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Final Analysis of Fixed-Duration Ibrutinib + Venetoclax for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma in the Phase 2 CAPTIVATE Study

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OBJECTIVE

To report final analysis results for patients treated with fixed-duration (FD) ibrutinib + venetoclax in the phase 2 CAPTIVATE study

CONCLUSIONS

Ibrutinib + venetoclax is an all-oral, once-daily, chemotherapy-free FD regimen for first-line treatment of chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL)

With long-term follow-up, durable progression-free survival (PFS) and overall survival is observed with ibrutinib + venetoclax treatment, including in patients with high-risk genomic features

Undetectable minimal residual disease at end of treatment is strongly associated with long-term PFS overall irrespective of high-risk genomic features

Ibrutinib-based retreatment provides durable responses in patients needing subsequent therapy after completion of FD ibrutinib + venetoclax

Together with the GLOW study, CAPTIVATE led to the availability of the ibrutinib + venetoclax FD regimen across 78 countries. We thank the patients whose participation made this possible

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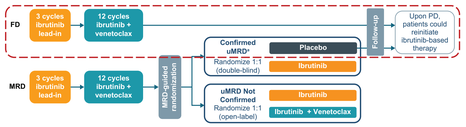
INTRODUCTION

- First-line, all-oral, once-daily ibrutinib + venetoclax for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) was investigated in 2 cohorts of the phase 2 CAPTIVATE study: minimal residual disease (MRD)–guided randomized discontinuation (MRD cohort) and Fixed Duration (FD cohort)[1,2]
- At the previous analysis with up to 5.5 years of follow-up, FD treatment with ibrutinib + venetoclax demonstrated sustained progression-free survival (PFS), including in patients with high-risk genomic features[3]
- Here, we report final analysis results for patients treated with FD ibrutinib + venetoclax in the FD cohort and in the MRD cohort placebo arm with up to 7 years of follow-up (median 5.75 years)

METHODS

- Patients aged ≤70 years with previously untreated CLL/SLL received 3 cycles of ibrutinib, then 12 cycles of ibrutinib + venetoclax (ibrutinib, 420 mg/day orally; venetoclax, 5-week ramp up to 400 mg/day orally)
  - Patients in the FD cohort received no further treatment (n=159)
  - Patients in the MRD cohort placebo arm with confirmed undetectable MRD (uMRD4, undetectable minimal residual disease [<10^{-4}]; n=43) received 1 additional cycle of ibrutinib + venetoclax during the MRD-guided randomization, then placebo treatment
- Analyses were performed to evaluate efficacy and safety in the pooled population of the FD cohort and MRD cohort placebo arms, as well as PFS in patient subgroups according to the presence or absence of high-risk genomic features at baseline
- Post hoc exploratory analyses of the FD cohort (n=159) were performed to evaluate PFS in patient subgroups based on MRD4 status at Cycle 7 (C7, after 3 cycles of ibrutinib and 3 cycles of ibrutinib + venetoclax) and at end of treatment (EOT; 3 cycles after the 15-cycle FD ibrutinib + venetoclax treatment [ie, day 1 of C19 for the FD cohort])
- In patients with confirmed progressive disease (PD), on-study retreatment included single-agent ibrutinib
  - FD cohort patients with PD occurring >2 years after EOT could be retreated with FD ibrutinib + venetoclax
- Serious adverse events (AEs) considered related to study treatment and second malignancies continued to be collected after completion of the FD treatment-emergent period (up to 30 days after last dose of study treatment or start of subsequent therapy, whichever occurred first)

CAPTIVATE Study Design



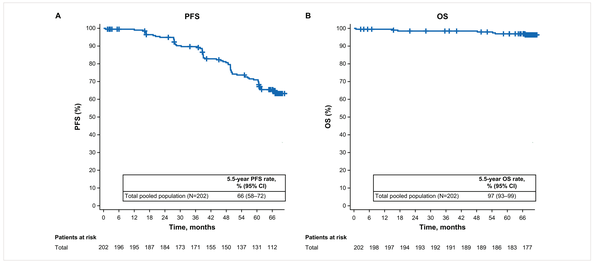
[a]Patients with confirmed uMRD4 (defined as uMRD <10^{-4} by 8-color flow cytometry serially over ≥3 cycles in both peripheral blood and bone marrow) after 12 cycles of ibrutinib + venetoclax were randomly assigned 1:1 to receive placebo or ibrutinib; the placebo arm was included in the current analysis.

