



LAL e LAM : DAY

Stato dell'arte delle Leucemie Acute

ED. CENTRO

31 marzo 2026 **Roma**

SESSIONE II:

EVOLUZIONE DELL'ALGORITMO TERAPEUTICO DEL PAZIENTE CON LAM

**Dalla diagnosi alla malattia refrattaria nel
paziente Fit**

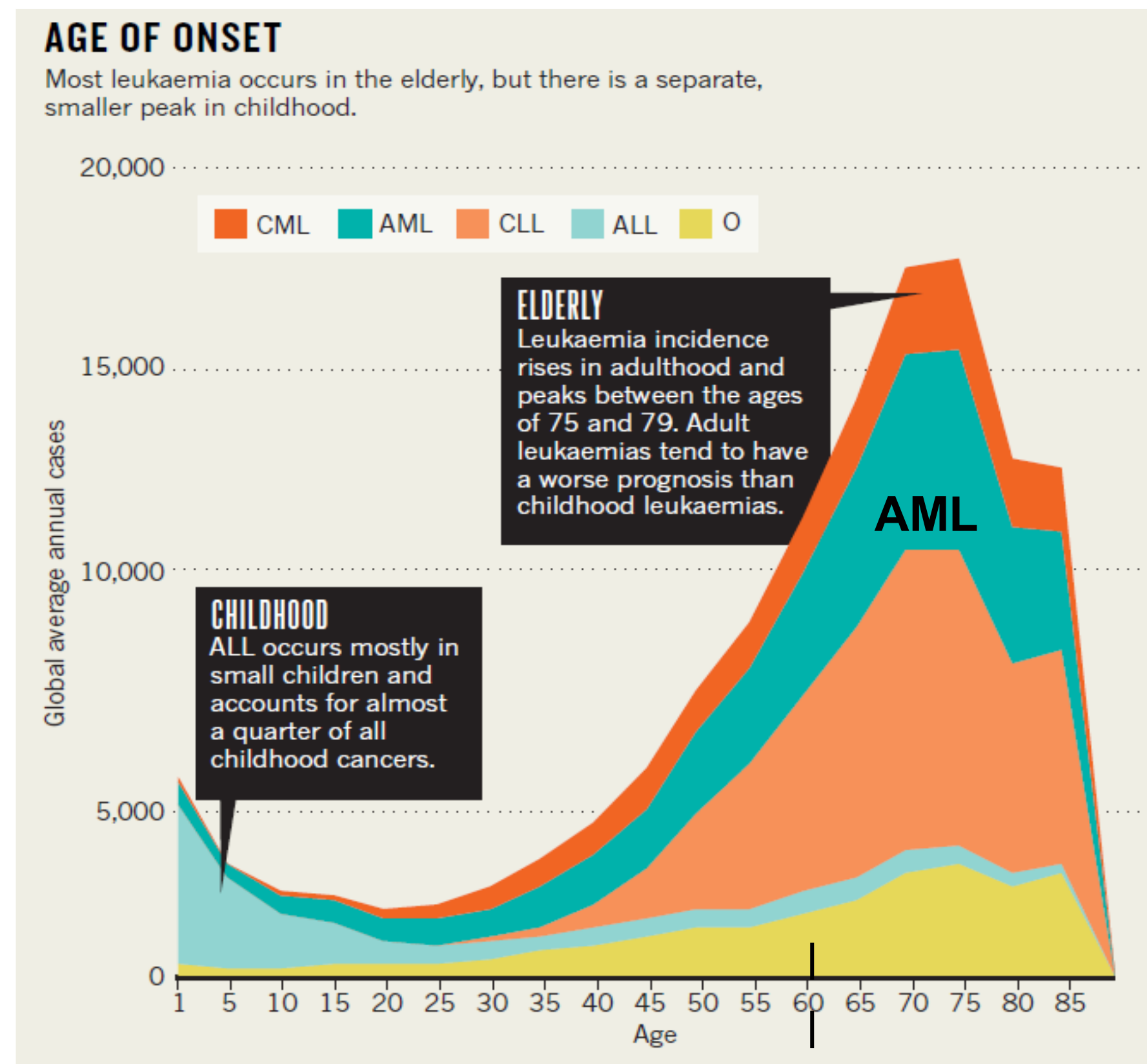
MARIA PAOLA MARTELLI, M.D., Ph.D.

(Ematologia, Università degli Studi di Perugia)

Disclosures of MARIA PAOLA MARTELLI

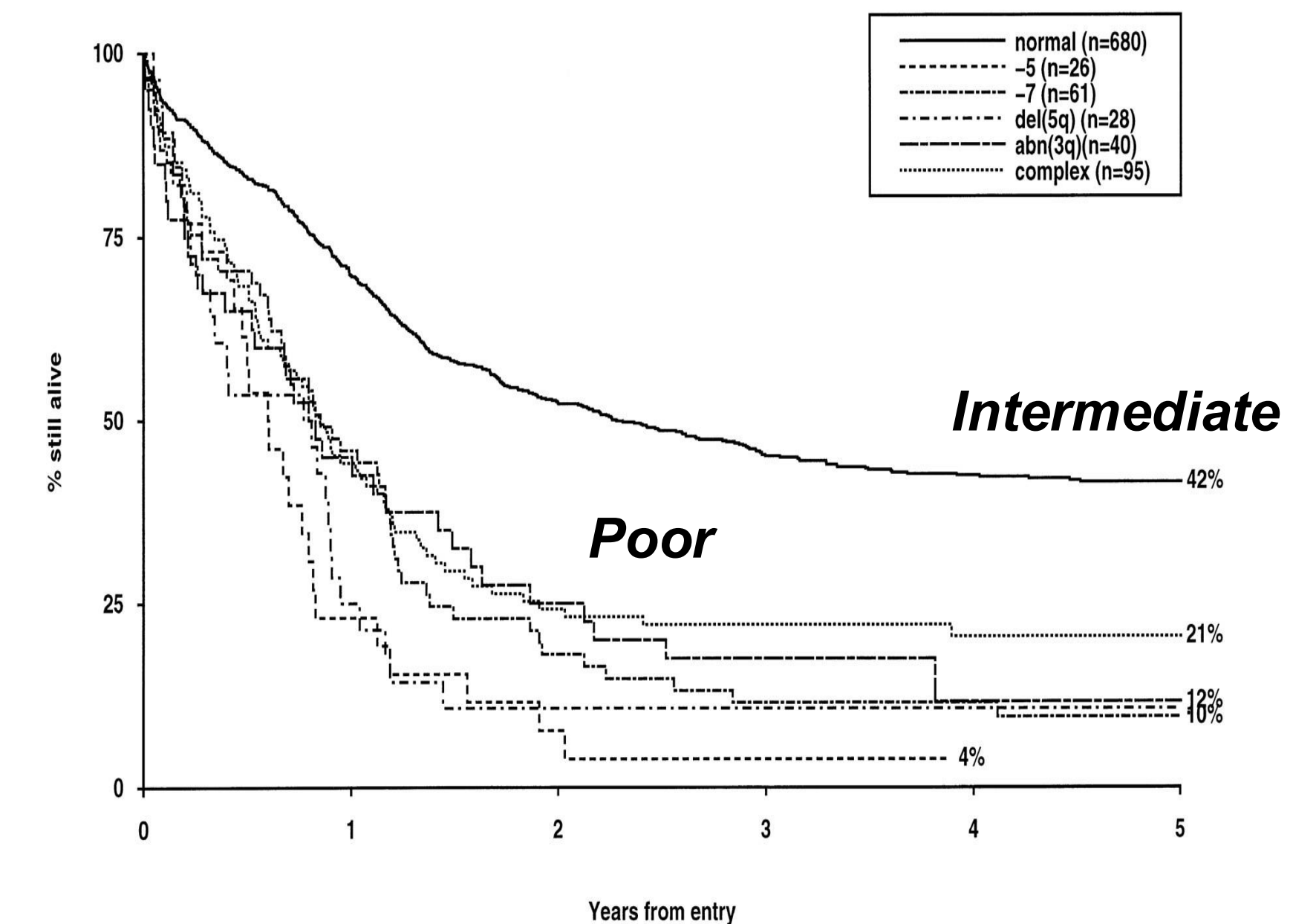
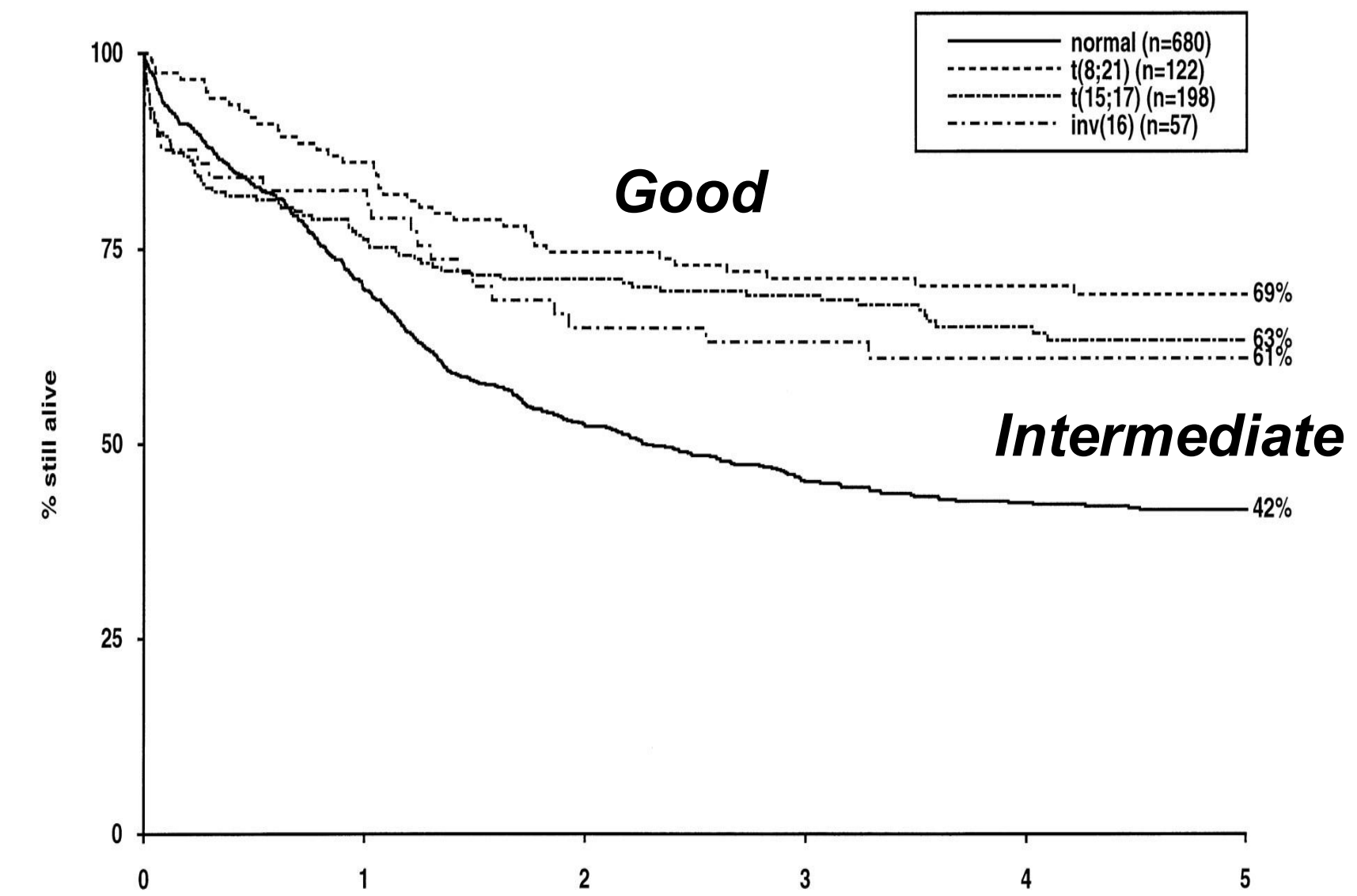
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie			X		X	X	
Amgen					X	X	
BMS					X	X	
Delbert			X				
Gilead						X	
Incyte						X	
Janssen						X	
Jazz Pharmaceuticals					X	X	
Novartis					X	X	
Otsuka					X	X	
Pfizer			X		X	X	
Roche						X	
Servier					X	X	

AML: a heterogeneous disease and an urgent medical need



NATURE | VOL 498 | 27 JUNE 2013

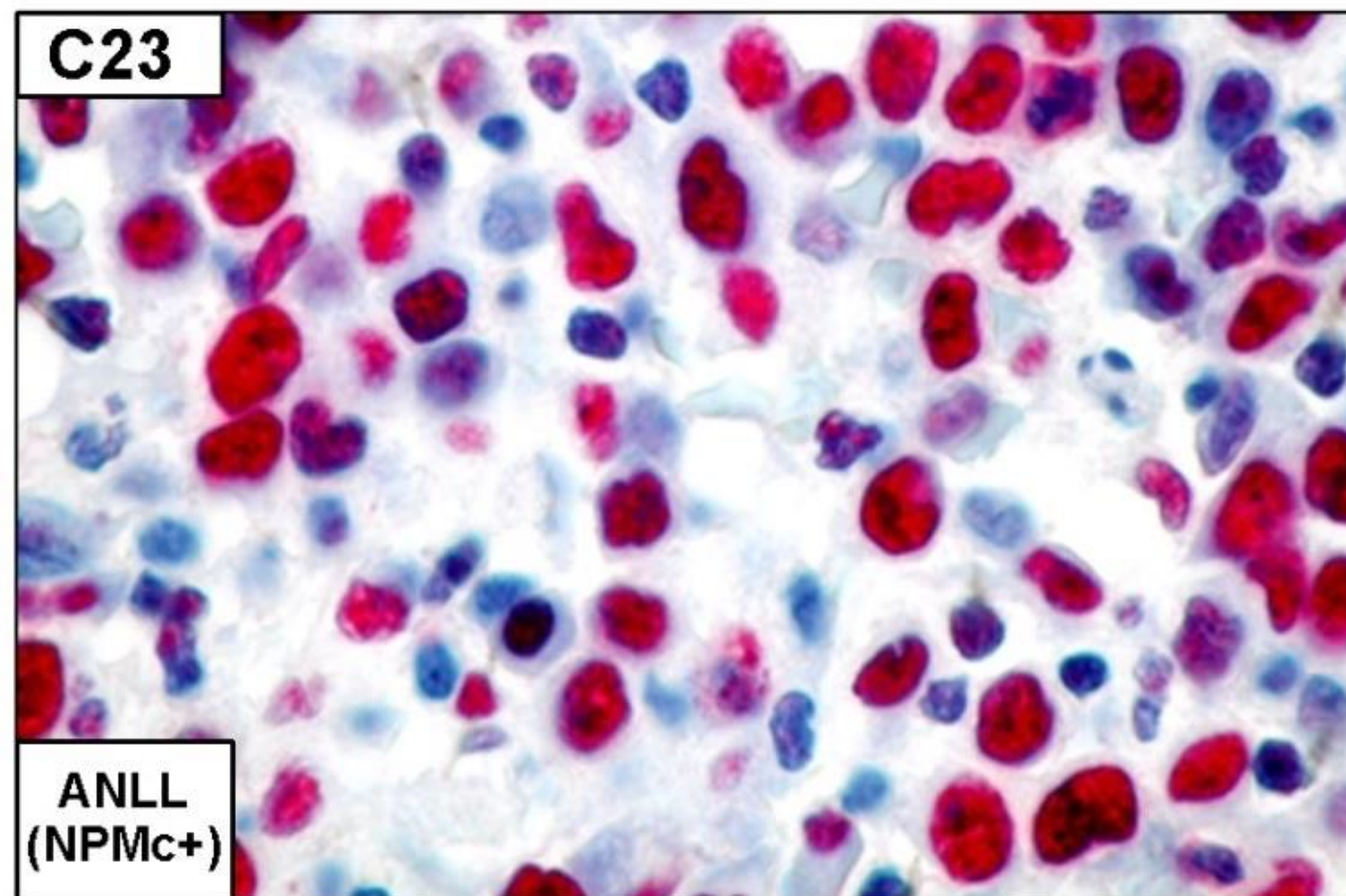
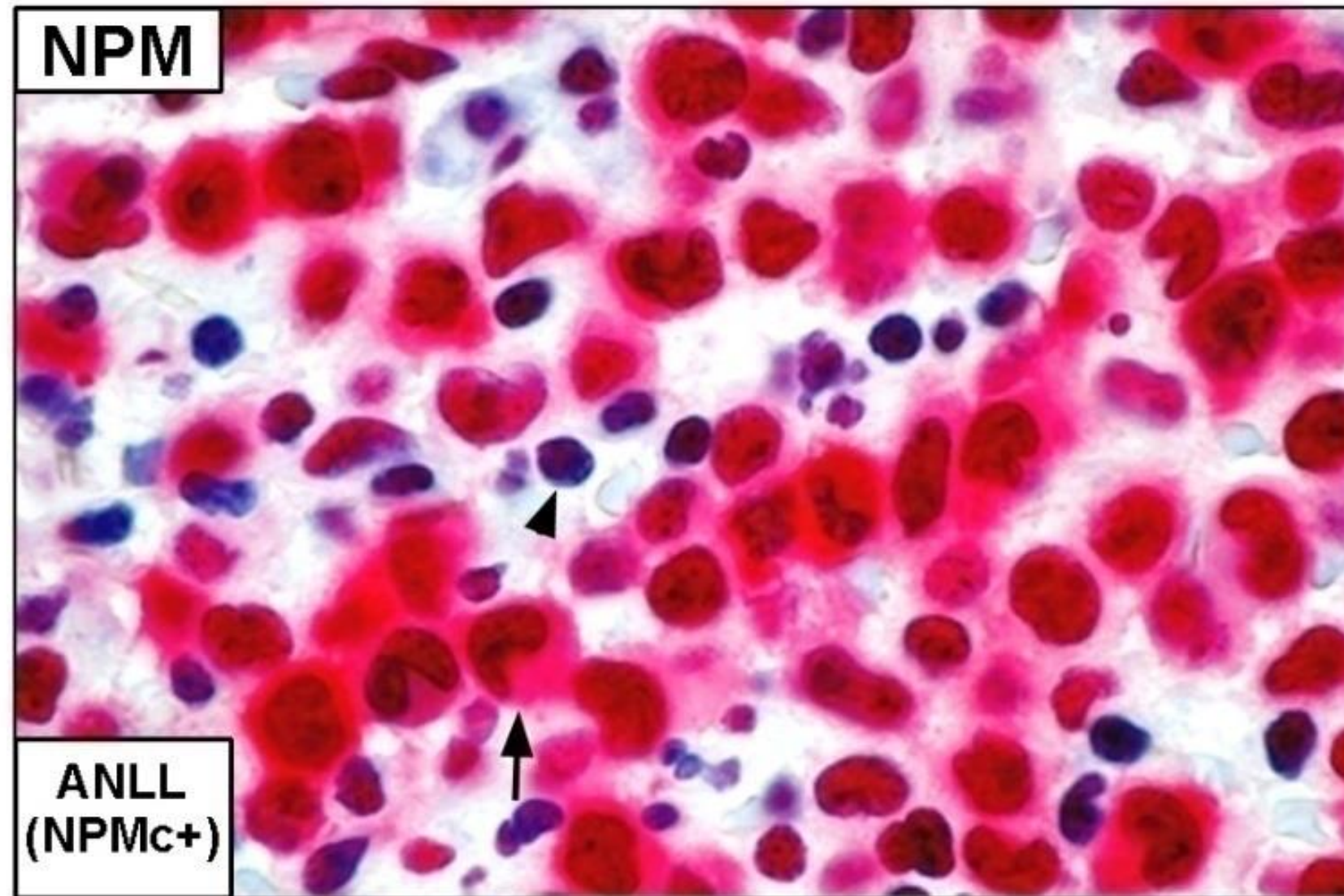
- 15-20000 new cases/year in EU/USA
- Rapidly rising incidence over age 50
- Most patients diagnosed over age 60 (median: 70 yrs)
- ~ 40% cure rates in younger
- Dismal outcome in older
- Treatment advances in the past recent years



Grimwade D et al. Blood 1998;92:2322-2333

✓ 2005

The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE

Cytoplasmic Nucleophosmin in Acute Myelogenous Leukemia with a Normal Karyotype

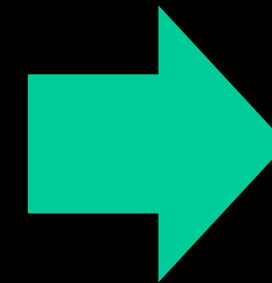
Brunangelo Falini, M.D., Cristina Mecucci, M.D., Ph.D., Enrico Tiacci, M.D., Myriam Alcalay, M.D., Ph.D., Roberto Rosati, Ph.D., Laura Pasqualucci, M.D., Roberta La Starza, M.D., Ph.D., Daniela Diverio, M.D., Emanuela Colombo, Ph.D., Antonella Santucci, M.D., Barbara Bigerna, Roberta Pacini, Alessandra Pucciarini, Ph.D., Arcangelo Liso, M.D., Marco Vignetti, M.D., Paola Fazi, M.D., Natalia Meani, Ph.D., Valentina Pettirossi, Ph.D., Giuseppe Saglio, M.D., Franco Mandelli, M.D., Francesco Lo-Coco, M.D., Pier-Giuseppe Pelicci, M.D., Ph.D., and Massimo F. Martelli, M.D., for the GIMEMA Acute Leukemia Working Party*

✓ 2008

Human Genome Project



February 2001



nature

Vol 456 | 6 November 2008 | doi:10.1038/nature07485

ARTICLES

DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome

Timothy J. Ley^{1,2,3,4*}, Elaine R. Mardis^{2,3*}, Li Ding^{2,3}, Bob Fulton³, Michael D. McLellan³, Ken Chen³, David Dooling³, Brian H. Dunford-Shore³, Sean McGrath³, Matthew Hickenbotham³, Lisa Cook³, Rachel Abbott³, David E. Larson³, Dan C. Koboldt³, Craig Pohl³, Scott Smith³, Amy Hawkins³, Scott Abbott³, Devin Locke³, LaDeana W. Hillier^{3,8}, Tracie Miner³, Lucinda Fulton³, Vincent Magrini^{2,3}, Todd Wylie³, Jarret Glasscock³, Joshua Conyers³, Nathan Sander³, Xiaoli Shi³, John R. Osborne³, Patrick Minx³, David Gordon⁸, Asif Chinwalla³, Yu Zhao¹, Rhonda E. Ries¹, Jacqueline E. Payton⁵, Peter Westervelt^{1,4}, Michael H. Tomasson^{1,4}, Mark Watson^{3,4,5}, Jack Baty⁶, Jennifer Ivanovich^{4,7}, Sharon Heath^{1,4}, William D. Shannon^{1,4}, Rakesh Nagarajan^{4,5}, Matthew J. Walter^{1,4}, Daniel C. Link^{1,4}, Timothy A. Graubert^{1,4}, John F. DiPersio^{1,4} & Richard K. Wilson^{2,3,4}

Acute myeloid leukaemia is a highly malignant haematopoietic tumour that affects about 13,000 adults in the United States each year. The treatment of this disease has changed little in the past two decades, because most of the genetic events that initiate the disease remain undiscovered. Whole-genome sequencing is now possible at a reasonable cost and timeframe to use this approach for the unbiased discovery of tumour-specific somatic mutations that alter the protein-coding genes. Here we present the results obtained from sequencing a typical acute myeloid leukaemia genome, and its matched normal counterpart obtained from the same patient's skin. We discovered ten genes with acquired mutations; two were previously described mutations that are thought to contribute to tumour progression, and eight were new mutations present in virtually all tumour cells at presentation and relapse, the function of which is not yet known. Our study establishes whole-genome sequencing as an unbiased method for discovering cancer-initiating mutations in previously unidentified genes that may respond to targeted therapies.

We used massively parallel sequencing technology to sequence the genomic DNA of tumour and normal skin cells obtained from a patient with a typical presentation of French-American-British (FAB) subtype M1 acute myeloid leukaemia (AML) with normal cytogenetics. For the tumour genome, 32.7-fold 'haploid' coverage (98 billion bases) was obtained, and 13.9-fold coverage (41.8 billion bases) was obtained for the normal skin sample. Of the 2,647,695 well-supported single nucleotide variants (SNVs) found in the tumour genome, 2,584,418 (97.6%) were also detected in the patient's skin genome, limiting the number of variants that required further study. For the purposes of this initial study, we restricted our downstream analysis to the coding sequences of annotated genes: we found only eight heterozygous, non-synonymous somatic SNVs in the entire genome. All were new, including mutations in protocadherin/cadherin family members (*CDH24* and *PCLKC* (also known as *PCDH24*)), G-protein-coupled receptors (*GPR123* and *EBI2* (also known as *GPR183*)), a protein phosphatase (*PTPRT*), a potential guanine nucleotide exchange factor (*KNDC1*), a peptide/drug transporter (*SLC15A1*) and a glutamate receptor gene (*GRIN1B*). We also detected previously described, recurrent somatic insertions in the *FLT3* and *NPM1* genes. On the basis of deep readcount data, we determined that all of these mutations (except *FLT3*) were present in nearly all tumour cells at presentation and again at relapse 11 months later, suggesting that the patient had a single dominant clone containing all of the mutations. These results demonstrate the power of whole-genome sequencing to discover new cancer-associated mutations.

AML refers to a group of clonal haematopoietic malignancies that predominantly affect middle-aged and elderly adults. An estimated 13,000 people will develop AML in the United States in 2008, and 8,800 will die from it¹. Although the life expectancy from this disease has increased slowly over the past decade, the improvement is predominantly because of improvements in supportive care—not in the drugs or approaches used to treat patients.

For most patients with a 'sporadic' presentation of AML, it is not yet clear whether inherited susceptibility alleles have a role in the pathogenesis². Furthermore, the nature of the initiating or progression mutations is for the most part unknown³. Recent attempts to identify additional progression mutations by sequencing of whole-genome DNA from AML cells yielded very few new and most were not recurrent^{4,5}. Exome sequencing yielded signatures that correlate with AML, but have not yet suggested new studies using array-based comparative single nucleotide polymorphism (SNP) arrays. Our study revealed very few recurrent submicroscopic variants in AML (M.J.W., manuscript 13). Together, these studies suggest that most of the relevant mutations that cause AML are not detected by current methods. We therefore believe that unbiased whole-genome sequencing will be required to identify most of the mutations that initiate AML. This approach has not been feasible because

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*These authors contributed equally to this work.

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(Ley T et al, Nature, 2008)

✓ 2013

The NEW ENGLAND JOURNAL of MEDICINE

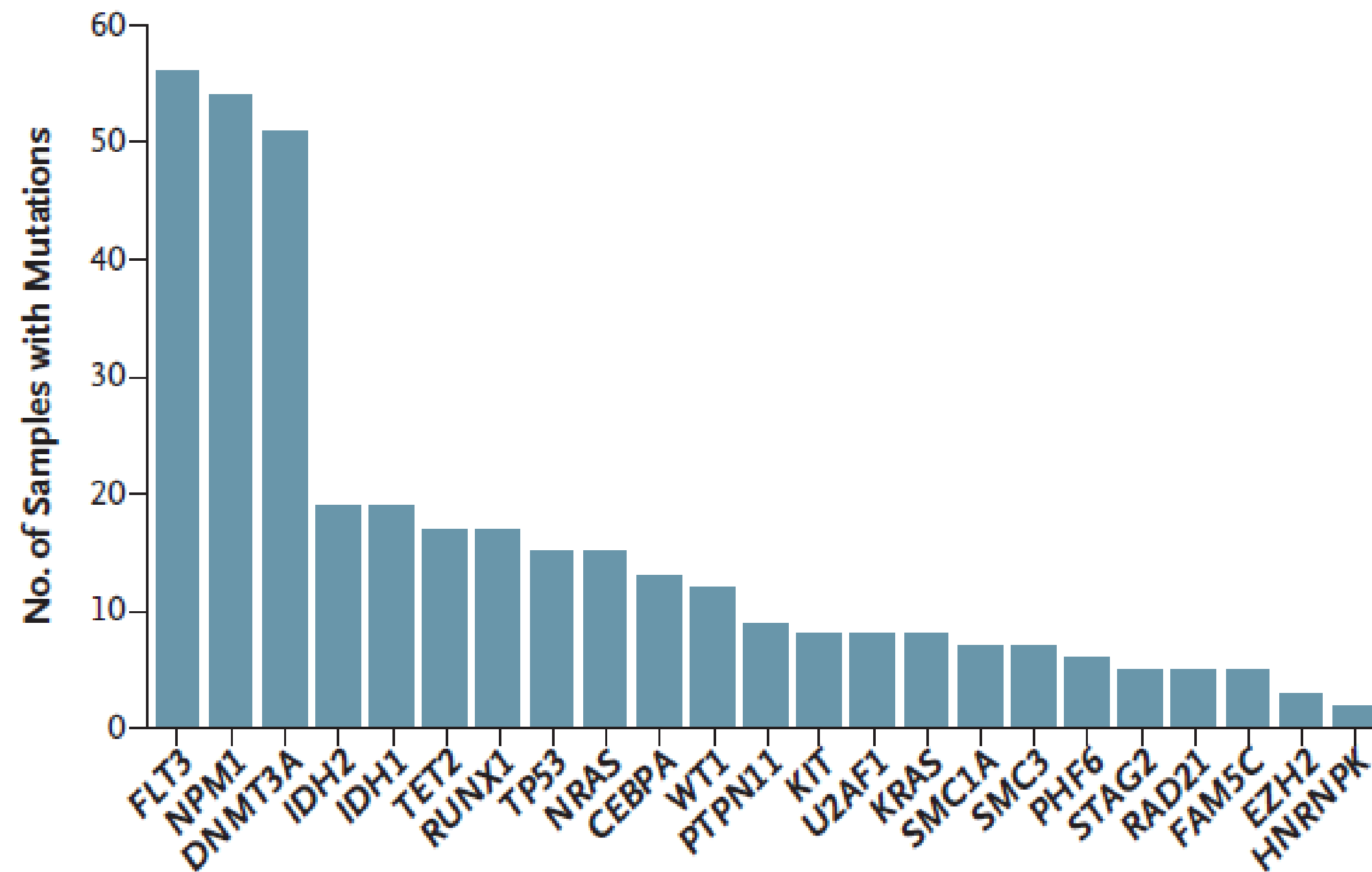
ESTABLISHED IN 1812

MAY 30, 2013

VOL. 368 NO. 22

Genomic and Epigenomic Landscapes of Adult De Novo Acute Myeloid Leukemia

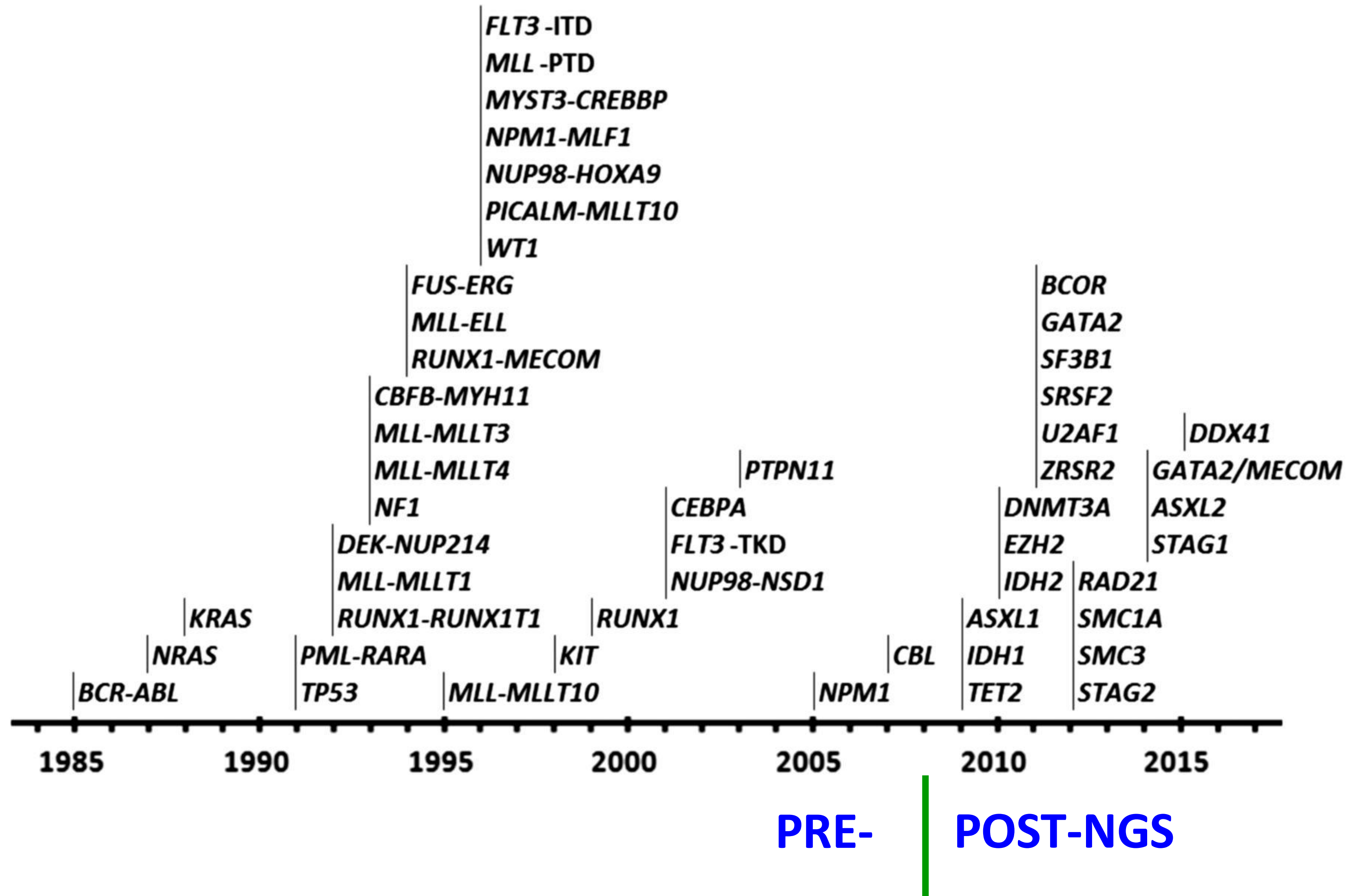
The Cancer Genome Atlas Research Network



