AML
IL BUONO, IL BRUTTO, IL CATTIVO
IL BUONO:
LEUCEMIE CORE BINDING FACTOR

Dr. Michele Gottardi
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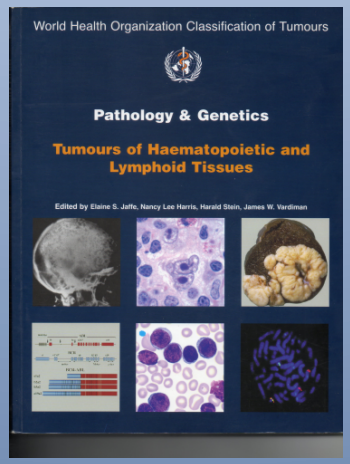
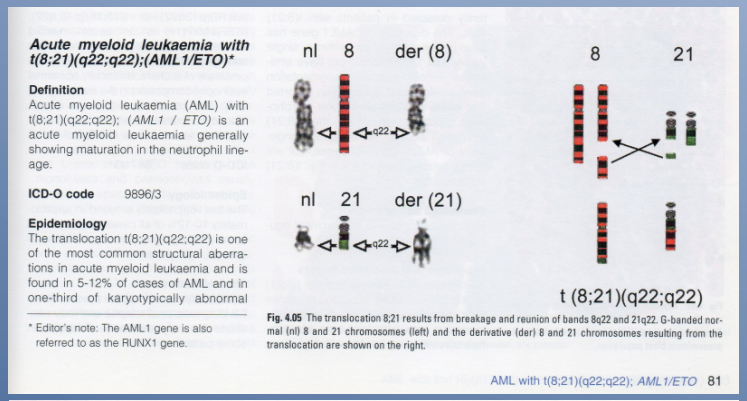
Treviso 24.11.18

IL BUONO:
LEUCEMIE CORE BINDING FACTOR





Acute myeloid leukaemia with t(8;21)(q22;q22);(AML1/ETO)*

Definition

Acute myeloid leukaemia (AML) with t(8;21)(q22;q22); (*AML1 / ETO*) is an acute myeloid leukaemia generally showing maturation in the neutrophil lineage.

ICD-O code 9896/3

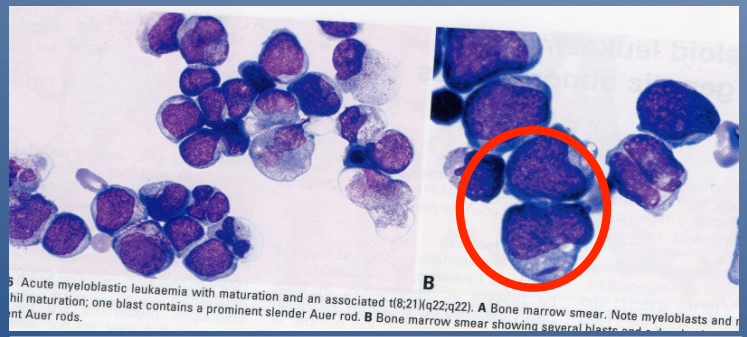
Epidemiology

The translocation t(8;21)(q22;q22) is one of the most common structural aberrations in acute myeloid leukaemia and is found in 5-12% of cases of AML and in one-third of karyotypically abnormal

* Editor's note: The AML1 gene is also referred to as the RUNX1 gene.

Fig. 4.05 The translocation 8;21 results from breakage and reunion of bands 8q22 and 21q22. G-banded normal (nl) 8 and 21 chromosomes (left) and the derivative (der) 8 and 21 chromosomes resulting from the translocation are shown on the right.

AML with t(8;21)(q22;q22); *AML1/ETO* 81



Acute myeloblastic leukaemia with maturation and an associated t(8;21)(q22;q22). **A** Bone marrow smear. Note myeloblasts and [illegible] maturation; one blast contains a prominent slender Auer rod. **B** Bone marrow smear showing several blasts [illegible] Auer rods.

