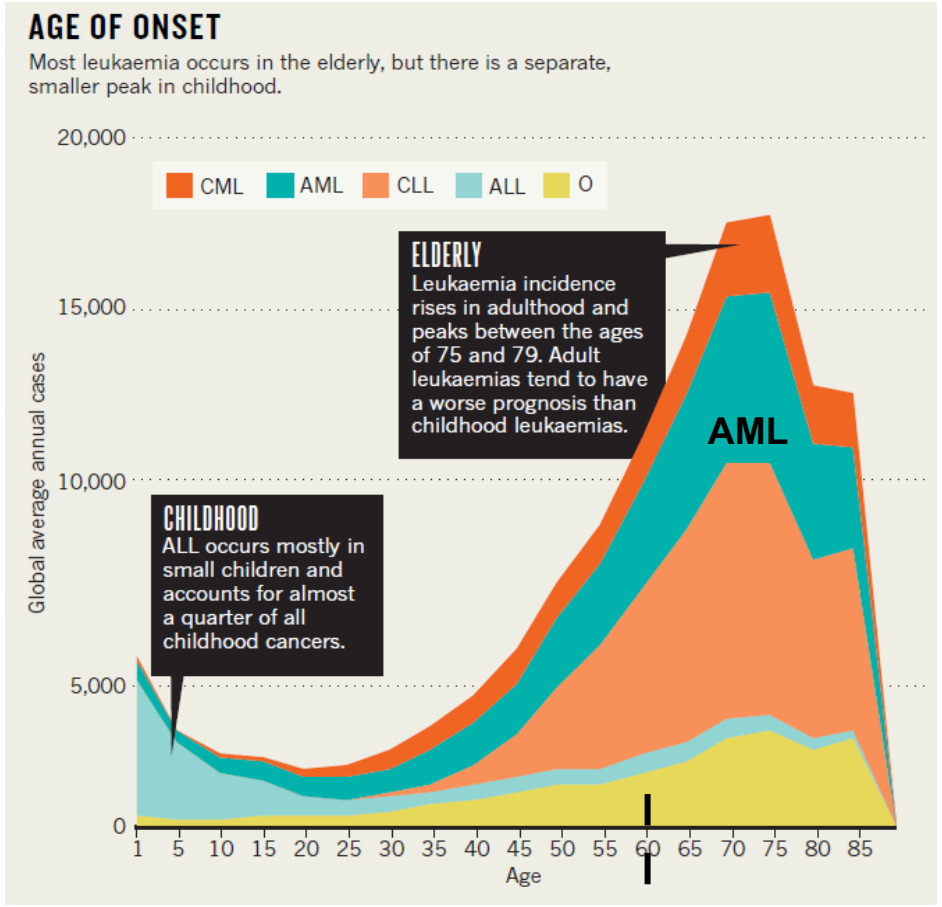
Should 'intermediate risk' AML patients receive gemtuzumab?

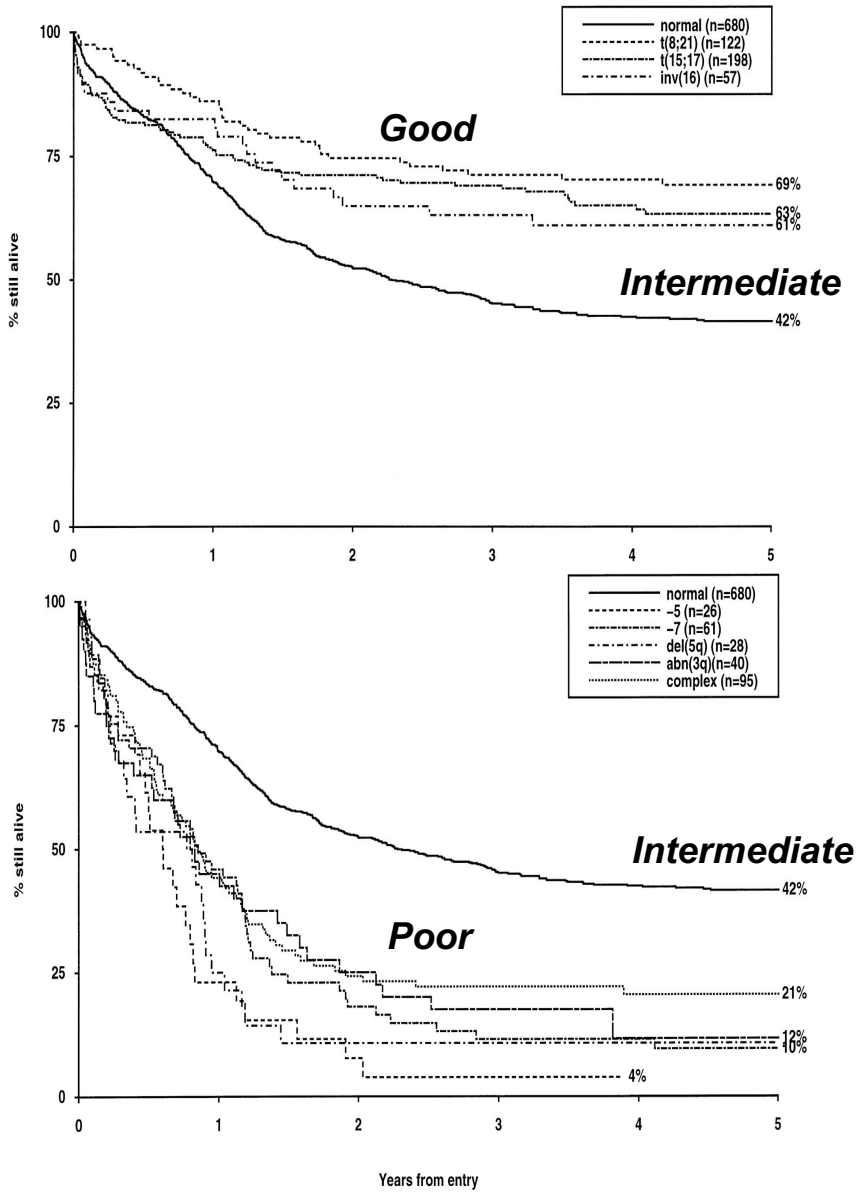
Maria Paola Martelli, M.D., Ph.D
(Ematologia, Università di Perugia)

Disclosures of Maria Paola Martelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie					x	x	
BMS						x	
Amgen					x	x	
Pfizer					x	x	
Jazz Pharmaceuticals					x	x	

AML: a heterogeneous disease and an urgent medical need

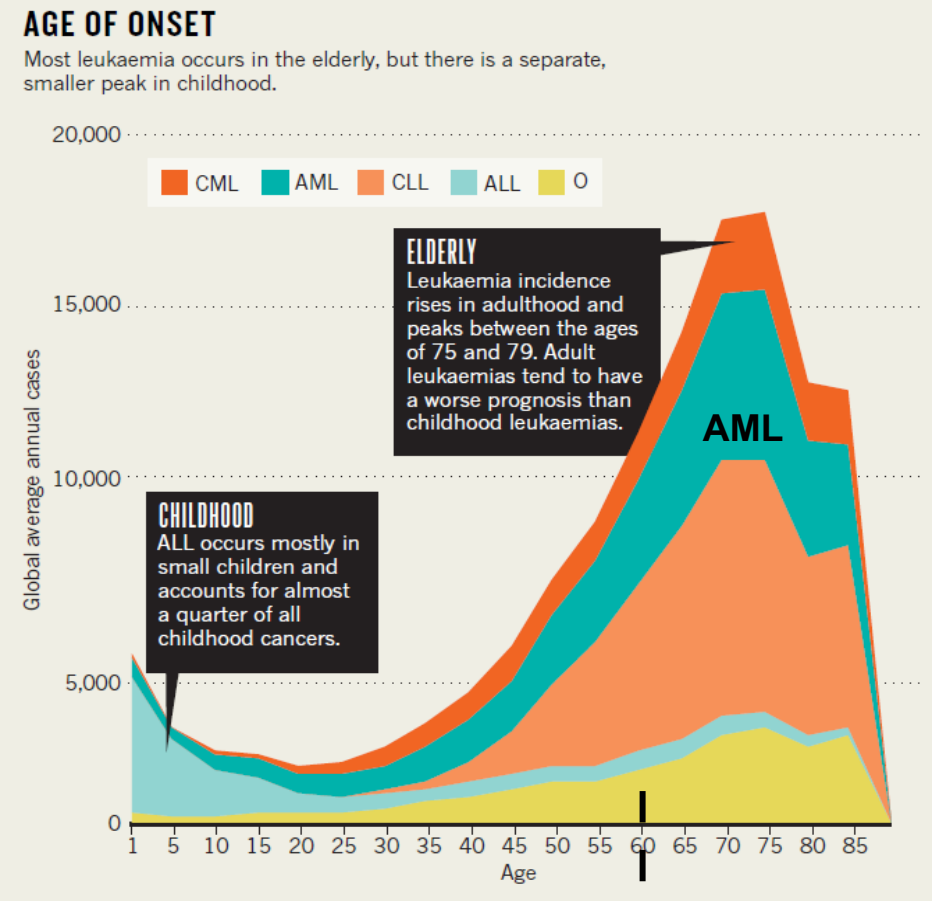


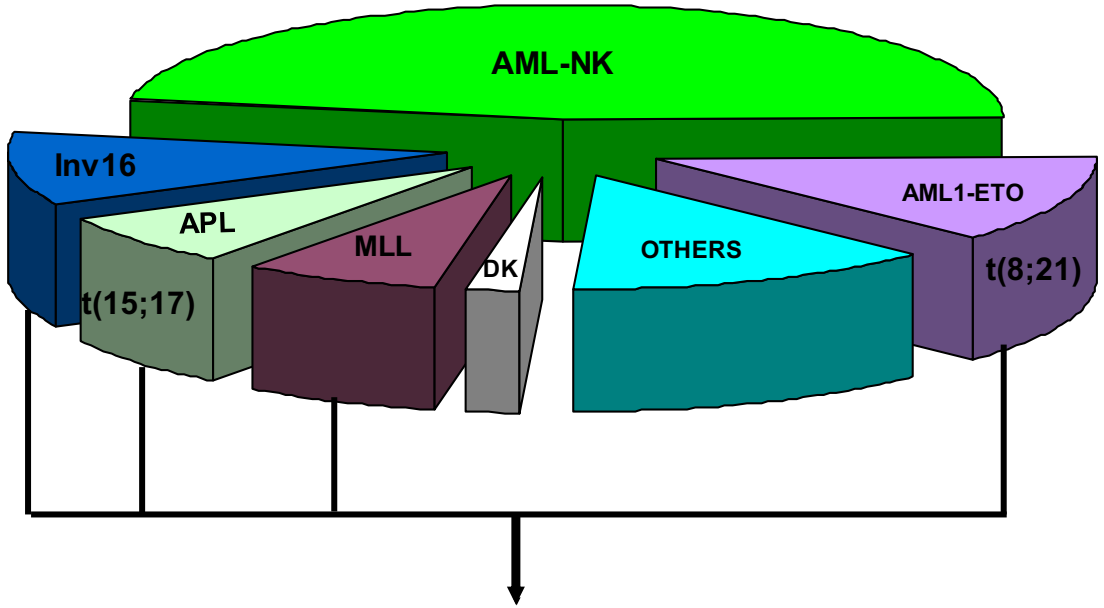


- 15-20000 new cases/year in EU/USA
- Rapidly rising incidence over age 50
- Most patients diagnosed over age 60 (median: 70 yrs)
- ~ 40% cure rates in younger
- Dismal outcome in older
- No major advances in treatment, until recently

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

AML: a heterogeneous disease and an urgent medical need





PROGNOSIS / MRD

- **15-20000 new cases/year in EU/USA**
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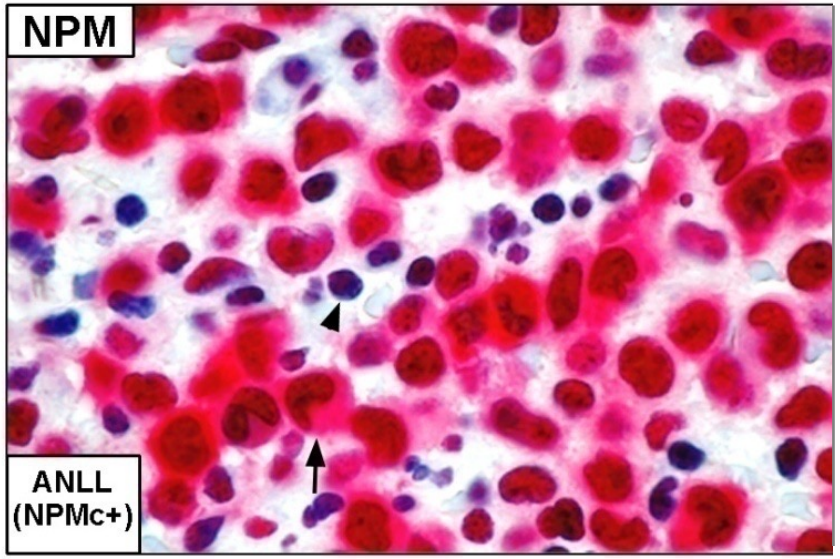
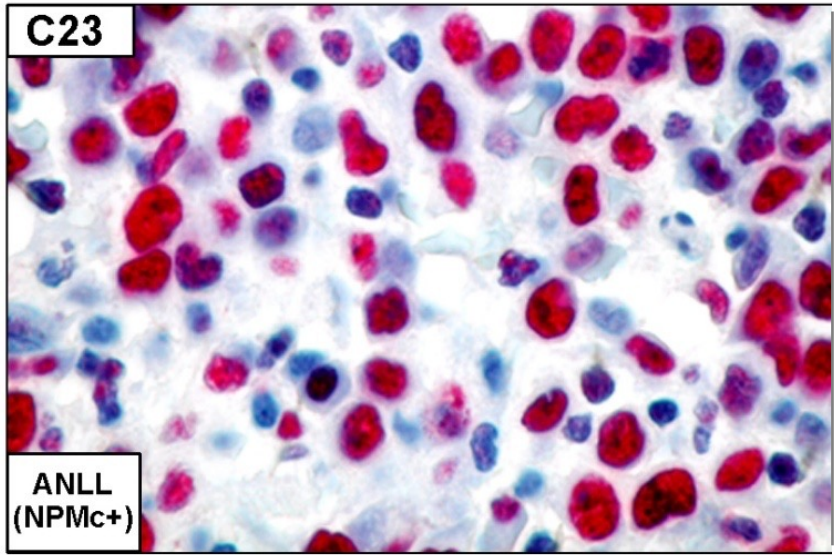
- **Most patients diagnosed over age 60 (median: 70 yrs)**
- **~ 40% cure rates in younger**
- **Dismal outcome in older**
- **No major advances in treatment, until recently**

