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First worldwide real-life data on fixed-duration Ibrutinib+Venetoclax treatment for previously untreated CLL/SLL patients: initial interim analysis of Spain's LI+VE observational study

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Key takeaway

To date, this is the first real-world study of I+V worldwide, providing initial results regarding the use of I+V in untreated patients with CLL/SLL based on clinical practice in Spain. Our findings are aligned with clinical trial data, supporting once-daily fixed-duration (FD) I+V effectiveness and safety across all patient profiles.

Conclusions

The patient population receiving I+V in this study is diverse and reflects how, in a real-world setting, previously untreated patients with CLL/SLL exhibit a high prevalence of cardiovascular disease and other comorbidities, with the majority receiving multiple concomitant medications.

The preliminary results of this real-world study suggest that I+V is an effective treatment for previously untreated CLL/SLL patients, including those with comorbidities, elderly and unfit characteristics. Nearly half of the patients (45.2%) achieved early confirmed clinical responses and no progressions were reported.

In this real-world study, ibrutinib lead-in significantly reduced the tumor burden category for TLS monitoring and prophylaxis. I+V was well tolerated, with a very low discontinuation rate and no discontinuations attributed to cardiovascular toxicity. Additionally, there were no treatment-related deaths or severe cardiovascular AEs. These early results may suggest a better tolerability of a FD regimen vs. continuous treatment. Future follow-up will shed light on this matter.

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Disclosure declaration

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Background

- Ibrutinib plus venetoclax (I+V) is the first all-oral, chemotherapy- free, once-daily fixed-duration (FD) therapy with EMA approval since August 2022 for previously untreated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) patients.[1]
- Due to their distinct and complementary mechanisms of action, I+V work synergistically to eradicate CLL by eliminating both dividing and resting leukemic subpopulations, inducing deep responses with time-limited therapy, enabling treatment-free remissions for patients.[2-4]
- Ibrutinib, alone or in combination with venetoclax, has significantly improved overall survival (OS) in CLL patients, with some trials demonstrating OS rates comparable to the age-matched healthy population.[5]
- I+V shows durable responses and manageable safety across all patient profiles in previously untreated CLL/SLL patients with high progression-free survival (PFS) and OS rates, even in elderly patients or those with high-risk genomic features.[4,6-9]
- Despite the evidence from clinical trials, real-world data on CLL/SLL patients treated with this regimen in routine practice remains scarce. In this context, the LI+VE study aims to provide the first real-life data on I+V FD combination worldwide.

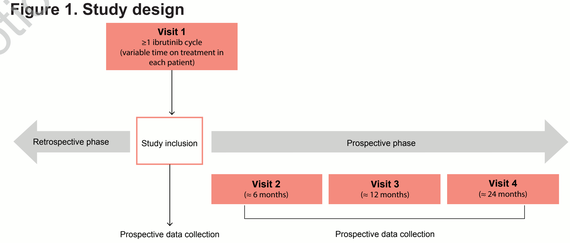
Objective

- To assess the effectiveness, safety, and clinical management of first-line I+V treatment in CLL/SLL patients in routine clinical practice in Spain.

Methods

- LI+VE is an ambispective, multicenter, observational study, conducted in 40 centers in Spain. Patients included in the study had to have been diagnosed with CLL/SLL, initiated first-line treatment with I+V according to clinical practice and have completed ≥1 cycle of ibrutinib before signing the informed consent form (visit 1).
- At the time of patients' inclusion in the study (Visit 1), a retrospective data collection was performed, which included characteristics of the patients as well as measures of the effectiveness, safety, and tolerability of I+V. During the prospective observational period, effectiveness and safety data will be collected at Visits 2, 3, and 4 **(Figure 1)**.
- The primary objective of this study is to describe PFS. Key secondary objectives include description of patients' characteristics, effectiveness in terms of response, OS, duration of treatment, time to next treatment, and safety.
- Here we present the first interim analysis, which describes the patients' baseline characteristics, preliminary clinical management, tolerability, and effectiveness of I+V treatment.