CD13/CD33/MPO/CD34
CD19
CD56

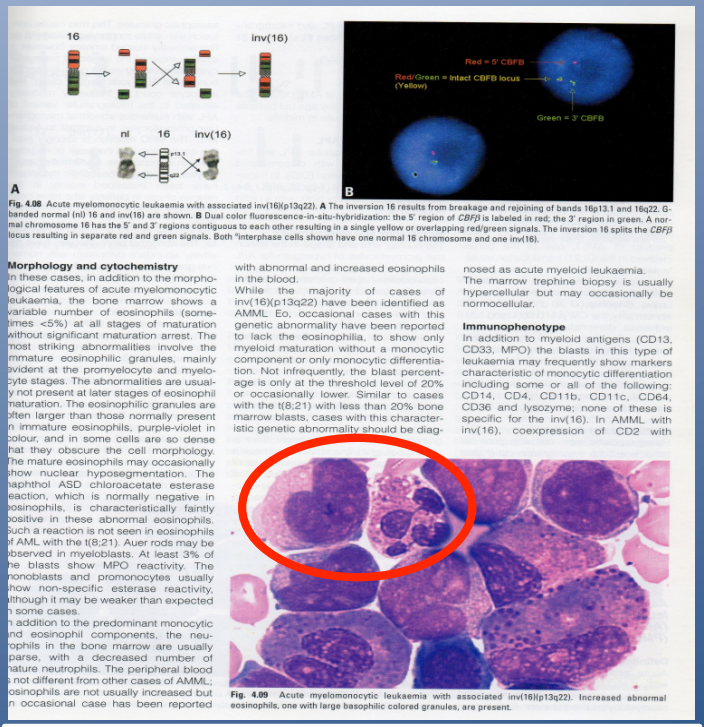


Fig. 4.08 Acute myelomonocytic leukaemia with associated inv(16)(p13q22). **A** The inversion 16 results from breakage and rejoining of bands 16p13.1 and 16q22. G-banded normal (nl) 16 and inv(16) are shown. **B** Dual color fluorescence-in-situ-hybridization: the 5' region of *CBFβ* is labeled in red; the 3' region in green. A normal chromosome 16 has the 5' and 3' regions contiguous to each other resulting in a single yellow or overlapping red/green signals. The inversion 16 splits the *CBFβ* locus resulting in separate red and green signals. Both *interphase cells shown have one normal 16 chromosome and one inv(16).

Morphology and cytochemistry

In these cases, in addition to the morphological features of acute myelomonocytic leukaemia, the bone marrow shows a variable number of eosinophils (sometimes <5%) at all stages of maturation without significant maturation arrest. The most striking abnormalities involve the immature eosinophilic granules, mainly evident at the promyelocyte and myelocyte stages. The abnormalities are usually not present at later stages of eosinophil maturation. The eosinophilic granules are often larger than those normally present in immature eosinophils, purple-violet in colour, and in some cells are so dense that they obscure the cell morphology. The mature eosinophils may occasionally show nuclear hyposegmentation. The naphthol ASD chloroacetate esterase reaction, which is normally negative in eosinophils, is characteristically faintly positive in these abnormal eosinophils. Such a reaction is not seen in eosinophils of AML with the t(8;21). Auer rods may be observed in myeloblasts. At least 3% of the blasts show MPO reactivity. The monoblasts and promonocytes usually show non-specific esterase reactivity, although it may be weaker than expected in some cases.

In addition to the predominant monocytic and eosinophil components, the neutrophils in the bone marrow are usually sparse, with a decreased number of mature neutrophils. The peripheral blood is not different from other cases of AMML; eosinophils are not usually increased but in occasional case has been reported with abnormal and increased eosinophils in the blood.

While the majority of cases of inv(16)(p13q22) have been identified as AMML Eo, occasional cases with this genetic abnormality have been reported to lack the eosinophilia, to show only myeloid maturation without a monocytic component or only monocytic differentiation. Not infrequently, the blast percentage is only at the threshold level of 20% or occasionally lower. Similar to cases with the t(8;21) with less than 20% bone marrow blasts, cases with this characteristic genetic abnormality should be diagnosed as acute myeloid leukaemia.

The marrow trephine biopsy is usually hypercellular but may occasionally be normocellular.

