### Title

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# Outcomes in high-risk subgroups after fixed-duration ibrutinib + venetoclax for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Up to 5.5 years of follow-up in the phase 2 CAPTIVATE study.

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**Background:** The phase 2 CAPTIVATE study evaluated first-line ibrutinib (Ibr) + venetoclax (Ven) for CLL/SLL in 2 cohorts: minimal residual disease (MRD)-guided randomized discontinuation (MRD cohort) and Fixed Duration (FD cohort). Ibr±Ven retreatment was allowed in patients (pts) who had progressive disease (PD). Here, we report outcomes for pts with high-risk genomic features from the FD cohort and retreatment outcomes in pts from the FD cohort and MRD cohort placebo arm. **Methods:** Pts aged ≤70 y with previously untreated CLL/SLL without restriction on genomic risk factors received 3 cycles of Ibr, then 12 cycles of Ibr+Ven (Ibr, 420 mg/d orally; Ven, 5-wk ramp up to 400 mg/d orally). On-study retreatment included single-agent Ibr (FD cohort or MRD cohort placebo arm); pts with PD >2 y after end of treatment (EOT) could be retreated with FD Ibr+Ven (FD cohort). **Results:** In the FD cohort (n=159) with a median follow-up of 61.2 mo (range, 0.8–66.3), 5-y PFS and OS rates (95% CI) were 67% (59–74) and 96% (91–98), respectively. 5-y PFS rates were higher in pts with undetectable MRD at 3 mo after EOT in peripheral blood (83%) or bone marrow (84%) vs those without (48% and 50%, respectively). 5-y PFS rates (95% CI) in pts with genomic risk factors were: del(17p)/mutated *TP53* 41% (21–59), complex karyotype 57% (37–72), del(11q) 64% (30–85), and unmutated IGHV 68% (50–80) (Table). In total, 18 second malignancies occurred in 13 pts (10 events in 8 pts during FD Ibr+Ven, 6 events in 4 pts after EOT and before retreatment, and 2 events in 2 pts during retreatment). Of 202 pts who completed Ibr+Ven (FD cohort, n=159; MRD cohort placebo arm, n=43), 63 have had PD to date; PD occurred >2 y after EOT in 43/63 pts (68%). 32/63 (51%) pts initiated retreatment with Ibr (n=25) or Ibr+Ven (n=7). With a median time on Ibr retreatment of 21.9 mo (range, 0.03–50.4), ORR was 86% in 22 evaluable pts (best response: 1 CR; 1 nodular PR; 17 PR; 2 SD; 1 PD [Richter transformation]). With a median time on Ibr+Ven retreatment of 13.8 mo (range, 3.7–15.1), ORR was 71% in 7 evaluable pts (best response: 1 CR; 4 PR; 1 PR with lymphocytosis; 1 SD). **Conclusions:** With up to 5.5 y of follow-up, FD Ibr+Ven continues to provide clinically meaningful PFS in pts with high-risk genomic features, as well as in the overall population. Ibr-based retreatment provides promising responses in pts needing subsequent therapy after the all-oral FD regimen of Ibr+Ven. Clinical trial information: NCT02910583. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

| FD cohort | With high-risk genomic feature[a] | | Without high-risk genomic feature[a] | |
|---|---|---|---|---|
| | n | 5-y PFS rate, % (95% CI) | n | 5-y PFS rate, % (95% CI) |
| del(17p)/mutated *TP53* | 27 | 41 (21–59) | 129 | 73 (64–80) |
| CK[b] | 31 | 57 (37–72) | 102 | 72 (61–80) |
| Unmutated IGHV[c] | 40 | 68 (50–80) | 44 | 85 (69–93) |
| del(11q)[c] | 11 | 64 (30–85) | 74 | 79 (67–87) |

[a]Among pts with known baseline status. [b]Defined as ≥3 chromosomal abnormalities. [c]Excluding pts with del(17p)/mutated *TP53* or CK.