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Safety and Efficacy of Dose-Modified Approaches of Fixed-Duration Ibrutinib+Venetoclax in Patients With Previously Untreated CLL: Primary Analysis of the Prospective Phase 2 TAILOR Study

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Key Takeaway

Results from the prospective TAILOR study support the use of reactive and proactive adjustment of Ibr dose within a FD Ibr+Ven regimen to manage AEs, providing treatment flexibility for patients with previously untreated CLL

Conclusions

Both reactive and proactive dose adjustment Ibr+Ven cohorts met the primary end point with a statistically significant improvement in ORR versus historical controls

When treated both per dose adjustment guidance (per prescribing information) and with proactive dose reductions, patients had manageable AE profiles, including low rates of AF and no cardiac deaths

Results from TAILOR further strengthen the clinical profile and dosing flexibility of Ibr+Ven in previously untreated CLL

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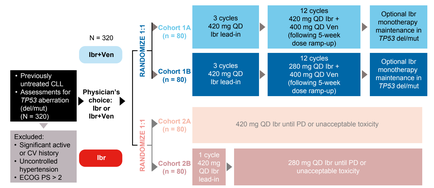
Introduction

- Fixed-duration (FD) ibrutinib + venetoclax (Ibr+Ven) has transformed first-line treatment of patients with chronic lymphocytic leukemia (CLL). Ibr+Ven has been studied in over 1200 patients in phase 2/3 studies with up to 5.7 years' median follow-up[1-8] and in over 500 patients in real-world (RW) studies[9-11]
- In a recent analysis, physicians indicated all-oral administration, quality-of-life advantages, and patient preference as key factors for FD Ibr+Ven initiation[12]
- Results from the phase 3 RESONATE-2 study show that Ibr dose can be modified to manage adverse events (AEs),[13] and RW studies have demonstrated that reduction of Ibr dose did not impact survival outcomes[14-17]
- Dose reduction guidance is now incorporated into Ibr prescribing information, which recommends Ibr dose reduction following AEs[18,19]
- TAILOR is the first study to prospectively evaluate outcomes using 2 clinical strategies to improve tolerability: reactive dose adjustment per label and proactive dose adjustment
- Results from the monotherapy cohorts of TAILOR revealed a near complete Bruton's tyrosine kinase occupancy (> 95%) when single-agent Ibr dose was proactively reduced following 1 cycle at full dose[20]
- Here we present the primary analysis from the FD Ibr+Ven cohorts of TAILOR, assessing efficacy and safety of reactive dose adjustment (per label) and proactive dose adjustment approaches in previously untreated CLL

Methods

- After physician choice of Ibr+Ven, patients were randomized 1:1 into reactive (1A) and proactive (1B) dose adjustment cohorts and dosed per approved label for 12 cycles of FD Ibr+Ven following a 3-cycle lead-in with Ibr 420 mg daily. Ven step-up and dosing were per label. Patients in 1B had Ibr dose proactively reduced to 280 mg daily after Ibr lead-in (**Figure 1**)
- The primary end point was best overall response rate (ORR) tested individually for each cohort versus a benchmark of > 75%, which represents a clinically meaningful ORR of 90% based on the GLOW and CAPTIVATE studies
- Secondary end points included progression-free survival (PFS), overall survival (OS), and safety
- TAILOR was not powered for comparisons between cohorts. Safety results are summarized using descriptive measures

Figure 1: TAILOR study design



CV, cardiovascular; del/mut, deletion/mutation; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; QD, once daily.

Results

Cohort 1A: Reactive dose adjustment

Patients

- Of 171 patients allocated to Ibr+Ven therapy, 86 were randomized to Cohort 1A. Patient characteristics are detailed in **Table 1**
- As of November 2025, 95.3% of the patients in Cohort 1A are still participating, while 1.2% have completed the study

