



education and research initiative on CLL

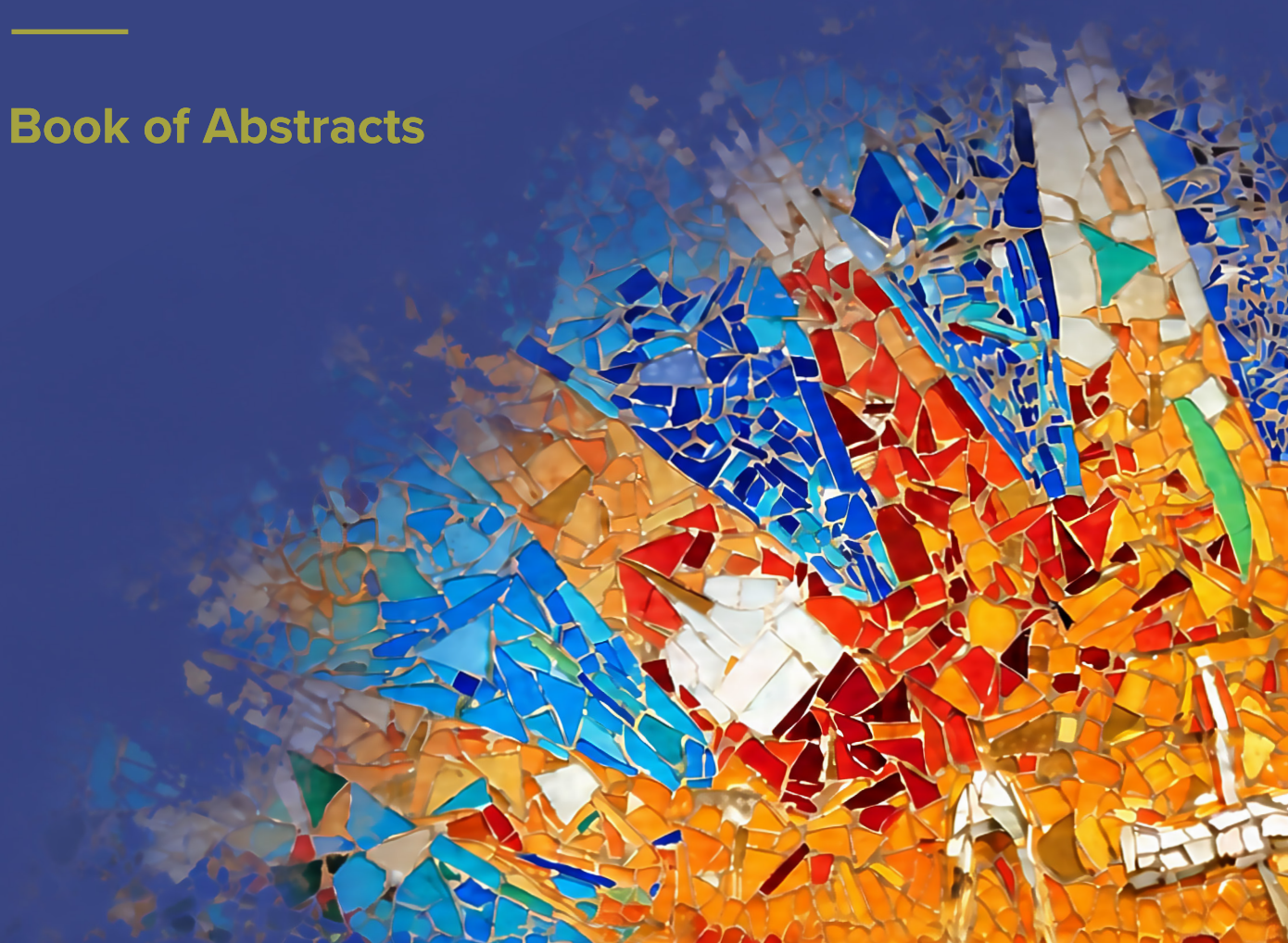
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New frontiers in CLL Research

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Book of Abstracts



P001

Biochemical and Functional characterization of Notch1 non-coding mutations using genome edited cell models

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Topic: Basic

Background: Chronic lymphocytic leukemia (CLL) is the most common adult leukemia and is characterized by a highly heterogeneous clinical course. Aberrant NOTCH1 signaling and NOTCH1 mutations are frequently observed in CLL and are associated with adverse prognosis, disease progression, and transformation. To date, mechanistic studies have mainly focused on coding mutations in exon 34 that disrupt the PEST domain, resulting in stabilization of the active Notch1 intracellular domain (NICD1). Recently, non coding mutations within the NOTCH1 3'untranslated region (3'UTR) have been identified. Patients harboring these lesions exhibit an even more aggressive clinical course than those with canonical coding NOTCH1 mutations. However, despite their link to NOTCH1 pathway activation and poor outcome, their functional impact and contribution to CLL biology remain poorly understood.

Material and methods: The NOTCH1-152 A>G mutation (g.139390152 A>G) was introduced into HG3 cells using CRISPR-Cas9 genome editing and validated by Sanger sequencing. Transcriptomic changes were characterized by RNA sequencing. Alternative splicing was assessed and expression of NOTCH1 target genes was quantified by qRT-PCR. Proteins of interest, including cleaved NICD1 and FBXW7 targets, were analyzed by Western blotting. Flow cytometry was used to assess surface marker expression. In addition, cells were treated with NOTCH agonists and antagonists to investigate the kinetics of NOTCH1 pathway activation and deactivation.

Results: In our CLL model, the most common NOTCH1 3'-UTR mutation (NOTCH1-152 A>G) generated indeed an alternatively spliced NOTCH1 transcript encoding a novel NICD1 152 protein variant lacking the PEST domain and containing a unique C terminus, consistent with activation of a cryptic splice acceptor site within the 3'-UTR. CRISPR Cas9 mediated introduction of a heterozygotic 152 A>G mutation into HG3 cells generated isogenic clones co expressing wild-type NICD1 and NICD1-152, resulting in increased overall NICD1 stability and accumulation of FBXW7 substrates, including c JUN. Mutant clones exhibited altered cellular morphology, enhanced proliferation, increased viability, and adaptive cell cycle responses under glutamine-deprived conditions. At baseline, NOTCH1 152 mutant clones displayed a distinct transcriptomic profile compared with wild-type HG3 cells, characterized by significant enrichment of NOTCH1/RBPJ target gene signatures as well as adhesion and transcription related programs, whereas inflammatory pathways were markedly downregulated. Upon experimental NOTCH1 stimulation, mutant clones demonstrated additional context dependent transcriptional remodeling superimposed on this baseline signature, linking the non coding NOTCH1 3'-UTR mutation to sustained yet dynamically regulated oncogenic NOTCH1 signature in CLL.

Conclusion: Our CRISPR Cas engineered NOTCH1-152 A>G model demonstrates that recurrent non-coding NOTCH1 3'UTR mutations defines a distinct CLL subgroup in which a non coding NOTCH1 lesion sustains oncogenic signaling through a degradation protection "sponge" mechanism involving FBXW7 and USP28. This mechanism provides a molecular explanation for the particularly aggressive clinical

course of affected patients and identifies a distinct high-risk biological subgroup of CLL. Therefore, NOTCH1-152 could serve as a prognostic tool for future precision diagnostics and risk stratification.

P002

A RiboCancer cell line panel reveals that CLL-associated Rps15 mutations translationally rewire transcription through codon-specific tRNA accommodation defects

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Topic: Basic

Background: Mutations in ribosomal proteins (RPs) are recurrently associated with oncogenesis, as illustrated by deletions of RPL5, RPL11 and RPL22 in hematological malignancies and solid tumors, as well as point mutations in RPL10 and RPS15 in T-cell acute lymphoblastic leukemia (T-ALL) and chronic lymphocytic leukemia (CLL), respectively. Previous studies have demonstrated that cancer-associated RP mutations can selectively rewire translation and create therapeutic vulnerabilities. For example, we previously showed that the T-ALL-associated RPL10 R98S mutation promotes hypertranslation of oncogenic transcripts including BCL2, thereby sensitizing leukemic cells to the BCL2 inhibitor venetoclax. In CLL, up to 20% of relapsed patients harbor missense mutations affecting the C-terminal tail of the ribosomal protein RPS15. This region plays a critical structural role in ribosomal decoding by facilitating aminoacyl-tRNA accommodation at the ribosomal tRNA accommodation (A) site. However, the impact of CLL-associated RPS15 mutations on translational dysregulation remains incompletely understood.

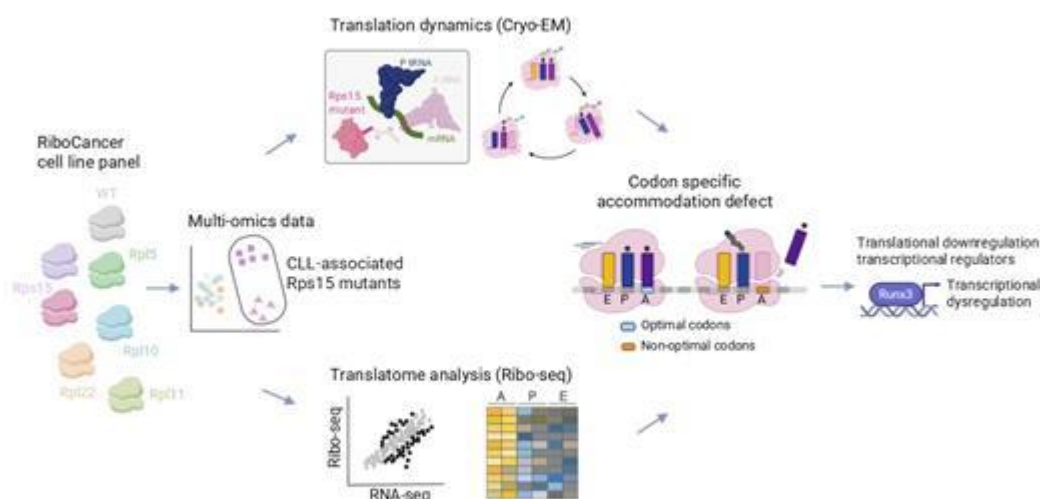
Material and methods: To systematically compare the translational consequences of the most prevalent cancer-associated RP lesions, we generated an isogenic CRISPR-Cas9-engineered RiboCancer cell line panel, including the CLL-associated RPS15 P131S and H137Y mutations. We performed an integrated multi-omics translome analysis combining total RNA-seq, Ribo-seq (sequencing of ribosome protected RNA), quantitative proteomics, and rRNA modification profiling. Structural consequences of RPS15 mutations were assessed by cryo-electron microscopy (cryo-EM) of translating ribosomes. Codon occupancy analyses and reporter assays were used to determine the impact of RPS15 mutations on translation elongation dynamics.

Results: Within the RiboCancer panel, RP loss-of-function lesions showed minimal translational rewiring. In contrast, RP point mutations induced substantial translational rewiring, with CLL-associated RPS15 mutations displaying the strongest phenotype and affecting the translation efficiency

of nearly 10% of expressed genes. Cryo-EM and biochemical analyses revealed that these mutations destabilize the RPS15 C-terminus tail and affect translation elongation cycle dynamics by deregulating aminoacyl-tRNAs accommodation at the ribosomal A-site. Ribo-seq analyses and translation reporter assays demonstrated that this defect was codon-specific, with 11 codons enriched among transcripts with reduced translation efficiency in RPS15-mutant cells. Transcripts with high occurrence of these hard-to-translate codons were enriched for genes involved in epigenetic and transcriptional regulation as well as DNA repair. Integration of our translome datasets identified RUNX3 as one of the most prominent translationally repressed transcription factors, with reduced protein expression and subsequent downregulation of many of its target genes involved in immune regulation. Consistent with these observations, RUNX3 downregulation was confirmed in a human CLL cellular model harboring RPS15 mutation.

Conclusion: By systematically comparing recurrent cancer-associated RP lesions, we have identified CLL-associated RPS15 mutations as potent drivers of translational rewiring. Mechanistically, these mutations impair aminoacyl-tRNA accommodation in a codon-specific manner, resulting in selective translational repression of genes involved in transcriptional regulation such as RUNX3. Our findings establish a mechanistic link between RPS15 mutations and translational dysregulation, providing new insights into how ribosome dysfunction contributes to CLL pathobiology.

Figure/Table 1



P003

Targeting apoptotic co-dependence in venetoclax-resistant CLL with a dual BCL2/BCLxL PROTAC degrader

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Topic: Basic

Background: Venetoclax has transformed the treatment of chronic lymphocytic leukemia (CLL), particularly after BTK inhibitor (BTKi) failure, but patients who progress after both BTKi and venetoclax have limited therapeutic options. Acquired BCL2 mutations can reduce venetoclax sensitivity but occur in only a minority of relapsed patients and often as minor subclones, suggesting that most resistant CLL cells escape through additional mechanisms. We hypothesized that genetic and non-genetic mechanisms of venetoclax resistance converge on mitochondrial apoptotic rewiring and adaptive BCL2/BCLxL co-dependence.

Methods: We analyzed 24 paired CLL samples collected before venetoclax and at relapse, including progression during continuous venetoclax therapy (“on ven”) and relapse after fixed-duration venetoclax discontinuation (“off ven”). Integrated analyses included single-cell RNA-seq, single-cell ATAC-seq, whole-exome sequencing, proteomics, spatial immunofluorescence, BH3 profiling, and drug sensitivity assays. Candidate resistance pathways were prioritized based on convergence across orthogonal datasets and tested for apoptosis priming using BAX/BAK activation, and cytochrome c release assays. The activity of the VHL-recruiting BCL2/BCLxL PROTAC WH25244 was compared with venetoclax and navitoclax in treatment-naïve, “on ven,” and “off ven” primary CLL samples, stromal co-culture models, and CRISPR engineered BCL2, BTK, and TP53 mutant cells.

Results: BCL2 mutations were detected in a subset of venetoclax-relapsed samples but were often subclonal, indicating that additional mechanisms contribute to clinical resistance. Integrated single-cell and proteomic analyses identified relapse-associated activation of NFκB, BCR, AKT, and MAPK signaling, with increased expression of BCLxL-associated survival programs. Spatial and stromal co-culture studies further supported a role for microenvironmental NFκB activation in promoting BCLxL expression. BH3 profiling showed that venetoclax-relapsed CLL cells retained BCL2 dependence but acquired increased BCLxL dependence, consistent with adaptive BCL2/BCLxL co-dependence. This pattern was most evident in “on ven” relapse, whereas “off ven” relapse showed a greater tendency to retain BCL2-dominant survival with emerging BCLxL contribution. Functional studies showed that prioritized resistance pathways contributed to BCLxL induction, altered apoptotic priming, and impaired venetoclax response.

WH25244 induced VHL-dependent BCLxL degradation and, depending on cellular context, BCL2 inhibition, dephosphorylation, or degradation. This remodeling of the apoptotic interactome triggered BAX/BAK activation, cytochrome c release, and apoptosis in venetoclax-resistant CLL cells. WH25244 remained active in engineered models expressing recurrent BCL2 mutations and in BTK- or TP53-mutant systems associated with increased BCLxL dependence. Compared with conventional BCLxL inhibition, WH25244 showed a more favorable therapeutic window in platelet studies, consistent with reduced platelet vulnerability to VHL-recruiting degrader activity.

Conclusions: Venetoclax resistance in CLL is driven by heterogeneous genetic, transcriptional, post-translational, and microenvironmental mechanisms that converge on mitochondrial apoptotic rewiring

and adaptive BCL2/BCLxL co-dependence. Integrated functional profiling distinguishes “on ven” and “off ven” relapse trajectories while identifying a shared therapeutic vulnerability in many resistant cases. These findings support dual BCL2/BCLxL targeting with WH25244 as a rational strategy for venetoclax-resistant and dual-refractory CLL, with potential relevance across B-cell malignancies.

P004

Genomic heterogeneity in CLL with del(11q): integrated analysis by chromosome banding analysis, optical genome mapping and NGS

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Topic: Basic

Introduction: In chronic lymphocytic leukemia (CLL), 11q22-q23 deletion [del(11q)] has been associated with adverse biological features. The minimally deleted region includes ATM, essential for DNA repair that is mutated in one third of cases. In 80–85% of cases, del(11q) coexists with BIRC3 deletion, whereas co-mutations are uncommon (<10%). Although its prognostic impact may have been attenuated with targeted therapies, its genomic context and associated complexity remain incompletely understood.

Objectives: (1) To define the clinicobiological characteristics of CLL patients with del(11q) included in a Spanish real-world cohort treated with targeted agents. (2) To describe 11q alterations and genomic complexity by chromosome banding analysis (CBA) and/or Optical Genome Mapping (OGM). (3) To analyse their mutational profile by NGS.

Patients and methods: A total of 434 CLL patients from 35 Spanish centers treated with BTK and/or BCL2 inhibitors, with or without anti-CD20 antibodies, between November 2021 and January 2026 were included. Eighty-nine patients with del(11q) detected by FISH were selected. Cytogenetic abnormalities were assessed in all cases by CBA, while OGM was performed in 64/89 cases. Genomic complexity by OGM (GC) was defined as ≥ 5 alterations of ≥ 5 Mb and/or rearrangements. NGS was performed in 31 patients using the SOPHiA DDM™ CLL Solution panel.

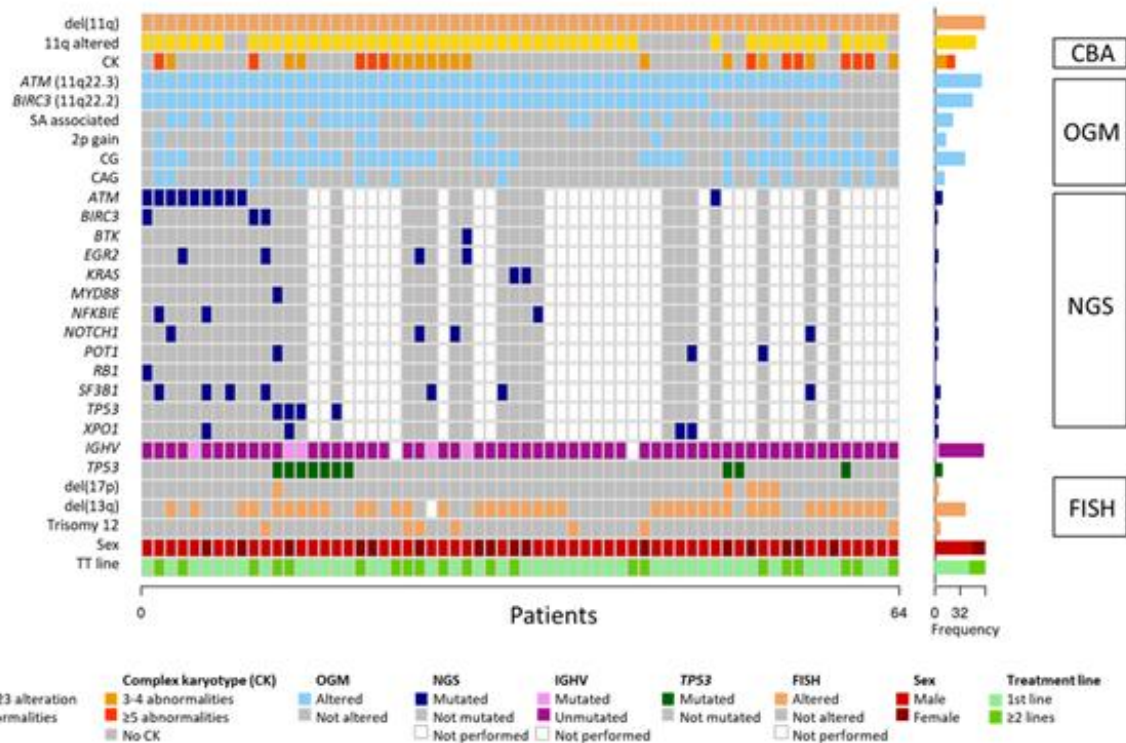
Results: Patients with del(11q) represented 20% (89/434) of the cohort, with 81% Binet B/C stage, 89% unmutated IGHV and TP53 alteration in 18%. Regarding treatment, 35% had received two or more treatment lines, and 29% received prior chemoimmunotherapy. CBA was abnormal in 88% and complex in 31%. In 66 (74%) cases, abnormalities involving 11q22-q23 were detected, including 55 deletions and 11 complex structural alterations (Figure).

OGM identified del(11q) in 59/64 cases, with discordant cases showing low infiltration (<15–20%). The median size of del(11q) was 33.6Mb (422Kb–42.6Mb). All deletions included ATM, and 81% also involved BIRC3, without clinicobiological differences. Multiple del(11q) events were detected in 7 patients, suggesting clonal heterogeneity. OGM allowed the characterization of structural alterations associated with del(11q) in 23 patients (38%), including simple (n=7) or multiple translocations (n=16), 15 of which were not identified by CBA. Gains of 2p involving REL and MYCN were observed in 24% of patients, five associated with cryptic t(2;11). GC was detected in 34/59 (58%) cases including 10 chromoanagenesis events: chromoplexy (n=5), chromothripsis (n=4), and chromoanasythesis (n=1). Among the 31 patients analyzed by NGS, 93% (29/31) had at least one mutation. ATM mutations were detected in 34% (11/31) of cases and were distributed across the gene, whereas BIRC3 mutations were detected in 3 (10%) cases, always associated with a concomitant deletion. Additional mutated genes included SF3B1(22%), TP53(13%), EGR2(13%), NOTCH1(13%), XPO1(10%), NFKBIE(10%), POT1(10%) and KRAS(6%) (Figure).

Conclusions: (1) Del(11q) in CLL is associated with an adverse biological profile and a high frequency of UM-IGHV. (2) OGM reveals wide structural variability at 11q22q23 and high GC in these patients. (3) CLL with del(11q) represents a genomically heterogeneous subgroup in which accompanying cytogenetic alterations and/or mutations may have clinical relevance.

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Figure/Table 1



P005

Resolving the genomic complexity of chronic lymphocytic leukemia using long-read whole-genome sequencing

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Topic: Basic

Background: Complex karyotype (CK) is a well-established marker of adverse prognosis in chronic lymphocytic leukemia (CLL). While advances in genomic profiling have enabled comprehensive detection of single-nucleotide variants (SNVs), structural variants (SVs) and copy number variants (CNVs), the molecular consequences of large-scale structural genome alterations remain insufficiently understood. To address this gap, we employed long-read nanopore sequencing to comprehensively investigate the SV architecture in CK-CLL cohort.

Material and methods: CK was characterized using IL-2/CpG-stimulated chromosomal banding and molecular cytogenomics (24XCyte mFISH, Metasystems; CytoScan HD Array, Thermo Fisher Scientific). High molecular-weight DNA was sequenced on PromethION platform (Oxford Nanopore Technologies). Somatic SVs and CNVs were identified using custom bioinformatics pipeline, involving the Delly and Severus variant callers in a tumor-only mode and visualised alongside variant allele frequencies and methylation profiles. Complex haplotype-specific rearrangements were resolved through local assembly.

Results: Based on the number of cytogenetic aberrations, 37 tested CK-CLL samples were stratified into a low/intermediate-CK group (3–4 aberrations; n = 19) and a high-CK group (≥5 aberrations; n = 18). Across these samples, nanopore sequencing achieved a median coverage of 37× and median N50 read length of 25 kb. SVs and CNVs were evaluated in all patients, and the resulting breakpoint landscapes were systematically analyzed. Initial results revealed substantial inter-patient variability in genomic complexity, variant composition, and distribution of affected chromosomes. In total, 7100 SV breakpoints were identified across the entire cohort (ranging from 90 to 520 per patient, with a median of 172). The low/intermediate-CK group accounted for 3170 SV breakpoints (ranging from 90 to 302, with a median of 148), while the high-CK group accounted for 3930 SV breakpoints (ranging from 112 to 520, with a median of 194). For CNVs, a total of 1361 breakpoints were detected (ranging from 8 to 149 per patient, with a median of 30). Of these, 488 CNV breakpoints were found in the low/intermediate-CK group (ranging from 8 to 58, with a median of 20), whereas the high-CK group exhibited 873 CNV breakpoints (ranging from 10 to 149, with a median of 42). In 28/37 cases, including 11 within the low/intermediate-CK group and 17 within the high-CK group, breakpoint clustering accompanied by copy-number oscillations indicated the presence of catastrophic genomic events, such as chromothripsis. Importantly, breakpoints directly disrupted previously reported CLL-associated genes in 25/37 cases including ANK1, ATM, BIRC3, MGA, NFKB2, PAX5, RB1, SETD2, and TP53. Complex rearrangements in six CLL-related genes were identified in 5/37 cases. TP53 was the most frequently affected gene, with structural intragenic alterations detected in five patients.

