# EHA Perspectives on Malignant Hematology

**Highlights from EHA2025 Congress held in Milan, Italy**
June 12 - 15, 2025

**European Hematology Association**

Supported by BeOne Medicines
and Eli Lilly and Company in the
form of an unrestricted grant


# Welcome

On behalf of the European Hematology Association (EHA), we are delighted to present one of the two EHA2025 Scientific Congress Reports, titled “EHA Perspectives on Malignant Hematology.”

These two Scientific Congress Reports have been developed as an initiative to provide our community with a concise overview of the most important works showcased at EHA2025. The new editions serve as an essential summary of scientific information and breaking news on the latest technological advancements in the field, relevant to clinicians, researchers, healthcare professionals, regulators, nurses, patients, payers, pharmaceutical representatives, and all stakeholders in hematology. Having introduced a new scientific content and formats at the EHA2025 Congress, the reports underscore the significance of the latest developments in the various fields of hematology.

This specific report focuses on malignant hematology including myeloid neoplasms, lymphoid malignancies, cellular and humoral immunotherapy, geriatric hematology, precision medicine, hematopoietic stem cells, artificial intelligence and other new frontiers and technologies in hematology, which are already driving advancements in clinical practice and patient care. Whether you attended the Annual Congress or not, and whether you are an EHA member or not, this is an important overview that you cannot afford to miss!

**Martin Dreyling**
EHA2025 Scientific Program Committee Chair

# Acknowledgements

EHA would like to extend a special thank you to the reviewers for the preparation of this report and their excellent guidance during EHA2025 in Milan, Italy.

- Dr. **Matteo Giovanni Della Porta**
  *Professor of Hematology at Humanitas University, and Head of Leukemia Unit – Cancer Center, Humanitas Research Hospital*
  *Milan, Italy*

- Dr. **Caroline Heckman**
  *Research Director at the Institute for Molecular Medicine Finland and University of Helsinki*
  *Helsinki, Finland*

- Dr. **Sirpa Leppä**
  *Professor, Department of Oncology, University of Helsinki and Helsinki University Hospital*
  *Helsinki, Finland*

- Dr. **Patricia Pérez-Galán**
  *Senior group leader at the Fundació de Recerca Clínic Barcelona-IDIBAPS*
  *Barcelona, Spain*

- Dr. **George Vassiliou**
  *Professor of Hematological Medicine at the University of Cambridge, Cancer Research UK Senior Fellow and Consultant Hematologist at Cambridge University Hospitals*
  *Cambridge, England*

- Dr. **Paresh Vyas**
  *Professor of Hematology, MRC Molecular Hematology Unit Weatherall Institute of Molecular Medicine, Radcliffe Department of Medicine University of Oxford and Oxford University Hospitals NHS Trust*
  *Oxford, England*

# Table of contents



# Disclaimer



# Expert videos

This scientific congress report was developed in collaboration with top experts in malignant hematology. While in Milan, some of the experts shared their personal highlights of the topics presented. Their videos can be viewed by clicking on the thumbnail at the beginning of the respective sections of the report.

# More from EHA

This scientific congress report not only highlights the top contributions to hematology within the topics listed above, but as of this year also highlights other EHA activities and assets related to these topics. At the end of each section, you will find icons which are linked to the related elements. Here is a list of the icons and what they represent:


Meeting


Education


Paper/Guideline


Podcast


Activity

# 01

# The genetic continuum of myeloid neoplasms: from CH to AML

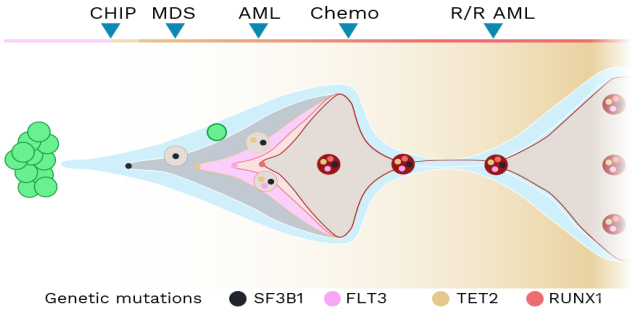
**Dr. George Vassiliou** shares his highlights on myeloid neoplasms from EHA2025

## Developing models to better understand pathophysiology and clonal evolution in MDS

Myelodysplastic syndromes (MDSs) are clonal blood disorders associated with abnormal blood cell production. They are characterized by peripheral blood cytopenia, increased apoptosis, and an increasing number of blasts in the bone marrow (BM). The 5-year survival rate of MDS is about 30%.[1]

Clonal hematopoiesis of indeterminate potential (CHIP) is a common age-associated phenomenon that can progress to MDS. Several mutations can cause MDS, including the MDS ring sideroblast (MDS-RS) subgroup, which is linked to *SF3B1* mutations.[2] Acquisition of additional mutations in subclones can eventually lead to acute myeloid leukemia (AML).

Clonal selection in progressive myeloid malignancy




R/R, relapsed and refractory.

To be able to intervene earlier and stop disease evolution through therapeutic means, researchers need reliable mouse models to study MDS. Using human mesenchymal stem cells (MSC) with MDS mutations in immunodeficient mice has a low success rate. However, Professor Bonnet's group developed a method using a gelatin-based scaffold with MSC and endothelial progenitor cells, with which they report MDS BM CD45+ engraftment rates ranging from 1 to 40%, and even 80% in some cases.[3] This model could help identify the factors that keep MDS cells alive, predict how well patients will respond to treatment, and study how the disease changes over time to improve treatment options for MDS.

## Exploring MDS/AML (MN) risks in *DDX41* pathogenic variant carriers

Not only is it important to understand the pathophysiology and clonal evolution of myeloid neoplasms (MNs) such as MDS, it is also of importance to understand patient predisposition and risk to such diseases to be able to identify patients and tailor treatments. For instance, it is estimated that 5–10% of all patients with MN have a genetic germline predisposition.[4] Germline *DDX41* mutations are the most frequent, accounting for 5% of MDS/AML cases. Patients with germline causal *DDX41* mutations tend to present at the same age as those with sporadic disease but have been shown to have longer survival compared to patients with MDS or AML and wild-type *DDX41*.[5]

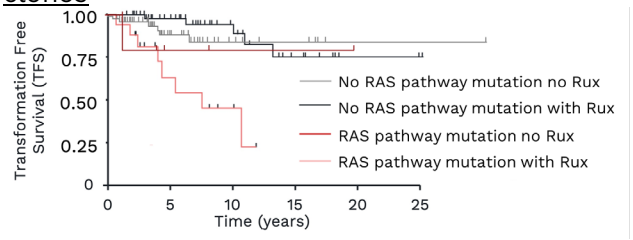
The heritable nature of this MN subpopulation needs to be considered when choosing hematopoietic stem cell transplant donors (who are often relatives). There is growing evidence on the risk of relapse when the donor carries a germline pathogenic variant in *DDX41*. A retrospective Japanese kin-cohort study found a low absolute risk before the age of 40, rising to

49% at 90 years of age. Moreover, the group noted patients with MDS and truncating variants of *DDx41* mutations rapidly progressed to AML.[6] For comparison, a UK Biobank study in the general population found the absolute MDS/AML risks were only 5.5% for men and 1.37% for women.[7] These findings justify monitoring recommendations for carriers. Therefore, Villy et al.[8] conducted a project spanning over 11 centers throughout France to identify and monitor families with *DDX41*-germline variants to estimate the cumulative risk of MDS/AML in carriers. The results of which are currently in review in the *European Journal of Human Genetics.* Further research in larger cohorts with a representative population is warranted.

## Clonal selection in MPN and its consequences

As with other MNs, myeloproliferative neoplasms (MPN) can also progress to secondary AML through clonal evolution. The process is driven by the acquisition of Janus kinase signal transducer and activator of transcription (*JAK*/*STAT*) activating mutations and clonal fitness.[9,10] Several mutations have been described as prognostic factors to predict overall survival (*K/NRAS,*[11] *NFE2*,[12] and *TP53*[13,14]), arterial thrombosis (*TET2* or *DNMT3A*) and resistance to treatment (*TET2, DNMT3A, ASXL1, EZH2, IDH1/2*); however, age is the only known risk factor for progression through clonal evolution. The expansion of certain clones is not driven solely by the acquisition of new mutations – the microenvironment also plays an important role, and is sometimes influenced by therapy. For example, the JAK inhibitor ruxolitinib drives the activation of *RAS* mutant clones by releasing them from oncogene-induced senescence. New data show[15], when comparing patients with no RAS pathway mutations not treated with ruxolitinib to patients with RAS pathway mutations not treated with ruxolitinib, no significant difference in transformation-free survival is seen (*P*=0.555). However, patients with RAS pathway mutations treated with ruxolitinib experienced a significantly shorter transformation-free survival than patients without RAS pathway mutations treated with ruxolitinib (*P*<0.0001). This suggests treatment exposure can drive clonal evolution in MPN, and the evaluation of clonal architecture may improve prognosis assessments and direct treatment choices in the future.

Ruxolitinib-driven expansion of *RAS*-mutated clones




## Antibody targeting of mutCALR in MPN

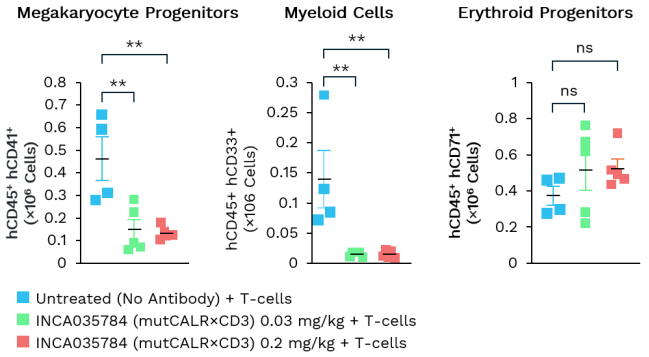
Mutant calreticulin (mutCALR) is the second most common driver mutation in MPN,[16, 17] generating a novel C-terminal tail which activates MPL/JAK2/STAT signaling at the plasma membrane, and promotes oncogenic proliferation. Wild-type CALR protein is not located on the cell surface due to the presence of an ER retention sequence (KDEL), which is lost in CALR-mut. Cell surface CALR is an MPN marker and can be selectively targeted. Moreover, a quarter of patients with essential thrombocythemia (ET) – a type of MPN – have CalR mutations, and most patients have one of two types (Type 1 and Type 2).[18-20] These patients often have a higher risk of transformation to myelofibrosis, but current therapies do not target driver mutations.[21] Two main strategies are currently being explored and were presented at EHA2025.[22]

First, targeting the oncogenic mut*CALR*/MPL with agents such as INCA33989 (a monoclonal antibody) to inhibit STAT signaling, prevent oncogenic proliferation, and induce apoptosis– thereby normalizing megakaryopoiesis, reducing disease-initiating cells, and preventing thrombocytosis and leukemic features. INCA33989 is currently undergoing clinical evaluation. In two Phase 1 dose-escalation studies (NCT05936359 – outside of the USA, NCT06034002 – within the USA only) 49 patients with ET were given INCA33989 doses ranging from 24 mg to 2500 mg. No dose-limiting toxicities were observed, but 3 cases of Gr≥3 lipase level increase were noted, which were classified as serious adverse events. Platelet counts normalized rapidly and sustainably in most patients, especially at doses ≥400 mg. Patients with Type 1 mutations responded at lower doses, but at higher doses (≥400 mg), patients with Type 2 mutations also responded well. Biomarker analysis showed a reduction of mutated stem/progenitor cells and megakaryocytes. Mascarenhas et al. conclude, "These findings support the potential of INCA33989 to provide durable hematologic responses and modify the disease of patients with mut*CALR* ET."[23]

Second, recruitment of T cells against mut*CALR* with JNJ-88549968 and INCA035784 (mutCALRxCD3 antibodies), to induce selective cytotoxicity, was also presented at EHA2025.[22, 24] Preclinical studies and *in vivo* mouse models have demonstrated tumor volume reduction and survival benefit associated with JNJ-88549968, prompting the initiation of a Phase 1 trial (NCT06150157).[22] The selectivity of INCA035784 for different forms of mutCALR was tested using a panel of cell lines that was developed using TF-1 parental cells as a base.[10] Adding in healthy donor T cells allowed testing of T-cell activation, T-cell-mediated toxicity, and proliferation. In the study, INCA035784 selectively bound to Type 1 and 2

mutCALR-expressing engineered TF-1 clones and activated T-cell-mediated functions. It did not bind to surface-exposed wild-type CALR nor induced non-specific cytokine secretion associated with cytokine-release syndrome in healthy donor peripheral blood mononuclear cells. Treatment in a xenograft model led to a reduction of myeloid cells (CD33+) and megakaryocytes (CD45+CD41+) in bone marrow. Psaila et al. conclude, "Overall, INCA035784 represents a promising approach for patients with MPN who lack curative treatment options."[24]

Efficacy of INCA035784 in an autologous myelofibrosis patient-derived xenograft model




## Novel ADC selectively delivers SMARCA2/4 degraders to MPN

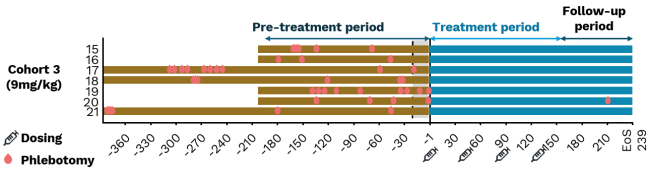
Mut*CALR* is not only a valuable target because of its role in signal transduction, but can also be used to selectively target cells with antibody-drug-conjugates (ADCs). Deregulated switch / sucrose non-fermentable (SWI/SNF) activity has been linked to AML, MDS, and MPN pathogenesis, and the SWI/SNF ATPases SMARCA2 and SMARCA4 are key therapeutic targets in MPN. A non-antagonizing, internalizing CALR antibody was identified and used as a basis for a new type of ADC that selectively internalizes in *CALR* mutant cells, but not healthy wild-type cells. The *CALR*-precision ADCs (pADCs) demonstrate selective SMARCA2/4 degradation and cytotoxicity in *CALR* mutant cells. The presence of soluble mutant CALR protein does not affect CALR pADC cytotoxicity, and thus does not seem to pose a risk to efficacy or safety. The CALR pADCs tested show a robust anti-tumor activity *in vivo* (mouse models) and were well tolerated, selectively targeting and eliminating mutant peripheral disease cells while sparing healthy ones. Similar findings were observed with a CDK9-degrading CALR pADC, demonstrating the broad potential of this modality across multiple payloads.[25]

## SANRECO, a Phase 1 study investigating divesiran in PV

Polycythemia Vera (PV) is marked by excessive production of red blood cells, iron deficiency, and often low hepcidin levels.[26] Divesiran is a novel GalNAc-conjugated siRNA targeting TMPRSS6, designed to increase hepcidin levels, promote iron redistribution, and restrict its availability for erythropoiesis in patients with PV. The Phase 1 results, presented by Kreyanskaya et al. at EHA2025, (N=21) suggest that treatment with divesiran reduces phlebotomy frequency during treatment and follow-up periods.[27]

Lower hematocrit and hemoglobin were seen across all dose levels, with dose-dependent increases in hepcidin and ferritin. The treatment was well-tolerated without dose-limiting toxicities. The most common treatment-emergent adverse events were injection-site reactions, anemia, and fatigue. An ongoing randomized, double-blind, Phase 1/2 study (NCT05499013) is currently evaluating the proportion of patients achieving hematocrit ≤45% without phlebotomies, along with improvement in PV-related symptoms.[27]

Phlebotomy rates before and under treatment in Cohort 3 (9 mg/kg dose)




New and emerging data presented at EHA2025 show that the understanding of molecular mechanisms in MPN not only continues grow but also facilitates the development of treatments – which aim to tackle malignancy in its early stages and in more targeted ways.

