CLL-057

Outcomes in High-Risk Subgroups After Fixed-Duration Ibrutinib + Venetoclax for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Up to 5.5 Years of Follow-Up in the Phase 2 CAPTIVATE Study

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OBJECTIVE

To report outcomes for patients with high-risk genomic features from the Fixed Duration (FD) cohort of the CAPTIVATE study and retreatment outcomes in patients from the FD cohort and minimal residual disease (MRD) cohort placebo arm

CONCLUSIONS

- Ibrutinib + venetoclax is an all-oral, once-daily, chemotherapy-free fixed-duration regimen for first-line treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma
- With up to 5.5 years of follow-up, median progression-free survival is still not reached with fixed-duration ibrutinib + venetoclax and correlates to achievement of undetectable MRD
- Patients with high-risk genomic features, including del(17p)/mutated *TP53*, complex karyotype, and unmutated IGHV, derive meaningful survival benefits from fixed-duration ibrutinib + venetoclax
- In patients relapsing after fixed-duration ibrutinib + venetoclax, retreatment with ibrutinib-based regimens yields durable responses with acceptable safety, even in patients with high-risk genomic features
- Based on the safety profiles of fixed-duration ibrutinib + venetoclax and ibrutinib-based retreatment, this treatment approach appears to have a positive benefit-risk profile

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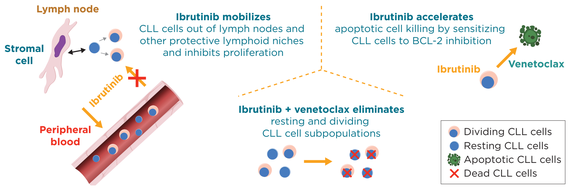
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INTRODUCTION

- Ibrutinib + venetoclax is approved for first-line treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in 78 countries across Asia, Europe, the Middle East, and South America, as well as Canada, Australia, and New Zealand

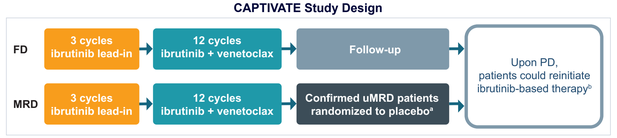
Ibrutinib and Venetoclax Work Synergistically Through Distinct and Complementary Modes of Action[1-3]



METHODS

- The phase 2 CAPTIVATE study (NCT02910583) evaluated first-line ibrutinib + venetoclax for CLL/SLL in 2 cohorts: minimal residual disease (MRD)-guided randomized discontinuation (MRD cohort) and Fixed Duration (FD cohort)
  - Patients aged ≤70 years with previously untreated CLL/SLL, without restriction on genomic risk features, 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)

CAPTIVATE Study Design



PD, progressive disease; uMRD, undetectable MRD.

[a]Patients with confirmed uMRD (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; only the placebo arm was included in the current analysis. [b]Patients with PD after completion of fixed-duration ibrutinib + venetoclax could reinitiate single-agent ibrutinib (FD cohort or MRD cohort placebo arm); patients with PD >2 years after treatment completion could reinitiate fixed-duration ibrutinib + venetoclax (FD cohort).

RESULTS

Outcomes for Patients With High-Risk Genomic Features From the FD Cohort

Baseline Characteristics of Patients in the FD Cohort

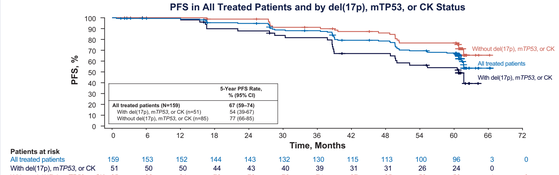
Characteristic	All Treated Patients N=159
Median age (range), years	60 (33–71)
Male, n (%)	106 (67)
Rai stage III/IV, n (%)	44 (28)
High-risk genomic features, n (%)	
ulGHV	89 (56)
del(17p)/mTP53	27 (17)
del(17p)[a]	20 (13)
del(11q)[b]	28 (18)
CK[c]	31 (23)
Any cytopenia, n (%)	54 (34)
ANC ≤1.5 × 109/L	13 (8)
Hemoglobin ≤11 g/dL	37 (23)
Platelet count ≤100 × 10^9/L	21 (13)
Bulky LN disease ≥5 cm, n (%)	48 (30)
Median ALC × 10^9/L (range)	70 (1–503)
ALC ≥25 × 10^9/L, n (%)	120 (75)

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CK, complex karyotype; LN, lymph node; mTP53, mutated *TP53*; ulGHV, unmutated IGHV.
[a]del(17p) status was missing for 3 patients. [b]Without del(17p) per Döhner hierarchy. [c]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics; CK status was missing for 26 patients.

