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

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Conclusions

- The LI+VE study confirms the effectiveness of fixed-duration I+V in a diverse real-world population of previously untreated CLL/SLL patients. Among patients with evaluable response data, the overall response rate was 98.4%, with a complete response observed in 60.3% of patients.
- With further follow-up, the LI+VE study continues to demonstrate I+V tolerability profile. The discontinuation rate remains low, and no discontinuations related to cardiovascular toxicity have occurred.
- Most AEs leading to dose reductions or temporary interruptions were either resolved or improved in patients with ≥2 comorbidities. Suggesting that even if these rates were higher vs. those with <2 comorbidities I+V is still manageable in more complex clinical profiles. Treatment modifications and temporary interruptions were similar in patients with baseline HTN and those without, suggesting that treatment management was comparable and feasible regardless of this baseline condition.
- Most AEs were grade 1–2, and serious events were infrequent. No new severe cardiac toxicity was observed. These preliminary results keep suggesting a better tolerability of a FD regimen vs. continuous treatment although future follow-ups will shed light on this matter. In the subgroups of patients with preexisting conditions, HTN or ≥2 comorbidities, the safety and tolerability profile was favorable as serious AEs of clinical interest were infrequent, supporting that this baseline traits would not have an impact on treatment tolerability.
- These preliminary findings reinforce the effectiveness and safety of I+V not only in fit patients but also in potentially vulnerable patients, including those with comorbidities, elderly and unfit characteristics who can also benefit thanks to an individualized patient management and selection. Further follow-up will provide insights into long-term outcomes.

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Background

- Ibrutinib plus venetoclax (I+V) represents the first and only all-oral, chemotherapy-free, once-daily fixed-duration (FD) regimen approved by the EMA (August 2022) for treatment-naïve patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).[1] There are currently over 1.000 patients treated with I+V in Spain in accordance with this approval.
- The synergistic mechanisms of action of I+V result in the targeting of both proliferating and quiescent leukemic cells. This enables deep responses with time-limited therapy that lead to sustained treatment-free remissions.[2-4]
- The GLOW trial showed a statistically significant difference in overall survival (OS) of I+V vs. chemoimmunotherapy (CIT), establishing I+V as the first FD regimen that demonstrates significant differences in OS vs QIT in first line CLL. Additionally, the CAPTIVATE trial demonstrated a 3-year progression free survival (PFS) of 88% and a best undetected minimal residual disease rate of 77%. These long-term data, confirm the durability of responses and favorable survival outcomes with an OS rate comparable to an age-matched general European population.[1, 5, 6, 9]
- I+V has demonstrated consistent efficacy and manageable safety across diverse patient subgroups, including elderly individuals and those with high-risk genomic features, with prolonged PFS and OS rates.[4, 7-10]
- While randomized trials have established the clinical value of I+V, real-world evidence remains limited. The LI+VE study is designed to address this gap by providing longitudinal, real-life data on the use of I+V FD therapy.
- This second interim analysis presents updated outcomes with an additional 6 months of prospective follow-up, offering further insights into the effectiveness and tolerability of the regimen in routine clinical practice.

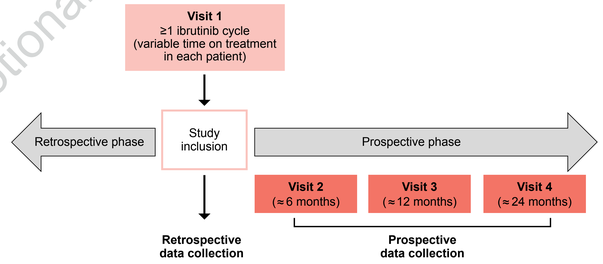
Objective

- To evaluate the effectiveness, safety and clinical management of first-line FD I+V treatment for patients with CLL/SLL, based on updated data from the six-month interim analysis of the LI+VE study, in routine clinical practice in Spain.

