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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

The Impact of Fitness and Dose Intensity on Safety and Efficacy Outcomes after Venetoclax-Obinutuzumab in Previously Untreated Chronic Lymphocytic Leukemia

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Introduction
Following the results of two phase-III studies, the CLL14 study, recruiting elderly and unfit patients (pts) with chronic lymphocytic leukemia (CLL), and the CLL13 study, recruiting younger and fit pts, venetoclax-obinutuzumab (Ven-Obi) is a standard of care for pts with treatment-naive CLL. However, it is unclear whether age and/or fitness have an impact on the tolerability and efficacy of Ven-Obi. Furthermore, the impact of dose reductions on response and survival has not been explored yet. Here, we present a pooled analysis detailing the toxicity and efficacy of Ven-Obi in pts treated within the CLL13 and CLL14 studies.

Methods
Patients randomized to the Ven-Obi arm in CLL14 (2015-2016) and CLL13 (2016-2019) with at least one dose of study drug were considered and categorized as fit or unfit pts (cumulative illness rating scale [CIRS] > 6 and/or creatinine clearance < 70 ml/min). Patients with *TP53* aberrations were excluded to ensure balanced features across the CLL13 and CLL14 populations. Correlations regarding minimal residual disease (MRD) in peripheral blood and response (both assessed at the end of treatment [EOT]) were assessed by chi² test. Progression-free survival (PFS) and overall survival (OS) were analyzed by Kaplan-Meier methodology and Cox proportional hazard regression modeling. Dose intensity was calculated as the relative fraction within the administered treatment cycles (excluding pts with treatment discontinuation due to PD/death). Adverse events were analyzed up to 28 days after EOT.

Results
In total, 410 pts were considered for this analysis, 228 from CLL13 and 182 from CLL14. The median observation time was 49 months (interquartile range [IQR] 37.0-65.8 months); for CLL13, median observation time was 38.9 months (IQR 33.8-46.3), and 66.7 months in CLL14 (IQR 64.4-70.8). Median age at enrollment was 67 years (IQR 58-73); 55.7% were grouped as unfit (median age 72), 44.3% as fit (median age 58) (**A**).
Overall response rate (ORR) was 89.5% in unfit and 96.1% in fit pts (p=0.011), CR rates were 51.8% and 54.1% (p=0.63), respectively. The undetectable MRD ($<10^{-4}$) rates were 80.3% in unfit and 85.1% in fit pts (p=0.2). The 3-year-PFS rates were 86.4% in unfit vs 87.5% in fit pts (HR 1.12, 95%-CI 0.70-1.81, p=0.63, **B**). The 3-year-OS was 91.8% in unfit vs 96.9% in fit pts (HR 2.02, 95% CI 0.90-4.55, p=0.088).
Adverse events (any grade) considered of interest included neutropenia, which occurred in 62.7% of unfit and 56.9% of fit pts (febrile neutropenia 4.4% in each group), respectively. Infusion-related-reactions (IRR) occurred in 44.3% of unfit and 56.9% of fit pts. Fatigue was reported in 15.8% of unfit and 35.9% of fit pts; headaches in 9.2% of unfit and 18.2% of fit pts. Infections occurred in 57.5% of unfit and 69.6% of fit pts; in particular, nasopharyngitis was reported for 10.5% of unfit and 24.3% of fit pts. Covid-19 occurred in 3 unfit (3 fatal) and 5 fit (2 fatal) pts. Other common adverse events were balanced between fit and unfit pts. Comparable patterns were also observed when comparing young vs older pts according to exploratory age cut-offs between 65 to 80 years.
Early venetoclax discontinuations for reasons other than PD or death (e.g., adverse events, withdrawal) were more common in unfit than in fit pts (15.8% vs 5.0%). Median time to early discontinuation was 6.3 months (3.1-8.7). Patients with early venetoclax discontinuation had a 3-year-PFS from EOT of 71.2%, compared with 83.0% in pts who completed venetoclax as planned (HR 2.25, 95%-CI 1.32-3.83, p=0.003). The 3-year-OS from the EOT was 84.3% and 94.0% (HR 2.48, 95%-CI 1.10-5.59, p=0.029), respectively.
Dose reductions <80% (excluding PD/death) occurred in 15.7% of all pts (14.7% unfit, 16.5% fit). ORR in pts with venetoclax dose intensity <80% was 82.5% and 95.9% in pts with dose intensity ≥80% (p<0.001). CR rates were 42.9% and 55.5% (p=0.066), uMRD rates were 76.2% and 85.3% (p=0.073). The 3-year-PFS from the EOT for pts with and without venetoclax dose intensity <80% was 81.0 % and 82.2%, respectively (HR 1.47, 95%-CI 0.84-2.57, p=0.175).