RESULTS

- In total, 202 patients completed FD ibrutinib + venetoclax (FD cohort, n=159; MRD cohort placebo arm, n=43)
  - In the total pooled population (median age, 60.0 years [range, 33–71]), high-risk genomic features at baseline were unmutated IGHV (uIGHV) in 119 patients (59%), del(17p)/mutated *TP53* in 29 (14%), and complex karyotype (CK; ≥3 abnormalities) in 35 (17%) (**Supplement**)
- At this final analysis, median follow-up was 68.9 months (range, 0.8–83.9) in the total pooled population and 69.0 months (range, 0.8–73.2) in the FD cohort

PFS and OS Outcomes in the Total Pooled Population

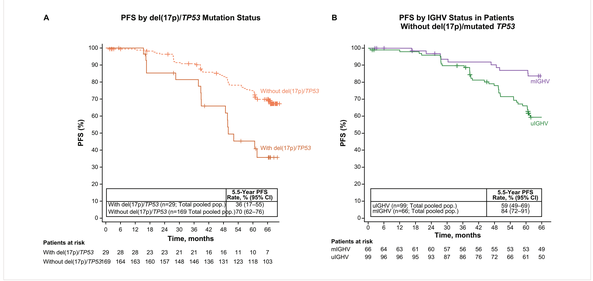
Overall Median PFS and OS Were Not Reached With Up to 7 Years of Follow-Up (Total Pooled Population)



OS, overall survival.

- Assessed in FD cohort patients only, 5.5-year PFS and OS rates were 60% (95% CI, 52–68) and 96% (95% CI, 91–98), respectively (**Supplement**)

Impact of del(17p)/mutated *TP53* and IGHV Status on Long-Term PFS (Total Pooled Population)

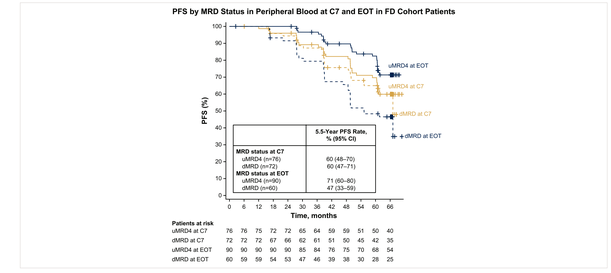


mIGHV, mutated IGHV.

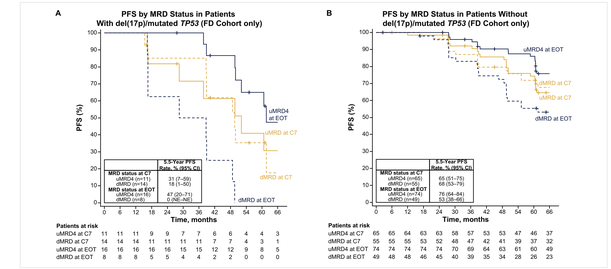
Correlation of MRD Status With PFS Outcomes in FD Cohort Patients

- Assessed in FD cohort patients only, uMRD4 rates in peripheral blood increased from 51% at C7 to 60% at EOT: uMRD4 rate in bone marrow was 60% at EOT
  - Increases in peripheral blood uMRD4 rates from C7 to EOT were particularly notable in patients with del(17p)/mutated *TP53* or CK5, and in patients with uIGHV to a lesser extent (**Supplement**)

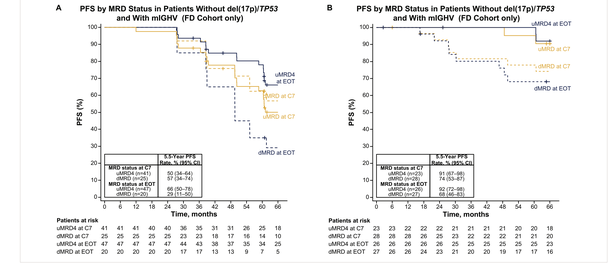
MRD Status in Peripheral Blood at EOT Is More Strongly Predictive for Long-Term PFS Than MRD Status at C7 (FD Cohort Patients)



MRD Status at EOT Is Predictive of Long-Term PFS Regardless of del(17p)/*TP53* Status (FD Cohort Patients)



MRD Status at EOT Is Predictive of Long-Term PFS Regardless of del(17p)/*TP53* Status (FD Cohort Patients)



