EHA Perspectives on Malignant Hematology

Presented at the EHA2025 Congress

Milan, Italy

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Table of contents

Supported by BeOne Medicines and Eli Lilly and Company
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Welcome & Objectives

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 format at the EHA2025 Congress, the reports underscore the significance of the latest developments in the various fields of hematology.

Martin Dreyling, EHA2025 Scientific Program Committee Chair

Objectives

The EHA Annual Congress is recognized as the second-largest global event in hematology. Beyond uniting hematology experts from around the world, the EHA Congress serves as a vital platform for disseminating groundbreaking scientific information and developments within the field of hematology. The congress reports are an initiative to give the hematology community a concise overview of the most critical work showcased at EHA2025.

01

The genetic continuum of myeloid neoplasms: from Clonal Hematopoiesis to Acute Leukemias

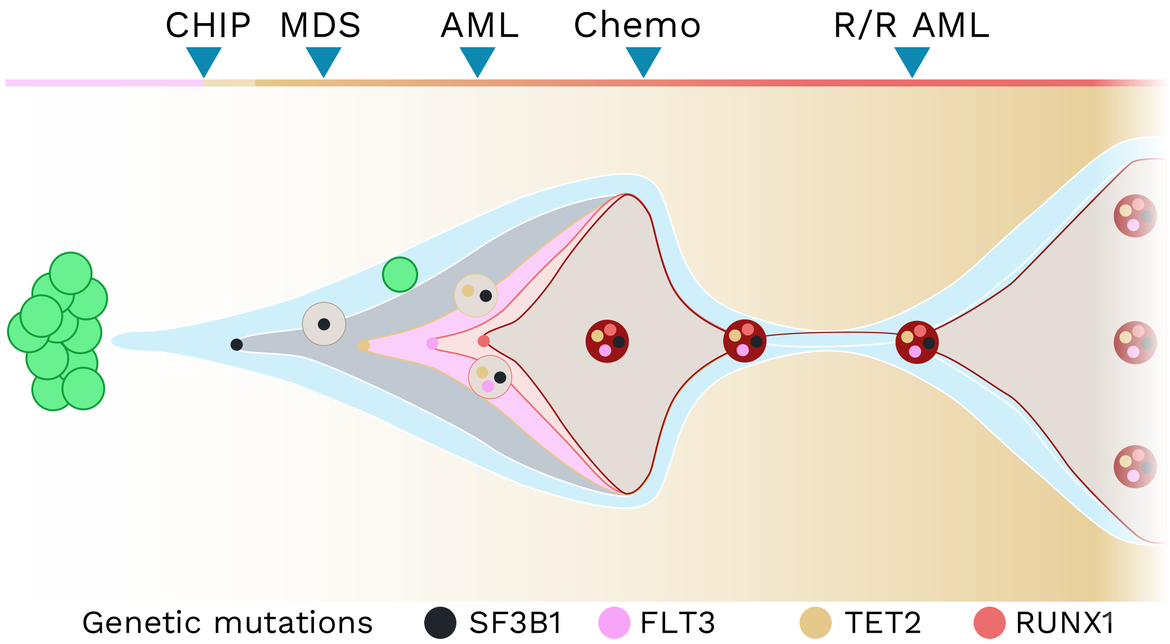
Section 1: The genetic continuum of myeloid neoplasms: from Clonal Hematopoiesis to Acute Leukemias

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
p115-1	Pathophysiology and clonal evolution in MDS	Dominique Bonnet
p266-1	Clonal selection in MPN and its consequence	Lina Benajiba
S145	Myeloid neoplasms risks for germline DDX41 pathogenic variants carriers	Marie-Charlotte Villy
p114-2	Antibody targeting of mutant CALR in MPN	Isabelle Plo
LBA4002	INCA33989 is a novel, first in class, mutant calreticulin-specific monoclonal antibody that demonstrates safety and efficacy in patients with essential thrombocythemia (ET)	John Mascarenhas
S212	INCA035784, A novel, equipotent T Cell–redirecting antibody for patients with myeloproliferative neoplasms carrying different types of calreticulin mutations	Beth Psaila
S211	Discovery of first-in-class precision antibody drug conjugates targeting mutant calreticulin for the treatment of myeloproliferative neoplasms	Norman Fultang
S224	SANRECO, an on-going Phase1/2 study evaluating divesiran, a novel GalNAC-conjugated siRNA, in patients with polycythemia vera	Marina Kremyanskaya

p115-1: Pathophysiology and clonal evolution in MDS

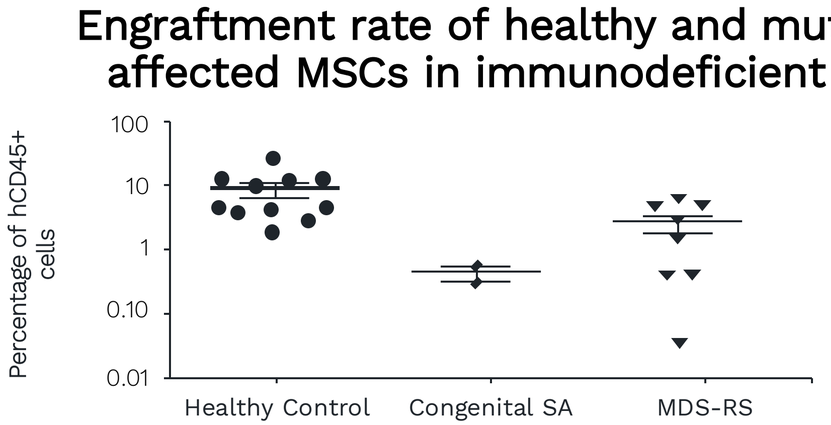
Clonal selection in progressive myeloid malignancy

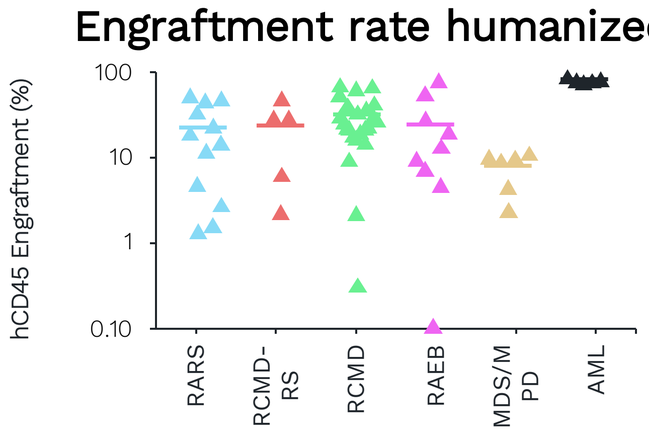


- Myelodysplastic syndromes (MDSs) are clonal blood conditions associated with abnormal blood cell production
  - Characterized by peripheral blood cytopenia, increased apoptosis, increasing number of blasts in BM
- MDS has a 5-year survival rate of only ~30% and its incidence increases with age
- Clonal hematopoiesis of indeterminate potential (CHIP) is a common age-associated phenomenon that can progress to MDS
- Several mutations can lead to MDS
  - One discernible subgroup, MDS ring sideroblast (MDS-RS), is associated with SF3B1 mutations
- Clonal transformation via acquisition of additional mutations can lead to AML

AML, acute myeloid leukemia; BM, bone marrow; MDS, myelodysplastic syndrome; MSC, myeloid stem cell; RS, ring sideroblast.
Bonnet D. Pathophysiology and clonal evolution in MDS. Oral presentation p115-1 at EHA2025.

p115-1: Pathophysiology and clonal evolution in MDS





- Reliable mouse models are needed to study MDS and develop strategies to intervene earlier and stop disease evolution
- Transplantation of human MDS HSPCs has been used in this context. However, engraftment rates of human HSPCs in combination with MSCs are low. Therefore new approaches are needed.
- Using a gelatin-based scaffold in combination with BM cells and growth factors provided an environment of cell attachment and growth.
- This led to the use of 3D scaffolds seeded with human MSC and EPCs, resulting in an engraftment rate of MDS BM CD45+ cells ranging from 1 to 40%, in some cases 80%
- MDS cells are highly dependent on humanized niches. Healthy MSCs could also provide the needed niche
- Goals: Identification of niche factors that maintain MDS cells, predict response to therapy with the new model, study disease transformation and improve treatment

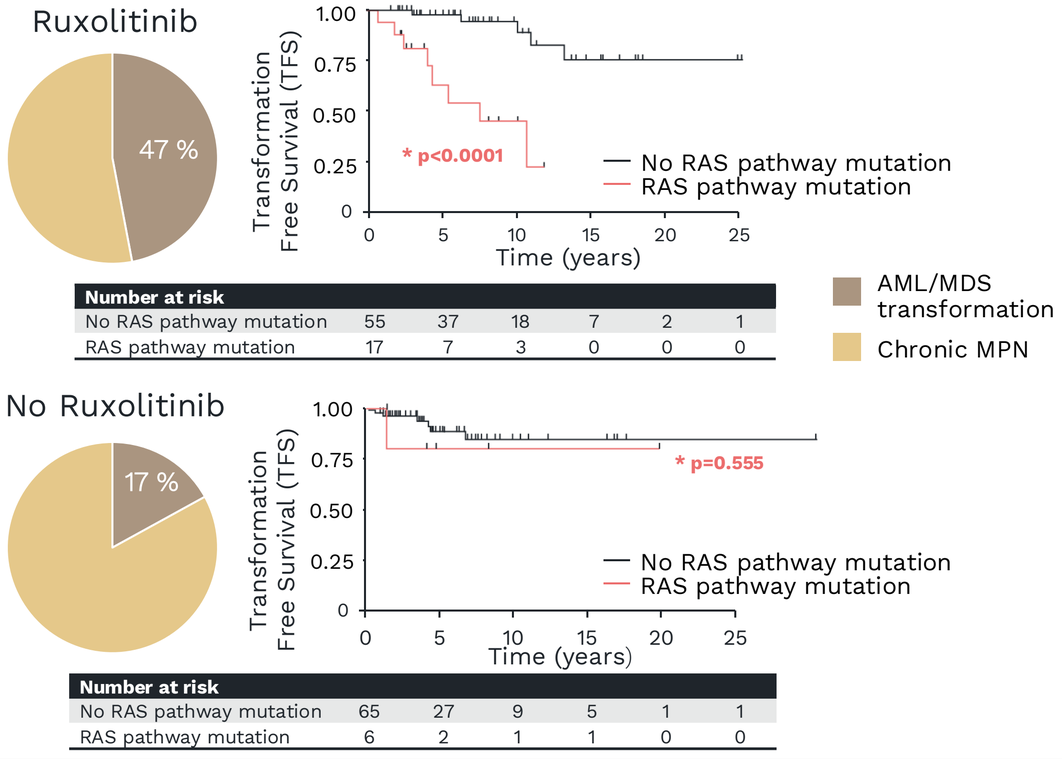
AML, acute myeloid leukemia; BM(FS), bone marrow (failure syndrome); HSPC, hematopoietic stem cell; MDS, myelodysplastic syndrome; MPD, myeloproliferative disease; MSC, myeloid stem cell; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ring sideroblast; RCMD, refractory cytopenia with multilineage dysplasia; RS, ring sideroblast.

Bonnet D. Pathophysiology and clonal evolution in MDS. Oral presentation p115-1 at EHA2025.

p266-1: Clonal selection in myeloproliferative neoplasms (MPNs) and its consequences

- MPNs can progress to secondary AML through clonal evolution, which is driven by acquisition of additional mutations (N/KRAS, NFE2 & TP53) and clone fitness
- Prognostic factors in patients with MPN include:
  - OS: K/NRAS, NFE2 and TP53 mutations, and complex mutational profiles
  - Arterial Thrombosis: TET2 or DNMT3A mutations
  - Resistance to treatment: TET2, DNMT3A, ASXL1, EZH2, IDH1/2 mutations
- Age is the only known risk factor for clonal evolution
- The microenvironment might drive the survival and expansion of mutant cells, e.g. via inflammation
- RAS mutant clone emergence occurs in JAK/STAT-activated and wild-type context
- JAK2 inhibition with ruxolitinib releases RAS-mutated cells from oncogene-induced senescence

Ruxolitinib enhances the expansion of RAS-mutated clones and exacerbates the risk posed by RAS mutation



AML, acute myeloid leukemia; JAK, janus kinase; MDS, myelodysplastic syndrome; MPN, myeloproliferative disorder; OS, overall survival.

Benajiba L. Clonal selection in MPN and its consequence. Oral presentation p266-1 at EHA2025.

S145: Exploring MN risks in *DDX41* pathogenic variant carriers

5–10% of all MN patients have a genetic germline predisposition[1]

- *DDX41* is the most frequent, accounting for 5% of MDS/AML
  - Affected patients present at a similar age as those with sporadic disease
- But it is a specific entity:
  - Associated with second hotspot tumor mutation in the other copy of *DDX41*
  - Has a better prognosis, with a higher response rate and longer survival

This is important because HSCT donors are often relatives

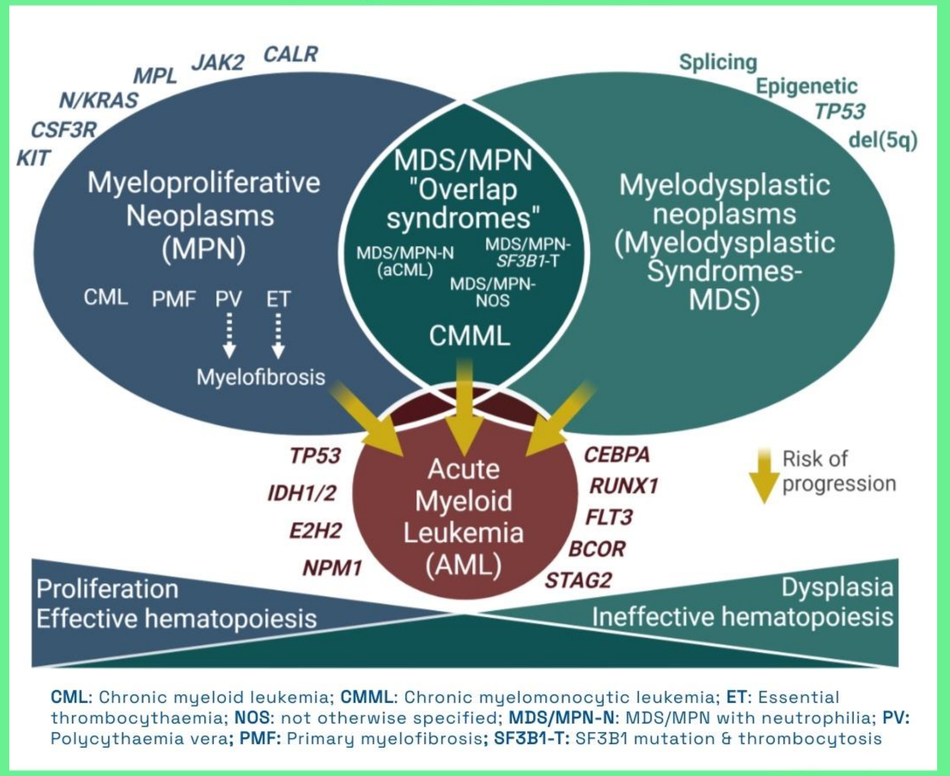
- There is growing evidence donor-derived MDS/AML when the donor carries a germline pathogenic variant in *DDX41*

Germline *DDX41* mutations define a unique subtype of MN

- Retrospective kin-cohort study in Japan found a low absolute risk before age 40, rising to 49% at age 90[2]
- UK Biobank study in the general population found absolute MDS/AML risk of 5.5% for men and 1.37% for women[3]

More from EHA #Thinking Thursday

Clinical and genetic continuum between MPN, MDS and AML



ThinkingThursday

AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; MN, myeloid neoplasm.

1. Khoury JD, et al. Leukemia 2022; 2. Makishima H, et al. Blood 2023;141(5):534-549; 3. Cheloor Kovilakam S, et al. Blood 2023;142(14):1185-1192.

Villy MC. Myeloid neoplasms risks for germline DDX41 pathogenic variants carriers. Oral presentation S145 at EHA2025.

S145: Exploring MN risk in *DDX41* pathogenic variant carriers

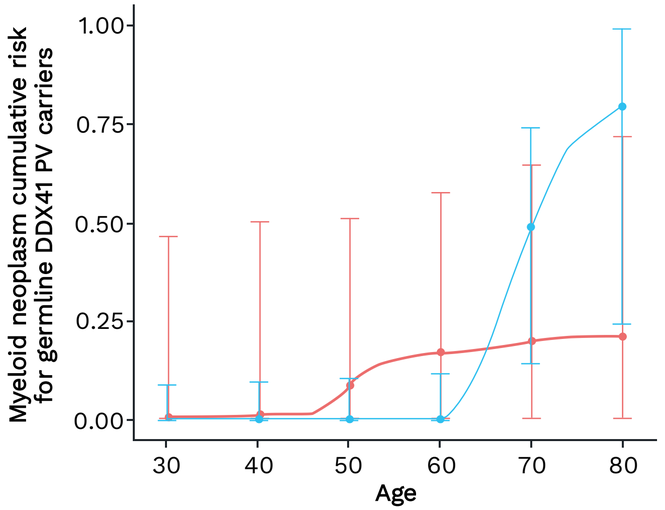
This study estimated the cumulative risk of MDS/AML in carriers:

- 11 centers in France
- 63 families with >1 genotyped relative
- 63 probands (MN, 70% males):
  - 22 MDS (median age 62 years)
  - 40 AML (median age 63.5 years)
  - 1 AA (17 years)

These findings justify monitoring recommendations for carriers

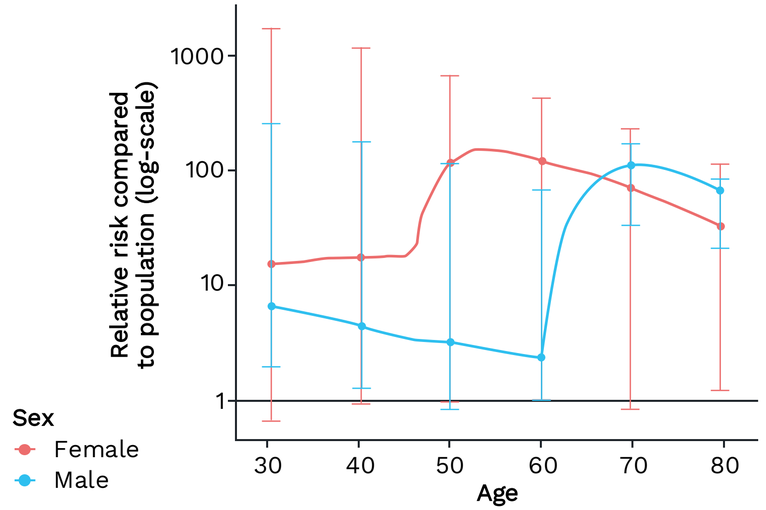
Absolute risk of MDS/AML for carriers

- Male: increases from age 60, reaching 80% at age 80
- Female: increases earlier, but lower risk (20% at age 80)



Relative risk of MDS/AML

- Up to 150 for females



AA, aplastic anemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; MN, myeloid neoplasm.

Villy MC. Myeloid neoplasms risks for germline DDX41 pathogenic variants carriers. Oral presentation S145 at EHA2025.

p114-2: Antibody targeting of mutant CALR in MPN

- Mutant CALR (mutCALR) is the second most common driver mutation in MPN,[1,2] 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 presence of a ER retention sequence (KDEL), which is lost in CALR-mut
- Cell surface CALR is thus a marker for MPN and can be selectively targeted
- Current immunotherapy strategies include:

1. Targeting the oncogenic mutCALR/MPL signaling

INCA33989 (Fc-silent, fully human IgG1 mAb)

- Binds the mutant C-terminus with high specificity and inhibits STAT signaling, prevents oncogenic proliferation, induces apoptosis, normalizes megakaryopoiesis, reduces disease-initiating cells, prevents thrombocytosis and leukemic features
- Phase 1 trials ongoing: NCT05936359, NCT06034002

2. Recruiting T-cells against mutCALR

JNJ-88549968 (mutCALRxCD3 T-cell redirecting mAb)

- Redirects T-cells to mutCALR cells, inducing selective cytotoxicity and has demonstrated tumor volume reduction and survival benefit in *in vivo* mouse models
- It is currently being tested in patients with mutCALR
- Phase 1 trial ongoing: NCT06150157

mAb, monoclonal antibody; MPN, myeloproliferative neoplasm.

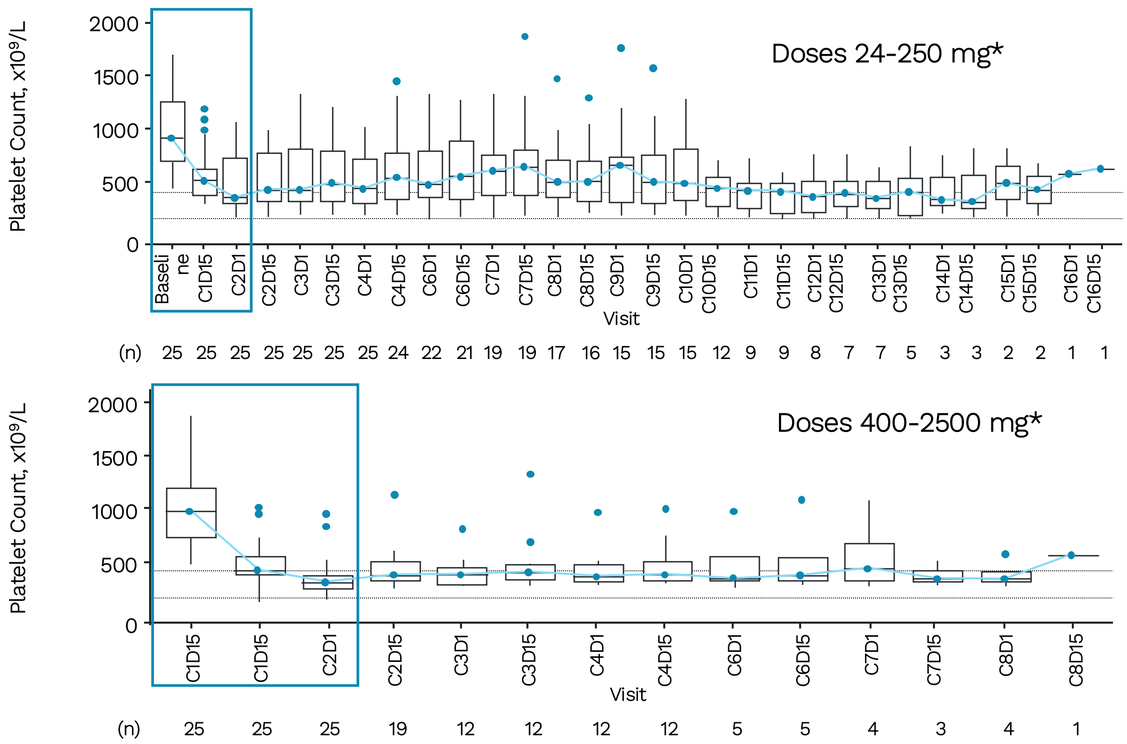
1. Klampfl et al. NEJM 2013; 2. Nangalia et al. NEJM 2013.

Plo I. Antibody targeting of mutant CALR in MPN. Oral presentation p114-2 at EHA2025.

LBA4002: INCA33989 normalizes thrombocyte counts in patients with essential thrombocythemia (ET)

- CalR mutations are found in 25% of patients with essential thrombocythemia (ET), a type of MPN; most patients have one of two mutations, Type 1 or 2
  - These patients have a higher risk of transformation to myelofibrosis; current therapies do not target driver mutations
- INCA33989 is a mAb targeting the mutCalR/TPO-R complex to inhibit cell signaling and proliferation, currently tested in two Phase 1 trials (NCT05936359, NCT06034002)
- In a study of N=49, patients received the drug at doses from 25 mg to 2500 mg
  - No DLTs but there were 3 SAEs (increased lipase levels)
  - Platelet counts normalized rapidly and sustainably in most patients, especially at doses ≥400 mg
  - Type 1 patients responded at lower doses, whilst type 2 responded well at higher doses (≥400 mg)
  - Biomarker analysis showed a reduction of mutated stem/progenitor cells and megakaryocytes

Platelet counts over the course of treatment



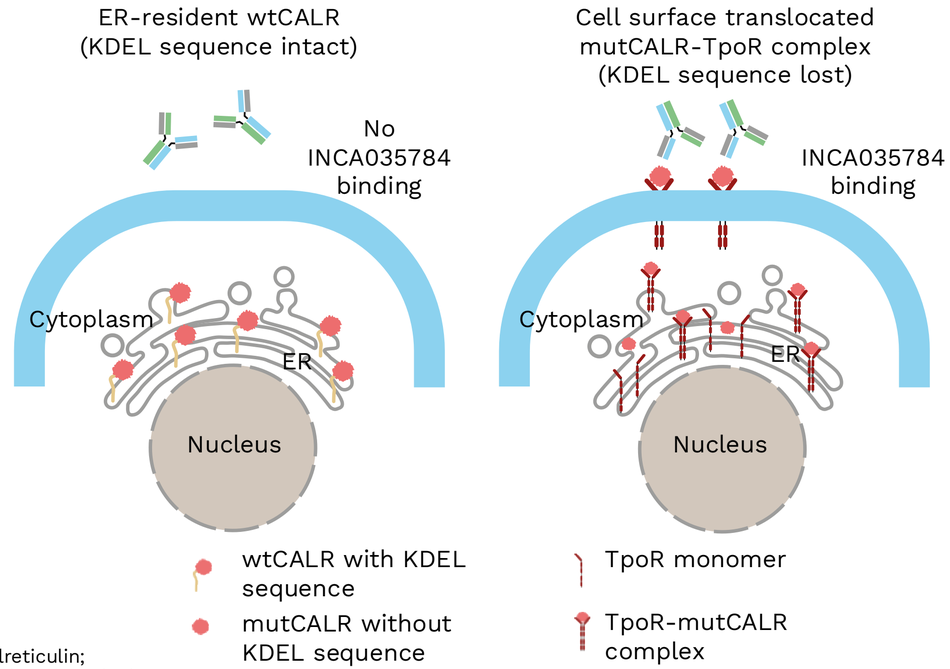
DLTs, dose limiting toxicity; mAb, monoclonal antibody; MPN, myeloproliferative neoplasm; SAEs, serous adverse events; TPO-R, thrombopoietin receptor

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.

S212: A novel, equipotent T-cell–redirecting Antibody for patients with MN carrying different calreticulin mutations

- INCA035784 is a mutCALRxCD3 bispecific, T-cell redirecting antibody
- It binds to the N-terminal domain of CALR, which remains intact despite C-terminal mutations, allowing it to target multiple forms of mutant CALR
- INCA035784 achieves specificity because wild-type *CALR* remains intracellular due to its ER retention signal (KDEL), which is absent in mut*CALR*, allowing surface expression of the mutCALR-TpoR complex.
- The selectivity of INCA035784 for different forms of mut*CALR* was tested using a panel of cell lines that was developed using TF-1 parental cells as a base
- Adding in healthy donor T cells allowed testing of T-cell activation, T-cell-mediated toxicity towards mutCALR CD34+ cells, and T-cell proliferation

Cell surface translocation of mutated CALR upon loss of KDEL sequence (ER retention signal)



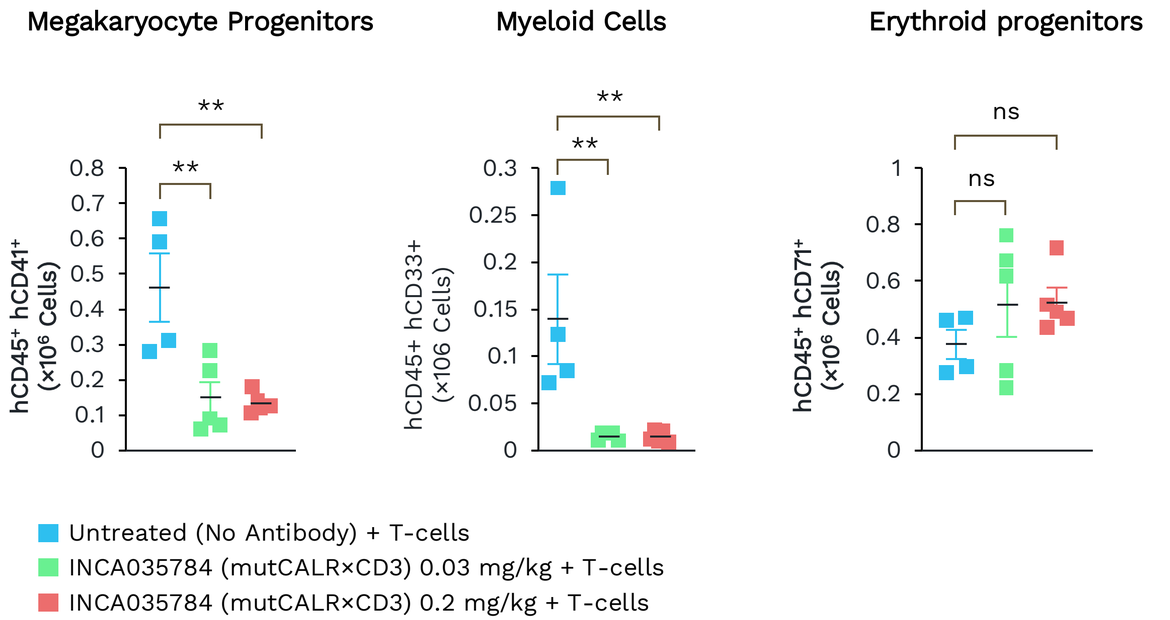
CALR, calreticulin;
ER, endoplasmic reticulum

Ab, antibody; CALR, **calreticulin; ER, endoplasmic reticulum;** MN, myeloid neoplasm.
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.

