

LAL e LAM : DAY

Stato dell'arte delle Leucemie Acute

ED. CENTRO

31 marzo 2026 **Roma**

EVOLUZIONE DELL'ALGORITMO TERAPEUTICO DEL PAZIENTE CON LAM

Esperienza di pratica clinica nel paziente FIT a rischio favorevole

DR. SAVERIA CAPRIA

DIPARTIMENTO DI ONCOLOGIA, EMATOLOGIA E PATOLOGIA MOLECOLARE

POLICLINICO UMBERTO I- SAPIENZA UNIVERSITA' DI ROMA

Patient Profile & Baseline

OCTOBER 2025

65-year-old male, Veterinarian

Former smoker (25 cig/day)

History: 2022 incidental monocytosis/neutropenia (external follow-up)

Performance Status: ECOG 0

Donor: 25-year-old HLA-haploidentical daughter

Clinical Presentation

Presentation: Fatigue, anemia, thrombocytopenia, and leukocytosis

Labs: Hb 11.7 g/dl, WBC $36.7 \times 10^3/\mu\text{L}$, PLTS $85 \times 10^3/\mu\text{L}$

Peripheral blood Smear: 50% myeloid blasts

Diagnosis: Acute Myeloid Leukemia (AML)

Diagnostic Workup & Fitness (HU pretreatment)

Marrow Blasts: 92% (Cyтомorphology)

Immunophenotype: CD45+, CD33+, CD38+, CD117+, CD123+

Genetics: Normal male karyotype; FISH neg (KMT2a, p53)

Molecular: NPM1-mutated (NPM-A), FLT3 wild-type

Fitness: LVEF 60%; Lung Function: Within normal limits

CT scan:

- **Mucosal inflammatory changes left maxillary sinus, ipsilateral ethmoid air cells.**
- **Lungs: Subpleural and posterobasal bilateral interstitial thickening.**
- **Emphysema: Small paraseptal emphysematous bullae in the upper lobes.**
- **Colon: Sigmoid diverticulosis with no signs of active inflammation**