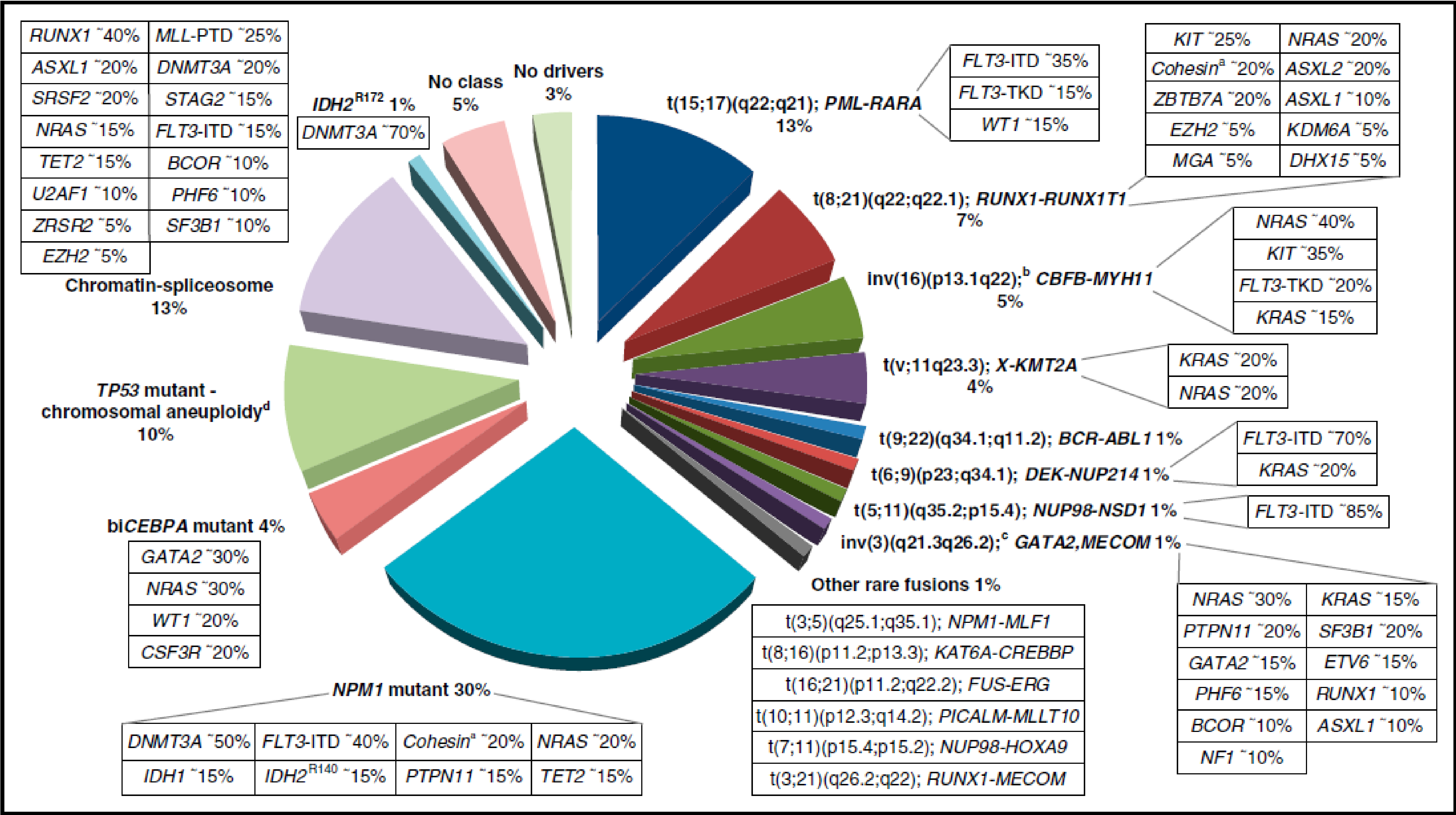
23
significantly
mutated genes
in 200 *de novo* AML

Ley T, et al. N Engl J Med 2013;368:2059-74.

Progress in defining the molecular landscape of AML

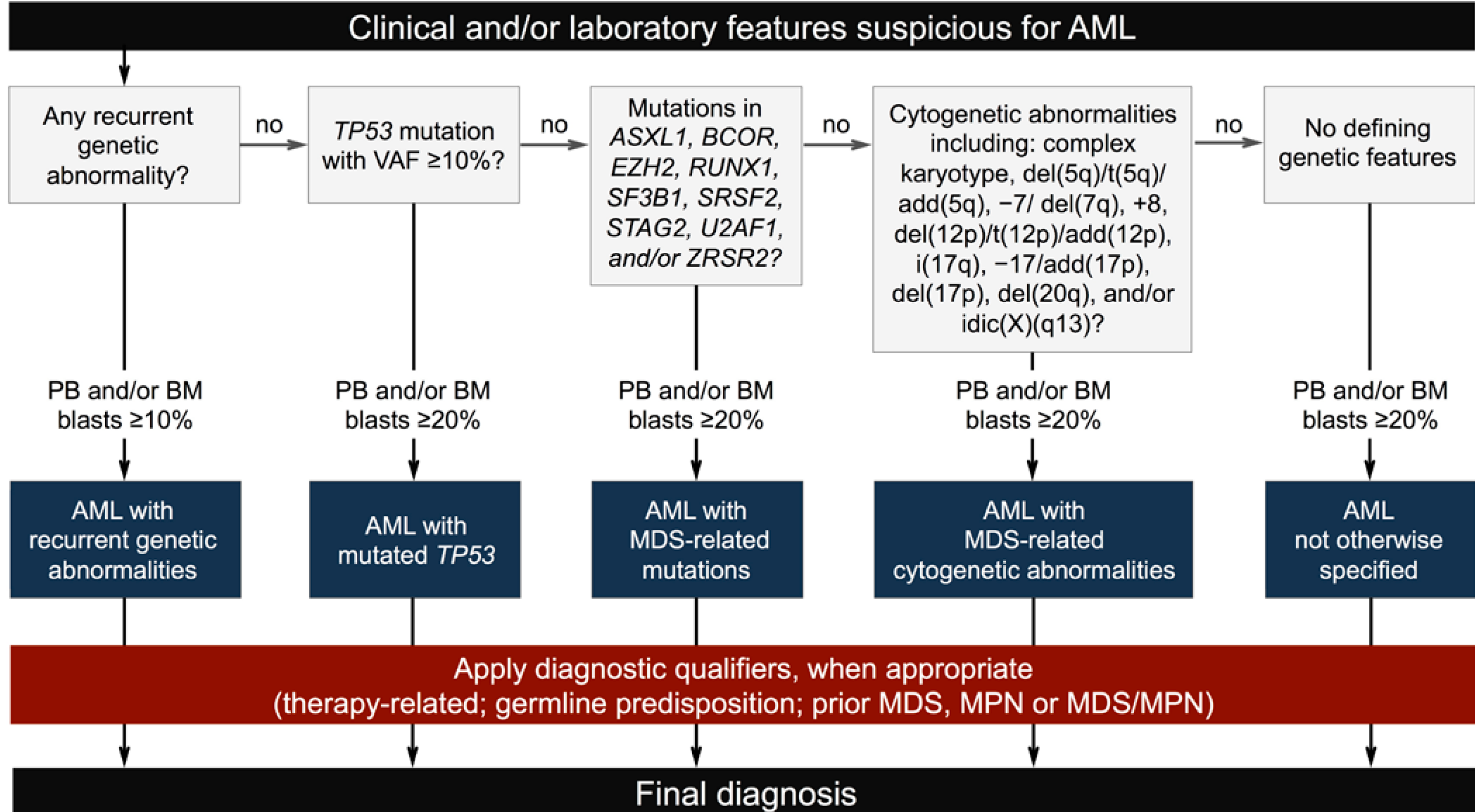


Molecular classes of AML and concurrent gene mutations



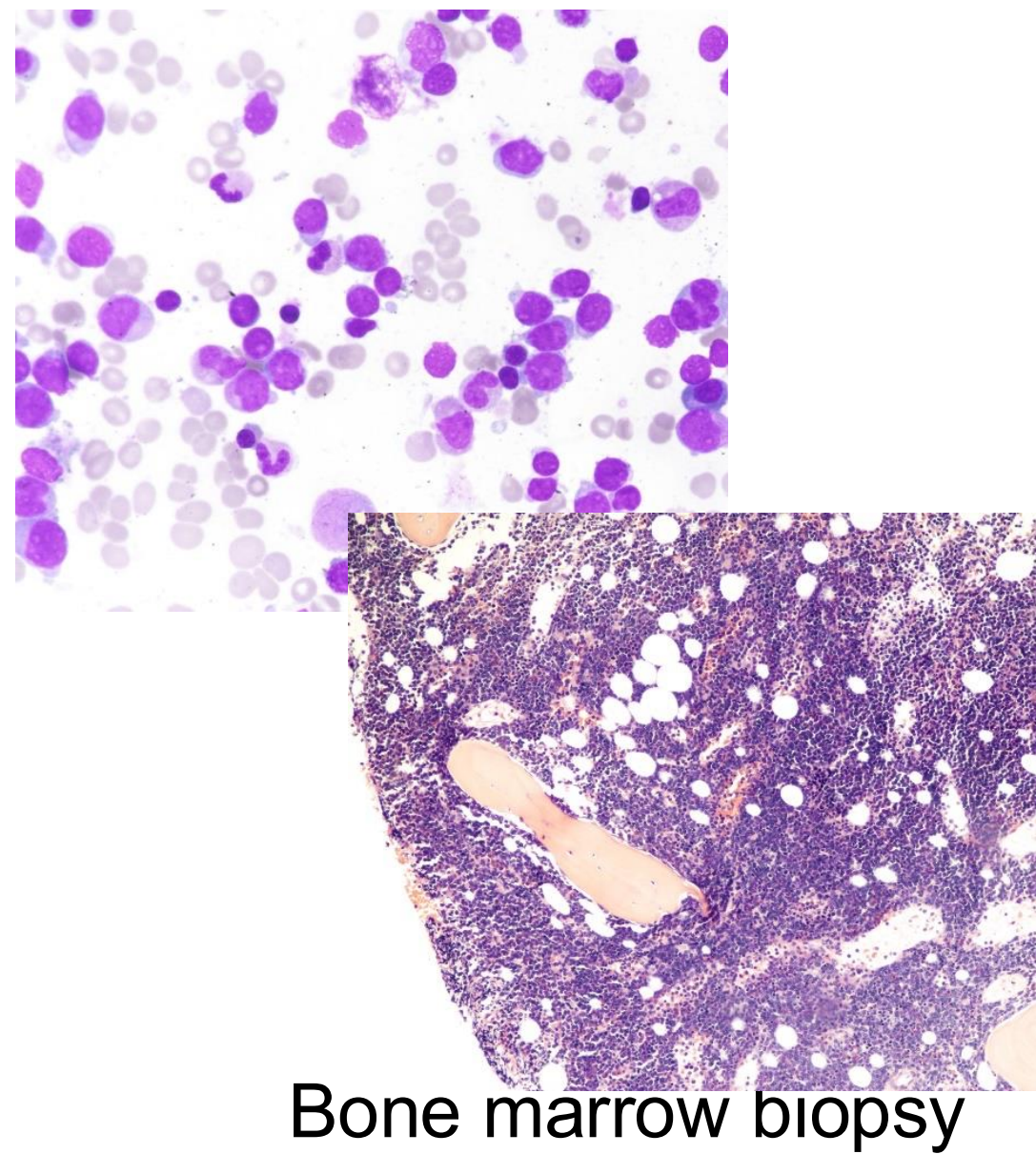
Dohner et al. *Blood* 2017

The ICC diagnostic flow-chart for AML

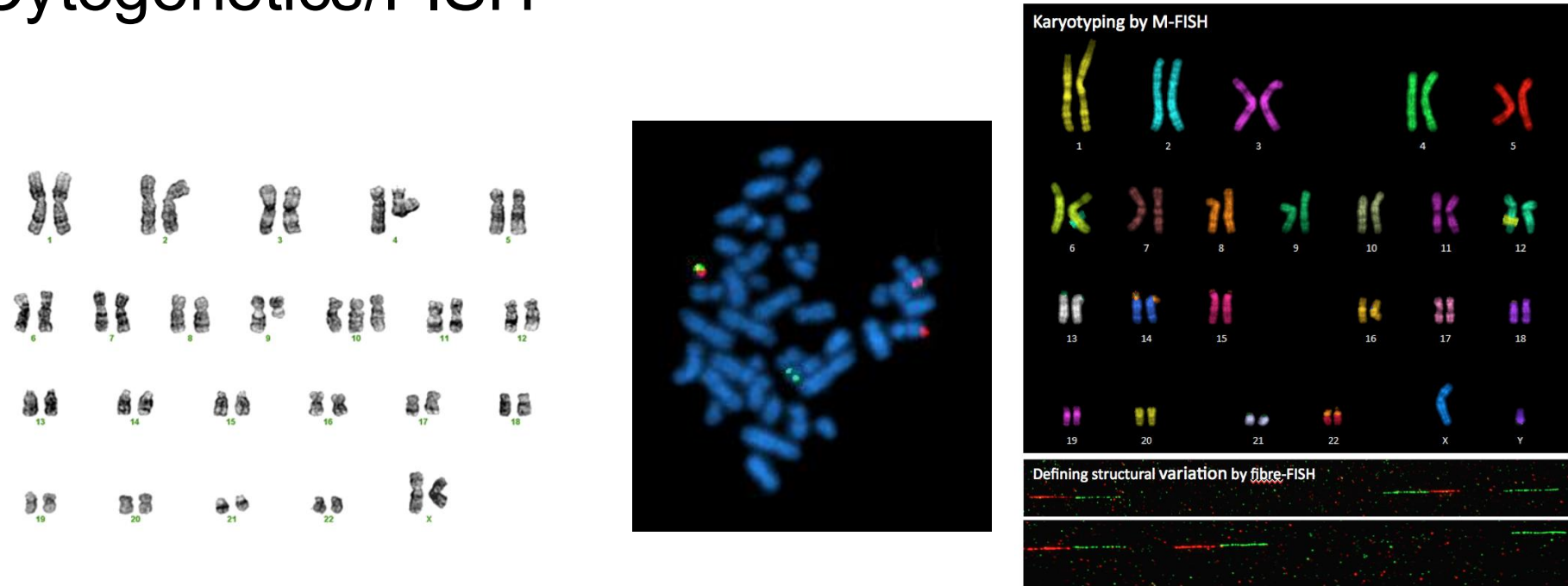


Current routine diagnostic workup in AML

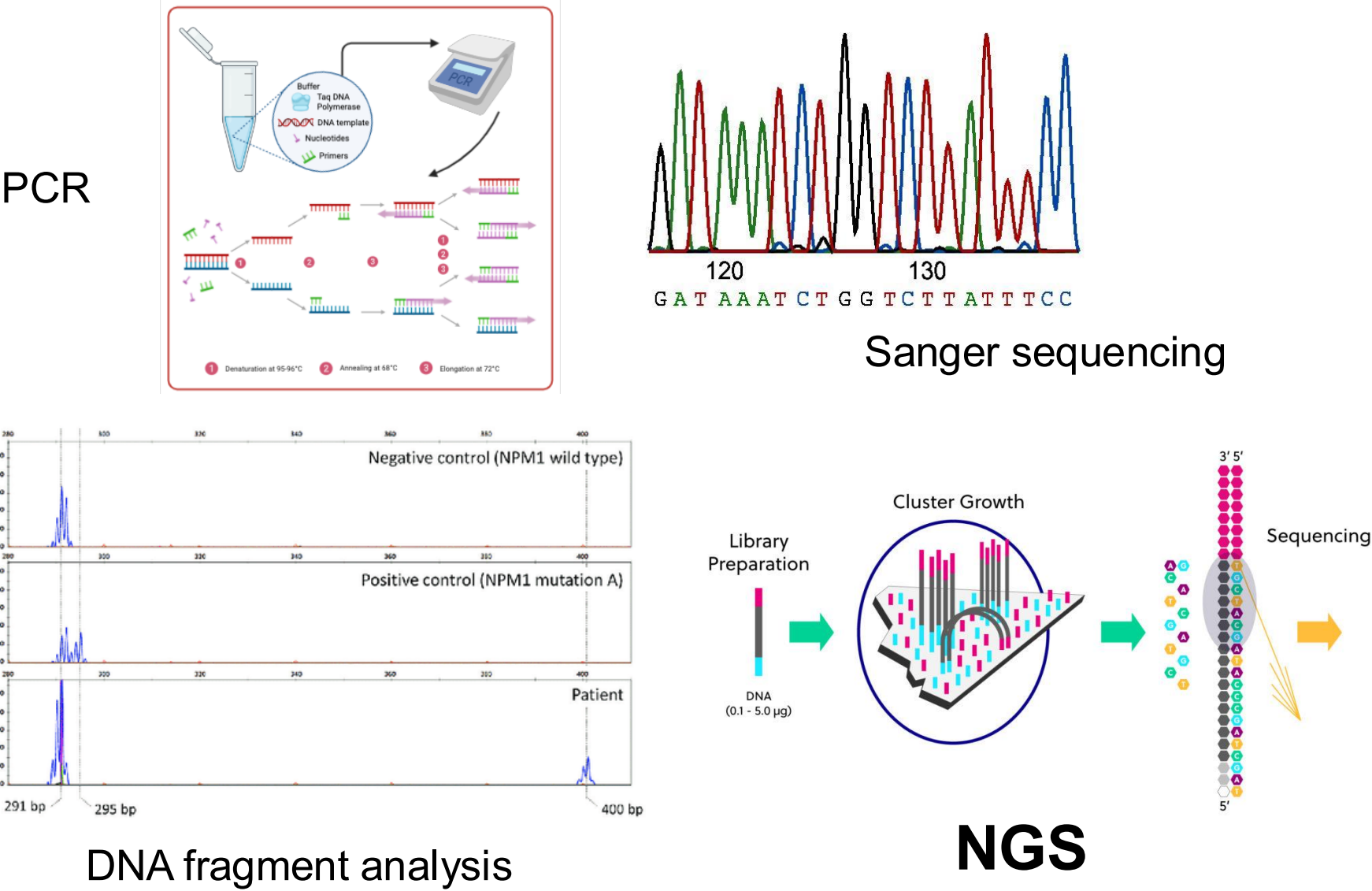
Cytomorphology



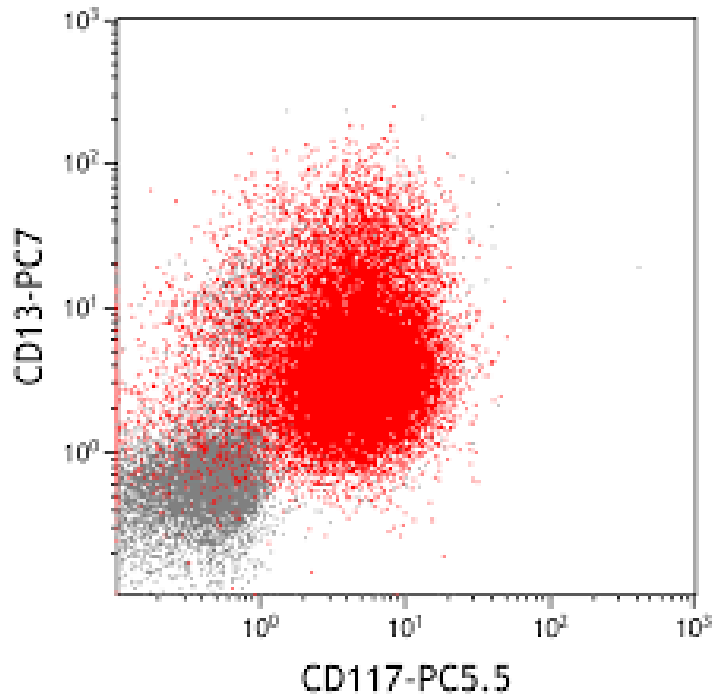
Cytogenetics/FISH



Molecular genetics



Multiparameter flow cytometry (MFC)



**AML.....
(according to
international
classifications
WHO/ICC)**

Gene mutations indicated for clinical testing in AML

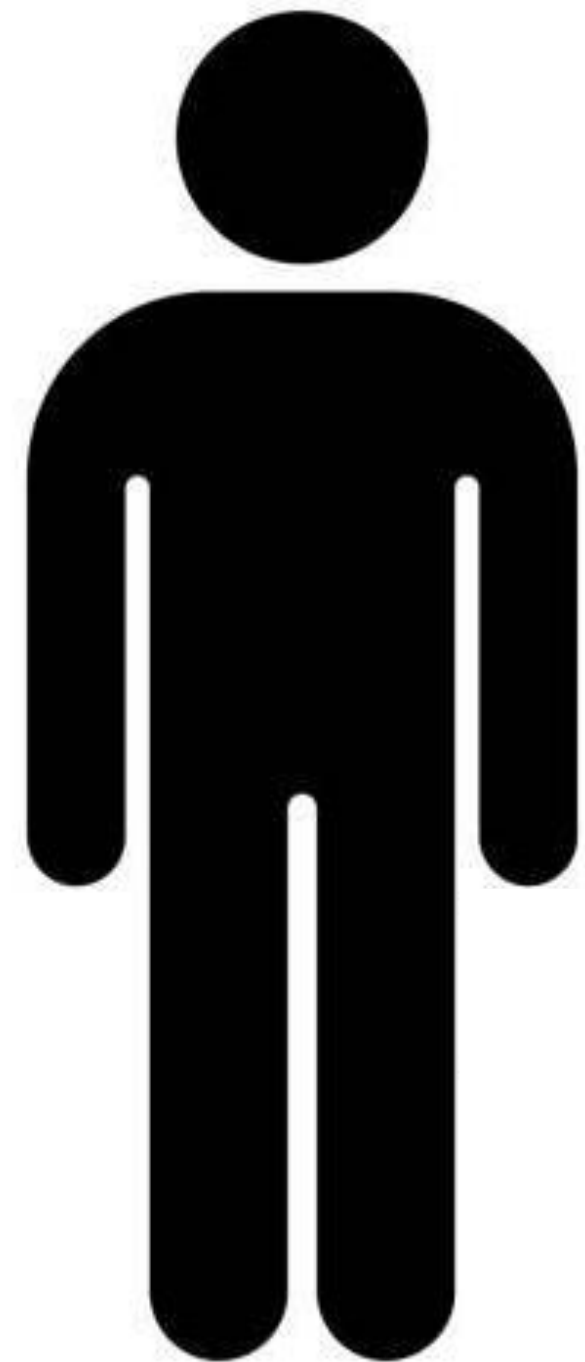
Indication	Single gene mutations	Structural variants*
AML	Genes required for diagnosis and risk stratification: ASXL1, BCOR, CEBPA, DDX41, EZH2, FLT3-ITD§, FLT3-TKD§, IDH1§, IDH2§, NPM1, RUNX1, SF3B1, SRSF2, STAG2, TP53, U2AF1, ZRSR2 Additional genes recommended to test for at diagnosis and for use in disease monitoring: ANKRD26, BCORL1, BRAF, CBL, CSF3R, DNMT3A, ETV6, GATA2, JAK2, KIT, KRAS, NRAS, NF1, PHF6, PPM1D, PTPN11, RAD21, SETBP1, TET2, WT1	BCR::ABL1§, CBFB::MYH11, DEK::NUP214, MECOM::R, KMT2A::R, NUP98::R, RUNX1::RUNX1T1, PML::RARA§

§Food and Drug Administration–approved targeted therapy.

- **diagnosis**
- **prognosis**
- **inform treatment**

Duncavage et al. *Blood* (2022) 140 (21): 2228–2247.

Treatment choices in AML patients: a matter of 'TARGET' and 'FITNESS'



**Chemioterapia di
induzione intensiva**

Terapia non intensiva

Terapia di supporto

**Arruolamento in trial
clinici**

Criteria for Unfitness

original reports

HEMATOLOGIC MALIGNANCY

Accuracy of SIE/SIES/GITMO Consensus Criteria for Unfitness to Predict Early Mortality After Intensive Chemotherapy in Adults With AML or Other High-Grade Myeloid Neoplasm



Raffaele Palmieri, MD¹; Megan Othus, PhD²; Anna B. Halpern, MD^{1,3}; Mary-Elizabeth M. Percival, MD, MS^{1,3}; Colin D. Godwin, MD, MPhil^{1,3}; Pamela S. Becker, MD, PhD^{1,3}; and Roland B. Walter, MD, PhD, MS^{1,3,4}

Table 3. Operation criteria to define unfitness to intensive chemotherapy in AML

- | | |
|----|--|
| 1. | An age older than 75 years |
| 2. | Congestive heart failure or documented cardiomyopathy with an EF $\leq$ 50% |
| 3. | Documented pulmonary disease with DLCO $\leq$ 65% or FEV1 $\leq$ 65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm |
| 4. | On dialysis and age older than 60 years or uncontrolled renal carcinoma |
| 5. | Liver cirrhosis Child B or C, or documented liver disease with marked elevation of transaminases ($>$ 3 times normal values) and an age older than 60 years, or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis |
| 6. | Active infection resistant to anti-infective therapy |
| 7. | Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver |
| 8. | ECOG performance status $\geq$ 3 not related to leukemia |
| 9. | Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy |

Abbreviations: AML, acute myeloid leukemia; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; FEV1, forced expiratory volume in 1 s.

Standard Intensive Chemotherapy (IC) in *fit* patients

INDUCTION (1 / 2)
('7+3' / others $\pm$ inhibitors / GO)



CR



CONSOLIDATION



$\pm$ Autologous/Allogeneic transplantation

**INDUCTION
TREATMENT**

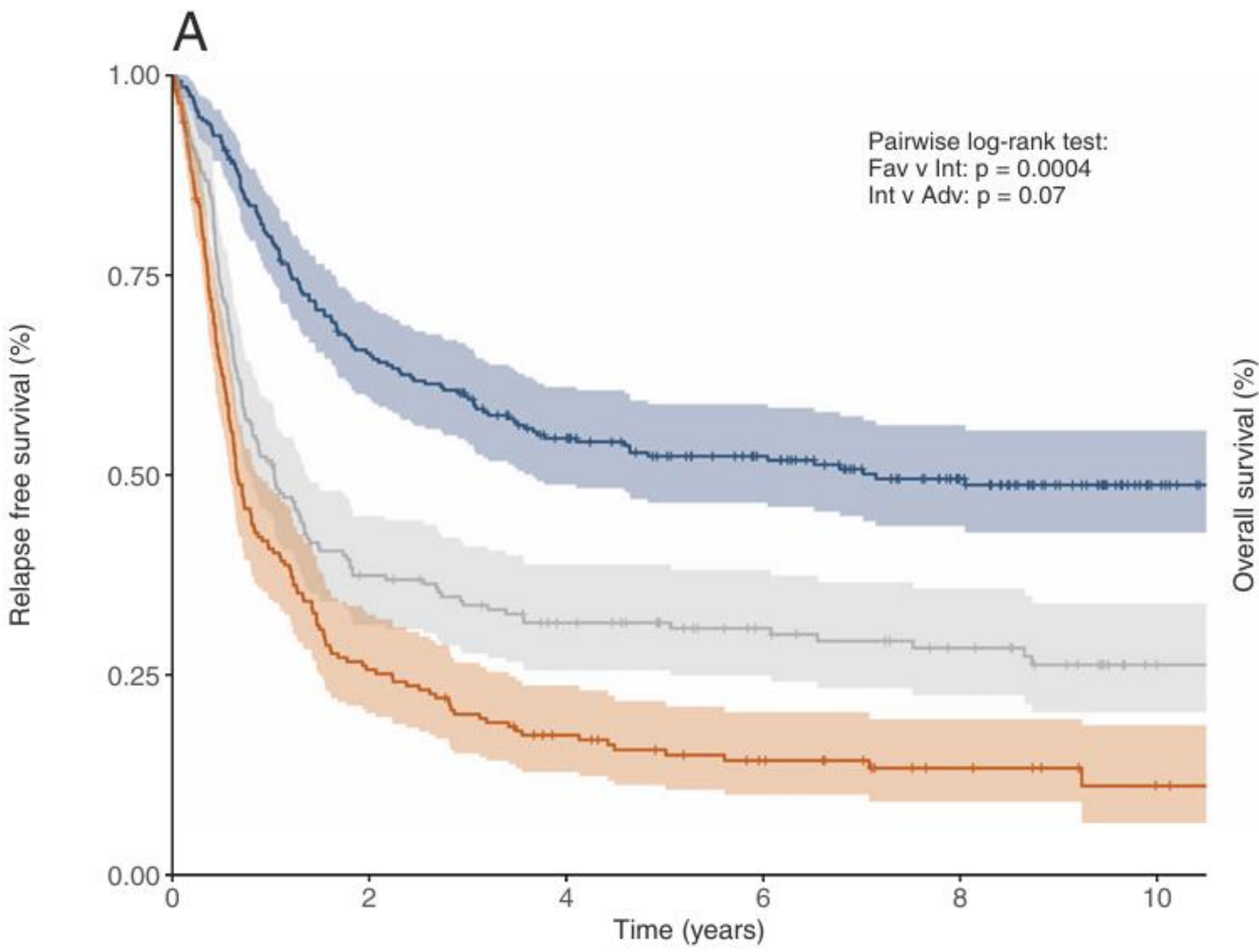
**POST-REMISSION
TREATMENT**

ELN 2022 risk stratification by genetics

Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/RUNX1::RUNX1T1†,‡ • inv(16)(p13.1q22) 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 TP53ª

The 2022 ELN guidelines were developed based on data from younger adults **receiving IC**

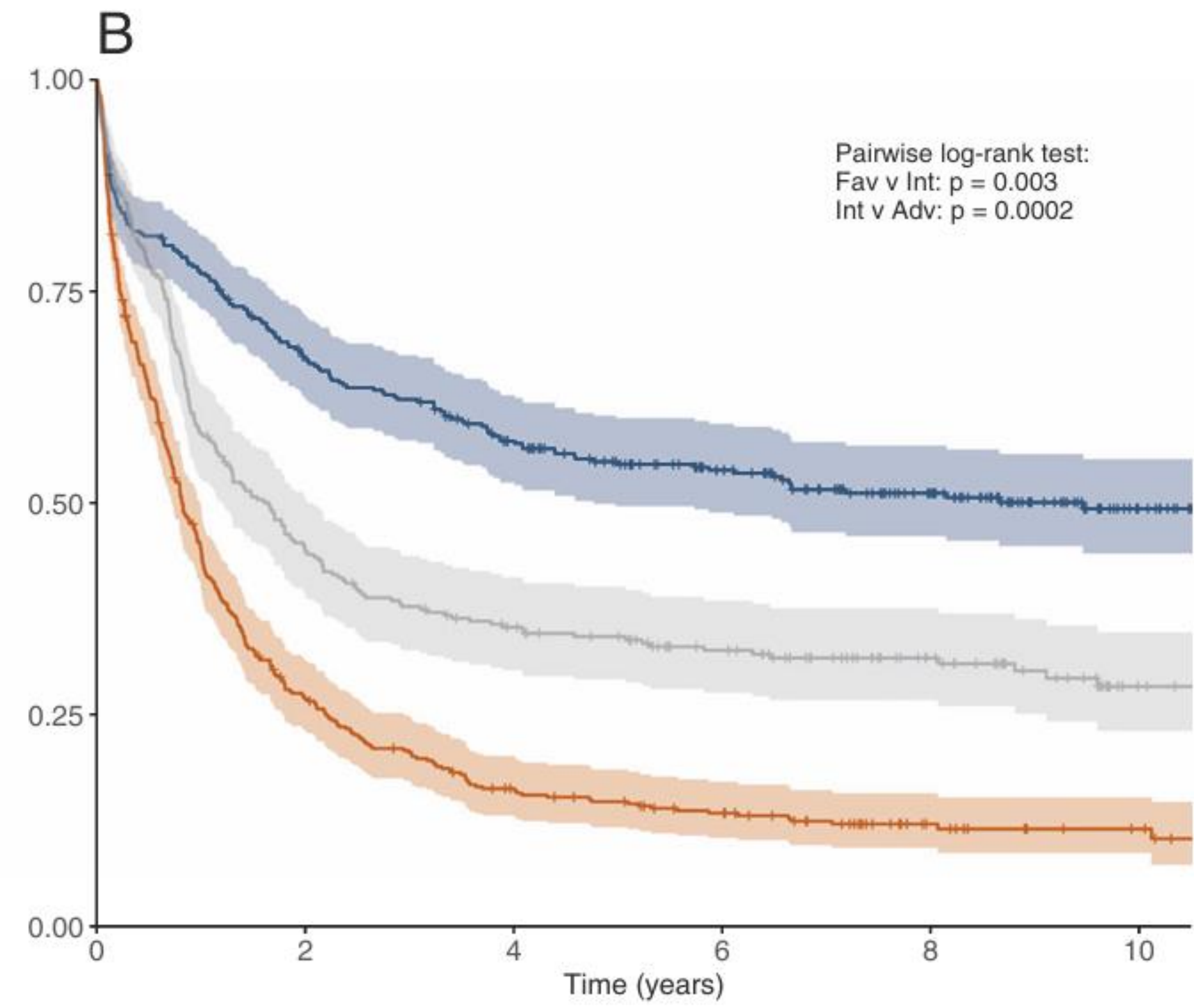
RFS



Number at risk

Strata	0	2	4	6	8	10
Favourable	265	169	129	103	66	27
Intermediate	198	72	54	40	30	13
Adverse	202	51	30	19	10	4

