



EHA2026

Perspectives on Hematology

Presented at the EHA2026 Congress
Stockholm, Sweden
June 11 - 14, 2026



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Welcome

On behalf of the European Hematology Association (EHA), we are delighted to present the EHA2026 Scientific Congress Report, entitled *EHA2026 Perspectives on Hematology*.

Following the previous two editions published in 2024 and 2025, this report has been developed to provide our community with a concise overview of the most important research and clinical advances presented at EHA2026. This new edition offers an essential summary of key scientific findings and late-breaking developments across the entire field of hematology, encompassing both malignant and non-malignant disorders, and is relevant to clinicians, researchers, healthcare professionals, pharmaceutical representatives, and all stakeholders in hematology.

Covering key clinical topics such as the latest advances in the treatment of acute myeloid leukemia, lymphomas, and multiple myeloma, as well as groundbreaking research in emerging areas, including the roles of epigenetics and the bone marrow niche in the pathogenesis of hematologic disorders, this report provides high-level, unbiased scientific information for the entire hematology community.

This downloadable slide deck, designed for reuse and dissemination, is also included to facilitate the sharing of scientific data presented at EHA2026.

Whether you attended the Annual Congress or not, and whether or not you are an EHA member, this report provides an important overview of the latest developments in hematology that you will not want to miss.

*Meritxell Alberich Jordà,
EHA2026 Scientific Program Committee Chair*

01

Targeted agents in AML: from induction to long-term maintenance and resistance



Section 1: Targeted agents in AML: from induction to long-term maintenance and resistance

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
p112-3	Current and future role of menin inhibitors in the treatment of AML	S. Garciaz
S130	Ziftomenib combined with intensive induction (7+3) for newly diagnosed <i>NPM1</i> -m or <i>KMT2A</i> -r Acute Myeloid Leukemia (AML): Long-term results from the KOMET-007 trial	A.M. Zeidan
p112-2	Translating menin biology into therapeutics: Biomarkers, resistance and combinations	S. Armstrong
S118	ZEB1 defines a targetable menin-inhibitor escape program in <i>KMT2A::MLLT3</i> AML	L. MacPhee
S556	Is HMA-Venetoclax the new standard of care for induction in fit older patients with AML? (Thematic Debate)	P. Vyas and C. Röllig
p146-1	Mechanisms of venetoclax resistance	C. Heckman
p146-2	New BCL2 inhibitors in myeloid diseases	M. Konopleva
S126	OPTI-AML: Prospective randomized Phase 2 trial of 28 versus 14 day schedule of venetoclax and azacitidine for 2 cycles in newly diagnosed genomically agnostic acute myeloid leukemia patients ≥60 years	U. Borate
p210-2	FLT3 inhibition in <i>FLT3</i> mutated AML: Current and emerging therapeutic strategies	B. Wouters
LB5005	Gilteritinib versus midostaurin in patients with newly diagnosed <i>FLT3</i> -mutated acute myeloid leukemia eligible for intensive therapy: results from the Phase 3 HOVON156/AML SG28-18/PASHA trial	M. Raaijmakers
p116-1	AML immunotherapy beyond allo and GO: Now prime time?	S. Tettamanti
S131	A Phase II randomized study of AK117 versus placebo in combination with venetoclax and azacitidine in previously untreated acute myeloid leukemia patients ineligible for intensive chemotherapy	H. Wang
PF515	Optimised CD33 (FL33) CAR-T cells in relapsed/refractory acute myeloid leukemia: a Phase 1/2 clinical trial	J. Pan
LB5007	First-in-class Switchable Allogeneic CAR-T therapy for CD123+ AML – Results from the Phase Ia RevSTAR-123 (AVC-201-01) Study	M. Wermke
p116-2	IL-1RAP CAR-T (NK CAR for AML and MDS)	C. Ferrand
PF493	CD7 CAR T-cell therapy in relapsed or refractory acute myeloid leukemia	Z. Defeng

p112-2/p112-3/S130: Targeting menin in AML

- Menin inhibitors are emerging as promising targeted therapies, with revumenib and ziftomenib already approved in R/R AML and several agents (e.g., bleximenib, enzominib, and BN-104) in clinical development.
- Combination strategies may deepen responses, as menin inhibitors with IC or Aza/Ven show strong early activity in ND and R/R AML.
- Updated analysis of the **KOMET-007** study showed that ziftomenib plus IC (7+3) was well tolerated and highly active in ND *NPM1*-mutated and *KMT2A*-r AML, with high CR rates, deep MRD-negative responses, manageable differentiation syndrome, and no median OS reached.
- Key challenges remain with the use of menin inhibitors, including limited durability of response, differentiation syndrome, QTc prolongation, resistance mutations, and the optimal sequencing of menin inhibitor-based regimens.
- We may be entering a new treatment paradigm in frontline AML, with triplet strategies that integrate targeted therapies. Ongoing clinical trials include Phase 3 trials in ND AML combining an Aza/Ven or 7+3 backbone with revumenib, bleximenib or ziftomenib.

Mechanism of menin inhibitors in AML

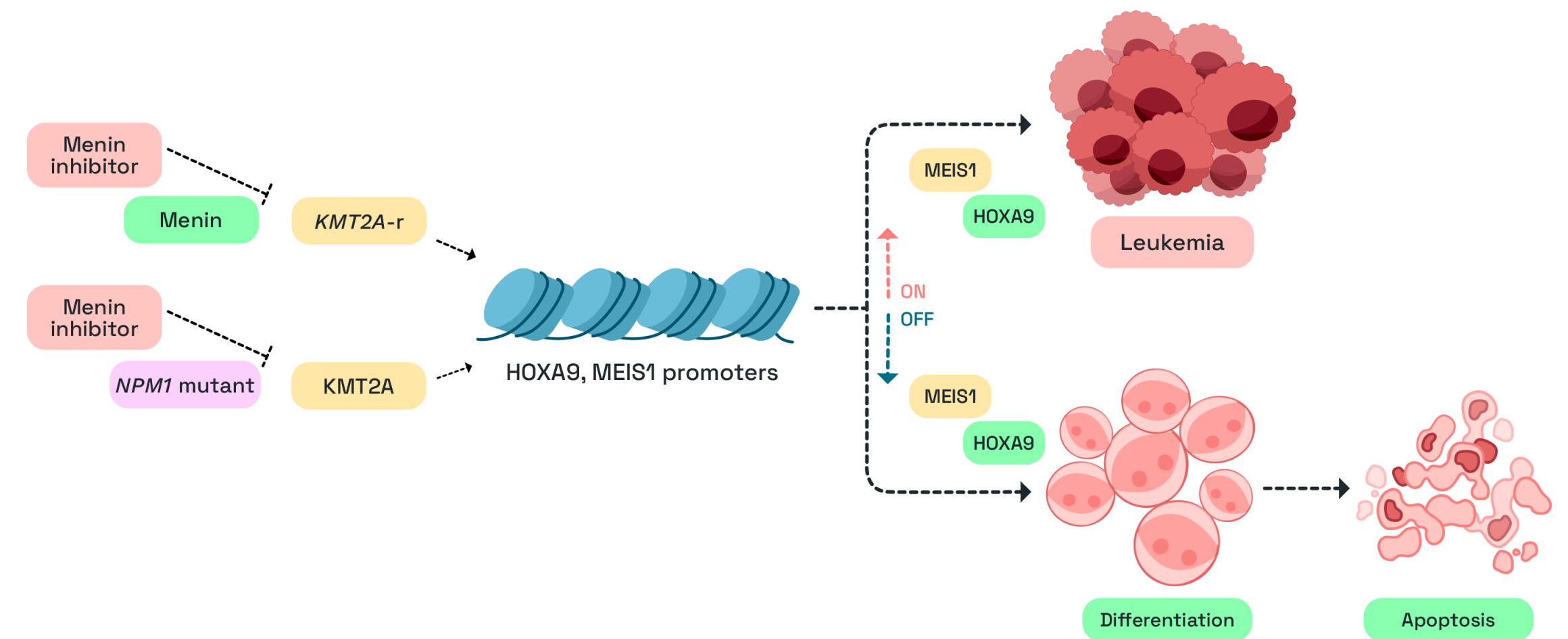


Figure 1.1 Menin inhibitors disrupt the menin-KMT2A oncogenic complex from anchoring to chromatin, switching off the aberrant HOXA9/MEIS1 expression, and promoting leukemic cell differentiation. Figure adapted/reproduced with permission from Garciaz. HOXA9, homeobox 9A gene; KMT2A, lysine methyltransferase 2A-rearrangement; NPM1, nucleophosmin 1 gene.

AML, acute myeloid leukemia; Aza/Ven, azacitidine and venetoclax; CR, complete response; HOX, homeobox gene; IC, intensive chemotherapy; KMT2A-r, lysine methyltransferase 2A gene rearrangement; MRD, minimal residual disease; ND, newly diagnosed; NPM1, nucleophosmin 1 gene; OS, overall survival; R/R, relapsed/refractory.

Garciaz S. Current and future role of menin inhibitors in the treatment of AML. Oral presentation p112-3 at EHA2026.

Zeidan AM. Ziftomenib combined with intensive induction (7+3) for newly diagnosed NPM1-m or KMT2A-r Acute Myeloid Leukemia (AML): Long-term results from the KOMET-007 trial. Oral presentation S130 at EHA2026.

Armstrong S. Translating menin biology into therapeutics: Biomarkers, resistance and combinations. Oral presentation p112-2 at EHA2026.

S556: When to use HMA/Ven or IC for selected fit AML

- Current treatment guidelines generally recommend IC as first-line therapy for AML patients who are eligible for intensive treatment. However, with multiple effective AML therapies available, it is increasingly questioned whether IC should be selected solely based on a patient's ability to tolerate it.
- The **PARADIGM** study suggested that Aza/Ven may benefit selected IC-eligible patients, with longer EFS, higher response rates, improved QoL, and less time in hospital compared with IC.
- OS was similar between the Aza/Ven and IC groups, possibly influenced by crossover, salvage therapy, and differences in transplant pathways.
- IC remains the preferred upfront treatment for key molecular subgroups, including CBF fusions, *FLT3* mutations, and selected *NPM1*-mutated AML, where strong evidence supports an intensive approach.
- Aza/Ven is not yet a new frontline standard for fit AML patients, as PARADIGM needs validation in larger trials and real-world datasets with longer follow-up.

First-line treatment for AML patients ineligible at diagnosis for intensive chemotherapy

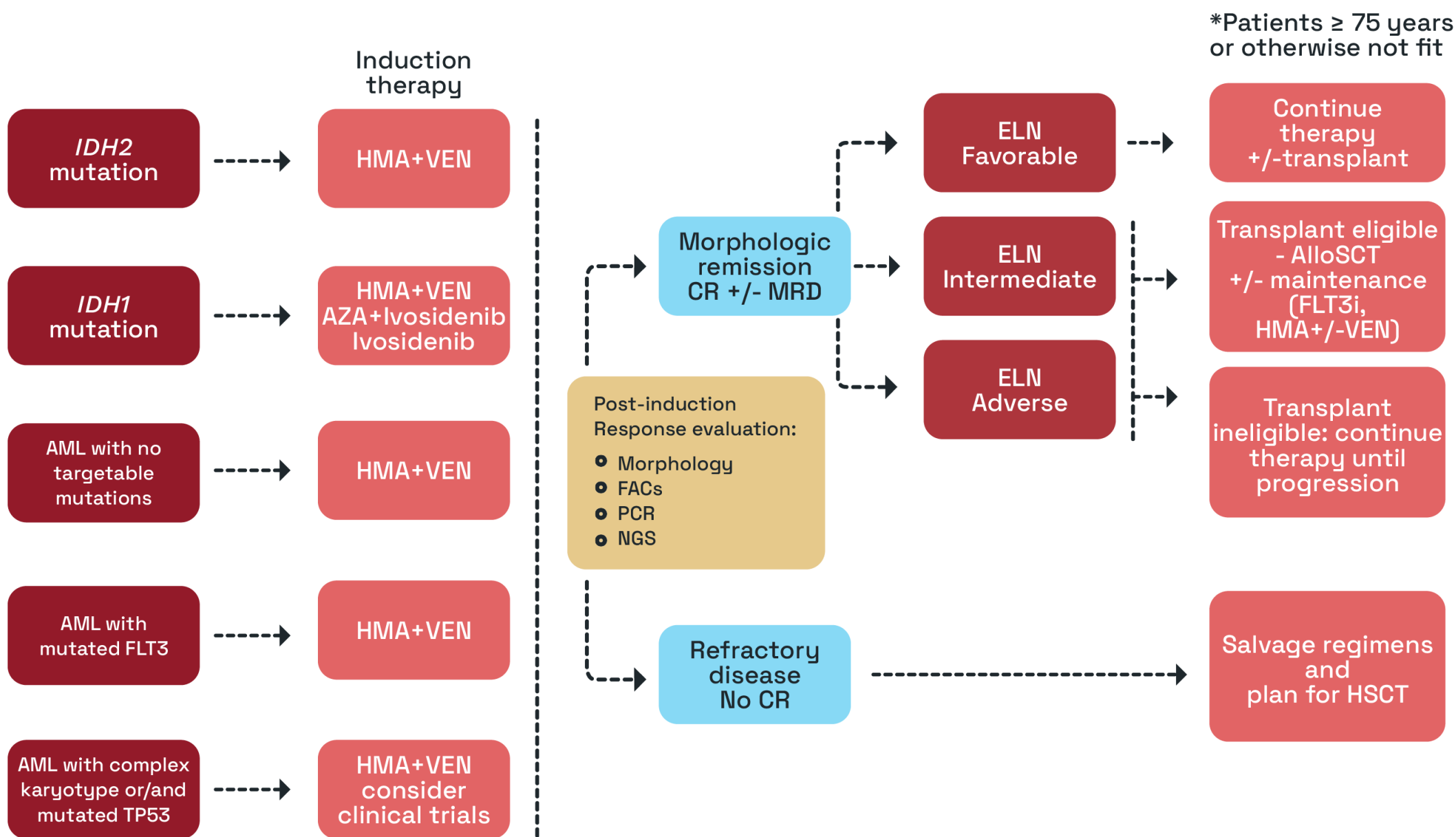


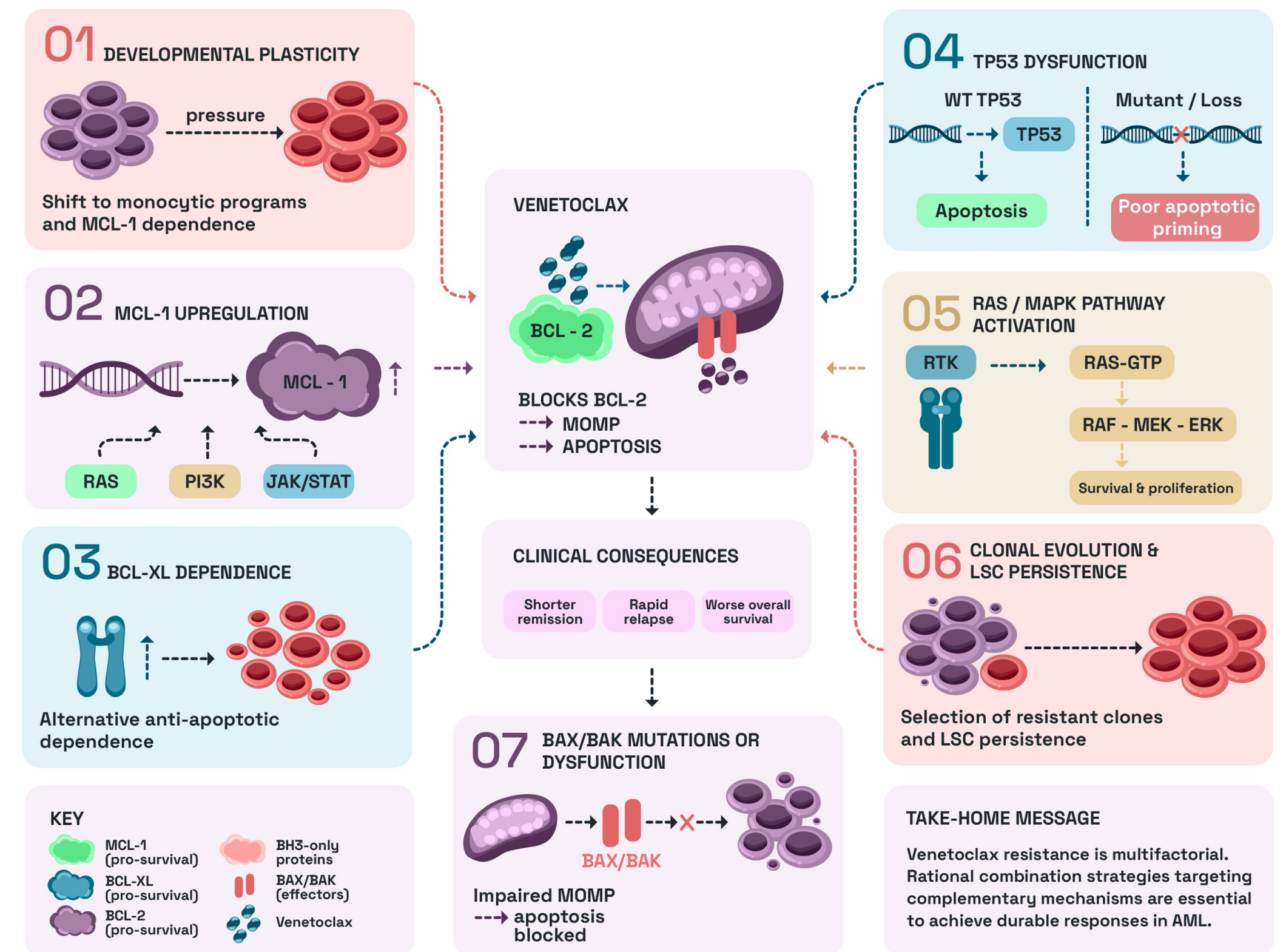
Figure 1.2 HMA + Ven is the standard induction therapy for most newly diagnosed AML patients not fit for IC. Figure adapted from Shimony S, et al. *Am J Hematol.* 2023;98(3):502-526. AlloSCT, allogeneic stem cell transplant; AML, acute myeloid leukemia; CR, complete response; ELN, European Leukemia Network; FLT3i, FLT3 inhibitor; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; IDH, isocitrate dehydrogenase; MRD, minimal residual disease; NPM1, nucleophosmin 1 gene; Ven, venetoclax.

AlloSCT, allogeneic stem cell transplant; AML, acute myeloid leukemia; Aza/Ven, azacitidine and venetoclax; CBF, core binding factor; CR, complete response; EFS, event-free survival; ELN, European Leukemia Network; FLT3i, FLT3 inhibitor; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; IDH, isocitrate dehydrogenase; MRD, minimal residual disease; NPM1, nucleophosmin 1 gene; OS, overall survival; QoL, quality of life; Ven, venetoclax. Figure adapted from Shimony S, et al. Acute myeloid leukemia: 2023 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2023;98(3):502-526. Vyas P et Röhlig C. Is HMA-Venetoclax the new standard of care for induction in fit older patients with AML? Thematic Debate S556 at EHA2026.

p146-1/p146-2: Overcoming venetoclax resistance in AML

- AML heterogeneity drives relapse, with resistant clones emerging despite Ven-based therapy.
- Ven resistance often reflects reduced BCL-2 dependence, with cells shifting toward MCL-1 or BCL-xL survival pathways.
- The apoptotic dependence of LSCs is determined by their state: primitive LSCs depend on BCL-2 and respond to Ven, whereas monocytic LSCs, which depend on MCL-1, tend to be resistant to Ven.
- High-risk molecular features contribute to Ven resistance, including *FLT3* or *RAS* activation, *TP53* mutations, complex karyotype, and acquired *BAX* mutations.
- Next-generation BCL2 inhibitors aim to overcome resistance, with sonrotoclax and lisaftoclax showing stronger BCL2 binding and early activity with Aza in newly diagnosed unfit AML.
- The development of advanced strategies, such as dual BCL-2/BCL-xL inhibitors (Necatoclax) and proteolysis-targeting chimeras (PROTACs) that promote BCL-xL degradation via the proteasome, aims to expand the therapeutic window.

Venetoclax resistance mechanisms



AML, acute myeloid leukemia; Aza, azacitidine; LSCs, leukemic stem cells; Ven, venetoclax.
Heckman C. Mechanisms of venetoclax resistance. Oral presentation p146-1 at EHA2026.
Konopleva M. New BCL2 inhibitors in myeloid diseases. Oral presentation p146-2 at EHA2026.

Figure 1.3 AML cells evade BCL-2 inhibition through multiple interconnected pathways.
Figure adapted/reproduced with permission from Heckman. LSC, leukemic stem cells; WT, wild-type.

S126: Comparison of different Venetoclax dosing schedules

- In the VIALE-A study, the 28-day Ven dosing schedules in the Aza/Ven regimen often required dose reductions due to cytopenias.
- OPTI-AML is the first prospective randomized Phase 2 trial comparing 14-day vs. 28-day Ven for 2 cycles in newly diagnosed older AML patients.
- The study did not show a clinically important difference in CR rates between the two arms.
- The CR rates were significantly higher in the *NPM1*m and *IDH1/2* subgroups with the 28-day Ven dosing regimen, but the small sample sizes limit interpretation.
- Interestingly, tolerability and toxicity profiles were similar and showed no favorable effect of the shorter 14-day venetoclax duration
- This study did not convincingly demonstrate that 14-day Ven dosing is equivalent to the 28-day regimen across all AML subgroups, given AML's heterogeneity.
- The authors concluded that, as novel Aza/Ven triplet combinations continue to be investigated, Ven duration should be optimized by molecular subtype and triplet partner rather than a uniform approach.

Primary endpoint from the OPTI-AML study

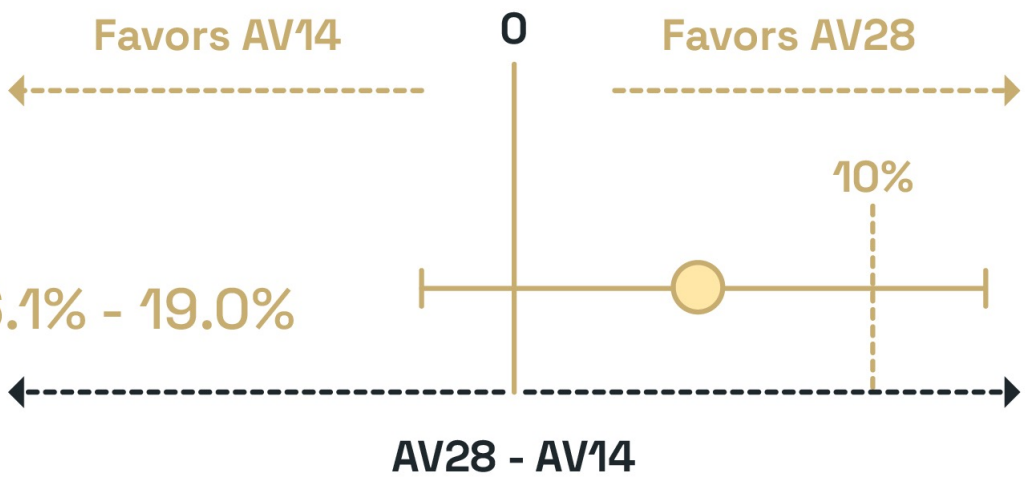
Complete Remission Rate:

AV14
43.0%

AV28
49.4%

Difference in CR Rates: 6.4%

90% Confidence Intervals: -6.1% - 19.0%



Key

● - point estimate

— - 90% CI

| - 0 (equal efficacy)

| - 10% (non inferiority margin)

Figure 1.4 The 14-day Aza/Ven dosing schedule (AV14) did not meet the criteria for non-inferiority (90% CI difference in CR rates <10%) compared to the 28-day Aza/Ven dosing schedule (AV28). Figure adapted/reproduced with permission from Borate. Aza/Ven, Azacitidine/Venetoclax; CI, confidence interval; CR, complete remission.

AML, acute myeloid leukemia; AV14, 14-day Aza/Ven dosing schedule; AV28, 28-day Aza/Ven dosing schedule; Aza/Ven, Azacitidine/Venetoclax; CI, confidence interval; CR, complete remission; IDH, isocitrate dehydrogenase; MRD, minimal residual disease; NPM1, nucleophosmin 1 gene
Borate U. OPTI-AML: Prospective randomized Phase 2 trial of 28 versus 14 day schedule of venetoclax and azacitidine for 2 cycles in newly diagnosed genomically agnostic acute myeloid leukemia patients ≥60 years. Oral presentation S126 at EHA2026.

p116-1/S131/LB5007: The immunotherapy landscape in AML

- The central challenge in AML immunotherapy is target antigen selection, as most AML antigens are also expressed on normal hematopoietic cells, creating risks of on-target off-tumor toxicity, antigen escape, and variable expression.
- Gemtuzumab ozogamicin (GO) remains the only approved ADC in AML; newer CD123-directed ADCs are being explored, especially in combination with Aza/Ven.
- Targeting the innate immune system with anti-CD47, magrolimab has had mixed results; a novel anti-CD47, AK117 in combination with Aza/Ven showed encouraging Phase 2 activity in newly diagnosed, IC-ineligible AML, with more durable responses than placebo + Aza/Ven (median OS, NR vs. 8.3 mo. with placebo) and a favorable safety profile.
- CD33 and CD123 CAR platforms are evolving with improved safety designs, switchable systems, and off-the-shelf approaches; **RevSTAR-123** showed early promise for switchable CD123 CAR T therapy in R/R AML, with low-grade CRS, no GvHD or ICANS, robust CAR T expansion, and early signs of clinical activity in heavily pretreated patients; the platform allows CAR T activity to be controlled through an adaptor-based on/off switch.

Target antigen choice for AML immunotherapy

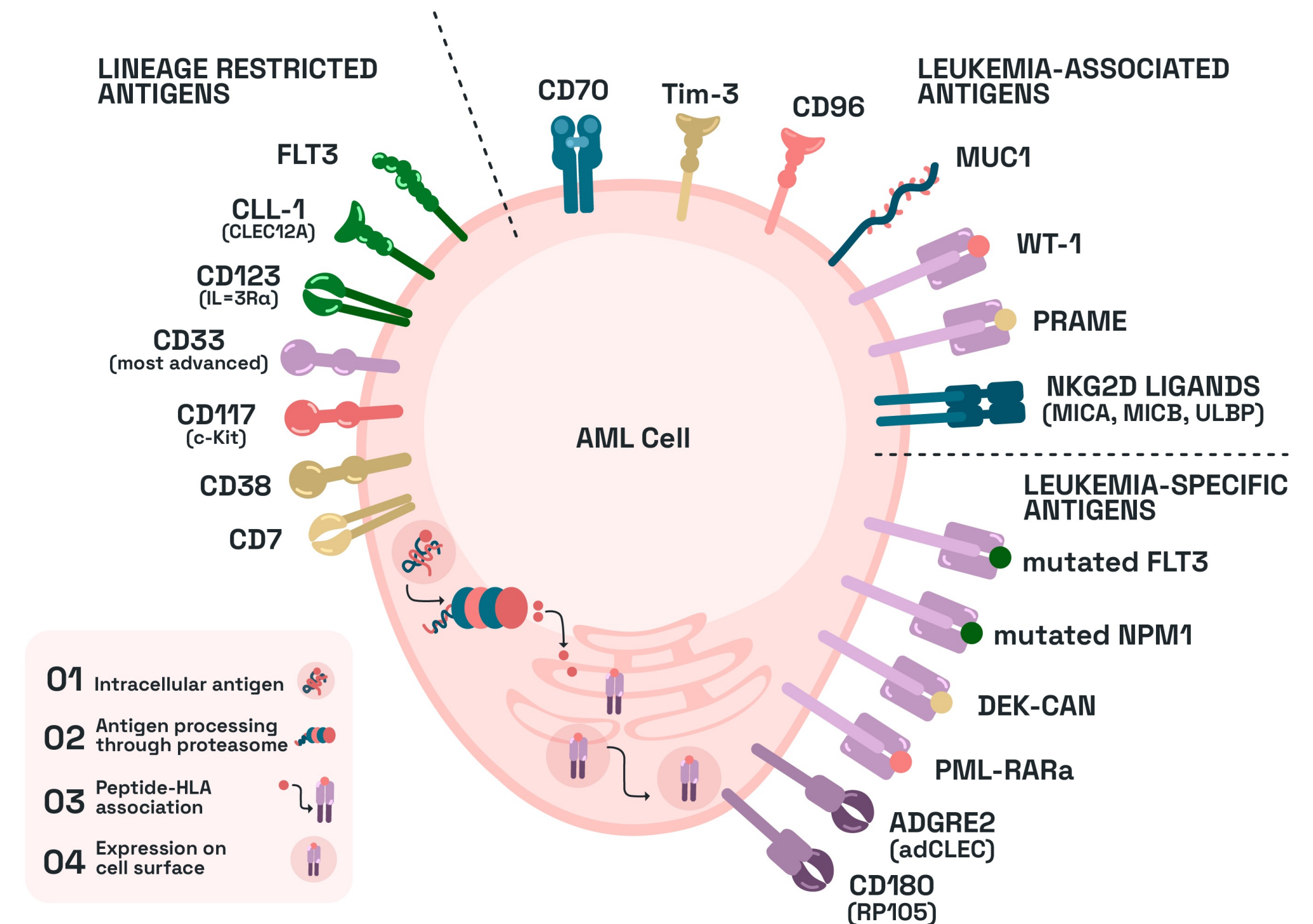


Figure 1.5 Antigen targets expressed in AML can be grouped into lineage-restricted, leukemia-associated, and leukemia-specific antigens, which differ in cellular localization and specificity. Figure adapted from Subklewe M, et al. *Seminars in Hematology*. 2025;62(3):209-217.

ADC, antibody drug conjugate; AML, acute myeloid leukemia; Aza/Ven, Azacitidine/Venetoclax; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; GvHD, graft versus host disease; IC, intensive chemotherapy; ICANS, immune effector cell-associated neurotoxicity syndrome; NR, not reached; OS, overall survival; R/R, relapsed/refractory. Figure adapted from Subklewe M, et al. *Seminars in Hematology*. 2025;62(3):209-217.

Tettamanti S. AML immunotherapy beyond allo and GO: Now prime time? Oral presentation p116-1 at EHA2026.

Wang H. A Phase II randomized study of AK117 versus placebo in combination with venetoclax and azacitidine in previously untreated acute myeloid leukemia patients ineligible for intensive chemotherapy. Oral presentation S131 at EHA2026.

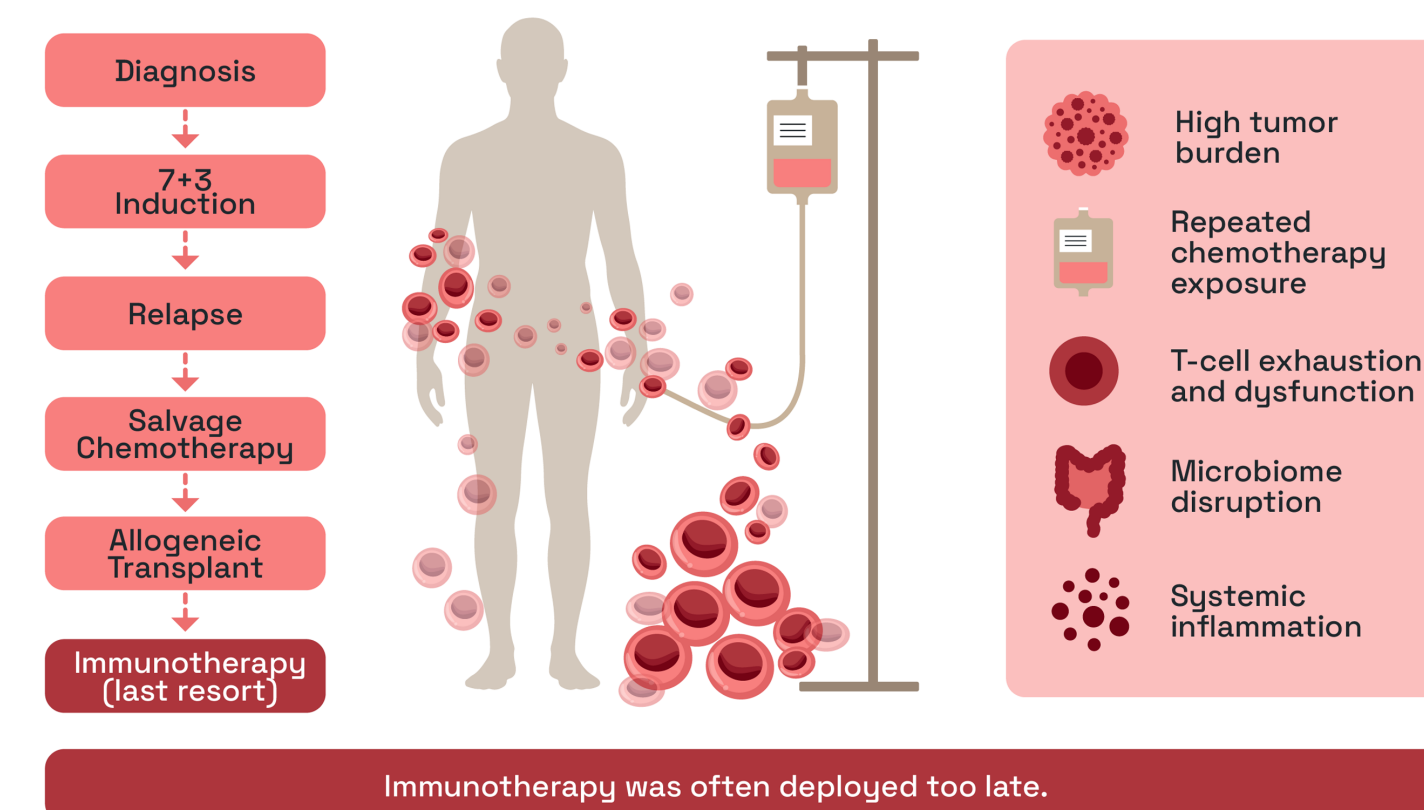
Wermke M. First-in-class Switchable Allogeneic CAR-T therapy for CD123+ AML – Results from the Phase Ia RevSTAR-123 (AVC-201-01) Study. Oral presentation LB5007 at EHA2026.

p116-1: Immunotherapy is moving earlier in the AML disease course

- AML immunotherapy has highlighted a key lesson: the challenge is not just activating the immune system, but doing so at the optimal time, in the appropriate patient, and within the right biological setting.
- AML immunotherapy is shifting from a late-stage rescue strategy to an approach aimed at earlier intervention and relapse prevention.
- Earlier use of immunotherapy may be more effective when the tumor burden is lower, the immune function is less compromised, and the disease can be detected through MRD.
- Improved molecular monitoring and targeted therapies now create opportunities to treat before overt relapse.
- Future strategies may combine precise immune targeting, LSC eradication, and microenvironment modulation.
- The goal is evolving from simply inducing remission to intervening before disease progression and relapse.