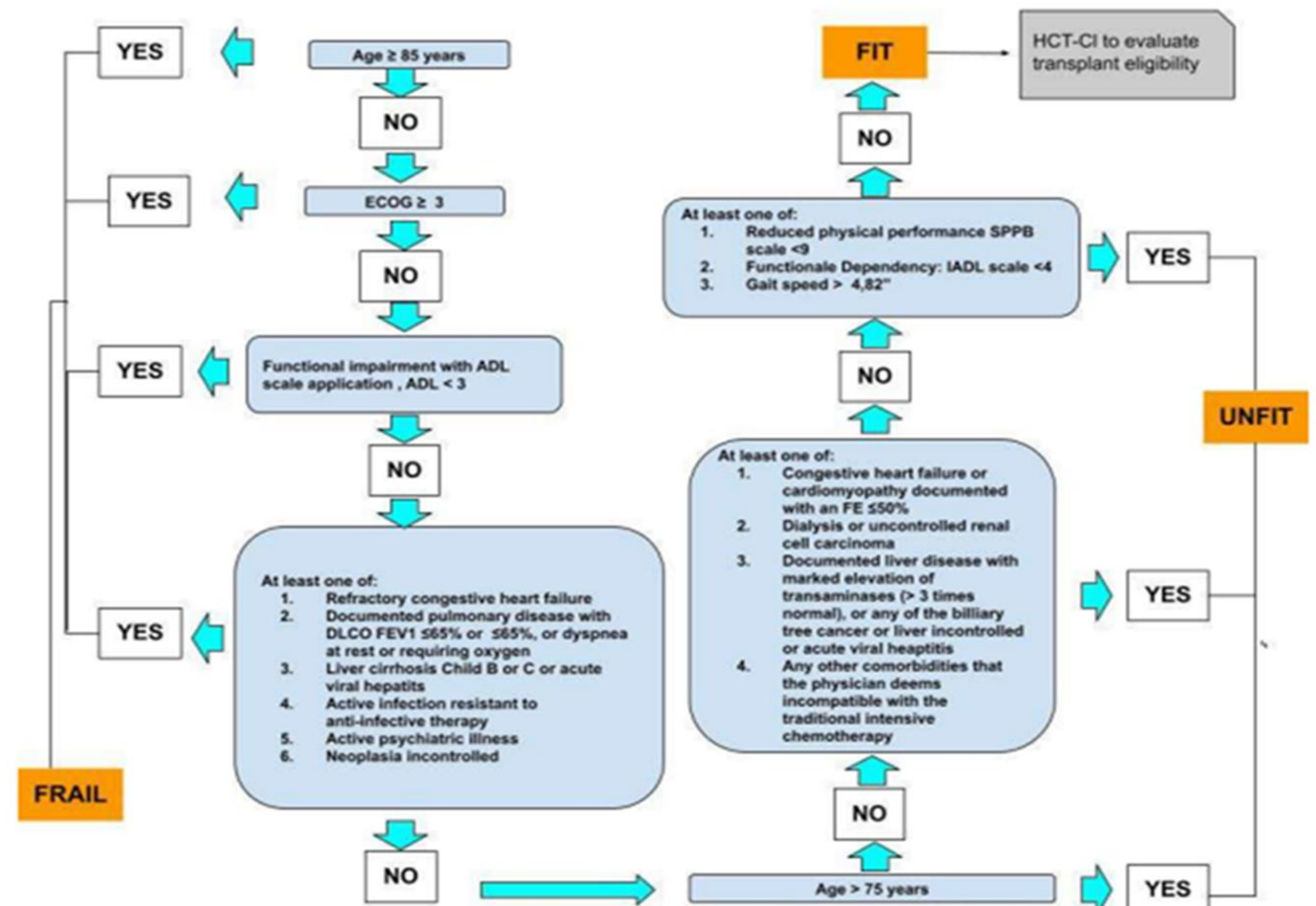
NPM1-mutated, FLT3-WT AML

ELN 2022 Risk: Favorable

Eligibility: FIT for intensive chemotherapy

Strategy: DNR-Ara-C (3+7) + Gemtuzumab Ozogamicin (GO)

Risk category†	Genetic abnormality
Favorable	- t(8;21)(q22;q22.1)/RUNX1::RUNX1T1†,‡ - inv(16)(p13.1;q22) or t(16;16)(p13.1;q22)/CBFB::MYH11†,‡ - Mutated NPM1†,§ without FLT3-ITD - bZIP in-frame mutated CEBPA
Intermediate	- Mutated NPM1†,§ with FLT3-ITD - Wild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions) - t(9;11)(p21.3;q23.3)/MLLT3::KMT2A†,¶ - Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	- t(6;9)(p23.3;q34.1)/DEK::NUP214 - t(v;11q23.3)/KMT2A-rearranged# - t(9;22)(q34.1;q11.2)/BCR::ABL1 - t(8;16)(p11.2;p13.3)/KAT6A::CREBBP - inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1) - t(3q26.2;v)/MECOM(EVI1)-rearranged −5 or del(5q); −7; −17/abn(17p) - Complex karyotype,** monosomal karyotype†† - Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2‡‡ - Mutated TP53*



Induction Phase & Complications

Regimen: DNR-Ara-C (3+7) + GO

Supportive therapy: filgrastim, acyclovir, posaconazole, TPN

D+3: Grade III/IV Hemorrhage (gingival, hematuria)

D+4: S. Aureus Sepsis (Pip/Tazo + Daptomycin)

D+27 & D+42: Febrile Neutropenia

Note: D+7 GO dose and final Ara-C dose omitted due to complications

Response Evaluation

Hematologic Recovery: ANC >0.5 (D+49), PLTS >50 (D+27)