Immunophenotype

In addition to myeloid antigens (CD13, CD33, MPO) the blasts in this type of leukaemia may frequently show markers characteristic of monocytic differentiation including some or all of the following: CD14, CD4, CD11b, CD11c, CD64, CD36 and lysozyme; none of these is specific for the inv(16). In AMML with inv(16), coexpression of CD2 with

Fig. 4.09 Acute myelomonocytic leukaemia with associated inv(16)(p13q22). Increased abnormal eosinophils, one with large basophilic colored granules, are present.

CD13/CD33/MPO/CD34
CD14/CD11b/CD11c/CD64/lysozyme
CD2

According to the WHO classification, patients with t(8;21) or inv(16) should be considered to have AML regardless the percentage of blasts

IL BUONO: LEUCEMIE CORE BINDING FACTOR

The Importance of Diagnostic Cytogenetics on Outcome in AML: Analysis of 1,612 Patients Entered Into the MRC AML 10 Trial

By David Grimwade, Helen Walker, Fiona Oliver, Keith Wheatley, Christine Harrison, Georgina Harrison, John Rees, Ian Hann, Richard Stevens, Alan Burnett, and Anthony Goldstone on behalf of the Medical Research Council Adult and Children's Leukaemia Working Parties

PROGNOSTIC SIGNIFICANCE OF CYTOGENETICS IN AML 2325

Table 2. CR Rates, Survival, and Relapse Risk by Individual Abnormalities

Abnormality	Total No.	CR and Reason for Failure: CR Rate %	Induction Deaths %	Resistant Disease %	Deaths in Remission % (SE)	Relapse Risk at 5 yr % (SE)	Overall Survival at 5 yr % (SE)
Overall	1,612	85	8	8	14 (1.1)	49 (1.5)	44 (1.3)
Favorable							
t(15;17)	[illegible]	87	[illegible]	[illegible]	13 (3.7)	37 (4.1)*	63 (3.6)*
t(8;21)	122	98*	2	0†	15 (3.4)	29 (4.5)*	69 (4.2)*
inv(16)	57	88	12	0	9 (4.3)	42 (7.4)	61 (6.5)†
Intermediate							
No abnormality	680	88	6	6	15 (1.7)	53 (2.3)	42 (1.9)
+8	148	84	7	8	12 (2.9)	44 (4.8)	48 (4.3)
11q23	60	87	7	7	9 (4.6)	47 (7.2)	45 (6.4)
+21	[illegible]	80	7	13	11 (6.2)	50 (9.0)	47 (7.7)
del (7q)	[illegible]	75	6	19	19 (10.9)	59 (10.5)	23 (8.1)
del (9q)	25	100	0	0	9 (5.8)	39 (10.1)	60 (9.8)
+22	22	91	5	5	13 (8.6)	51 (12.4)	59 (10.5)
Other numerical	219	76*	11	14*	19 (3.4)	60 (4.2)	29 (3.1)*
Other structural	366	76*	9	14*	14 (2.5)	51 (3.2)	35 (2.5)†
Adverse							
Complex	95	67*	13	20*	12 (4.9)	68 (6.2)*	21 (4.2)*
−7	[illegible]	54*	16†	30*	8 (8.0)	80 (7.1)*	10 (3.8)*
abn(3q)	[illegible]	63*	23†	15	20 (11.9)	85 (7.8)*	12 (6.2)*
del(5q)	28	57*	14	29*	14 (9.1)	85 (9.5)*	11 (5.8)*
−5	26	42*	12	46*	12 (11.7)	90 (9.8)†	4 (3.8)*

24% (CBF 15-20%)

60%

16%

The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial

David Grimwade, Helen Walker, Georgina Harrison, Fiona Oliver, Stephen Chatters, Christine J. Harrison, Keith Wheatley, Alan K. Burnett, and Anthony H. Goldstone, on behalf of the Medical Research Council Adult Leukaemia Working Party

Table 2. Characterization of

	Total
Total	1065
Alone	
With the following:	
t(15;17)	[illegible]
t(8;21)	23
inv(16)	12
+8	109
7q−	48
+21	26
9q−	24
+22	15
11q23	11
Other structural	295
Other numerical	277
−7	87
5q−	80
−5	55
abn(3q)	27
Complex	146

7% (CBF 5%)

