HEMATOLOGIA
Número Educacional

th LAG-CLL Meeting 2026

Latin American Group on
Chronic Lymphocytic Leukemia

16-17 ABRIL 2026 HILTON HOTEL Mendoza, Argentina

Volumen 30 • Número Extraordinario
ABRIL 2026

Sociedad Argentina de Hematología

HEMATOLOGÍA

ÓRGANO DE DIFUSIÓN DE LA SOCIEDAD ARGENTINA DE HEMATOLOGÍA

Esta revista se encuentra indizada en: SCIELO, NÚCLEO BÁSICO, LATINDEX, DIALNET, LILACS, SIIC Data Bases, BIREME BRASIL, REDIB, DOAJ.

ISSN: 2250-8309 (versión en línea)

VOLUMEN 30 Nº EXTRAORDINARIO • Abril 2026 • Publicada en Abril de 2026 • Buenos Aires, Argentina

Edición: **Sociedad Argentina de Hematología**: Julián Alvarez 146 - C1414 DRD - TEL/FAX: (54-11) 4855-2452 / 2485

www.sah.org.ar / e-mail: **revista@sah.org.ar** / contacto: **Mariela Escalante**

Hematología se distribuye cuatrimestralmente en forma gratuita a los miembros de la Sociedad Argentina de Hematología

Se publica en abril, agosto y diciembre de cada año

Registro de la Propiedad Intelectual Nº 155751

VOLUMEN 30 • Nº EXTRAORDINARIO

6th LAG-CLL Meeting
Latin American Group on Chronic Lymphocytic Leukemia

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Welcome to the 6th LAG-CLL Meeting in 2026!

HEMATOLOGÍA
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5th Latin American Congress on
Chronic Lymphocytic Leukemia
Noviembre 2024

The LAG-CLL Meeting is the biennial flagship event of the Latin American Group on Chronic Lymphocytic Leukemia, born out of the growing interest in CLL in the region. Bringing together leaders in basic and clinical research, it has evolved into a unique platform for the exchange of biological and clinical data in Latin America.

Since its inception in 2013, the meeting has expanded with each edition: the first three meetings took place in Uruguay, Brazil and Argentina, respectively; the 2022 meeting was held online, and in 2024, it went back to an in-person format, turning into a regional benchmark in the field.

We will meet again on **April 16 and 17, 2026**, for a new edition, featuring two days of intense networking and outstanding academic discussions on CLL.. This time the setting will be the beautiful city of **Mendoza, Argentina**, at the foot of the Andes, recognized worldwide as the cradle of the Argentinian Vineyards.

This will be a golden opportunity to strengthen ties in the scientific community, inspire new collaborations, share advances in research, exchange ideas and deepen our knowledge on CLL, Join us for an unforgettable experience of science, discussion and networking in the heart of the Andes.

LAG-CLL Meeting 2026 Authorities

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Oral presentations

OP 1 (#40)

Dissecting the role of the notch1/msi2/c-myc pathways in chronic lymphocytic leukemia progression

Querol Rivas, Juliana[1]; Fernández, Gabriel[2]; Payque, Eugenia[1]; Uría, Rita[1]; Dos Santos, Gimena[3]; Márquez, María Elena[4]; Landoni, Ana Inés[5]; Irigoín, Victoria[6]; Muxi, Pablo[7]; Oliver, Carolina[8]; de Galvez, Gabriela[6]; Kescherman, Francis[3]; Gabus, Raúl[5]; Oppezzo, Pablo[1]; Chiorazzi, Nicholas[9]; Ferrer, Gerardo[10]; Palacios, Florencia[1]

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HEMATOLOGÍA
Volumen 30 - Número Extraordinario 6th Latin American Congress on Chronic Lymphocytic Leukemia
Abril 2026

Introduction

RNA-binding proteins (RBPs) are key regulators of post-transcriptional gene expression and are frequently dysregulated in cancer. Among them, elevated Musashi2 (MSI2) levels have been associated with several malignancies. Our group previously reported increased MSI2 expression in tumor B cells from patients with chronic lymphocytic leukemia (CLL) and poor clinical outcomes. In CLL, MSI2 promotes cell survival and tumor growth [1]. Recently, we demonstrated that: 1) NOTCH1 signaling pathway induces MSI2 expression by repressing its negative regulator, KLF4 and 2) MSI2 inhibits tumor-cell migration within an activated tumor microenvironment [2], suggesting that NOTCH1/MSI2 signaling retains leukemic cells within proliferative niches where they receive survival signals, thereby supporting tumor clone growth.
In CLL, NOTCH1 signaling induces transcription of the oncogene c-MYC, an oncoprotein highly expressed in patients with poor clinical outcomes. Given our previous findings and the knowledge that MSI2 regulates c-MYC translation in other cancers [3,4], we investigated whether a coordinated NOTCH1/MSI2/c-MYC regulatory pathway operates in leukemic clones from CLL patients.

Aims

To define how the NOTCH1/MSI2/c-MYC pathway mechanistically drives post-transcriptional regulation in CLL and to determine how this pathway contributes to the expansion and progression of the leukemic clone.

Methodology

Peripheral blood samples from CLL patients were obtained following informed consent and institutional Ethics Committee approval. Cells stored in the Uruguayan CLL Group Biobank were used for the molecular and cellular biology experiments.

Results

First, we determine MSI2 and c-MYC expression levels in 10 B-CLL samples. Analysis revealed a positive correlation between MSI2/c-MYC protein levels($r=0.47$; $p=0.029$), where patients with poor outcomes show higher levels of both proteins.
In-vitro studies of CLL B cells from 13 patients treated for 24h with a MSI2 inhibitor showed that blocking MSI2 function reduced c-MYC protein levels($p=0.0042$). Consistently, TCL1 mice treated with the inhibitor showed reduced c-MYC protein levels in CD19+CD5+ cells. RNA immunoprecipitation assays in primary CLL cells confirmed direct binding of MSI2 to c-MYC mRNA.
Because NOTCH1 transcriptionally activates c-MYC, we evaluated combined inhibition of NOTCH1 and MSI2. 13 CLL samples were treated with both inhibitors, showing that dual inhibition led to a greater reduction in c-MYC levels than either inhibitor alone($p\leq0.0001$), suggesting a potential strategy to reduce tumor cell viability.

Conclusions

We propose that NOTCH1/MSI2/c-MYC signaling pathways drives proliferation of leukemic B cells in CLL. NOTCH1 induces MSI2 expression by repressing KLF4 and promotes c-MYC transcription, while MSI2 binds c-MYC mRNA and enhances its translation. Disrupting this pathway may offer a targeted therapeutic strategy for certain patients and may open new avenues for highly targeted CLL therapies.

OP 2 (#58)

Transcriptome-wide characterization of sf3b1-mutated chronic lymphocytic leukemia reveals event-specific splicing patterns and potential novel candidate targets.

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Introduction
In chronic lymphocytic leukemia (CLL), SF3B1 mutations occur in 10–20% of cases and are associated with a more aggressive clinical course. SF3B1 encodes a core component of the U2 small nuclear ribonucleoprotein (U2 snRNP) complex essential for pre-mRNA splicing. Most transcriptomic studies of SF3B1 mutation consequences have relied on poly(A)-selected RNA-seq, limiting intron retention detection and focusing mainly on event frequency rather than affected genes, isoforms, and functional consequences. Therefore, a comprehensive total RNA–based analysis may provide a broader view of splicing alterations, refining molecular signatures and identifying clinically relevant biomarkers.

Objective(s)
To systematically characterize the transcriptomic impact of SF3B1 mutations in CLL and identify consistent splicing alterations with potential clinical relevance.

Methodology
High-depth public total RNA-seq data (rRNA-depleted; n=74; >250M reads/sample; PRJEB56000) were analyzed. After quality control, five samples were excluded (final n=69). Reads were aligned with STAR. Differential splicing analysis between SF3B1 wild-type (n=64) and mutated (n=5) samples was performed using rMATS-turbo. Enrichment and directionality were evaluated with Fisher's exact and non-parametric tests, with Benjamini–Hochberg correction.

Results
We identified 337 significant differential splicing events. Relative to the background distribution of detected events, significant alterations were most strongly enriched for Intron Retention (RI; OR=9.73, FDR<1×10^-30), followed by A3SS, while Skipped Exons (SE) were depleted in this dataset. SF3B1-mutated samples exhibited a structured profile of event types. Although A3SS and Mutually Exclusive Exons (MXE) represented the majority of affected events in this group, directionality analysis revealed that RI and A5SS events were more frequently excluded in SF3B1-mutated samples compared to wild-type, whereas MXE events were more frequently included. In contrast, despite being highly represented in the SF3B1-mutated group, A3SS showed no consistent directional shift between groups. These coordinated alterations segregated mutated and wild-type samples by unsupervised clustering. Filtering for low intra-group Percent Spliced In (PSI) variability identified canonical SF3B1 targets (e.g., DLG1, MAP3K8, BRD9) alongside novel candidate genes implicated in tumorigenesis and therapy resistance not previously described in CLL.

Conclusions
High-depth total RNA sequencing reveals a structured splicing landscape associated with SF3B1 mutations in CLL. In addition to the expected A3SS alterations, pronounced enrichment and directional bias of Intron Retention events highlight a broader impact of SF3B1 mutations on RNA processing. Together, these alterations delineate a consistent pattern of differential splicing at the gene level and highlight candidate genes for further functional investigation and potential molecular stratification.

OP 3
(#66)

Detection of occurrent somatic hypermutation and associated gene expression profile in single b cells of follicular lymphoma and mouse models.

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Somatic Hypermutation (SHM) is essential for antibody affinity maturation, yet it is traditionally analyzed as a cumulative population outcome. To capture individual mutational events in real-time, we developed a single-cell RNA and B-cell receptor sequencing pipeline (scSHM). We applied this to tumor cells from classical follicular lymphoma (cFL), a malignancy arrested at the germinal center stage. We identified 1,238 "occurrent" SHM events, new mutations arising within single-cell mRNA transcripts, occurring in 1.11% of cFL cells. These events were significantly absent in chronic lymphocytic leukemia (CLL) controls. Neovariant-carrying cells exhibited a distinct transcriptional profile characterized by elevated AICDA expression and the coordinated upregulation of mismatch repair (MMR) and base excision repair (BER) pathways.

To validate these findings, we utilized mouse models representing a gradient of AID expression: knockout Aicda-/- (0x), heterozygous Aicda+/- (0.5x), WT (1x), and Aicda-Gfp BAC transgenic (3x). The frequency of events increased in correlation with AID dosage, with the 3x cohort effectively recapitulating the human cFL mutational and transcriptional signature. By comparing "original" (germline-matching) and "neovariant" (mutated) nucleotides, we demonstrated that 91.3% of events disrupted canonical AID motifs, supporting the directional polarity of the mutations. Analysis of 344 murine events showed a significant preference for Complementarity-Determining Regions (CDRs) and WRCY/WA hotspots. Our results demonstrate that high mutational pressure triggers a specialized DNA repair response, offering novel insights into the functional cooperation between AID and repair machinery in germinal center B-cell neoplasms.

OP 4
(#56)

Mutational and clonal landscape of chronic lymphocytic leukemia using next-generation sequencing: a multicenter real-world cross sectional study in Argentina.

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Introduction

Chronic lymphocytic leukemia (CLL) is an heterogeneous disease with a complex molecular landscape. Next-generation sequencing (NGS) enables the identification of prognostically relevant mutations, although it is still not standardized in clinical practice. In Argentina, real-world genomic data remain limited.

Objectives

To characterize the mutational profile of CLL Argentine patients undergoing NGS and to explore its association with clinical and therapeutic setting.

Methods

This multicenter, retrospective, observational study included CLL patients from public and private centers in Argentina diagnosed according to iwCLL criteria (1) who, after providing a writteng informed consent, uderwent NGS testing. Samples were obtained from peripheral blood and analized in a centralized laboratory using the SOPHiA Genetics Community CLL Clonality Solution and the SOPHiA DDM™ Platform, covering 23 CLL-related genes. Clinical data were collected using standardized forms. Continuous variables were described using median and interquartile range (IQR), and categorical variables using frequencies and percentages. Associations between categorical variables were evaluated using Fisher´s exact test. JAMOVI Statistics v2.6.44.

Results

A total of 83 patients underwent NGS between June 1, 2025 and February 1, 2026. Baseline characteristics: median age at diagnosis was 60 years (IQR 52-69); 54.2% were male. RAI stage distribution was 0 (20.5%) I (36.5%) II (16.9%) III (15.7%) IV (10.8%). At NGS, 68.7% were treatment-naïve and 31.3% relapsed/refractory. Eight samples were nonconclusive; therefore, 75 patients were evaluable. A total of 84% (63/75) harbored more than one mutation. IGHV was mutated in 29.3% (22/75), unmutated in 61.3% (46/75), and unmutated borderline in 9.3% (7/75). The most frequent variants reported were NOTCH1 28% (21/75), SF3B1 21.3% (16/75), TP53 18.7% (14/75) and ATM 17.3% (13/75). Additional less frequent alterations were also observed. When stratified according to the clinical timing of index NGS, TP53 mutations were significantly more frequent in relapsed/refractory compared with treatment-naïve patients (36% vs 10%, p=0.01). No significant associations were observed for NOTCH1 and SF3B1 (table 1). Median TP53 variant allele frequency (VAF) was similar between groups (14.9% vs 15%). Clonal variants were defined with a VAF ≥10%. A total of 64.3% (9/14) were classified as clonal and 35.7% (5/14) as subclonal <10%, according to international recommendations (1-3).

Conclusions

This real-world Argentine cohort highlights the genomic complexity of CLL across diverse healthcare settings. TP53 mutations were more prevalent in relapsed/refractory cases, without a corresponding increase in overall mutational burden or VAF expansion, probably indicating selective enrichment rather than widespread clonal escalation. These results underscore the importance of NGS for risk stratification and emphasize the need for broader access to molecular testing in Latin America.

OP 5
(#42)

Concomitant use of venetoclax 100mg and ketoconazole is clinically equivalent to venetoclax 400mg for treating relapsed or refractory chronic lymphocytic leukemia (CLL).

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Introduction

Venetoclax, a selective BCL-2 inhibitor, shows significant efficacy in CLL with durable responses and improved survival. Metabolized primarily by CYP3A4, its co-administration with strong CYP3A4 inhibitors like ketoconazole can elevate plasma levels, necessitating dose adjustments to avoid toxicity, especially tumor lysis syndrome. In Brazil, limited access to venetoclax prompted a strategy to combine 100 mg of venetoclax with ketoconazole to enhance availability.

Objective

Compare the efficacy and safety of low-dose venetoclax plus ketoconazole ("Ketoven" protocol) versus standard-dose venetoclax (400 mg), with or without rituximab, in patients with relapsed/refractory CLL.

Method

This real-world analysis included 114 patients from the Brazilian CLL Registry. All patients initiated venetoclax on day 22 of cycle 1 with a five-week ramp-up (20–200 mg). Then, for up to 24 cycles patients received either venetoclax 100 mg plus ketoconazole 200 mg daily - ´´Ketoven´´ protocol (n = 24) or venetoclax 400 mg daily (n = 90). Rituximab (375 mg/m² in cycle 1 and 500 mg/m² in cycles 2–6) was administered to 76 patients. All patients had at least six months of follow-up at the data cutoff.