Bone Marrow (D+55): Hematological CR; NPM-A: 51.329×10^{-4}

Consolidation & PBSC Mobilization

Consolidation: DNR/Ara-C/GO

Prophylaxis: Posaconazole, Acyclovir, Daptomycin (S. Aureus sinusopathy)

Toxicity: D+10 febrile neutropenia: Ceftazidime-Avibactam, tygecicline, gentamicin (Rectal swab: Klebsiella p. KPC+)

Mobilization: Filgrastim 10μg/kg

Collection (D+16): 4.11×10^6 CD34+/kg

Post-consolidation MRD: NPM1 4×10^{-4}

Therapeutic Strategies & Rationale

Option 1: GO-based Approach

Based on ALFA-0701 data.

Allows maintenance with oral HMA (QUAZAR trial).

Option 2: MRD-driven Strategy

Supported by GIMEMA 1310 and 1819.

Goal: Tailor Allogeneic Stem Cell Transplant (allo-SCT) based on disease clearance.

Option 3: Intensive Consolidation/Allo-SCT

Not suitable for this patient due to favorable risk and excellent molecular response.....

But Does it tell the whole story?

Core Question:

Would baseline NGS data
have altered the treatment path?

Diagnostic Impact:

Identification of MDS-associated mutations could have reclassified the case as "Secondary AML," potentially making the patient eligible for CPX-351.

CPX-351 vs daunorubicin, cytarabine, and gemtuzumab ozogamicin in older adults with non-adverse-risk AML: the NCRI AML18 trial

Knapper S. Blood, 2026

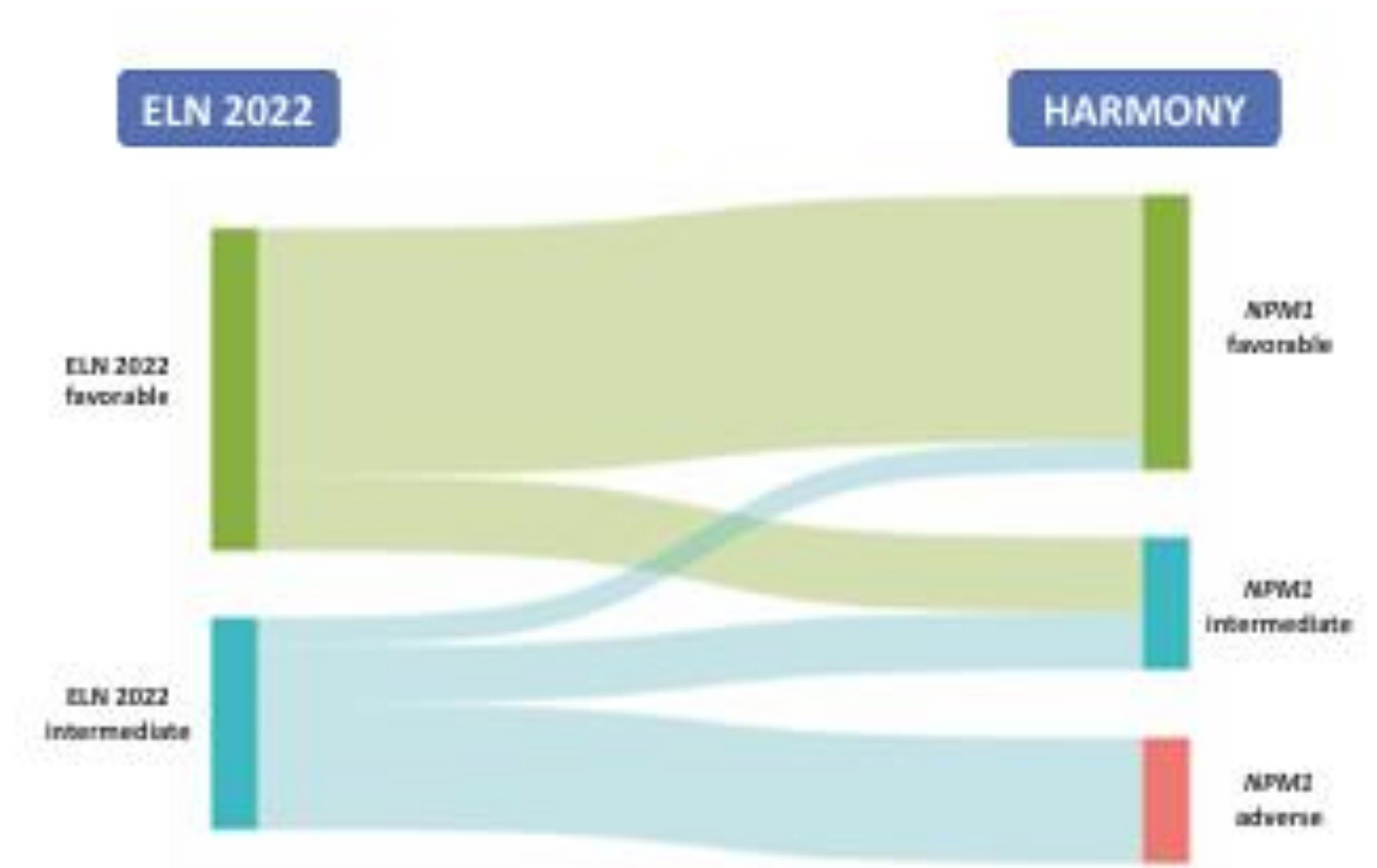
- Fit patients with AML aged >60 y without known adverse-risk cytogenetics, were randomized DA chemotherapy plus gemtuzumab against CPX-351
- Response and survival were better with DAGO, including in those patients with MDS-related mutations