Immunotherapy

2010 - 2015 Immunotherapy in a cytotoxic era



2025 - 2030 Immunotherapy in a biology-driven era

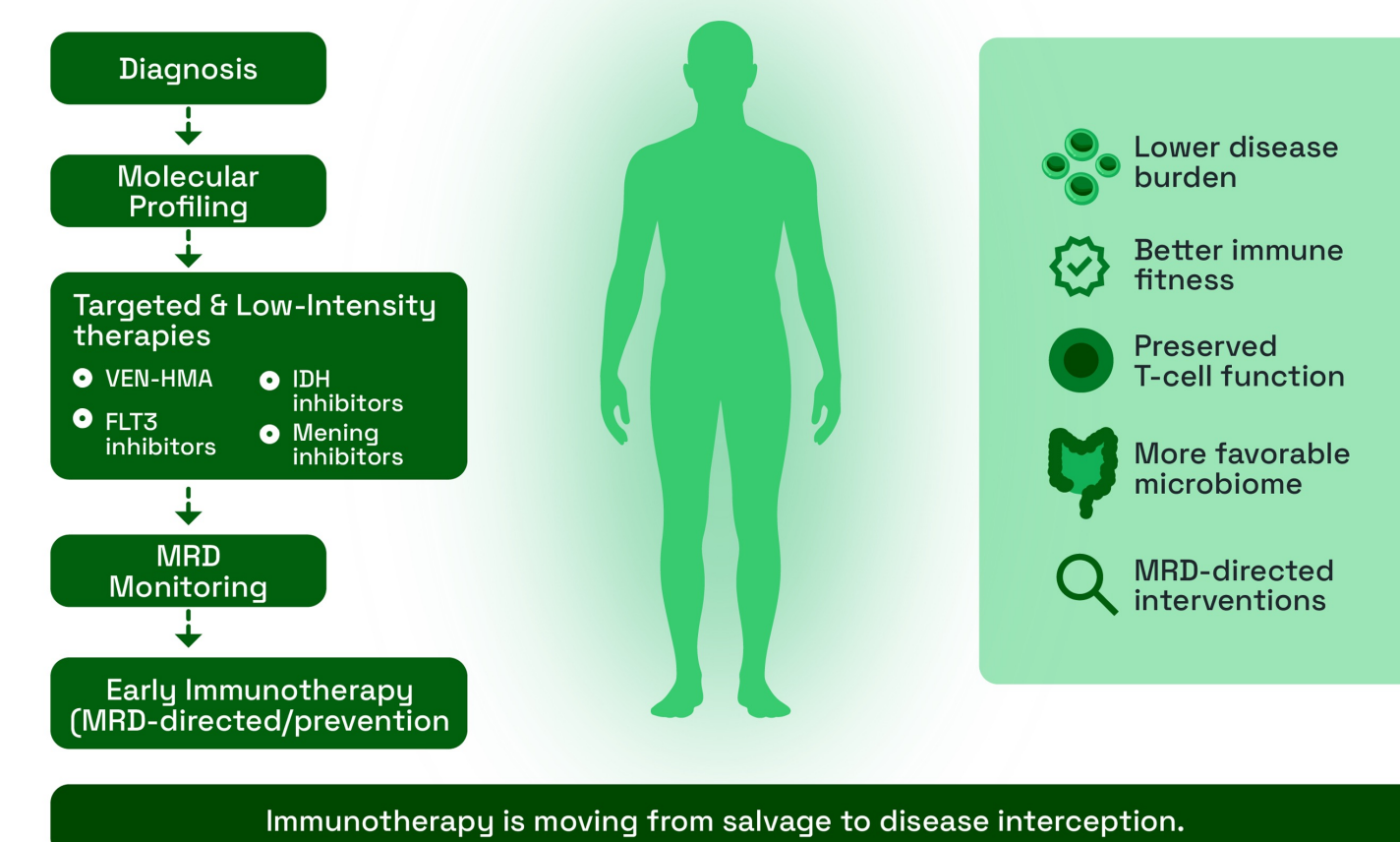


Figure 1.6 Conceptual shift in AML immunotherapy from late-stage salvage treatment to earlier, biology-driven intervention. Figure adapted/reproduced with permission from Tettamanti. AML, acute myeloid leukemia; HMA, hypomethylating agent; IDH, isocitrate dehydrogenase; MRD, measurable residual disease; VEN, venetoclax.

02

Using new agents for lymphoid neoplasms in clinical practice



Section 2: Using new agents for lymphoid neoplasms in clinical practice

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
S235	Results from EPCORE DLBCL-1: randomized Phase 3 study of epcoritamab (epcor) vs investigator's choice chemoimmunotherapy (CIT) in patients with relapsed/ refractory large B-cell lymphoma (R/R LBCL)	C. Fox
S103	Replacement of high dose combination chemotherapy with blinatumomab in newly diagnosed pediatric high-risk B-cell ALL improves efficacy and safety in the randomized Phase 3 AIEOPO-BFM ALL 2017 trial	M. Schrappe
S236	Vispa-cel, an allogeneic anti-CD19 CAR-T cell therapy with a PD-1 knockout, in patients with relapsed/ refractory B cell non-hodgkin lymphoma (ANTLER Phase 1 clinical trial)	S. Schuster
LB5006	CD20 dual targeting CAR-T therapy, in relapsed/refractory B-Cell NHL	L. Fan
S101	Tafasitamab plus lenalidomide and R-CHOP for patients with previously untreated diffuse large B-cell lymphoma (DLBCL): results from the Phase 3 frontmind study	G. Lenz
S239	Golcadomide (golca), a potential, first-in-class oral CELMoD + pola-RCHP in patients (pts) with newly diagnosed aggressive B-cell lymphoma (A-BCL): safety and 12-month efficacy from a Phase 1b study	M. Bouzani
S104	CD5 inhibition as a generalizable strategy to amplify T cell-mediated anti-tumor effects of bispecific T-cell engagers	Y. Li
S225	Mosunetuzumab for early relapse of follicular lymphoma in the Nordic countries (MERLIN, NLG-FL6/ML43841)	M. Brodtkorb
S228	Surovatamig (AZD0486) Plus Rituximab in Previously Untreated Follicular Lymphoma (FL):Initial Safety Data from the Phase 3 SOUNDTRACK-F1 Trial	C.Y. Cheah
S227	Golcadomide (golca), a potential, first-in-class, oral celmod ±rituximab (R) in patients (pts) with relapsed/refractory (R/R) follicular lymphoma (FL): Phase (ph) 1/2 study long-term follow-up (f/u).	D. Morillo Giles
p557-2	Fixed duration therapy in CLL	S. Stilgenbauer
p557-3	MRD-adapted therapy in CLL	T. Munir
LB5001	Fixed-duration pirtobrutinib plus venetoclax–rituximab versus venetoclax–rituximab for patients with previously treated CLL/SLL: A Phase 3, randomized trial (BRUIN CLL-322)	M. Davids
S152	BGB-16673, a bruton tyrosine kinase (BTK) degrader, in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): a Phase 1 CADAnCe-101	S. Stilgenbauer
S150	Updated efficacy and safety data from an ongoing Phase 1a/b trial of the BTK degrader bexobrutideg (NX-5948) in patients with CLL/SLL across lines of therapy	T. Munir

S235/S103: Bispecific T-cell engagers (BiTEs) in aggressive B-cell malignancies

- EPCORE DLBCL-1: randomized Phase 3 trial
 - CD20/CD3-BiTE epcoritamab vs. CIT in patients with various RR de novo or transformed (L)BCLs.
 - New data show improved 2-year PFS (30% vs. 13%) and OS (HR: 0.76) after accounting for subsequent therapies and excess COVID-19 mortality during the SARS-CoV-2 pandemic.
- AIEOP-BFM ALL 2017: randomized Phase 3 trial
 - Investigated the replacement of two cycles of chemo with the CD19/CD3-BiTE blinatumomab within the standard treatment regimen in young patients with newly diagnosed B-ALL.
 - Significant EFS benefit with the study drug; in the experimental phase, a marked reduction in the risk of serious AEs, particularly infections was seen.

Mechanism of action of bispecific T-cell engagers (BiTEs)

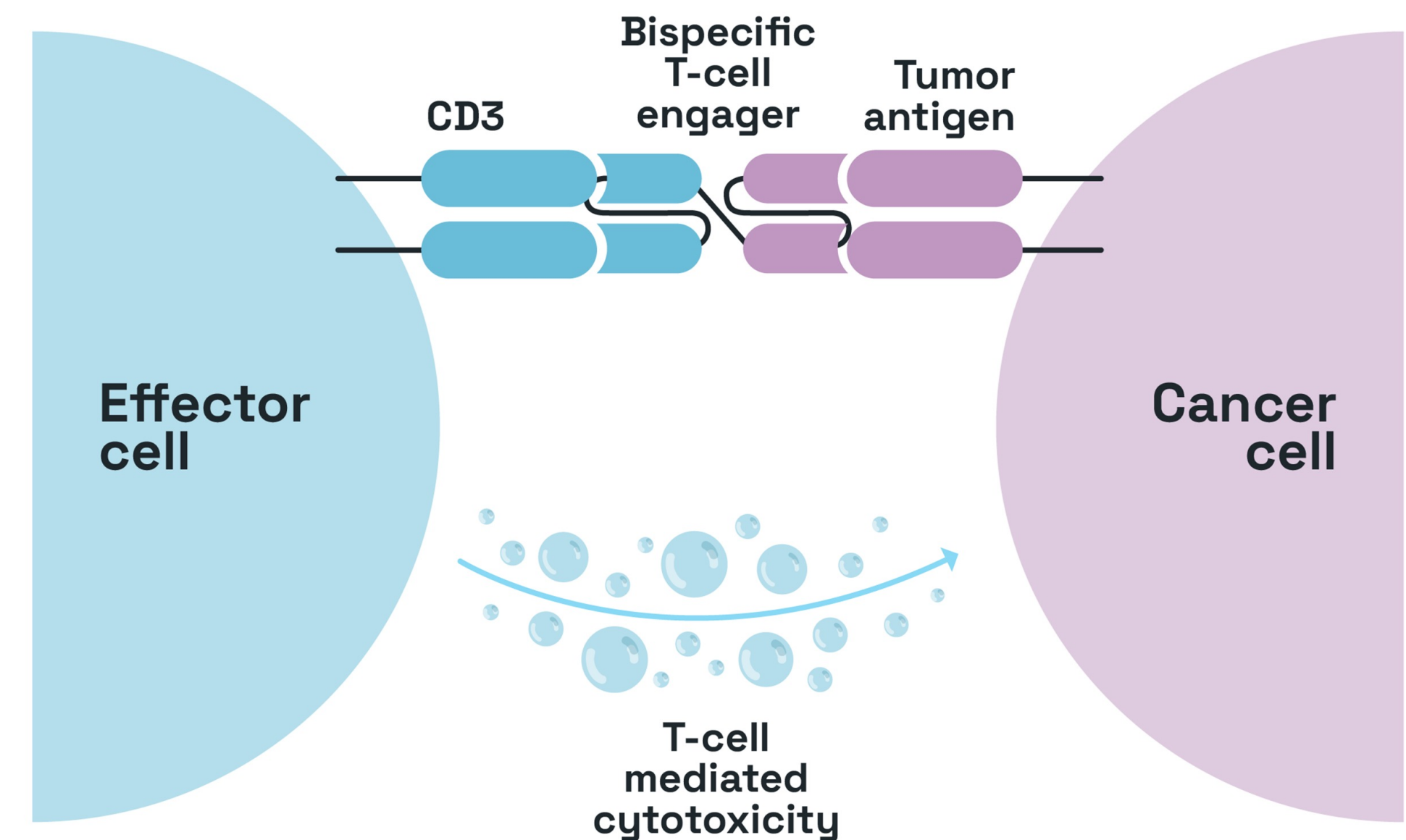


Figure 2.1 Created with BioRender. BiTE, bispecific T-cell engager.

AE, adverse event; B-ALL, B-cell acute lymphoblastic leukemia; CIT, chemoimmunotherapy; EFS, event-free survival; LBCL, large B-cell lymphoma; OS, overall survival; PFS, progression-free survival.

Fox C. Results from EPCORE DLBCL-1: randomized Phase 3 study of epcoritamab (epcor) vs investigator's choice chemoimmunotherapy (CIT) in patients with relapsed/ refractory large B-cell lymphoma (R/R LBCL). Abstract S235 at EHA2026.

Schrappe M. Replacement of high dose combination chemotherapy with blinatumomab in newly diagnosed pediatric high-risk B-cell ALL improves efficacy and safety in the randomized Phase 3 AIEOP-BFM ALL 2017 trial. Abstract S103 at EHA2026.

S236/LB5006: CAR-T cell therapies in aggressive B-cell lymphoma

- **ANTLER: Phase 1 trial**
 - Vispacabtagene regedleucel, an allogeneic CAR-T cell product with PD-1 and T-cell receptor knockouts, was tested in patients with RR LBCL in 2L+.
 - CR rate was 66%, median PFS was 17.1 months; safety data is consistent with other CAR-T cell therapies → on par performance with autologous CAR-T products.
- **NCT07002112: Phase 1 trial**
 - LB2501, a lentiviral vector that generates CD19/CD20 dual-targeting CAR-T cells *in vivo*, was tested in 6 patients with aggressive BCL.
 - ORR was 100%, CR rate was 83%; CRS Gr1-2 in 100% of patients but no Gr≥3 CRS; neutropenia Gr≥3 in 5/6 patients; genetic analysis showed a highly polyclonal cell profile and no CAR transduction in non-T lymphocytes.

Progression-free survival in patients with R/R LBCL in the ANTLER trial

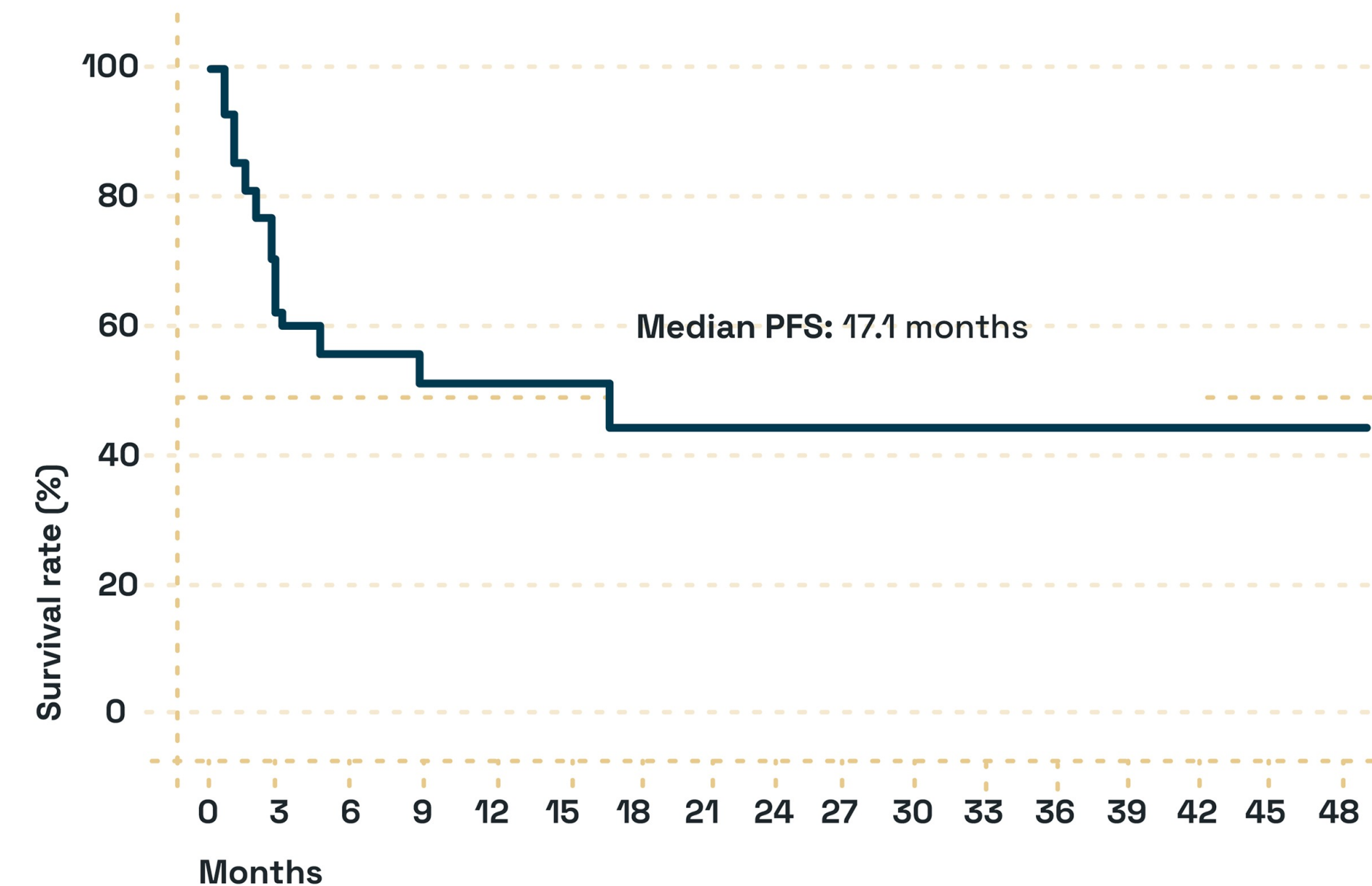


Figure 2.2 Adapted/reproduced with permission from Schuster. PFS, progression-free survival.

2L, second line; CAR, chimeric antigen receptor; CR, complete response; Gr, grade; LBCL, large B-cell lymphoma; ORR, objective response rate, PFS, progression-free survival; RR, relapsed or refractory.

Schuster S. Vispa-cel, an allogeneic anti-CD19 CAR-T cell therapy with a PD-1 knockout, in patients with relapsed/ refractory B cell non-hodgkin lymphoma (ANTLER Phase 1 clinical trial). Oral presentation S236 at EHA2026.
Fan L. CD20 dual targeting CAR-T therapy, in relapsed/refractory B-Cell NHL. Oral presentation LB5006 at EHA2026.

S101/S239/S104: Innovative combination treatments and new synergisms in aggressive B-cell lymphoma

- FrontMIND: Phase 3 trial
 - Addition of CD19 mAb tafasitamab and lenalidomide to R-CHOP vs R-CHOP in previously untreated DLBCL.
 - Moderately improved PFS (3-year PFS: 67.3% vs. 60.7%); higher risk of Gr $\geq$ 3 AE (86.7% vs. 76.1%) and serious AE (50.1% vs. 38.9%).
- CC-220-DLBCL-001: Phase 1b trial
 - CELMoD golcadomide at doses of 0.2 mg or 0.4 mg as an addition to Pola-R-CHP for patients with newly diagnosed aggressive BCL.
 - At 0.4 mg, CR rate was 89% across BCL subgroups, uMRD rate was 83%; 12-month DOR was 95.8%; rate of neutropenia Gr $\geq$ 3 was 83%.
- CD5 is a negative regulator for blinatumomab-mediated T-cell activity
 - CD5⁻ T-cells show enhanced blinatumomab-induced activation compared with CD5⁺ T-cells.
 - CD5 is druggable, making CD5 inhibition a promising candidate in the search for synergistic treatment combinations.

Treatment responses in individual patients with newly diagnosed aggressive B-cell lymphoma to golcadomide 0.4 mg + POLA-R-CHP

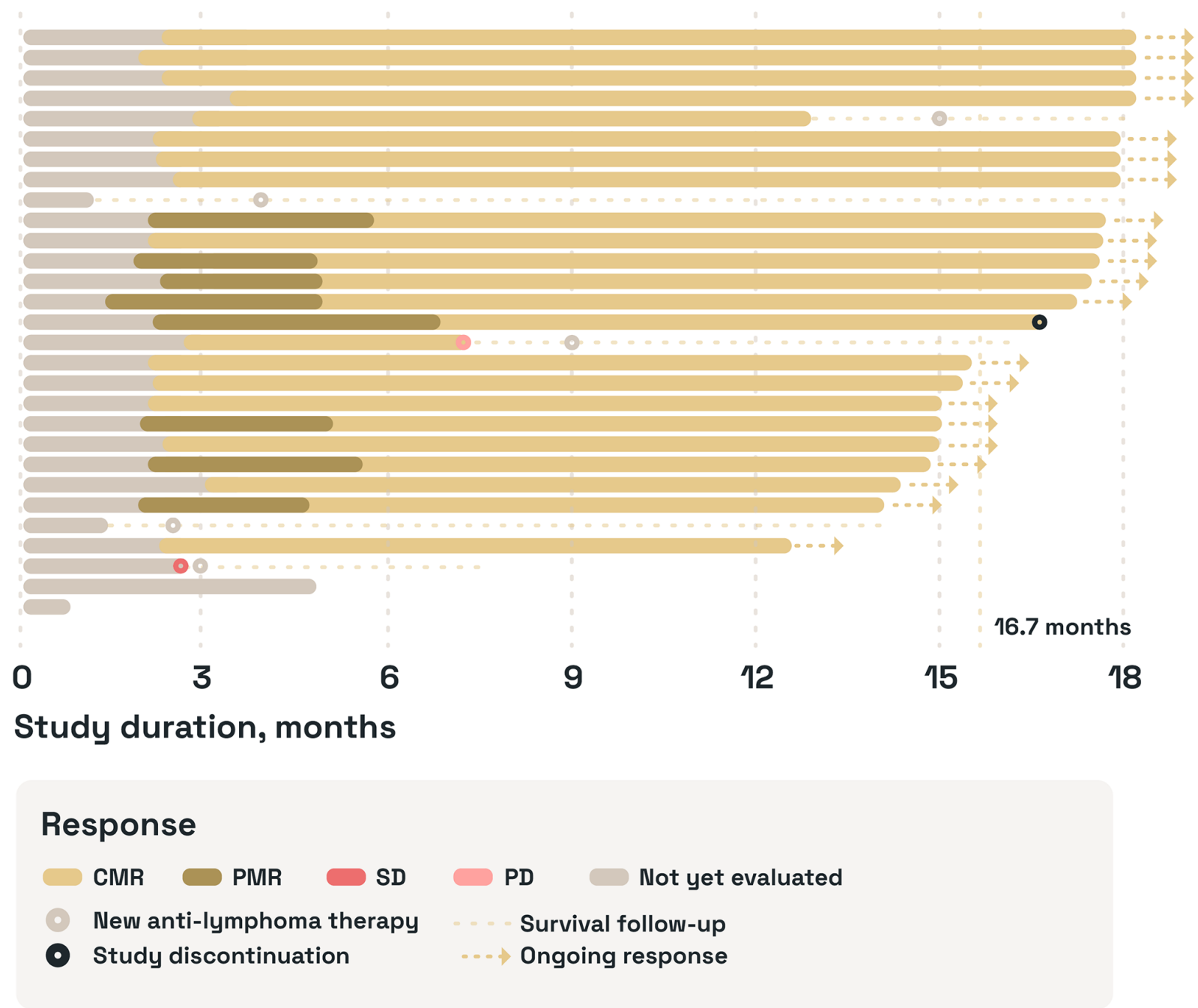


Figure 2.3 Reproduced with permission from Bouzani. CMR, complete metabolic response; PD, progressive disease; PMR, partial metabolic response; POLA-R-CHP, polatuzumab vedotin rituximab, cyclophosphamide, hydroxydaunorubicin, prednisone; SD, stable disease.

AE, adverse event; DLBCL, (diffuse large) B-cell lymphoma; C, cyclophosphamide; CR, complete response; DOR, duration of response; Gr, grade; H, hydroxydaunorubicin; len, lenalidomide; mAb, monoclonal antibody; MRD, minimal residual disease; O, oncovin; P, prednisone; Pola, polatuzumab vedotin; R, rituximab.

Lenz G. Tafasitamab plus lenalidomide and R-CHOP for patients with previously untreated diffuse large B-cell lymphoma (DLBCL): results from the Phase 3 frontmind study. Oral presentation S101 at EHA2026.

Bouzani M. Golcadomide (golca), a potential, first-in-class oral CELMoD + pola-RCHP in patients (pts) with newly diagnosed aggressive B-cell lymphoma (A-BCL): safety and 12-month efficacy from a Phase 1b study. Oral presentation S239 at EHA2026.

Li Y. CD5 inhibition as a generalizable strategy to amplify T cell-mediated anti-tumor effects of bispecific T-cell engagers. Oral presentation S104 at EHA2026.

S225/S228/S227: Innovations in follicular lymphoma (FL) treatment

- **MERLIN:** Phase 2 trial on the CD20/CD3 BiTE Mosunetuzumab
 - Patients with FL who relapsed within 2 years or were primary refractory to 1L treatment
 - ORR = 83%, CR rate = 65%; few progressions in patients with CR; no cases of CRS Gr $\geq$ 3, but 14% had Gr 3–4 infections
- **SOUNDTRACK-F1:** Phase 3 trial on the CD19/CD3 BiTE surovatamig
 - Surovatamig (2.4 mg or 7.2 mg) + R vs chemo + R in patients with ND FL high tumor burden
 - ORR = 100%, CR rate = 95%; manageable safety overall, similar between dose levels, but 11.6% of patients had Gr $\geq$ 3 infections including one lethal event
- **CC-99282-NHL-001:** Phase 1/2 trial on the CELMoD Golcadomide
 - Golca 0.2 or 0.4 mg + R in heavily pretreated patients with FL
 - ORR = 100% and 91%, and CR = 75% and 64%, in patients exposed to lenalidomide and T-cell-redirecting therapies, respectively; rate of neutropenia Gr $\geq$ 3 was 68%.
 - GOLSEEK-4 trial on 0.4 mg golca + rituximab in 2L FL treatment is underway

Response to 2.4 mg and 7.2 mg surovatamig in patients with newly diagnosed follicular lymphoma

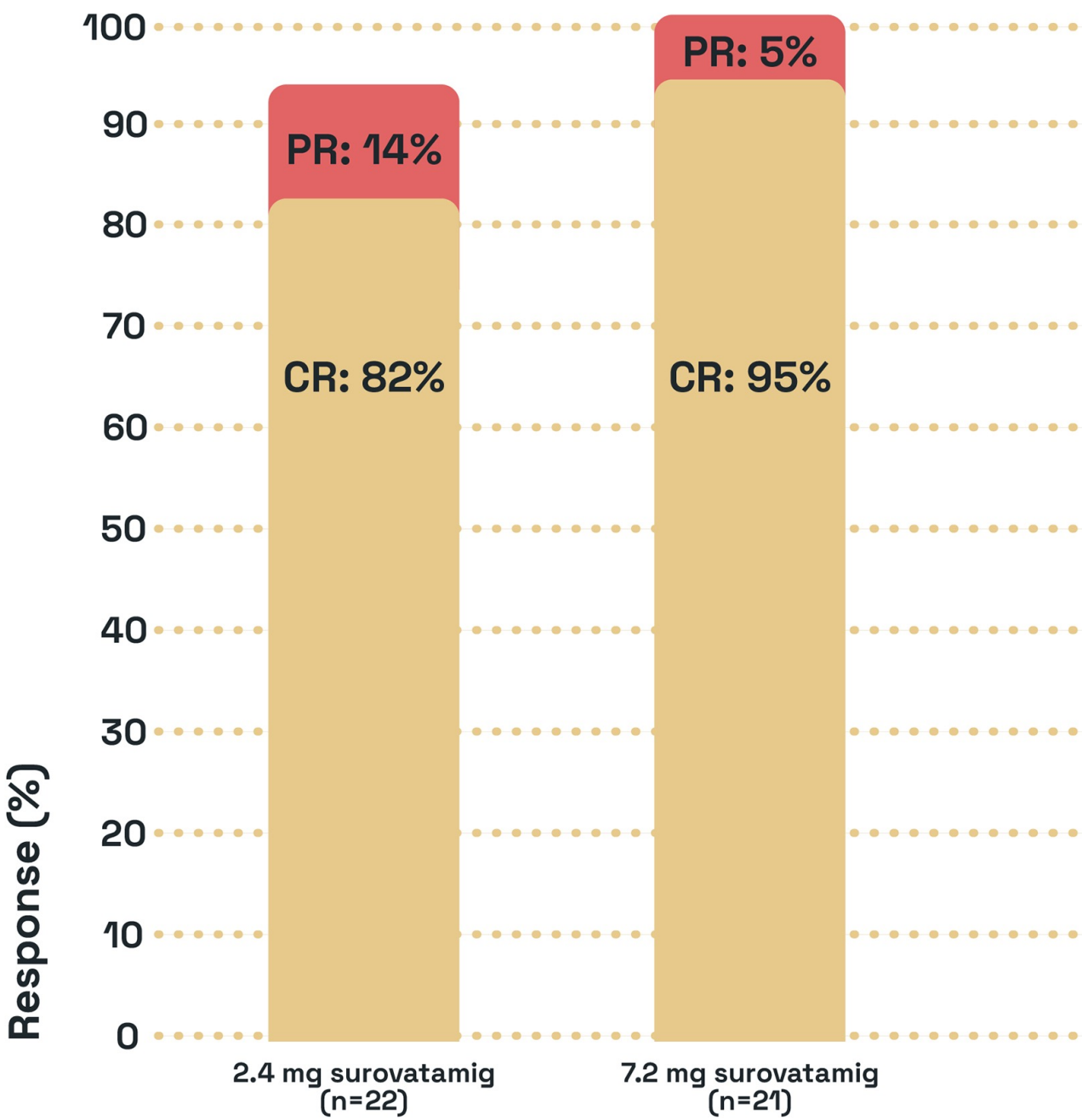


Figure 2.4 Adapted/reproduced with permission from Cheah. CR, complete response; PR, partial response.

1L, first line; 2L, second line; BiTE, bispecific T-cell engager; CELMoD, cereblon E3 ligase modulator; CR, complete response; CRS, cytokine release syndrome; Gr, grade; (ND)FL, (newly diagnosed) follicular lymphoma; ORR, objective response rate; R, rituximab.

Brodtkorb M. Mosunetuzumab for early relapse of follicular lymphoma in the Nordic countries (MERLIN, NLG-FL6/ML43841). Oral presentation S225 at EHA2026.

Cheah CY. Surovatamig (AZD0486) Plus Rituximab in Previously Untreated Follicular Lymphoma (FL): Initial Safety Data from the Phase 3 SOUNDTRACK-F1 Trial. Oral presentation S228 at EHA2026.

Morillo Giles D. Golcadomide (golca), a potential, first-in-class, oral celmod $\pm$ rituximab (R) in patients (pts) with relapsed/refractory (R/R) follicular lymphoma (FL): Phase (ph) 1/2 study long-term follow-up (f/u). Oral presentation S227 at EHA2026.

p557-2/p557-3: Minimal residual disease – a guide for treatment decision making in chronic lymphocytic leukemia (CLL)?

- uMRD is usually defined as $<10^{-4}$ cancer cells per healthy cell; it has seen increasing use in clinical trials, but its value in treatment guidance is unclear.
 - At a debate at EHA2026, Stefan Stilgenbauer and Talha Munir debated whether fixed or MRD-guided treatment duration is preferable.
-
- **Contra (Stilgenbauer)**
 - Among the VO, IV, and I treatment regimens, the latter showed the highest uMRD rate (73.3%) but slightly poorer OS in the CLL-17 trial.¹
 - uMRD has not been shown to be an independent prognostic marker in any clinical trial.
 - In the quest to achieve uMRD, overtreatment becomes a greater risk of death than CLL progression; it might be time to de-escalate, not escalate treatment.
 - **Pro (Munir)**
 - The duration of fixed treatment schedules is arbitrary, and uMRD is a plausible marker to indicate the correct duration.
 - CLL is a slow-growing tumor, so deep uMRD well below 10^{-4} could mean a functional cure in some cases.
 - The risk of serious AEs such as cardiac toxicity is highest in the first 2-3 years of treatment, but does not rise much higher as treatment is continued²
-
- In parallel with the debate, the audience voted on MRD guidance in 1L CLL therapy; 53.7% voted against it, while 46.3% supported its use.

1L, first line; BM, bone marrow; I, ibrutinib; O, obinutuzumab; PB, peripheral blood; V, venetoclax; uMRD, undetectable minimal residual disease.