Results

The median age was 66 years, and 61% of patients were male. Venetoclax was administered predominantly in the second line (45%), followed by the third (26%), fourth (22%), and fifth line or beyond (7%).

The overall response rate (ORR) was 97%, with similar rates observed in the Ketoven group (96%) and the standard treatment group (98%). No grade ≥2 hepatic toxicity attributable to ketoconazole was reported.

After a median follow-up of 21 months (range, 6–92), the median time to next treatment (TTNT) and median overall survival (OS) were not reached. The 2-year TTNT rate was 73%. Patients receiving venetoclax in later lines had a significantly shorter 2-year TTNT compared with those treated in the second line (59% vs. 89%; P=0.03). A trend toward shorter TTNT was observed in patients harboring del(17p)/TP53 mutations (44% vs. 74%; P=0.06).

At 2 years, TTNT was 77% in the Ketoven protocol group and 73% in the standard protocol group (P=0.39). Likewise, TTNT did not significantly differ between patients treated with rituximab-based combinations and those receiving venetoclax monotherapy (75% vs. 72%; P=0.45). After adjustment for del(17p)/TP53 mutations and treatment line, TTNT remained similar between patients treated with and without ketoconazole.

The 2-year OS rate was 77%, with no significant difference between groups (74% in the standard treatment group vs. 77% in the ketoconazole combination group).

Conclusion

Low-dose venetoclax plus ketoconazole demonstrated similar efficacy and tolerability to standard-dose venetoclax in patients with relapsed or refractory CLL. This cost-saving approach may be a viable alternative in settings with limited resources. Further prospective studies are needed to validate these findings and support broader implementation.

OP 6 (#77)

Ibrutinib maintenance after first-line chemoimmunotherapy in CLL: a prospective multicenter study.

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Background
Although targeted, fixed-duration regimens have reshaped frontline chronic lymphocytic leukemia (CLL) management, chemoimmunotherapy (CIT) remains widely used in several regions due to heterogeneous access to novel agents. A substantial proportion of patients treated with CIT achieve clinical remission but remain measurable residual disease (MRD)-positive. The potential role of maintenance therapy to deepen response and prolong disease control in this setting remains uncertain. Methods: We conducted a prospective, multicenter, single-arm phase 2 study evaluating ibrutinib maintenance in patients with CLL who achieved complete (CR) or partial remission (PR) within 12 months after first-line CIT and had detectable MRD. Ibrutinib was administered at 420 mg daily until disease progression or unacceptable toxicity. MRD was assessed using standardized 8-color flow cytometry in peripheral blood and bone marrow (sensitivity $\geq 10^{-4}$). The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), time to next treatment (TTNT), MRD kinetics, and safety. Results: Forty patients from nine centers were enrolled. Median age was 59 years; 62.5% were in CR and 37.5% in PR at maintenance initiation. Among MRD-positive patients at baseline, 23.5% achieved undetectable MRD and 85% experienced at least a 1-log reduction in MRD levels. All patients who initiated maintenance in PR converted to CR. After a median follow-up of 100 months, 48-month PFS was 65%, OS was 78%, and TTNT was 76%. Adverse events were predominantly grade 1–2; grade ≥3 toxicities were infrequent. Asymptomatic atrial fibrillation occurred in 8% of patients.

Summary/Conclusion
Ibrutinib maintenance following first-line CIT resulted in MRD reduction, response deepening, and durable disease control in this prospective cohort. While contemporary frontline strategies increasingly favor fixed-duration targeted combinations, these findings suggest that maintenance BTK inhibition may represent a pragmatic consolidation approach in settings where access to novel frontline regimens remains limited. Further comparative studies are warranted.

EP 20
(#62)

Oral microbiome structural alterations are associated with beta-2-microglobulin levels in chronic lymphocytic leukemia

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Introduction

Beta-2-microglobulin (B2M) is a well-established prognostic biomarker in chronic lymphocytic leukemia (CLL) that reflects tumor burden and systemic immune activation. There is emerging evidence of bidirectional interactions between host immunity and the microbiome. However, the relationship between systemic disease activity in CLL and alterations in the oral microbiome is not well understood.

Objectives

To investigate the association between serum B2M levels and oral microbiome diversity and community structure in patients with CLL.

Methods

This prospective cohort study collected oral biofilm samples at baseline (C1) from patients with confirmed CLL. DNA extraction included negative controls to monitor contamination. Microbiome profiling was performed using 16S rRNA gene sequencing. Alpha diversity was assessed using ASV richness, Faith's phylogenetic diversity (PD), the Shannon index, and the Gini–Simpson index. Beta diversity was evaluated using weighted UniFrac distances and compared using PERMANOVA. Differential abundance analysis was conducted using ANCOM-BC2 with false discovery rate (FDR) correction. Statistical significance was defined as $p < 0.05$.

Results

Sixty-two patients were included in the analysis. Elevated B2M levels (>3.5 mg/L) were observed in 8.1% of patients. Patients with elevated B2M levels demonstrated significantly reduced ASV richness compared to patients with normal B2M levels ($p = 0.048$) and a trend toward reduced phylogenetic diversity (Faith's PD, $p = 0.059$). Shannon and Gini-Simpson indices did not differ between groups, suggesting preservation of evenness despite reduced richness.Beta diversity analysis revealed significant global compositional differences between groups (weighted UniFracPERMANOVA, $p = 0.038$), indicating structural shifts in microbial communities associated with a greater systemic disease burden.
No individual taxa remained significant after FDR correction. However, Catonella showed a non-significant trend toward higher abundance in patients with normal B2M levels.

Conclusions

This exploratory prospective study found that elevated B2M levels were associated with reduced oral microbial richness and global community structural alterations in CLL. Although the differential taxa did not remain significant after correction for multiple testing, the observed shifts in diversity suggest a potential link between systemic disease burden and oral microbial ecology. These findings support the hypothesis that immune-microbiome interactions may reflect or contribute to disease activity in CLL, and they warrant validation in larger cohorts through mechanistic investigation.

EP 21
(#78)

Impact of new targeted therapies in CLL patients with unmutated igvh and overexpression of aid.

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Introduction

Chronic lymphocytic leukemia (CLL) shows marked clinical and molecular heterogeneity, hindering accurate prediction of disease progression. Despite multiple prognostic tools, reliable risk stratification remains limited. Activation-induced cytidine deaminase (AID) is aberrantly expressed in peripheral blood from patients with poor outcomes, mainly in unmutated CLL (U-CLL). Although AID drives somatic hypermutation and class-switch recombination in B cells, off-target activity can induce oncogenic mutations and chromosomal translocations.

We identified a novel CLL subgroup (SG_1) defined by unmutated B-cell receptors with specific IGHV rearrangements (IGHV1-02, IGHV1-69, IGHV3-30, IGHV4-39), positive AID expression and the shortest time to first treatment (TTFT). This subset comprises ~36% of U-CLL and can be prospectively identified by combining AID mRNA analysis with IGHV profiling in routine diagnostics.

Objective

To evaluate treatment response in this subset of patients, comparing chemoimmunotherapy with novel targeted therapies.

Method

In this work, we characterized CLL patients based on AID expression and its association with immunoglobulin heavy chain gene (IgVH) status/use. To assess AID expression, we used specific AID TaqMan probes. Assay sensitivity and the cut-off value were established using a calibration curve generated from synthetic cloned AID. cDNA from the Daudi cell line was included as a positive control, and pooled PBMC cDNA from 12 age-matched healthy donors as a negative control. This approach defined the minimum and maximum detectable AID transcript levels. Based on ROC curve analysis (sensitivity and specificity >99%), the cut-off for AID positivity was set at 7.000 CN. IGHV family subgroups and their association with AID expression were identified by unsupervised K-means clustering.

PB samples were prospectively collected from patients meeting the clinical and immunophenotypic criteria for CLL, in accordance with the iwCLL guidelines. The cohort included 312 patients (follow up = mean 5 years). Overall survival was analyzed by Kaplan-Meier (IBM SPSS Statistics v15.0).

Results

In SG_1, patients treated with chemoimmunotherapy had a median overall survival of 69 months, whereas median survival was not reached in those receiving novel targeted therapies (ibrutinib, venetoclax, or venetoclax plus obinutuzumab). Although no statistically significant difference was observed (likely due to the limited number of patients treated with targeted agents), these findings suggest that SG_1 which requires earlier treatment, may achieve improved progression-free survival with novel therapies. Ongoing studies aim to expand the cohort treated with targeted agents and to compare treatment responses between SG_1 (AID-positive, specific IGHV rearrangements, shorter TTFT) and subgroup 2 (same IGHV families, AID-negative and longer TTFT).

EP 22 (#79)

From indolent to lethal: clinical and pathological determinants of richter transformation, high risk case series.

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Richter transformation represents one of the most dramatic and devastating turning points in the course of chronic lymphocytic leukemia. A disease that often follows an indolent trajectory can suddenly evolve into an aggressive lymphoma, leading to rapid clinical deterioration and a profound change in prognosis. Despite major advances in targeted therapies and immunotherapy, outcomes after transformation remain poor. We sought to better understand how this transformation presents in real-world practice, how it manifests pathologically, how it is managed, and what short-term outcomes patients experience in a tertiary cancer center.

We conducted a retrospective descriptive case series including four consecutive patients diagnosed between 2018 and 2024 with biopsy-confirmed transformation. Comprehensive clinical data — including comorbidities, laboratory findings, imaging studies, histopathology, and treatment strategies — were collected from electronic medical records. Continuous variables are presented as median (range), and categorical variables as absolute numbers and percentages. Given the limited sample size, no comparative statistical testing was performed.

The median age at transformation was 69 years (range 62–77), and most patients were male. All had advanced chronic lymphocytic leukemia at the time of transformation, either clinically or biologically, including high-risk genomic features. Histopathology confirmed diffuse large B-cell lymphoma in three patients, while one showed early transformation features. Tumor proliferation indices were markedly elevated (70–95%), reflecting highly aggressive disease biology.

Half of the patients developed severe SARS-CoV-2 pneumonia complicated by multiorgan failure requiring invasive mechanical ventilation. In one critically ill patient, lymphoma-directed therapy could not be initiated. Three patients received salvage immunochemotherapy with dose-adjusted or platinum-based regimens, achieving partial response in two cases. Severe infectious complications were frequent. One patient was referred for hematopoietic stem cell transplant evaluation due to high-risk features.

Conclusions
Richter transformation remains a catastrophic and biologically complex complication of chronic lymphocytic leukemia. Our experience highlights three key determinants of adverse outcome: aggressive tumor proliferation, vulnerability to severe infections, and organ dysfunction limiting therapeutic options. Early biopsy of rapidly progressive lymphadenopathy and proactive infection mitigation strategies are essential. Even in the modern therapeutic era, overall survival after transformation remains limited, underscoring the urgent need for more effective and innovative treatment approaches.

EP 23
(#67)

Hodgkin lymphoma in patients with chronic lymphocytic leukemia: results from a multicenter collaboration in Argentina.

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Abril 2026

Introduction

Richter transformation (RT), defined as the development of an aggressive lymphoma in the context of chronic lymphocytic leukemia (CLL), remains a therapeutic challenge in these patients. The occurrence of Hodgkin lymphoma (HL) as a form of RT is uncommon (5–10% of RT cases), but well recognized. The biology of this entity is poorly understood, and patients are typically older and present with multiple comorbidities. Most published data consist of small series in the international literature.

Objective To describe the epidemiological and clinical characteristics, as well as outcomes, of patients with CLL who developed Hodgkin lymphoma across eight centers.

Materials and Methods

This was a retrospective, observational, multicenter study including patients older than 18 years with a prior diagnosis of CLL who developed HL between January 1, 2021 and January 1, 2025, with a minimum follow-up of 12 months. Data were obtained from medical records. Continuous variables were summarized using mean and interquartile range (IQR), and categorical variables were expressed as numbers and percentages. Survival analysis was performed using the Kaplan–Meier method. Statistical analysis JAMOVI statistics v2.6.44.

Results

A total of n=13 patients with a prior diagnosis of CLL who developed classical Hodgkin lymphoma (cHL) were included. The median age at HL diagnosis was 68 years (IQR: 64–72), and all patients were older than 60 years. At the time of RT, three patients had not received prior CLL treatment, and two had received two or more previous lines of therapy. Baseline characteristics at the time of transformation are shown in Table 1. Overall, 92.3% (12/13) were diagnosed at advanced stages (stage IIB, III, or IV), and 46.1% (6/13) had extranodal involvement (Bone, Bone Marrow, Lungs and Liver). Only one patient was diagnosed at stage I, presenting with a bulky mediastinal mass (>7.5 cm). B symptoms were present in 84.6% (11/13) of patients.

The median time from CLL diagnosis to HL transformation was 72 months (IQR: 28–107). As first-line therapy for HL, 92.3% (12/13) received ABVD-based regimen. Progression-free survival at 36 months was 61.5% (8/13). Median overall survival at 36 months was not reached, with an estimated overall survival from RT of 76.9% (Figure 1). Three deaths were recorded, all attributable to HL progression. This data compares favorably with the largest series to date published by Paul J. Hampel (1).

Conclusions

In our series, RT to HL in patients with CLL occurred at significantly older ages compared to de novo HL, with a variable interval from initial CLL diagnosis. Advanced-stage disease and extranodal involvement predominated. Prognosis was consistent with previously published data, showing better survival compared to transformation to diffuse large B-cell lymphoma, but worse outcomes compared to de novo HL. It's important to have data from LATAM in this unusual presentation of RT.

EP 24
(#65)

Long-term survival and cumulative incidence of secondary malignancies in chronic lymphocytic leukemia: a two-center cohort from Córdoba, Argentina.

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Volumen 30 - Número Extraordinario 6th Latin American Congress on Chronic Lymphocytic Leukemia
Abril 2026

Introduction
As survival improves in chronic lymphocytic leukemia (CLL), late complications, particularly secondary malignancies, are becoming increasingly clinically relevant. Despite extensive reports from North American and European cohorts, large-scale data from Latin American populations remain limited.

Objectives
To characterize long-term survival and the cumulative incidence of secondary malignancies in an Argentine CLL cohort.

Methodology
We conducted a retrospective study of 210 consecutive CLL patients followed at two tertiary-care centers in Córdoba, Argentina (Hospital Privado Universitario de Córdoba and Hospital Raúl Ángel Ferreyra). Clinical and staging data at diagnosis were collected. Overall survival (OS) was calculated from the date of diagnosis to death or last follow-up, estimated using the Kaplan–Meier method, and compared using the log-rank test. The cumulative incidence of secondary malignancies was estimated using a competing risks approach (event: secondary malignancy; competing event: death without secondary malignancy). Univariable Cox models explored associations with OS, and multivariable Cox models were adjusted for age, sex, ECOG performance status, LDH at diagnosis, and Rai stage.

Results
Median age was 68 years; 62% were male and 82% were diagnosed incidentally. The median time from diagnosis to initiation of first-line therapy was 20 months (95% CI: 12–28). With a median follow-up of 71 months, median OS was not reached, with 2- and 5-year OS rates of 95% and 80%, respectively. In multivariable analysis, predictors of worse OS were older age (HR: 1.06 per year; p = 0.001), worse ECOG (HR: 1.86 per point; p = 0.005), elevated LDH at diagnosis (HR: 2.07; p = 0.036), higher Rai stage (HR: 1.33 per stage; p = 0.024), and del(11q) (HR: 3.01; p = 0.003).

