Ven-Obi arm still had uMRD ($<10^{-4}$ by NGS in peripheral blood), 22 (10.2%) had low (L)-MRD ($\geq 10^{-4}$ and $< 10^{-2}$) and 23 (10.6%) high (H)-MRD ($\geq 10^{-2}$), compared to 4 (1.9%) uMRD, 9 (4.2%) L-MRD and 18 (8.3%) H-MRD in the Clb-Obi arm.

Overall, 48 deaths were reported in the Ven-Obi arm (9 PD related) and 70 in the Clb-Obi arm (26 PD related); at 6-year-OS rate was 78.7% in the Ven-Obi and 69.2% in the Clb-Obi arm (HR 0.69 [0.48-1.01], p=0.052). Second primary malignancies were reported in 30 patients in the Ven-Obi and 18 in the Clb-Obi arm; cumulative incidences 6 years after randomization were 14.2% and 8.5%, respectively (p=0.071). Two Richter transformations were reported in the Ven-Obi arm and four in the Clb-Obi arm. No new safety signals were observed.

Summary/Conclusion:

These data confirm a long-term PFS benefit of fixed-duration Ven-Obi treatment compared to Clb-Obi, including patients with high-risk CLL. Five years after completing Ven-Obi, over half of patients remained in remission, and over 60% had not required second-line treatment. The 1-year Ven-Obi regimen is an effective fixed-duration option for patients with CLL and coexisting conditions.