## More from EHA

Review your knowledge with our Campus course on “MDS, MPN, and AML: Unraveling Commonalities and Innovations” and get ready for the upcoming 2nd EHA SWG meeting on “MDS/MPN/AML: Commonalities and Differences” in April 2026 to advance your knowledge and dive deeper into the development of the novel therapeutic approaches. Need to unplug from your computer? Listen to our podcast exploring the genetics of progression from MDS to AML.

CAMPUS course on MDS, MPN, & AML: Unraveling Commonalities & Innovations

EHA SWG 2nd meeting on MDS/MPN/AML

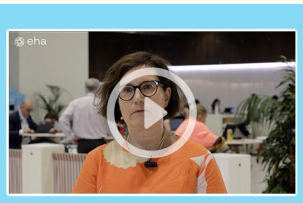
From MDS to AML: Genetics of Progression

## References


1. Zeidan AM, et al. Epidemiology of myelodysplastic syndromes: Why characterizing the beast is a prerequisite to taming it. *Blood*. 2019;34:1-15.
2. Mian SA, et al Spliceosome mutations exhibit specific associations with epigenetic modifiers and proto-oncogenes mutated in myelodysplastic syndrome. *Haematologica*. 2013;98(7):1058-1066.
3. Bonnet D. Pathophysiology and clonal evolution in MDS. Oral presentation p115-1 at EHA2025.
4. Khoury JD, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia*. 2022;36(7):1703-1719.
5. Sébert M et al. Germline DDX41 mutations define a significant entity within adult MDS/AML patients. *Blood.* 2019;134(17):1441-1444.
6. Makishima H, et al. Germ line DDX41 mutations define a unique subtype of myeloid neoplasms. *Blood*. 2023;141(5):534-549.
7. Cheloor Kovilakam S, et al. Prevalence and significance of DDX41 gene variants in the general population. *Blood.* 2023;142(14):1185-1192.
8. Villy MC. Myeloid neoplasms risks for germline DDX41 pathogenic variants carriers. Oral presentation S145 at EHA2025.
9. Jaiswal S. et al. Age-related Clonal Hematopoiesis Associated with Adverse Outcomes. *N Engl J Med*. 2014;371:2488-2498.
10. Genovese G. et al. Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence. *N Engl J Med*. 2014;371:2477-2487.
11. Santos FPS, et al. Prognostic impact of RAS-pathway mutations in patients with myelofibrosis. *Leukemia.* 2020;34(3):799-810.
12. Marcault C et al. Impact of NFE2 mutations on AML transformation and overall survival in patients with myeloproliferative neoplasms. *Blood.* 2021;138(21):2142-2148.
13. Gagelmann N et al. Impact of TP53 on outcome of patients with myelofibrosis undergoing hematopoietic stem cell transplantation. *Blood*. 2023;141(23):2901-2911.
14. Rolles B et al. TP53 mutations and Their Impact on Survival in Patients with Myeloproliferative Neoplasms. ASH 2023:3160.
15. Benajiba L. Clonal selection in MPN and its consequence. Oral presentation p266-1 at EHA2025.
16. Klampfl T, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med.* 2013;369(25):2379-2390.
17. Nangalia J, et al. Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. *N Engl J Med.* 2013;369(25):2391-2405.
18. Guglielmeli P et al. CALR mutation burden in essential thrombocythemia and disease outcome. *Blood*. 2024;143:1310-1314.
19. Klampfl T et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med*. 2013;369:2379-2390.
20. Nangalia J et al. Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. *N Engl J Med*. 2013;369:2391-2405.
21. Yacoub et al. Disease and Clinical Characteristics of Patients With a Clinical Diagnosis of Essential Thrombocythemia Enrolled in the MOST Study. *Clin Lymphoma Myeloma Leuk*. 2021;21:461-469.
22. Plo I. Antibody targeting of mutant CALR in MPN. Oral presentation p114-2 at EHA2025.
23. Mascarenhas J. INCA33989 is a novel, first in class, mutant calreticulin-specific monoclonal antibody that demonstrates safety and efficacy in patients with essential thrombocythemia (ET). Oral presentation LBA4002 at EHA2025.
24. Psaila B. INCA035784, a novel, equipotent T cell–redirecting antibody for patients with myeloproliferative neoplasms carrying different types of calreticulin mutations. Oral presentation S212 at EHA2025.
25. Fultang N. Discovery of first-in-class precision antibody drug conjugates targeting mutant calreticulin for the treatment of myeloproliferative neoplasms. Oral presentation S211 at EHA2025.
26. Ginzburg YZ, et al. Dysregulated iron metabolism in polycythemia vera: etiology and consequences. *Leukemia.* 2018;32:2015-2116.
27. Kremyanskaya M. SANRECO, an on-going Phase1/2 study evaluating divesiran, a novel GalNAc-conjugated siRNA, in patients with polycythemia vera. Oral presentation S224 at EHA2025.

# 02

# Monoclonal antibodies versus cellular immunotherapy - the next round



**Dr. Sirpa Leppä** shares her highlights on monoclonal antibodies & immunotherapy from EHA2025

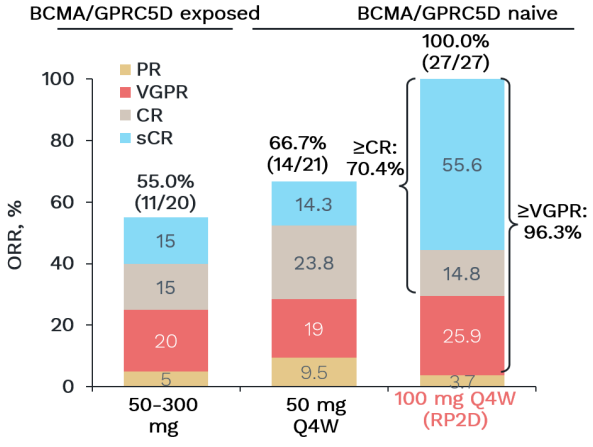
## Dual antigen targeting with bispecific antibodies in Multiple Myeloma

While bispecific antibodies, also known as T-cell engagers (TCE), have been a great step forward in hematological oncology, most patients eventually relapse and develop resistance. As with other treatment approaches, targeting multiple antigens offers a promising strategy to overcome resistance mechanisms.

At this year's EHA congress, the Phase 1 RedirecTT-1 trial was presented, which explores a dual TCE approach, combining talquetamab (αGPTC5D) and teclistamab (αBCMA). As monotherapy, each agent achieved overall response rates (ORRs) of ~40% in patients with triple-class exposed relapsed/refractory (R/R) multiple myeloma (MM) and extramedullary disease (EMD). EMD is associated with poor outcomes. The median overall survival (OS) in triple-class exposed patients (IMiD, proteasome inhibitors, αCD38) is only 7.2 months.[1] Preliminary data suggest that dual targeting leads to a higher ORR and deeper and more durable response, likely by mitigating antigen-related escape. In the second phase of the trial, an ORR of 78.9% and complete response (CR) rate of 54.4% were observed, with many responses continuing to deepen over time. The median progression-free survival (PFS) reached 15.4 months, and the 12-month OS rate was 74.5%. Regarding safety, cytokine release syndrome (CRS) Gr1-2 occurred in 77.8% of patients, usually during step-up dosing. Immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in 12.2%, mostly Gr1-2, with two cases of Gr3/4. Other frequent adverse events (AEs) included cytopenia and infections. Overall, the results suggest that the combination exceeds the efficacy of each individual drug without exacerbating AEs.

In contrast to the use of two separate antibodies, another presented ongoing phase 1 trial[2] evaluates JNJ-5322, a trispecific antibody with high affinity for BCMA and GPRC5D and low affinity for CD3.[3] The study aims to determine safety, the recommended Phase 2 dose (RP2D), and preliminary efficacy. The study population includes BCMA-exposed (17.7%), GPRC5D-exposed (3.4%), and BCMA/GPRC5D-naïve patients (80.3%). The RP2D was determined to be 5 mg in step-up dosing, followed by 100 mg once every 4 weeks (Q4W). In the BCMA/GPRC5D-exposed group receiving 50-300 mg, the ORR was 55% and CR rate was 30%. In BCMA/GPRC5D-naïve patients, the ORR and CR rates were 100% and 70.4%, respectively. At RP2D, 12-month PFS was 95%. With prophylactic tocilizumab, only 20% of patients experienced Gr1 CRS at RP2D.

Response rates in different patient collectives




VGPR, very good partial response; sCR, sustained CR.

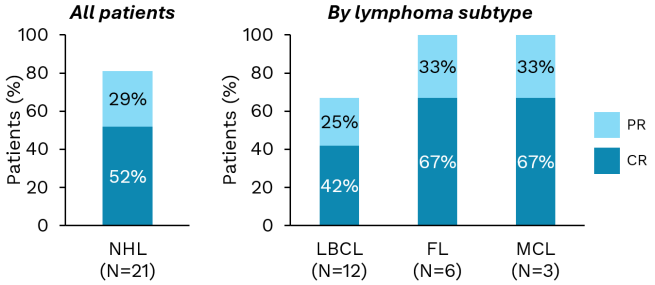
## The impact of CAR T in R/R B-ALL – challenges and novel advances

Tumor burden impacts the OS and toxicity of CAR T cell therapies, possibly due to lack of expansion in high-burden settings, or as a reflection of suboptimal infusion timing.[4-7] As discussed at this year's EHA congress, bridging to CAR T therapy is an important consideration,[8,9] but experience shows that intensive chemotherapy is unlikely to be beneficial and may increase infection rate. Despite cell persistence, relapse remains a challenge, particularly in patients at high risk of CD19 antigen loss and with high leukemic burden prior to therapy. For this patient group, stem cell transplantation (SCT) after CAR T therapy is an option. To address toxicity and relapse risk, autologous CAR T is being investigated in earlier treatment lines. In addition, novel platforms are being developed to extend therapeutic benefit, including strategies such as preloading CAR cells with a bispecific antibody and exploring natural killer (NK) CARs.[10]

## Armored CARs in lymphoma

Interleukin (IL)-18 is a known growth factor for T cells and could improve activity and proliferation of therapeutic T cell products. Indeed, a first-in-human trial of huCART19-IL18 cells in a single patient with follicular lymphoma and diffuse large B cell lymphoma (FL/DLBCL) achieved sustained CR at a microdose of 3 million cells.[11,12] Results from the subsequent Phase 1 clinical trial (NCT04684563) in B cell lymphoma patients with previous αCD19 CAR T cell therapy were presented at the congress and showed preliminary ORR of 80% at 3 months across all subtypes and a response rate of 100% in patients who had previously received a CD28-based CAR T cell product.[12,13] The study revealed several findings, including (preliminary) confirmation of the high efficacy of IL-18 CAR T cell therapies, but also indicated that the success of this CAR T cell therapy depends on the choice of the previous CAR type, i.e., 4-1BB versus CD28. A follow-on trial is currently underway (NCT05989204).

3-month response to huCART19-IL18

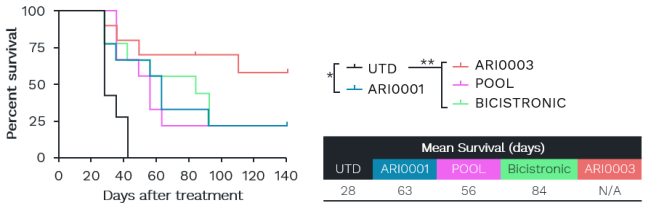



LBCL, large B cell lymphoma; NHL, non-Hodgkin lymphoma; PR, partial response.

## Next-generation CAR T in lymphoma: Dual specificity to counter tumor escape

CD19 CAR T resistance in lymphoma may result from low or heterogenous antigen density on lymphoma cells. BCMA, typically targeted in MM, also shows potential as an antigen in B cell lymphomas. At EHA2025, Dr. Sonia Guedan presented ARI-0003, a dual-targeting BCMA/CD19 CAR T product developed for the treatment of non-Hodgkin lymphoma (NHL).[14] It is created via co-transduction of two CAR vectors (CD19 and BCMA in a ~4:1 ratio), which resulted in enhanced T-cell proliferation, functionality, and anti-tumor efficacy, and prolonged survival in pre-clinical Burkitt lymphoma models. It outperformed CD19 CAR (ARI-0001) in pre-clinical lymphoma models and offers a promising approach for patients relapsing after CD19 CAR Tcell therapy. A first-in-human Phase 1 trial of ARI-0003 in patients with NHL is currently ongoing.

