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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Comparison of Venetoclax Based Treatments for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

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Background: Venetoclax (Ven) is a BCL-2 inhibitor that produces deep responses with high rates of undetectable minimal residual disease (uMRD) for patients (pts) with chronic lymphocytic leukemia (CLL) (Al-Sawaf et al. 2020). Currently, ven is FDA approved as either monotherapy (mono) or in combination (combo) with rituximab (R) In patients with relapsed/refractory (R/R) CLL (Seymour et al. 2018). However, the optimal ven based treatment (tx) for pts with R/R CLL either as mono, or in combo with anti-CD20 monoclonal antibody (mab), or bruton tyrosine kinase inhibitor (BTKi) is uncertain. We performed a single institution retrospective analysis of pts with R/R CLL treated with ven based regimens evaluating efficacy of different ven based txs.

Methods: 98 pts with R/R CLL treated between the years of 2012 and 2023 were evaluated. Ven based treatment consisted of ven mono or in combo with R, obinutuzumab (G), or ibrutinib (BTKi) with standard ven dose ramp up to a maximum dose of 400mg daily. R and G were administered per FDA standard dosing. Ibrutinib was administered as 420mg daily, as either fixed or continuous duration tx. Response assessment was performed using iwCLL criteria. Minimal residual disease (MRD) was assessed by multi-parametric peripheral blood flow cytometry with a sensitivity of 10^{-4}. Time-to-event analyses were performed with the Kaplan-Meier method, with log-rank test used to assess statistically significant differences between variables. Hazard ratios (HR) were calculated by use of Cox proportional modelling.

Results: The pts had a median age of 68 years (range; 46-89). Rai stage at time of tx initiation with ven: I 14.2%; II 36.3%; III 8.8%; Stage IV 40.7%. The median number of previous txs was 4 (range; 1-14). Pts harbored the following cytogenetic abnormalities: del(13q) 50.5%; del(11q) 18.5%; trisomy 12 15.5%; normal 15.5%; del(17p)/TP53 mutation 24.7%; and complex in 33%. Seventy percent of pts harbored an unmutated immunoglobulin heavy chain. 25.5% of pts had genomic complexity, with $\geq$ 5 gene mutations.

43.9% of pts were treated with ven mono; 19.4% were treated with venR; 25.5% of pts were treated with venG; and 11.2% of pts were treated with ven + BTKi. The median number of months of ven based tx was 16.3 (range; 0.9-118.6). 14.3% of pts currently remain on ven. 60.8% of pts had progression after ven based tx; with 62.2% requiring additional tx. 15.3% of pts developed Richter's Transformation. The best overall response for the cohort was: CR 67%; PR 24.5%; SD 1.1%; and PD 7.4%. The best MRD response for the whole cohort was uMRD 76.8%; low MRD 19.5; and high MRD 3.6%. uMRD as best MRD response occurred in 66.7% of ven mono; 82.4% of venR; 86.4% of venG; and 70% of ven + BTKi treated pts.

With a median follow-up of 52 months (mo), the median progression-free survival (PFS) for the whole cohort was 67.8 mo. Ven combo had superior PFS to ven mono; median PFS 76.6 vs 58.9 mo ($p = 0.04$; HR 0.5037; 95% CI 0.2583 - 0.9635). Among the combination treatment approaches, there was a trend for improved PFS for venG compared to ven mono; median PFS not reached (NR) vs 58.9 mo ($p = 0.08$; HR 0.4385; 95% CI 0.1608 - 1.0240). Similarly, there was also a trend to improved PFS for ven + BTKi compared to ven mono; median PFS NR vs 58.9 mo ($p = 0.07$; HR 0.2895; 95% CI 0.0462 - 0.9950). Both the presence of del17p/TP53 mutation; and the presence of MRD (+MRD) 12 months after stopping ven based tx were associated with inferior PFS. The median PFS for pts without del17p/TP53 mutation vs with del17p/TP53 mutation was 118 vs 39.7 mo ($p < 0.0001$; HR 0.2242; 95% CI 0.0533 - 0.8366). Median PFS for pts with uMRD vs +MRD 12 months after ven was NR vs 42.8 mo ($p = 0.0001$; HR 0.0689; 95% CI 0.0037 - 0.3810).

Conclusions **:** In a high-risk population of pts with R/R CLL, we found that ven based tx leads to durable remissions, with high rates of uMRD. Combo approaches with the addition of either an anti-CD20mab or BTKi led to improved PFS. While venR is the current FDA approved combo regimen for pts with R/R CLL, we found that there was a trend for improved PFS with either venG or ven + BTKi compared to ven mono. Both the presence of a del17p/TP53 mutation and the presence of MRD 12 months after stopping ven based tx significantly adversely affected PFS. However, pts who maintained uMRD 12 months after

completing ven, had exceptionally durable long-term remission. This has possible implications for employing MRD adapted txs for pts with CLL.

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Figure 1

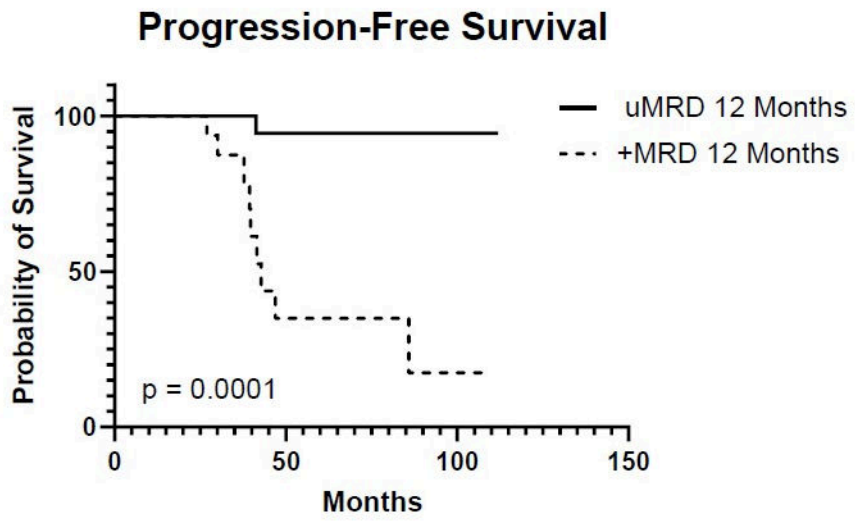

Table 1

Treatment	Median PFS (months)	p value	Hazard Ratio (95% CI)
Ven Combo vs Ven Mono	76.6 vs 56.9	0.04	0.5037 (0.2583 - 0.9635)
VenR vs Ven Mono	67.8 vs 56.9	0.19	0.7154 (0.2969 - 1.5600)
VenG vs Ven Mono	NR vs 56.9	0.08	0.4385 (0.1608 - 1.0240)
Ven + BTKi vs Ven Mono	NR vs 56.9	0.07	0.2895 (0.0462 - 0.9950)
No del17p/TP53 mutation vs del17p/TP53 Mutation	118 vs 39.7	<0.0001	0.2242 (0.0533 - 0.8366)
uMRD vs +MRD 12 months post ven	NR vs 42.8	0.0001	0.0689 (0.0037 - 0.3810)

Figure 1

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