OS

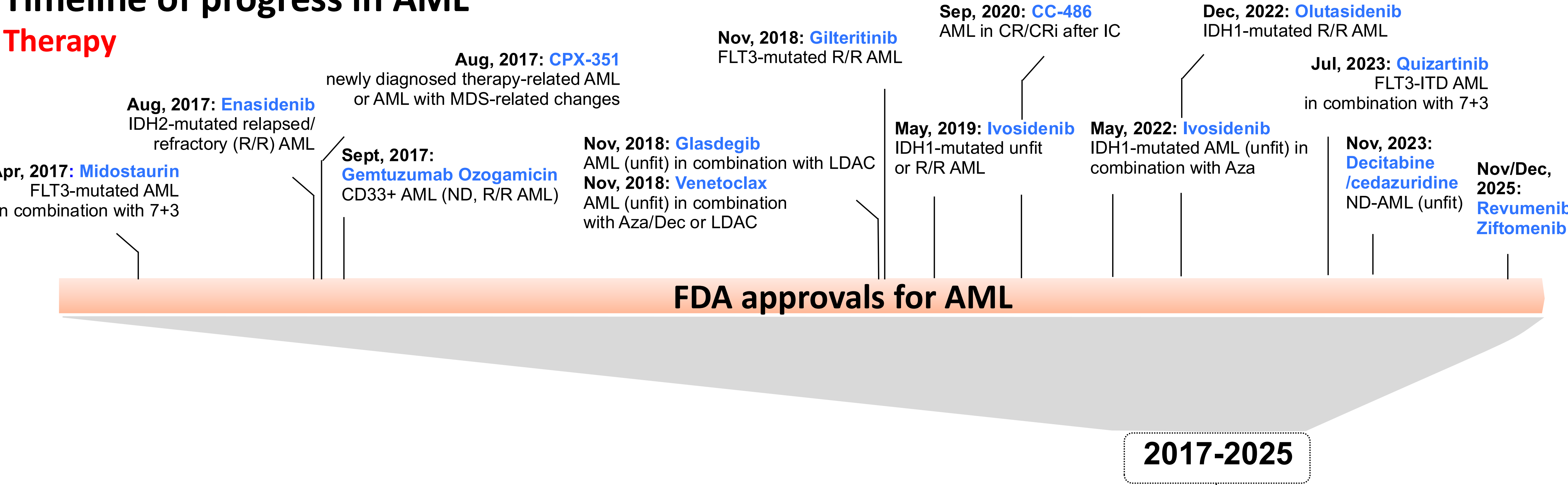


Number at risk

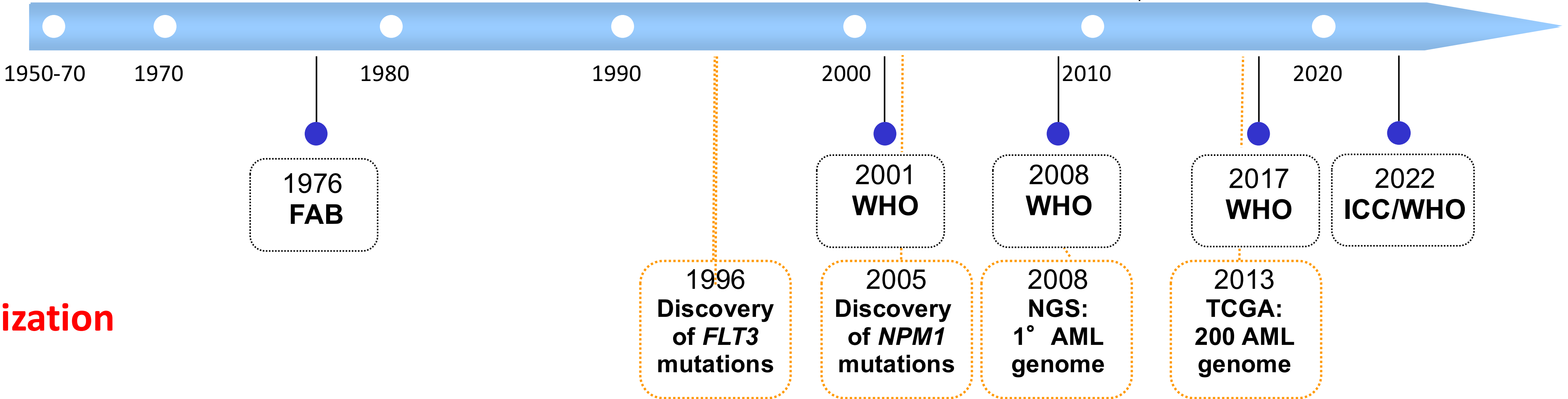
Strata	0	2	4	6	8	10
Favourable	363	237	193	152	107	52
Intermediate	302	130	98	75	48	20
Adverse	453	116	65	47	21	11

Timeline of progress in AML

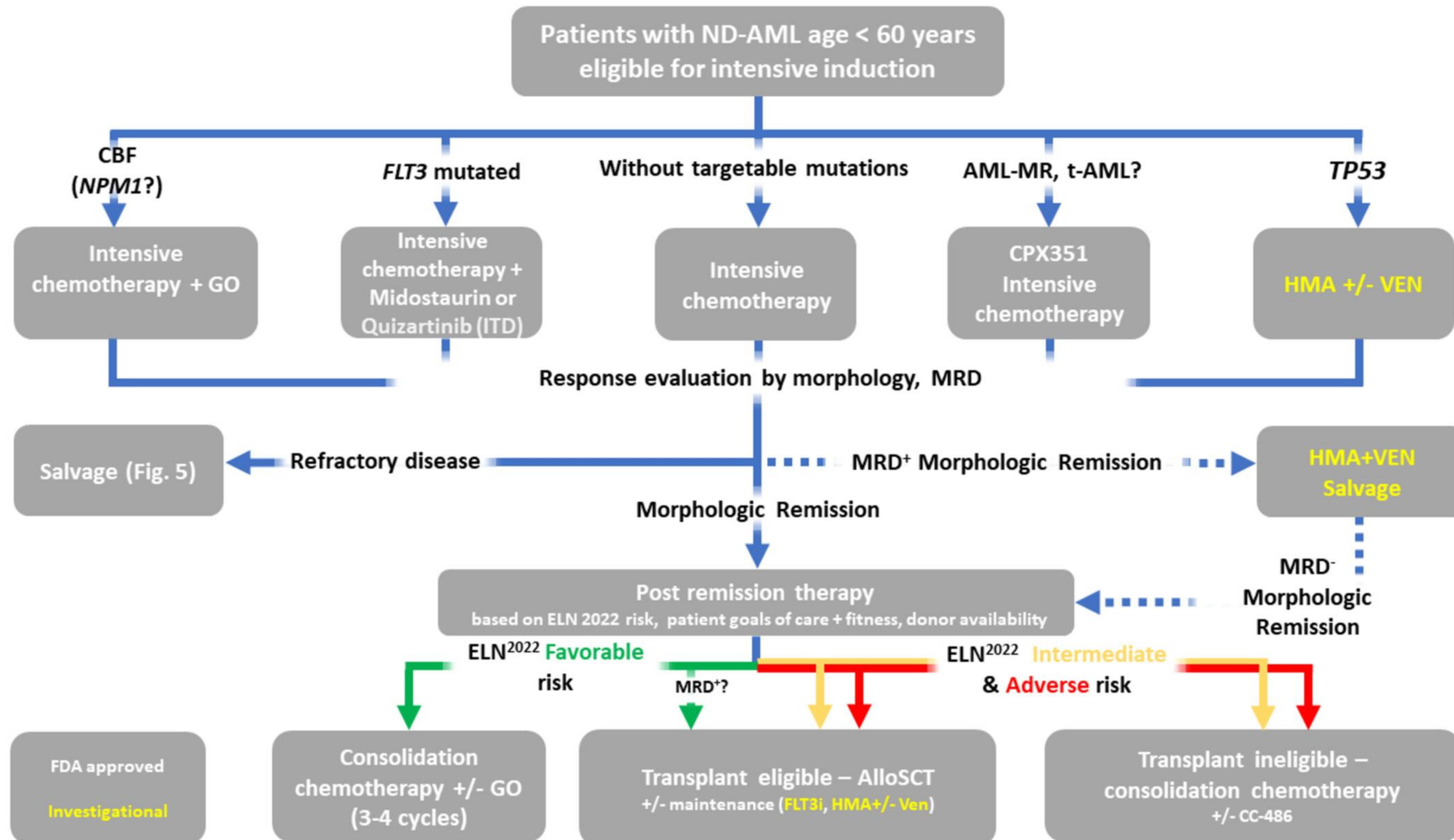
Therapy



Classification and molecular characterization

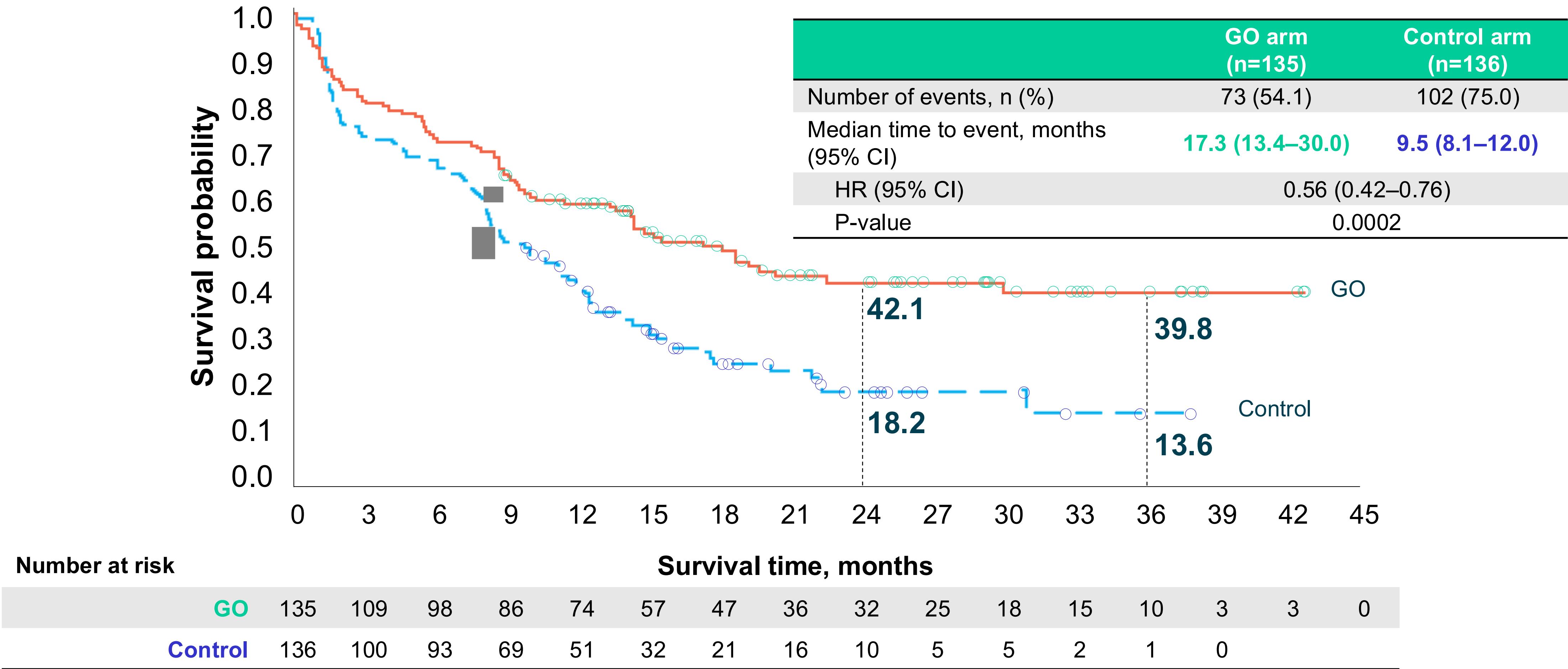


Acute Myeloid Leukemia: 2025 Update on Diagnosis, Risk-Stratification, and Management



Shimony, Stahl, Stone. American J Hematol, 100(5):860-891, 2025

ALFA-0701: Event-free survival (primary endpoint)

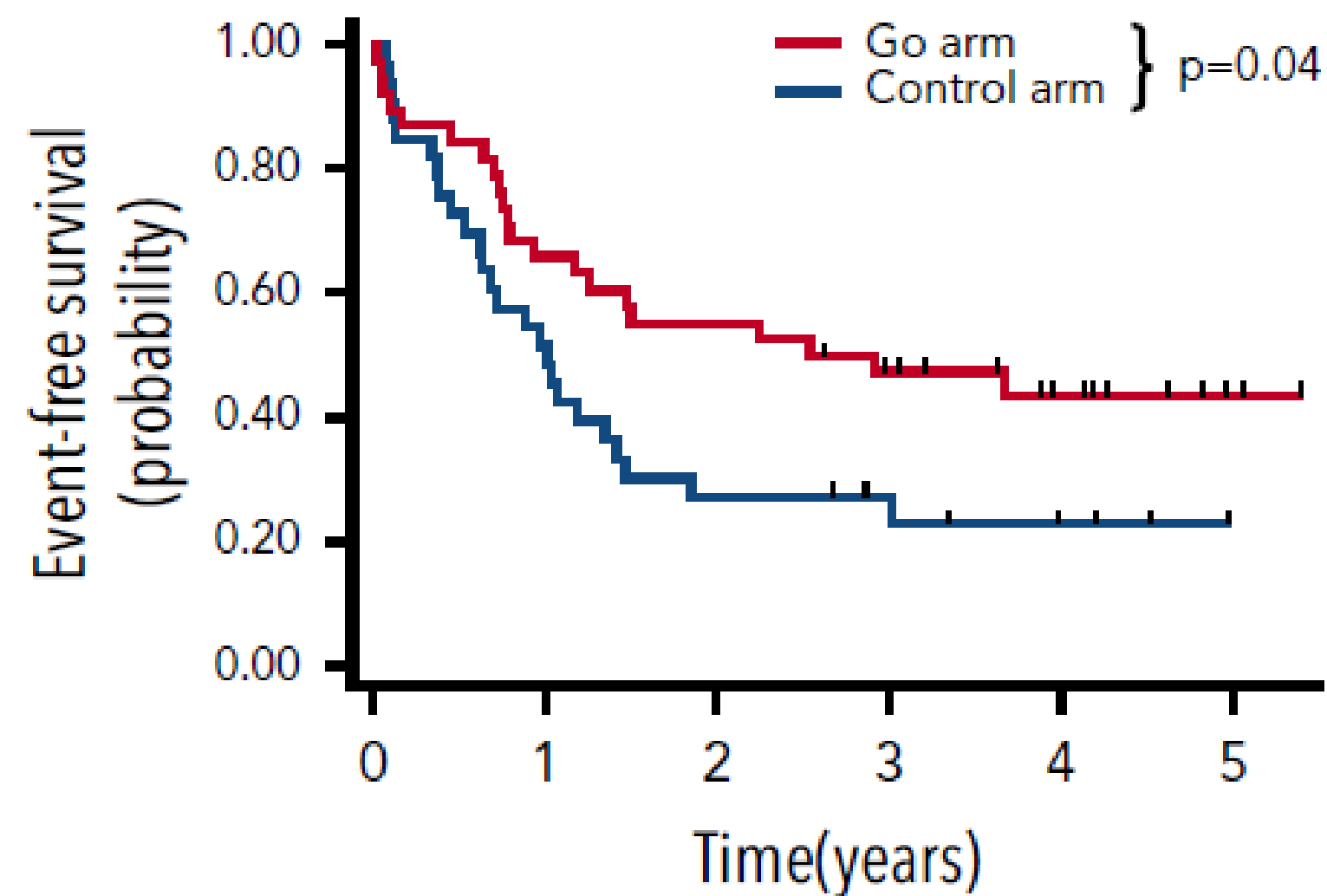


Adapted from Lambert *et al.* 2019
Modified intention-to-treat population; Data cut-off date: 1 August 2011
CI, confidence interval; GO, gemtuzumab ozogamicin; HR, hazard ratio
Lambert J *et al. Haematologica* 2019;104:113–119

Benefit of GO according to ELN classification

A

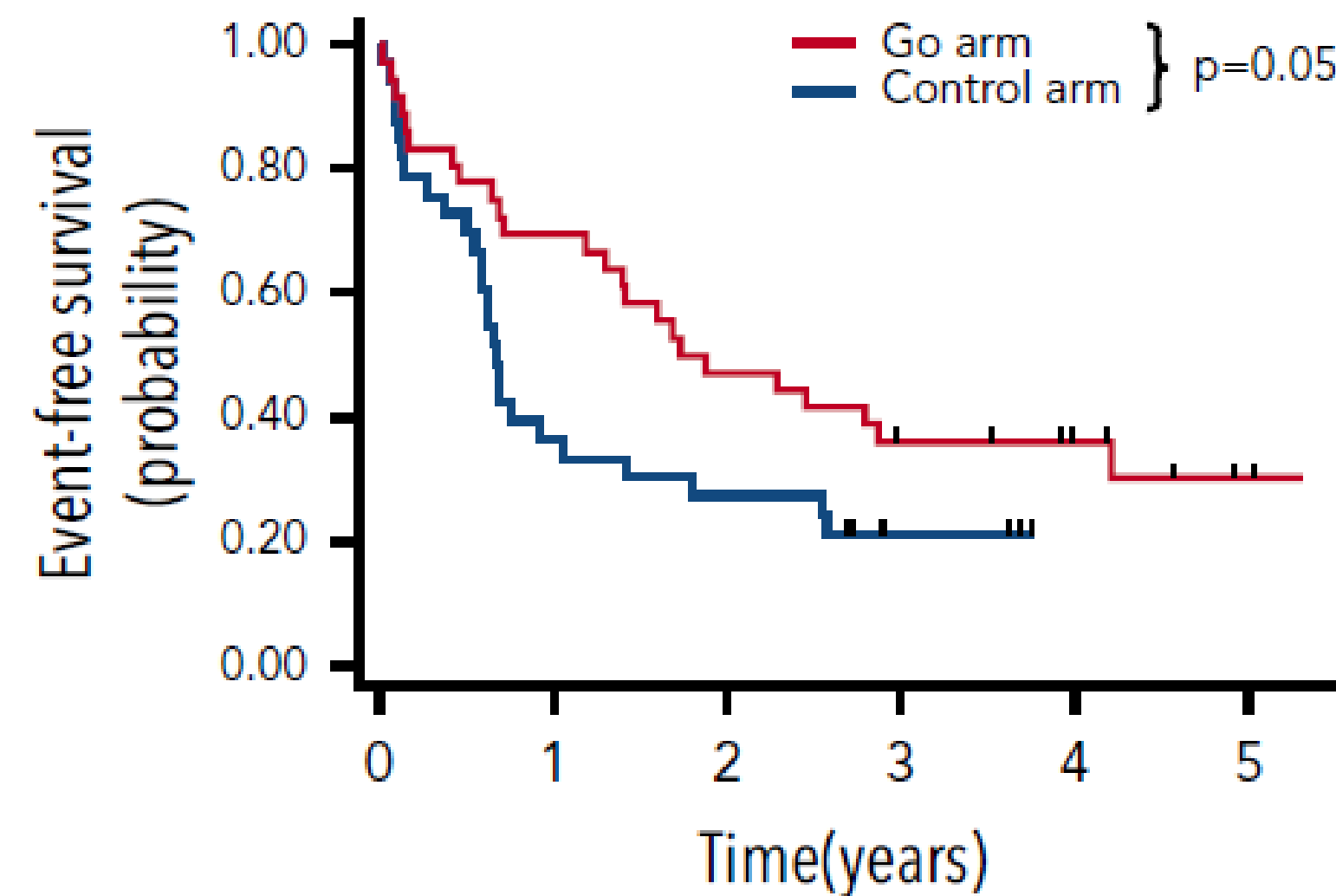
ELN-Favorable



Number at risk						
Control arm	33	17	9	6	3	0
Go arm	38	25	21	16	10	2

B

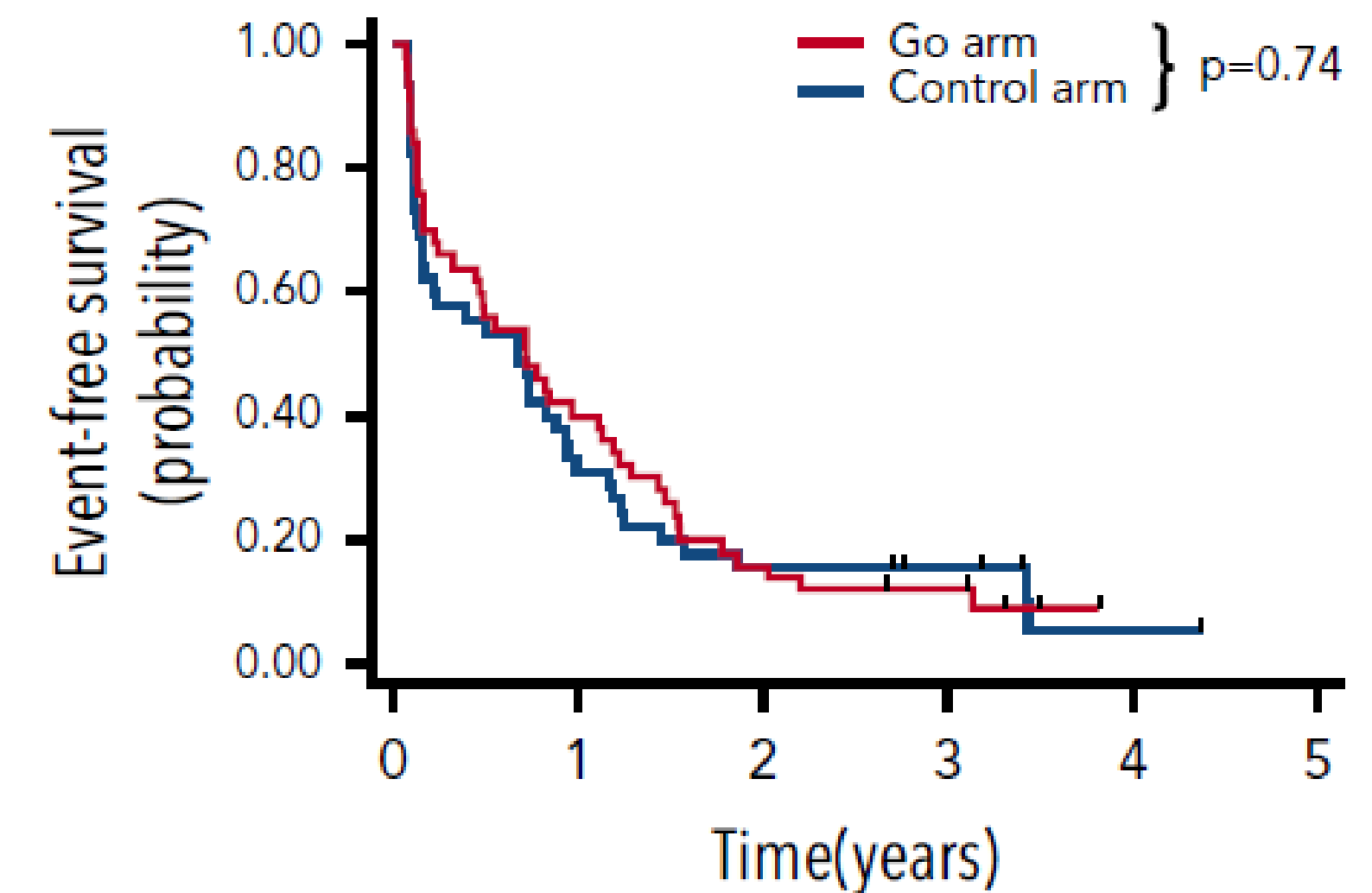
ELN-Intermediate



Number at risk						
Control arm	33	12	9	3	0	0
Go arm	36	25	17	11	7	2

C

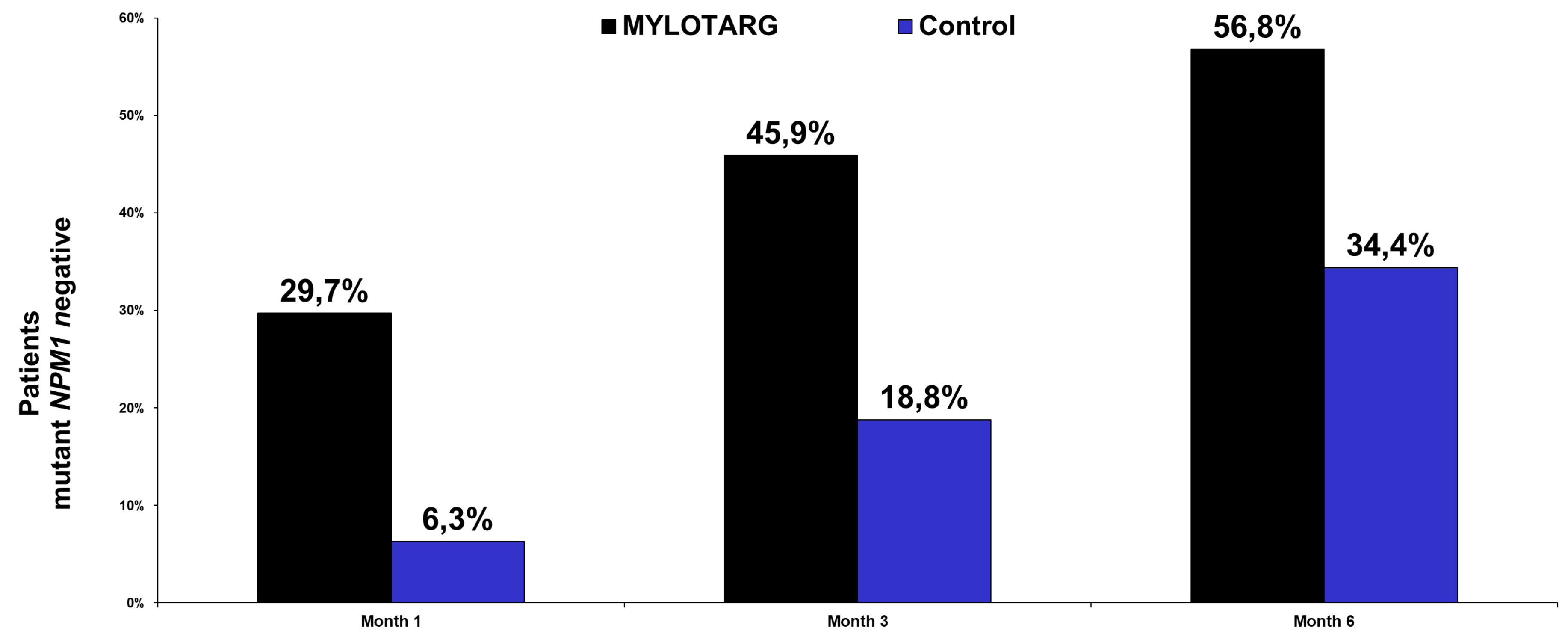
ELN-Adverse



Number at risk						
Control arm	45	14	7	5	1	0
Go arm	50	20	8	5	0	0

EFS according to ELN 2017 subgroups

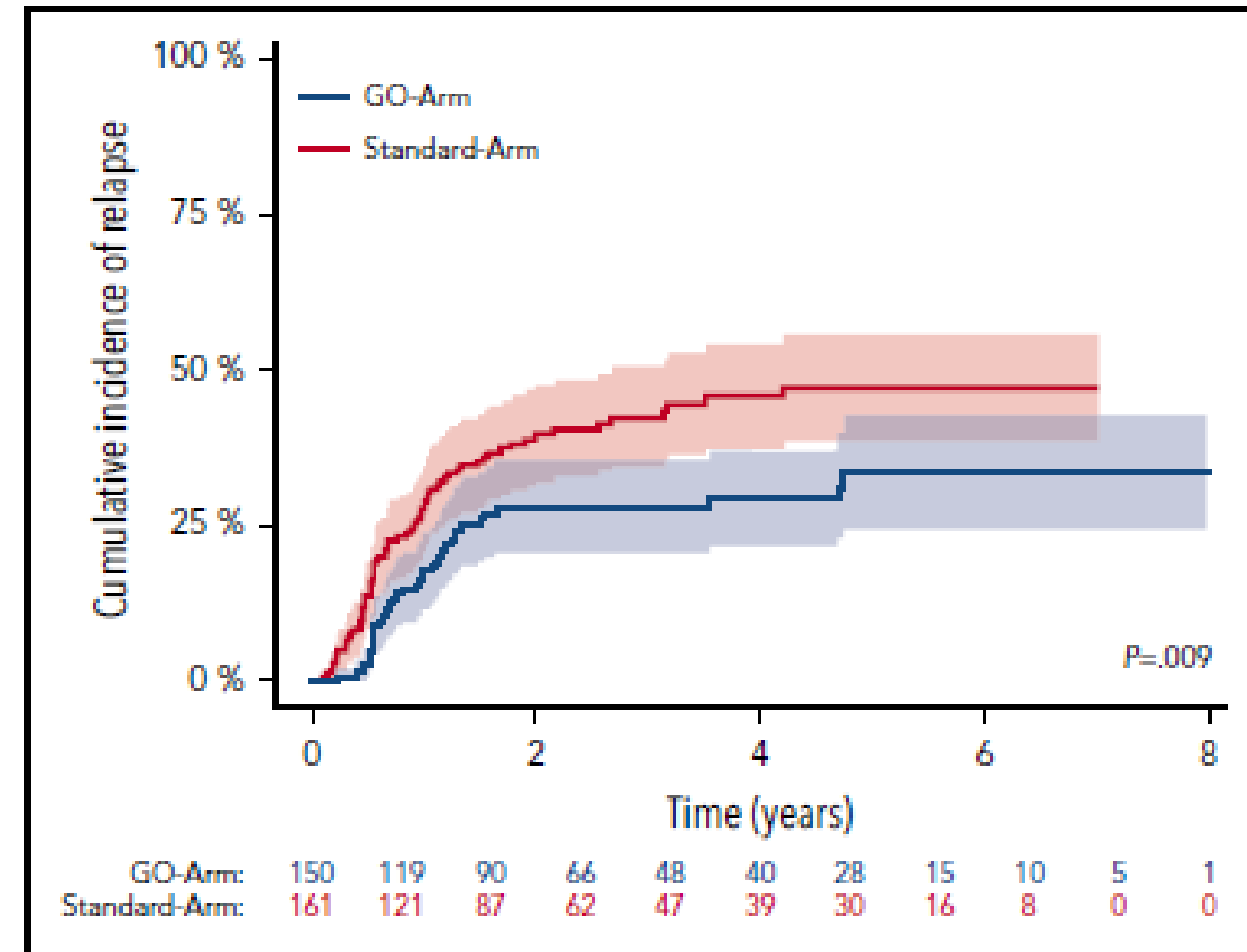
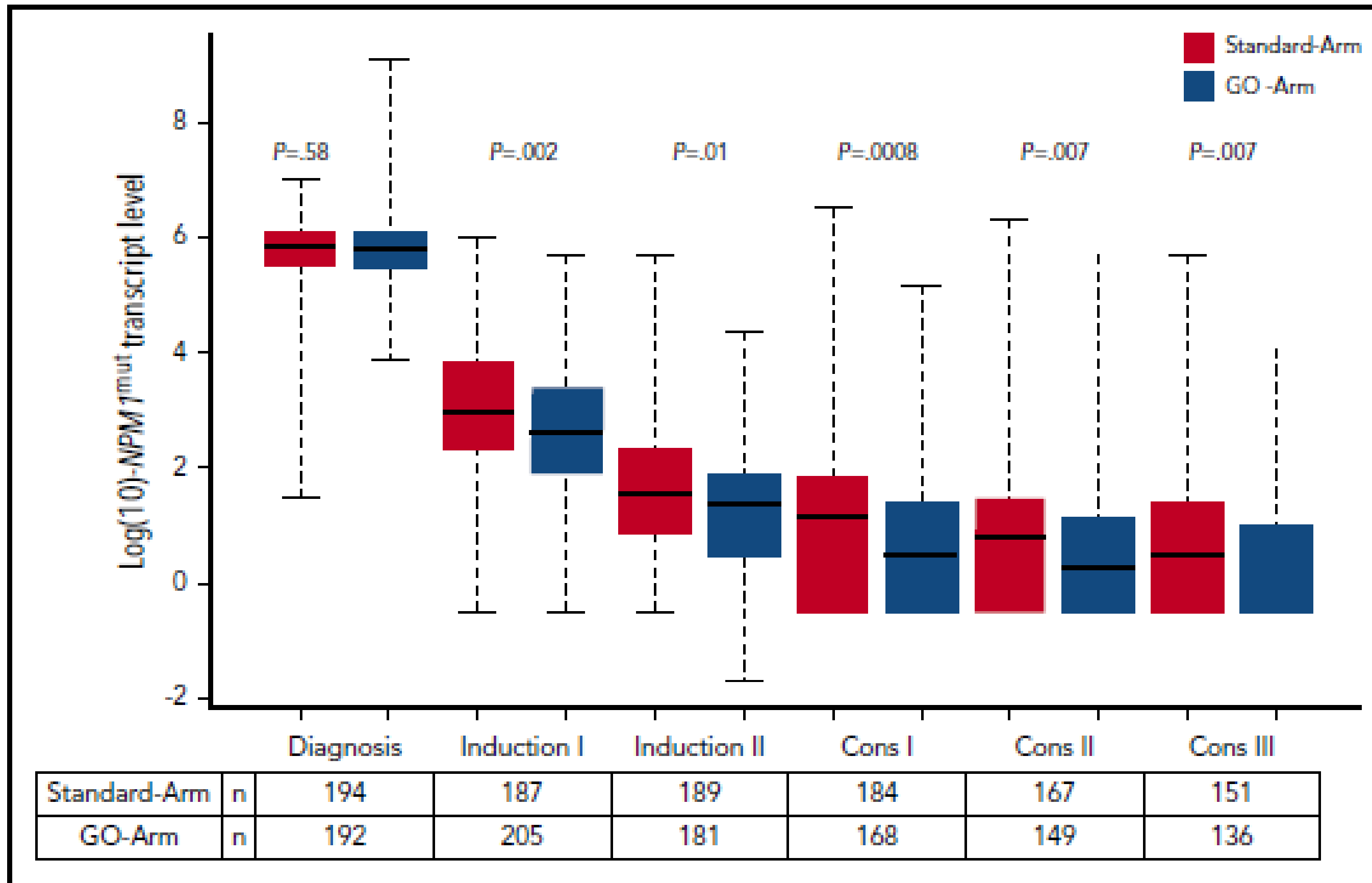
Higher MRD-negativity* rates in patients experiencing CR/CRp following GO (*NPM1*)



