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IBROMICS: A Real-World Study Of Clinical And Biological Parameters Determining Response In Patients With Chronic Lymphocytic Leukemia (CLL) Treated In First Line With Single Agent Ibrutinib

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Key Takeaway

We report a final analysis of the first prospective Real-World (RW) study of patients with CLL receiving 1L single-agent ibrutinib in routine practice in Spain, IBROMICS. Ibrutinib outcomes aligned with clinical trials and prior RW studies, showing effectiveness irrespective of high-risk CLL, including *del(17p)/TP53*. Ibrutinib exhibits dual therapeutic effects in CLL by directly targeting malignant B cells and partially restoring immune function. It not only disrupts the survival and proliferation of CLL cells but also enhances immune surveillance and impacts clones with high-risk mutations.

Conclusions

No significant differences in PFS or OS were observed among high-risk patient subgroups, including those with *del(17)p*, *TP53* mutations, u*IGHV*, and complex karyotype, indicating that the presence of these characteristics did not significantly compromise the effectiveness of ibrutinib.

A significant decrease in VAF greater than 10% was observed in 80-100% of patients with *TP53, SF3B1, XPO1, and NOTCH1* mutations, demonstrating that Ibrutinib has an impact on clones harboring mutations in these genes.

In the analysis of predictive markers for treatment response, both clinical and genetic/immunological parameters were evaluated; however, none showed a significant association with treatment effectiveness or toxicity.

Increased IgA evolution may suggest improved immunological surveillance. CD4+, CD8+, and normal B cell values increased, highlighting immune restoration in the real-world setting, with potential implications for antiviral and antitumor responses.

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Poster

Narrated poster video

Supplementary material

https://www.congresshub.com/EHA2025/Oncology/Ibrutinib/Garcia-Vela

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Introduction

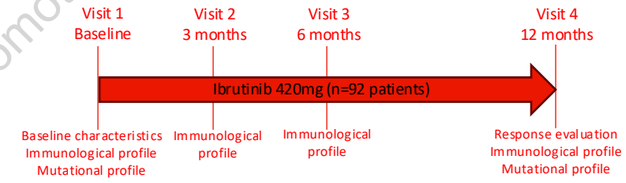
- Chronic Lymphocytic Leukemia (CLL) is a heterogeneous disease influenced by microenvironment and immune system.[1]
- Ibrutinib has transformed CLL management by combining sustained control of clonal proliferation with partial restoration of adaptive immunity—a dual mechanism that differentiates it from other therapies with limited immunomodulatory impact.[2,3]

Objectives

- The primary objective of this study was to analyze the possibility of predicting progression-free survival (PFS) and overall survival (OS) from clinical, cytogenetic, molecular, and immunological data in patients with CLL treated with first-line single-agent ibrutinib.
- Secondary endpoints were to analyze the clinical characteristics, therapeutic response, and progress of patients, to determine predictive markers of response and the evolution of immune reconstitution patterns. Also, to determine molecular and immunological profiles in CLL patients associated with different toxicity profiles.

Methods

- IBROMICS is a prospective, observational real-world study, including patients from 42 Spanish centers with active CLL according to iwCLL criteria (2018), starting 1L ibrutinib treatment from September 2022 to September 2023 [12 months (12m) follow-up].
- Clinical, immunological, and molecular data (30 gene NGS panel) were analysed.



Results

- Of 92 patients recruited in 42 centers in Spain from September 2022 to September 2023, 91 were included (62.6% male). Demographic data and baseline characteristics are included in Table 1.
- Population median age was 71.0 (47-90) years (38.5% >75). Most of the population had ECOG 0-1 (97.8%) and Rai stage 0-II (82.2%). High-risk mutations were very prevalent [u*IGHV*: 59/91 (64.8%), *del(17p)* or *TP53* mutations (*TP53m*): 26/90 (28.9%) and complex karyotype: 7/67 (10.4%)]. 87.9% (80/91) of the patient population had baseline comorbidities, the most common being hypertension (45.1%), dyslipidemia (25.3%), and diabetes (22.0%).

Table 1. Demographic data and baseline characteristics

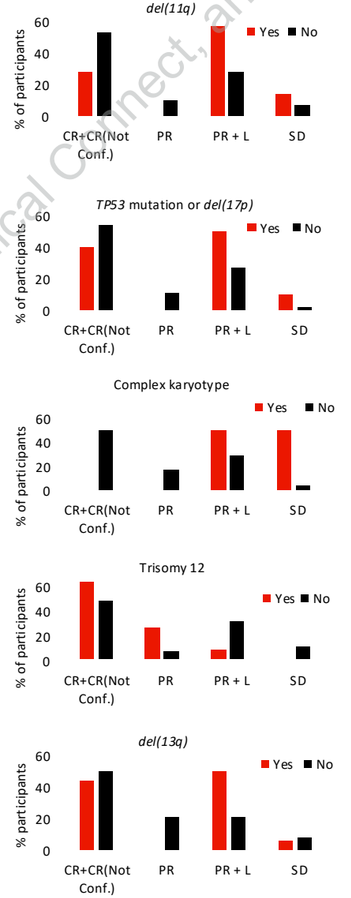
Characteristics	
Demographic and clinical	
Male (n=91), n (%)	57 (62.6%)
Median age (Min,Max) (n=90), years	71 (47, 90)
ECOG 0-2 (n=89), n (%)	88 (98.9%)
Rai Stage 0 (n=90), n (%)	20 (22.2%)
Rai Stage I-II (n=90), n (%)	54 (60.0%)
Mutational profile, n (%)	
IGHV unmutated (n=91)	59 (64.8%)
del(17p)/TP53m (n=90)	26 (28.9%)
Complex Karyotype (n=67)	7 (10.4%)
del(11q) (n=74)	14 (18.9%)
Trisomy 12 (n=74)	20 (27.0%)
del(13q) (n=82)	37 (45.1%)
Cytopenia (n=91), n (%)	
Hemoglobin ≤10 g/dL	42 (46.2%)
Platelets count ≤ 100,000/mm³	41 (45.1%)
Comorbidities (n=91), n (%)	80 (87.9%)
Hypertension	41 (45.1%)
Dyslipidemia	23 (25.3%)
Diabetes mellitus	20 (22.0%)