55%

38%

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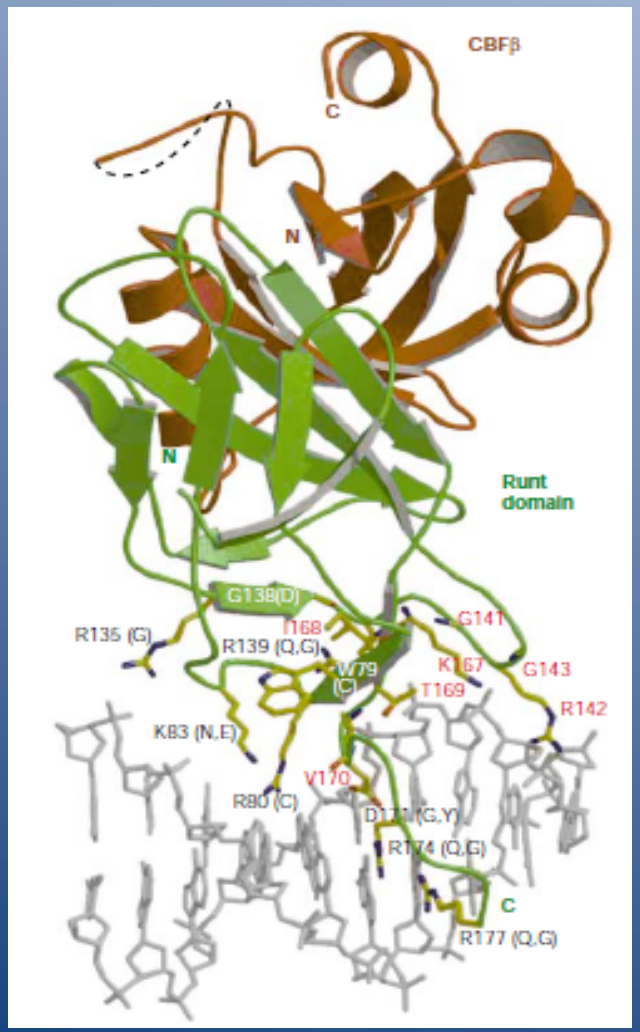
Table 2. CR Rates, Survival, and Relapse Risk by Individual Abnormalities