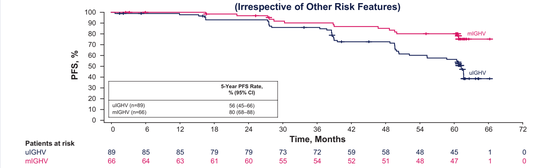
- At the time of analysis, median time on study was 61.2 months (range, 0.8–66.3)

Overall Median PFS in the FD Cohort Was Not Reached With Up to 5.5 Years of Follow-Up

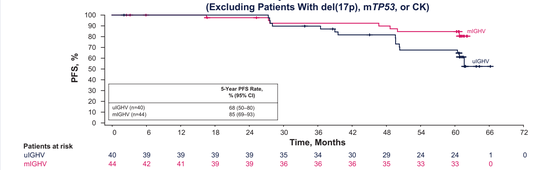
PFS in All Treated Patients and by del(17p), mTP53, or CK Status



PFS by IGHV Mutation Status (Irrespective of Other Risk Features)



PFS by IGHV Mutation Status (Excluding Patients With del(17p), mTP53, or CK)

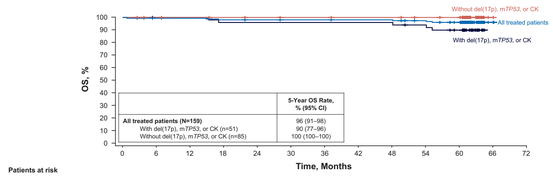


mIGHV, mutated IGHV; PFS, progression-free survival.

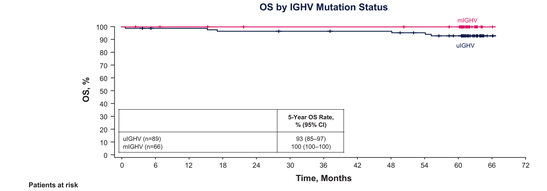
- 5-year PFS rates (95% CI) by individual high-risk genomic features were
  - With del(17p)/m*TP53* (n=27): 41% (21–59); without del(17p)/m*TP53* (n=129): 73% (64–80)
  - With CK (n=31): 57% (37–72); without CK (n=102): 72% (61–80)
  - With del(11q) (excluding patients with del(17p)/m*TP53* or CK; n=11): 64% (30–85); without del(11q) (n=74): 79% (67–87)
- High 5-year PFS rates were achieved in patients with unmutated IGHV in the FD cohort
  - Presence of del(17p), m*TP53*, and/or CK had a substantial impact on PFS in patients with uIGHV and mIGHV
- 5-Year PFS rates were improved in patients who achieved uMRD4 (<10^{-4} by 8-color flow cytometry) in peripheral blood (PB) or bone marrow (BM) in the FD cohort (**Supplementary Figure 1**)
  - In high-risk genomic subgroups with del(17p)/m*TP53*, CK, or uIGHV, 5-year PFS rates were also consistently higher in patients with uMRD4 in PB or BM at 3 months after end of treatment (EOT) than in those without uMRD4 (**Supplementary Table 1**)

5-Year OS Rates Were ≥90% Regardless of Genomic Risk Features in the FD Cohort

OS in All Treated Patients and by del(17p), mTP53, or CK Status



OS by IGHV Mutation Status



OS, overall survival.

- 5-year OS rates were ≥95% regardless of MRD status in PB or BM at 3 months after EOT or in PB at 12 months after EOT

Safety in the FD Cohort

- Serious adverse events (AEs) considered related to study treatment and second malignancies continued to be collected after completion of fixed-duration treatment
- No new related serious AEs were reported since the previous analysis[4]
- In total, 18 second malignancies occurred in 13 patients
  - 10 events in 8 patients during the treatment-emergent adverse event (TEAE) period (up to 30 days after last dose of study treatment or start of subsequent therapy, whichever occurred first) for fixed-duration ibrutinib + venetoclax
  - 6 events in 4 patients after the TEAE period and before retreatment
  - 2 events in 2 patients during the TEAE period for ibrutinib-based retreatment