1. Al-Sawaf O. Fixed-duration versus continuous targeted treatment for previously untreated chronic lymphocytic leukemia: Results from the randomized CLL17 trial. Oral presentation 1 at ASH2025. 2. Munir T. IGHV Unmutated Status, Low Tumor Lysis Risk Disease and BRAF Mutated Status Are Predictors for Early MRD Responders Treated with MRD Defined Ibrutinib with Venetoclax: Report of the UK NCRI FLAIR Study. Oral presentation 585 at ASH2024. Stilgenbauer S. Fixed duration. Oral presentation p557-2 at EHA2026; Munir T. MRD-adapted. Oral presentation p557-3 at EHA2026.

LB5001/S152/S150: Novel BTK-targeting agents in CLL

- **BRUIN CLL-322:** Phase 3 trial on the ncBTKi pirtobrutinib
 - Patients previously treated with a cBTKi received P+VR or VR
 - Improved 24-month PFS: 86.9% vs. 71.8%, higher rate of uMRD6: 52.1% vs. 35%; safety profiles in both treatment arms were similar
- **CaDAnCe-101:** Phase 1 trial on the BTK degrader tacabrutideg
 - Patients, including some pretreated with c- and ncBTKis were enrolled
 - ORR of 93% in cBTKi-exposed and 75% in c- and ncBTKi-exposed patients; across subgroups, mPFS = 24.4 months, 24-month OS ~ 80%.
- **NX-5948-301:** Phase 1a/b trial on the BTK degrader bexobrutideg
 - BTKi-pretreated patients ± prior Bcl-2i exposure in Phase 1a; additionally, in Phase 1b BTKi-naïve and treatment-naïve patients
 - Phase 1a: ORR = 83%, mPFS = 22.1 months; Phase 1b: ORRs = 92.9% and 84.2%, respectively, in Bcl-2i-naïve and BTKi-naïve patients at a mFU of ~5 months; more patients expected to respond at longer FU

Progression-free survival
across all dose levels in
the CADAnCe-101 trial

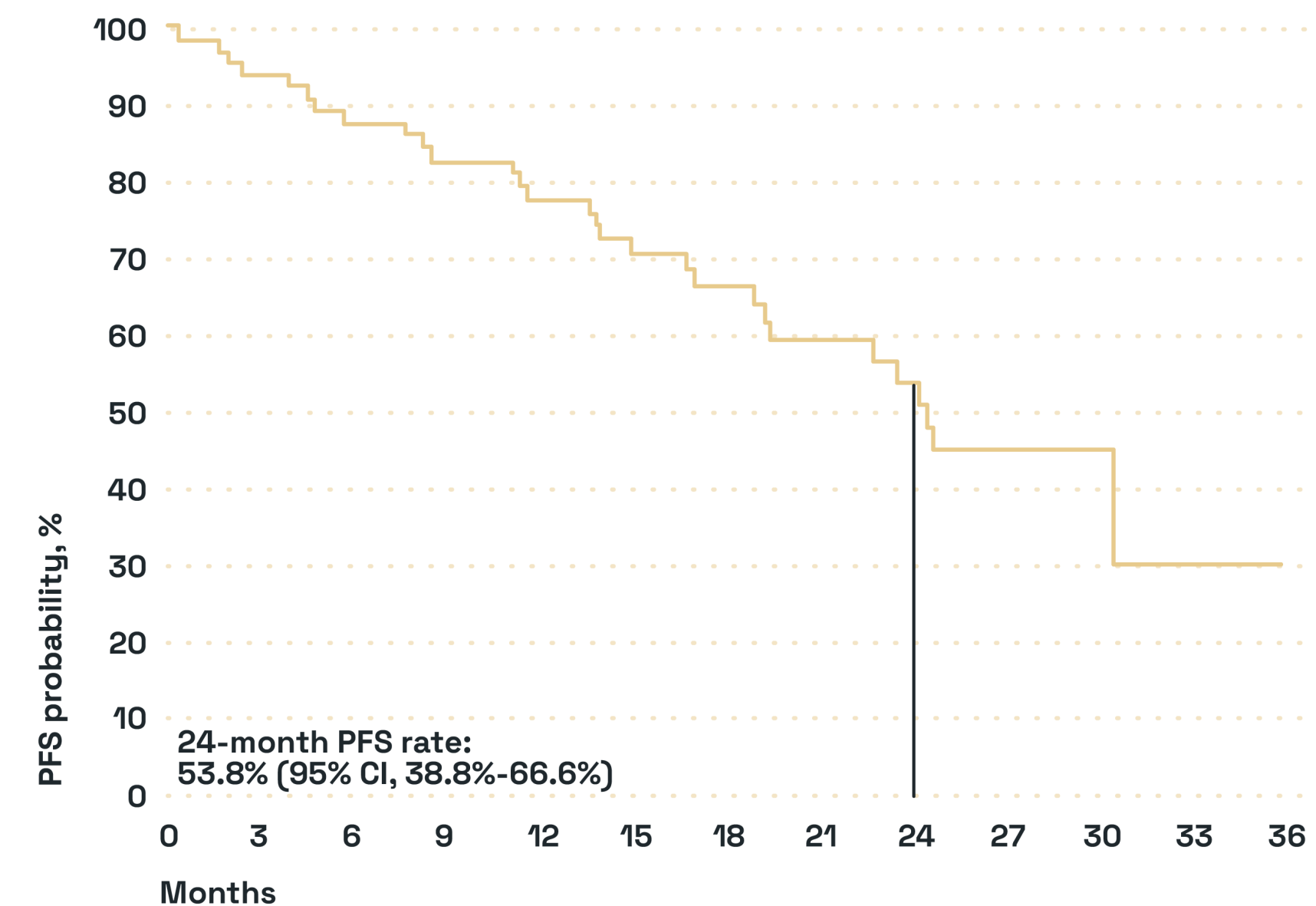


Figure 2.5 Adapted/reproduced with permission from Stilgenbauer. CI, confidence interval; PFS, progression-free survival.

Bcl-2i, Bcl2-inhibitor; (n)cBTKi, (non-)covalent BTKi; (m)FU, (median) follow up; ORR, objective response rate; OS, overall survival; P, pirtobrutinib; (m)PFS, (median) progression-free survival; R, rituximab; V, venetoclax; uMRD6, undetectable minimal residual disease, 10^{-6} cancer cells per healthy cell.
Davids M. Fixed-duration pirtobrutinib plus venetoclax–rituximab versus venetoclax–rituximab for patients with previously treated CLL/SLL: A Phase 3, randomized trial (BRUIN CLL-322). Oral presentation LB5001 at EHA2026.
Stilgenbauer S. BGB-16673, a bruton tyrosine kinase (BTK) degrader, in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): a Phase 1 CADAnCe-101. Oral presentation S152 at EHA2026.
Munir T. Updated efficacy and safety data from an ongoing Phase 1a/b trial of the BTK degrader bexobrutideg (NX-5948) in patients with CLL/SLL across lines of therapy. Oral presentation S150 at EHA2026.

03

Multiple myeloma: navigating the what, when, and who of treatment



Section 3: Multiple myeloma: navigating the what, when, and who of treatment

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
LB5004	Mezigdomide, carfilzomib, and dexamethasone (mezikd) vs carfilzomib and dexamethasone (kd) in relapsed/refractory multiple myeloma (RRMM): results from the Phase 3 SUCCESSOR-2 trial	M.A. Dimopoulos
S195	MajesTEC-9: A phase 3 study of teclistamab monotherapy vs pomalidomide/bortezomib/dexamethasone or carfilzomib/dexamethasone (pvd/kd) in patients (pts) with relapsed refractory multiple myeloma (RRMM)	C. Touzeau
S100	Phase 3, randomized study of talquetamab (Tal) plus daratumumab (Dara) ± pomalidomide (Pom) vs Dara plus Pom and dexamethasone (dpd) in relapsed/refractory multiple myeloma (RRMM): MonumentAL-3	P.M. Voorhees
S185	Successful in vivo CAR-T generation and minimal residual disease (MRD) clearance with KLN-1010 across diverse baseline T cell phenotypes in relapsed/refractory multiple myeloma (RRMM)	A. Spencer
p106-2	High-risk cytogenetics: Definition and treatment options	L.B. Leyboldt
p264-3	Treatment of (Ultra-) high risk multiple myeloma in clinical practice in 2026	M. Kaiser
S207	Aggressive smoldering curative approach evaluating novel therapies (ASCENT): a phase 2 trial of induction, consolidation, and maintenance in high-risk smoldering multiple myeloma	S.K. Kumar
LB5008	Teclistamab improves depth of response and PFS versus lenalidomide-dexamethasone in high-risk smoldering multiple myeloma: results from the phase 2 immunoprism trial	O. Nadeem
S205	Safety and efficacy of elranatamab as early intervention in patients with high-risk smoldering myeloma: First results from the phase 2 ERASMM (EMN34) study	C. Touzeau

LB5004: Next generation agents expanding treatment options in MM

- Cereblon E3 ligase modulators (CELMoDs), such as iberdomide and mezigdomide, are next-generation immunomodulatory drugs (IMiDs), developed to overcome IMiD resistance and to enhance immune activation.¹
- The Phase 3 randomized **SUCCESSOR-2** trial evaluated mezigdomide plus carfilzomib (K) and dexamethasone (d) (MeziKd) vs. Kd alone in anti-CD38 monoclonal antibody- and lenalidomide-exposed patients with RRMM.
- Study design: two-staged, first optimized the mezigdomide dose and then compared the efficacy and safety of MeziKd against Kd, with PFS as the primary endpoint.
- MeziKd significantly reduced the risk of progression or death by 52% (HR 0.48, 95% CI 0.36–0.63), also, superior PFS2 with MeziKd demonstrated sustained clinical benefit beyond first progression (HR 0.53, 95% CI 0.39-0.72)
- The safety profile of MeziKd was consistent with previous studies on mezigdomide, with no new safety signals reported.

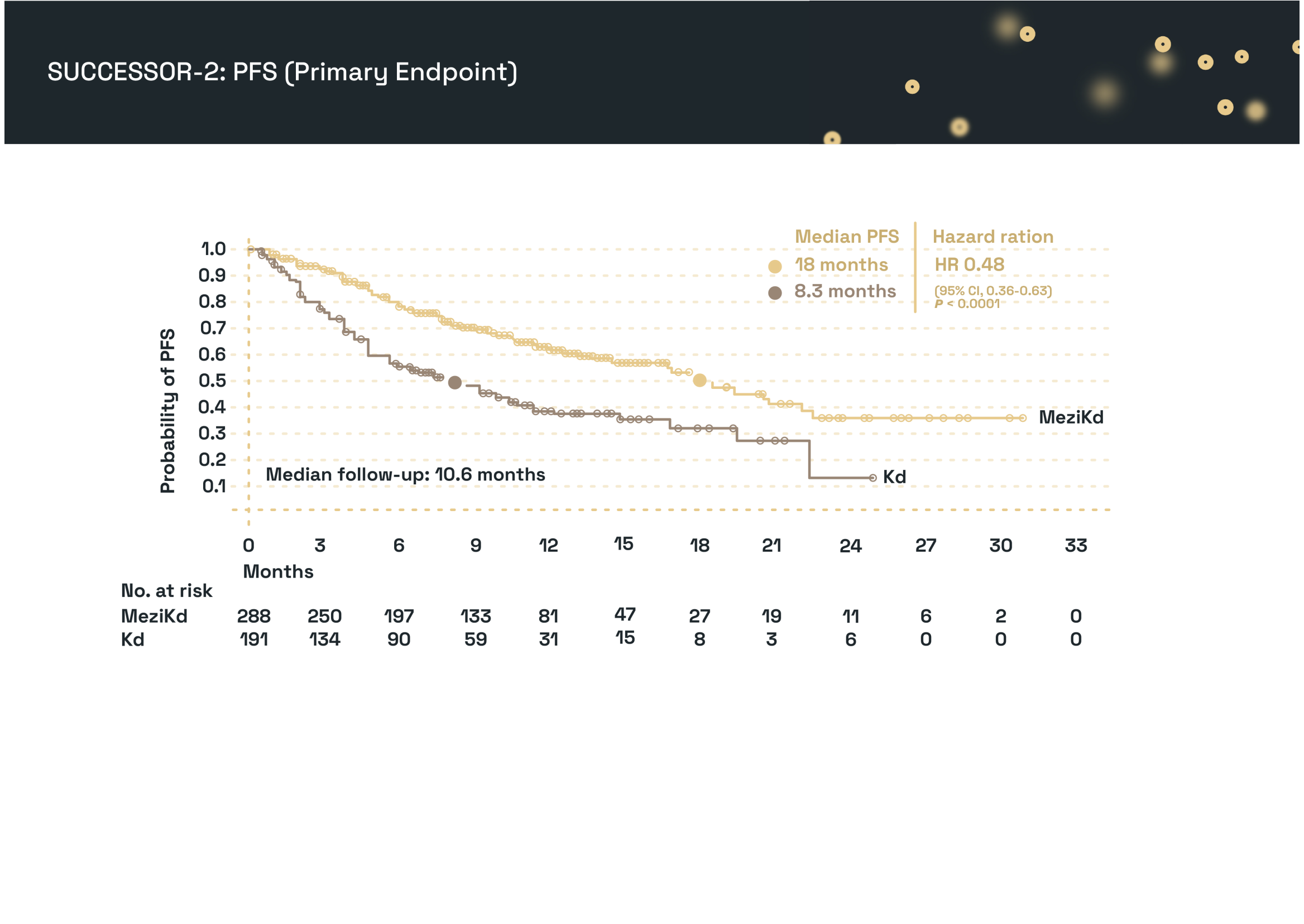


Figure 3.1 MeziKd significantly reduced progression risk in RRMM in the second-line setting and beyond. Figure adapted/reproduced with permission from Dimopoulos. CI, confidence interval; PFS, Progression-free survival; MeziKd, mezigdomide plus carfilzomib and dexamethasone; Kd, carfilzomib and dexamethasone.

CELMoD, Cereblon E3 ligase modulator; CI, confidence interval; d, dexamethasone; HR, hazard ratio; IMiDs, immunomodulatory drugs; K, carfilzomib; PFS, progression-free survival.
1. Watson, E. R. et al. Molecular glue CELMoD compounds are regulators of cereblon conformation. *Science*. 2022;378:549–553.
Dimopoulos MA. Mezigdomide, carfilzomib, and dexamethasone (mezikd) vs carfilzomib and dexamethasone (kd) in relapsed/refractory multiple myeloma (RRMM): results from the phase 3 SUCCESSOR-2 trial. Oral presentation LB5004 at EHA2026.

S195/S100: Bispecific antibodies reshaping the RRMM setting

- The MajesTEC-9 Phase 3 randomized study
 - 2L+ teclistamab (BCMAxCD3 BsAb) monotherapy, in RRMM setting, vs. standard Pvd or Kd triplet regimens, with PFS as the primary endpoint.
 - Teclistamab significantly improved PFS, with a 71% reduction in the risk of disease progression or death (HR 0.29, 95% CI 0.23–0.38) and OS (HR 0.60, 95% CI 0.43–0.83) in a highly exposed population.
 - The safety profile was consistent with the known profile of teclistamab monotherapy.
- The MonumenTAL-3 Phase 3 randomized study
 - 2L+ talquetamab (GPRC5DxCD3 BsAb) + Dara and pom (Tal-DP) vs. DPd in patients with RRMM, with PFS as the primary endpoint.
 - Tal-DP and Tal-D significantly improved PFS (HR 0.28, 95% CI 0.20–0.40 for Tal-DP; HR 0.33, 95% CI 0.24–0.46 for Tal-D), and OS (HR 0.47, 95% CI 0.30–0.73 for Tal-DP; HR 0.51, 95% CI 0.33–0.78 for Tal-D).
 - The safety profile was consistent with that of the individual agents.

MonumenTAL-3: PFS (Primary Endpoint)

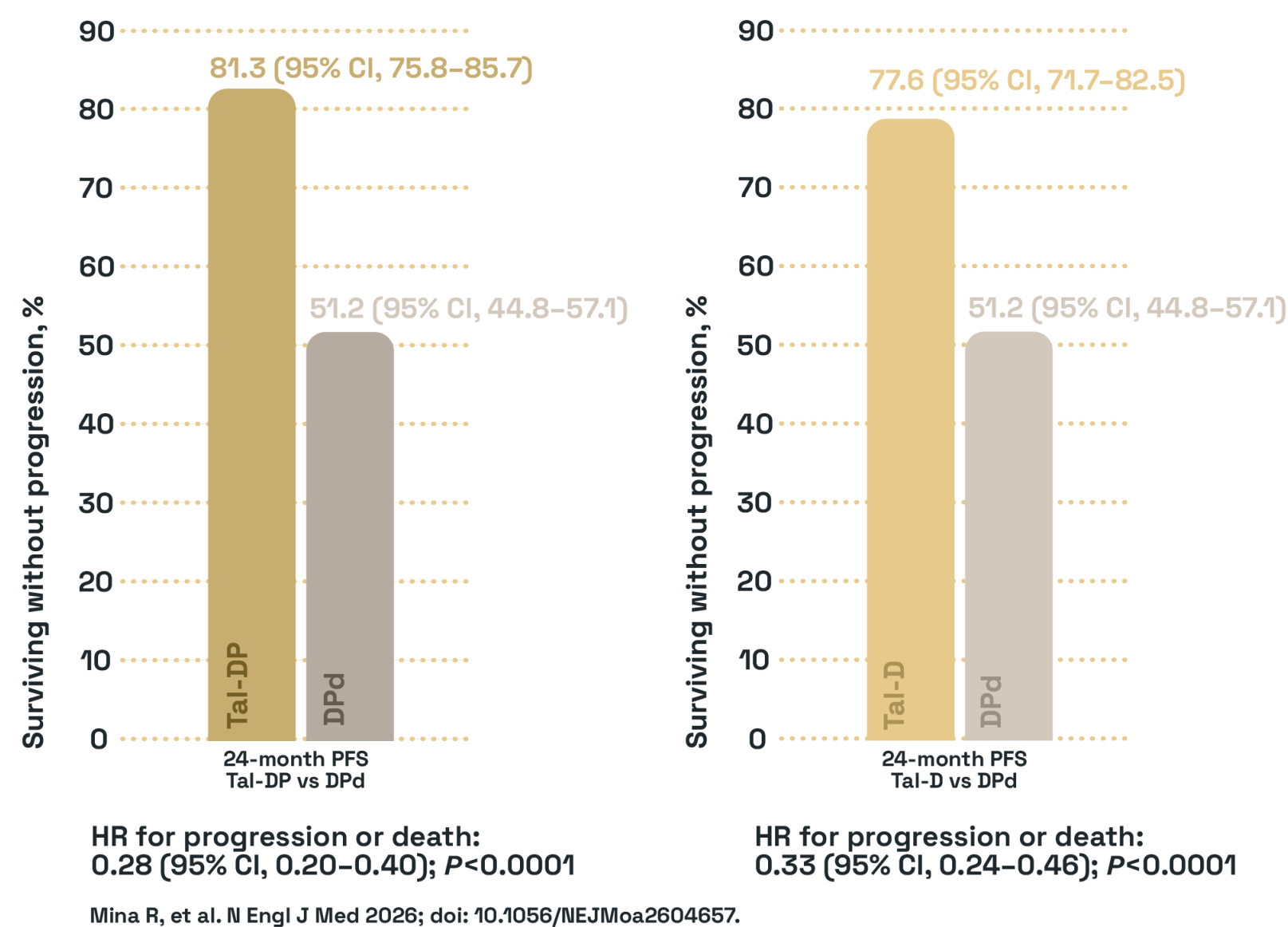


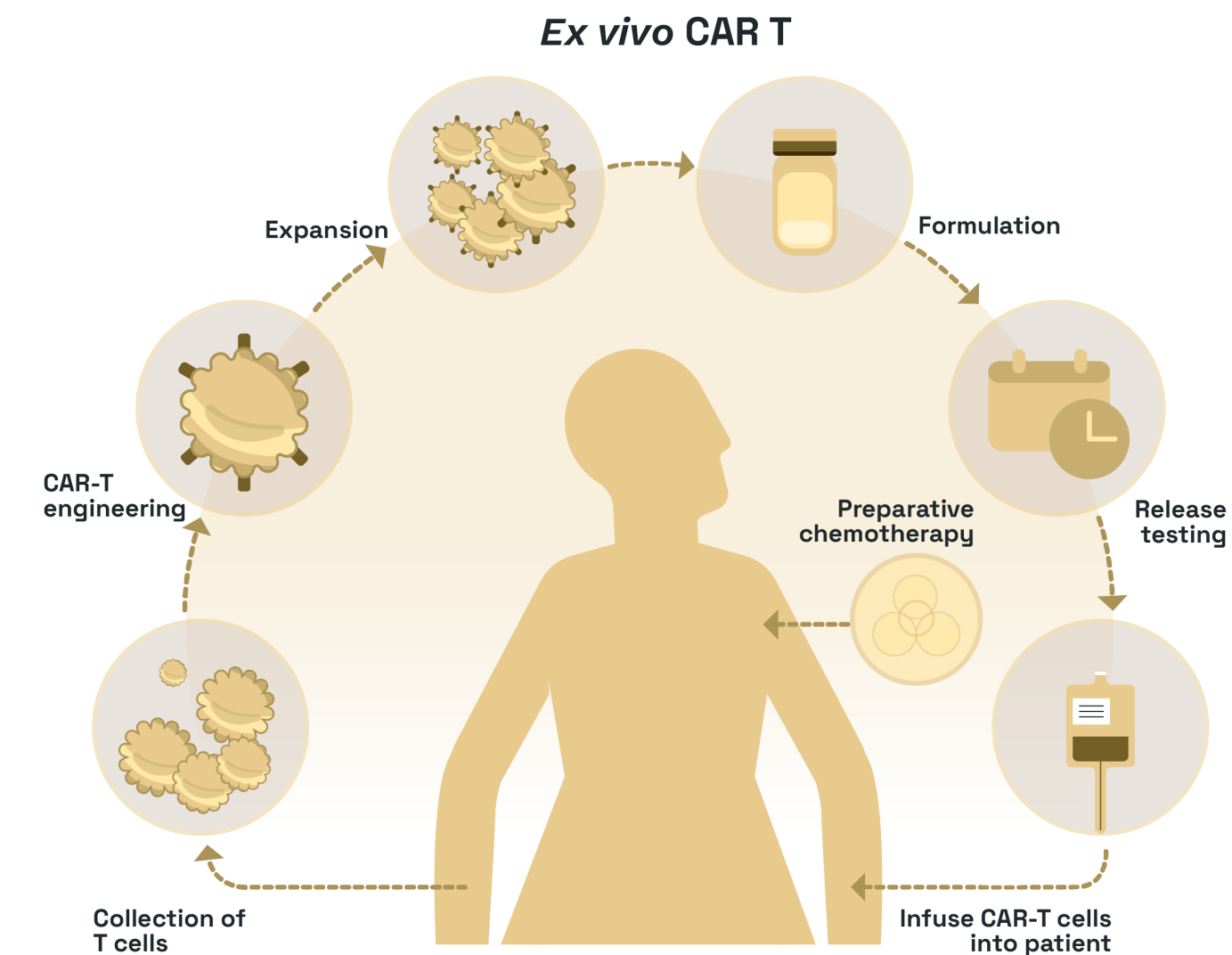
Figure 3.2 Combination-based immunotherapy with talquetamab significantly improved PFS in the 2L and beyond in RRMM. Figure adapted/reproduced with permission from Voorhees. CI, confidence interval; DPd, daratumumab pomalidomide dexamethasone; HR, hazard ratio; PFS, progression-free survival; RRMM, relapsed or refractory multiple myeloma; Tal, talquetamab; TAL-DP, talquetamab daratumumab pomalidomide.

2L+, second line or later; BCMA, B-cell maturation antigen; CI, confidence interval; D, daratumumab; d, dexamethasone; DPd, daratumumab pomalidomide dexamethasone; GPRC5D, G protein-coupled receptor class C group 5 member D; HR, hazard ratio; Kd, carfilzomib dexamethasone; P, pomalidomide; PFS, progression-free survival; Pvd, pomalidomide bortezomib dexamethasone; RRMM, relapsed or refractory multiple myeloma; Tal, talquetamab; TAL-DP, talquetamab daratumumab pomalidomide. Touzeau C. MajesTEC-9: A phase 3 study of teclistamab monotherapy vs pomalidomide/bortezomib/dexamethasone or carfilzomib/dexamethasone (Pvd/Kd) in patients (pts) with relapsed refractory multiple myeloma (RRMM). Oral presentation S195 at EHA2026. Voorhees PM. Phase 3, randomized study of talquetamab (Tal) plus daratumumab (Dara) ± pomalidomide (Pom) vs Dara plus Pom and dexamethasone (DPd) in relapsed/refractory multiple myeloma (RRMM): MonumenTAL-3. Oral presentation S100 at EHA2026.

S185: Towards simplified cell therapy: Emerging *in vivo* CAR-T approaches

Expanding the reach of CAR-T cells
with *in vivo* gene delivery^{1,2}

- *In vivo* CAR-T cell approaches use targeted delivery systems such as lentiviral vectors and lipid nanoparticles to introduce CAR-encoding genetic material into endogenous T cells, enabling CAR-T cell generation directly in the peripheral blood.¹
- The inMMycAR Phase 1 study of KLN-1010
 - Investigation of KLN-1010, a modified lentiviral vector generating anti-BCMA CAR-T cells directly in the peripheral blood, in heavily pretreated (3L+) RRMM.
 - Safety and tolerability, together with determination of the recommended Phase 2 dose, were primary endpoints.
 - KLN-1010 achieved consistent *in vivo* CAR-T generation, expansion, and clinical efficacy across a range of baseline T cell profiles.
 - Deep, ongoing BM MRD-negative responses observed.
 - A manageable safety profile, including limited cytopenias and no severe TE infections without lymphodepletion.



***In vivo* CAR T with KLN-1010 lentiviral particles**

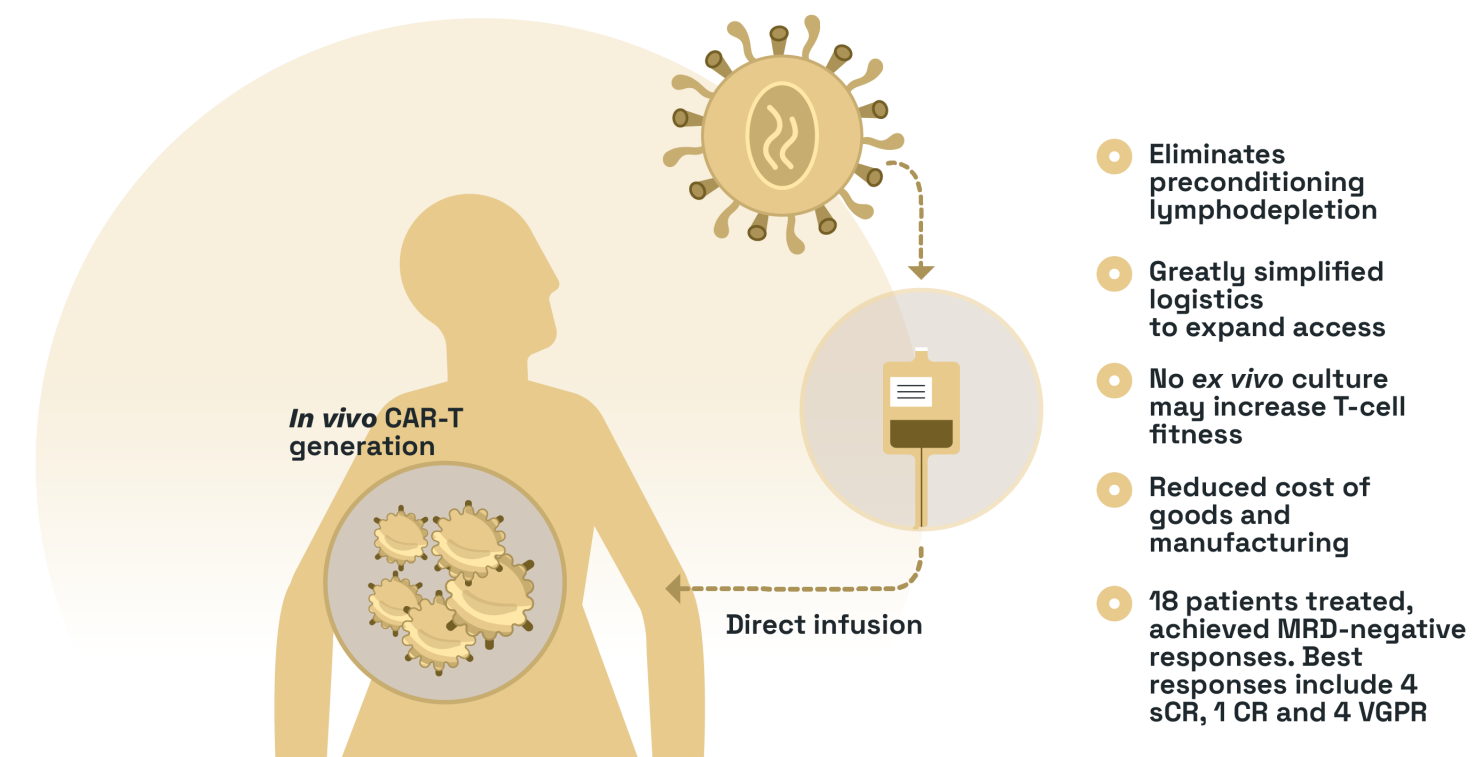


Figure 3.3 Expanding the reach of CAR-T cells with *in vivo* gene delivery.

Figure adapted/reproduced with permission from Bot and Spencer. CAR, chimeric antigen receptor; CR, complete response; MRD, minimal residual disease; VGPR, very good partial response.

3L+, third line or later; BCMA, B-cell maturation antigen; BM, bone marrow; CAR, chimeric antigen receptor; CR, complete response; MRD, minimal residual disease; TE infections, treatment-emergent infections; VGPR, very good partial response.

1. Bot A, et al. In vivo chimeric antigen receptor (CAR)-T cell therapy. *Nat Rev Drug Discov.* 2026;25:116-137. 2. Najibi AJ. T cell-specific in vivo transduction with preclinical candidate KLN-1010 generates BCMA-directed CAR-T cells with potent anti-multiple myeloma activity (abstract #48).

Poster presented at: AACR Annual Meeting; April 5-10, 2024.

Spencer A. Successful in vivo CAR-T generation and minimal residual disease (MRD) clearance with KLN-1010 across diverse baseline T cell phenotypes in relapsed/refractory multiple myeloma (RRMM). Oral presentation S185 at EHA2026.

p106-2/p264-3: The role of advanced risk stratification in MM

- High-risk multiple myeloma is defined by specific combinatorial genetic and clinical features that require NGS-based assessment.¹
- These patients have markedly inferior outcomes with standard regimens, necessitating intensified, risk-adapted, and early innovative treatment strategies.
- A careful upfront assessment of defined risk factors, including NGS and gene expression profiling, is necessary to help guide a more risk-adapted treatment approach and overcome poor-prognosis disease features.
- The Phase 2 **OPTIMUM** trial: intensive, daratumumab-based multi-agent regimen (Dara-CVRd with transplant and consolidation / maintenance) markedly improves PFS and OS vs. SOC in patients with ultra-high-risk newly diagnosed multiple myeloma, demonstrating that biologically risk-adapted, upfront combination therapy can overcome poor-prognosis disease features.