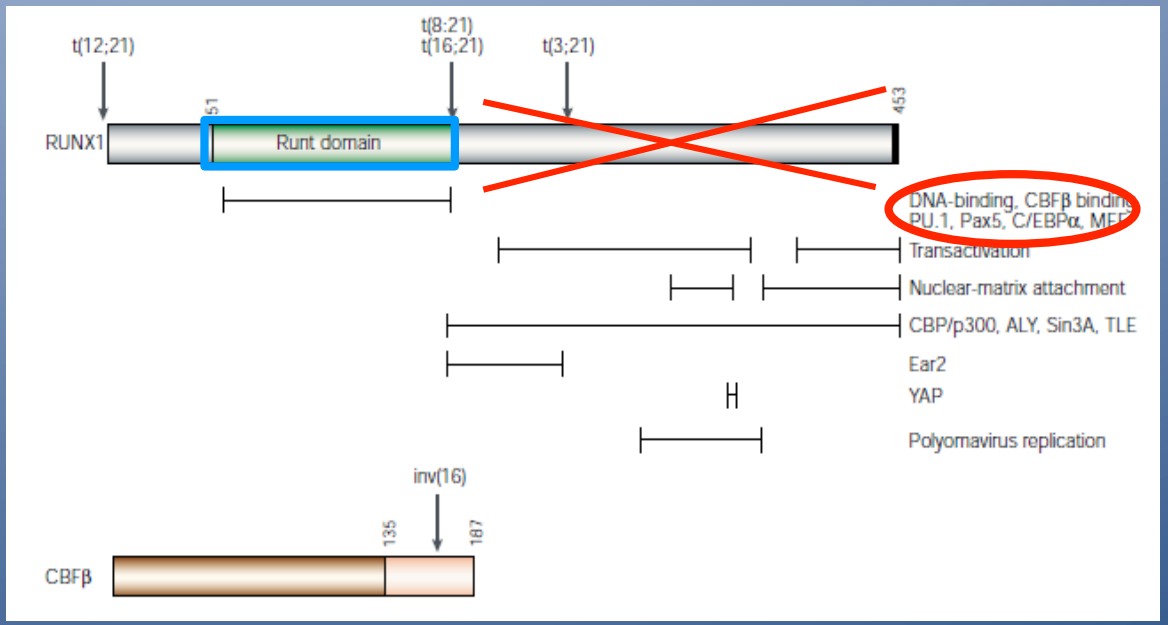
Abnormality	Total No.	CR and Reason for Failure: CR Rate %	Induction Deaths %	Resistant Disease %	Deaths in Remission % (SE)	Relapse Risk at 5 yr % (SE)	Overall Survival at 5 yr % (SE)
Overall	1,612	85	8	8	14 (1.1)	49 (1.5)	44 (1.3)
Favorable							
t(15;17)	198	87	11	2	13 (3.1)	37 (4.1)*	63 (3.6)*
t(8;21)	122	98*	2	0†	15 (3.4)	29 (4.5)*	69 (4.2)*
inv(16)	57	88	12	0	9 (4.3)	42 (7.4)	61 (6.5)†
Intermediate							
No abnormality	680	88	6	6	15 (1.7)	53 (2.3)	42 (1.9)
+8	148	84	7	8	12 (2.9)	44 (4.8)	48 (4.3)
11q23	60	87	7	7	9 (4.6)	47 (7.2)	45 (6.4)
+21	45	80	7	13	11 (6.2)	50 (9.0)	47 (7.7)
del (7q)	32	75	6	19	19 (10.9)	59 (10.5)	23 (8.1)
del (9q)	25	100	0	0	9 (5.8)	39 (10.1)	60 (9.8)
+22	22	91	5	5	13 (8.6)	51 (12.4)	59 (10.5)
Other numerical	219	76*	11	14*	19 (3.4)	60 (4.2)	29 (3.1)*
Other structural	366	76*	9	14*	14 (2.5)	51 (3.2)	35 (2.5)†
Adverse							
Complex	95	67*	13	20*	12 (4.9)	68 (6.2)*	21 (4.2)*
−7	61	54*	16†	30*	8 (8.0)	80 (7.1)*	10 (3.8)*
abn(3q)	40	63*	23†	15	20 (11.9)	85 (7.8)*	12 (6.2)*
del(5q)	28	57*	14	29*	14 (9.1)	85 (9.5)*	11 (5.8)*
−5	26	42*	12	46*	12 (11.7)	90 (9.8)†	4 (3.8)*