	GO	Control	GO	Control	GO	Control
Pts assessed	37	32	34	31	30	29
Pts mut <i>NPM1</i> neg	11	2	17	6	21	11

*MRD negative <0.1% *NPM1*mut copy number/*ABL* copy number × 100 (%);

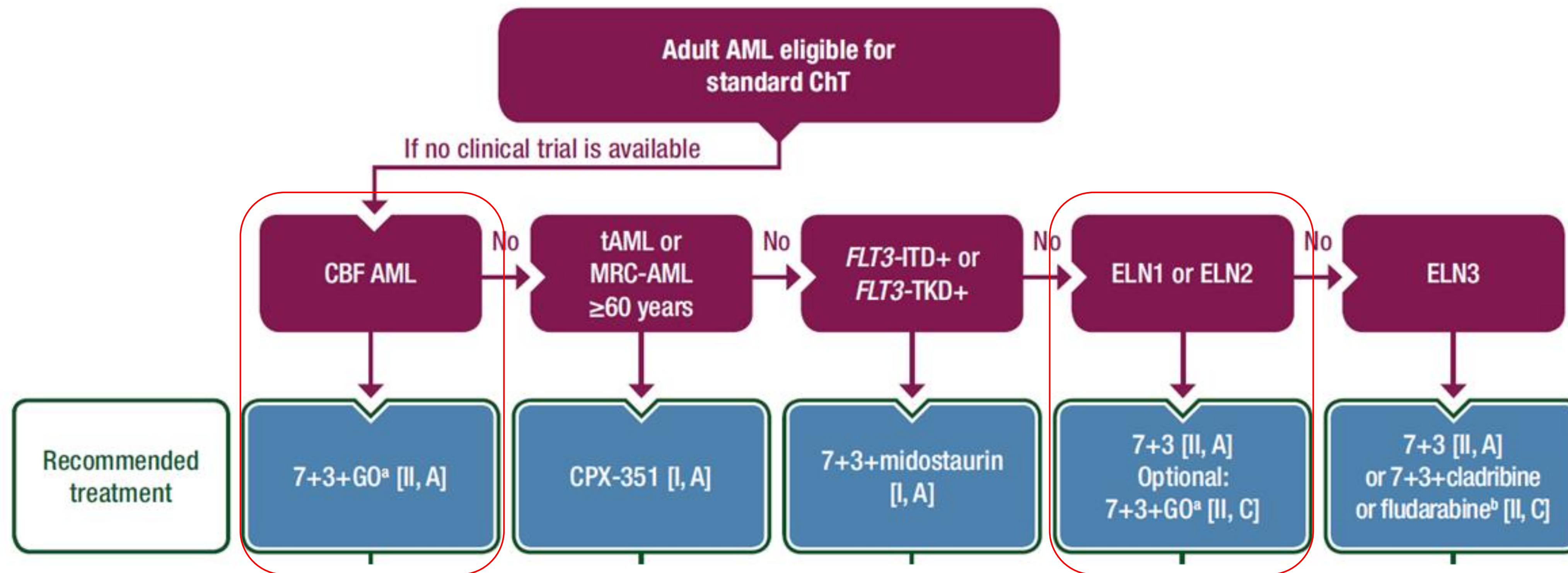
✓ GO given to intensive therapy led to better clearance of NPM1-mut transcript level, resulting in a lower relapse rate



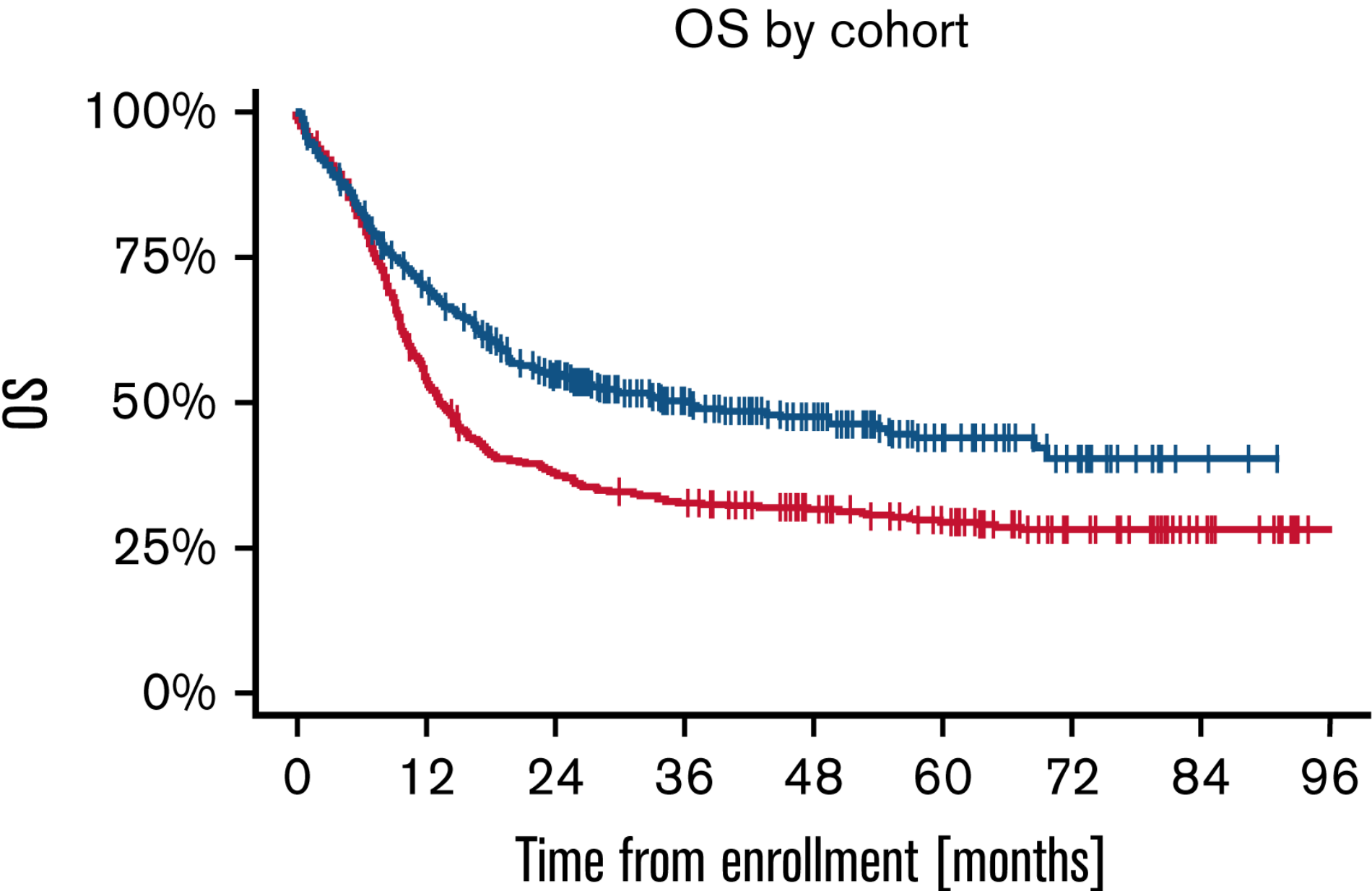
Shwoerer et al. Blood. 2020;136(26):3041-3050

ESMO 2020: Acute myeloid leukaemia in adult patients

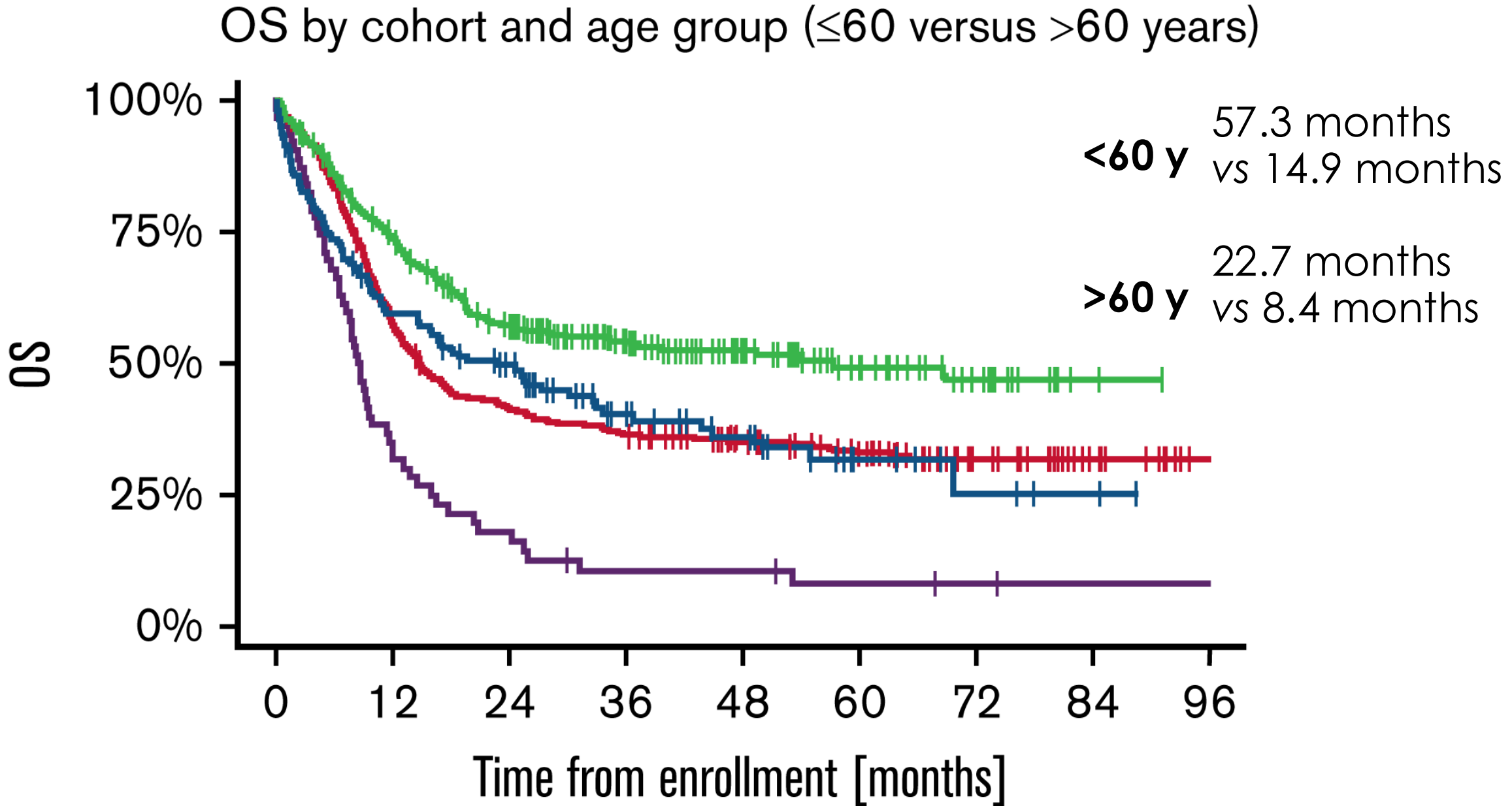
First-line treatment of AML patients eligible for standard induction and consolidation ChT (FIT)



Midostaurin plus IC for younger and older patients with ND-AML and *FLT3*-ITD



Cohort									
Historical	415	220	152	130	106	88	62	40	28
16–10	440	290	211	128	80	41	19	4	0

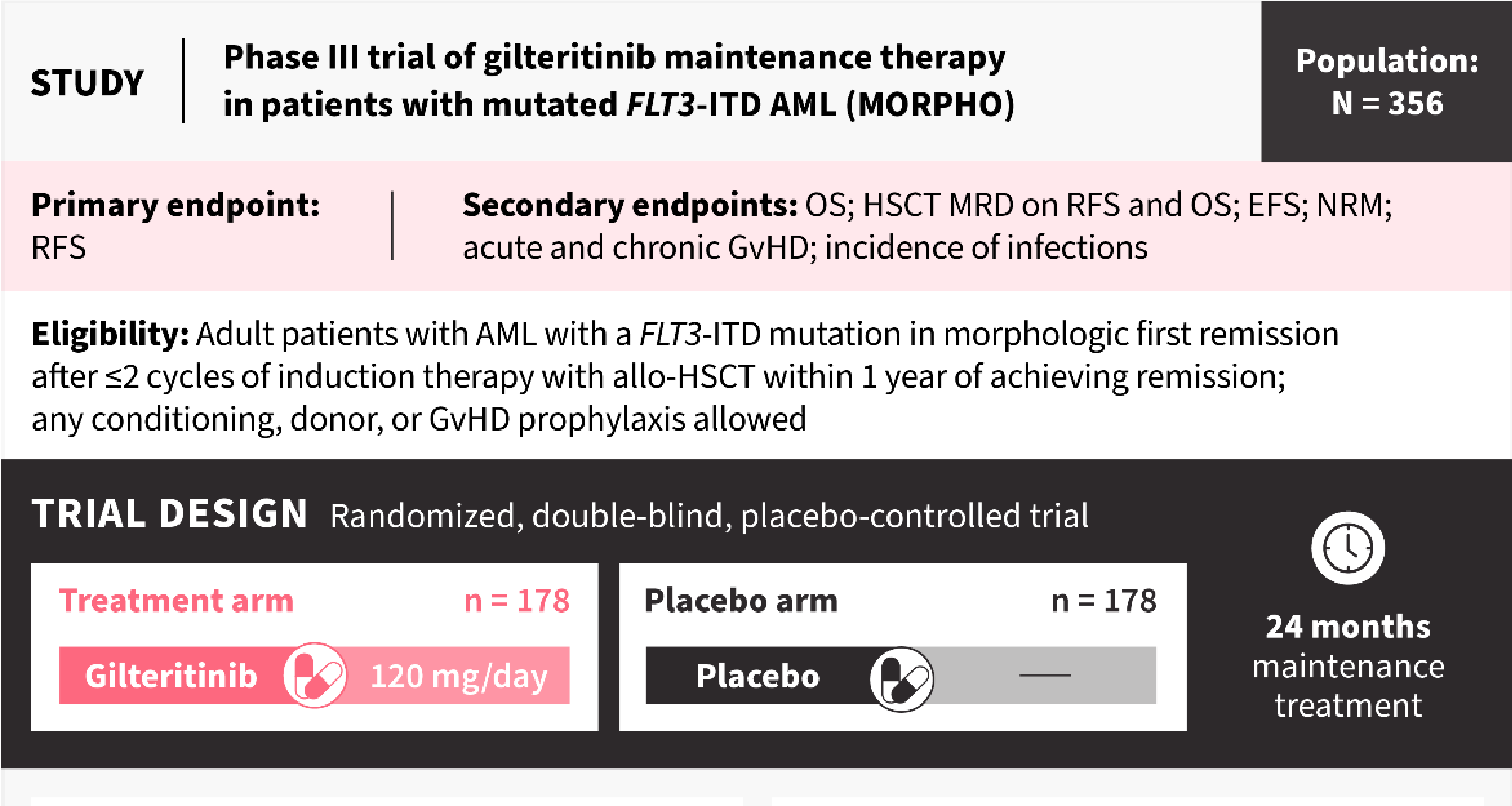


Cohort									
Historical (≤ 60)	352	201	142	125	101	85	60	39	27
16–10 (≤ 60)	312	217	155	95	60	33	15	2	0
Historical (>60)	63	19	10	5	5	3	2	1	1
16–10 (>60)	128	73	56	33	20	8	4	2	0

Key Points

- Midostaurin as adjunct to chemotherapy significantly improves outcome in younger and older patients with AML and *FLT3*-ITD
- The data provide evidence for the use of midostaurin as the standard of care also for older patients with *FLT3*-mutated AML

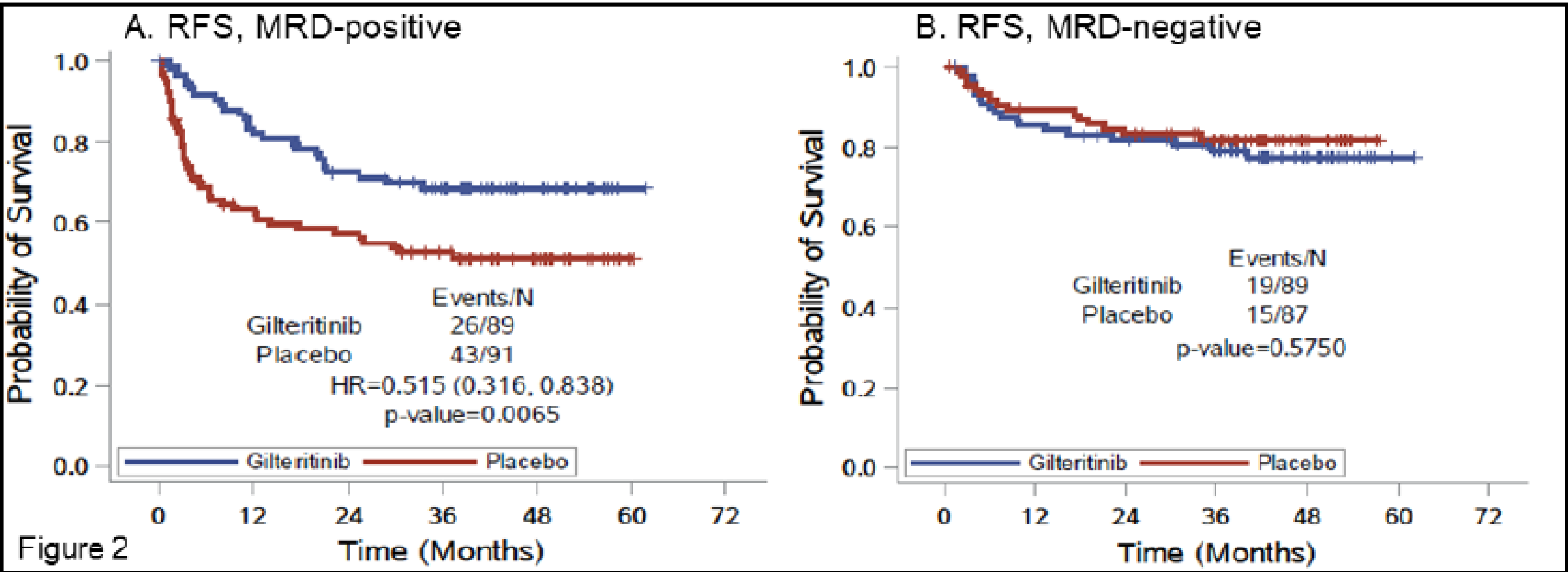
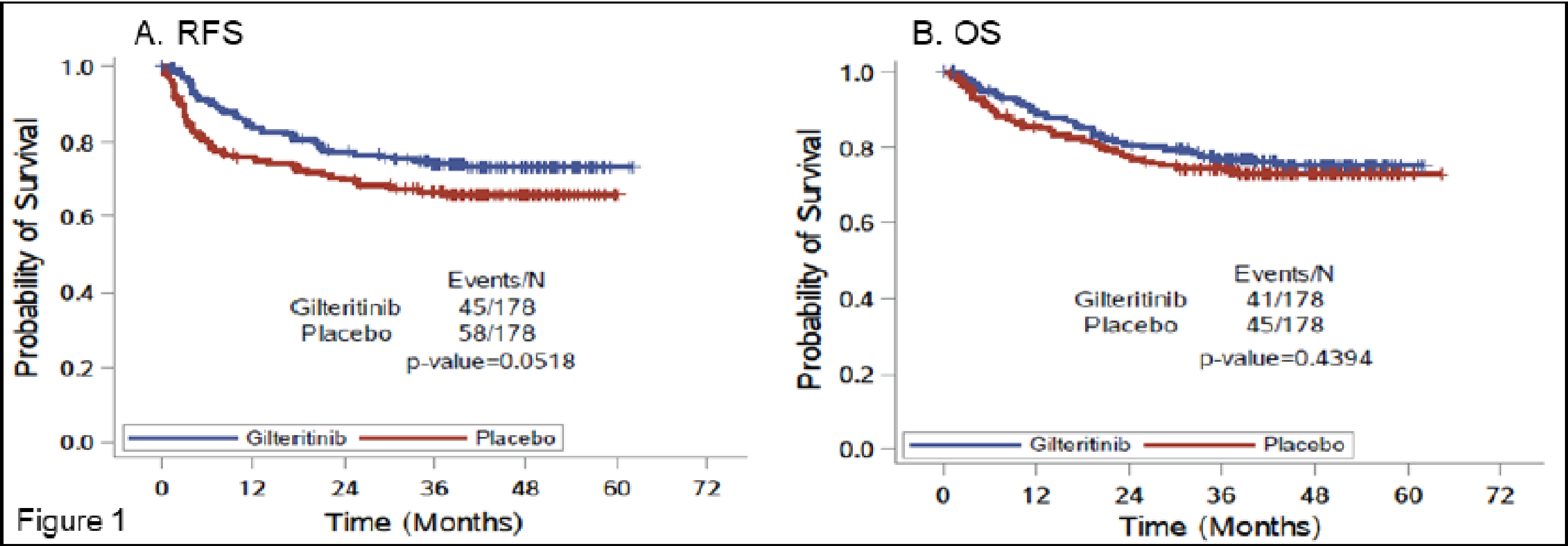
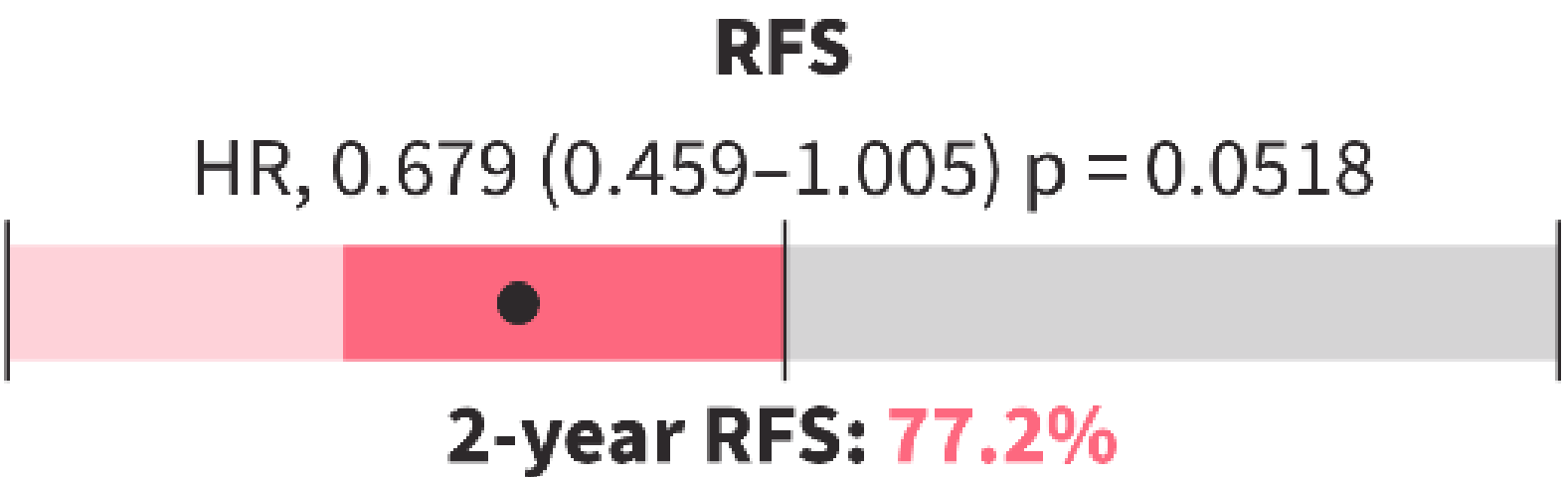
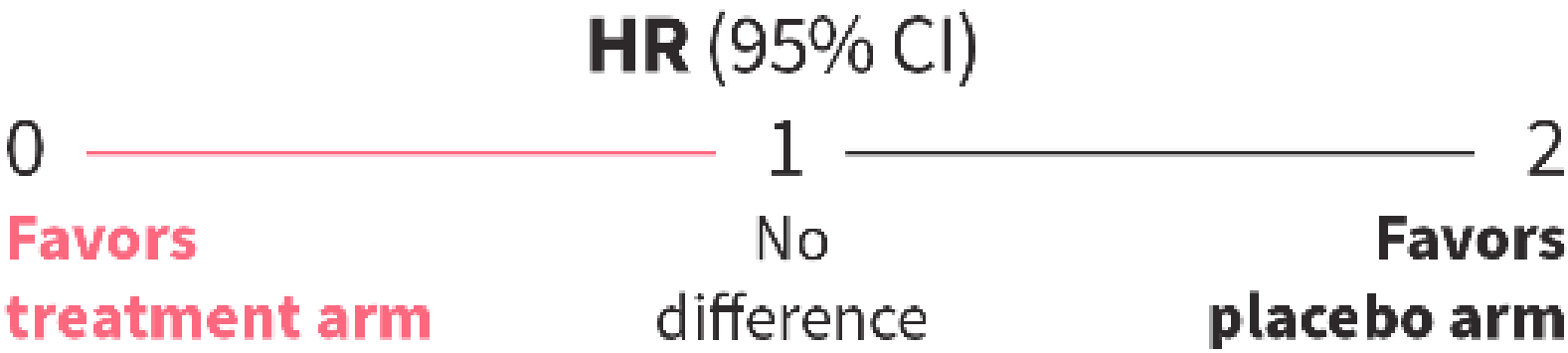
Phase III trial of gilteritinib maintenance therapy in patients with mutated *FLT3*-ITD AML (MORPHO)



- In March 2023, Astellas announced disappointing top-line results from the Phase III MORPHO clinical trial.
- The data showed that the study did not meet its pre-defined primary endpoint of relapse-free survival (RFS) for patients treated with gilteritinib compared to placebo.