Survival of mice with Burkitt lymphoma




## T-cell engagers and CAR T cell therapy in AML

The success of allogeneic SCT – largely due to its graft-versus-leukemia effect – provides a strong rationale for the use of TCEs and CAR T cells in acute myeloid leukemia (AML).[15] Prof. Marion Subklewe provided an in-depth overview of this topic. To date, a total of 27 clinical trials on TCEs in AML have been conducted, primarily targeting lineage-restricted antigens (CD33, CD123, CLL1, FLT3), but also leukemia-associated antigens (CD70 and Wt1). While responses are observed, they are usually not sustained and on-target-off-leukemia toxicity remains a challenge.[16-25] TCEs are now being explored as part of combination treatments in both pre-clinical and clinical studies – for example in combination with venetoclax and azacitidine, which does not impair T-cell function.[26] Novel TCE targets in AML include CD38, csGRP78, and ILT3–CD3, and a leader sequence peptide derived from Cathepsin G/HLA-A02.01.[27-30] Other approaches are bridging to allogenic hematopoietic SCT,[31,32] or to augment TCE efficacy through targeted co-stimulation using antibody constructs.

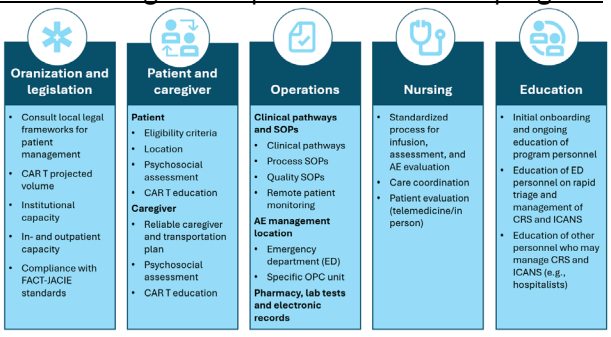
Many of the barriers limiting TCE effectiveness also hinder the broader success of CAR T cell therapy in AML, including intrinsic T-cell

dysfunction and the immunosuppressive tumor microenvironment (TME).[33] Further challenges involve crosstalk between CAR T cells and blasts in the AML niche and the release of pro-inflammatory cytokines, which may contribute to resistance. The rapidly progressive nature of AML also poses logistical issues for autologous manufacture. Compared to B cell acute lymphoblastic leukemia, which sees response rates of 80-90%, CAR T cell studies in AML only report disease responses of 30–50%. To overcome these obstacles, new strategies focus on armoring CAR T cells through cytokine secretion, improving bone-marrow homing ("self-driving" CARs), or limiting toxicity via on-off signaling. Notably, the CLEAR-AML study, investigating a CD371-targeting, IL-18-secreting CAR T cell product, has shown promising responses.[34]

## Outpatient CAR T therapy: There's no place like home

CRS and ICANS are common AEs in the days following CAR T cell infusion and can lead to readmission rates as high as 88%. However, clinical experience has shown that outpatient management can be both feasible and safe if early intervention strategies are in place to prevent and manage CRS, ICANS, and macrophage activation syndrome. During her presentation, Dr. Alexandra Martínez-Roca highlighted that the caregiver-patient dynamic is central for the success of the outpatient CAR T cell therapy. Caregivers play a critical role in outpatient monitoring and must be well-informed. As such, education for both patients and caregivers is essential to maintaining safety throughout the treatment journey. Importantly, not every patient is suited for the outpatient approach, and careful patient selection based on clinical, logistical, and psychosocial criteria is crucial.[35]

Establishing an outpatient CAR T cell program




## CAR T cell atlas may help unravel CAR T regulatory mechanisms

CAR T cells have revolutionized the cancer immunotherapy field. Yet, while initial responses are often good, maintaining long-term efficacy remains a challenge, especially in MM.[36] A better understanding of underlying molecular mechanisms might drive therapeutic advances. In his presentation, Dr. Juan R. Ridríguez-Madoz introduced a newly developed atlas for CD19 CAR T cells designed to uncover mechanisms associated with cell persistence and expansion.[37,38] The first version of the CAR T cell atlas comprises data from 415,000 cells from more than 100 patients with different hematological diseases. It includes CAR T cell products targeting different antigens (CD19, BCMA, APRIL). The atlas enables researchers to identify mechanisms of both resistance and response. For example, the memory phenotype of the infusion product correlates with better responses. Beyond this, the atlas can be used to generate new data-driven hypotheses – such as around age- or gender-related differences – and allows detection of cells related to therapy toxicity. Ongoing research aims to validate the identified mechanisms.

## Bispecific antibodies versus CAR T for R/R MM

Newer treatment modalities are changing the landscape for patients with R/R MM who have received multiple prior therapies. There are numerous unresolved questions regarding the optimal sequence and application of the new agents throughout the course of treatment, including: Which treatment modality is superior in certain patient populations? Which one offers a better safety profile and greater efficacy? Are there specific patient populations that would derive more benefit from one method over the other? Which should be administered earlier, and would its use prevent the employment of the alternative?

At EHA2025, Dr. Elena Zamagni, together with Dr. Philippe Moreau and Dr. Paula Rodriguez-Otero, attempted to answer some of these questions in a debate entitled "BCMA bsAb vs CAR T in MM".[39-41] Before the debate began, the audience was asked to choose their preferred treatment in clinical practice between CAR T and bispecific antibody (bsAb) therapy. Around 50% felt less or not comfortable choosing either one of the two, highlighting the ongoing uncertainty in decision-making.

Dr. Philippe Moreau argued in favor of therapy using BCMA bsAb in patients with R/R MM. Currently, two BCMA-targeting (teclistamab and elranatamab) and one GPRC5D-targeting (talquetamab) bsAbs are available for the management of heavily pretreated patients with R/R MM. BCMA is preferentially expressed during B lymphoid maturation and is either not expressed or expressed at low levels in normal cells. On the other hand, the role of GPRC5D in healthy tissue is less clear, but it is highly expressed in MM

compared to other cancers. The advantages of bsAbs are that they're readily available and can be accessed quickly, making them suitable for community hospitals and outpatient settings. They are also a good fit for patients who are frail, elderly, or have kidney problems, which can increase their real-world use. However, there are some challenges with bsAbs. For one, about a third of patients do not respond to them, and the reasons for this resistance are unclear. Another challenge is that it is not yet clear how to combine bsAbs with CAR T therapies. Additionally, there is a risk of target loss, such as when BCMA or GPRC5D levels decrease. Optimizing treatment schedules is also a challenge. Some researchers are exploring the use of bsAbs as bridging therapies, but there is still a risk of infection, which can be managed with intravenous Ig. Reducing costs and developing new treatments, like cevostamab and FCRH5, are also areas of focus for the future.

Next, Dr. Paula Rodriguez-Otero presented her arguments in support of CAR T cell therapy. Currently, six CAR T cell treatments have been authorized by the FDA, 4 of which are for MM. The most recently approved and one with better outcomes was ciltacabtagene autoleucel (cilta-cel) for patients with R/R MM. In its pivotal trial CARTITUDE-1, cilta-cel showed a median PFS of 43.9 months and a median OS in long-term follow-up of 60.7 months. CARTITUDE-4 tested the use of cilta-cel in earlier treatment lines and showed superiority to standard-of-care treatments. The advantages of CAR T cell therapy include longer treatment-free intervals, improved T-cell fitness in earlier lines, leading to better CAR T efficacy, more options for bridging therapy in earlier disease stages, and less refractory or aggressive disease. Current challenges with CAR T therapy include its limited suitability for patients with urgent needs or access issues, manufacturing delays, and limited availability in Europe, which remains a significant barrier.

In conclusion, the debate participants agreed that patient selection needs to be tailored to each individual, and both treatments have their benefits for specific patient groups, disease stage, and practical considerations.

## More from EHA

Interested to know more on the aspects of CAR-T cell therapy? Learn all about it on the new EHA Campus CAR-T Program. Explore the challenges and opportunities of point-of-care CAR-T manufacturing in this dedicated podcast, and don't forget to sign up for the 8th CAR-T meeting in Palma de Mallorca in February 2026.

CAMPUS CAR T-cell Therapy Program

Point-of-care CAR T-cell Manufacturing

EBMT-EHA 8th European CAR T-cell Meeting

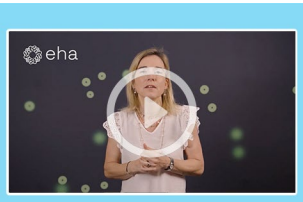
## References


1. Kumar S, et al. Phase 2 Study of Talquetamab + Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma and Extramedullary Disease: RedirecTT-1. Abstract LB4001, presented at EHA2025.
2. https://www.clinicaltrials.gov/study/NCT05652335 [accessed 30 June 2025]
3. Popat R. First-in-human study of JNJ-79635322 (JNJ-5322), a novel, next-generation trispecific antibody, in patients with relapsed/refractory multiple myeloma: initial Phase 1 results. Oral presentation s100 at EHA2025.
4. Shah BD, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: Phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *Lancet.* 2021;398(10299):491-502.
5. Roddie C. Oral abstract 7000 at ASCO 2023.
6. Roddie C, et al. Obecabtagene Autoleucel in Adults with B-Cell Acute Lymphoblastic Leukemia. *N Engl J Med.* 2024;391(23):2219-2230.
7. Shah BD. Oral presentation 7010 at ASCO 2022.
8. Perica K, et al. Impact of bridging chemotherapy on clinical outcome of CD19 CAR T therapy in adult acute lymphoblastic leukemia. *Leukemia.* 2021;35:3268-3271.
9. Lin C, et al. Oral presentation 3502 at ASH 2023.
10. Shah BJ. Cell therapy: CAR T and NK cells for R/R B cell precursor and T ALL. Oral presentation p251-3 at EHA2025.
11. Clinical Trials NCT04684563.
12. Svoboda J, et al. Enhanced CAR T-Cell Therapy for Lymphoma after Previous Failure. *N Engl J Med.* 2025;392(18):1824-1835.
13. June C. Armored CAR T in lymphoma: resistance mechanisms and efficacy. Oral presentation p109-1 at EHA2025.
14. Guedan S. Next-Generation CAR-T: Dual specificity to counter tumor escape in lymphoma. Oral presentation p196-2 at EHA2025.
15. Subklewe M. BiTE molecules in AML therapy. Oral presentation p141-1 at EHA2025.
16. Ravandi F, et al. Safety and tolerability of AMG 330 in adults with relapsed/refractory AML: a Phase 1a dose-escalation study. *Leuk Lymphoma.* 2024;65(9):1281-1291.
17. Subklewe, et al. ASH 2019 #833.
18. Westervelt, et al. ASH 2019 #834.
19. Uy GL, et al. Flotetuzumab as salvage immunotherapy for refractory acute myeloid leukemia. *Blood.* 2021;137(6):751-762.
20. Boyiadzis M, et al. First-in-human study of JNJ-63709178, a CD123/CD3 targeting antibody, in relapsed/refractory acute myeloid leukemia. *Clin Transl Sci.* 2023;16(3):429-435.
21. Ravandi, et al. ASH 2020 #460.
22. Mascarenhas, et al. EHA2020 #538.
23. Labrijn AF, et al. Bispecific antibodies: a mechanistic review of the pipeline. *Nat Rev Drug Discov.* 2019;18(8):585-608.

24. Stein AS et al, An open-label, first-in-human, dose-escalation study of SAR443579 administered as single agent by intravenous infusion in patients with relapsed or refractory acute myeloid leukemia (R/R AML), B-cell acute lymphoblastic leukemia (B-ALL) or high-risk myelodysplasia (HR-MDS). Abstract 3329, presented at ASH 2022
25. Bajel et al, First-in-Human Study of the CD123 NK Cell Engager SAR443579 in Relapsed or Refractory Acute Myeloid Leukemia, B-Cell Acute Lymphoblastic Leukemia or High Risk-Myelodysplasia: Updated Safety, Efficacy, Pharmacokinetics and Pharmacodynamics. Abstract 3474, presented at ASH 2023.
26. Haenel G, et al. Combining venetoclax and azacytidine with T-cell bispecific antibodies for treatment of acute myeloid leukemia: a preclinical assessment. *Leukemia*. 2024;38(2):398-402.
27. Zhong X, Ma H. Targeting CD38 for acute leukemia. *Front Oncol*. 2022:12:1007783.
28. Zeng X, et al. A novel bispecific T-cell engager using the ligand-target csGRP78 against acute myeloid leukemia. *Cell Mol Life Sci*. 2024;81(1):371.
29. Lin et al. Preclinical Characterization of NGM936, a Novel Bispecific T Cell Engager Targeting ILT3 for the Treatment of Acute Myeloid Leukemia With Monocytic Differentiation. Abstract 4082, presented at ASH 2022.
30. Shi et al. AML Immunotherapy Using a Novel Tcrm-Based Bispecific Antibody That Targets a Leader Sequence Peptide Derived from Cathepsin G. Abstract 1415, presented at ASH 2023.
31. Volta L, et al. A single-chain variable fragment-based bispecific T-cell activating antibody against CD117 enables T-cell mediated lysis of acute myeloid leukemia and hematopoietic stem and progenitor cells. *Hemasphere*. 2024;8(11):e70055.
32. Rasouli M. An Immunotherapy For Rapid Bone Marrow Conditioning And Leukemia Depletion That Allows Efficient Hematopoietic Stem Cell Transplantation. Oral Abstract s129 at EHA2025.
33. Ghorashian S. CAR T cell therapy in AML. Oral presentation p141-2 at EHA2025.
34. Geyer et al., CD371-Targeted CAR T-Cells Secreting Interleukin-18 Exhibit Robust Expansion and Disease Clearance in Patients with Refractory Acute Myeloid Leukemia. ASH 2024 #2070
35. Martínez Roca A. Outpatient CAR-T therapy. Oral presentation p213-3 at EHA2025.
36. Rodriguez-Madoz J, et al. A functional CAR-T cell atlas to unravel regulatory mechanisms of CAR-T cells. Oral presentation s276 at EHA2025.
37. Bai Z, et al. Single-cell CAR T atlas reveals type 2 function in 8-year leukaemia remission. *Nature*. 2024;634(8034):702-711.
38. Li X, et al. A single-cell atlas of CD19 chimeric antigen receptor T cells. *Cancer Cell*. 2023;41(11):1835-1837.
39. Zamagni E. BCMA bsAb vs CAR T in MM. Thematic Debate p552-0 at EHA2025;
40. Moreau P. BCMA bsAb vs CAR T in MM. Thematic Debate p552-1 at EHA2025;
41. Rodríguez-Otero P. BCMA bsAb vs CAR T in MM. Thematic Debate p552-2 at EHA2025

# 03

# Microenvironment and next-generation modeling in lymphoid malignancies




**Dr. Patricia Pérez-Galán** shares her highlights on lymphoid malignancies from EHA2025

## Patient-derived 3D lymphoma models

Establishing preclinical models for B-cell lymphoma is challenging due to the complex interactions between lymphoma cells and the tumor microenvironment (TME). Currently, three main approaches are used to recapitulate a robust preclinical 3D lymphoma system: cell lines, mouse models, and patient-derived cells. PDLS, or patient-derived lymphoma spheroids, is a robust *in vitro* model that combines lymphoma cells, monocytes, autologous T cells, and a specific cytokine cocktail.[1]

PDLS is a valuable model for characterizing disease pathology, predicting patient responses to drug testing, and discovering new targets, as well as understanding mechanisms of drug resistance. Biomimetic components, such as natural or synthetic hydrogels that resemble the extracellular matrix, form scaffolds to provide structure to the 3D culture systems, supporting spheroid growth. One example is a patient-derived lymphoma tumoroid (PDLT) cultured from a tumor biopsy sample, rat collagen, and stromal cells, which are stimulated with IL-4, resulting in tumoroids approximately 1 mm in size containing CD19+ and CD3+ cells.