Twenty-four secondary malignancies were recorded (11%), with skin cancer being the most frequent (45%), followed by lung cancer (12%), and breast, renal, and pancreatic cancers (8% each). The median time from CLL diagnosis to the development of a secondary malignancy was 50.1 months (range: 11.1–223.2), with a cumulative incidence of secondary malignancies of 1%, 9%, and 15% at 2, 5, and 10 years, respectively (Figure 1). Incidence was higher in treated than in untreated patients, although the difference did not reach statistical significance (15% vs. 7%; RR: 2.05; p≈0.08).

Conclusions
In this Argentine cohort, CLL patients achieved sustained long-term survival. However, secondary malignancies represent a clinically relevant late complication, with increasing incidence over time and numerically higher rates among treated patients. These findings support close oncologic surveillance as an integral component of long-term CLL management.

EP 26 (#41)

Aid expression along with bcr-bias define a subgroup of unmutated-chronic lymphocytic leukemia patients with a shorter time to first treatment.

Rodríguez Zraquia, Santiago[1]; Chifteian, Mercedes[2]; Payque, Eugenia[2]; Souto, Jorge[2]; Uría, Rita[2]; Medina, David[3]; Álvarez, Diego[4]; Dos Santos, Gimena[5]; Oliver, Carolina[6]; Irigoin, Victoria[7]; Remedi, Victoria[8]; Lema, Virginia[9]; Ranero, Sabrina[10]; Grille, Sofía[11]; Dighiero, Guillermo[2]; Festari, Florencia[12]; Navarrete, Marcelo[13]; Oppezzo, Pablo[2].

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Abril 2026

Introduction

Chronic lymphocytic leukemia (CLL) cell proliferation and survival are largely sustained by tumor microenvironment (TME) signaling and antigen (Ag) stimulation (1). Activated B cells express activation-induced cytidine deaminase (AID), a mutagenic enzyme essential for adaptive immune response.

Our previous work shows that integrating AID mRNA expression with IGHV mutational profile finds four distinct subgroups within unmutated patients (U-CLL). SG_1 includes patients expressing AID, specific IGHV rearrangements and shortest time to first treatment (TTFT). SG_2 patients share the same IGHV families, lack AID expression and display the longest TTFT. SG_3 and SG_4 carry different IGHV rearrangements, are AID-positive and -negative, respectively and exhibit intermediate TTFT (2).

We hypothesize that the shorter TTFT observed in SG_1 is driven by constitutive Ag stimulation leading to an activated TME (aTME) and sustained AID expression that promote off-target mutations and disease progression.

To test this idea, we compared SG_1 and SG_2 by analyzing the physicochemical and structural properties of the complete paratope, integrating heavy- and light-chain CDR3 regions. We evaluated key aTME-associated molecules and assessed AID mutational burden through whole-exome sequencing (WES) with disease progression.

Objective

To investigate the role of AID activity in U-CLL.

Methodology

PBMCs were collected from patients with informed consent and Ethics Committee approval and stored at the Uruguayan Biobank of CLL.

Results

Despite sharing unmutated IGHV families SG_1 and SG_2 differ in the physicochemical and secondary structural properties of their BCRs, consistent with different antigen- or epitope-driven selective pressures.

Evaluation of an aTME included key molecules involved in proliferation (c-MYC), migration (CCL3, CCL4, and CD49d), and survival (BCL-2 and MCL-1). In all cases, protein expression levels and the percentage of the proliferative fraction (PF) were significantly higher in SG_1 compared with SG_2.

Given the high AID expression in SG_1, we further analysed specific transcription factors (TFs) regulating AID expression. HoxC4, SP-1, and NF-κB were significantly upregulated in SG_1 relative to SG_2. Finally, WES identified three pathways significantly enriched in genes harbouring AID off-target mutations: IFN-α, IFN-γ, and KRAS. Ongoing studies are underway to define the functional impact of these AID-related mutations on these pathways and CLL progression.

Conclusions

Overall, this work underscores a key role of antigen-driven BCR engagement in a specific subgroup of U-CLL (36% within U-CLL and 15% of the total CLL cohort) and supports the hypothesis that shorter TTFT is associated with an aTME and sustained AID expression. Furthermore, we demonstrate that high AID levels correlate the upregulation of specific TFs, and provide mechanistic evidence linking AID activity to disease progression in this newly defined subgroup of U-CLL.

EP 27
(#28)

Baseline clinical characteristics of patients with chronic lymphocytic leukemia (cll) from 11 latin american countries: a real-world registry analysis.

Oliver, Carolina[1]; Arrais, Celso[2]; Villela, Luis[3]; Roa, Macarena[4]; Rivarola, Sofia[5]; Cardozo, Lorena6; Torres, María Alejandra[7]; Castro, Denisse[8]; Valvert, Fabiola[9]; Trujillo Loisaza, Daniela[10]; Garcia Salgado, Anelys[11]; Irigoin, Victoria[12]; Porobelli, Leila[13]; Cugliari, Silvana[14]; von Glasenapp, Alana[6]; Peña, Camila[4]; Paredes, Sally[8]; Buccheri, Valeria[15]; Lema, Virginia[16]; Miroli, Augusto[17]; Alvarez, Jose[18]; Colturato, Maura[19]; Landoni, Ana Ines[20]; B Oliveira, Gislaine[21]; B Oliveira, Guislaine[21]; Zerga, Marta22; Ranero, Sabrina[23]; Pavlovsky, Miguel[24]; Cristaldo, Nancy[25]; Fogliato, Laura[26]; Custidiano, María del Rosario[27]; Leao, Danielle[28]; Orlova, María[29]; Barroso Duarte, Fernando[30]; Macchiavello, Etelvina[31]; Pose Cabarcos, Julio32; Fortier, Sergio[33]; Laviano, Julia[34]; Pagano, Clarisa[35]; Hamerschlak, Neslon[36]; Figueiredo, Vera[37]; Perez Jacobo, Fernando[38]; Robles, Arianna[39]; Otanez, Melani[40]; Stemelin, German[5]; Oliday, Rosa[41]; Idrobo, Henry[10]; Beltran, Brady[42]; Castillos, Jorge[43]; Chiattone, Carlos[44]; Malpica, Luis[45].

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Background: CLL is clinically heterogeneous, and access to diagnostic/prognostic tools varies widely across Latin America (LATAM). We analyzed baseline presentation, available cytogenetic/molecular testing, and real-world outcomes from a collaborative LATAM CLL registry to better define regional patterns of care and risk stratification. We also compared outcomes by healthcare sector (public vs private) as a proxy for differential access.

Methods: Retrospective data were collected for 4,649 patients diagnosed between 2000–2024 across 11 LATAM countries (Argentina, Brazil, Chile, Colombia, Cuba, Guatemala, Mexico, Paraguay, Peru, Uruguay, Venezuela), integrating the Brazilian Registry of CLL and GELL-CLL. Clinical stage, performance status, comorbidity burden, laboratory biomarkers, FISH/TP53 results, treatment-free survival (TFS) and overall survival (OS) were analyzed.

Results: Median age was 67 years (range 21–106) and 58.6% were male. Binet stage (n=4,249): A 62.1%, B 21.7%, C 16.5. Rai stage (n=3,875): 0 36.2%, 1 23.0%, 2 11.1%, 3 5.9%, 4 7.1. ECOG (n=2,756): 0 60.7%, 1 29.2%, ≥2 10.1. CIRS (n=1,648): median 4; ≥1 comorbidity 35.4%. Elevated LDH occurred in 29.0% (864/2,983) and elevated β2-microglobulin in 46.3% (1,050/2,269). A 4-probe FISH panel (n=634) showed del(13q) 19%, trisomy 12 (+12) 16%, del(11q) 13%, and del(17p) 19%; isolated del(17p) testing was positive in 12.0% (122/1,015). TP53 mutations were detected in 16.4% (56/342); IGHV status was not systematically captured. After median follow-up of 49 months, median TFS was 38 months and was longer in private versus public centers (46 vs 31 months; P=0.01). Among patients with del(17p) data (n=921), TFS was shorter with del(17p) (13 vs 25 months; P=0.005). In patients with a complete 4-probe panel (n=543), the shortest TFS occurred with del(17p) (23 months) and del(11q) (20 months), followed by +12 (31 months) and normal FISH (33 months), while del(13q) had the longest TFS (60 months). Median OS was not reached. Five-year OS was lower in public versus private centers (88% vs 93%; P=0.03), with elevated β2-microglobulin (85% vs 96%; P<0.0001), and with elevated LDH (83% vs 92%; P<0.0001); OS declined by Binet stage (A 95%, B 85%, C 72%). With del(17p) data (n=921), 5-year OS was 79% with del(17p) versus 89% without (P=0.001).

Conclusion: This large, multicenter, real-world registry demonstrates early-stage predominance yet meaningful high-risk biology in LATAM CLL (del(17p), TP53 mutations, high LDH/β2-microglobulin) with adverse outcomes. Findings reinforce the prognostic value of established biomarkers while highlighting persistent gaps in comprehensive risk stratification. Expanding access to molecular diagnostics and strengthening clinician education are critical to enable risk-adapted, evidence-based CLL care across Latin America.

EP 28 (#32)

Sustained efficacy and continued favourable survival of zanubrutinib in treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma: 6-year follow-up in the phase 3 sequoia study.

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SEQUOIA (NCT03336333) evaluated zanubrutinib (zanu) in treatment-naive (TN) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Updated results for arms A (zanu) vs B (bendamustine + rituximab [BR]) and arm C (zanu) with a median follow-up (FU) of ~6yrs are presented.

Patients (pts) without del(17p) were randomized to receive zanu (arm A) or BR (arm B). Pts with del(17p) received zanu in arm C. This analysis reported investigator-assessed progression-free survival (PFS), time to second PFS event or death (PFS2), and overall survival (OS). PFS and OS analyses were also adjusted for COVID-19 impact.

In arms A and B, 479 pts received zanu (n=241) or BR (n=238); baseline demographics were well balanced between arms. As of April 30, 2025, median FU was 72.8mo (range, 0.0-90.0). Zanu demonstrated sustained PFS superiority vs BR (HR, 0.28; 95% CI, 0.20-0.38; P<.0001). At 72mo, PFS rates (95% CI) were 74% (67.2-79.1) for zanu and 32% (25.2-39.9) for BR; after COVID-19 adjustment, rates were 77% (70.1-81.8) and 33% (25.5-40.4), respectively. At 72mo, PFS2 rates (95% CI) were 84% (78.2-87.8) for zanu and 76% (69.9-81.6) for BR. OS (95% CI) at 72mo was 84% (78.7-88.2) for zanu and 80% (74.4-85.2) for BR; after COVID-19 adjustment, OS was 88% (82.5-91.2) and 82% (95% 76.1-86.7), respectively. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 72% of zanu pts and 74% of BR pts. Exposure-adjusted incidence rates (EAIR) for adverse events (AEs) of interest (per 100 person-mo) were atrial fibrillation/flutter (zanu vs BR: 0.16 vs 0.10), hypertension (0.46 vs 0.36) and infections (3.40 vs 3.37), which were comparable between zanu and BR, while neutropenia (0.34 vs 2.95) was higher with BR and hemorrhage (1.57 vs 0.32) and major hemorrhage (0.18 vs 0.05) were higher with zanu.

Arm C included 111 pts [110 with confirmed del(17p)] who received zanu; median FU was 76.7mo (range, 5.0-86.9). PFS rate at 72mo (95% CI) was 64% (53.6-72.8) and after COVID-19 adjustment was 65% (54.3-73.5). Estimated 72mo (95% CI) PFS2, OS and OS with COVID-19 adjusted rates were 82% (73.6-88.3), 83.2% (74.7-89.1) and 85.0% (76.7-90.5), respectively. The safety profile in arm C was similar to arm A. In arm C, 74% of pts experienced grade ≥3 AEs. The EAIR for select AEs of interest (per 100 person-mo) were atrial fibrillation/flutter 0.15, hypertension 0.38, infections 4.16, neutropenia 0.35, hemorrhage 2.03 and major hemorrhage 0.17.

With 6 yrs of FU, zanu continues to demonstrate robust efficacy and a favorable safety profile in TN CLL/SLL. Zanu demonstrated sustained superiority vs BR with a 72% reduction in risk of progression or death. Long-term outcomes were robust in both pts with del(17p) and without del(17p), with comparable PFS, PFS2, and OS. These data support zanu as an effective and tolerable frontline treatment in TN CLL/SLL, regardless of del(17p) status, including pts with high-risk disease.

EP 29
(#64)

First-line venetoclax-based regimens versus chemoimmunotherapy in chronic lymphocytic leukemia: a real-world analysis from the brazilian cll registry.

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Background
Venetoclax, a selective BCL-2 inhibitor, has reshaped the treatment landscape of chronic lymphocytic leukemia (CLL), especially in combination with anti-CD20 monoclonal antibodies. While randomized trials such as CLL14 have shown the superiority of venetoclax-obinutuzumab (VenO) over chlorambucil-obinutuzumab in elderly, comorbid patients, real-world comparisons of venetoclax-based therapies and chemoimmunotherapy (CIT) across broader populations remain limited, particularly in Latin America.

Objective
To assess the effectiveness and safety of venetoclax-based regimens as first-line therapy in CLL, compared to standard CIT, using real-world data from the Brazilian CLL Registry.

Methods
This retrospective multicenter study included patients with CLL treated in the frontline setting with either venetoclax-based regimens (with or without anti-CD20 antibodies) or standard CIT (e.g., FCR, BR, or chlorambucil-based combinations) between 2016 and 2024. Patients with <3 months of follow-up or incomplete data were excluded.

Results
A total of 482 patients were analyzed. Median age was 65 years (range 27–92). Elevated β2-microglobulin was seen in 63% of the 214 tested. IGHV status was available for 194 patients (40%), with 124 (63%) unmutated. del(17p) and/or TP53 mutation was available in 259 patients (54%), with 12 (5%) positive.
Venetoclax-based regimens were used in 59 patients (12%): 37 received VenO and 22 VenR (4%). CIT was used in 88%: FCR in 230 (48%), R-chlorambucil in 87 (18%), G-chlorambucil in 67 (14%), and R-bendamustine in 39 (8%).
After a median follow-up of 33 months, median time to next treatment (TTNT) was not reached in all groups except R-chlorambucil (28 months). Three-year TTNT rates were: R-chlorambucil 34%, G-chlorambucil 51%, R-bendamustine 78%, FCR 67%, VenR 77%, and VenG 83%. TTNT was significantly higher with venetoclax-based regimens (80%) versus CIT (58%, P=0.006). Three-year overall survival (OS) was similar (87% in both, P=0.75).

Conclusion
In this real-world Brazilian cohort, venetoclax-based regimens showed favorable outcomes and manageable toxicity compared to CIT in the frontline setting, including among high-risk patients. These results support the expanding role of time-limited targeted regimens in clinical practice and stress the importance of access to novel fixed-duration therapies in resource-limited environments. Updated analyses with longer follow-up and broader inclusion will be presented at the meeting.

EP 30 (#61)

Fixed-duration first-line strategies in chronic lymphocytic leukemia: a multinational real-world analysis from the gell latin american group and the brazilian registry of cll.