Phase III trial of gilteritinib maintenance therapy in patients with mutated FLT3-ITD AML (MORPHO)

EFFICACY

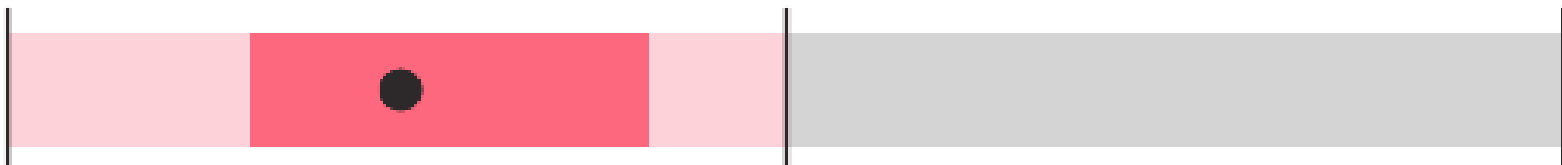


Phase III trial of gilteritinib maintenance therapy in patients with mutated FLT3-ITD AML (MORPHO)



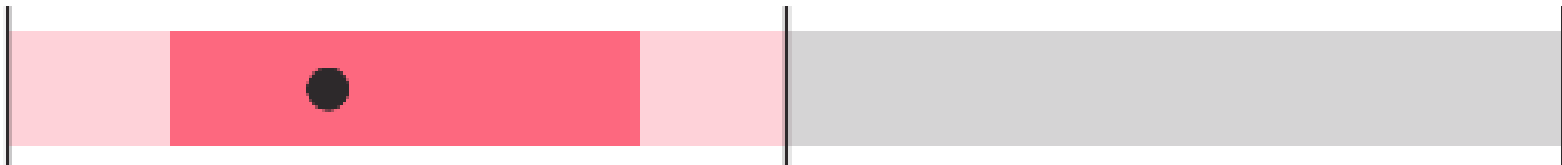
RFS in MRD+ patients

HR, 0.515 (0.316–0.838) $p = 0.0065$

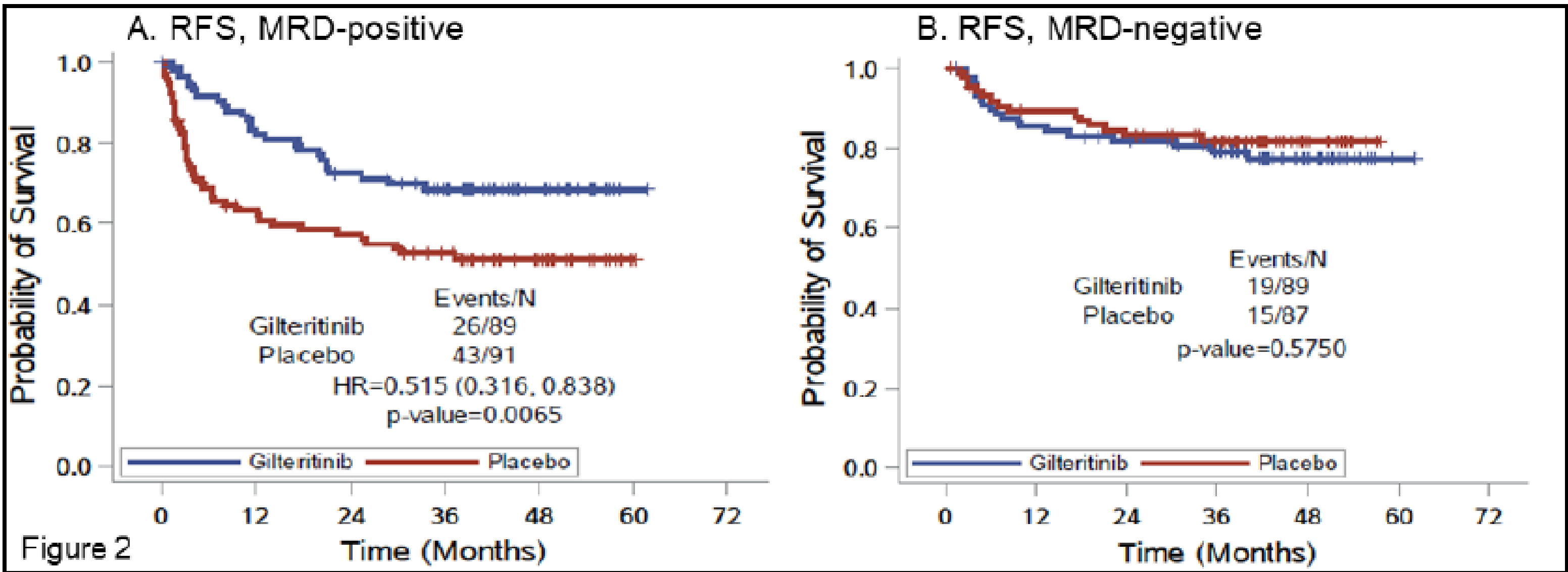
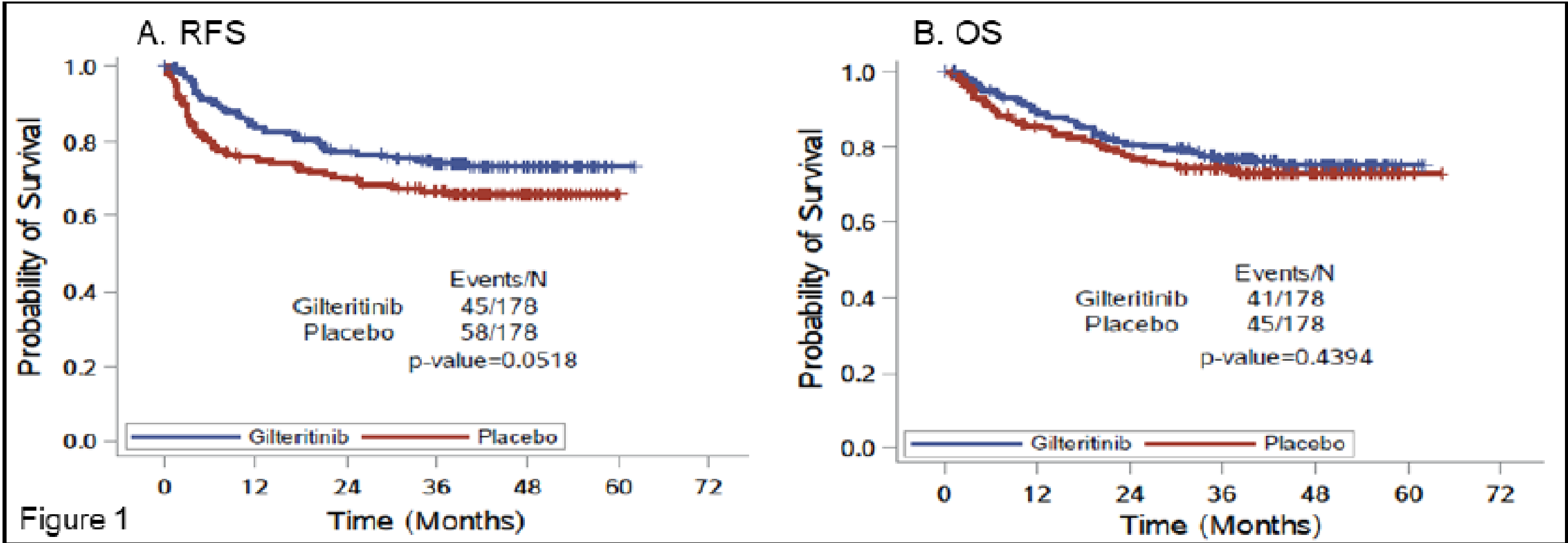


RFS in MRD+ patients who received MAC

HR, 0.418 (0.213–0.818) $p = 0.0087$

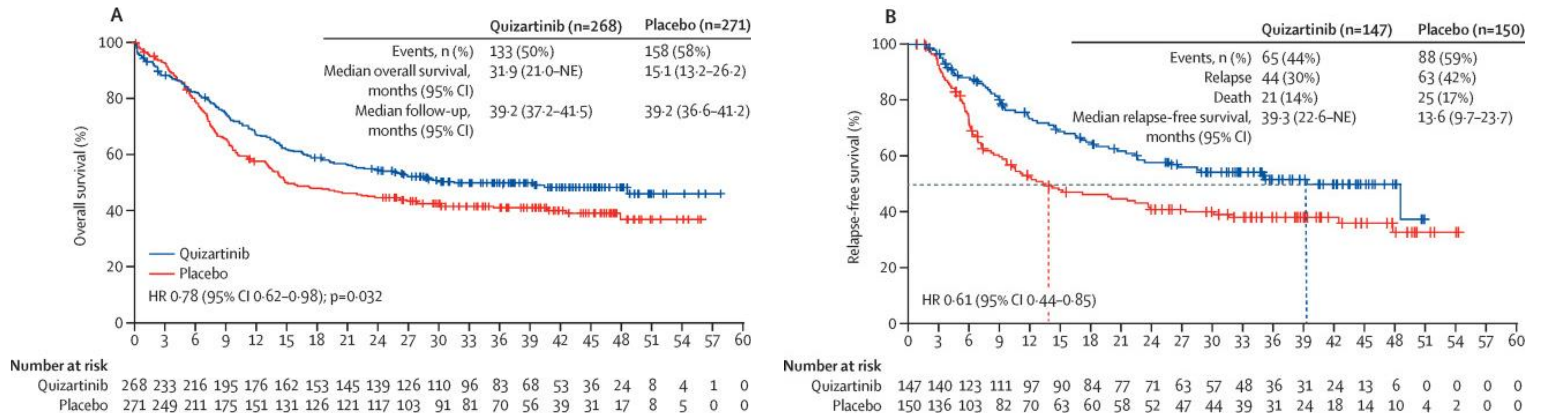


- Gilteritinib maintenance therapy could be the standard of care for patients with FLT3-ITD AML MRD+ pre- or post-allo-HSCT



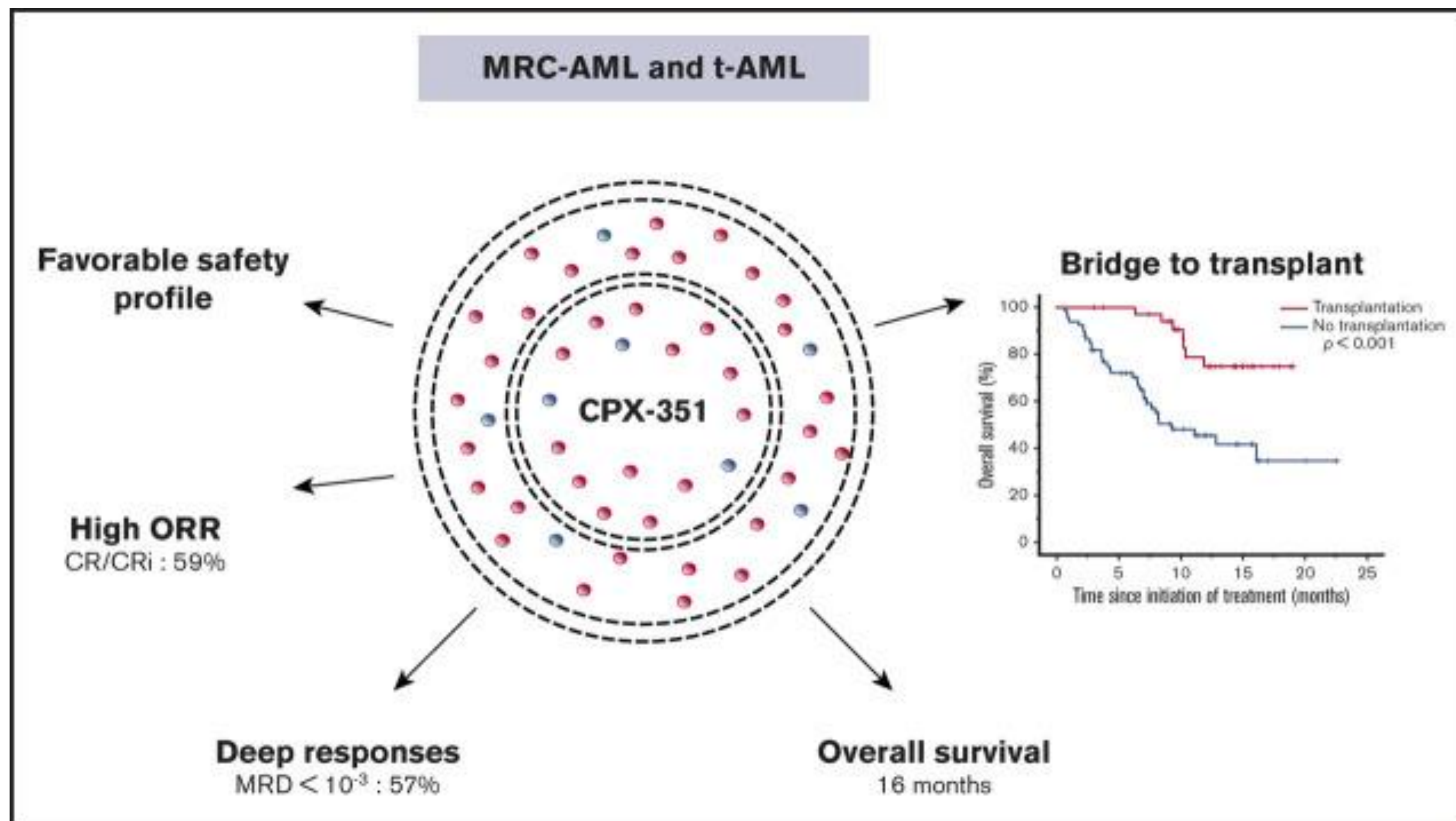
QuANTUM-First : FDA-approved QUIZARTINIB (July, 2023)

Quizartinib plus chemotherapy in newly diagnosed patients with *FLT3*-ITD-positive AML(QuANTUM-First): a randomised, doubleblind, placebo-controlled, phase 3 trial



QuANTUM-First is the first trial to evaluate the efficacy and safety of the potent and selective *FLT3*-ITD type 2 inhibitor quizartinib in patients aged **18–75 years** with *FLT3*-ITD-positive newly diagnosed AML alongside standard induction and consolidation chemotherapy, including allo-HCT, then single-agent continuation therapy for up to 3 years.

CPX-351 : high CR rates in otherwise resistant MRC- and t-AML



Main reference (Registration study)

- Lancet JE, et al. J Clin Oncol 2018; 36: 2684

Main references ('real-life-experience):

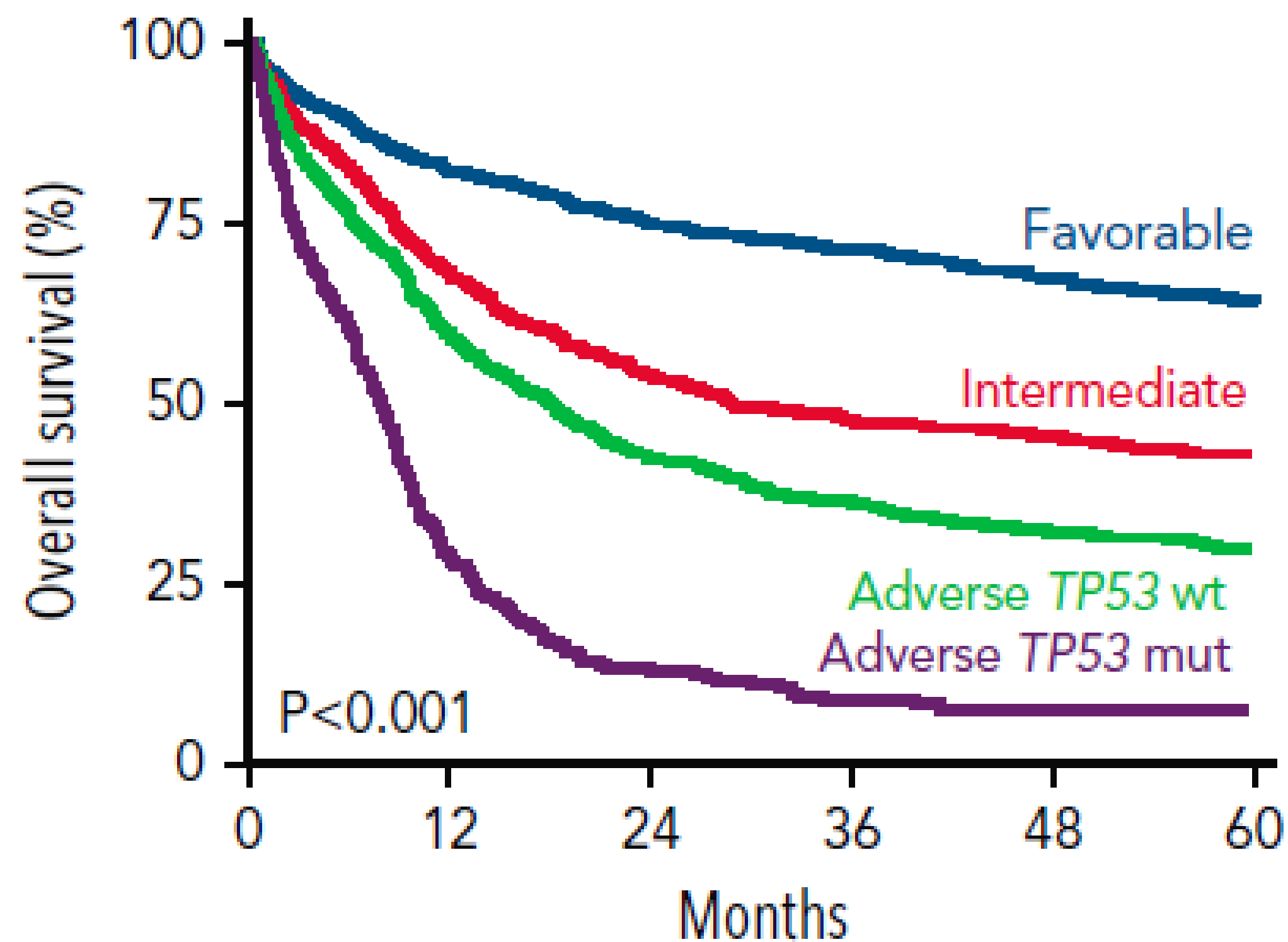
- Rautenberg C, et al. (2021) Blood cancer journal, 11(10), 164.

- Chiche E, et al. (2021) Blood Adv, 5(1), 176.

- Guolo F, et al. (2020) Blood cancer journal, 10(10), 96.

Chiche E, et al. (2021) Blood Adv, 5(1), 176.

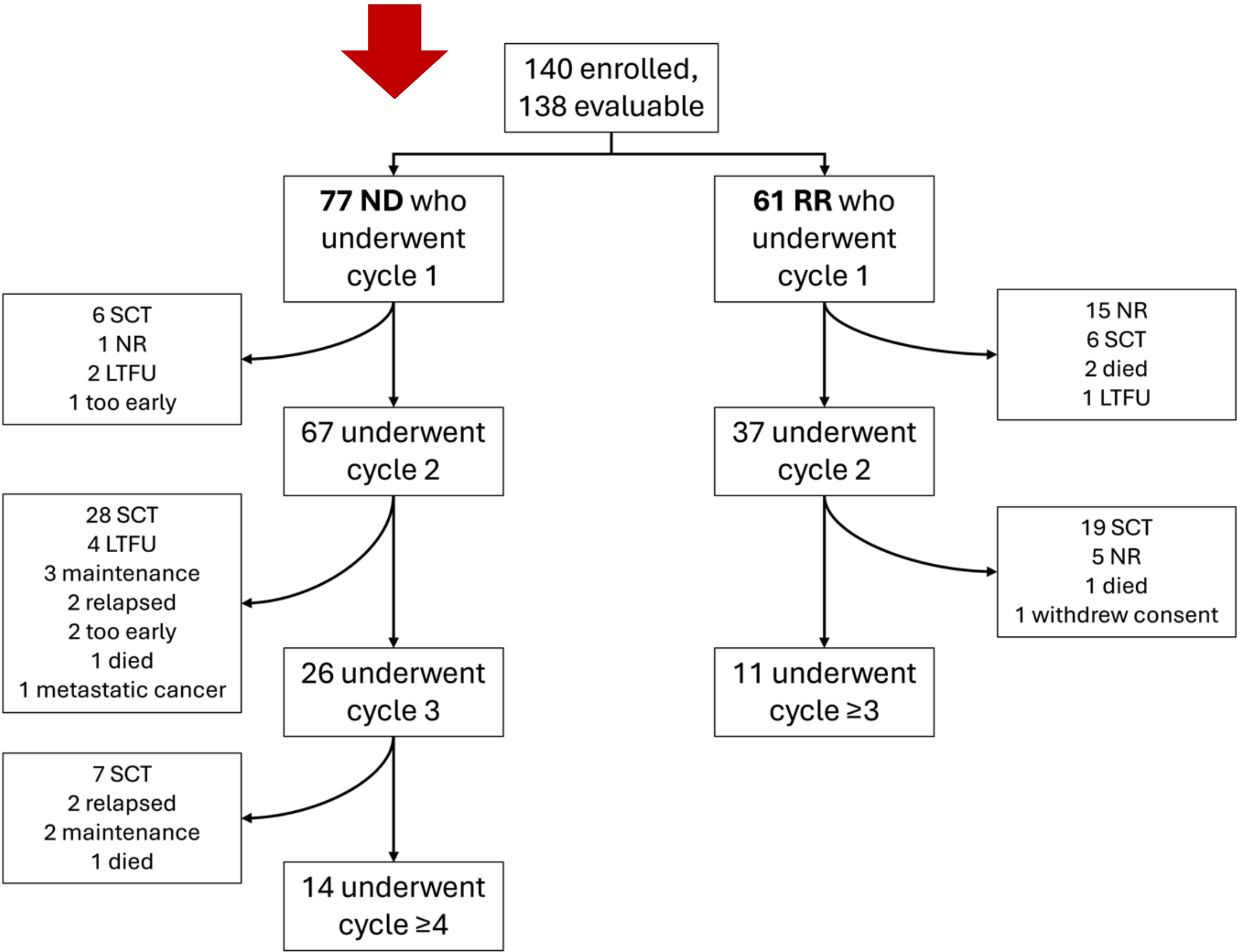
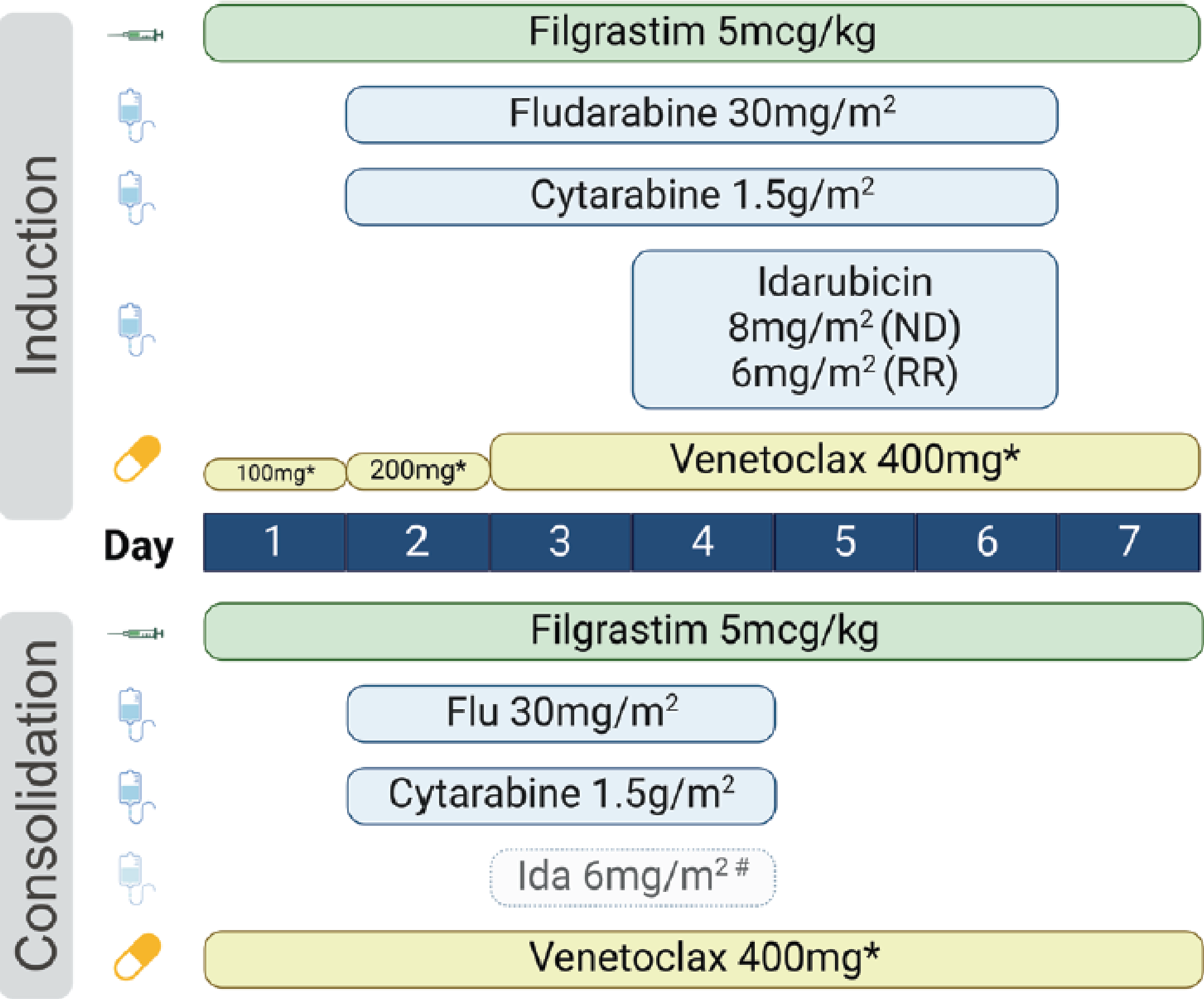
ELN 2022 risk stratification with *TP53* mutation defining a unique ‘very adverse’ subgroup within high-risk AML



No. at risk:						
Favorable	713	581	520	432	313	228
Intermediate	602	402	308	236	162	115
Adverse <i>TP53</i> wt	655	386	267	201	142	89
Adverse <i>TP53</i> mut	230	65	28	15	9	5

IC + venetoclax in ND (and R/R) AML

FLAG-IDA + VEN, NCT03214562

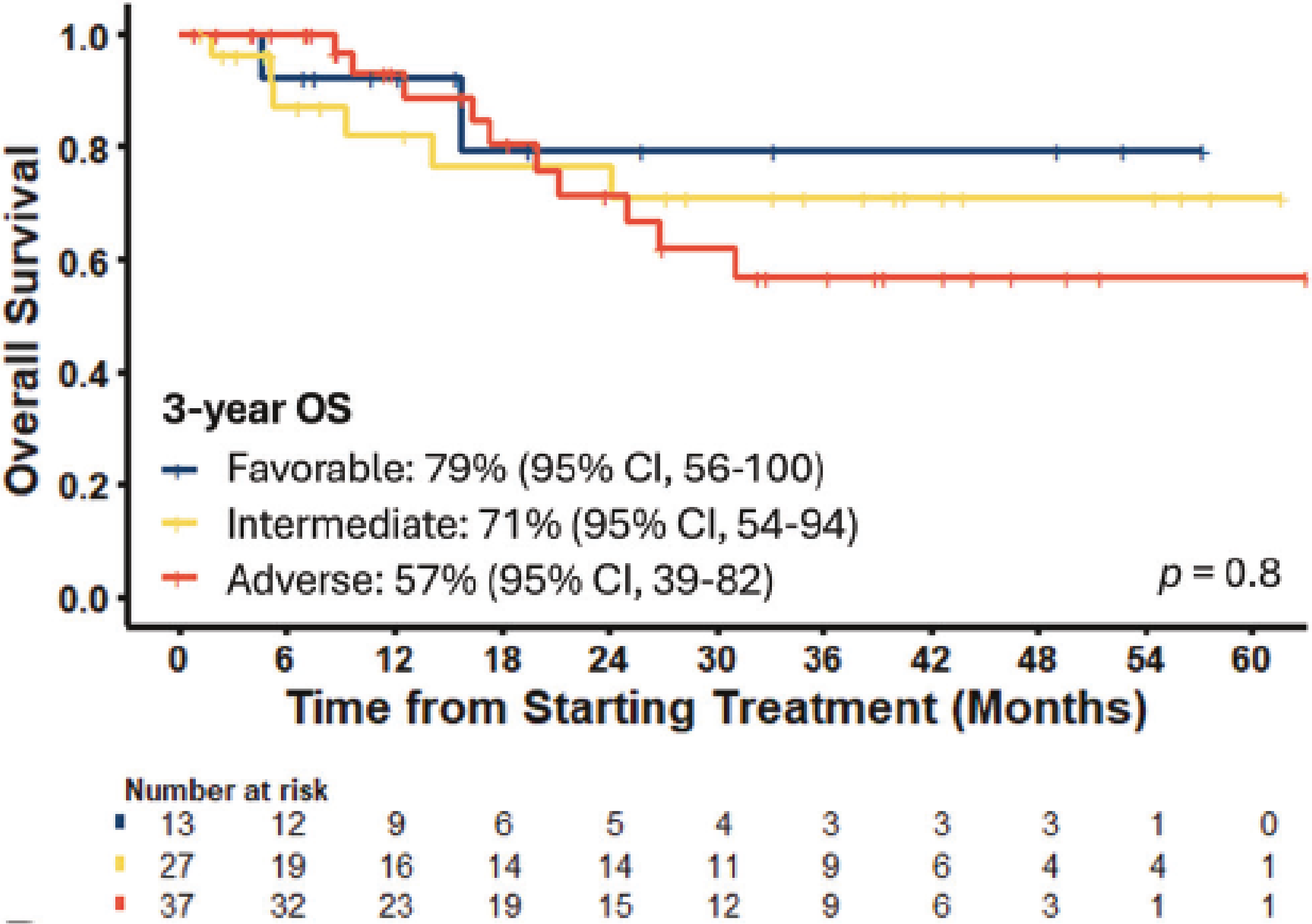
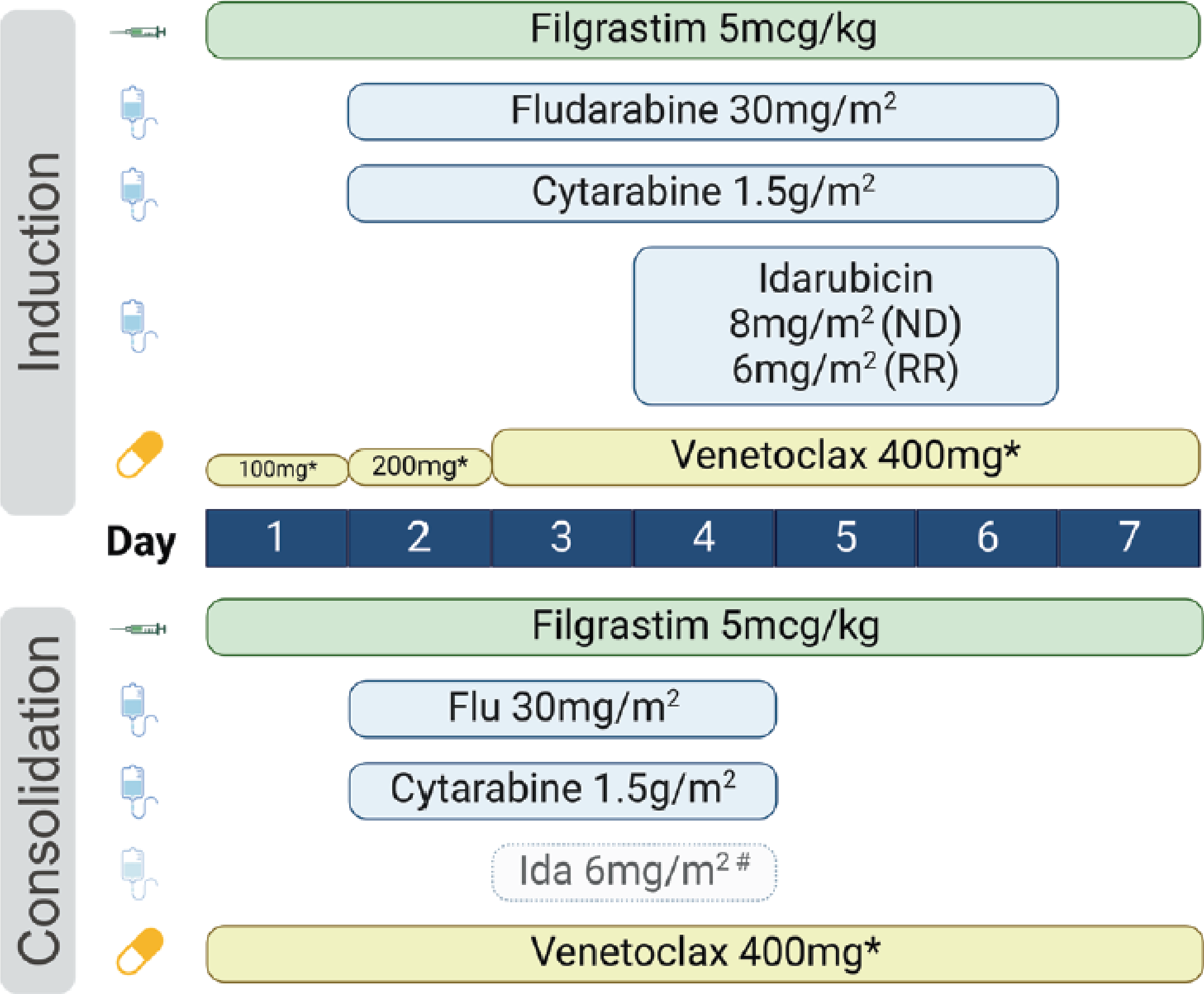


DiNardo et al. *Leukemia* (2025). <https://doi.org/10.1038/s41375-025-02531-8>.

