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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 Takeaways

This is the first interim analysis of the prospective study IBROMICS conducted in a Spanish real-world setting and designed to determine the effects of front-line single agent ibrutinib treatment beyond direct anti-tumor activity, including early restoration of immune surveillance and mutational landscape of 1L CLL patients.

Conclusions

Here, we report the first prospective real-world evidence study in patients with CLL treated with front-line single agent ibrutinib in routine clinical practice in Spain.

The results of this study suggest an early partially restored immune surveillance, including trends to decreased memory cells and increased naïve T lymphocytes, underscoring ibrutinib's therapeutic effects beyond direct tumor targeting. Future follow-up will help elucidate longer term implications of immune modulation on treatment outcomes.

This study will contribute to a deeper understanding of ibrutinib's role in CLL management, emphasizing the significance of considering different factors (clinical, molecular, and immunological) in optimizing patient care.

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Introduction

- B-cell Chronic Lymphocytic Leukemia (CLL) is a heterogeneous disease that represents 30-40% of adult leukemias.[1]
- Recent studies emphasize the role of the leukemic microenvironment and immune system in disease evolution.[2]
- Ibrutinib has shown significant efficacy in CLL treatment due to its direct antitumor effects and its ability to partially restore immune system function.[3]

Objectives

- To explore the immune reconstitution patterns and the distribution of mutational profiles in patients with CLL treated with front-line single agent ibrutinib in routine clinical practice.
- The present study focuses on the prospective description of these patterns at baseline and after 3 months of treatment.

Methods

- IBROMICS is a multicenter, prospective, non-interventional study. Efficacy variables (OS and PFS); clinical characteristics; cytogenetic profile; safety variables; clinical, genetic and immunological markers, mutational profile and immune competence will be described.
- The study included patients with active CLL and IWCLL indication for treatment starting first-line single agent ibrutinib in routine clinical practice.
- Here, we report the first interim analysis of patients' clinical, immunological, and genetic data at baseline and after 3 months of Ibrutinib treatment.

Results

- Of 92 patients recruited in 42 centers in Spain from September 2022 to September 2023, 2 were excluded from the analysis for non-compliance with inclusion criteria. Demographic data and baseline characteristics are included in **Table 1**.

Table 1. Demographic data and baseline characteristics

Characteristics	
Demographic and clinical	
Male (n=90), n (%)	56 (62.2%)
Age (n=90), median (Q1, Q3)	71.0 (62.0, 78,0)
ECOG 0 (n=85), n (%)	56 (65.9%)
Mutational profile, n (%)	
IGHV unmutated (n=89), n (%)	56 (62.9%)
Del17p (n=90), n (%)	11 (12.2%)
TP53 (n=90), n (%)	15 (16.7%)
Del11q (n=90), n (%)	11 (12.2%)
Trisomy 12 (n=90), n (%)	20 (22.2%)
Del13q (n=90), n (%)	32 (35.6%)
Complex karyotype (n=90), n (%)	3 (3.3%)

- 87.8% (79/90) of the patient population had baseline comorbidities, the most common being hypertension in 40/90 (44.4%) patients, dyslipidemia in 23/90 (25.6%), and diabetes in 20/90 (22.2%).
- Regarding the genetic profile (**Figure 1**), 56/89 (69.2%) patients presented mutations in any CLL-related gene, and the most frequently mutated (>10% of patients) were: TP53 (12/46, 26.1%), NOTCH1 (11/46, 23.9%), ATM (10/46, 21.7%), and SF3B1 (9/46, 15%).
- 20/65 (30.8%) patients had no mutations at baseline in CLL-related genes. 19/65 (29.2%) had one mutation, 11/65 (16.9%) had 2 and 9/65 (13.8%) had 3 mutations; but one patient displayed up to 7 different mutations (**Figure 1**).