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Background
Venetoclax-based fixed-duration regimens have redefined the standard of care for chronic lymphocytic leukemia (CLL). However, chemoimmunotherapy (CIT) remains widely used across Latin America due to heterogeneous access to targeted agents. Real-world comparative data evaluating fixed-duration strategies in contemporary Latin American practice are limited.

Objective
To compare the real-world effectiveness of venetoclax-based regimens and CIT as fixed-duration, first-line therapies for CLL in Latin American centers participating in the GELL group and the Brazilian CLL Registry.

Methods
This retrospective multinational study included treatment-naïve CLL patients who initiated fixed-duration frontline therapy between 2020 and 2025. To minimize calendar-time bias associated with venetoclax adoption, comparative analyses were restricted to patients treated from 2020 onwards. Patients received venetoclax-based regimens or CIT (FCR/BR or chlorambucil plus an anti-CD20 antibody combination). The primary endpoint was time to next treatment (TTNT), and the secondary endpoint was overall survival (OS). Multivariable Cox regression models were used to adjust for age, del(17p)/TP53 aberrations, and year of treatment initiation.

Results
Of the 279 patients, 88 received venetoclax-based therapy, 138 received FCR/BR, and 53 received chlorambucil plus an anti-CD20 antibody combination. The median age was 65 years. TP53 aberrations (del[17p] and/or TP53 mutation) were assessed in 193 patients and detected in 21 (11%). After a median follow-up period of 21 months, the two-year TTNT rate was 84% for patients receiving venetoclax-based therapy, compared to 74% for those receiving FCR/BR and 51% for those receiving chlorambucil-based CIT. Adjusted analyses revealed that venetoclax-based therapy was associated with improved TTNT compared to chlorambucil-based CIT (hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.34–0.69) and FCR/BR (HR, 0.55; 95% CI, 0.38–0.81). Two-year OS was 93% for venetoclax-based therapy, 87% for FCR/BR, and 80% for chlorambucil-based CIT. Multivariable analyses revealed that venetoclax-based therapy was associated with improved OS compared to chlorambucil-based CIT (HR: 0.64; 95% CI: 0.41–0.99) and FCR/BR (HR: 0.55; 95% CI: 0.33–0.91).

Conclusion
In this contemporary, multinational, Latin American cohort, fixed-duration, venetoclax-based regimens were associated with superior effectiveness compared with chlorambucil-based CIT, as well as improved short-term outcomes versus FCR/BR. These findings support the expansion of modern fixed-duration strategies across Latin America while highlighting the continued impact of treatment access on frontline CLL care.

EP 31
(#63)

Survival in very elderly (>75 years) patients with chronic lymphocytic leukemia: multinational real-world analysis from latin america.

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Intro: Very elderly patients (>75 years) with chronic lymphocytic leukemia (CLL) represent a growing yet persistently underrepresented population in randomized trials evaluating targeted therapies. Real-world data focused specifically on this age group remain scarce, and multinational evidence from Latin America is lacking.

Objective: To evaluate overall survival (OS) and treatment patterns in very elderly (>75 years) patients with CLL treated in clinical practice across Latin America, and to assess whether modern therapeutic strategies are associated with improved survival in this population.

Methodology: We analyzed patients aged >75 years who initiated first-line therapy between 2010 and 2024 within the multinational GELL registry, including centers from 10 Latin American countries. Kaplan–Meier methods and log-rank testing were used for survival comparisons. Restricted mean survival time (RMST) at 36 months was calculated to mitigate bias related to differential follow-up. Multivariable Cox proportional hazards models adjusted for age, ECOG performance status, and year of treatment initiation. Given treatment heterogeneity, three mutually exclusive groups were defined for comparative survival analyses: chlorambucil monotherapy, chlorambucil plus anti-CD20 antibody, and continuous Bruton tyrosine kinase inhibitor (iBTK) monotherapy.

Results: A total of 365 patients were included. Median age was 80 years (range 75–102), 57.1% were female, and 25.5% had Binet stage C disease. ECOG>1 was documented in 24% of evaluable patients. Median follow- up was 42mo (95% CI 36.2–47.1), and median OS in the overall cohort was 62mo (95% CI 51.7–NA). Most common treatments were chlorambucil monotherapy (39.5%), chlorambucil plus anti- CD20 (19.2%), and iBTK monotherapy (15.7%). Among 271 patients, 101 deaths occurred. At 36 months, OS was 78.2% for chlorambucil plus anti-CD20, 59.5% for iBTK, and 55.4% for chlorambucil monotherapy (log-rank p=0.03). iBTK monotherapy was ibrutinib (84.2%) and acalabrutinib (15.8%). del(17p) was more frequent with iBTK (7/38, 18.4%) than with chlorambucil plus anti-CD20 (2/32, 6.2%) or chlorambucil alone (0/19, 0%). Median OS was 76 months for chlorambucil plus anti-CD20 versus approximately 42mo for chlorambucil monotherapy and iBTK monotherapy. In multivariable analysis (n=182), chlorambucil plus anti-CD20 remained independently associated with improved OS compared with chlorambucil monotherapy (HR 0.44; 95%; p=0.007), while iBTK monotherapy was not significantly associated with improved survival (HR 0.71; 95%; p=0.27). ECOG performance status was independently prognostic (HR 0.43 for ECOG 0–1; p=0.001). Sensitivity analyses yielded consistent estimates.

Conclusion: In this multinational real-world cohort of CLL patients, chlorambucil plus anti- CD20 was associated with improved OS versus chlorambucil alone, even after adjustment for age, performance status, and treatment era. Continuous iBTK monotherapy showed no significant survival benefit. Retrospective study should be interpreted cautiously.

EP 32
(#57)

Bruton tyrosine kinase inhibitors as frontline therapy in latin american patients with chronic lymphocytic leukemia: pooled analysis from the gell and the brazilian chronic lymphocytic leukemia cohort.

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Introduction: Access to targeted agents for chronic lymphocytic leukemia (CLL) is heterogeneous across Latin America, and real-world use of first line Bruton tyrosine kinase inhibitors (BTKi) in Latin American countries has not been well described.

Objective: To describe baseline characteristics, subsequent treatment patterns, and survival outcomes of Latin American patients receiving frontline BTKi in routine practice.

Methodology: Retrospective analysis including adults with CLL treated with a BTKi as initial therapy in centers participating in GELL-CLL cohort (Argentina, Chile, Colombia, Guatemala, Mexico, Paraguay, Peru, Uruguay, and Venezuela) and from the Brazilian CLL Registry, representing a collaborative regional Latin American analysis.

Results: Among 1282 patients who received frontline treatment between 2015 and 2024, 198(15%) received a BTKi as initial therapy and comprised the study cohort. Median age was 69 years(39–103), 52% were male, and 82% were treated in private centers. Frontline BTKi was ibrutinib in 168(76%), acalabrutinib in 48(22%), and zanubrutinib in 5(2%); anti-CD20 was added in 4%. Binet stage was A 50%, B 34%, and C 16%. Among those assessed, elevated LDH occurred in 32%(47/154) and elevated beta-2 microglobulin in 46%(59/125). Among those tested, del(17p) was detected in 33%(49/149), and TP53 mutations in 34%(23/67). Either del(17p) and/or TP53 testing was available in 69% of patients, with an abnormality detected in 36%(55/152). Median follow-up: 28 months(3–119) and median time from diagnosis to treatment: 2 months (0–22). Median OS and PFS were not reached. Due to the small number of patients treated with second-generation BTKIs, formal comparative survival analyses were not performed. Presence of 17p deletion was not associated with OS differences. Forty-two patients (21%) received second-line therapy: 53% due to progression, 33% due to toxicity, and 14% due to Richter's transformation. Among patients progressing after first line BTKi, venetoclax-based regimens were the preferred second-line approach (21/22, 96%). Patients discontinuing ibrutinib due to toxicity most commonly switched to a second-generation BTKi (13/14, 93%), while one patient received venetoclax–obinutuzumab.

Conclusions: In this large Latin American real-world cohort, patients treated with BTKi as initial therapy were predominantly managed in private centers, and approximately one-third of tested patients harbored del(17p) and/or TP53 abnormalities. Despite the encouraging outcomes, access to targeted therapies and comprehensive molecular testing remains un even throughout Latin America. While outcomes were promising for BTKi-treated patients, comparative interpretation between agents is limited by sample size. These results support the need for improving equitable access to these therapies and standardized biomarker assessments in Latin America to enhance CLL treatment outcomes and reduce disparities.

EP 33 (#37)

Younger age at diagnosis is associated with shorter time to first treatment in an uruguayan real-world cohort of chronic lymphocytic leukemia.

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Introduction

Chronic lymphocytic leukemia (CLL) is typically a disease of older adults, although a minority of patients present at a young age. Median age at diagnosis is 73 years, and only 27% of patients are younger than 65 (SHU CLL registry). The last SEER report 9% of CLL cases occur in patients younger than 55 years, highlighting an important and often underrecognized subgroup within the CLL population. In 2024 our group presented the outcomes of 20 young CLL patients and suggested that this population needed earlier treatment. In Uruguay, local real-world evidence is still limited so, we expanded our data in order to contextualize time-to-first-treatment (TTFT) in routine practice.

Objective

To describe TTFT according to age at diagnosis in a national Uruguayan CLL cohort from GURU-CLL.

Methodology

Retrospective, multicenter cohort including patients diagnosed after 2000 and treated after 2010, or diagnosed after 2010 regardless of treatment status, from CASMU, COSEM, Hospital Británico, Hospital de Clínicas, Hospital Maciel, and Hospital Militar. Of 534 registered patients, 485 had complete data for TTFT analyses. Age at diagnosis was categorized as ≤50 years, 51–65 years, and ≥66 years. TTFT: time from diagnosis to first CLL therapy.

Results

Among 485 evaluable patients, 227 needed first line treatment. Men 308 and 177 women. Median age was 67 years old (33-94). We observed typical cytogenetic aberrations in 59% of cases. IGHV mutational profile was 53% mutated, clinical Binet A stage depict 66%, B: 20% and C: 14%. Public system: 259 (53,4%) and private: 226 (46,6%). The median follow up: 62 months (0,2-295).

In table 1 we show the characteristic of the patients according to the age group. The percentage of young CLL (≤50 years) was 7%. There are not differences in sex, LDH, B2 microglobulin, citogenetics, mutational IGVH status or management at the beginning. We found differences in ECOG status, with elderly patients being less fit, and in stage at diagnosis: younger patients more frequently presented with advanced Binet or RAI stages and higher lymphocyte counts. They also exhibited a higher proportion of TP53 alterations; however, the limited number of cases precludes definitive conclusions regarding this association.

Patients aged ≤50 years (n=34) showed the shortest TTFT (median 10.3 months; 95%CI 0.0–21.2), compared with those aged 51–65 years (n=171; median 58.5 months; 95%CI 41.4–75.6) and ≥66 years (n=280; median 102.6 months; 95%CI 52.5–152.6). Overall median TTFT was 69.4 months (95%CI 51.0–87.9). TTFT differed significantly across age strata (log-rank χ^2=16.1; df=2; p<0.001).

Conclusions

In this Uruguayan real-world cohort, younger patients (≤50 years) experienced a markedly shorter TTFT, potentially related to more advanced stage and grater lymphocytosis at diagnosis. Ongoing studies aim to dissect the biological mechanisms driving microenvironmental signaling and T-cell–mediated immune dynamics in this cohort.

EP 35
(#59)

Treatment patterns, and survival outcomes of patients aged >80 years with cll: data from the brazilian registry of cll (rbllc).

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Volumen 30 - Número Extraordinario 6th Latin American Congress on Chronic Lymphocytic Leukemia
Abril 2026

Introduction

Very elderly patients (>80 years) with chronic lymphocytic leukemia (CLL) are underrepresented in prospective trials, and real-world data in this population remain scarce.

Objective

To describe characteristics, treatment patterns, and survival of patients starting first-line therapy at age >80 years in the Brazilian CLL Registry.

Methodology

We conducted a retrospective analysis of patients enrolled in the Brazilian CLL Registry who were diagnosed between 1999 and 2022. Individuals aged >80 years at diagnosis were identified, and those who initiated first-line therapy were included in analyses.

Results

Among 5,130 registered patients, 560 (10.9%) were >80 years at diagnosis; 468 initiated first-line therapy and were included in survival analyses. Median age at treatment initiation was 84 years (IQR 82–87), and 52.1% were male. At therapy start, 60.9% were aged 80–84 years, 26.9% 85–89 years, and 12.2% >90 years. Rai stage was available in 76.1%, with 21.1% classified as high-risk (III–IV). ECOG performance status was reported in 44.4%, of whom 25.5% had ECOG >1. CIRS was documented in 22.2%, with 72.1% scoring >6, indicating substantial comorbidity burden. Among tested patients, del(17p) was detected in 14.9% and TP53 mutation in 11.1%. Median time from diagnosis to treatment was 12 months (IQR 1.6–37.9); 49.8% initiated therapy more than 12 months after diagnosis, and 45.1% received >2 treatment lines. First-line therapy was predominantly chlorambucil-based (70.9%), including chlorambucil monotherapy in 56.2% and chlorambucil combined with an anti-CD20 antibody in 14.7%. Uptake of targeted therapies was limited: BTK inhibitor–based regimens were administered in 5.8%, primarily ibrutinib (3.8%) and less frequently acalabrutinib (1.9%), while venetoclax-based therapy accounted for 3.2%. Anti-CD20 monotherapy was used in 2.1% of patients, whereas FCR-like and bendamustine-based regimens were uncommon (2.1% and 0.6%, respectively). The adoption of targeted agents was confined to the contemporary era; 21.8% of patients initiating therapy after 2015 received BTK inhibitor– or venetoclax- based regimens, although chemotherapy-based approaches remained the predominant strategy. Early mortality (<6 months) was 5.8%. Median overall survival from first-line initiation was 104.5 months (95% CI 85.1–115.1). Estimated OS at 12, 24, and 36 months was 89.8%, 82.6%, and 74.4%, respectively. ECOG >1 was independently associated with inferior OS (HR 2.22, 95% CI 1.42–3.49; p<0.001).

Conclusion

In this large Brazilian real-world cohort, 11% of patients with CLL were >80 years at diagnosis. Biological and comorbidity data were available for a limited subset of patients, reflecting real-world documentation constraints over the study period. Despite advanced age and substantial comorbidity burden among evaluable cases, early mortality was low and median OS was 8.7 years. Treatment remained predominantly chlorambucil-based, with limited use of targeted agents. These findings provide meaningful real-world evidence.

EP 36
(#49)

Frontline therapy patterns and outcomes in chronic lymphocytic leukemia: a real-world, multicenter analysis from latin america.

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Abril 2026

Background: Access to novel therapies for chronic lymphocytic leukemia (CLL) varies throughout Latin America. Many centers still rely on chemoimmunotherapy (CIT) or suboptimal regimens due to cost and availability issues. Real-world data comparing CIT and targeted therapies in this region are limited and urgently needed to inform clinical decisions and policy.

Methods: We conducted a retrospective analysis of CLL patients who received first-line therapy in 10 Latin American countries (Argentina, Brazil, Chile, Colombia, Cuba, Mexico, Paraguay, Peru, Uruguay, and Venezuela) between 2010 and 2024. We grouped treatment regimens into six categories: a) venetoclax- based combinations with or without anti-CD20 antibodies; b) Bruton tyrosine kinase (BTK) inhibitors; c) standard CIT, including fludarabine, cyclophosphamide, and rituximab (FCR), or bendamustine and rituximab (BR); d) fludarabine and cyclophosphamide without rituximab (FC); e) rituximab or obinutuzumab combined with chlorambucil (R/G-chlorambucil); and f) suboptimal regimens, including chlorambucil monotherapy, R-CHOP, R-CVP, or any other nonstandard or unsupported combinations.