In a previous publication by Dobano-López et al., a PDLS model was generated using patient-derived cells from a follicular lymphoma (FL) patient.[2] The PDLS model recapitulated the proliferation of B and T cells in disc-shaped 3D structures, along with macrophages exhibiting an intermediate M1/M2 phenotype. The most relevant B-cell transcriptional pathways were recapitulated similarly to those in FL lymph nodes, and the T-cell compartment preserved the spectrum of

phenotypes in both CD4 and CD8 populations. Researchers used the FL-PDLS model to evaluate dual-targeting CD19/BCMA CAR T cells for treating non-Hodgkin lymphoma.[3] A similar PDLS model has also been shown to replicate the lymph node TME in other conditions, such as mantle cell lymphoma.[4]

Although the FL-PDLS model does not recapitulate intra- and inter-lymph node variability, nor clonal evolution over time, FL-PDLS might evolve in the future to recreate a complete TME *in vitro* by integrating other TME components.

## Pola-R-GemOx shows OS benefit in R/R DLBCL

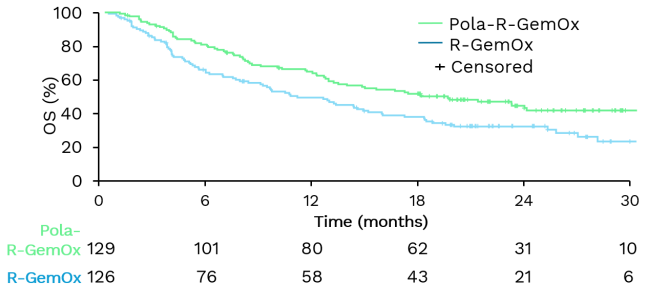
Polatuzumab vedotin is a CD79b-directed antibody-drug conjugate (ADC) that is already approved in the European Union for the use in both frontline and relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), with the latter indication involving its combination with bendamustine and rituximab.[5] Despite available therapies, alternative treatment options are still needed for patients with R/R DLBCL.

At the EHA2025 plenary session, Dr. Matthew Matasar presented the results of the POLARGO trial (NCT04182204). This global, randomized Phase 3 study evaluated the efficacy and safety of polatuzumab vedotin combined with rituximab, gemcitabine, and oxaliplatin (Pola-R-GemOx) compared to rituximab, gemcitabine, and oxaliplatin (R-GemOx) in patients with R/R DLBCL who had received at least one prior line of treatment and were not eligible for autologous stem cell transplantation.[6]

Following a safety run-in phase involving 15 patients, a total of 255 patients were randomized in a 1:1 ratio to receive either Pola-R-GemOx or R-GemOx alone. Pola-R-GemOx showed a significant improvement in the primary endpoint of overall survival (OS), with a median OS increase of 7 months compared to R-GemOx alone (hazard ratio: 0.60 (95% CI: 0.43–0.83), *P*=0.0017). Despite

higher rates of peripheral neuropathy and infections, the treatment remained tolerable and effective, providing a valuable alternative that avoids T-cell depleting bendamustine. These findings support adding polatuzumab vedotin to GemOx regimens for selected patients, broadening options beyond traditional salvage therapies.

OS with Pola-R-GemOx versus R-GemOx




Gem, gemcitabine; Ox, oxaliplatin; Pola, polatuzumab vedotin; R, rituximab.

## Mosunetuzumab SC induced high response rates in MZL patients

Another significant clinical trial in lymphoma, presented at EHA2025, was the Phase 2 MorningSun study. This Phase 2 basket study (NCT05207670) presented by Dr. John Burke investigated the efficacy and safety of the subcutaneous (SC) formulation of monsunetuzumab (Mosun), a bispecific CD20/CD3-targeting antibody, in treatment-naïve patients with symptomatic marginal zone lymphoma (MZL).[7] Currently, Mosun is approved as a fixed-duration intravenous (IV) therapy for R/R follicular lymphoma.

Mosun SC was administered with step-up dosing in cycle 1 (5mg on day 1, 45mg on days 8 and 15), followed by 45mg on day 1 of each 21-day cycle for up to 17 cycles or until disease progression or unacceptable toxicity. Cytokine release syndrome (CRS) mitigation involved Mosun SC step-up dosing in the first cycle, with mandatory corticosteroid prophylaxis for cycles 1 and 2, and optional for later cycles.

After a median follow-up of 18 months, the primary endpoint of overall response rate (ORR) was 78%, with a complete metabolic response (CMR) of 64%. At the time of analysis, progression-free survival (PFS) rates were 90.5% at 6 months and 83.6% at 12 months, with a median PFS not yet reached. The most frequent adverse events (AEs) included injection-site reactions, fatigue, diarrhea, neutropenia, and manageable CRS.

Researchers concluded that compared to intravenous Mosun, Mosun SC offered similar efficacy with manageable CRS. Besides the absence of mandatory hospitalization and the option to administer Mosun SC in community outpatient settings, these results support further research into Mosun SC as first-line therapy for MZL.

## Resistance to targeted therapies in CLL

Patients with chronic lymphocytic leukemia (CLL) show varied disease progression, with some patients never needing treatment, while others require treatment immediately after diagnosis. A subset of these patients experience only brief remissions before declining rapidly.

Although small molecule inhibitors that target the abnormal signaling pathways and molecular defects in CLL have improved survival rates, treatment resistance can develop later due to the tumor's intrinsic heterogeneity, persistence of the leukemic clone, and the supportive tumor microenvironment that promotes the survival of the disease clone.[8]

The development and progression of CLL involve complex interactions with the tumor microenvironment (TME), not just the intrinsic properties of leukemia cells. Herishanu Y, et al. previously identified the lymph node (LN) as the key site in CLL pathogenesis, serving as a location for CLL cell activation and tumor growth.[9] CLL cells in the LN showed upregulation of gene signatures compared to those in peripheral blood, indicating activation of the B-cell receptor (BCR) and nuclear factor-κB pathways.

Furthermore, whole genome sequencing analysis conducted by Kasar S, et al. on a cohort of CLL patients revealed that the most frequently mutated gene showed a mutational pattern consistent with activation-induced cytidine deaminase (AID) activity.[10] As B-cells develop, AID induces deamination of cytosine to uracil. Resolution of these lesions by the error-prone DNA polymerase can result in either canonical or non-canonical AID. It has been found that non-canonical AID activity plays a greater role in the early stages of CLL development, while mutations related to normal AID become more significant later in the development of CLL. Overall, AID expression levels do not differ between patients with and without subclonal expansion.[11] On the other hand, T-cell-mediated immune surveillance is an important factor that may restrict clonal evolution in the LN. In conclusion, these data highlight the disruption of tumor microenvironment interactions and the inhibition of BCR signaling as potential therapeutic approaches for CLL.

## BGB-16673, a novel BTK degrader, shows activity in R/R CLL/SLL

Bruton's tyrosine kinase inhibitors, or BTKi, have transformed the treatment of B-cell leukemia, including CLL and small lymphocytic lymphoma, and are established as leading drugs in the treatment of both treatment-naïve (TN) and relapsed or refractory (R/R) CLL/SLL patients. However, continuous therapy with BTKi may lead to intolerance or the development of resistance due to mutations causing clinical relapse.[12,13]

BGB-16673 is a BTK degrader, offering an alternative mechanism for interrupting the BCR signaling. It is an orally available BTK-targeting chimeric degradation activation compound (CDAC) designed to degrade wild-type BTK and multiple mutant forms.

At EHA2025, Dr. Lydia Scarfò presented the updated efficacy and safety data from the CaDAnCe-101 phase 1 trial investigating the use of BGB-16673 in patients with R/R CLL/SLL who had at least one line of therapy (including a BTKi).[14]

In the open-label, dose-escalation part 1a phase, up to 72 patients with select relapsed/refractory B-cell malignancies were first enrolled and treated with BGB-16673 orally at different doses between 50 and 600 mg once daily in 28-day cycles. Part 1b was the safety expansion phase, comprising up to 120 patients with CLL/SLL as well as other B-cell malignancies. The results from 66 enrolled patients with a median follow-up of 15.6 months was presented in this analysis. Regarding baseline characteristics, the cohort included patients with unfavorable biological biomarkers such as Binet stage C (46.8%), unmutated IGHV (77.6%), 17p deletion (del[17p]) and/or TP53 (65.2%), and complex karyotype (≥3 abnormalities; 50.0%). Mutations present included BTK (38.1%), PLCG2 (15.9%), and a combination of both (7.9%).

BGB-16673 had a favorable safety profile and was well tolerated with the most common grade ≥3 AEs being neutropenia (24%), pneumonia (11%) and thrombocytopenia (5%). Serious adverse events were reported in 45.5% of patients, 12.1% of which were related to treatment. Four patients had TEAEs that led to death, but none were related to therapy. Nine patients discontinued BGB-16673, 2 of which were due to treatment-related TEAEs.

The overall response rate (ORR) was 84.8%, which included a 4.5% complete response (CR)/CR with incomplete marrow recovery (CRi) rate, a 66.7% partial response (PR) rate, and a PR with lymphocytosis (PR-L) rate of 13.6%. At 1 year, the progression-free survival rate was 77.4%.

These data suggested that BGB-16673 is relatively safe, well-tolerated, and demonstrated encouraging antitumor activity in patients with R/R CLL/SLL. Importantly, responses were observed regardless of baseline mutations and other high-risk features, suggesting broad applicability for this drug in a challenging patient population.

Overall, the new data presented at EHA2025 helps us make more informed decisions on how to best treat patients with lymphoid malignancies. This includes utilizing new preclinical models and testing novel drugs to gain a deeper understanding of how tumors develop resistance and interact with their surrounding microenvironment.

## More from EHA

Visit the EHA Campus to discover the initial modules of our brand-new Lymphoma Program and stay tuned for upcoming modules. Check the 2025 ESMO-EHA guidelines on Peripheral T- and NK-cell lymphomas.

CAMPUS Lymphoma Program

Peripheral T- & natural killer-cell lymphomas: ESMO-EHA Clinical Practice Guideline for diagnosis, treatment, & follow-up

## References


1. Pérez-Galán P. 3D lymphoma models. Oral presentation p151-1 presented at EHA2025.
2. Dobano-López C, et al. Patient-derived follicular lymphoma spheroids recapitulate lymph node signaling and immune profile uncovering galectin-9 as a novel immunotherapeutic target. *Blood Cancer J.* 2024;14(1):75.
3. Guedan S. Next-Generation CAR-T: Dual specificity to counter tumor escape in lymphoma. Oral presentation p196-2 at EHA2025
4. Araujo-Ayala F, et al. A novel patient-derived 3D model recapitulates mantle cell lymphoma lymph node signaling, immune profile and in vivo ibrutinib responses. *Leukemia*. 2023 Jun;37(6):1311-1323.
5. https://www.ema.europa.eu/en/medicines/human/EPAR/polivy [accessed 16 June 2025].
6. Matasar M. Polatuzumab vedotin, rituximab, gemcitabine and oxaliplatin (Pola-R-GemOx) for relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): results from the randomized Phase III Polargo trial. Oral presentation s101 at EHA2025.
7. Burke M. MorningSun: open-label Phase II trial of the efficacy and safety of subcutaneous mosunetuzumab (mosun sc) as frontline (1L) treatment in symptomatic patients with marginal zone lymphoma (MZL). Oral presentation s232 at EHA225.
8. Sun C. The impact of the CLL microenvironment. Oral presentation p257-1 at EHA2025.
9. Herishanu Y, et al. The lymph node microenvironment promotes B-cell receptor signaling, NF-kappaB activation, and tumor proliferation in chronic lymphocytic leukemia. *Blood* 2011;117(2):563-74.
10. Kasar S, et al. Whole-genome sequencing reveals activation-induced cytidine deaminase signatures during indolent chronic lymphocytic leukaemia evolution. *Nat Commun.* 2015;6:8866.
11. Sun C, et al. The immune microenvironment shapes transcriptional and genetic heterogeneity in chronic lymphocytic leukemia. *Blood Adv.* 2023;7(1):145-158.
12. Woyach JA, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med.* 2014;370:2286-2294.
13. Wang E, et al. Mechanisms of Resistance to Noncovalent Bruton's Tyrosine Kinase Inhibitors. *N Engl J Med.* 2022;386:735-743.
14. Scarfo L. Updated efficacy and safety of the bruton tyrosine kinase (BTK) degrader BGB-16673 in patients (pts) with relapsed or refractory (r/r) CLL/SLL: results from the ongoing phase (ph) 1 CaDAnCe-101 study. Oral presentation s158 at EHA2025.