S212: INCA035784 represents a promising approach for patients with CALR-mutant MPN who lack curative treatment options

- INCA035784 selectively binds to Type 1 and 2 mut*CALR*-expressing engineered TF-1 clones, and promotes T-cell-mediated functions
- INCA035784 does not bind to surface-exposed wild-type CALR or induce non-specific cytokine secretion associated with CRS in healthy donor PBMCs
- Efficacy was tested in an MF patient-derived xenograft model
  - INCA035784 treatment seems to causes a reduction in myeloid cells (CD33+) and megakaryocytes (CD45+CD41+) in the BM but does not seem to affect the erythroid cell progenitor population (CD71+)

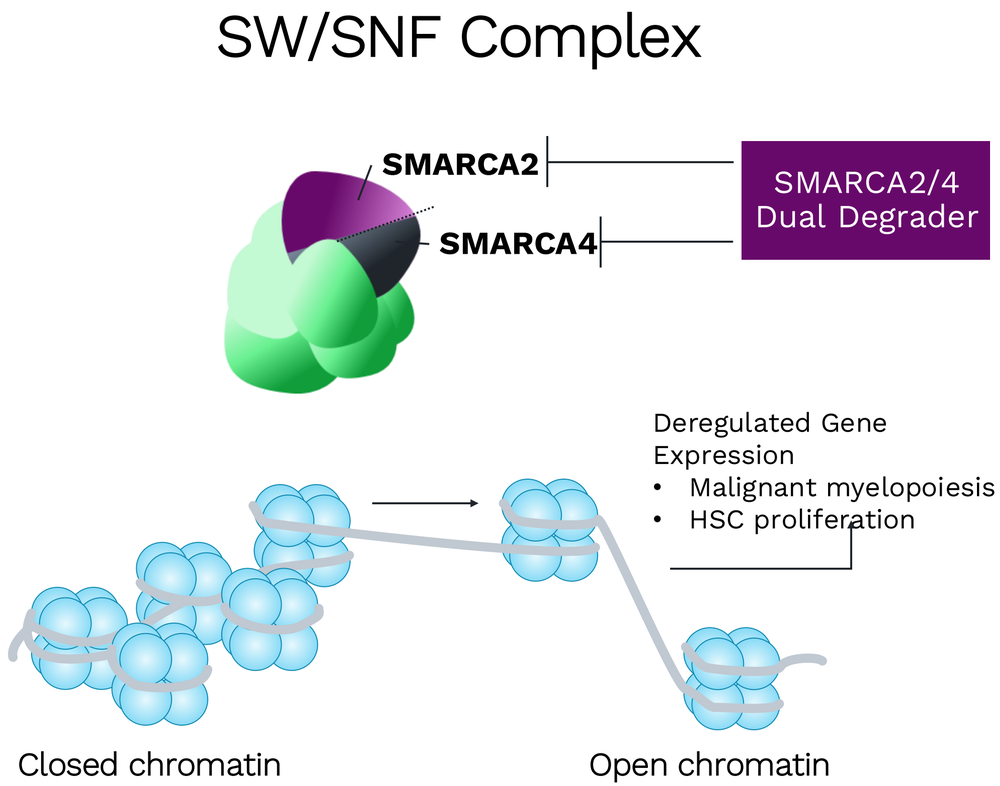
Efficacy in an autologous MF patient-derived xenograft model



**P<0.01 vs the untreated group (1-way ANOVA), Data points represent the mean and error bars represent the standard error of the mean.
Ab, antibody; BM, bone marrow; CALR, calreticulin; CRS, cytokine-release syndrome; MF, myelofibrosis; MN, myeloid neoplasm; MPN, myeloproliferative neoplasm; PBMC, peripheral blood mononuclear cell; TNF, tumor necrosis factor.
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 EHA 2025.

S211: Results of a first-in-class precision antibody drug conjugate targeting mutant calreticulin for MPN

- Deregulated SWI/SNF activity has been linked to AML, MDS, and MPN pathogenesis
- SWI/SNF ATPases SMARCA2 and SMARCA4 are key therapeutic targets in MPN
- Mutated calreticulin (CALR) is the second most common mutation in MPN
- In complex with thrombopoietin receptor (TPO-R) it is located on the cell surface and can be targeted
- A non-antagonizing, internalizing CALR Ab was identified from a screen of CALR mAb, which is selectively internalized by CALR mutant cells
- This antibody was used to develop a pADC



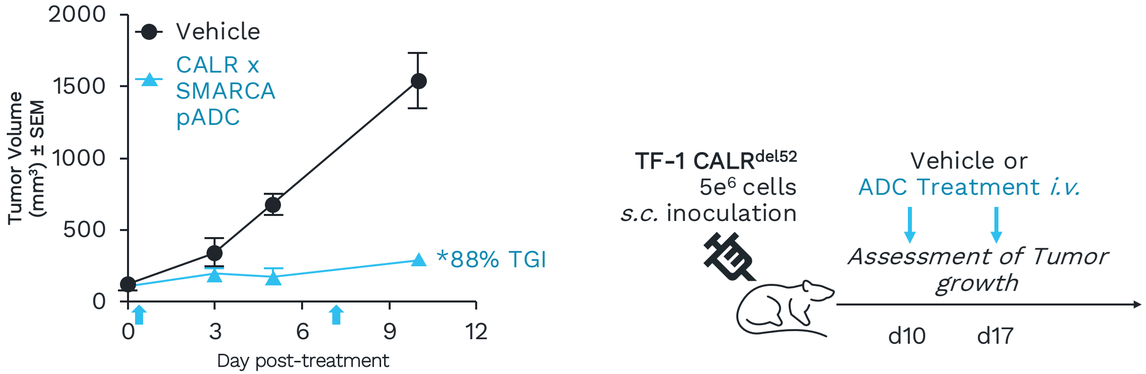
(p)ADC, (precision) antibody drug conjugate; AML, acute myeloid leukemia; CALR, calreticulin; ET, essential thrombocythemia; mAb, monoclonal antibody; MDS, myelodysplastic syndrome; MF, myelofibrosis; MPN, myeloproliferative neoplasm; SWI/SWF, switch/sucrose non-fermentable.

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.

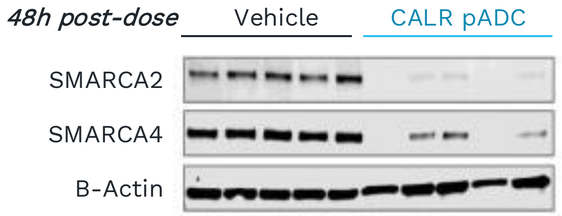
S211: Results of a first-in-class precision antibody drug conjugate targeting mutant calreticulin for MPN

- CALR 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 – posing no risk to efficacy or safety
- CALR pADCs have robust anti-tumor activity *in vivo* and are 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

Robust tumor growth inhibition



Target degradation in tumor tissue



Ab, antibody; CALR, calreticulin; MPN, myeloproliferative neoplasm; pADC, precision antibody degrader complex.

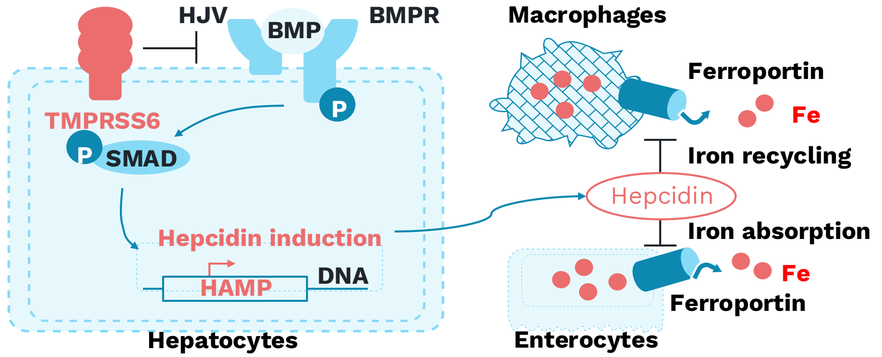
Fultang N. Discovery of first-in-class precision antibody drug conjugates targeting mutant calreticulin for the treatment of myeloproliferative neoplasms. Oral presentation S211 at EHA2025.

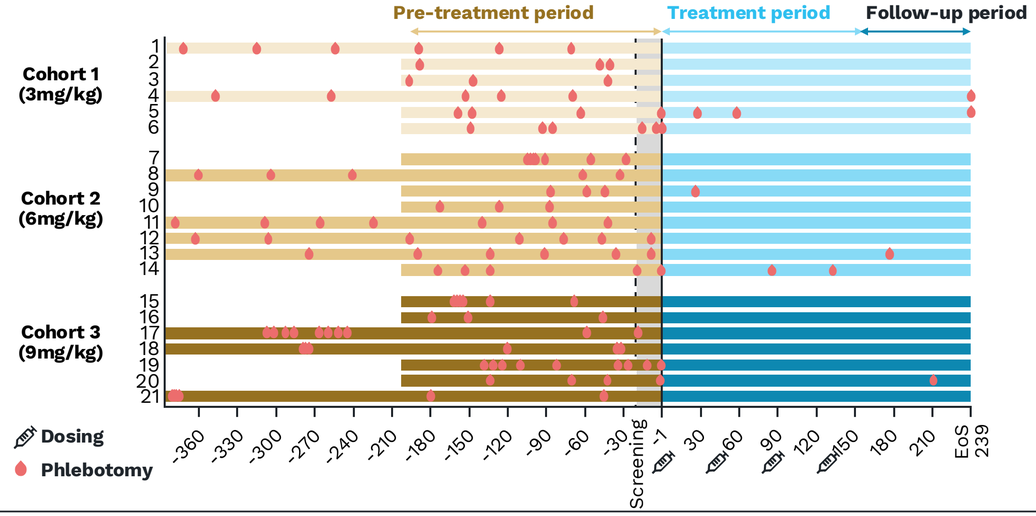
S224: First data from the Phase 1 SANRECO study on divesiran, a GalNAc-conjugated siRNA, in Polycythemia Vera (PV)

- PV is marked by excessive RBC production, elevated hematocrit, and frequent iron deficiency, and patients often have low hepcidin levels[1]
- 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

Phase 1 results (N=21) suggest:

- Treatment with divesiran **reduces phlebotomy frequency** during treatment and follow-up periods
- **Lower hematocrit and hemoglobin** were seen across all dose levels
- Dose-dependent **increases in hepcidin and ferritin** were seen
- **Well-tolerated safety profile** without dose-limiting toxicities; most common TEAEs: injection site reactions, anemia, fatigue
- Ongoing Phase 1/2 study (NCT05499013): Randomized, double-blind trial evaluating the proportion of patients achieving HCT ≤45% without phlebotomies, along with improvement in PV-related symptoms





GalNAc, N-acetylgalactosamine; HCT, hematocrit; PV, polycythemia vera; RBC, red blood cell; TEAE, treatment-emergent adverse event.

1. Ginzburg et al. 2018 Leukemia 32:2015-2116.

Kremyanskaya M. SANRECO, an on-going Phase 1/2 study evaluating Divesiran, a novel GalNAc-conjugated siRNA, in patients with polycythemia vera. Oral presentation S224 at EHA2025.

Conclusion

- MN exists across a genetic continuum – suggesting bone marrow failure syndromes such as MDS and acute conditions like AML can share genetic abnormalities and transition into one another through clonal evolution
- This year's EHA offered new insights into the biology of hematological malignancies and better models for research, including:
  - Gelatin-based scaffolds in combination with BM cells and growth factors have been explored as an environment of cell attachment and growth in MDS – leading to increased engraftment rates in mice
  - Age is the only known risk factor for clonal evolution, but the microenvironment might drive survival and expansion of mutant cells through inflammation
  - Up to 10% of all MN patients have a genetic germline predisposition, most often DDX41; carriers have a cumulative risk of MDS or AML, which justifies monitoring
- New data specifically on CalR-targeting antibodies
  - INCA33989 – a mAb targeting the mutCalR/TPO-R complex – normalizes thrombocyte counts in patients with ET
  - A first-in-class precision Ab drug conjugate also targeting mutant CALR in MPN presented animal models demonstrating robust tumor growth inhibition
  - INCA035784 – a mutCALR-N-domain-specific T-cell redirecting Ab – represents a promising approach for MPN patients who lack curative treatment options
- Data on new ways of tackling chronic bone marrow diseases
  - Divesiran in PV shows reduced rates of phlebotomy, lower hematocrit and hemoglobin – with a well-tolerated safety profile
  - Mutant CALR is the second most common driver mutation in MPN, and current immunotherapies target the oncogenic signaling or recruit T cells against the mutants

AML, acute myeloid leukemia; BM, bone marrow; CARL,; calreticulin; ET, essential thrombocythemia; MDS, myelodysplastic syndrome; MN, myeloid neoplasm; MPN, myeloproliferative neoplasm; PV, polycythemia vera; TPO, thrombopoietin

02

Monoclonal antibodies versus cellular immunotherapy: the next round

Section 2: Monoclonal antibodies versus cellular immunotherapy: the next round

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
LBA4001	Phase 2 study of talquetamab + teclistamab in patients with relapsed/refractory multiple myeloma and extramedullary disease: RedirecTT-1	Shaji Kumar
S100	First-in-human study of JNJ-79635322 (JNJ-5322), a novel, next-generation tri-specific antibody, in patients with relapsed/refractory multiple myeloma: Initial Phase 1 results	Rakesh Popat
p251-3	Cell therapy: CAR T and NK cells for R/R B cell precursor and T ALL	Bijal D. Shah
p109-1	Armored CAR T in lymphoma: Resistance mechanisms and efficacy	Carl June
p196-2	Next-Generation CAR T: Dual specificity to counter tumor escape in lymphoma	Sonia Guedan
p141-1	BiTE molecules in AML therapy	Marion Subklewe
p141-2	CAR T cell therapy in AML	Sara Ghorashian
p213-3	Outpatient CAR T therapy	Alexandra Martínez-Roca
S276	A functional CAR T cell atlas to unravel regulatory mechanisms of CAR T cells	Juan Roberto Rodriguez-Madoz
S552	BCMA bsAb vs CAR T in MM - Thematic Debate	Elena Zamagni Philippe Moreau Paula Rodrígues-Otero

LB4001: RedirecTT-1: Dual-targeting in R/R MM and Extramedullary disease

EMD is associated with poor outcomes: mOS in triple-class exposed patients is 7.2 months

- RedirecTT-1 combines talquetamab (GPTC5D) and teclistamab (BCMA), each of which, as monotherapy, achieves an ORR of ~40% in triple-class exposed R/RMM
- Preliminary Phase 1 data suggest dual targeting leads to higher ORR and greater depth and durability of response, likely by mitigating antigen-related escape
- Phase 2 of the program is the largest dedicated Phase 2 study in patients with true EMD

Talquetamab and teclistamab are first-in-class BsAb approved as monotherapies for triple-class exposed R/R MM

Step up doses* administered 2–4 days apart

- Tal 0.4 mg/kg Tec 1.5 mg/kg
- Tal 0.06 mg/kg Tec 0.3 mg/kg
- Tal 0.01 mg/kg Tec 0.06 mg/kg

Tal 0.8 mg/kg Q2W SC + Tec 3.0 mg/kg Q2W SC*

until disease progression

Primary endpoint

- ORR† (EMD response assessed by central radiology review of whole-body PET-CT scans)

Secondary endpoints

- ≥VGPR, ≥CR, and sCR rate†
- Time to response,† DOR,† PFS, and OS
- Safety
- PK, immunogenicity

Option to reduce dosing frequency for both agents to monthly dosing after:

- ≥VGPR and minimum 4 cycles of therapy, or
- 6 cycles, per investigator discretion

*Tal and Tec were administered on the same day, 30 (±10) minutes apart, for all step-up and full treatment doses. †Response was assessed by an independent review committee per IMWG criteria. BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; EMD, extramedullary disease; MM, multiple myeloma; mOS, median overall survival; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; Q2W, once every 2 weeks; R/R, relapsed/refractory; SC, subcutaneous; VGPR, very good partial response.

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.

LB4001: RedirecTT-1: Dual-targeting in R/R MM and Extramedullary disease

Efficacy:

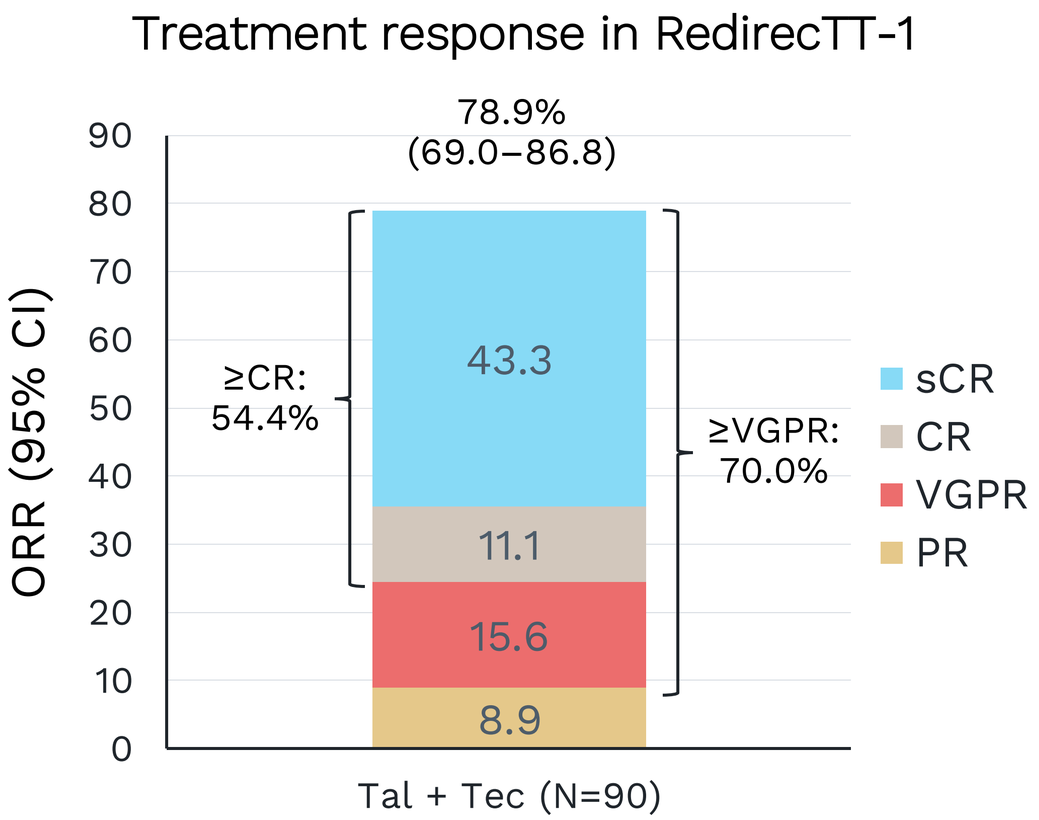
- In Phase 2, ORR was 78.9% and CR rate was 54.4%
- Responses often continued to deepen over time
- mPFS: 15.4 months; OS rate at 12 months: 74.5%

Safety:

- CRS Gr1-2 occurred in 77.8% of patients, usually during step-up dosing
- ICANS in 12.2%, mostly Gr1-2 but 2 cases Gr3/4
- Other frequent AEs included cytopenia and infections

Conclusion:

Combination exceeded the efficacy of each drug without exacerbating AE

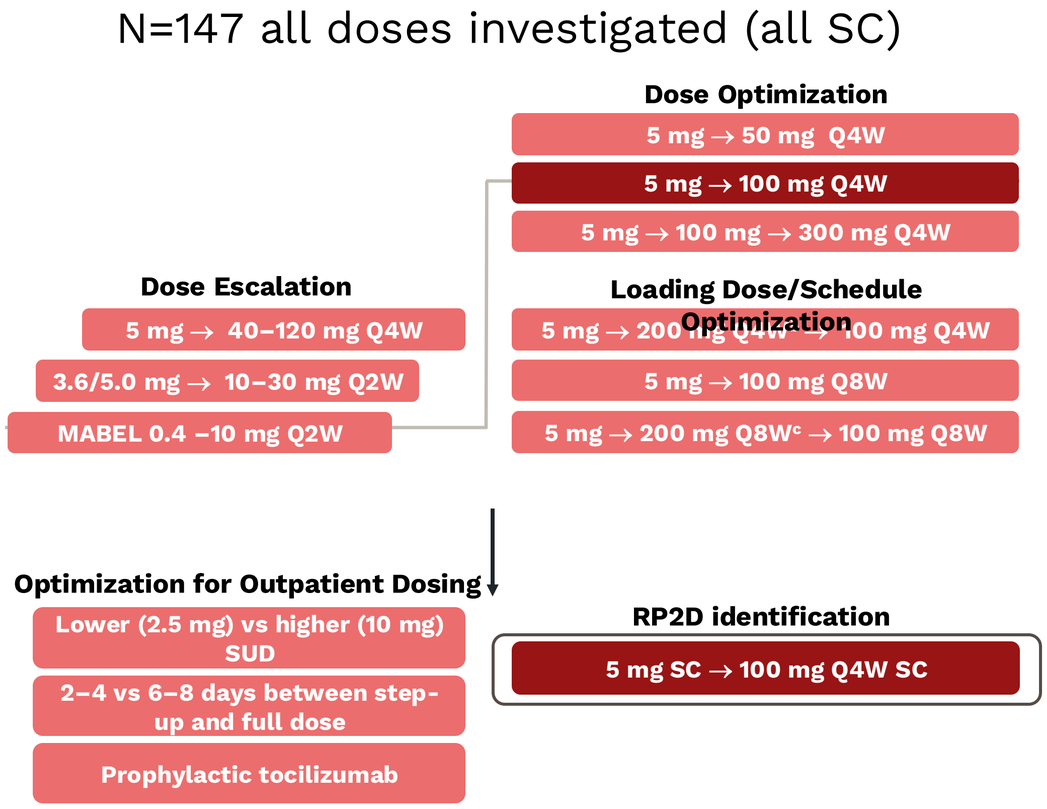


AE, adverse event; CR, complete response; EMD, extramedullary disease; Gr, grade; ICANS, immune effector cell-associated neurotoxicity syndrome; MM, multiple myeloma; mPFS, median progression-free survival; ORR, overall response rate; OS, overall survival.

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.

S100: First-in-human study of JNJ-79635322 (JNJ-5322), a trispecific BCMA/GPRC5D-targeting antibody, in R/R MM

- Triple-class exposed patients with R/R MM have poor survival outcomes[1]
- Dual bispecific antibodies talquetamab (BCMA/CD3) + teclistamab (GPRC5D/CD3) achieved an ORR of 80% in the Phase 1 RedirecTT trial[2]
- JNJ-5322 is a trispecific antibody with high affinity for BCMA and GPRC5D and low affinity for CD3
- Phase 1 trial of the drug examined the dose level
  - The study population included BCMA-exposed (17.7%) and GPRC5D-exposed (3.4 %) and BCMA/GPRC5D-naïve patients (80.3%)
  - The recommended Phase 2 dose was determined to be 5 mg SUD and 100 mg Q4W



BCMA, B-cell maturation antigen; CD3, cluster of differentiation 3; CRS, cytokine release syndrome; GPRC5D, G-protein coupled receptor family C group 5 member D; Gr, grade; ICANS, immune effector cell associated neurotoxicity syndrome; ORR, overall response rate; (m)PFS, (median) progression free survival; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; R/R MM, relapsed or refractory multiple myeloma; SUD, step-up dose.

1. Mateos MV et al., Leukemia 2024;38:2554-60. 2. Cohen Y et al., NEJM 2025;9(392):139-49.

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.

S100: JNJ-5322 achieves 55-70% CR in patients with R/R MM

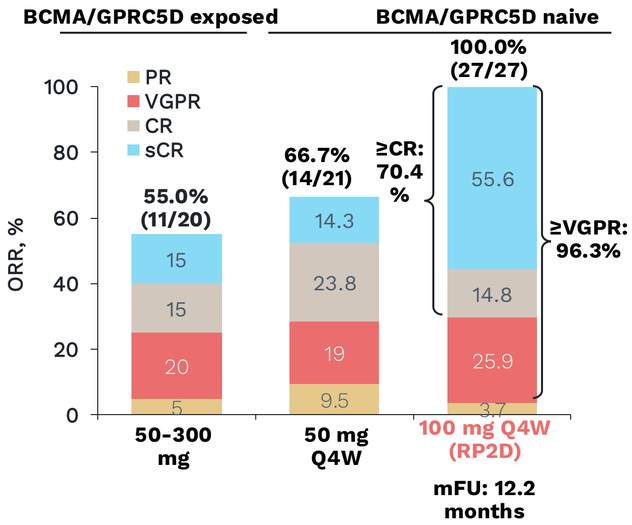
Efficacy

- In the BCMA/GPRC5D-exposed group receiving 50-300mg, ORR was 55% and CR was 30%
- In BCMA/GPRC5D naïve patients, the ORR was 100% and CR was 70.4% in the RP2D group (100mg Q4W)
- PFS with RP2D at 12 months was 95%

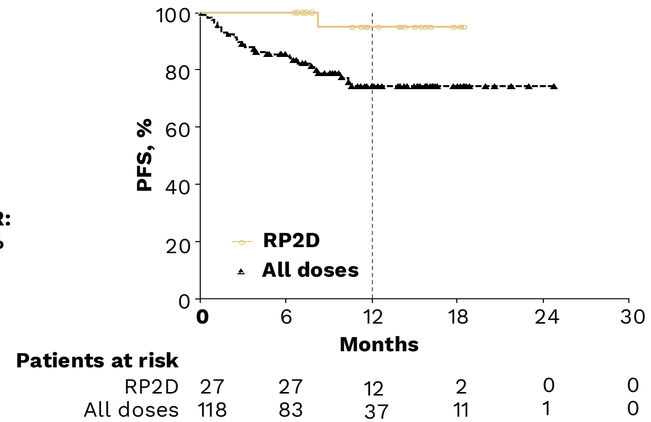
Safety:

- Among the patients receiving RP2D without prophylactic tocilizumab, 69.2% experienced G1/2 CRS (no G≥3 CRS or any grade ICANS)
- In the RP2D group with prophylactic tocilizumab, only 20% had G1 CRS
- 33.3% of patients had G≥3 infections at RP2D

Response rates by previous therapy



PFS all doses vs RP2D



BCMA, B-cell maturation antigen; CD3, cluster of differentiation 3; CRS, cytokine release syndrome; GPRC5D; G-protein coupled receptor family C group 5 member D; G, grade; ICANS, immune effector cell associated neurotoxicity syndrome; ORR, overall response rate; (m)PFS, (median) progression free survival; (VG)PR, (very good) partial response; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; RRMM, relapsed or refractory multiple myeloma; SUD, step-up dose.

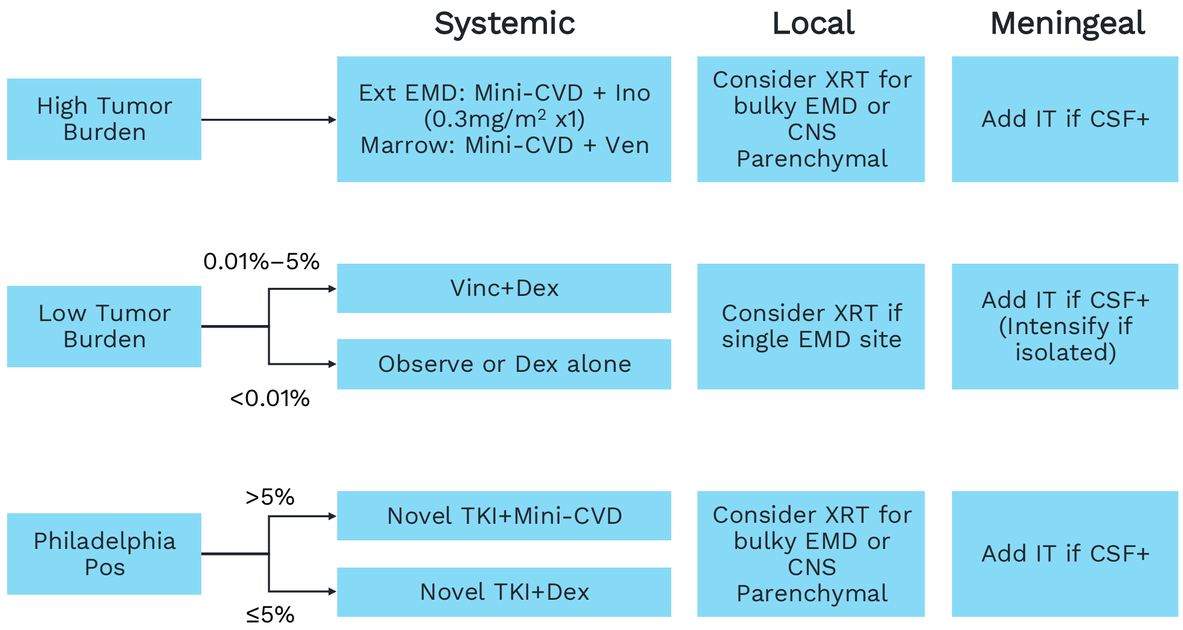
1. Mateos MV et al., Leukemia 2024;38:2554-60. 2. Cohen Y et al., NEJM 2025;9(392):139-49.
Popat R. First-in-human study of JNJ-79635322 (JNJ-5322), a novel, next-generation trispecific antibody, in patients with relapsed/refractory multiple myeloma: initial Phase 1 results. Oral presentation S100 at EHA2025.

p251-3: The impact of CAR T in R/R B-ALL – challenges and novel advances

Two αCD19 CAR T cell therapies (KTE-X19 and Obecabtagene autoleucel) in R/R B-ALL report similar responses[1-3]

- Tumor burden impacts toxicity,[1,4] possibly due to lack of expansion in high-burden settings, or a reflection on infusion timing; it also impacts OS[1,2,5]
- Bridging is an important consideration,[6,7] but more intensive CT is unlikely to be of benefit, and may increase the infection rate
- Persistence is seen,[2,8] but patients still relapse; this aligns with the previous experience[9,10]
- Late transplantation is associated with high relapse and NRM[11]
- Transplant is favored in those at high risk of CD19 antigen loss, with limited therapeutic options to manage post-CAR T relapse, with a high burden prior to infusion, or without a good maintenance option
- Autologous CAR T is established as the SoC for R/R B-ALL and is rapidly moving to earlier lines to mitigate toxicity and relapse

"How I Bridge"



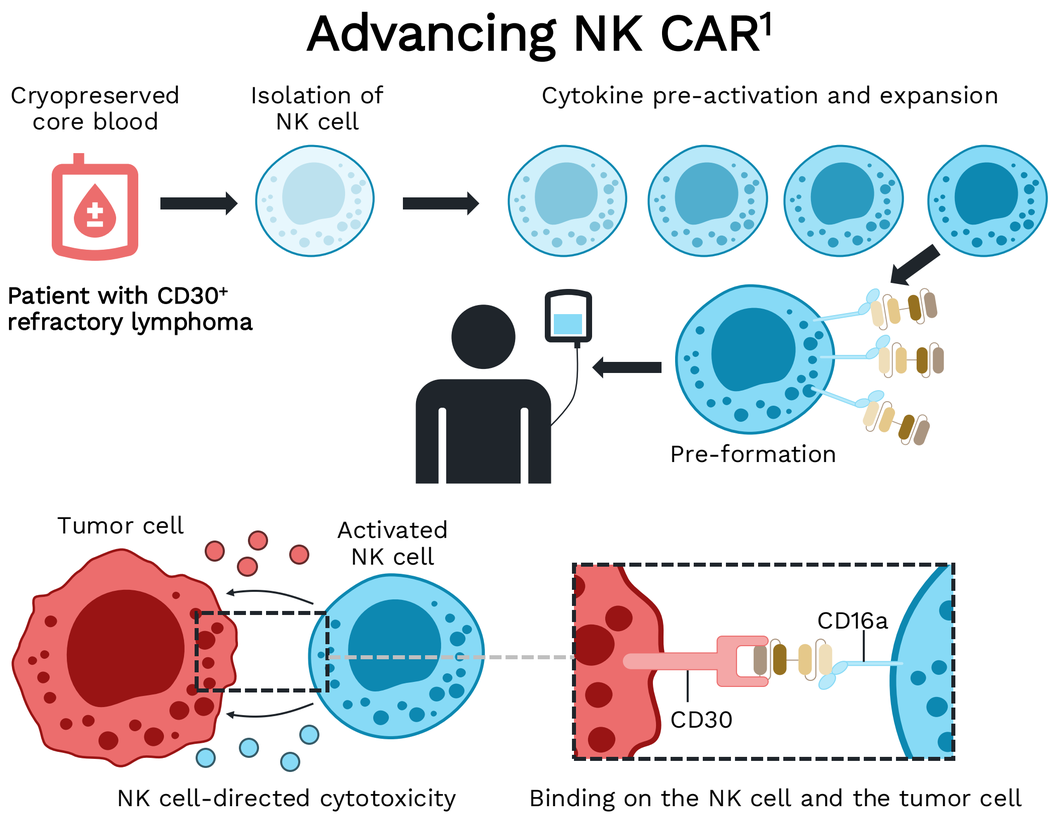
B-ALL, B cell acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CAR T, chimeric antigen receptor T-cell; CT, chemotherapy; NRM, non-relapse mortality; OS, overall survival; R/R, relapsed/refractory; SoC, standard of care.