Figure 1. Study design



Results

Patient characteristics

At cut-off date of November 11th, 2024, 93 patients were included in this study. The median age was 63 (range: 41-84) years, with 29.7% ≥70 years. A high proportion of patients (69.8%) had cardiovascular (CV) risk factors, with hypertension (63.3%) being the most common. Overall, 61.2% pts were at medium/high CV risk. Most of the patients had ≥1 comorbidity (66.3%) of which 49.1% had ≥2 co-existing diseases. In particular, CV comorbidity was present in 15.1%. In addition, 30.2% and 28.3% of patients had nervous system and gastrointestinal disorders, and 13.2% had respiratory disorders and previous or concomitant neoplasms **(Table 1)**. The most common reason for I+V initiation was lymph node enlargement (63.1%), followed by the presence of systemic symptoms (31.0%).

Table 1. Demographics and baseline characteristics of the patients

Characteristic	Value (N=93)
Age (years), median (range) [n= 91]	63 (41-84)
≥70 years	27 (29.7)
Male, n (%) [n= 92]	63 (68.5)
Histology, n (%) [n= 86]	
Chronic lymphocytic leukemia	75 (87.2)
Small lymphocytic lymphoma	11 (12.8)
RAI stage 0-II, n (%) [n= 87]	59 (67.8)
ECOG n (%) [n= 88]	61 (69.3)
0	46 (52.3)
1	13 (14.8)
2	2 (2.3)
Not done	27 (30.7)
Bulky disease ≥5 cm, n (%) [n= 83]	26 (31.3)
ALC x 10^9/L, median (range)	54.4 (1.5-391.4)
High-risk genomic features, n (%) [n= 86]	
Unmutated IGHV	47 (54.7)
del(11q)	10 (11.6)
del(17p)/mutated TP53	5 (5.8)
Unmutated IGHV/del(17p)/TP53 mutation/del(11q)	52 (60.5)
Cardiovascular risk, n (%) [n= 85]	
High	10 (11.8)
Medium	42 (49.4)
Low	33 (38.8)
Cardiovascular risk factors (>20%), n (%) [n= 86]	60 (69.8)
Hypertension	38 (63.3)
Dyslipidemia	34 (56.7)
Obesity	13 (21.7)
Diabetes Mellitus	12 (20.0)
Active Smoking	12 (20.0)
Patients with comorbidities (>10%), n (%) [n= 80]	53 (66.3)

The number of patients with available data is shown in square brackets. CV risk according Online calculator 'Fundación Española del Corazón'. ALC, Absolute lymphocyte count.

Concomitant medications

The majority of patients were receiving concomitant medication at I+V treatment initiation (78.2%), with more than half of patients (55.9%) receiving ≥3 medications. The most commonly used drugs were antihypertensives (43.5%) and proton pump inhibitors (33.9%).

Patient status at Visit 1

At Visit 1, all patients were alive, and 93.1% remained on treatment, with a median time on treatment of 9.8 months (range: 2.3–17.4) and a median of 6 completed cycles. Three patients had completed the I+V regimen. In addition, 85.1% had completed the 3-cycle ibrutinib lead-in. Of the 19 patients with a documented response, 16 (84.2%) achieved a complete response, while 3 (15.8%) had a partial response, according to the iwCLL2018 criteria as per routine clinical practice. No cases of disease progression were reported **(Table 2)**.

Table 2. Treatment status and clinical responses at visit 1

Variable	Value (N=93)
Treatment with ibrutinib+venetoclax	
Venetoclax initiation, n (%) [n= 93]	69 (74.1)
Ramp-up completed, n (%) [n= 68]	59 (86.8)
Achieved 400 mg daily at the end of ramp-up	56 (94.9)
Time on treatment (months), median (range) [n= 87]	9.8 (2.3-17.4)
Treatment cycles completed, median (range) [n= 87]	6 (0-16)
Response assessment performed, n (%) [n=86]	42 (48.8)
Confirmed response (iwCLL2018)	19 (45.2)
Complete response	16 (84.2)
Partial response	3 (7.1)
Disease progression	0 (0.0)
Survival status	
Alive, n (%) [n= 88]	88 (100.0)