Unravelling co-mutational patterns with prognostic implications in *NPM1* mutated adult acute myeloid leukemia

a HARMONY study *Hernandez-Sanchez, Leukemia 2026*

NPM1 prognosis is influenced by co-mutations (e.g., DNMT3A, FLT3, or "secondary-type" mutations).

Triple-positive status (FLT3/DNMT3A/*NPM1*) carries a significantly worse prognosis.



Added prognostic value of secondary AML-like gene mutations in ELN intermediate-risk older AML: ALFA-1200 study results

Claude Gardin,¹ Cécile Pautas,² Elise Fournier,³ Raphaël Itzykson,⁴ Emilie Lemasle,⁵ Jean-Henri Bourhis,⁶ Lionel Adès,⁴ Jean-Pierre Marolleau,⁷ Jean-Valère Malfuson,⁸ Lauris Gastaud,⁹ Emmanuel Raffoux,⁴ Juliette Lambert,¹⁰ Thorsten Braun,¹ Xavier Thomas,¹¹ Sylvain Chantepie,¹² Thomas Cluzeau,¹³ Stéphane de Botton,⁶ Céline Berthon,¹⁴ Nicolas Boissel,⁴ Nicolas Duployez,³ Christine Terré,¹⁵ Régis Peffault de Latour,⁴ Mauricette Michallet,¹¹ Karine Celli-Lebras,¹⁶ Claude Preudhomme,³ and Hervé Dombret⁴

Received: 11 May 2024 | Revised: 27 July 2024 | Accepted: 4 August 2024
DOI: 10.1002/cam4.70102

RESEARCH ARTICLE

Influence of genetic co-mutation on chemotherapeutic outcome in *NPM1*-mutated and *FLT3-ITD* wild-type AML patients

Yujiao Zhang | Baoyi Yuan | Yun Huang | Ling Jiang | Fang Liu |
Jiaying Cheng | Zhiquan Long | Xuejie Jiang

www.nature.com/leu

Check for updates

Leukemia

ARTICLE OPEN

Acute Myeloid Leukemia

Differential prognostic impact of myelodysplasia-related gene mutations in a European cohort of 4978 intensively treated AML patients