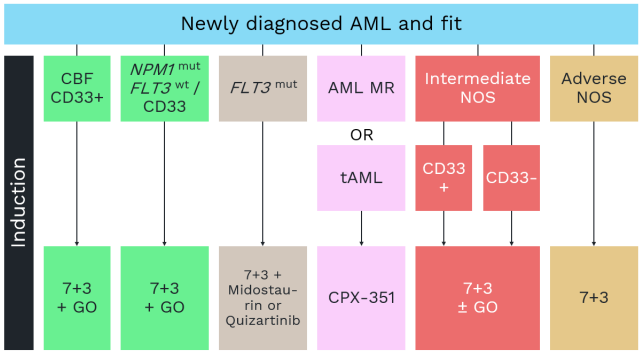
# 04

# Genomics and new treatments for AML

## Beyond IC and HMA in AML

Over the past 50 years, induction chemotherapy (IC) for acute myeloid leukemia (AML) has remained largely unchanged since the introduction of the "7+3" regimen, which includes cytarabine and an anthracycline. Although complete remission (CR) rates with conventional induction are quite favorable, long-term survival remains poor,[1] except perhaps in younger and fit patients who can undergo allogeneic hematopoietic stem cell transplant (HSCT). As a result, there has been significant research into possible changes to AML treatment, particularly in new strategies that build on the 7+3 approach.[2]
Gemtuzumab ozogamicin (GO), an antibody-drug conjugate (ADC) consisting of a CD33-targeted monoclonal antibody (mAb) chemically linked to a calicheamicin-based cytotoxic warhead, has been approved for patients with previously untreated CD33 antigen-positive AML in combination with standard frontline IC.[3] In a randomized phase 3 trial, ALFA-0701, GO combined with daunorubicin and cytarabine demonstrated a significant improvement in event-free survival (EFS), with particular benefit in patients with core binding factor (CBF) AML.[4]
Other combinations include the use of targeted agents, such as FMS-like tyrosine kinase 3 (FLT3) inhibitors like midostaurin or quizartinib, for AML with a *FLT3* mutation.[5] Targeting isocitrate dehydrogenases (IDH) 1/2, which affects approximately 20% of AML patients, is an emerging strategy to promote clinical responses in AML. IDH1/2 inhibitors, ivosidenib and enasidenib, are currently being studied in combination with IC in large Phase 3 clinical trials in newly diagnosed AML patients with IDH1/2 mutations.[6] AML cells also express BCL-2, enabling them to sequester pro-apoptotic proteins and evade apoptosis. The B-cell lymphoma 2 inhibitor (BCL-2i) venetoclax, combined with IC, demonstrated a high composite complete response (cCR) rate of 95% in both newly diagnosed and relapsed/recurrent cases of AML.[7]
Overall, the integration of targeted treatments into frontline IC for newly diagnosed, fit adults with AML is promising, and the landscape is likely to continue evolving.

Treatment stratification for newly diagnosed AML patients who are fit for intensive therapy




Hypomethylating agents (HMA) such as azacitidine or decitabine combined with venetoclax is the standard of care for patients with newly diagnosed AML, who are ineligible for IC, but are associated with lower OS as compared to patients treated with IC regimens.[8] Another combination of IDH1 inhibitor ivosidenib and azacitidine showed encouraging clinical activity in an early stage trial involving patients with newly diagnosed *IDH1*-mutated AML.[9] Although some ongoing trials exist in this challenging-to-treat patient population, further improvements are necessary, particularly for patients with high-risk genetic mutations such as *TP53*, *FLT3*, and *RAS*.[10]
The VIALE-A trial results have established the combination of venetoclax plus azacitidine as a new standard of care for older and unfit patients

with AML. However, data from real-world settings have highlighted its value, especially in maintaining the quality of life for elderly patients with AML.[11]

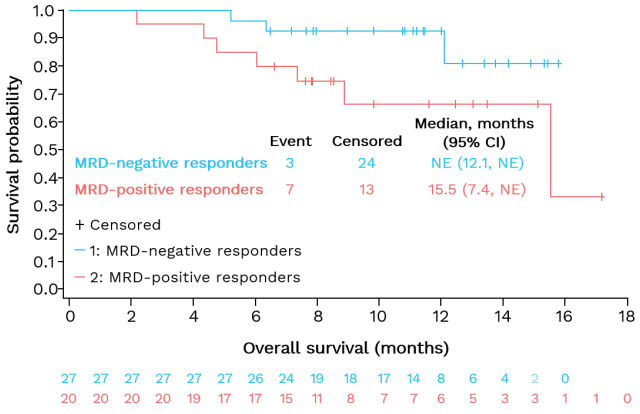
## An all-oral decitabine-cedazuridine + venetoclax in older AML patients

As in-hospital treatment is a significant burden for elderly patients, the Phase 1/2 ASCERTAIN-V (NCT04975919) trial tested an all-oral decitabine-cedazuridine (DEC-C) plus venetoclax (Ven) treatment regimen in patients with a median age of over 75 years, who were ineligible for IC. All patients received oral DEC-C on Days 1–5 plus Ven 400 mg daily in 28-day cycles after Cycle 1 VEN ramp up.

Dr. Gail Roboz presented the data of this trial at EHA2025, showing that across the phase 1 (n = 30), phase 2A (n = 58), and phase 2B (n = 101) portions of the trial, the complete response (CR) rates were 40.0%, 37.9% and 46.5% respectively.[12] The median OS was 15.5 months in the phase 2B portion after a follow-up of 11.2 months.

Patients with CR (n=44) underwent evaluation for minimal residual disease (MRD). The results revealed that 55.1% (n = 27) of patients achieved MRD negativity at some point; for those who were MRD negative, the median OS was not estimable (NE), and for those who were MRD positive, the median OS was 15.5 months.

Overall survival in MRD-negative and MRD-positive responders under oral decitabine-cedazuridine + venetoclax therapy




Regarding safety data, 86.7%, 91.4%, and 98.0% of patients in phases 1, 2A, and 2B, respectively, experienced grade 3 or higher adverse events. The most common severe adverse events were related to myelosuppression, including anemia (25.9%), neutropenia (20.6%), febrile neutropenia (20.6%), and thrombocytopenia (14.3%).

Since many patients on ven/aza combination experience neutropenia and therapy-related myelosuppression, dose adjustments were also analyzed as part of the study. Patients completed a median of 4, 5, and 4 cycles of treatment in the phase 1, 2A, and 2B portions, respectively. It was observed that 3.3% of patients in phase 1 underwent bone marrow examinations, which then increased to 15.5% in phase 2A and to 31.7% in phase 2B.

Based on these results, the researchers concluded that an all-oral regimen of DEC-C + Ven resulted in comparable safety, response, and survival rates to parenteral azacitidine plus VEN in newly diagnosed elderly AML patients ineligible for IC. Compared with standard dosing, early BM examination and subsequent dose reductions in DEC-C and/or VEN during post-remission treatment cycles were linked to better long-term outcomes and tolerability. The treatment plan will now be tested in a large Phase 3 trial.

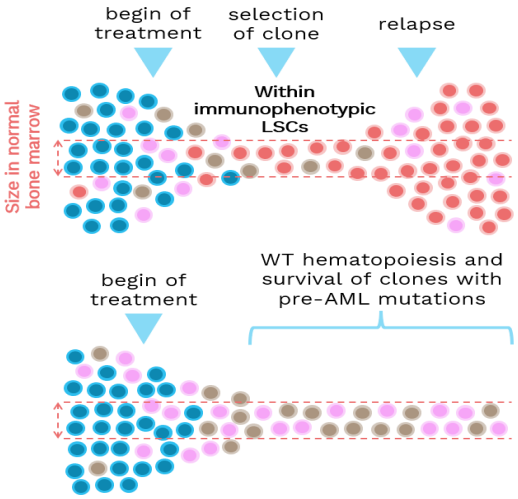
## Tumor heterogeneity and clonal selection

Relapse after treatment is rooted in tumor heterogeneity and clonal selection. In patients with relapsed and refractory (R/R) disease, AML clones carrying different resistance mechanisms might already exist before the start of the next therapy. The use of single-cell multi-omics has been instrumental in better identifying quiescent stem-like cells and leukemia stem cells, which are responsible for resistance to therapeutic approaches and relapse after treatment.[13]

Clonal evolution in AML patients was monitored through single-cell RNA sequencing of bone marrow samples to observe gene expression changes between clones and relate them to their changing dominance over time. It was found that resistant clones can, but do not necessarily have to, undergo genetic evolution. The clone that eventually caused relapse was often present from the start.

In patients with long-term remissions, normal hematopoiesis and only clones with pre-AML mutations were observed after treatment. If early clonal selection can be detected using scalable, cost-effective technologies, such as single-cell approaches, many relapses may be potentially preventable.

Difference between patients who relapse and patients with sustained remission



## Combination treatments counter tumor resistance mechanisms

AML relapse in patients treated with venetoclax doublets can occur through various mechanisms, including upregulation or mutations in BCL2 family proteins, *FLT3*, *RAS*, and *MAPK*, new *TP53* mutations, and expansion of monocytic clones, among other factors. As a result, several new agents have been approved or are being developed to target these issues. To achieve more lasting and effective remissions, personalized, patient-specific combinations targeting specific abnormalities are likely needed, and may also help reduce primary and secondary resistance to venetoclax-based treatments.

## Menin inhibitors as combination treatments in AML

Menin inhibitors are new and promising agents currently in clinical development that target the HOX/MEIS1 transcriptional program, which is critical for leukemogenesis in *KMT2A*-rearranged (*KMT2A*-r) and *NPM1*-mutated (*NPM1*-m) AML. Menin inhibitors currently in clinical development for AML include revumenib, ziftomenib, bleximenib, BMF-219, and DSP-5336, with revumenib being furthest along in clinical development.[14]

New data from several of the previously mentioned menin inhibitors were presented at the EHA2025. Dr. Harry Erba presented the findings from the KOMET-007 dose-escalation trial, which evaluated ziftomenib 600 mg daily in combination with 7+3 induction chemotherapy or venetoclax/azacitidine (ven/aza) in 82 patients with *NPM1*-m and *KMT2A*-r AML (NCT05735184).[15] The safety profile was similar to that of 7+3 alone, and the combination therapy achieved higher response rates, including durable responses.

| Efficacy | NPM1-m (n = 49) | KMT2a-r (33%) |
|---|---|---|
| cCR (%) | 90 | 89 |
| CR MRD- (%) | 71 | 88 |
| mOS (months) | NR | NR |
| mDoCR (months) | NR | 25.6 |
| Alive at data cutoff (%) | 96 | 88 |

Another abstract presented data on bleximenib (JNJ-75276617), which was also tested in combination with ven/aza in newly diagnosed and relapsed or refractory AML with *KMT2A/NPM1* alterations in a Phase 1b trial (NCT04811560).[16] At the RP2D of 100 mg twice daily, bleximenib combination achieved an ORR of 82% and a cCR of 59% in patients with R/R AML. The newly diagnosed patient population showed an ORR of 90% and a cCR rate of 75%.

Grade 3 or higher events were mostly confined to myelosuppression, such as neutropenia.

| Subgroup | CR rate at 100 mg (%) |
|---|---|
| ND AML | 75.0 |
| R/R AML | 59.1 |
| Prior VEN eposure | 28.6 |
| No prior VEN eposure | 73.3 |
| KMT2A-r | 71.4 |
| NPM1-m | 57.1 |

And finally, the sub-study from the BEAT AML Master Trial (BAMT) was presented by Dr. Joshua Zeidner.[17] Revumenib was also tested in combination with ven/aza in only newly diagnosed AML patients in a dose-escalation and expansion trial (NCT06652438). A total of 43 patients with *NPM1*-m or *KMT2A*-r were treated with revumenib in combination at two doses (113 mg and 163 mg) taken orally twice daily. No maximum tolerated dose was identified, and no patients discontinued revumenib due to adverse events. Efficacy was consistent with other menin combination treatments.

| Efficacy | DL1 (n=21) | DL2 (n=22) |
|---|---|---|
| ORR (%) | 90.5 | 86.4 |
| CR (%) | 61.9 | 72.7 |
| 1y-OS rate (%) | 63 | |

Overall, menin inhibitors are a promising new class of treatments for *KMT2A*-r and *NPM1*-mutated AML. Early results from ongoing clinical trials look encouraging in terms of response rates and safety, particularly in patients who have been heavily treated. However, more research is needed to confirm these findings, identify patient subgroups that may benefit most from these treatments, and determine the best timing and dosage for these new medicines.

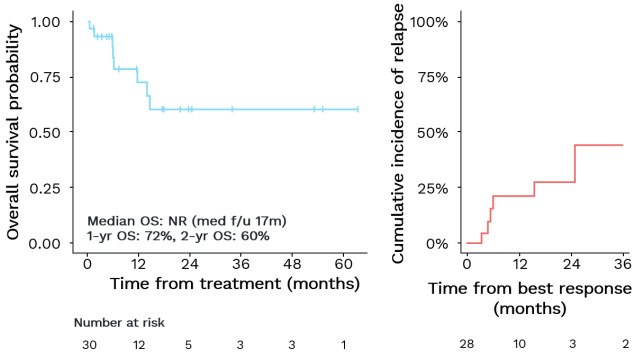
Additionally, menin inhibitors appear to work well in combination with other agents, such as venetoclax and azacitidine, making both classes of drugs more effective and potentially improving outcomes for *KMT2A*-r and *NPM1*-mutated AML, especially in older patients and those with R/R AML.