1. Shah BD, et al. Lancet 2021;398(10299):491-502; 2. Roddie C, et al. N Engl J Med 2024;391(23):2219-2230; 3. https://www.fda.gov/vaccines-blood-biologics/aucatzyl [accessed 22 June 2025]; 4. Roddie C, oral presentation at ASCO 2023; abstract 7000; 5. Shah BD, oral presentation 7010 presented at ASCO 2022; 6. Perica K, et al. Leukemia 2021;35:3268-3271; 7. Lin C, et al. oral presentation 3502 presented at ASH 2023; 8. Shah BD, et al. J Hematol Oncol 2022;15:170; 9. Wierda WG, oral presentation 887 presented at ASH 2024; 10. Siddiqi T, et al. Lancet 2023;402(10402):641-654; 11. Yanada M, et al. Ann Hematol 2021;100(12):3017-3027.

Shah BJ. Cell therapy: CAR T and NK cells for R/R B cell precursor and T ALL. Oral presentation p251-3 at EHA2025.

p251-3: The impact of CAR T in R/R B-ALL – challenges and novel advances

- Novel platforms are being actively developed, extending therapeutic benefit
- Novel approaches include preloading CAR cells with a bispecific and NK CARs
- Optimization of outcomes will necessitate reflection on impact



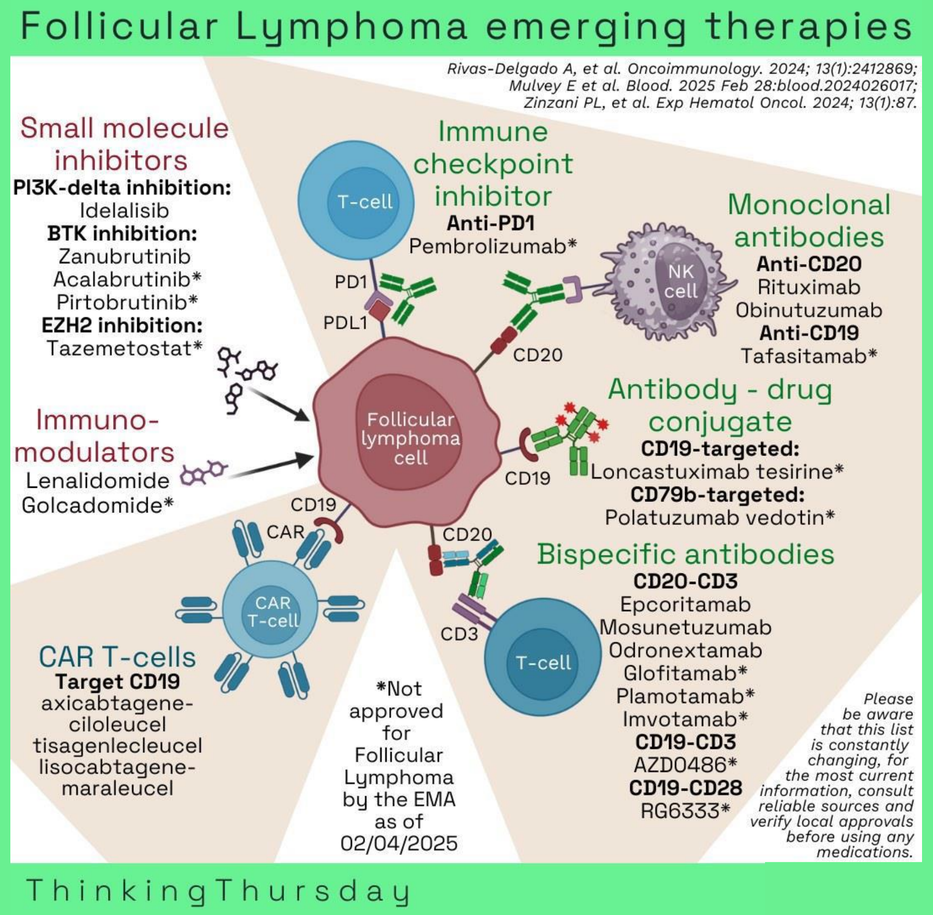
B-ALL, B-cell acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CAR T, chimeric antigen receptor T-cell; NK, natural killer; R/R, relapsed/refractory.

1. Nieto Y et al. Nat Med. 2025 31:1987–1993.
Shah BJ. Cell therapy: CAR T and NK cells for R/R B cell precursor and T ALL. Oral presentation p251-3 at EHA2025.

p109-1: Next-generation armored CARs and TRUCKs in lymphoma

- First study using an armored CAR T product secreting IL18[1] – a known growth factor for T cells
- Treatment is feasible, well tolerated, and results in durable responses in patients with R/R lymphomas who progress after prior anti-CD19 CAR
- Peak huCART19-IL18 expansion and responses are affected by prior CAR co-stimulatory domain type (4-1BB vs. CD28)
- IL18 enhances CAR T efficacy by cell intrinsic/extrinsic mechanisms, including modification of the tumor microenvironment
- Follow-on trial is underway (NCT05989204)

More from EHA #Thinking Thursday



CAR, chimeric antigen receptor; CAR T, chimeric antigen receptor T-cell; IL18, interleukin 18; IL36, interleukin 36; TME, TME, tumor microenvironment; TRUCK: T cell redirected for antigen-unrestricted cytokine-initiated killing.

1 Svoboda et al. N Engl J Med 2025;392(18):1824-1835.

June C. Armored CAR T in lymphoma: resistance mechanisms and efficacy. Oral presentation p109-1 at EHA2025.

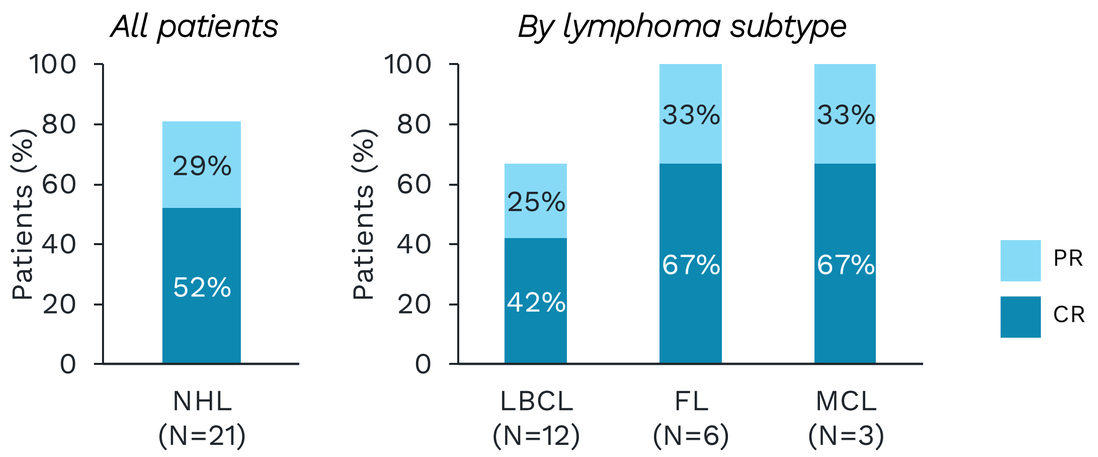
p109-1: Next-generation armored CARs could deliver durable responses and reprogram the TME in lymphoma

- Cytokines can enhance the anti-tumor activity of CAR T cells, e.g. by promoting survival or improving their activity in suppressive tumor microenvironments
- IL18 is a known growth factor for T cells, which may impact proliferation
- Cytokine-releasing CAR T cells are termed “T cell redirected for antigen-unrestricted cytokine-initiated killing” (TRUCK); TRUCKs are a subset of the class of “armored CAR T cells”

huCART19-IL18:

- First in-human trial in a 56-year-old woman with FL/DLBCL achieved sustained CR at a microdose of 3 million cells[1,2]

3-month response to huCART19-IL18[2]



Safety, feasibility, and preliminary efficacy assessed in R/R lymphoma after previous anti-CD19 CAR T cell therapy (N=21)

- 80% overall response at 3 months across all subtypes[2]
- 100% response rate in patients previously treated with CD28 co-stimulatory domain-based therapy

CAR, chimeric antigen receptor; CAR T, chimeric antigen receptor T-cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IL18, interleukin 18; PR, partial response; R/R, relapsed/refractory; TME, tumor microenvironment; TRUCK: T cell redirected for antigen-unrestricted cytokine-initiated killing.

1. Clinical Trials NCT04684563; 2. Svoboda et al. N Engl J Med 2025;392(18):1824-1835.

June C. Armored CAR T in lymphoma: resistance mechanisms and efficacy. Oral presentation p109-1 at EHA2025.

p196-2: Next-generation CAR T cells in lymphoma: Dual specificity to counter tumor escape

Rationale for dual targeting of CD19/BCMA CAR T cells (ARI-0003):[1]

- CD19 CAR T resistance in lymphoma may result from low/ heterogeneous antigen density on lymphoma cells
- BCMA, typically targeted in MM, also shows potential as an antigen in B-cell lymphomas
- Dual targeting with ARI-0003 aims to enhance coverage and confer therapeutic advantages for the treatment of NHL

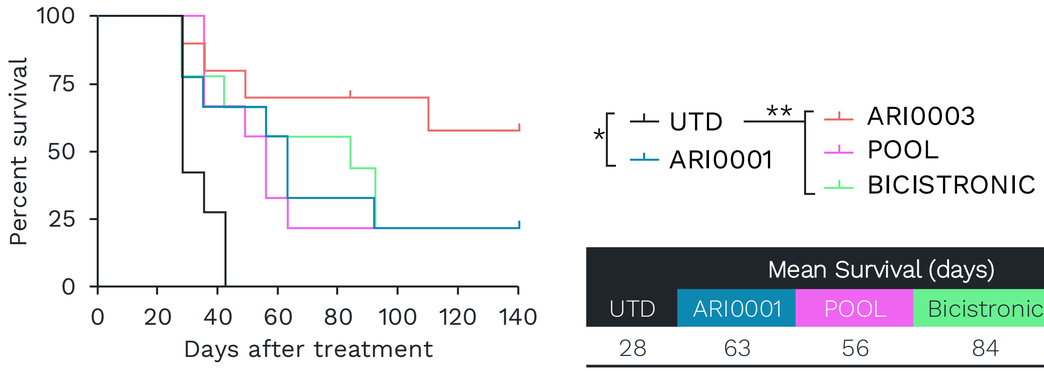
Design and pre-clinical highlights:

- ARI-0003 created via co-transduction of two CAR vectors (CD19 & BCMA in a ~4:1 ratio)
- Enhanced T-cell proliferation, functionality, and anti-tumor efficacy, and prolonged survival in Burkitt lymphoma models
- Prolonged survival after relapse to CD19 CAR T cell therapy

Clinical translation:

- Co-transduction strategy ensures stable dual CAR expression and effective cytotoxicity
- Outperforms CD19 CAR (ARI-0001) in pre-clinical lymphoma models and offers a promising approach for patients relapsing after CD19 CAR T therapy → First-in-human Phase 1 trial of ARI-0003 in patients with NHL is ongoing

Efficacy of ARI-0003 in NSG mice with Burkitt lymphoma



Mean Survival (days)				
UTD	ARI0001	POOL	Bicistronic	ARI0003
28	63	56	84	N/A

Academic CAR T cell development program:

- ARI-0001 (adult ALL): targeting CD19
- ARI-0002 (MM): targeting BCMA
- **ARI-0003 (lymphoma): dual-targeting CD19 & BCMA**
- ARI-007 (T-cell malignancies): targeting CD7
- ARI-HER2 (HER2+ breast cancer): targeting HER2

Over 500 patients treated with academic CAR T cells

ALL, acute lymphoblastic leukemia; BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor T-cell; MM, multiple myeloma.

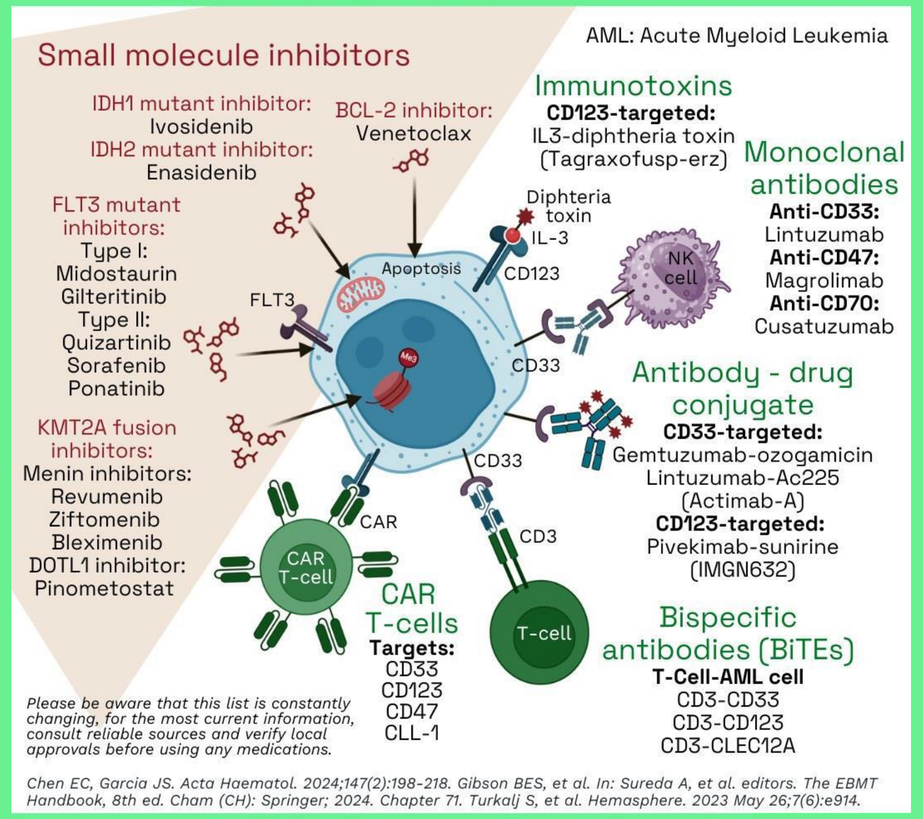
1. Bachiller M et al., *Mol Ther*. 2025 Jan 8;33(1):317-335.

Guedan S. Next-Generation CAR-T: Dual specificity to counter tumor escape in lymphoma. Oral presentation p196-2 at EHA2025.

p141-1: Strong rationale for T-cell engagers in AML is driving novel targets

- Blinatumumab is a CD19 TCE approved in R/R and MRD-positive B-cell precursor ALL, and used as consolidation therapy independent of MRD status
- The success of allogeneic SCT (Graft-vs.-leukemia effect) demonstrates a strong rationale for TCE in AML
- TCE recruits T cells by binding to the epsilon subunit of the CD3 complex
- 27 clinical trials with TCE have been conducted in AML; mostly directed against lineage-restricted antigens (CD33, CD123, CLL1, FLT3), but also leukemia-associated antigens (CD70 and Wt1)
- On-target-off-leukemia toxicity is a challenge
- Responses are observed, but not sustained[1-10]
- TCEs as part of combination treatments are being explored in clinical and pre-clinical studies (e.g., +VEN/AZA, which does not impair TC function)[11]

More from EHA #Thinking Thursday

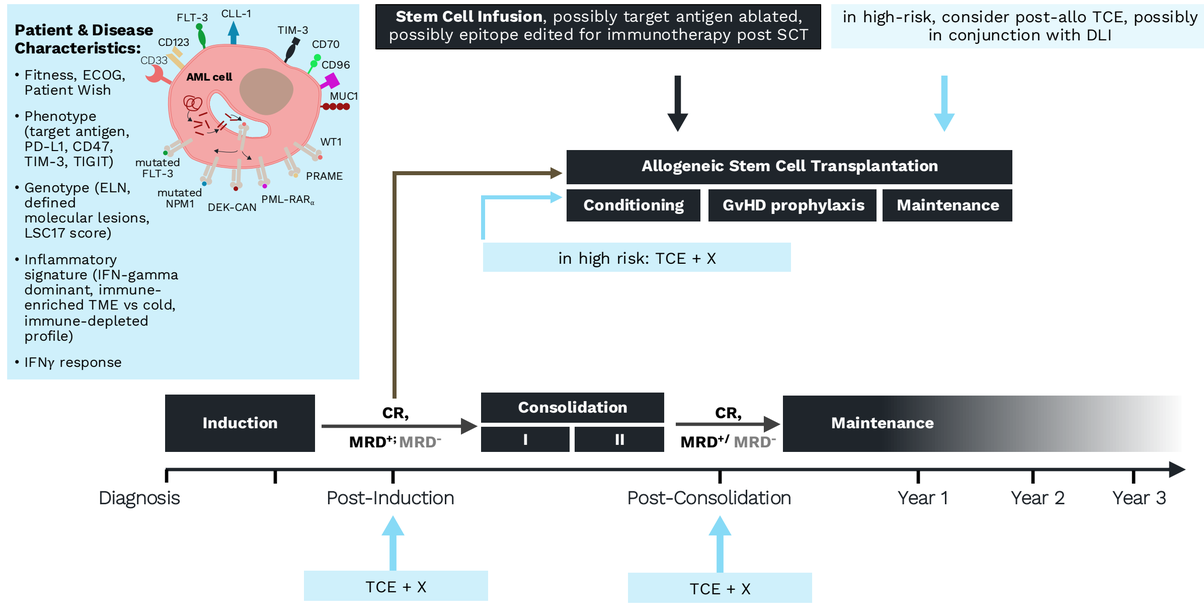


ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MRD, minimal residual disease; R/R, relapsed/refractory; SCT, stem cell transplantation; TCE, T-cell engager. 1. Ravandi, et al. Leuk Lymphoma 2024;65(9):1281-91. 2. Subklewe, et al. ASH 2019 #833. 3. Westervelt, et al. ASH 2019 #834. 4. Uy, et al. Blood 2021;137(6):751-62. 5. Boyiadzis, et al. Clin Transl Sci 2023;16(3):429-35. 6. Ravandi, et al. ASH 2020 #460. 7. Mascarenhas, et al. EHA2020 #538. 8. Labrijn, et al. Nat Rev Drug Discov 2019;18(8):585-608. 9. Stein et al, ASH 2022. 10. Bajel et al, ASH 2023 #3474. 11. Haenel et al., Leukemia. 2024 Feb;38(2):398-402.
Subklewe M. BiTE molecules in AML therapy. Oral presentation p141-1 at EHA2025.

p141-1: Strong rationale for TCE in AML is driving novel targets

- Novel targets for TCE in AML include CD38, csGRP78, and ILT3–CD3, and a leader sequence peptide derived from Cathepsin G/HLA-A02.01[1-4]
- Aim to increase efficacy and overcome resistance due to dim target antigen expression, loss of target antigen, or escape of target antigen variants
- It may also be possible to:
  - Bridge to allogenic HSCT and integrate hematotoxicity into the concept[5,6]
  - Augment TCE efficacy through targeted co-stimulation using Ab constructs
  - Employ combinatorial strategies
- Integrating patient- and AML-related variables such as phenotype, genotype, and inflammatory signature will help identify the most suitable platform for each individual patient

Use early (CR1) & in low disease burden (MRD+/MRD-) in a smart combination



Integrate TCE post-induction (7 + 3 + X) or after 1-2 cycles of VEN/AZA – in parallel or sequentially

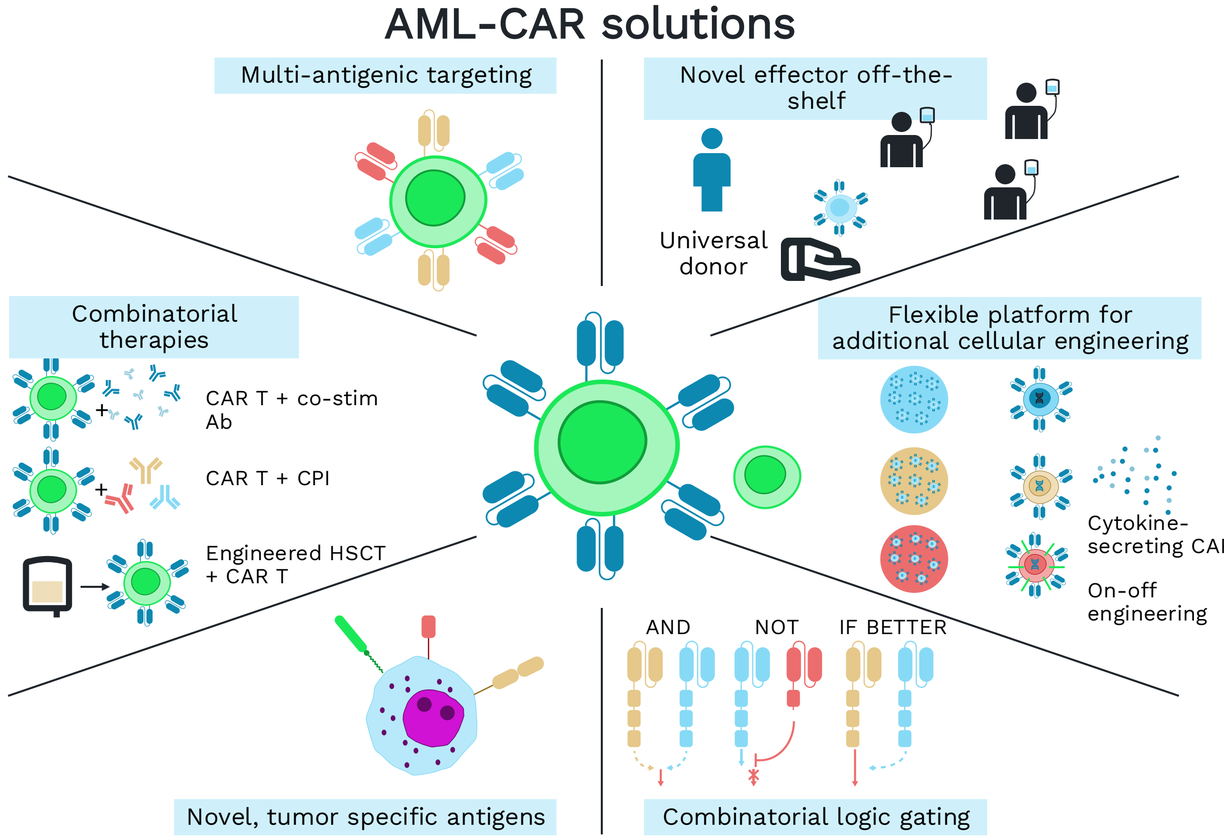
Ab, antibody; AML, acute myeloid leukemia; BiTE, Bispecific T-cell Engager; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease; TCE, T-cell engager.

1. Zhong X et Ma H. Front Oncol. 2022:12:1007783; 2. Zeng et al. Cell Mol Life Sci 2024;81(1):371; 3. Lin et al. ASH 2022; 4. Shi et al. ASH 2023; 5. Volta et al. Hemasphere 2024;8(11):e70055; 6. Rasouli M. Oral presentation s129 at EHA 2025.

Subklewe M. BiTE molecules in AML therapy. Oral presentation p141-1 at EHA2025.

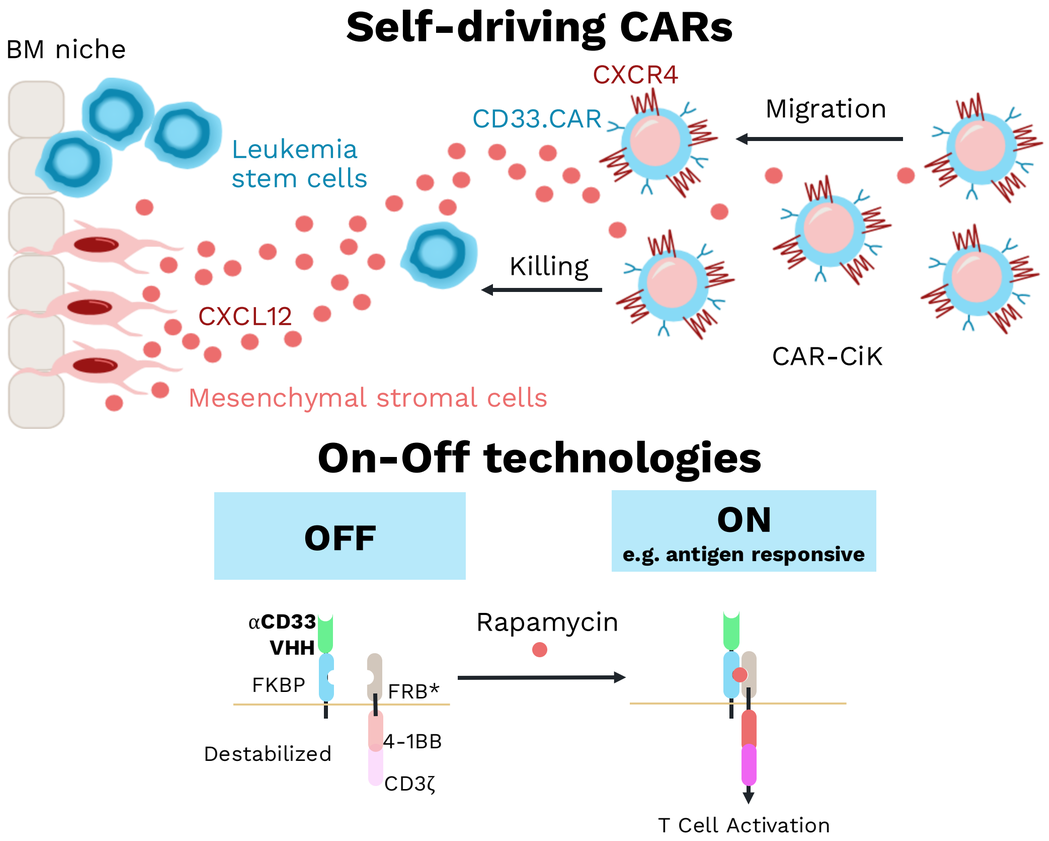
p141-2: Immunotherapies represent a powerful platform to overcome unmet clinical need in chemo-resistant AML

- There are many challenges in AML therapy, including some related to intrinsic T-cell dysfunction and the immunosuppressive TME
- Further challenges include
  - Cross-talk between CAR T cells and blasts in the AML niche
  - Release of pro-inflammatory cytokines, which may drive resistance
  - Logistical issues for autologous manufacture with a rapidly progressing leukemia
- Early CAR T cell studies reported a limited disease response rate of 30–50% compared to the 80–90% seen in targeting B-ALL
- It is important to recognize the limited response rates and address this with novel approaches



AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; CART-T, chimeric antigen receptor T-cell; TME, tumor microenvironment.
Ghorashian S, et al. CAR T cell therapy in AML. Oral presentation p141-2 at EHA2025.

p141-2: Innovations in CAR T cell technology are needed to unlock its potential in chemo-resistant AML

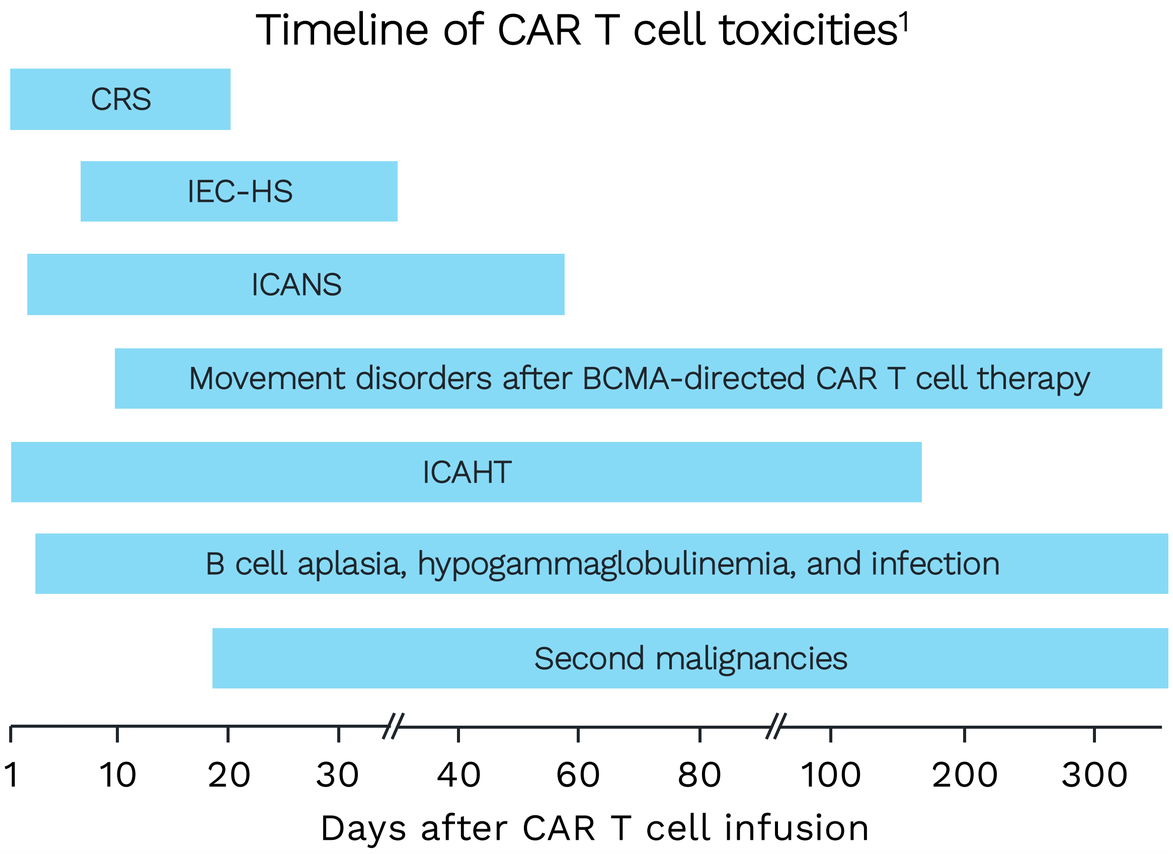


- Additional engineering of CAR effector cells allows modulation of function
  - Such as armoring anti-tumor efficacy through cytokine secretion
  - Or limiting toxicity through on-off signaling
- The study CLEAR-AML investigates a CD371-targeting, IL-18 secreting CAR T cell product, which delivered promising responses; a proportion of patients bridged to transplant[1]
- Self-driving CARs generated by co-transduction with CXCR4 support selective homing to the AML BM niche and enhance control of the AML burden[2]
- On-off technologies: next-generation CARs with separate antigen binding and signaling subunits
- Careful patient selection and optimization of therapeutic pathways will be needed
- Unlocking the full potential of immunotherapies will require combinatorial therapy, iterative design, and evolution of the regulatory and commercial landscape

AML, acute myeloid leukemia; BM, bone marrow; CAR, chimeric antigen receptor; MRD, minimal residual disease.
1. Geyer et al., ASH 2024. abstract 2070; 2. Biondi M, et al. Blood 2023;141(21):2587-2598.
Ghorashian S, et al. CAR T cell therapy in AML. Oral presentation p141-2 at EHA2025.

p213-3: Outpatient CAR T cell therapy: There's no place like home

- Readmission rates can be as high as 88% after CAR T cell therapy
- CRS and ICANS are common AEs in the days after infusion
- Outpatient management of CAR T cell therapy is a feasible and safe approach
- Early intervention for the prevention and management of CRS, ICANS, and MAS must be considered



AE, adverse event; BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICAHT, immune effector cell-associated hematotoxicity; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; MAS, macrophage activation syndrome.