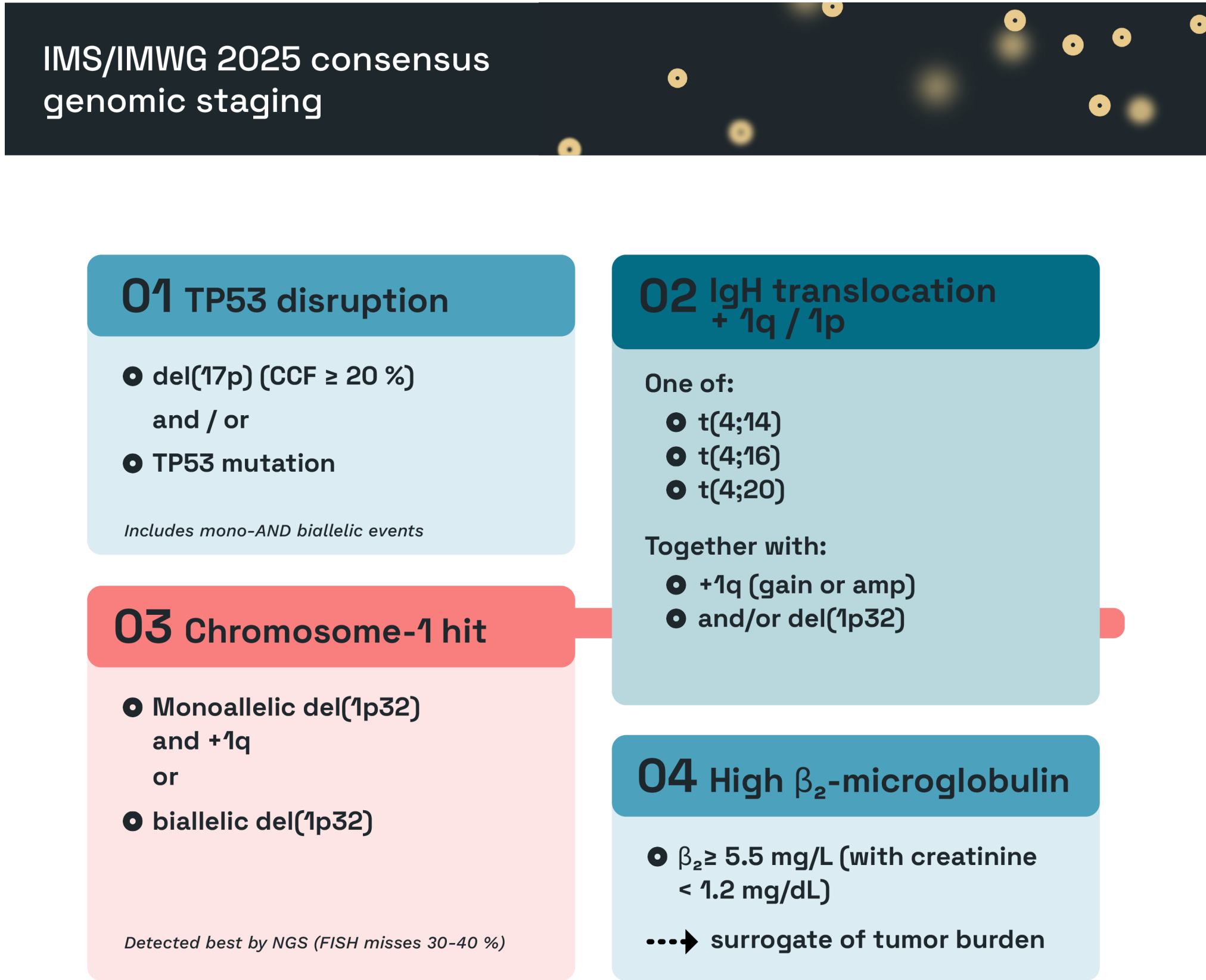


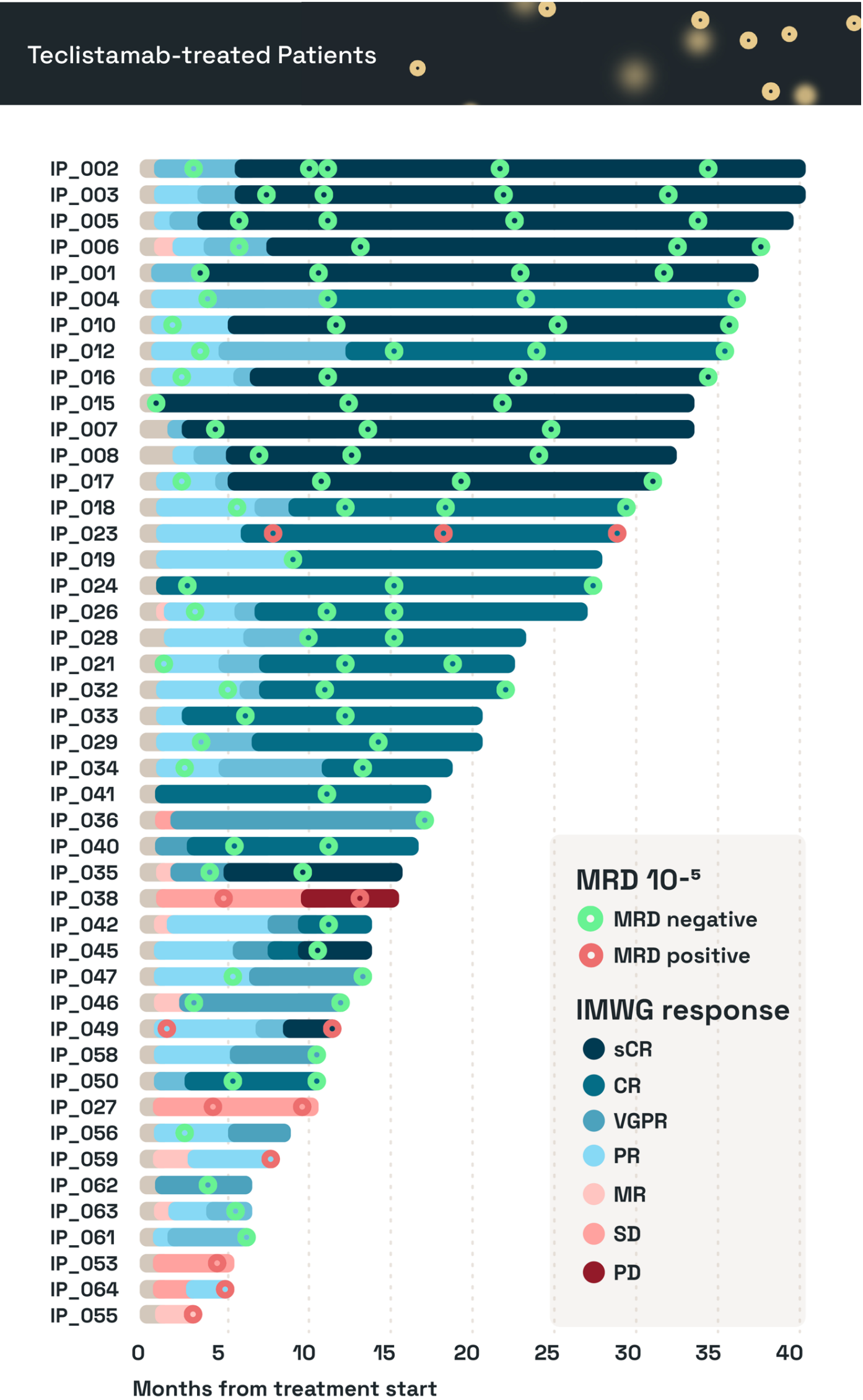
Figure 3.4 The new IMS/IMWG 2025 consensus genomic staging scheme includes combinatorial logic. Figure reproduced with permission from Leyoldt. CCF, cancer cell fraction; del, deletion; IgH, immunoglobulin heavy chain; NGS, next-generation sequencing.

CCF, cancer cell fraction; Dara-CVRd, daratumumab cyclophosphamide bortezomib lenalidomide dexamethasone; del, deletion; IgH, immunoglobulin heavy chain; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; SOC, standard of care.
1. Avet-Loiseau H, et al. International Myeloma Society/International Myeloma Working Group Consensus Recommendations on the Definition of High-Risk Multiple Myeloma. *J Clin Oncol.* 2025;43,2739-2751.
Leyoldt LB. High-risk cytogenetics: Definition and treatment options. Oral presentation p106-2 at EHA2026.
Kaiser M. Treatment of (Ultra-) high risk multiple myeloma in clinical practice in 2026. Oral presentation p264-3 at EHA2026.

S207/LB5008/S205: Intensified treatment strategies in high-risk smoldering MM

- The Phase 2 ASCENT study: Single-arm study of Dara-KRd in high-risk smoldering MM (HR-SMM), with CR rates as the primary endpoint.
- Results: MRD negativity in 52 out of 87 enrolled patients (60%) by IMWG definition. PFS rate for 3 years was 89.9% (95% CI 82.3–98.3%).
- The safety profile was consistent with previous studies on active MM.
- The randomized Phase 2 Immuno-PRISM study: Fixed-duration teclistamab (BCMAxCD3 BsAb) vs. standard therapy (Rd) in HR-SMM, with CR rates as primary endpoint
- Results: superior CR rate (75.6% vs. 0%) and improved PFS compared to Rd (median not reached, 2-year estimated PFS 92% vs. 51%; P=0.007). MRD negativity rate of 82% at a 10⁻⁵ threshold in all patients in the ITT population, while MRD negativity was sustained in all patients at a median follow-up of 23.4 months.
- For safety, the overall profile was favorable, with no high-grade CRS events or neurological toxicities observed.
- The Phase 2 ERASMM study: Fixed-duration elranatamab (BCMAxCD3 BsAb) in HR-SMM, with CR rate as primary endpoint
- Elranatamab induced high response rates, with the CR rate increasing from 30% at six cycles to 72% overall at a median follow-up time of 14 months. MRD negativity rate reached 90%, indicating deep disease control, with no progression to active myeloma observed.
- No new safety signals were observed with elranatamab monotherapy in HR-SMM patients compared to those with RRMM.

Figure 3.5 Teclistamab showed increased, deep response rates in patients with HR-SMM. Figure reproduced with permission from Nadeem. CR, complete response; MR, minimal response; MRD, minimal residual disease; PD, progressive disease; PFS, progression-free survival; PR, partial response; RRMM, relapsed or refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.



2L+, second line or later; CI, confidence interval; CR, complete response; D, daratumumab; d, dexamethasone; HR, hazard ratio; ITT, intend-to-treat; K, carfilzomib; MR, minimal response; MRD, minimal residual disease; P, pomalidomide; PD, progressive disease; PFS, progression-free survival; PR, partial response; Pvd, pomalidomide bortezomib dexamethasone; RRMM, relapsed or refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; Tal, talquetamab; VGPR, very good partial response.

Kumar SK. Aggressive smoldering curative approach evaluating novel therapies (ASCENT): a phase 2 trial of induction, consolidation, and maintenance in high-risk smoldering multiple myeloma. Oral presentation S207 at EHA2026.

Nadeem O. Teclistamab improves depth of response and PFS versus lenalidomide-dexamethasone in high-risk smoldering multiple myeloma: results from the phase 2 immunoPRISM trial. Oral presentation LB5008 at EHA2026.

Touzeau C. Safety and efficacy of elranatamab as early intervention in patients with high-risk smoldering myeloma: First results from the phase 2 ERASMM (EMN34) study. Oral presentation S205 at EHA2026.

04

Toward a personalized
therapeutic approach
for patients with
chronic myeloid
malignancies



Section 4: Toward a personalized therapeutic approach for patients with chronic myeloid malignancies

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
p113-2	Targeting cardiovascular risk in MPN novel findings after use of large data sets	M. Lucijanic
P113-3	Modern approaches to ET and PV	F. Palandri
LB5002	Selinexor plus ruxolitinib in Janus kinase inhibitor–naïve myelofibrosis: Phase 3 SENTRY trial.	C. Harrison
P266-1	Targeting of Hepcidin friend and foe in PV and MF	R. Mesa
S215	Efficacy and safety of luspatercept in patients with myelofibrosis on janus kinase inhibitors who require red blood cell transfusions: primary analysis of the phase 3 INDEPENDENCE trial	F. Passamonti
S306	RALLY-MF: Initial efficacy of a phase 2 study of DISC-0974, an anti-hemojuvelin antibody, to treat anemia in myelofibrosis	N. Gangat
P266-2	What can we expect from mutation targeted therapies in MPN?	B. Psaila
S216	Mutant calreticulin–specific monoclonal antibody, INCA033989, is well tolerated and achieves robust spleen, anemia, and molecular responses in patients (pts) with myelofibrosis (MF)	C. Harrison
P270-1	Quality of life and symptoms: Translating clinical trial outcomes to clinical practice in hematological malignancies	E. Oliva

p113-2/p113-3: Shift toward biologically driven treatment strategies

- Essential thrombocythemia (ET) and polycythemia vera (PV) are driven by JAK-STAT pathway activation, primarily due to JAK2, CALR, or MPL mutations. PV is characterized by an increased red blood cell count, while ET features an elevated platelet count.
- Key risks include thrombosis, myelofibrosis (MF) progression, and leukemic transformation, while current risk models do not adequately capture patient diversity.
- The **ZEBRA score**, a novel MF-specific risk tool, may assist treatment decisions when combined with existing MPN thrombosis risk stratification methods. It assesses anisocytosis, leukocyte count, absolute lymphocyte and monocyte counts, along with comorbidities, and performs well for arterial and venous events across MF subtypes.^{1,2}
- Emerging approaches, including interferons, JAK inhibitors, epigenetic therapies, and CALR-targeted immunotherapies, are shifting treatment toward targeted, biology-driven care with improved long-term outcomes and quality of life.
- The **SERENITY Phase 3 trial** demonstrates that dual inhibition of JAK STAT and XPO1 signaling with selinexor plus ruxolitinib provides superior clinical and molecular responses compared to ruxolitinib alone in JAK inhibitor-naïve myelofibrosis, supporting a synergistic, disease modifying therapeutic strategy with manageable safety.

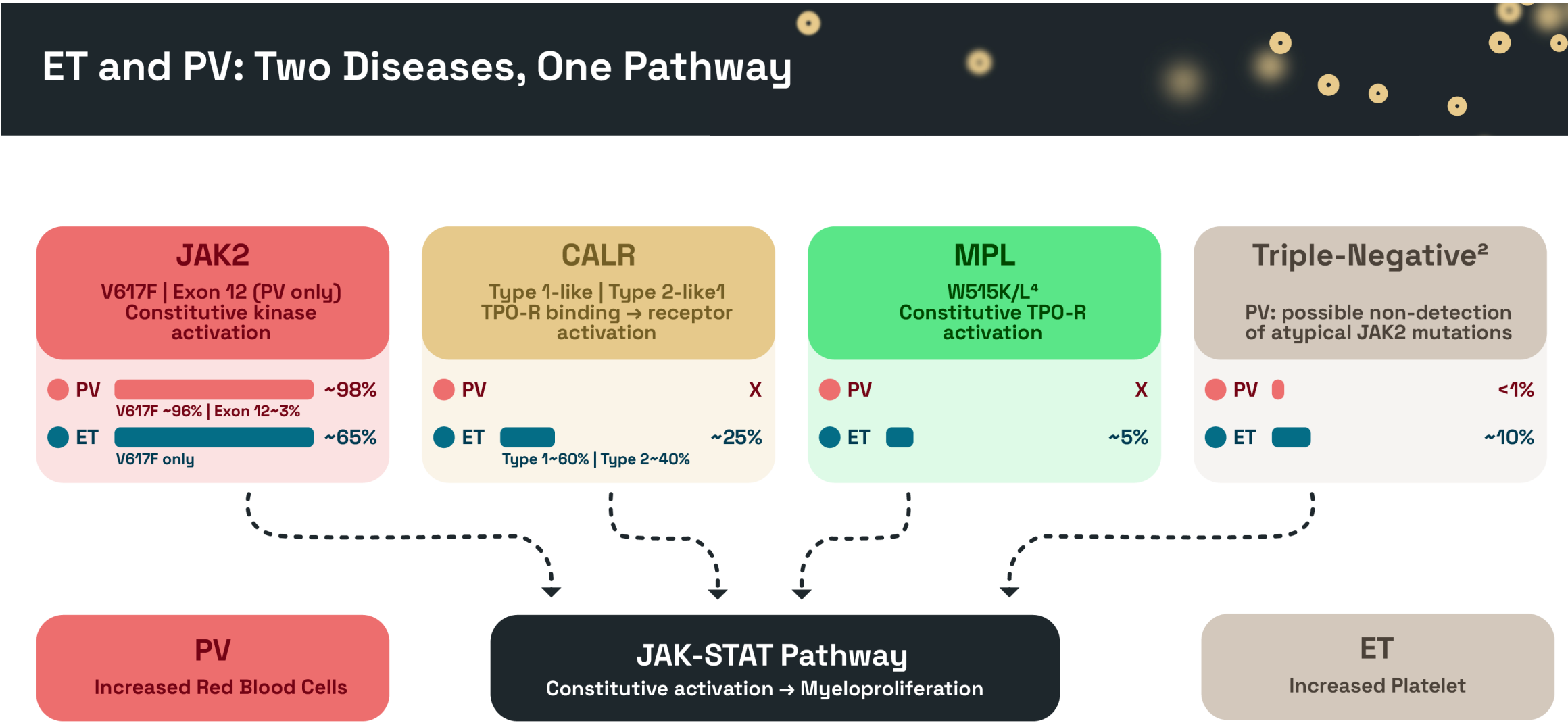


Figure 4.1 ET and PV are both driven by JAK-STAT pathway activation. Figure adapted/reproduced with permission from Palandri. CALR, calreticulin; ET, essential thrombocythemia; JAK, Janus kinase; MPL, myeloproliferative leukemia protein; PV, polycythemia vera.

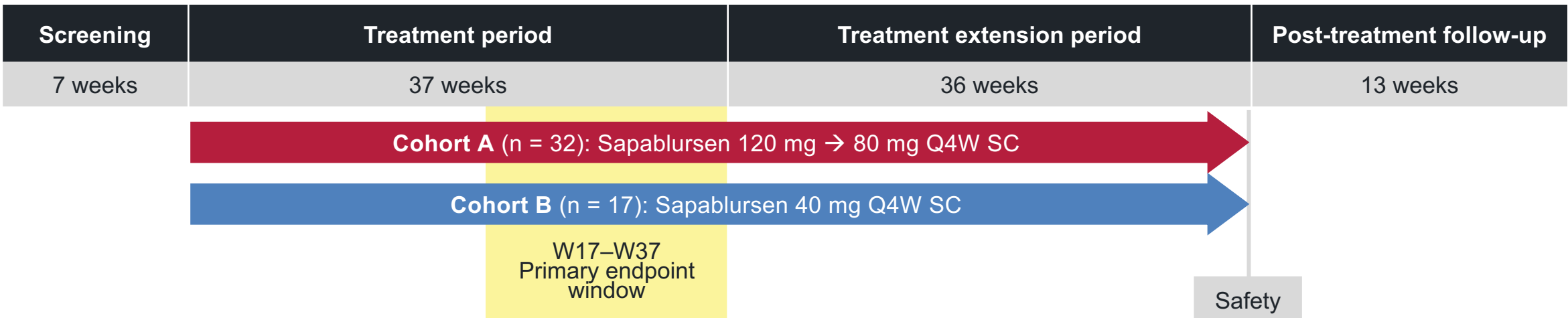
CALR, calreticulin; ET, essential thrombocythemia; JAK, Janus kinase; JAK2, Janus kinase 2; MPL, myeloproliferative leukemia protein; PV, polycythemia vera; STAT, signal transducer and activator of transcription; TPO-R, thrombopoietin receptor.
1. Marchetti, M. et al. Appropriate management of polycythaemia vera with cytoreductive drug therapy: European LeukemiaNet 2021 recommendations. *Lancet Haematol.* 2022;9:e301–e311. 2. Pasquer, H. et al. Distinct clinico-molecular arterial and venous thrombosis scores for myeloproliferative neoplasms risk stratification. *Leukemia.* 2024;38:326–339.
Lucijanac, M. Targeting cardiovascular risk in MPN novel findings after use of large data sets. Oral presentation p113-2 at EHA2026.
Palandri, F. Modern approaches to ET and PV. Oral presentation p113-3 at EHA2026.
Harrison, C. Selinexor plus ruxolitinib in Janus kinase inhibitor-naïve myelofibrosis: Phase 3 SENTRY trial. Oral presentation LB5002 at EHA2026.

p266-1: Targeting iron homeostasis: a central lever in MPN management

- Hepcidin is the key regulator of systemic iron homeostasis and erythropoiesis, making it an attractive therapeutic target in MPN.¹
- Increasing hepcidin levels, for example via mimetics like rusfertide or Tmprss6 inhibition, can reduce erythrocytosis and phlebotomy needs in PV.
- Conversely, lowering hepcidin through pathways such as ACVR1, hemojuvelin, or activin/BMP/SMAD signaling enhances iron availability and improves anemia in MF.
- The Phase 2a **IMPRSSION** study evaluates the safety and efficacy of sapablursen, a Tmprss6 inhibitor, for hematocrit control, reducing phlebotomy rate, and improving symptoms in patients with PV.
- Sapablursen significantly reduced the frequency of phlebotomy, increased serum hepcidin, controlled hematocrit, and improved symptoms of PV, altogether with an acceptable safety profile.

IMPRSSION: Multicenter, Randomized, Open-Label Trial of Sapablursen in Patients With Phlebotomy-Dependent PV

- Key inclusion criteria:**
- Clinical diagnosis of PV (WHO diagnostic criteria – JAK2 mutation required²)
 - Phlebotomy dependent
 - No eligibility restrictions based on hematocrit level
- Key endpoints:**
- Primary: Reduction in the weekly rate of phlebotomies
 - Secondary: Change in mean MPN-SAF-TSS score
 - Safety: AEs, vital signs, ECG, and clinical laboratory tests



ACVR1, activin A receptor type 1; AE, adverse event; BMP, bone morphogenetic protein; ECG, electrocardiogram; ET, essential thrombocythemia; MPN, myeloproliferative neoplasm; MPN-SAF-TSS, MPN-Symptoms Assessment Form-Total Symptom Score; PV, polycythemia vera; SMAD, small mothers against decapentaplegic; Tmprss6, transmembrane protease serine 6; WHO, World Health Organization.
1. Camaschella, C., Nai, A. & Silvestri, L. Iron metabolism and iron disorders revisited in the hepcidin era. *Haematologica*. 2020;105:260–272. 2. Barbui T, et al. Polycythemia vera treatment algorithm 2018. *Blood Cancer J*. 2018; 8(1):3. doi: 10.1038/s41408-017-0042-7.
Mesa, R. Targeting of Hepcidin friend and foe in PV and MF. Oral presentation p266-1 at EHA2026.

S215/S306: Emerging agents for anemia control

- The Phase 3 INDEPENDENCE trial
 - Luspatercept, an erythroid maturation agent, compared to placebo in MF patients with anemia requiring blood transfusions while on JAKi therapy, with blood cell transfusion independence (RBC-TI) for ≥ 12 consecutive weeks as primary endpoint.
 - Clinically meaningful improvements in RBC-TI, transfusion burden (TB), and Hb levels with luspatercept vs. placebo in higher-risk MF and high TB who were receiving JAKi therapy. RBC-TI ≥ 12 response was achieved by 23.1% of luspatercept-treated patients.
 - The luspatercept safety profile was manageable and consistent with that expected in advanced MF.
- The Phase 2 RALLY-MF study
 - DISC-0974, a hemojuvelin Ab, in patients with primary, post-ET or post-PV MF, across different transfusion dependence groups, focusing on transfusion needs, hematologic responses, safety, and patient-reported outcomes.
 - DISC-0974 led to reduced hepcidin and increased iron mobilization. In non-transfusion dependent (TD) participants, 55% achieved a mean hemoglobin increase of 1.5 g/dL for at least 12 weeks. In TD low participants, 64% achieved transfusion independence (TI) for over 16 weeks, with increases maintained during continuation, and an increase in Hb after DISC-0974 dosing was correlated with improvement in patient-reported outcomes.
 - DISC-0974 was safe and well tolerated.

DISC-0974 is an investigational first-in-class mAb that blocks the co-receptor hemojuvelin and decreases hepcidin expression

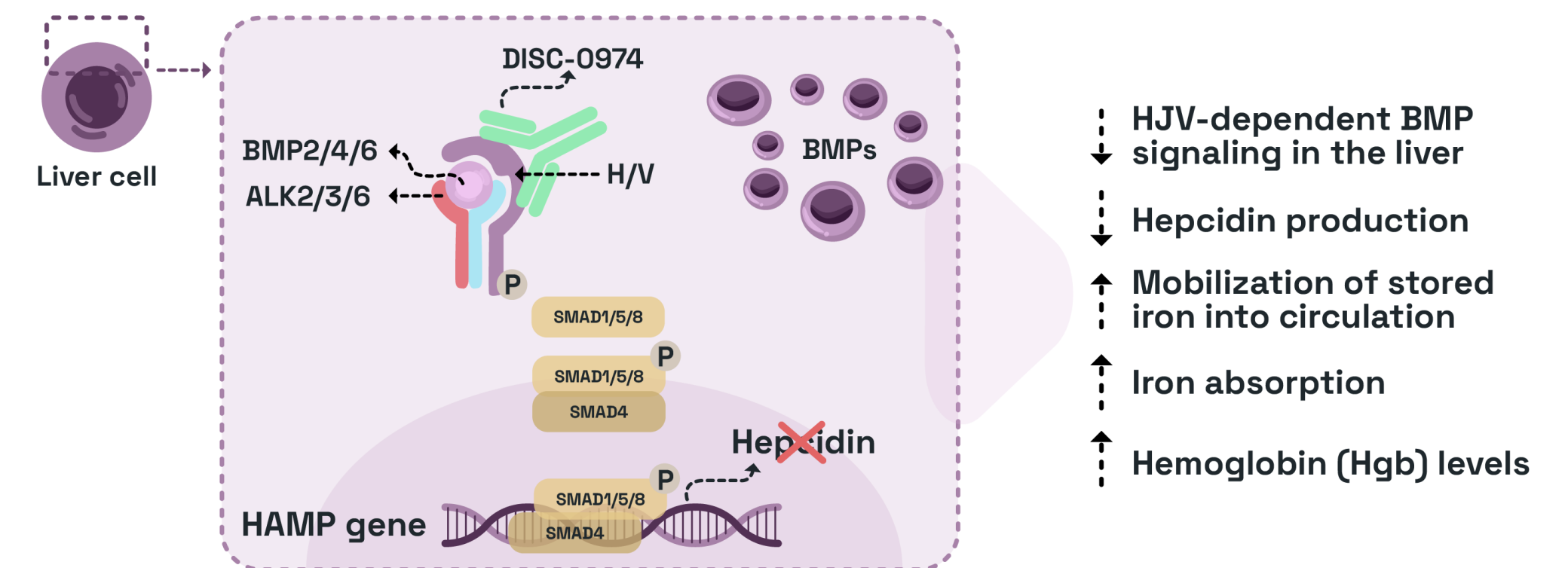


Figure 4.2 Inhibition of hemojuvelin reduces hepcidin levels, leading to mobilization of stored iron into the circulation and fostering increased hemoglobin levels. Figure adapted/reproduced with permission from Gangat.

Ab, antibody; ET, essential thrombocythemia; Hb, hemoglobin; JAKi, Janus kinase inhibitor; MF, myelofibrosis; PV, polycythemia vera; RBC-TI, red blood cell transfusion independence; TB, total bilirubin; TD, transfusion dependence; TI, transfusion independence. Passamonti, F. Efficacy and safety of luspatercept in patients with myelofibrosis on janus kinase inhibitors who require red blood cell transfusions: primary analysis of the phase 3 INDEPENDENCE trial. Oral presentation S215 at EHA2026. Gangat, N. RALLY-MF: Initial efficacy of a phase 2 study of DISC-0974, an anti-hemojuvelin antibody, to treat anemia in myelofibrosis. Oral presentation S306 at EHA2026.

p266-2/S216: Towards Clone-selective therapies: Mutation-driven targeting in MPN

- Current standard therapies for MPNs show limited selectivity for the malignant clone, with effects on variant allele frequency (VAF) often being transient or difficult to interpret.
- Mutant CALR represents a highly specific therapeutic target, with emerging immunotherapies such as monoclonal antibodies, BiTEs, ADCs, and CAR-T cells under clinical investigation.
- Meaningful clinical benefit depends on true targeting of malignant stem cells, as only sustained VAF reduction correlates with improved long-term outcomes such as event-free survival.
- Phase 1 studies of INCA033989, a mAb that selectively targets mutCALR in complex with TPO-R
 - In patients harboring a CALR exon-9 mutation with high-risk MF and ET, assessment of safety, dosing, and early efficacy, monotherapy and combination with ruxolitinib, with focus on dose-limiting toxicities, TEAEs, spleen reduction, and molecular response.
 - Overall, 84% (n=70) patients were still receiving treatment and 16% (n=13) discontinued (adverse event (n=3); lack of efficacy (n=3); physician decision (n=3); progressive disease (n=3); withdrawal by patient (n=1).
 - No dose-limiting toxicities were observed; the maximum tolerated dose was not reached. Results show rapid and robust spleen, symptom, and anemia responses, as well as a mutant CALR VAF reduction.

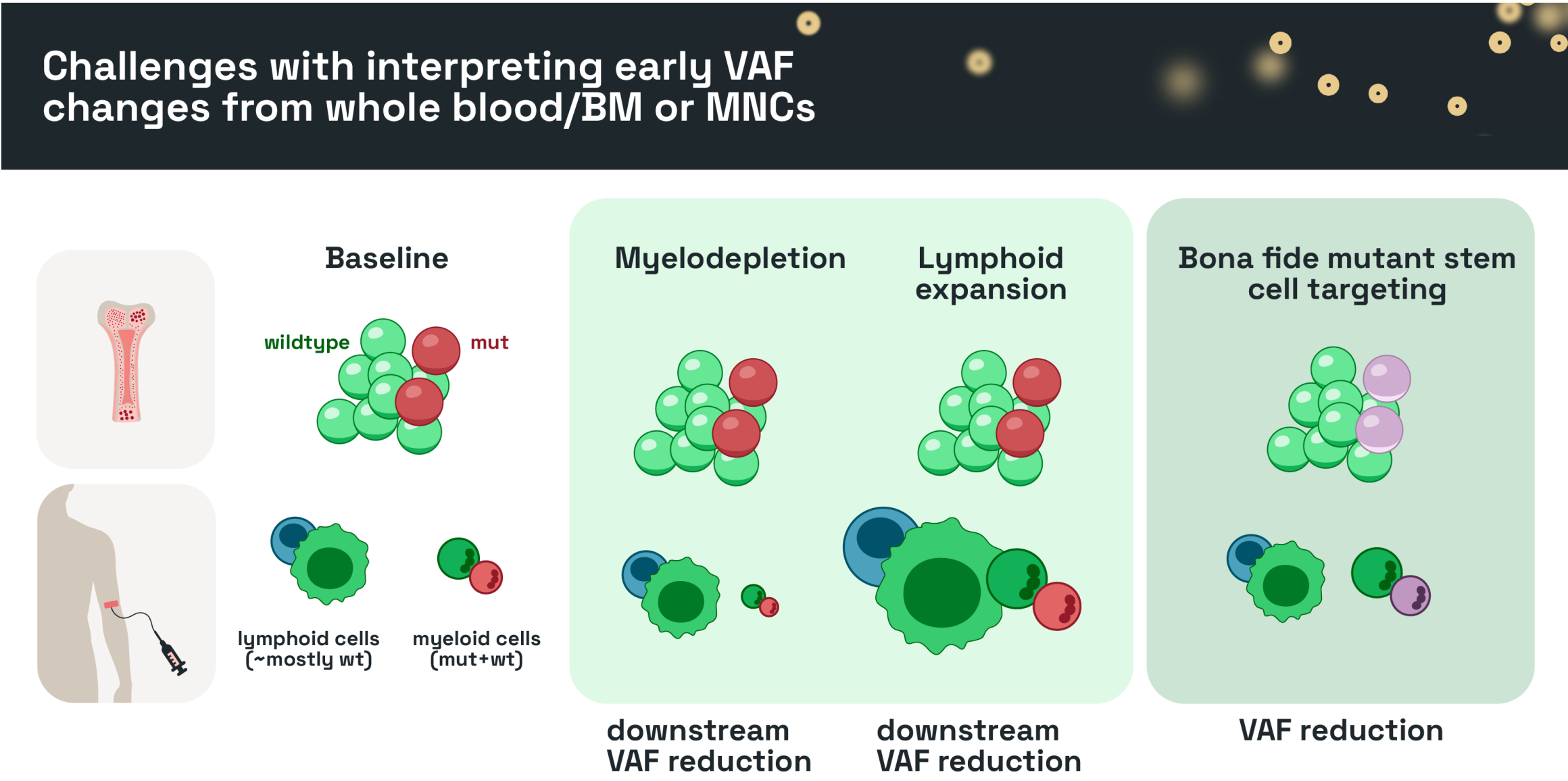


Figure 4.3 Variant allele frequency (VAF) reduction from peripheral blood can be misleading, as treatment may deplete myeloid or expand lymphoid cells, altering the malignant clone ratio and causing apparent VAF decrease without effectively targeting the bone marrow clone. Figure adapted/reproduced with permission from Psaila. BM, bone marrow; MNC, mononuclear cells; mut, mutant; VAF, variant allele frequency; wt, wild type.

ADCs, antibody-drug conjugates; BiTEs, bispecific T-cell engagers; CALR, calreticulin; CAR-T, chimeric antigen receptor T cell; ET, essential thrombocythemia; JAK, Janus kinase; JH1, Janus homology domain 1; JH2, Janus homology domain 2; MF, myelofibrosis; STAT, signal transducer and activator of transcription; TEAEs, treatment-emergent adverse events; TPO-R, thrombopoietin receptor; VAF, variant allele frequency.
Psaila, B. What can we expect from mutation targeted therapies in MPN? Oral presentation p266-2 at EHA2026.
Harrison, C. Mutant calreticulin-specific monoclonal antibody, INCA033989, is well tolerated and achieves robust spleen, anemia, and molecular responses in patients (pts) with myelofibrosis (MF). Oral presentation S216 at EHA2026.

p270-1: Capturing what matters: The role of patient-reported outcomes in MPN

- MPNs are linked to significant symptom burdens that clinicians often underestimate or overlook, and which may not be fully captured by lab values. Therefore, patient-reported outcomes (PRO) are crucial for assessing the impact of treatment.
- Various PRO instruments exist but are used inconsistently, prompting EHA guidelines to standardize selection, implementation, and reporting in MPN trials.
- Key conclusions:
 - MF has the most robust evidence base: MF-SAF v4.0 conditionally preferred for MF symptom endpoints.
 - PV and ET require subtype-specific approaches: the use of MPN-SAF TSS/MPN-10 is conditionally preferred, and supplementing with key symptoms such as pruritus or microvascular burden is proposed.
 - PROs must be integrated into the trial design, including prespecifying the construct, instrument, timing, analysis, interpretation, and reporting.
- Overall, MPN management is evolving toward an integrated approach that combines disease biology, hematologic control, and patient-centered outcomes.

