**Consistently High 5.5-Year Progression-Free Survival Rates** in Patients With and Without Bulky Baseline Lymphadenopathy ≥5 cm Are **Associated With High Undetectable** Minimal Residual Disease Rates **After First-Line Treatment With Fixed-Duration Ibrutinib Plus Venetoclax for Chronic Lymphocytic Leukemia/Small** Lymphocytic Lymphoma in the Phase 2 CAPTIVATE Study

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### OBJECTIVE

To evaluate baseline lymph node size, extent of lymph node and depth of minimal residual disease (MRD) responses, and outcomes after fixed-duration ibrutinib + venetoclax

# CONCLUSIONS

Ibrutinib + venetoclax is an all-oral, once-daily, chemotherapy-free, fixedduration regimen for first-line treatment of chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) that provides durable progression-free survival (PFS) and overall survival (OS) with long-term follow-up

In patients with or without bulky baseline lymphadenopathy  $\geq 5$  cm, similarly durable long-term PFS and OS outcomes were observed and associated with similarly high rates of undetectable MRD (<10<sup>-4</sup>; uMRD4) at end of treatment (EOT)

Assessed at EOT, maximal residual lymph node longest diameter ≤1.5 versus ≤2 cm cutoffs were associated with similar 5.5-year PFS outcomes while uMRD4 status was more strongly correlated with PFS than lymph node response subgroups

Similarly, long-term PFS was associated most strongly with uMRD4 status while response per International Working Group on Chronic Lymphocytic Leukemia criteria (complete response vs partial response) had a minor impact, which was seen only in patients with detectable MRD

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The safety profile of fixed-duration ibrutinib + venetoclax was similar independent of lymph node bulk at baseline

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https://www.congresshub.com/ASH2024/Oncology/Ibrutinib/ Wierda

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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)<sup>1,2</sup>
- With up to 5.5 years of follow-up, fixed-duration treatment with ibrutinib + venetoclax demonstrated sustained progression-free survival (PFS), including in patients with high-risk genomic features<sup>3</sup>
- Achievement of complete response (CR) per International Working Group on CLL (iwCLL) criteria, requiring the absence of lymph nodes >1.5 cm in diameter,<sup>4,5</sup> is well established as an independent predictor of improved PFS and overall survival (OS) in patients with CLL treated with chemoimmunotherapy<sup>6-8</sup>
- Several studies have shown that achievement of undetectable MRD (<10<sup>-4</sup>; uMRD4) with chemoimmunotherapy is a stronger predictor of PFS than achievement of CR9-11
- Detectable MRD (dMRD) remains present in many patients despite achievement of CR<sup>9-11</sup>
- Bulky lymph nodes can develop scar tissue that may contribute to residual lymphadenopathy >1.5 cm, thereby preventing achievement of CR per iwCLL criteria<sup>12</sup>
- The association of CR and/or uMRD4 with PFS and OS remains to be clarified in patients treated with fixedduration ibrutinib + venetoclax

## RESULTS

### **Baseline Lymph Node Longest Diameter (LDi) Correlated Well With Baseline Lymph Node Sum of the** Product of Diameters (SPD)



• As lymph node longest diameter (LDi) is correlated with sum of the product of diameters, is used in the iwCLL response criteria, and is readily applied in daily clinical practice, LDi was used to explore the potential impact of bulky baseline disease on outcomes

### **Baseline Characteristics**

- Of 202 patients who completed fixed-duration ibrutinib + venetoclax in the FD cohort (n=159) or MRD cohort placebo arm (n=43), 66 (33%) had baseline LDi ≥5 cm
- Baseline characteristics were generally balanced in patients with baseline LDi <5 vs</li> ≥5 cm (**Supplement**). Notable differences included:
- Unmutated IGHV in 54% vs 70%
- del(11q) in 14% vs 26%
- del(17p)/mutated TP53 in 18% vs 8%
- Complex karyotype ( $\geq$ 3 aberrations) in 15% vs 21%

### Safety Profile According to Baseline Lymph Node Longest Diameter (LDi <5 cm vs ≥5 cm)

Treatment-emergent AEs, n (%)	Baseline LDi <5 cm n=136	Baseline LDi ≥5 cm n=66	Total N=202
Any AE	135 (99)	66 (100)	201 (99.5)
Most frequent AEs <sup>a</sup>	<u> </u>		
Diarrhea	88 (65)	38 (58)	126 (62)
Nausea	64 (47)	23 (35)	87 (43)
Neutropenia	60 (44)	21 (32)	81 (40)
Arthralgia	44 (32)	21 (32)	65 (32)
Headache	42 (31)	14 (21)	56 (28)
Muscle spasms	35 (26)	19 (29)	54 (27)
Fatigue	38 (28)	16 (24)	54 (27)
Upper respiratory tract infection	32 (24)	20 (30)	52 (26)
Increased tendency to bruise	32 (24)	9 (14)	41 (20)
Vomiting	29 (21)	12 (18)	41 (20)
Grade ≥3 AEs	87 (64)	38 (58)	125 (62)
Serious AEs	30 (22)	15 (23)	45 (22)
AEs leading to discontinuation	4 (3)	4 (6)	8 (4)
AEs leading to dose reduction	29 (21)	13 (20)	42 (21)

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BM, bone marrow; CRi, complete response with incomplete bone marrow recovery; PB, peripheral blood. <sup>a</sup>Assessed in evaluable patients with non-missing data at EOT.