1. Brudno JN, Kochenderfer JN. Nat Rev Clin Oncol 2024;21(7):501-521.

Martínez Roca A. Outpatient CAR-T therapy. Oral presentation p213-3 at EHA2025.

p213-3: Outpatient CAR T cell therapy: There's no place like home

- Caregivers play an important role in the outpatient setting
- Education for patients and caregivers is key to maintaining procedure safety
- Adequate selection of patients is mandatory
- Continuous training for HCPs is imperative

Establishing an outpatient CAR T cell program[1]

Organization and legislation

- Consult legal frameworks for patient management
- CAR T projected volume
- Institutional capacity for investment
- In- and outpatient capacity
- Compliance with FACT-JACIE standards

Patient and caregiver

Patient

- Eligibility criteria
- Location
- Psychosocial assessment
- CAR T education

Caregiver

- Reliable caregiver and transportation plan
- Psychosocial assessment
- CAR T education

Operations

Clinical pathways and SOPs

- Clinical pathways
- Process SOPs
- Quality SOPs
- Remote patient monitoring

AE management location

- Emergency department (ED)
- Specific OPC unit

Pharmacy, Lab tests and electronic records

Nursing

- Standardized process for infusion, assessment, and AE evaluation
- Care coordination
- Patient evaluation (telemedicine/in person)

Education

- Initial onboarding and ongoing education of program personnel
- Education of ED personnel on rapid triage and management of CRS and ICANS
- Education of other personnel who may manage CRS and ICANS (e.g., hospitalists)

CART-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome; ED, emergency department; HCP, healthcare professional; ICANS, immune effector cell-associated neurotoxicity syndrome; MAS, macrophage activation syndrome.

1. Navneet SM et al., JCO Oncol Pract. 2025 Apr 18:OP2500062.

Martínez Roca A. Outpatient CAR-T therapy. Oral presentation p213-3 at EHA 2025.

S276: CAR T cell atlas may help unravel CAR T regulatory mechanisms

- CAR T cells have revolutionized the cancer immunotherapy field
- Despite good initial responses, long-term efficacy is impaired, especially in MM
- A better understanding of molecular mechanisms might drive therapeutic advances
- Some mechanisms are associated with persistence and expansion
- This is the idea behind the generation of an atlas, which has been done for CD19 CAR T cells[1,2]

Human atlas

~ 500.000 cells

Coming from 24 tissues or organs

Allowed the identification of over

400

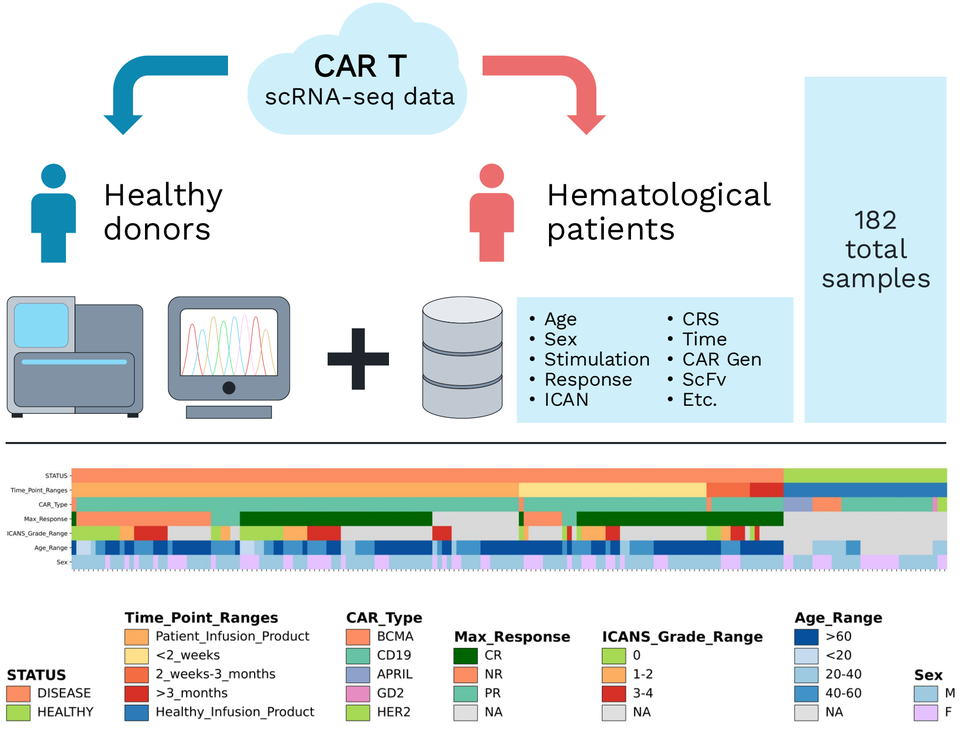
cell types

CART-T, chimeric antigen receptor T-cell; MM, multiple myeloma.

1. Bai Z, et al. Nature 2024;634(8034):702-711; 2. Li X, et al. Cancer Cell 2023;41(11):1835-1837.

Rodriguez-Madoz J, et al. A functional CAR-T cell atlas to unravel regulatory mechanisms of CAR-T cells. Oral presentation S276 at EHA2025.

S276: CAR T cell atlas may help unravel CAR T regulatory mechanisms



Summary

13
Public datasets

>1 M
Cells

14
Healthy donors

102
Patients

First version of a CAR T cell atlas of 415,000 cells from >100 patients with different hematological diseases

- Targeting different antigens (CD19, BCMA, APRIL)
- It allows identification of mechanisms of resistance and response
- Memory phenotype of the infusion product correlated with better responses
- The atlas can be used to generate new data-driven hypotheses, e.g. around age- or gender-related differences
- Also allows detection of cells related to therapy toxicity
- Ongoing research will validate identified mechanisms of response and resistance

APRIL, A proliferation-inducing ligand; BCMA, B-cell maturation antigen; CART-T, chimeric antigen receptor T-cell.

Rodriguez-Madoz J, et al. A functional CAR-T cell atlas to unravel regulatory mechanisms of CAR-T cells. Abstract S276 at EHA 2025.

S552: Thematic debate – BCMA bispecific antibodies vs. CAR T therapies as key options for R/R MM

Bispecific antibodies:

Therapies
- BCMA: Teclistamab (Majestec-1)[1], elranatamab (MagnetisMM-3)[2], linvoseltamab (LinkedMM-1)[3]; BCMA in earlier lines (Majestec-3, MagnetisMM-5)[4,5]
- GPRC5D: Talquetamab (MonumenTAL-1)[6]
- BCMA + GPRC5D: Trispe JNJ-5322[7]

Advantages
- Off-the-shelf, large access, outpatient-compatible, guidelines for optimal use
- Suitable for older, frail, or renal-impaired patients
- Real-life data confirm results of pivotal trials

Challenges
- Resistance mechanisms in non-responders are unclear
- Concerns with target downregulation, infection risk, cost, and sequencing

CAR T cell therapy:

Therapies
- Cilta cel (CARTITUDE-1)[8]
- Early-line use (CARTITUDE-4, KarMMa-3)[9,10] shows superiority over SoC, which led to the approval of Cilta-cel in 2L (the setting of bispecific antibodies)

Advantages
- Deep and durable responses, prolonged treatment-free intervals
- Most effective when used earlier in the disease course
- Less refractory/aggressive disease

Challenges
- Manufacturing time, limited access, and reimbursement
- Less suitable for rapidly progressing cases

- Both treatment approaches are complementary and essential
- Optimal use depends on patient characteristics, disease stage, and logistical factors
- Ongoing trials aim to clarify sequencing and combination strategies

BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor T-cell; MM, multiple myeloma; R/R, relapsed/refractory. 1. Moreau P et al., NEJM. 2022 Aug 11;387(6):495-505. 2. Lesokhin AM et al., Nat Med. 2023 Sep;29(9):2259-2267. 3. Bumma M et al., JCO. 2024 Aug 1;42(22):2702-2712. 4. Matteos MV et al., Hemasphere. 2022 Jun 23;6(Suppl):1891-1892. 5. https://www.clinicaltrials.gov/study/NCT05020236 [accessed 27 June 2025]. 6. Chari A et al., NEJM. 2022 Dec 15;387(24):2232-2244. 7. https://www.clinicaltrials.gov/study/NCT05652335 [accessed 27 June 2025]. 8. Berdeja JG et al., *Lancet*. 2021 Jul 24;398(10297):314-324. 9. San-Miguel J et al., *NEJM*. 2023 Jul 27;389(4):335-347. 10. Rodriguez-Otero P et al., *NEJM*. 2023 Mar 16;388(11):1002-1014.
Zamagni E. BCMA bsAb vs CAR T in MM. Thematic Debate p552-0 at EHA2025; Moreau P. **BCMA bsAb vs CAR T in MM. Thematic Debate p552-1 at EHA2025;** Rodríguez-Otero P. **BCMA bsAb vs CAR T in MM. Thematic Debate p552-2 at EHA2025.**

Conclusion

- Data from RedirecTT-1 exploring dual-targeting in R/R MM and EMD showed deepening responses over time, with the combination exceeding the individual efficacy of each drug without exacerbating AE
- Data for a first-in-human study of a trispecific BCMA/GPRC5D-targeting antibody in R/R MM showed 55–70% CR and 100% ORR
- Autologous CAR T is SoC for R/R B-ALL and is moving to earlier lines; novel approaches include bi-specific preloading, and NK CAR
- Next-generation armored CARs and TRUCKs in lymphoma could deliver durable responses and reprogram the TME
- A next-generation CAR T harnessing dual specificity (CD19/BCMA) to counter tumor escape outperforms CD19 CAR T in pre-clinical lymphoma models
- Strong rationale for BCEs, TCEs and CAR T therapies in AML is driving novel targets, but requires further innovations to unlock the potential of immunotherapy in AML
- Establishing outpatient programs for CAR T is feasible but requires knowledge of common toxicities post-infusion
- EHA 2025 showcased new work on a CAR T cell atlas that may help unravel mechanisms associated with CAR T persistence and expansion and drive novel therapeutics
- A thematic debate considered BCMA bispecifics and CAR T as key options for R/R MM, concluding both options are complementary and essential

AML, acute myeloid leukemia; B-ALL, B-cell acute lymphocytic anemia; BCMA, B-cell maturation antigen; BCE, bispecific T-cell engager; CAR T, chimeric antigen receptor T-cell; CD, cluster of differentiation; EMD, extramedullary disease; MM, multiple myeloma; NK, natural killer (cell); R/R, relapsed/refractory; SoC, standard of care; TCE, tri-specific T-cell engager; TRUCK, T cells redirected for antigen-unrestricted cytokine-initiated killing.

03

Microenvironment and next-generation modeling in lymphoid malignancies

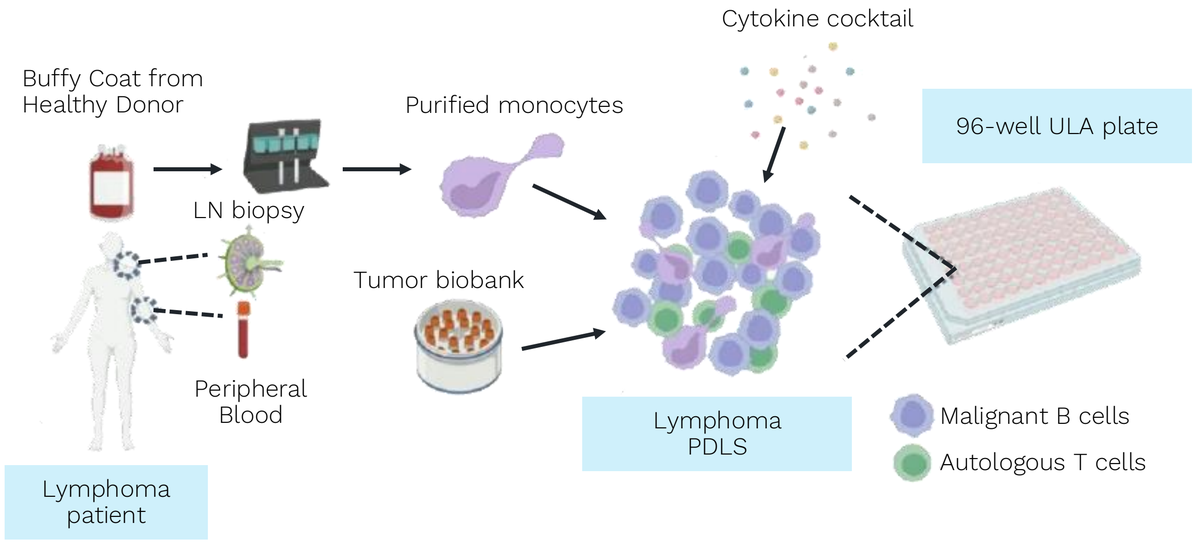
Section 3: Microenvironment and next-generation modeling in lymphoid malignancies

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
p151-1	3D lymphoma models	Patricia Perez Galan
S101	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 3 POLARGO trial	Matthew Matasar
S232	MORNINGSUN: Open-label Phase 2 trial of the efficacy and safety of subcutaneous mosunetuzumab (MOSUN SC) as frontline (1L) treatment in symptomatic patients with marginal zone lymphoma (MZL)	John M. Burke
p257-1	The impact of the CLL microenvironment	Clare Sun
S158	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	Lydia Scarfò

p151-1: Generation of patient-derived 3D lymphoma models

Procedure for creating patient-derived lymphoma spheroids



- B-cell lymphoma is challenging to model because it is a complicated network between lymphoma cells and other cells of the lymph node
- Three approaches for lymphoma models: Cell line models, mouse models and patient-derived
- **Types of patient-derived models**
  - Patient-derived lymphoma spheroids (PDLS): Mixture of lymphoma cells, monocytes, autologous T cells and a cytokine cocktail
  - FL-PDLS: cells proliferate, monocytes differentiate into an intermediate M1/M2 macrophage phenotype
  - Transcriptional program is similar to FL, and the T-cell compartment behaves similar in terms of gene expression of T cells in FL
  - MC-PDLS: recapitulates LN expression signature, monocytes differentiate into M2

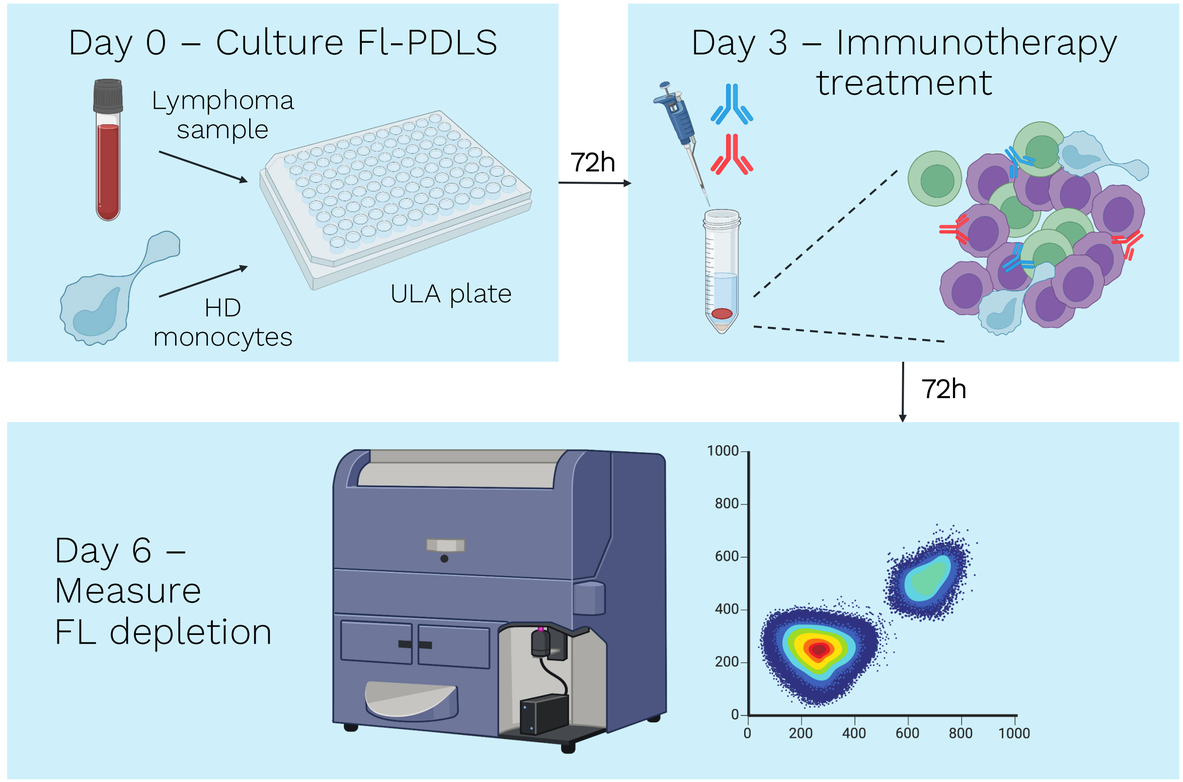
FL, follicular lymphoma; LN, lymph node; MC, mantle-cell lymphoma; PDLS, patient-derived lymphoma spheroids
Image created with BioRender.com.
Pérez-Galán P, 3D lymphoma models. Oral presentation p151-1 presented at EHA2025.

p151-1: Use of 3D lymphoma models for drug screening

- FL-PDLS is a useful model for drug screening
- Replicates the response of the FL patient it was derived from, including the development of resistance
- The FL-PDLS model was used to test a dual CD19-BCMA CAR T cell product (ARI0003)[1]
- **Patient-derived models with scaffold**
  - Uses natural or synthetic hydrogels
  - Patient-derived lymphoma tumoroids (PDLT): Tumor biopsy sample (incl. TME), rat collagen I and stromal cells are cultured with IL-4

    → 1 mm tumoroids containing CD19+ and CD3+ cells
  - Important parameters to verify: Pore size and stiffness (mimicking FL lymph node)
  - Other scaffolding systems: Alginate-based model[2] and biopsy samples with Vitrogel RGD[3]

In-vitro drug testing with PDLS



BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor; CD, cluster of differentiation; FL, follicular lymphoma; HD, healthy donor; IL-4, interleukin 4; LN, lymph node; PDLS, patient-derived lymphoma spheroids; PDLT, patient-derived lymphoma tumoroids; RGD, arginine-glycine-aspartic acid peptide; TME, tumor microenvironment; ULA, ultra-low attachment. Image created with BioRender.com.

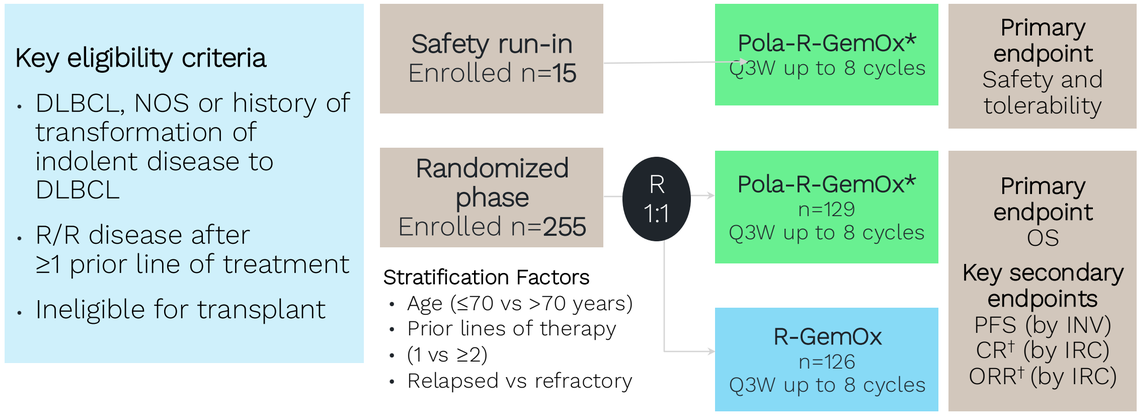
1. Guedan S. Next-Generation CAR T: Dual specificity to counter tumor escape in lymphoma. Oral presentation p196-2 at EHA2025. 2. Lamaison C et al., *Blood Adv.* 2021 Dec 14;5(23):5372-5386. 3. Santamaria-Martinez A et al., Nat Commun. 2024 Dec 9;15(1):10650.

Perez-Galan P, 3D lymphoma models. Oral presentation p151-1 presented at EHA2025.

S101: Polatuzumab vedotin + R-GemOx for R/R DLBCL: Results from the randomized Phase 3 POLARGO trial

- Polatuzumab is a CD79b-directed mAb, approved for the treatment of ND and R/R DLBCL in combination with other drugs[1]
- Polatuzumab vedotin is an ADC that targets CD79b+ cells and disrupts microtubule function

Phase 3 POLARGO trial: Pola-R-GemOx vs. R-GemOx in transplant ineligible patients with R/R DLBCL



Efficacy

- ORR was roughly doubled with Pola-R-GemOx vs. R-GemOx per IRC
- OS subgroup analysis favored Pola-R-GemOx across the board and independent of cell origin

Safety

- Similar safety profile, however:
- There were more deaths in the R-GemOx (56%) arm compared to the Pola-R-GemOx arm (29.7%) due to progression
- Pola-R-GemOx was associated with more G5 AEs (11.7% vs. 4%, half of which were COVID-19-related); Pola-R-GemOx was associated with numerically more thrombocytopenia, anemia, hepatic toxicity and peripheral neuropathy

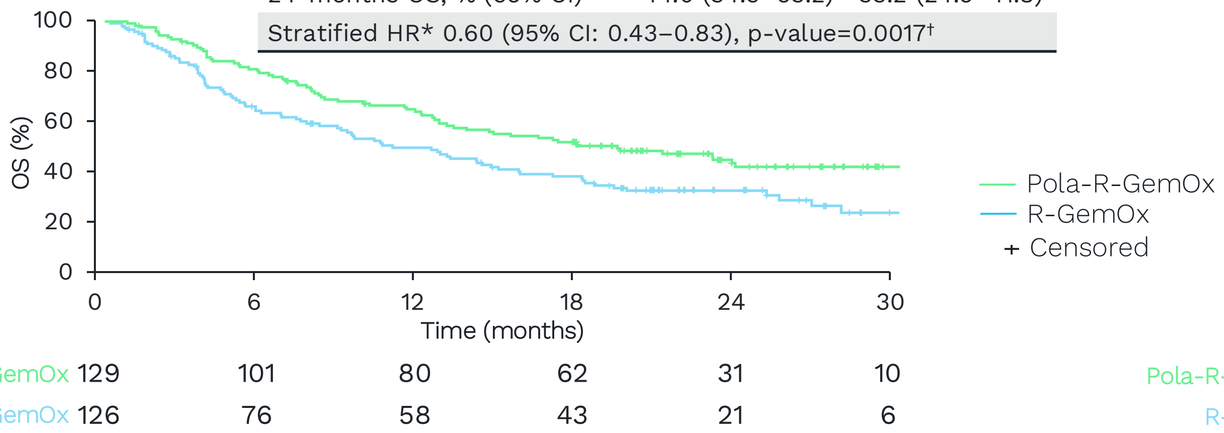
ABC, activated B-cell-like; ADC, antibody drug conjugate; AE, adverse event; CD, cluster of differentiation; CR, complete response; DLBCL, diffuse large cell B-cell lymphoma; GCB, germinal center B-cell; Gr, grade; HR, hazard ratio; IRC, (per) independent review committee; mAb, monoclonal antibody; ORR, overall response rate; (m)OS, (median) overall survival; PN, peripheral neuropathy; R/R relapsed/ refractory.

1. https://www.ema.europa.eu/en/medicines/human/EPAR/polivy [accessed 16 June 2025].
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 3 Polargo trial. Oral presentation S101 at EHA2025.

S101: Phase 3 POLARGO trial: Pola-R-GemOx demonstrates superior response and survival over R-GemOx

Median OS follow-up: 24.6 months (95% CI: 23.0–26.0)

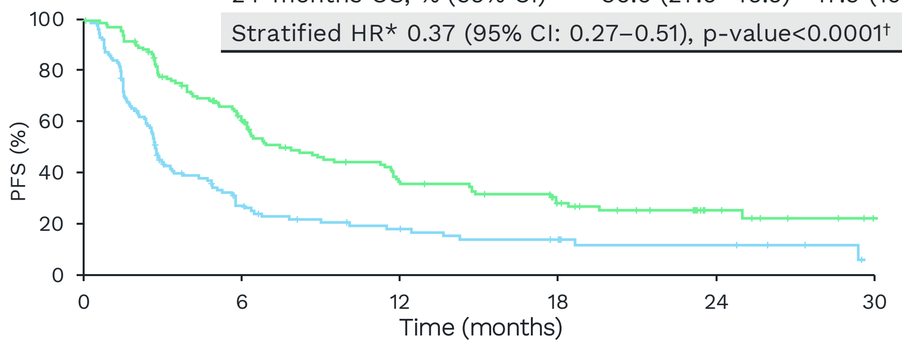
	Pola-R-GemOx (n=129)	R-GemOx (n=126)
Median OS, months (95% CI)	19.5 (13.3–NE)	12.5 (8.9–15.8)
24-months OS, % (95% CI)	44.0 (34.9–53.2)	33.2 (24.5–41.8)
Stratified HR* 0.60 (95% CI: 0.43–0.83), p-value=0.0017†		



Pola-R-GemOx	129	101	80	62	31	10
R-GemOx	126	76	58	43	21	6

Median PFS follow-up: 18.7 months (95% CI: 17.8–23.3)

	Pola-R-GemOx (n=129)	R-GemOx (n=126)
Median OS, months (95% CI)	7.4 (8.2–11.7)	2.7 (2.4–3.3)
24-months OS, % (95% CI)	36.6 (27.6–45.5)	17.9 (10.3–25.5)
Stratified HR* 0.37 (95% CI: 0.27–0.51), p-value<0.0001†		



Pola-R-GemOx	129	69	38	23	9	2
R-GemOx	126	26	14	8	5	NE

Parameter	Pola-R-GemOx (n=129)	R-GemOx (n=126)
ORR	52.7%	24.6%
CR	40.3%	19.0%
PR	12.4%	5.6%

Conclusion

Consistent benefit of adding Pola-V despite AEs, offers a chance to avoid bendamustine and its negative effect on subsequent cellular therapies.

ABC, activated B-cell-like; ADC, antibody drug conjugate; AE, adverse event; CD, cluster of differentiation; CR, complete response; DLBCL, diffuse large cell B-cell lymphoma; GCB, germinal center B-cell; Gr, grade; HR, hazard ratio; IRC, (per) independent review committee; mAb, monoclonal antibody; ORR, overall response rate; (m)OS, (median) overall survival; PN, peripheral neuropathy; R/R relapsed/ refractory.

1. https://www.ema.europa.eu/en/medicines/human/EPAR/polivy [accessed 16 June 2025].

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 3 Polargo trial. Oral presentation S101 at EHA2025.

S232: Subcutaneous Mosunetuzumab in symptomatic patients with MZL: First results from the MorningSun study

Mosunetuzumab (Monsun SC) is a bispecific antibody, binding CD20 and CD3 on the surface of T-cells and tumor cells.

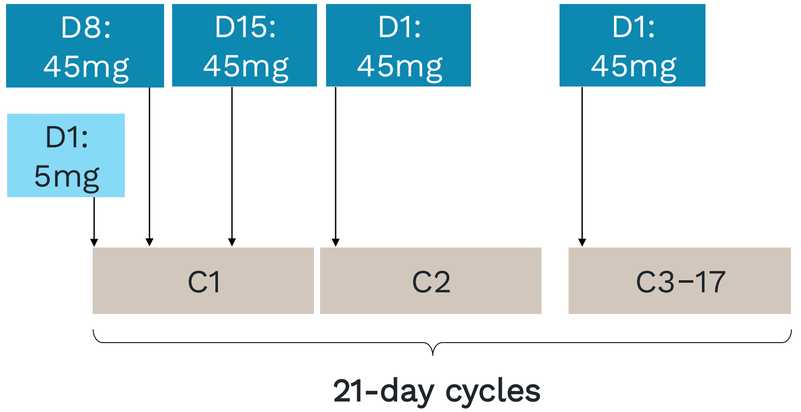
Study Design

- The Phase 2 MorningSun basket study (NCT05207670) investigates the efficacy and safety of Monsun in treatment-naïve patients with symptomatic MZL
- CRS mitigation consisted of Monsun SC step-up dosing in C1, with corticosteroid prophylaxis mandatory in C1 and C2 (optional thereafter).

Endpoints

- Primary: ORR by Lugano criteria
- Key secondary: PFS, DOR, DOCR, TTR, safety

Mosunetuzumab SC administration



Patients were treated for up to 17 cycles unless disease progression or unacceptable toxicity occurred.

- 21 (58%) patients completed the study
- Median treatment duration was 51 (4-58) weeks
- Median number of cycles: 17 (1-17)

C, cycle; DOR, duration of response; DOCR, duration of complete response; ECOG, Eastern Cooperative Oncology Group; MZL, marginal zone lymphoma; ORR, overall response rate; PFS, progression-free survival; TTR, time to response.

Burke M. MorningSun: open-label Phase 2 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 EHA2025..

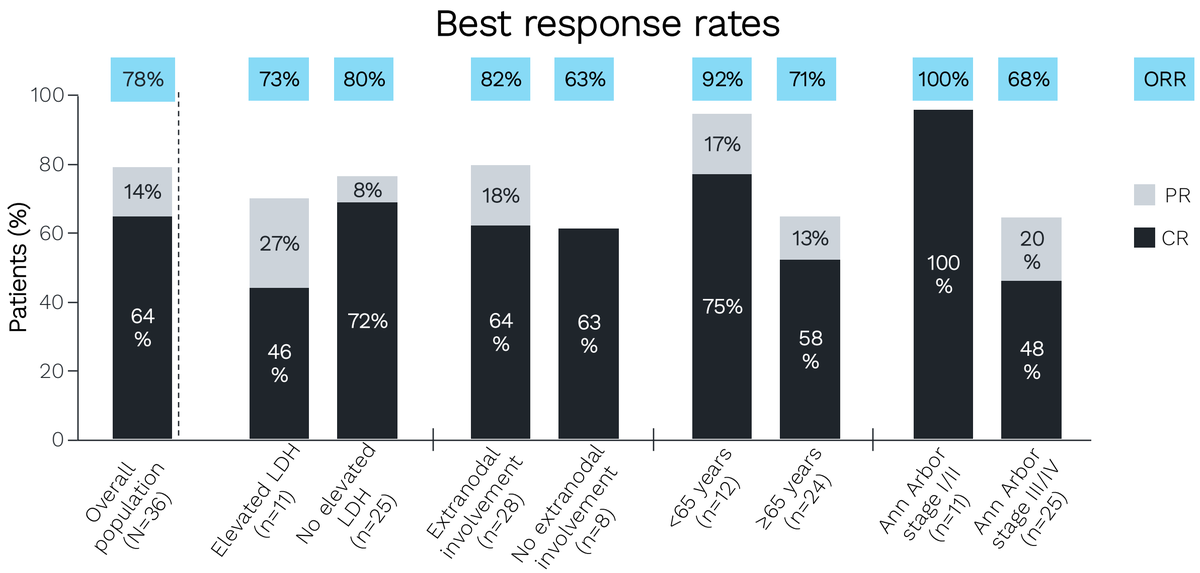
S232: Subcutaneous Mosunetuzumab in symptomatic patients with MZL: First results from the MorningSun study

Efficacy

- Clinically meaningful, durable responses were observed at 18-month follow-up and at the time of the analysis, 23 (64%) patients were still in CMR
- CR rates were consistent across high-risk subgroups
- DOR and DOCR event-free rates at 12 months were 92% and 100%, respectively; however, mDOR and mDOCR were not reached
- PFS rates: 90.5% at 6 months, 83.6% at 12 months; mPFS was not reached

Safety

- The most frequent AEs were injection site reactions (72%, all G1/2), fatigue, diarrhea, neutropenia, and CRS.