Table 1: Patient baseline characteristics

Characteristic		N = 86
Age, years	Overall median (range) ≥ 65, n (%)	63 (42-82) 37 (43.0)
Sex, n (%)	Female Male	34 (39.5) 52 (60.5)
Geographical region, n (%)	North America Europe	26 (30.2) 60 (69.8)
Diagnosis, n (%)	CLL SLL	78 (90.7) 8 (9.3)
Binet stage, n (%)	 A B C	n = 76 12 (14.0) 39 (45.3) 25 (29.1)
ECOG PS, n (%)	0 1	63 (73.3) 23 (26.7)
CIRS total score, n (%)	≤ 6 > 6	82 (95.3) 4 (4.7)
***TP53*/del17p aberration, n (%)**		14 (16.3)
Unmutated IGHV status,[a] n (%)		n = 67 31 (36.0)
Cytopenia,[b] n (%)		40 (46.5)
Elevated LDH,[c] n (%)	> ULN	37(43.0)
Serum β-2 macroglobulin, n (%)	≤ 3.5 > 3.5	37 (43.0) 49 (57.0)
High-risk status,[d] n (%)		37 (43.0)
Prior documented cardiac history, n (%)		38 (44.2)
Number of hypertension medications prescribed, n (%)	0 1-2	50 (58.1) 36 (41.9)

[a]Missing in 3 patients. [b]Cytopenia is defined as yes if hemoglobin ≤ 110 g/L, platelet counts ≤ 100 × 10^9/L, or absolute neutrophil count ≤ 1.5 × 10^9/L is observed. [c]Missing in 5 patients. [d]High-risk population: patients with *TP53* mutation, del17p, del11q, or unmutated IGHV status at baseline.
CIRS, Cumulative Illness Rating Scale; LDH, lactate dehydrogenase; SLL, small lymphocytic lymphoma; ULN, upper limit of normal.
Percentages calculated with the number of intention-to-treat patients as denominator.

Efficacy

- This cohort demonstrated statistically significant benefit through ORR, with a rate of 94.2% (95% confidence interval [CI], 87-98%)
  - This cohort consistently demonstrated treatment benefit in ORR across patient subgroups, including in patients with del17p/*TP53* (**Figure 2**)
- 12-month PFS/OS rates were both 98.8% (**Figure 3**); 1 patient had progressive disease

Figure 2: ORR

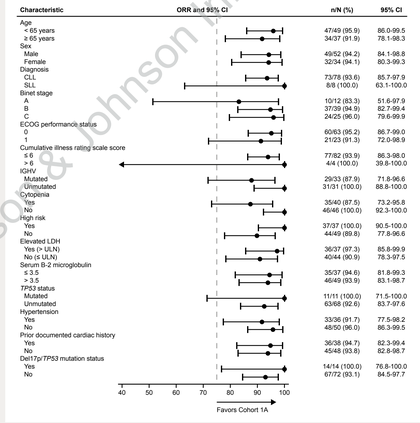
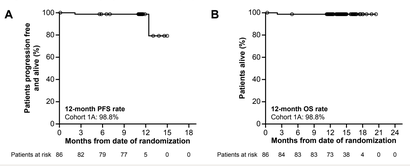


Figure 3: PFS (A) and OS (B)



Safety

- Overall, any-grade and grade ≥ 3 treatment-emergent AEs (TEAEs) were reported in 95.3% and 48.2% of patients, respectively. After Ibr lead-in, these were reported in 91.8% and 41.2% of patients, respectively (**Table 2**)
- AEs led to Ibr discontinuation in 4.7% and reduction of Ibr dose in 20.0%
- 1 death occurred due to intracranial hemorrhage during lead-in, deemed related to Ibr

Table 2: Adverse events of interest (N = 85)

Adverse event, n (%)	Any-grade	Grade ≥ 3
≥ 1 AE after Cycle 3	78 (91.8)	35 (41.2)
≥ 1 AE overall	81 (95.3)	41 (48.2)
Infections and infestations[a]	44 (51.8)	2 (2.4)
Neutropenia	33 (38.8)	26 (30.6)
Arthralgia	18 (21.2)	2 (2.4)
Hypertension	9 (10.6)	2 (2.4)
Atrial fibrillation	4 (4.7)	2 (2.4)

[a]System organ class.