Conclusion: Using whole-genome long-read sequencing, we comprehensively characterized somatic genomic alterations in CK-CLL. Our data reveal marked inter-patient heterogeneity and identified recurrently affected chromosomes, chromothripsis-associated regions, and key driver genes disrupted by large structural and copy-number alterations. These findings refine our understanding of the genomic architecture of CK-CLL and highlight the potential value of comprehensive SV profiling for accurate molecular characterization and patient risk stratification.

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P007

Uncovering the genetic and epigenetic landscape of IGH::BCL2-translocated chronic lymphocytic leukemia

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Topic: Basic

While the IGH::BCL2-translocation is present in ~85% of follicular lymphoma (FL) cases (Yunis et al., 1987), it occurs in only 2-4% in chronic lymphocytic leukemia (CLL) and is the most common translocation (Braekeleer et al., 2016; Fang et al., 2019; Nguyen-Khac et al., 2011). In CLL, the IGH::BCL2-translocation is associated with mutated IGHV and trisomy 12 (Baseggio et al., 2012; Tang et al., 2013). Although IGH::BCL2-translocation has not been linked to worse outcomes in the chemotherapy era, evidence with novel agents remains limited (Put et al., 2009).

A total of 87 CLL with IGH::BCL2 translocation detected by fluorescence in situ hybridisation (FISH) were studied. Breakpoints at the BCL2 and IGH loci were sequenced in 12 cases using whole genome sequencing (WGS). Chromosomal aberrations detected by FISH (n=84), recurrently mutated genes detected by targeted capture-based sequencing (n=85) and the IGHV mutation status (n=87) were analysed. DNA methylation analyses were performed for 37 cases using the 850K EPIC BeadChip array. For analysis of association with clinical outcome a cohort consisting of 3834 previously untreated CLL patients (41 with IGH::BCL2-translocation) enrolled in clinical trials of the German CLL Study group (GCLLSG) was studied.

WGS data showed that 64% of IGH::BCL2-translocations are associated with aberrant VDJ recombination at the IGH locus (9/14 translocations, two cases have translocation on two alleles) followed by aberrant class-switch recombination in 29% (4/14) and somatic hypermutation in 7% (1/14). In chromosome 18q21, 29 % (8/28) of breakpoints mapped upstream of BCL2, 7% (2/28) in intron 1, 32 % (9/28), in exon 3 and 32% (9/28) of breakpoints downstream of BCL2. In the DNA methylation analyses, the cohort was enriched for memory-like CLL (m-CLL) suggesting a mature B-cell as origin. IGH::BCL2-translocated CLL grouped together with the m-CLL without IG-translocation with mutated IGHV in the UMAP analysis and separately from other unmutated CLL with and without IG-translocations. In 80% (70/87) of cases the IGHV locus was hypermutated. Interestingly, we observed somatic hypermutation in the BCL2 locus in 9 cases of 12 sequenced cases with translocation breakpoints all located downstream of BCL2, in line with the hypothesis that IGH-associated hypermutation machinery continues beyond the translocation breakpoint into the juxtaposed BCL2 locus. Other recurrent CLL aberrations, including NOTCH1 (7%, 6/85) and TP53 (5%, 4/85) mutations, were markedly underrepresented, while ATM, SF3B1, and RPS15 mutations were absent entirely. Based on FISH data, IGH::BCL2-translocated cases had a significant enrichment of trisomy 12 (45%, 38/84) relative to the general CLL population. In a first line cohort of 3834 patients from pooled 12 clinical GCLLSG trials IGH::BCL2 was not associated with shorter PFS or OS. In those patients treated with venetoclax based time limited therapies (n=982, 13 with IGH::BCL2) we observed numerically shorter PFS (HR 1.89, 95% CI 0.88-3.95, p=0.097).

Our multi-OMICS study of IGH::BCL2-translocated CLL provides evidence for a molecularly distinct subgroup with mature B-cell origin, IGHV hypermutation, and enrichment of trisomy 12 and 18, but

near-absence of typical adverse markers. Numerically shorter PFS with venetoclax-based regimens suggests this entity may warrant dedicated prospective evaluation.

P008

Breaking survival circuits: IKAROS-dependent miR-29c and miR-145 regulation restrains apoptosis resistance in CD5 positive B-1 cells

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Topic: Basic

Background: Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of mature CD5 positive B cells with impaired apoptosis. Murine CD5 positive B-1 cells share phenotypic and functional features with CLL-related B-cell biology and represent a useful model to investigate intrinsic mechanisms controlling survival and apoptosis. IKAROS, encoded by *Ikzf1*, is a lymphoid transcription factor that interacts with chromatin remodeling complexes, including histone deacetylases, and has been implicated in B-cell malignancies. To explore IKAROS-regulated post-transcriptional mechanisms, we focused on apoptosis-related microRNAs and their functional contribution to B-1 cell viability.

Material and methods: Public CLL-related datasets and miRNA target prediction analyses were used as exploratory bioinformatic support to prioritize apoptosis-associated miRNA networks. Murine B-1 cells were subjected to IKAROS knockdown, followed by analysis of cell viability, apoptosis-related proteins, HDAC1 and c-MYC expression. miRNA profiling was performed to identify IKAROS-regulated miRNAs. HDAC dependency was assessed using trichostatin A. Functional reconstitution assays were performed by overexpressing miR-29c and miR-145, individually or in combination, followed by evaluation of viability and apoptosis-related targets.

Results: Bioinformatic analyses supported the relevance of miRNA-mediated regulation of apoptosis-related pathways in CLL-associated biology and highlighted potential interactions involving miR-29c, miR-145 and survival-related targets. In B-1 cells, IKAROS knockdown increased cell viability and induced a pro-survival molecular profile, characterized by increased HDAC1, c-MYC and BCL-2 expression, together with reduced cleaved CASPASE-3. miRNA profiling identified miR-29c and miR-145 as downregulated after IKAROS knockdown. HDAC inhibition restored miR-29c expression but did not rescue miR-145, suggesting partially distinct regulatory mechanisms within the IKAROS-HDAC-miRNA axis. Functionally, miR-29c reconstitution reduced BCL-2 expression and increased BAX, whereas miR-145 reconstitution reduced c-MYC, MCL-1 and BCL-2 expression and increased miR-29c levels. Combined overexpression of miR-29c and miR-145 reduced B-1 cell viability, supporting a cooperative role for these miRNAs in restraining the anti-apoptotic phenotype induced by IKAROS loss.

Conclusions: These findings identify an IKAROS-HDAC dependent miR-29c and miR-145 axis that limits CD5 positive B-1 cell viability by modulating apoptosis-related pathways. Although generated in a murine B-1 cell model, this mechanism may be relevant to the study of apoptosis resistance in CLL-related B-cell biology and supports further investigation of IKAROS-regulated miRNA networks in primary CLL samples.

P009

Activation of PTPRG phosphatase drives apoptosis in Richter transformation cells by disrupting their hyper-adhesive features

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Topic: Basic

Background: In chronic lymphocytic leukemia (CLL), neoplastic cells actively recirculate between peripheral blood and lymphoid organs, via integrins and chemokine receptors. Activating the receptor tyrosine phosphatase PTPRG, using the cell-penetrating peptide P1-WD, has been shown to modulate kinase phosphorylation of specific targets, and interfere with chemotaxis and adhesion of CLL cells, finally activating the apoptotic pathway.

At variance with CLL, Richter transformation (RT) predominantly involves secondary lymphoid organs, suggesting that microenvironmental interactions drive disease progression. However, the mechanisms governing homing and adhesion in RT remain poorly defined. This study aimed to define and characterize the genetic and molecular mechanisms controlling RT cells localization.

Material and methods: The study exploited a cohort of primary CLL samples, four patient-derived xenograft (RT-PDX) models, and the U-RT1 cell line. Transcriptomic profiling (RNA-seq) was performed on RT cells isolated from peripheral blood and secondary lymphoid organs of systemic mouse models of RT, to identify differentially expressed genes and enriched gene ontologies. The expression of integrins and chemokines receptors were validated by flow cytometry, western blot, and real-time PCR. Transwell and in vitro assays were used to study migration and VCAM-1 and ICAM-1 mediated adhesion, both spontaneous as well as induced by CXCL12, CCL19 and CCL21. Cytoskeletal polarization was assessed by wide-field microscopy. The effects of PTPRG activation via the P1-WD peptide (versus the control peptide P1) on downstream signaling and apoptosis were evaluated by phosphoproteomic profiling, immunoblotting, time-lapse Caspase-3 immunofluorescence, and Annexin V-based flow cytometry.

Results: RNA-seq analysis revealed a distinct adhesion-related transcriptional signature in blood-derived RT cells. Compared to CLL, RT cells displayed the upregulation of CD49d and downregulation of CXCR4 and CCR7, although all receptors remained detectable, both at mRNA and protein levels. Functionally, RT cells exhibited a spontaneous hyper-adhesive phenotype, preferentially engaging VCAM-1 with marked cytoskeletal polarization, while remaining completely non-responsive to chemokines in migration and adhesion assays, suggesting a chemokine-uncoupled phenotype.

PTPRG activation via P1-WD peptide selectively disrupted the VCAM-1-mediated adhesion, unlike the control peptide (P1) that showed no effects. Moreover, phosphoproteomic profiling revealed a PTPRG-dependent STAT5A dephosphorylation and BCL2 hyperphosphorylation, shifting cells toward programmed death. Consistently, functional assays and immunoblots confirmed a significant increase in apoptosis following P1-WD treatment, which spared healthy normal B-cells.

Conclusions: RT cells exhibit a unique hyper-adhesive, chemokine-unresponsive phenotype that underlines a strict microenvironmental dependency. PTPRG activation effectively disrupts this adhesion, while selectively triggering apoptosis. These findings identify hyper-adhesion as a driver of RT pathogenesis and highlight PTPRG activation as a switch-on mechanism to target RT lymphoma cells.

P010

Longitudinal serum proteomics reveals immune dynamics in Relapsed/Refractory CLL on Venetoclax plus Epcoritamab

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Topic: Basic

Relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) remains challenging to treat, partly due to T-cell dysfunction associated with high disease burden. T-cell-engaging therapies such as CAR T cells show limited efficacy in CLL, whereas the CD3×CD20 bispecific Epcoritamab (Epcor) has shown promising activity as monotherapy, which may be further enhanced when combined with standard-of-care agents such as BCL2-inhibitor Venetoclax (Ven). We hypothesized that Ven debulking improves T-cell function, providing a rationale for the Ven-Epcor combination. Preliminary data from the HOVON165/AETHER trial (ClinicalTrials.gov NCT05791409) indeed showed high proportions of patients reaching undetectable measurable residual disease (80% at cycle 6 (C6)) and a 100% overall response rate with 60% complete nodal responses at C9 (Kater et al., EHA 2026, S153). To define how Ven debulking, alone and combined with Epcor, reshapes the circulating immune microenvironment and whether this leads to a state supporting T-cell-redirecting therapy, we longitudinally profiled the serum proteome and immunophenotyped circulating T and CLL cells.

Serum and PBMCs were collected at baseline (before treatment), after the Ven ramp-up pre-Epcor (C1D1), and after 3 (C4D1) and 5 (C6D1) cycles of Ven plus Epcor. The serum proteome (~1,000 inflammation- and immune-related proteins) was profiled by proximity extension assay (Olink Reveal); patient paired timepoints were compared by Wilcoxon signed-rank test, with differentially expressed proteins defined as Benjamini-Hochberg-adjusted $P < 0.05$ and $|\Delta\text{NPX}| \geq 0.5$ (log2; ~1.4-fold). PBMCs were immunophenotyped by spectral flow cytometry using 38-marker T cell and 35-marker CLL/immunophenotyping panels.

Paired analyses of samples from 16 enrolled patients were performed. Comparison of serum obtained at the end of Ven ramp-up with baseline identified 271 significantly altered proteins, predominantly reflecting decreased B-cell/CLL-associated proteins consistent with effective disease debulking. Interestingly, 5 proteins increased following Ven monotherapy, including T-cell activation markers CD40L and FLT3L. During combination therapy (C4D1/C6D1 vs C1D1), 77 proteins changed significantly, indicating a shift toward an active immune and tissue-remodeling state. B-cell/CLL associated proteins further declined (CD20, CD22, CD79b, TCL1A, FCRL2, FCRL3, BAFF-R, TACI), confirming continued CLL depletion. In parallel, proteins associated with myeloid activation (CLEC6A, CD300e), T-cell support (IL-7, DNAM-1, CD40L), chemotaxis (CCL26), and tissue-remodeling (VEGF-A, epiregulin and CCN1)

increased. Collectively, these data indicate a transition from a CLL-dominated serum profile toward one characterized by myeloid and T-cell engagement. Spectral flow cytometry confirmed CLL cell depletion, while T cells remained stable in absolute counts and as percentages of non-CLL cells from baseline through C1D1-C6D1, including stable proportions of memory/effector subsets and unchanged Treg frequencies. These changes resulted in a >1000-fold increase in the T-cell-to-tumor-cell ratio (C1D1 vs C6D1). T cells displayed increased cytotoxic potential, with higher granzyme-B expression in both CD4⁺ and CD8⁺ compartments, without induction of exhaustion markers (TIM-3, LAG-3, PD-1). In R/R CLL, Ven debulking depletes B-cell/CLL-associated serum proteins while raising markers consistent with early T-cell activation. Adding Epcor shifts the proteome toward an innate/myeloid, chemokine, and tissue-remodeling signature alongside sustained CLL depletion. This remodeling yields a higher T-cell-to-tumor ratio and greater cytotoxicity without signs of exhaustion, creating an immune state supportive for T cells.

P011

Boosting CD20xCD3 bispecific antibody therapy with Interleukin-10 in the E μ -TCL1 mouse model

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Topic: Basic

Chronic antigen stimulation, together with an immunosuppressive microenvironment, drives progressive T cell exhaustion and dysfunction in chronic lymphocytic leukemia (CLL). The exhausted T cell compartment not only contributes to immune escape but also undermines the efficacy of T cell-directed immunotherapies, such as chimeric antigen receptor (CAR) T-cell and bispecific antibody (BsAb) therapies. Previous work from our group identified interleukin-10 (IL-10) as a promising therapeutic candidate capable of preventing T cell exhaustion and reprogramming the immunosuppressive phenotype of myeloid cells in the E μ -TCL1 mouse model. We therefore hypothesize that the addition of stabilized IL-10-Fc to the CD20xCD3 BsAb treatment regimen will enhance its therapeutic efficacy against CLL by creating a more favorable anti-tumor immune microenvironment.

The fully immunocompetent E μ -TCL1 adoptive transfer model of CLL (TCL1-AT) was treated with CD20xCD3 BsAb in combination with IL-10-Fc. CLL engraftment was confirmed in blood prior to treatment initiation. Equimolar doses of IL-10-Fc and IgG-Fc control protein were administered by i.p. injections 3 times per week for the first 3 weeks and once weekly thereafter. The CD20xCD3 BsAb was injected i.v. once weekly. Disease progression was monitored in peripheral blood, and lymphoid tissues were analyzed by flow cytometry at a predefined endpoint or upon reaching the humane endpoint in the survival study.

The combination of IL-10-Fc and BsAb significantly reduced CLL load in blood to minimal levels within 2 weeks of treatment, outperforming both monotherapies. At the experimental endpoint, malignant CLL cells were depleted by the combination therapy, which was not achieved by the BsAb monotherapy. This was reflected by lower spleen weights and almost undetectable frequencies of malignant CD5⁺CD19⁺ cells in all lymphoid organs. Overall, the combination therapy achieved superior long-term disease control and significantly prolonged survival of mice. The therapeutic efficacy of the combination was accompanied by increased frequencies of memory T cells across organs and reduced expression of exhaustion-associated markers, including PD-1, TIM-3, and CD39 on cytotoxic T cells. As previously observed, IL-10-Fc treatment induced a loss of NK cells and polarization of monocytes towards an inflammatory phenotype, irrespective of BsAb addition.

Our study demonstrates the benefit of combining CD20xCD3 BsAb with IL-10-Fc in the TCL1-AT mouse model, highlighting its potential for clinical translation. These findings support the idea of IL-10 as a promising candidate for next-generation cancer immunotherapy, with the potential to enhance anti-tumor immune responses and improve therapeutic outcomes.

P012

The role of BCR stereotypy and NOTCH1 mutations in regulating adhesion and chemotaxis in chronic lymphocytic leukemia

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Topic: Basic

Introduction: Chronic lymphocytic leukemia (CLL) is the most common adult leukemia and is characterized by the progressive accumulation of mature monoclonal B lymphocytes within the peripheral blood and lymphoid organs. It is characterized by remarkable biological heterogeneity that underlies its highly variable clinical course. Among the major determinants of disease behavior are stereotyped B-cell receptors (BCRs) and recurrent genetic alterations, including activating NOTCH1 mutations, both of which influence leukemic cell interactions with the microenvironment and are associated with disease aggressiveness. Although the contribution of BCR signaling and NOTCH1 activation to CLL pathogenesis has been extensively studied, whether the biological consequences of NOTCH1 mutation depend on the underlying BCR stereotype remains poorly understood. In particular, it is unknown whether acquisition of a NOTCH1 mutation can functionally reprogram an indolent stereotyped CLL subset toward a more aggressive phenotype. The aim of this study was to we investigate the impact of NOTCH1 mutation across distinct stereotyped BCR subsets.

Materials and Methods: Engineered MEC1 cell models expressing representative aggressive (IGHV1-69 and IGLV3-21) or indolent (IGHV4-34) stereotyped BCRs were generated by first disrupting the endogenous immunoglobulin heavy- and light-chain loci using CRISPR/Cas9, followed by lentiviral transduction of the corresponding stereotyped BCRs. Activating NOTCH1 mutations, mapping in the PEST domain of the protein, were subsequently introduced into each model by CRISPR/Cas9 genome editing. Global transcriptomic changes were analyzed by bulk RNA sequencing. Integrins and chemokine receptors expression was evaluated at both the transcript and protein levels using gene expression analysis and flow cytometry, respectively. Functional consequences were assessed using migration assays and intravenous xenotransplantation into NOD/SCID/gamma chain-/- (NSG) mice.

Results and Discussion: Transcriptomic profiling demonstrated that the introduction of NOTCH1 mutation results in a shift in gene expression compared to the wild-type (WT) clones, showing the greatest impact on the indolent IGHV4-34 stereotype, resulting in a profile resembling that of the aggressive stereotypes. Genes involved in cell migration, adhesion, cytoskeletal organization, and chemokine signaling were prominently enriched. This transcriptional reprogramming was accompanied by increased expression of adhesion- and trafficking-associated molecules, including CD49d, ITGB1 and CCR7, resulting in enhanced migration toward CCL19. These in vitro data were confirmed in vivo. Three weeks after intravenous injection of MEC1 cells in NSG mice, NOTCH1-mutated IGHV4-34 cells showed increased accumulation in the bone marrow, spleen, liver, and kidneys compared to the wild-type counterpart, resembling the distribution pattern of the aggressive stereotyped models.

Conclusion: Our findings demonstrate that activating NOTCH1 mutation exerts its strongest biological effect in the indolent IGHV4-34 stereotyped background, driving transcriptional and functional reprogramming toward an aggressive, microenvironment-interactive phenotype. These results suggest that NOTCH1 mutation can overcome the intrinsic indolent characteristics of specific CLL stereotypes

by enhancing migratory capacity and tissue homing, providing new insight into the context-dependent role of NOTCH1 mutations in CLL progression.

P013

TP53 Aberrations and Clinical Outcomes in Richter Transformation: A Retrospective Analysis in the Era of Targeted Agents

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Topic: Prediction

Background: Richter Transformation (RT)—the evolution of chronic lymphocytic leukemia (CLL) into an aggressive lymphoma—remains a formidable therapeutic challenge, particularly for patients previously treated with targeted agents. This study evaluates the clinical and molecular characteristics, therapeutic approaches, and clinical outcomes of RT cases at our institution, with a specific focus on the prognostic impact of TP53 aberrations.

Materials and Methods: We conducted a retrospective analysis of 12 consecutive patients diagnosed with RT following a prior CLL diagnosis (2012–2025). RT was confirmed via histopathology and immunophenotyping. Data collection included demographics, prior CLL therapies, RT histological subtypes, and molecular/genetic profiles (unmutated IGHV, del(17p), TP53 mutations, and complex karyotype). Treatment responses were assessed using Lugano 2014 criteria; overall survival (OS) was calculated from the date of RT diagnosis.

Results: The median age at RT diagnosis was 66 years (range: 56–86). Most patients (91.7%) were pretreated for CLL, including seven (58.3%) previously exposed to BTK inhibitors. Adverse molecular features were prevalent: TP53 mutations in 41.7%, del(17p) in 33.3%, and complex karyotype in 25%. Histological subtypes included DLBCL (66.7%), Hodgkin-like (25%), and mixed-type (8.3%). First-line RT interventions consisted of chemo-immunotherapy (n=6), targeted combinations (n=4), and cellular therapies (n=2). The overall response rate (ORR) was 41.7%. Patients harboring TP53 aberrations experienced significantly inferior outcomes, with a median OS of 5.2 months versus 13.8 months in TP53 wild-type cases. All patients who died or were lost to follow-up (n=6) belonged to the DLBCL subgroup and presented with high-risk molecular features.

Conclusion: This real-world series underscores the aggressive nature of RT in heavily pretreated CLL patients, identifying TP53 aberrations as the most critical adverse prognostic factor. Despite the shift toward targeted therapies, outcomes in high-risk RT remain suboptimal. These findings highlight the urgent need for early identification of high-risk clones and the integration of novel, non-chemotherapeutic strategies.

P014

Prognostic Significance of Baseline Liver Enzyme Patterns in Chronic Lymphocytic Leukemia: A Nationwide Real-World Cohort Study

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Topic: Prediction

Background: Chronic lymphocytic leukemia (CLL) is clinically heterogeneous, and additional routine biomarkers may improve real-world baseline risk assessment. Liver biochemical abnormalities may reflect hepatocellular injury, cholestasis, hepatic infiltration, systemic inflammation, comorbidity, or occult organ vulnerability. Whether baseline cholestatic and hepatocellular liver enzyme patterns have distinct prognostic implications in newly diagnosed CLL remains unclear.

Materials and Methods: We conducted a retrospective nationwide cohort study using linked electronic health records from Clalit Health Services, the largest healthcare provider in Israel. Adults diagnosed with CLL between 2004 and 2025 were included if liver biochemistry was available within ± 3 months of diagnosis. Patients with documented pre-existing liver disease were excluded. Cholestatic elevation was defined as alkaline phosphatase (ALP) and/or gamma-glutamyl transferase (GGT) above the contemporaneous laboratory-specific upper limit of normal (ULN). Hepatocellular elevation was defined as alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) above the ULN. Outcomes included overall survival (OS), time to first treatment (TTFT), and infection-related hospitalization burden. OS and TTFT were analyzed using Kaplan-Meier methods and multivariable Cox models. Hospitalization burden was analyzed using negative binomial regression with log follow-up time as an offset.

Results: A total of 3,448 patients with newly diagnosed CLL were included. Median age was 72.1 years, 55.0% were male, and median follow-up was 74.9 months. During follow-up, 1,374 patients (39.8%) died and 727 (21.1%) required first CLL-directed treatment. Baseline cholestatic elevation was present in 567 patients (16.4%), including 206 with isolated ALP elevation, 260 with isolated GGT elevation, and 101 with concurrent ALP plus GGT elevation. Hepatocellular elevation was present in 207 patients (6.0%).

Patients with cholestatic elevation had higher comorbidity burden, higher absolute lymphocyte and white blood cell counts, lower hemoglobin, higher lactate dehydrogenase, and higher β_2 -microglobulin. Patients with concurrent ALP plus GGT elevation had the most adverse baseline profile. In contrast, hepatocellular elevation was not associated with higher mortality or treatment requirement in unadjusted comparisons.

In multivariable analysis, cholestatic elevation independently predicted inferior OS (hazard ratio [HR], 1.21; 95% CI, 1.05–1.39; $P=.008$), whereas hepatocellular elevation did not (HR, 1.22; 95% CI, 0.93–1.59; $P=.145$). Neither cholestatic nor hepatocellular elevation independently predicted TTFT. Cholestatic elevation was independently associated with higher infection-related hospitalization rates (incidence rate ratio [IRR], 1.33; 95% CI, 1.14–1.56; $P<.001$) and higher rates of infection-related hospitalized days (IRR, 1.45; 95% CI, 1.15–1.83; $P<.001$).