## Decitabine, venetoclax, and quizartinib triplet combination in *FLT3-ITD* mutated AML

FMS-like tyrosine kinase 3 (FLT3) is a tyrosine kinase receptor that plays a vital role in hematopoietic cell survival, proliferation and differentiation. *FLT3* mutations occur in 20-30% of patients with AML and indicate poor treatment outcomes. Quizartinib is a second-generation *FLT3* inhibitor currently being tested in Phase 3 trials. Pre-clinical data indicate that quizartinib and Ven could act synergistically. Therefore, a Phase 1/2 trial was launched to determine the

RP2D of quizartinib combined with decitabine (DEC) and Ven in patients with *FLT3*-mutated AML, in both newly diagnosed (ND) and R/R settings, who were ineligible for IC. Dr. Musa Yilmaz demonstrated that quizartinib at a dose of 30 mg had no dose-limiting toxicity, with high remission rates seen in both ND (94%) and R/R (61%).[18] The median OS was not reached in the ND patients after a median follow-up of 17 months with a 1-yr OS rate of 72%. In the R/R patient group, the median OS was 6.3 months with the 1-yr OS rate at 20%. Regarding safety data, the delayed neutrophil recovery could be mitigated by reducing VEN and quizartinib to 14 days and grade 3 QTcF prolongation was uncommon (4%). Combining DEC, VEN, and quizartinib showed promising activity in high-risk patients, with additional data needed to better understand the use of the triplet combination in both frontline and relapsed/refractory settings for AML patients.

Probability of survival and relapse




## Sonrotoclax in treatment-naïve and R/R AML

Venetoclax has been a groundbreaking drug used to treat various blood cancers, including AML. However, with prolonged treatment, cancer cells can develop mechanisms to resist venetoclax. Sonrotoclax is a next-generation BCL-2 Inhibitor with higher selectivity and potency, capable of inhibiting both wild-type and *G101V*-mutated BCL-2.[19]

At EHA 2025, a poster abstract was presented in which researchers tested the combination of sonrotoclax plus azacitidine in treatment-naïve and R/R MDS and AML patients.[20] In this Phase 1b/2 dose escalation and expansion trial (BGB-11417-103), multiple dosing schemes of sonrotoclax were tested, ranging from 40–320 mg and from 10 to 28 days in a 28-day cycle. Across all dosing schemes, the overall response rate was 75%, with a CR of 60% for treatment-naïve patients and 60% in the R/R populations, with a CR of 43%. Adverse events related to myelosuppression occurred frequently, with neutropenia Gr≥3 affecting 90% of treatment-naïve and 84% of R/R patients. Overall, 15.2% and 11.8% of patients discontinued treatment.
Considering the high-risk patient profile enrolled in the study, the authors concluded that the combination treatment was effective and had an acceptable safety profile in both treatment-naïve and R/R settings.

Overall, EHA2025 provided valuable insights into cutting-edge treatment approaches in AML. These included exploring alternatives to the current standard of induction chemotherapy and hypomethylating agents, and testing more effective treatment combinations based on a tumor's unique characteristics. A deeper understanding of tumor heterogeneity and clonal selection is the foundation for developing treatments after relapse in AML, as well as for exploring new strategies to combine treatments and prevent resistance. The congress also presented new data on all-oral treatment regimens for elderly and unfit patients, along with early clinical trial results of menin inhibitors added to standard treatments. Additionally, the data from triplet combinations and sonrotoclax combinations show promise for the future of AML treatment, highlighting the need to optimize their use in a safe and effective manner to further improve patient outcomes.

## More from EHA

Check out the EHA SWG Preceptorship on AML diagnostics, planned to take place in October 2025. Gain more insights on potentialities for cellular therapies in myeloid malignancies with our podcast focused on CAR-T and AML.

EHA-SWG Pilot Preceptorship on AML diagnostics

CAR T-cell Therapy in AML: State of the Art

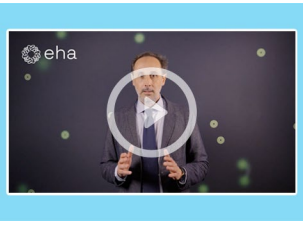
## References


1. Büchner T, et al. Acute Myeloid Leukemia (AML): different treatment strategies versus a common standard arm--combined prospective analysis by the German AML Intergroup. J Clin Oncol. 2012;30(29):3604-3610.
2. Röllig C. Beyond 3 plus 7. Oral presentation p126-1 at EHA2025.
3. Döhner H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf

of the ELN. *Blood.* 2022;140(12):1345-1377.
4. Lambert J, et al. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, Phase III ALFA-0701 trial. *Haematologica.* 2019;104(1):113-119.
5. Erba HP, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, Phase 3 trial. *Lancet*. 2023;401(10388):1571-1583.
6. A Study of Ivosidenib or Enasidenib in Combination With Induction Therapy and Consolidation Therapy, Followed by Maintenance Therapy in Patients With Newly Diagnosed Acute Myeloid Leukemia or Myedysplastic Syndrome EB2, With an IDH1 or IDH2 Mutation, Respectively, Eligible for Intensive Chemotherapy (HOVON150AML). ClinicalTrials.gov ID NCT03839771. Last Accessed 1st July 2025. www.clinicaltrials.gov/study/ NCT03839771.
7. DiNardo CD, et al. Long term results of venetoclax combined with FLAG-IDA induction and consolidation for newly diagnosed and relapsed or refractory acute myeloid leukemia. *Leukemia.* 2025;39(4):854-863.
8. Cherry EM, et al. Venetoclax and azacitidine compared with induction chemotherapy for newly diagnosed patients with acute myeloid leukemia. *Blood Adv.* 2021;5(24):5565-5573.
9. Montesinos P, et al. Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia. *NEJM*. 2022;386(16):1519-1531
10. DiNardo C. Beyond HMA+venetoclax. Oral presentation p126-2 at EHA2025.
11. Gangat N et Tefferi A. Venetoclax in the treatment of acute myeloid leukemia: Beyond VIALE-A. *Am J Hematol*. 2024;99:515–518.
12. Roboz G. All-oral decitabine-cedazuridine (DEC-C) + venetoclax (VEN) in ND AML patients: Phase 1/2 clinical trial results. Oral presentation s135 at EHA2025.
13. Vyas P. New combination therapies. Oral presentation p250-3 at EHA2025.
14. Candoni A, Coppola G. A 2024 Update on Menin Inhibitors. A New Class of Target Agents against KMT2A-Rearranged and NPM1-Mutated Acute Myeloid Leukemia. *Hematol Rep.* 2024;16(2):244-254.
15. Erba H. Ziftomenib combined with intensive induction chemotherapy (7+3) in newly diagnosed NPM1-M or KMT2A-r acute myeloid leukemia (AML): Updated Phase 1a/b results from KOMET-007. Oral presentation S136 at EHA2025.
16. Wei AH. RP2D determination of bleximenib in combination with VEN+AZA: phase 1b study in nd & r/r aml with *KMT2A/NPM1* alterations. Abstract s137 at EHA2025.
17. Zeidner J. Azacitidine, venetoclax, and revumenib for newly diagnosed older adults with acute myeloid leukemia (AML) and NPM1 mutation or KMT2A Rearrangement: updated results from the Beat AML consortium. Oral presentation s138 at EHA2025.
18. Yilmaz N. Phase I/II study of decitabine, venetoclax, and quizartinib triplet combination in FLT3-ITD mutated AML. Abstract S142 presented at EHA2025.
19. Yunhang G, et al. Discovery of the Clinical Candidate Sonrotoclax (BGB-11417), a Highly Potent and Selective Inhibitor for Both WT and G101V Mutant Bcl-2. *J Med Chem.* 2024;67(10):7836-7858.
20. Montesinos P. Updated safety and antileukemic activity data for sonrotoclax (BGB-11417), a potent and selective BCL2 inhibitor, in patients with relapsed/refractory acute myeloid leukemia. PF491 at EHA2025.

# 05

# Geriatric hematology: from HSC to AI




**Dr. Matteo Della Porta** shares his highlights on geriatric hematology from EHA2025

## "InflammAging" and clonal hematopoiesis: Microbial and inflammatory drivers of HSC aging

Prof. Markus Manz provided a detailed overview of the emerging concept of "InflammAging" – the chronic inflammatory state that accompanies aging, affecting hematopoietic stem cell (HSC) function and promoting clonal hematopoiesis. He highlighted age-associated gut microbiome dysbiosis as a key contributor, as it increases intestinal permeability and allows microbial products to enter circulation, ultimately triggering chronic bone marrow (BM) inflammation.[1] Continuous exposure to inflammatory signals such as infections and microbial metabolites leads to HSC exhaustion, differentiation bias, and reduced regenerative potential.[1,2] Over time, this inflammatory stress environment promotes accumulation of mutations, loss of diversity, and expansion of mutant clones – hallmarks of clonal hematopoiesis of indeterminate potential and age-related clonal hematopoiesis. Mutations in genes like *Tet2* and *Dnmt3a* are particularly common in this context.[3-5] In addition, inflammation not only favors these mutant clones but also increases the risk for malignant transformation, especially when compounded by secondary hits.

Elevated interleukin (IL)-1 signaling in aged BM has emerged as a key pathway driving HSC dysfunction and clonal dominance.[5,6] Experimental models

have shown that blocking IL-1 or removing microbial stimuli (e.g., in germ-free or IL1R1-deficient mice) can protect against age-related HSC decline.[6] These findings highlight the role of inflammation and microbial signals in shaping the aging hematopoietic niche. Targeting IL-1 signaling and microbiome-derived inflammation may offer new therapeutic strategies to mitigate hematopoietic aging and reduce the risk of clonal progression to leukemia.[7]

## A deep learning model can predict the chronological age of HSC/MPPs from single-cell transcriptomic data

To explore the impact of aging on hematopoietic stem and progenitor cells (HSCPs), researchers presented their results from an analysis of six publicly available single-cell RNA-seq datasets, through which they created a comprehensive atlas of ~193,000 CD34+ Lin- HSCPs across the human lifespan. A subset of ~64,000 HSC/multipotent progenitors (MPPs) was identified based on the expression of established markers such as AVP, HOPX, and MLLT3. Using matrix factorization, seven molecular programs were defined that captured functional heterogeneity of HSC/MPPs. These programs showed age- and disease-specific enrichment, including in myelodysplastic syndromes (MDS), myelofibrosis, and B-cell precursor acute lymphoblastic leukemia (BCP-ALL). The trained model predicted premature aging signatures in BCP-ALL HSC/MPPs, but not in MDS, suggesting distinct mechanisms of transcriptional age reprogramming. This approach may guide future therapeutic strategies targeting aging pathways that contribute to age-related regenerative decline and hematologic malignancies.[8]

## Immune effector dysfunction scores: A prognostic index in AML

Technological advances have enabled deeper characterization of the tumor microenvironment (TME) in acute myeloid leukemia (AML), revealing mechanisms that contribute to disease progression. Prior work identified natural killer (NK)-like senescent CD8+ T cells as markers of poor response. Building on these insights, a presentation at this year's EHA congress introduced an immune effector dysfunction (IED) prognostic index, which stratifies AML cells into senescence/NK-high and senescence/NK-low groups based on gene expression.[9] The IED signature was found to be largely expressed by T and NK cells in the TME. In the BEAT-AML2 real-world cohort, high IED scores were associated with poor survival outcomes in patients treated with intensive chemotherapy. When combined with AML stemness markers (e.g., LSC17), the IED index helped distinguish between subgroups with excellent (IED-low/stemness-low) or poor outcomes.[10]

Single-cell profiling further identified a population of TEMRA/senescent-like (SenL) T cells enriched in AML and associated with poor response to chemotherapy. These cells were associated with Type I/II interferon signaling, oxidative phosphorylation, fatty acid metabolism, and reactive oxygen species production, and were likely induced by AML tumor cells rather than representing bystander T cell infiltration. High IED scores (NK-like CD8+ TEMRA states) also correlated with poor response to midostaurin (*in vitro*), venetoclax (*ex vivo*), and pembrolizumab plus azacitidine. Furthermore, BM from ipilimumab non-responders showed enriched TEMRA-like cells overexpressing NK cell markers and chemokines that reshape the TME. Targeting BM inflammation and senescence may enhance the efficacy of AML therapies.

## The future of AI in the intersection of hematology and geriatrics

With rising life expectancy, more people, including geriatric patients, are living with hematologic malignancies. These individuals often face multiple comorbidities and medications, making treatment planning, especially around drug interactions, challenging. Yet, of the over 1,000 US Food and Drug Administration (FDA)-approved artificial intelligence (AI)-enabled medical devices, only 2% are in hematology, and just three address geriatric care.[11,12] This presentation explored how AI could help to fill this gap and shape the future of geriatric hematology. Potential applications include automation in microscopy, blood and cell analysis, karyotyping, and genomic interpretation, enabling more accurate distinction between malignant and non-malignant cases. Large language models (LLMs) are already used for morphology-based diagnostics, with AI-proposed results accepted in 75% of 21,926 cases.[13] Looking further ahead, AI may become part of real-time workflows, such as history-taking, documentation, and diagnosis, where it already outperforms physicians in accuracy (92% versus 74%). Clinical adoption of this potential is still underutilized. By 2030, integrated diagnostic dashboards may combine lab results, minimal residual disease, genomics, and digital twin simulations to support dynamic prognostication and therapy guidance. Ultimately, AI will likely enhance, not replace, clinical care by simplifying workflows and enabling clinicians to spend more time with patients.[13]

## LLM-assisted decision-making in geriatric hematology

The different dimensions of the complex profiles of geriatric patients are often overlooked by current decision-making tools. LLMs offer new potential to address these by analyzing medical histories, test results, and literature to provide personalized treatment recommendations. Tools such as CancerLLM and RadOnc-GPT have shown promise in improving phenotype extraction from pathology reports and helping geriatric oncologists to stay up-to-date with the latest scientific evidence.[14,15] LLMs can also effectively assist with note taking.[16] During her talk, Dr. Esther Lueje emphasized that these models offer great promise, but their use does not come without risks, such as hallucinations, clinical errors, challenges with unstructured data, and the need for staff training and data privacy protections. When used wisely, however, AI can support clinical judgement and reduce administrative burden, allowing clinicians return to what matters most: patient care.[17]

## More from EHA

Mark on your agenda the EHA SWG meeting in November 2025 and the EHA ReCon 2026, both events focusing on age-related changes in hematopoiesis and associated clinical disorders. On the clinical side, get up to date on hematology and aging patients through the EHA Campus Program dedicated to treating older adults.