- **Normal karyotype AML represent about 50% of all AML cases**

✓ 2005





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

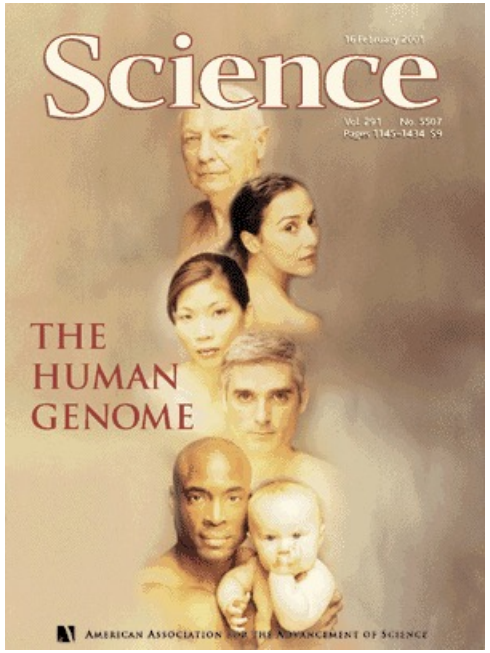
Cytoplasmic Nucleophosmin in Acute Myelogenous Leukemia with a Normal Karyotype

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*

N ENGL J MED 352;3 WWW.NEJM.ORG JANUARY 20, 2005

✓ 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 Fulton[3], Michael D. McLellan[3], Ken Chen[3], David Dooling[3], Brian H. Dunford-Shore[3], Sean McGrath[3], Matthew Hickenbotham[3], Lisa Cook[3], Rachel Abbott[3], David E. Larson[3], Dan C. Koboldt[3], Craig Pohl[3], Scott Smith[3], Amy Hawkins[3], Scott Abbott[3], Devin Locke[3], LaDeana W. Hillier[3,8], Tracie Miner[3], Lucinda Fulton[3], Vincent Magrini[2,3], Todd Wylie[3], Jarret Glasscock[3], Joshua Conyers[3], Nathan Sander[3], Xiaoqi Shi[3], John R. Osborne[3], Patrick Minx[3], David Gordon[8], Asif Chinwalla[3], Yu Zhao[1], Rhonda E. Ries[1], Jacqueline E. Payton[5], Peter Westervelt[1,4], Michael H. Tomasson[1,4], Mark Watson[3,4,5], Jack Baty[6], 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 (*GRINL1B*). 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 it[1]. 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 pathogenesis[2]. Furthermore, the nature of the initiating or progression mutations is for the most part unknown[3]. Recent attempts to identify additional progression mutations by extensively re-sequencing tyrosine kinase genes yielded very few previously unidentified mutations, and most were not recurrent[4,5]. Expression profiling studies have yielded signatures that correlate with specific cytogenetic subtypes of AML, but have not yet suggested new initiating mutations[6–8]. Recent studies using array-based comparative genomic hybridization and/or single nucleotide polymorphism (SNP) arrays, although identifying important gene mutations in acute lymphoblastic leukaemia[9,10] have revealed very few recurrent submicroscopic somatic copy number variants in AML (M.J.W., manuscript in preparation, and refs 11–13). Together, these studies suggest that we have not yet discovered most of the relevant mutations that contribute to the pathogenesis of AML. We therefore believe that unbiased whole-genome sequencing will be required to identify most of these mutations. Until recently, this approach has not been feasible because of the high cost of conventional

[1]Department of Medicine, [2]Department of Genetics, [3]The Genome Center at Washington University, [4]Siteman Cancer Center, [5]Department of Pathology and Immunology, [6]Division of Biostatistics, and [7]Department of Surgery, Washington University School of Medicine, St. Louis, Missouri 63108, USA. [8]Department of Genome Sciences, University of Washington, Seattle, Washington 98195, USA.
*These authors contributed equally to this work.

(Ley et al, Nature, 2008)

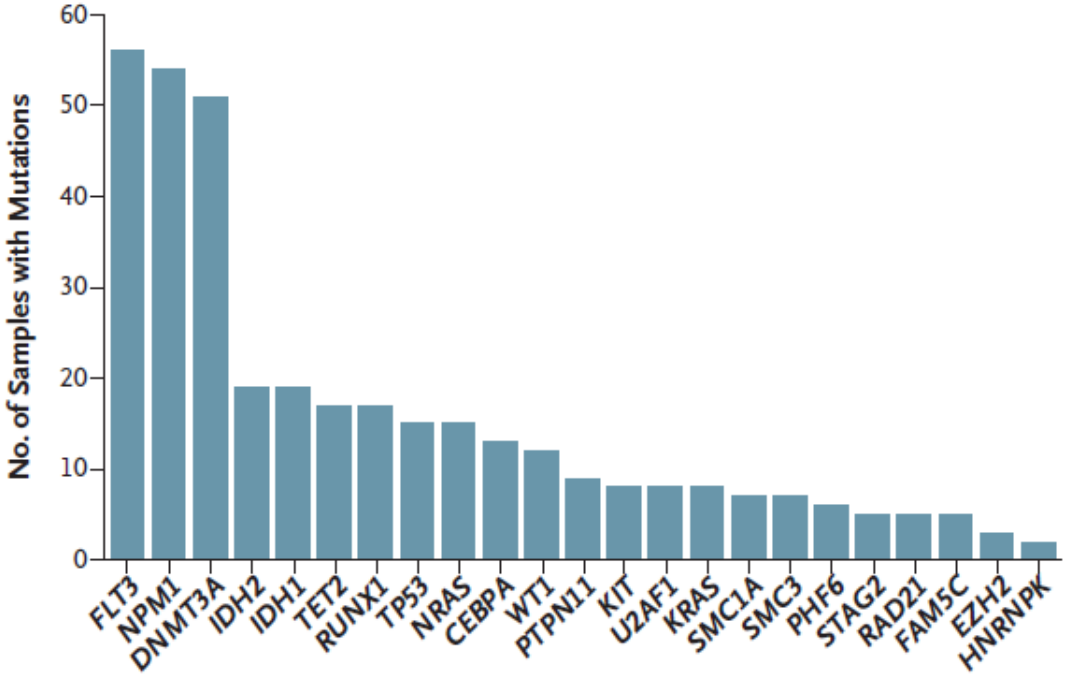
✓ 2013

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

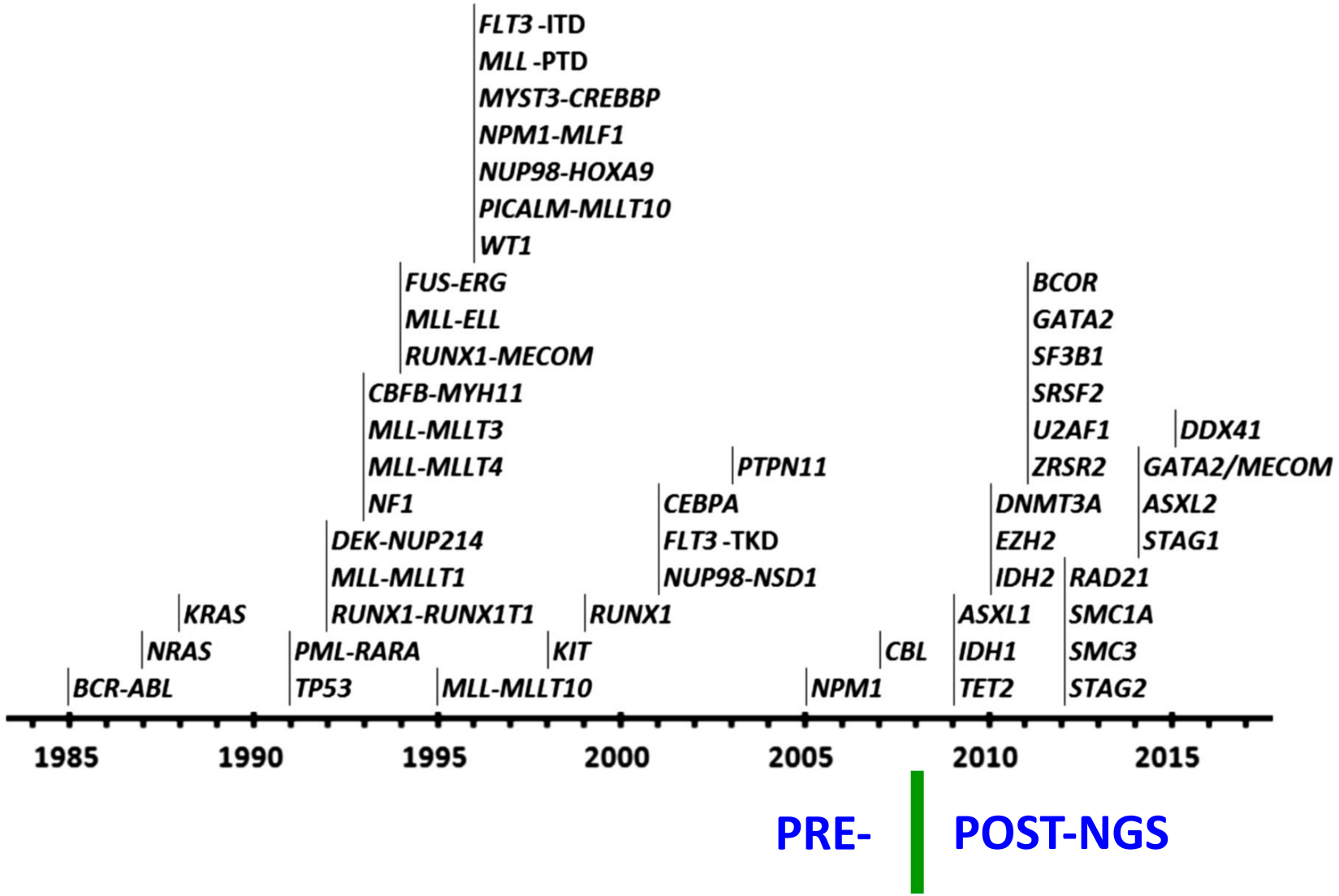
The Cancer Genome Atlas Research Network



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



David Grimwade et al. Blood 2016;127:29-41

AML risk stratification by genetics: ELN 2010 and 2017

Standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
*	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I*	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse†
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	−5 or del(5q); −7; abnl(17p); complex karyotype‡

2010 ELN recommendations

Dohner et al. Blood, 2010;115:453-474

2017 ELN 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 or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

2017 ELN recommendations

Dohner et al. Blood, 2017;129:424-447

blood®
Special Report

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Strategies for developing or refining a classification of hematologic neoplasms

Arber et al. *Blood*. 2022;140(11):1200-1228; Cazzola and Sehn. *Blood*. 2022;140 (11):1193–1199.