Results: Of the 2,133 patients who received treatment after 2010, the most common guideline-recommended regimens were FCR or BR (n = 521; 24.4%), BTK inhibitors (n = 188; 8.8%), chlorambucil plus anti-CD20 (n = 177; 8.3%), and venetoclax-based regimens (n = 89; 4.2%). However, 899 patients (42.1%) received suboptimal therapies, most commonly chlorambucil monotherapy (n = 552; 25.9%), FC (n = 259; 12.1%), and lymphoma-like regimens, such as CHOP or CVP ± anti-CD20 (n = 300; 14.1%). To analyze outcomes in the era of targeted therapies, we included 1,282 patients treated between 2015 and 2024. The median follow-up was 34 months (range, 0–119). Progression-free survival (PFS) at 3 years was 51%, with median PFS not reached. When stratified by treatment group, the 3-year PFS was 75% for venetoclax-based regimens, 67% for FCR/BR, 65% for BTK inhibitors, 48% for FC, 43% for R/G- chlorambucil, and 33% for suboptimal regimens. FISH testing for del(17p) and/or TP53 mutation was performed in 571 patients (44.5%), with abnormalities identified in 77 patients (13.5%). Of those 77 patients, 50 (65%) received targeted therapies (venetoclax- or BTK-based), while 27 (35%) received CIT or other treatments.

Conclusions: In this Latin American real-world cohort, non–CLL-directed regimens (e.g., CHOP/CVP) and chlorambucil monotherapy were frequent and associated with inferior outcomes, supporting their abandonment. Anti-CD20 addition improved FC-based results. FCR and targeted therapy (venetoclax or BTK inhibitors) showed broadly comparable effectiveness, but this should be interpreted cautiously due to retrospective design and likely selection/risk imbalances. These findings highlight an urgent need to expand access to modern agents and strengthen evidence-based CLL education across the region.

EP 37 (#35)

Institutional experience in patients with chronic lymphocytic leukemia: a retrospective observational study.

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Abril 2026

Background
Chronic lymphocytic leukemia (CLL) is the most common lymphoid malignancy in adults and is characterized by the clonal proliferation and accumulation of mature B lymphocytes. Its clinical course is heterogeneous, ranging from indolent disease to aggressive forms requiring early treatment. Prognostic factors such as IGHV mutational status and cytogenetic abnormalities detected by FISH, including del(17p) and del(11q), play a key role in risk stratification and therapeutic decision-making.

Objectives
To describe demographic characteristics, clinical stage at diagnosis, availability of prognostic testing, and treatment patterns in patients with CLL at our institution.

Methods
We conducted a retrospective, observational, descriptive study including adult patients (≥18 years) diagnosed with CLL according to iwCLL criteria at Hospital Central de San Isidro between 2020 and 2025. Data were collected from electronic medical records and laboratory databases. Continuous variables were expressed as median and interquartile range, and categorical variables as absolute and relative frequencies.

Results
A total of 52 patients were included. Median age at diagnosis was 69.5 years (IQR 64–77), with a predominance of males (57.7%). Most patients were diagnosed at early stages: 44.2% were Rai stage 0 and 77% were Binet stage A. Prognostic molecular testing was limited. IGHV mutational status was not assessed in 98% of patients. FISH analysis was performed in only 13 patients (25%), revealing high-risk abnormalities in a subset, including del(17p) in 4 cases and del(11q) in 1 case. Figuire 1.
Regarding management, 28 patients (54%) remained under active surveillance. Twenty-two patients (42.2%) required treatment. The most frequently used regimen was ibrutinib (45.5%), followed by rituximab-bendamustine (31.8%). Other regimens included Rituximab-Ibrutinib, Obinutuzumab-Venetoclax, Fludarabine- Cyclophosphamide and Rituximab (FCR) and Chlorambucil. At last follow-up, 41 patients (79%) were alive, 8 (15%) were lost to follow-up, and 3 (5.8%) died from causes unrelated to CLL, including infections and secondary malignancies.

Conclusions
In this institutional cohort, most patients were diagnosed at early stages, consistent with the indolent nature of CLL. Access to prognostic molecular testing was limited, restricting optimal risk stratification. Among tested patients, del(17p) was the most frequent high-risk abnormality. Most patients remained under observation, while treated patients predominantly received Bruton tyrosine kinase inhibitors. Access to targeted therapies was influenced by insurance coverage and authorization processes, highlighting the impact of healthcare access on treatment selection. Improving access to molecular testing is essential to optimize risk stratification and individualized treatment strategies.

EP 38
(#55)

Obinutuzumab-induced acute thrombocytopenia (oiat). Report of four cases.

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Volumen 30 - Número Extraordinario 6th Latin American Congress on Chronic Lymphocytic Leukemia
Abril 2026

Introduction
Obinutuzumab (O) is an anti-CD20 monoclonal antibody used in the treatment of B-cell malignancies. On rare occasions, O may induce sudden-onset, severe thrombocytopenia (OIAT). We describe four cases of OIAT and review the potential pathogenic mechanisms, management and outcome of this rare but life-threatening complication.

Patients
Case 1: 64-year-old female with a previous history of rheumatoid arthritis. Chronic lymphocytic leukemia (CLL) was under active surveillance for ten years. Two episodes of autoimmune hemolytic anemia were treated with corticosteroids and low-dose rituximab. Due to a third hemolytic crisis, the CLL14 protocol (O-Venetoclax) was proposed as first-line treatment. She experienced an acute thrombocytopenia with a drop in platelet counts from 144 G/L to 10 G/L the day after the first dose of 100 mg of Obinutuzumab.
Case 2: 79-year-old female. Newly diagnosed CLL with lymphocytosis, large retroperitoneal lymphadenopathy, and 17p deletion in 29 % of cells. She received one cycle of R-CHOP as debulking and then started the CLL14 protocol. An acute thrombocytopenia with a drop in her platelet count from 203 G/L to 5 G/L was documented the day after initiating O.
Case 3: 60-year-old male with a history of chronic obstructive pulmonary disease (COPD). Newly diagnosed stage IIB CLL with unmutated IGHV and high-risk CLL-IPI. Initiated CLL14 protocol with a baseline platelet count of 138 G/L. Developed shortness of breath and transient hypoxia after the first 100 mg dose of O, requiring oxygen therapy and intravenous steroids. Platelet count dropped to 31 G/L on day 3 and to 20 G/L. Dexamethasone 40 mg was administered daily for four days, after which platelets recovered. Treatment was resumed without further complications, and the patient completed six cycles of O and is currently continuing Venetoclax monotherapy.
Case 4: 72-year-old male with CLL diagnosed in 2009 (13q deletion, mutated IGHV). Under observation for over ten years, until the development of B symptoms, splenomegaly, and mild anemia prompted initiation of the CLL14 protocol. Experienced rapid lymphocyte reduction and tumor lysis syndrome following the first 100 mg dose of O, leading to withholding of the subsequent 900 mg dose. Platelet count dropped from 116 G/L to 23 G/L. Treated with dexamethasone 20 mg, with recovery to 55 G/L by day 8. Subsequent O doses consistently induced platelet count declines (nadir 15 G/L), each managed with a single dose of dexamethasone. No bleeding occurred, and the patient completed therapy with undetectable MRD.

Discussion
OIAT is a low-incidence entity, and it is notable for severe thrombocytopenia very early (within the first 24 hours) after the first O infusion. It is not limited to the initial cycle.Recovery occurs within a few days without severe bleeding. The exact mechanism of thrombocytopenia caused by O is unclear, but it may involve immune-mediated processes.

Final Comment
OIAT is a rare but life-threatening complication. Physicians should be aware of it and detect and treat it early after O.

EP 39
(#60)

Effectiveness of subcutaneous cladribine in hairy cell leukemia: a multicenter real-world study from brazil.

Santos Azevedo, Fernanda[1]; Justino, Caio[1]; Cunha, Gabriel[1]; Seiwald, Maria Cristina[1]; Tavares, Ana Paula[1]; Perobelli, Leila[2]; Marques, Fernanda[1]; Leão Cordeiro de Farias, Danielle[3]; Silveira, Talita[4]; Arraias-Rodrigues, Celso[1].

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Volumen 30 - Número Extraordinario 6th Latin American Congress on Chronic Lymphocytic Leukemia
Abril 2026

Introduction

Hairy cell leukemia (HCL) is an indolent B-cell lymphoproliferative disorder. Clinical manifestations include cytopenias and susceptibility to infections. Purine analogues remain the standard first-line therapy and achieve high complete response(CR) rates. Cladribine can be administered intravenously (IV) or subcutaneously (SC) with comparable efficacy and safety.

Objective

The aim of this study is to evaluate the efficacy and safety of SC cladribine in patients (pts) with HCL.

Methods

This retrospective study included pts diagnosed with HCL between July 1998 and February 2026 at five institutions that participate in the Brazilian CLL Database. Response was assessed according to established HCL criteria. Overall survival (OS) and time to next treatment(TTNT) were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox regression analysis was performed to identify factors associated with poorer survival.

Results

116 pts were included in this cohort. Classical HCL was diagnosed in 115 pts (99%), and one had variant HCL. Eighty percent were male. The median age at diagnosis was 51 years (range, 29–90). The median hemoglobin level was 10.1 g/dL (range, 3.5–15.1) and the median platelet count was 64 $\times 10^9$/L (range, 12–346 $\times 10^9$/L). Monocytopenia was present in 98%. After a median follow-up of 59 months (range, 3–334), five-year OS was 92%. Age greater than 75 years and hemoglobin less than 10 g/dL were associated with poorer survival. 94 pts (81%) required first-line therapy. Cladribine was the most frequently used regimen (95%), administered IV in 61 cases (68%) and SC in 28 cases (32%). Rituximab was combined with cladribine in four cases (IV administration). SC cladribine was administered in the outpatient setting. Overall response rate was 98%, and CR was achieved in 88%. Among pts who received cladribine, the median follow-up period after first-line therapy was 58 months (range, 3–332). Five-year OS was 94%, with no significant difference between IV and SC administration (95% vs.93%, respectively). Median TTNT was not reached, and there was no difference by route of administration. Only 20 of the 89 pts treated with cladribine required second-line therapy, with a median time to second-line treatment of 106 months. Retreatment with cladribine, with or without Rituximab, was performed in 13 cases (65%). Rituximab monotherapy was administered in four pts, chemotherapy and splenectomy in one case each, and allogeneic hematopoietic stem cell transplantation in one patient.

Conclusions

This multicenter, real-world study represents the largest reported HCL cohort in Latin America. First-line cladribine treatment produced high complete remission rates; SC cladribine demonstrated efficacy comparable to IV administration. Importantly, SC cladribine enables full outpatient treatment. These findings support the use of ambulatory SC cladribine as an effective, safe, economic, and pragmatic first-line treatment strategy.

Basic translational

EP 1
(#25)

Multicenter study of epidemiological and molecular characteristics in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma in baja California Sur, Mexico.

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Introduction
Chronic lymphocytic leukemia is a hematologic neoplasm derived from B-cell lineage lymphocytes and is highly prevalent representing 25–30% of leukemias in adults. At the international level, the epidemiology and genetic characteristics of this disease have been widely described; however, in Mexico, especially in Baja California Sur, information remains limited.

Objective
To describe characteristics by sex, age, molecular features, and treatment in patients with CLL from Baja California Sur, Mexico (HGZ1 IMSS , Hospital Juan María Salvatierra and Clínica Médica del Cortés).

Methodology
Multicenter study including public and private hospitals in the state of Baja California Sur, Mexico, from March 2020 to September 2025, with a confirmed diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma established through bone marrow or peripheral blood immunophenotypingwith or without NGS/FISH analysis of specific mutations.

Results
A total of 29 patients were included, with an H:M ratio of 2.6:1, a maximum age of 82 years, a minimum age of 39 years, a mean age at diagnosis of 68.2 years, and FISH/NGS characterization performed in 80% of the total population (23/29). More than half of the patients had at least one genetic alteration, with the most frequent alteration identified being del13q14 IGVH in 52.2% (10/23) of the studied patients. Trisomy 12 was identified in 8.7% (2/23), 11q ATM deletion 4.3% (1/23), and a frequency of only 4.3% of TP53 mutation del17p31.1, (1/23). For treatment purposes, 27% of the patients are on active treatment, with the most commonly used regimen being Ibrutinib + Venetoclax (4), followed by ibrutinib monotherapy (2), acalabrutinib monotherapy (1), and Venetoclax + Obinutuzumab (1). The rest of the population is under surveillance after first-line treatments or without current treatment criteria.

Conclusions
This multicenter study represents the first clinical and cytogenetic description of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in the state of Baja California Sur, Mexico, demonstrating a predominantly older adult population, with a clear male predominance and a mean age at diagnosis comparable to that reported internationally.

Molecular characterization by FISH/NGS was performed in 80% of patients, with deletion 13q14 identified as the most frequent alteration.

Overall, these results underscore the need to strengthen local epidemiological registries, promote systematic access to molecular studies, and continue generating regional evidence to optimize prognostic stratification and therapeutic decision-making in patients with CLL in Baja California Sur.

In the medium term, the objective is to obtain more in-depth information on treatment response rates, progression-free survival, and time to next treatment based on this specific population census.

EP 2
(#29)

Geographic pattern of immunoglobulin gene rearrangements in argentinean patients with chronic lymphocytic leukemia. Over 10 years experience from a single institution.

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Abril 2026

Introduction
The IGHV (immunoglobulin heavy variable) mutational status (MS) is one the most important prognostic factors in chronic lymphocytic leukemia (CLL). It allows to stratified patients into mutated (M) (<98% identity to germline) or unmutated (U) (= or >98%), with different outcome.

Objective
To characterize IGHV-IGHD-IGHJ rearrangements and stereotyped receptors in a large series of Argentinean CLL patients, in order to identify possible differences in immunoglobulin gene usage compared to Caucasian and Chinese cohorts.

Methodology
Immunoglobulin gene rearrangements, stereotyped receptors and R110 mutation in lambda light chain were analyzed by RT-PCR and bidirectional Sanger sequencing. FISH (Fluorescence In Situ Hybridization) analysis was also performed. Statistical analysis was done using the SPSS v.26 software; p-values <0.05 were considered as statistically significant. The study was approved by the Institutional Ethics Committee.