Marius Bill^{1,2,3,4,34}, Jan-Niklas Eckardt^{1,34}, Konstanze Döhner⁵, Maximilian-Alexander Röhnert¹, Christian Rausch⁶, Klaus H. Metzeler⁷, Karsten Spiekermann⁶, Sebastian Stasik¹, Alexander A. Wurm^{1,2,3,4}, Tim Sauer⁸, Sebastian Scholl⁹, Ulf Schnetzke⁹, Andreas Hochhaus⁹, Martina Crysandt¹⁰, Tim H. Brümmendorf¹⁰, Utz Krug¹¹, Bernhard Wörmann¹², Hermann Einsele¹³, Wolfgang Hiddemann⁵, Dennis Görlich¹⁴, Cristina Sauerland¹⁴, Björn Steffen¹⁵, Andreas Neubauer¹⁶, Andreas Burchert¹⁶, Kerstin Schäfer-Eckart¹⁷, Wolfgang E. Berdel¹⁸, Christoph Schliemann¹⁸, Stefan W. Krause¹⁹, Mathias Hänel²⁰, Maher Hanoun²¹, Martin Kaufmann²², Lars Fransecky²³, Jan Braess²⁴, Johannes Schetelig¹, Jan Moritz Midecke¹, Lars Bullinger¹², Michael Heuser^{25,26}, Felicitas Thol²⁶, Hubert Serve¹⁵, Claudia D. Baldus²³, Uwe Platzbecker⁷, Carsten Müller-Tidow⁸, Jan Vánka²⁷, Jiří Šrámek^{28,29}, Barbora Weinbergerova³⁰, Jiri Mayer³⁰, Pierre-Yves Dumas³¹, Sarah Bertoli³², Eric Delabesse³², Christian Récher³², Arnaud Pigneux³¹, Tobias Herold^{6,33}, Arnold Ganser²⁶, Hartmut Döhner⁵, Martin Bornhäuser^{1,2,3,4}, Christian Thiede¹ and Christoph Röllig^{1,25}

Article

The Prognostic Impact of Additional Molecular and Cytogenetic Abnormalities on AML Patients with *NPM1*- and/or *FLT3-ITD* Mutations Receiving Intensive Chemotherapy: Real-World Data from the Greek Registry

Ioanna Lazana¹, Maria Papathanassiou², Ioannis Konstantellos¹, Tatiana Tzenou³, Anastasia Kopsaftopoulou⁴, Maria Liga⁵, Vasiliki Violaki⁶, Lydia Kyriazopoulou⁷, Konstantinos Gkirkas¹, Apostolia Papalexandri², Eleni Plata⁴, Evrydiki Michalis⁸, Theoni Leonidopoulou⁹, Maria Garofalaki³, Anastasia Sioni¹⁰, Irene Tziotziou³, Chrysavgi Lalayanni², Dimitrios Kiouisiafes⁹, Theodoros P. Vassilakopoulos⁴, Eleni Kapsali⁷, Alexandros Spyridonidis⁵, Ioannis Baltadakis³, Maria Angelopoulou⁴, Ioanna Sakellari^{2,†} and Panagiotis Tsirigotis^{1,*,†}

Cancer Medicine WILEY

Mutations highly specific for secondary AML are associated with poor outcomes in ELN favorable risk *NPM1*-mutated AML

Onyee Chan,¹ Najla Al Ali,¹ Hammad Tashkandi,² Austin Ellis,² Somedeb Ball,¹ Justin Grenet,³ Caroline Hana,⁴ Yehuda Deutsch,⁴ Ling Zhang,² Mohammad Hussaini,² Jinming Song,² Seongseok Yun,¹ Chetasi Talati,¹ Andrew Kuykendall,¹ Eric Padron,¹ Alison Walker,¹ Gail Roboz,³ Pinkal Desai,³ David Sallman,¹ Kendra Sweet,¹ Rami Komrokji,¹ and Jeffrey Lancet¹