Methods

- LI+VE is an ambispective, multicenter, observational study conducted across 40 centers in Spain. This is study is conducted in collaboration with a CRO ensuring rigorous management and quality of data. Eligible patients were diagnosed with CLL/SLL, initiated first-line treatment with FD I+V according to routine clinical practice, and had completed ≥1 cycle of ibrutinib prior to signing the informed consent form (Visit 1).
- At inclusion (Visit 1), retrospective data were collected, including patient demographic characteristics as well as initial measures of effectiveness, safety, and tolerability. During the prospective follow-up, data are collected at Visits 2, 3, and 4, corresponding to key timepoints in the treatment and post-treatment phases (**Figure 1**).
- The primary objective of the study is to describe PFS. Key secondary objectives include characterization of patient profiles, assessment of treatment response, OS, duration of treatment, time to next treatment, and safety.
- This second interim analysis presents updated data at 6 months, including clinical management, tolerability, and effectiveness of I+V treatment in routine practice.

Figure 1. Study design.



Results

Patient characteristics

- At the cut-off date of April 21st, 2025, a total of 93 patients were included in the LI+VE study (CLL: 87.8%; SLL: 12.2%). The median age was 63 years (range: 41–84), with 29.3% aged ≥70 years. The majority of patients were male (68.5%) and presented with Rai stage 0–II (71.1%). Among those with available ECOG performance status, 97.0% had an ECOG of 0–1. Cardiovascular (CV) risk factors were present in 69.7% of patients, with hypertension (HTN) being the most frequent (62.9%). Moderate/high CV risk was observed in 60.2% of patients. Comorbidities were reported in 68.7% of patients, with 49.1% having ≥2 co-existing conditions. CV comorbidity was specifically present in 15.1%. Genomic risk status was available for 90 patients, of whom 54.4% had unmutated *IGHV* and 4.5% had del(17p)/TP53 mutations.

Table 1. Demographics and baseline characteristics of the patients.

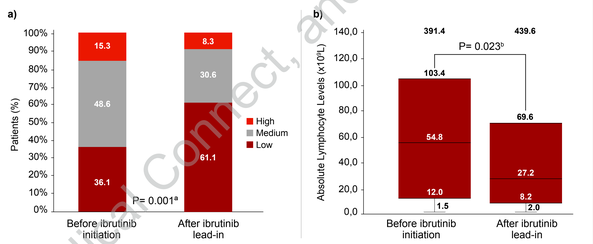
Characteristics	Value (N=93)
Age (years), median (range) [92]	63 (41-84)
≥70 years	27 (29.3)
Male, n (%) [92]	63 (68.5)
Histology, n (%) [90]	
Chronic lymphocytic leukemia	79 (87.8)
Small lymphocytic lymphoma	11 (12.2)
RAI stage 0-II, n (%) [90]	64 (71.1)
ECOG 0-1, n (%) [66]	64 (97.0)
Bulky disease ≥5 cm, n (%) [86]	28 (32.6)
ALC x 10^9/L, median (range) [76]	54.8 (1.5-391.4)
High-risk genomic features, n (%)	
Unmutated *IGHV* [90]	49 (54.4)
del(11q) [90]	10 (11.1)
del(17p) and/or mutated TP53 [89]	4 (4.5)
Unmutated *IGHV*/del(17p)/TP53 mutation/del(11q) [89]	54 (60.7)
Cardiovascular risk, n (%) [88]	
High	10 (11.4)
Medium	43 (48.9)
Low	35 (39.8)
Cardiovascular risk factors (>15%), n (%) [89]	62 (69.7)
Hypertension	39 (62.9)
Dyslipidemia	25 (40.3)
Obesity	13 (21.0)
Active Smoking	13 (21.0)
Diabetes Mellitus	12 (19.4)
Patients with comorbidities, n (%) [83]	57 (68.7)
≥2 comorbidities	28 (49.1)
Concomitant medications, n (%) [93]	71 (76.3)
≥ 3 medications	43 (60.6)

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

Patient status at Visit 2

- At the time of analysis, 72 out of 93 patients (77.4%) had completed Visit 2, with a median of 11 (range: 6-16) treatment cycles completed. A total of 23 (24,7%) patients had finalized the FD I+V regimen, one patient had initiated second-line therapy. Venetoclax ramp-up was completed in 64 (68.8%) patients. No clinical or laboratory TLS occurred.
- 81.8% (9/11) of patients with a high risk of TLS prior to treatment shifted to medium or low TLS risk categories after ibrutinib lead-in. Only 8.3% remained in the high TLS risk category (p=0.001); (**Figure 2a**). Lymphocyte levels decrease significantly after ibrutinib lead-in from a median of 54.8 x 10^9/L (range: 1.5-391.4) to 27,2 x 10^9/L (range: 2.0-439.6) (p=0.023) (**Figure 2b**).