Conclusions: Baseline cholestatic, but not hepatocellular, liver enzyme elevation independently predicted inferior OS and greater infection-related hospitalization burden in newly diagnosed CLL,

without independently predicting TTFT. Routine ALP and GGT measurement may identify a clinically vulnerable subgroup and serve as a simple adjunct to baseline risk assessment in CLL.

P015

When the sample makes the difference: The importance of proper sample preparation for TP53 mutation status determination in chronic lymphocytic leukemia

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Topic: Prediction

Background: According to the latest ERIC recommendations for the management of patients with chronic lymphocytic leukemia (CLL), assessment of TP53 aberration status should be performed whenever treatment is being considered, both in frontline and the relapsed/refractory settings. As TP53 aberrations have a direct impact on therapeutic decision-making, obtaining reliable diagnostic results is of utmost importance. Determination of TP53 mutational status involves multiple analytical steps leading to the final result, and in this study we demonstrate that appropriate pre-analytical sample processing is one of the key factors required to ensure accurate and reliable results.

Material and methods: Peripheral blood from a patient with CLL was processed using two approaches prior to DNA isolation: mononuclear cells (CLL1) and purified CD19+ B cells (CLL2). The proportion of CLL B lymphocytes was determined by flow cytometry. DNA extracted from both cell fractions were analyzed using a custom NGS panel (xGen Custom Panel, IDT) covering the entire coding region of TP53 (exons 2–11, including splice sites ± 10 bp). Libraries were prepared using the Illumina DNA Prep with Enrichment workflow and sequenced on the Illumina MiniSeq platform. Bioinformatic analysis and variant interpretation were performed using DRAGEN Enrichment, Franklin, Seshat and IGV software. The assay was validated for detection of variants with a variant allele frequency (VAF) $\geq 1\%$. To assess the reproducibility and reliability of the assay, both samples were sequenced in duplicate in two independent sequencing runs.

Results: Flow cytometric analysis revealed that CLL B cells constituted 53% of peripheral blood lymphocytes. Both samples fulfilled all predefined NGS quality criteria, confirming the reliability of the sequencing results. A pathogenic TP53 frameshift mutation, c.626_627del, p.(Arg209LysfsTer6), was detected in both samples, with a VAF of 57.06% in CLL1 and 94.78% in CLL2. In addition, a second pathogenic TP53 frameshift mutation, c.825_826del, p.(Ala276LeufsTer29), was identified exclusively in CLL2 at a VAF of 1.59%. The variant was supported by adequate sequencing depth ($>750\times$) and coverage. To exclude a potential false-positive result, the low-VAF variant was inspected using IGV software and subsequently confirmed by repeat sequencing (VAF 1.36%). Duplicate analysis demonstrated good assay reproducibility, with coefficients of variation of 1.38% and 9.62% for the high- and low-frequency variants, respectively.

Conclusions: Pre-analytical sample processing significantly influences the detection of TP53 mutations in CLL. DNA isolated from mononuclear cells containing insufficient proportions of CD19+ leukemic cells may result in false-negative findings, particularly for low-frequency variants. Enrichment of CD19+ cells improves analytical sensitivity and enables the detection of clinically relevant low-burden TP53 mutations. Although the clinical significance of low-VAF TP53 mutations remains a subject of ongoing debate, this study underscores the critical importance of appropriate sample selection and standardized pre-analytical processing for accurate molecular diagnostics and informed personalized treatment decisions in CLL.

P017

Characterization of IGHV Stereotypy and Its Association with TP53 Status and Cytogenetic Abnormalities in a Croatian CLL Cohort

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Topic: Prediction

Background: Chronic lymphocytic leukemia (CLL) is characterized by marked biological and clinical heterogeneity. As therapeutic options expand, accurate genetic and phenotypic characterization has become essential for risk assessment. IGHV mutational status is a key biological and prognostic marker in CLL, while stereotyped VH CDR3 immunoglobulin gene rearrangements further define subsets of patients with distinct biological and clinical features. Therefore, we performed a comprehensive analysis of a Croatian CLL cohort to characterize immunoglobulin gene stereotypy and evaluate its association with TP53 status and cytogenetic alterations, aiming to identify biologically distinct CLL subgroups.

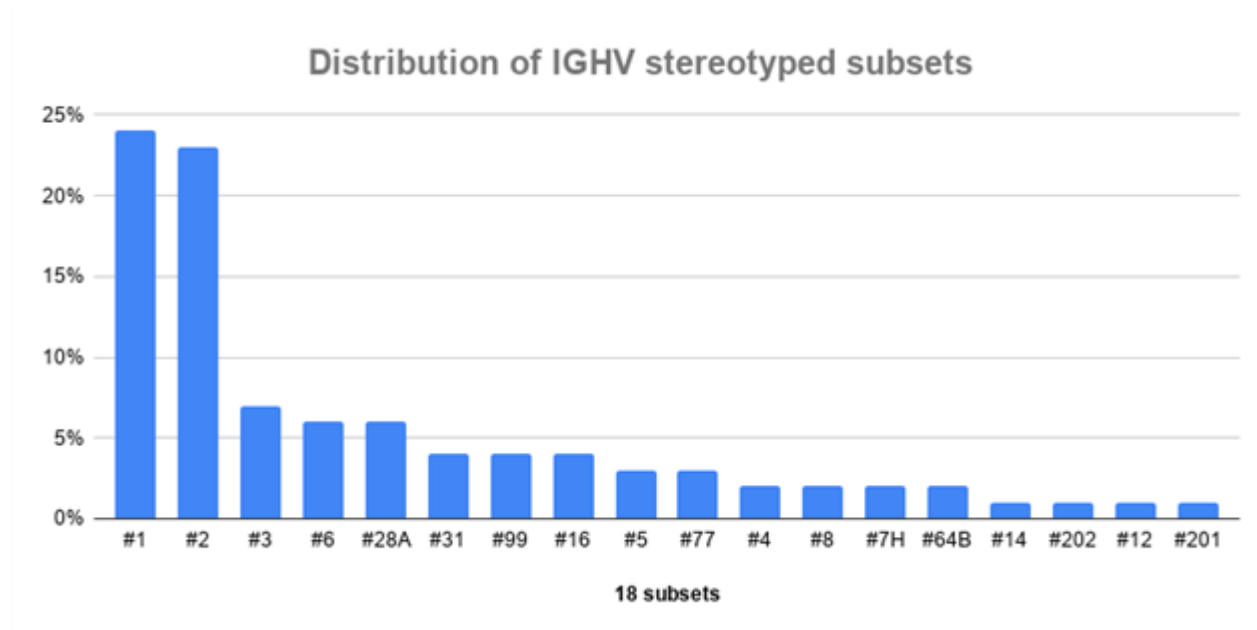
Material and methods: IGHV mutational status was analyzed in 778 patients from a Croatian CLL cohort between June 2022 and March 2026. Importantly, this cohort consisted of patients referred for IGHV mutational status testing at the time of disease progression and/or before the initiation of therapy. IGHV mutational status was determined by Sanger sequencing according to ERIC recommendations, and sequences were subsequently assessed for stereotypy. Available cytogenetic and TP53 mutational status data were retrieved to evaluate their association with IGHV stereotypy. Cytogenetic abnormalities were classified as del(13q14)/RB1, del(11q22.3)/ATM, del(17p13.1)/TP53 and/or monosomy 17, trisomy 12. Cytogenetic abnormalities were assessed using conventional G-banded karyotyping and fluorescence in situ hybridization (FISH). TP53 mutational status was determined by next-generation sequencing.

Results: Of 778 CLL patients, 520 (66.8%) were classified as U-CLL, 231 (29.7%) as M-CLL, 22 (2.8%) as borderline-mutated, and 5 (0.6%) showed two identifiable IGHV clones. Stereotyped VH CDR3 rearrangements were identified in 94/778 patients (12.1%) and distributed across 18 different subsets, with subsets #1, #2, and #3 being the most frequent and together comprising 53/94 stereotyped cases (56.4%). BCR stereotypy was more frequently observed in U-CLL than in M-CLL cases, with 74/520 U-CLL patients (14.2%) and 18/231 M-CLL patients (7.8%) assigned to stereotyped subsets. Clinically unfavorable stereotyped subsets were mostly associated with unmutated IGHV status. Of note, the two borderline-mutated cases assigned to stereotyped subsets both belonged to subset #2. Subsets #2, #3, and #28A showed predominant usage of specific IGHV gene rearrangements, while subset #1 was characterized by heterogeneous IGHV rearrangement patterns. Among 79 cases with available cytogenetic data, del(13q14)/RB1 was the most frequent cytogenetic abnormality overall (34/79, 43.0%) and within subset #2 (11/22 cases), where del(11q22.3)/ATM was also common (6/22 cases). In contrast, subset #1 showed a higher burden of TP53-related cytogenetic alterations, including del(17p)/TP53 or monosomy 17 in 6/23 cases. TP53 point mutations were detected in 6/43 tested cases (14.0%).

Conclusions: IGHV stereotypy is associated with distinct molecular and cytogenetic patterns within this Croatian CLL cohort. The enrichment of IGHV stereotypy among U-CLL cases may reflect restricted, germline-like B-cell receptor repertoires and antigen-driven selection, while subset-specific

cytogenetic and TP53-related patterns suggest that stereotyped subset assignment may provide additional biological information beyond IGHV mutational status alone.

Figure/Table 1



P019

Improved MRD Detection and Immune Profiling in R-Ven Treated Relapsed CLL: Insights from the “DEDALUS” Study

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Topic: MRD

Background: Fixed-duration Rituximab and Venetoclax (R-Ven) has redefined outcomes in chronic lymphocytic leukemia (CLL), achieving high rates of deep molecular responses. However, as therapeutic efficacy increases, so does the need for ultra-sensitive minimal residual disease (MRD) monitoring. The "DEDALUS" protocol evaluated the concordance between multiparametric flow cytometry (MFC) and next-generation sequencing (NGS) for MRD assessment in relapsed/refractory (R/R) CLL patients, while simultaneously exploring the treatment's impact on the immune microenvironment.

Materials and Methods: Twenty-two R/R CLL patients treated with R-Ven underwent MRD monitoring using ERIC-compliant MFC (sensitivity 10^{-4}) and LymphoTrack NGS (sensitivity 10^{-5}). Clinical response was monitored via advanced ultrasonography. MRD and immunological parameters were longitudinally assessed at months 1, 6, 12, and 18, or upon treatment discontinuation.

Results: Twenty patients (91%) achieved complete remission (CR), with 15 patients showing undetectable MRD (uMRD) by both methods at the first assessment. Notably, in two cases of partial response (PR), NGS identified low-level residual IGH clonality (3–45 clonal cells per 10^6) that was missed by MFC. Throughout treatment, venetoclax induced sustained B-cell depletion and a significant reduction in CD4+ T-cells, leading to an inverted CD4/CD8 ratio in 25% of the cohort. NGS-based MRD results demonstrated a stronger correlation with clinical outcomes than MFC, particularly in cases of low-level residual disease.

Conclusion: The R-Ven regimen confirms high efficacy in achieving deep, durable remissions in R/R CLL. While MFC remains a cost-effective and accessible tool, NGS provides superior sensitivity and prognostic precision. These findings highlight the importance of high-sensitivity molecular monitoring and suggest that future research should integrate digital PCR for IGH rearrangements as a non-invasive biomarker, alongside further investigation into the immunomodulatory effects of venetoclax.

P020

Real-World Measurable Residual Disease Assessment in Chronic Lymphocytic Leukemia Patients Treated with Novel Agents

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Topic: MRD

Introduction: Chronic lymphocytic leukemia (CLL) is a clinically heterogeneous disease with a highly variable course. In recent years, continuous Bruton tyrosine kinase inhibitors and time-limited venetoclax-based regimens have improved outcomes and enabled deeper responses in CLL. However, despite the growing recognition of measurable residual disease (MRD) as a sensitive marker of treatment response, MRD-guided therapeutic strategies have not yet been fully integrated into routine clinical practice, and their role continues to be investigated in ongoing clinical studies. In this study, we aimed to assess the real-world utilization of MRD evaluation in CLL patients receiving novel targeted therapies.

Material and methods: Patients with a diagnosis of CLL who were followed in the Hematology Clinic of Ankara Bilkent City Hospital and treated with novel targeted agents were retrospectively reviewed. MRD analysis had been performed using multiparameter flow cytometry on peripheral blood and/or bone marrow samples. MRD negativity was defined as a disease burden below the 10^{-4} threshold.

Results: A total of 28 patients with CLL (including 4 with SLL) who received novel targeted therapies were identified, with treatment initiation dates ranging from September 2011 to March 2025. Of these, 6 were female and 22 were male, with a median age of 56 years (range, 36–75). Novel targeted therapies were administered in the first-line setting in 12 patients (venetoclax-based therapy in 8 patients and ibrutinib in 4 patients) and in the relapsed/refractory setting in 16 patients, at a median follow-up of 67 months. MRD assessment was performed in 3 patients in the first-line setting and in 3 patients in the relapsed/refractory setting. MRD assessment was performed using peripheral blood samples in 4 patients and bone marrow samples in 2 patients. MRD evaluation was conducted at the end of treatment in 3 patients, during post-treatment follow-up in 2 patients, and during ongoing treatment in 1 patient. High MRD positivity was observed in 2 patients, while MRD negativity was achieved in 4 patients. In one patient with high MRD positivity following first-line chemotherapy, a novel targeted therapy was initiated, whereas in the relapsed/refractory setting, treatment was continued in a patient with high MRD positivity. Among patients who achieved MRD negativity, treatment was discontinued in 2 patients, while it was continued in the remaining patients. MRD assessment was not performed in patients receiving BTK inhibitors or in those diagnosed with SLL.

Conclusions: MRD assessment was performed in a limited proportion of patients treated with novel targeted therapies in real-world clinical practice, and was more frequently utilized in selected clinical scenarios, particularly in patients receiving venetoclax-based regimens. The heterogeneity in timing and patient selection highlights the lack of standardized MRD-guided strategies outside clinical trials. Larger real-world studies are needed to better define the role of MRD in guiding treatment decisions in CLL.

P021

Undetectable minimal residual disease and survival association in ~ 4000 first-line chronic lymphocytic leukemia patients: artificial intelligence–assisted patient-level analyses

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Topic: MRD

Background: Minimal residual disease (MRD) assessment in chronic lymphocytic leukemia (CLL) may inform clinical decision making and accelerate therapy development. However, heterogeneity in treatment regimens and methodologies challenges validation of MRD as a surrogate for survival, especially given recent data (AMPLIFY, CLL17) showing Bruton tyrosine kinase and B-cell lymphoma 2 inhibitor doublets (BTKi–BCL2i) achieve longer progression-free survival (PFS) despite lower undetectable MRD (uMRD) rates.

Aim: Leveraging artificial intelligence (AI)-supported approaches, we built a framework for literature review, data extraction, and cross-trial harmonization enabling evaluation of MRD and survival. We tested MRD–survival associations using trial and patient (pt)-level data from 3927 first-line (1L) CLL pts.

Methods: An AI-supported literature review identified time-limited 1L CLL trials reporting MRD and Kaplan-Meier (KM) plots of PFS/overall survival (OS) stratified by MRD status. MRD was quantified by flow cytometry, next-generation sequencing, or allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) within 6 months post-end of treatment (EOT). Sample size, median age, follow-up, regimen, MRD methods, and outcomes were extracted for harmonization. If needed, individual survival data were reconstructed from digitized KM curves with validated AI and quality control. uMRD was defined at 10^4 sensitivity in the peripheral blood. Cox models estimated hazard ratios (HR) and 95% confidence intervals (CIs).

Results: In total, 3927 pts from 11 global 1L studies were included (2215 uMRD pts). Baseline characteristics: 61 y median age, 61% unmutated immunoglobulin heavy-chain variable region gene (uIGHV), 10% del17p, 53.5% chemoimmunotherapy (CIT)-treated, 44.6% venetoclax (Ven)-based treated. Across the entire study cohort, uMRD was associated with longer PFS (HR 0.20; 95% CI 0.18–0.22 [n=3927]) and OS (HR 0.35; 95% CI 0.29–0.42 [n=3136]). In subgroup analyses, uMRD was associated with improved PFS in pts treated with CIT, Ven-based combinations, and BTKi–BCL2i doublets (HR 0.18; 95% CI 0.16–0.21 [n = 2402], HR 0.29; 95% CI 0.24–0.35 [n = 1525], HR 0.38; 95% CI 0.23–0.65 [n = 379]). Further, in the BTKi–BCL2i subgroup, uMRD was associated with significantly longer PFS in pts with uIGHV but not mutated IGHV (HR 0.21; 95% CI 0.09–0.46 [n=167], HR 0.87; 95% CI 0.37–2.08 [n = 124]). Notably, detectable MRD (dMRD) pts on BTKi–BCL2i doublets had longer PFS vs dMRD pts on CIT/Ven–obinutuzumab (HR 0.43; 95% CI 0.34–0.54). uMRD's prognostic value was not impacted by MRD methods within the confinement of 10^{-4} assay sensitivity.

Summary/Conclusion: Across ~4000 1L CLL pts, uMRD was associated with longer PFS and OS. Similar to CLL17 and AMPLIFY, these data indicate that EOT MRD status is informative within a given treatment approach, but less so for cross-regimen comparisons. This analysis supports further exploration of EOT MRD as a potential intermediate endpoint for survival in 1L CLL. AI was instrumental in conducting this work efficiently, and further work will provide regulatory-grade evidence.

P022

Tacabrutideg (BGB-16673), a Bruton tyrosine kinase (BTK) degrader, in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): a phase 1 CaDAnCe-101 study update

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Topic: Clinical Trial

Background: Tacabrutideg (BGB-16673) is a BTK degrader that blocks signaling by tagging BTK for degradation through the cell's proteasome pathway, leading to tumor regression. CaDAnCe-101 (BGB-16673-101; NCT05006716) is an ongoing open-label, phase 1/2, study evaluating tacabrutideg monotherapy in patients with B-cell malignancies. Here we report updated safety and efficacy for phase 1 of CaDAnCe-101 in patients with R/R CLL/SLL.

Material and Methods: Eligible patients had R/R CLL/SLL (≥ 2 prior therapies), ECOG PS of 0-2 (0-1 in the EU), and adequate organ function. In the US, EU, and Australia, patients must have previously received a covalent BTKi. Tacabrutideg was administered orally once daily. Primary phase 1 objectives were to assess safety/tolerability and establish the maximum tolerated dose and recommended expansion dose. Secondary objectives included overall response rate (ORR) per iwCLL 2018 criteria with the partial response (PR) with lymphocytosis (PR-L) modification and per the 2014 Lugano criteria (SLL).

Results: As of December 15, 2025, data cutoff, 67 patients with R/R CLL/SLL received tacabrutideg (50 mg, n=1; 100 mg, n=22; 200 mg, n=17; 350 mg, n=15; 500 mg, n=12). Median age was 70 (range, 47-91) years, median lines of prior therapy was 4 (range, 2-10). Prior therapies included covalent BTKis (n=63 [94.0%]), noncovalent BTKis (n=14 [20.9%]), and BCL2 inhibitors (n=55 [82.1%]). At baseline, 77.1% (37/48) of patients had CLL/SLL with unmutated IGHV, 65.7% (44/67) had del(17p) and/or TP53 mutation, 37.9% (25/66) had BTK mutation, and 15.2% (10/66) had PLCG2 mutation. Median study follow-up was 24.1 (range, 0.3-37.7) months; 35 patients (52.2%) remained on treatment at data cutoff.

Any-grade treatment-emergent adverse events (TEAEs) occurred in 97.0%; those reported in $\geq 25\%$ were fatigue (37.3%), contusion (bruising) (32.8%), diarrhea (29.9%), and neutropenia/neutrophil count decreased (29.9%). Grade ≥ 3 TEAEs occurred in 61.2%; (in $\geq 5\%$) were infections (34.3%), neutropenia/neutrophil count decreased (25.4%), and thrombocytopenia/platelet count decreased (7.5%). TEAEs led to dose reduction in 9 patients (13.4%) and treatment discontinuation in 12 patients

(17.9%), 4 (6.0%) of whom had treatment-related TEAEs (subdural hemorrhage, peripheral swelling and ecchymosis, maculopapular rash, and disseminated aspergillosis). Among 67 patients, 5 (7.5%) had TEAEs leading to death (all infections; one in the context of progressive disease [PD]).

Among 67 patients, the ORR ($\geq$ PR-L) was 85.1% (n=57), $\geq$ PR was 77.6% (n=52); complete response (CR)/CR with incomplete marrow recovery rate was 3.0% (n=2). At the 200-mg dose, ORR was 94.1% (16/17), with 1 CR. Median time to first response was 2.8 (range, 2.0-19.4) months; median duration of response was 20.7 (range, 0-27.6) months. Responses were observed in patients previously treated with cBTKi and BCL2i (40/43 [93.0%]) and cBTKi, BCL2i, and ncBTKi (9/12 [75.0%]), and those with del(17p) and/or TP53 mutation (35/44 [79.5%]), with BTK mutations (19/25 [76.0%]), and with PLCG2 mutation (9/10 [90.0%]). The 18-month PFS rate was 65.2% (95% CI, 50.9%-76.2%); 21 patients (31.3%) had PD, and 5 (7.5%) died.

Conclusions: Tacabrutideg demonstrated a manageable safety profile with durable responses in patients with R/R CLL/SLL, including in difficult-to-treat CLL/SLL. Tacabrutideg (200 mg) is being evaluated in ongoing phase 2 and 3 studies. ©EHA2026.

P023

Tacabrutideg (BGB-16673) versus idelalisib plus rituximab, bendamustine plus rituximab, or venetoclax plus rituximab re-treatment in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: the phase 3 CaDAnCe-302 trial

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Topic: Clinical Trial

Background: Novel therapies, including Bruton tyrosine kinase inhibitors (BTKis) and B-cell lymphoma 2 inhibitors (BCL2is), have meaningfully improved patient outcomes in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). However, CLL/SLL remains incurable, and most patients will experience disease relapse following a BTKi or BCL2i. Tacabrutideg (BGB-16673) is a Bruton tyrosine kinase (BTK) degrader that blocks signaling by tagging BTK for degradation through the cell's proteasome pathway, leading to tumor regression. Data from CaDAnCe-101 (BGB-16673-101, NCT05006716), an ongoing phase 1/2 study, demonstrate that tacabrutideg has a tolerable safety profile and can achieve responses in heavily pretreated patients with relapsed/refractory (R/R) CLL/SLL, including those with prior BTKi treatment and BTK resistance mutations. Here, CaDAnCe-302, an ongoing phase 3 study that will evaluate the efficacy and safety of tacabrutideg monotherapy vs investigator's choice (IC; idelalisib + rituximab, bendamustine + rituximab, or venetoclax + rituximab re-treatment) in patients with CLL/SLL previously exposed to BTK and BCL2 inhibitors, is described.

Material and Methods: CaDAnCe-302 (BGB-16673-302, NCT06846671) is a global, open-label, randomized, phase 3 clinical study conducted across approximately 137 sites in 14 countries. Eligible patients are ≥18 years of age with a confirmed diagnosis of CLL/SLL that has relapsed after treatment with a covalent BTKi and a BCL2i or is refractory to these treatments. Prior treatment with a noncovalent BTKi is also required in regions where they are approved and available. Patients are excluded if they have prolymphocytic leukemia or history of, or currently suspected, Richter transformation, have received an autologous stem cell transplant or chimeric antigen receptor T-cell therapy in the last 3 months, or had prior exposure to any BTK protein degraders. Approximately 250 patients are planned to be enrolled and randomized 3:2 to receive either tacabrutideg once daily (arm A) or IC of idelalisib + rituximab (for CLL only), bendamustine + rituximab [for CLL/SLL without del(17p) or TP53 mutation], or venetoclax + rituximab re-treatment (arm B) until disease progression or intolerance. For patients to be considered for venetoclax + rituximab re-treatment, the best overall response of the last BCL2i-based regimen should be partial response or better, with the last BCL2i dose being ≥1 year prior to the most recent disease progression, and the patient should have been able to tolerate previous BCL2i treatment. Patients in arm B will be given the option to cross over to tacabrutideg treatment after confirmation of progressive disease by both the investigator and independent review committee (IRC). The primary endpoint is progression-free survival (PFS), as

determined by IRC per modified 2018 International Workshop on CLL criteria (for CLL) or Lugano classification (for SLL). Overall survival is the key secondary endpoint; additional secondary endpoints include PFS in patients with prior exposure to noncovalent BTKis by IRC, PFS by investigator, overall response rate by IRC and investigator, rate of partial response with lymphocytosis or higher by IRC and investigator, duration of response by IRC and investigator, time to next treatment, and safety/tolerability per NCI CTCAE v5.0. Recruitment is ongoing. © American Society of Hematology (2025). Reused with permission.