AML risk stratification by genetics: ELN 2017 and 2022

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	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
*	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
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	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

2017 ELN recommendations

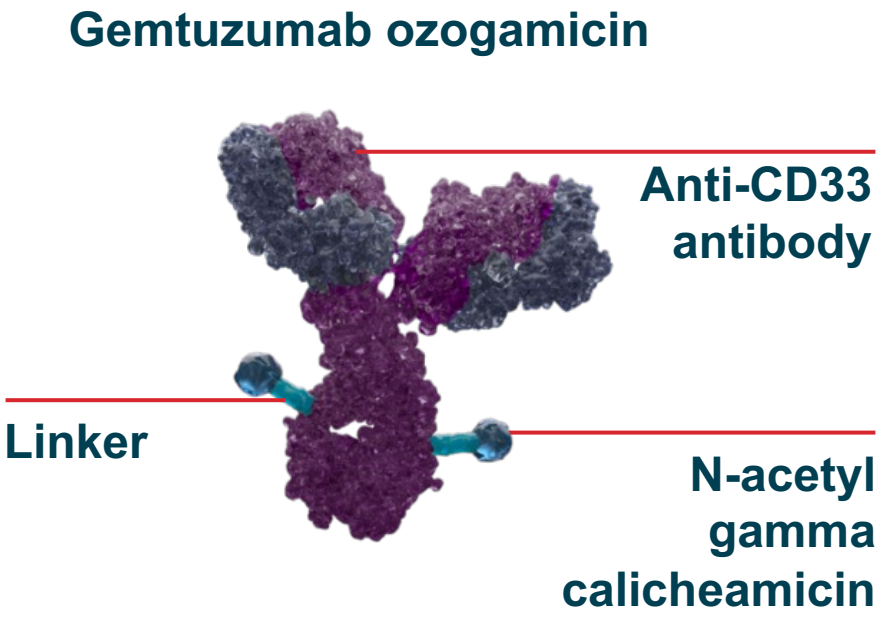
Dohner et al. Blood, 2017;129:424-447

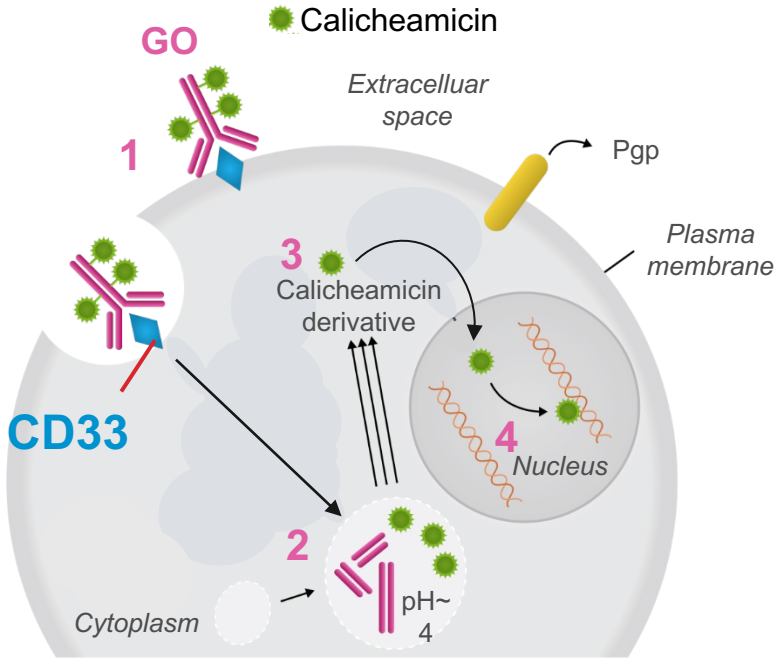
Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*†,‡
	• inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*†,‡
*	• Mutated *NPM1*†,§ without *FLT3*-ITD
	• bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD
	• Wild-type *NPM1* with *FLT3*-ITD (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 *TP53*[a]

2022 ELN recommendations

Dohner et al. Blood, 2022;140:1345-1377

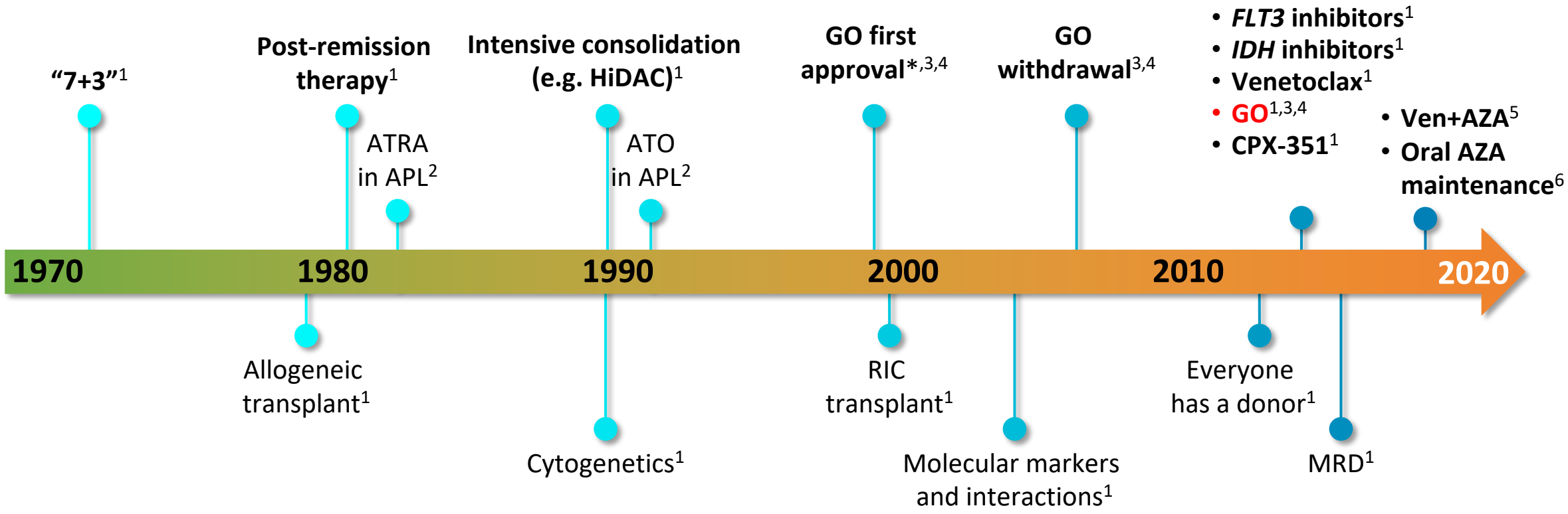
Gemtuzumab ozogamicin (GO): Mechanism of action





1. GO binds to CD33 antigens on leukaemic blasts
2. Once bound, the GO/CD33 complex is internalised by receptor-mediated endocytosis
3. Calicheamicin is released from the antibody–drug complex and acts as a potent cytotoxic agent
4. Calicheamicin causes double-strand DNA breaks, causing the cell to undergo apoptosis

Major advances in AML over the past 5 decades

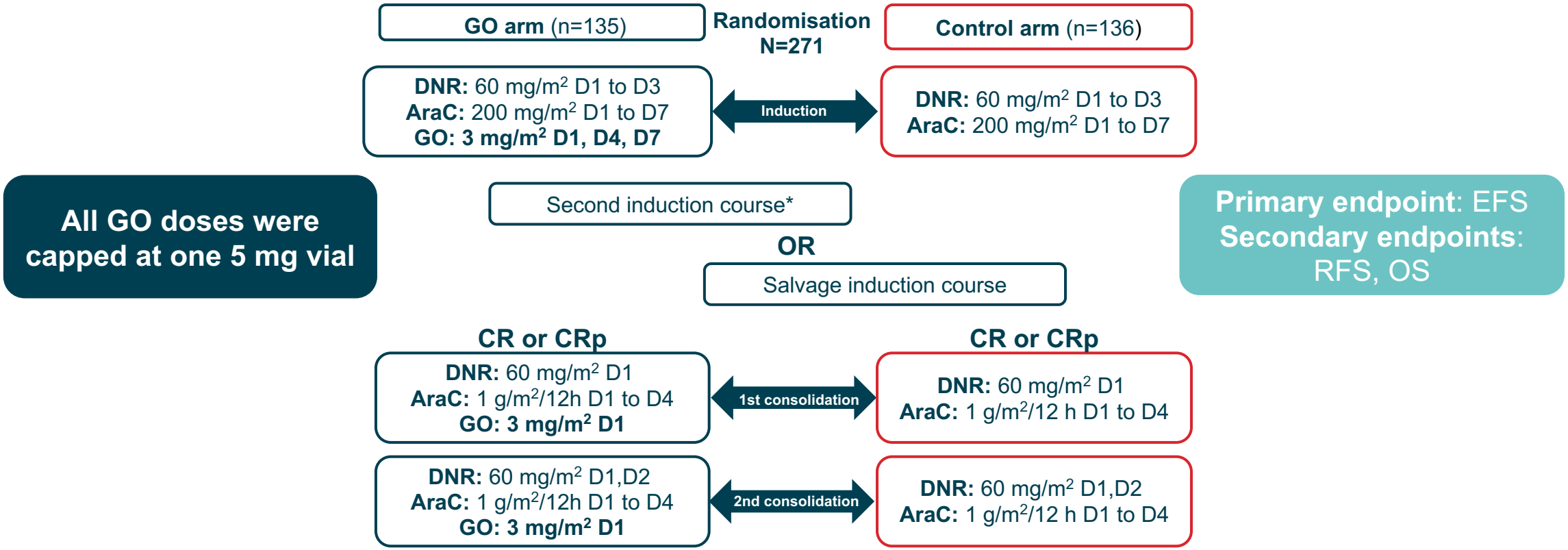


* EMA orphan designation and FDA approval in 2000;
AlloSCT, allogeneic stem cell transplant; APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA; all-trans retinoic acid; GO, gemtuzumab ozogamicin; AZA, oral azacitidine; HiDAC, high-dose cytarabine; RIC, reduced-intensity conditioning.

1. Rowe JM. *Best Pract Res Clin Haematol* 2019; **32:**101094; 2. Wang ZY & Chen Z. *Blood* 2008; **111:**2505–2515; 3. Ali S, *et al. Oncologist* 2019; **24:**e171–e179;
4. FDA News Release. Sept 01, 2017. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-mylotarg-treatment-acute-myeloid-leukemia (accessed 09/2020);
5. DiNardo CD, *et al. N Engl J Med* 2020; **383**:617–629; 6. Wei AH, *et al. Blood* 2019; **134:**LBA-3.

ALFA-0701: Phase III study design

Randomisation: Untreated patients with AML, aged 50–70 years[1,2]

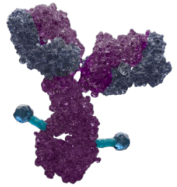


***If a second induction is required, GO should not be administered during second induction therapy. Only DNR and AraC should be administered during the second induction cycle: DNR should be infused at a dose of 35 mg/m²/day on Days 1 and Day 2, and AraC at a dose of 1 g/m²/every 12 hours on Day 1 to Day 3[3]**

AML, acute myeloid leukaemia; AraC, cytarabine; CR, complete remission; CRp, complete remission with incomplete platelet recovery; DNR, daunorubicin; EFS, event-free survival; GO, gemtuzumab ozogamicin; OS, overall survival; RFS, relapse-free survival

1. Lambert J *et al. Haematologica* 2019;104:113–119; 2. Lambert J *et al. Haematologica* 2019;104:113−119.(Suppl.); 3. Pfizer Limited. gemtuzumab ozogamicin Summary of Product Characteristics last update

Gemtuzumab ozogamicin EU label



GO is indicated for combination therapy with DNR and AraC for the treatment of patients age 15 years and above with previously untreated, *de novo* CD33-positive AML, except APL

Dosing and administration

		Day 1	2	3	4	5	6	7
Induction*	**GO 3 mg/m²/dose**	▶			▶			▶
	DNR 60 mg/m²/day	▶	▶	▶				
	AraC 200 mg/m²/day	▶	▶	▶	▶	▶	▶	▶
Second induction (if required)*	**GO should not be administered during second induction**							
	DNR 35 mg/m²/day	▶	▶					
	AraC 1 g/m² q12h/day	▶	▶	▶				
Up to two consolidation courses can be given for patients in CR following induction								
Consolidation course 1	**GO 3 mg/m²/dose**	▶						
	DNR 60 mg/m²/day	▶						
	AraC 1 g/m² q12h/day	▶	▶	▶	▶			
Consolidation course 2	**GO 3 mg/m²/dose**	▶						
	DNR 60 mg/m²/day	▶	▶					
	AraC 1 g/m² q12h/day	▶	▶	▶	▶			

Rationale for the use of fractionated doses of gemtuzumab ozogamicin

GO was developed in the relapsed AML setting[1]

Phase II studies

9 mg/m² **9 mg/m²**

30%

Response rate

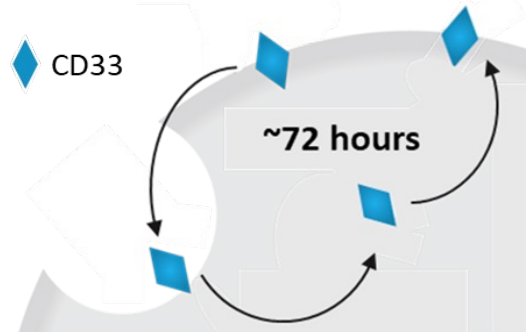
Excessive toxicity

Responses observed at 1–4 mg/m² [2]

Phase I study	Dose level, mg/m²							
	0.25	0.5	1	2	4	5	6	9
Patients per dose group, n	4	3	4	3	6	6	8	7
CR, n	–	–	1	–	1	–	–	1

Adapted from: Sievers *et al* 1999

Re-expression of CD33 sites occurred every ~72 hours[3]

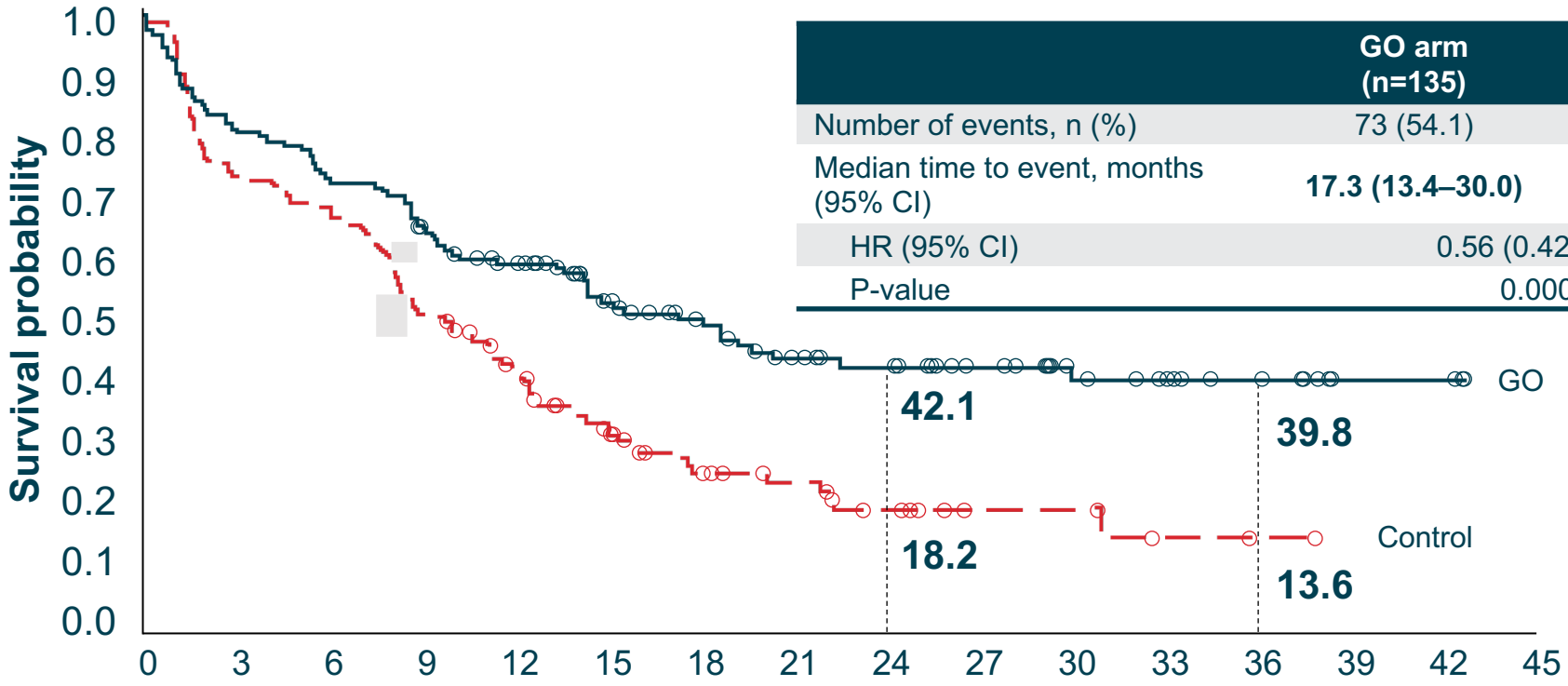


Frequent GO dosing may facilitate prolonged saturating serum levels and more efficient drug targeting