IC + venetoclax in ND (and R/R) AML

FLAG-IDA + VEN, NCT03214562

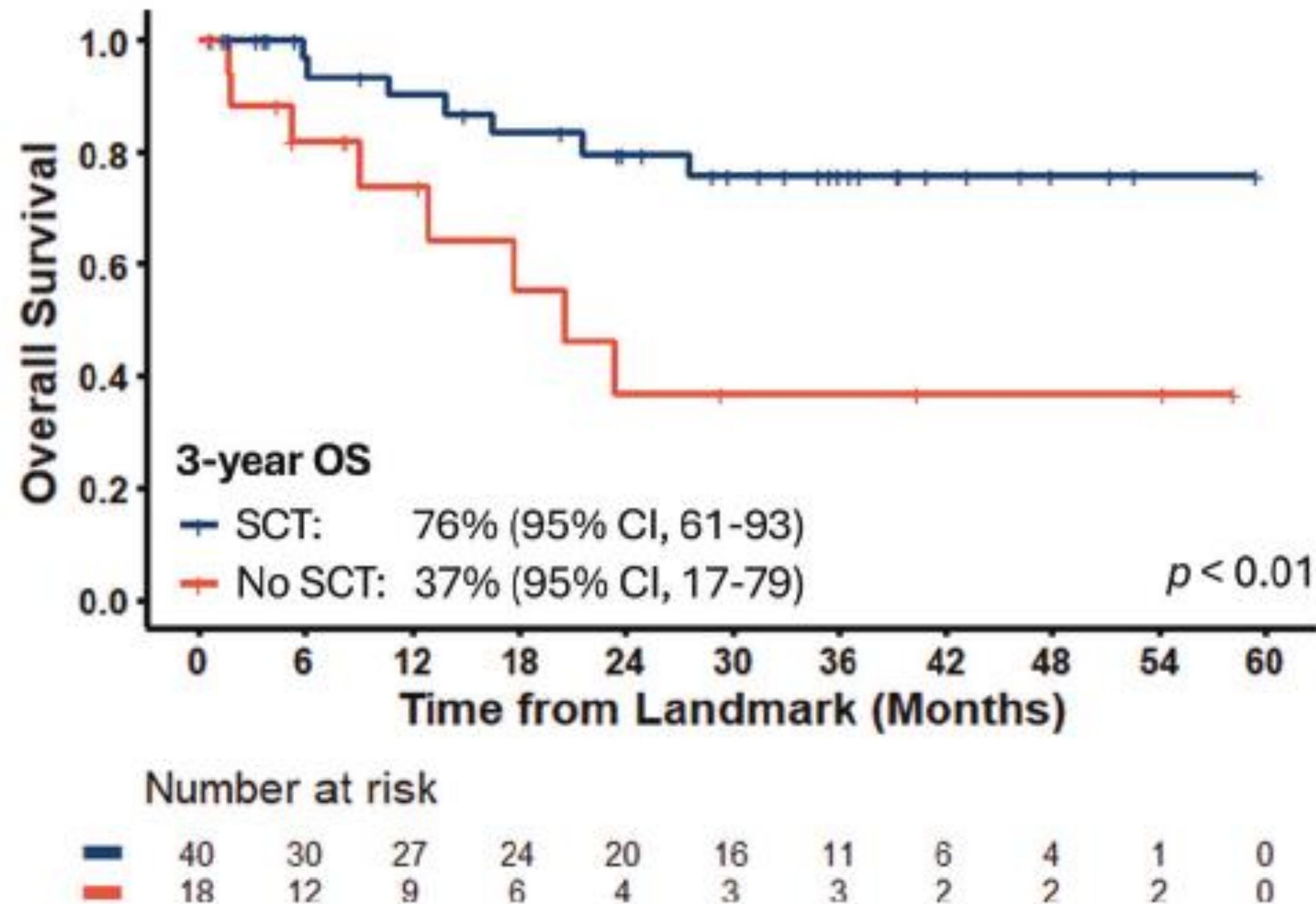
• ND-AML, ELN 2022



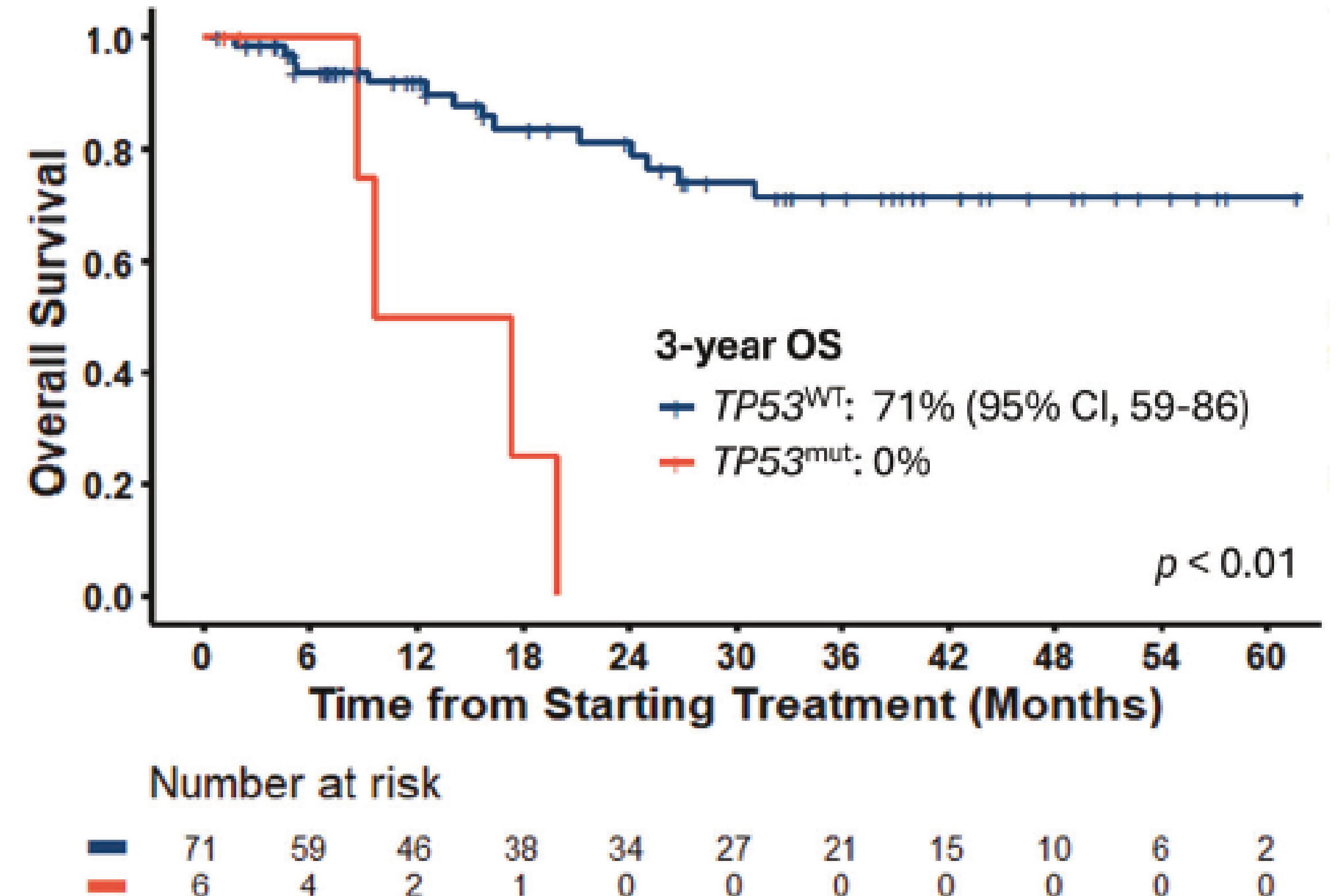
DiNardo et al. *Leukemia* (2025). <https://doi.org/10.1038/s41375-025-02531-8>.

IC + venetoclax in ND (and R/R) AML

- Int-Adv risk ND-AML, ELN 2022

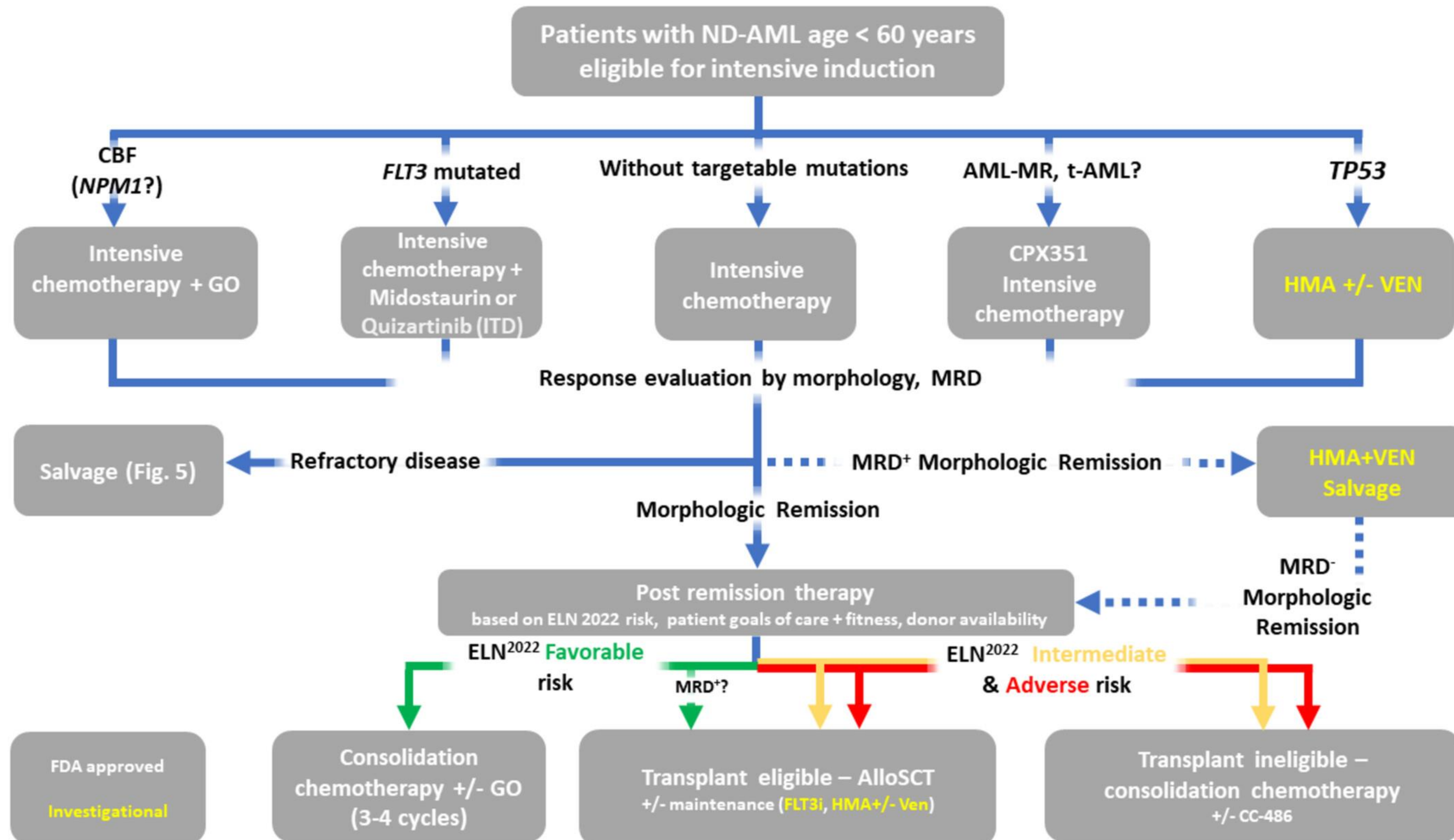


- TP53*-mut ND-AML, ELN 2022



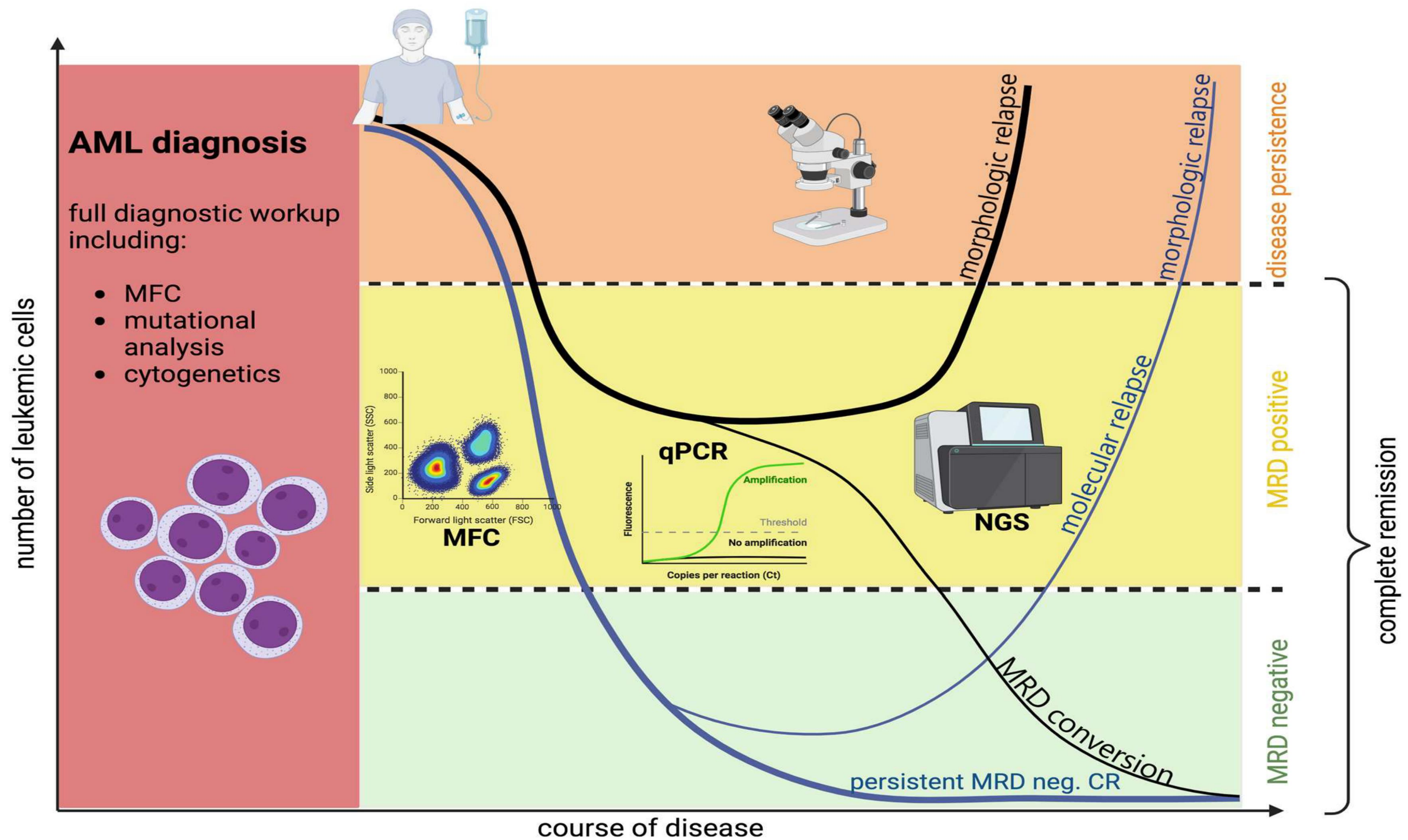
DiNardo et al. *Leukemia* (2025). <https://doi.org/10.1038/s41375-025-02531-8>.

Acute Myeloid Leukemia: 2025 Update on Diagnosis, Risk-Stratification, and Management



Shimony, Stahl, Stone. American J Hematol, 100(5):860-891, 2025

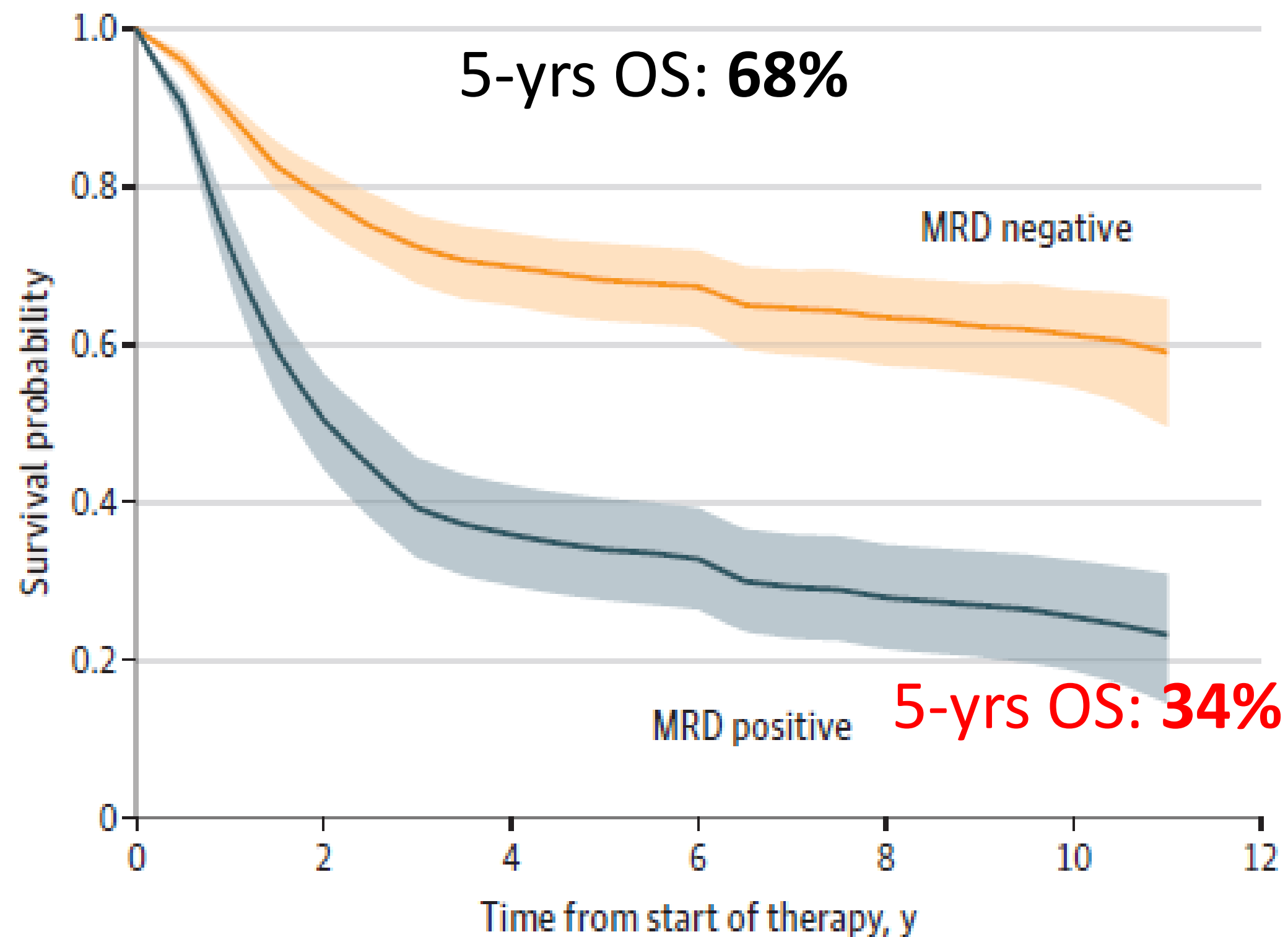
Eradication of the ‘founding clone’ and MRD negativity: the goal of therapy



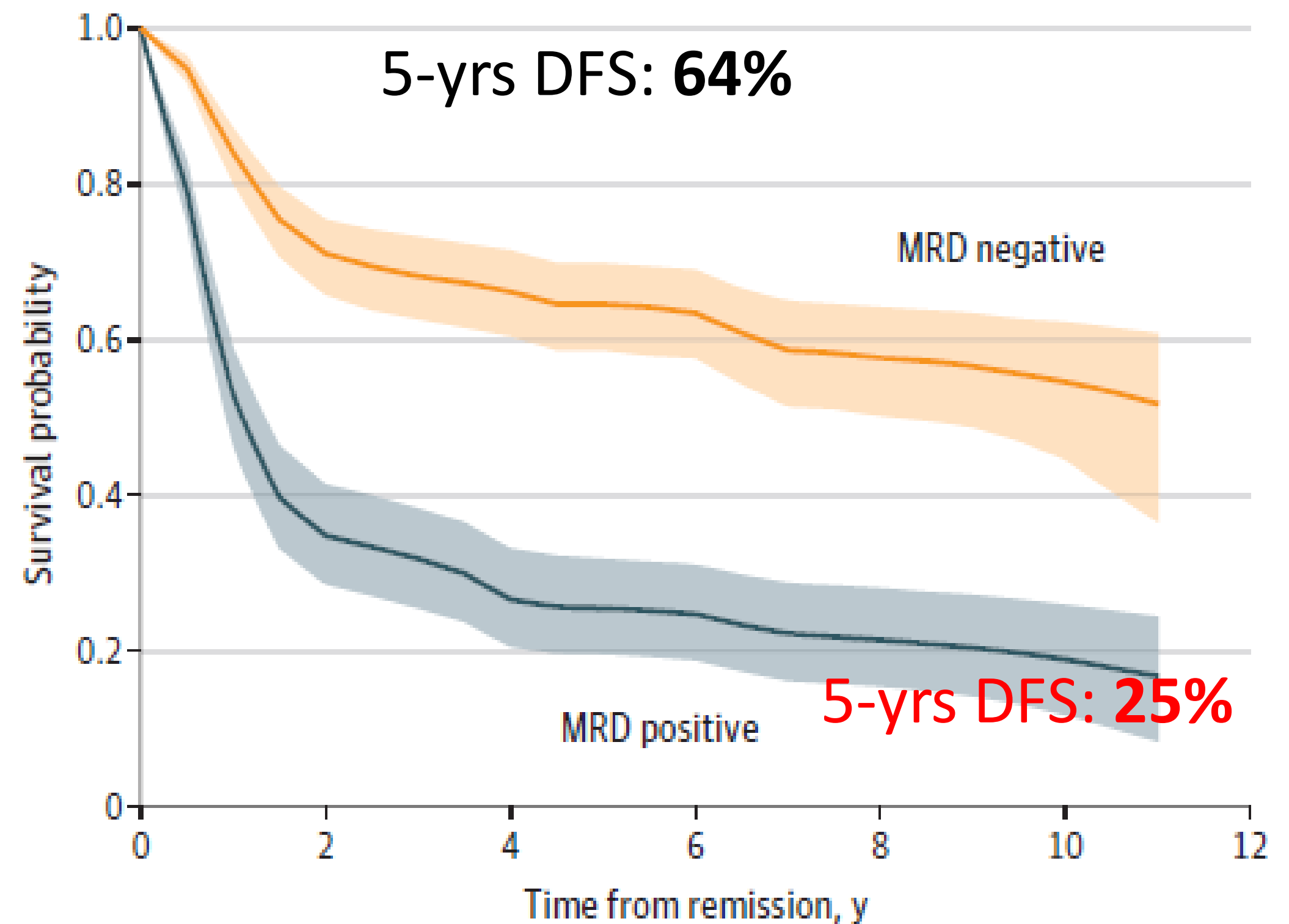
Association of Measurable Residual Disease With Survival Outcomes in Patients With Acute Myeloid Leukemia

A Systematic Review and Meta-analysis

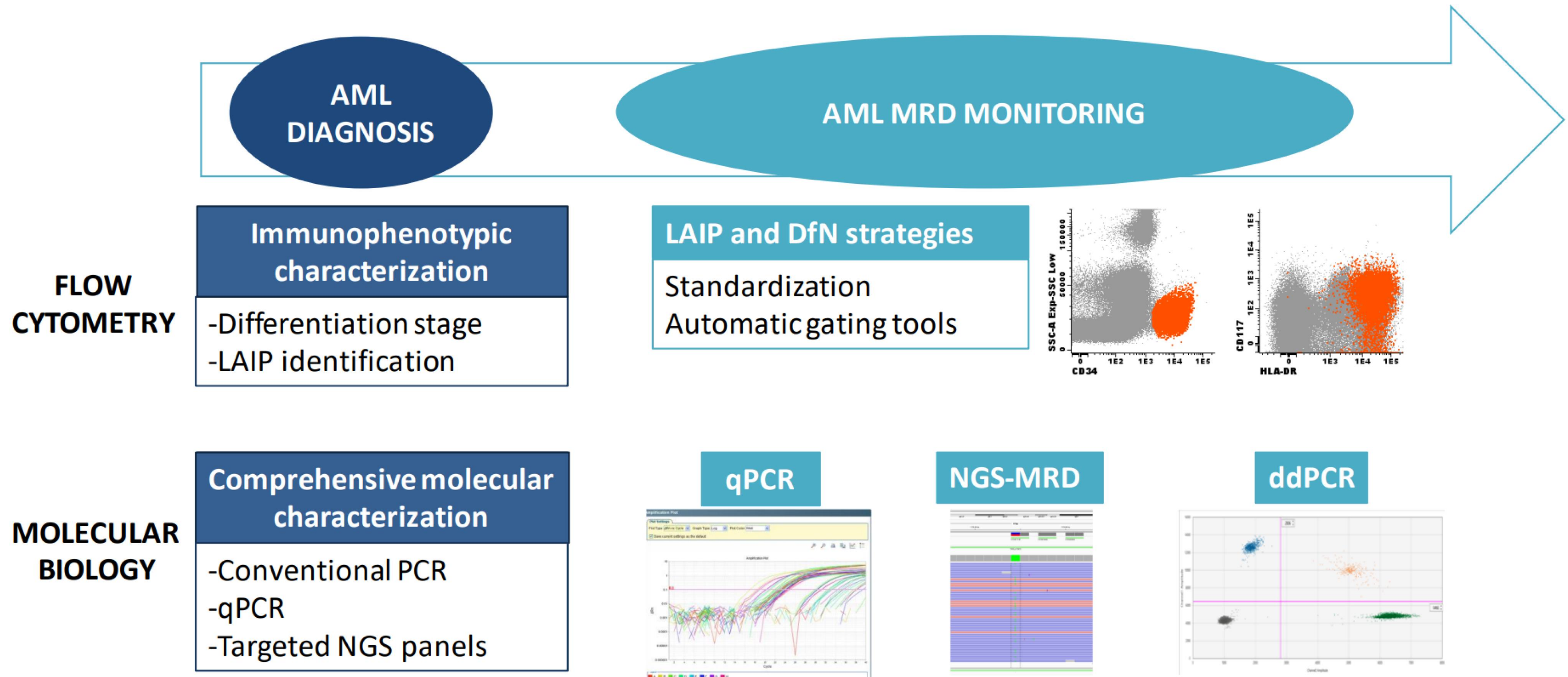
A Overall survival



B Disease-free survival



Tools for diagnosis and monitoring of AML



Guijarro et al. *Curr. Oncol.* 2023, 30(6), 5201-5213

2025 Consensus from the ELN-DAVID MRD Working Party

2025 Update on MRD in Acute Myeloid Leukemia:
A Consensus Document from the ELN-DAVID
MRD Working Party

1

Genetic ELN Risk Groups

Favorable

Intermediate

Adverse

2

Choice of Assay

Flow cytometry

qPCR

High-sensitivity NGS

3

MRD Assessment

Time point

Tissue

4

Technical Recommendations

Standardization

Analysis strategy

Cutoffs

5

Definitions for MRD Results

Negative

Low-level positive

Positive

Optimal

Warning

High risk of treatment failure

Prognosis

Treatment guidance

Clinical trials

5

Clinical Recommendations

MRD burden

Qualitative MRD response

Prognosis

Treatment guidance

Clinical trials

Created with BioRender.com Bachas C. (2026) <https://BioRender.com/82o7yaw>

Conclusions: The 2025 ELN MRD consensus recommendation for AML provides a unified framework for standardizing and clinically applying MRD assessment in AML. It outlines preferred assay selection, analysis strategies, and key parameters including timing, tissue type, and cutoffs across molecular subtypes, and defines MRD levels with corresponding clinical recommendations to enhance patient care.

Cloos et al. DOI: 10.1182/*blood*.2025031480

blood

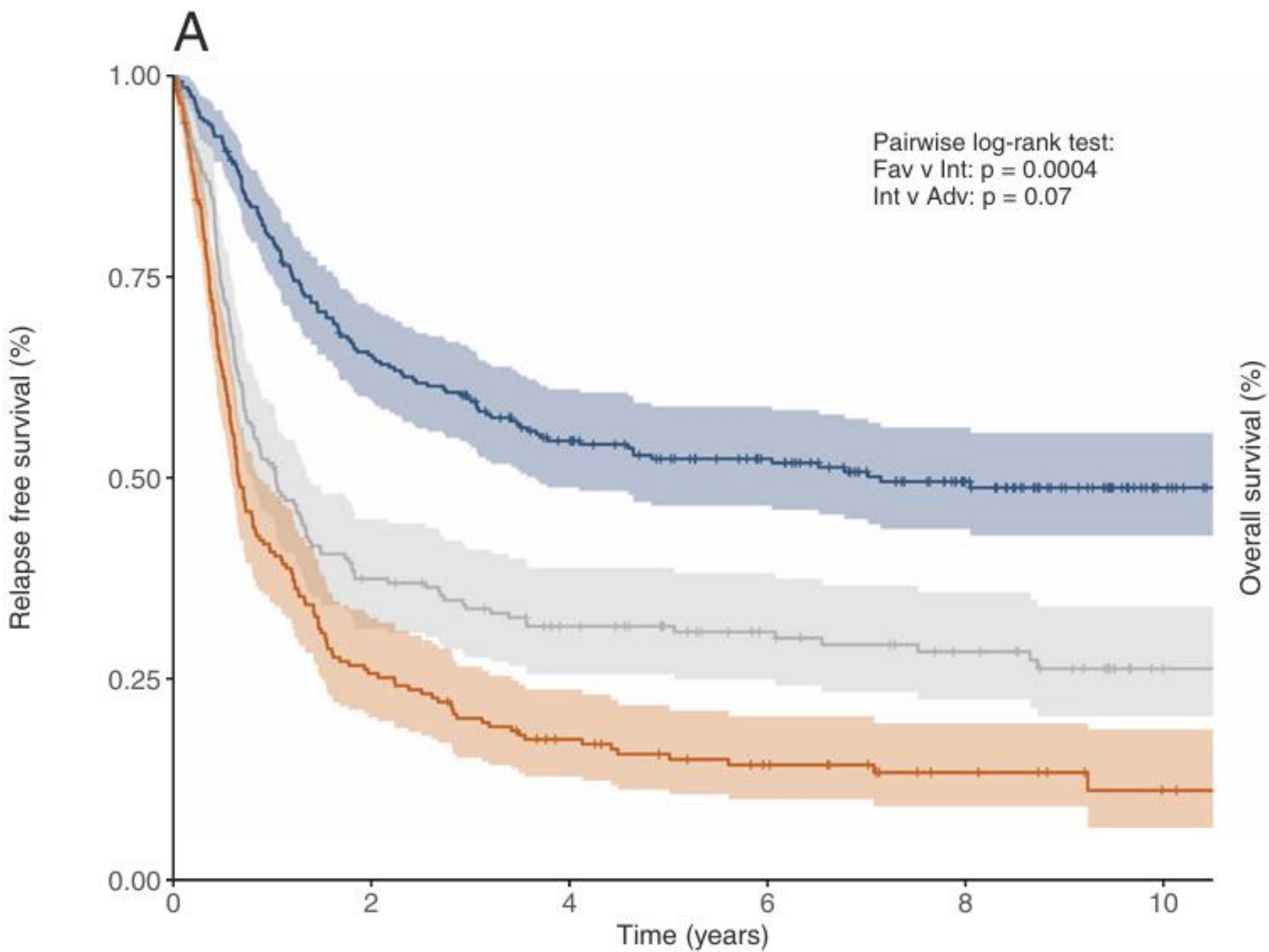
Visual Abstract

ELN risk	Subgroup	Assay	Diagnosis	After 2 cycles or before HCT	EOT	Follow-up (see footnotes for frequency and duration during follow-up)
Favorable	mutNPM1 without FLT3-ITD	qPCR	PB (if blasts ≥20%) or BM*	PB	BM	PB or BM†
	RUNX1::RUNX1T1	qPCR	BM‡	BM	BM	PB or BM§
	CBFB::MYH11	qPCR	BM‡	BM	BM	PB or BM§
	PML::RARA	qPCR	PB (if blasts ≥20%) or BM*	Not recommended	BM	Only if MRD positive at EOT, and in chemotherapy-treated high-risk APL even when MRD negative; BM*,
	CEBPA bZIP in-frame	MFC	PB (if blasts ≥20%) or BM*	See recommendation B13		
Intermediate	FLT3-ITD and NPM1wt	FLT3-ITD UHS-NGS if available; otherwise MFC	PB (if blasts ≥20%) or BM*	FLT3-ITD UHS-NGS: BM > PB MFC: BM	FLT3-ITD UHS-NGS§: BM > PB MFC: BM	FLT3-ITD UHS-NGS¶: PB or BM* MFC: BM (every 3 mo for 12 mo)
	FLT3-ITD and mutNPM1	qPCR for mutNPM1 and, if available, FLT3-ITD UHS-NGS	PB (if blasts ≥20%) or BM*	mutNPM1 qPCR: PB FLT3-ITD UHS-NGS: BM > PB	mutNPM1 qPCR: BM FLT3-ITD UHS-NGS¶: BM > PB	mutNPM1-qPCR: PB or BM* FLT3-ITD UHS-NGS¶: PB or BM*
	KMT2A::MLLT3, other fusion genes#	qPCR if available or MFC	PB (if blasts ≥20%) or BM*	qPCR and MFC: BM	qPCR and MFC: BM	qPCR: PB or BM* MFC: BM (every 3 mo for 12 mo)
	Other (with LAIP/DfN)	MFC	PB (if blasts ≥20%) or BM*	BM	BM	BM (every 3 mo for 12 mo)
	Other (with gene mutation)**	UHS-NGS if available and MFC	PB (if blasts ≥20%) or BM*	See recommendations C12 and C13 and supplemental Table 7	See recommendations C12 and C13 and supplemental Table 7	After alloHCT (only validated genes)†† BM > PB*,‡‡
Adverse	Fusion genes (eg, KMT2A::X)	qPCR if available or MFC	PB (if blasts ≥20%) or BM*	qPCR and MFC: BM	qPCR and MFC: BM	qPCR: see recommendation C6 MFC: BM (every 3 mo for 12 mo)
	Other (with LAIP/DfN)	MFC	PB (if blasts ≥20%) or BM*	BM	BM	BM (every 3 mo for 12 mo)
	Other (with gene mutation)**	UHS-NGS	PB (if blasts ≥20%) or BM*	See recommendations C12 and C13 and supplemental Table 7	See recommendations C12 and C13 and supplemental Table 7	After alloHCT (only validated genes)†† BM > PB*,‡‡

Cools J. et al. *Blood* 2026; 147 (11): 1147–1167.