P024

Pirtobrutinib in Treatment-Naïve Patients with CLL/SLL: Pooled Results from BRUIN CLL-313 and BRUIN CLL-314

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Topic: Clinical Trial

Background: Pirtobrutinib, a highly selective, non-covalent Bruton tyrosine kinase inhibitor (BTKi), is approved globally for patients (pts) with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) previously treated with a covalent BTKi. BRUIN CLL-313 and BRUIN CLL-314 are open-label, randomised phase 3 studies evaluating pirtobrutinib for therapy of pts with CLL/SLL, including in the treatment-naïve (TN) setting [versus bendamustine plus rituximab (BendaR; CLL-313, NCT05023980) and versus ibrutinib (CLL-314, NCT05254743)].

Material and Methods: Pooled data from TN CLL pts randomised to receive pirtobrutinib from CLL-313 and CLL-314 were used to assess efficacy [overall response rate (ORR), progression-free survival (PFS) and overall survival (OS)] and safety. PFS and OS estimates were calculated by the Kaplan-Meier method. All pts (253) randomized within each study to receive pirtobrutinib are included in efficacy analyses and all pts (252) who received pirtobrutinib treatment are included in safety analyses.

Results: A total of 253 TN pts, median age of 66 yrs, were assigned to receive pirtobrutinib (CLL-313 n=141; CLL-314 n=112); all but one received treatment. Among pts with evaluable samples 134/233 (58%) had unmutated IGHV, 14/253 (6%) had del(17p) and 21/220 (10%) had mutated TP53. Efficacy was consistent between the two studies (Table). Overall, ORR was 93.3%. Median PFS was not reached; the 24-month PFS rate was 93.2% (95%CI, 89.1-95.8). Median OS was also not reached; the 24-month OS rate was 97.5% (95%CI, 94.6-98.9). Median duration of therapy was 29.1 months. Treatment discontinuation due to TEAEs occurred in 4.8% of pts with 1.6% treatment related. Any-grade infection occurred in 59.9% of pts; neutropenia in 18.3% and grade ≥3 bleeding in 2.4%. Any-grade hypertension occurred in 10.7% of pts and atrial fibrillation/flutter was reported in 2.8%.

Conclusions: In 253 TN pts with CLL randomised on two phase 3 studies, pirtobrutinib showed a high ORR and favorable 24-month PFS and OS rates. The safety profile was consistent with prior studies

using pirtobrutinib in more heavily treated pts, with low rates of atrial fibrillation/flutter, hypertension and TEAE-related discontinuations. These findings reinforce the potential of pirtobrutinib as a meaningful and clinically relevant treatment option for pts with TN disease.

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Figure/Table 1

Efficacy of Pirtobrutinib in TN patients with CLL/SLL

	Parameter	CLL-313 N = 141	CLL-314 N = 112	Pooled TN pts N=253
ORR	ORR, % (95% CI)	94.3 (89.1, 97.5)	92.0 (85.3, 96.3)	93.3 (89.5, 96.0)
PFS	24-month PFS rates, % (95% CI)	92.7 (86.8, 96.0)	94.3 (87.8, 97.4)	93.2 (89.1-95.8)
	Median FU, months	28.1	22.4	27.7
OS	24-month OS rates, % (95% CI)	97.8 (93.3, 99.3)	97.2 (91.5, 99.1)	97.5 (94.6-98.9)
	Median FU, months	32.7	26.7	29.5

ORR includes a best response of partial response or better

P025

Fixed duration pirtobrutinib plus venetoclax–rituximab versus venetoclax–rituximab for patients with previously treated CLL/SLL: A phase 3, randomised study (BRUIN CLL-322)

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Topic: Clinical Trial

Background: Venetoclax-rituximab (VR) is the current standard of care (SOC) fixed-duration therapy for relapsed/refractory (R/R) CLL; however, prospective data are limited in patients (pts) previously treated with covalent BTK inhibitors (cBTKis), the most commonly used first-line SOC. Pirtobrutinib, a highly selective noncovalent (nc) BTKi, has demonstrated efficacy in first-line, second-line, and more heavily pretreated R/R CLL, including pts with prior cBTKi exposure, leading to global regulatory approvals. The synergy of dual inhibition of BTK and BCL2 combined with anti-CD20 therapy provides rationale for adding pirtobrutinib to VR (PVR) to deepen responses and improve outcomes in R/R CLL, particularly in the post-cBTKi setting. We compared the efficacy and safety of fixed-duration PVR v VR in pts with R/R CLL.

Material and Methods: Pts were randomized 1:1 (PVR:VR), stratified by del(17p) status and prior cBTKi exposure. Pts with prior ncBTKi or BCL2i exposure were excluded. Both arms received venetoclax (25 cycles [C]) and rituximab (6C); PVR arm also received fixed-duration pirtobrutinib (28C), with a 3C pirtobrutinib-rituximab lead-in before venetoclax initiation. The primary endpoint was IRC-assessed PFS (iwCLL 2018). Secondary endpoints included INV-assessed PFS, OS, TTNT, ORR, and safety. MRD

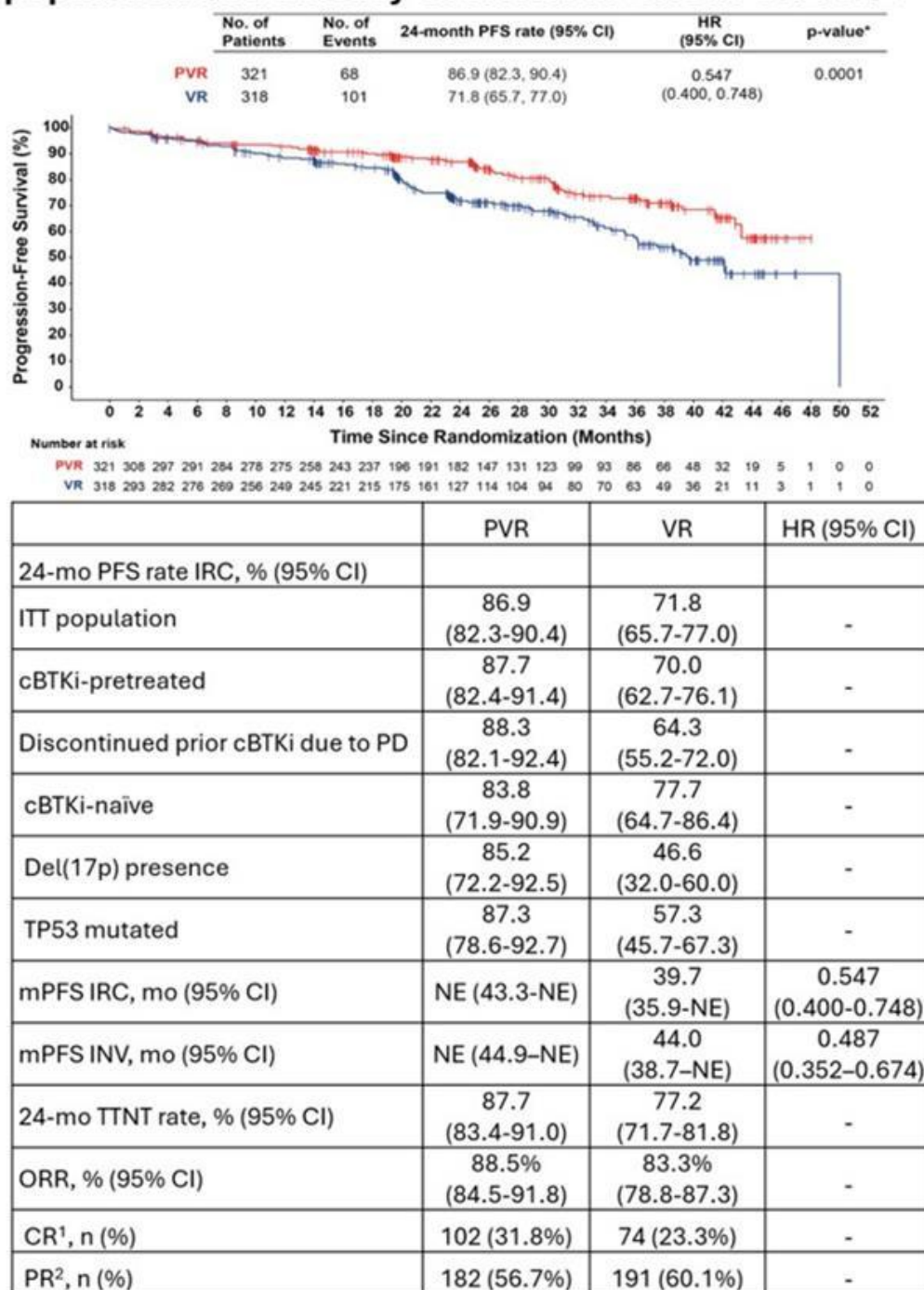
analyses (clonoSEQ) were exploratory. This planned interim analysis tested PVR superiority in IRC-PFS using a group sequential approach to control type I error. Data cutoff: 2Feb2026.

Results: 639 pts were randomised (PVR:n=321; VR:n=318); median age: 68 years (range, 32-87); median number of prior line of therapies: 2 (range, 1-9). 510 (79.8%) pts had prior cBTKi exposure; 362/510 (71.0%) had discontinued cBTKi due to progressive disease (PD). PVR demonstrated superiority in IRC-PFS v VR in the ITT population (HR=0.547; 95%CI, 0.400-0.748; P=0.0001; Figure); median follow-up: 27.3 months (95%CI, 25.49-29.86); 24-month PFS: 86.9% with PVR v 71.8% with VR. The PFS benefit with PVR was consistent across prespecified subgroups, including pts with prior cBTKi exposure, those who discontinued prior cBTKi due to PD, and pts with del(17p)/TP53 mutation. TTNT favored PVR (HR=0.498; 95%CI, 0.352-0.704). OS data are immature (HR, 0.891; 95% CI, 0.568-1.398). Peripheral blood undetectable (u) MRD4 rates at end of treatment were higher with PVR in pts with evaluable samples (101/117 [86%] v 71/117 [61%]; P<0.001). Rates of any grade (G) AEs (PVR v VR: 99.7% v 98.1%) and G≥3 AEs (78.8% v 73.0%) were similar between arms, including low rates of any G atrial fibrillation/flutter (3.5% v 2.6%), hypertension (12.0% v 7.4%), and hemorrhage (14.2% v 10.6%). G≥3 clinical AEs of interest included neutropenia (50.3% v 43.7% [febrile neutropenia 2.2% v 3.5%]) and tumor lysis syndrome (0.9% v 3.9%). Discontinuation rates due to treatment-related AEs were similar for PVR v VR (5.4% v 5.1%).

Conclusions: PVR showed a statistically significant and clinically meaningful improvement in IRC-PFS compared with VR in previously treated CLL, with higher uMRD rates and a similar safety profile. BRUIN CLL-322 provides the first randomized phase 3 data for any BTKi as part of a fixed-duration regimen in R/R CLL, including in pts previously treated with cBTKi, and establishes fixed-duration PVR as a potential new SOC for R/R CLL.

Figure/Table 1

Kaplan–Meier estimate of IRC-assessed PFS in ITT population and efficacy overview in BRUIN CLL-322



*Two-sided P values are based on the stratified log-rank test, stratified by prior cBTKi experience and del(17p)

¹ CR includes incomplete bone marrow recovery. ² PR includes nodular partial remission.

CR, complete response; INV, investigator; IRC, independent review committee; mo, months; mPFS, median progression-free survival; NE; ORR, overall response rate; PD, progressive disease; PR, partial response; TTNT, time to next treatment

The study was presented at the European Hematology Association - 31st Congress; June 11-14, 2026; Stockholm, Sweden

P026

18F-FDG-PET/CT to assess metabolic disease activity of chronic lymphocytic leukemia during first line treatment with ibrutinib, venetoclax and obinutuzumab (HOVON 158 trial)

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Topic: Clinical Trial

Background: Treatment for chronic lymphocytic leukemia (CLL) has improved with the introduction of targeted therapy, such as ibrutinib and venetoclax, resulting in deep remissions. Currently, CT is the standard imaging modality for CLL, providing anatomical information on lymph node involvement. 18F-FDG-PET/CT (FDG-PET/CT) on the other hand, is not routinely used in CLL but may provide complementary metabolic information on disease activity before and during treatment, although the expected low FDG avidity of CLL may complicate image analysis. Therefore, we explored the feasibility of visual and quantitative assessment of FDG uptake in CLL patients before and during treatment with ibrutinib, venetoclax, and obinutuzumab.

Methods: In the HOVON-158 trial, 85 untreated CLL patients received 16 cycles of venetoclax and ibrutinib. Patients with persistent measurable residual disease (MRD) in bonemarrow received 6 additional cycles of obinutuzumab and ibrutinib. FDG-PET/CT scans and assessment were performed at baseline, after cycle 8 (C8), after cycle 15 (C15), and 9 months after registration. Representative target lesions were selected on CT (max 6 per patient, size >1.5x1cm). Visual assessment of FDG uptake in target lesions was performed by three reviewers, employing the Deauville score (DS). Tumor uptake for each target lesion (DS ≥ 2) was derived from a volume of interest (sphere) on FDG-PET/CT using SUVpeak. Inter-reader variability in visual assessment of the hottest-lesion (i.e. target lesion with the highest FDG uptake on FDG-PET/CT) at baseline (n=33) and C8 (n=34) were evaluated employing overall agreement (OA) and weighted kappa.

Results: At baseline, low FDG uptake was observed on FDG-PET/CT (DS 2–5; Figure 1), with a median SUVpeak of 2.2 (IQR 1.6–2.7). Over time, FDG uptake decreased further, resulting in significantly fewer target lesions that could be quantified (baseline: n=365 vs. 9 months: n=21; p<0.001). The OA among the three reviewers assigning the exact same DS for the hottest lesion was 55.2% (95% CI: 0.418–0.677) at baseline and 57.8% (95% CI: 0.454–0.694) at C8. Weighted kappa values in DS assessment were 0.621 at baseline and 0.481 at C8, overall indicating ‘moderate’ to ‘substantial’ inter-reader agreement.

Conclusion: The feasibility of visualizing and quantifying FDG uptake in CLL is challenging due to the low metabolic activity of the disease, resulting in low FDG uptake within lesions. During treatment, lesion visualization became increasingly challenging as therapy further reduced FDG uptake. This contributed to a moderate inter-reader variability, partly due to the use of DS criteria, which appears not to be directly transferable from aggressive lymphomas to CLL. These findings indicate that further studies are warranted to explore more advanced assessment methods (e.g. radiomics) for FDG-PET/CT to quantify metabolic activity of CLL and ultimately improve understanding of disease activity and prognosis.

Figure/Table 1

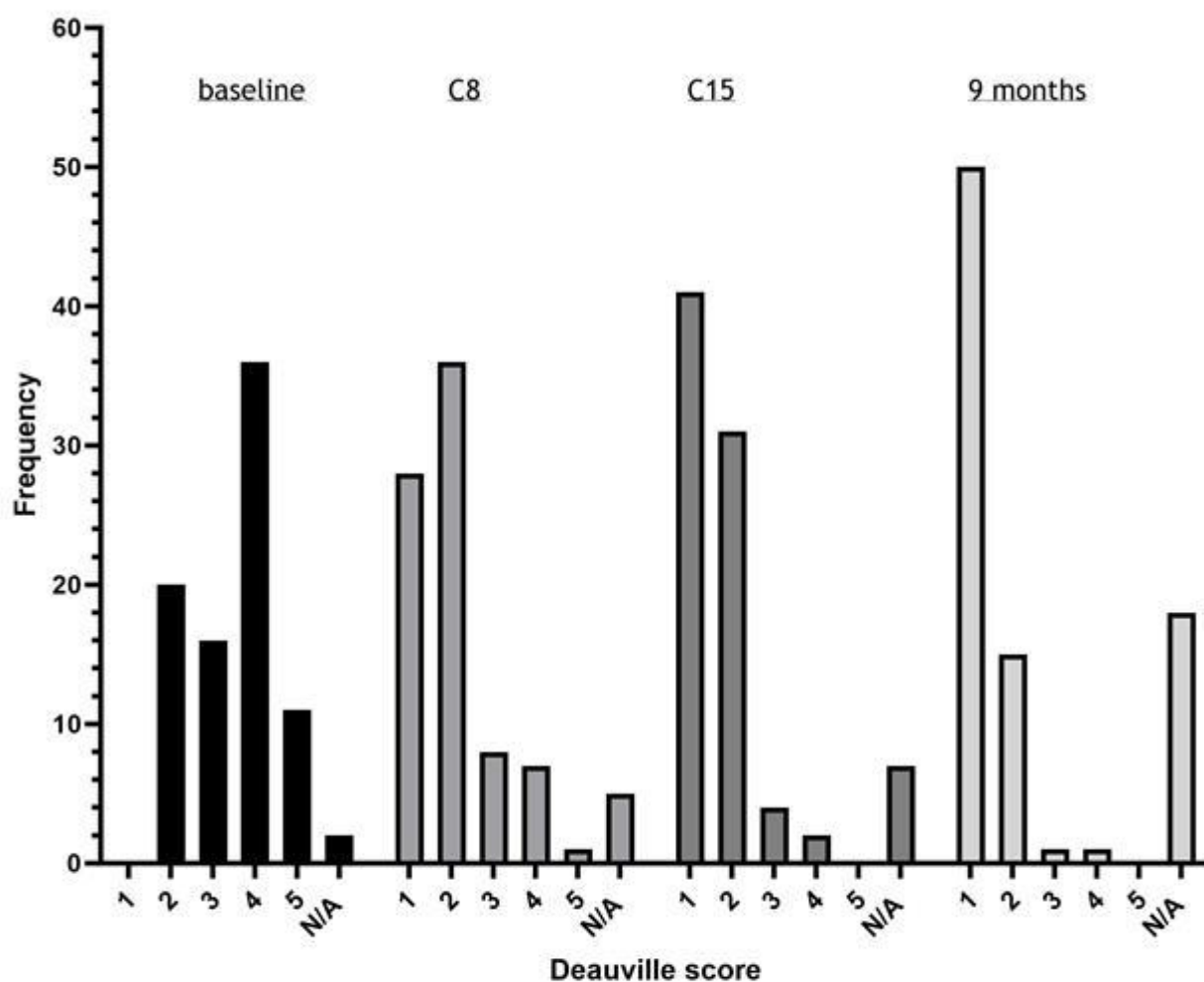


Figure 1: Deauville score based on hottest target lesion (adjudicator assessment)
N/A = not available

P028

First-line treatment of CLL/SLL with the all-oral combination of sonrotoclax and zanubrutinib achieves undetectable minimal residual disease rates of >90%, including in patients with del(17p)/TP53

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Topic: Clinical Trial

Background: Oral, fixed-duration BTKi-BCL2i combinations are effective, convenient first-line options for CLL. However, current regimens, including those using 2nd-generation BTKi, can be limited by low uMRD rates. Upgrading the BCL2i component of BTKi-BCL2i with sonrotoclax, a next generation BCL2i with ~14x pharmacological potency vs venetoclax, may lead to improved uMRD rates. Here, we report safety and efficacy results in patients with treatment-naïve CLL/SLL treated with zanubrutinib + sonrotoclax (320 mg cohort) in a phase 1/1b study (NCT04277637), with a median follow-up of 30.9 months (range, 3.1-41.9 months).

Material and Methods: Study treatment consisted of lead-in zanubrutinib 320 mg QD for 8-12 weeks, after which sonrotoclax was added with ramp-up to target dose (320 mg QD). Patients were treated until progression, unacceptable toxicity, or protocol-defined elective discontinuation after 96 weeks of combination treatment at target dose. Primary endpoint was safety. Secondary endpoints included overall response rate (ORR). Exploratory endpoints included blood uMRD4 rates per flow cytometry and next generation-sequencing (NGS).

Results: Of 86 patients in the sonrotoclax 320 mg cohort, 45 (52%) remained on treatment at data cut-off. Of patients who discontinued sonrotoclax, 85% (34/40) did so due to protocol-defined elective discontinuation. The most common (≥30%) treatment-emergent adverse events (TEAEs) were neutropenia (38%), contusion (38%), COVID-19 (33%), and upper respiratory tract infection (30%). Neutropenia was the most common grade ≥3 TEAE (29%). No TLS occurred, and no AEs led to death. In 84 efficacy-evaluable patients, the ORR was 100%, with 46 (55%) achieving complete response.

Median time to response was 2.6 months (range, 1.5-9.1 months). No patients in the 320 mg cohort had progression (estimated 30-month PFS: 100%). The best uMRD4 rate assessed by flow cytometry was 99% (83/84) and 100% (10/10) in patients with del(17p)/TP53 mutations. Median time from reaching so sonrotoclax target dose to uMRD was 3.0 months (range, 2.3-27.4 months), and the best uMRD4 rates by weeks 24, 48 and 96 were 81% (69/85), 91% (63/69) and 98% (55/56), respectively. No patient with uMRD4 reverted to detectable MRD4. In the NGS evaluable set, best uMRD5 ($<10^{-5}$) was 86% (66/77). Updated results will be presented.

Conclusions: Sonrotoclax + zanubrutinib was well tolerated and achieved uMRD rates of >90%, including in patients with high-risk cytogenetics, and is being evaluated in two phase 3 clinical trials (NCT06073821, NCT07277231).

P029

Preemptive Short-Term Venetoclax + Acalabrutinib for Newly Diagnosed CLL Patients Assessed as High Risk of Infection or CLL Treatment by the CLL-TIM Algorithm: Analysis of the PreVent-ACaLL Trial

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Topic: Clinical Trial

Background: Watchful waiting is standard for patients with early-stage chronic lymphocytic leukemia (CLL). Clinical trials have tested preemptive treatment for high-risk asymptomatic patients without demonstrating benefit. However, patients with asymptomatic CLL not meeting iwCLL criteria for treatment have higher incidence of severe infections, leading to increased morbidity and mortality. We present the primary analysis of the PreVent-ACaLL trial, the first randomized trial testing short term venetoclax + acalabrutinib to improve grade ≥ 3 infection-free, treatment-free survival (IF-TFS) for patients newly diagnosed with CLL assessed at high risk by the data-driven CLL-TIM algorithm.

Methods: PreVent-ACaLL (NCT03868722) is a multicenter, randomized, phase-2 trial, including newly diagnosed patients with high risk of infection and/or treatment within 2 years from diagnosis by the machine-learning based CLL-TIM algorithm (Agius et al., Nat Comm, 2020). Based on CLL-TIM, patients were classified into four categories: High Risk/High Confidence (HR-HC), High Risk/Low Confidence (HR-LC), Low Risk/Low Confidence (LR-LC) and Low Risk/High Confidence (LR-HC).

HR-HC patients were randomized 1:1 between venetoclax + acalabrutinib for three cycles (28 days) or observation.

The primary outcome was the proportion of patients with Grade ≥ 3 -Infection-free survival (IFS) in the treatment arm compared to the observation arm. The secondary outcome was Grade ≥ 3 -Infection-free, treatment-free survival (IF-TFS).

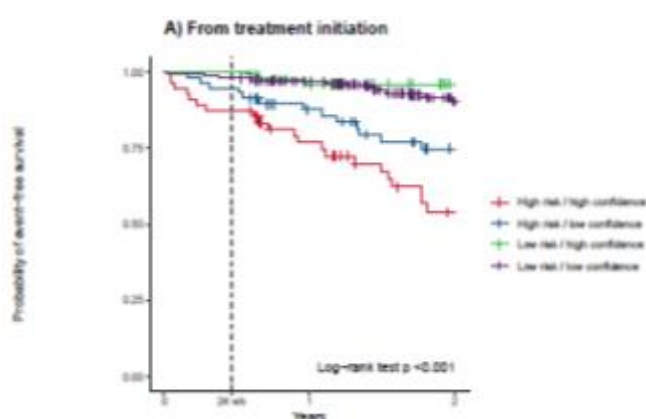
Results: In total, 596 patients were prescreened, 574 assessed by CLL-TIM, resulting in 131 (23%) assessed as low risk, high confidence; 289 (50%) as low risk, low confidence; 59 (10%) as high risk, low confidence; and 95 (17%) as high risk, high confidence. Of the latter, 55 (58%) were not randomized due to patient or physician decision. The remaining 40 (42%) high risk, high confidence patients were randomized; 22 to the treatment arm and 18 to observation; 68, 87% had IGHV unmutated status, 13% had TP53 aberration.