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

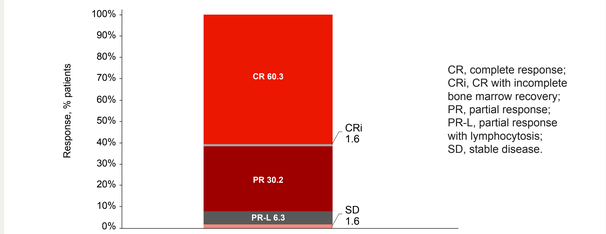


[a]Marginal homogeneity test; [b]Wilcoxon.

Effectiveness

- After a median follow-up of 15.2 months from I initiation, response data were available for 63/93 patients. According to iwCLL2018 criteria and routine clinical practice, 39 patients (61.9%) achieved a complete response, 23 (36.5%) a partial response, and 1 patient (1.6%) showed stable disease (**Figure 3**). One patient experienced disease progression after permanently discontinuing treatment due to an AE not related to treatment. The 6-month OS and PFS rates were 100% and 98.9%, respectively. One patient required a subsequent treatment.

Figure 3. Best overall response.



Treatment modifications

- At the time of analysis, I dose was reduced to 280 mg in 2 out of 93 patients (2.2%) due to thrombocytopenia and neutropenia. V dose reductions occurred in 9 patients (9.7%), with a total of 12 dose reductions (DRs) (1 to 100 mg, 4 to 200 mg, and 7 to 300 mg) (**Table 2**). The causes were diarrhea (n=6), neutropenia (n=2), abdominal pain (n=1), thrombocytopenia (n=1), nephrotoxicity (n=1), and food poisoning (n=1). All adverse events (AEs) leading to I DRs were resolved or partially improved. Among those leading to V DRs, 83.3% were resolved in 66.7% of patients or partially improved in 33.3%. Temporary treatment interruptions occurred in 33/93 patients (35.5%), affecting I in 26/33 cases (78.8%), V in 12/33 (36.4%), and both agents in 10/33 (30.3%). The main reasons were neutropenia (24.2%) and infections (12.1%). AEs leading to treatment interruptions were resolved (20) or partially resolved (6). Permanent treatment discontinuation was reported in 2 patients (2.2%). No CV toxicity leading to discontinuation was observed.
- DRs and treatment interruptions were generally manageable across subgroups.
- Among patients with ≥2 comorbidities, 5 (18.5%) experienced DRs, I was reduced in one patient (3.7%) and V in four patients (14.8%). The AE leading to the I reduction was thrombocytopenia and was partially resolved. All V-related AEs were resolved (75.0%) or partially improved (25.0%) following dose adjustment. Temporary treatment interruptions occurred in 44.4% of this subgroup of patients. All of AEs leading to temporary interruption due to treatment toxicity in this subgroup of patients were resolved (76.5%), or notably or partially improved (23,5%). (**Table 2**).
- In patients with arterial HTN, DRs were reported in 5 (13.2%) of them, I was reduced in two patients (5.3%) and V in four patients (10.5%). The AEs leading to I reductions were resolved or partially resolved. 85,7% of those leading to V reduction were resolved or partially resolved. Temporary interruptions occurred in 31.6% of HTN patients, slightly lower than in non-HTN patients (43.8%) (**Table 2**). All of AEs leading to temporary interruption due to treatment toxicity in this subgroup of patients were resolved of the AE (50.0%), or notably or partially improved (50.0%).

Table 2. Dose modification, interruption and discontinuation of therapy.