Conclusions

- Safety and CRS profiles were manageable and show Mosun Sc could be considered in an outpatient setting
- Data support further exploration of Mosun Sc in patients with MZL

(S)AE, (serious) adverse event; C, cycle; CMR, complete metabolic response; CR, complete response; CRS, cytokine release syndrome; (m)DOR, (median) duration of response; (m)DOCR, (median) duration of complete response; ECOG, Eastern Cooperative Oncology Group; G, grade; LDH, lactate dehydrogenase; ORR, objective response rate; (m)PFS, (median) progression free survival; PR, partial response..

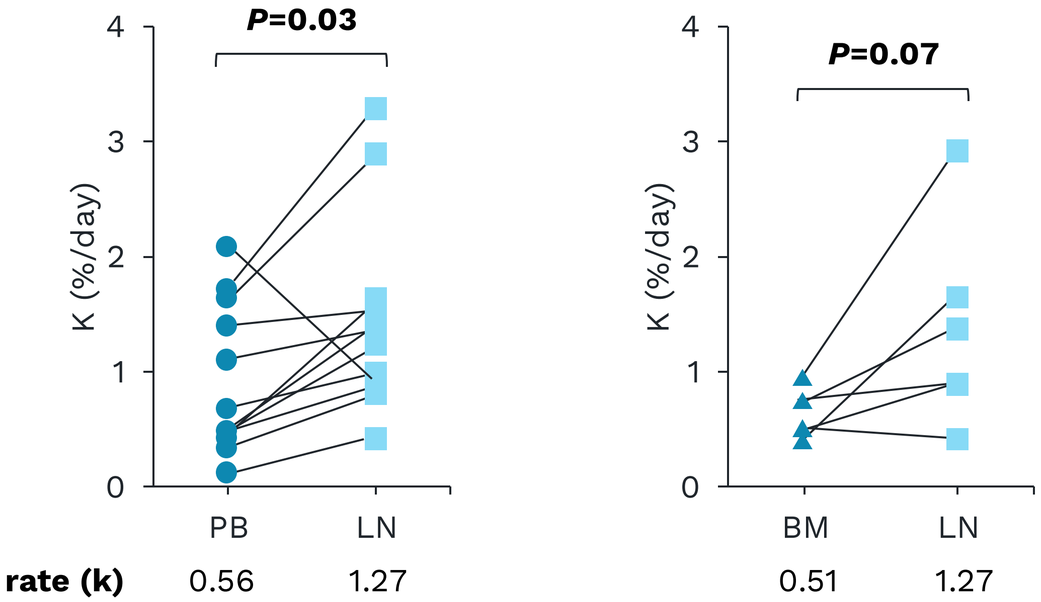
Burke M. MorningSun: open-label Phase 2 trial of the efficacy and safety of subcutaneous mosunetuzumab (mosun sc) as frontline (1L) treatment in symptomatic patients with marginal zone lymphoma (MZL). Oral presentation S232 at EHA2025..

p257-1: The impact of the CLL microenvironment

- Hallmarks of CLL include inflammatory milieu, migration and homing, survival and proliferation, and immune evasion
- Gene expression of CLL cells depends on the environment: BCR and NF-κB signatures are upregulated in lymph nodes[1]
- Cell division rate is 2x higher in LN compared to PB[2]
- Single-cell RNA-seq of CLL lymph nodes[3]:
  - 0.4-1% of cells are in a proliferative state
  - 2.2-4.3% are activated, the rest are quiescent
- Activation in CLL cells correlates with the presence of M2 macrophages[3]
- CLL cells migrate towards CXCL12 and bind via CXCR4, which is downregulated after the interaction[4]

Median birth rate (k)

Figure adapted from Herndon et al. [2]



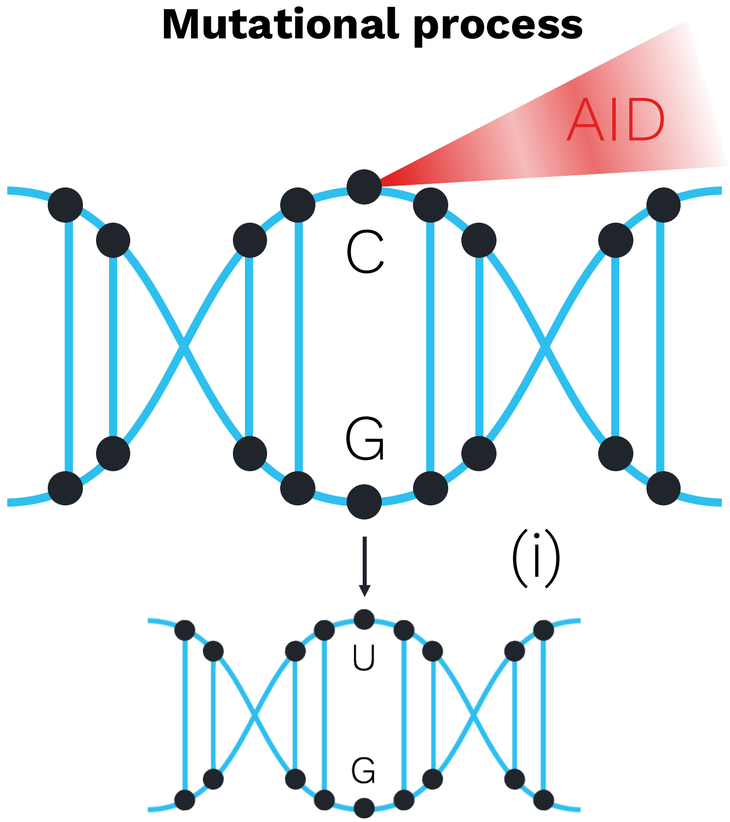
AID, activation-induced cytidine deaminase; BCR, B-cell receptor; BTKi, bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; LN, lymph node; PB, peripheral blood.

1. Herishanu Y et al., Blood. 2011 Jan 13;117(2):563-74.; 2. Herndon TM et al., Leukemia. 2017 Jun;31(6):1340-1347.; 3. Sun C et al., Blood Adv. 2023 Jan 10;7(1):145-158.; 4. Burger JA et al., Blood. 1999 Dec 1;94(11):3658-67

Sun C. The impact of the CLL microenvironment. Oral presentation p257-1 at EHA2025.

p257-1: The impact of the CLL microenvironment

- AID is active in CLL cells
  - Non-canonical AID activity is more relevant in early CLL development[1]
  - Subclonal canonical AID-related mutations become more important in later development[1]
- Subclonal expansion (and thus disease progression) occurs mostly in lymph nodes[2]
  - AID expression levels do not differ between patients with/without subclonal expansion overall[2]
- T-cell inflammatory response is stronger in stable CLL compared to CLL with subclonal outgrowth[2]
- During progression, resistant subclones emerge, which are heterogeneous across compartments[3]



AID, activation-induced cytidine deaminase; BCR, C cell receptor; BTKi, bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; LN, lymph node; PB, peripheral Blood.
Image adapted from Oppezzo P, et al. *Front Oncol.* 2021;11:634383.
1. Kasar S et al., Nat Commun. 2015 Dec 7:6:8866. 2. Sun C et al., Blood Adv. 2023 Jan 10;7(1):145-158. 3. Sun C et al., ASH 2023.
Sun C. The impact of the CLL microenvironment. Oral presentation p257-1 at EHA2025.

S158: BGB-16673 is a novel BTK degrader and under investigation in patients with R/R CLL or SLL: Phase 1 CaDAnCe-101 study

BTKis have revolutionized treatment for patients with CLL/SLL, but many patients experience disease progression due to resistance mutations[1-3]

- BGB-16673 is a BTK degrader and thus offers an alternative mechanism of interrupting BTK signaling
- The CaDAnCe-101 Phase 1 clinical trial investigates BGB-16673 in patients with R/R CLL/SLL

Study design

Patients who meet the 2018 iwCLL criteria for treatment, who have had ≥2 lines of therapy (including a cBTKi if approved for the disease), ECOG PS 0-2 and adequate organ function

- Primary endpoints: safety/tolerability, MTD & RDFE
- Secondary endpoints: PK, PD, preliminary antitumor activity

Part 1: Monotherapy dose finding

Part 1a: Dose escalation

Selected R/R B-cell malignancies
(MZL, FL, MCL, CLL/SLL, WM, DLBCL, RT)
n≤72
Oral, daily intake, 28-day cycle[a]
Doses: 50 mg, 100 mg, 200 mg, 350 mg, 500 mg, 600 mg

Part 1b: Safety expansion

Selected R/R B-cell malignancies
(MZL, MCL, CLL/SLL, WM)
n≤120

Based on the results of CaDAnCe-101 (see next slide), BGB-16673 is being evaluated in ongoing Phase 2 and Phase 3 studies in R/R CLL

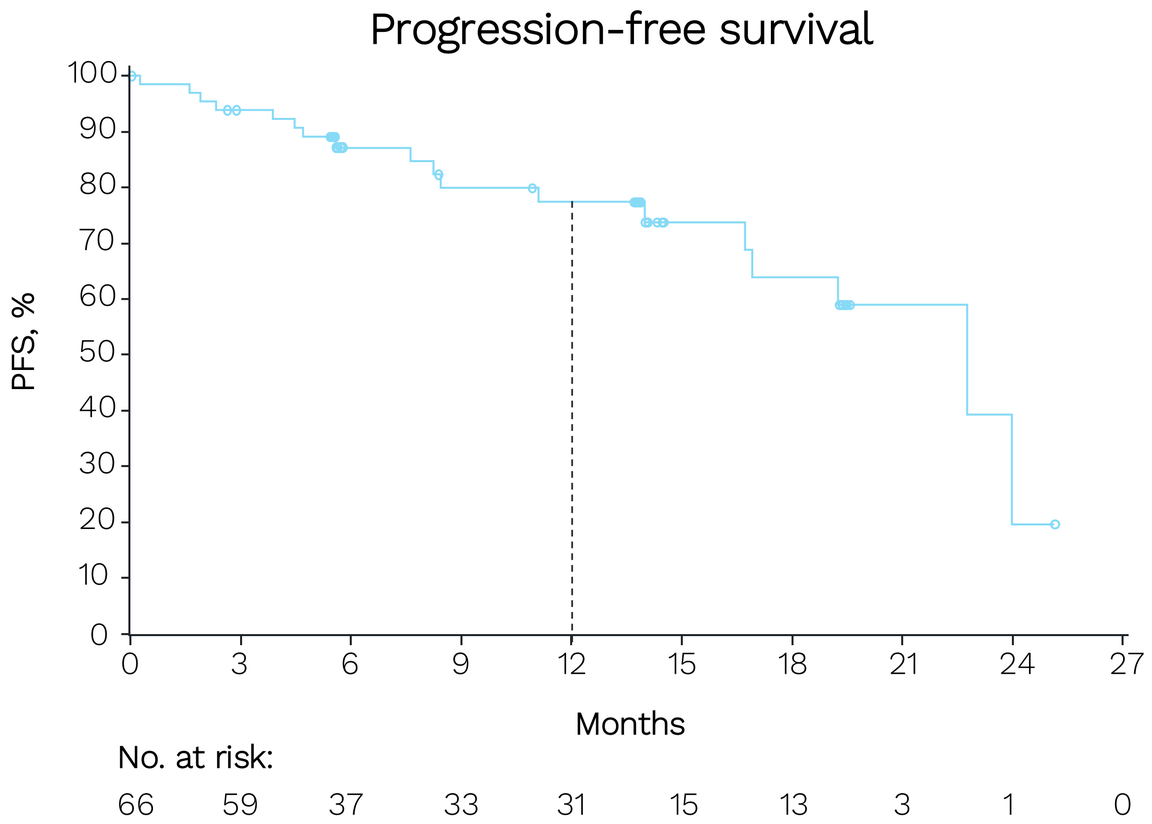
[a]Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation.

BTK(i), bruton tyrosine kinase (inhibitor); CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; iwCLL, international workshop on chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; PS, performance status; RDFE, recommended dose for expansion; R/R, relapsed/refractory; RT, richter's transformation; SLL, small lymphocytic lymphoma; WM, waldenström's macroglobulinemia

1. Moreno C et al., *Hematol Am Soc Hematol Educ Program*. 2020;2020:33-40; 2. Woyach JA et al., *N Engl J Med*. 2014;370:2286-2294; 3. Wang E et al., *N Engl J Med*. 2022;386:735-743.

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.

S158: BGB-16673 is efficacious in patients with CLL/SLL who relapsed under BTKi treatment



Safety

- Most AEs were G1/2; Most common (≥5%) G≥3 AEs were neutropenia (24%), pneumonia (11%) and thrombocytopenia (5%)
- Two treatment discontinuations due to AEs

Efficacy

- ORR was 84.8% across dose levels (50-500 mg; n=66) and 93.8% at 200 mg (n=16)
- PFS rate at 12 months was 77.4% (median follow-up: 15.6 months)

Conclusion

- BGB-16673 is a safe and effective drug in heavily pre-treated patients with CLL/SLL who relapsed under BTKi treatment

AEs, adverse events; BTKi, bruton tyrosine kinase inhibitor; CLL/SLL, chronic lymphocytic leukemia/ small lymphocytic lymphoma; G, grade; ORR, overall response rate; PFS, progression-free survival

1. Moreno C et al., *Hematol Am Soc Hematol Educ Program*. 2020;2020:33-40; 2. Woyach JA et al., *N Engl J Med*. 2014;370:2286-2294; 3. Wang E et al., *N Engl J Med*. 2022;386:735-743.

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.

Conclusion

- New 3D models of lymphoma recapitulate many important aspects of tumor biology, including gene expression in different environments, and are already advancing drug development
- Results were also shared at EHA for the Phase 3 POLARGO trial in R/R DLBCL, with Pola-R-GemOx demonstrating superior response and survival over R-GemOx.
- First results from the MorningSun study of SC mosunetuzumab in MZL show clinically meaningful and durable responses at 18-month follow-up with manageable safety and CRS profiles.
- Insights into the CLL microenvironment suggest that resistant subclones emerge, which are heterogeneous across compartments.
- Phase 1 CaDAnCe-101 results for BGB-16673 – a novel BTK degrader – proved efficacy in patients with CLL/SLL who relapsed under BTKi treatment.

BCMA, B-cell maturation antigen; BTK(i), bruton kinase (inhibitor); CLL, chronic lymphocytic leukemia; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; Pola-R-HemOx, Polatuzumab vedotin – Rituximab-Gemcitabin-Oxaliplatin; R/R, relapsed/refractory; SC, subcutaneous; SLL, small lymphocytic lymphoma.

04

Genomics and new treatments for AML

Section 4: Genomics and new treatments for AML

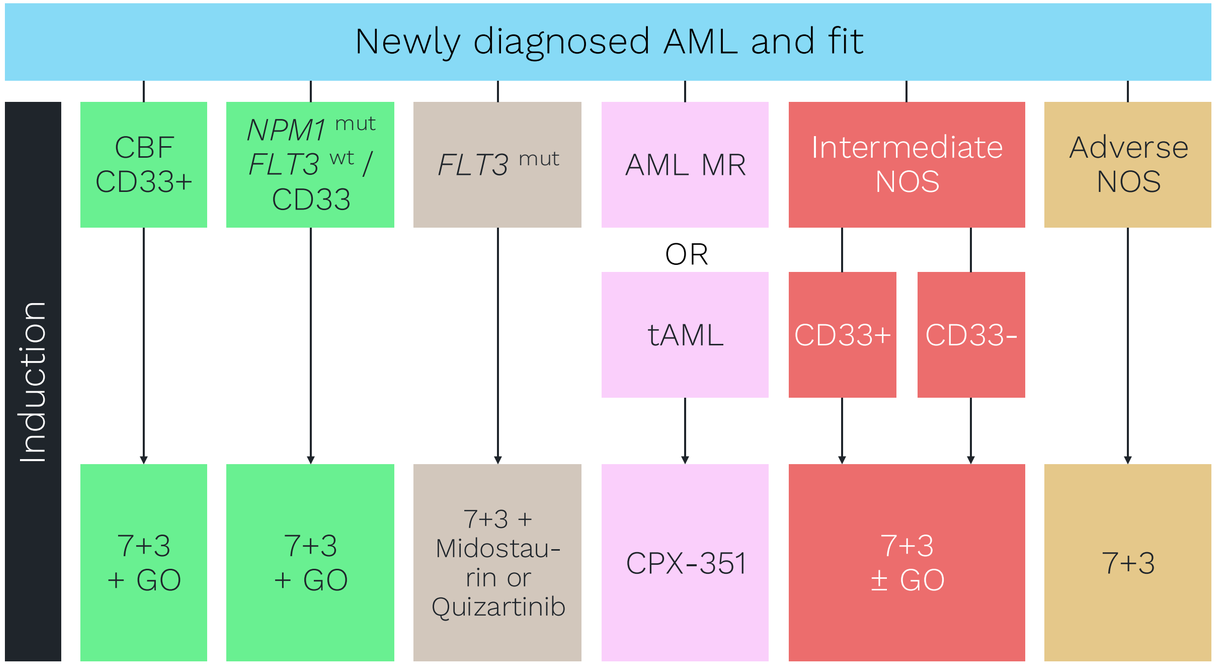
Overview of selected presentations

Presentation ID	Presentation Title	Presenter
p126-1	Beyond 3 plus 7	Christoph Röllig
p126-2	Beyond HMA + venetoclax	Courtney DiNardo
S135	All-oral decitabine-cedazuridine (DEC-C) + venetoclax (VEN) in patients with newly diagnosed acute myeloid leukemia (AML) ineligible for induction chemotherapy: Phase 1/2 clinical trial results	Gail Roboz
p250-3	New combination therapies	Paresh Vyas
S136	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	Harry Erba
S137	RP2D determination of bleximenib in combination with VEN+AZA: Phase 1b study in ND & R/R AML with KMT2A/NPM1 alterations	Andrew H. Wei
S138	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	Joshoa Zeidner
S142	Phase 1/2 study of decitabine, venetoclax, and quizartinib triplet combination in FLT3-ITD mutated AML	Musa Yilmaz
PF477	Updated safety and antileukemic activity data for sonrotoclax (BGB-11417), a potent and selective BCL2 inhibitor, in treatment-naïve patients with acute myeloid leukemia unfit for intensive chemotherapy	Jake Shortt
PF491	Updated safety and anti-leukemic activity data for sonrotoclax (BGB-11417), a potent and selective BCL2 inhibitor, in patients with relapsed/refractory acute myeloid leukemia	Pau Montesinos

p126-1: Genotype-sensitive AML therapy with combination treatments using 7+3 chemotherapy as a basis

- 7+3 chemotherapy (cytarabine + anthracycline) was introduced in 1973 and has been largely unchanged in clinical practice; modifications did not significantly improve responses and survival[1]
- Incorporating ADC GO improves results in favorable and intermediate genetics, with better results in CBF AML[2]
- The FLT3 inhibitor midostaurin helps in patients with AML with *FLT3* mutations regardless of age[3]; Quizartinib seems to be better in young but not older patients[4]
- Liposomal formulation of 7+3 (CP-351) is more efficacious in tAML and sAML[5] and particularly in MDS-related mutations
- IDH1/2 inhibitors (ivosidenib, enasidenib) are currently being studied[6]
- BCL2i venetoclax in combination with high intensity chemo showed a high CRc (95%)[7]
- Menin inhibitors are in clinical development,[8] as are other alternatives to 7+3[9]

Treatment stratification for newly diagnosed patients fit for intensive therapy



ADC, antibody-drug-conjugate; (t/s)AML, (therapy-related/secondary) acute myeloid leukemia; AZA, Azacitidine; CBF, core binding factor; CRc, composite complete response; DEC, decitabine; GO, gemtuzumab ozogomycin; LDAC, low-dose cytarabine; MDS, myelodysplastic disorder; VEN, venetoclax. 1. Büchner T et al., J Clin Oncol. 2012 Oct 10;30(29):3604-10. 2. Lambert J et al., Haematologica. 2019 Jan;104(1):113-119. 3. Döhner H et al., Blood. 2022 Sep 22;140(12):1345-1377. 4. Erba HP et al., Lancet. 2023 May 13;401(10388):1571-1583. 5. Lancet JE et al., Lancet Haematol. 2021 Jul;8(7):e481-e491. 6. NCT03839771. 7. DiNardo CD et al., Leukemia. 2025 Apr;39(4):854-863. 8. Candoni & Coppola, Hematol Rep. 2024 Apr 18;16(2):244-254. 9. Cherry EM et al., Blood Adv. 2021 Dec 28;5(24):5565-5573.
Röllig C. Beyond 3 plus 7. Oral presentation p126-1 at EHA2025.

p126-2: Induction chemotherapy ineligible patients: Beyond HMA + venetoclax

- Improvements on VEN+AZA are needed for patients with high-risk genetics, e.g. with *TP53, FLT3* and *RAS* mutations

Quality of life

- Oral therapy (DEC-C + VEN) for elderly patients translates to more time spent at home and not hospital[1]

Targeted treatment

- *IDH1* mut AML patients benefit from Ivosidenib and quizartinib instead of or in addition to venetoclax with azacitidine[2,3]
- Menin inhibitors are being evaluated + AZA/VEN for newly diagnosed patients and in patients with R/R disease[4]

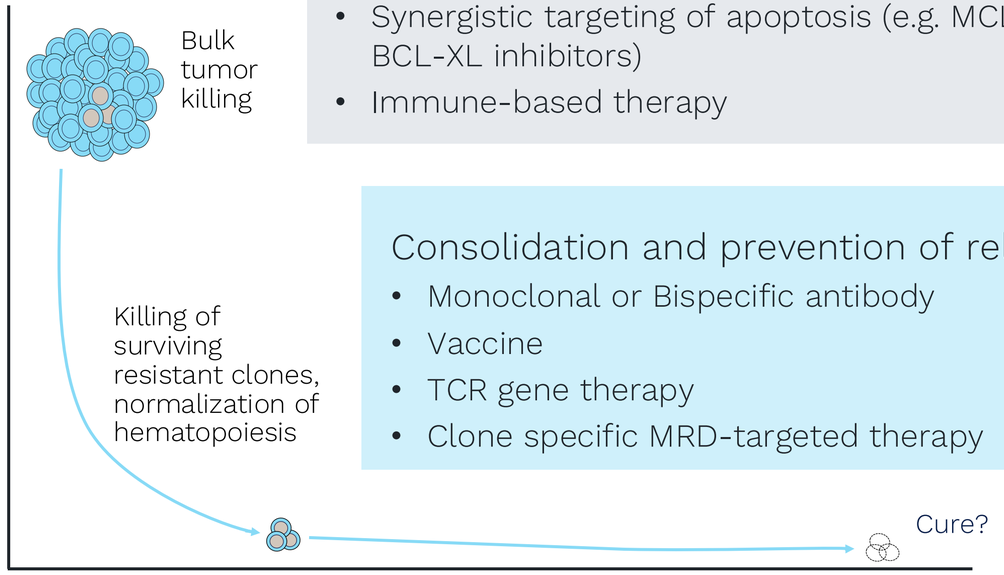
Mutation-informed treatment

- *RAS*m patients: intermediate intensity approach with cladribine + cytarabine + VEN consolidation[5]

Conclusions

- Strategies to move beyond HMA + VEN are triplet regimens, intermediate intensity, immunotherapy and novel agents

The basis: VEN + HMA



Targeted and mutation-informed additions:

- Mutation-specific targeted agent (e.g. *FLT3*, *IDH1/2)*
- Synergistic targeting of apoptosis (e.g. MCL-1 or BCL-XL inhibitors)
- Immune-based therapy

Consolidation and prevention of relapse:

- Monoclonal or Bispecific antibody
- Vaccine
- TCR gene therapy
- Clone specific MRD-targeted therapy

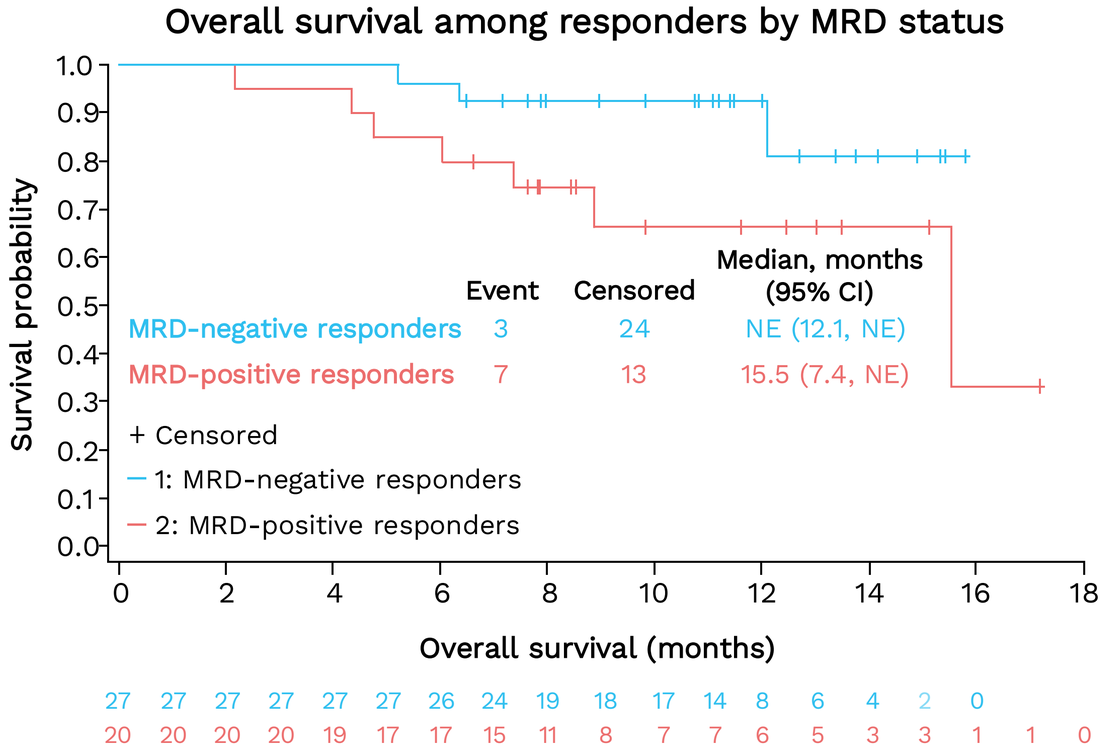
AML, acute myeloid leukemia; AZA, Azacitidine; DEC, decitabine; DEC-C, decitabine-cedazuridine; HMA, hypomethylating agent; MRD, minimal residual disease; TCR, T-cell receptor; VEN, venetoclax

1. Roboz G. Oral presentation S135, presented at EHA2025. 2. Montesinos P et al., NEJM. 2022 Apr 21;386(16):1519-1531. 3. Yilmaz N. Abstract 220, presented at ASH2024. 4. Wei AH. Oral presentation S137 presented at EHA 2025. 5. Kadia TM et al., JCO. 2022 Nov 20;40(33):3848-3857.

DiNardo C. Beyond HMA+venetoclax. Oral presentation p126-2 at EHA2025.

S135: Oral decitabine-cedazuridine (DEC-C) + venetoclax (VEN) is a viable alternative for older, newly diagnosed patients with AML

- Inpatient treatment is a great burden for elderly patients
- The Phase 1/2 clinical trial ASCERTAIN-V looked at an all-oral DEC-C + VEN treatment regimen in patients with a median age of ≥75y, ineligible for intensive induction chemotherapy[1,2]
- In Phase 2b (N=101), 46.5% of patients achieved CR, 80% still had CR at 9 months
- mOS was 15.5 months in Phase 2b; patients who achieved MRD$^-$ had excellent survival (median not reached, see figure)
- Most frequent G≥3 AEs were associated with myelosuppression (anemia: 25.9%, neutropenia: 20.6%, febrile neutropenia: 20.6%, thrombocytopenia: 14.3%)
- No drug-drug interactions were noted
- Based on these results, the treatment regimen was recommended for Phase 3 evaluation



AE, adverse event; AML, acute myeloid leukemia; CI, confidence interval; CR, complete response; G, grade; MRD, minimal residual disease; (m)OS, (median) overall survival; NE, not evaluated.

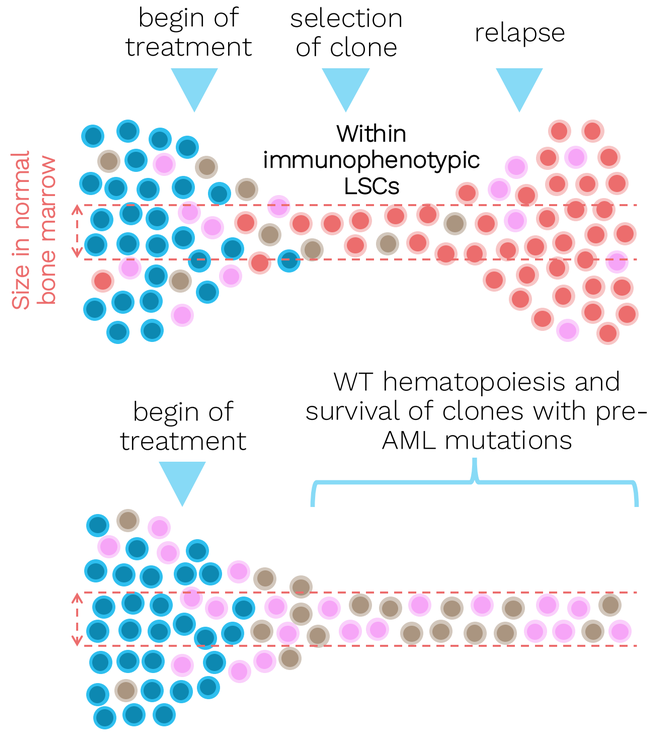
1. DiNardo CD et al. Lancet Oncol. 2018;19:216–28. 2. Wei AH et al. J Clin Oncol. 2019;37:1277–84.