¹Department of Malignant Hematology and ²Department of Hematopathology, Moffitt Cancer Center, Tampa, FL; ³Division of Hematology and Oncology, Weill Cornell Medical College, New York, NY; and ⁴Department of Malignant Hematology and Cellular Therapy at Memorial Healthcare System, Moffitt Cancer Center, Pembroke Pines, FL

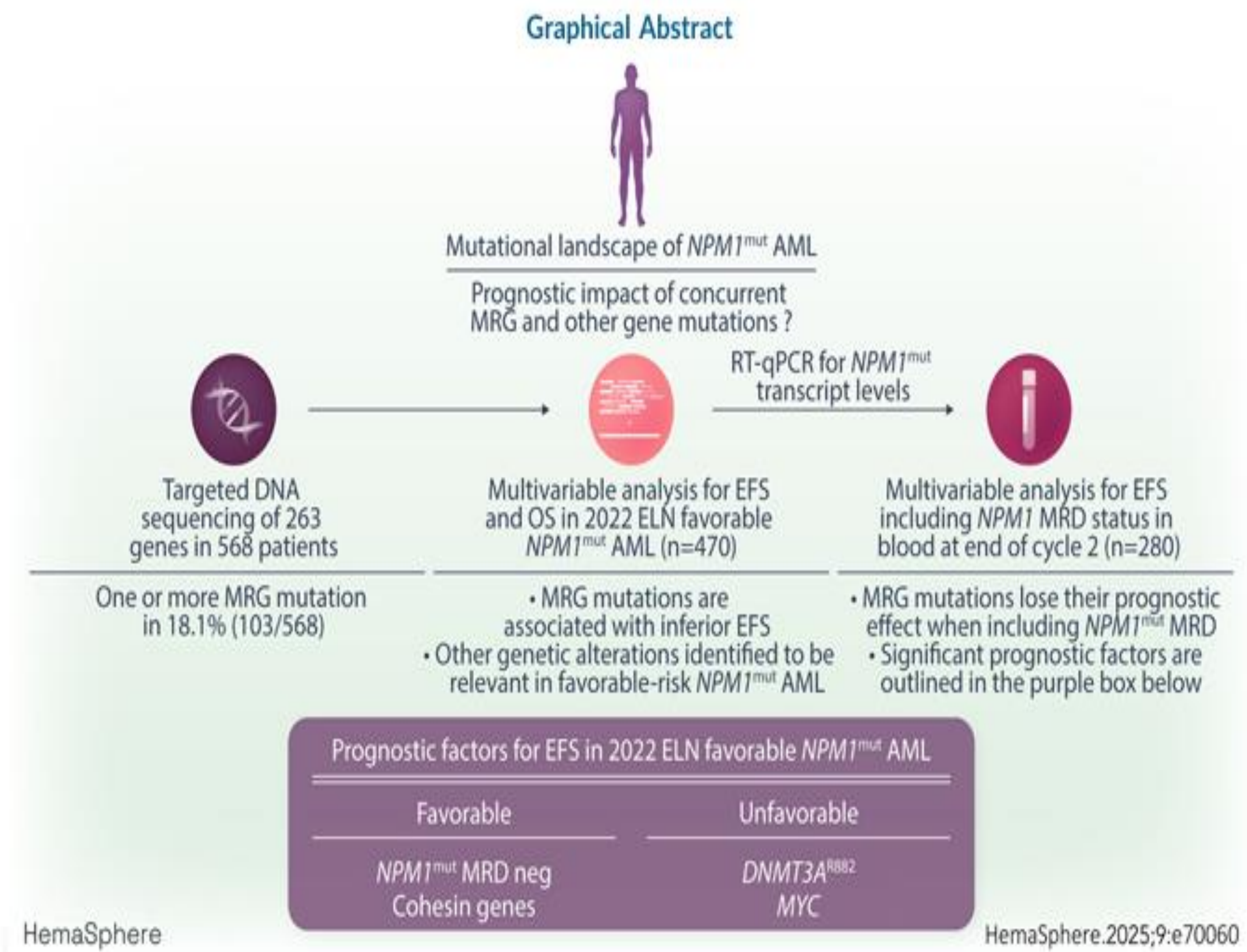
ARTICLE OPEN

Unravelling co-mutational patterns with prognostic implications in *NPM1* mutated adult acute myeloid leukemia – a HARMONY study