In induction, the recommended dose of GO is 3 mg/m²/dose (up to a maximum of one 5 mg vial) infused over a 2-hour period on Days 1, 4 and 7 in combination with daunorubicin 60 mg/m²/day infused over 30 minutes on Day 1 to Day 3, and AraC 200 mg/m²/day by continuous infusion on Day 1 to Day 7. AML, acute myeloid leukaemia; C_{max}, peak serum concentration; CR, complete remission; GO, gemtuzumab ozogamicin

1. Sievers EL *et al. J Clin Oncol* 2001;19:3244−3254; 2. Sievers EL *et al. Blood* 1999;93:3678−3684; 3. Caron PC *et al. Blood* 1994;83:1760−1768

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



	GO arm (n=135)	Control arm (n=136)
Number of events, n (%)	73 (54.1)	102 (75.0)
Median time to event, months (95% CI)	**17.3 (13.4–30.0)**	**9.5 (8.1–12.0)**
HR (95% CI)	0.56 (0.42–0.76)	
P-value	0.0002	

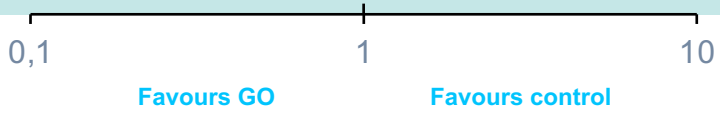
Number at risk

GO	135	109	98	86	74	57	47	36	32	25	18	15	10	3	3	0
Control	136	100	93	69	51	32	21	16	10	5	5	2	1	0		

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

ALFA-0701: Event-free survival by subgroup

Subgroup	Hazard ratio (95% CI)
Primary EFS	0.56 (0.42–0.76)
Age, years	
<60	0.52 (0.29–0.92)
≥60	0.56 (0.39–0.80)
Sex	
Male	0.57 (0.37–0.88)
Female	0.55 (0.35–0.85)
ECOG PS	
0–1	0.56 (0.41–0.78)
≥2	0.62 (0.26–1.51)
***FLT3*-ITD**	
Positive	0.33 (0.13–0.83)
Negative	0.51 (0.30–0.87)

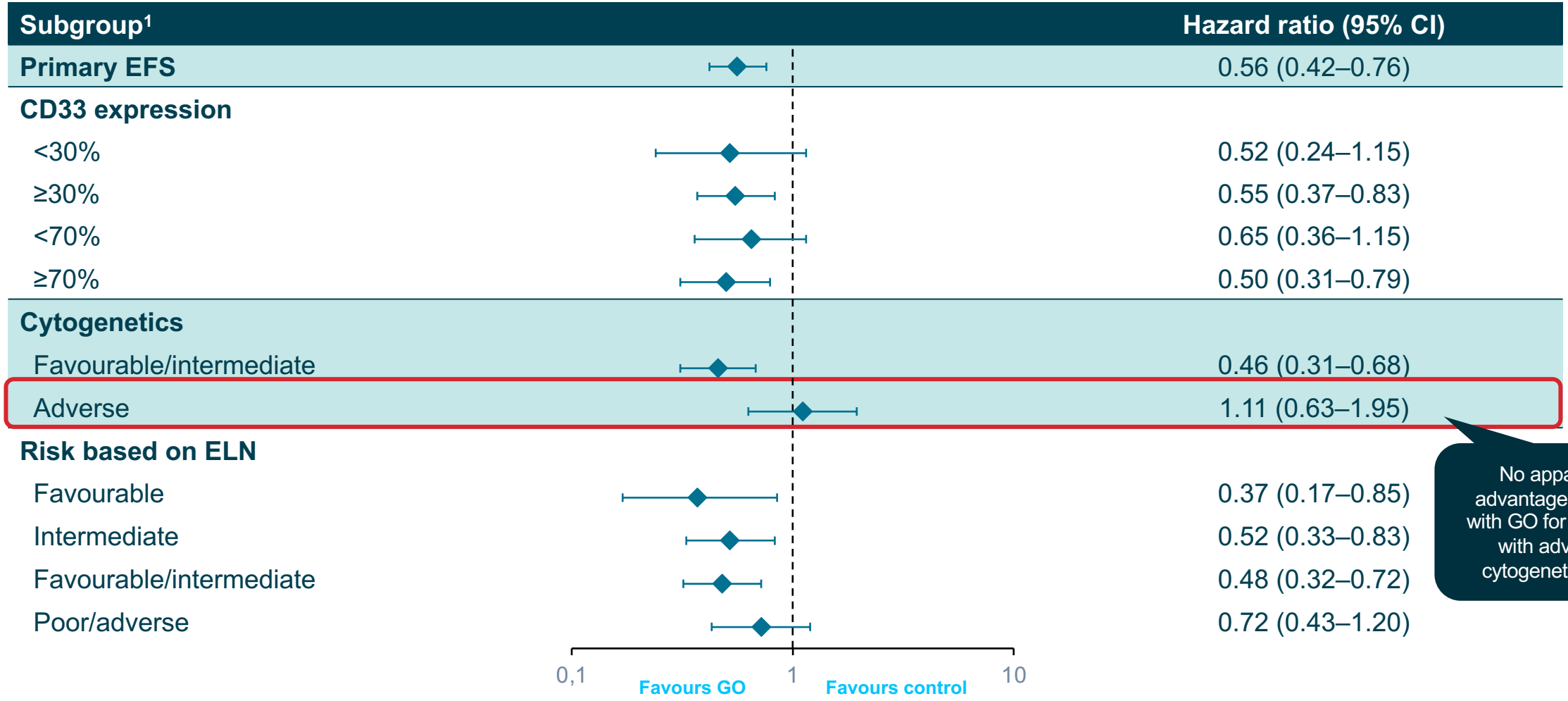


Adapted from: Lambert *et al*. 2019. (Suppl.)

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; GO, gemtuzumab ozogamicin

Lambert J *et al. Haematologica* 2019;104:113−119.(Suppl.)

ALFA-0701: Event-free survival by subgroup (cont'd)



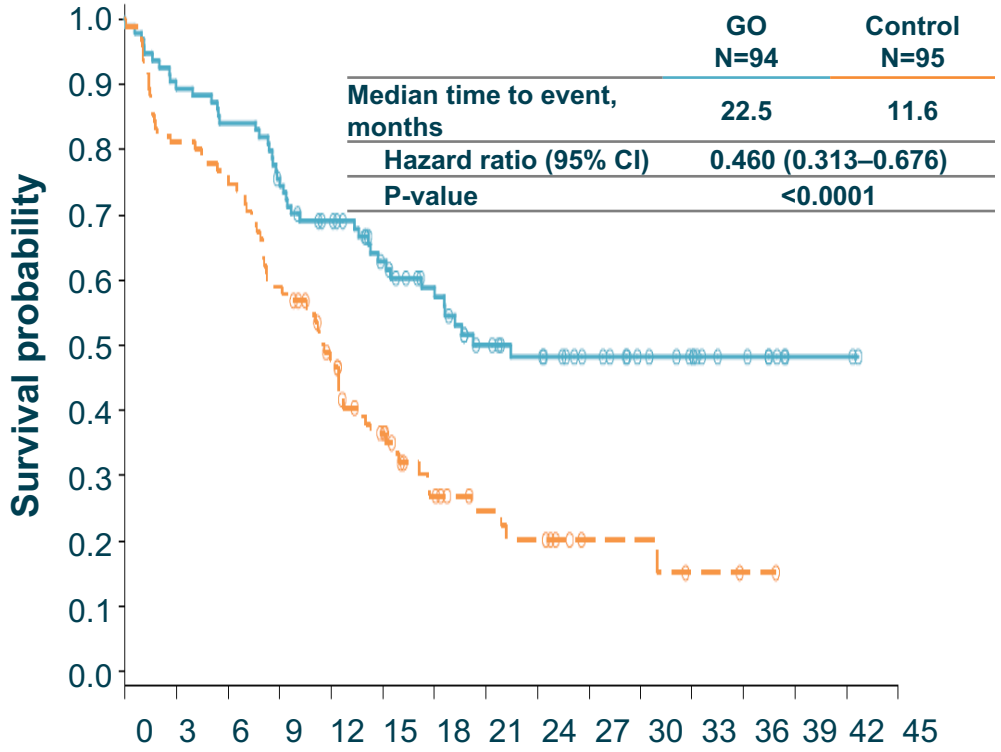
Adapted from: Lambert *et al*. 2019. (Suppl.)

CI, confidence interval; EFS, event-free survival; ELN, European LeukemiaNet; GO, gemtuzumab ozogamicin

1. Lambert J *et al. Haematologica* 2019;104:113−119. (Suppl.); 2. Lambert J *et al. Haematologica* 2019;104:113−119

This advantage in EFS with GO was not apparent for patients with adverse cytogenetic risk

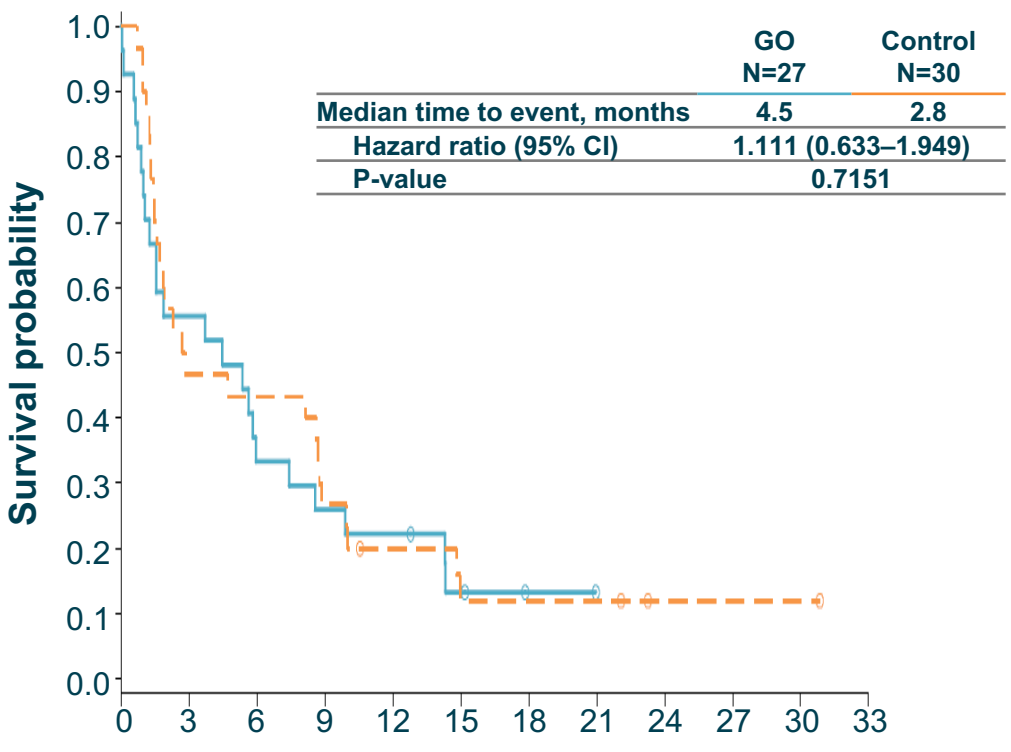
Favourable/intermediate



	GO N=94	Control N=95
Median time to event, months	22.5	11.6
Hazard ratio (95% CI)	0.460 (0.313–0.676)	
P-value	<0.0001	

No. at risk																
GO	94	84	79	70	61	49	41	31	27	21	16	13	8	2	2	0
Control	95	77	73	56	41	27	16	11	9	4	4	2	1	0		