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

p250-3: Tumor heterogeneity and clonal selection are the basis for relapse after treatment

- In patients with R/R disease, multiple resistance mechanisms are present before the subsequent therapy
- Clonal evolution is the basis for resistance to therapy
- IDH1 inhibitor ivosidenib + AZA + VEN[1] was used to investigate the clonal basis of treatment failure and response to treatment
- Single-cell sequencing of BM samples was performed, gene expression changes between clones were investigated and correlated with their dominance
  - Resistant clones can but do not have to undergo genetic evolution
  - Clonal selection can be detected early and the expansion of clones can be traced over the course of treatment/relapse
- Identification of different clones has the potential to identify resistant clones early and scalable, cost-effective single-cell approaches are needed so that the right therapy can be chosen (or developed) to help more patients in the future

Difference between patients who relapse and patients with sustained remissions



- The resistant clone is present from the beginning
- Features of sensitive clones
  - LSC/HSC self-renewal
  - Genes sensitive to menin inhibition
- Features of resistant clones
  - Inflammatory response: TNFα and NFκB
  - AP-1 complex and early response

AML, acute myeloid leukemia; AZA, Azacitidine; HSCs, hematopoietic stem cells; LSCs, leukemia stem cells; R/R, relapsed/refractory; VEN, venetoclax; WT, wildtype

1. Lachowiez CA et al., Blood Cancer Discov 2023 Jul 5;4(4):276-293.

Vyas P. New combination therapies. Oral presentation p250-3 at EHA2025.

p250-3: Combination treatments counter tumor resistance mechanisms

- Classical chemotherapy is limited by its side effects and is too toxic for elderly and frail patients
- Monotherapy with targeted agents shows only modest efficacy in R/R disease; e.g., with menin inhibitors, CR rates of 20-30% and DORs of 4-6 months[1] can be achieved
- Combinations of targeted therapies with chemotherapy or a combination of multiple targeted agents may lead to deeper and more durable responses, e.g.:
  - Menin inhibitor combination therapies are currently in Phase 3 testing, achieving much higher rates of CR (as we will see below)
  - In a study of IDH1 inhibitor ivosidenib + AZA in IDG1-m AML, significant improvement of survival over azacitidine monotherapy (mOS = 29.3 vs. 7.9 months) was noted[2]
  - With additional venetoclax (IVO/VEN/AZA), an even better response was seen (CR rate = 94% in ND and 83% in R/R AML)[2]

New combination treatments for patients with AML in this section

- Ziftomenib and 7+3 chemotherapy in newly diagnosed AML
- Bleximenib and AZA/VEN in newly diagnosed and R/R AML
- AZA/VEN + Revumenib in newly diagnosed AML
- Decitabine, venetoclax, and quizartinib triplet combination in FLT3-ITD mutated AML
- SONROTOCLAX (BGB-11417) in treatment-naïve patients and patients with R/R AML

AML, acute myeloid leukemia; AZA, Azacitidine; CR, complete response; DEC-C, decitabine-cedazuridine; DOR, duration of response; IVO, ivosidenib; mOS, median overall survival; R/R, relapsed/refractory; VEN, venetoclax

1. Aldoss I et al., Oral abstract 211 presented at ASH2024; 2. Lachowiez CA et al., Blood Cancer Discov 2023 Jul 5;4(4):276-293.

Vyas P. New combination therapies. Oral presentation p250-3 at EHA2025.

S136: Menin inhibitors in AML (1)

Introduction

- Most tumors eventually develop resistance to targeted therapy
- Menin inhibitors are new and promising agents currently in clinical development that target the HOX/MEIS1 transcriptional program
- They are critical for leukemogenesis in *KMT2A*-rearranged (KMT2Ar) and in *NPM1*-mutated AMLs
- Menin inhibitors are being tested both for the treatment of AML patients with newly diagnosed and R/R disease

AML, acute myeloid leukemia; KMT2A, histone-lysine N-methyltransferase 2A; R/R, relapsed/refractory

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

S136 & S137: Menin inhibitors in combination with chemotherapy and targeted agents are active in newly diagnosed (ND) and R/R AML

Phase 1 clinical trials in the ND and R/R setting

Ziftomenib and 7+3 chemotherapy in ND AML

- Dose escalation trial (N=82) in *NPM1*-m and *KMT2A*-r patients
- 600 mg dose chosen
- Safety: AE profile similar to 7+3 alone[1]

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

- Based on results, Phase 3 was recommended

Bleximenib and AZA/VEN in ND and R/R AML

- Dose escalation trial (ND: N=40; R/R: N=85)
- 100 mg chosen
- Safety: Almost all G≥3 AEs related to myelosuppression (overall rate = 96%)

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

- Phase 3 trial is now enrolling (NCT06852222)

AE, adverse event; AML, acute myeloid leukemia; AZA, azacitidine; (c)CR, (composite) complete response; (m)DoCR, (median) duration of complete response; Gr, grade; ND, newly diagnosed; (m)OS, (median) overall survival; R/R, relapsed/refractory; VEN, venetoclax.

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
Wei AH. RP2D determination of bleximenib in combination with VEN+AZA: Phase 1b study in ND & R/R AML with KMT2A/NPM1 alterations. Oral presentation S137 at EHA2025

S138: Menin inhibitors in combination with chemotherapy and targeted agents are active in newly diagnosed (ND) and R/R AML

Phase 1 clinical trial in the ND setting

AZA/VEN + Revumenib in ND AML

- Dose escalation + expansion trial (N=43) in older, unfit ND AML patients
  - 113mg (DL1) and
  - 163 mg (DL2)

  in the expansion cohort
- Safety: No MTD identified; no patients discontinued Revumenib due to AEs

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

- Differences in 1y-OS between patients with *KMP2A*-r (83%) and *NPM1*-m (55%)
- Conclusions:
  - The treatment regimen is safe and effective
  - VEN should be reduced preemptively after the achievement of remission to mitigate AEs

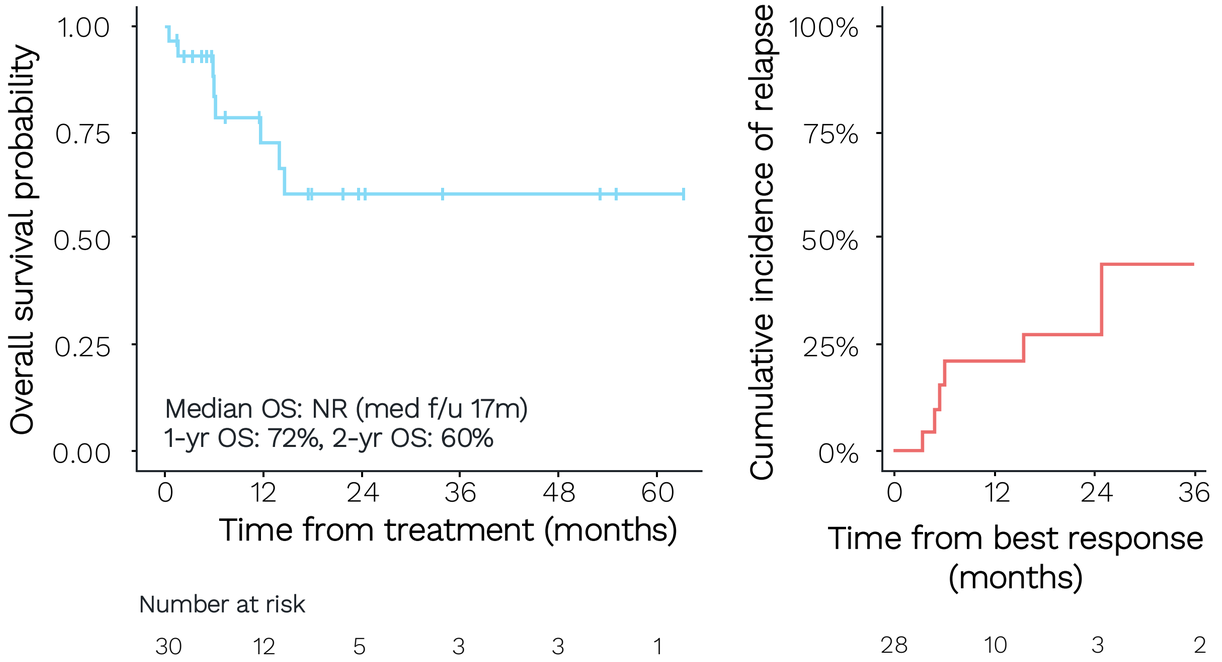
AE, adverse event; AML, acute myeloid leukemia; AZA, azacitidine; (c)CR, (composite) complete response; DL, dose level; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; ND, newly diagnosed; OS, overall survival; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; VEN, venetoclax.

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.

S142: Phase 1/2 study of decitabine, venetoclax, and quizartinib triplet combination in *FLT3-ITD* mutated AML

- *FLT3* mutations occur in 20-30% of patients with AML and indicate poor treatment outcomes[1]
- Quizartinib is a second-generation FLT3 inhibitor currently tested in Phase 3 trials[2,3]
  - Pre-clinical data indicate that quizartinib and venetoclax acts synergistically
- A Phase 1 trial aims to establish the RP2D of quizartinib in combination with DAC + Ven in patients with *FLT3*m AML (newly diagnosed and R/R) and collected data on CR, MRD and OS
- 30 mg chosen as RP2D, no dose-limiting toxicity
- 94% of ND and 61% of R/R pts achieved CR; 60% and 27% were MRD- at best response
- 30% and 37% bridged to ASCT
- mOS was not reached in newly diagnosed patients and 6.3 months in patients with R/R disease

Overall survival and cumulative incidence of relapse of patients with newly diagnosed *FLT3-ITD* mutated AML



AML, acute myeloid leukemia; ASCT, autologous stem cell transplant; CR, complete response; DAC, decitabine; f/u, follow-up; MRD, minimal residual disease; (m)OS, (median) overall survival; ND, newly diagnosed; NR, not reached; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; VEN, venetoclax

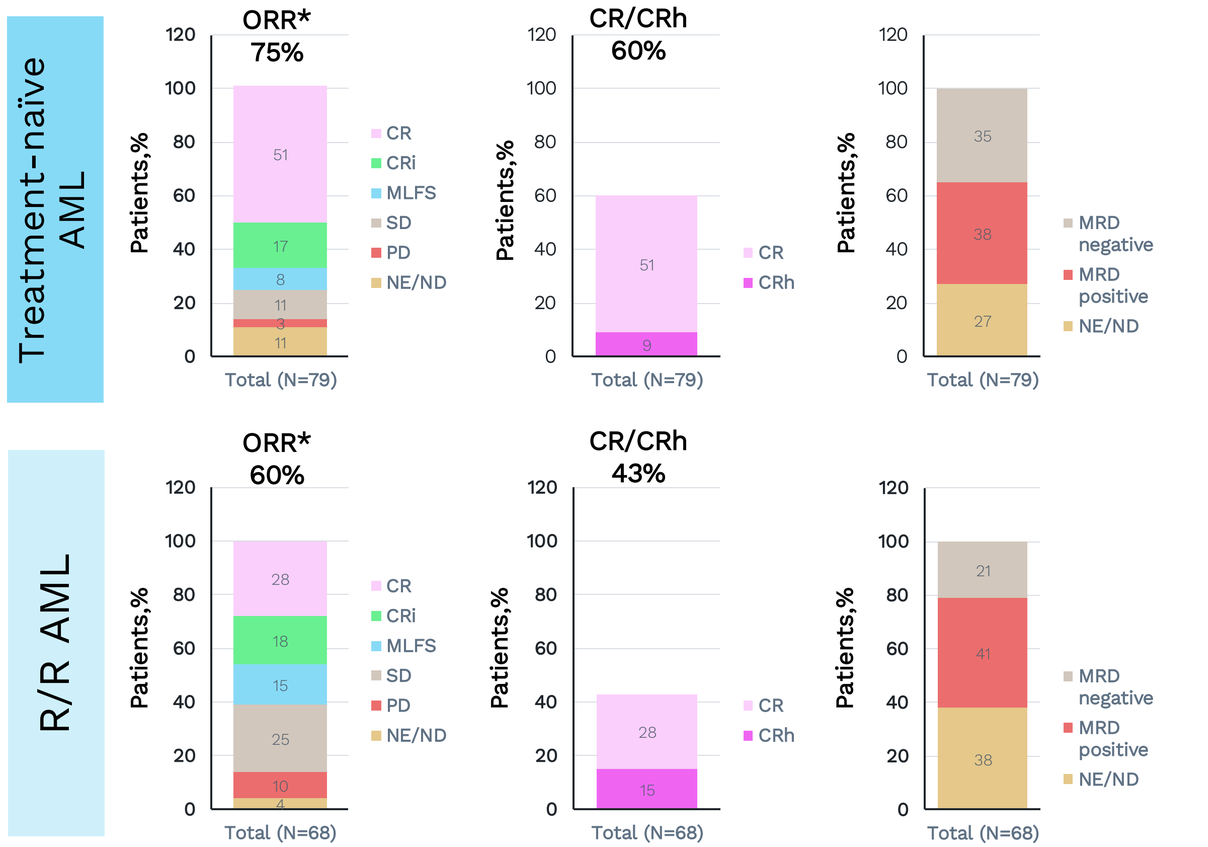
1. Kottaridis et. al, Leukemia & Lymphoma, 2003;44(6):905-913. 2. Erba HP et al., Lancet. 2023 May 13;401(10388):1571-1583. 3. Cortes JE etr al., Lancet Oncol. 2019 Jul;20(7):984-997. 4. Mali RS et al., Haematologica. 2021 Apr 1;106(4):1034-1046.

Yilmaz M. Phase 1/2 study of decitabine, venetoclax, and quizartinib triplet combination in FLT3-ITD mutated AML Oral presentation S142 at EHA2025.

PF477 & PF491: Sonrotoclax (BGB-11417) in treatment-naïve patients and R/R AML

- The BCL-2i venetoclax has improved outcomes for treatment-naïve, chemotherapy-ineligible patients[1]
- Sonrotoclax (S) is a next-generation BCL-2i with higher selectivity and potency[1,2]
- S+AZA was tested in the BGB-11417-103 Phase 1b/2 dose escalation and expansion trial in treatment-naïve[2] and R/R MDS and AML patients[1]
- Dosing: 40-320 mg for 10 to 28 days in a 28-day cycle
- Across all dosing schemes, the ORR for treatment-naïve patients was 75%, and 60% in R/R patients; with CR/CRh rates of 60% and 43%, respectively
- AEs related to myelosuppression (e.g. neutropenia G≥3: 90% in treatment-naïve, 84% in R/R) occurred frequently
- 15.2% of treatment-naïve and 11.8% R/R patients discontinued treatment
- Conclusion: The treatment is effective and was tolerated by most patients in the treatment-naïve and R/R settings

Response rates among treatment-naïve and R/R patients with AML receiving a combination of sonrotoclax plus azacitidine



*ORR included CR, CRi, MLFS and PR
AZA, azacitidine; CR, complete response; CRh, CR with partial hematologic recovery; CRi, CR with incomplete recovery; Gr, grade; MDS, myelodysplastic syndrome; MRD, minimal residual disease; MLFS, morphologic leukemia-free state; ND, not determined; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/ refractory; SD, stable disease.

1. **Montesinos P, et al. 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.**
2. **Shortt J, et al. Updated safety & antileukemic activity data of Sonrotoclax (BGB-11417), a potent and selective BCL2 inhibitor, in treatment-naive patients with acute myeloid leukemia unfit for intensive chemotherapy. PF477 at EHA2025.**

Conclusion

- This year’s EHA offered insights into tumor heterogeneity and clonal selection as the basis for relapse after treatment in AML, and new ways of combining treatments to avoid resistance
- 7+3 chemotherapy as a basis for combination treatments
- Strategies to move beyond HMA + VEN include triplets, intermediate intensity, immunotherapy, and novel agents
- Oral decitabine-cedazuridine + venetoclax is a viable alternative for older patients with newly diagnosed AML: in Phase 2b 46.5% achieved CR
- Menin inhibitors are being taken into Phase 3 based on initial dose escalation trials
- A Phase 1/2 study of decitabine, venetoclax, and quizartinib triplet in FLT3-ITD mutated AML showed 94% of ND and 61% of RR pts achieved CR
- Sonrotoclax in treatment-naïve and R/R AML was safe and effective and tolerated by most patients

AML, acute myeloid leukemia; CR, complete response; HMA, hypomethylating agent; ND, newly diagnosed; R/R, relapsed/refractory; VEN, venetoclax.

05

Geriatric hematology: from HSC to AI

Section 5: Geriatric hematology: from HSC to AI

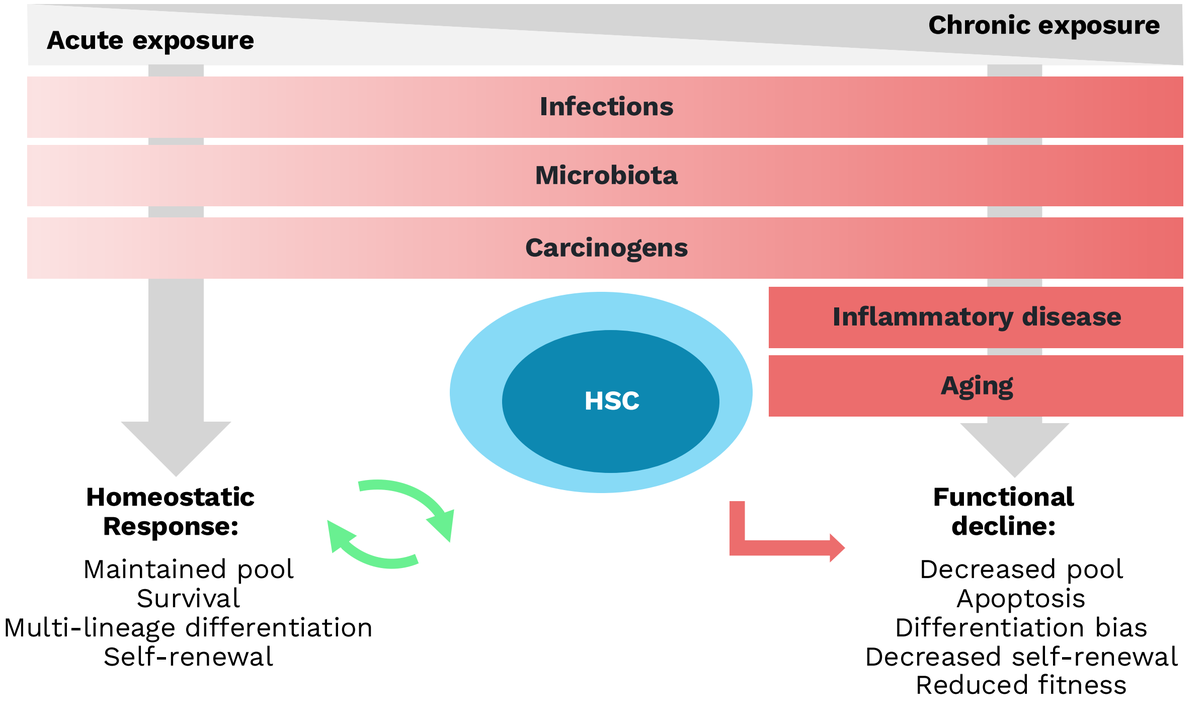
Overview of selected presentations

Presentation ID	Presentation Title	Presenter
p101-1	Aging in HSCs	Markus G. Manz
S332	Stem cell aging clock: A deep learning driven framework for predicting stem cell age	Guanlin Wang
p101-3	BM inflammation: Effects on clinical outcome and immune response in myeloid malignancies	Sergio Rutella
p252-1	The future of AI in the intersection of hematology and geriatrics	Torsten Haferlach
p252-2	LLM-assisted Decision-Making in geriatric hematology	Esther Lueje

p101-1: “InflammAging” and clonal hematopoiesis: Microbial and inflammatory drivers of HSC aging

- Aging is linked with chronic inflammation (“**InflammAging**”)
- Age-related gut microbiome dysbiosis increases intestinal permeability, allowing microbial products to enter the bloodstream and trigger bone marrow (BM) inflammation[1]
- Chronic inflammatory signaling (e.g., infections, microbial metabolites) drives HSC exhaustion, differentiation bias, and reduced regenerative potential[1]
- HSCs in aging are associated with accumulated mutations, loss of diversity, and clonal expansion[2]
- Clonal hematopoiesis (CHiP/ARCH) is more frequent with age and inflammation (*Tet2*- or *Dnmt3a*-mutant HSPCs)[3-5]
- Inflammation promotes pre-leukemic clonal expansion and may contribute to malignant transformation
- IL-1 signaling is upregulated in aged BM and plays a central role in promoting HSC dysfunction and clonal dominance[5,6]
- Blocking IL-1 or removing microbial triggers can protect against HSC aging (shown in germ-free and *IL1R1*-deficient mice)[6]

Aging-related impacts on HSC function



ARCH, age-related clonal hematopoiesis; BM, bone marrow; CHiP, clonal hematopoiesis of indeterminate potential; HSC, hematopoietic stem cell; HSPC, hematopoietic stem and progenitor cell.

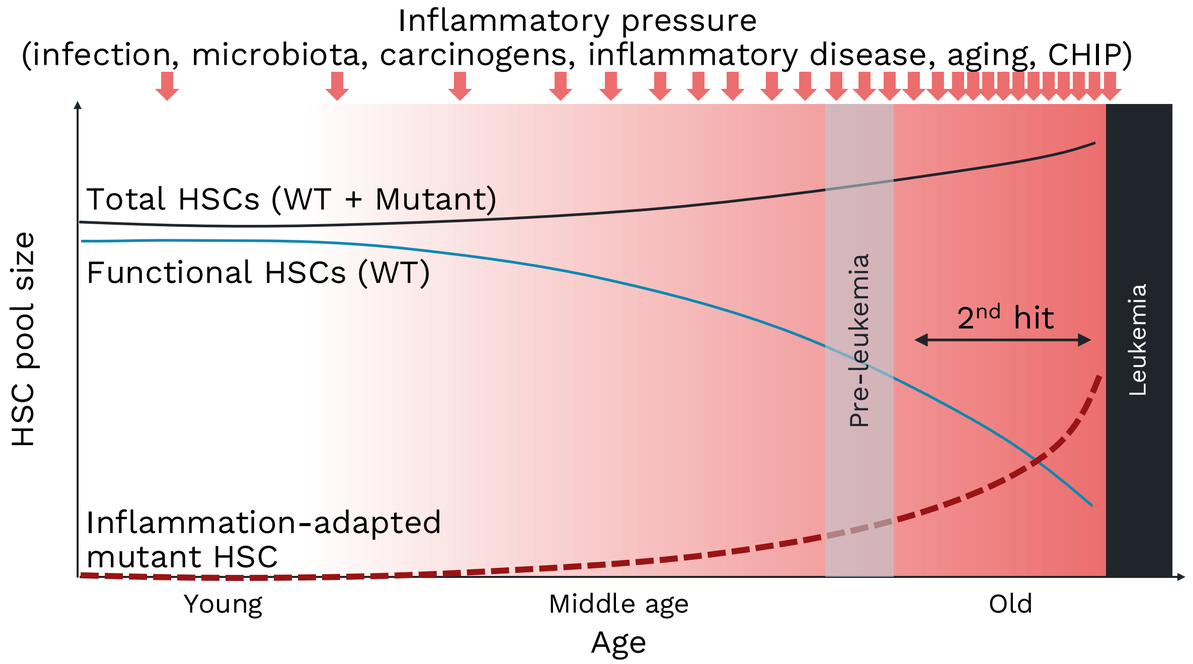
1. Balmer et al., J Immunol 2014. 2. Caiado, F., Pietras, E.M. & Manz M.G. JEM 2021. 3. Meisel et al., Nature 2018. 4. Hormaechea-Agulla D et al. Cell Stem Cell 2021. 5. Caiado et al. Blood 2023. 6. Kovtonyuk et al. Blood 2022.

Manz MG. Aging in HSCs. Oral presentation p101-1 at EHA2025.

p101-1: “InflammAging” and clonal hematopoiesis: Microbial and inflammatory drivers of HSC aging

- The interplay of aging, inflammatory cytokines, and microbial signals shapes the hematopoietic niche, promoting clonal hematopoiesis and contributing to systemic disease and malignant transformation[1]
- Therapeutic outlook: Targeting IL-1 signaling and microbiome-derived inflammation may offer new strategies to prevent or reverse hematopoietic aging and its complications

Inflammation in aging as a driver of (pre-) leukemia

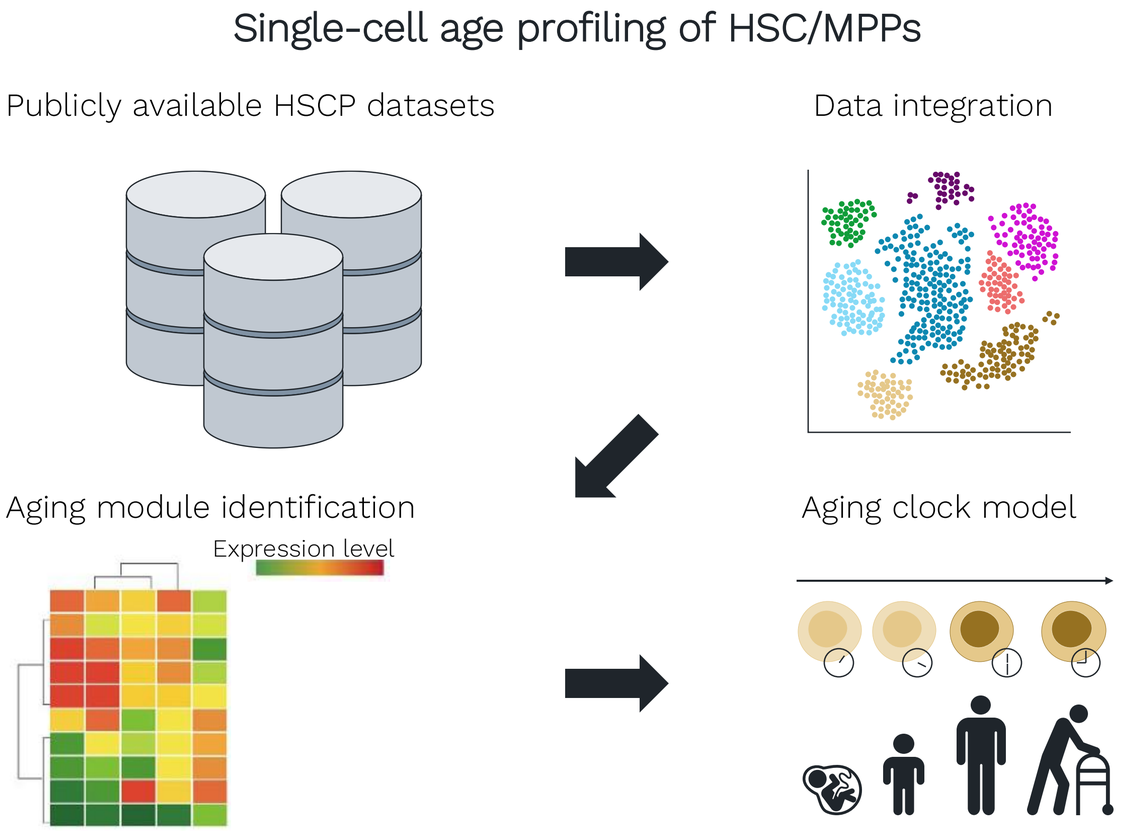


CHiP, clonal hematopoiesis of indeterminate potential; HSC, hematopoietic stem cell; IL, interleukin; WT, wildtype.

1. Caiado, F., Pietras, E.M. & Manz M.G. JEM 2021.

Manz MG. Aging in HSCs. Oral presentation p101-1 at EHA2025.

S332: A deep learning model can predict the chronological age of HSC/MPPs from single-cell transcriptomic data



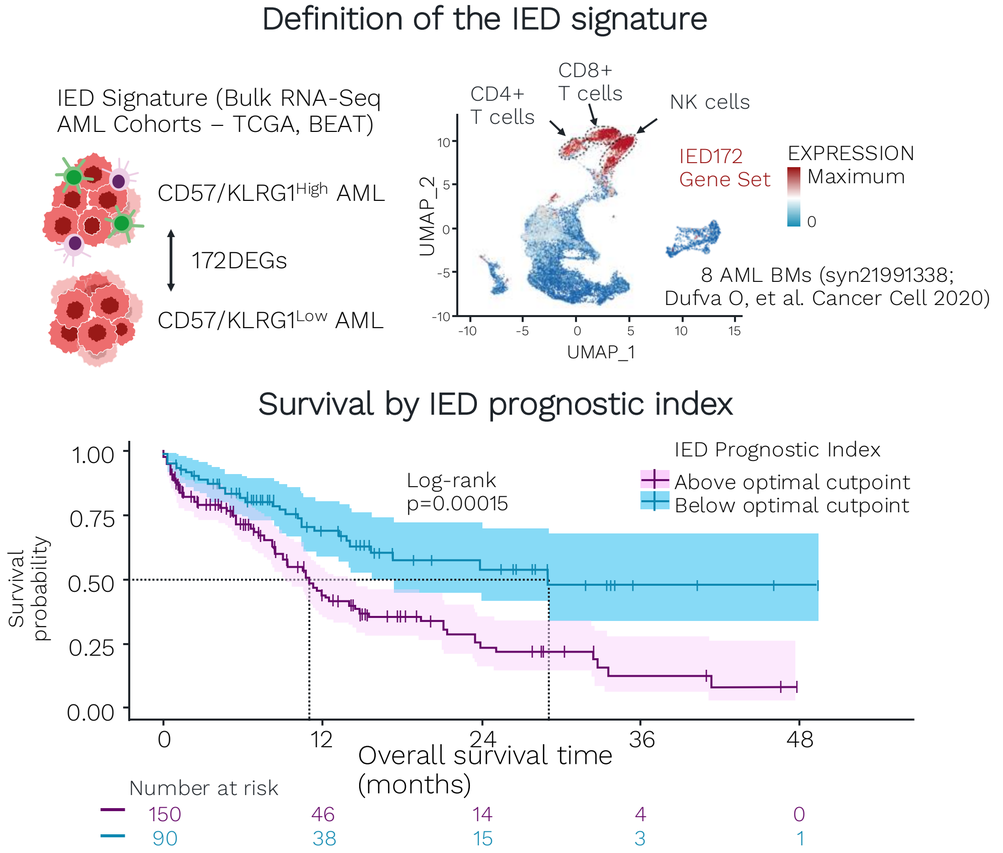
- Wang et al. integrated six published scRNA-seq datasets to build a comprehensive single-cell atlas of ~193,000 CD34+ Lin- HSPCs across the human lifespan, from fetal to geriatric stages
- A subset population of ~64,000 HSC/MPPs was identified and validated based on the expression of established markers (e.g., *AVP*, *HOPX*, *MLLT3*)
- Seven molecular programs underlying HSC/MPP functional heterogeneity were identified using a matrix factorization method
- These programs showed age- and disease-specific enrichment, including in MDS, myelofibrosis and BCP-ALL
- The trained aging clock model predicted chronological age shifts in BCP-ALL HSC/MPPs, which aged prematurely, but not in MDS, suggesting transcriptional age reprogramming of malignant cells
- **This model may inform therapeutic strategies targeting aging pathways that drive age-related regenerative decline and hematological malignancies**

BCP-ALL, B-cell precursor acute lymphoblastic leukemia; CD34+, cluster of differentiation 34 positive; HSC, hematopoietic stem cell; HSPC, hematopoietic stem and progenitor cell; Lin-, lineage negative; MDS, myelodysplastic syndrome; MPP, multipotent progenitor; scRNA-seq, single-cell RNA sequencing.

