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Dose and BTK Occupancy Relationship in the Prospective Phase 2 TAILOR Study: Exploratory End Point Analysis of the Ibrutinib Monotherapy Cohorts in Patients With Previously Untreated Chronic Lymphocytic Leukemia

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Key Takeaway

In this prospective phase 2 study in patients with previously untreated CLL, high BTK occupancy levels were maintained after proactively reducing Ibr dose to 280 mg QD after 1 cycle with 420 mg QD, with concomitant lower serum Ibr concentration in patients randomized to the proactively dose reduced cohort

Conclusions

- Both study cohorts had a postbaseline BTK occupancy exceeding 99%, demonstrating sustained BTK inhibition
- Posttreatment Ibr plasma concentrations were lower after dose reduction in the prospective dose reduced cohort
- Additional analyses are needed to determine whether sustained BTK occupancy in the prospectively dose reduced cohort correlates with an overall clinical benefit in patients with untreated CLL

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Poster

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Acknowledgments
This study was funded by Johnson & Johnson and PCYC, an AbbVie company. Professional medical writing and editorial assistance were provided by Bradley Richardson, PhD, of Parexel, funded by Johnson & Johnson.

Disclosures
Jacqueline C Barrientos reports attendance at advisory boards for AbbVie, BeOne Medicines, AstraZeneca, Merck, J&J, Lilly, and Bristol Myers Squibb; and honoraria from BeOne Medicines.

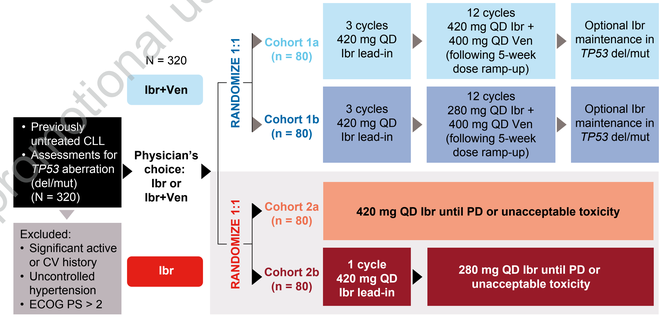
Introduction

- Continuous Bruton's tyrosine kinase inhibitor (BTKi) treatment with ibrutinib (Ibr) is a standard of care option for patients (pts) with previously untreated chronic lymphocytic leukemia (CLL), including pts with high-risk cytogenetics
  - Ibr is the only BTKi that has demonstrated survival benefits comparable with an age-matched general population[1]
- The RESONATE-2 trial demonstrated sustained progression-free survival (PFS) benefits, with up to 10 years of follow-up, in first-line pts with CLL treated with Ibr. Ibr dose modification improved or resolved adverse events (AEs) in ≥ 85% of pts[2,3]
- Additionally, real-world (RW) evidence has shown that Ibr dose modification may enhance overall tolerability and decrease side effects without impacting efficacy
- Previous research has shown that total BTK protein levels decrease during Ibr treatment[4]
- In support of clinical and real-world data, model-based research has demonstrated sustained BTK inhibition when Ibr is reduced to 280 mg following an initial 28-day cycle at 420 mg, and pilot clinical data have shown that the biological activity of Ibr can be retained following similar dose modification approaches[5,6]

Methods

- In the phase 2 TAILOR Ibr monotherapy cohort, pts were randomized 1:1 to receive Ibr 420 mg once daily (QD; **Cohort 2a**) or 1 cycle of Ibr 420 mg QD followed by Ibr 280 mg QD (**Cohort 2b**) until progression or intolerability
- Blood samples were taken from pts in Cohorts 2a and 2b at screening, Cycle (C) 1 Day (D) 14, and C4D1 to assess predose BTK occupancy
- Ibr plasma concentration was assessed using samples at predose, 2 hours (h), and 4 h after dosing at C1D14/C4D1
- Results were summarized using descriptive statistics, Ibr plasma concentrations calculated as geometric means, and BTK occupancy as median of data from the specified cohort/time point

Figure 1: TAILOR study design



CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease.

Results

Patients

- All results are from the ibrutinib monotherapy Cohorts 2a and 2b (Figure 1)
- Blood samples from 41 pts were evaluated
- Pts had a median age of 73 years (range, 53-84), and 75.6% were aged ≥ 65 years
- 65.9% of pts were from Europe and 34.1% from North America
- Of 41 pts, 7 had a *TP53*/del17p aberration and 21 of 32 assessed pts had unmutated IGHV

Table 1: Baseline patient characteristics

Characteristic	Cohort 2a + 2b (N = 41)
Median age, years (range)	73 (53-84)
Sex, n (%)	
Female	15 (36.6)
Male	26 (63.4)
Race, n (%)	
Black or African American	1 (2.4)
White	38 (92.7)
Not reported	2 (4.9)
Geographical region, n (%)	
North America	14 (34.1)
Europe	27 (65.9)
ECOG PS, n (%)	
0	27 (65.9)
1	11 (26.8)
2	3 (7.3)
CIRS total score, n (%)[a]	
≤ 6	38 (92.7)
> 6	2 (4.9)
7-12	2 (4.9)
***TP53*/del17p aberration, n (%)**	7 (17.1)
Unmutated IGHV status, n (%)	21 (51.2)[b]

CIRS, Cumulative Illness Rating Scale.
[a]40 pts assessed. [b]32 pts assessed.