For prospective validation of CLL-TIM; a significant difference in IF-TFS was observed for HR-HC versus both LR groups; the HR-HC group also had significantly worse outcomes than the HR-LC group ($p > 0.045$) (fig 1). Though not trained on survival, the HR-HC 2-year survival (88.7%) was also significantly lower than LR groups ($p > 0.03$).

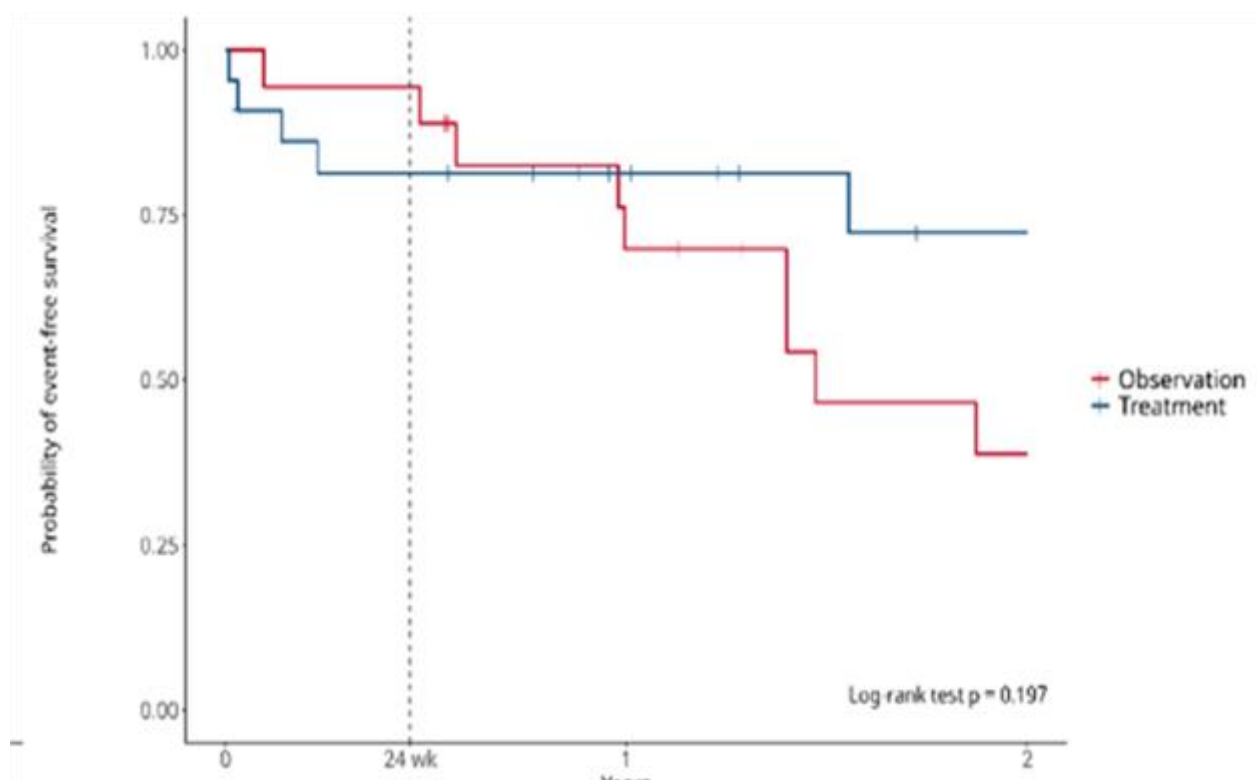
For the randomized patients, the estimated IFS was 78% versus 100% at 24 weeks and 72% versus 78% at 2 years, in the treatment and observation arms, respectively. Thus, non-inferiority of IFS for treatment as compared to observation per protocol was not met. The IF-TFS was 81% versus 94% at 24 weeks and 72% versus 39% at 2 years, in the treatment and observation arms, respectively (fig 2). No difference in overall survival appeared between study arms with 1 fatality in each arm (gastric cancer in the treatment arm and uterine cancer in observation) during the 2 years.

Conclusion: The CLL-TIM algorithm is prospectively validated for identification of patients with newly di-agnosed CLL at high risk of infection or CLL treatment. Preemptive treatment with short-term venetoclax + acalabrutinib for high-risk patients increases grade ≥ 3 infections during treat-ment, while improving IF-TFS at 2 years. Thus, further refinement of early interventions in-cluding infection prophylaxis during treatment are warranted.

Figure/Table 1



Figure/Table 2



P030

Second primary malignancies in patients with chronic lymphocytic leukemia treated with targeted therapies in three phase-III trials of the German CLL Study Group

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Topic: Clinical Trial

Background: Despite advancements in targeted therapies, second primary malignancies (SPM) remain a major challenge for patients (pts) with chronic lymphocytic leukaemia (CLL) contributing to morbidity.

Aims:

The aim of this pooled analysis is to identify risk factors for the development of SPM in pts with treatment-naïve CLL treated in phase-III trials of the German CLL Study Group.

Methods: Data from phase-III trials (CLL12, CLL13, CLL14) were pooled in 5 cohorts: venetoclax-based (ven) (n=677, CLL13-GVe, CLL13-RVe, CLL14-GVe), ibrutinib (BTKi) (n=170, CLL12-I), BTKi-ven-based (n=231, CLL13-GIVe), chemoimmunotherapy (CIT) (n=430, CLL13-FCR, CLL13-BR, CLL14-GCib) or untreated (n=320, CLL12-Placebo/Watch and wait). SPM (excluding benign neoplasia and non-melanoma skin cancer; NMSC) were reported until end of study. Follow-up adjusted incidence rates of SPM were calculated based on time from study entry to first SPM or last observation and reported per 1,000 patient-months (pt-mo). Multivariable logistic regression was used to identify prognostic factors for SPM development. Overall survival was assessed using Cox proportional hazards regression with SPM as time-dependent covariate.

Results: With a median observation time of 68.4 months (mo) (IQR 58.6 – 78.5 mo) a total of 214 SPMs were reported in 202 of 1,828 pts (11%). Of those, 150 were solid (70%), 39 Richter Transformations (RT, 18%) and 21 haematological (hem, 10%). Thirty-eight (18%) SPMs were fatal (26 solid, 9 RT, 3 haematological).

In the multivariate analysis, age >65 years (odds ratio [OR] 2.17, 95% confidence interval [CI] [1.61 – 2.94]) and male sex (OR 1.92, 95% CI [1.34 – 2.74]) were suggested as risk factors for SPM development in the pooled cohort. In the untreated cohort, del17p (OR 14.59 [2.74 - 77.63]) and del11q (OR 5.25 [2.02 – 13.68]) were identified as risk factors for SPM development. Risk factors for each cohort are depicted in Fig. 1.

Details for each cohort are listed in Table 1.

Overall survival was shorter for pts with vs pts without SPM in all cohorts: ven (hazard ratio [HR] 8.86 [5.38 – 14.60]), BTKi (HR 10.95 [2.88 – 41.71]), BTKi-ven (HR 22.18 [6.84 – 71.91]), CIT (HR 4.65 [2.82 – 7.66]), untreated (HR 15.87 [6.56 – 38.40]).

Conclusion: With the caveat of a very heterogeneous pooled analysis population including a total of 1,828 treated and untreated CLL pts from 3 phase-III trials, SPM occurred in 11% of all pts with follow-up adjusted incidence rates ranging from 1.4 to 2.2 per 1,000 pt-mo across various treatment cohorts and 1.6 in the untreated cohort. Higher age and male gender were suggested as risk factors for SPM. Since 18% of all documented SPMs are fatal, SPMs remain a challenge in the era of targeted therapies and a continuous surveillance is recommended.

Figure/Table 1

Table 1: Follow-up adjusted incidence rate, SPM frequency per treatment cohort, median time to first SPM and SPMs with CTC grade 5. Bold numbers represent significantly higher or lower follow-up adjusted incidence rates compared to the other listed SPM categories.

Cohort	Number of SPMs	Number of pts with SPMs (%)	Number of pts with SPMs CTC grade 5 (%)	Follow-up adjusted incidence rate per 1,000 pt-mo, 95% CI				Median time to first SPM (months)
				All SPMs	Solid	RT	Hem	
Ven	77	73 (10.8)	9 (1.3)	1.78 [1.40-2.24]	1.26 [0.94-1.62]	0.37 [0.21-0.58]	0.07 [0.01-0.17]	22.1
BTKi	15	15 (8.8)	2 (1.2)	1.44 [0.81-2.38]	1.25 [0.66-2.01]	0.09 [0.00-0.34]	0.00 [NE]	20.5
BTKi-ven	29	29 (12.6)	5 (2.2)	2.15 [1.44-3.09]	1.31 [0.78-1.98]	0.21 [0.04-0.51]	0.56 [0.24-1.02]	31.6
CIT	59	53 (12.3)	11 (2.6)	2.11 [1.58-2.76]	1.38 [0.96-1.87]	0.49 [0.26-0.80]	0.30 [0.13-0.55]	24.6
untreated	34	32 (10.0)	7 (2.2)	1.59 [1.09-2.25]	1.34 [0.88-1.89]	0.29 [0.11-0.56]	0.05 [0.00-0.18]	30.1

Figure/Table 2

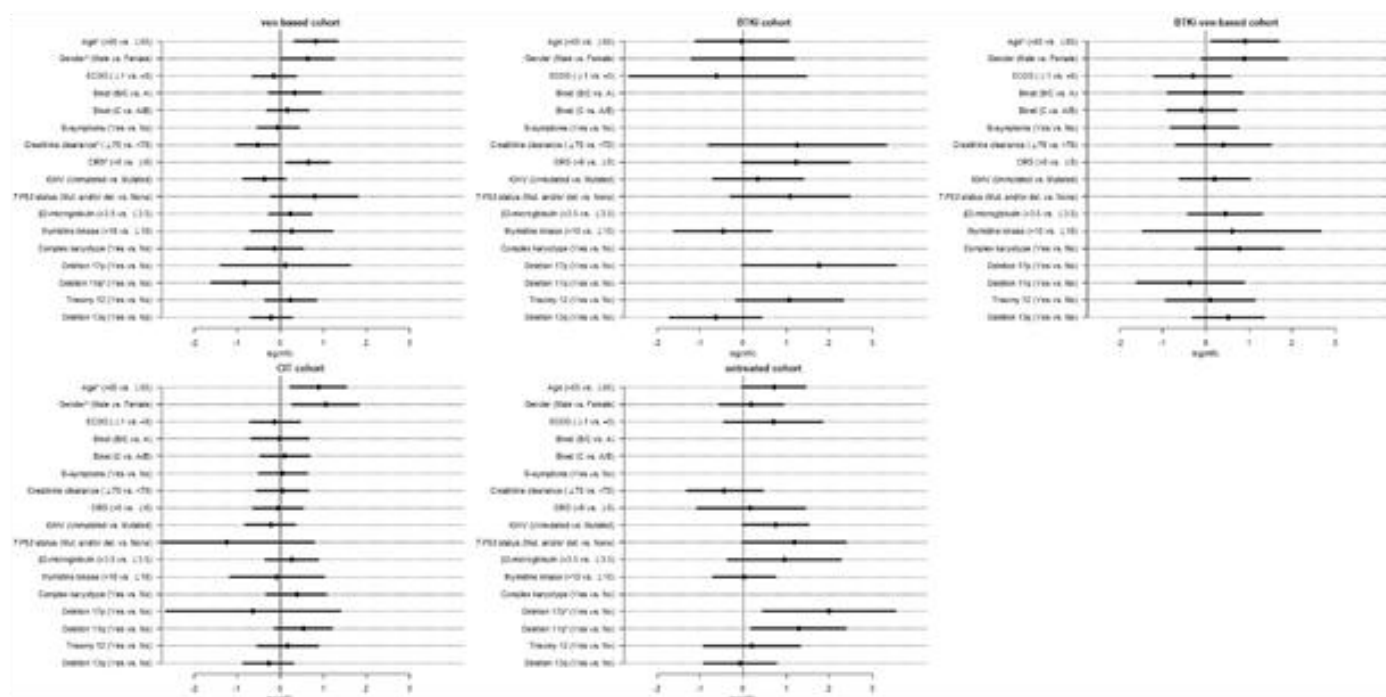


Figure 1: Forest plot of risk factors for each treatment cohort analyzed by univariable analysis. ECOG: Eastern Cooperative Oncology Group; CLL-IPI: international prognostic index for patients with chronic lymphocytic leukaemia; *: significant risk factors for SPM in multivariable analysis.

P032

Cardiovascular Toxicity, Risk Predictors and Dose Modulation in Patients with CLL Treated with BTKi: A Multicenter Real-World Analysis

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Topic: Real-world

Background: Bruton tyrosine kinase inhibitors (BTKi) are a cornerstone in CLL, but cardiovascular (CV) toxicity remains a major concern. Real-world comparative data on first- vs second-generation BTKi (2gBTKi), including timing, predictors of CV events and the impact of dose modulation, are limited.

Aim: To assess the incidence and timing of atrial fibrillation (AF), hypertension (HTN), congestive heart failure (CHF) and bleeding, identify clinical and heart ultrasound predictors, and evaluate the impact of dosing strategies.

Methods: We retrospectively analysed 410 CLL patients treated with BTKi-based regimens across three Italian centres. Baseline CV risk factors, echo features and treatment characteristics were collected. Cumulative incidence (CI) of CV events was estimated using competing-risk analysis. Overall survival (OS) and progression free survival (PFS) were analysed using Kaplan-Meier and multivariable (MV) Cox models, with dose reduction as a time-dependent covariate.

Results: Baseline characteristics are summarised in table 1. Median follow-up was 32 months. At 30 months, OS/PFS were 87.1%/79% for I, 87.2%/82% for 2gBTKi, and 95%/86% for I+V. In MV analyses, age>80 years (OS p=.038; PFS p<.001) and starting at reduced dose (OS p=.002; PFS p=.046) were independent predictors of inferior outcomes, considering that patients starting at reduced dose were significantly older (p<.001). In addition, complex karyotype adversely impacted PFS (p=.03). Dose reduction due to AEs occurred in 61 patients, at a median of 8 months (range 1–107), and was not associated with inferior PFS (p=0.45) or OS (p=0.51).

Median time-to-CV-event differed: bleeding was early (98 days, IQR 46.5-369), whereas AF and HTN occurred later (14.0 months, IQR 5.8-24.3 and 14.5 months, IQR 9.0-26.8), and CHF at 11.5 months (IQR 6.8-35.0). AF incidence was higher with I compared to 2gBTKi (24-month CI: 13.6% vs 4.4%, p=.018), while no differences were observed for HTN, bleeding or CHF. In MV analysis, AF was associated with baseline AF (p<.001), smoking (p=.002) and atrial dilatation (p=.013), whereas 2gBTKi reduced AF risk (p=.009). HTN was associated with left ventricular remodelling (p<.001), and CHF with age >80 years (p=.02).

Conclusions: 2gBTKi showed a more favourable CV profile, particularly for AF. Clinical and heart ultrasound features identify patients at higher risk of CV events, supporting tailored baseline assessment and monitoring. Inferior outcomes observed in patients starting at reduced dose may reflect baseline frailty, while dose reduction during therapy does not appear to compromise survival outcomes.

Figure/Table 1

Table 1. Main characteristics of our cohort population.

Characteristics	N (%) N=410
Therapy	
Ibrutinib monotherapy	211 (51)
Ibrutinib + venetoclax	60 (15)
Second generation BTKi	139 (34)
- Acalabrutinib	79 (19)
- Zanubrutinib	60 (15)
Age	72 years (range 65-93)
Sex F/M	157 (38)/253 (62)
Treatment naïve	262 (64)
Relapsed/refractory	148 (36)
Low dose of drug at baseline	55 (13)
IGHV um	237 (70)
Unknown	72 (17)
TP53 mut	124 (32)
Unknown	25 (6)
Del(17p)	85 (21)
Unknown	7 (1)
Complex Karyotype	84 (20)
Unknown	110 (27)
Echocardiography available at baseline	344 (84)
Baseline CV comorbidities	272 (66)
- Hypertension	216 (53)
- Atrial fibrillation	42 (10)
- Other arrhythmias	21 (5,1)
- Valvular heart diseases	62 (15)
- Tobacco smoking	53 (13)
- Dyslipidaemia	110 (27)
- Diabetes	59 (14)
- Atrial dilatation	125 (36)
- Left ventricular remodelling	116 (34)
- Antiplatelets therapy	55 (13)
- Anticoagulants	54 (13)

P033

Long-Term Follow-Up for Safety and Efficacy of Zanubrutinib in Elderly (≥80 Years) Treatment-Naïve CLL/SLL Patients, Including Those With del(17p): Subgroup Analysis from the SEQUOIA Trial

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Topic: Real-world

Background: Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) predominantly affects older adults, with a median age at diagnosis of 72 years (yrs). Advancing age, comorbidities, and poor performance status can limit tolerability and effectiveness of treatment. However, clinical data in this population remain limited and with short follow-up. This subgroup analysis of SEQUOIA (NCT03336333) assessed efficacy and safety of zanubrutinib in patients aged ≥80yrs with CLL/SLL.

Materials and Methods: SEQUOIA enrolled TN pts with CLL/SLL considered unsuitable for FCR, defined as age ≥65yrs and/or CIRS >6, creatinine clearance <70 mL/min, and/or a recent history of serious or multiple infections. In Cohort 1/1a, pts without del(17p) were randomized 1:1 to receive continuous zanubrutinib (Arm A) or six cycles of BR (Arm B). Cohort 2 (Arm C) included pts with del(17p), all of whom received continuous zanubrutinib. This post hoc subgroup analysis included pts aged ≥80yrs from both cohorts who received zanubrutinib.

Results: A total of 38 pts treated with zanubrutinib (Arm A: 28 pts; Arm C: 10 pts) were aged ≥80yrs at study entry. Median age was 81yrs (range; 80–87) and 23 (60.5%) were male. Del(17p) and/or TP53 mutations were present in 14 (36.8%) pts, complex karyotype (≥3 copy-number aberrations) was detected in 4/24 (16.7%) evaluable pts, and 14 (36.8%) and 22 (57.9%) pts had mutated or unmutated IGHV, respectively. As of 31 Oct 2025, the median follow-up was 78.8mo (range; 5.0–92.1). The overall response rate was 100%, with a complete response rate of 18.4%. Estimated investigator-assessed progression free survival (PFS) rate (95% CI) at 72mo was 63.8% (44.6–77.8). Estimated overall survival (OS) rate (95% CI) at 72mo was 75.8% (58.6–86.6).

Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 78.9% of pts. TEAE of interest (any grade/grade ≥3) included atrial fibrillation/flutter (15.8%/0%), major hemorrhage (21.1%/13.2%), hypertension (28.9%/18.4%) and infections (76.3%/36.8%). TEAEs leading to treatment discontinuation occurred in 39.5% of pts, and TEAEs leading to death were observed in 13.2% of pts; infection (two cases; pneumonia and meningitis cryptococcal) was the only TEAE leading to death in >1 pt. In total, 36.8% pts remain on zanubrutinib.

Conclusion: Very elderly pts remain underrepresented in CLL trials despite the disease predominantly affecting older adults, making dedicated evaluation in this age group essential. SEQUOIA includes one of the largest populations of patients aged ≥80 yrs in a ph3 setting and provides the longest follow-up in this subgroup. Pts aged ≥80 yrs achieved durable benefit from zanubrutinib, with 64% of pts alive and progression free at 6yrs despite advanced age and high risk characteristics. The tolerability profile observed in this subgroup is as expected for a very elderly population and is comparable to the established safety profile reported for zanubrutinib. These results support the use of zanubrutinib as an effective first-line treatment for pts with TN CLL/SLL, including those aged ≥80yrs.

P034

Understanding patients' perspectives and preferences for first-line chronic lymphocytic leukemia (CLL) treatment across Europe

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Topic: Real-world

Background: Following a cancer diagnosis, patients may use digital social community platforms to seek information and share personal experiences, needs, and concerns. Systematic collection and analysis of patient-generated online content can provide valuable insights into the patient voice. Artificial intelligence enables the processing and extraction of meaningful insights from large volumes of unstructured online data. Digital listening leverages real-world insights by highlighting common themes and trends over time of topics important to patients. This analysis aimed to understand patient perspectives on factors influencing first-line CLL treatment choice and the extent of patient involvement in treatment decision-making using AI-based Semantic-NLP technology.

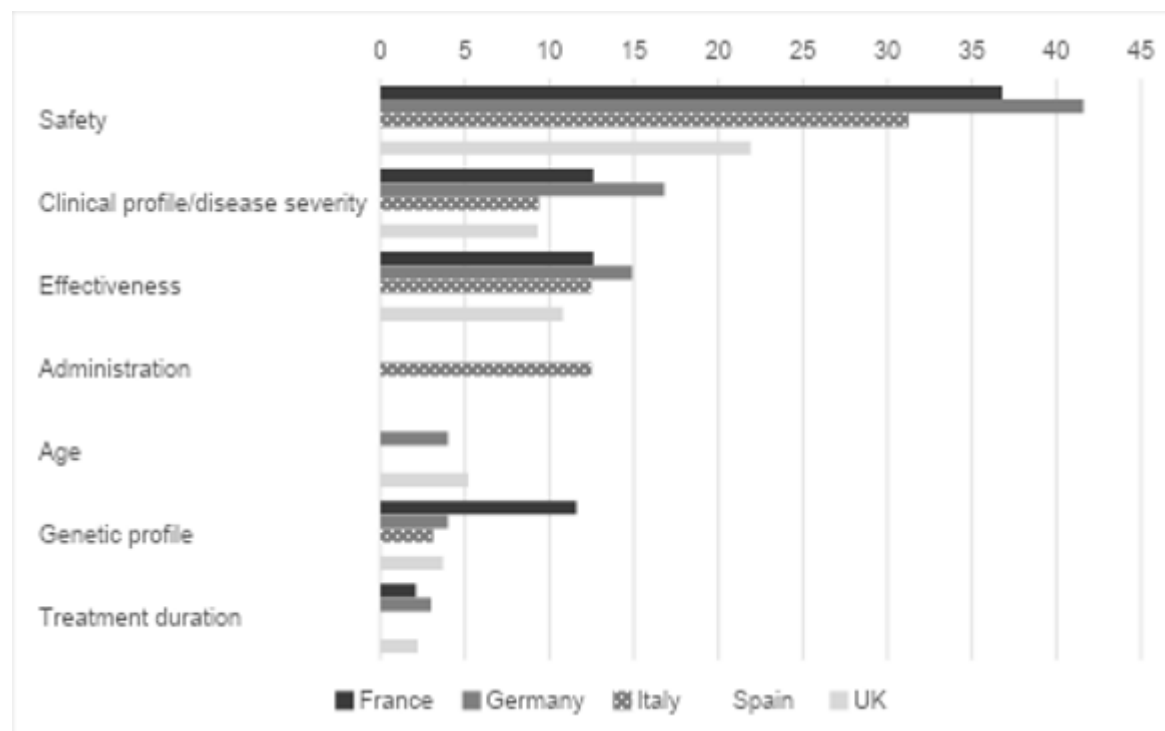
Material and methods: A multilingual ontology-based AI information extraction system, Semantic Hub, was used to identify the patient "voice" from online posts in France, Germany, Italy, Spain, and the United Kingdom. Data related to patients and first-line treatments in CLL were collected from social community platforms and other online patient platforms (i.e. Facebook, Instagram, HealthUnlocked.com) between January 1, 2020 and December 31, 2025. Key medical concepts, including factors influencing treatment choice and treatment decision-making, were extracted from the data, grouped into thematic categories, and analyzed using both qualitative and quantitative approaches.

Results: A total of 44,451 messages from 2,699 individuals were detected across the five countries. The semantic analysis revealed that treatment decisions were generally guided by hematologists. In the UK and Germany, out of 1,090 and 629 authors, respectively, only 7% and 11% explicitly reported that they were involved in the decision-making for their choice of treatment. Of note, in Germany, patients posted that physicians rarely asked about their personal priorities. Safety and effectiveness were the primary drivers of treatment choice among patients with CLL across the five countries, and these factors remained consistent over time.

Treatment duration was the lowest ranking criteria influencing treatment choice across the five countries (Figure). Notably, in the UK, patients mentioned that those who chose a fixed-duration treatment were influenced by their hematologists' recommendation and the expectation of achieving a deep remission.

