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

Paolo Ghia, MD, PhD,[1,2] Paul M. Barr, MD,[3] John N. Allan, MD,[4] Tanya Siddiqi, MD,[5] Alessandra Tedeschi, MD,[6] Thomas J. Kipps, MD, PhD,[7] Susan M. O'Brien, MD,[8] Ryan Jacobs, MD,[9] Xavier C. Badoux, MBBS, FRACP, FRCPA,[10] Livio Trentin, MD,[11] Masa Lasica, MBBS, FRACP, FRCPA,[12] Dennis Carney, MBBS, FRACP, FRCPA,[13] Anna Elinder Camburn, MBChB, FRACP, FRCPA,[14] Javier De la Serna, MD,[15] Edith Szafer-Glusman, PhD,[16] Cathy Zhou, MS,[16] Jutta K. Neuenburg, MD, PhD,[16] James P. Dean, MD, PhD,[16] William G. Wierda, MD, PhD,[17] Constantine S. Tam, MBBS, MD[18]

[1]Università Vita-Salute San Raffaele, Milan, Italy; [2]IRCCS Ospedale San Raffaele, Milan, Italy; [3]Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA; [4]Weill Cornell Medicine, New York, NY, USA; [5]City of Hope National Medical Center, Duarte, CA, USA; [6]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [7]Moores Cancer Center, UC San Diego Health, La Jolla, CA, USA; [8]UCI Health, Chao Family Comprehensive Cancer Center, Orange, CA, USA; [9]Levine Cancer Institute, Charlotte, NC, USA; [10]Ministry of Health, Kogarah, NSW, Australia; [11]Univeristy of Padua, Padua, Italy; [12]St Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [13]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [14]North Shore Hospital, Auckland, New Zealand; [15]Hospital Universitario 12 de Octubre, Madrid, Spain; [16]AbbVie, North Chicago, IL, USA; [17]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [18]Alfred Hospital and Monash University, Melbourne, VIC, Australia

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 (OS) is observed with ibrutinib + venetoclax treatment, including in patients with high-risk genomic features

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

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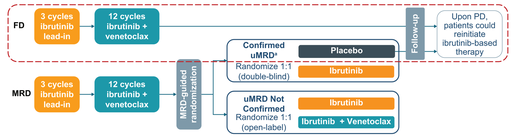
INTRODUCTION

- 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

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 FD cohort and MRD cohort placebo arm patients, 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; day 1 of C19 for the FD cohort and C16 for the MRD 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



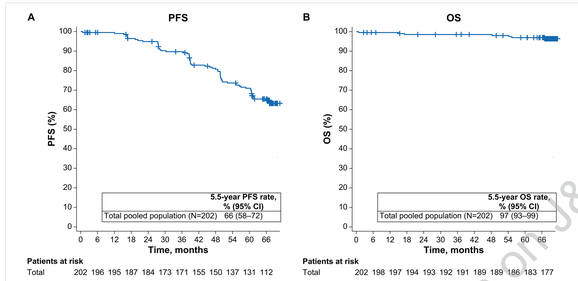
[a]Patients with confirmed uMRD4 (defined as uMRD $<10^{-4}$ by 8-color flow cytometry serially over ≥3 cycles in both peripheral blood and bone marrow) after 12 cycles of ibrutinib + venetoclax were randomly assigned 1:1 to receive placebo or ibrutinib; the placebo arm was included in the current analysis.

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)

PFS and OS Outcomes in the Total Pooled Population

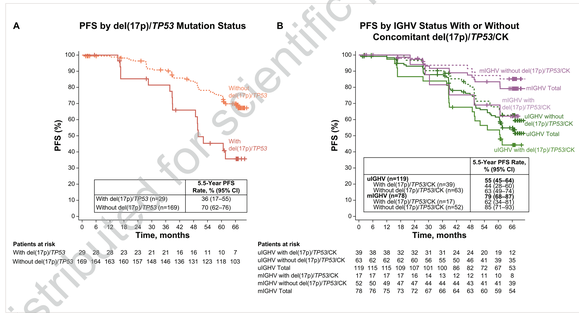
Overall Median PFS and OS Were Not Reached With Up to 7 Years of Follow-Up (Total Pooled Population)



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

Impact of del(17p), Mutated *TP53*, and CK on Long-Term PFS Overall and in Patients With uIGHV and mIGHV (Total Pooled Population)

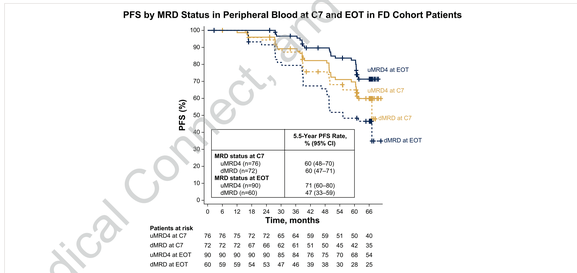


mIGHV, mutated IGHV.