Results
A total of 1123 CLL patients (686 males; mean age: 65.7 years; Rai stages: 0: 31.5%, I-II: 49.8%, III-IV: 18.7%) were analyzed. We found 1143 IGHV-IGHD-IGHJ productive rearrangements (PR): 1123 single and 20 double (1.8%), 11 with concordant MS and 9 discordant. According to germline identity, 659 (57.7%) PR were M and 484 U (42.3%). A shorter time to first treatment was observed in U patients compared to M cases (p=0.0001). The most frequent families found were VH3(43.3%)>VH4(27.5%) >VH1(20.4%), showing significant differences compared to Caucasian and Chinese patients [1-3] (Figure1a). VH1 was associated to U (p<0.0001) while VH3 and VH4 to M state (p<0.001 each). Figure1b shows the most common IGHV genes used in the Argentinean series and their comparison with Caucasian and Chinese cohorts. IGHV1-69, IGHV3-11 and IGHV4-39 were significantly associated to U (p<0.01), while IGHV3-23, IGHV3-7, IGHV3-74 and IGHV4-34 to M state (p<0.001), displaying similar propensity towards mutations and the same clinical impact than other series. Concerning stereotyped subsets of clinical relevance, subset #2 was present in 2.6% of PR, subset #1 (1.6%), subset #4 (1.2%) and subset #8 (0.5%). Differences between Argentinean and Chinese patients in IGHV subsets #2, #4 and #8 were found (p<0.03) (Figure1c). R110 in subset #2 showed 12 positive and 1 negative case [4]. FISH analysis showed 51% del13q14, 30% trisomy 12, 14% del11q22 and 20% del17p13 in our cohort.

Conclusions
Our results present the largest series of IGHV studies in Argentine CLL patients performed in a single institution. Our cohort showed different frequencies in families, IGHV genes and stereotyped receptors compared to Eastern and Western series. Interestingly, Argentinean patients, unlike Caucasian population, displayed VH3>VH4>VH1 family distribution, similar to those observed in Eastern populations, but with a less usage of VH1, suggesting diverse specific antigens implicated in CLL pathogenesis in this geographic region.

EP 3
(#34)

Detection of infrequent variants in patients with chronic lymphocytic leukemia.

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Introduction
In recent years, the contribution of new genomic technologies for high-throughput analysis in chronic lymphocytic leukemia (CLL), allowed the detection of multiple variants in driver genes that cluster into distinct signaling pathways.

Objective
To detect the presence of infrequent variants (IVs) in genes associated to CLL in order to deepen the biological characterization of the disease.

Methodology
A total of 70 patients with CLL (37 men; mean age: 64.97 years) were evaluated. Analysis of variants was performed by Sanger sequencing and/or using the SOPHiA DDM™ Platform Community CLL Clonality Solution NGS (next-generation sequencing) panel. For the variants categorization, the recommendations of the ClinGen/CGC/VICC consortium were used [1], except for those of the TP53 gene, that follow the ERIC (European Research Initiative on CLL) recommendations [2-3]. The variants found were then evaluated in ColabPro (developed by Google) using the AlphaGenome model to assess their functional impact. The study was approved by the Institutional Ethics Committee.

Results
Fifty-nine patients (84.3%) presented variants in genes associated with CLL. A total of 114 variants were found, which were categorized as Pathogenic/Oncogenic (65/114; 57%), Probably Pathogenic/Probably Oncogenic (42/114; 36.8%) and Variant of Uncertain Significance (7/114; 6.2%). The most affected genes were TP53, NOTCH1, SF3B1 and ATM, which together account for 68.4% (78/114) of total alterations. The analysis of variants showed that 27.2% (31/114) of them were very infrequent or novel in CLL: TP53, BIRC3, NOTCH1, SF3B1 and FBXW7 (12.9% each), ATM (9.7%), RB1 (6.5%), POT1, EGR2, PLCG2, NFKBIE, MYD88 and KRAS (3.2% each) (Table 1). Of the 31 variants found, 17 (54.8%) were missense, 10 (32.2%) frameshift, 2 (6.5%) nonsense, and 2 (6.5%) splicing. The analysis of the functional impact of the IVs detected that 90% of them affect the splicing mechanism, BIRC3 variants lead to the activation of matrix metalloproteinases (MMP8, MMP3, MMP10), NOTCH1 alterations showed persistent signal gain for the Lipocalin family (LCN6, LCN8) and a modulation of WRAP53 was found in response to the TP53 alterations. The evaluation of IGHV mutational status found that 64.5% (40/62) of the patients presented were unmutated IGHV, of which 40% (16/40) had IVs.

Conclusions
To our knowledge, this is the first analysis of IVs in CLL patients of our country. Interestingly, 12 variants from different genes were novel in this pathology. The bioinformatic analysis showed that BIRC3 variants would have a role in the remodeling of tumor microenvironment and alterations in NOTCH1 would participate in metabolic reprogramming. These findings emphasize the importance of further deepening the molecular study of patients with CLL, to gain a better understanding of this pathology and to obtain new information for the design of novel therapeutic agents.

EP 4
(#38)

Mutational profile of Chronic Lymphocytic Leukemia patients from Rio de Janeiro, Brazil.

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HEMATOLOGÍA
Volumen 30 - Número Extraordinario 6th Latin American Congress on Chronic Lymphocytic Leukemia
Abril 2026

Introduction

Chronic Lymphocytic Leukemia (CLL) is the most prevalent leukemia among adults in Western countries and is characterized by the clonal proliferation of dysfunctional mature CD5+, CD23+, CD19+, CD2-, and FMC7- B cells in the bone marrow, peripheral blood, and secondary lymphoid organs. Patients may remain asymptomatic for years, whereas others present with a rapid onset of symptoms, leading to disease progression and transformation [1]. In this context, prognostic markers play a critical role in clinical decision-making and patient management. The mutational status of the immunoglobulin heavy chain variable region (IGHV) gene is a well-established genomic marker in CLL, in which patients classified as CLL-M (mutated IGHV) generally exhibit a more indolent disease course, whereas patients classified as CLL-UM (unmutated IGHV) have a poorer prognosis[2]. In addition, mutations in the TP53, SF3B1, NOTCH1, MYD88, BIRC3, and ATM genes have been recognized as indicators of disease progression and unfavorable prognosis[3]. Recent studies highlight the heterogeneity of the disease across different populations[4,5].

Objectives

This study aimed to characterize the genomic profile of CLL patients from a Brazilian hospital, a comparative analysis of the mutational profiles of the IGHV gene and the TP53, SF3B1, NOTCH1, MYD88, BIRC3, and ATM genes with an international database.

Methodology

A total of 78 CLL patients from Rio de Janeiro - Brazil were analyzed, with approval from the institutional Ethics Committee. DNA samples were subjected to Sanger sequencing of the IGHV gene to determine mutational status, and patients were classified as CLL-M (mutated IGHV) or CLL-UM (unmutated IGHV). Next-generation sequencing (NGS) was performed using a six-gene panel to identify pathogenic (P), likely pathogenic (LP), and variants of uncertain significance (VUS). The results were correlated with disease progression and prognosis and were also compared with an international cohort.

Results

Among the 78 patients analyzed, a potentially pathogenic variant not previously described in other populations was identified in NOTCH1 (Q1057E), detected in 35% of patients. Additionally, 56% of patients were classified as CLL-UM (poorer prognosis), representing a statistically higher frequency than that described in the literature. The Brazilian cohort also showed a higher risk of harboring variants in the ATM, TP53, and NOTCH1 genes, with a proportionally greater number of pathogenic variants in ATM and TP53.

Conclusion

Overall, these findings enabled the genomic characterization of Brazilian CLL patients by identifying a novel variant and assessing the risk of disease progression in the Brazilian cohort, highlighting the genetic heterogeneity of the Brazilian population compared with international cohorts.

EP 5 (#71)

Comprehensive characterization of TP53 alterations in Chronic Lymphocytic Leukemia (CLL): contribution of molecular cytogenetics and sequencing (sanger/ngs).

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HEMATOLOGÍA
Volumen 30 - Número Extraordinario 6th Latin American Congress on Chronic Lymphocytic Leukemia
Abril 2026

Introduction

TP53 alterations are among the most relevant prognostic markers in CLL; because they are associated with chemoresistance, assessment prior to treatment initiation is mandatory. Combining FISH and sequencing provides a more complete evaluation by identifying 17p deletion (del(17p)), TP53 mutations, and cases consistent with biallelic involvement (del(17p) with a concomitant mutation). As CLL commonly displays clonal heterogeneity, sequencing sensitivity is critical to detect mutations in minor subclones and to avoid underestimating TP53 status.

Objectives

To describe TP53 alterations in a CLL cohort, assessing the complementarity between FISH and sequencing, and the impact of analytical sensitivity on detecting low-frequency variants.

Methodology

Observational, descriptive, retrospective study including CLL patients evaluated between 2018–2025. del(17p) was assessed by FISH, and TP53 exon variants were analyzed by Sanger sequencing and/or NGS.

Results

A total of 630 FISH tests were performed, with del(17p) detected in 11.9% (75/630). TP53 mutational analysis was performed by Sanger sequencing in 85 patients and by NGS in 31 patients. Mutations were detected in 5.9% of Sanger-tested patients (5/85) and 16.1% of NGS-tested patients (5/31). Among NGS-detected mutations, 75% (6/8) showed a VAF <10%. Regarding methodological complementarity, 67/630 patients underwent paired evaluation by FISH and molecular testing (41 by Sanger and 26 by NGS), identifying two cases with del(17p) and a concomitant mutation; additionally, two FISH+/Sanger– cases were observed.

Conclusions

Integrating FISH and sequencing provides a more complete assessment of TP53 status in CLL by offering complementary information on del(17p) and exon variants. Detection of VAF <10% variants, together with cases showing two TP53 mutations by NGS, highlights the value of higher analytical sensitivity for identifying minor subclones. In the subgroup with paired testing, combined results identified cases with del(17p) and a concomitant mutation, consistent with biallelic involvement. Moreover, the occurrence of del(17p) without detectable mutations in Sanger-tested cases (FISH+/Sanger–)—considered theoretically unlikely—supports the advantage of more sensitive approaches such as NGS for mutation detection. Overall, these findings support an integrated strategy to optimize TP53 detection and interpretation in CLL.

EP 6
(#72)

Genetic characterization of CLL patients using a next generation sequencing (NSG) gene panel: first experience in argentina.

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Volumen 30 - Número Extraordinario 6th Latin American Congress on Chronic Lymphocytic Leukemia
Abril 2026

Introduction
Chronic lymphocytic leukemia (CLL) is a genetically heterogeneous disease that features several recurrent mutations associated with clinical course and evolution, most of which affect key signaling pathways and cellular processes (1). The advent of Next Generation Sequencing (NGS) facilitated the detection of mutations, even at very low subclonal levels, and have illustrated different patterns of clonal evolution (2,3). Since CLL remains largely incurable and its course difficult to predict, it is essencial to understand its heterogeneous features and eventually proceed to more tailor-made therapeutic approaches.

Objectives
1) To demonstrate the usefulness of a NGS gene panel for the study of genetic alterations in CLL patients.
2) To describe the mutation and copy number variations (CNV) profile in a cohort of Argentine patients.

Methodology
CLL patients were studied using a panel of 23 target genes (CLL Conality Solution-SOPHIA Genetics), sequencing in NS2000 (Illumina) and bioinformatics analysis (DDM-SOPHIA Genetics). DNA was obtained from peripheral blood (PB) and bone marrow (BM) samples. IGH rearrangement and IGHV mutational status were analyzed following ERIC recommendations (4). Del(17p), del(11q) and del(13q) were assesed by FISH, and TP53 mutations by Sanger/NGS.

Results
This cohort includes 16 CLL patients (M:F=3:1; median age: 63 yrs. (57–77)). Twenty-three gene variants (var) in 7 genes were detected in 10 pts: TP53 (7), SF3B1 (5), BIRC3 (6), POT1 (2), NOTCH1 (1), FBXW7 (1) and XPO1 (1) (table 1). The number of mutated genes per patient was: 1 in 5 pts, 2 in 4 pts and 3 in 1pts. Variant allelic frequencies (VAF) ranges between 2 and 51.1. More than one variant within a single gene were detected in 5 patients: TP53 (2 var in 3 pts), SF3B1 and BIRC3 (2 var in 1 pt each). IGHV gene distribution available in 16 pts: IGHV1 (38%), IGHV4 (31%), IGHV3 (25%) and IGHV6 (6%). IGHV gene SHM status was: mutated (38%), unmutated (38%), borderline (25%). NGS-based CNV were available in 10 pts and detected in 70% of them: losses on chr. 13 (4 pts) and chr. 17 (1 pt), and gains on chr. 12 (3 pts). All patients were tested by FISH for del17p, only detected in one patient, coincidentally with CNV. Del13q was not detected by FISH in 2/3 patients with 13q losses according to CNV results.

Conclusions
This is the first experience in Argentina using an NGS gene panel in CLL patients. Thirteen of 16 pts (81%) carried any genetic alteration and, although merely descriptive, the relative frequency of mutations is consistent with other series reported. The VAF of different mutations in a single sample allows estimation of subclones. NGS also enables the determination of the immunoglobulin heavy variable (IGHV) gene somatic hypermutation (SHM) status and detects CNV, outperforming traditional methods as Sanger sequencing and FISH in a single assay.

EP 7 (#75)

Distribution of ighv mutational status and detection of IGLV3-21^R110 mutation in CLL patients.

Bender, María Eugenia[1]; Bender, Andrea[1]; Giuliani, Macarena[1]; Gasparini, Nehuen[1]; Torreguitart, Federico[1]; Lang, Cecilia[1]; Iommi, Paula[1]; Pombo, Pablo[1]; Miranda, Julieta[1]; Agriello, Evangelina[1]; Lopez Ares, Lisa[2]; Taborda, Gustavo[2]; Crescitelli, Franco[3]; Vargas, Lorena[4]; Raña, Pablo[5]; Cabanne, Vanina[5]; Brandt, Martin[3]; Vazquez, Mercedes[5]; Rios Sant, Florencia[5]; Lopez, Tatiana[5]; Rios Part, Maria del Carmen[6]; Halac, Alejandra[7]; Espina, Bibiana[7]; Venchi, Rosana[2]; Sanhueza, Diego[2]; Jones, Laura[8]; Rosende, Silvina[9]; Gregorio, Carina[10]; Boughen, Santiago[3]; Beccacece, Martin[3]; Kowalyszyn, Ruben[11]; Egozcue, Cecilia[12]; Muller, Katja[13].

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Volumen 30 - Número Extraordinario 6th Latin American Congress on Chronic Lymphocytic Leukemia
Abril 2026

Introduction

Chronic lymphocytic leukemia (CLL) is a hematological neoplasm with a heterogeneous clinical course that primarily affects older adults. IGHV mutational status is one of the most relevant prognostic factors: patients with mutated IGHV (CLL-M) have a better prognosis than those with unmutated IGHV (CLL-NM). Certain IGHV genes predominate in CLL and can form highly homologous B-cell receptors (stereotyped bcrs); subsets #1, #2, #4 and #8 being the most frequent(1). It has been shown that B cells expressing IGLV3-21 can acquire the R110 point mutation, which can induce constitutive BCR activation and confer aggressive behavior regardless of IGHV status(2). However, the prevalence and clinical impact of this alteration are not fully characterized.

Aims

To evaluate the distribution of rearrangements and the IGHV status, and to evaluate the prevalence and clinical behavior of the IGLV3-21^R110 mutation in CLL patients.

Materials and methods

A retrospective analysis was performed on a cohort of CLL patients studied between 2020 and the present. IGH rearrangement and IGHV status were analyzed from DNA obtained from peripheral blood, bone marrow, or lymph nodes using FR1 (BIOMED-2)/leader primer amplification and bidirectional Sanger sequencing. Sequences were aligned using IMGT/V-QUEST and subset assignment was performed using arrest/assign-subsets, following ERIC recommendations(3). IGLV3-21^R110 mutation was evaluated in cases with IGHV3-21 by allele-specific PCR. Del(17p) and trisomy 12 were assessed by FISH, and TP53 mutations by Sanger/NGS. The Kaplan–Meier method and the log-rank test were used for the analysis of TTFT.