CORE-BINDING FACTORS IN HAEMATOPOIESIS AND LEUKAEMIA

NATURE REVIEWS | CANCER

Nancy A. Speck and D. Gary Gilliland‡*





The core-binding factor leukemias: lessons learned from murine models

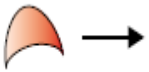
James R Downing

AML1–/–

No definitive hematopoiesis

Fetal liver

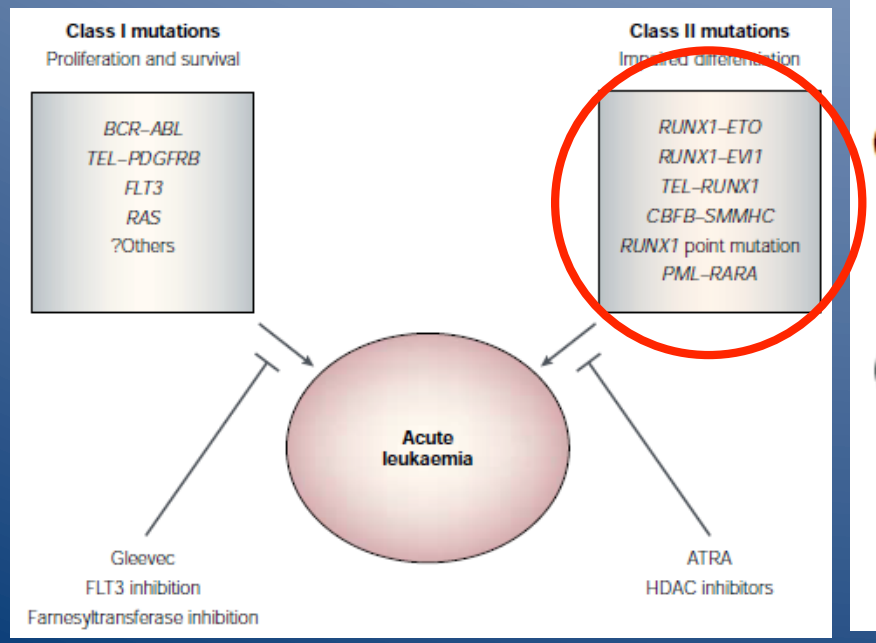
AML1–ETO KI

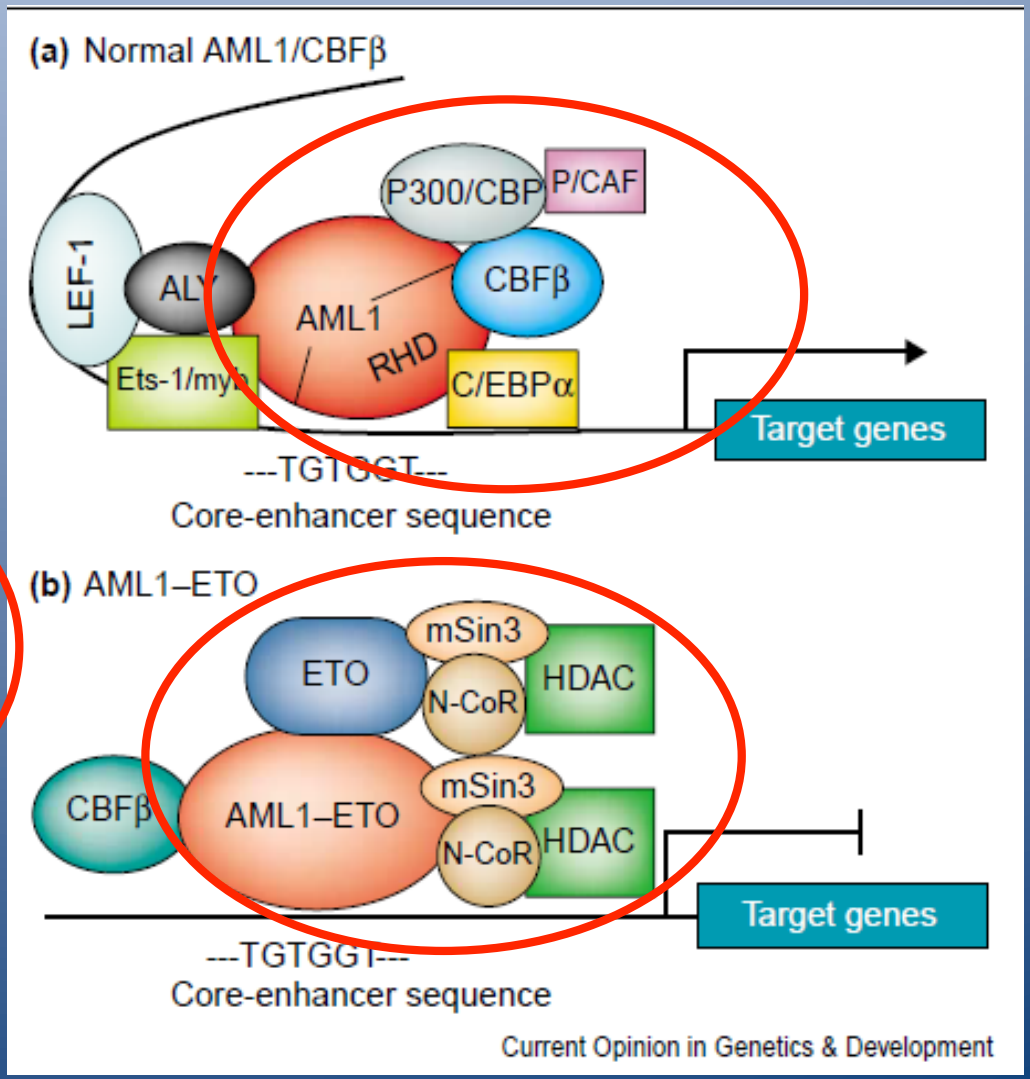


Fetal liver

- Marked reduction in definitive hematopoiesis
- Increased self-renewal capacity
- Impaired differentiation
- No overt leukemia