Adverse

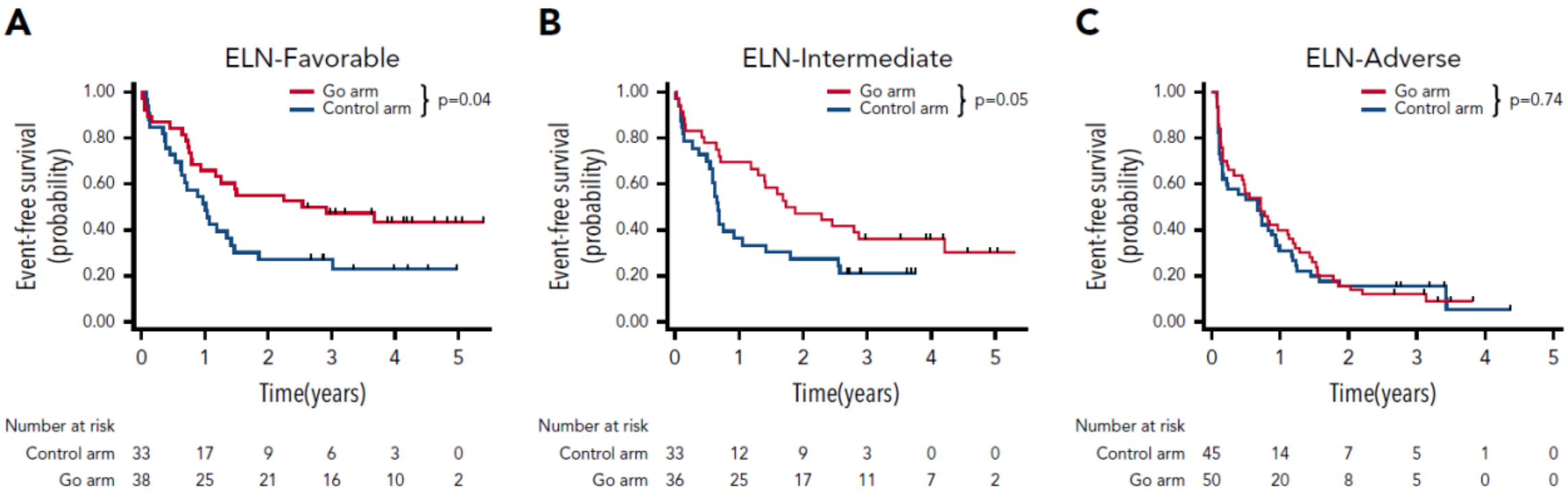


	GO N=27	Control N=30
Median time to event, months	4.5	2.8
Hazard ratio (95% CI)	1.111 (0.633–1.949)	
P-value	0.7151	

27	15	9	7	6	3	1	0					
30	14	13	8	5	3	3	3	1	1	1	0	

CI, confidence interval; EFS, event-free survival
Lambert J et al, Haematologica 2018

Benefit of GO according to ELN classification

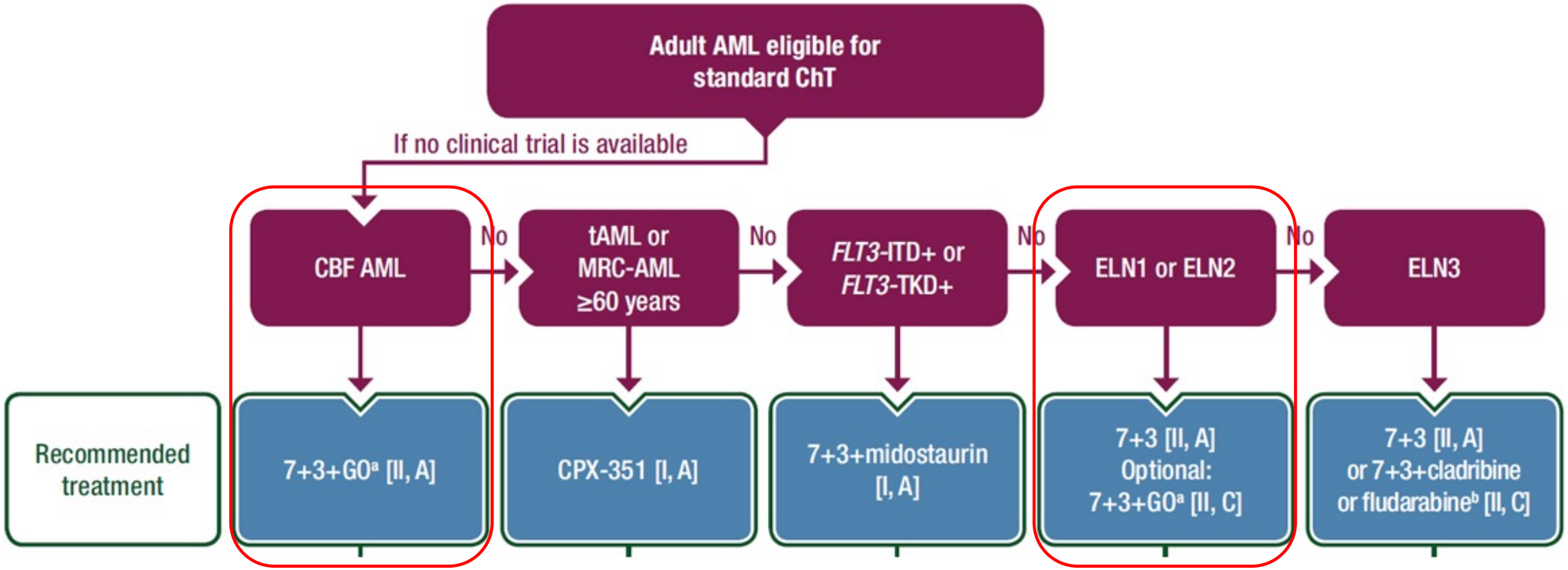


EFS according to ELN 2017 subgroups

Fournier E et al, (Blood. 2020;135(8):542-546)

ESMO 2020: Acute myeloid leukaemia in adult patients

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



M. Heuser et al, Annals of Oncology, Feb 2020

NCCN 2020: Treatment recommendations for newly diagnosed patients fit for intensive chemotherapy

Induction

Age < 60 years

Favorable-risk cytogenetics
- 7+3 **or**
- **7+3 and 3 total doses of MYLO* 3 mg/m^2 given on Days 1, 4, and 7 if CD33-positive**

Intermediate-risk cytogenetics and *FLT3*mt (ITD or TKD)
- 7+3 and midostaurin

Other recommendations for intermediate-/poor-risk disease
- **7+3 and 3 total doses of MYLO* 3 mg/m^2 given on Days 1, 4, and 7 if CD33-positive, intermediate-risk AML**
- Various chemotherapy regimens, including: 7+3 or 7+3 with cladribine or HiDAC with Ida or DNR or fludarabine, HiDAC, Ida, and G-CSF

tAML, antecedent MDS/CMML, AML-MRC
- 7+3 or CPX-351

Age ≥ 60 years (candidate for intensive therapy)

Favorable-risk cytogenetics
- 7+3 or
- **7+3 and 3 total doses of MYLO* 3 mg/m^2 given on Days 1, 4, and 7 if CD33-positive**

***FLT3*mt (ITD or TKD)**
- 7+3 and midostaurin

Unfavorable-risk cytogenetics (exclusive of AML-MRC)
- Venetoclax and DEC or AZA or LDAC or
- Low-intensity therapy (AZA, DEC)

Other recommendations for intermediate-/poor-risk disease
- 7+3
- **7+3 and 3 total doses of MYLO* 3 mg/m^2 given on Days 1, 4, and 7 if CD33-positive, intermediate-risk AML**

tAML, antecedent MDS/CMML, AML-MRC
- CPX-351

MYLOTARG in combination with 7+3 is recommended for use in patients with CD33-positive AML with favorable-risk and intermediate-risk cytogenetics (both < and ≥ 60 years):

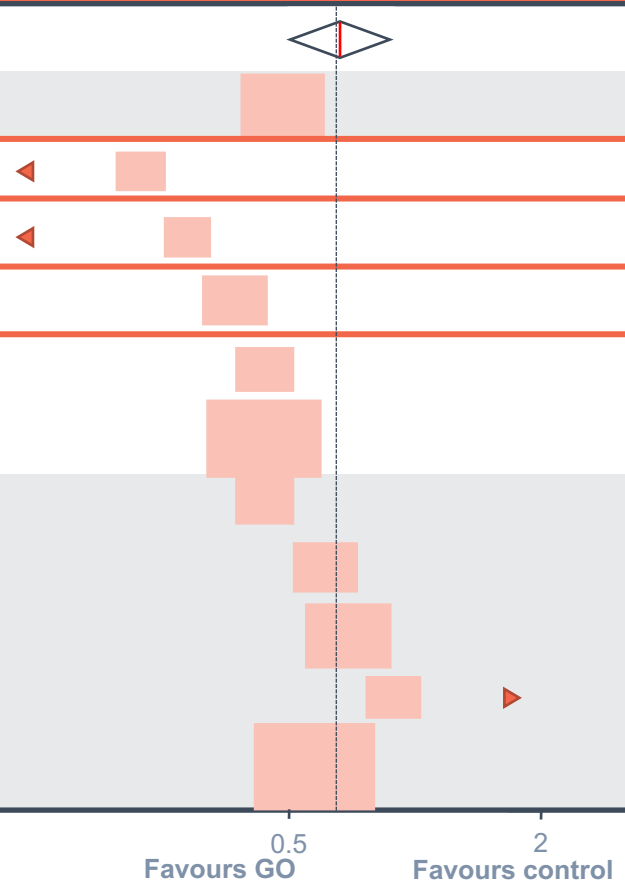
Induction:
- 7+3 and 3 total doses of MYLOTARG 3 mg/m^2 (up to one 4.5 mg vial) given on Days 1, 4, and 7

NCCN Guidelines Version 3. 2020. Acute Myeloid Leukemia

Benefit of GO according to mutation profile

ALFA-0701: Retrospective analysis of event-free survival by mutational profile

	Gene	Number of patients	Hazard ratio (95% CI)
	Overall	235	0.68 (0.51–0.92)
	NPM1	80	0.48 (0.28–0.83)
Signalling	*FLT3*-TKD	19	0.20 (0.05–0.78)
Signalling	*KRAS*	19	0.27 (0.09–0.84)
Signalling	*FLT3*-ITD	49	0.36 (0.18–0.72)
Signalling	*NRAS*	33	0.43 (0.19–0.95)
Signalling	Overall	117	0.43 (0.28–0.65)
Methylation	*IDH2*	31	0.43 (0.16–1.17)
Methylation	*TET2*	47	0.62 (0.33–1.18)
Methylation	*DNMT3A*	67	0.70 (0.40–1.22)
Methylation	*IDH1*	26	0.91 (0.41–2.02)
Methylation	Overall	133	0.58 (0.39–0.87)

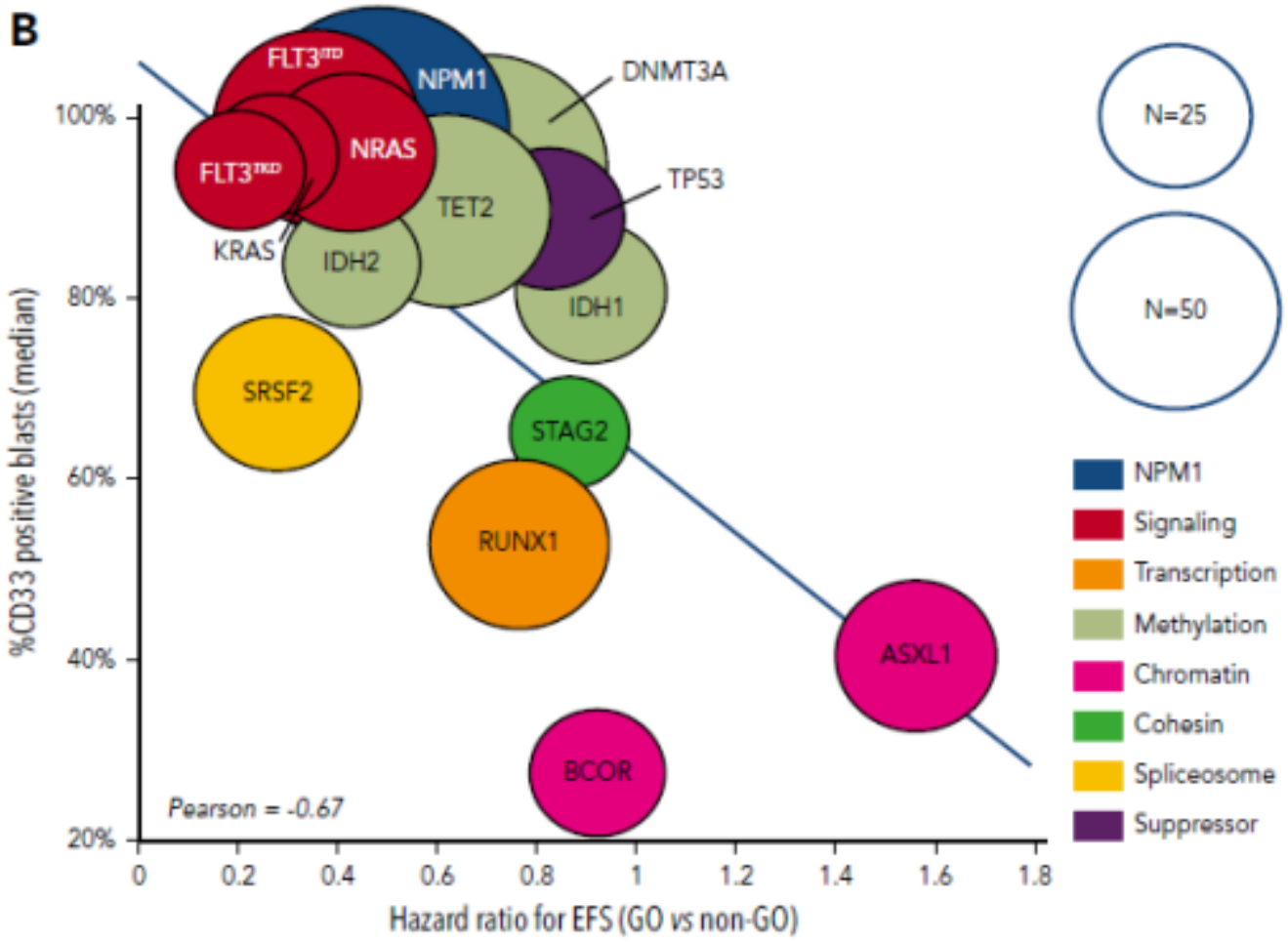


Adapted from Fournier *et al.* 2020

ALFA, Acute Leukemia French Association; CI, confidence interval; GO, gemtuzumab ozogamicin; ITD, internal tandem duplication; TKD, tyrosine kinase domain