Cohort 1B: Proactive dose adjustment

Patients

- Of 171 patients allocated to Ibr+Ven therapy, 85 were randomized to Cohort 1B. Patient characteristics are detailed in **Table 3**
- As of November 2025, 94.1% of the patients in Cohort 1B are still participating, while 1.2% have completed the study

Table 3: Patient baseline characteristics

Characteristic		N = 85
Age, years	Overall median (range) ≥ 65, n (%)	63 (33-83) 38 (44.7)
Sex, n (%)	Female Male	25 (29.4) 60 (70.6)
Geographical region, n (%)	North America Europe	28 (32.9) 57 (67.1)
Diagnosis, n (%)	CLL SLL	83 (97.6) 2 (2.4)
Binet stage, n (%)	 A B C	n = 83 11 (12.9) 46 (54.1) 26 (30.6)
ECOG PS, n (%)	0 1	55 (64.7) 30 (35.3)
CIRS total score, n (%)	≤ 6 > 6	78 (91.8) 7 (8.2)
***TP53*/del17p aberration, n (%)**		8 (9.4)
Unmutated IGHV status,[a] n (%)		n = 69 35 (41.2)
Cytopenia,[b] n (%)		44 (51.8)
Elevated LDH,[c] n (%)	> ULN	38 (44.7)
Serum β-2 macroglobulin,[d] n (%)	≤ 3.5 > 3.5	33 (38.8) 50 (58.8)
High-risk status,[e] n (%)		44 (51.8)
Prior documented cardiac history, n (%)		36 (42.4)
Number of hypertension medications prescribed, n (%)	0 1-2	51 (60.0) 34 (40.0)

[a]Missing in 3 patients. [b]Cytopenia is defined as yes if hemoglobin ≤ 110 g/L, platelet counts ≤ 100 × 10^9/L, or absolute neutrophil count ≤ 1.5 × 10^9/L is observed. [c]Missing in 5 patients. [d]High-risk population: patients with *TP53* mutation, del17p, del11q, or unmutated IGHV status at baseline.
Percentages calculated with the number of intention-to-treat patients as denominator.

Efficacy

- This cohort demonstrated statistically significant benefit through ORR, with a rate of 89.4% (95% CI, 81-95%)
  - This cohort consistently demonstrated treatment benefit in ORR across patient subgroups, including in patients with del17p/*TP53* (**Figure 4**)
- 12-month PFS/OS rates were 97.6%/98.8% (**Figure 5**); 1 patient had progressive disease

Figure 4: ORR

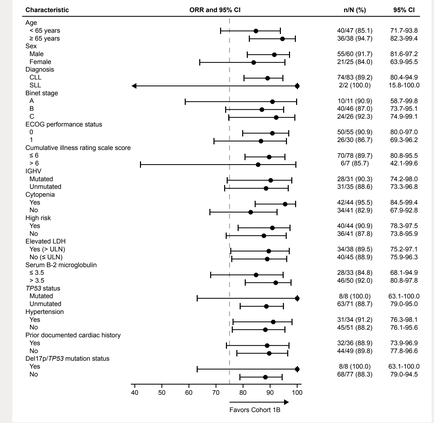
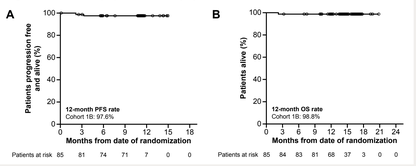


Figure 5: PFS (A) and OS (B)



Safety

- Overall, any-grade and grade ≥ 3 TEAEs were reported in 94.1% and 50.6% of patients, respectively. After Ibr lead-in, these were reported in 83.5% and 42.4% of patients, respectively (**Table 4**)
- AEs led to Ibr discontinuation in 11.8% and reduction of Ibr dose in 11.8%
- 1 death occurred due to pneumonia during lead-in, deemed unrelated to Ibr

Table 4: Adverse events of interest (N = 85)

Adverse event, n (%)	Any-grade	Grade ≥ 3
≥ 1 AE after Cycle 3	71 (83.5)	36 (42.4)
≥ 1 AE overall	80 (94.1)	43 (50.6)
Infections and infestations[a]	27 (31.8)	7 (8.2)
Neutropenia	20 (23.5)	13 (15.3)
Arthralgia	15 (17.6)	1 (1.2)
Hypertension	14 (16.5)	4 (4.7)
Atrial fibrillation	7 (8.2)	6 (7.1)

[a]System organ class.

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