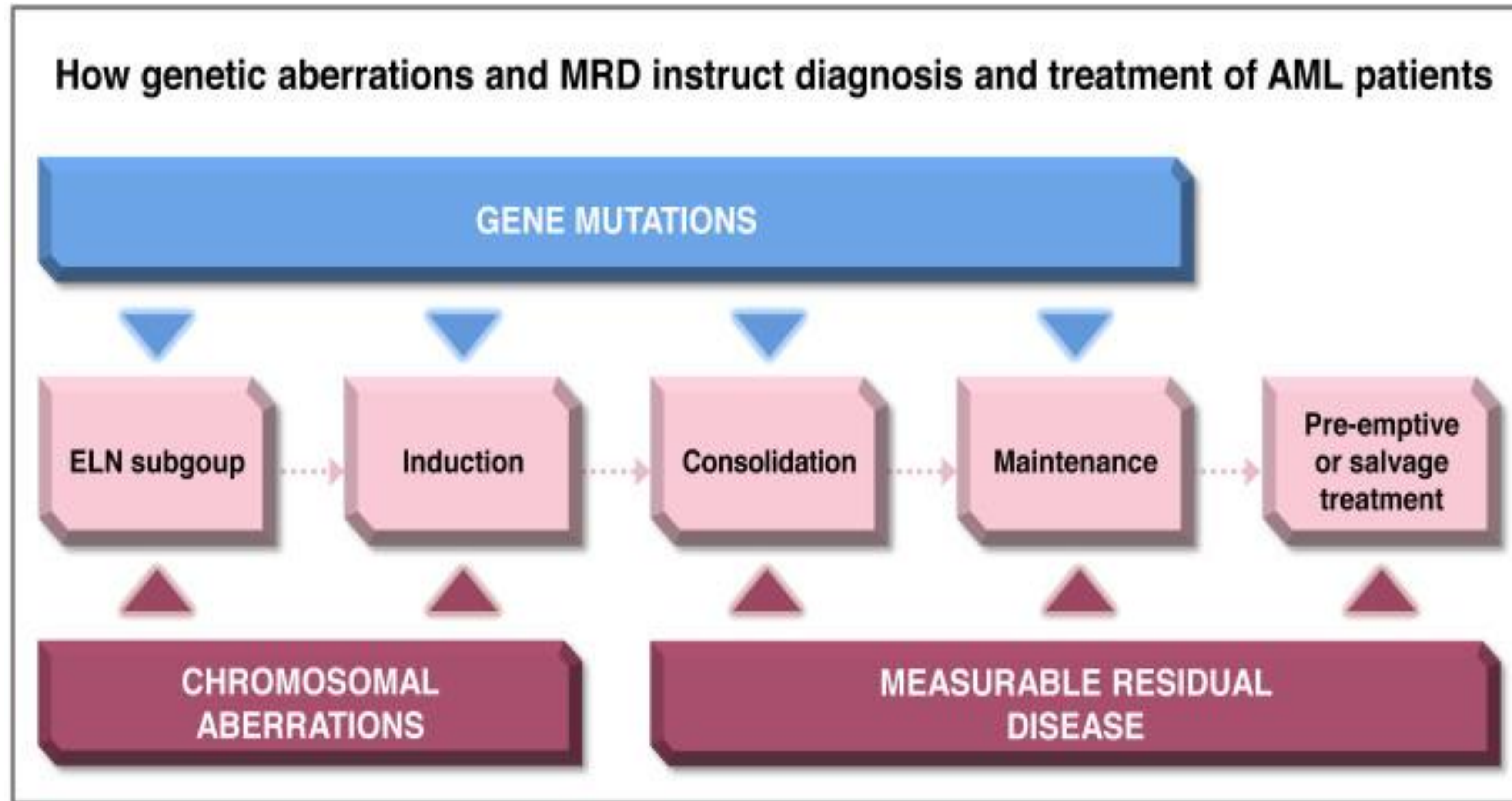
Alberto Hernández-Sánchez^{1,2,3}, Ángela Villaverde Ramiro^{2,3,4}, Eric Sträng⁵, Amin T. Turki^{6,7}, María Abáigar^{2,3,4}, Jurjen Versluis⁸, Ian Thomas⁹, Marta Sobas¹⁰, Javier Martínez Elicegui^{2,3}, Gastone Castellani^{11,12}, Axel Benner¹³, Raúl Azibeiro^{1,2}, Jesse M. Tetters¹⁴, Rabea Mecklenbrauck^{15,16}, Joaquín Martínez-López¹⁷, Marta Pratcorona¹⁸, Ken I. Mills¹⁹, Guillermo Sanz^{20,21}, Maria Teresa Voso²², Lehmann Sören^{23,24}, Christoph Röllig²⁵, Christian Thiede²⁵, Klaus H. Metzeler²⁶, Konstanze Döhner²⁷, Michael Heuser^{15,28}, Torsten Haferlach²⁹, Peter JM Valk⁸, Nigel Russell³⁰, Jesús María Hernández-Rivas^{1,2,3,4}, Brian Huntly³¹, Gert Ossenkoppele¹⁴, Hartmut Döhner²⁷ and Lars Bullinger^{32,33}