Conclusion: This analysis demonstrated that the safety and effectiveness of a treatment were the top priorities for patients, with treatment duration being the lowest priority, when discussing treatment choices for first-line CLL. Insights also revealed that shared decision-making between patients and their healthcare providers remains limited. Further research warrants validating these findings across a wide range of CLL patients beyond social community platforms as there may be a reporting bias from patients who are more motivated to share their experiences online.

Figure/Table 1



P036

Patient-Reported Outcomes and Disease Progression in Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: A Systematic Literature Review and Gap Analysis

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Topic: Real-world

Background: Progression-free survival is a key endpoint in oncology, however the German Federal Joint Committee (G-BA) and other health technology assessment (HTA) bodies have questioned its direct patient relevance as a standalone endpoint. Other therapy areas have developed patient-relevant endpoints that combine disease progression with symptoms. To inform the development of a patient-focused progression endpoint in hematology trials, it is necessary to understand how patients are impacted by progression. This study aimed to identify patient-reported disease symptoms related to disease progression in chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

Material and Methods: A systematic literature review (SLR) was conducted to identify evidence on CLL/SLL-related symptoms and patient-reported outcomes (PROs). Searches were conducted in Embase, MEDLINE, MEDLINE In-Process, and the Cochrane Library for publications from January 2015 to October 2025. Targeted supplementary searches were also performed through December 2025, including Google Scholar, conference proceedings, clinical trial registries, and relevant professional society, government, and regulatory agency websites, as well as reference lists of identified SLRs. Only studies published in English were included. Eligible studies either reported an association between symptoms and disease progression or used CLL/SLL-validated PRO instruments assessing symptoms or clinically relevant events.

Results: A total of 3510 unique publications were identified, of which 3420 were excluded during title and abstract screening. Of the 90 publications screened in full, 40 met at least one of the inclusion criteria; an additional conference abstract was identified through hand searching. Two publications explicitly assessed the relationship between a CLL/SLL PRO measure and disease progression as part of randomized controlled trials. The first publication reported global health status and fatigue before and after disease progression among 428 patients randomized to chlorambucil or chlorambucil with ofatumumab who had at least one PRO measurement. No changes were observed at progression compared with the pre-progression assessment in either arm. The second publication reported a post-hoc analysis among the 560 patients with relapsed/refractory CLL/SLL with at least one evaluable PRO who were randomized to zanubrutinib or ibrutinib. Results demonstrated that longitudinal deterioration in patient-reported fatigue, insomnia, and nausea/vomiting was significantly associated with increased risk of disease progression, irrespective of treatment received. While pain deterioration (worsening of pain) was associated with increased risk of disease progression, the association did not reach statistical significance. The remaining 39 publications reported on 88 distinct PROs assessing 38 distinct symptoms or domains. The most frequently reported symptoms and domains included fatigue, physical functioning, pain, gastrointestinal symptoms, emotional and social functioning, and overall symptom burden. None of these 39 publications explored an association between symptoms and progressive disease.

Conclusions: Evidence linking patient-reported symptoms with disease progression in CLL/SLL remains limited. These findings highlight the need for further research and consensus-building to develop a symptomatic progression composite endpoint that could support future clinical trials and HTA decision-making. ©EHA2026.

P037

Subsequent Therapies and Time to Second Progression-free Survival Events in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Previously Treated with Zanubrutinib or Bendamustine-rituximab

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Topic: Real-world

Background: Cohort 1 of the phase 3 SEQUOIA trial assessed zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor (BTKi), compared with bendamustine-rituximab (BR) in treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL/SLL) without del(17p). Zanubrutinib previously demonstrated sustained superiority in progression-free survival (PFS) and time to next treatment (TTNT) vs BR. However, evidence regarding outcomes on subsequent therapies after progressive disease (PD) on zanubrutinib remains limited. Here, we present results on follow-up therapies after zanubrutinib, including second progression-free survival events (PFS2).

Material and Methods: Patients without del(17p) were randomized to receive continuous zanubrutinib or six cycles of BR. Patients who received BR could crossover to receive zanubrutinib after PD. All patients were followed post-PD for details on any subsequent anti-CLL treatments. This analysis evaluated PFS, TTNT, TTNT or death (TTNT-D) and PFS2. P-values are descriptive.

Results: In total 479 patients were randomized; 241 to zanubrutinib and 238 to BR. Baseline demographics and disease characteristics were well balanced between the arms. As of 31 October 2025, median follow-up was 78.7 months (range, 0.0-96.0). Sustained PFS superiority with zanubrutinib vs BR was observed (HR, 0.28; 95% CI, 0.21-0.38; P<.0001) with 78-month PFS estimates of 70.9% (95% CI, 64.2-76.6) for zanubrutinib and 28.6% (95% CI, 21.7-35.8) for BR. After adjustment for COVID, 78-month PFS estimates were 73.7% (95% CI, 67.0-79.3) for zanubrutinib and 29.0% (95% CI, 22.1-36.3) for BR. Overall, 211/241 (87.6%) of patients treated with zanubrutinib had not received subsequent therapy and 34 patients had died without subsequent therapy. TTNT and TTNT-D favored zanubrutinib over BR (HR, 0.23 [95% CI, 0.15- 0.35; P<.0001] and 0.37 [0.27-0.50; P<.0001], respectively). Overall, 24/241 (10.0%) zanubrutinib patients and 82/238 (34.5%) BR patients had PD after study treatment and received subsequent therapy. Of the 24 zanubrutinib patients receiving subsequent therapy after PD, 13 (54.2%) received B-cell lymphoma 2 inhibitor (BCL2i)-based regimens, 8 (33.3%) received chemoimmunotherapy (CIT) (including anti-CD20 antibody monotherapy), and 3 (12.5%) received BTKi. Of the 82 BR patients receiving subsequent therapy after PD, 77 (93.9%)

received BTKi (including 71 crossover patients), 3 (3.7%) received BCL2i-based regimens and 2 (2.4%) received CIT. Median time from PD following first therapy to initiation of next therapy was 2.1 months for zanubrutinib (range 0-25.7) and 7.4 months (0.3-48.0) for BR. Zanubrutinib patients who had PD and received subsequent BCL2i-based therapy had a median follow-up of 33.5 months from initiation of next line therapy. Among these patients, 10 remain alive and without PD, two had died, and one had PD. Overall, PFS2 significantly favored zanubrutinib over BR (HR, 0.66; 95% CI, 0.45-0.98; $P < .05$) with 78-month PFS2 estimates of 81.3% (95% CI, 75.6-85.8) vs 73.8% (67.2-79.3), respectively.

Conclusions: PFS2 remained superior with zanubrutinib despite broad use of novel subsequent therapy (including crossover) in BR patients. Importantly, BCL2i-based salvage after initial zanubrutinib achieved high PFS rates at almost 3 years of follow-up. Together, these findings support that initial zanubrutinib provides durable benefit while preserving sensitivity to effective subsequent therapy. ©EHA2026.

P038

Treatment-Characteristic Preferences Among Individuals with Chronic Lymphocytic Leukemia and Hematologists: A Qualitative Study in Europe

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Topic: Real-world

Background: Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in adults. Novel targeted therapies, including Bruton tyrosine kinase (BTK) inhibitors (acalabrutinib, ibrutinib, and zanubrutinib) and B-cell lymphoma 2 inhibitors (venetoclax) have substantially improved outcomes for patients with CLL. Although treatment choice is often personalized based on disease characteristics, genetic markers and patient fitness, other treatment characteristics, such as side effect profile or treatment duration, may affect patient preference. This study explored the most and least relevant treatment characteristics for treatment selection among patients with CLL and hematologists treating CLL in Europe.

Material and Methods: Qualitative interviews were conducted with independently recruited patients with CLL and hematologists with experience treating CLL in the United Kingdom, Ireland, Germany, France, Italy, and Spain. Patients were required to be currently taking a continuous BTK inhibitor (acalabrutinib, ibrutinib, or zanubrutinib for ≥6 months). Eligible participants completed a background questionnaire followed by a 60-minute qualitative interview. Interviews followed semi-structured guides that included open-ended questions on treatment experiences as well as a ranking exercise on the characteristics that were most and least relevant to treatment choice.

Results: A total of 33 patients and 14 hematologists completed the ranking exercise. When patients ranked treatment characteristics from most to least relevant when choosing a treatment for CLL, ‘effectiveness and relief of symptoms’ was ranked first: “First and foremost, a therapy must be effective – that is fundamental. If a treatment is administered, it should lead to a reduction in the signs of the disease”. ‘Side effects’ and ‘impact on quality of life’ were tied as the second most relevant treatment characteristics for patients. ‘Duration of therapy’ and ‘dose frequency’ were ranked as least relevant for patients: “...[duration of therapy] doesn’t matter so much to me because I don’t care...whatever is more effective for me, if I have to take it continuously, I take it, and if I have to do it another way, I do it”. Hematologists also ranked ‘effectiveness and relief of symptoms’ as the most relevant treatment characteristic: “It is really important for the patient – especially if they have symptoms – that the disease is treated first, and therefore effectiveness with alleviation of symptoms comes first”. ‘Side effects’ and ‘impact on quality of life’ were ranked second and third, respectively. Some hematologists tied these characteristics to the effectiveness of the treatment: “...[effectiveness and relief of symptoms] impacts on daily activities [and] quality of life. I don’t really think you can completely divorce those and call them separate characteristics because I think if patients’ symptoms are better, they’re able to do more and their quality of life improves”. Unlike patients, hematologists ranked ‘duration of therapy’ higher than ‘mode of administration’ and ‘dose frequency’, which were ranked as least relevant.

Conclusions: Treatment effectiveness and symptom relief were ranked as the most relevant characteristic when choosing a CLL treatment from both the patient and hematologist perspective.

These findings highlight the importance of communication regarding patient preferences in treatment choice to facilitate shared decision-making. ©EHA2026.

P040

Accelerated chronic lymphocytic leukemia (aCLL) in the targeted therapy era: clinical, genomic and imaging correlations

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Topic: Real-world

Patients with accelerated chronic lymphocytic leukemia (aCLL) share some clinicopathological features of those with Richter transformation (RT), and yet patients with aCLL may respond to targeted therapy whilst those with RT are generally refractory.

To evaluate the clinical course of aCLL in the era of targeted therapy and to identify supportive diagnostic markers, we retrospectively studied 270 consecutive patients diagnosed by tissue biopsy as CLL (57%), aCLL (17%), or RT (26%) between March 2010 and March 2026 at Hospital Clínic de Barcelona and Hospital Universitario de Salamanca. The biopsy was performed at any time during the follow-up of the disease. At the time of biopsy, we reviewed biochemical parameters, FISH, karyotype, next-generation sequencing, flow cytometry, blood smear, and FDG PET/CT data when available.

Between CLL and RT, aCLL showed intermediate values for high LDH levels (CLL=18%, aCLL=44%, RT=60%, $p<0.001$) and advanced Rai stage $\geq$ III (CLL=11%, aCLL=26%, RT=30%, $p=0.002$). The highest frequency of unmutated IGHV was observed in aCLL (CLL=63%, aCLL=86%, RT=72%, $p=0.01$). In addition, the frequency of del(17p)/TP53 mutations (CLL=14%, aCLL=41%, RT=49%, $p<0.001$), del(9p) (CLL=2%, aCLL=17%, RT=19%, $p=0.009$) and complex karyotype defined as ≥ 3 alterations (CLL=14%, aCLL=45%, RT=60%, $p<0.001$) were also more frequent in aCLL compared with CLL, but were slightly less prevalent than in RT.

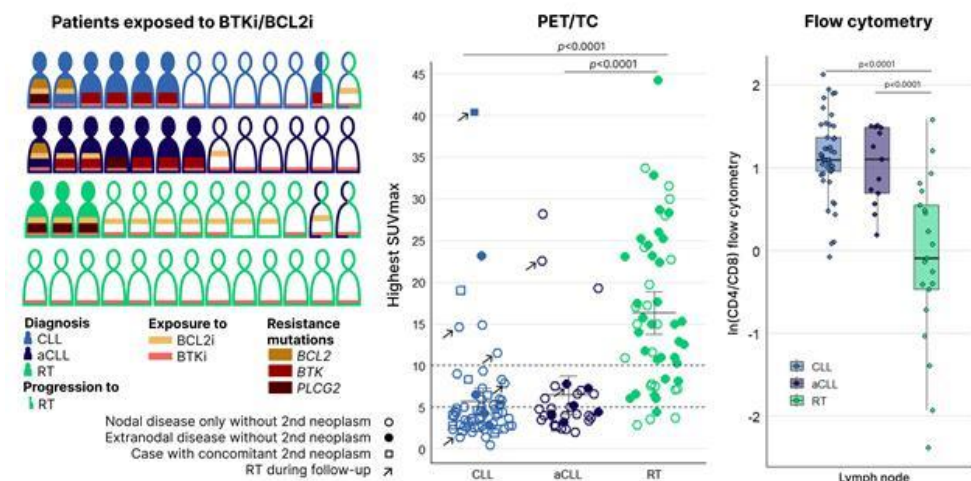
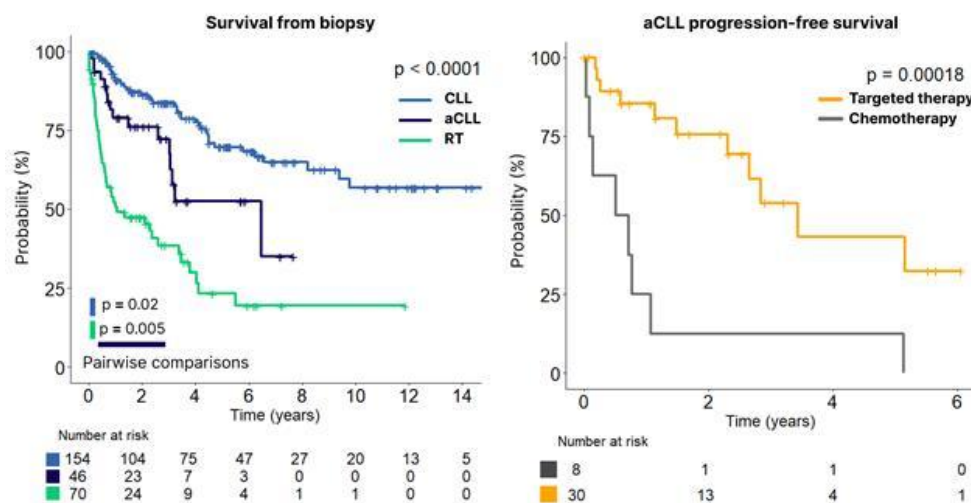
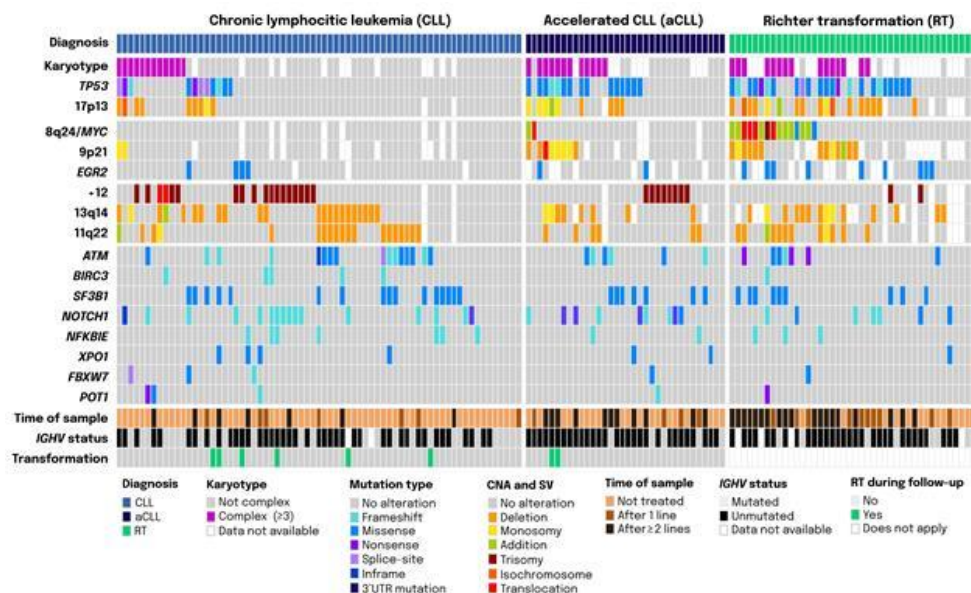
Notably, 8q24/MYC alterations were markedly less frequent in CLL/aCLL than in RT (CLL=0%, aCLL=5%, RT=36%, $p<0.001$), whereas BTK/PLCG2/BCL2 mutations were more frequent in CLL/aCLL (CLL=54%, aCLL=47%, RT=13%, $p=0.01$). Lymph node flow cytometry demonstrated a higher loge(CD4/CD8) ratio in CLL and aCLL compared with RT (median 1.1 in CLL, 1 in aCLL, -0.1 in RT, $p<0.001$), a difference not observed in peripheral blood. Peripheral blood smears showed a lower monocyte count in aCLL compared with RT (median 6 in CLL, 6 in aCLL, 15 in RT, $p=0.008$), with similar prolymphocyte percentages ($p=NS$).

FDG PET/CT analysis showed lower SUVmax in CLL/aCLL compared with RT (mean 6 in CLL, 7 in aCLL, 17 in RT, $p<0.001$), as well as reduced extranodal uptake (CLL=8%, aCLL=20%, RT=60%, $p<0.001$), enabling the definition of a combined diagnostic threshold for RT: SUVmax between 5 and 10 plus extranodal uptake or SUVmax ≥ 10 , with 84% sensitivity and 86% specificity.

After a median follow-up of 4.4 years, aCLL showed progression-free survival (PFS) and post-biopsy survival intermediate between CLL and RT (aCLL HR 2, 95% CI 1.1-3.7, RT HR 5, 95% CI 3.5-7.7; $p<0.001$). Compared with a historical cohort (Giné et al., 2010), post-biopsy survival significantly improved in CLL and aCLL but not in RT, likely reflecting the introduction of targeted therapies. This was further supported by improved PFS in aCLL patients treated with targeted agents versus chemotherapy (HR 0.2, 95% CI 0.1-0.5, $p<0.001$) in the present cohort.

In conclusion, aCLL generally responds favorably to target agents, making accurate distinction from RT essential. Beyond histopathology, key auxiliary diagnostic variables include BTK/BCL2 mutations, MYC/8q24 alterations, PET/CT SUVmax and extranodal involvement, as well as lymph node flow cytometry.

Figure/Table 1



Figure/Table 2

Characteristic at the time of biopsy	All patients (n=270)	Histological result of the biopsy			P value
		CLL (n=154, 57%)	aCLL (n=46, 17%)	RT (n=70, 26%)	
Age in years, median (range)	69 (29-94)	71 (29-93)	65 (42-86)	68 (40-94)	NS
Male sex, n (%)	171 (63)	103 (67)	26 (57)	42 (60)	NS
N° of previously lines of treatment, n (%)					
Untreated	178 (66)	130 (84)	26 (57)	22 (31)	<0.0001
1 line	39 (14)	14 (9)	7 (15)	18 (26)	
2 lines	23 (9)	5 (3)	5 (11)	13 (19)	
≥3 lines	30 (11)	5 (3)	8 (17)	17 (24)	
Previously received treatments, n (%)					
Continue BTKi base treatment	50 (54)	9 (36)	14 (70)	27 (56)	NS
Finite BCL2i base treatment	17 (18)	2 (8)	6 (30)	9 (19)	NS
Chemotherapy	73 (78)	23 (96)	16 (80)	34 (71)	NS
PI3Kδi	6 (6)	1 (4)	2 (10)	3 (6)	NS
Allogeneic HSCT	6 (6)	1 (4)	0	5 (10)	NS

P041

Expression Profile of miR-17-92 Cluster in Treatment-Naïve Chronic Lymphocytic Leukaemia and Association with IGHV Mutation Status and Cytogenetic Abnormalities: A Single-Centre Study from India

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Topic: Real-world

Background: The miR-17-92 cluster (oncomiR-1) is an oncogenic microRNA cluster that consists of miR-17, miR-18a, miR-19a, miR-19b, miR-20a, and miR-92a, and is frequently overexpressed in several cancers. They have been implicated in tumorigenesis and disease progression, but their specific roles in chronic lymphocytic leukaemia (CLL) remain poorly defined. This study evaluated miR-17-92 cluster expression in treatment-naïve CLL patients and its association with IGHV mutation status and cytogenetic abnormalities.

Methods: Peripheral blood samples were collected from 70 treatment-naïve CLL patients and 20 healthy controls. Expression levels of all miRNAs in the miR-17-92 cluster were quantified by real-time PCR, while IGHV mutation status was determined according to ERIC guidelines, and cytogenetic analysis was performed by fluorescent in situ hybridization.

Results: Descriptive analysis showed variation in median miRNA expression across modified Rai and Binet stages. The highest median expression of miR19a, miR92a, miR20a and miR18a in Intermediate-risk, and miR17a and miR19b in High-risk. Binet staging association with miR19a, miR92a, and miR19b showed the highest median expression in stage B; miR20a and miR18a in stage A; and miR17a in stage C, as shown in Figures 1 & 2.

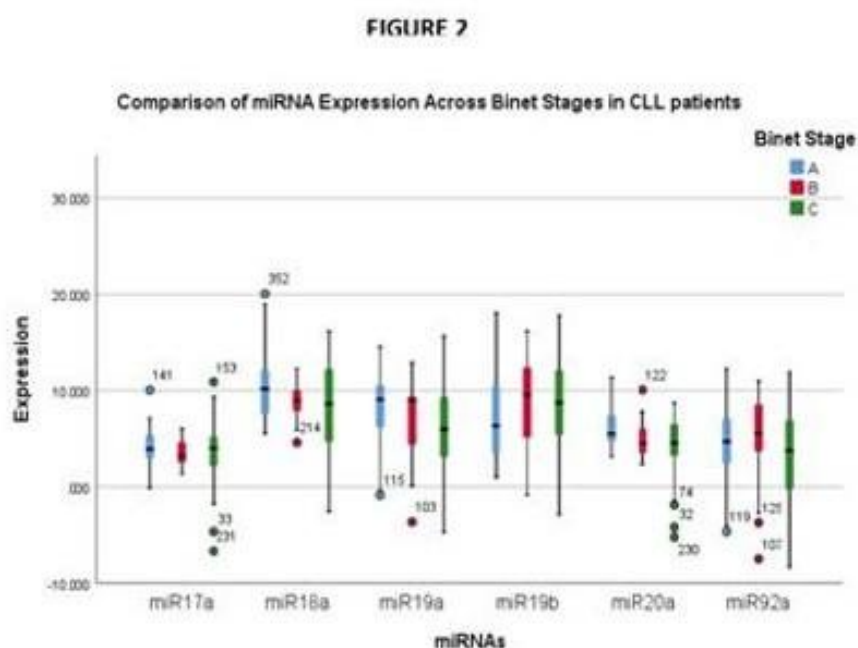
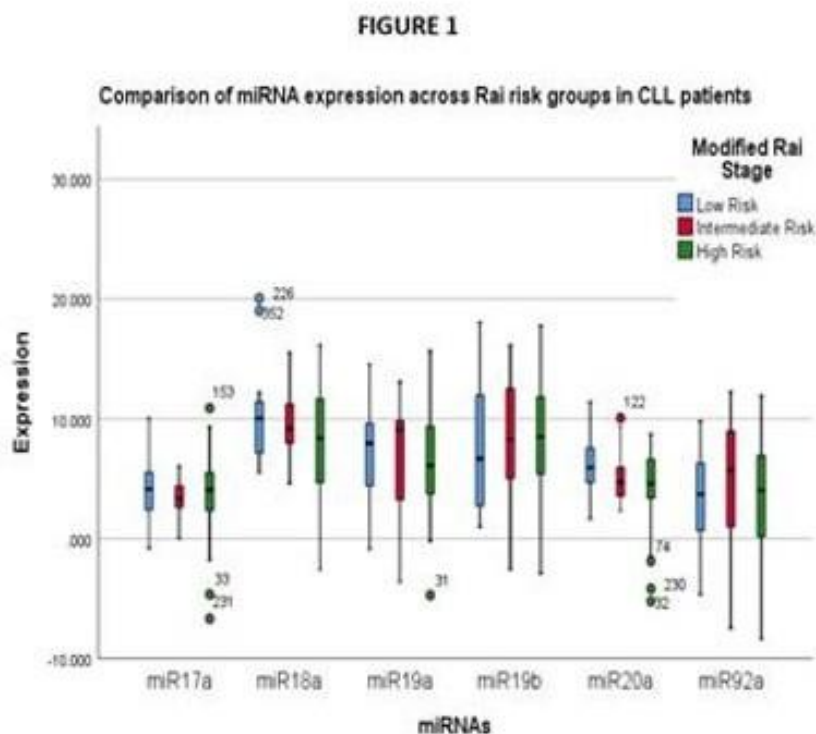
Based on the normality assessment, miR17a, miR19a, miR20a, and miR92a were analysed using the Mann–Whitney U test, while miR18a and miR19b were compared using the independent-samples t-test. All six miRNAs showed significantly higher expression in CLL patients than in healthy controls (all $p < 0.001$). Specifically, the Mann–Whitney U test demonstrated significant differences for miR19a ($U = 127.0$), miR20a ($U = 214.5$), miR17a ($U = 161.0$), and miR92a ($U = 192.0$) (all $p < 0.001$). The independent-samples t-test also revealed significantly higher expression of miR19b ($t(87.997) = 12.425$, $p < 0.001$) and miR18a ($t(85.723) = 19.299$, $p < 0.001$) in CLL patients compared with healthy controls, as shown in Figure 3.