LAL e LAM DAY

RFS

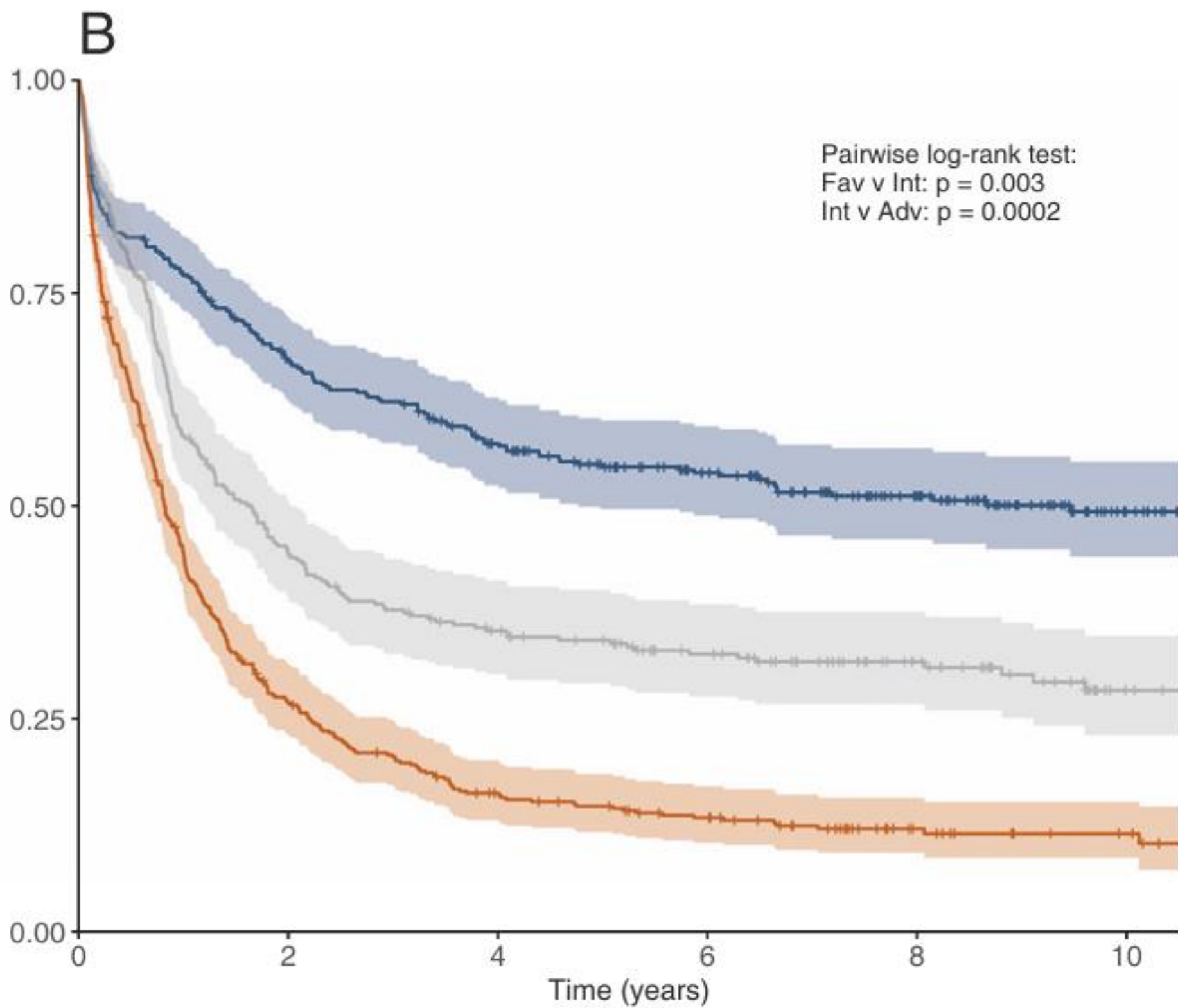


Number at risk

Favourable	265	169	129	103	66	27
Intermediate	198	72	54	40	30	13
Adverse	202	51	30	19	10	4

Time (years)

OS



Number at risk

Favourable	363	237	193	152	107	52
Intermediate	302	130	98	75	48	20
Adverse	453	116	65	47	21	11

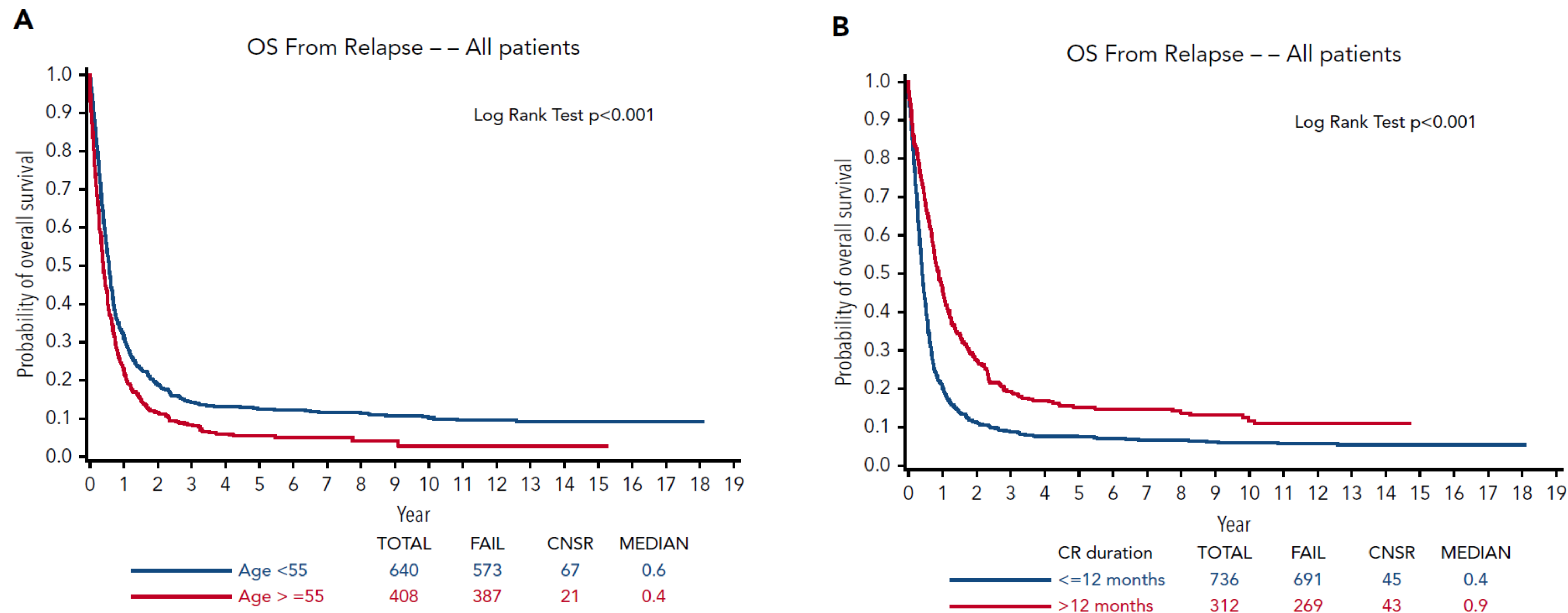
Time (years)

Definitions of R/R AML according to the 2022 ELN recommendations

Refractory disease	Failure to achieve CR, CRh, or CRi after Two courses of intensive induction for intensively treated patients or A defined landmark (eg, 180 d) after starting nonintensive therapy
Relapsed disease	After prior achievement of CR, CRh, or CRi Increase of blasts to $\geq 5\%$ Development of extramedullary disease Reappearance of blasts in the blood in at least 2 peripheral blood samples at least 1 wk apart
MRD relapse	Conversion from MRD negativity to MRD positivity (independent of method) Increase of MRD copy numbers ≥ 1 log10 between any 2 positive samples in patients with CR, CRh, or CRi in MRD detectable at low levels by qPCR

Patients not responding to a first cycle of 7+3 should be considered for a regimen containing higher doses of cytarabine

OS from relapse. Stratified by (A) age and (B) duration of first CR from ECOG-ACRIN trials (1984-2008)



Therapeutic options for R/R AML

Common salvage regimens in patients not responding to initial induction or with relapsed disease who are candidates for intensive therapy	
Gilteritinib (AML with <i>FLT3</i> mutation)	Gilteritinib 120 mg PO QD d1-28, q4 wk, until disease progression
Intermediate-dose cytarabine# (with or without anthracycline)	Cytarabine 1000-1500 mg/m ² IV over 3h q12h d1-3 (500-1000 mg/m ² in patients ≥ 60y); with or without daunorubicin 60 mg/m ² IV d1-3; idarubicin 8-10 mg/m ² IV d3-5; or mitoxantrone 8-10 mg/m ² IV d1-3
FLAG-IDA**	Fludarabine 30 mg/m ² IV d2-6; cytarabine 1500-2000 mg/m ² IV over 3h, starting 4h after fludarabine infusion, d2-6; idarubicin 10 mg/m ² IV d2-4; G-CSF 5 µg/kg SC d1-5; additional G-CSF may be administered starting 7 d after end of chemotherapy until WBC count > 0.5 × 10 ⁹ /L Consider dose reduction in patients ≥60 y: fludarabine 20 mg/m ² ; cytarabine 500-1000 mg/m ² ; idarubicin 8 mg/m ²
MEC	Mitoxantrone 8 mg/m ² IV d1-5; etoposide 100 mg/m ² IV d1-5; cytarabine 1000 mg/m ² IV d1-5
CLAG-M	Cladribine 5 mg/m ² IV d1-5; cytarabine 2000 mg/m ² IV d1-5 (starting 2h after cladribine infusion); mitoxantrone 10 mg/m ² IV d1-3; G-CSF 300 µg SC d0-5
Allogeneic HCT	Consider transplantation for patients with primary refractory disease, for patients in second CR (or CRh, CRi) or with major cytoreduction but still active disease following salvage therapy. Consider second transplantation under certain conditions. Perform early HLA typing.
Salvage options if not a candidate for intensive chemotherapy	
Gilteritinib (AML with <i>FLT3</i> mutation)††	120 mg PO QD d1-28, q4 wk, until disease progression
Ivosidenib (AML with <i>IDH1</i> mutation)‡‡	500 mg PO QD d1-28, q4 wk, until disease progression
Enasidenib (AML with <i>IDH2</i> mutation) ^a	100 mg PO QD d1-28, q4 wk, until disease progression

Diagnostic work up for R/R AML pts: BM assessment, mutational analysis *

1. Question: Possibility of enrollment into clinical trial?
If yes, 1st priority

2. Question: Is the patient a candidate for allogeneic HCT?

Yes

No

Mutation agnostic therapies

Targeted therapies *

Mutation agnostic therapies

Step1 *

Salvage therapies: e.g. FLAG-IDA, MEC, HAM
(possibly with the addition of Venetoclax)

Step 1

FLT3 mutated: Gilteritinib
IDH1 mutated: Ivosidenib[#]
Olutasidenib[#]
IDH2 mutated: Enasidenib[#]

Step 1

No standard therapy
• --> clinical trials best choice
• Change agents
(e.g. HMA/VEN if no prior VEN)
• BSC

rapid

Step 2: Allogeneic HCT[¶]

If no allogeneic HCT
continue treatment

Step 3: Consider maintenance therapy

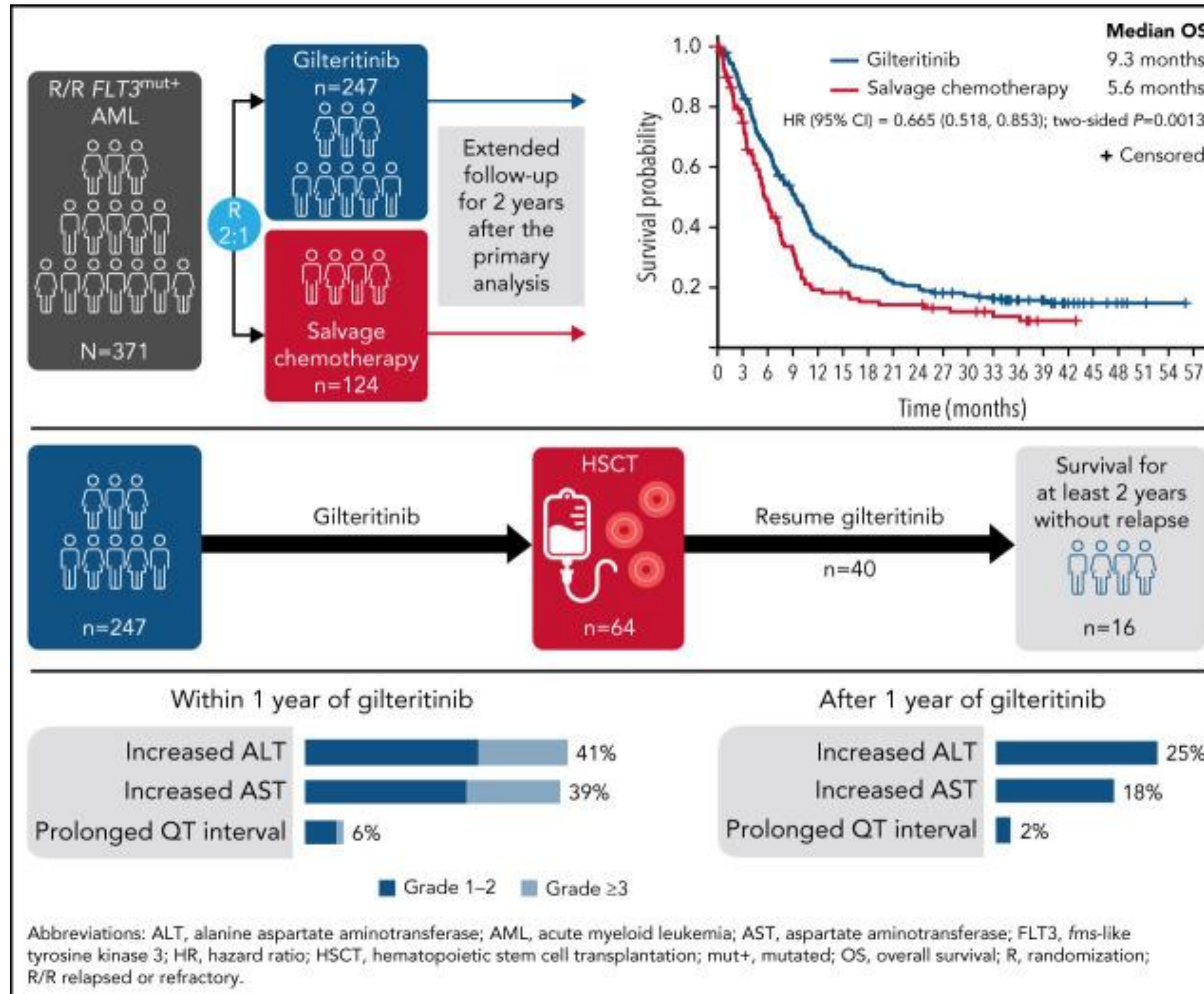
* re-testing for *FLT3*

* Some patients might go directly to allogeneic HCT or receive lower intensity regimens
¶ Consider DLIs for relapse post alloHCT, second alloHCT only indicated in selected pts
approved by FDA but not EMA for R/R AML pts

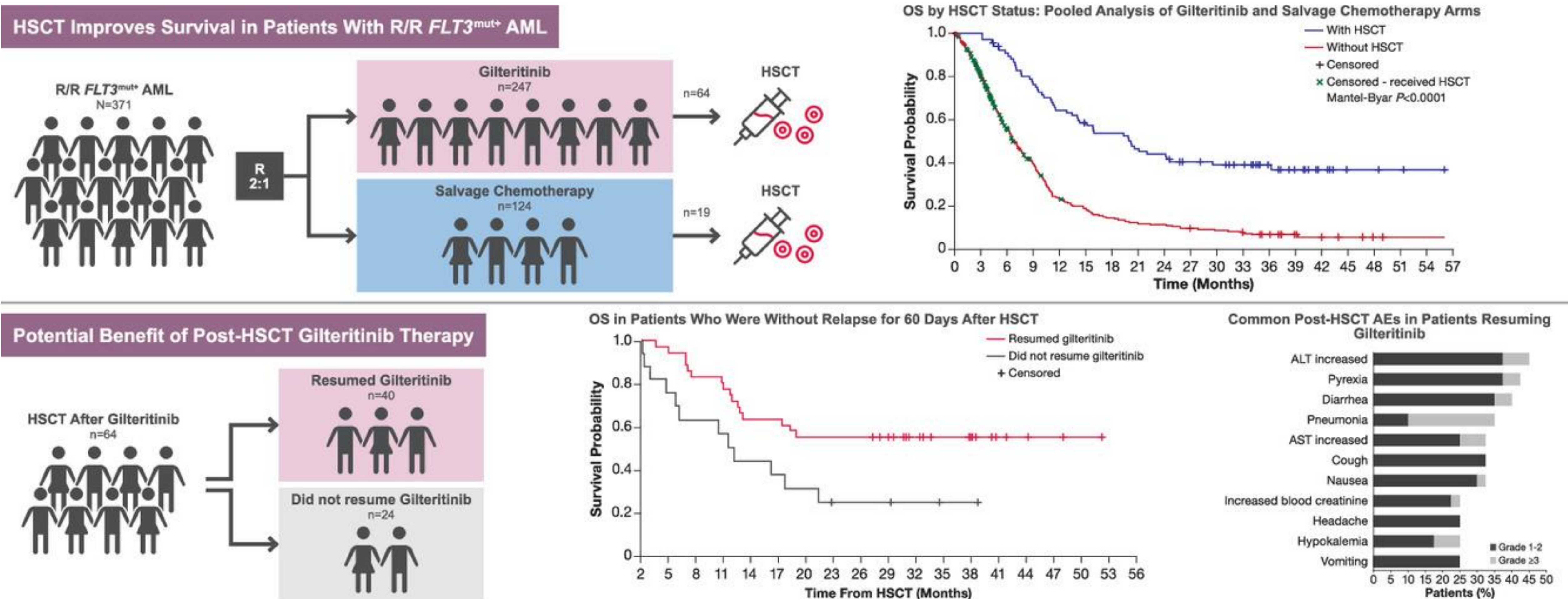
Question

How the mutational profile influence our treatment options at relapse? *FLT3*-mutations...

ADMIRAL TRIAL follow-up

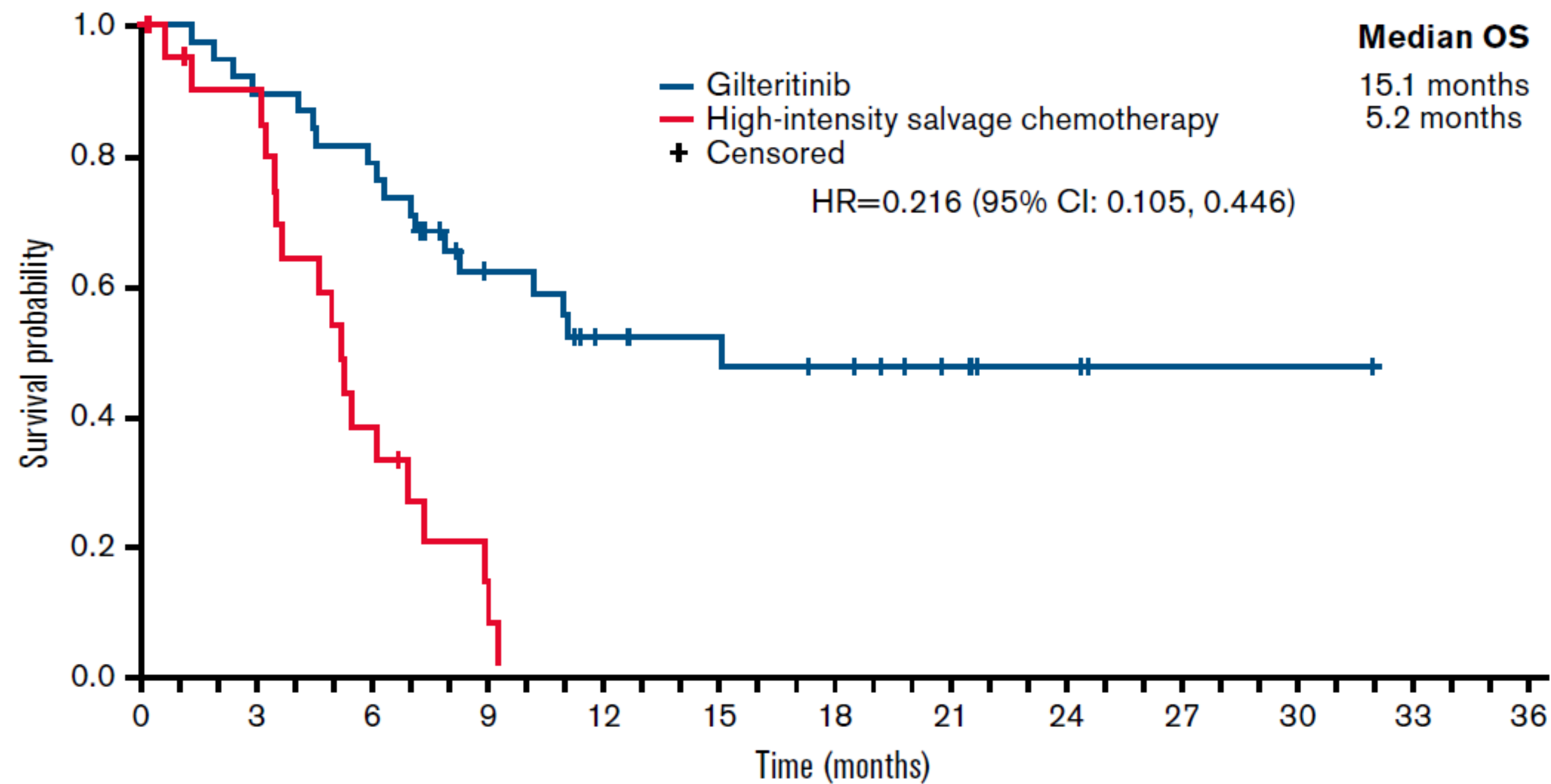


Outcomes in Patients with *FLT3*-Mutated R/R Acute Myelogenous Leukemia Who Underwent Transplantation in the Phase 3 ADMIRAL Trial of Gilteritinib versus Salvage Chemotherapy



AE, adverse event; ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; *FLT3*, *fms*-like tyrosine kinase 3; HSCT, hematopoietic stem cell transplantation; mut+, mutated; OS, overall survival; R, randomization; R/R, relapsed or refractory.

OS in *FLT3*, *DNMT3A* and *NPM1* co-mutated patients

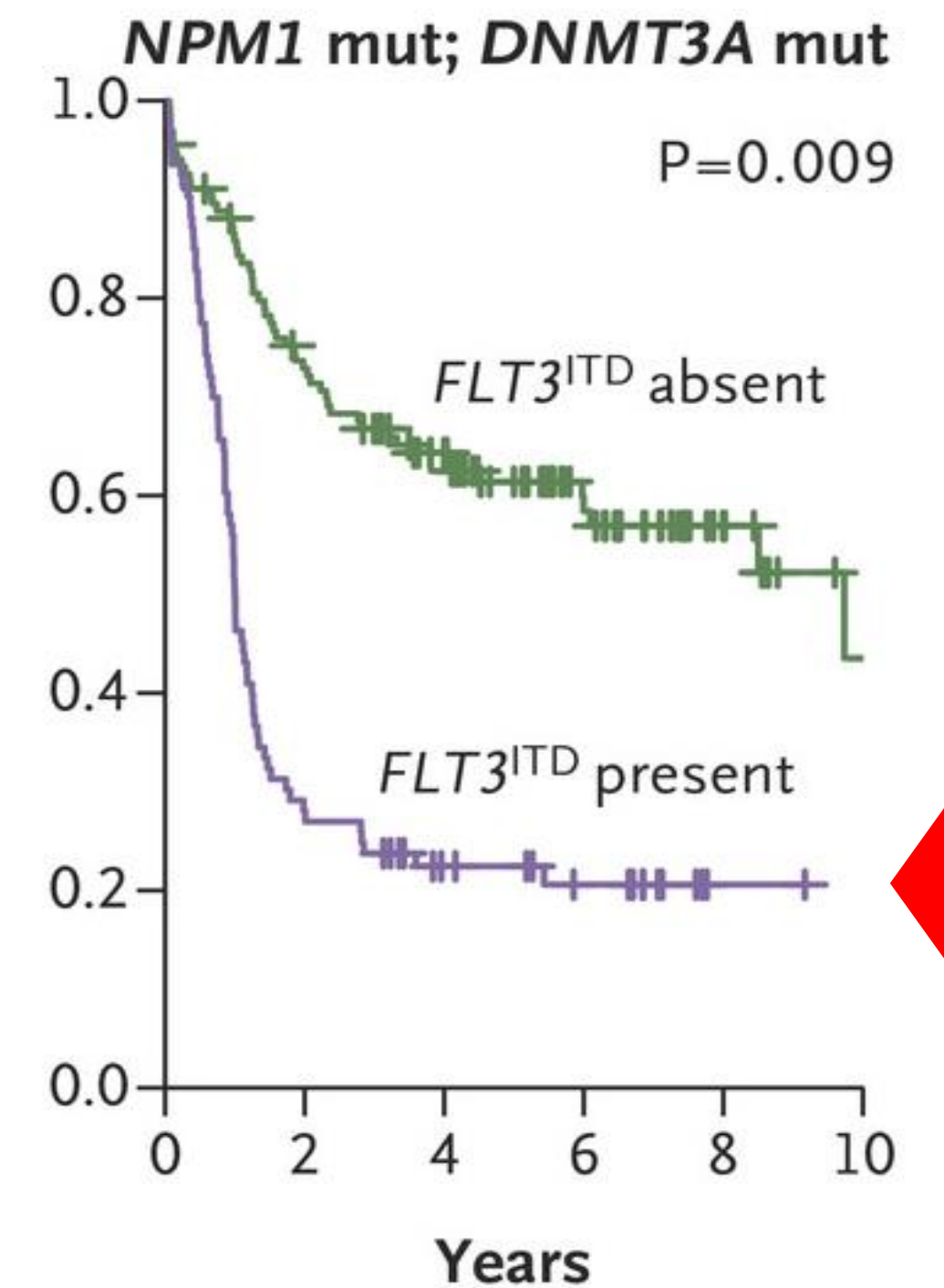


Patients at risk, n

Gilteritinib	37	33	29	18	12	11	9	5	3	1	1	0	0
High-intensity salvage chemotherapy	21	17	7	2	0	0	0	0	0	0	0	0	0

In patients eligible for high-intensity chemotherapy, the most pronounced survival benefit was in patients with both *DNMT3A* and *NPM1* co-mutations

Smith et al *Blood Adv.* 2022



Papaemmanuil et al. *N Engl J Med* 2016

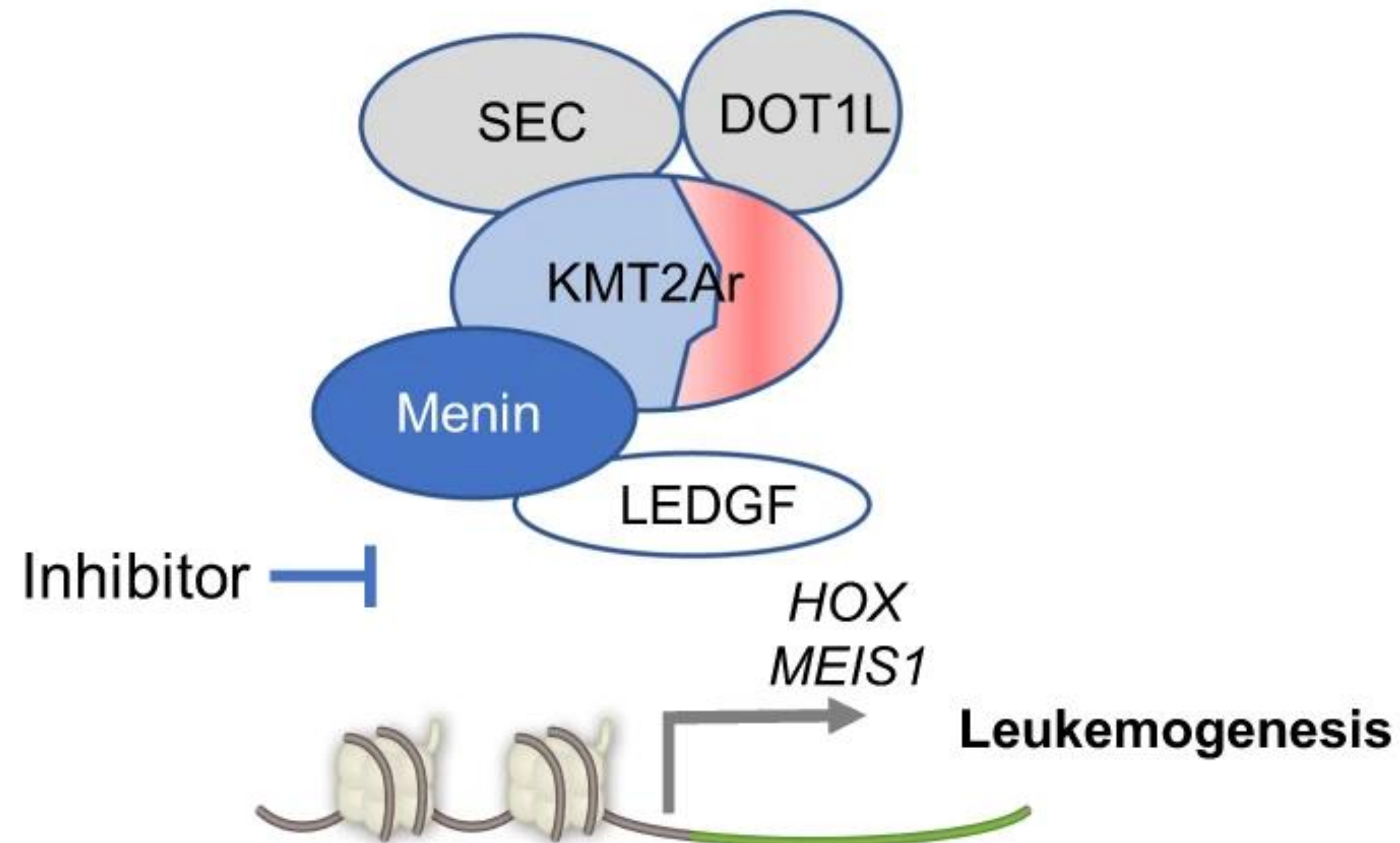
Question

How the mutational profile influence our treatment options at relapse? *NPM1*-mutations or *KMT2A*-r...