Current Opinion in Genetics & Development





Granulocyte inducer C/EBPα inactivates the myeloid master regulator PU.1: possible role in lineage commitment decisions

Venkateshwar A. Reddy, Atsushi Iwama, Guergana Iotzova, Mathias Schulz, Annika Elsasser, Rajani K. Vangala, Daniel G. Tenen, Wolfgang Hiddemann, and Gerhard Behre

BLOOD, 15 JULY 2002 • VOLUME 100, NUMBER 2

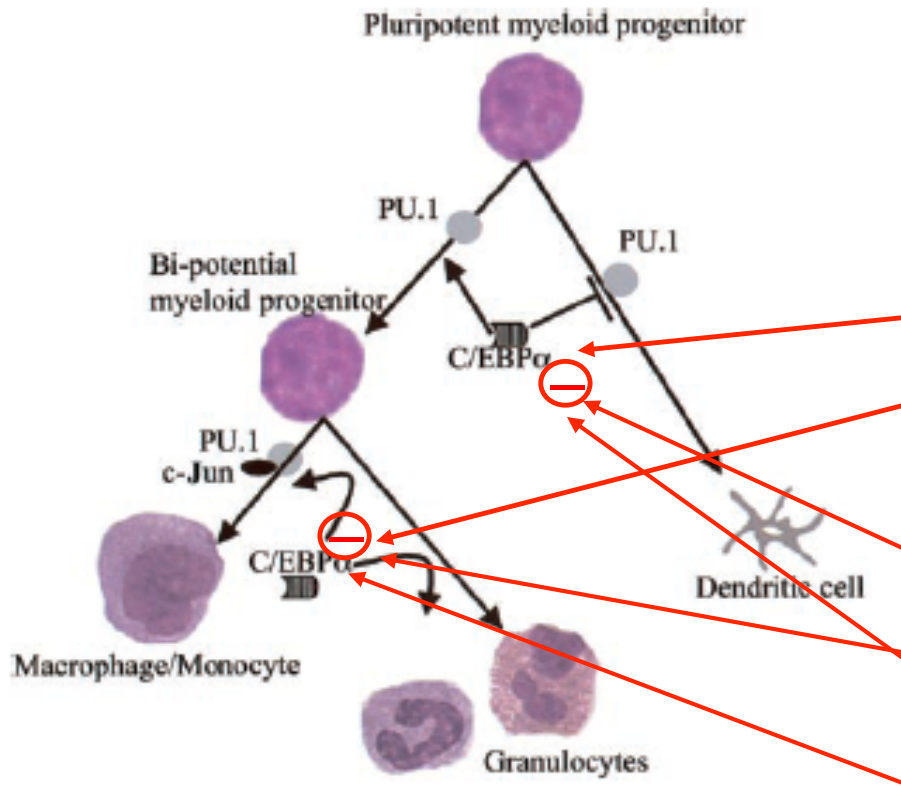


Figure 9. Model of C/EBPα modulating PU.1 activity and its effect on target genes of PU.1. C/EBPα interacts with PU.1. This interaction is between the β3-β4 region of the DNA-binding domain of PU.1 and the leucine zipper of the DNA-binding domain of C/EBPα. C/EBPα displaces the coactivator c-Jun from binding to PU.1. C/EBPα blocks PU.1 function and down-regulates its target genes. C/EBPα blocks PU.1-induced dendritic cell differentiation and drives the cells to granulocytes.

20. Pabst T, Mueller BU, Schoch C, et al. AML1-ETO downregulates the granulocytic differentiation factor C/EBPalpha in t(8;21) myeloid leukemia. Nat Med. 2001;7:444-451.