SWG - From Aging Hematopoietic Stem Cells to Age-related Diseases: Opportunities for Intervention

ReCon: From cradle to grave: normal & malignant hematopoiesis in young & aged settings

Hematology of the Aging Patient: Dispelling Myths Program

## References


1. Balmer ML, et al. Microbiota-derived compounds drive steady-state granulopoiesis via MyD88/TICAM signaling. *J Immunol.* 2014;193(10):5273-5283.
2. Caiado F, et al. Inflammation as a regulator of hematopoietic stem cell function in disease, aging, and clonal selection. *J Exp Med.* 2021;218(7):e20201541.
3. Meisel M, et al. Microbial signals drive pre-leukaemic myeloproliferation in a Tet2-deficient host. *Nature.* 2018;557(7706):580-584.
4. Hormaechea-Agulla D, et al. Chronic infection drives Dnmt3a-loss-of-function clonal hematopoiesis via IFNγ signaling. *Cell Stem Cell.* 2021;28(8):1428-1442.e6.
5. Caiado F, et al. Aging drives Tet2+/- clonal hematopoiesis via IL-1 signaling. *Blood.* 2023;141(8):886-903.
6. Kovtonyuk LV, et al. IL-1 mediates microbiome-induced inflammaging of hematopoietic stem cells in mice. *Blood*. 2022;139(1):44-58.
7. Manz MG. Aging in HSCs. Oral presentation p101-1 at EHA2025.
8. Wang G. STEM CELL AGING CLOCK: A DEEP LEARNING DRIVEN FRAMEWORK FOR PREDICTING STEM CELL AGE. Oral abstract s332 at EHA202.
9. Rutella S, et al. Immune dysfunction signatures predict outcomes and define checkpoint blockade-unresponsive microenvironments in acute myeloid leukemia. *J Clin Invest.* 2022;132(21):e159579.
10. Rutella S. BM inflammation; effects on clinical outcome and immune response in myeloid malignancies. Oral presentation p101-3 at EHA2025.
11. Muralidharan V, et al. A scoping review of reporting gaps in FDA-approved AI medical devices. *NPJ Digit Med.* 2024;7(1):273.
12. www.fda.gov.
13. Haferlach T. The future of AI in the intersection of hematology and geriatrics. Oral presentation p252-1 at EHA2025.
14. Li et al. *arXiv.* 2024:2406;10459.
15. Liu Z, et al. *arXiv.* 2023;abs/2309.10160.
16. Dayan R et al., Age against the machine-susceptibility of large language models to cognitive impairment: cross sectional analysis *BMJ.* 2024;387:e081948.
17. Lueje E. LLM-assisted decision-making in geriatric hematology. Oral presentation p252-2 at EHA2025.

# 06

# The new frontiers of genomic and functional techniques for precision medicine in hematology

## The future role of AI in hematology diagnostics

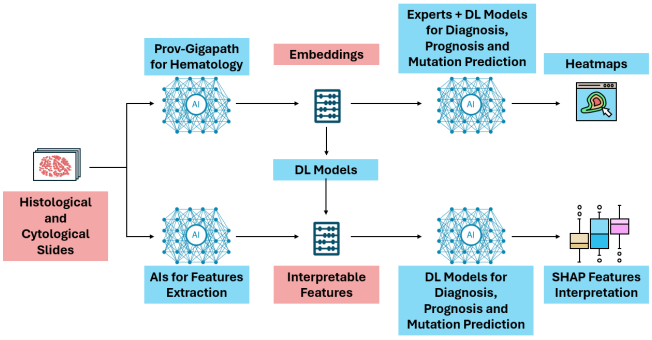
The integration of artificial intelligence (AI) into hematology diagnostics is a promising approach to tackling challenges inherent to manual diagnostic methods, such as peripheral blood and bone marrow (BM) smear analyses. These traditional techniques may be impacted by inter- and intra-observer variability, can lead to delayed diagnoses, and are often associated with a flat learning curve for operators. In contrast, AI excels at processing large amounts of data and identifying complex patterns, making it a powerful tool for cell and disease classification, digital biomarker discovery, and response prediction and risk stratification. A key advancement is the use of large language models (LLM) and foundational models that can integrate different data sources, such as imaging, clinical notes, or genomic information into a unified diagnostic framework.[1]

At this year's EHA congress, the Articulate Medical Intelligence Explorer (AMIE) was presented as a compelling example of an LLM system optimized for physician-patient AI-assisted diagnostic dialogue. In a recently published study, AMIE consistently outperformed unassisted physicians in diagnostic accuracy across various top-n predictions, and enhanced clinician performance when used as a supportive tool.[2] Furthermore, AMIE's soft skills were preferred by patients, receiving higher patient preference scores than primary care physicians (PCPs) across key patient-related metrics such as empathy, understanding and addressing patient concerns, and maintaining patient welfare.[3] These findings highlight the transformative role that AI systems like AMIE could play in improving both diagnostic accuracy and patient interaction in hematology.

## The role of digital pathology in personalized medicine for hematological malignancies

Building on the potential of LLMs in diagnostic support, digital pathology represents another frontier where AI is advancing precision medicine in hematology. AI-based digital pathology is transforming the analysis of histological and cytological images in hematological malignancies by detecting patterns and converting complex, high-dimensional visual information into interpretable numerical features.[4] A recent study explored the potential of AI-based digital pathology to improve personalized prognostic and predictive approaches.[5,6] The system is built on a newly defined framework for digital pathology in hematology, called PATHroclus, which was presented at the congress and includes data from 1,688 patients with myeloid neoplasms (MN). A fine-tuned foundation model was trained on this large and diverse dataset to analyze whole slide images, extract morphological features, and distinguish between specific clinical entities. In addition, a mixture-of-experts approach was applied to enhance the efficiency and scalability across different clinically relevant tasks.

PATHroclus – an innovative framework for digital pathology in hematology




The model achieved a high diagnostic accuracy (AUROC >0.91), indicating that the extracted features are clinically relevant. It also accurately predicted specific genomic profiles based on morphological patterns, demonstrating the model's ability to capture the biological background of the disease. These morphological features were integrated into an innovative prognostic tool for personalized prediction of overall survival (OS) and leukemia-free survival (LFS). Importantly, incorporating digital pathology into clinical, genomic, and karyotype data raised the C-index for OS prediction from 0.82 to 0.88, and for LFS from 0.80 to 0.90, highlighting its added prognostic value.

The PATHroclus platform supports federated learning, enabling collaborative model training without sharing raw patient data across institutions. Supported by the EHA, the platform will be deployed as the basis for a virtual atlas of hematological malignancies, aiming to improve diagnostic standards and reproducibility across Europe.

## Bringing AI into clinical practice in hematology

In hematology, many existing AI models have relied on image analysis.[7,8] However, recent advances in LLMs are shifting this landscape. LLMs support medical reasoning, add additional context, and can be used to structure unstructured data, such as imaging results or pathology reports.[9] New vision language models extend this further by supporting image interpretation and enabling applications in biomarker quantification and discovery. The ESMO Scale of Biomarkers with AI (EBAI) initiative is actively investigating how AI can be used for the quantification and prediction of existing biomarkers and for the identification of novel AI-based biomarkers that provide prognostic information or predict treatment response.

In his talk, Prof. Jakob Kather emphasized the potential of enhancing LLMs with external tools such as web search, calculators, imaging AI, pathology AI, or other specialist AI software. Access to structured knowledge sources like PubMed, radiology reports, or histological analyses can further improve their performance. When LLMs are linked with such other tools, they create integrated AI agents that mimic how clinicians gather information for complex clinical decisions. This enables the automation of virtually any computer-based task humans normally do. The next critical step is to validate these AI agents in clinical trials and real-world patient cases. While high-quality evidence supports the usefulness of AI products,[10] it is important to recognize that models remain sensitive to subtle cues and nuances, and that privacy and compliance concerns must be carefully considered when entering patient data into commercial AI models.

## Precision hematology through NGS immunogenetics across diagnosis, prognosis, theranostics, and monitoring

As precision medicine continues to shape the hematological field, advances in genomic technologies such as next-generation sequencing (NGS) are contributing to more refined and individualized approaches in hematology. Prof. Anton Langerak highlighted recent developments in this area. NGS immunogenetics enables in-depth profiling of immunoglobulin (IG) and T-cell receptors (TR), providing insights into antigen receptor diversity and clonality.[11] This approach allows precise differentiation between polyclonal, oligoclonal, and monoclonal populations, supporting the identification of precision markers in hematologic malignancies.[12,13] Standardized protocols for IG/TR clonality testing are now established and facilitate a range of clinical applications. In lymphoma diagnostics, NGS helps distinguish relapses from new disease by comparing clonal profiles. In chronic lymphocytic leukemia (CLL), the identification of stereotyped subsets, such as subset #2 and #8, offers prognostic insights, while immunoglobulin light chain variable region (IGLV) stereotypy may also serve as a theranostic marker. NGS-based immunoglobulin heavy chain variable region (IGHV) assays for minimal residual disease (MRD) detection offer high sensitivity and enhance prognostic risk stratification. Furthermore, early detection studies, such as the EPIC cohort in CLL and the LOGIC study in non-Hodgkin lymphoma (NHL), demonstrate that NGS can identify preclinical clones before clinical onset, supporting its role in screening and risk prediction.

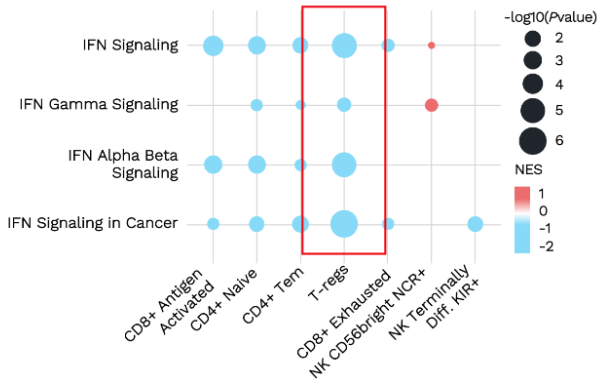
## Multimodal analysis of newly diagnosed AML reveals associations between genetic lesions and immunophenotypes

The immunophenotypic landscape of acute myeloid leukemia (AML) is highly heterogeneous, with no universal leukemic marker and limited inter-patient similarity.[14] The presented study used a comprehensive approach to map immunophenotypic diversity in newly diagnosed AML.[15] Researchers analyzed over 50 million cells from 520 BM aspirates collected at diagnosis using a 5-tube flow cytometry assay and a novel unsupervised clustering algorithm (MSGMM). This approach enabled the construction of a phenotypic atlas of AML, revealing seven different immunophenotypic clusters based on expression patterns of key myeloid markers.
These clusters aligned with specific genotypes. For example, patients with more mature CD34-negative blasts were predominantly associated with *NPM1* mutations. Importantly, leukemia-associated immunophenotypes (LAIPs), which are mostly absent in healthy BM, were identified and stratified. These patterns are clinically actionable, with implications for targeted therapy.

## Exploring the interplay between inflammation and immune escape in MDS, with insights from single-cell multi-omics

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal HSC neoplasms characterized by myelodysplasia, ineffective hematopoiesis, cytopenia, and increased risk of AML.[16,17] While *TP53* mutations account for approximately 10% of all MDS mutations and are known to drive an immunosuppressive tumor microenvironment (TME),[18,19] the presented study focused on characterizing non-mutational p53 dysfunction in MDS by using an integrated single-cell multi-omics approach to stratify the immunological BM environment according to p53 dysfunction.[20] Performing CITEseq, transcriptional profiling, and high-dimensional flow cytometry across patient data, the researchers identified an MDS subset with transcriptional and immunophenotypic hallmarks of p53 dysfunction despite the absence of *TP53* mutations. This subset showed reduced expression of p53 target genes and exhibited distinct features in hematopoietic stem and progenitor cells (HSPCs), including altered antigen presentation, increased levels of PD-L1 expression, and upregulated TNF-α and TGF-β signaling. Notably, p53 dysfunction was not associated with IFNγ-driven regulatory T cell expansion via CD34+ progenitors but appeared to be linked to chronic myeloid-derived inflammation.

CITEseq multi-omics analysis




These findings reveal a novel connection between inflammatory signaling and immune escape mechanisms in MDS with p53 dysfunction, independent of *TP53* mutation. Importantly, this points to a potential therapeutic responsiveness to immune-based therapies in this patient subgroup, especially when combined with anti-inflammatory strategies.

## Biomarker-driven immunotherapy in LBCL: The BIO-CHIC trial

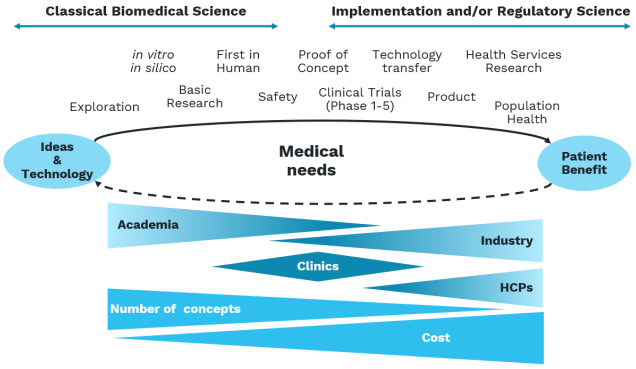
The BIO-CHIC (NGL-LBC-6) Phase 2 trial represents a precision medicine approach in patients <65 years with high-risk large B-cell lymphoma (LBCL), using biomarker-based stratification to guide risk-adapted chemoimmunotherapy and early central nervous system (CNS) prophylaxis.[21,22] Patients were stratified by biological risk factors, including single *MYC* rearrangements, double-hit lymphoma (HDL), *TP53* deletion or overexpression, *MYC/BCL2* co-expression, and CD5 positivity. High-risk patients received DA-EPOCH-R, while low-risk patients received R-CHOEP-14. Results from the trial, presented at the EHA congress, showed favorable five-year outcomes across the cohort (FFS: 75%, PFS: 83%, OS: 89%), with only slightly lower survival in the high-risk group. However, *TP53* alterations and high pre-treatment circulating tumor DNA (ctDNA) levels were associated with worse prognosis.
ctDNA analysis demonstrated a strong correlation between tumor burden, treatment response, and relapse risk. ctDNA positivity at end-of-treatment (EOT) predicted relapse, while ctDNA negativity indicated durable remission and clarified false-positive PET findings. As such, ctDNA emerged as a powerful biomarker for risk stratification, outperforming clinical scores like age-adjusted International Prognostic Index (aaIPI) and allowing for the early detection of chemoresistance. Combining this approach with genomic classifiers like LymphGen, which defines diffuse large B-cell lymphoma (DLBCL) into distinct genetic subtypes, allows for biology-based precision therapy selection.