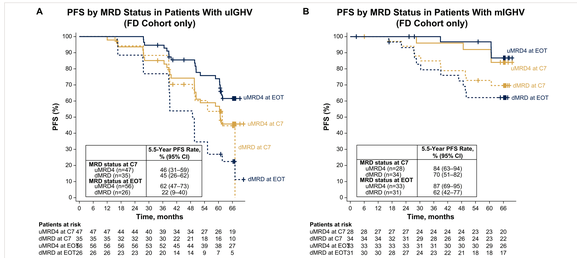
Correlation of MRD Status With PFS Outcomes in FD Cohort Patients

- Assessed in FD cohort patients only, uMRD4 was achieved in peripheral blood in 51% of patients at C7 and 60% at EOT, and in bone marrow in 60% of patients at EOT
  - uMRD4 rates at C7 were not significantly different in patients with versus without uIGHV, del(11q), or in the pooled high-risk subgroup with ≥1 high-risk genomic feature (uIGHV, del(17p), mutated *TP53*, and/or CK) (**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 IGHV Status and Also Predictive at C7 in Patients With mIGHV



EOT, end of treatment.

- EOT uMRD4 status in peripheral blood was also strongly predictive for long-term PFS in subgroups of patients with or without ≥1 high-risk genomic feature, defined as uIGHV, del(17p), mutated *TP53*, and/or CK (**Supplement**)
- C7 and EOT uMRD4 status in peripheral blood were similarly and strongly predictive of long-term PFS in patients free of uIGHV/del(17p)/mutated *TP53*/CK high-risk features, similar to those with mIGHV (**Supplement**)

No Resistance-Associated Mutations Identified at PD

- In the total pooled population 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
  - Two patients were found with subclonal *BCL2 A113G* mutations of unclear significance, with variant allele frequencies of only 8% and 9.3%, respectively
  - One of these 2 patients was retreated with FD ibrutinib + venetoclax and achieved partial response (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
  - The other patient did not receive retreatment on study

Ibrutinib-Based Retreatment

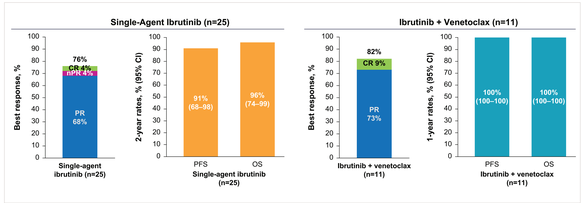
- 73% of patients remained free from next-line treatment at the 5.5-year landmark time point (95% CI, 66–79) (**Supplement**)
- In total, 36 patients (who met International Workshop on Chronic Lymphocytic Leukemia [iwCLL] criteria for treatment) initiated retreatment with either single-agent ibrutinib (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

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.

Safety of Ibrutinib-Based Retreatment Shows No New Safety Signals

TEAEs[a], n (%)	Single-agent ibrutinib n=25	FD ibrutinib + venetoclax n=11
Any AE	22 (88)	11 (100)
Most frequent AEs[b]		
COVID-19	6 (24)	2 (18)
Diarrhea	5 (20)	4 (36)
Hypertension	5 (20)	5 (45)
Grade 3 or 4 AEs	9 (36)	4 (36)
AEs leading to discontinuation	1 (4)	0
AEs leading to dose reduction	0	0

[a]TEAEs were collected until 30 days after the last dose of study treatment or the start of subsequent therapy, whichever occurred first. [b]Occurring in ≥20% of patients who received single-agent ibrutinib or ibrutinib + venetoclax.