No significant association was observed between the expression of any of the six miRNAs and IGHV mutation status (all $p > 0.05$). Likewise, no significant differences in miRNA expression were found according to the presence or absence of del13q, del11q, or del17p (all $p > 0.05$). However, trisomy 12 was significantly associated with increased expression of miR20a ($p = 0.006$) and miR17a ($p = 0.014$) as shown in Figure 4, whereas no significant association was observed with miR19a, miR92a, miR19b, or

miR18a expression. Both IGHV mutation status and FISH cytogenetic abnormalities were analysed using the Mann–Whitney U test.

Conclusion: This study demonstrated significant dysregulation of the miR-17-92 cluster in newly diagnosed CLL patients compared with healthy controls. No significant association was observed between miR-17-92 cluster expression and IGHV mutation status & Del(17p). However, miR-17 and miR-20a showed significant associations with trisomy 12.

Figure/Table 1



Figure/Table 2

FIGURE 3

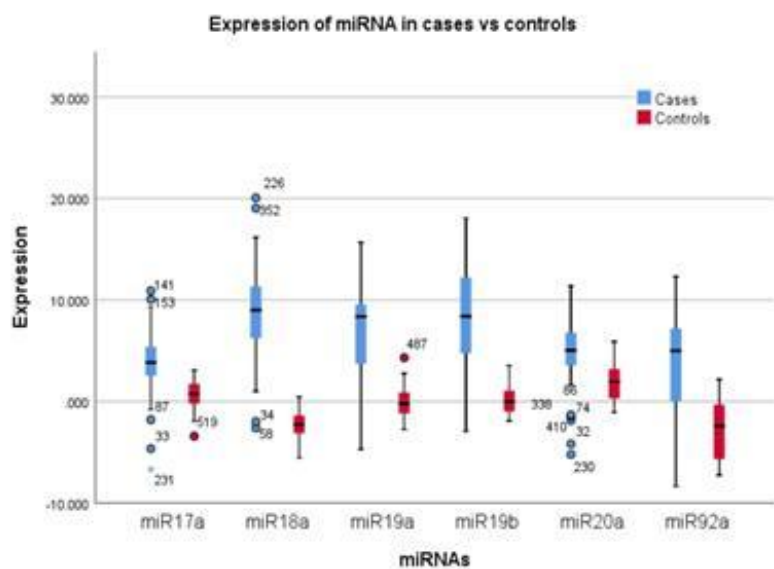
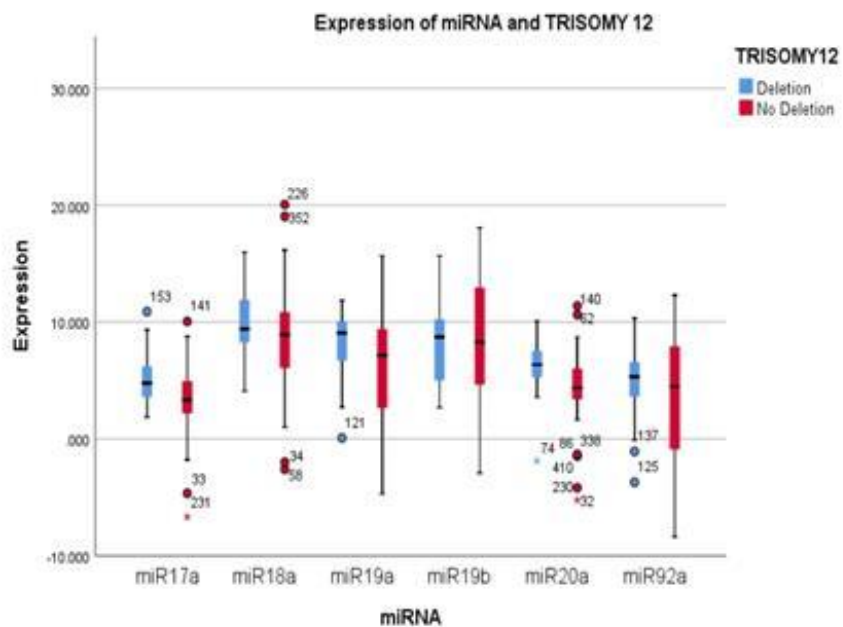


FIGURE 4



P042

IGHV Mutational Status and Gene Usage in Egyptian CLL/SLL Patients: A Three-Year Multicenter Study

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Topic: Real-world

Background: Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common adult leukemia in Western countries, characterized by monoclonal B-cell expansion with highly variable clinical behavior. Population-level data on IGHV gene usage and mutational frequencies from the Middle East and North Africa (MENA) region remain scarce, limiting our understanding of potential geographic and ethnic differences in disease biology.

Aims: To describe the IGHV mutational status distribution, specific gene and gene family usage, sequence germline homology characteristics, and demographic correlates in a large multicenter Egyptian CLL/SLL cohort across 3 years (2023–2026), and to identify trends over time in a rapidly expanding national molecular diagnostic network.

Methods: A retrospective observational analysis was performed on all patients referred for IGHV rearrangement testing in COLORS MEDICAL LABORATORY (CML) laboratory, Egypt. Written consent for IGHV testing was obtained from all patients. Peripheral blood samples from patients with confirmed CLL/SLL by flowcytometry scoring or Immunohistochemistry. Samples were processed using fragment analysis following PCR amplification with IGH Somatic Hypermutation Assay v2.0 for ABI (Invivoscribe, USA). Clonal IGH rearrangements were identified, sequenced, and aligned against the IMGT/V-QUEST database. Mutational status was defined as: Non-Mutated (U-CLL) $\geq 98\%$ germline homology; Mutated (M-CLL) $< 97.2\%$; Borderline 97.2–97.9%. Anonymized results were recorded across two discrete periods: 2023–2025 (720 entries) and 2026 (290 entries). Samples yielding more than one clonal peak (polyclonal) or failing amplification were excluded from the mutational analysis cohort.

Results: A total of 1,010 samples were submitted across both periods. After excluding invalid/polyclonal (n=115), unproductive (n=41), and pending/unresolved (n=58) cases, 796 cases with decisive IGHV mutational status were analyzed (2023–2025: n=567; 2026: n=229).

The patient cohort was predominantly male (59% male, 41% female in 2023–2025), with a mean age of 60.6 years (range 29–90). Disease presentation peaked in the 60–69-year age group (n=188 decisive cases, 33.1%), with a secondary peak in the 50–59-year group (n=145, 25.6%). Male predominance was more pronounced in U-CLL (60.9% male) than in M-CLL (53.3% male), which showed a near-equal sex distribution.

Mean sequence homology was 99.76% (U-CLL), 92.73% (M-CLL), and 97.66% (Borderline) in 2023–2025, and 99.83%, 93.06%, and 97.45% respectively in 2026, confirming consistent classification stringency across periods. The minimum homology observed in the M-CLL group was 81.2%.

IGHV1-69 was the most frequently rearranged gene in both periods (14.1% and 13.1% respectively), followed by IGHV4-34 (7.8%; 8.7%). IGHV3 was the dominant gene family in 2023–2025 (39.2%) and increased further in 2026 (42.8%), while IGHV4 family usage declined slightly (22.0% to 26.6% adjusted for the expanded cohort). Notably, IGHV3-23 and IGHV3-33 rose to third and fourth position in 2026 (6.1% each), genes previously linked with specific CLL stereotyped subsets.

Conclusions: This is, to our knowledge, the largest Egyptian CLL/SLL IGHV mutational dataset reported to date, encompassing 796 decisive results across a multicenter national network. U-CLL predominates in this population (68.5% overall), a ratio broadly consistent with published Northern European

registries. IGHV1-69 dominance in both periods aligns with its global recognition as the most common CLL-associated gene and its established association with adverse outcomes.

P043

Richter Transformation: Past and Present - A Single-Center 25-Years Experience

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Topic: Real-world

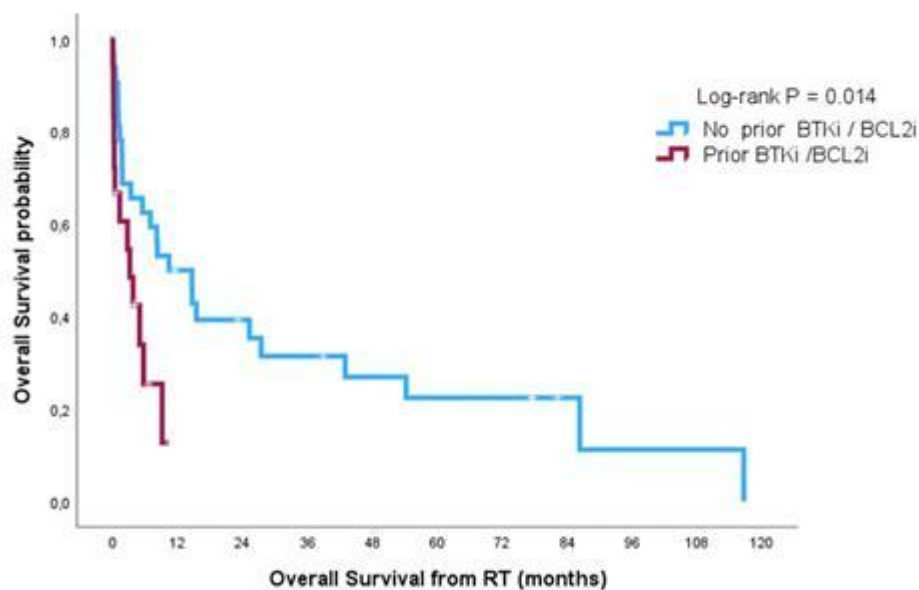
Background: Richter transformation (RT) is the clonal evolution of chronic lymphocytic leukemia (CLL) into an aggressive lymphoma—most commonly diffuse large B cell lymphoma (DLBCL) or, less often, Hodgkin lymphoma (HL)—and remains associated with poor survival.

Material and methods: We retrospectively analyzed 960 consecutive CLL patients followed at our center between 2000 and 2024. Sixty patients developed RT; histologic confirmation was available in 50. We assessed clinical features, treatment patterns, outcomes, and prognostic factors.

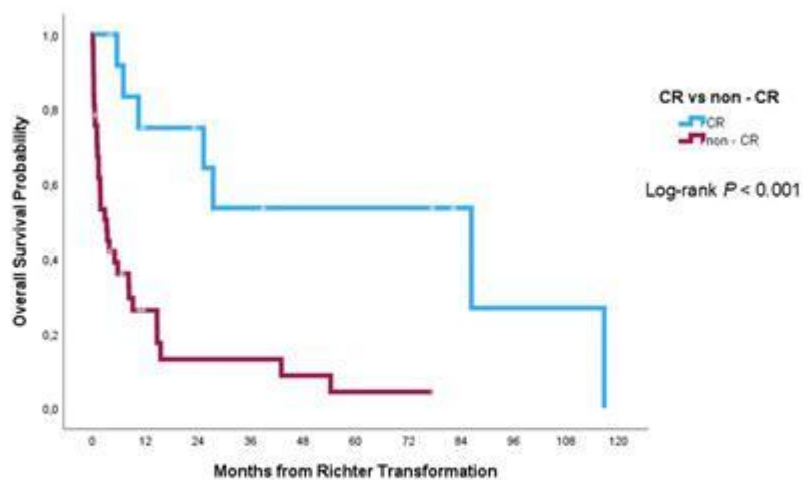
Results: Median age was 62.4 years at CLL diagnosis and 69.4 years at RT. Median time from CLL diagnosis to first CLL treatment was 12.4 months. Three groups of RT were identified: a) RT after watch and wait, b) RT after prior CLL therapy, and c) de novo RT (concurrent CLL and RT). Median time to RT was 90.9 months and was shorter in watch and wait versus previously treated patients (30.7 vs 114.5 months, $p < 0.001$) and in SLL versus CLL/atypical CLL (16.7 vs 95.3 months, $p = 0.014$). Histology was aggressive B cell lymphoma in 80% (DLBCL/high grade 74%, Burkitt 6%) and HL in 14%. Bone marrow involvement occurred in 35% (14/40) of aggressive B cell cases; hypercalcemia in 29%. Among 44 previously treated CLL patients, 22 had received BTK inhibitors (BTKi) and/or BCL2 inhibitors (BCL2i). First line RT therapy for aggressive B cell lymphoma was mainly R CHOP-based ($n = 33$). Subsequent treatments included platinum based chemotherapy ($n = 4$), BTKi ($n = 13$), venetoclax based combinations ($n = 3$), PD 1 inhibitors ($n = 4$), and bispecific antibodies ($n = 2$); one patient underwent allogeneic stem cell transplantation (died from infection) and one received CAR T cell therapy (ongoing CR). HL RT was treated with ABVD/AVD ($n = 3$) or nivolumab AVD ($n = 3$). Overall response rate to first line RT therapy was 37.3% (CR 27.5%, PR 9.8%), with higher CR rates in de novo RT ($p = 0.03$). Prior exposure to targeted agents (BTKi/BCL2i) was associated with lower CR rates ($p = 0.021$); only 2/10 patients exposed to both BTKi and BCL2i achieved CR. Patients with ≤ 2 prior CLL treatment lines had higher CR rates (33.3% vs 5.5%, $p = 0.044$) and superior OS (14.6 vs 1.27 months, $p < 0.001$). Median OS was 116.4 months from CLL diagnosis and 5.3 months from RT; 23.3% were alive at last follow up. Adverse prognostic factors for OS after RT included prior BTKi/BCL2i exposure (3.1 vs 10.4 months, $p = 0.014$, figure 1), ≥ 3 prior treatment lines, aggressive B cell histology, bone marrow involvement, and failure to achieve CR after first line RT therapy (strongest predictor, figure 2). Patients diagnosed from 2016 onwards showed a non significant trend towards improved OS after RT (14.6 vs 3.3 months, $p = 0.088$).

Conclusion: RT occurred in 6.2% of CLL patients and was associated with a dismal prognosis. RT arising after BTKi/BCL2i exposure and/or multiple prior lines represents a particularly high risk entity; achieving CR with first line RT therapy is the strongest favorable prognostic factor.

Figure/Table 1



Figure/Table 2



P044

Next-Generation Sequencing approach for Immunoglobulin Heavy Variable (IGHV) Somatic Hypermutation Analysis in Chronic Lymphocytic Leukemia-establishment and validation in Low-Resource Settings

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Topic: Real-world

Background: In Chronic Lymphocytic Leukemia (CLL), the mutational load of immunoglobulin genes of heavy chain (IGHV) is one of the most relevant prognostic markers. The current gold standard method for IGHV based mutational status utilizes BIOMED-2 protocol followed by Sanger sequencing, however, it does not provide insight into subclonal architecture and intraclonal diversity. Technological advances enabled the development of NGS based assays for assessment of IGHV-SHM in CLL, however, the associated cost limits its adaptation in low-resource countries. The objective of the study is to establish and validate a cost-effective NGS based protocol for detection of SHM status in CLL in low resource settings.

Methodology: The genomic DNA from peripheral blood of 64 CLL cases was amplified using IGHV leader primer set (Septenville et al, 2022). Paired end sequencing (2X300) was carried out on Miseq i100 Plus. To assess the assay specificity, that data was compared with sequences obtained using FR1 primers with Sanger sequencer. The clones, mutational status and stereotype subsets were analyzed using <https://app.vidjil.org/>, <http://www.imgt.org> (cut off $\leq 2\%$) and Arrest assign subset tool respectively. Productive rearrangements with clone size $\geq 5\%$ were analyzed in the current study.

Results: The median age of the analyzed cases was 60 years with 12 females and 52 males. 39/64 cases were in early stage (Rai stage 0-2) and 25/64 were in late stages (Rai stage 3-4). With a median time to first treatment of 9.5 months, 48 cases received treatment. With a median follow up of 56 months, 49 cases died and 5 were lost to follow up.

The NGS assay identified at least one productive clone in all the cases, however, in one case, the clone size was only 1.4%. 11% cases had double and 5% had triple productive rearrangements. Sanger sequencing had a failure rate in 12.5% cases. In double and triple productive cases, the clonal rearrangements were not identical in 5/7 cases and 3/3 cases respectively.

The NGS based assay resulted in productive clones in all sequencing failed cases; the clonotypes in these cases were same from both the techniques.

SHM analysis by NGS for single productive rearrangement cases revealed 23 cases as mutated and 22 cases as unmutated. Mutation status of 08/64 cases could not be compared due to non-availability of productive clones in these using Sanger. Comparison of NGS with Sanger yielded 96% similarity in IGHV identity. The mutation status by NGS vs sanger sequencing was discordant in 4/6 cases of double productive and 3/3 cases of triple productive rearrangements.

Both Sanger sequencing and NGS identified subset#1 in two cases, subset# 4 in one case, and subset#202 in one case. In addition, NGS identified subset#8 in one patient, which was not detected by Sanger sequencing.

Discussion and Conclusion: NGS provides a comprehensive characterization of all clones enabling detailed analysis of the subclonal architecture of CLL and identification of subsets. NGS based assay shows improved performance in identification of productive clones as compared to Sanger because of longer sequence determination allowing more precise determination of the identity percentage.

P045

Population-based real-world analysis of CLL/SLL treatment and outcomes in Norway

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Topic: Real-world

Background: The treatment landscape for chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) evolved rapidly following the introduction of novel oral targeted therapies but no study has yet described these changes in Norway. Therefore, this study aimed to describe current patient characteristics and treatments in CLL and SLL in Norway.

Methods: This retrospective real-world study used data, extracted between January 1, 2008, and 31 December 2024, from the Norwegian Patient Registry (NPR), Prescribed Drug Registry, Cause of Death Registry, and Cancer Registry to describe patient characteristics, treatment patterns and survival outcomes; data for patients with an incident CLL/SLL diagnosis between 2014 and 2024 are reported here.

Results: Of the 7089 patients identified with at least one CLL or SLL diagnosis in the NPR, 2471 (34.9%) received first-line (1L) therapy, with 613 (8.6%) and 164 (2.3%) patients receiving second- (2L) and third-line (3L) therapy, respectively. Among the treated patients, 51.4% started 1L therapy ≥ 3 months after diagnosis, with a median (Q1, Q3) time of 3.5 (0.5, 26.3) months between diagnosis and 1L start. Median patient age at diagnosis among the treated patients was 70.3 (62.2, 76.9), 69.8 (62.0, 76.4) and 68.3 (60.7, 73.4) years for those starting 1L, 2L, and 3L therapy, respectively.. The proportion of patients with lymphadenopathy and Binet stage C increased from 23.8% to 32.9% and from 2.1% to 6.7%, respectively, between 1L and 3L. The most common 1L therapies were chemoimmunotherapy (CIT; 31.2%), anti-CD20 antibodies (21.6%) and chemotherapy (15.1%), and the most common 2L treatments were Bruton's tyrosine kinase inhibitors (BTKi; 24.1%), CIT (15.5%) and chemotherapy (11.1%), with other CLL/SLL-related therapy also prevalent (26.3%). For the subgroup of patients who initiated treatment in 2023–2024 (n=630), the most common 1L therapies were CIT (30.8%), anti-CD20 antibodies (28.3%), and BTKi (10.6%), and the most common 2L therapies (among 217 patients) were BTKi (28.1%), CIT (14.3%), and B-cell lymphoma 2 inhibitors + anti-CD20 antibodies (10.1%), with other CLL/SLL-related therapy also prevalent (25.3%) in the 2L. Median overall survival from the start of 1L, 2L, and 3L therapy was 8.2 (95% CI 7.7, not estimable), 4.8 (3.6, 6.0) and 2.8 (2.1, 5.8) years, respectively, and median time to next treatment or death at the time of starting 1L, 2L and 3L therapy was 4.3 (4.0, 4.7). 2.4 (2.0, 2.9) and 1.8 (1.0–3.2) years, respectively.

Conclusions: This data highlights increasing use of targeted therapies in Norwegian patients with CLL/SLL, with most treated patients only receiving one or two lines of therapy for CLL/SLL. CIT use remains prevalent, even in 2023–2024, which may reflect limited access due to reimbursement requirements in Norway.

P047

Molecular Testing in Chronic Lymphocytic Leukemia: Initial Findings in Indonesia

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Topic: Real-world

Background: Chronic lymphocytic leukaemia (CLL) is a clonal mature B-cell neoplasm characterised by lymphocytosis of B-cells with a distinct immunophenotype, generally more common in Western countries, with lower rates observed in Asian populations.¹ The lower rate of incidence is also observed in Indonesia, although CLL incidence may be underreported in Indonesia because of the indolent course of disease. The advent of next-generation sequencing (NGS) technologies, coupled with gene copy number analysis, has enabled exploration of the CLL genome, uncovering genetic lesions that recurrently target this leukemia.² Indonesia has started to set up molecular testing for CLL using NGS in 2025. This study aimed to describe the molecular profile of CLL in Indonesia.

Material and methods: This is a prospective study. The samples were recruited consecutively from all patients previously diagnosed with CLL who were referred for targeted NGS testing. NGS test was performed using SOPHiA DDM™ Community Clonality Solution CLL which combines an optimized next-generation sequencing (NGS) workflow and the analytics of the SOPHiA DDM™ Platform. The instrument used was Illumina MiSeq System. All data was analysed descriptively.

Results: 29 CLL patients were referred to Dharmais National Cancer Center Clinical Pathology Laboratory during the study period (July 2025-June 2026), 21 were male and 8 female. Of the 29 CLL patients, mutations were found in 21 patients. The most prevalent mutations were MYD88 (6/21), TP53 and BIRC3 (4/21), ATM (3/21), and NOTCH1 (2/21). MYD88 was found as single mutation in 5 patients. TP53 was found as single mutation in 2 patients. BIRC3 was the only gene affected in 4 patients, but 3 patients had 2 mutations each. Other mutations found were ATF1, SF3B1, CXCR4, POT1 and RB1.

IGHV was mutated in 15 patients, unmutated in 5 patients, not determined in 8 patients and discordant in 1 patient. 4 patients showed IGLV3-21 rearrangement; 3 with mutated IGHV and 1 with unmutated IGHV.

Conclusion: Five genes were most commonly mutated in CLL cases in our study, with MYD88 as the most prevalent. Our findings showed that the landscape of mutation in CLL cases in Indonesia may differ from other regions, while also emphasised the need for more precise diagnostics to differentiate between true CLL or other circulating CD5+ lymphomas such as lymphoplasmacytic lymphoma and mantle cell lymphomas.

P048

Predictors of Long Remissions in Patients with CLL: A Real-World Study Conducted By ERIC

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Topic: Real-world

Background: Chronic lymphocytic leukemia (CLL) has a highly variable clinical course: while some patients need multiple treatments, others achieve a durable response to first-line therapy (1L tx) and need no further intervention. The aim of this study is to describe (i) the clinicobiological characteristics and treatment patterns in an unselected patient population, (ii) the characteristics of a smaller subset of patients who remain treatment-free for more than 8 years and (iii) identify factors associated with long remissions.

Material and Methods: This secondary analysis utilized data from a retrospective observational cohort of adult consecutively treated patients with CLL who initiated 1L tx between November 2014 and December 2023. The data cutoff was February 2025. Univariable and multivariable analyses were performed using mixture cure models to identify factors associated with time to second-line treatment (2L tx) (event), simultaneously assessing both the risk [odds ratio (OR)] and the timing of the event [hazard ratio (HR)].