Wang G. Stem cell aging clock: a deep learning driven framework for predicting stem cell age. Oral presentation S332 at EHA2025.

p101-3: Immune effector dysfunction (IED) scores: A prognostic index in AML

- Technological advances enable a comprehensive characterization of the TME and the identification of mechanisms underlying disease
- Previous studies had shown that NK-like senescent CD8⁺ T cells are functionally impaired and predict poor responses in AML
- Building on this, the Rutella lab had defined an **immune effector dysfunction (IED) prognostic index,** dividing AML cells into senescence/NK^{high} and senescence/NK^{low} and identifying differentially expressed genes[1]
  - Genes in the IED signature were largely expressed by T cells and NK cells in the AML TME
- IED scores predicted poor survival outcomes in patients from the BEAT-AML2 real-world cohort treated with intensive chemotherapy
- The IED prognosticator, when combined with gene signatures of AML stemness (e.g, LSC17 score), was able to define subgroups outcomes
  - Excellent survival outcomes were observed in IED^{low}/stemness^{low}
  - This finding establishes a link between AML stemness and impaired anti-AML immune responses
- The prognostic power of the IED score was further confirmed in pediatric AML using bulk RNA-seq data from ~1,900 patients



AML, acute myeloid leukemia; CD8⁺, cluster of differentiation 8-positive; IED, immune effector dysfunction; LSC17, leukemia stem cell 17-gene signature; NK, natural killer; TME, tumor microenvironment.

1. Rutella S, *et al.* Journal of Clinical Investigation 2022.

Rutella S. BM inflammation; effects on clinical outcome and immune response in myeloid malignancies. Oral presentation p101-3 at EHA2025.

p101-3: Bone marrow inflammation has effects on clinical outcomes and immune responses in AML

Single-cell profiling identifies dysfunctional T-cell states in AML

- Rutella et al. built a single-cell atlas of T-cell states in newly diagnosed AML to better understand their impact on clinical outcomes
- A population of T_{EMRA}/senescent-like (SenL) T-cells associated with poor responses to chemotherapy was identified and further characterized:
  - T_{EMRA}/SenL T-cells were more abundant in AML samples than in those from healthy donors
  - T_{EMRA}/SenL T-cells were enriched in Type I and Type II IFN signaling, along with metabolic pathways related to OXPHOS, fatty acid metabolism, and ROS production
  - T_{EMRA}/SenL T-cells overexpress genes associated with antigen-specific $CD8^+$ T-cells found in various solid tumors, suggesting that T_{EMRA} states may be induced by AML tumor cells, rather than representing bystander T-cell infiltration

Gene signatures of IED (NK-like $CD8^+$ T_{EMRA} states) and inflammation may confer resistance to molecular targeted therapies:

- BM samples from patients with AML who did not respond to midostaurin *in vitro* had significantly higher IED scores
  - Overexpressed genes in samples from resistant patients were enriched in immune and pro-inflammatory pathways, including IFNɣ and IFNα signaling
- High IED scores correlated with poor *ex vivo* response to venetoclax in BM samples from BEAT-AML2 patients, suggesting that immune senescence may also impair response to BCL2i
- In BM samples from patients treated with pembrolizumab + azacitidine, high IED scores correlated with low response rates
- In patients with AML who did not derive any clinical benefit from ipilimumab immunotherapy, BM samples were enriched in T_{EMRA}-like cells overexpressing NK cell markers and chemokines that recruit Tregs and M2-type monocytes to the TME

Novel treatments targeting BM inflammation and senescence may enhance the efficacy of AML therapies

AML, acute myeloid leukemia; BCL2i, B-cell lymphoma 2 inhibitor; BM, bone marrow; $CD8^+$, cluster of differentiation 8-positive; IED, immune effector dysfunction; IFN, interferon; NK, natural killer; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; SenL, senescent-like; TME, tumor microenvironment; T_{EMRA}, terminally differentiated effector memory T cells re-expressing CD45RA; Treg, regulatory T cell.

Rutella S. BM inflammation; effects on clinical outcome and immune response in myeloid malignancies. Oral presentation p101-3 at EHA2025.

p252-1: The future of AI in the intersection of hematology and geriatrics

Rising prevalence and complexity in geriatric hematology

Why will AI be needed in hematology?

- As the life expectancy of patients with hematological malignancy increases, so does the number of patients
- Elderly patients often take multiple routine medications daily, in addition to treatments for hematologic malignancies
- Accounting for drug-drug interactions is a major challenge:
  - Treatment options based on patient genotype
  - Distinct scoring systems for patients aged ≥60 years
  - Dynamic prognostic models
- There are over 1,000 FDA-approved AI-enabled medical devices, 76% are in radiology, and 2% are in hematology. There are only 3 FDA-approved devices to address geriatric health.[1,2]

AI-driven diagnostic tools with potential in hematology

- Automated microscopes and blood / cell analysis
- Batch karyotyping, and molecular genetics (variant annotation and NGS interpretation)
- WTS and WGS, using datasets trained on thousands of genomes and transcriptomes to differentiate malignant from non-malignant signatures, and different hematological malignancies from each other
- LLMs can generate diagnostic reports and secondary LLMs may be used to evaluate the first.
- LLMs are already used for morphology-based diagnostics
  - For example, 21,926 cases were processed using LLMs and the first AI-generated proposal was accepted in 75% of cases

AI, artificial intelligence; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BCP-ALL, B-cell precursor acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; FL, follicular lymphoma; HZL, hairy zone lymphoma; LLM, large language model; MDS, myelodysplastic syndromes; MM, multiple myeloma; MPN, myeloproliferative neoplasms; NGS, next-generation sequencing; WGS, whole genome sequencing; WTS, whole transcriptome sequencing; XGBoost, eXtreme Gradient Boosting.

1. Muralidharan *et al*. NPJ Digit Med, 2024. 2. www.fda.gov.

Haferlach T. The future of AI in the intersection of hematology and geriatrics. Oral presentation p252-1 at EHA2025.

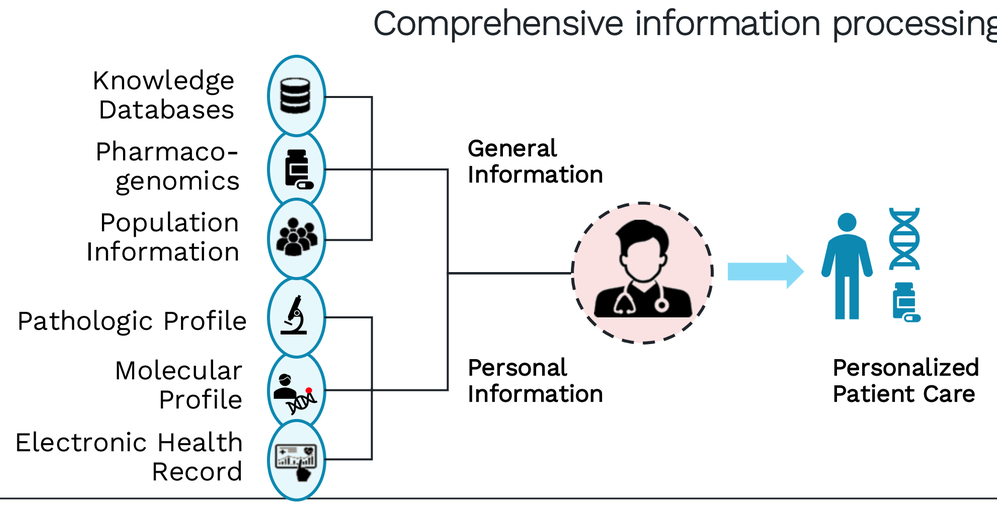
p252-1: The future of AI in the intersection of hematology and geriatrics

AI implementation in hematolgy

- One might envision a future where AI will offer real-time coaching to clinicians, suggesting relevant history-taking questions and physical findings to examine
- These technologies will also assist in listening to and documenting clinical encounters, effectively generating clinical notes and organizing next steps and investigations
- Despite AI outperforming physicians in diagnostic accuracy (92% vs. 74%), its potential remains underutilized, largely because physicians often disregard AI input and lack
adequate training in how to interact effectively with AI tools
- By 2030, integrated diagnostic dashboards are expected to support dynamic prognostication via automated workflows, real-time risk models based on lab results, MRD, and multi-omics profiling, and therapy guidance using digital twin scenarios

AI supports, and doctors decide

- AI will play a role in hematology by enabling truly personalized therapy through genetic profiling, treatment timing, and toxicity prediction
- AI will enhance, not replace, clinical care by streamlining workflows and empowering clinicians to spend more time communicating with patients



AI, artificial intelligence; MRD, minimal residual disease.

Haferlach T. The future of AI in the intersection of hematology and geriatrics. Oral presentation p252-1 at EHA2025.

p252-2: LLM-assisted decision-making in geriatric hematology

Unmet need in the management of geriatric patients

- Complex individuals with multiple comorbidities, frailty, cognitive changes, and social vulnerabilities
- Current decision-making tools often overlook these dimensions and there is a lack of models that integrate social, clinical, and functional data into real-time recommendations. Moreover, clinicians face limited resources and time constraints.
- Large language models (LLMs) can analyze medical histories, test results, and scientific literature to provide personalized treatment recommendations.
  - CancerLLM, a model trained on over 2.6 million clinical notes and 500,000 pathology reports, has demonstrated improved phenotype extraction and diagnostic generation in oncology[1]
- LLMs can also synthesize evidence.
  - RadOnc-GPT, specialized in radiation oncology[2] enables geriatric oncologists to stay up-to-date with the latest evidence
- LLMs can translate medical terminology into understandable language for patients and LLMs can be used for note-taking

Pitfalls currently exist and need to be considered, such as:

1. Hallucinations and clinical errors
2. The need for medical oversight
3. Challenges with unstructured data
4. Technical and organizational barriers (staff training and implementation costs)
5. Patient data needs to be safeguarded in AI applications.
6. If clinicians want to utilize AI tools, they need to learn the language of these tools.

Better prompting = better clinical support.

The recommendations generated by AI need to be reviewed and final clinical decisions should always be made by the HCP.

Clinicians didn't become doctors to fill out forms but to help patients. If AI is used wisely, doctors can return to that purpose.

1. Li, Mingchen, et al. arXiv preprint arXiv. 2024:2406;10459. 2. Liu, Z., et al. ArXiv. 2023;abs/2309.10160.
Lueje E. LLM-assisted decision-making in geriatric hematology. Oral presentation p252-2 at EHA2025.

Conclusion

- Aging is linked with chronic inflammation, but targeting IL-1 and the microbiome may represent a new strategy to prevent or even reverse hematopoietic aging.
- New insights from data presented at EHA2025 suggest that deep-learning models can predict chronological age from single-cell transcriptomic data, which could inform therapeutic strategies targeting aging pathways.
- Immune effector dysfunction (IED) scores predict poor survival outcomes and could be used in a prognostic index for AML.
- BM inflammation has effects on clinical outcomes and immune responses in AML; targeting BM inflammation and senescence may enhance therapy efficacy
- AI will be important at the intersection of hematology and geriatrics to deal with polypharmacy and potential drug interactions, as well as to support diagnosis.
- LLM may assist in analyzing medical histories, test results, and scientific literature to provide personalized treatment recommendations.

AI, artificial intelligence; AML, acute myeloid leukemia; BM, bone marrow; LLM, large language model.

06

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

Section 6: The new frontiers of genomic and functional techniques for precision medicine in hematology

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
p502-1	AI in hematology diagnostics	Jan-Niklas Eckardt
p255-4	Digital pathology for personalized medicine in hematological malignancies	Matteo Giovanni Della Porta
p201-3	Artificial intelligence in hematology: Opportunities, pitfalls and how to bring it to clinical practice	Jakob Kather
p282-1	NGS immunogenetics	Anton Langerak
S121	Multimodal analysis of newly diagnosed acute myeloid leukemia patients reveals associations between genetic lesions and immunophenotypes	Tim Mocking
S171	The interplay between inflammation and immune escape in MDS with P53 dysfunction evolution: Insights from single-cell multi-omics	Matteo Zampini
p269-2	Biomarker-driven trials: Immunotherapy prediction in lymphoma	Sirpa Leppä
p282-2	Implementation science in diagnostics	Elizabeth Macintyre

p502-1: The future role of AI in hematology diagnostics

Cell- and disease-level classifications in hematology rely on manual diagnostics such as peripheral blood and BM smears

- May be impacted by inter- and intra-observer variability
- Can result in a longer time to diagnosis
- Operators tend to have a flat learning curve

AI is better than humans at processing large volumes of data and noticing patterns

- AI image data can be used for cell and disease classification, as digital biomarkers, and for response prediction and risk marker identification
- Large-language and foundational models collate different aspects

AI system AMIE: Diagnostic accuracy and patient preference

AMIE is an LLM system optimized for physician-patient AI-assisted diagnostic dialogue

- AMIE achieves the correct diagnosis more often than an unassisted physician[1]
- And patients prefer the soft skills of AMIE to a PCP[2]

AI, artificial intelligence; AMIE, Articulate Medical Intelligence Explorer; BM, bone marrow; LLM, large language model; PCP, primary care physician.

1. McDuff D, et al. Nature 2025;642(8067):451-457; 2. Tu et al. Nature 2025;642(8067):442-450.

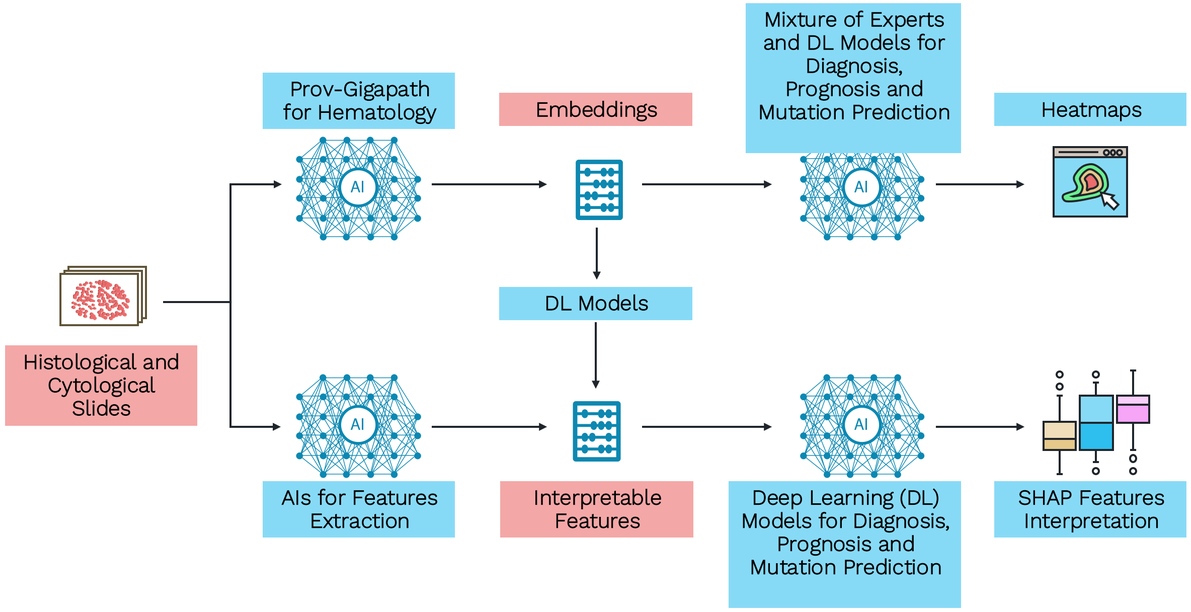
Eckardt J-N. AI in hematology diagnostics. Oral presentation p502-1 at EHA 2025.

p255-4: The role of digital pathology in personalized medicine for hematological malignancies

AI-based digital pathology has improved the use of tumor biopsy data

- It can detect patterns and convert complex image information into numerical features
- This study explored a personalized prognostic/predictive model
- A foundation model was pretrained on a large and diverse dataset and was used to extract specific clinical entities from whole slide imaging features[1,2]
- Based on digital pathology in 1,688 patients with MN: PATHroclus

PATHroclus – an innovative framework for digital pathology in hematology



AI, artificial intelligence; MN, myeloid neoplasm.

1. Asti G, et al, Blood 2024;144:3598; 2. Xu H, et al. Nature 2024;630:181-188.

Della Porta MG. Digital pathology for personalized medicine in hematological malignancies. Oral presentation p255-4 at EHA 2025.

p255-4: The role of digital pathology in personalized medicine for hematological malignancies

- Correct diagnosis was predicted with overall AUROC >0.91, suggesting that extracted features capture clinically relevant information
- Specific genomic profiles were predicted with high accuracy, underlining the capability to capture the biological background
- Morphological features were integrated into an innovative prognostic tool for personalized prediction of OS and leukemia-free survival
- EHA supports the deployment of the federated PATHroclus platform

Preliminary data provide proof-of-concept that digital pathology is able to capture clinically and biologically relevant information

- This will help refine diagnosis and prognostication at the individual patient level

Variables	Overall Survival C-Index	Leukemia-Free Survival C-Index
Clinical	0.78	0.68
Clinical + Genomic + Karyotype	0.82	0.80
Clinical + Genomic + Karyotype + **Digital Pathology**	0.88	0.90

AI, artificial intelligence; AUROC, area under the receiver operating characteristic; EHA, European Hematology Association; OS, overall survival.

Della Porta MG. Digital pathology for personalized medicine in hematological malignancies. Oral presentation p255-4 at EHA 2025.

p201-3: Bringing AI into clinical practice in hematology

- AI is being positioned as a decision-making tool in healthcare – and this use is the leading reason for investment in AI technologies
- AI is already approved in medical devices and for shadow use[1]
- In hematology, many models have relied on image analysis – for example, differentiating BM cell morphologies[2,3]

- LLMs support medical reasoning and add additional context, and can be used to structure unstructured data
- New vision language models can support image interpretation
- ESMO has an initiative to investigate biomarkers with AI – for quantification and prediction, as well as novel AI-based biomarkers that might be able to provide prognostic information or predict treatment response

AI, artificial intelligence; BM, bone marrow.

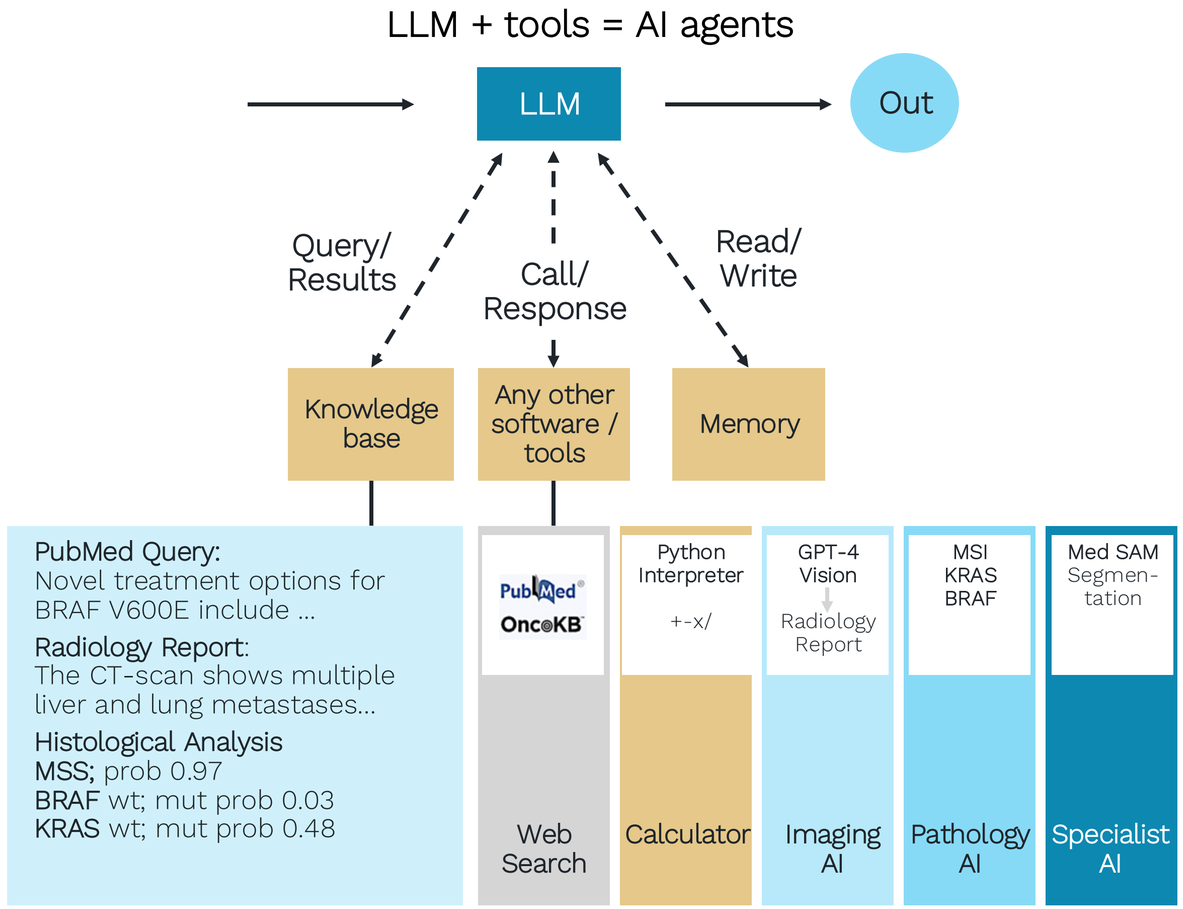
1. Blease et al. BMJ 2024; 2. Matek et al. Blood 2021; 3. Eckardt JN, et al. Leukemia 2021.

Kather J. Artificial intelligence in hematology: Opportunities, pitfalls, and how to bring it to clinical practice. Oral presentation p201-3 at EHA 2025.

p201-3: AI agents: Bringing LLMs together with other automated tools

- LLMs can be enhanced with external tools – linking models to other pieces of software or workflow tools
  - Anything a human does with a computer can be automated
  - Combining outputs from various tools with LLMs enables AI agents to become oncology decision makers
- The next step is to validate these AI agents in real-world patient cases and clinical trials

- There is already high-quality evidence for the usefulness of AI products[1] but with new technologies comes new dangers, such as:
  - AI models care sensitive to subtle cues and nuances
  - Privacy/compliance considerations when entering patient data into commercial AI models



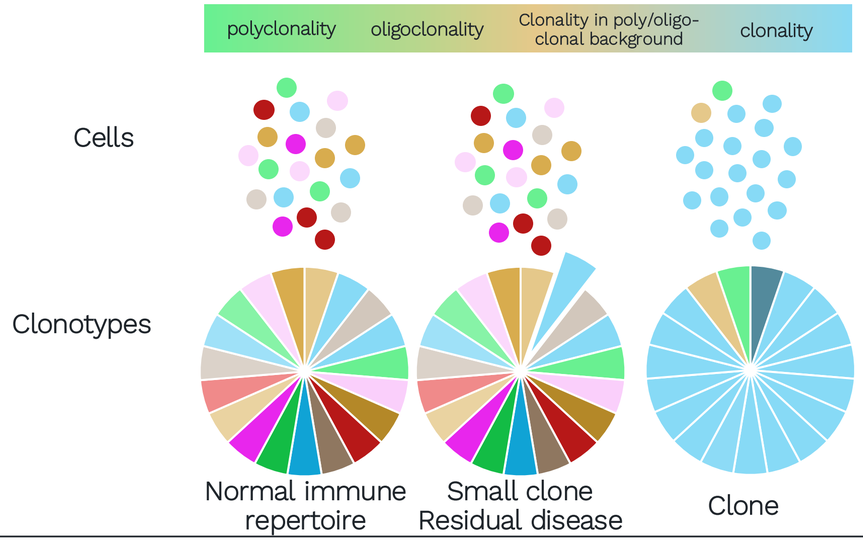
AI, artificial intelligence; LLM, large-language model.

1. Lång K, et al. Lancet Oncol 2023;24(8):936-944.

Kather J. Artificial intelligence in hematology: Opportunities, pitfalls, and how to bring it to clinical practice. Oral presentation p201-3 at EHA 2025.

p282-1: Precision hematology through NGS immunogenetics across diagnosis, prognosis, theranostics, and monitoring

- NGS immunogenetics enables in-depth profiling of immunoglobulin (IG) and T-cell receptors (TR) and uncovering antigen receptor diversity and clonality, supporting the identification of precision markers
- Protocols for NGS-based IG/TR clonality testing are now established



Clinical applications and impact of NGS immunogenetics

- Lymphoma diagnostics:
  IG/TR profiling helps distinguish new disease from relapses
- CLL stereotyping:
  Identification of stereotyped CLL subsets (e.g., #2, #8) provides prognostic insights; IGLV stereotypy may serve as a prognostic and theranostic marker (e.g., CAR T targeting principle)
- MRD monitoring:
  IGHV NGS-based MRD detection assays offer high sensitivity in detecting residual disease and contribute to better prognostic risk stratification
- Early detection & screening:
  NGS can detect preclinical clones in CLL (EPIC cohort) and supports early NHL detection in at-risk populations (LOGIC study)

CAR T, chimeric antigen receptor T cell; CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain variable region; IGLV, Immunoglobulin light chain variable region; MRD, minimal residual disease; NGS, next-generation sequencing.

Langerak, J Immunol 2017; Langerak, Meth in Mol Biol 2022.

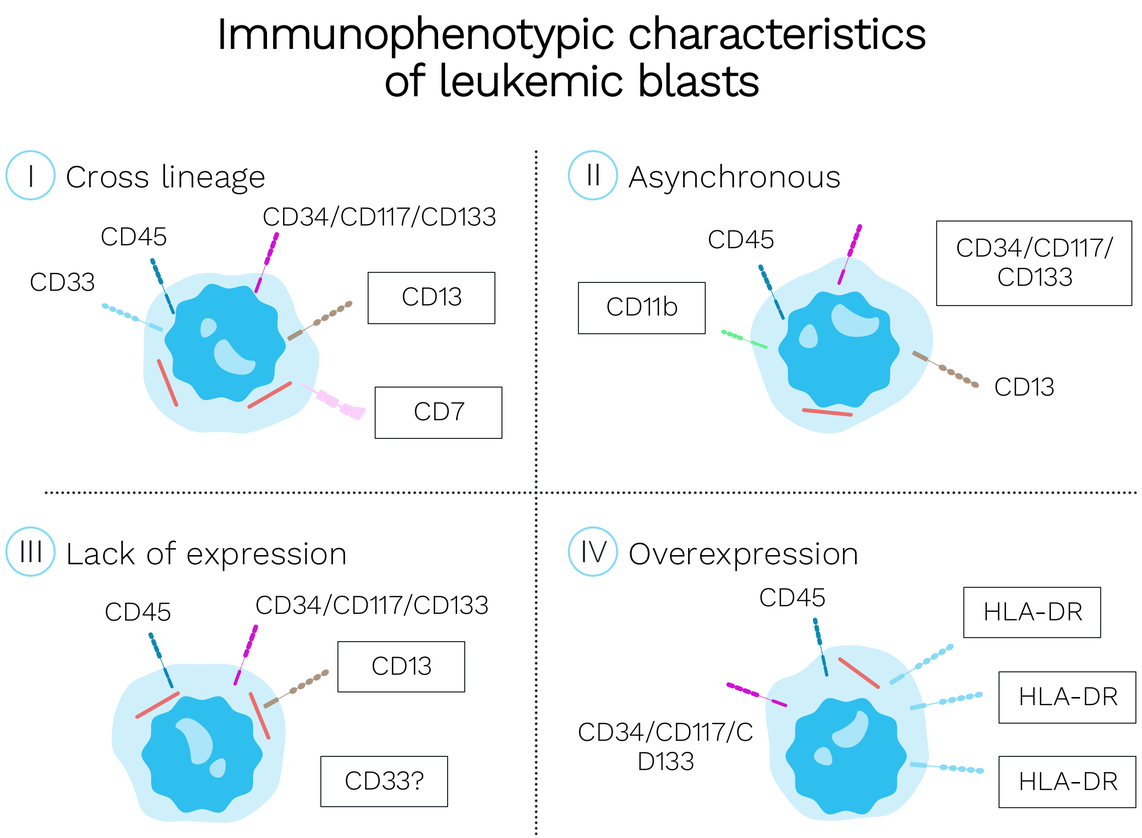
Langerak A. NGS immunogenetics. Abstract p282-1 presented at EHA2025.

S121: Multimodal analysis of newly diagnosed AML reveals associations between genetic lesions and immunophenotypes

- The immunophenotypic landscape of AML is heterogeneous
- There is no single leukemic cell marker, and limited inter-patient similarity
- Most insights come from small single-marker studies
- LAIP are rarely found on healthy cells, and are targetable

Mapping the phenotypic atlas is an unsupervised method that can be used to identify patterns

- Data from 502 BM aspirates at diagnosis
- Clustered >50 million cells using an algorithm
- Stratified patients into clusters

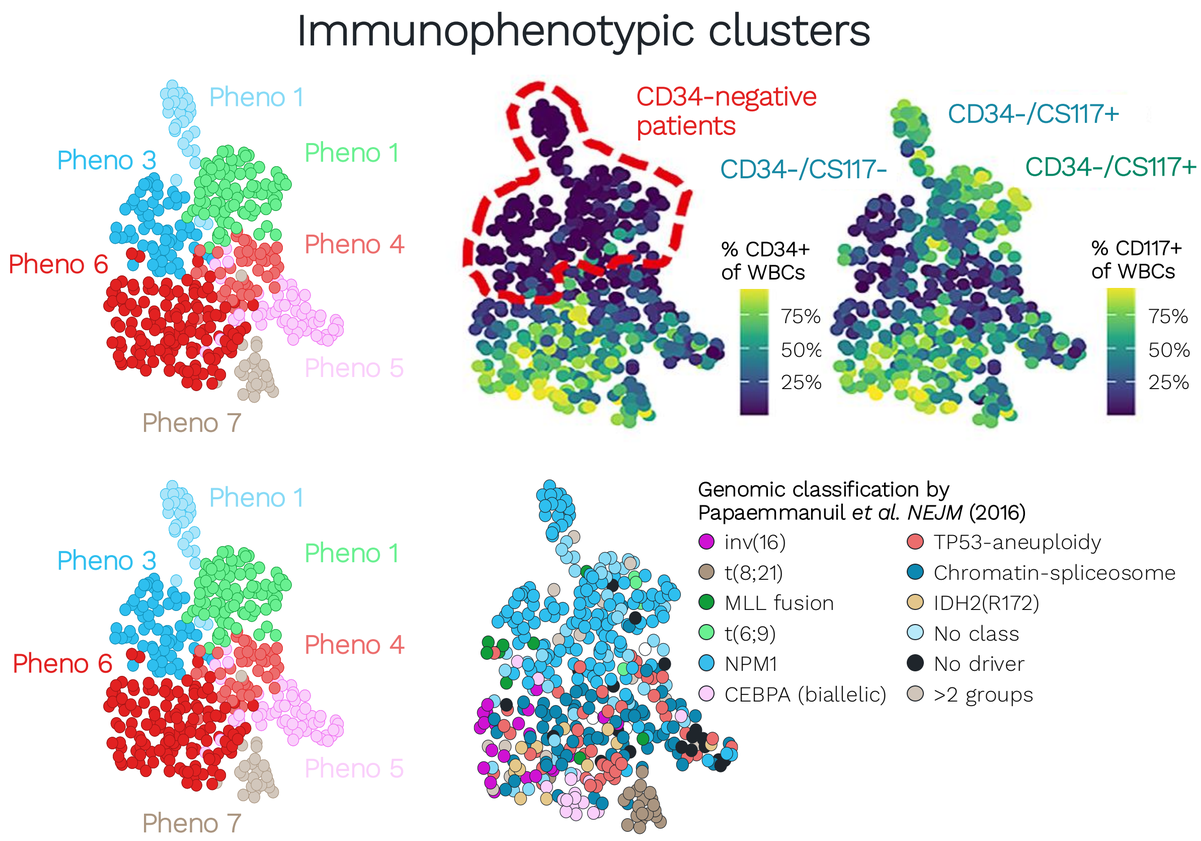


AML, acute myeloid leukemia; BM, bone marrow; LAIP, leukemia-associated immunophenotype.