Results

A total of 814 patients were included in this analysis (median age 66 years; M:F 1.8:1). Among them, 55.7% were classified as CLL-M, 38.1% as CLL-NM, and 6.2% as borderline (CLL-B). The IGHV gene distribution was as follows: IGHV3 (44.7%), IGHV4 (27.6%), IGHV1 (20.9%), IGHV2 (2.9%), IGHV5 (2.5%), and IGHV6 (1.3%). The most frequent IGHV genes were IGHV4-34 (12.3%), IGHV1-69 (11.7%), and IGHV3-21 (6.1%). A stereotyped BCR subset was assigned to 11.7% (3.8% CLL#2 and 0.6% CLL#8). Time to first treatment (TTFT) was significantly shorter (p=0.001) in CLL-NM (median 12 months) compared to CLL-M (36 months).
IGLV3-21^R110 was evaluated in 39 patients from the IGHV3 family, resulting in 27 positive cases (6 LLC-NM, 9 LLC-M and 12 LLC-B), found mainly in IGHV3-21 cases and less frequently in IGHV3-23 and IGHV3-66. None of these patients had del(17p) or trisomy 12. Patients with IGHV3-21^R110 were observed to have shorter TTFT than the rest of the IGHV3 patients studied.

Conclusions

The distribution of IGHV rearrangements observed in this cohort was consistent with previous reports in the literature. Molecular studies are essential for the diagnosis and risk stratification of patients with CLL, enabling more precise therapeutic decision-making. The high frequency of IGLV3-21^R110 among cases carrying IGHV3-21 and its association with shorter TTFT further underscore the clinical relevance of its detection.

EP 8
(#30)

The S100A9/emmprin axis is involved in Chronic Lymphocytic Leukemia progression and offers novel therapeutic opportunities.

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Volumen 30 - Número Extraordinario 6th Latin American Congress on Chronic Lymphocytic Leukemia
Abril 2026

Introduction

Chronic Lymphocytic Leukemia (CLL) is characterized by clonal expansion of CD5+ B cells. Disease progression is driven by tumor–microenvironment (TME) interactions within SLOs that promote survival, proliferation, and therapeutic resistance.

We identified the pro-inflammatory protein S100A9 enriched in serum-derived exosomes from IGHV-unmutated patients with active disease1. Both S100A9 and its receptor EMMPRIN (Extracellular metalloproteinase inducer) are overexpressed in leukemic cells, and activation of the S100A9–EMMPRIN axis induces NF-κB and PI3K/AKT signaling, promoting survival and proliferation, supporting its potential as a therapeutic target2.

As EMMPRIN induces metalloproteinases (MMPs), this axis may enhance leukemic migration. CLL infiltration into BM and SLOs depends on basement membrane degradation mediated by MMPs such as MMP9, associated with TME-driven progression3. BTK inhibitors (BTKi) disrupt these interactions by promoting leukemic egress, reducing the proliferative fraction, downregulating NF-κB, PI3K/AKT, CCL3, and CCL4, impairing tissue re-entry, and inducing tumor cell death4. Therefore, as the S100A9/EMMPRIN axis drives proliferation and induces MMPs, we investigated its contribution to migration and modulation by BTKi.

Hypothesis and Aims

The S100A9/EMMPRIN axis drives CLL progression by activating NF-κB and PI3K/AKT signaling and promoting leukemic migration to supportive niches. As BTKi efficacy relies on disrupting proliferation and homing, we aim to validate S100A9/EMMPRIN axis as an additional target to enhance BTKi efficacy.

Methodology

CLL samples were collected with informed consent and Ethics Committee approval and stored in the GURU-LLC Biobank. In vitro S100A9 stimulation and BTK inhibition were performed using PBMCs from untreated patients; ex-vivo analyses were conducted in PBMCs from BTKi-treated patients.

Results

S100A9 stimulation upregulates SP1 and EMMPRIN, increasing MMP2, MMP9, CCL3, and CCL4 expression, mediators of extracellular matrix remodeling, migration, and TME interactions. These effects (higher SP1, EMMPRIN, and MMP9 expression) are enriched in proliferative (CXCR4dim/CD5high) and dividing (CXCR4high/CD5high) fractions5 compared with the quiescent fraction (CXCR4high/CD5dim).

In vitro BTKi treatment downregulates SP1 and EMMPRIN, reducing MMP2/9 and CCL3/4 expression, impairing invasive behavior. Consistently, CLL cells from BTKi-treated patients show decreased activation of the SP1–EMMPRIN–MMP9 axis, particularly within proliferative and dividing fractions, along with reduced homing gene expression.

Conclusions

The S100A9/EMMPRIN axis drives CLL progression by enhancing proliferation and homing capacity. BTK inhibition suppresses this pathway, impairing lymph node re-entry and promoting leukemic cell death. Ongoing studies aim to define its role in BTKi-refractory patients and evaluate combined targeting strategies to overcome resistance.

EP 9
(#33)

The sphingosine kinase 2 (SPHK2) inhibitor opaganib reduces venetoclax resistance in a murine xenograft model of Chronic Lymphocytic Leukemia (CLL).

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Abril 2026

Introduction
Treatment of CLL patients with the BCL-2 inhibitor venetoclax (VEN) has shown efficacy, but the emergence of resistant cells is a current complication. We reported that co-culture of CLL cells with activated autologous T cells (aaT) promotes leukemic clone activation and VEN resistance [(1,2)]. VEN-resistant cells overexpress SPHK2, whose inhibition reduces aaT-induced CLL activation, proliferation and VEN resistance, and resensitizes already resistant CLL cells in vitro [(3)].

Objective
To evaluate in vivo treatment with VEN in combination with an SPHK2 inhibitor (opaganib) in a murine xenograft model of primary cells from CLL patients.

Methods
95 NSG mice were injected with peripheral blood mononuclear cells from 6 CLL patients, 3 with mutated IGHV (M-IGHV), and 3 with unmutated IGHV (U-IGHV), along with aaT cells [(4)]. After 2 weeks, human $CD45^+CD19^+$ cell detection confirmed engraftment, enabling 3-week treatment of 4 groups: control, VEN, opaganib, and VEN+opaganib. We euthanized the mice and assessed spleen, bone marrow, and peripheral blood by flow cytometry (Fig. A). Statistical analyses were made using Kruskal-Wallis followed by Dunn test.

Results
Analysis of spleens from the four treatment groups revealed no differences in leukemic cell counts between VEN-treated and control mice, suggesting that in this murine model, CLL cells became resistant to VEN (B). Mice treated with opaganib monotherapy did not diminish disease burden, but the combination VEN+opaganib, reduced splenic $hCD45^+CD19^+CD5^+$ cell counts by 50% compared to controls (Fig. B). We found a trend toward a greater effect in mice with U-IGVH cells, without reaching statistical significance. Few CLL cells were found in bone marrow and blood, with no significative differences among groups. No significant variations in BCL-2 expression were found in any of the 4 treatment groups.
VEN+opaganib reduced the number of T cells (CD3+) compared to controls in the spleens of mice injected with cells from U-IGHV patients (Fig. C). When evaluating $CD4^+$ and $CD8^+$ T-cell separately, both cell counts exhibited a downward trend in the VEN+opaganib and opaganib groups, reaching significance only for $CD8^{+-}$ cells from U-IGHV patients (Fig. D). Interestingly, CD8+ T cells in the VEN+opaganib group showed lower PD1 expression compared to the control group (Fig. F), suggesting a possible restorative effect of the combination treatment on this T cell subpopulation.

Conclusion
We here identified the murine xenograft model with primary cells from CLL patients as a value tool to study venetoclax resistance in vivo. This in vivo preclinical trial positions the SPHK2 inhibitor opaganib as a potentially useful therapeutic agent to overcome VEN resistance on CLL patients.

EP 11
(#45)

Inhibitory receptor lair-1 expression in normal b cells and chronic lymphocytic leukemia (CLL).

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Abril 2026

Introduction

B-cell receptor (BCR) signaling is a central pathogenetic pathway in CLL. Most CLL cells express BCRs of IgM and IgD isotypes, which are key in the activation and survival of the leukemic clone. On the other hand, LAIR-1 (Leukocyte-Associated Ig-like Receptor 1) is an inhibitory receptor, expressed by most immune cells. When activated, it delivers inhibitory signals that decrease B-cell activation and reduce BCR signaling. LAIR-1 exhibits heterogeneous expression in CLL and is currently the focus of multiple clinical trials for the treatment of cancer.

Objectives

To analyze the expression of IgM/IgD in different subgroups of CLL and their relationship with key genes involved in the inhibition of BCR signaling like LAIR1.

Methodology

For IGHV analysis, RT-PCR reaction and bidirectional sequencing were used. Sequences were analyzed using the IMGT/V-Quest and IG BLAST–NIH. The CLL phenotype were assessed by 8-color flow cytometry. The transcriptome of patients and healthy controls was analyzed using bioinformatics tools based on mRNA public datasets obtained from GEO-NCBI-NIH (Gene Expression Omnibus), of the U.S. National Institutes of Health. The datasets were analyzed using the GEO2R tool. Differentially expressed genes (DEGs) were obtained by applying the Benjamini & Hochberg (FDR) method with an adjusted p-value cutoff of 0.05 and a log2 fold-change threshold of 0.58.

Results

In our patient cohort (M:54 and F:39, mean age 67), 63% of cases showed mutated IGHV(M) and 37% unmutated(UM). Analysis of IGHV families: VH3(58%), followed by VH1(24%), VH4(11%), VH2(2%), VH5(3%), VH6(1%), and VH7(1%), showing a distribution similar to other Latin American series. VH3(68%) and VH4(78%) families were more frequent in M-CLL, whereas VH1 was associated with UM-CLL(71%). In 22 fresh CLL samples (14M-CLL, 9U-CLL), IgM/IgD expression were analyzed. The percentage of IgD was significantly greater than that of IgM in both groups ($p<0.05$). Additionally, IgD expression was higher in the U-CLL compared to the M-CLL group, although this difference did not reach statistical significance. Subsequently, LAIR expression was analyzed from datasets (GSE36907, GSE16065) and compared among groups of normal B lymphocytes with different levels of IgD expression and CLL patients (M-UM). 1.The $IgM^+IgDlow/-CD27^+$ normal B-cells showed a 2.5-fold lower expression of LAIR compared to the $IgM^+IgD^+CD27^+$ phenotype (p=ns). 2. In the naïve B-cell phenotype ($IgM^+IgD^+CD27^+$), LAIR expression was two-fold higher compared to the $IgM^+IgD^+CD27^+$ (memory) group, $p<0.05$. 3. No differences were observed between M and UM CLL patients. 4. LAIR gene expression showed 2.0 fold increase in Mutated IgHV3-23 compared to Mutated non IgHV3-23, $p<0.05$.

Conclusions

LAIR expression in CLL is not associated with global IGHV mutational status but appears linked to B-cell differentiation state and specific IGHV family usage, particularly IGHV3-23, suggesting that inhibitory signaling balance may be shaped by clonal immunogenetic features rather than by surface IgM/IgD levels alone.

EP 14
(#46)

Epitranscriptomic regulation of leukemic b cells from Chronic Lymphocytic Leukemia patients: the role of methyltransferase 3 and musashi 2.

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Abril 2026

Introduction

Epitranscriptomic regulation is essential for maintaining cellular homeostasis, and its dysregulation has been linked to cancer. Proteins that add chemical modifications to RNA, as well as those that recognize and bind RNA molecules, play critical roles in determining the fate of messenger RNA (mRNA). Two such proteins, RNA methyltransferase (METTL3) [1] and mRNA-binding oncoprotein Musashi 2 (MSI2) [2], promote the survival of chronic lymphocytic leukemia (CLL) cells and are highly expressed in patients with poor clinical outcomes. Therefore, we hypothesize that METTL3's action on target mRNAs may influence MSI2 function and contribute to disease progression.

Aim

To determine how epitranscriptomic regulation influences the progression of CLL, by investigating the regulatory mechanisms of METTL3/MSI2 in CLL and evaluating the combined effects of MSI2 and METTL3 inhibition or downregulation on CLL cell viability.

Methodology

Blood samples from patients with CLL were used, following informed consent and approval by the institutional Ethics Committee. The cells stored in the Uruguayan CLL Group Biobank were used for the performance of in vitro experiments. Molecular and cellular biology techniques were carried out.

Results

Higher MSI2 and METTL3 protein levels were observed in leukemic B-cells from poor clinical outcome CLL patients (n=15, p<0,03), with even greater expression in recently divided cells defined as CXCR4DimCD5Bright cells (n=15, p<0,0067). We identified a positive correlation between METTL3 and MSI2 expression at protein (n=15, p=0,016) and mRNA levels (n=188, p<0,0001), supporting the hypothesis of a functional connection between these two proteins. Pharmacological inhibition of METTL3 (STM2457, SCT-15) or genetic silencing with small interference RNA (siMETTL3) reduced cell viability and proliferation in MEC1 cells and in primary CLL samples. Furthermore, METTL3 protein reduction by a specific METTL3 PROTAC-degrader [3] in MEC1s cells resulted in reduced BCL2 expression and enhanced apoptosis, further supporting the role of METTL3 in leukemic cell survival.

Based on these findings, we are currently evaluating whether combined inhibition or downregulation of MSI2 and METTL3 produces additive or synergistic antitumor effects, with the aim of extending these studies to patient-derived xenograft models.

Conclusions

Our results demonstrate that METTL3 and MSI2 are co-expressed and functionally associated in CLL, particularly in aggressive disease. Inhibiting METTL3 reduces leukemic cell viability and promotes apoptosis, highlighting its role in CLL survival. Ongoing studies will determine whether dual targeting of METTL3 and MSI2 enhances antitumor effects. Overall, the METTL3/MSI2 axis emerges as a promising therapeutic target in CLL.

EP 15
(#47)

Modulation of the cation channel transmembrane protein 176a (tmem176a) as a potential strategy to enhance inflammasome activation and induce tumor cell death in Chronic Lymphocytic Leukemia.

dos Santos, Gimena[1]; Guazzone, Vanesa[2]; Rammauro, Florencia[3]; Uriepero, Angimar[1]; Uria, Rita[1]; Prieto, Daniel[4]; Palacios, Florencia[1]; Marquez, María Elena[1]; Landoni, Ana Inés[5]; Ranero, Sabrina[6]; Oliver, Carolina[7]; Irigoin, Victoria[7]; Russo, Sofía[3]; Segovia, Mercedes[3]; Hill, Marcelo[3]; Oppezzo, Pablo[1].

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Abril 2026

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by the progressive accumulation of monoclonal CD5⁺B lymphocytes with defective programmed cell death, including resistance to apoptosis and pyroptosis. Specifically, pyroptosis is executed by gasdermin D (GSDMD) pores, which assemble following inflammasome activation. Inflammasomes are cytosolic multiprotein complexes that activate caspase-1 which then cleaves GSDMD. NLRP3 inflammasome activation is negatively regulated by the cation channel transmembrane protein TMEM176A/B. We previously reported elevated TMEM176A expression mainly in patients with active CLL (patients with progressive CLL), associated with reduced caspase-1 activation and impaired GSDMD cleavage.