Fournier E *et al. Blood* 2020;135:542–546

Benefit of GO and correlation with CD33 expression



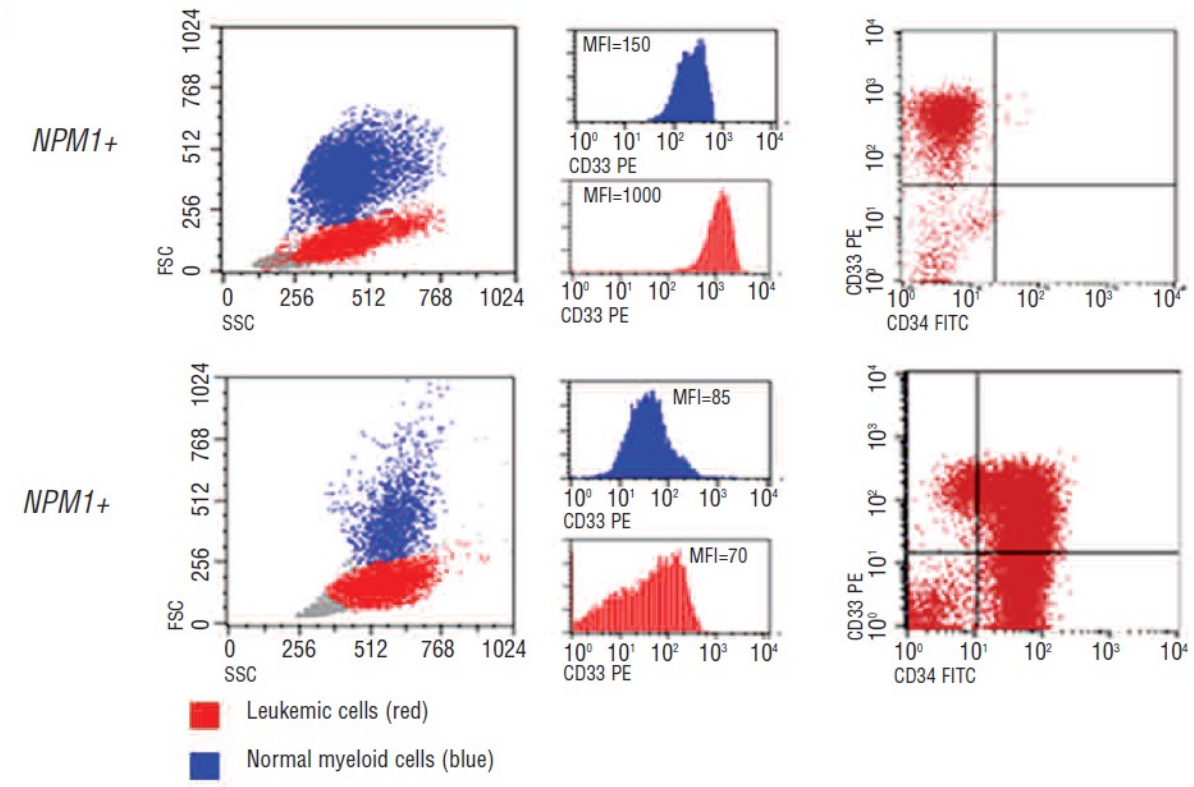
The correlation between the HRs and CD33 expression on AML blasts. Each circle represents a subgroup of patients with a mutation. The size of each circle is proportional to the number of patients.

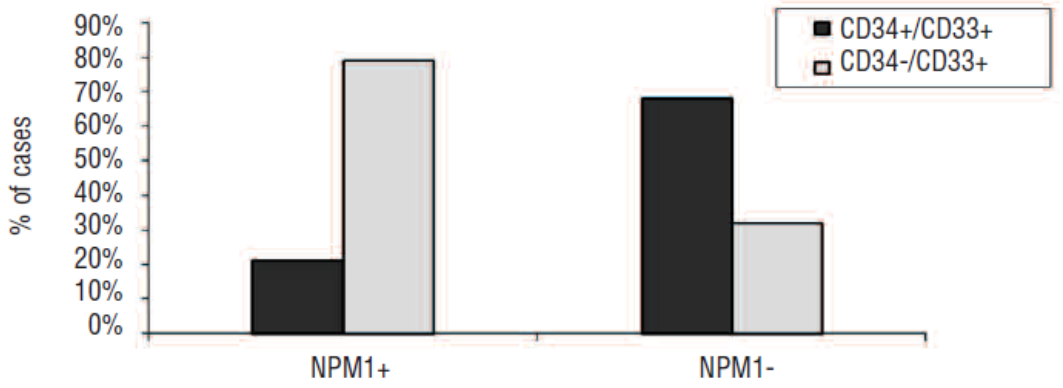
Fournier E et al, (Blood. 2020;135(8):542-546)

High CD33 expression levels in acute myeloid leukemia cells carrying the nucleophosmin (*NPM1*) mutation

Maria Stefania De Propris,[1] Sara Raponi,[1] Daniela Diverio,[1] Maria Laura Milani,[1] Giovanna Meloni,[1] Brunangelo Falini,[2] Robin Foà[1] and Anna Guarini[1]

[1]Division of Hematology, Department of Cellular Biotechnologies and Hematology, "Sapienza" University of Rome; and [2]Institute of Hematology, University of Perugia, Italy



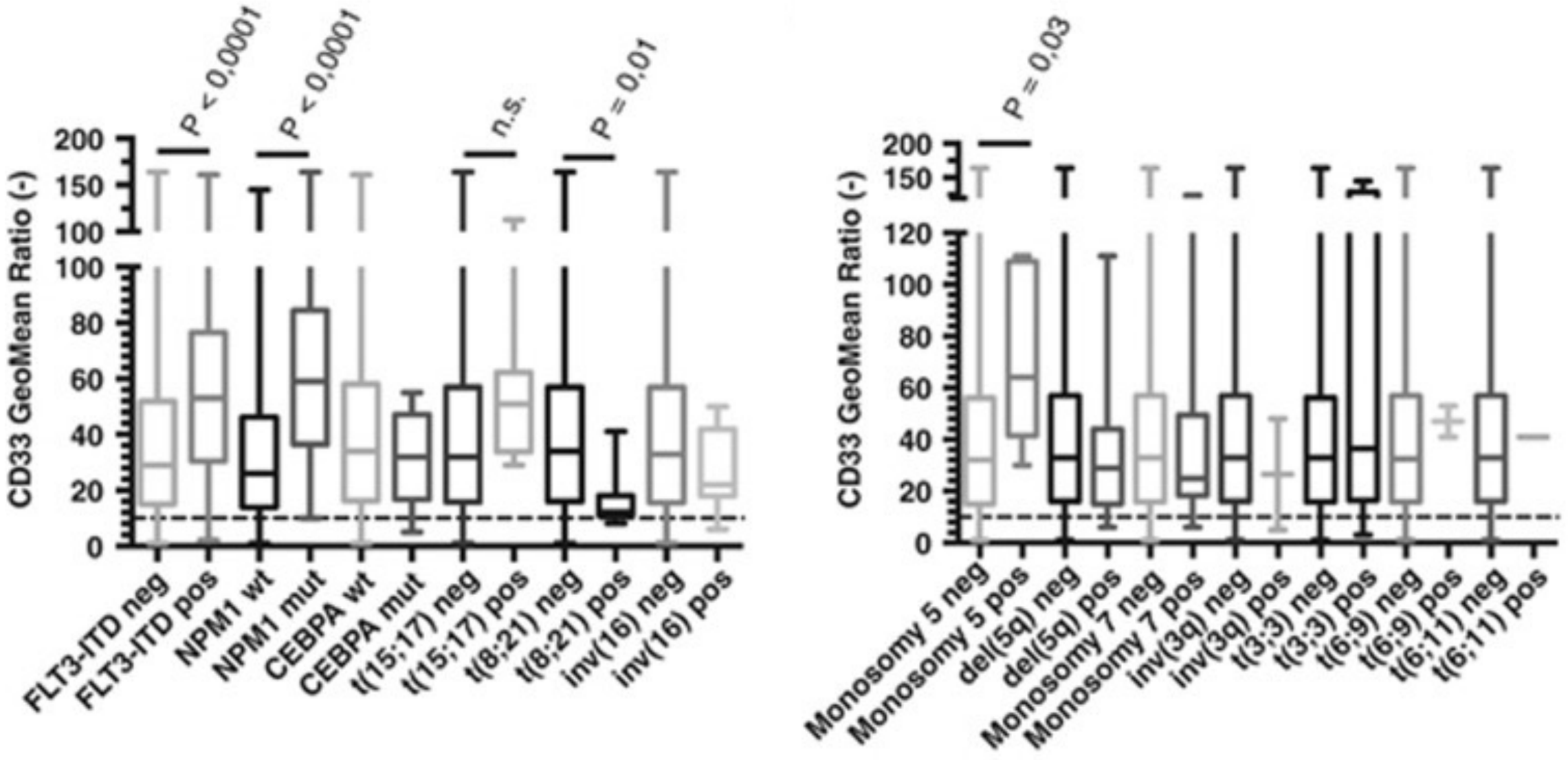


- CD34/CD33 expression in *NPM1*+ and *NPM1*- AML cells

- different expression intensity (MFI) of CD33 between leukemic cells and normal myeloid cells

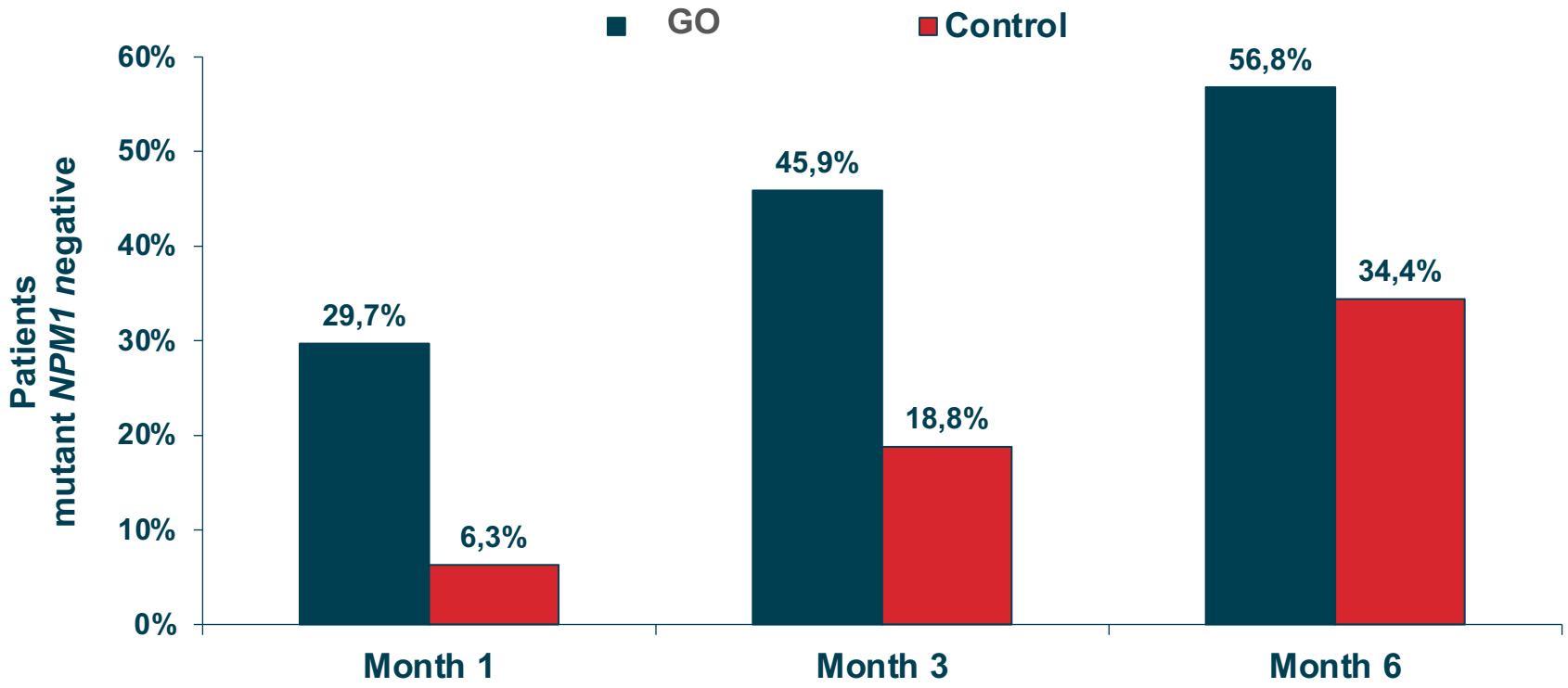
De Propris MS et al. Haematologica 2011;96(10):1548-1551

CD33 expression in AML



Ehninger A et al. Blood Cancer J. 2014 Jun 13;4(6):e218

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



	Month 1		Month 3		Month 6	
	GO	Control	GO	Control	GO	Control
Pts assessed	37	32	34	31	30	29
Pts mut*NPM1* neg	11	2	17	6	21	11