## Translating diagnostic innovation in hematology through multidisciplinary implementation

While classical biomedical science drives innovation, implementation science ensures these advances reach patients through structured integration into clinical practice, ultimately achieving clinical benefit for individual patients.[23] The Biomedical Alliance in Europe, comprising 35 medical societies and over 400,000 healthcare professionals, promotes the role of implementing science in delivering patient-centered precision medicine.[24] At this year's EHA congress, Prof. Elizabeth Macintyre introduced the core principles of implementation science and emphasized their particular relevance in hematology, where diagnostic workflows increasingly span histology, genomics, immunology, and hematology, raising questions about how to define a consistent and clinically meaningful diagnosis.

Successful implementation of diagnostic innovations in hematologic malignancies relies on the development of national diagnostic networks. Existing examples include the UK's SIHMDS or France's GBMHM and LBMR networks, which focus on national guidelines, health technology assessment (HTA) and real-world molecular test evaluations.[24,25] Across Europe, broader implementation efforts must consider differences in population size and language diversity. Successful diagnostic implementation requires multi-stakeholder collaboration and regulatory expertise, training in implementation and regulatory science, development of coordinated diagnostic networks, support from governmental and non-profit initiatives, and development of HTA and regulatory assessment methods. Importantly, efficiency and standardization should not come at the cost of academic innovation and development.

Translating research into patient benefits




## More from EHA

The EHA Topic-in-Focus Preceptorship on Precision Medicine will take place in October 2025: application for travel grant will close on July 15, 2025. You can also explore the joint BSH/EHA guideline on the use of NGS in the diagnosis of rare inherited anemias, and the EHA Campus Program on Gene Therapy Techniques. Finally, if you are a researcher whose focus is on precision medicine approaches, check out the EHA Topic in Focus Research Grant opportunities: last call for applications opened on June 9, 2025.

TIF: Preceptorship on Precision Medicine

The Use of Next-generation Sequencing in the Diagnosis of Rare Inherited Anaemias: A Joint BSH/EHA Good Practice Paper

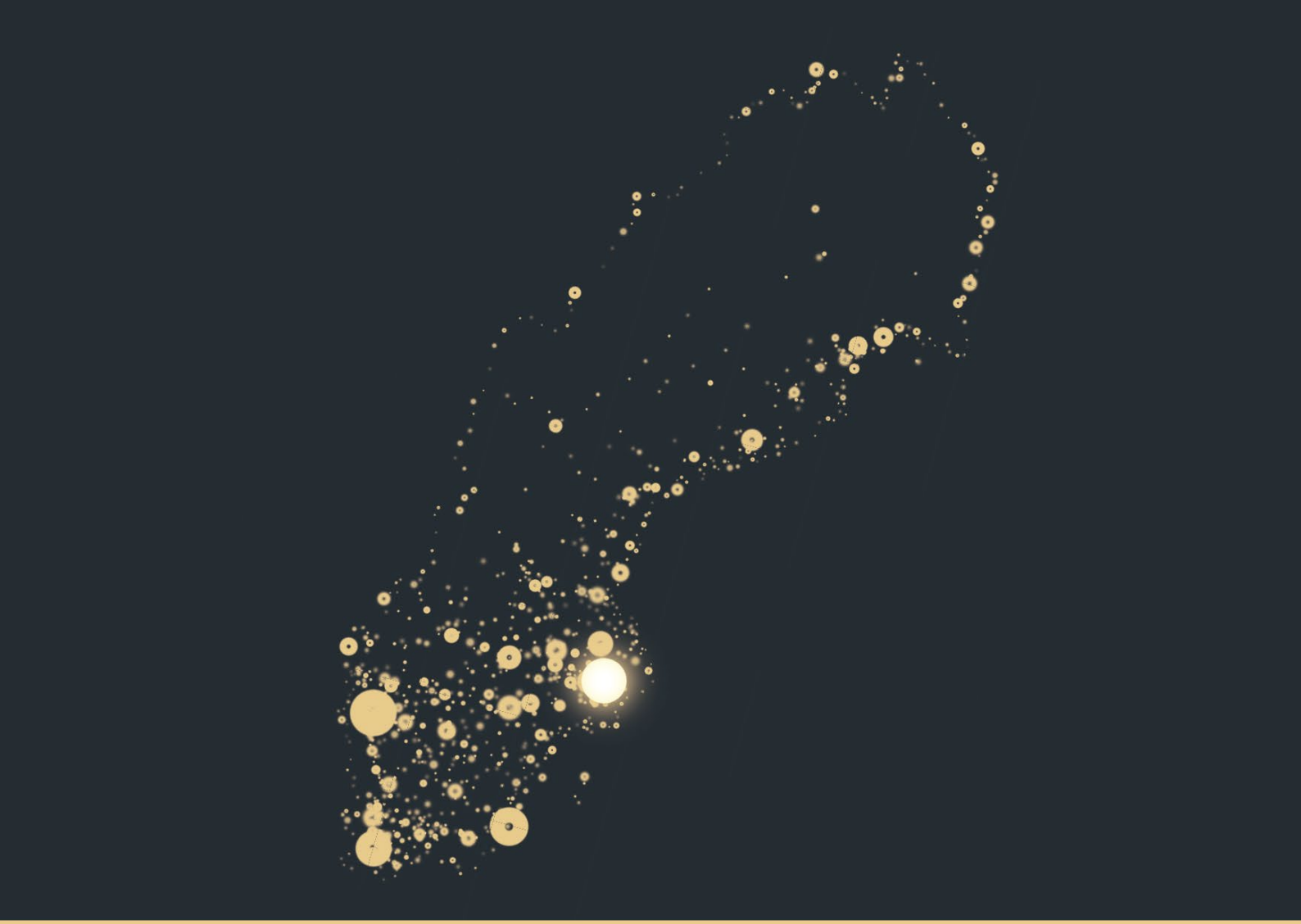
EHA Gene Therapy Techniques Program

Topic in Focus research Grants

## References


1. Eckardt JN. AI in hematology diagnostics. Oral presentation p502-1 at EHA2025.
2. McDuff D, et al. Towards accurate differential diagnosis with large language models. *Nature* 2025;642(8067):451-457.
3. Tu T, et al. Towards conversational diagnostic artificial intelligence. *Nature* 2025;642(8067):442–450.
4. Della Porta MG. Digital pathology for personalized medicine in hematological malignancies. Oral presentation p255-4 at EHA2025.
5. Asti G, et al. Artificial Intelligence-Powered Digital Pathology to Improve Diagnosis and Personalized Prognostic Assessment in Patient with Myeloid Neoplasms. *Blood* 2024;144:3598.
6. Xu H, et al. A whole-slide foundation model for digital pathology from real-world data. *Nature* 2024;630:181-188.
7. Matek C, et al. Highly accurate differentiation of bone marrow cell morphologies using deep neural networks on a large image data set. *Blood* 2021;138(20):1917–1927.
8. Eckardt JN, et al. Deep learning detects acute myeloid leukemia and predicts NPM1 mutation status from bone marrow smears. *Leukemia* 2022;36(1):111-118.
9. Kather J. Artificial intelligence in hematology: Opportunities, pitfalls, and how to bring it to clinical practice. Oral presentation p201-3 at EHA2025.
10. Lång K, et al. Artificial intelligence-supported screen reading versus

standard double reading in the Mammography Screening with Artificial Intelligence trial (MASAI): a clinical safety analysis of a randomised, controlled, non-inferiority, single-blinded, screening accuracy study. *Lancet Oncol.* 2023;24(8):936-944.
11. Langerak A. NGS immunogenetics. Abstract p282-1 presented at EHA2025.
12. Langerak AW, et al. High-Throughput Immunogenetics for Clinical and Research Applications in Immunohematology: Potential and Challenges. *J Immunol*. 2017;198(10):3765-3774.
13. Langerak AW. Immunogenetics. *Meth in Mol Biol. Springer Protocols* 2022.
14. Papaemmanuil E, et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. *N Engl J Med*. 2016;374(23):2209-2221.
15. Mocking T. Multimodal analysis of newly diagnosed acute myeloid leukemia patients reveals associations between genetic lesions and immunophenotypes. Oral presentation S121 at EHA2025.
16. Cazzola M. Myelodysplastic Syndromes. *N Engl J Med.* 2020;383(14):1358-1374.
17. Dunn WG, et al. Clonal hematopoiesis and hematological malignancy. *J Clin Invest.* 2024;134(19):e180065.
18. Sallman DA, et al. Impact of TP53 mutation variant allele frequency on phenotype and outcomes in myelodysplastic syndromes. *Leukemia* 2016;30(3):666-673.
19. Daver NG, et al. TP53-Mutated Myelodysplastic Syndrome and Acute Myeloid Leukemia: Biology, Current Therapy, and Future Directions. *Cancer Discov.* 2022;12(11):2516-2529.
20. Zampini M. The interplay between inflammation and immune escape in MDS with p53 dysfunction evolution: insights from single-cell multi-omics. Oral presentation s171 at EHA2025.
21. Leppä S, et al. Biomarker-adapted treatment in high-risk large B-cell lymphoma: long-term follow-up of a Nordic phase II trial. *Hemasphere*. 2025;9(5):e70139.
22. Leppä S. Biomarker-driven trials: Immunotherapy prediction in lymphoma. Oral abstract p269-2 presented at EHA2025.
23. Macintyre E. Implementation science in diagnostics. Oral abstract p282-1 presented at EHA2025.
24. https://www.biomedeurope.org
25. Cayuela JM, et al. Implementation science in hemato-oncology molecular diagnostics in France via the Groupe des Biologistes Moléculaire des Hémopathies Malignes (GBMHM). *HemaSphere* 2025;9(4):e70121.



# EHA2026 Congress

June 11 - 14, 2026
Stockholm, Sweden

eha

# Let's meet at EHA**2026**

## where we connect the global hematology community.

EHA2026 will once again offer an exceptional scientific program, featuring a seamless flow of engagement across Plenary Sessions—including the Opening Ceremony, Plenary Abstract Session, and Presidential Sessions—alongside carefully curated Sponsor Sessions spread throughout each Congress day.

With a comprehensive program and two poster sessions, we look forward to sharing the latest clinical and research updates in hematology with you.

Join us in the city renowned for celebrating scientific achievement to explore the latest advancements in hematology, and engage with leading experts at the cutting edge of scientific progress.

**Save the date for EHA2026 to ensure you stay at the forefront of hematology.**

**Stay informed with updates on the EHA website.**

**ehaweb.org**

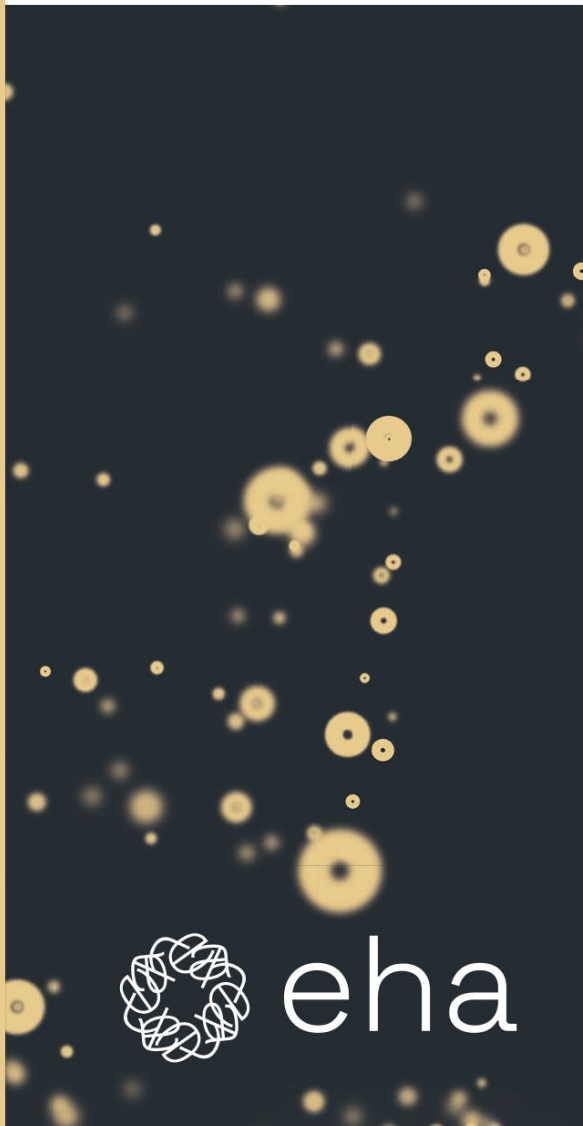
**Key dates:**

**March 1, 2026**
- Abstract submission deadline
- Grant application deadline

**May 4, 2026**
- Early registration deadline

**May 7, 2026**
- Late-breaking abstract submission deadline

**June 11 - 14, 2026**
- EHA2026 Congress in Stockholm, Sweden



**Publisher**
European Hematology Association - EHA Executive Office
Koninginnegracht 12b | 2514 AA The Hague | The Netherlands

**Imprint**
Production: infill healthcare communication GmbH
Medical writing and editing: Marie Farrow, MA (Oxon); Vishal Hegde, PhD; Amy Kenyon, PhD; Melissa Koch, MSc; Júlia Melià Alomà, PhD; Anette Minarzyk, Dipl Biol; Stephan Rudolph, PhD; Sofia Urner, PhD; and Sven Vanselow, PhD
Graphics: Heidrun Bahmann, Bastian Höfer, Nele Honnef, Martin Jöckel, Luke Lehnen, Daniel Nikolay, Max Runald, and Sascha Tkacz



**ehaweb.org**