Abstract: S201

Title: FINAL 7-YEAR FOLLOW UP AND RETREATMENT SUBSTUDY ANALYSIS OF MURANO: VENETOCLAX-RITUXIMAB (VENR)-TREATED PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (R/R CLL)

Abstract Type: Oral Presentation

Session Title: MM and CLL final analyses/long term follow up of clinical trials

Background:

The Phase 3 MURANO trial (NCT02005471) reported superior progression-free survival (PFS) and overall survival (OS) with fixed-duration VenR vs bendamustine (B)R in patients (pts) with R/R CLL. At the 5-year update, the median (m)PFS was 53.6 vs 17.0 months ($P<0.0001$), and 5-year OS rates were 82.1% vs 62.2% ($P<0.0001$) in pts treated with VenR vs BR, respectively (Seymour et al. Blood 2022).

Aims:

We report the final analyses of MURANO, with 7 years median follow-up (FU): specifically, updated PFS and OS, with minimal residual disease (MRD) evaluation, in pts treated in the main study, as well as in VenR-retreated pts in the substudy.

Methods:

Pts with R/R CLL were randomized to VenR (Ven 400mg daily for 2 years + monthly R for the first 6 months) or BR (6 months). In the substudy (2018 onwards), pts with progressive disease (PD) received VenR (same schedule as main study) as either re-treatment or as crossover from BR. PFS data are by investigator assessment. Peripheral blood MRD was measured centrally by allele-specific oligonucleotide-PCR and/or flow cytometry, with a $<10^{-4}$ threshold for undetectable (u)MRD.

Results:

Baseline characteristics are presented in the Table. At final data cutoff (3 August 2022), VenR-treated pts (n=194) had a mPFS (95% confidence interval [CI]) of 54.7 months (52.3, 59.9) vs 17.0 months (15.5, 21.7) for BR-treated pts (n=195; hazard ratio [HR] 0.25). Seven-year PFS rates (95% CI) were 23.0% (16.1, 29.9) with VenR, while no pts treated with BR remained progression-free at this time point; 7-year OS rates (95% CI) were 69.6% (62.8, 76.5) with VenR and 51.0% (43.3, 58.7) with BR (HR 0.53). Median time to next treatment with VenR was 63.0 months vs 24.0 months with BR (HR 0.30); 37.1% of VenR-treated pts have not received subsequent anti-CLL treatment.

Among VenR-treated pts who had uMRD at end of treatment (EOT) without PD (n=83/118; 70.3%), mPFS (95% CI) from EOT was 52.5 months (44.5, 61.5) vs 18.0 months (8.5, 29.3; p<0.0001) in pts who were MRD+ at EOT (n=35; 29.7%). Fourteen (16.9%) pts had no PD nor confirmed MRD conversion at the 7-year update; in the 63 (75.9%) pts who had MRD conversion, median time to conversion (95% CI) was 19.4 months (8.7, 28.0). Among 63 pts who converted, 39 subsequently had PD or died; median time from conversion to PD (95% CI) was 28.3 months (23.2, 35.0).

In the substudy (n=34), 25 pts received VenR re-treatment (Table), 92.0% of whom had at least one of the following high-risk features: *IGHV*-unmutated disease, genomic complexity, or del(17p) and/or *TP53* mutations (Wu et al. EHA 2021); despite this, 14/25 (56.0%) achieved uMRD at EOT in the main study. Best overall response rate (ORR) to re-treatment was 72.0% and mPFS (95% CI) was 23.3 months (15.6, 24.3). Median (range) time between the last Ven dose in the main study and Ven ramp-up in the substudy was 2.3 (1.2–3.1) years. Eight (32.0%) pts achieved uMRD at the re-treatment end of combination treatment; however, no pts retained their uMRD status at the re-treatment EOT.

No new safety findings were observed since the 5-year data cut.

Summary/Conclusion:

In this final long-term analysis of the MURANO trial, PFS and OS benefits for VenR over BR were sustained. Furthermore, achievement of uMRD was associated with prolonged PFS. In VenR-treated pts in the substudy, ORR was high and uMRD was still attainable in this high-risk population. Overall, these data continue to support the use of fixed-duration VenR in R/R CLL, and suggest that re-treatment with VenR is a viable option for pre-treated pts.

Table. Baseline characteristics and efficacy of pts in the main study and the substudy

	Main study		Substudy
	Pts treated with VenR (n=194)	**Pts treated with BR (n=195)**	**Pts retreated with VenR (n=25)**
Baseline characteristics			
Mean age, years (SD)	63.9 (10.5)	64.4 (9.6)	65.8 (8.3)
Number of prior cancer therapy, n (%)			
1	111 (57.2)	117 (60.0)	0 (0.0)
2	58 (29.9)	43 (22.1)	20 (80.0)
≥3	25 (12.9)	35 (17.9)	5 (20.0)
del(17p) and/or TP53 mutation (aCGH), n (%)			
mutated	53 (27.3)	55 (28.2)	14 (56.0)
unmutated	104 (53.6)	98 (50.3)	9 (36.0)
unknown	37 (19.1)	42 (21.5)	2 (8.0)
GC, n (%)	n=48	n=46	n=20
3–4	34 (70.8)	29 (63.0)	3 (15.0)
≥5	14 (29.2)	17 (37.0)	8 (40.0)
IGHV, n (%)	n=180	n=180	n=23
mutated	53 (29.4)	51 (28.3)	2 (8.7)
unmutated	123 (68.3)	123 (68.3)	21 (91.3)
unknown	4 (2.2)	6 (3.3)	0 (0.0)
Efficacy results			
Median follow-up, months	85.7	85.7	33.4
Best ORR, %	93.3	67.7	72.0
uMRD at EOCT of main study, n (%)	121 (62.4)	26 (13.3)	16 (64.0)
uMRD at EOCT of substudy, n (%)	N/A	N/A	8 (32.0)
uMRD at EOT of main study, n (%)	83 (70.3)*	N/A	14 (56.0)
uMRD at EOT of substudy, n (%)	N/A	N/A	0 (0.0)
Median PFS, months (95% CI)	54.7 (52.3, 59.9)	17.0 (15.5, 21.7)	23.3 (15.6, 24.3)
3-year OS rate, % (95% CI)	88.4 (83.8, 93.0)	78.9 (72.8, 84.9)	53.1 (25.1, 81.0)

* Pts who completed 2 years of ven without PD (n=118)

aCGH, array comparative genomic hybridization; BR, bendamustine-rituximab; CI, confidence interval; del(17p), deletion in chromosome 17p; EOCT, end of combination treatment; EOT, end of treatment; GC, genomic complexity; *IGHV*, immunoglobulin heavy chain gene; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; pts, patients; SD, standard deviation; *TP53*, tumor protein P53; uMRD, undetectable minimal residual disease; Ven(R), venetoclax-(rituximab)

Keywords: Retreatment, Chronic lymphocytic leukemia, Minimal residual disease (MRD), Venetoclax