• EOT uMRD4 rates in patients with EOT longest diameter of  $\leq 1.5$  cm and  $\leq 2$  cm, respectively, were consistently high at 71% and 69% in peripheral blood, and 72% and 70% in bone marrow (**Supplement**) - Corresponding uMRD4 rates in patients with EOT longest diameter >2 cm were 71% in peripheral blood and 68% in bone marrow

AE, adverse event.

<sup>a</sup>Occurring in  $\geq$ 20% of patients overall.

### **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 (n=43) received 1 additional cycle of ibrutinib + venetoclax during the MRD-guided randomization
- Post hoc exploratory analyses were performed to evaluate response per iwCLL criteria, uMRD4, PFS, and OS in patient subgroups defined by maximal lymph node longest diameter (LDi) at baseline and at end of treatment (EOT; Cycle 19, Day 1 visit [FD cohort] or Cycle 16, Day 1 visit [MRD cohort placebo arm])
- Treatment-emergent safety outcomes were evaluated in patient subsets defined by baseline lymph node LDi
- At the time of this analysis, the median time on study was 69 months (range, 1–84)







<sup>a</sup>Patients with confirmed uMRD (defined as uMRD [<10<sup>-4</sup> 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.

nPR, nodular partial response; PR, partial response.

Patients at risk

dMRD

Event, n (%)

% (95% CI)

5.5-year PFS rate,

 PFS rates according to bone marrow MRD status were very consistent with those according to peripheral blood MRD status across subgroups by iwCLL response category (Supplement)

uMRD4

PR/nPR

n=60

15 (25)

6 12 18 24 30 36 42 48 54 60 66 72

Time, months

29 29 28 27 22 21 18 17 14 13 12

CR/CRi 73 73 73 73 73 69 68 64 63 59 57 48

CR/CRi 26 26 26 26 26 25 25 21 21 16 15 13

75 (64–84) 75 (62–85) 54 (33–71) 46 (28–63)

CR/CRi

n=73

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PR/nPR

PR/nPR

n=29

16 (55)

dMRD

CR/CRi

n=26

12 (46)

**Consistently High 5.5-Year Progression-Free Survival Rates in Patients With and Without Bulky** Baseline Lymphadenopathy ≥5 cm Are Associated With High Undetectable Minimal Residual Disease **Rates After First-Line Treatment With Fixed-Duration Ibrutinib Plus Venetoclax for Chronic Lymphocytic** Leukemia/Small Lymphocytic Lymphoma in the Phase 2 CAPTIVATE Study

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# **SUPPLEMENTAL INFORMATION**

## **Baseline Characteristics According to Presence or Absence of Bulky Lymphadenopathy at Baseline (Longest Diameter** <5 cm vs ≥5 cm)

Characteristic	Baseline LDi <5 cm n=136	Baseline LDi ≥5 cm n=66	Total N=202		
Median age (range), years	59.5 (33–71)	60.0 (39–69)	60.0 (33–71)		
Sex, n (%)					
Male	82 (60)	49 (74)	131 (65)		
Female	54 (40)	17 (26)	71 (35)		
Rai stage III/IV, n (%)	40 (29)	19 (29)	59 (29)		
High-risk genomic features, n (%)					
Unmutated IGHV	73 (54)	46 (70)	119 (59)		
del(17p)/mutated TP53ª	24 (18)	5 (8)	29 (14)		
del(17p)	18 (13)	3 (5)	21 (10)		
del(11q) <sup>b</sup>	19 (14)	17 (26)	36 (18)		
Complex karyotype <sup>c</sup>	21 (15)	14 (21)	35 (17)		
Any cytopenia	47 (35)	26 (39)	73 (36)		
ANC ≤1.5 × 10 <sup>9</sup> /L	12 (9)	6 (9)	18 (9)		
Hemoglobin ≤11 g/dL	33 (24)	18 (27)	51 (25)		
Platelet count ≤100 × 10⁰/L	16 (12)	9 (14)	25 (12)		
Median ALC × 10 <sup>9</sup> /L (range)	65.0 (1–503)	62.8 (1–429)	64.4 (1–503)		
ALC ≥25 × 10 <sup>9</sup> /L, n (%)	106 (78)	46 (70)	152 (75)		

ALC, absolute lymphocyte count; ANC, absolute neutrophil count.

<sup>a</sup>del(17p)/*TP53* status was missing for 4 patients.

<sup>b</sup>Without del(17p) per Döhner hierarchy.

<sup>o</sup>Defined as  $\geq$ 3 abnormalities by conventional CpG-stimulated cytogenetics; complex karyotype status was missing for 30 patients.

## EOT uMRD4 Rates According to EOT Residual Lymph Node Longest Diameter (LDi ≤1.5 cm, ≤2 cm, or >2 cm)



<sup>a</sup>Assessed in evaluable patients with non-missing data at EOT.

# Long-Term PFS Impact of Combined EOT Bone Marrow MRD **Status and Residual Lymph Node Longest Diameter** $(LDi \le 1.5 \text{ cm}, >1.5 \text{ to} \le 2 \text{ cm}, >2 \text{ cm})$



# EOT Bone Marrow MRD Status Is More Predictive Than iwCLL **Response for Long-Term PFS**



CR, complete response; CRi, complete response with incomplete bone marrow recovery; iwCLL, International Working Group on Chronic Lymphocytic Leukemia; nPR, nodular partial response; PR, partial response.