Results: Among 3,360 patients with CLL, median age was 65 [interquartile range (IQR): 58-73] years at diagnosis and 69 (IQR:62-76) years at first-line treatment; 63.1% were male. Unmutated IGHV genes were present in 56% (1463/2614), TP53 mutations in 13.5% (254/1880), and del(17p) in 12.3% (350/2471) prior to 1L tx. The overall response rate to 1L tx was 85% (CR 36.8%); transformation occurred in 5.1% and 26.7% had died after a median follow-up of 38 (IQR: 16-65) months from 1L tx.

1L tx consisted mainly of chemoimmunotherapy (CIT) (52.1%) [fludarabine-cyclophosphamide-rituximab: 596 (17.7%), bendamustine-rituximab: 443 (13.2%), chlorambucil-obinutuzumab: 238 (7.1%)], continuous targeted therapy (24.4%) [ibrutinib: 559 (16.7%), acalabrutinib: 207 (6.2%), and zanubrutinib: 18 (0.5%)] and time-limited targeted therapy (11.3%) [venetoclax- obinutuzumab: 199 (5.9%) and venetoclax-ibrutinib: 87 (2.6%)]. Overall, 31% of cases received 2L tx and that was mainly targeted-agents-based (704, 70.9%). Median TTNT-D was 49.9 (95% CI:48-52) months and median OS from first-line treatment was 115.7 (95% CI:99-not estimable) months.

In multivariable analysis, male sex, unmutated IGHV genes, TP53 aberrations and del(11q) predicted the need for a 2L tx [OR: 1.28 (95% CI:1.01-1.64), 3.89 (95% CI:3.01-5.04, 2.6 (95% CI:1.85-3.64), 2.05 (95% CI:1.4-3)] while older age (continuous variable) and TP53 aberrations were associated with a shorter time until 2L tx (HR 1.01, 95% CI: 1-1.02, HR 1.44, 95% CI:1.01-2.07), respectively).

Patients with at least 8 year-follow-up after 1L tx (n=90) and no need for 2L tx had lower frequencies of unmutated IGHV genes [36.4% (24/66) vs 56%], TP53 mutations [3.8% (2/52) vs 13.5%], del(17p) [4.3% (3/70) vs 12.3%], complex karyotype with ≥ 5 abnormalities [0% (0/36) vs 7.4% (78/1053)] and del(11q) [5.9% (4/68) vs 16.9% (379/2236)] compared to overall cohort. These patients were mainly treated with CIT (66, 73%).

Conclusions: Our study underscores that patients with mutated IGHV genes and without other adverse-prognosis biomarkers (i.e., TP53 aberrations, del(11q) and complex karyotype) are expected to achieve long-term remissions with most available therapies. Consequently, while targeted therapies remain the standard of care for these patients, treatment selection should prioritize regimens with the most favorable safety profiles.

P049

Real-world treatment patterns and outcomes in CLL/SLL in Denmark

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Topic: Real-world

Background: The novel oral targeted therapies have shifted the treatment landscape for chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL). However, population-based evidence on the extent of this change is lacking. We investigated the treatment landscape and outcomes for patients with CLL/SLL in a publicly funded health system in the Nordics; results for Denmark are reported here.

Methods: This retrospective real-world evidence study used healthcare data, extracted between January 1, 2008, and December 31, 2024, from the Danish National Patient Register (DNPR), National Prescription Register, and Cause of Death Register to describe patient characteristics and to assess CLL/SLL treatment patterns and survival outcomes. Findings for patients with an incident CLL/SLL diagnosis between January 1, 2014, and December 31, 2024, are reported here.

Results: Overall, 7137 patients with an incident diagnosis of CLL/SLL between 2014 and 2024 were identified. During the study period, 1847 (25.9%) of 7137 patients received first-line (1L) treatment, 449 (6.3%) received second-line (2L) treatment and 98 (1.4%) received third-line (3L) treatment. The initial diagnosis was CLL in 5729 (80.3%) patients, SLL in 1350 (18.9%) patients and CLL + SLL in 58 (0.8%) patients. Median (Q1, Q3) age at diagnosis was 72.1 (64.3, 78.7) years and 4408 (61.8%) patients were male. The proportion of males increased with each treatment line, from 66.8% at the start of 1L treatment to 69.9% and 74.5% at 2L and 3L, respectively. Relative to patients who received treatment, patients who did not receive treatment during the study period were older at diagnosis (median age 72.7 [64.9, 79.2] vs 70.0 [62.4, 76.4] years) and a higher proportion were female (40.2% vs 33.3%) and had CLL as their initial diagnosis (81.9% vs 75.8%). Among treated patients, 71% waited ≥ 3 months before starting 1L treatment, with a median time from diagnosis to 1L start of 15.9 (1.9, 40.4) months. The most common 1L treatments were chemotherapy (35.1%), anti-CD20 antibodies (10.3%) and Bruton's tyrosine kinase inhibitors (BTKi) (9.9%), with other CLL/SLL-related medications also commonly used (15.8%); for 2L, the most common treatments were: BTKi (22.3%), B-cell lymphoma 2 inhibitors (BCL2i) (19.6%) and BCL2i + anti-CD20 (8.9%) antibodies. Among patients initiating 1L treatment in 2023 or 2024 (n=466), the most common treatment types were anti-CD20 (20.2%), chemotherapy (19.5%) and BCL2i + anti CD20 (19.5%), and the most common 2L therapies initiated during the same two years (among 135 patients) were BCL2i + anti-CD 20 (24.4%), BTKi (18.5%) and anti-CD20 antibodies (17.8%). Median overall survival (years) for the main population from starting 1L, 2L, and 3L treatment was 9.1 (95% CI 7.9–not estimable [NE]), NE (5.6–NE), and 2.1 (1.4–NE), respectively. Median time (years) to next treatment or death from the start of 1L, 2L, and 3L treatment, was 4.1 (3.8–4.6), 3.8 (2.8–4.7), and 1.7 (1.3–4.2), respectively.

Conclusions: This study demonstrated that during the available follow-up period, most treated patients only received one or two lines of therapy for CLL/SLL, with data highlighting that targeted therapies are used frequently in the 2L.

P050

Molecular Genetic Alterations and Clinical Correlations in Chronic Lymphocytic Leukemia Patients from Indian Subcontinent

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Topic: Real-world

Background: Molecular and cytogenetic abnormalities significantly impact the course of chronic lymphocytic leukaemia (CLL), a disease characterized by substantial clinical and biological heterogeneity. Data from the Indian subcontinent remains limited. To investigate the molecular genetic profiling (Cytogenetic abnormalities such as del 13q, del 11q, trisomy 12, del 17p and molecular abnormalities such as IGHV, TP53, NOTCH1, MYD88, SF3B1, FBXW7, ATM) and its association with clinical and hematological characteristics in patients of CLL.

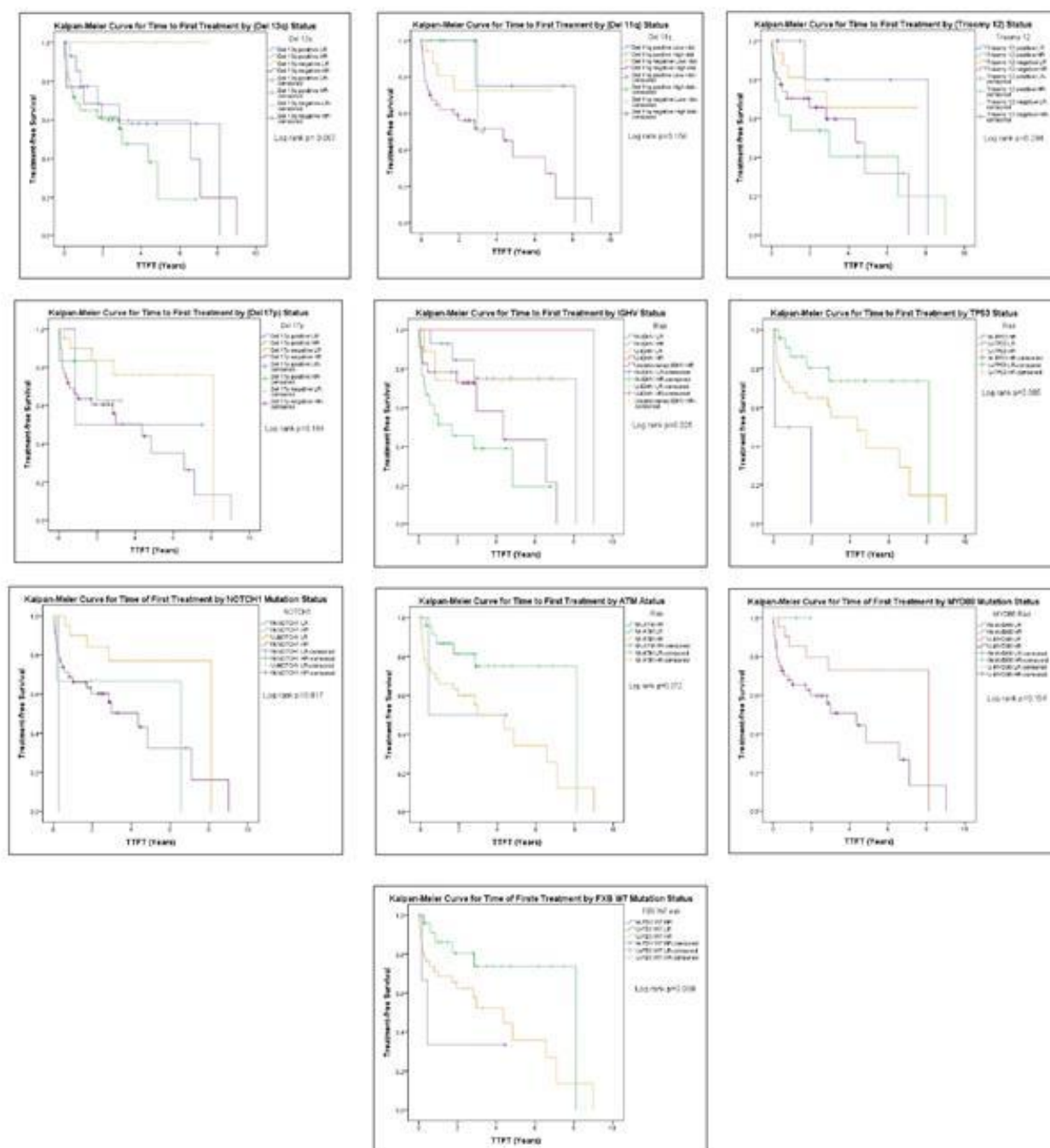
Methods: 70 newly diagnosed CLL patients treated at a North Indian tertiary care facility between 2017 and 2024 were included in this ambispective study, with follow-up continuing until 2025. Clinical, hematological, cytogenetic, and molecular baseline characteristics were examined. Fluorescence In Situ Hybridization (FISH) trisomy 12, del(13q), del(11q), and del(17p). Immunoglobulin heavy chain variable region (IGHV) mutation analysis and Next-Generation Sequencing (NGS) for TP53, NOTCH1, ATM, SF3B1, MYD88, and FBXW7 were performed at external reference laboratories. Cox proportional hazards regression and Kaplan-Meier analysis were used to evaluate time to first treatment (TTFT).

Results: Males predominated (male:female ratio 2.88:1), with a median age of 62 years at diagnosis. With 46% of patients in high-risk Rai stages and 44% in Binet stage C, the majority of patients had advanced disease. Del(13q) was the most common cytogenetic abnormality (69%), followed by trisomy 12 (30%), del(11q) (19%), and del(17p) (13%). 52.9% of patients had mutated IGHV. Mutations in TP53, NOTCH1, ATM, SF3B1, MYD88, and FBXW7 were found in 5.8%, 17.1%, 5.7%, 8.5%, 2.8%, and 4.3% of cases, respectively. 48 months was the median TTFT. Although not independently significant on Cox regression, unmutated IGHV was linked to significantly shorter TTFT on Kaplan-Meier analysis ($p=0.026$). Early treatment initiation was significantly correlated with TP53 mutation ($p=0.005$). On Cox regression, Del(13q) continued to be linked to shorter TTFT, whereas NOTCH1 and ATM displayed comparable patterns.

Conclusion: Patients with CLL in this Indian cohort presented at a comparatively younger age and with more advanced-stage disease than western populations. The most reliable indicator of the need for early treatment was found to be the presence of a TP53 mutation. These results underscore the importance of integrating clinical staging with molecular and cytogenetic profiling to enhance risk assessment and inform treatment decisions in the Indian population.

Special characters: Chronic Lymphocytic Leukaemia (CLL), Immunoglobulin heavy chain variable region (IGHV), Cytogenetic abnormalities, Molecular abnormalities, Time to First Treatment (TTFT).

Figure/Table 1



P051

Treatment patterns and patient outcomes in CLL/SLL in Finland: real-world evidence

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Topic: Real-world

Background: The novel oral targeted therapies have changed the treatment landscape for chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). This study described the treatment landscape and patient outcomes for CLL/SLL across Scandinavia, with results for Finland reported here.

Methods: This retrospective real-world study utilizing Finnish data, from January 1, 2010, through to December 31, 2024, from the Care Register for Health Care (Hilmo), electronic health records (EHR) of university hospitals, e-Prescription Registry, and Cause of Death Registry was conducted to describe patient demographics and characteristics and to assess treatment patterns and survival outcomes in CLL/SLL. Findings for patients with an incident CLL/SLL diagnosis between January 1, 2014, and December 31, 2024, are reported.

Results: Overall, 4806 patients were identified in Hilmo. Median (Q1, Q3) patient age at diagnosis was 71.5 (63.6, 78.5) years, there were 2979 (62.0%) males, and first diagnosis type was CLL in 4642 (96.6%) patients, SLL in 149 (3.1%) and CLL + SLL in 15 (0.3%). Of the 4806 patients, 1256 received first-line (1L) treatment during the study, with 293 and 71 receiving second-line (2L) and third-line (3L) treatment, respectively. Median patient age at diagnosis decreased with each treatment line, from 69.4 (61.9, 75.8) years for 1L treatment to 68.0 (60.8, 73.1) and 66.1 (59.4, 72.5) years for 2L and 3L, respectively. Among treated patients, 75.7% waited ≥ 3 months between diagnosis and 1L start; median time from diagnosis to 1L start was 17.9 (3.2, 42.9) months. There were some variation between regions in Finland in median time from diagnosis to 1L start, it being 24.0 (2.7, 44.7) months for Western Finland (n= 223), 15.5 (3.0, 40.3) for Southern Finland (n=463), 17.7 (4.0, 44.1) for Eastern Finland (n=188), 17.7 (2.1, 42.4) for Northern Finland (n=160) and 20.5 (7.2, 50.8) for Inland Finland (n=221). Across Finland, the most common 1L treatments were chemoimmunotherapy (CIT) (20.3%), B-cell lymphoma 2 inhibitors (BCL2i) (15.9%), chlorambucil-based medication (15.0%) and Bruton's tyrosine kinase inhibitors (BTKi) (14.6%); the most common 2L treatments were BTKi (34.1%), BCL2i (15.4%) and CIT (11.3%). Patients who started 1L treatment in 2023 or 2024 (n=354) most commonly received BCL2i (37.9%), BTKi (22.0%), or BCL2i + anti-CD20 medication (19.2%). In the same two years, the most common 2L treatments (among 96 patients) were BTKi (47.9%), BCL2i (18.8), and BCL2i + anti-CD20 (10.4%). Median overall survival (OS) from diagnosis was 10.4 years (95% CI 9.6–not estimable [NE]), while median OS (years) from initiation of 1L, 2L, and 3L treatment was 6.9 (6.3–9.0), 5.3 (3.9–NE), and 4.3 (1.7–NE) years, respectively. Median time to next treatment or death was 3.5 years (3.3–3.9) from 1L start, 2.9 years (2.4–3.9) from 2L start, and 1.9 years (1.3–4.1) from 3L start.

Conclusions: This study highlights the changing CLL/SLL treatment landscape in Finland, with increased use of targeted treatments in recent years, and suggests regional variation in time to treatment start.

P052

Distinct Toxicity Profiles but Comparable Severe Adverse Events with Venetoclax-Based Regimens and Second-Generation BTK Inhibitors in Older Patients with Chronic Lymphocytic Leukaemia: A Real-World Cohort Study

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Topic: Real-world

Background: Chronic lymphocytic leukaemia (CLL) predominantly affects older adults, in whom severe, treatment-limiting toxicity matters as much as efficacy. Two strategies with equal efficacy but distinct toxicities are available: continuous second-generation Bruton tyrosine kinase inhibitors (BTKi) and fixed-duration venetoclax-based regimens. Older patients are underrepresented in clinical trials, and real-world data have rarely assessed toxicity by treatment line or compared the strategies directly. The primary objective was to compare adverse events of special interest (AESI) between these two

treatment pathways; secondary objectives included grade 1–2 adverse events (AEs) and event-free survival (EFS).

Methods: This retrospective, multicentre cohort study enrolled patients aged ≥ 65 years who initiated venetoclax-based therapy or a second-generation BTKi (acalabrutinib or zanubrutinib) between 2019 and 2025. AESI were predefined as grade 3–5 infections, grade 3–5 cardiovascular events and grade 3–5 bleeding. All AEs were graded according to CTCAE v5.0 and compared using Fisher's exact test with Benjamini–Hochberg correction (q value), and stratified by treatment setting (treatment-naïve [TN] vs relapsed/refractory [R/R]). EFS, defined as the time from treatment initiation to death from any cause, disease progression, or grade 3–5 infection, whichever occurred first, was estimated using the Kaplan–Meier method and compared using log-rank tests and Cox proportional-hazards models, before and after inverse-probability-of-treatment weighting (IPTW).

Results: Of 715 patients, 386 received venetoclax-based therapy and 329 a second-generation BTKi (median age 73 and 74 years, respectively). Among haematological toxicities, grade 3–4 neutropenia was markedly more frequent with venetoclax in both settings (TN 52.8% vs 6.1%, OR 17.06; R/R 52.0% vs 9.8%, OR 9.86; both $q < 0.001$). Grade 3–4 thrombocytopenia was more frequent with venetoclax in the first line only (TN 13.5% vs 2.5%, OR 5.96, $q = 0.001$). Grade 3–4 anaemia did not differ between strategies in either line (TN 8.0% vs 8.6%, $q = 1.000$; R/R 14.3% vs 11.4%, $q = 0.853$). AESI were comparable between treatment strategies in both lines of therapy: grade 3–5 infections (TN 11.7% vs 10.2%; R/R 26.0% vs 18.9%), grade 3–5 cardiovascular events (TN 3.7% vs 2.5%; R/R 2.7% vs 3.8%) and grade 3–5 bleeding (TN 1.2% vs 3.6%; R/R 0% vs 1.5%) showed no significant differences (all $q \geq 0.4$) (Table 1). Among grade 1–2 AEs, infections were more frequent with venetoclax in the first line (41.1% vs 22.3%, OR 2.42, $q = 0.002$), whereas low-grade bleeding was more frequent with BTKi in both lines (TN 6.1% vs 0%, $q = 0.006$; R/R 9.8% vs 0.4%, OR 0.04, $q < 0.001$). EFS was comparable before adjustment (log-rank $p = 0.14$) and modestly favoured BTKi after IPTW (weighted $n = 482$; $p = 0.016$; HR venetoclax vs BTKi 1.61) (Figure 1).

Conclusions: The AESI — grade 3–5 infections, grade 3–5 cardiovascular events and grade 3–5 bleeding — did not differ between venetoclax-based therapy and second-generation BTKi in either treatment line. We observed more frequent grade 3–4 neutropenia (in both TN and R/R) and thrombocytopenia (in TN) with venetoclax-based therapy. Low-grade infections were more frequent with venetoclax and low-grade bleeding with BTKi. EFS modestly favoured BTKi after IPTW.

Figure/Table 1

Table 1. Severe (grade ≥ 3) AEs, including AESI, by treatment strategy and treatment line

AEs (grade)	Venetoclax n (%)	BTKi n (%)	OR (95% CI)	q	Higher in
TN					
Neutropenia, grade 3–4	86 (52.8)	12 (6.1)	17.06 (8.67–36.37)	< 0.001	Ven-based
Thrombocytopenia, grade 3–4	22 (13.5)	5 (2.5)	5.96 (2.13–20.65)	0.001	Ven-based
Anaemia, grade 3–4	13 (8.0)	17 (8.6)	0.92 (0.40–2.08)	1.000	-
Infections, grade 3–5	19 (11.7)	20 (10.2)	1.17 (0.57–2.40)	1.000	-
Cardiovascular events, grade 3–5	6 (3.7)	5 (2.5)	1.47 (0.37–6.19)	0.874	-
Bleeding, grade 3–5	2 (1.2)	7 (3.6)	0.34 (0.03–1.81)	0.506	-
R/R					
Neutropenia, grade 3–4	116 (52.0)	13 (9.8)	9.86 (5.17–20.22)	< 0.001	Ven-based
Thrombocytopenia, grade 3–4	28 (12.6)	8 (6.1)	2.22 (0.95–5.83)	0.273	-
Anaemia, grade 3–4	32 (14.3)	15 (11.4)	1.31 (0.65–2.71)	0.853	-
Infections, grade 3–5	58 (26.0)	25 (18.9)	1.50 (0.86–2.67)	0.437	-
Cardiovascular events, grade 3–5	6 (2.7)	5 (3.8)	0.70 (0.17–2.97)	0.874	-
Bleeding, grade 3–5	0 (0.0)	2 (1.5)	NE	0.416	-

Bold q = significant (Benjamini–Hochberg); Abbreviations: AE, adverse event; AESI, adverse event of special interest; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; NE, not estimable; OR, odds ratio; q, Benjamini–Hochberg-adjusted p value; R/R, relapsed/refractory; TN, treatment-naïve; Ven-based, venetoclax-based.

Figure/Table 2

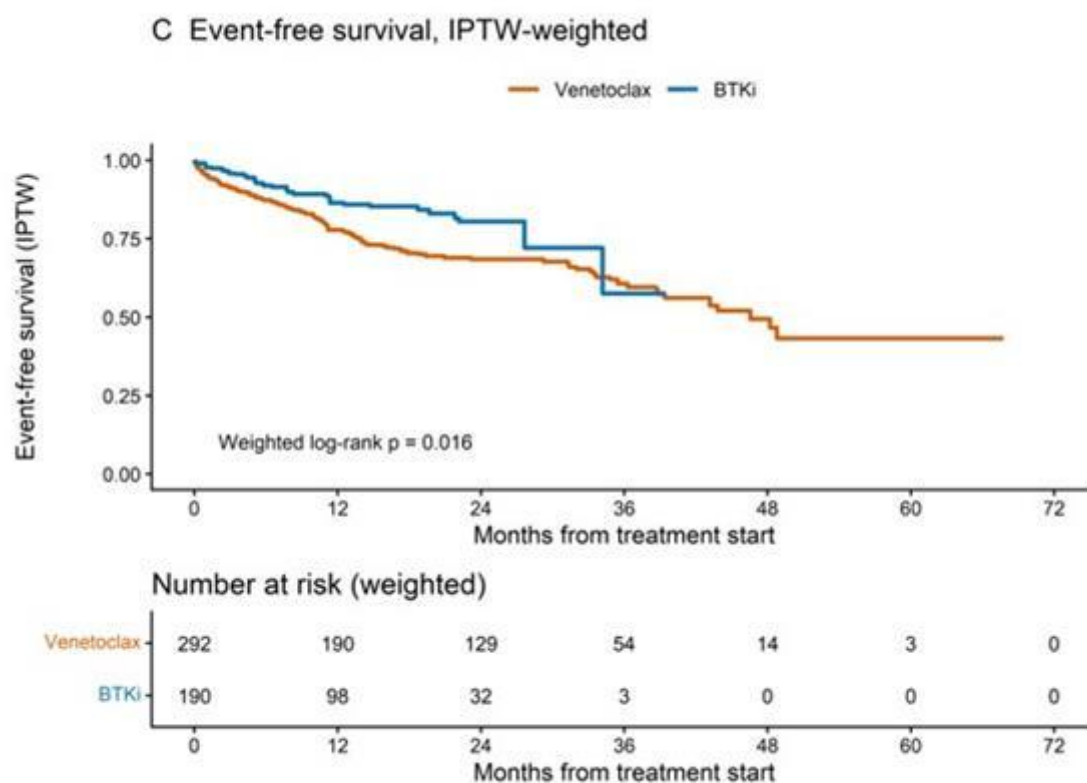


Figure 1. IPTW-weighted Kaplan–Meier curves for EFS in the pseudo-randomised population

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