The challenges of young MPN patients

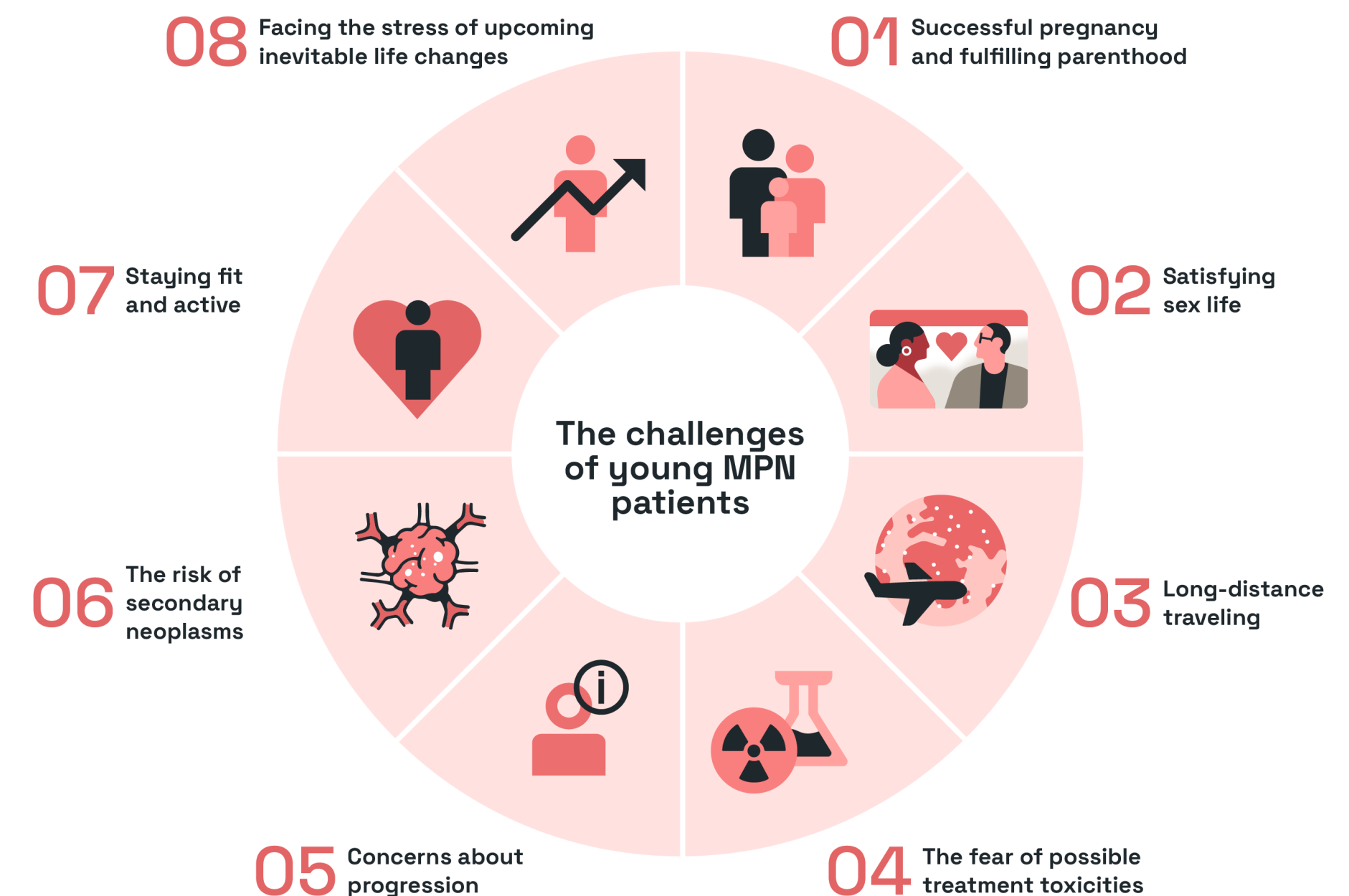


Figure 4.4 The symptom burden of a chronic disease can be clinically invisible, highlighting the importance of incorporating PROs into clinical trial designs. Figure adapted/reproduced with permission from Oliva.

05

Epigenetics in hematologic malignant (and non-malignant) diseases



Section 5: Epigenetics in hematologic malignant (and non-malignant) diseases

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
P153-1	Histone modification in acute leukemia	A. Radziskeuskaya
P153-2	Role of 3D chromatin organization in acute leukemia	F. Boccalatte
S332	Nanopore-based genomic and epigenomic profiling for pediatric hematologic malignancies using targeted adaptive sampling long-read sequencing: interim report of the JCCG-WGS study	S. Kato
S333	Nanoleukemia - a hierarchical classification framework for hematopoietic neoplasms integrating epigenetic and genetic information from whole genome nanopore sequencing	M. Schöning
P196-2	Diagnostic and prognostic implications of the DNA methylome of lymphoid neoplasms	J.I. Martíin-Subero
P282-1	Heterogeneity in transcriptional/ epigenetic dependencies in ALL	S. Richardson
S260	Integrated metabolic and epigenetic profiling uncovers distinct immune-escape programs and targetable vulnerabilities in post-transplant AML relapse	S. Tameni
P192-4	PLZF dysfunction drives LINE-1 retrotransposon derepression and genomic instability in hematopoietic progenitor cell	H. Xiao

p153-1/p153-2: Mechanisms of genomic interaction and epigenetic regulation in cancer

- Histone modification is a key mechanism for epigenetic regulation.
- Histone acetylation loosens chromatin and makes genes accessible for translation.
- Aberrant histone acetylation can drive cancer development and progression by activating oncogenes:
 - KAT6a/p300 fusion protein, result of a chromosomal translocation, occurs in a subset of AML.
 - It induces H3/H2B multi-acetylation of key leukemia promoters through KAT6A-driven p300 redistribution.
- At the **3D chromatin level**, gene regulation occurs through the spatial proximity of enhancer and silencer elements to gene promoters.
- These interactions are not strictly tied to proximity in the chromosomal base sequence, but rather to proteins that organize chromatin.
- HiChIP analysis reveals the strength of interactions between different chromatin elements and the hubness of interaction networks.
 - CD1 locus was identified as an important hub driving the expression of key surface antigens in T-ALL; MYCN was found to be a hub for proto-oncogene expression in ETP-ALL.

Matrix of chromatin interactions and illustration of 3D chromatin organization

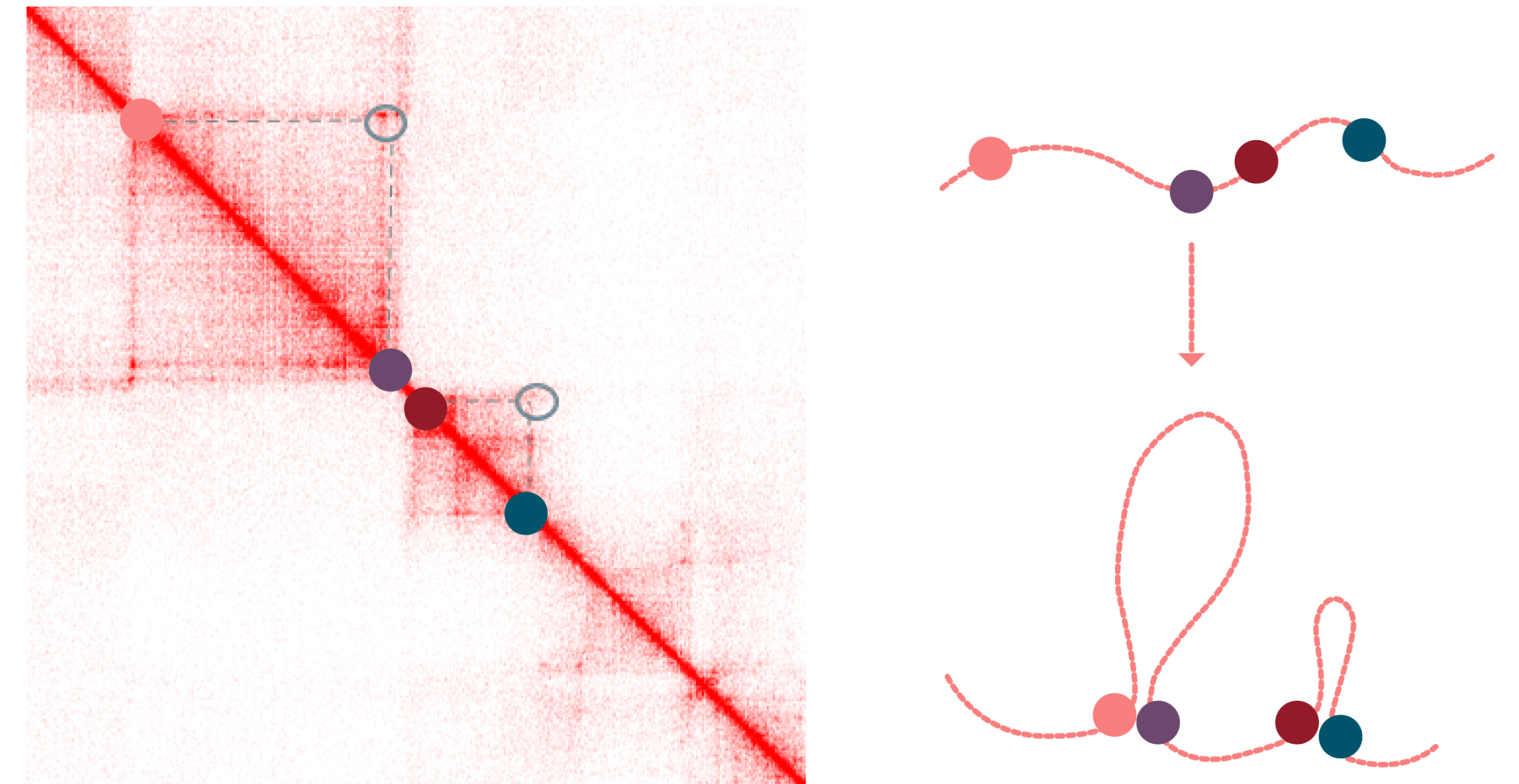


Figure 5.1 Left: Matrix of chromatin interactions, generated with Hi-C genomic analysis. Right: Illustration of 3D chromatin organization and interaction of distant genetic elements. Reproduced with permission from Boccalatte.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CD1, cluster of differentiation 1; ETP-ALL, early T-cell precursor ALL; H2B, histone 2B; H3, histone 3; HiChIP, Hi-C chromatin immunoprecipitation; KAT6a, lysine acetyltransferase 6; MYCN, myelocytomatosis oncogene N; p300, protein 300; T-ALL, T-cell ALL.

Radzisheuskaya A. Histone modification in acute leukemia. Oral presentation p153-1 at EHA2026.

Boccalatte F. Role of 3D chromatin organization in acute leukemia. Oral presentation p153-2 at EHA2026.

S332/S333: Nanopore-based genomic and epigenomic cancer profiling

- Unlike conventional NGS sequencing, nanopore sequencing is sensitive to cytosine methylation and can more reliably identify SVs and CNVs thanks to longer sequence reads.
- **TAS-LRS** was used in a study of 87 patient samples with various hematological malignancies, focusing on the identification of SVs and CNVs of clinical relevance.
- Findings relevant to diagnosis, prognosis and for therapeutic targets were found in 78%, 47% and 55% of cases, respectively; one patient was retrospectively reclassified as having AML.
- The novel, nanopore-based workflow **nanoLeukemia** integrates epigenetic and genetic information for entity classification and diagnostic risk stratification into a single test.
- In a benchmark vs. the standard workflow, concordance was 91.7% for epitype classification and 97.2% for risk stratification, thereby achieving statistical non-inferiority.
- Future work will involve creating nanopore-based databases and expanding the application of TAS-LRS and nanoLeukemia methods to additional cancer entities.

Genomic profiling with TAS-LRS in patients with hematological malignancies

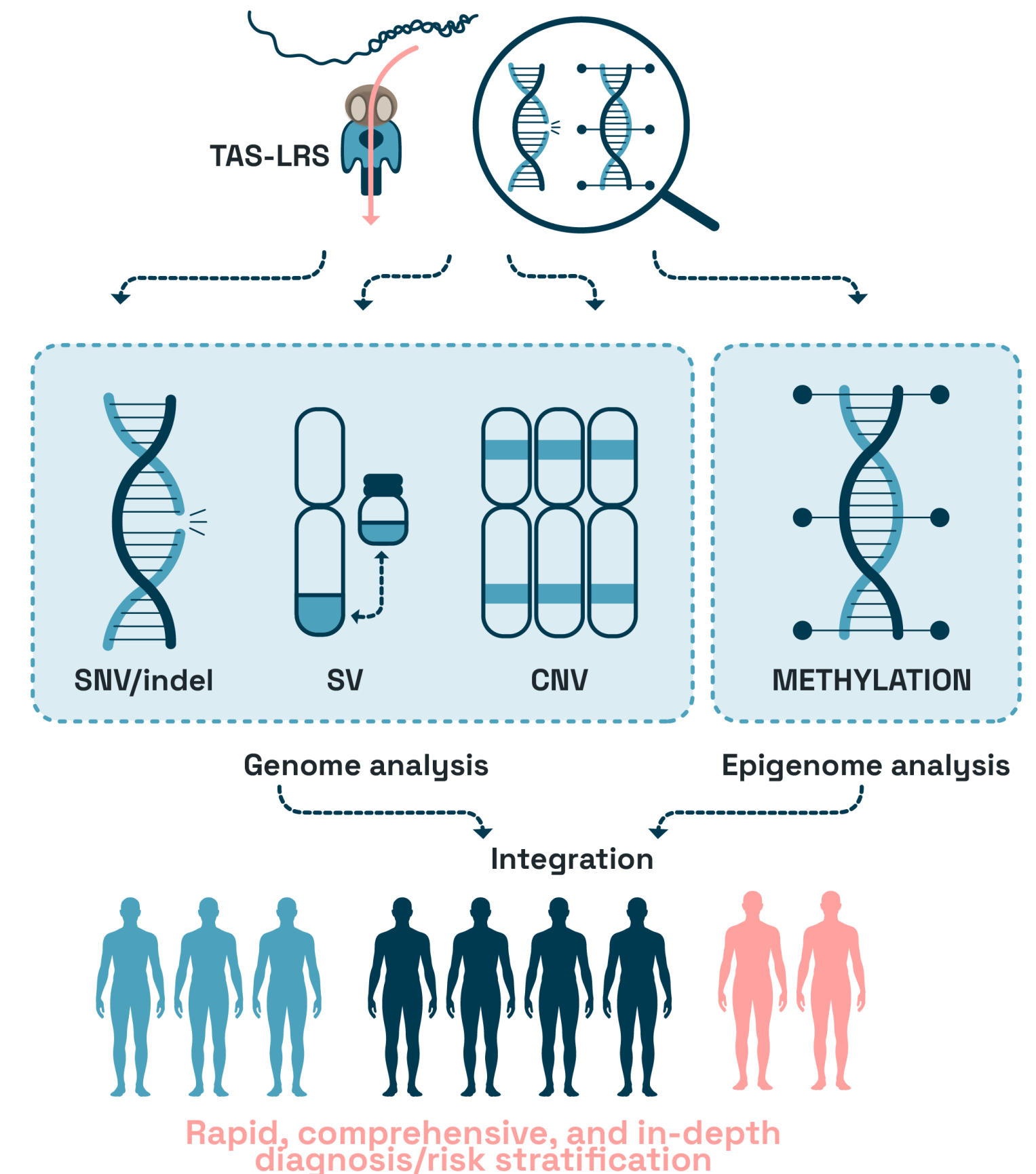


Figure 5.2 Reproduced with permission from Kato. CNV, copy number variation; SNV, single-nucleotide variation; SV, structural variant; TAS-LRS, targeted adaptive sampling long-read sequencing.

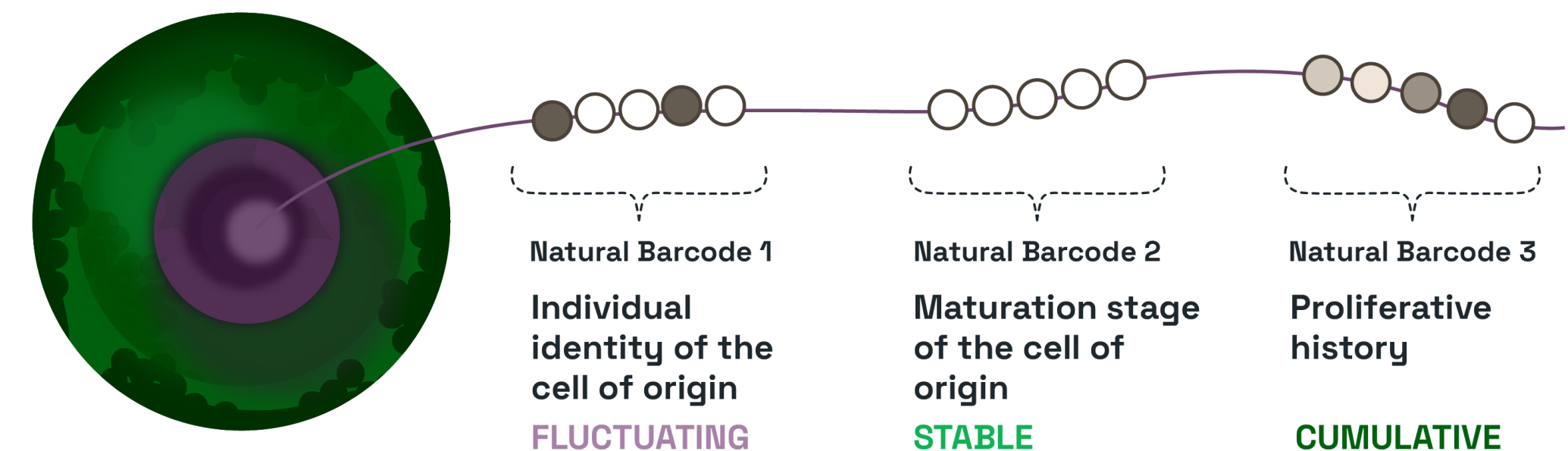
AML, acute myeloid leukemia; CNV, copy number variation; NGS, next-generation sequencing; SV, structural variant; TAS-LRS, targeted adaptive sampling long-read sequencing.

Kato S. Nanopore-based genomic and epigenomic profiling for pediatric hematologic malignancies using targeted adaptive sampling long-read sequencing: interim report of the JCCG-WGS study. Oral presentation S332 at EHA2026.
Schönung M. Nanoleukemia - a hierarchical classification framework for hematopoietic neoplasms integrating epigenetic and genetic information from whole genome nanopore sequencing. Oral presentation S333 at EHA2026.

p196-2: DNA methylation provides insights into cancer evolution and prognosis

- 95% of CpG methylation sites do not correlate with gene expression; these sites can provide valuable information about the origin and development of (tumor) cells.
- Comprehensive methylation analysis in CLL patient samples identified a third type of CLL with intermediate prognosis between U-CLL and M-CLL, consisting mostly of M-type cells with low levels of IGHV mutation.
- With the help of the new mathematical model **EVOFLUX** three types of methylation “barcodes” were identified that provide information on the tumor cell of origin, its maturation stage, and the tumor’s proliferative history.
- These data reveal tumor growth rate independent of other genetic markers, with significant implications for prognostication and treatment decision making.
- EVOFLUX is applicable to all types of hematological and solid cancers and, if verified, could transform oncologic research and prognostication.

The hidden message of DNA methylation patterns



“Epigenetic identity and memory as natural barcodes that can refine classification and prognosis in lymphoid neoplasms”

Figure 5.3 Reproduced with permission from Martín-Subero.

p282-1/S260: Epigenomic and metabolomic weak points in acute leukemias

Identification of gene pairs for synthetic lethality in ALL

- In B-cell ALL, over 200 “first-hit” mutations have been identified overalls, making it difficult to develop broadly applicable mutation-directed therapies.
- B-cell malignancies have characteristic interactions between their genetic elements arising from genomic rearrangements that occur during B-cell development.
- A study identified master regulators in patient samples that could serve as targets for future therapies; besides *BCL2*, the identified genes include *TUBA1B* and *AURK*.

Metabolic rewiring in AML drives T-cell inhibitory relapse

- Post-transplant AML relapses are characterized by either HLA II downregulation or T-cell inhibition.
- Using bulk RNA-seq, ATAC-seq, and CUT&Tag-seq, a metabolically rewired, pro-oxidative state was identified in T-cell inhibitory relapses.
- The oxidative milieu leads to immune cell exhaustion and lactate-mediated derepression of inhibitory ligands.

Disproportional enrichment of metabolic pathway alterations in T-cell inhibitory relapses vs. HLA class II downregulation relapses

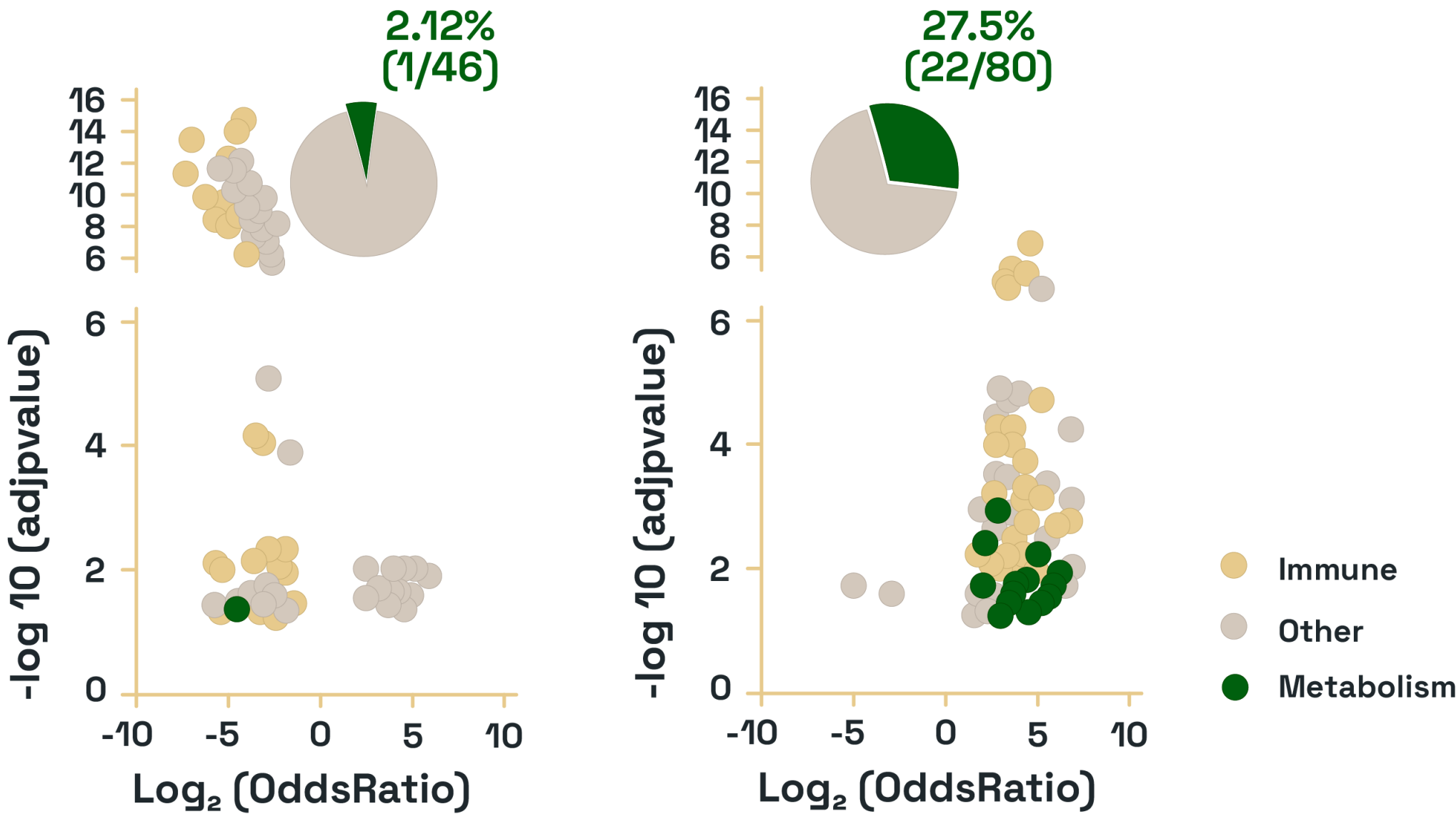


Figure 5.4 Pathway enrichment analysis in leukemic blasts shows downregulation of immune pathways in relapses with HLA II-downregulation (left) and upregulation of metabolic pathways in T-cell inhibitory relapses (right). Reproduced with permission from Tameni. HLA, human leukocyte antigen.

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ATAC-seq, Assay for Transposase-Accessible Chromatin using sequencing; AURK, aurora kinase (gene family); B-ALL, B-cell ALL; BCL2, B-cell lymphoma 2 (gene); CUT&Tag-seq, Cleavage Under Targets and Tagmentation sequencing; TUBA1B, Tubulin alpha-1B gene.

Richardson S. Heterogeneity in transcriptional/ epigenetic dependencies in ALL. Oral presentation p282-1 at EHA2026.

Tameni S. Integrated metabolic and epigenetic profiling uncovers distinct immune-escape programs and targetable vulnerabilities in post-transplant AML relapse. Oral presentation S260 at EHA2026.

06

Complement-targeted treatments in hematology



Section 6: Complement-targeted treatments in hematology

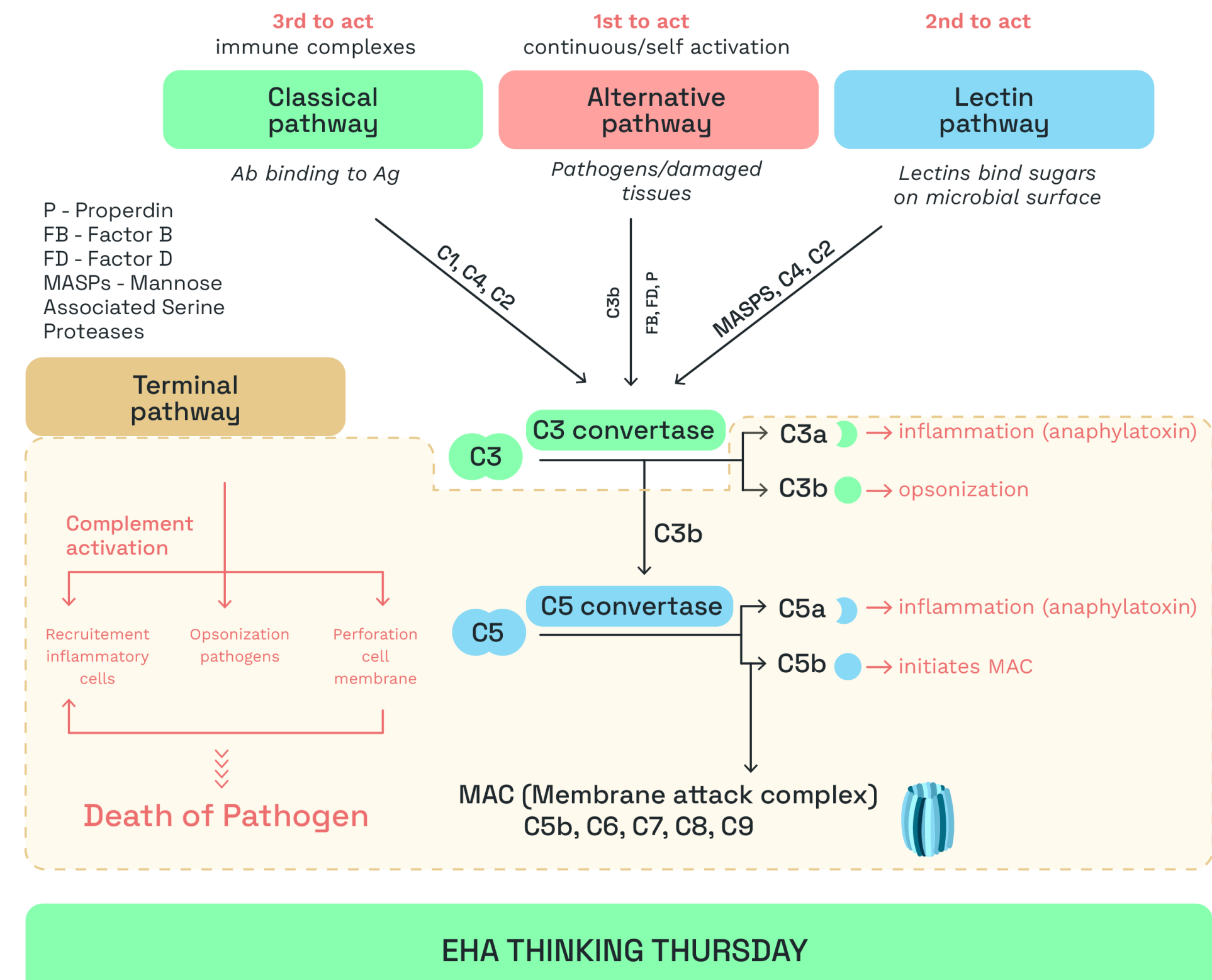
Overview of selected presentations

Presentation ID	Presentation Title	Presenter
P105-1	Complement biology, pathology and therapeutic opportunity	D.C. Mastellos
PS1797	Long-term hematologic control and safety in patients with paroxysmal nocturnal hemoglobinuria treated with iptacopan: 6-year follow-up from phase 2 studies and rollover extension program	A. Risitano
PS1779	Real-World Outcomes of Iptacopan in Paroxysmal Nocturnal Hemoglobinuria (PNH) Patients: Insights from the French Early Access Program	R. Peffault de Latour
PF697	3-year efficacy and safety of crovalimab in patients with paroxysmal nocturnal hemoglobinuria (PNH) naïve to complement inhibitors: Long-term data from the phase III COMMODORE 2 trial	N. Obara
S181	A phase III study of a head-to-head comparison of a factor b inhibitor HSK39297, versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria naïve to complement inhibition	Y. Zhang
PS1787	Oral MY008211A demonstrates superior efficacy versus eculizumab in complement inhibitor-naïve Chinese patients with paroxysmal nocturnal hemoglobinuria (PNH)	F. Zhang
P105-2	Cold agglutinin disease (CAD) and anti-complement therapies	S. Berentsen
PS1952	Sutimlimab in patients with cold agglutinin disease and prior rituximab exposure: a post-hoc analysis of the phase 3 CADENZA study	M. Michel
P105-3	Hyperhemolytic syndrome: Risk factors and management in sickle cell disease	F. Pirenne
PS2373	Targeting the complement alternative pathway attenuates acute vaso-occlusive crisis in sickle cell disease	T.T. Maciel

p105-1: A paradigm shift in complement biology

- The complement system has long been recognized as a crucial component of innate immunity, essential for host defense and tissue maintenance.
- Complement system activation through the classical, alternative, and lectin pathways, all converging on C3 and C5 convertase formation, drives inflammation, opsonization, and MAC-mediated pathogen killing.
- However, growing evidence indicates that complement is involved in **many fundamental biological processes** beyond its traditional functions, including the fine-tuning of B- and T-cell responses and the interface between innate and adaptive immunity.
- Although complement is crucial in regulating inflammation and adaptive immune activation, dysregulation can also cause significant collateral damage.
- Such improper responses may result in abnormal thrombo-inflammatory activity, immune imbalance, vascular endothelial inflammation, and organ injury.

Complement pathways



Ab, antibody; Ag, antigen; FB, Factor B; FD, Factor D; MAC, membrane attack complex; MASPs, mannose-associated serine protease.
Figure adapted from EHA Thinking Thursdays. <https://sway.cloud.microsoft/ckFlxaf1Pnr41jmX> (Last accessed June 2026).
Mastellos DC. Complement biology, pathology and therapeutic opportunity. Oral presentation p105-1 at EHA2026.

Figure 6.1 Complement system activation through the classical, alternative, and lectin pathways, all converging on C3 and C5 convertase formation to drive inflammation, opsonization, and MAC-mediated pathogen killing. Figure from EHA Thinking Thursdays. Ab, antibody; Ag, antigen; FB, Factor B; FD, Factor D; MAC, membrane attack complex; MASPs, mannose-associated serine protease.

PS1797/PS1779/PF697/S181/PS1787:

Long-term data for complement inhibitors in PNH

- PNH treatment is expanding beyond C5 inhibition to proximal complement targets to improve control of both intravascular and extravascular hemolysis.
- C5 inhibitors block MAC formation, but C3 fragment deposition can still promote extravascular clearance by macrophages.
- **Iptacopan**, an oral Factor B inhibitor, showed sustained benefit for up to 6 years, with maintained Hb levels, transfusion independence, LDH control and no new safety findings.
- French real-world data showed rapid Hb normalization from Day 15 and 100% transfusion independence by Month 12.
- **Crovalimab**, an anti-C5 Ab, showed sustained disease control and tolerability over >3 years with 4-weekly SC dosing.
- Switching between crovalimab and other C5 inhibitors caused mostly mild-to-moderate transient immune complex reactions.
- New oral Factor B inhibitors, **HSK39297** and **MY008211A**, showed superior Hb outcomes vs. IV eculizumab in Phase 3 trials.
- Overall, newer oral and SC inhibitors may improve hemolysis control, reduce transfusion burden, and increase treatment convenience.