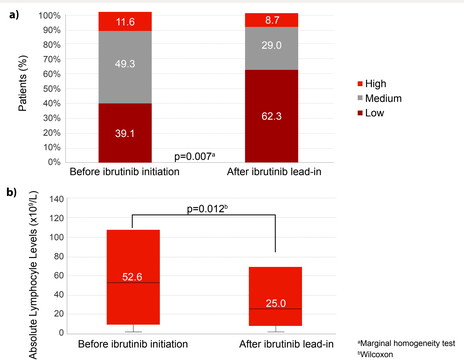
The number of patients with available data is shown in square brackets. iwCLL, International Workshop on Chronic Lymphocytic Leukemia

TLS risk category and indication for hospitalization

At cut-off date, 75.0% (6/8) of patients with a high risk of TLS prior to treatment shifted to medium or low TLS risk categories after ibrutinib lead-in. Only 8.7% remained in the high TLS risk category (p=0.007); **(Figure 2a)**. Lymphocyte levels decrease significantly after ibrutinib lead-in from a median of 52.6x109/L (range: 1.5-391.4) to 25.0 x109/L (range: 1.3-439.6) (p=0.012) **(Figure 2b)**.

Only 6 patients were hospitalized during the venetoclax ramp-up phase, all for TLS monitoring and prophylaxis per venetoclax prescribing information. No clinical or laboratory TLS occurred.

Figure 2. Impact of single-agent ibrutinib lead-in on TLS risk category (a) and on lymphocytes count (b)



Treatment modifications

Dose reductions were infrequent, ibrutinib was reduced in only 2 patients (2.2%) due to arrhythmia (n=1) and neutropenia (n=1) and venetoclax was reduced in 5 patients (5.4%) due to diarrhea (n=2), abdominal pain (n=1), thrombocytopenia (n=1) and food poisoning (n=1) **(Table 3)**. As a result of dose flexibility, all adverse events (AEs) leading to ibrutinib dose reductions were resolved. Among those resulting in venetoclax dose reductions 67% were resolved (n=3) or partially resolved (n=1). Treatment was permanently discontinued in 1 patient. No cardiovascular toxicity leading to discontinuation was reported.

Table 3. Dose modification, and discontinuation of therapy

Characteristic	Value (N=93)
Dose reductions, n (%) [n= 93]	6 (6.5)
Ibrutinib (280mg/day) (cycle 3 and 8)	2 (2.2)
Venetoclax (cycles 4-7)	5 (5.4)
100 mg/day	1 (20.0)
200 mg/day	2 (40.0)
300 mg/day	2 (40.0)
Discontinuation of therapy (pyoderma gangrenosum), n (%) [n= 93]	1 (1.1)

Safety

Overall, I+V was well tolerated. 51/93 patients (54.8%) experienced ≥1 AEs. The rate of AEs generally decreased over time. The most common all grade AEs were diarrhea (15%), and neutropenia (13%). AEs were grade 1-2 in the majority of patients (60%), and the most common grade ≥3 AE was neutropenia (9.7%). Filgrastim was used in 16% of patients. **Table 4** shows the description of AEs.

Table 4. Adverse events

AEs	Any grade	Grade 3/4
Patients with any AE, n (%)	51 (54.8)	18 (19.4)
Most common AEs (≥ 5%), n (%)		
Diarrhea	14 (15.1)	2 (2.2)
Neutropenia	12 (12.9)	9 (9.7)
Infection	11 (11.8)	2 (2.2)
Bleeding (including contusion)	10 (10.8)	1 (1.1)
Nausea	6 (6.5)	0 (0.0)
Arthralgia	5 (5.4)	0 (0.0)
Headache	5 (5.4)	0 (0.0)
Other AEs of clinical interest, n (%)		
Arrhythmia	1 (1.1)	1 (1.1)
Atrial fibrillation	2 (2.2)	0 (0.0)
Palpitations	1 (1.1)	0 (0.0)
Hypertension	2 (2.2)	0 (0.0)
TLS	0 (0.0)	0 (0.0)
Second primary malignancy	0 (0.0)	0 (0.0)
SAEs, n (%)	10 (10.8)	9 (9.7)

AE, adverse event; TLS,tumor lysis syndrome; SAE; severe adverse event

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B-cell malignancies