Mocking T. Multimodal analysis of newly diagnosed acute myeloid leukemia patients reveals associations between genetic lesions and immunophenotypes. Oral presentation S121 at EHA2025.

S121: Multimodal analysis of newly diagnosed AML reveals associations between genetic lesions and immunophenotypes

- 7 clusters globally defined by myeloid marker expression patterns
- Immunophenotypic clustering aligned with genotype
- More mature CD34-negative patients were mostly the NPM1 group
- Some genetic subgroups have more phenotypic similarity
- *NPM1+IDH* and t(8;21) harbor distinct leukemic cell-surface signatures at diagnosis



AML, acute myeloid leukemia; NPM1, nucleophosmin 1.

1. Papaemmanuil E, et al. N Engl J Med 2016;374(23):2209-2221. 2. Mocking et al. HemaSphere 2025.

Mocking T. Multimodal analysis of newly diagnosed acute myeloid leukemia patients reveals associations between genetic lesions and immunophenotypes. Oral presentation S121 at EHA2025.

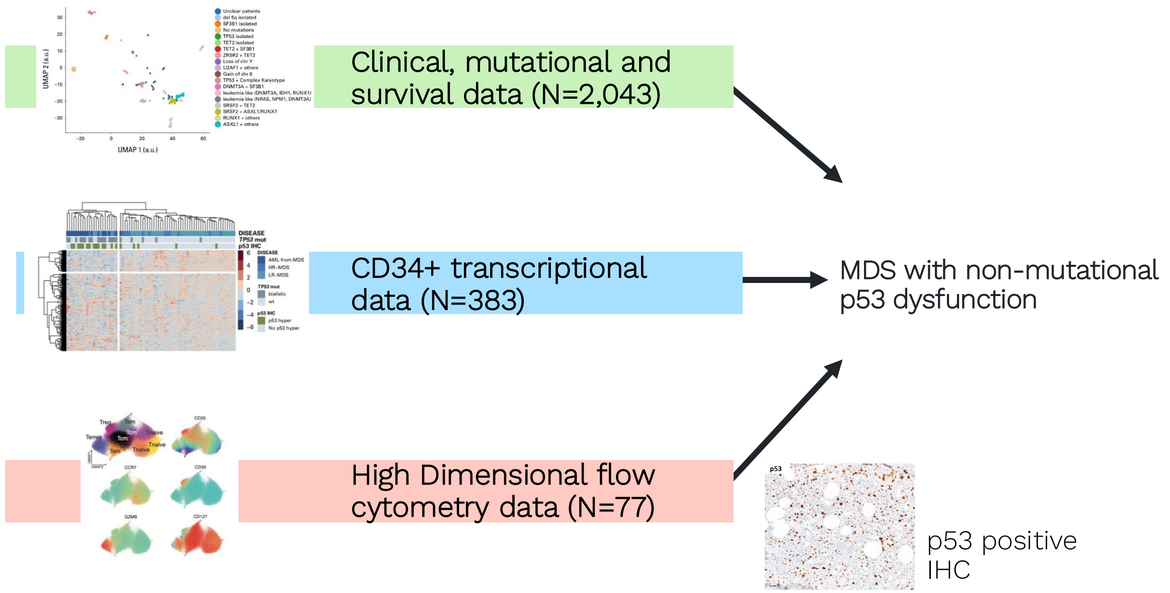
S171: Exploring the interplay between inflammation and immune escape in MDS, with insights from single-cell multi-omics

- MDS is a heterogeneous group of clonal HSC neoplasms characterized by myelodysplasia, ineffective hematopoiesis, cytopenia, and increased AML risk[1,2]
- *TP53* accounts for 10% of all MDS mutations, and gives rise to an immunosuppressive TME[3,4]

This work aimed to identify non-mutational p53 dysfunction in MDS

- Immunological BM environment stratified according to p53 dysfunction
- Performed CITEseq and FACS-based immunophenotypic enrichment

Identification approach of non-mutational p53 dysfunction in MDS



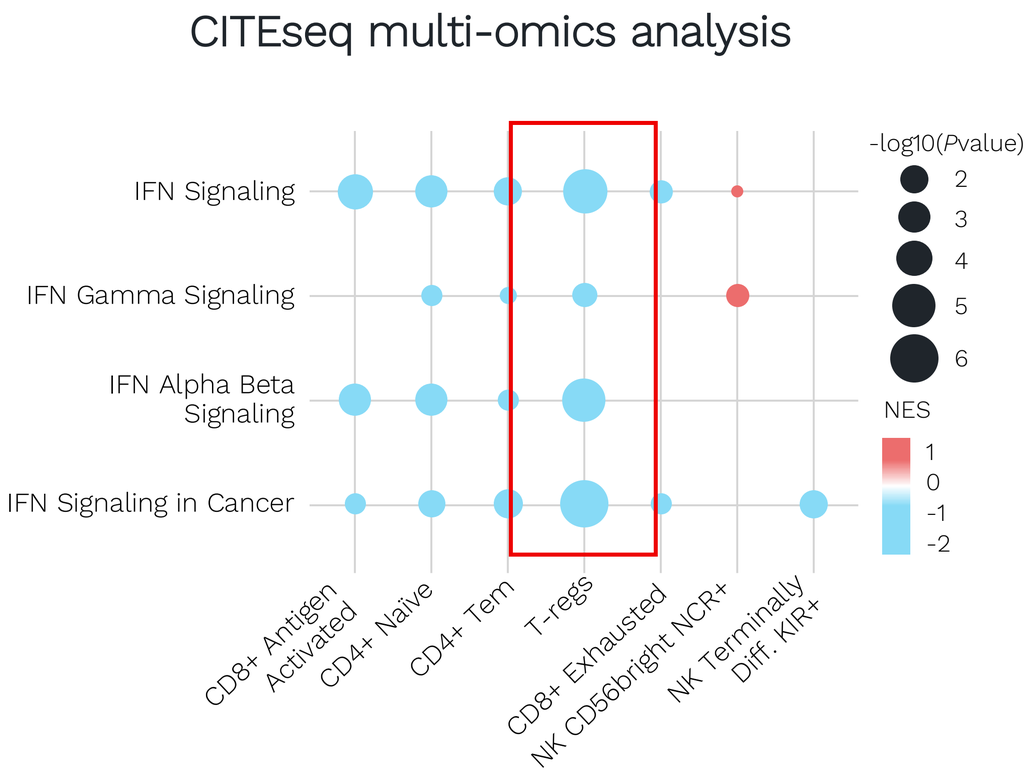
AML, acute myeloid leukemia; BM, bone marrow; HSC, hematopoietic stem cell; IHC, immunohistochemistry; MDS, myelodysplastic syndrome; TME, tumor microenvironment.

1. Cazzola M. N Engl J Med 2020;383(14):1358-1374; 2. Dunn WG, et al. J Clin Invest 2024;134(19):e180065; 3. Sallman DA, et al. Leukemia 2016;30(3):666-673; 4. Daver NG, et al. Cancer Discov 2022;12(11):2516.

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 EHA 2025.

S171: Exploring the interplay between inflammation and immune escape in MDS, with insights from single-cell multi-omics

- CITEseq confirmed lower expression of p53 target genes in p53 dysfunction
- HSPC in p53 dysfunction show:
  - Altered antigen presentation
  - Increased levels of PD-L1, driving immunosuppression
  - Upregulation of TNF-a and TGF-b signaling
- p53 dysfunction does not fuel an IFNγ-driven T-reg expansion via CD34+ progenitors, but appears linked to chronic myeloid-derived inflammation
- These findings reveal a novel connection between inflammatory signaling and immune escape mechanisms in p53-dysfunctional MDS

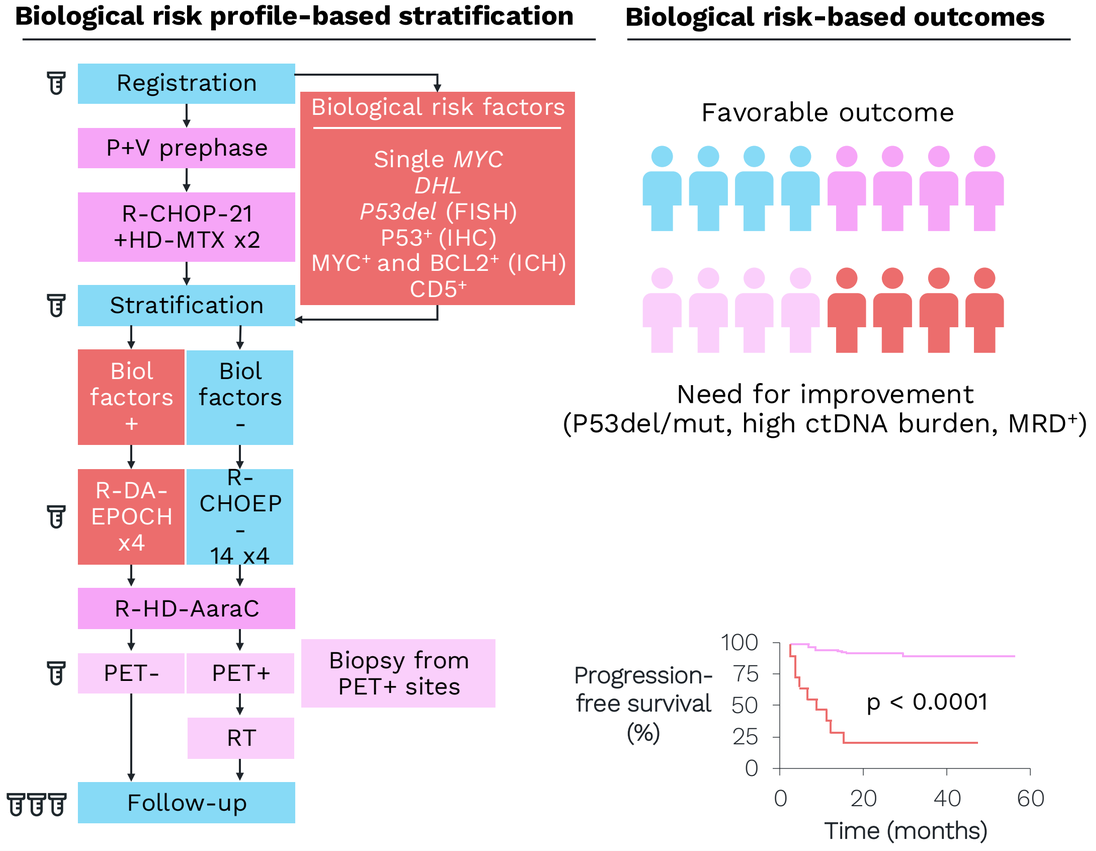


HSPC, hematopoietic stem and progenitor cell; IFN, interferon; MDS, myelodysplastic syndrome.

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 EHA 2025.

p269-2: Biomarker-driven immunotherapy in LBCL: The BIO-CHIC trial

- Biomarker-driven approaches aim to personalize lymphoma treatment by using genetic and biological risk factors to address molecular vulnerabilities
- **NLG-LBC-6 (BIO-CHIC)**: Phase 2 trial in patients <65 years with high-risk large B-cell lymphoma (LBCL) using risk-adapted chemoimmunotherapy with early CNS prophylaxis
- Patients were stratified by biological risk factors
  - High-risk: Treatment with DA-EPOCH-R
  - Low-risk: Treatment with R-CHOEP-14
- 5-year outcomes (all patients): FFS 75%, PFS 83%, OS 89%; slightly lower outcomes for high-risk group, but intensified therapy was effective in many subtypes
- High pre-treatment ctDNA levels, 17p/TP53 deletion, and TP53 mutations were associated with worse outcomes



BCL2, B-cell lymphoma 2; CD5, cluster of differentiation 5; CHOEP, cyclophosphamide + doxorubicin + vincristine + etoposide + prednisone; CNS, central nervous system; ctDNA, circulating tumor DNA; DA-EPOCH, dose-adjusted etoposide prednisone vincristine cyclophosphamide doxorubicin; DHL, double hit lymphoma; FFS, failure-free survival; FISH, fluorescence in situ hybridization; HD-AraC, high-dose cytarabine; HD-MTX, high-dose methotrexate; IHC, immunohistochemistry; LBCL, large B-cell lymphoma; MRD, minimal residual disease; MTX, methotrexate; MYC, myelocytomatosis oncogene; OS, overall survival; PFS, progression-free survival; PET, positron emission tomography; R, rituximab; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; RT, radiotherapy; TP53, tumor protein p53. Leppä S, et al. *Hemasphere.* 2025;9(5):e70139.

Leppä S. Biomarker-driven trials: Immunotherapy prediction in lymphoma. Oral abstract p269-2 presented at EHA2025.

p269-2: Role of ctDNA and molecular subtypes in predicting response in DLBCL

- ctDNA analysis revealed strong correlation between tumor burden, treatment response, and relapse risk
  - High pretreatment ctDNA were associated with worse outcomes
  - ctDNA positivity at EOF predicted relapse
  - ctDNA negativity at EOF indicated durable remission and helped address false-positive PET findings
- ctDNA should be used as a biomarker for risk stratification, offering:
  - Better prognostic accuracy than aaIPI
  - Early detection of chemoresistance and potential to avoid overtreatment
- DLBCL molecular subtypes show distinct genetic profiles and signaling dependencies, enabling targeted treatment strategies
  - **MCD/C5/MYD88 lymphomas (ABC signature)**
  - **EZB/C3/BCL2 lymphomas (GCB signature)**
  - Ibrutinib + R-CHOP leads to improved survival in younger patients with non-GCB DLBCL (PHOENIX)
  - Ibrutinib + R-CHOP benefits MCD-like and BN2-like subgroups (Guidance-1)
  - Bortezomib + R-CHOP benefits the ABC subgroup (REMoDL-B)
- The LymphGen algorithm classifies DLBCL into 7 genetic subtypes, guiding rational biology-based therapy selection

→ Integrating molecular profiling and ctDNA enables precision treatment and uncovers subgroup-specific responses in DLBCL

ABC, activated B-cell; aaIPI, age-adjusted International Prognostic Index; BCL2, B-cell lymphoma 2; C3, cluster 3; C5, cluster 5; ctDNA, circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; EOF, end of frontline; EZB, EZH2 and BCL2 mutations; GCB, germinal center B-cell; LymphGen, lymphoma genetics classifier; MCD, MYD88 and CD79B mutations; MRD, measurable residual disease; MYD88, myeloid differentiation primary response 88; PET, positron emission tomography; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone.

Leppä S, et al. *Hemasphere.* 2025;9(5):e70139.
Leppä S. Biomarker-driven trials: Immunotherapy prediction in lymphoma. Abstract p269-2 presented at EHA2025.

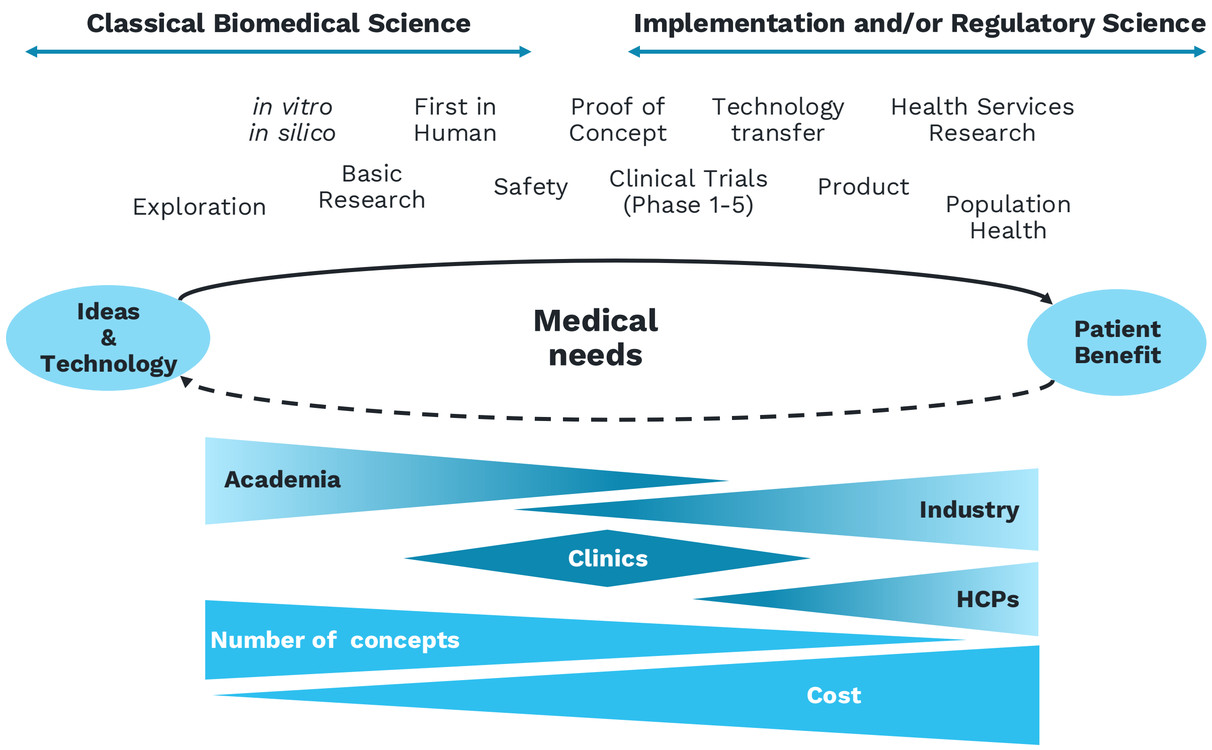
p282-2: Translating diagnostic innovation in hematology through multidisciplinary implementation

Implementation science focuses on translating medical innovations into real-world clinical benefits for individual patients

- The **Biomedical Alliance in Europe**, uniting 35 medical societies representing >400,000 HCPs, promotes patient-centered precision medicine through structured implementation efforts[1]

Challenges in diagnostic implementation

- Diagnostics in hematologic malignancies involve increasingly complex workflows across histology, genomics, immunology, and hematology, making the definition of a consistent and clinically meaningful diagnosis more challenging
- Effective implementation in hematology diagnostics requires collaboration across disciplines and policymakers



HCP, healthcare professional.

1. https://www.biomedeurope.org.

Macintyre E. Implementation science in diagnostics. Oral abstract p282-2 presented at EHA2025.

p282-2: National and European strategies for coordinated implementation of onco-hematology diagnostics

National example models

- **UK (SIHMDS):** 27 integrated labs aiming to improve diagnostic accuracy and consistency
- **France (GBMHM)**: Established in 2003; achievements include development of national prescribing guidelines, creation of EQA, and heath-economic HTAs (e.g., evaluating molecular tests and targeted NGS utility in real-world settings)[1]
- **France (LBMR)**: Ongoing initiative (2021-2026) focused on strengthening expertise, data collection, education, and network coordination
- **European context:** Europe-wide diagnostic models need to consider differences in population size and language diversity

Successful diagnostic implementation requires:

- Multi-stakeholder collaboration and regulatory expertise
- Training in implementation/regulatory hematology
- Building coordinated diagnostic networks
- Support from governmental and NGO initiatives (e.g., GBMHM)
- Development of HTA & regulatory assessment methods
- A balance with academic innovation and development

EQA, external quality assessment; GBMHM, Group of Molecular Biologists for Hematological Malignancies; HTA, health technology assessment; LBMR, Laboratory Medical Biology Reference; NGO, non-governmental organizations; NGS, next-generation sequencing; SIHMDS, specialist integrated hematological malignancy diagnostic services

1. Cayuela, JM et al. HemaSphere 2025;9(4):e70121.

Macintyre E. Implementation science in diagnostics. Abstract p282-2 presented at EHA2025.

Conclusion

- AI is better than humans at processing large volumes of data and noticing patterns, and achieves the correct diagnosis more often than an aided physician.
- The leading reason for investment in AI technologies is its use as a decision-making tool in healthcare.
- Digital pathology will play an important role in personalized medicine for hematological malignancies, and preliminary data suggest the ability to capture clinically and biologically relevant information.
- LLMs can be brought together with other automated tools to create AI agents.
- Precision hematology through NGS immunogenetics will have applications in diagnosis, prognosis, theranostics, and disease monitoring.
- Data presented at EHA2025 from a multimodal analysis of newly diagnosed AML reveals associations between genetic lesions and immunophenotypes.
- Novel connections have also been made between inflammatory signaling and immune escape mechanisms in p53-dysfunctional MDS.
- The BIO-CHIC trial aims to personalize lymphoma treatment by using genetic and biological risk factors to address molecular vulnerabilities; results suggest intensified therapy is effective in many subtypes.
- Integrating molecular profiling and ctDNA enables precision treatment and uncovers subgroup-specific responses in DLBCL.
- Effective implementation in hematology diagnostics requires collaboration across disciplines and with policymakers.
- There will be a need for both National and European strategies for the coordinated implementation of onco-hematology diagnostics.

AI, artificial intelligence; ctDNA, circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; LLMs, large language models; MDS, myelodysplastic syndrome; NGS, next-generation sequencing

07

Appendix

Abbreviations

AA	aplastic anemia
aaIPI	age-adjusted International Prognostic Index
ABC	activated B-cell-like
(p)ADC	(precision) antibody drug conjugate
AE	adverse event
AI	artificial intelligence
AID	activation-induced cytidine deaminase
ALL	acute lymphoblastic leukemia
AMIE	Articulate Medical Intelligence Explorer
(t/s)AML	(therapy-related/secondary) acute myeloid leukemia
APRIL	A proliferation-inducing ligand
ARCH	age-related clonal hematopoiesis
AUROC	area under the receiver operating characteristic
AZA	Azacitidine
Ab	antibody
B-ALL	B cell acute lymphoblastic leukemia
BCL2i	B-cell lymphoma 2 inhibitor
BCMA	B-cell maturation antigen
BCP-ALL	B-cell precursor acute lymphoblastic leukemia
BCR	B-cell receptor
BM	bone marrow
BM(FS)	bone marrow (failure syndrome)
BTKi	bruton tyrosine kinase inhibitor
BiTE	Bispecific T-cell Engager
BsAb	bispecific antibody
C	cycle
CALR	calreticulin
CAR	chimeric antigen receptor
CAR T	chimeric antigen receptor T-cell
CBF	core binding factor
CD	cluster of differentiation
CHOEP	cyclophosphamide + doxorubicin + vincristine + etoposide + prednisone;
CHiP	clonal hematopoiesis of indeterminate potential
CLL/SLL	chronic lymphocytic leukemia/ small lymphocytic lymphoma
CML	chronic myeloid leukemia
CMR	complete metabolic response
CR	complete response
CRS	cytokine-release syndrome
CT	chemotherapy
ctDNA	circulating tumor deoxyribonucleic acid
DA-EPOCH	dose-adjusted etoposide prednisone vincristine cyclophosphamide doxorubicin
DEC	decitabine
DEC-C	decitabine-cedazuridine
DHL	double hit lymphoma
DL	dose level
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DOCR	duration of complete response
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
ED	emergency department
EHA	European Hematology Association
EMD	extramedullary disease
EOF	end of frontline
EQA	external quality assessment
ER	endoplasmic reticulum
ET	essential thrombocythemia
FFS	failure-free survival
FISH	fluorescence in situ hybridization
FL	follicular lymphoma
GBMHM	Group of Molecular Biologists for Hematological Malignancies
GCB	germinal center B-cell
GO	gemtuzumab ozogomycin
GPRC5D	G-protein coupled receptor family C group 5 member D
GalNAc	N-acetylgalactosamine
Gr	grade
HCP	healthcare professional
HCT	hematocrit
HD	healthy donor
HD-AraC	high-dose cytarabine
HD-MTX	high-dose methotrexate
HMA	hypomethylating agent
HR	hazard ratio
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplantation
HSPC	hematopoietic stem and progenitor cell
HTA	health technology assessment
HZL	hairy zone lymphoma
ICAHT	immune effector cell-associated hematotoxicity
ICANS	immune effector cell-associated neurotoxicity syndrome
IEC-HS	immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome
IED	immune effector dysfunction
IFN	interferon
IGHV	immunoglobulin heavy chain variable region
IGLV	Immunoglobulin light chain variable region
IHC	immunohistochemistry
IL	interleukin
IRC	(per) independent review committee
IVO	ivosidenib
iwCLL	international workshop on chronic lymphocytic leukemia
JAK	janus kinase

Abbreviations

LAIP	leukemia-associated immunophenotype
LBCL	large B-cell lymphoma
LBMR	Laboratory Medical Biology Reference
LDAC	low-dose cytarabine
LDH	lactate dehydrogenase
LLM	large language model
LN	lymph node
LSCs	leukemia stem cells
LymphGen	lymphoma genetics classifier
mAb	monoclonal antibody
MAS	macrophage activation syndrome
MC/MCL	mantle-cell lymphoma
MDS	myelodysplastic syndrome
MF	myelofibrosis
MM	multiple myeloma
MN	myeloid neoplasm
mOS	median overall survival
MPD	myeloproliferative disease
MPN	myeloproliferative disorder
MPP	multipotent progenitor
MRD	minimal residual disease
MSC	myeloid stem cell
MTD	maximum tolerated dose
MTX	methotrexate
MYC	myelocytomatosis oncogene
MYD88	myeloid differentiation primary response 88
MZL	marginal zone lymphoma
ND	newly diagnosed
NGO	non-governmental organizations
NGS	next-generation sequencing
NK	natural killer
NPM1	nucleophosmin 1
NRM	non-relapse mortality
ORR	overall response rate
OS	overall survival
OXPHOS	oxidative phosphorylation
PB	peripheral blood
PBMC	peripheral blood mononuclear cell
PCP	primary care physician
PD	pharmacodynamics
PDLS	patient-derived lymphoma spheroids
PDLT	patient-derived lymphoma tumoroids
PET	positron emission tomography
(m)PFS	(median) progression-free survival
PK	pharmacokinetics
PN	peripheral neuropathy
PR	partial response
PS	performance status
PV	polycythemia vera
Q2W	once every 2 weeks
R	rituximab
R-CHOP	rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone;
R/R	relapsed/refractory
RAEB	refractory anemia with excess blasts
RARS	refractory anemia with ring sideroblast
RBC	red blood cell
RCMD	refractory cytopenia with multilineage dysplasia
RDFE	recommended dose for expansion
RGD	arginine-glycine-aspartic acid peptide
ROS	reactive oxygen species
RP2D	recommended phase 2 dose
RS	ring sideroblast
RT	richter's transformation
RT	radiotherapy
SAEs	serous adverse events
SC	subcutaneous
scRNA-seq	single-cell RNA sequencing
SCT	stem cell transplantation
SIHMDS	specialist integrated hematological malignancy diagnostic services
SUD	step-up dose
SWI/SWF	switch/sucrose non-fermentable
SenL	senescent-like
SoC	standard of care
TCE	T-cell engager
TEAE	treatment-emergent adverse event
TEMRA	terminally differentiated effector memory T cells re-expressing CD45RA
TME	tumor microenvironment
TNF	tumor necrosis factor
TP53	tumor protein p53
TPO-R	thrombopoietin receptor
TTR	time to response
Treg	regulatory T cell
ULA	ultra-low attachment
VEN	venetoclax
VGPR	very good partial response
WGS	whole genome sequencing
WM	waldenström's macroglobulinemia
WT	wildtype
WTS	whole transcriptome sequencing
XGBoost	eXtreme Gradient Boosting

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

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Patricia Pérez-Galán

Senior group leader

Fundació de Recerca Clínic Barcelona-IDIBAPS

Barcelona, Spain

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

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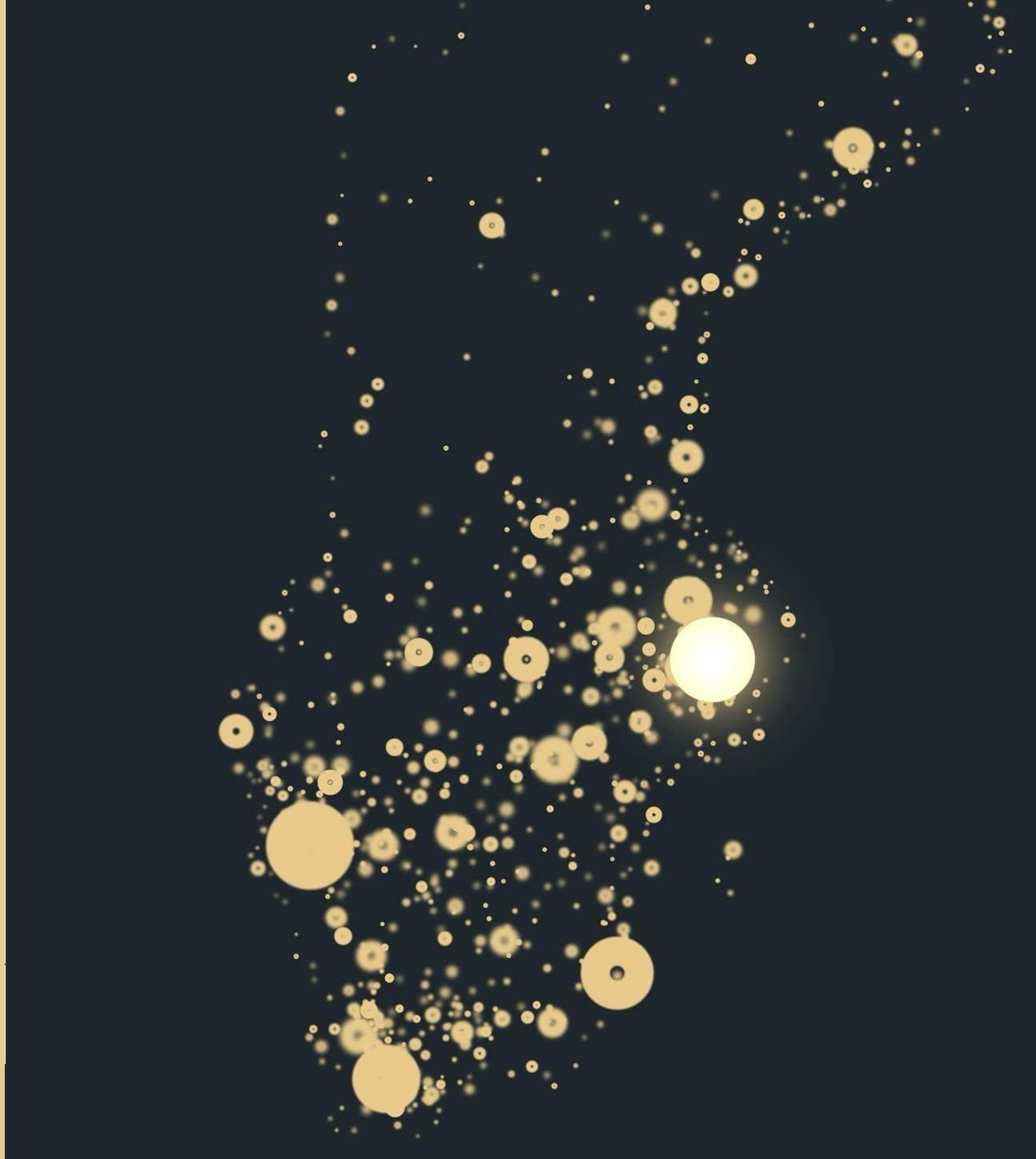

Publisher

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

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