Ibrutinib plasma concentration at C1D14 and C4D1

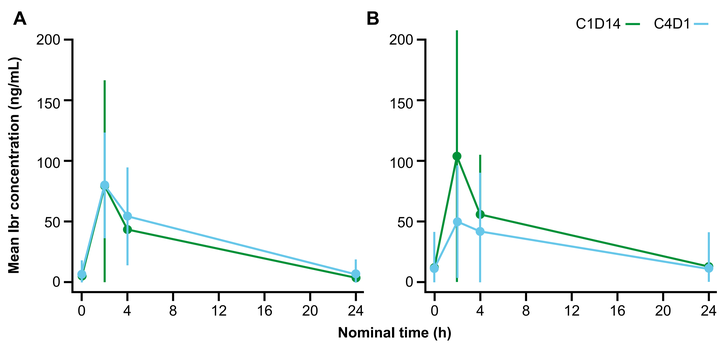
- Mean Ibr plasma concentration in Cohort 2a was similar between C1D14 and C4D1 (Table 2, Figure 2A)
- At C1D14, Ibr plasma concentration was similar between Cohorts 2a and 2b (Table 2)
- In Cohort 2b, mean Ibr plasma concentration was lower at C4D1 compared with C1D14 (Table 2, Figure 2B)
- At C4D1, Ibr plasma concentration was lower for Cohort 2b versus 2a (Table 2)
- Interindividual variability in Ibr plasma concentration was high within both cohorts (Table 2, Figure 2) and plasma concentration at 24 h was assumed to be similar to predose due to steady state conditions (Figure 2)

Table 2: Predose and postdose Ibr plasma concentration at Cycle 1 and 4[a]

Gmean (%CV), ng/mL	Cycle 1 Day 14			Cycle 4 Day 1		
Sample time point	**Predose**	**2 h**	**4 h**	**Predose**	**2 h**	**4 h**
Patients, n	17	17	17	17	16	16
Cohort 2a	3.05 (103.96)	44.38 (110.02)	34.45 (66.15)	3.29 (157.25)	68.14 (53.49)	40.94 (72.69)
Cohort 2b	4.58 (206.39)	47.54 (165.04)	35.86 (86.34)	3.05 (252.50)	27.13 (91.33)	21.19 (112.79)

Gmean, geometric means; %CV, coefficient of variation.
[a]Data from evaluable pts.

Figure 2: Mean Ibr plasma concentration in Cohort 2a (A) and Cohort 2b (B)[a]



Mean ± standard deviation concentration time plots Cohorts 2a and 2b.
[a]Data from evaluable pts.

Median BTK occupancy

- Median predose BTK occupancy was similar between Cohorts 2a (n = 17) and 2b (n = 23) at C1D14 (99.8% [range, 98.7-100.0%] and 99.8% [range, 92.9-100.0%]), and C4D1 (99.8% [range, 98.3-100%] and 99.8% [range, 96.9-100.0%]) (Figure 3)
- Combined median C1D14 and C4D1 BTK occupancy was 99.8% for Cohort 2a and 99.8% for Cohort 2b (Figure 4)
- BTK occupancy was observed to be nearly complete for all Ibr plasma concentration levels measured at predose C1D14 and C4D1

Figure 3: BTK occupancy in Cohorts 2a and 2b

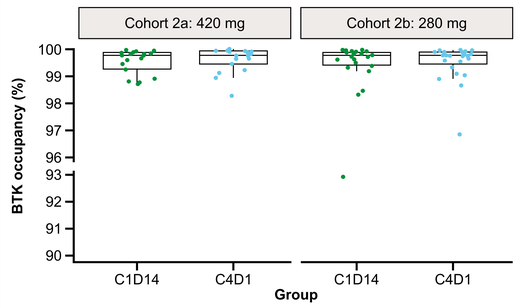
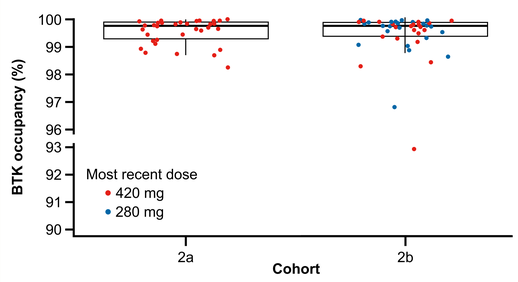


Figure 4: Postbaseline combined BTK occupancy in Cohorts 2a and 2b[a]



[a]BTK occupancy assessed predose, combining C1D14 and C4D1.
Data from evaluable pts.

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B-cell Malignancies

Presented by JC Barrientos at the 67th ASH Annual Meeting; December 6-9, 2025; Orlando, FL, USA