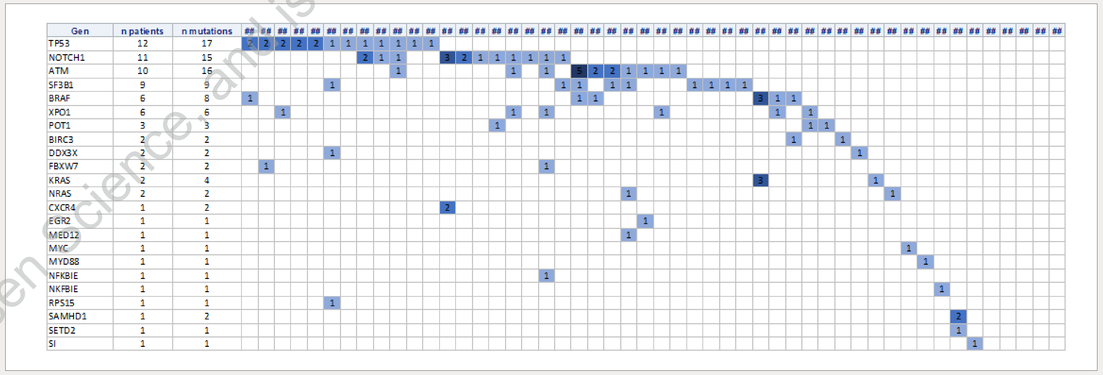

Figure 1. Baseline gene mutations (n=46)

- As to T cell maturation stages, single agent ibrutinib treatment decreased the median percentage of two of the main memory subpopulations of CD8+ T lymphocytes: CD8+ T central memory (TCM) from 13.2% (Q1-Q3, 7.8-25.9) to 12.8% (Q1-Q3, 4.5-21.0) (p=0.0124) and CD8+ T effector memory (TEM) from 3.3% (Q1-Q3, 0.7-12.8) to 1.2% (Q1-Q3, 0.8-5.9) (p=0.0476), but increased CD8+ NAÏVE from 33.3% (Q1-Q3, 17.7-51.1) to 39.0% (Q1-Q3, 27.7-60.8) (p=0.0290) (paired data). The CD4+/CD8+ ratio, typically disbalanced in CLL patients, was 1.33 at baseline and 1.25 at 3 months. (**Figure 2**).
- CD3 positive T lymphocytes decreased from a median of 8.0% (Q1-Q3, 4.9-15.6) at baseline to 7.9% (Q1-Q3, 5.4-32.6) at 3 months (paired data, p=0.0708).

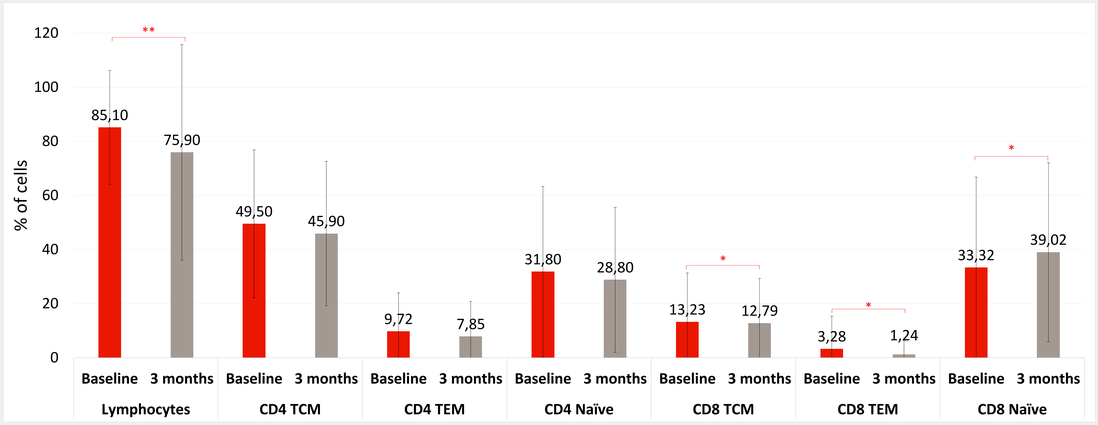

Figure 2. Evolution (paired data) in immunological profile from baseline and after 3 months of treatment with single agent ibrutinib. % of cells: median (IQR); IQR=Q3-Q1. n=47 (Lymphocytes), n=47 (CD4), n=45 (CD8). Change from baseline (paired data): * p<0.05, ** p<0.001, Wilcoxon test

ECOG: Eastern Cooperative Oncology Group; IWCLL: International Workshop on Chronic Lymphocytic Leukemia; OS: Overal Survival ; PFS: Progression-Free Survival

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B-cell Malignancies

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