*MRD negative <0.1% NPM1mut copy number/ABL copy number × 100 (%);
ABL, Abelson murine leukaemia viral oncogene homolog; CR, complete remission; CRp, complete remission with partial haematological recovery of peripheral blood counts; MRD, minimal residual disease; mutNPM1, mutant Nucleophosmin 1; NPM1, Nucleophosmin 1; pts, patients
Lambert J et al, Haematologica 2018

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Regular Article

MYELOID NEOPLASIA

Impact of gemtuzumab ozogamicin on MRD and relapse risk in patients with *NPM1*-mutated AML: results from the AMLSG 09-09 trial

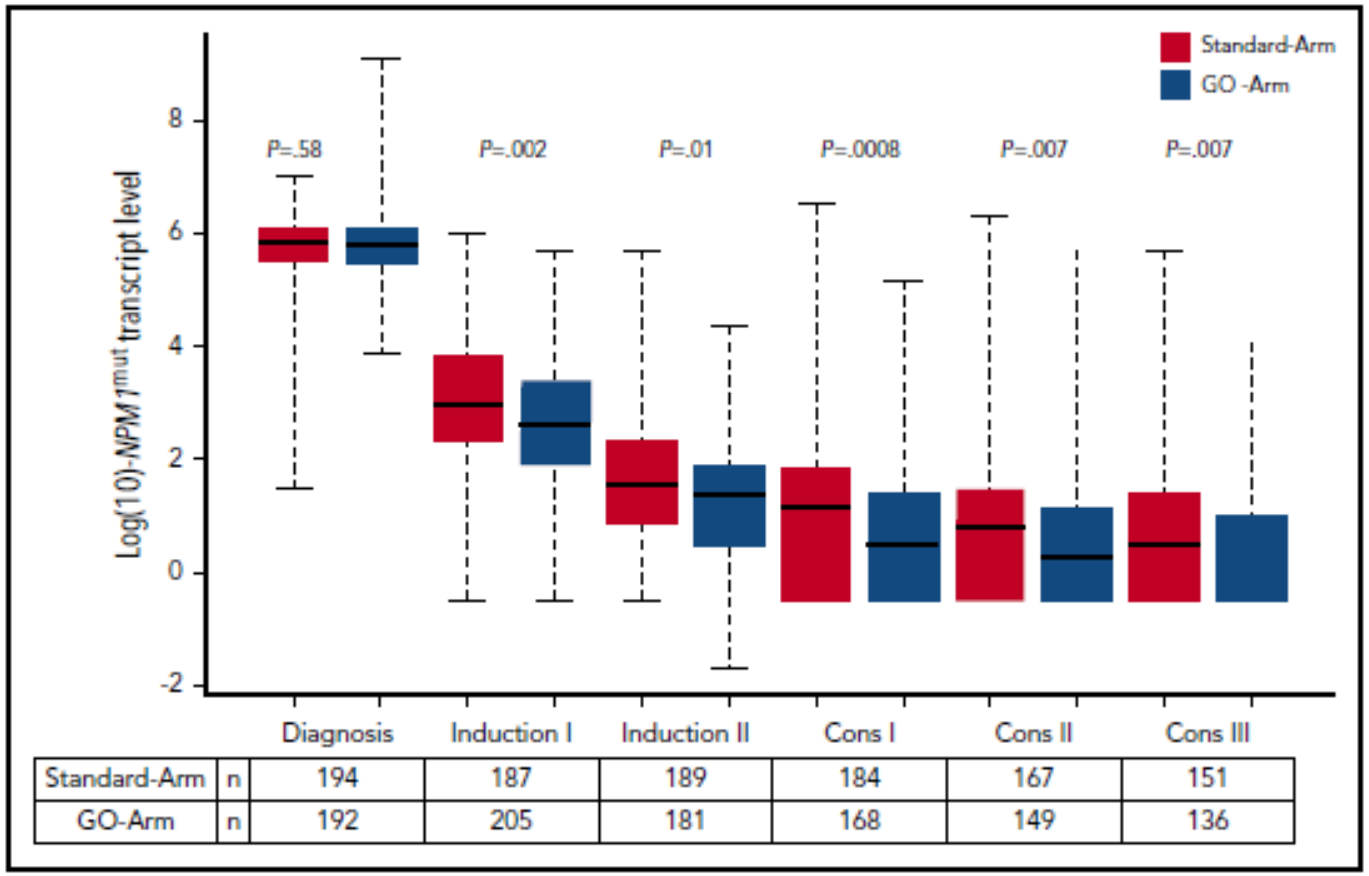
Silke Kapp-Schwoerer,[1] Daniela Weber,[1] Andrea Corbacioglu,[1] Verena I. Gaidzik,[1] Peter Paschka,[1] Jan Krönke,[1] Frauke Theis,[1] Frank G. Rücker,[1] Maria-Veronica Teleanu,[1] Ekaterina Panina,[1] Nikolaus Jahn,[1] Julia Herzig,[1] Lena Kubanek,[1] Anika Schrade,[1] Gudrun Göhring,[2] Walter Fiedler,[3] Thomas Kindler,[4] Thomas Schroeder,[5] Karin T. Mayer,[6] Michael Lübbert,[7] Mohammed Wattad,[8] Katharina S. Götze,[9] Heinz A. Horst,[10] Elisabeth Koller,[11] Gerald Wulf,[12] Jan Schleicher,[13] Martin Bentz,[14] Jürgen Krauter,[15] Lars Bullinger,[16] Julia Krzykalla,[17] Axel Benner,[17] Richard F. Schlenk,[18,19] Felicitas Thol,[20] Michael Heuser,[20] Arnold Ganser,[20] Hartmut Döhner,[1] and Konstanze Döhner[1]

KEY POINTS

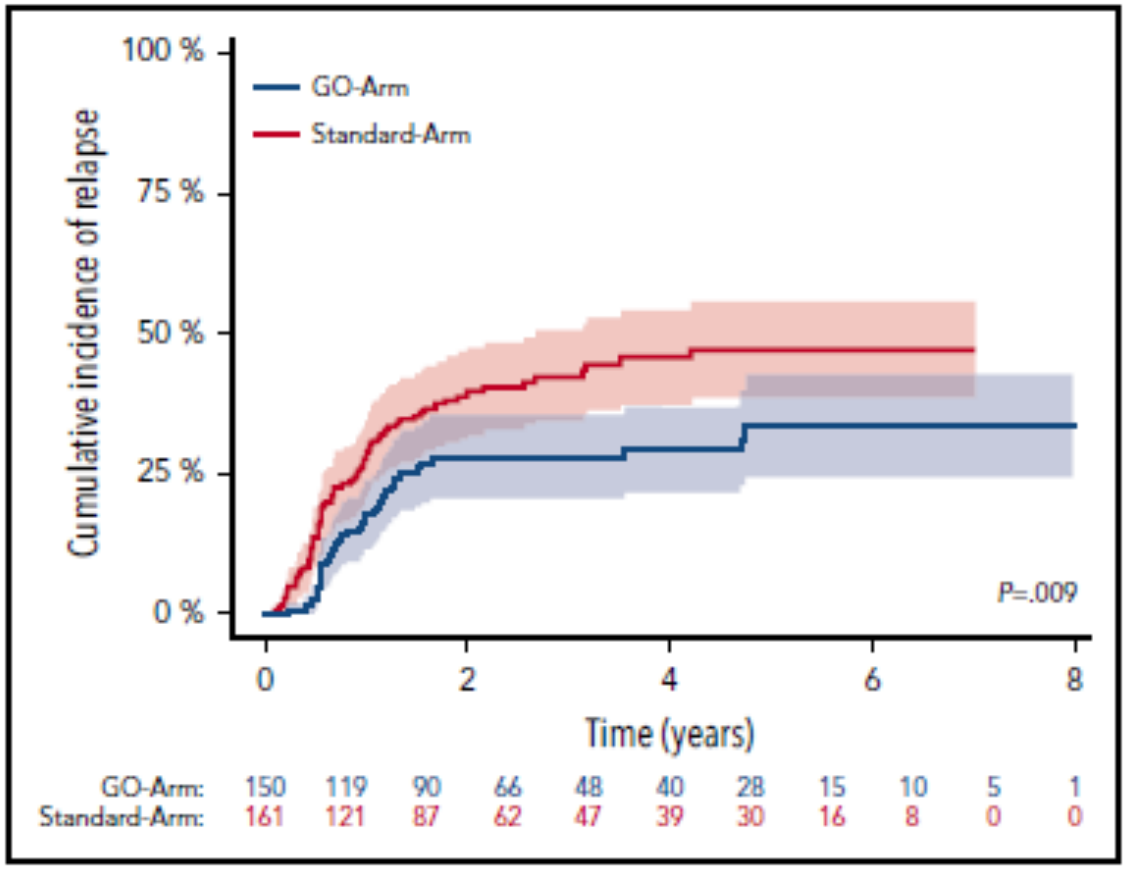
- **Measurable residual disease monitoring is of prognostic relevance in *NPM1*^{mut} acute myeloid leukemia patients.**
- **Gemtuzumab ozogamicin given to intensive therapy led to better clearance of *NPM1*^{mut} transcript level, resulting in a lower relapse rate.**

✓ The AMLSG 09-09 trial was a prospective randomized study of the German-Austrian AML Study Group (AMLSG) for adult patients with newly diagnosed NPM1-mut AML eligible for intensive chemotherapy. Treatment on the Standard-Arm included 2 cycles of induction therapy with ATRA, idarubicin, cytarabine, and etoposide, followed by up to 3 consolidation cycles of high-dose cytarabine with ATRA. On the GO-Arm, GO was given on day 1 (3 mg/mq) during the 2 induction cycles and the first consolidation cycle.

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



Standard-Arm	n	194	187	189	184	167	151
GO-Arm	n	192	205	181	168	149	136

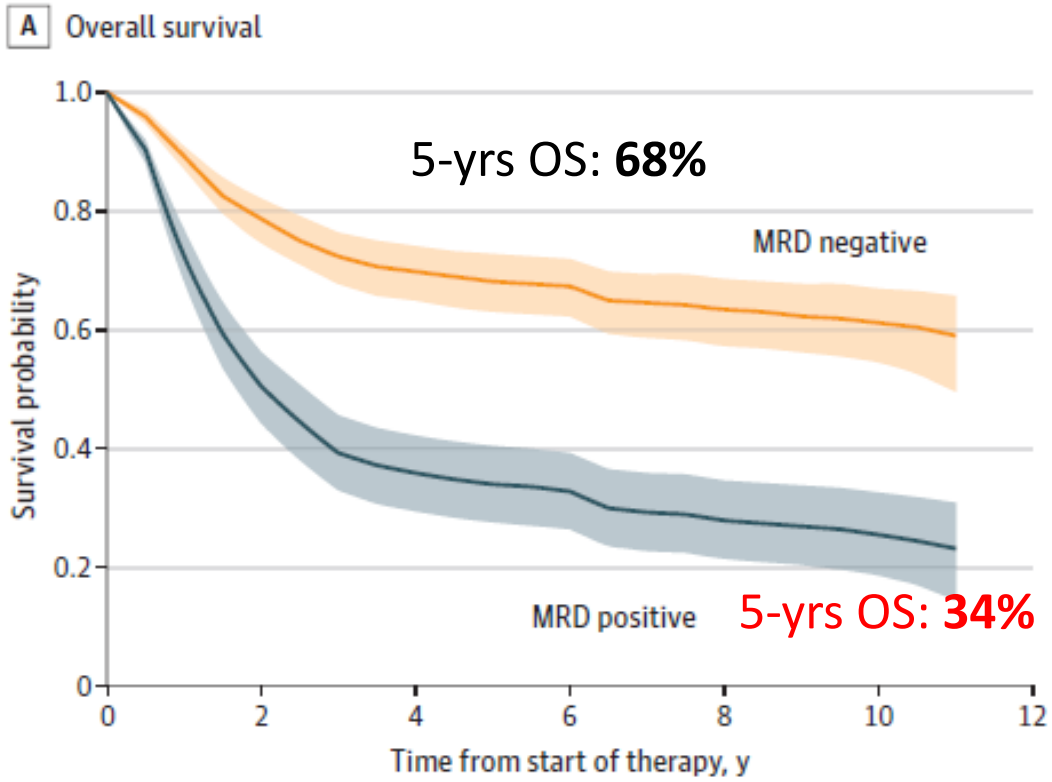


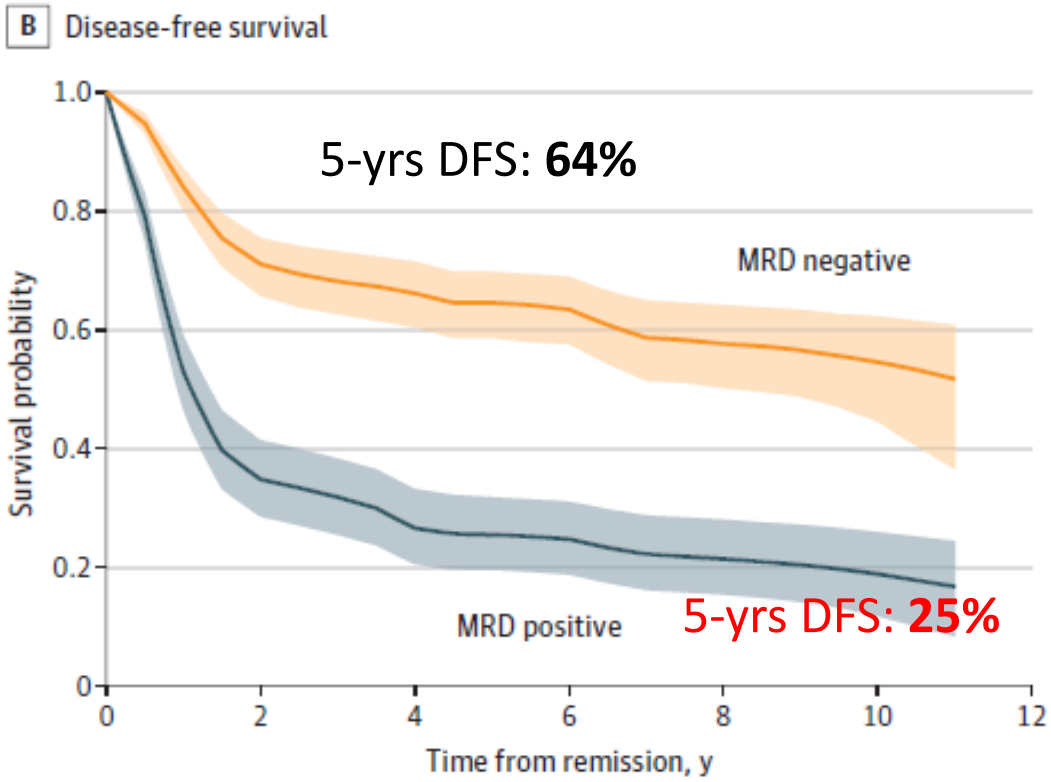
Shwoerer et al. Blood. 2020;136(26):3041-3050