- The 12m Progression Free Survival (PFS) was 93.4% and was not influenced by the clinical or genetic characteristics studied. IgA increased from baseline to 12m (mean [SD] 92.2 (91.7) to 130.8 (103.3) mg/dL; p=0.0001), while there were no statistically significant changes for IgG and IgM (**Figure 1**). Overall response rate (ORR) at 12 m was 93.3%. Efficacy was similar regardless of *IGHV* status or *del(17p)/TP53* mutations (**Figure 2**).

Figure 1. IgA profile from baseline to 12 months of ibrutinib treatment

IgA profile from visit 1 (baseline) to visit 4, after 12 months of ibrutinib treatment. IgA mg/dL levels, Paired data, n=38 (visit 1), n=27 (visit 2), n=30 (visit 3), n=38 (visit 4). Change Visit 4-Visit 1 =38,6mg/dL, p-value <0.0001

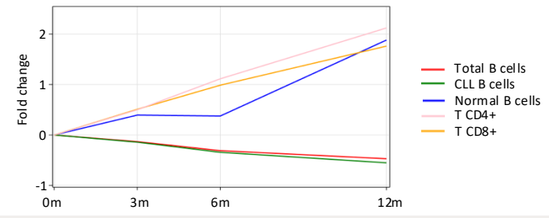
Figure 2. Treatment response by genomic aberrations



Therapeutic response from visit 2 to visit 4, after 12 months of ibrutinib treatment. % of participants,
del(11q) n=7 (Yes), n=28 (No); *TP53m/del(17q)* n=10 (Yes), n=26 (No);
Complex karyote n=2 (Yes), n=28 (No); Trisomy 12 n=11 (Yes), n=25 (No),
del(13q) n=16 (Yes), n=24 (No)
Complete Response+ Complete Response Not Confirmed by MO or TAC [CR+ CR(Not Conf.)], Partial response (PR), Partial response with lymphocytosis (PR+L), Stable Disease (SD)

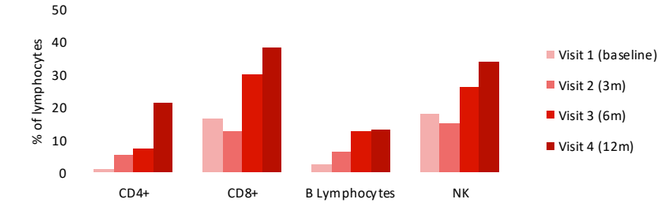
- The percentage of CLL B cells significantly decreased, while the proportion of normal B cells increased (**Figure 3**; p<0.001). CD4+ and CD8+ T cells relative values also increased (**Figure 3**; p<0.0001).

Figure 3. Fold change in B and T cells at 3, 6 and 12 months of ibrutinib treatment



- The percentage of patients with normal lymphocyte relative values increased from 1.2% to 21.3% for CD4+, from 16.7% to 38.2% for CD8+ and from 2.4% to 13.1% for B cells. Immune restoration for CD4+ and CD8+ was comparable in high-risk and non-high-risk patients (**Figure 4**).

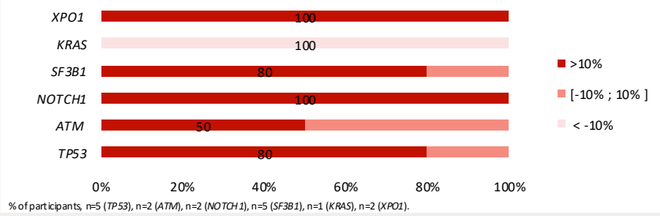
Figure 4. Evolution in immunological profile from baseline to 12 months of ibrutinib treatment



n=84 (visit 1), n=71 (visit 2), n=67 (visit 3), n=61 (visit 4).

- One patient developed a *BTK* mutation at 12 m [*T474I*, variant allele frequency (VAF) 2.5%]. Among *TP53m* pts, 4 out of 5 (80%) exhibited a significant reduction in VAF >10% within the first year of treatment. Similar reductions were noted in other mutations [*ATM* 1 out of 2 pts (50%), *NOTCH1* 2/2 (100%), *SF3B1* 4/5 (80%), *XPO1* 2/2 (100%)], while only 1 pt had an increased VAF >10%, in *KRAS* (**Figure 5**).

Figure 5. Reduction of VAF from baseline to 12 months of ibrutinib treatment



% of participants, n=5 (*TP53*), n=2 (*ATM*), n=2 (*NOTCH1*), n=5 (*SF3B1*), n=1 (*KRAS*), n=2 (*XPO1*).

- A total of 82.4% of patients experienced ≥1 TEAE (Treatment-Emergent Adverse Events) [53.8% related with ibrutinib, as arthralgia: 14/91 (2 grade (gr)≥3); bleeding 9/91 (0 gr≥3); atrial fibrillation: 7/91 (1 gr≥3)]. No significant correlation was found between mutation emergence and disease progression, nor with the appearance of toxicity.

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B-cell Malignancies