Mechanism of extravascular hemolysis in patients with PNH receiving C5 inhibitors

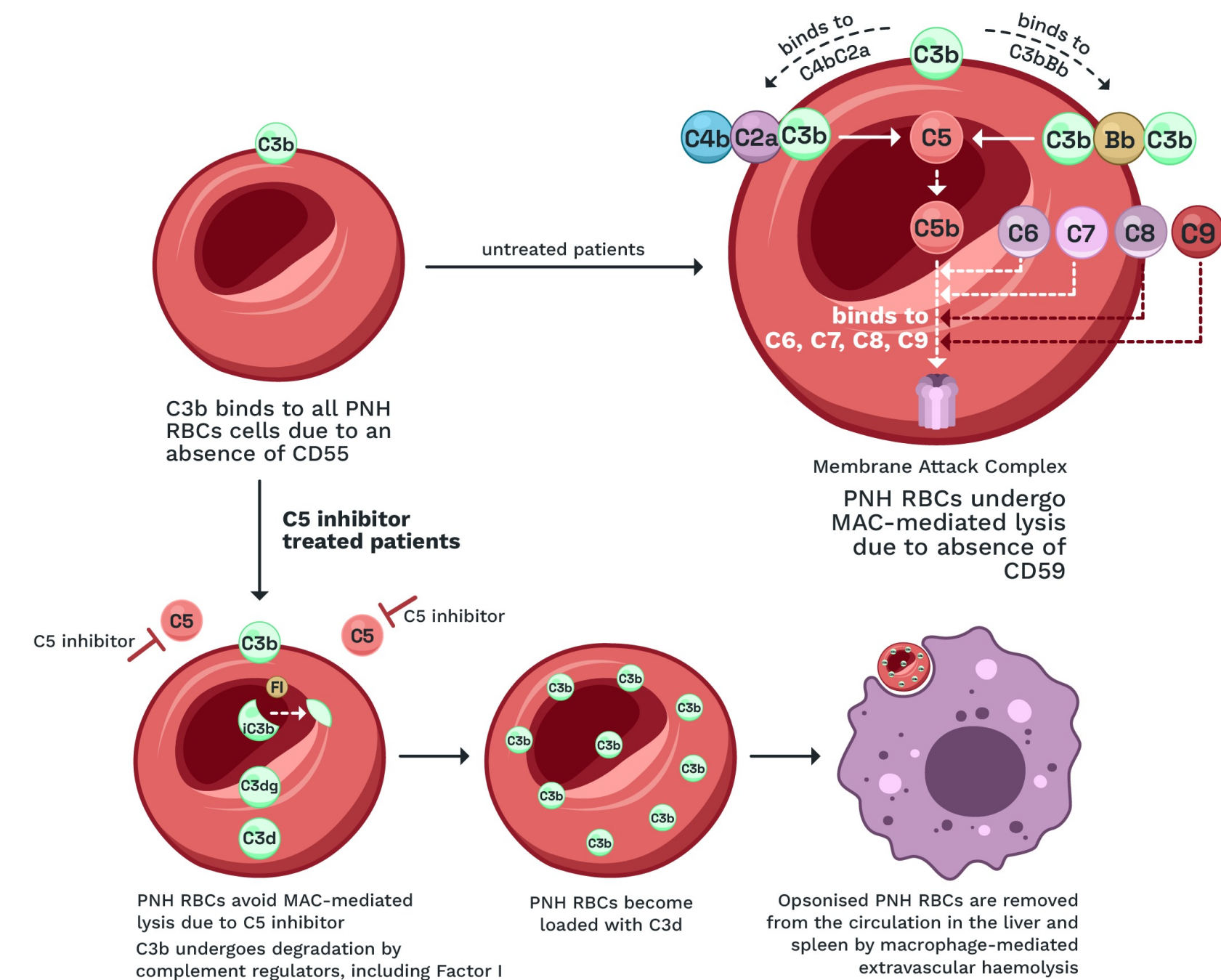


Figure 6.2 In PNH, RBCs lack the complement regulators CD55 and CD59, making them vulnerable to MAC-mediated intravascular hemolysis. C5 inhibitors block MAC formation, but C3 fragment deposition can still promote extravascular clearance by macrophages. Figure adapted from Kelly RJ, et al. *Drugs*. 2025;85(11):1413-1428. FI, factor I; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

FI, factor I; Hb, hemoglobin; IV, intravenous; LDH, lactate dehydrogenase; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SC, subcutaneous.

Figure adapted from Kelly RJ, et al. *Drugs*. 2025;85(11):1413-1428.

Risitano A. Poster PS1797 at EHA2026; Peffault de Latour R. Poster PS1779 at EHA2026; Obara N. Poster PF697 at EHA2026; Zhang Y. Oral presentation S181 at EHA2026; Zhang F. Poster PS1787 at EHA2026.

p105-2/PS1952: Complement-mediated pathogenesis in CAD

- In CAD, the pathophysiology involves CA binding to RBCs at low temperature, impairing microcirculation. In severe cases, it activates complement via the classical pathway, promoting extravascular hemolysis and, in some cases, MAC-mediated intravascular hemolysis.
- Patients often have fatigue, anemia, and cold-induced circulatory symptoms; most require systemic treatment; rituximab remains commonly used, but responses are limited and often short-lived.
- Sutimlimab selectively inhibits C1s and showed rapid and sustained benefit in the **CADENZA study**, with increased Hb, fast inhibition of hemolysis, and meaningful improvements in PROs in patients with or without prior RBC transfusion.
- *Post-hoc* CADENZA data analysis showed consistent efficacy after prior rituximab, suggesting that previous rituximab exposure does not reduce response to sutimlimab in CAD patients.
- Relapse may occur after discontinuing sutimlimab, highlighting the importance of ongoing therapy or exploring new treatment options such as BTKi, novel complement inhibitors, cytokine inhibitors, plasma cell-directed therapies, and anti-BCMA T-cell engagers.

Pathophysiology in CAD

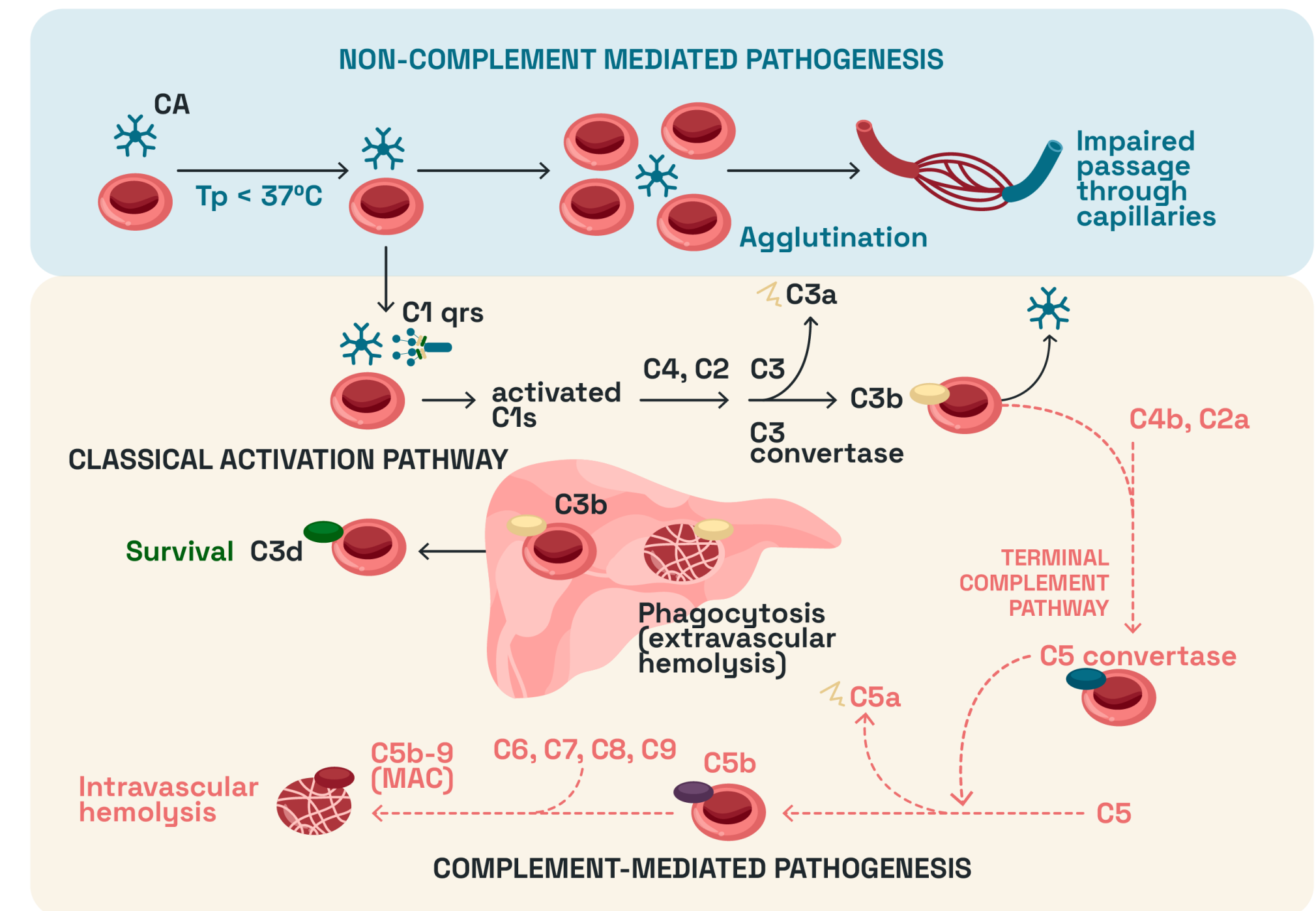


Figure 6.3 At low temperatures, CA binds RBCs, impairing microcirculation. In severe disease, it activates complement via the classical pathway, promoting C3b deposition, extravascular hemolysis, and, in some cases, MAC-mediated intravascular hemolysis. Figure adapted from Berentsen S. *Hematology Am Soc Hematol Educ Program*. 2025;2025(1):295-304. CA, cold agglutinin; MAC, membrane attack complex.

BCMA, B-cell maturation antigen; BTKi, Bruton's tyrosine kinase inhibitor; CA, cold agglutinin; CAD, cold agglutinin disease; C1s, complement component 1s; Hb, hemoglobin; MAC, membrane attack complex; PROs, patient-reported outcomes; RBCs, red blood cells.

Figure adapted from Berentsen S. *Hematology Am Soc Hematol Educ Program*. 2025;2025(1):295-304.

Berentsen S. Cold agglutinin disease (CAD) and anti-complement therapies. Oral presentation p105-2 at EHA2026.

Michel M. Sutimlimab in patients with cold agglutinin disease and prior rituximab exposure: a post-hoc analysis of the phase 3 CADENZA study. Poster PS1952 at EHA2026.

p105-3/PS2373: Role of complement in driving post-transfusion HHS in SCD

- SCD is characterized by chronic hemolysis that requires regular RBC transfusions, which can trigger DHTR, especially in alloimmunized patients.
- DHTR can progress to HHS due to the rapid destruction of both transfused and native RBCs, leading to Hb levels falling below pre-transfusion levels.
- Degradation products such as Hb, heme, and RBC fragments from hemolysis can activate the complement system via C3, triggering the alternative pathway and exacerbating vascular and tissue injury.
- A study examined the effects of Factor B inhibition (iptacopan), C5 blockade (BB5.1), and combined inhibition in an HbSS mouse model.
- Dual inhibition provided the most comprehensive suppression of complement-mediated injury, underscoring the role of complement activation in acute VOC injury.

Heme-induced complement-mediated lysis of RBCs

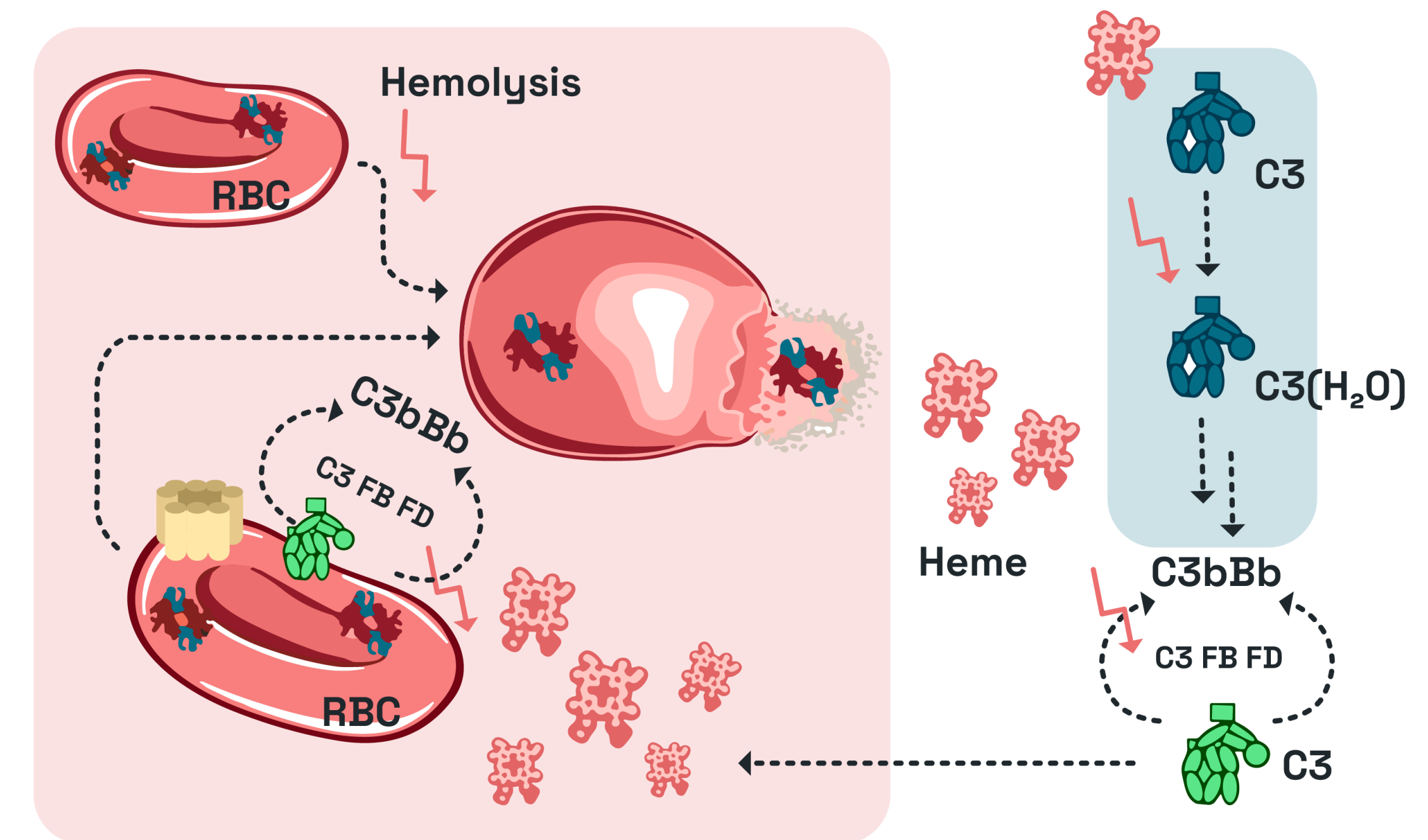


Figure 6.4 adapted from Merle NS, et al. *Transfusion Clinique et Biologique*. 2019;26(2):116-124 and reproduced courtesy of Dr. Lubka Roumenina.

C3(H₂O), hydrolyzed C3; C5, complement 5; DHTR, delayed-type hemolytic transfusion reaction; FB, factor B; FD, factor D; Hb, hemoglobin; HbSS, homozygous sickle hemoglobin; HHS, hyperhemolytic syndrome; RBCs, red blood cells; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Figure adapted from Merle NS, et al. *Transfusion Clinique et Biologique*. 2019;26(2):116-124 and reproduced courtesy of Dr. Lubka Roumenina.

Pirenne F. Hyperhemolytic syndrome: Risk factors and management in sickle cell disease. Oral presentation p105-3 at EHA2026.

Maciel TT. Targeting the complement alternative pathway attenuates acute vaso-occlusive crisis in sickle cell disease. Poster PS2373 at EHA2026.

07

Bleeding disorders: from replacing to balancing



Section 7: Bleeding disorders: from replacing to balancing

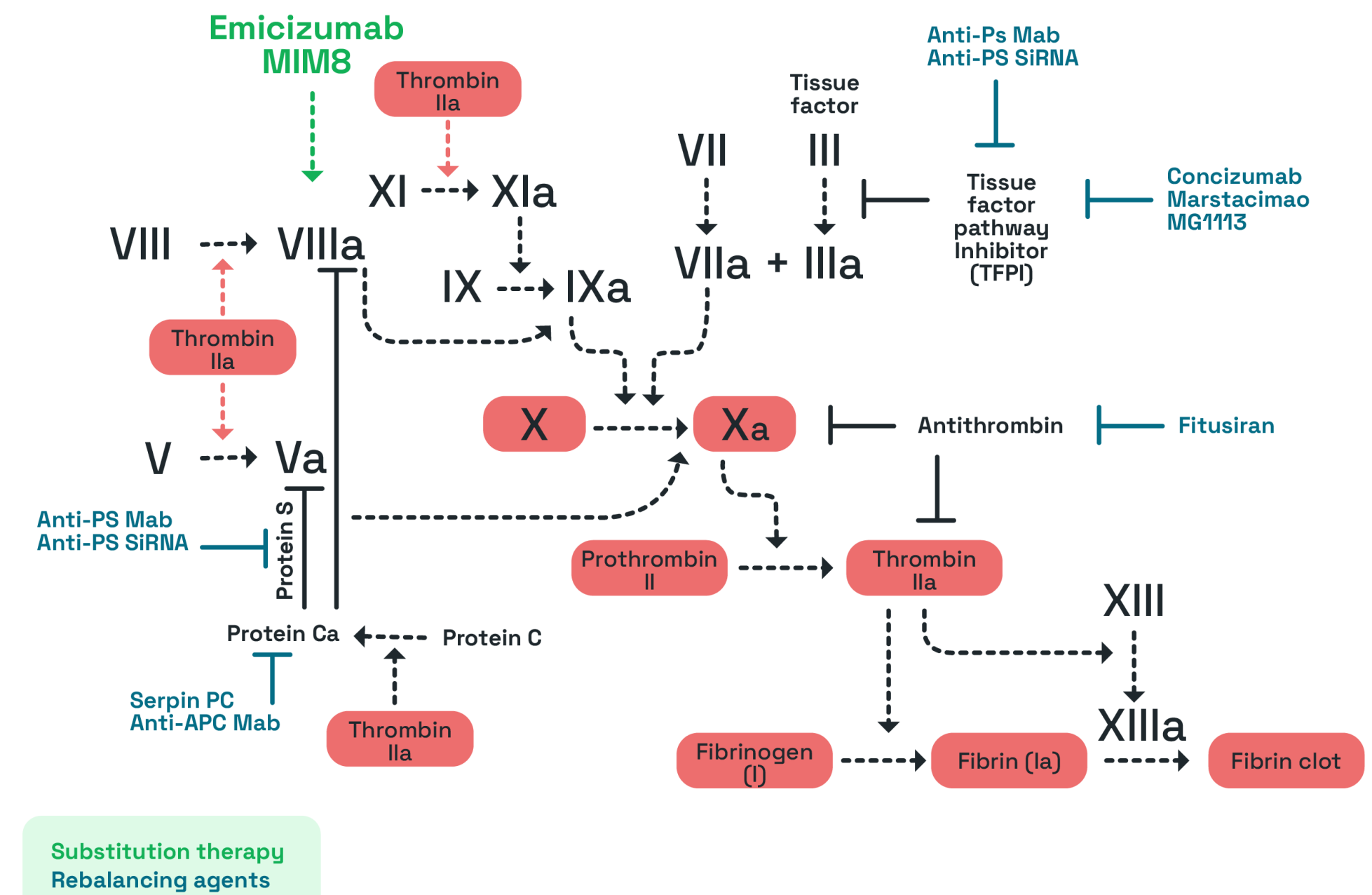
Overview of selected presentations

Presentation ID	Presentation Title	Presenter
P202-3	Future of hemophilia care	P. Chowdary
PF1359	Matching-adjusted indirect comparison of RIX-FP versus marstacimab for the prophylaxis of severe hemophilia B	B. Guillet
PF1365	Eliciting expert recommendations on the dosing of factor replacement therapy with marstacimab for breakthrough bleeding & perioperative situations in haemophilia: Interim results of a delphi study	H.K. Kim
P141-2	Translating Genetic Innovation into Hemophilia Care	W. Miesbach
PS2461	Evolving treatment priorities in hemophilia: Physician and patient perspectives on convenience, quality of life, and the emerging role of rebalancing agents across the US and EU5	S. Hendry
S332	Heavy menstrual bleeding in mild-to-moderate bleeding disorders: Investigating prevalence and risk-factors using machine learning	T. Dreier
LB5003	BCMA CAR-T cell therapy induces comprehensive immune resetting and durable remission in refractory Primary immune thrombocytopenia	J. Shu

p202-3/PF1359: Hemophilia: current challenges and opportunities

- Severe hemophilia can lead to frequent bleeding, joint damage, and disability.
- Factor replacement remains central to hemophilia care, but regular IV prophylaxis creates a high treatment burden despite options with factors with extended half-life.
- Non-factor therapies are transforming care through SC administration and mechanisms beyond direct factor replacement
- **Substitution therapy** includes factor mimetics, such as emicizumab, that substitute FVIII function and reduce bleeding and treatment complexity in hemophilia A.
- **Rebalancing agents** reduce natural anticoagulants such as AT, TFPI, protein C, or protein S and may benefit both hemophilia A and B.
- Approved rebalancing agents include fitusiran, concizumab, and marstacimab, although thrombosis risk remains an important safety consideration.
- MAIC data suggested lower bleeding rates with rIX-FP than marstacimab in severe hemophilia B previously treated with FIX prophylaxis.
- Extending rIX-FP dosing from 7 to 14 days may reduce administration burden while maintaining strong prophylactic efficacy.

Hemophilia novel therapeutics



Adapted from: Young, G. HemaSphere 7(6):p e911, June 2023.

EHA THINKING THURSDAY

AT, antithrombin; EHA, European Hematology Association; FIX, Factor IX; FVIII, Factor VIII; IV, intravenous; MAIC, matching-adjusted indirect comparison; rIX-FP, recombinant Factor IX albumin fusion protein; SC, subcutaneous; TFPI, tissue factor pathway inhibitor.
Figure adapted from Young G. *Hemasphere*. 2023;7(6):e911.
Chowdary P. Future of hemophilia care. Oral presentation p202-3 at EHA2026.
Guillet B. Matching-adjusted indirect comparison of rIX-FP versus marstacimab for the prophylaxis of severe hemophilia B. Poster PF1359 at EHA2026.

Figure 7.1 Substitution therapy replaces deficient clotting activity by mimicking FVIII activity, while rebalancing agents enhance thrombin generation by inhibiting natural anticoagulant pathways such as antithrombin, TFPI, protein C, or protein S. Figure from EHA Thinking Thursdays (adapted from Young G. *Hemasphere*. 2023;7(6):e911). APC, activated protein C; mAb, monoclonal antibody; siRNA, small interfering RNA; TFPI, tissue factor pathway inhibitor.

p202-3/PF1365/p141-2: Non-factor therapies shift hemophilia care toward thrombin rebalancing

- Hemophilia is increasingly viewed as impaired thrombin generation, not only FVIII or FIX deficiency.
- Treatment goals are shifting from factor replacement to improving hemostatic protection through enhanced thrombin generation.
- Non-factor therapies may provide effective long-term prophylaxis with lower treatment burden.
- These agents add new management challenges, especially for BTB, surgery, and switching between therapies.
- Thrombotic risk remains a key safety concern with rebalancing approaches.
- Reported thrombotic events may result from drug-drug interactions, excessive procoagulant effects, or unmasking of baseline patient risk factors.
- An expert consensus highlighted individualized dosing strategies for BTB and surgery with marstacimab.
- Gene therapy offers a potential one-time functional cure for hemophilia, but its broader use depends on resolving key uncertainties around response variability, durability, liver toxicity, long-term vector safety, and standardized care delivery.

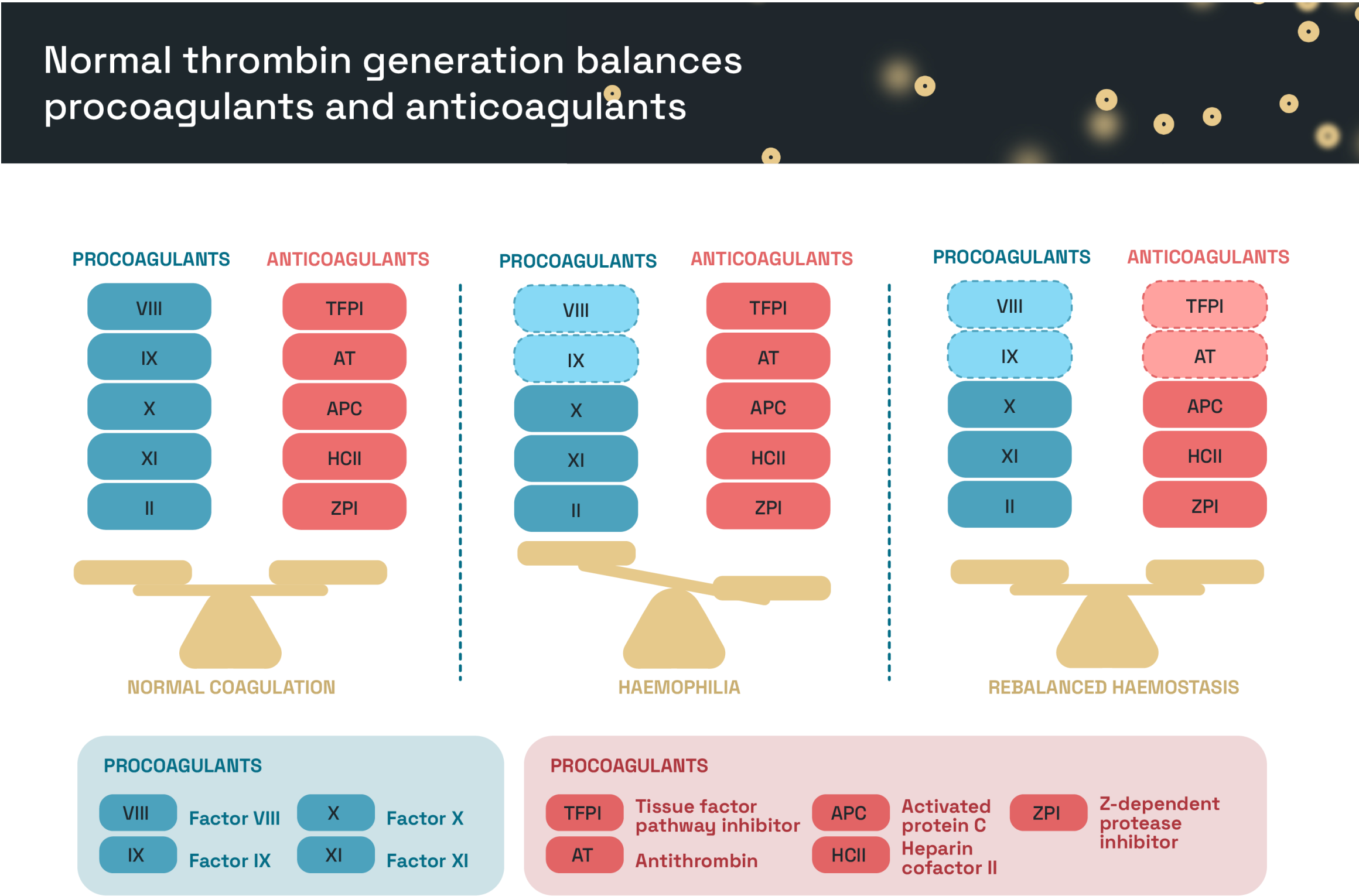


Figure 7.2 Hemophilia disrupts the balance between procoagulant and anticoagulant factors due to FVIII or FIX deficiency, and treatment aims to restore hemostasis through factor replacement, mimetics, or anticoagulant reduction. Figure adapted from Berg HM van den et al. *N Engl J Med.* 2023;389(9):853-856. APC, activated protein C; AT, antithrombin; HCII, heparin cofactor II; TFPI, tissue factor pathway inhibitor; ZPI, Z-dependent protease inhibitor; VIII, Factor VIII; IX, Factor IX; X, Factor X; XI, Factor XI; II, Factor II/prothrombin.

APC, activated protein C; AT, antithrombin; BTB, breakthrough bleed; HCII, heparin cofactor II; TFPI, tissue factor pathway inhibitor; ZPI, Z-dependent protease inhibitor; VIII, factor VIII; IX, factor IX; X, factor X; XI, factor XI; II, factor II/prothrombin.
Figure adapted from Berg HM van den et al. *N Engl J Med.* 2023;389(9):853-856.
Chowdary P. Future of hemophilia care. Oral presentation p202-3 at EHA2026.
Kim HK. Eliciting expert recommendations on the dosing of factor replacement therapy with marstacimab for breakthrough bleeding & perioperative situations in haemophilia: Interim results of a delphi study. Poster PF1365 at EHA2026.
Miesbach W. Translating Genetic Innovation into Hemophilia Care. Oral presentation p141-2 at EHA2026.

p202-3/PS2461: Personalized therapy is redefining hemophilia care

- Hemophilia care is shifting from standardized prophylaxis to personalized, patient-centered treatment.
- The key question is no longer only whether therapy prevents bleeds, but which option best fits the individual patient.
- Treatment choice should consider efficacy, lifestyle, preferences, treatment burden, adherence, and life-stage needs.
- Zero ABR is becoming the minimum standard, with the broader goal of near-normal daily life.
- Treatment burden reflects the balance between care-related workload and the patient's capacity to manage it.
- Physicians increasingly rank dosing frequency, route of administration, and adherence alongside efficacy.
- Shared decision-making is essential as more therapies, including rebalancing agents, become available.
- New assessment tools are needed to capture quality of life, convenience, mental well-being, and real-world treatment impact.

Balancing life and treatment burden in hemophilia

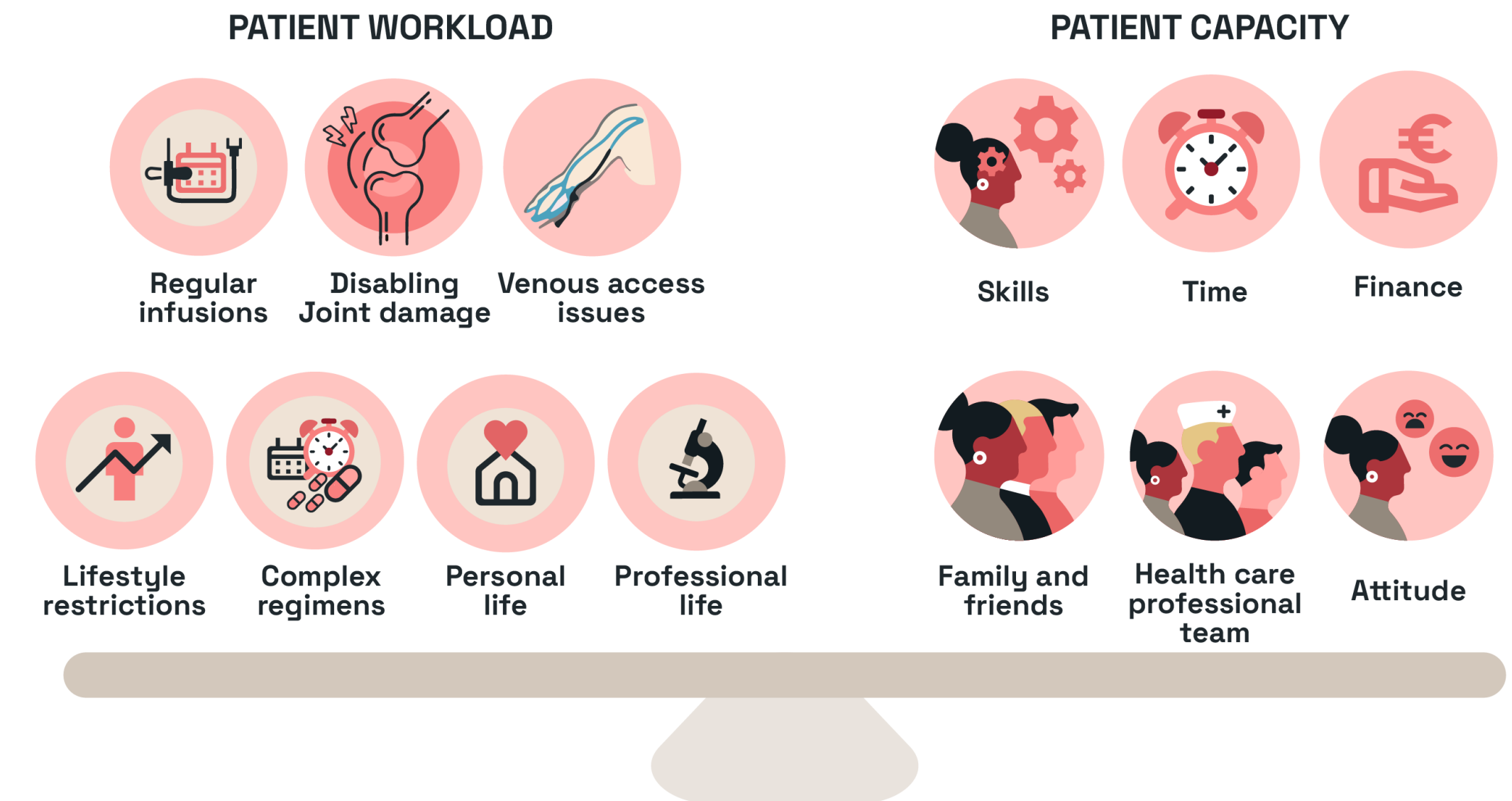


Figure 7.3 Treatment burden in hemophilia reflects the balance between care-related workload and a patient's capacity to manage these demands. Figure adapted/reproduced with permission from Chowdary.

ABR, annualized bleeding rate.

Chowdary P. Future of hemophilia care. Oral presentation p202-3 at EHA2026.

Hendry S. Evolving treatment priorities in hemophilia: Physician and patient perspectives on convenience, quality of life, and the emerging role of rebalancing agents across the US and EU5. Poster PS2461 at EHA2026.