No Resistance-Associated Mutations Were Identified at PD

- In the total pooled population (FD and MRD-placebo cohorts) with a median follow-up of more than 5.5 years, 64/202 patients (32%) had PD after FD ibrutinib + venetoclax treatment
- No patients had resistance-associated mutations in *BTK* or *PLCG2* at PD among 53 patients with available samples
  - 2 patients were found with subclonal *BCL2 A113G* mutations of unclear significance at PD: variant allele frequencies were only 8% and 9.3%, respectively
  - Patient 1: Achieved partial response with FD ibrutinib + venetoclax retreatment (complete response was not confirmed due to missing bone marrow assessment). In this patient the *BCL2 A113G* mutation variant allele frequency spontaneously decreased to 6.7% before retreatment and was not detectable at the time of eventual relapse after retreatment
  - Patient 2: Did not receive retreatment in the study

Ibrutinib-Based Retreatment

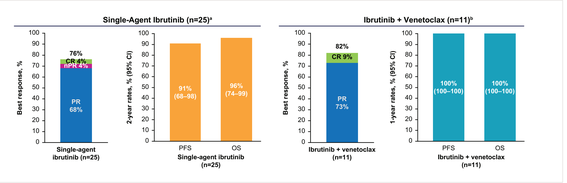
- 73% of patients remained free from next-line treatment at the 5.5-year landmark time point (95% CI, 66–79) (**Supplement**)
- In total, 36 patients (who met International Workshop on Chronic Lymphocytic Leukemia [iwCLL] criteria for treatment) initiated retreatment with either single-agent ibrutinib (n=25) or FD ibrutinib + venetoclax (n=11)
- At final analysis, median duration of follow-up was 28.4 months (range, 3.7–59.1) from the start of retreatment with single-agent ibrutinib and 15.2 months (range, 7.4–29.3) from the start of retreatment with FD ibrutinib + venetoclax, as expected due to the later eligibility to retreat with FD ibrutinib + venetoclax
  - Median duration of retreatment was 27.0 months (range, 1.1–59.1) with single-agent ibrutinib and 13.8 months (range, 6.7–18.3) with FD ibrutinib + venetoclax
- No new safety signals were observed during retreatment, relative to the safety profile of 1L treatment with single-agent ibrutinib or FD ibrutinib + venetoclax (**Supplement**)
- Across the entire study period, including any retreatment received on study, secondary malignancies occurred in 24 patients: non-melanoma skin cancers occurred in 16 patients, and other cancers occurred in 14 patients (**Supplement**)

Patients Who Initiated Ibrutinib-Based Retreatment: Study Baseline Characteristics

Characteristic	Single-agent ibrutinib n=25	FD ibrutinib + venetoclax n=11	All retreated patients n=36
Median age (range), years	56.0 (39–71)	63.0 (49–69)	58.5 (39–71)
Male, n (%)	16 (64)	8 (73)	24 (67)
Rai stage III/IV, n (%)	4 (16)	2 (18)	6 (17)
High-risk genomic features, n (%)			
uIGHV	20 (80)	8 (73)	28 (78)
del(17p)/TP53	4 (16)	6 (55)	10 (28)
del(11q)[a]	7 (28)	1 (9)	8 (22)
CK (≥3 abnormalities)[b]	8 (32)	3 (27)	11 (31)
CK (≥5 abnormalities)[b]	5 (20)	2 (18)	7 (19)
Bulky LN disease, n (%)			
≥5 cm	9 (36)	2 (18)	11 (31)
≥10 cm	1 (4)	1 (9)	2 (6)

LN, lymph node.
[a]Without del(17p) per Döhner hierarchy. [b]By conventional CpG-stimulated cytogenetics.

Ibrutinib-Based Retreatment Confers Promising Overall Response Rates, PFS, and OS in Patients Needing Subsequent Treatment



CR, complete response; nPR, nodular partial response; PR, partial response.
[a]Of the 6 nonresponders, 4 patients achieved stable disease with reintroduced treatment duration ranging from 6.2–19.4 months; 1 patient was discontinued after reassessment of the putative progressive lesion as not PD, and 1 patient was diagnosed with Richter transformation after 1.1 month on retreatment.
[b]Of the 2 nonresponders, both achieved stable disease with reintroduced treatment duration of 9.9 and 25.9 months, respectively.

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