Impact of myelodysplasia-related and additional gene mutations in intensively treated patients with *NPM1*-mutated AML

Sibylle Cocciardi¹ | Maral Saadati² | Nina Weiß¹ | Daniela Späth¹ |
Silke Kapp-Schwoerer¹ | Isabelle Schneider¹ | Annika Meid¹ | Verena I. Gaidzik¹ |
Sabrina Skambraks¹ | Walter Fiedler³ | Michael W. M. Kühn⁴ | Ulrich Germing⁵ |
Karin T. Mayer⁶ | Michael Lübbert⁷ | Elli Papaemmanuil⁸ | Felicitas Thol⁹ |
Michael Heuser⁹ | Arnold Ganser⁹ | Lars Bullinger^{10,11,12} | Axel Benner² |
Hartmut Döhner¹ | Konstanze Döhner¹ 



Mutation- and MRD-informed treatment decisions for the transplant-eligible AML patient



Michael Heuser and Rabia Shahswar. Hematology 2024

Case Management & Decision Making

- **Patient Profile:**
 - NPM1+ / FLT3- AML (Mylotarg eligible).
 - History of unexplained leukocytosis/monocytosis (suspected prior MDS).
 - Satisfactory disease clearance (4 NPM1 copies).
- **Selected strategy:** 2nd consolidation cycle followed by maintenance.

Future Outlook & Monitoring

Risk Profile: Despite "favorable" risk, the absence of CBF and presence of potential co-mutations require caution.

MRD Monitoring: Strict follow-up of the NPM1 signal mandatory.

Relapse Strategy:

In case of molecular relapse, the patient remains a candidate for allo-SCT given the age and Performance Status (PS).

Current strategy preserves the transplant option for a later stage if needed.

Beyond intensive CHT in NPM1-mutated AML?

PARADIGM (Fathi A. Blood 2025;146:6–7)

- A phase 2 randomized multi-center study comparing azacitidine and venetoclax to conventional induction chemotherapy for newly diagnosed fit adults with acute myeloid leukemia".

VINCENT (NCT05904106)

- A randomized-controlled trial evaluating venetoclax plus azacitidine versus intensive chemotherapy in patients with newly diagnosed, NPM1-mutated AML

VICTOR (EudraCT: 2020–000,273-24)

- Venetoclax combined with low-dose cytarabine compared to standard of care intensive chemotherapy vo the treatment of favourable risk adult acute myeloid leukemia