08

Gene-targeted therapies of hemoglobinopathies



Section 8: Gene-targeted therapies of hemoglobinopathies

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
S102	Efficacy and safety of mitapivat in sickle cell disease: results from the global, randomized, phase 3 RISE UP trial	B. Andemariam
S290	PHASE 1/2 hibiscus kids study of etavopivat in pediatric patients with sickle cell disease: safety and efficacy findings from the complete first cohort	B. Ogutu
S299	Etavopivat reduces transfusion requirements in adults and adolescents with transfusion-dependent alpha- or beta-thalassemia: results from the open-label phase 2 gladiolus study	A. Lal
S297	Etavopivat improves hemoglobin levels in adults and adolescents with non-transfusion-dependent alpha- or beta-thalassemia: results from the open-label phase 2 gladiolus study	S. Sheth
PF1232	Durable clinical benefits with exagamlogene autotemcel for over 6 years in patients aged 12 to 35 years with sickle cell disease with recurrent vaso-occlusive crises	S. Grupp
PS2345	Durable clinical benefits with exagamlogene autotemcel for pediatric patients (5-11 years) with transfusion-dependent beta-thalassemia and sickle cell disease with recurrent vaso-occlusive crises	F. Locatelli
S288	Durable clinical benefits with RM001 (autologous HBG1/2 promoter-modified CD34+ hematopoietic stem and progenitor cells) for transfusion-dependent beta-thalassemia	H. Xu
PS2332	Ristoglogene autogetemcel treatment restored red blood cell health and function in patients with sickle cell disease, with sickling and rheology parameters comparable to sickle cell trait	P.S. Chockalingam

S102: Mitapivat raises Hb and improves function in patients with SCD

- RISE UP is a clinical trial on the safety and efficacy of mitapivat, a pyruvate kinase activator, in patients with SCD of any subtype who had Hb levels of 5.5–10.5 g/dL at screening.
- From Week 24 onwards, 40.6% of patients in the study arm and 2.9% in the control arm had an Hb level increase of at least 1 g/dL
- Markers of hemolysis decreased significantly in the study cohort (mean indirect bilirubin decrease: 16%)
- VOC trend was positive but not statistically significant (2.62 vs. 3.05 events per year, $P=0.1213$).
- The treatment was well tolerated; rates of adverse events and treatment discontinuations were similar between study and control arms.

Hemoglobin response to mitapivat and placebo in the RISE UP trial

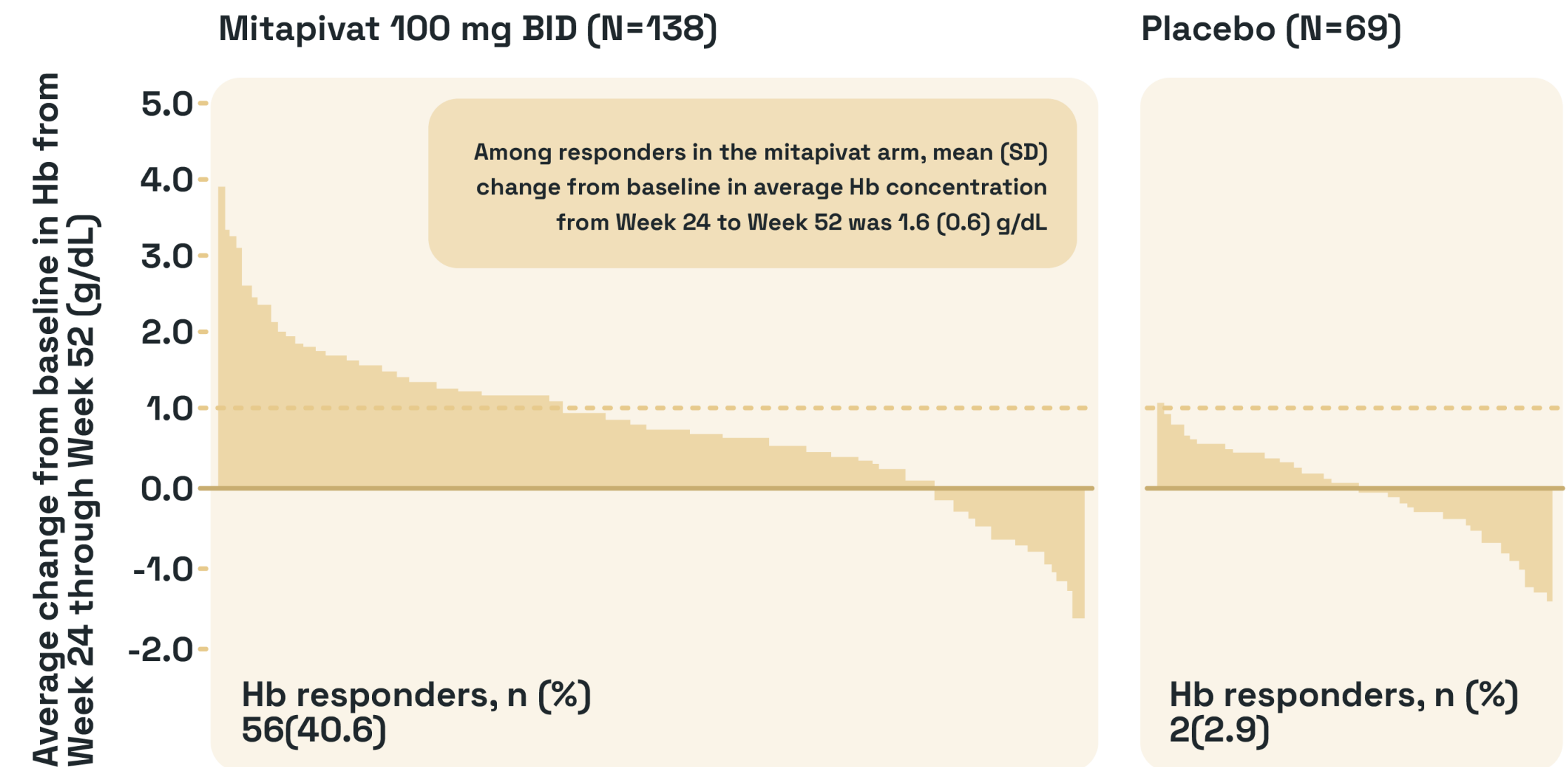


Figure 8.1 Reproduced with permission from Andemariam. BID, twice daily; Hb, hemoglobin; SD, standard deviation.

Hb, hemoglobin; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Andemariam B. Efficacy and safety of mitapivat in sickle cell disease: results from the global, randomized, phase 3 RISE UP trial. Oral presentation S102 at EHA2026.

S299/S297/S290: Etavopivat improves Hb levels and decreases need for transfusion in patients in α/β -thalassemia and SCD

- The GLADIOLUS study tested etavopivat in adult and adolescent patients with SCD (Cohort A), and transfusion-dependent (Cohort B), and independent thalassemia patients (Cohort C).
- Cohort B:
 - 89% of patients achieved $\geq 20\%$ reduction, and 79% achieved $\geq 33\%$ reduction over any 12-week period under treatment.
 - No significant change to serum ferritin and LIC levels.
- Cohort C:
 - Hb increase ≥ 1 g/dL in 50% of participants at week 12 and in 37.5% at week 48
 - Significant improvement of markers for ineffective erythropoiesis
- The treatment was generally well tolerated in both cohorts, but liver-related AEs should be noted.
- HIBISCUS KIDS enrolled pediatric patients aged 12-17 with severe SCD who had Hb levels of 5.5-10.5 g/dL.
 - Mean Hb increase of 1.46 g/dL at Week 2 and 1.37 g/dL at Week 24;
 - 20% decrease in VOCs normalized over time
 - Sustained improvements in hemolysis markers.

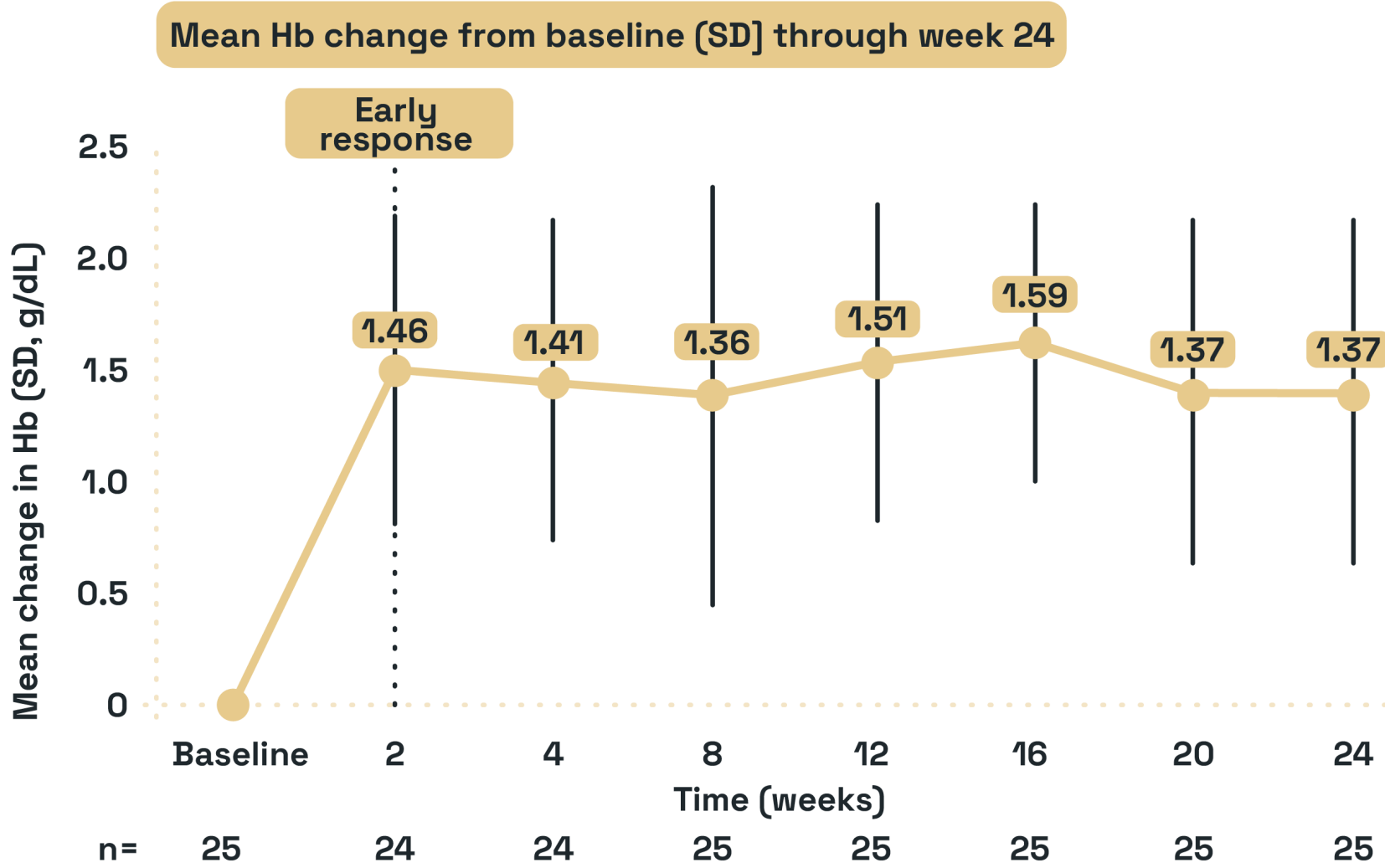
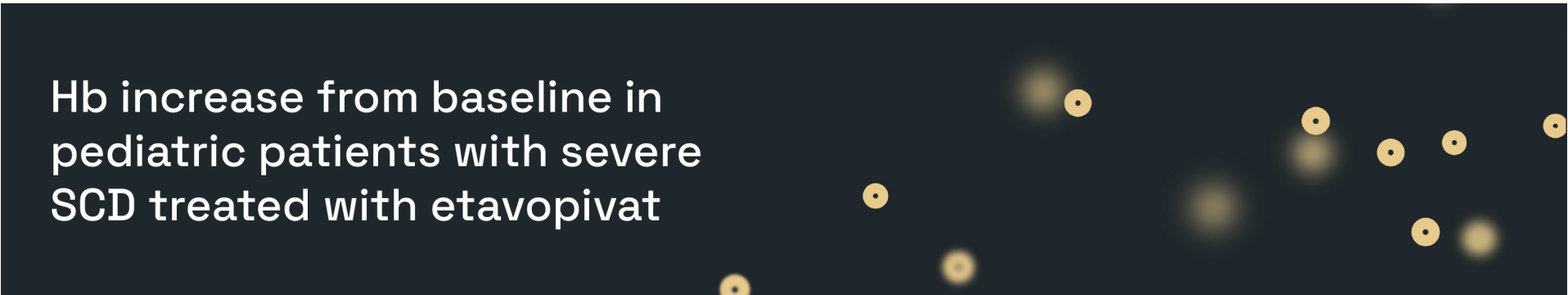


Figure 8.2 Reproduced with permission from Ogutu. Hb, hemoglobin; SD, standard deviation.

AE, adverse event; Hb, hemoglobin; LIC, liver iron concentration; RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Lal A. Etavopivat reduces transfusion requirements in adults and adolescents with transfusion-dependent alpha- or beta-thalassemia: results from the open-label phase 2 gladiolus study. Oral presentation S299 at EHA2026.
Sheth S. Etavopivat improves hemoglobin levels in adults and adolescents with non-transfusion-dependent alpha- or beta-thalassemia: results from the open-label phase 2 gladiolus study. Oral presentation S297 et EHA2026.
Ogutu B. PHASE 1/2 hibiscus kids study of etavopivat in pediatric patients with sickle cell disease: safety and efficacy findings from the complete first cohort. Oral presentation S290 et EHA2026.

PF1232/PS2345: Exagamglogene autotemcel (exa-cel): CRISPR-Cas9-based gene therapy for patients with SCD and β -TDT

- Exa-cel is a non-viral, CRISPR-Cas9-based drug for ex vivo CD34+ autologous stem cell editing, which permanently reactivates HbF expression
- CLIMB SCD-121/131 trials (N=46): patients ≥ 12 years with SCD
 - After treatment, ~40% HbF in peripheral blood
 - Freedom from VOC and VOC-related hospitalization in 100% of evaluable patients
- CLIMB SCD-151 (N=11): patients with SCD aged 5–11
 - Of 8 evaluable patients, all achieved freedom from VOC and VOC-related hospitalization for at least 12 months
 - Hb level normalization, hemolysis markers, and AE consistent with the adult and adolescent cohorts in CLIMB SCD-121/131
- CLIMB THAL-141 (N=15): patients with TDT aged 5–11 years
 - Transfusion independence rates >90% among participants following treatment
- Across CLIMB trials, AEs were mostly related to busulfan conditioning; one patient each died due to infection in CLIMB SCD-121 and CLIMB THAL-141; no malignancies occurred during follow-up

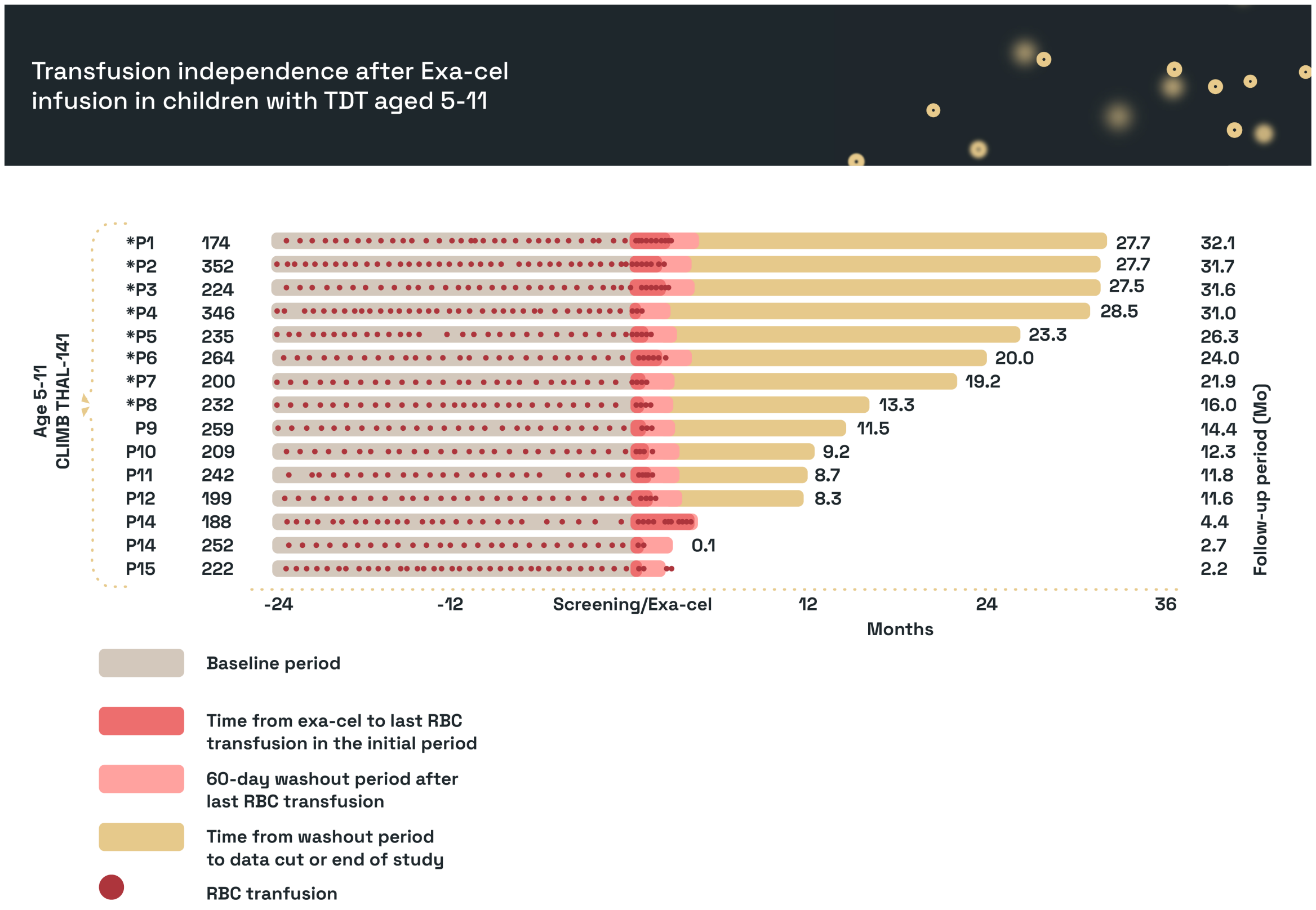


Figure 8.3 Figure reproduced with permission from Locatelli. RBC, red blood cell; TDT, transfusion-dependent β -thalassemia.

AE, adverse event; HbF, fetal hemoglobin; SCD, sickle cell disease; VOC, TDT, transfusion-dependent β -thalassemia; vaso-occlusive crisis.

Grupp S, et al. Durable clinical benefits with exagamglogene autotemcel for over 6 years in patients aged 12 to 35 years with sickle cell disease with recurrent vaso-occlusive crises. Poster presentation PF1232 at EHA2026.
Locatelli F. Durable clinical benefits with exagamglogene autotemcel for pediatric patients (5-11 years) with transfusion-dependent β -thalassemia and sickle cell disease with recurrent vaso-occlusive crises. Poster presentation PS2345 at EHA2026.

S288/PS2332: Long-term benefits in TDT and SCD with novel gene therapies

- RM001 is a cell therapy based on CRISPR-Cas9 modification of autologous CD34+ HSC and progenitor cells for permanent HbF expression
 - Across three trials in patients with TDT (IIT, Phase 1, Phase 2; N=47), total Hb and iron metabolism normalized in all patients (to 12.2 g/dL in Phase 2)
 - High level of on-target editing, no detectable off-target editing at tested sites
- Ristoglogene autogetemcel uses base editing to induce permanent HbF reactivation in CD34+ HSCs and RBC progenitors
 - Phase 1/2 BEACON trial investigates risto-cel in patients with severe SCD aged 12–35 (N=44)
 - One month after risto-cel treatment >98% of non-transfused patient RBCs expressed HbF at a mean level of 63.5%
 - Blood rheology markers (percentage of dense RBC, point of sickling) improved substantially; hemolysis markers normalized in all patients
- For both treatments, safety results were consistent with busulfan conditioning; no deaths were reported in the follow-up periods

Durable and sustainable HbF expression in patients post RM001 infusion

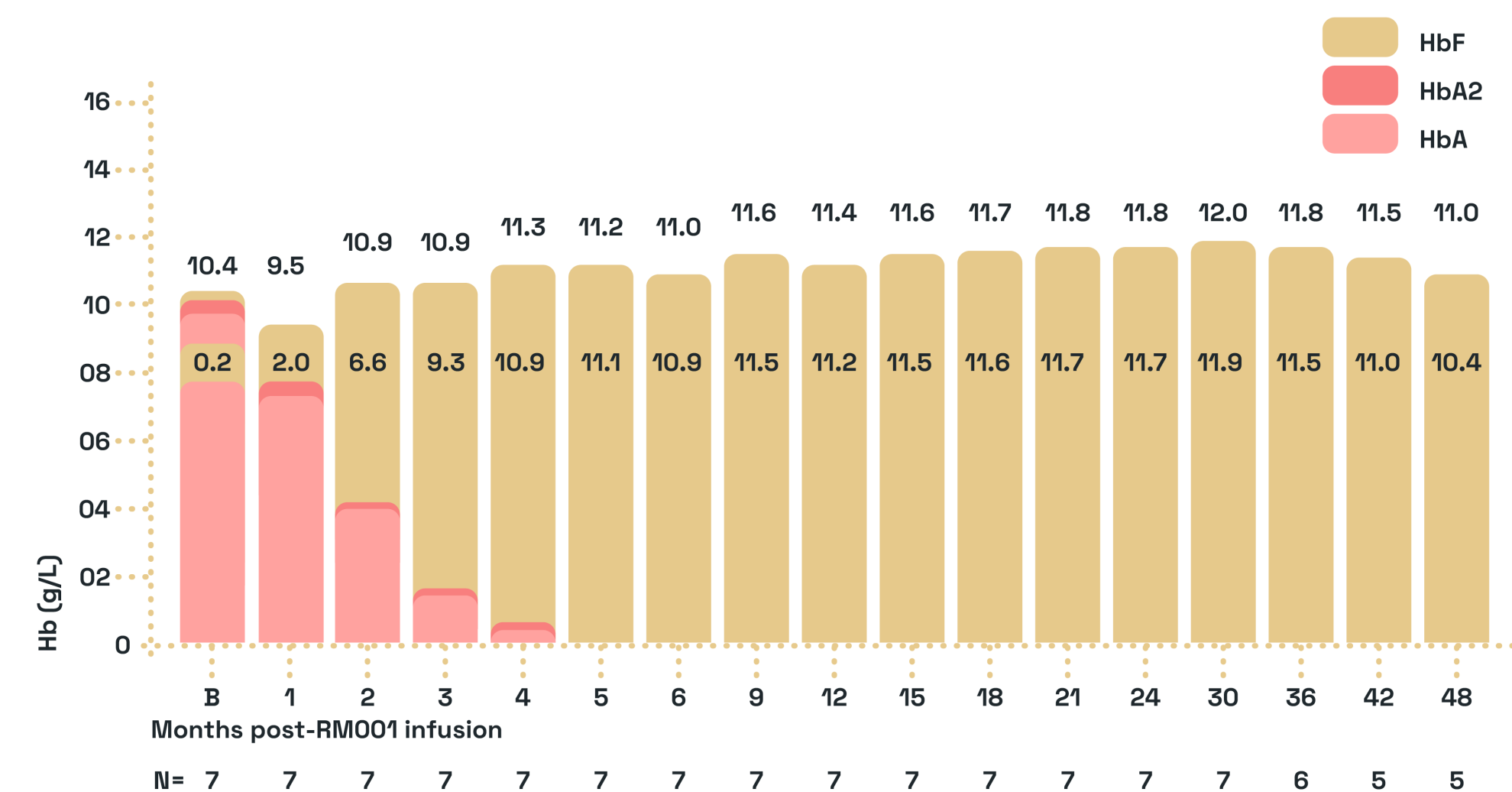


Figure 8.4 Reproduced with permission from Xu.

AE, adverse event; auto-HSCT, autologous hematopoietic stem cell transplantation; Hb, hemoglobin; HbF, fetal hemoglobin; HSC, hematopoietic stem cell; RBC, red blood cell; SCD, sickle cell disease; TDT, transfusion-dependent β -thalassemia.
Xu H. Durable clinical benefits with RM001 (autologous HBG1/2 promoter-modified CD34+ hematopoietic stem and progenitor cells) for transfusion-dependent β -thalassemia. Oral presentation S288 at EHA2026.
Chockalingam PS, et al., ristoglogene autogetemcel treatment restored red blood cell health and function in patients with sickle cell disease, with sickling and rheology parameters comparable to sickle cell trait. Poster presentation PS2332 at EHA2026.

09

HSC: the lifelong
importance of the
niche in health and
disease



Section 9: HSC: the lifelong importance of the niche in health and disease

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
P272-4	The leukemic niche	C. Lo Celso
P191-4	Regulation of hematopoietic stem cells quiescence and proliferation by the bone marrow niche during regeneration	T.C. Luis
P152-1	Regeneration and ageing in the niche	M.C. Florian
P193-2	Perturbation of leukemic stem cell states reveals a TGFβ-driven niche remodeling program in AML	K. Prummel
P105-2	Engineered BM niches	A. Garcia-Garcia
P272-2	Engineering the stem cell microenvironment	P. Bourguine

p272-4: HSC–bone marrow niche dynamics in stress

- HSCs sustain lifelong blood and immune cell production through self-renewal and multilineage differentiation. HSC's function is regulated by specialized BM niches, which adapt during homeostasis, infection, and malignancy.
- Cavity-wide intravital microscopy enables visualization of HSCs, megakaryocytes, leukemic cells, and immune-cell interactions within the mouse BM.
- Using this imaging technique, megakaryocytes can be visualized in the mouse BM (see figure, shown in green), including cells extending proplatelets and the rare migrating megakaryocyte after platelet depletion with activating antibodies.
- This technique was then implemented to visualize HSCs response to stress.
- **Key findings:** In malaria-induced inflammation in mice, many HSCs were lost, but a subset survived and remained functional – indicating that HSCs response to inflammatory stress is highly heterogeneous.

Images from the cavity-wide intravital microscopy of mouse BM

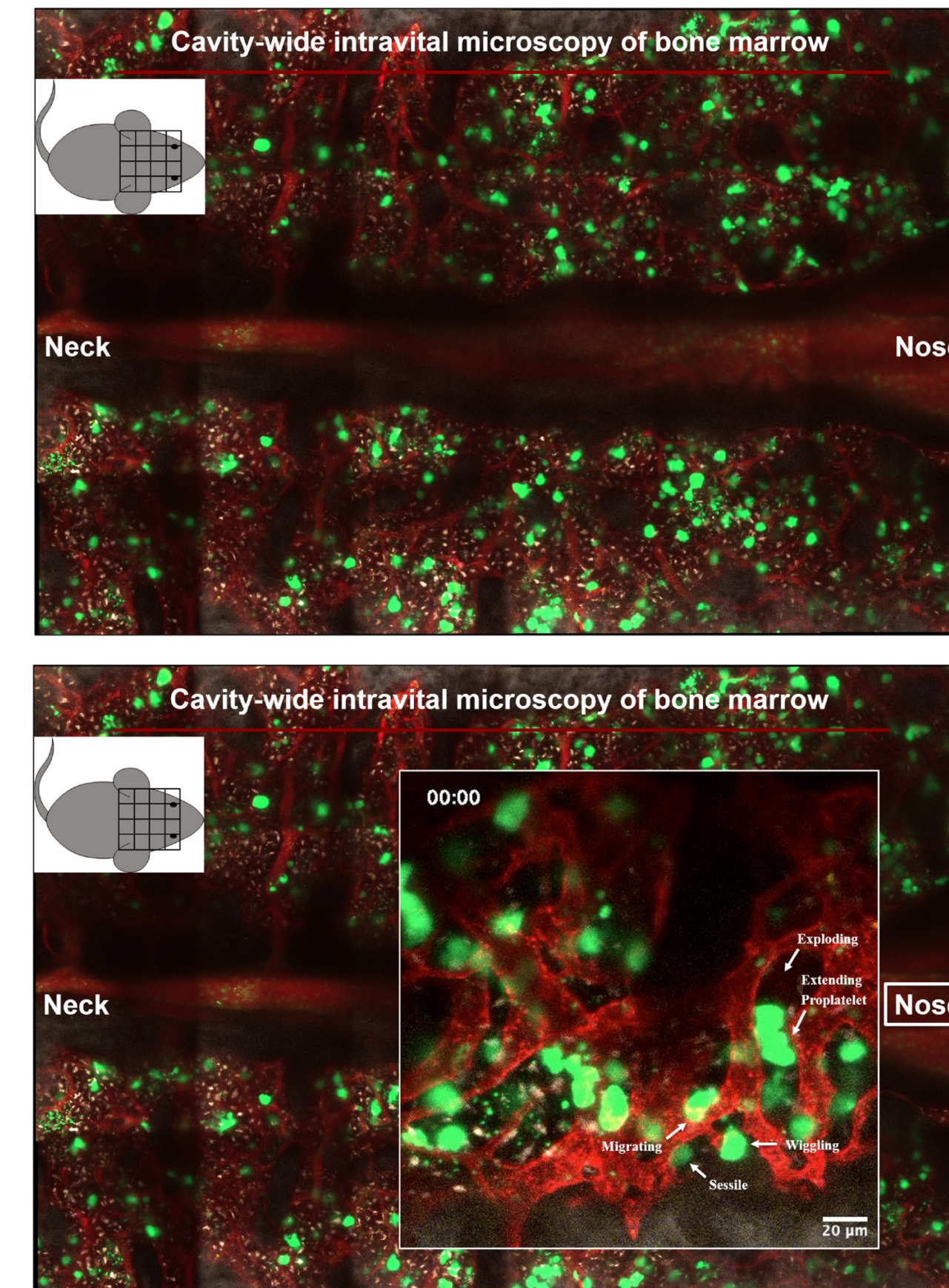


Figure 9.1 Images from the cavity-wide intravital microscopy of mouse BM. Images reproduced with permission from Lo Celso. BM, bone marrow.

p191-4/p152-1: Niche remodeling and aging of HSC

- Regulation of HSC activity
 - Hoxb5+Vwf+ HSC are immobile (non-migratory) in homeostasis and post AT within the BM, even when highly proliferating.
- Regeneration and aging in the BM Niche
 - Notch signaling activation is not homogeneous in the HSC pool, and it is triggered by sinusoidal expression of the Notch ligand Jag2.
 - With aging, reduced Jag2 expression in the niche lowers Notch activity; HSC then upregulate Jag2, causing *cis*-inhibition of Notch signaling.¹
 - This switch promotes expansion of myeloid-biased HSC and reduces hematopoietic regeneration.

Key results from young vs. aged mice in relation to Jag2, sinusoid, and Notch activity

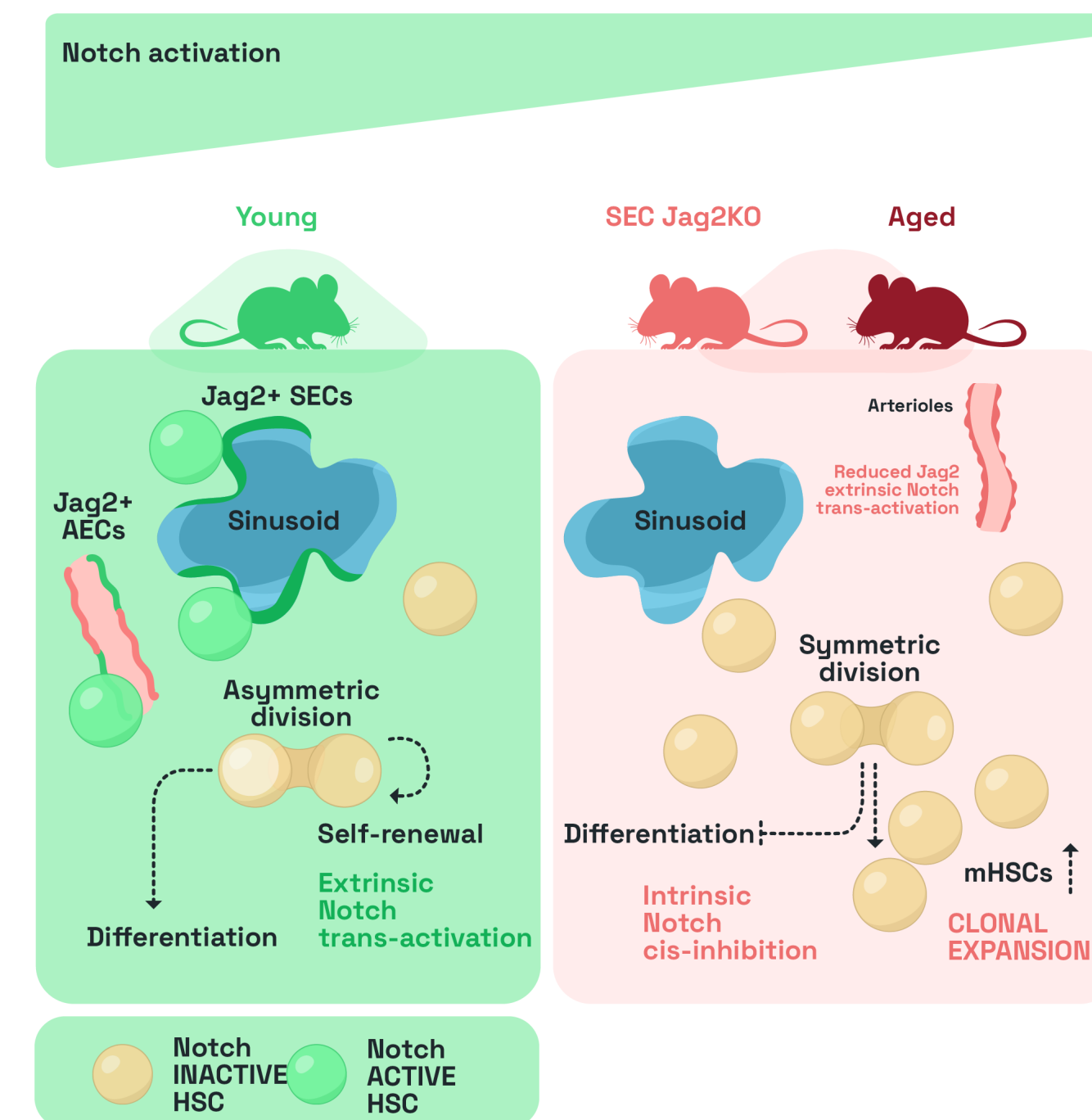


Figure 9.2 Reduction of BM Jag2 expression at sinusoids decreases Notch activity, whereupon HSC themselves upregulate Jag2, which *cis*-inhibits Notch signaling, resulting in the expansion of myeloid HSC. Figure adapted/reproduced with permission from Matteini. mHSC, myeloid hematopoietic stem cells.