Second Malignancies Across the Entire Study Period

- Second malignancies occurred in 24 patients across the entire study period:
  - During the TEAE period for first-line FD ibrutinib + venetoclax in 12 patients (8 non-melanoma skin cancers and 6 other cancers)
  - After the initial TEAE period and before retreatment started in 9 patients (4 non-melanoma skin cancers and 7 other cancers)
  - During the TEAE period for ibrutinib-based retreatment in 4 patients (4 non-melanoma skin cancers and 1 other cancer)

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[1]University Vita-Salute San Raffaele, Milan, Italy; [2]Department of Medicine, Division of Hematology, University of Rochester Medical Center, Rochester, NY; [3]UK Medical Consult Ltd, Cambridge, UK; [4]City of Hope National Medical Center, Duarte, CA; [5]Department of Medical Oncology, Regina Elena National Cancer Institute, Rome, Italy; [6]Moores Cancer Center, UC San Diego Health, La Jolla, CA; [7]UC Health, Chao Family Comprehensive Cancer Center, Orange, CA; [8]UC Irvine Cancer Center, Orange, CA; [9]UC Irvine Cancer Center, Orange, CA; [10]Dana-Farber Cancer Institute, Boston, MA; [11]Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy; [12]Hematology and Lymphoid Malignancies Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy; [13]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [14]Department of Medical Oncology, Alfred Health, Melbourne, Victoria, Australia; [15]Department of Haematology, University of Cambridge, Cambridge, UK; [16]Department of Clinical Hematology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

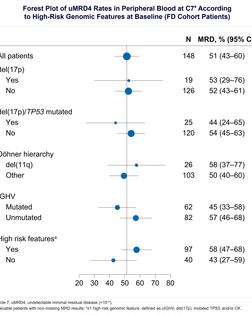
SUPPLEMENTAL RESULTS

Baseline Characteristics in Patients Treated With Fd Ibrutinib + Venetoclax (Total Pooled Population)

Characteristic	Total Pooled Population (N=202)
Median age (range), years	60.0 (33–71)
Male, n (%)	131 (65)
Rai stage III/IV, n (%)	59 (29)
High-risk genomic features, n (%)	
*u*IGHV	119 (59)
del(17p)/*TP53*	29 (14)
del(11q)[a]	36 (18)
CK (≥3 abnormalities)[a]	35 (17)
CK (≥5 abnormalities)[a]	19 (9)
Bulky LN disease ≥5 cm, n (%)	66 (33)

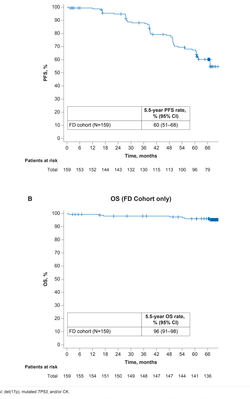
CK, complex karyotype; LN, lymph node; *u*IGHV, unmutated IGHV;
[a]Without del(11q) per Döhner hierarchy; [b]By conventional cytogenetics; CK status was missing for 30 patients (15%).

Forest Plot of uMRD4 Rates in Peripheral Blood at C7[a] According to High-Risk Genomic Features at Baseline (FD Cohort Patients)



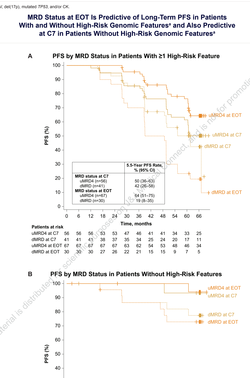
C7, cycle 7; uMRD4, undetectable minimal residual disease (<10⁻⁴);
[b]It evaluable patients with non-missing MRD results; [b]1 high-risk genomic feature, defined as *u*IGHV, del(17p), mutated *TP53*, and/or CK.

PFS and OS in the FD Cohort Only

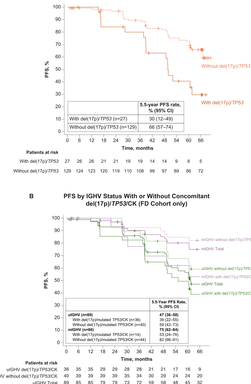


*u*IGHV, del(17p), mutated *TP53*, and/or CK.

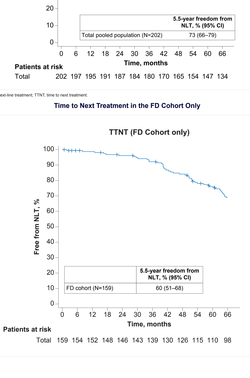
MRD Status at EOT Is Predictive of Long-Term PFS in Patients With and Without High-Risk Genomic Features[a] and Also Predictive at C7 in Patients Without High-Risk Genomic Features[a]



PFS by Mutation Status in the FD Cohort Only



Time to Next Treatment in the Total Pooled Population



NLT, next-line treatment; TTNT, time to next treatment.

Time to Next Treatment in the FD Cohort Only

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