Objective

To elucidate the role of TMEM176A/NLRP3 inflammasome axis in CLL and identify it as a potential therapeutic target.

Methodology

PBMCs from CLL patients were obtained after informed consent and stored in the of CLL Biobank. Flow cytometry and PCR were performed to evaluate TMEM176A modulation in CLL cells treated with TMEM176 inhibitor as (+)-BayK8644 (monotherapy) or (+)-BayK8644 and ibrutinib (dual therapy). Active caspase-1 was quantified as a readout of the NLRP3 inflammasome activation. TCL-1 mice housed at Institut Pasteur de Montevideo were used for the adoptive transfer model of CLL. Survival and tumor clone evolution were assessed after monotherapy or dual-agent therapy. Ethics Committee approval was granted for both human and animal studies.

Results

Given the high expression of TMEM176A in progressive CLL cells and the well-established role of tumor microenvironment-tumor clone interactions promoting proliferation and survival, we evaluated inflammasome activation in primary CLL cells stimulated with CD40L/IL4. TMEM176A expression and AKT phosphorylation were increased upon stimulation, but caspase-1 activation was downregulated. Pharmacological inhibition of TMEM176A with (+)-BayK8644 and of the AKT pathway with triciribine induced caspase-1 activation in primary CLL cells. Furthermore, the combination of (+)-Bayk8644 and ibrutinib was more effective than monotherapy in inducing caspase-1 activation and cell death. In the TCL1 model, monotherapy with (+)-BayK8644 -and more prominently its combination with ibrutinib- synergistically enhanced leukemic cell death, resulting in significantly prolonged survival compared to control groups.

Conclusions

TMEM176A mediates escape from cell death in CLL downstream of microenvironment-driven AKT activation. CD40L/IL4 stimulation enhances AKT phosphorylation and TMEM176A expression, suppressing inflammasome activation and pyroptosis. Targeting AKT or TMEM176A restores caspase-1–dependent cell death, supporting a PI3K/AKT/TMEM176A regulatory axis controlling inflammasome activity. Combination therapy with (+)-BayK8644 and ibrutinib synergistically induces leukemic cell death in vitro and in vivo, revealing a therapeutic strategy to overcome microenvironment-mediated survival signals in CLL.

EP 16
(#50)

Combined bet and bcl-2 or btk inhibition induces broad transcriptional reprogramming and enhances cell death in poorly responsive CLL cells.

Lins Pansonato, Bruna[1]; Carvalho, José Leilton[2]; Amoedo, Pedro[2]; Camargo, Anamaria[2]; Asprino, Paula[2]; Masotti, Cibele[2]; Bettoni, Fabiana[2]; Azevedo, Fernanda[2]; Molla, Vinicius[2]; Pfister, Verena[2]; Arrais-Rorigues, Celso[2]; Amano, Mariane[1].

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Abril 2026

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by transcriptional programs that sustain B-cell receptor signaling and resistance to apoptosis. Although iBTK and iBCL-2 inhibitors have significantly improved outcomes, complete remissions remain uncommon, particularly in high-risk or poorly responsive cases. Bromodomain and extra-terminal (BET) proteins regulate the transcription of oncogenic drivers, such as MYC and TCL1A, via super-enhancer activity. Although BET inhibition (iBET) has demonstrated antitumor activity in other hematologic malignancies, its role in CLL is not fully understood.
Objective: Evaluate the transcriptional and functional effects of BET inhibition combined with BTK or BCL-2 inhibition in primary CLL cells and determine whether these combinations enhance cytotoxicity in poorly responsive samples.

Methods

Peripheral blood mononuclear cells from CLL patients were treated in vitro with iBET alone or in combination with iBTK (n=48) or iBCL-2 (n=49). Apoptosis was assessed by Annexin V/propidium iodide staining. RNA sequencing (n=32) and RT-qPCR were performed to characterize transcriptional changes. The cutoff for defining poorly responsive samples was set at a BCL-2 inhibitor–to–DMSO ratio ≤ 3. Statistical analyses were conducted using parametric or nonparametric tests, as appropriate.

Results

The combination of iBET and iBTK induced apoptosis, though it did not significantly increase cytotoxicity compared to iBTK alone. However, the combination significantly downregulated transcriptional programs associated with disease progression and survival, including MYC, TCL1A, IKZF3, and BCL2. In contrast, the combination of iBET and iBCL-2 significantly increased apoptosis in poorly responsive CLL samples (mean apoptosis 70% vs. 58% with iBCL-2 alone; $p<0.05$). This effect was not observed in highly sensitive samples. Transcriptomic profiling revealed that iBET-containing combinations induced broad transcriptional reprogramming, which was characterized by the suppression of MYC-driven and anti-apoptotic gene signatures. Similar transcriptional patterns were observed in the iBET+iBTK and iBET+iBCL-2 conditions. No significant differences in response were detected between IGHV-mutated and unmutated samples.

Conclusion

BET inhibition induces transcriptional reprogramming of oncogenic networks in CLL and selectively enhances cytotoxicity when combined with BCL-2 inhibition in poorly responsive samples. These findings support the further investigation of BET inhibitors as combination therapies to overcome resistance to targeted treatments in CLL.

EP 17
(#73)

Impact of gene editing of histones 1.3 and 1.4 in TCL1-355 cells.

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Abril 2026

Introduction
Chromatin activation is associated with disease progression in chronic lymphocytic leukemia (CLL). Histones 1 (H1) modulate the conformation of the chromatin and play a key role in the epigenetic regulation of several biological processes. Overexpression of the mutagenic enzyme AID in a murine model enhances CLL disease aggressiveness and introduces mutations in genes encoding for H1.3 and H1.4 (1). Our goal is to study the role of H1.3 and H1.4 in CLL and hypothesize that H1 levels and mutant variants affect the phenotype and function of leukemic cells.

Methods
The structural impact of murine H1.3 S90R, H1.4 A164S and H1.4 A167V key mutations were evaluated using homology-based modelings on a nucleosome template, machine-learning predictors of stability and protein–DNA affinity, and normal-mode analysis (NMA) of conformational flexibility. The murine CLL line TCL1-355 was used to generate H1.3 and H1.4 stable knock outs (KO) cells by CRISPR/Cas9 technology. End point PCR was used to evaluate the excision of the targeted genomic DNA. Gene expression levels of hist1h1d and hist1h1e (encoding murine H1.3 and H1.4) were evaluated by qPCR. Proliferation was analysed by cell count. Expression of CD69 was assessed by flow cytometry.

Results
In silico analyses indicated that H1.3 S90R and H1.4 A164S/A167V mutations do not grossly disrupt the global fold of H1 but rather fine-tune its local dynamics and interaction with DNA. NMA-based flexibility analysis revealed a localized decrease in backbone mobility (local rigidification) around the three mutation sites. We efficiently edited the genomic DNA region of the targeted H1 genes obtaining single and double KO TCL1-355 cells. Compared to controls, TCL1-355 H1.4 KO cells lacked expression of hist1h1e and upregulated hist1h1d gene levels ($n=3$, $p<0.05$). TCL1-355 H1.3 KO cells showed significantly lower levels of transcripts for hist1h1d and upregulated hist1h1e gene levels ($n=6$, $p<0.05$). Impaired expression of hist1h1d led to increased cell proliferation and to enhanced CD69 expression in single H1.3 KO cells ($n=6$, $p<0.05$). Ibrutinib, used at 1uM for 72 hs, impaired the proliferation in the control TCL1-355 group but this effect was not observed in single H1.3 nor double H1.3+H1.4 KO cells ($n=6$, $p<0.05$).

Conclusion
H1 mutations primarily alter the local geometry and dynamics of the H1–DNA interface, rather than globally destabilizing the histone fold, thereby potentially modulating chromatin compaction and higher-order organization. H1.3 impairment in the TCL1-355 cell line enhances activation, proliferation and suppression of the anti-proliferative effect induced by Ibrutinib. These effects are not rescued by upregulation of H1.4, and are not detected in H1.4 KO cells. In line with our previous results in MEC-1 cells KO for H1.3 (2), we propose that this specific H1 subtype could be involved in CLL disease aggressiveness and in loss of sensitivity to BTK inhibition.

EP 18
(#76)

Quantitative analysis of clonal expansion and repertoire structure in CLL using long-read ighv sequencing.

Sarmiento Varon, Lindybeth[1]; Aldridge, Jacqueline[2]; Gonzalez Puelma, Jorge[3]; Torres Almoacid, Jorge[2]; Cardenas, Sofia[4]; Uribe Paredes, Roberto[5]; Navarrete, Marcelo[3].

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Abril 2026

Introduction

IGHV mutational status is an established prognostic marker in chronic lymphocytic leukemia (CLL). However, conventional testing does not quantify clonal dominance nor provide detailed information on mutation distribution patterns and the structure of the residual B-cell repertoire. Long-read sequencing enables full-length VDJ reconstruction and quantitative analysis of immunogenomic architecture from clinical samples.

Objective

To characterize clonal expansion patterns and repertoire structure in CLL using long-read IGHV sequencing.

Methodology

Fifty-one CLL patients and twelve healthy donors were analyzed. Full-length IGHV libraries were generated using template-switching amplification and sequenced on Oxford Nanopore platforms. Clonotype assignment and SHM calculation were performed using a dedicated bioinformatic workflow. Analyses included clonal space (CS) distribution, frequency of expanded (1–5%) and hyperexpanded (>5%) clonotypes, Hill diversity indices (0D–2D), mutation density distribution, CDR3 length and amino acid charge, and modeling of antigen selection pressure and SHM targeting across framework and CDR regions. Group comparisons were performed using non-parametric tests ($p<0.05$).

Results

Long-read sequencing enabled estimation of clonal space distribution, with CS values of 0.66 in M-CLL and 0.71 in UM-CLL. Differences in clonotype frequency distribution were observed between CLL samples and healthy donors, with expanded categories more frequently represented in CLL

Mutation density profiling showed differences in SHM distribution between M-CLL and UM-CLL. Modeling of antigen selection pressure and SHM targeting showed variation in replacement/silent mutation patterns across framework and CDR regions between subgroups.

Diversity analysis indicated reduced shared rearrangements and skewed clonotype frequency distributions in CLL. The non-clonal B-cell compartment showed longer CDR3 sequences and higher mean amino acid charge compared to healthy donors. Intraclonal diversification was observed within dominant rearrangements.

Conclusions

Long-read IGHV sequencing allows quantitative assessment of clonal expansion and repertoire structure in CLL from a single dataset. These analyses provide additional descriptive parameters beyond conventional mutational status classification and may contribute to a more detailed characterization of clonal and residual repertoire features.

EP 19 (#27)

Altered phenotype and functional profile of kir+ virtual memory cd8+ t cells in chronic lymphocytic leukemia (CLL).

Rodríguez Galán, María Cecilia[1]; Salvador, Iñaki[2]; Mallorqui, Sofia[2]; Rodriguez, Cecilia[3]; Erguin, Maite[2]; Serna, Angel[2]; Abrisqueta, Pau[2]; Bosch, Francesc[2]; Crespo, Marta[2].

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Introduction
In this ongoing project, we expanded our work initiated in Argentina in 2025, where we demonstrated that a subset of CD8+ T cells known as Virtual Memory T cells (TVM) can express either KIR or NKG2A in a mutually exclusive manner and respond independently of TCR stimulation. We previously showed that KIR+ TVM—but not NKG2A+ TVM—are significantly reduced in frequency in patients with CLL compared with healthy donors (HD) ($p<0.01$). Moreover, KIR+ TVM from CLL displays lower expression of the transcription factors EOMES and HELIOS ($p<0.01$), both essential for functional and regulatory programs, which correlates with reduced levels of granzymes and perforin ($p<0.05$).

Objective
To extend the comparative analysis between CLL and HD by evaluating chemokine and cytokine receptor expression, exhaustion markers, and functional molecules using a 35-color spectral flow cytometry panel.

Methodology
Spectral flow cytometry in Dr. Bosch laboratory at VHIO, Barcelona.

Results
Comparison of a CLL patient with an HD revealed a markedly altered distribution of CD8+ T-cell subsets. Naïve T cells were nearly absent in CLL, accompanied by a pronounced expansion of Terminally Differentiated Effector Memory T (TEMRA) cells. Regarding functional capacity, KIR+ TVM from HD showed higher frequencies of EOMES and CD56 expression than those from CLL. Interestingly, KIR+ TVM from CLL exhibited increased expression of CXCR3 and IL7R, suggesting a Tc-like profile with enhanced migration toward inflamed tissues and lymph nodes. Their elevated IL7R expression may indicate improved survival and potential homing to lymph nodes and bone marrow, where IL-7 is abundant. Notably, this IL7R upregulation was specific to KIR+ TVM in CLL and was not observed in conventional CD8+ T-cell subsets. However, KIR+ TVM from CLL also displayed higher levels of exhaustion markers (PD-1, TIM-3, TIGIT) compared with HD.

Conclusions
This comparative analysis of CD8+ T-cell subsets reveal substantial differences in functional, migratory, cytokine-dependence, and exhaustion profiles, particularly within the KIR+ TVM compartment in CLL versus HD. The study is ongoing, with plans to expand the cohort and include functional assays to assess the prognostic and clinical implications of these alterations. Future work will also evaluate whether different CLL treatments can restore any of these parameters.

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HEMATOLOGÍA

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HEMATOLOGY JOURNAL REGULATIONS

HEMATOLOGÍA

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We will accept the publication of articles from non-Spanish-speaking authors written in English.
The current sections of Revista Hematología are:

1. Original articles
2. My opinion
3. Anatomo-clinic discussion of the hematology fellowships
4. Editorial
5. Updates and/or reviews
6. Pediatric hematology
7. New drugs in hematology
8. Brief communications
9. Laboratory
10. History of hematology
11. Case reports
12. Images in hematology
13. Letters to the Editor

1) **Original articles** must be unpublished. They should not have been submitted simultaneously to another journal without knowing the decision of acceptance or denial from Revista Hematología.
The articles should be in Word format, double-spaced, in Times New Roman font 12, with wide margins of 3cm with a maximum of 4,000 words, including tables and references. All illustrations, figures and tables and their respective legend, should be placed in the appropriate places in the text, instead of at the end.
The articles arrangement should be as follows:
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- Authors:
  - The list of authors should be included in a separate line, separated by commas, beginning with the complete last name and the initials of the name.
  - Institutional affiliation: it will include the institution name (without abbreviations) where the work has been carried out for each author.

Example:
Pérez V1; González C2
1 Servicio Hematología, Hospital Milstein. Buenos Aires, Argentina
2 Servicio de Hematología, Hospital Fernández. Buenos Aires, Argentina
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Note: The statement of authorship should only be included in **research articles** with multiple authors, but not in those with only one author.
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- Summary:
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References must be visible in the text in parentheses, and subscript. The journal adopts the criteria established by the APA Standards (www.normasapa.com)

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3) Share Ownership
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Animal models
If works in animal models are accepted, the authors should send the appropriate certificate of approval from the project issued by CICUAL (Institutional Committee for the Care and Use of Laboratory Animals).

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REVISTA HEMATOLOGÍA

http://revistahematologia.com.ar/
ISSN 0329-0379

Entidad editora SOCIEDAD ARGENTINA DE HEMATOLOGÍA
Julián Álvarez 146 - Ciudad Autónoma de Bs As - Argentina
(54-11) 4855-2452 / 2485
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