PD and Richter Transformation in the FD Cohort and MRD Cohort Placebo Arm

- In total, 202 patients completed fixed-duration ibrutinib + venetoclax (FD cohort, N=159; MRD cohort placebo arm, n=43)
  - Only 63 patients have had PD to date
  - 61 patients had CLL PD, including 2 patients who subsequently experienced Richter transformation (RT) during retreatment
  - 2 patients had RT
  - PD occurred >2 years after EOT in most patients (43/63; 68%)
- In the 4 patients with RT, time from first dose to RT was
  - Patient 1: 12.7 months (0.2 months before EOT)
  - Patient 2: 28.1 months (14.3 months after EOT)
  - Patient 3: 50.9 months (after 1.0 months of single-agent ibrutinib retreatment)
  - Patient 4: 55.3 months (after 27 months of single-agent ibrutinib retreatment)

Study Entry Baseline Characteristics: Patients With RT

Characteristic	Patient 1 (DLBCL)	Patient 2 (HD)	Patient 3 (DLBCL)	Patient 4 (DLBCL)
Age, years	68	58	48	55
Sex	Male	Male	Male	Female
Rai stage	I	II	IV	I
Time from CLL diagnosis to study enrollment, months	46.5	13.3	6.3	9.4
Bulky LN disease ≥5 cm	Y	Y	N	N
High-risk genomic features				
ulGHV	Y	Y	Y	Y
del(17p)/mTP53	N	N	Y	N
del(11q)[a]	N	Y	N	N
CK[b]	Y	N	Y	Y

DLBCL, diffuse large B-cell lymphoma; HD, Hodgkin disease.
[a]Without del(17p) per Döhner hierarchy. [b]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.

Retreatment Outcomes in the FD Cohort and MRD Cohort Placebo Arm

- Of 61 patients with CLL PD after completion of fixed-duration ibrutinib + venetoclax, 32 (52%) initiated retreatment with single-agent ibrutinib (n=25) or ibrutinib + venetoclax (n=7)
- Median time on retreatment on study was 21.9 months (range, 0.0–50.4) for single-agent continuous ibrutinib and 13.8 months (range, 3.7–15.1) for 15-month fixed-duration ibrutinib + venetoclax

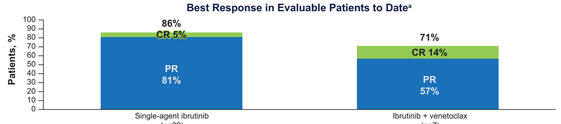
Study Entry Baseline Characteristics: Retreated Patients

Characteristic	Single-Agent Ibrutinib (n=25)	Ibrutinib + Venetoclax[a,b] (n=7)	All Retreated Patients (n=32)
Median age (range), years	56 (39–71)	63 (49–69)	59 (39–71)
Male, n (%)	15 (60)	6 (86)	21 (66)
Rai stage III/IV, n (%)	4 (16)	2 (29)	6 (19)
High-risk genomic features, n (%)			
ulGHV	20 (80)	5 (71)	25 (78)
del(17p)/mTP53	5 (20)	5 (71)	10 (31)
del(11q)[c]	6 (24)	1 (14)	7 (22)
CK[d]	9 (36)	2 (29)	11 (34)
Bulky LN disease ≥5 cm, n (%)	10 (40)	1 (14)	11 (34)

[a]Per protocol, only patients with PD >2 years after completion of treatment were eligible to reinitiate ibrutinib + venetoclax. [b]4 patients exited the study during ibrutinib + venetoclax retreatment and completed retreatment off study. [c]Without del(17p) per Döhner hierarchy. [d]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.

Promising Responses Were Observed With Ibrutinib-Based Retreatment in Evaluable Patients to Date[a]

Best Response in Evaluable Patients to Date[a]



CR, complete response; PR, partial response.
[a]3 patients who initiated single-agent ibrutinib retreatment had not yet undergone response assessment.

AEs With Ibrutinib-Based Retreatment Were Consistent With Known Safety Profiles for Single-Agent Ibrutinib and Ibrutinib + Venetoclax

Characteristic	Single-Agent Ibrutinib (n=25)	Ibrutinib + Venetoclax[a] (n=7)
Any AE	18 (72)	7 (100)
Most frequent AEs[a]		
COVID-19[b]	5 (20)	2 (29)
Diarrhea	5 (20)	3 (43)
Hypertension	4 (16)	4 (57)
Pyrexia	3 (12)	0
Upper respiratory tract infection	3 (12)	0
Nausea	1 (4)	2 (29)
Grade 3/4 AEs	6 (24)	2 (29)
Serious AEs	5 (20)	0
AEs leading to discontinuation	1 (4)	0
AEs leading to dose reduction	0	0

[a]Occurring in ≥10% of patients with single-agent ibrutinib or ≥2 patients with ibrutinib + venetoclax. [b]All events were grade 1/2.

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