Characteristics	Total (N=93)	< 2 comorbidities (N=59)	≥ 2 comorbidities (N=27)	Non-HTN (N=48)	HTN (N=38)
Dose reductions, n (%)	10 (10.8)	5 (8.5)	5 (18.5)	5 (10.4)	5 (13.2)
Ibrutinib (280mg/day)	2 (2.2)	1 (1.7)	1 (3.7)	0 (0.0)	2 (5.3)
Venetoclax	9 (9.7)	5 (8.5)	4 (14.8)	5 (10.4)	4 (10.5)
100 mg/day	1 (11.1)	1 (20.0)	0 (0.0)	1 (20.0)	0 (0.0)
200 mg/day	4 (44.4)	3 (60.0)	1 (25.0)	2 (40.0)	2 (50.0)
300 mg/day	6 (66.7)	3 (60.0)	3 (75.0)	2 (40.0)	4 (100.0)
Temporary interruption, n (%)	33 (35.5)	21 (35.6)	12 (44.4)	21 (43.8)	12 (31.6)
Ibrutinib	26 (78.8)	16 (76.2)	9 (75.0)	16 (76.2)	9 (75.0)
Venetoclax	12 (36.4)	4 (19.0)	8 (66.7)	7 (33.3)	5 (41.7)
Both	10 (30.3)	7 (33.3)	3 (25.0)	7 (33.3)	3 (25.0)
Discontinuation of therapy, n (%)	2 (2.2)	2 (3.4)	0 (0.0)	1 (2.1)	1 (2.6)

HTN, hypertension.

Safety

- Overall, I+V was well tolerated. At the time of analysis, 70/93 patients (75.3%) experienced ≥1 adverse event (AE). The most common all-grade AEs were diarrhea (30.1%), and neutropenia (24.7%), and infection (21.5%). In most cases AEs were grade 1–2 (75.7%), with neutropenia being the most frequent grade ≥3 AE (15.1%).
- Among other AEs of clinical interest included cardiac events such as HTN (5.4%), atrial fibrillation (3.2%), arrhythmia (2.2%), and palpitations (1.1%), they were all generally low grade 1-2. While infections were common overall, the most frequent specific events were upper respiratory tract infection (12.9%) and urinary tract infection (5.4%). Additionally, one case of intestinal sepsis not related to treatment occurred, which resulted in patient death. No new cases of severe cardiac toxicity were reported during this follow-up.

Table 6. Adverse events in patients treated with ibrutinib + venetoclax (N=93).

AEs	Any grade	Grade 3/4
Patients with any AE, n (%)	70 (75.3)	17 (18.3)
Most common AEs (≥5%), n (%)		
Diarrhea	28 (30.1)	3 (3.2)
Neutropenia	23 (24.7)	14 (15.1)
Infection	20 (21.5)	4 (4.3)
Bleeding (including contusion)	11 (11.8)	1 (1.1)
Thrombocytopenia	10 (10.8)	2 (2.2)
Nausea	6 (6.5)	0 (0.0)
Arthralgia	5 (5.4)	0 (0.0)
Headache	5 (5.4)	0 (0.0)
Lymphocytosis	5 (5.4)	3 (3.2)
Asthenia	5 (5.4)	0 (0.0)
Fatigue	5 (5.4)	1 (1.1)
Hypertension	5 (5.4)	1 (1.1)
Second primary malignancy	5 (5.4)*	0 (0.0)
Other AEs of clinical interest, n (%)		
Atrial fibrillation	3 (3.2)	0 (0.0)
Arrhythmia	1 (1.1)	1 (1.1)
Palpitations	1 (1.1)	0 (0.0)
TLS	0 (0.0)	0 (0.0)
SAEs, n (%)	14 (15.1)	13 (14.0)

AE, adverse event; TLS, tumor lysis syndrome; SAE; severe adverse event. *breast (n=2), glioblastoma (n=1), melanoma (n=1), and urothelial (n=1).

- Among patients with ≥2 comorbidities no AEs of clinical interest related to CV toxicity were reported. Regarding HTN, 3 events occurred, all grade 1. No discontinuation of therapy was reported in this subgroup.
- Among patients with baseline HTN AEs of clinical interest related to CV toxicity included 3 events of atrial fibrillation, all grade 2. No grade ≥3 CV toxicity events were reported in this subgroup. One patient discontinued therapy in this subgroup. Other cardiac events such as arrhythmia, palpitations, cardiac failure were only observed in the non-HTN group all reported as grade 1 and at low frequencies (≤1.9%) except for one case of grade 3 arrhythmia. In the subgroup with baseline HTN, worsening of HTN was infrequent, with only one patient experiencing grade 3 HTN. On the other hand, there was only one new case of grade 2 HTN reported in the subgroup without baseline HTN.

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