Targeting *HOX/MEIS1* through menin inhibition

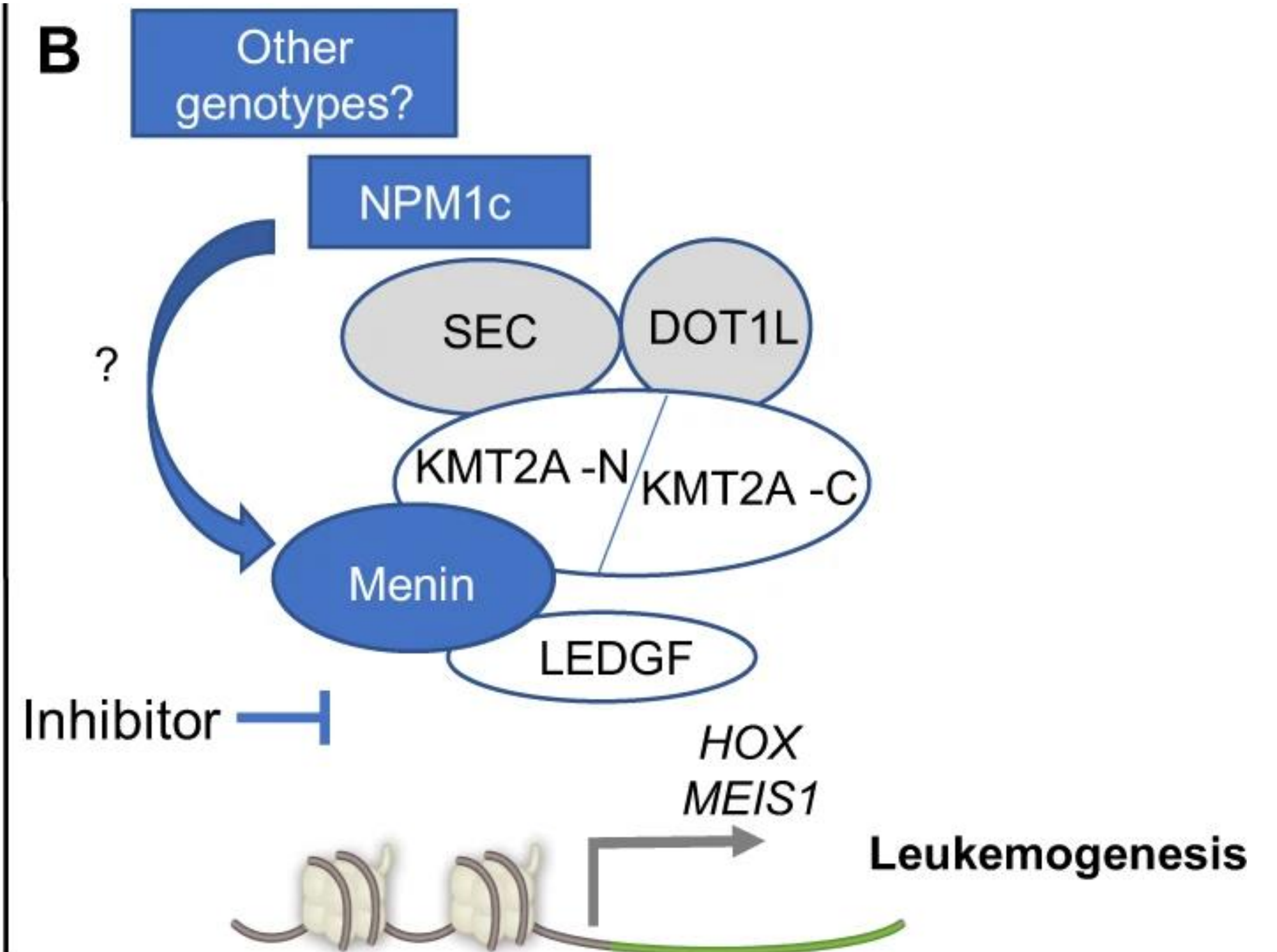
- ***MLL*-rearranged AML**

A



- ***NPM1*-mutated AML**

B



Menin Inhibition With Revumenib for *KMT2A*-Rearranged Relapsed or Refractory Acute Leukemia (AUGMENT-101)

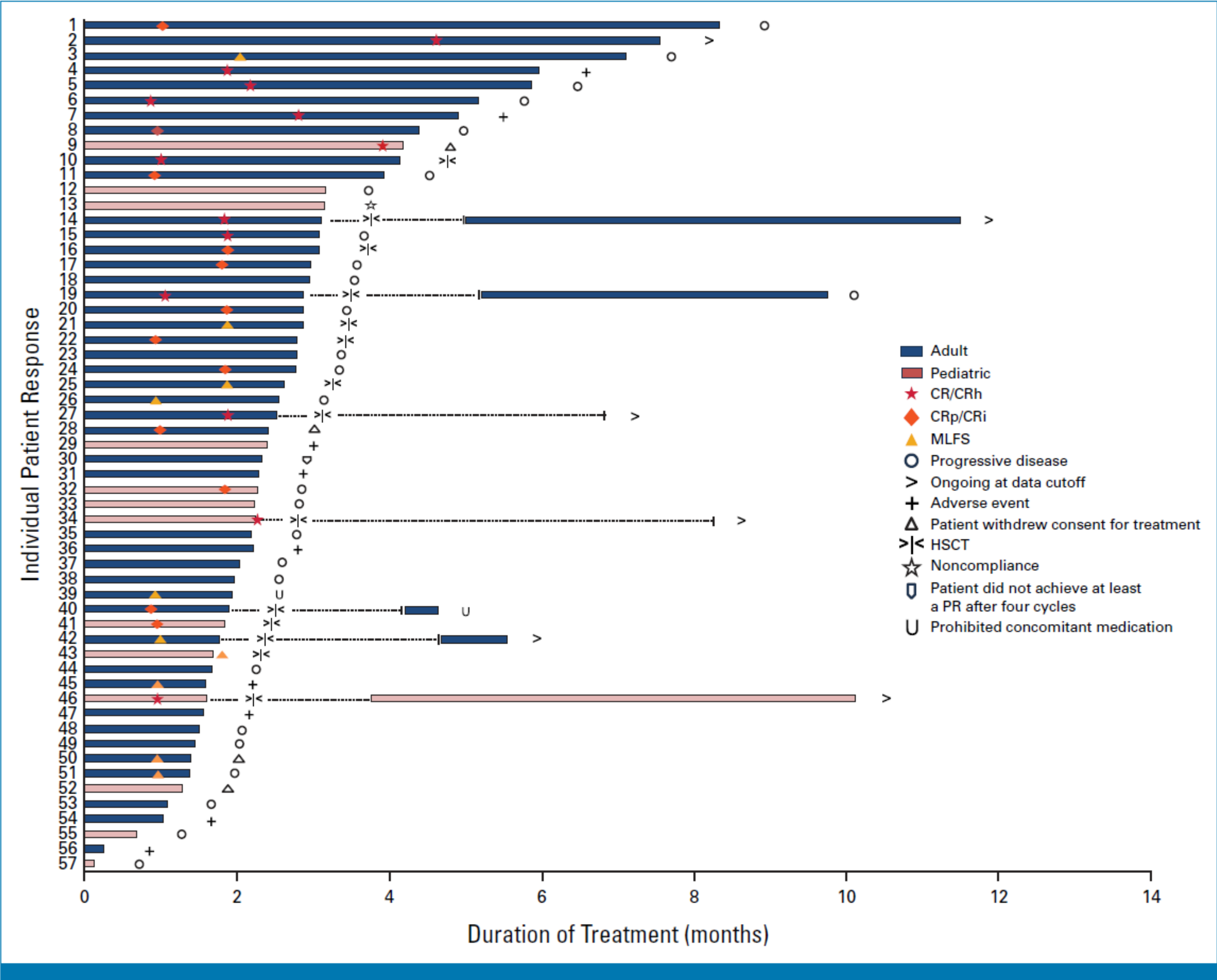
Ghayas C. Issa, MD¹ ; Ibrahim Aldoss, MD²; Michael J. Thirman, MD³ ; John DiPersio, MD, PhD⁴ ; Martha Arellano, MD⁵; James S. Blachly, MD⁶ ; Gabriel N. Mannis, MD⁷; Alexander Perl, MD⁸ ; David S. Dickens, MD⁹ ; Christine M. McMahon, MD¹⁰; Elie Traer, MD, PhD¹¹ ; C. Michel Zwaan, MD, PhD¹² ; Carolyn S. Grove, MBBS, PhD, FRACP, FRCPA¹³ ; Richard Stone, MD¹⁴ ; Paul J. Shami, MD¹⁵; Ioannis Mantzaris, MD¹⁶; Matthew Greenwood, MBBS, FRACP, FRCPA¹⁷ ; Neerav Shukla, MD¹⁸ ; Branko Cuglievan, MD¹; Tibor Kovacsovics, MD¹⁹; Yu Gu, PhD²⁰; Rebecca G. Bagley, MA²⁰; Kate Madigan, MD²⁰; Yakov Chudnovsky, PhD²⁰; Huy Van Nguyen, PharmD²⁰; Nicole McNeer, MD, PhD²⁰; and Eytan M. Stein, MD¹⁸ 

DOI <https://doi.org/10.1200/JCO.24.00826>

Issa et al. *J Clin Oncol* 2024

Response

Parameter	Efficacy Population (n = 57)
Overall response rate, No. (%) ^a	36 (63.2)
95% CI	49.3 to 75.6
Time to first response, months, median (range)	0.95 (0.9-2.0)
Duration of response, months, median (range)	4.3 (1.9-NR)
CR + CRh rate, No. (%)	13 (22.8)
95% CI	12.7 to 35.8
P value, one-sided	0.0036
Time to first CR + CRh, months, median (range)	1.87 (0.9-4.6)
Duration of CR + CRh, months, median (95% CI)	6.4 (3.4 to NR)
CRc, No. (%) ^b	25 (43.9)
95% CI	30.7 to 57.6
Best response, No. (%)	
CR	10 (17.5)
CRh	3 (5.3)
CRi	1 (1.8)
CRp	11 (19.3)
Morphological leukemia-free state	10 (17.5)
Partial remission	1 (1.8)
Progressive disease	4 (7.0)
No response	14 (24.6)
Other ^c	3 (5.3)
MRD negative rate within evaluable patients ^d	
Within CR + CRh, No. (%)	7/10 (70.0)
Within CRc, No. (%)	15/22 (68.2)
Time to negative MRD status for patients with CR + CRh, months, median (range)	1.08 (1.0-3.9)

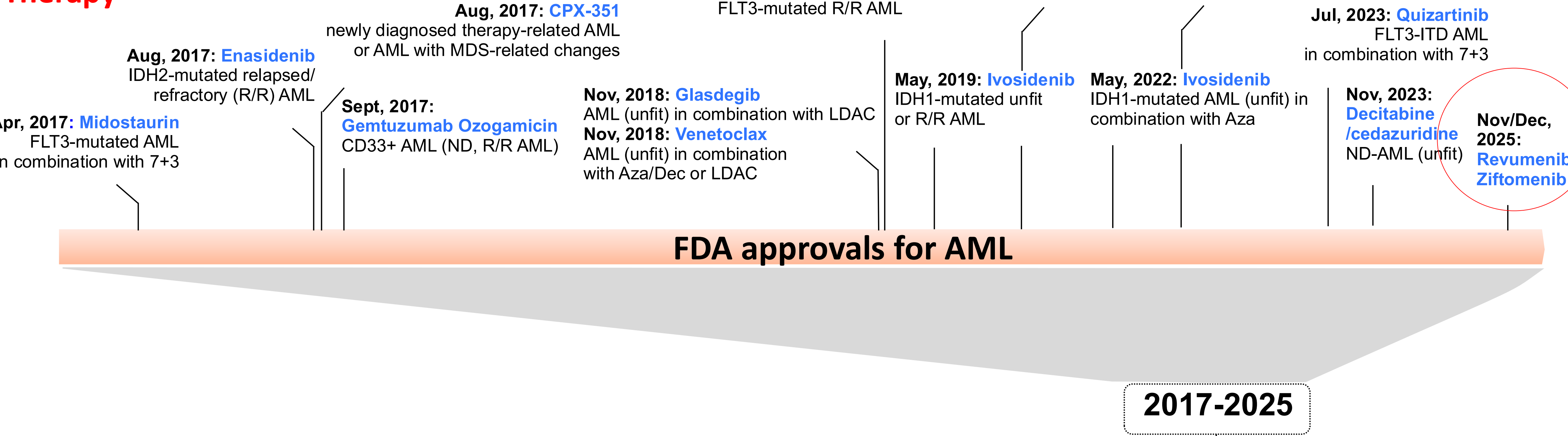


Summary of menin inhibitors as monotherapy for R/R AL

	Revumenib		Ziftomenib		Bleximenib		Enzomenib	
Trial	AUGMENT-101		KOMET-001		cAMeLot-1		Phase 1 Study	
	NCT04065399		NCT04067336		NCT04811560		NCT04988555	
Population	R/R Acute Leukemia		R/R AML		R/R Acute Leukemia		R/R Acute Leukemia	
Therapeutic Oral Dose(s)	160 mg BID; 270 mg BID		600 mg daily		90 mg BID; 100 mg BID		200 mg BID; 300 mg BID; 400 mg BID	
Subtype	<i>KMT2Ar</i>	<i>NPM1m</i>	<i>KMT2Ar</i>	<i>NPM1m</i>	<i>KMT2Ar</i>	<i>NPM1m</i>	KMT2Ar 300 mg BID	<i>NPM1m</i> 200–400 mg BID
n (efficacy)	97	64	18	112	9	12	15	25
ORR	64%	47%	17%	35%	48%		73%	52%
CR/CRh	23%	23%	11%	25%	33%	33%	40%	44%
TTR	2.0 months	1.8 months	1.7 months	2.8 months	1.4 months		1.0 months*	1.8 months
DOR	6.4 months	4.7 months	2.1 months	3.7 months	6 months		12.5 months*	5.7 months
Median OS	8.0 months	4.0 months	NR	6.1 months	NR		11.8 months*	8.5 months
HSCT	34%	8%	NR	15%	14%		33%*	12%
n (safety)	116	84		112		31		116
CYP450 Interaction?	Yes			No		No		Minimal
Gr. ≥3 QTC	13%	23%		0		0		2.6%
DS (Any)	27%	19%		24%		19%		13%
Gr. ≥3 FN	39%	33%		22%		#		27%

Timeline of progress in AML

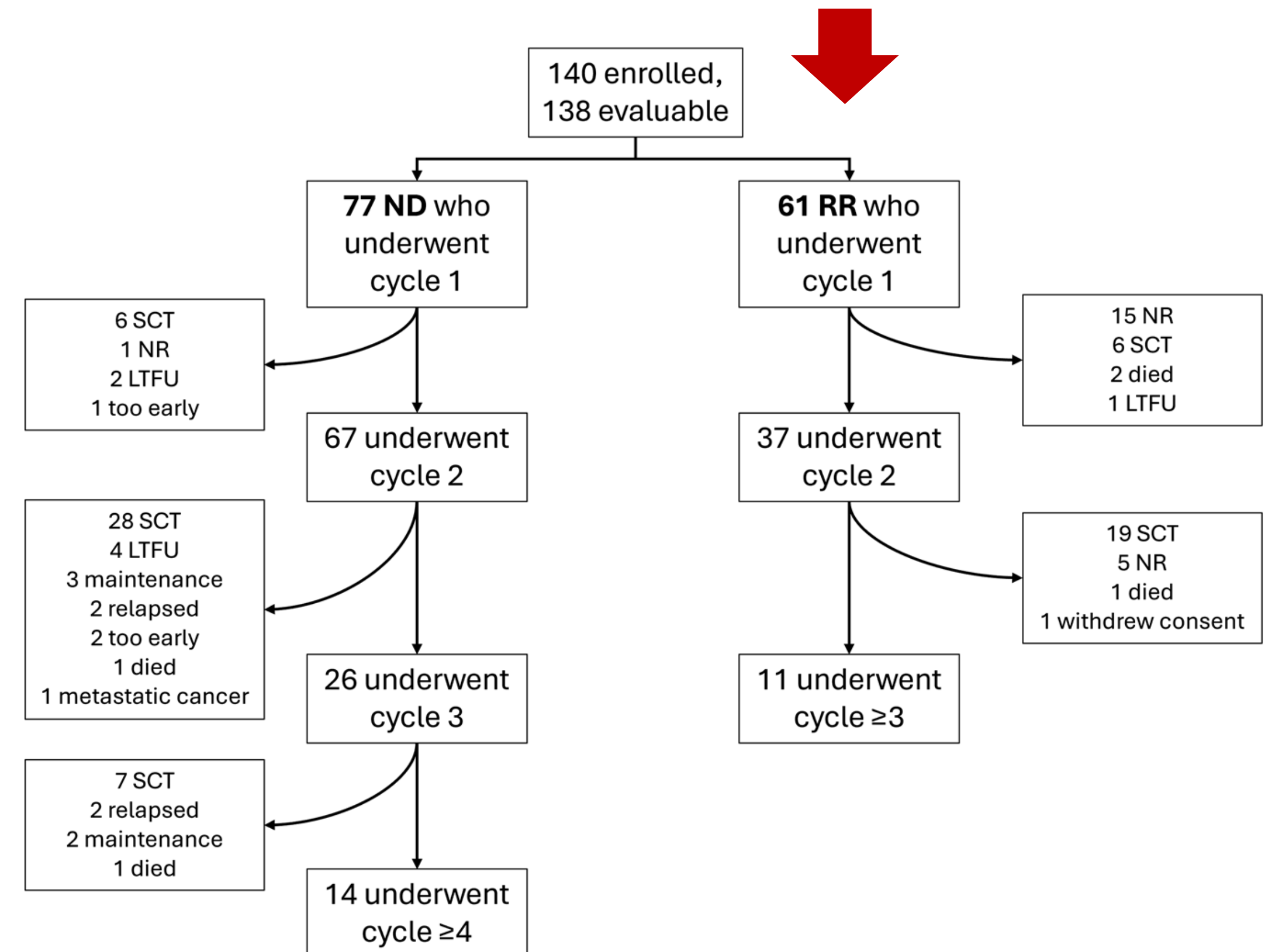
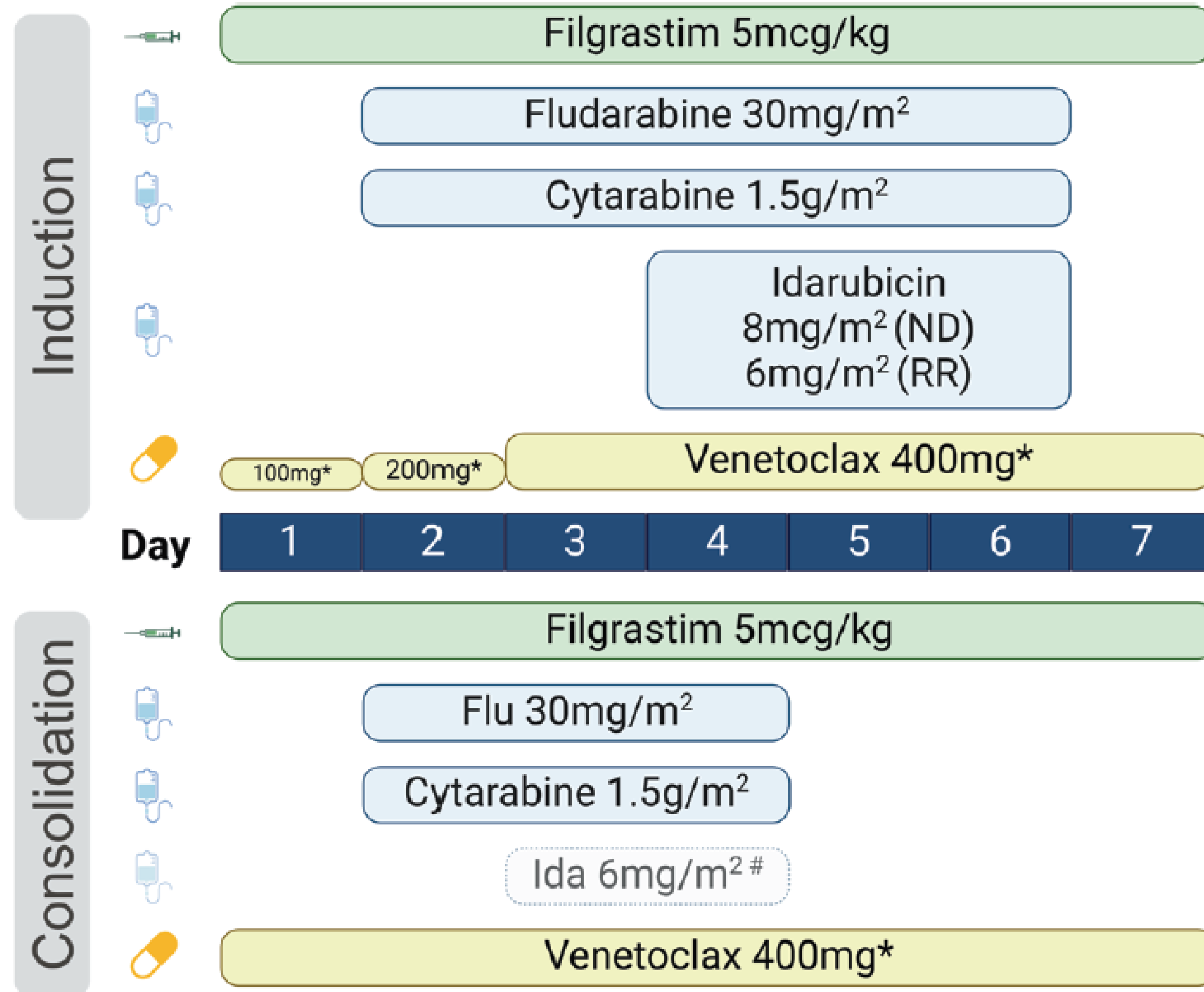
Therapy



Classification and molecular characterization

IC + venetoclax in R/R AML

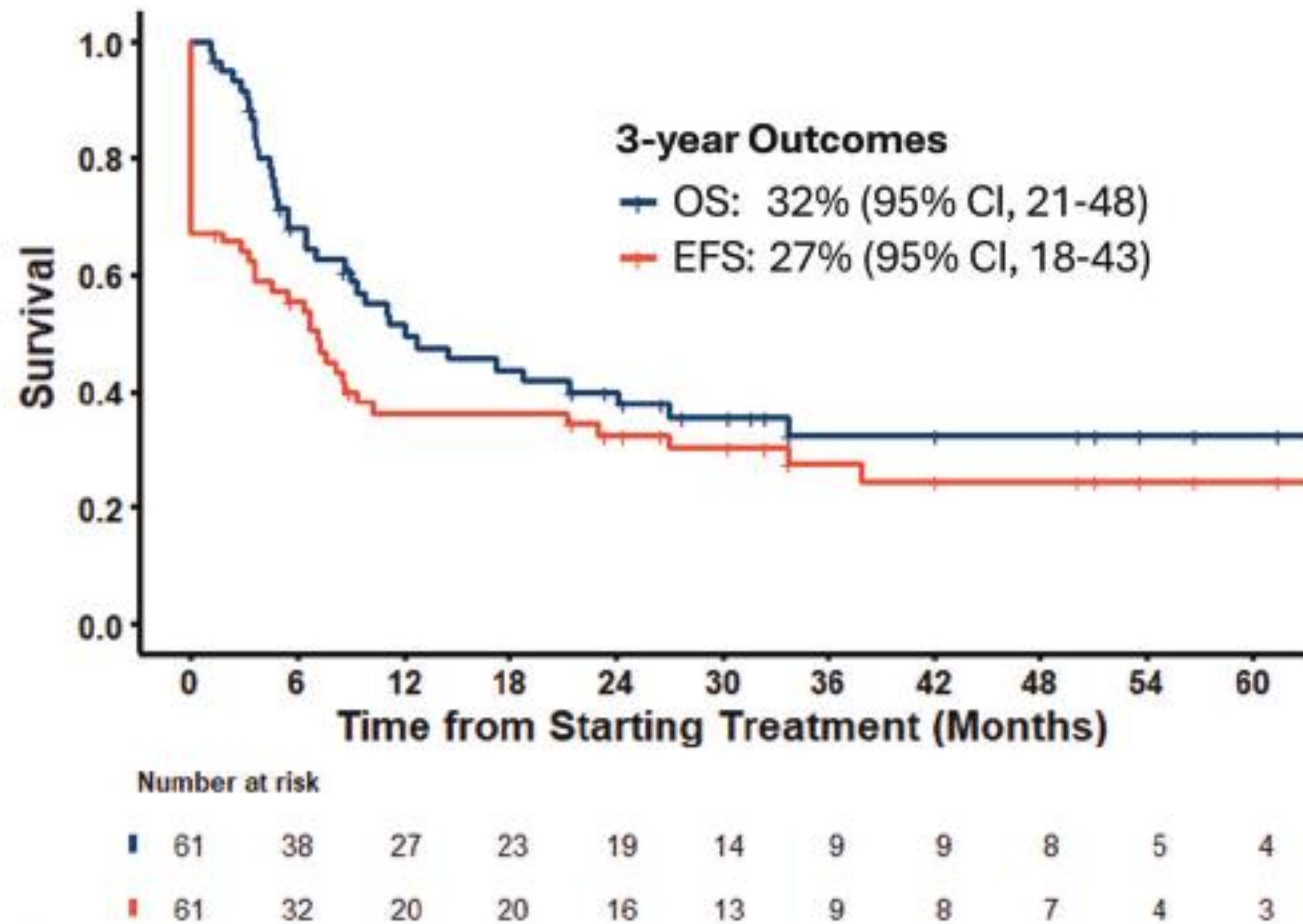
FLAG-IDA + VEN, NCT03214562



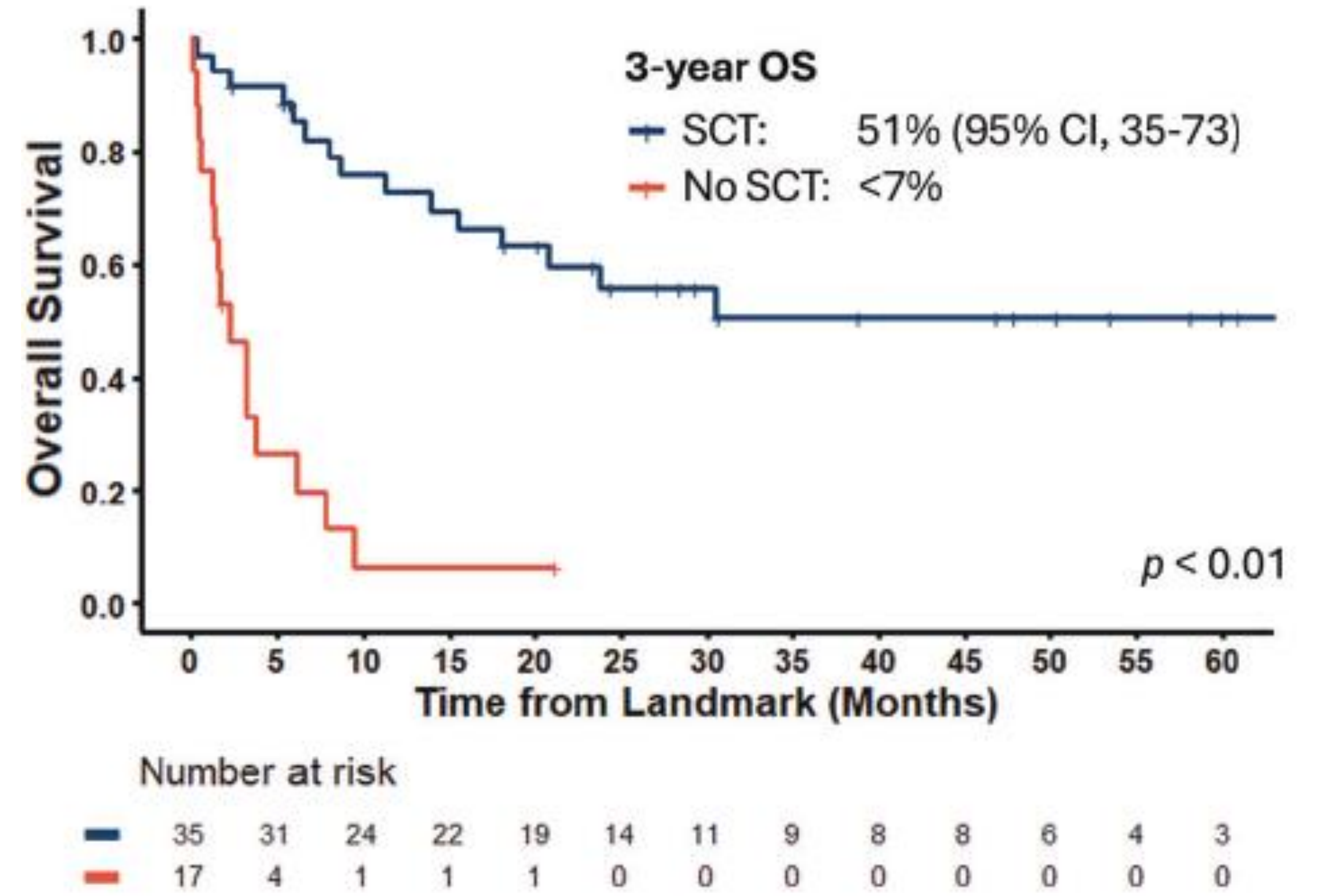
DiNardo et al. *Leukemia* (2025). <https://doi.org/10.1038/s41375-025-02531-8>.

IC + venetoclax in R/R AML

- R/R AML

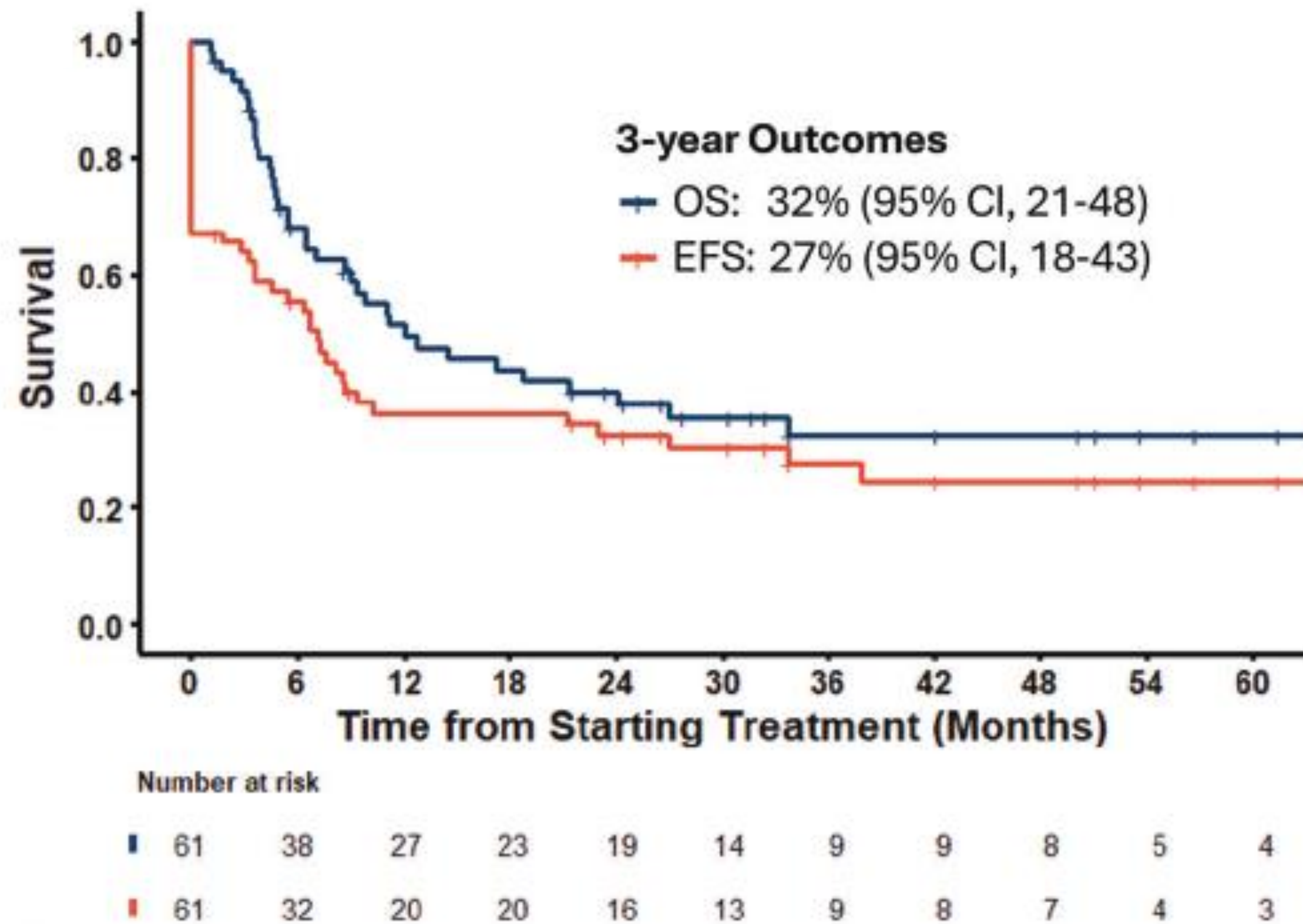


- R/R AML: yes-SCT vs no-SCT

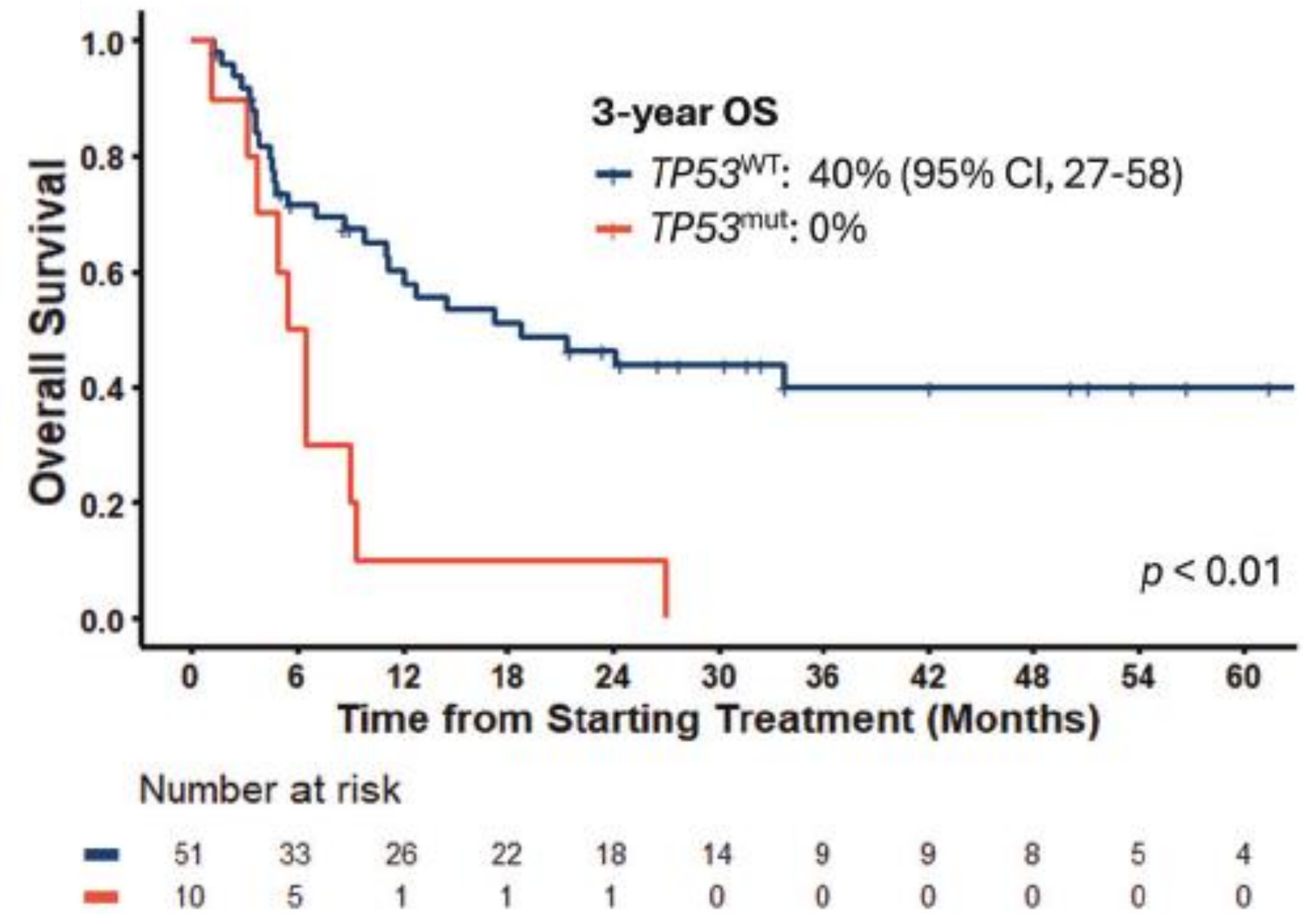


IC + venetoclax in R/R AML

- R/R AML



- TP53*-mut R/R AML



TAKE-HOME MESSAGES

Guiding principles for relapsed or refractory AML

1. Enroll patients on clinical trials, when available
2. Perform molecular testing to identify potential for targeted therapy and drug development
3. Decipher mechanisms of treatment resistance
4. Avoid reinduction attempts with multiple sequential courses of intensive cytotoxic chemotherapy
5. Ensure appropriate patients proceed to allogeneic HCT, ideally when patients are MRD–