Conclusion
This analysis confirms the feasibility and efficacy of Ven-Obi for both fit and unfit pts with CLL. The incidence of toxicities was comparable between both patient groups, although IRR and fatigue were more common in fit pts. Reduced venetoclax dose intensity had no impact on PFS, suggesting that dose modifications may have limited impact on long-term clinical outcomes.

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A

Characteristic	Unfit		Fit		Total	
	N	%	N	%	N	%
Age (years)	**228**		**181**		**409**	
Median	72		58		67	
Sex, N (%)	**228**		**181**		**409**	
Female	92	40.4	31	17.1	123	30.1
Male	136	59.6	150	82.9	286	69.9
Total CIRS score	**228**		**181**		**409**	
Median	8.0		2.0		5.0	
Binet stage, N (%)	**228**		**181**		**409**	
A	56	24.6	43	23.8	99	24.2
B	80	35.1	74	40.9	154	37.7
C	92	40.4	64	35.4	156	38.1
Chromosomal aberration, N (%)	**228**		**181**		**409**	
del(17p)	0	0	0	0	0	0
del(11q)	37	16.2	39	21.5	76	18.6
Trisomy 12	48	21.1	34	18.8	82	20.0
No del(17p)/ del(11q)/ trisomy12/ del(13q)	53	23.2	37	20.4	90	22.0
del(13q) alone	90	39.5	71	39.2	161	39.4
IGHV mutational status, N (%)	**217**		**172**		**389**	
Unmutated	122	56.2	108	62.8	230	59.1
Mutated	95	43.8	64	37.2	159	40.9
Serum β2-microglobulin (mg/L)	**219**		**179**		**398**	
Median	4.1		3.9		3.9	

B

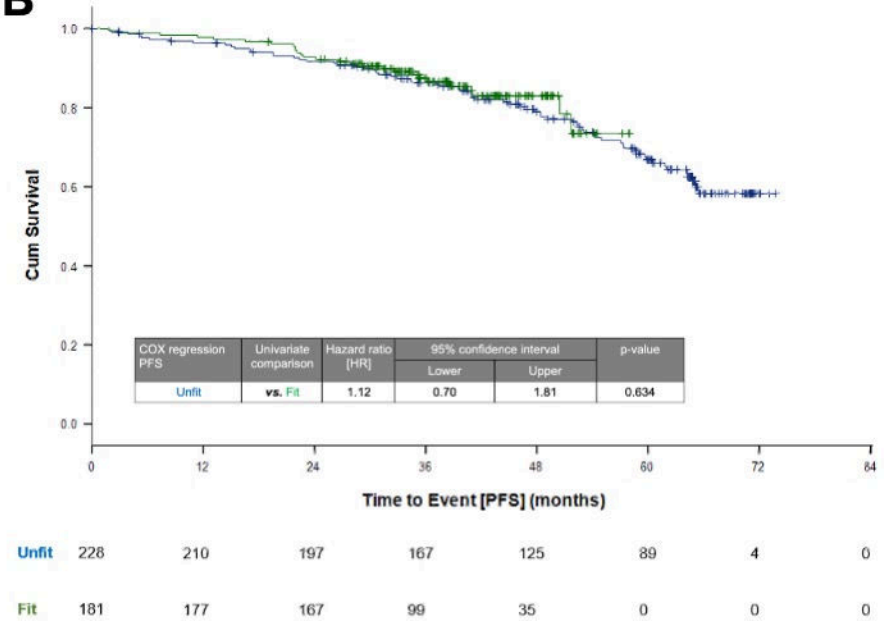

Figure 1