Title

Relapse after First-Line Fixed Duration Ibrutinib + Venetoclax: High Response Rates to Ibrutinib Retreatment and Absence of BTK Mutations in Patients with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) with up to 5 Years of Follo...

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ORAL ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Relapse after First-Line Fixed Duration Ibrutinib + Venetoclax: High Response Rates to Ibrutinib Retreatment and Absence of BTK Mutations in Patients with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) with up to 5 Years of Follow-up in the Phase 2 Captivate Study

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Background:CAPTIVATE (PCYC-1142) is a multicenter phase 2 study of ibrutinib + venetoclax as first-line treatment for CLL/SLL in 2 cohorts: minimal residual disease (MRD)-guided randomized-discontinuation (MRD cohort) and Fixed Duration (FD cohort). Results from the FD cohort with 4 years of follow-up (Barr, ASCO 2023) showed 4-year progression-free survival (PFS) and overall survival (OS) rates of 79% and 98%, respectively. After completing fixed-duration treatment, ibrutinib-based retreatment was allowed per protocol in patients with an indication for treatment after experiencing progressive disease (PD). Here, we report retreatment outcomes in patients from the FD cohort or the MRD cohort placebo arm, as well as updated results with an additional year of follow-up (up to 5 years) from the FD cohort.

Methods: Patients aged ≤70 years with previously untreated CLL/SLL received 3 cycles of ibrutinib, then 12 cycles of combined ibrutinib + venetoclax (ibrutinib, 420 mg/day orally; venetoclax, standard 5-week ramp up to 400 mg/day orally). Response was assessed by investigators per International Workshop on CLL (iwCLL) 2008 criteria. Duration of response (DOR), PFS, and OS were estimated using Kaplan-Meier methodology. Per protocol, on-study retreatment included single-agent ibrutinib; patients with PD >2 years after treatment completion could be retreated with the FD regimen (3 cycles of ibrutinib + 12 cycles of ibrutinib + venetoclax).

Results: Of 202 patients treated with fixed-duration ibrutinib + venetoclax in the FD cohort (n=159) or the MRD cohort placebo arm (n=43), 53 have had PD to date (Table 1), with PD occurring >2 years after completion of treatment in the majority of patients (33/53 [62%]). Of the 40 patients with available samples at PD, one had an acquired resistance-associated mutation in *BCL2* (A113G); no other patient had clinically relevant mutations in *BTK, BCL2*, or *PLCG2*. A total of 22 patients have initiated retreatment on study with single-agent ibrutinib. With a median time on retreatment of 17 months (range, 0-45), overall response rate (ORR) in 21 evaluable patients was 86% (with best responses of complete response [CR], n=1 [5%]; partial response [PR], n=17 [81%]; PR with lymphocytosis, n=1 [5%]; stable disease, n=1 [5%]; PD [Richter transformation], n=1 [5%]). The most frequent adverse events (AEs; occurrence ≥10%) during single-agent ibrutinib retreatment were COVID-19 (n=6, all grade 1/2), diarrhea (n=5), hypertension (n=4), and pyrexia (n=3). No dose reductions or discontinuations due to AEs occurred among retreated patients. Eighteen patients have not received subsequent treatment, 7 patients have initiated other subsequent therapies, and 6 patients have started retreatment with ibrutinib + venetoclax (time on retreatment, 5-15 months). Best responses in patients retreated with ibrutinib + venetoclax are CR, n=2; PR, n=3; and SD, n=1. Response data for the patient with *BCL2* (A113G) is pending.

To date, with a median time on study of 56 months (range, 1-61) for patients in the FD cohort, the 54-month PFS and OS rates were 70% (95% CI, 62-77) and 97% (95% CI, 93-99), respectively. Best response rates remained unchanged from the

4-year follow-up analysis (CR, including CR with incomplete bone marrow recovery [CRi], 58%; ORR, 96%). In patients who achieved CR/CRi (n=92), median duration of CR/CRi was not reached; 90/92 patients (98%) achieved durable CR/CRi (lasting ≥12 cycles). PFS in patients with high-risk features was promising (Table 2), but it was numerically lower in the subset with del(17p)/mutated *TP53* (54-month rate, 45% [95% CI, 25-64]). Serious AEs considered related to study treatment and second malignancies continued to be collected after completion of fixed-duration treatment. One AE of basal cell carcinoma occurred during this additional year of follow-up. In total, second malignancies have occurred in 8% of patients since completion of ibrutinib + venetoclax treatment.

Conclusion: Ibrutinib-based retreatment results in the CAPTIVATE study show promising responses in patients needing subsequent therapy after receiving this all-oral, once-daily fixed-duration regimen for first-line treatment of CLL/SLL. With up to 5 years of follow-up, fixed-duration ibrutinib + venetoclax continues to provide deep remissions with clinically meaningful PFS, including in patients with high-risk genomic features.

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Table 1. Baseline Characteristics of Patients With PD After Fixed-Duration Ibrutinib + Venetoclax

	Patients With PD (n=53)	Patients With PD Who Have Received Ibrutinib-Based Retreatment[a] (n=28)
Median age (range), years	60 (38–71)	62 (39–71)
Male, n (%)	37 (70)	19 (68)
Rai stage III/IV, n (%)	10 (19)	5 (18)
High-risk genomic features, n (%)		
Unmutated IGHV	41 (77)	22 (79)
del(17p)/mutated *TP53*	12 (23)	9 (32)
Complex karyotype[b]	12 (23)	10 (36)
del(11q)	14 (26)	7 (25)
Any cytopenia, n (%)	14 (26)	9 (32)
ANC ≤1.5 x 10^9/L	2 (4)	0
Hemoglobin ≤11 g/dL	11 (21)	7 (25)
Platelet count ≤100 × 10^9/L	4 (8)	2 (7)
Lymph node diameter ≥5 cm, n (%)	19 (36)	9 (32)
Median ALC × 10^9/L (range)	70 (1–368)	74 (1–297)
ALC ≥25 × 10^9/L, n (%)	41 (77)	22 (79)

[a]Single-agent ibrutinib (n=22) or fixed-duration ibrutinib + venetoclax (n=6).
[b]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.

Table 2. FD Cohort: PFS in Patients With High-Risk Features

	54-Month PFS Rate, % (95% CI)
All patients (n=159)	70 (62–77)
del(17p)/mutated *TP53* (n=27)	45 (25–64)
Complex karyotype (n=31)[a]	60 (41–79)
Unmutated IGHV (n=40)[b]	68 (50–80)
del(11q) (n=11)[b]	64 (30–85)

[a]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.
[b]Excluding patients with del(17p)/mutated *TP53* or complex karyotype.

Figure 1

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