JAMA Oncology | Original Investigation

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

A Systematic Review and Meta-analysis





Short NJ et al. JAMA 2020

Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials

Robert K Hills, Sylvie Castaigne, Frederick R Appelbaum, Jacques Delaunay, Stephen Petersdorf, Megan Othus, Elihu H Estey, Hervé Dombret, Sylvie Chevret, Norbert Ifrah, Jean-Yves Cahn, Christian Récher, Lucy Chilton, Anthony V Moorman, Alan K Burnett

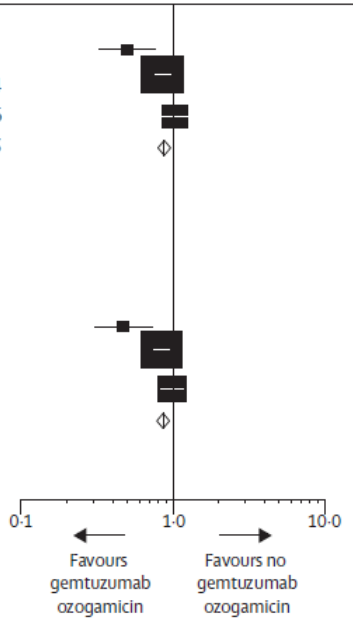
- ✓ a meta-analysis including **3325 patients** from **five open-label randomized phase III** controlled trials (MRC AML15, NCRI AML16, SWOG S0106, GOELAMS-AML 2006 IR and ALFA-0701) highlighted the benefit of the addition of GO on the risk of relapse (RR) and on OS (RR: OR: 0.81, 95% CI: 0.73–0.90, $p = 0.0001$; 5-year OS: OR: 0.90, 95% CI: 0.82–0.98, $p = 0.01$)

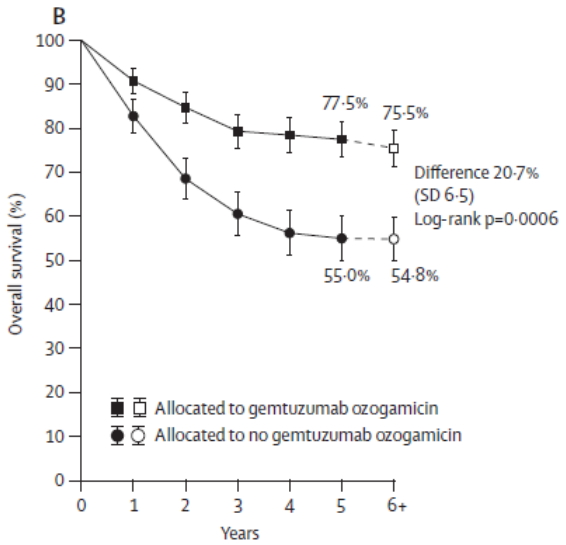
Hills et al. *Lancet Oncol* 2014; 15: 986–96

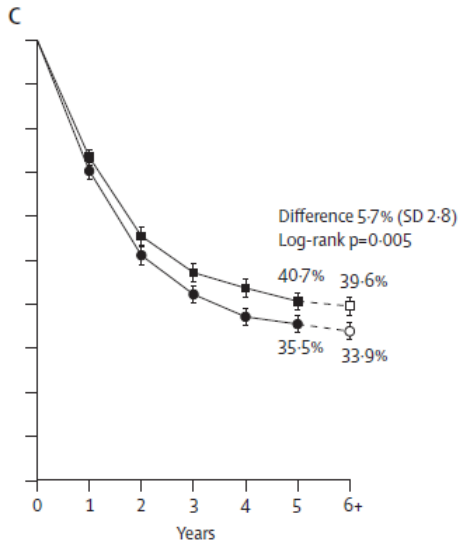
Overall survival stratified by cytogenetic characteristics

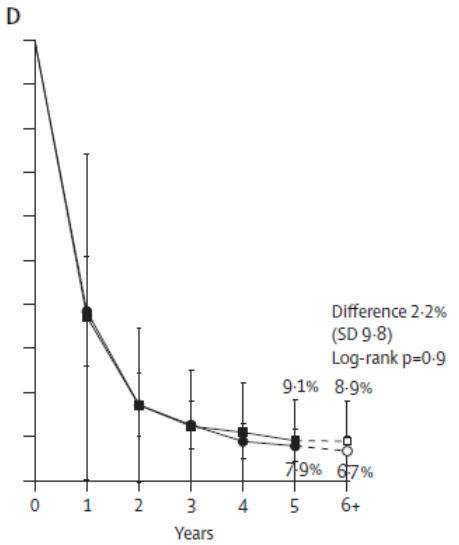
A

	Events/patients: Gemtuzumab ozogamicin group	Events/patients: No gemtuzumab ozogamicin group	o–e	Variance	OR (95% CI)	p value
Original coding						
Favourable	32/125	54/126	−14·3	20·5	0·50 (0·32–0·77)	
Intermediate	549/962	596/964	−44·2	284·4	0·86 (0·76–0·96)	
Adverse	223/261	227/256	3·1	110·6	1·03 (0·85–1·24)	
Subtotal	**804/1348**	**877/1346**	**−55·4**	**415·5**	**0·88 (0·79–0·96)**	**0·007**
Test for heterogeneity between subgroups: χ^2=9·6; p=0·008						
Test for trend between subgroups: χ^2=7·8; p=0·005						
Revised MRC coding[12]						
Favourable	30/122	54/124	−15·5	20·6	0·47 (0·31–0·73)	
Intermediate	506/911	559/916	−45·3	264·6	0·84 (0·75–0·95)	
Adverse	260/299	258/284	−1·2	127·6	0·99 (0·83–1·18)	
Subtotal	**796/1332**	**871/1324**	**−61·9**	**412·8**	**0·86 (0·78–0·95)**	**0·002**
Test for heterogeneity between subgroups: χ^2=10·1; p=0·006						
Test for trend between subgroups: χ^2=7·7; p=0·006						









Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

Hills et al. *Lancet Oncol* 2014; 15: 986–96

ALFA-0701: Persistent thrombocytopenia and platelet recovery

- Severe persistent thrombocytopenia was defined as platelet count <50,000/mm^3 at 45 days (after Day 1 of the respective treatment phase) in patients experiencing CRp
  - 20 patients discontinued GO as a result of persistent thrombocytopenia*

Laboratory abnormality	GO arm	Control arm
Severe persistent thrombocytopenia		
Evaluable patients	108	101
Patients with persistent thrombocytopenia, n (%)	22 (20.4)	2 (2.0)
Median time to platelet recovery to 50,000/µl		
During induction, days	34	29
During consolidation 1, days	32	27
During consolidation 2, days	36.5	30

Adapted from Lambert et al. 2019
*As per protocol, patients with platelets <100,000/mm3 14 days after the planned start date of their next treatment course were required to discontinue GO
CRp, complete remission with incomplete platelet recovery; GO, gemtuzumab ozogamicin
Lambert J et al. Haematologica 2019;104:113–119

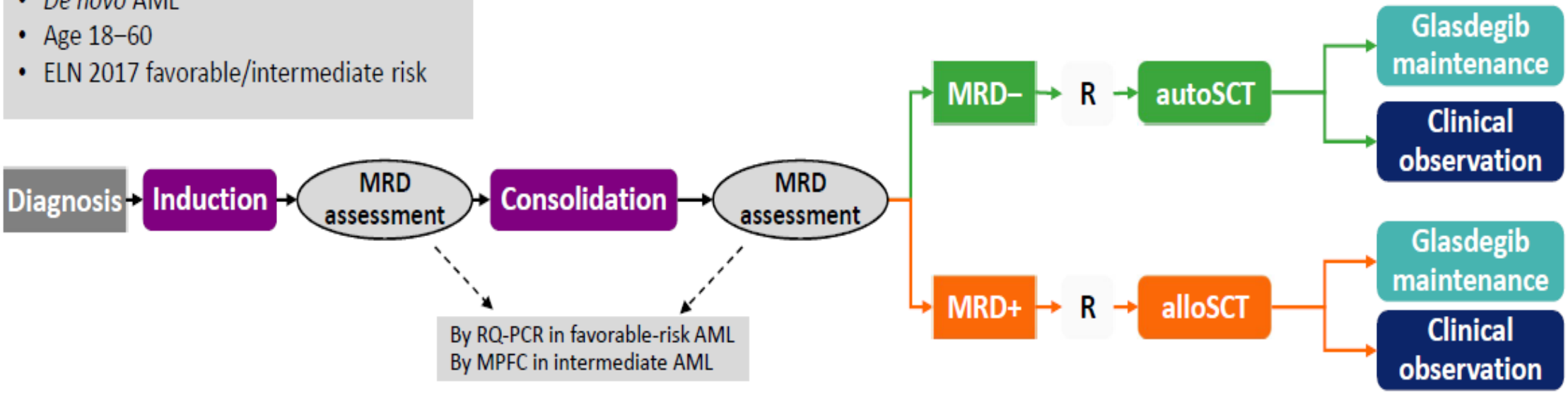
ALFA-0701: AEs of special interest

	GO arm (n=131), n (%)	Control arm (n=137), n (%)
Infections:* Severe (Grade ≥3)[1]	102 (77.9)	106 (77.4)
Haemorrhage: All grades (Grade ≥1), total†[1]	118 (90.1)	107 (78.1)
Grade 3	23 (17.6)	12 (8.8)
Grade 4	4 (3.1)	0
Grade 5	3 (2.3)	1 (0.7)
VOD: All grades (Grade ≥1), total†[1]	6 (4.6)	2 (1.5)‡
Grade 3	2 (1.5)	1 (0.7)
Grade 4	1 (0.8)	1 (0.7)
Grade 5	2 (1.5)	0

Adapted from Lambert *et al.* 2019
As treated study population
Only severe (i.e., Grade ≥3) infections and all-grade haemorrhage, VOD and other AEs that led to permanent discontinuation of study drugs were collected and reported.
AEs were graded in accordance with the NCI CTCAE v3.0 and coded by the MedDRA v18.0 dictionary[1]
*Infections refer to infections and infestations as defined for system organ class; †Coded MedDRA preferred terms for AEs indicating haemorrhage (standardised MedDRA queries for haemorrhage [excluding laboratory results] [narrow]) and VOD (includes the preferred term of veno-occlusive liver disease and VOD) were clustered[2]; ‡The 2 patients in the control arm received GO during the follow-up phase of the study, as part of the compassionate use programme after having relapsed before developing VOD[1]
AE, adverse event; GO, gemtuzumab ozogamicin; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute, Common Terminology Criteria for Adverse Events; VOD, veno-occlusive disease
1. Lambert J *et al*. *Haematologica* 2019;104:113–119; 2. Lambert J *et al*. *Haematologica* 2019;104:113–119 (Suppl.)

New GIMEMA AML1819 study (ELN2017 FR and IR pts, <60aa)

- *De novo* AML
- Age 18–60
- ELN 2017 favorable/intermediate risk



Two co-primary endpoints:

1. % MRD-negative after consolidation treatment
2. Disease-free survival in patients randomized to glasdegib maintenance or clinical observation

Induction
- GO: 3 mg/m^2 D1, 4, 7*
- Daunorubicin : 60 mg/m^2 D1–3
- Ara-C: 200 mg/m^2 D1–7

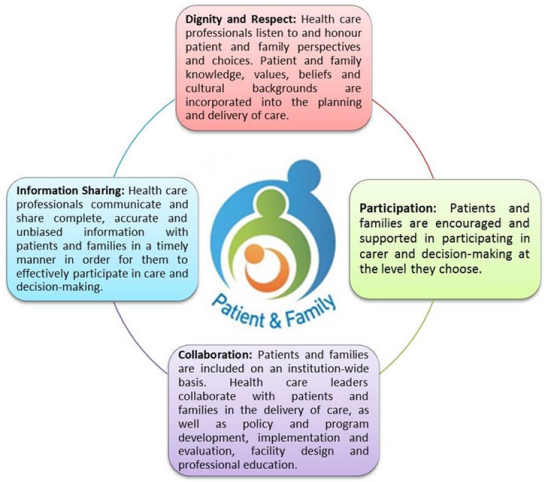
Consolidation
- GO: 3 mg/m^2 D1*
- Daunorubicin : 50 mg/m^2 D4–6
- Ara-C: 500 mg/m^2 BID, D1–6

Maintenance post-transplant
- Glasdegib 100 mg/day, orally, for up to 1 year or until toxicity/relapse

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

* Flat dose capped at 5 mg.

Acknowledgements



Patients

and Families

Hematology - CREO (Centro Ricerche Emato-Oncologiche)

All the clinical and research Hematology team

fondazione GIMEMA
FRANCO MANDELLI

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SÌ ALLA VITA!

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