AT, acute thrombocytopenia; BM, bone marrow; HSC, hematopoietic stem cells; Jag2, jagged2; mHSCs, myeloid hematopoietic stem cells.

1. Matteini F, et al. A Notch trans-activation to cis-inhibition switch underlies hematopoietic stem cell aging. *Blood*. 2026;147(2):164-179.

Luis TC. Regulation of hematopoietic stem cells quiescence and proliferation by the bone marrow niche during regeneration. Oral presentation p191-4 at EHA2026.

Florian MC. Regeneration and ageing in the niche. Oral presentation p152-1 at EHA2026.

p193-2: LSC and niche interactions in AML

- A model is proposed wherein the AML LSC-TGF β -CREB3L1-THBS1 axis acts as a driver of BM niche remodeling. Specifically, a subset of LSCs is proposed to secrete high levels of TGF β , which activated TGF β signaling in stromal cells, and promotes the establishment of a niche that supports AML cells maintenance and retention.
- Sustained TGF- β signaling induces a CREB3L1-dependent transcriptional program that remodels the stromal compartment towards a pro-fibrotic, THBS1-high phenotype, accompanied by altered MSC lineage commitment.

TGF β -driven niche remodelling in AML

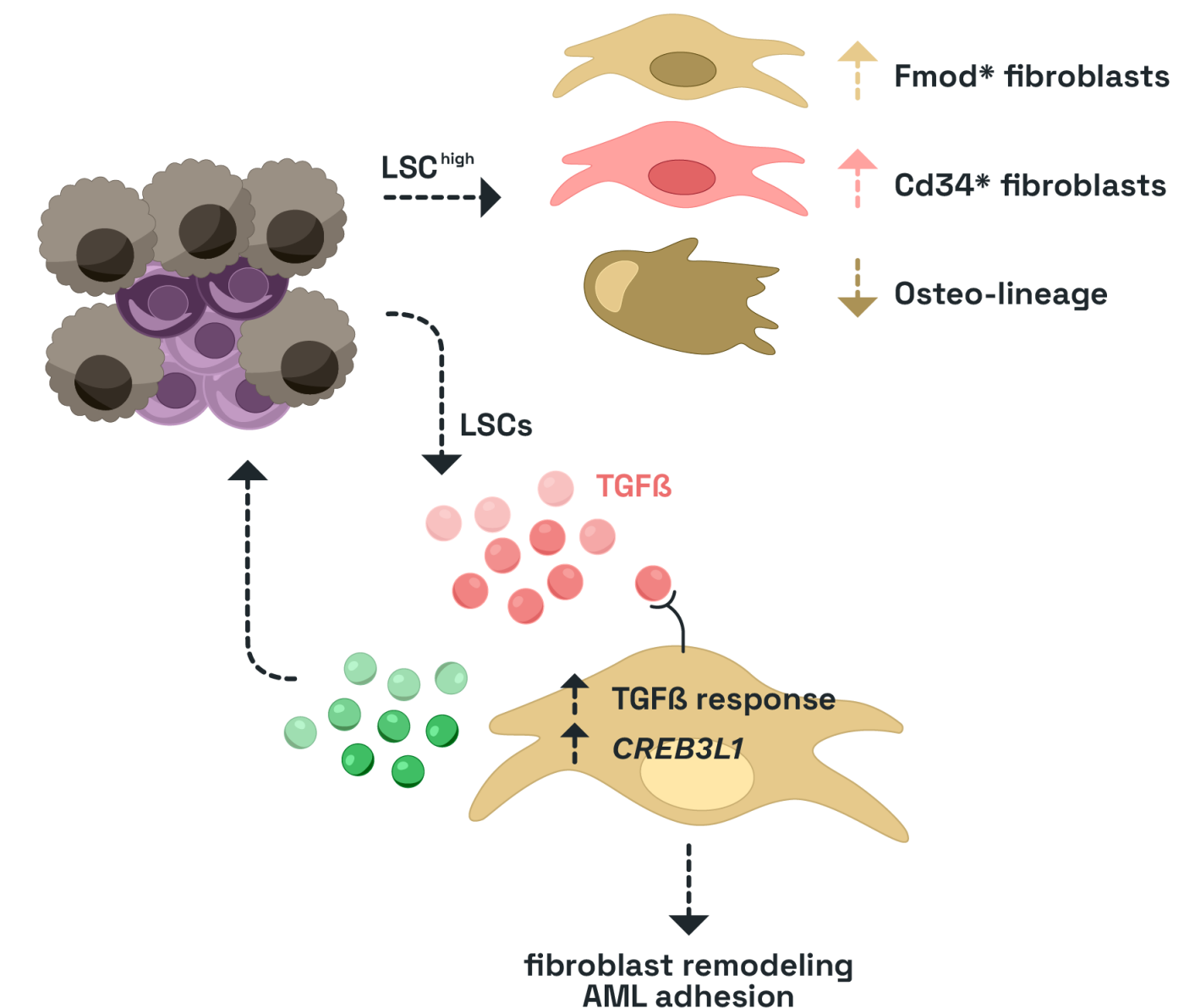


Figure 9.3 Proposed framework for LSC-TGF β -CREB3L1-THBS1 axis. Figure adapted/reproduced with permission from Prummel. AML, acute myeloid leukemia; LSC, leukemic stem cells.

p150-2/p272-2: Engineered BM niches

- Human 3D organotypic models eliminate the final implantation step of the traditional tissue engineering paradigm and are instead used as *in vitro* platforms to study human tissue biology.
- Another important feature of the platform is its ability to generate patient-specific BM niches.
 - As a proof of concept, a patient-derived niche generated from an AML sample carrying a RUNX1 mutation was used to evaluate the response to the targeted inhibitor R05-335. Whereas the patient-specific 3D niche protected AML cells from cytarabine-induced cytotoxicity, the antileukemic activity of R05-335 observed in conventional 2D cultures was not recapitulated in the 3D model.
 - These findings suggest that patient-specific organotypic BM niches may provide a more physiologically relevant platform for evaluating therapeutic responses and identifying microenvironment-mediated drug resistance.
- A separate analysis revealed that CAR-T cells preferentially homed to the hOss niche; however, the humanized niche markedly impaired CAR-T cell function and protected AML cells from CAR-T-mediated clearance (unpublished data).
- Collectively, these findings suggest that the hOss model more faithfully recapitulates the immunosuppressive human BM microenvironment than conventional murine models. As such, it represents a valuable platform for evaluating immunotherapies and investigating mechanisms of microenvironment-mediated resistance.

Engineering 3D organotypic models

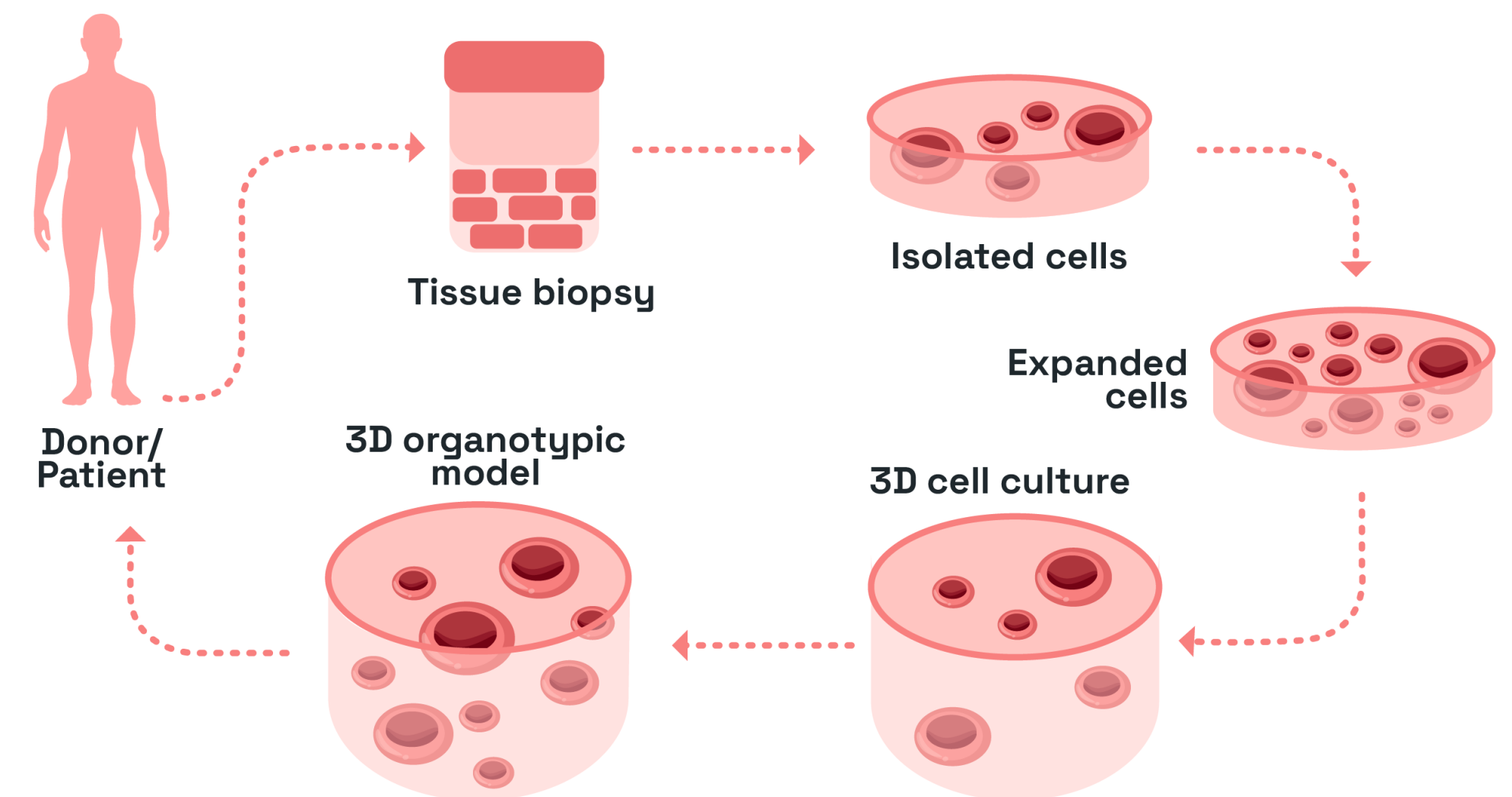


Figure 9.4 Using this method, the step of re-implanting the cellular graft back to the patient/donor is eliminated. Figure adapted/reproduced with permission from Garcia-Garcia.

10

AI real-world impact in
hematology: hype or
hope?



Section 10: AI real-world impact in hematology: hype or hope?

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
S563	Transforming diagnosis by AI? (Thematic Debate)	C. Haferlach and K. Stamatopoulos
p514	Machine learning directly in the clinic (Spotlight Talk)	C. Niemann
PF1421	Distinguishing myeloproliferative neoplasms and predicting JAK2 and CALR mutation status from bone marrow whole slide images using self-supervised vision transformers and multi-instance learning	J.-N. Eckardt
PF1427	Prediction of SF3B1 mutation from digitized bone marrow aspiration smears of myelodysplastic syndromes using supervised machine learning	T. Lanamtieng
S331	Deciphering the epigenetic landscape of mature T-cell lymphomas and leukemias: integrating ATAC-seq and machine learning for precision diagnostics	E. Julia
S334	A bimodal framework for reliable and accessible acute leukemia machine learning classification using gene expression and DNA methylation data	M.A. Lysenkova Wiklander

S563: AI real-world impact in hematology: The debate

- At EHA2026, a highly interactive and engaging debate addressed AI in hematology. Claudia Haferlach argued for the use of AI, and Kostas Stamatopoulos presented the counter arguments.

Pro-AI:

- AI can relieve hematologists of routine tasks, allowing them to focus more on complex cases.
- AI can also improve the integration of multimodal data, potentially leading to improved diagnostics and multiple. Many AI models in this context are already cleared for use in both the European Union and the United States.

Against AI:

- Various critical considerations and risks include geopolitical and economic inequalities in AI research and development, as well as AI acting as a “black box” with a lack of transparency, which need to be considered.

In conclusion, the speakers on either side of the debate shared some common ground: **AI will matter and has the potential to transform diagnosis.**

- Hematologists were encouraged to approach AI with a proactive mindset, to engage, and to take small steps to incorporate it into clinical practice.

AI has already transformed diagnosis in hematology

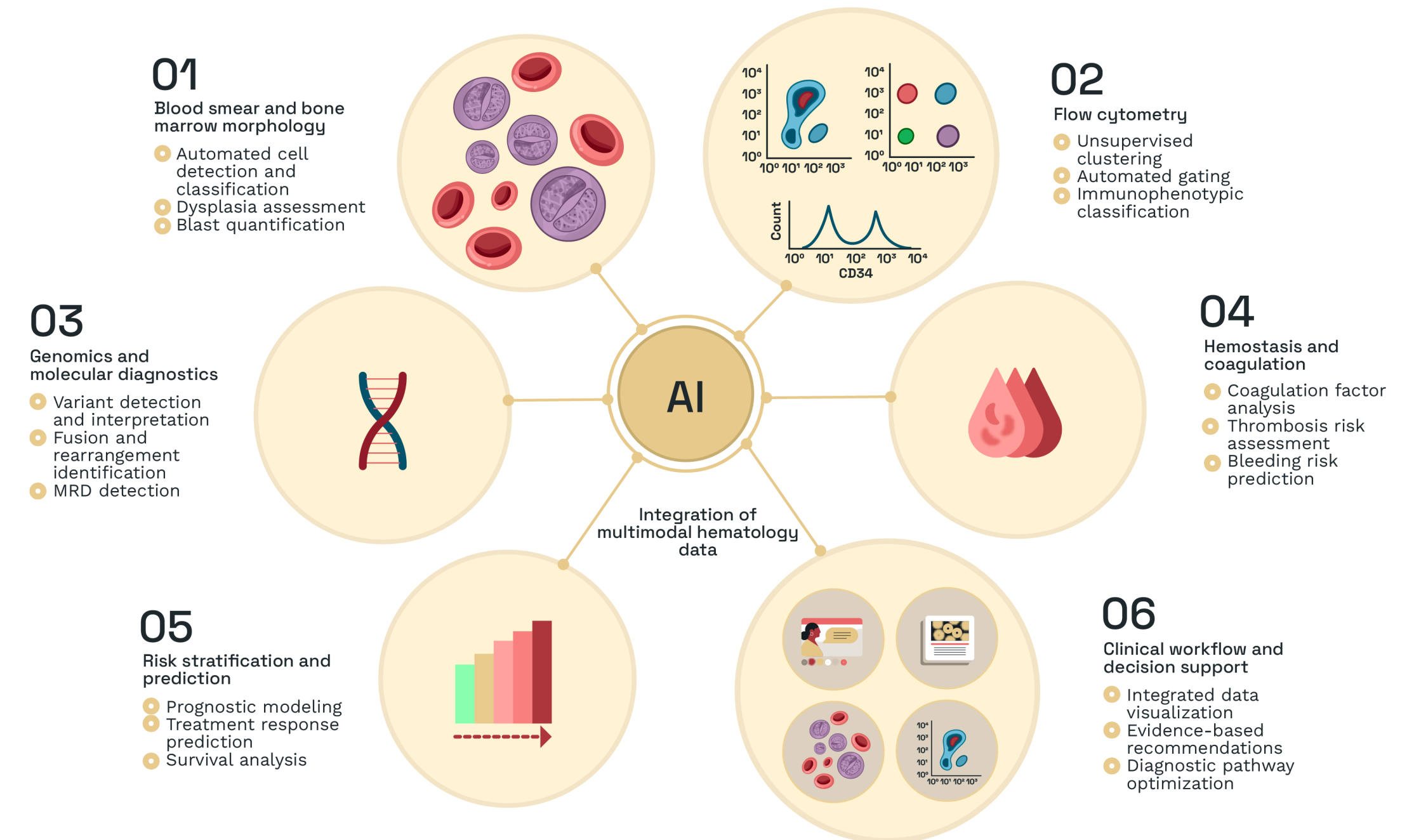


Figure 10.1 Applications of AI in hematology. Figure adapted from Haferlach. AI, artificial intelligence.

AI, artificial intelligence.

Haferlach C. Transforming diagnosis by AI? Debate S563 at EHA2026.

Stamatopoulos K. Transforming diagnosis by AI? Debate S563 at EHA2026.

p514: Machine learning directly in the clinic

- Spotlight talk: CLL-TIM, an AI-based predictive model¹
- The model was developed with the clinically relevant goal of identifying patients at risk of infection or CLL treatment within 2 years of diagnosis.
- The model development is fully data-driven and incorporates an ensemble algorithm of 28 different machine learning algorithms.
- To increase trustworthiness and explainability, it also includes a confidence estimate to indicate whether HCPs can rely on the model's prediction.
- Furthermore, it includes personalized risk factors for the individual patient, which can be used to make predictions (the physician can assess whether these matter from a clinical perspective).
- Interestingly, this model has now been deployed in the Danish electronic health record registry.

Results from CLL-TIM from its deployment in the Danish registry



Figure 10.2 Reproduced with permission from Niemann.

AI, artificial intelligence; CLL-TIM, chronic lymphocytic leukemia treatment-infection model; HCP, healthcare professional.

1. Agius R, et al. Machine learning can identify newly diagnosed patients with CLL at high risk of infection. *Nat Commun.* 2020;11:363.

Niemann C. Machine learning directly in the clinic. Oral presentation p514 at EHA2026.

S334/PF1427: AI in hematology: Specific applications

- MLOmix, an end-to-end framework for training and deploying explainable machine learning models was developed using GEX and array-based DNAm data.
- This framework was used to implement PALLAS, a multi-modal classifier used to predict subtypes of pediatric ALL and AML.
- *SF3B1* mutation status can be predicted with an AI-based model from digitized bone marrow aspiration smears from MDS patients using single-cell features and gradient boosting.

Workflow of development: MLOmix and PALLAS

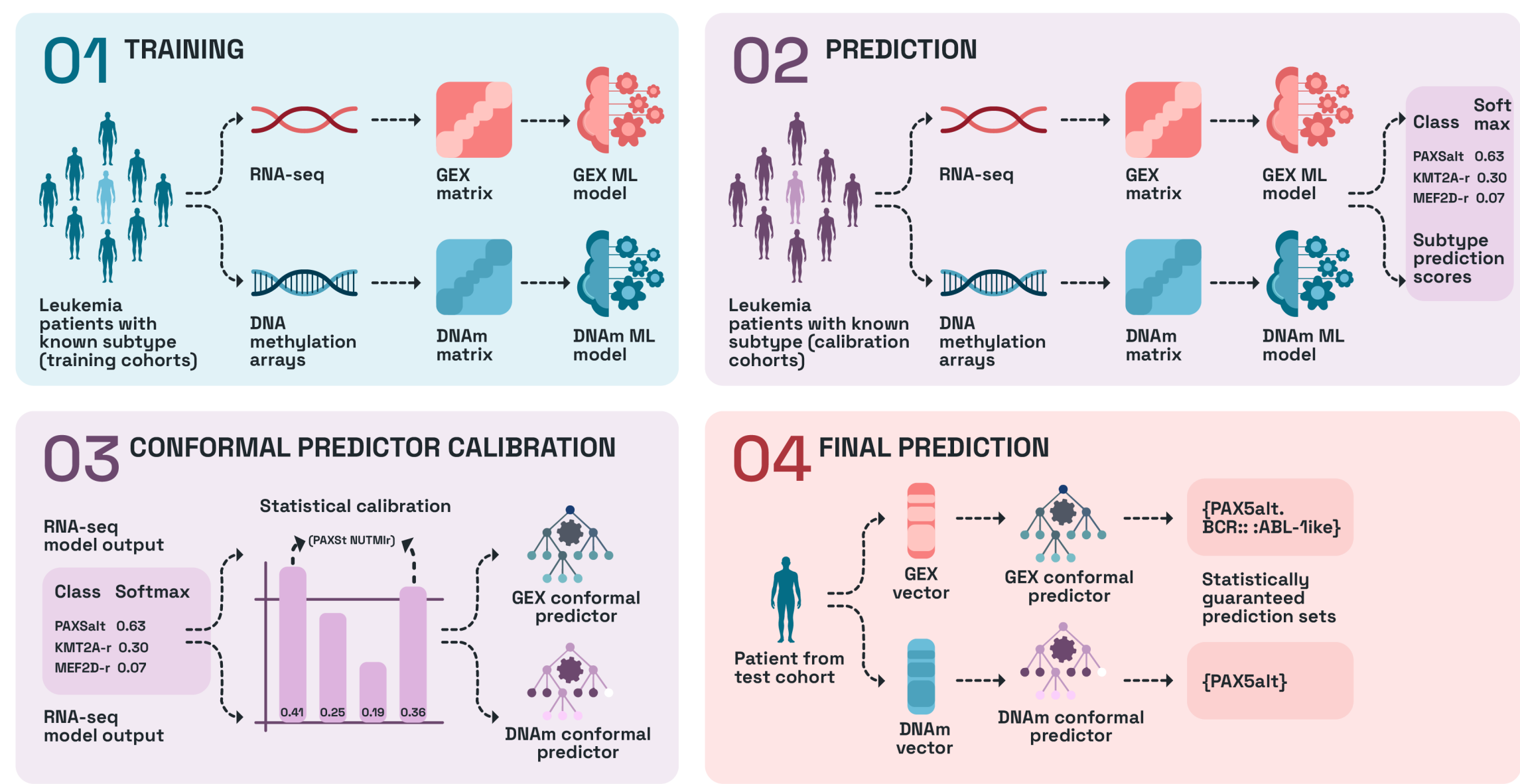


Figure 10.3 Workflow of development: MLOmix and PALLAS (pan acute leukemia learning and subtyping).15 DNAm, DNA methylation; GEX, gene expression; ML, machine learning.

AI, artificial intelligence; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; DNAm, DNA methylation; GEX, gene expression; MDS, myelodysplastic syndrome; PALLAS, pan acute leukemia learning and subtyping.
 Lysenkova Wiklander M. A bimodal framework for reliable and accessible acute leukemia machine learning classification using gene expression and DNA methylation data. Oral presentation S334 at EHA2026.
 Lanamtieng T. Prediction of SF3B1 mutation from digitized bone marrow aspiration smears of myelodysplastic syndromes using supervised machine learning. Poster presentation PF1427 at EHA2026.

S331/PF1421: AI in hematology: Specific applications

- A machine learning-based AI algorithm trained on ATAC-seq data revealed 12 clusters of epigenetic groups of lymphoid malignancies.
- Each epigenetic cluster was predominantly composed of one MTCN subtype, showing high concordance with initial pathological diagnoses.
- A deep learning-based AI model was able to accurately differentiate between PV, ET, and PMF based on bone marrow smear image data alone.

Results from the machine learning algorithm and ATAC-seq for MTCN clustering

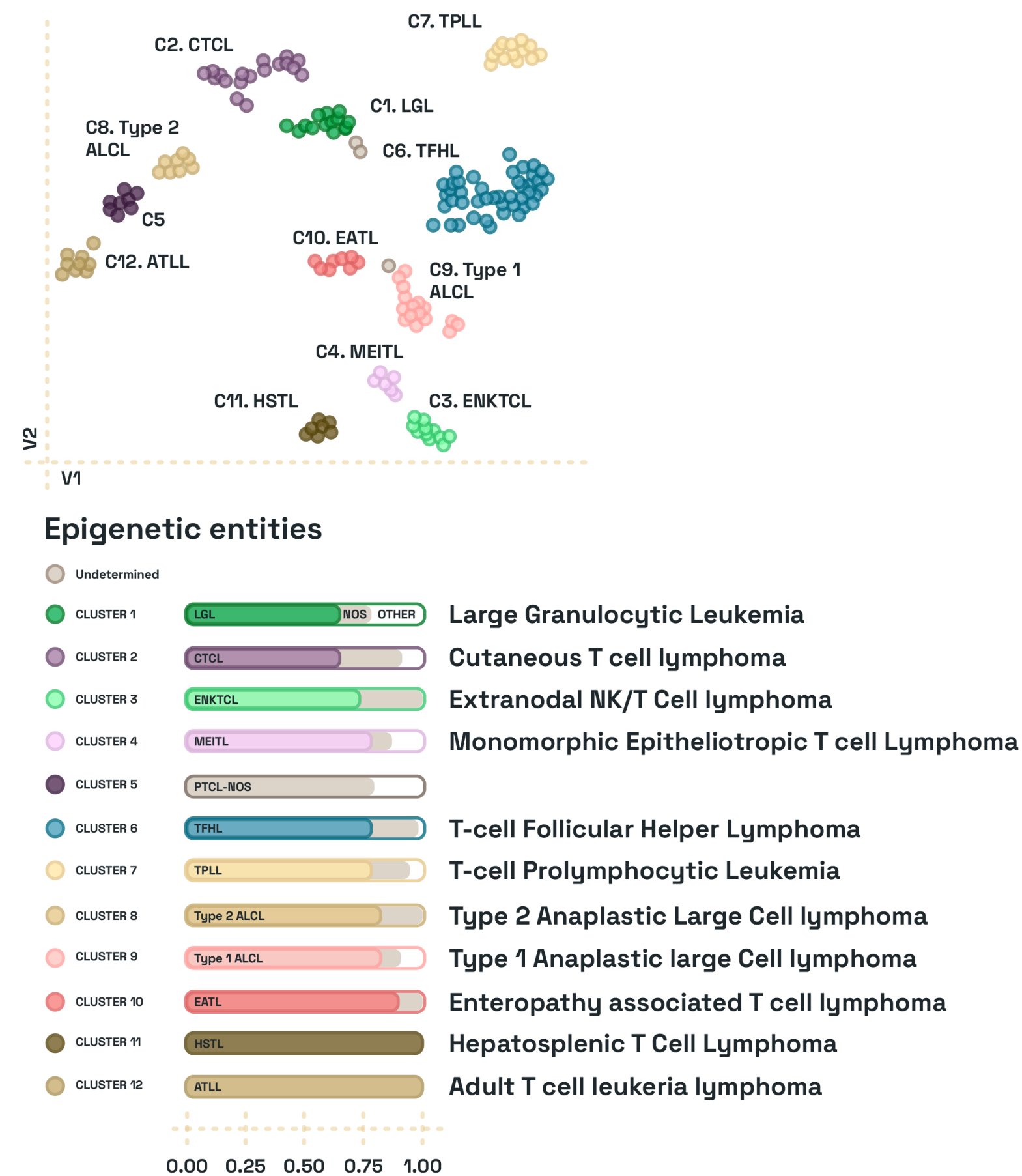


Figure 10.4 Results showed epigenetic groups highly concordant with initial pathological diagnoses. Figure adapted/reproduced with permission from Julia. ATAC-seq, assay for transposase-accessible chromatin using sequencing; MTCN, mature T-cell neoplasm.

AI, artificial intelligence; ATAC-seq, assay for transposase-accessible chromatin using sequencing; ET, essential thrombocythemia; MTCN, mature T-cell neoplasm; PMF, primary myelofibrosis; PV, polycythemia vera.
 Eckardt J-N. Distinguishing myeloproliferative neoplasms and predicting JAK2 and CALR mutation status from bone marrow whole slide images using self-supervised vision transformers and multi-instance learning. Poster presentation PF1421 at EHA2026.
 Julia E. Deciphering the epigenetic landscape of mature T-cell lymphomas and leukemias: integrating ATAC-seq and machine learning for precision diagnostics. Oral presentation S331 at EHA2026.

EHA2026 Perspectives Congress Report. Topic and Expert information

Information on Topic and Respective Expert

Topic number	Topic name	Expert name
1	Targeted agents in AML: from induction to long-term maintenance and resistance	Prof Christoph Röllig
2	Using new agents for lymphoid neoplasms in clinical practice	Prof Anastasios Stathis
3	Multiple myeloma: navigating the what, when, and who of treatment	Dr Cyrille Touzeau
4	Toward a personalized therapeutic approach for patients with chronic myeloid malignancies	Dr Marta Sobas
5	Epigenetics in hematologic malignant (and non-malignant) diseases	Prof Ruud Delwel
6	Complement-targeted treatments in hematology	Dr Marta Morado
7	Bleeding disorders: from replacing to balancing	Dr Johannes Thaler
8	Gene-targeted treatments of hemoglobinopathies	Dr Erfan Nur
9	HSC: the lifelong importance of the niche in health and disease	Dr Simona Valletta
10	AI real-world impact in hematology: hype or hope?	Dr Marina Martello

Acknowledgements

EHA would like to extend a special thank you to the reviewers for the preparation of this report and their excellent guidance during EHA2026 in Stockholm, Sweden.



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Acknowledgements

EHA would like to extend a special thank you to the reviewers for the preparation of this report and their excellent guidance during EHA2026 in Stockholm, Sweden.



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Acknowledgements

EHA would like to extend a special thank you to the reviewers for the preparation of this report and their excellent guidance during EHA2026 in Stockholm, Sweden.



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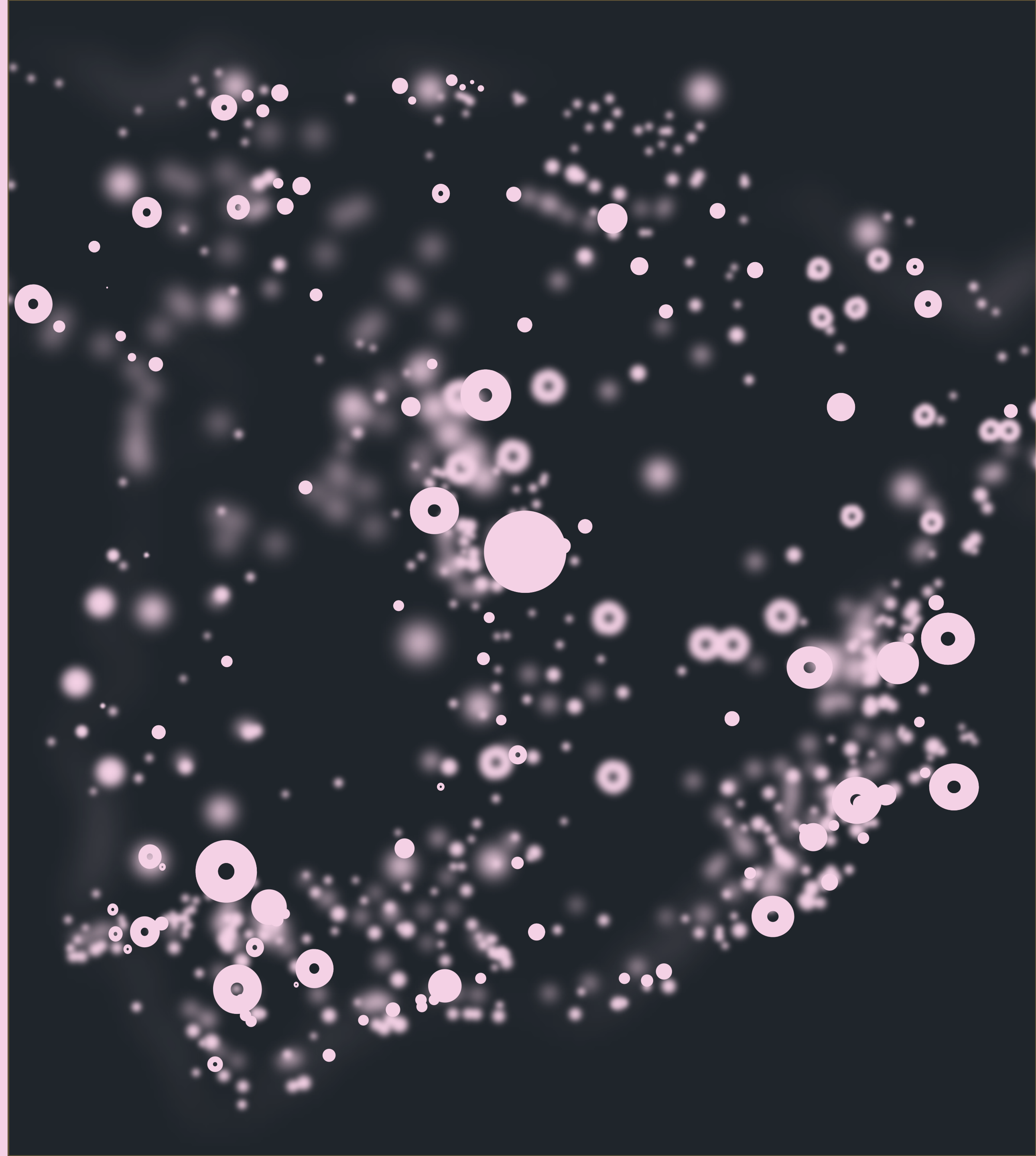
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Publisher

European Hematology Association

EHA Executive Office

Koninginnegracht 12b | 2514 AA The Hague | The Netherlands

Imprint

Production: European Hematology Association

Medical writing and editing:

infill healthcare communication GmbH

Melissa Koch, Marie Farrow, Vishal Hegde, Revati Mulay, Lisa Rusyn, and Sven Vanselow

European Hematology Association

Wilson Lim and Enrica Orsini