28. Truong BT, Lee YJ, Lodie TA, et al: CCAAT/enhancer binding proteins repress the leukemic phenotype of acute myeloid leukemia. Blood 101: 1141-1148, 2003

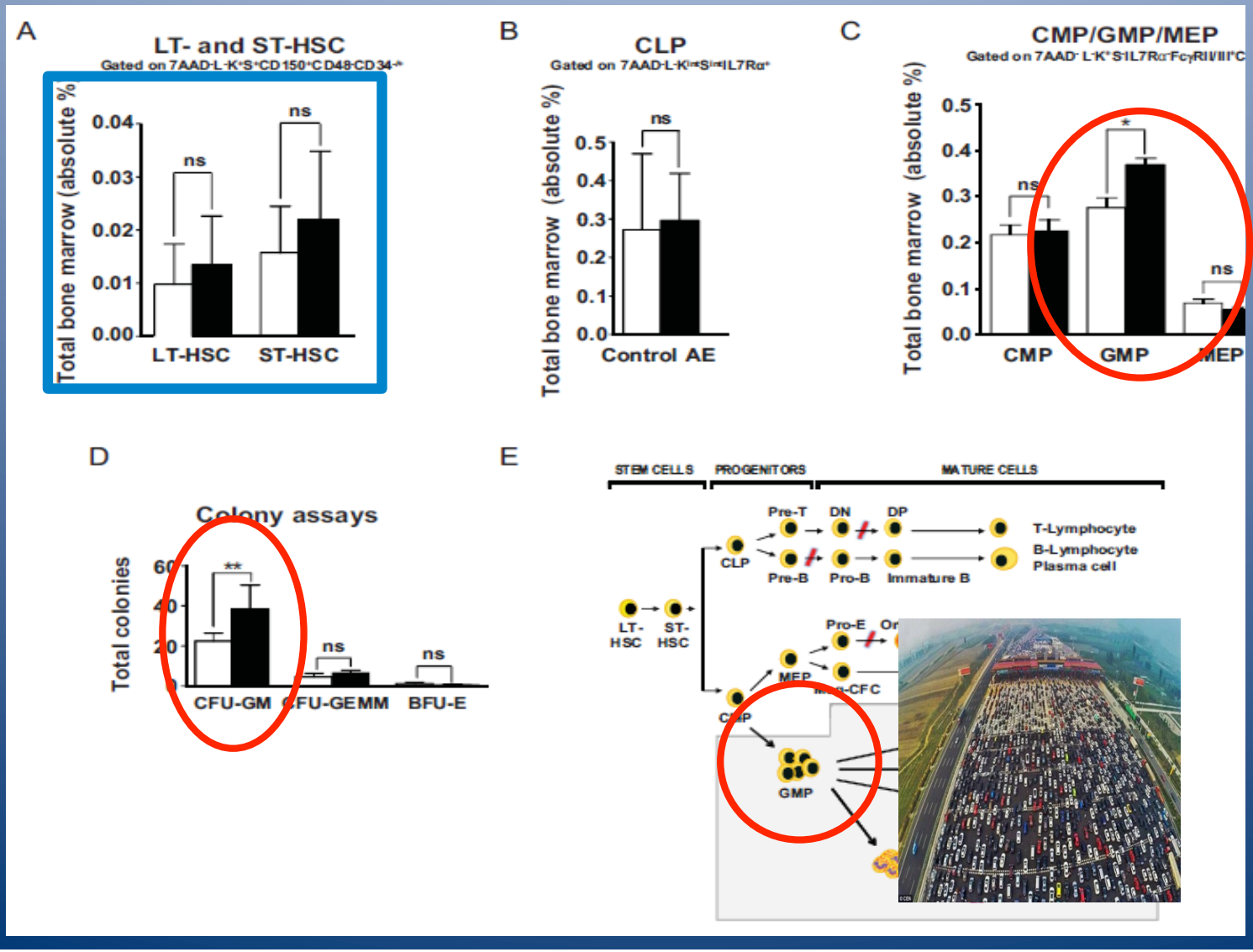
PML-RAR

26. Westendorf JJ, Yamamoto CM, Lenny N, et al: The t(8;21) fusion product, AML-1-ETO, associates with C/EBP-alpha, inhibits C/EBP-alpha-dependent transcription, and blocks granulocytic differentiation. Mol Cell Biol 18:322-333, 1998

CBF-B/MYH

Instruction of haematopoietic lineage choices, evolution of transcriptional landscapes and cancer stem cell hierarchies derived from an AML1-ETO mouse model

EMBO Molecular Medicine



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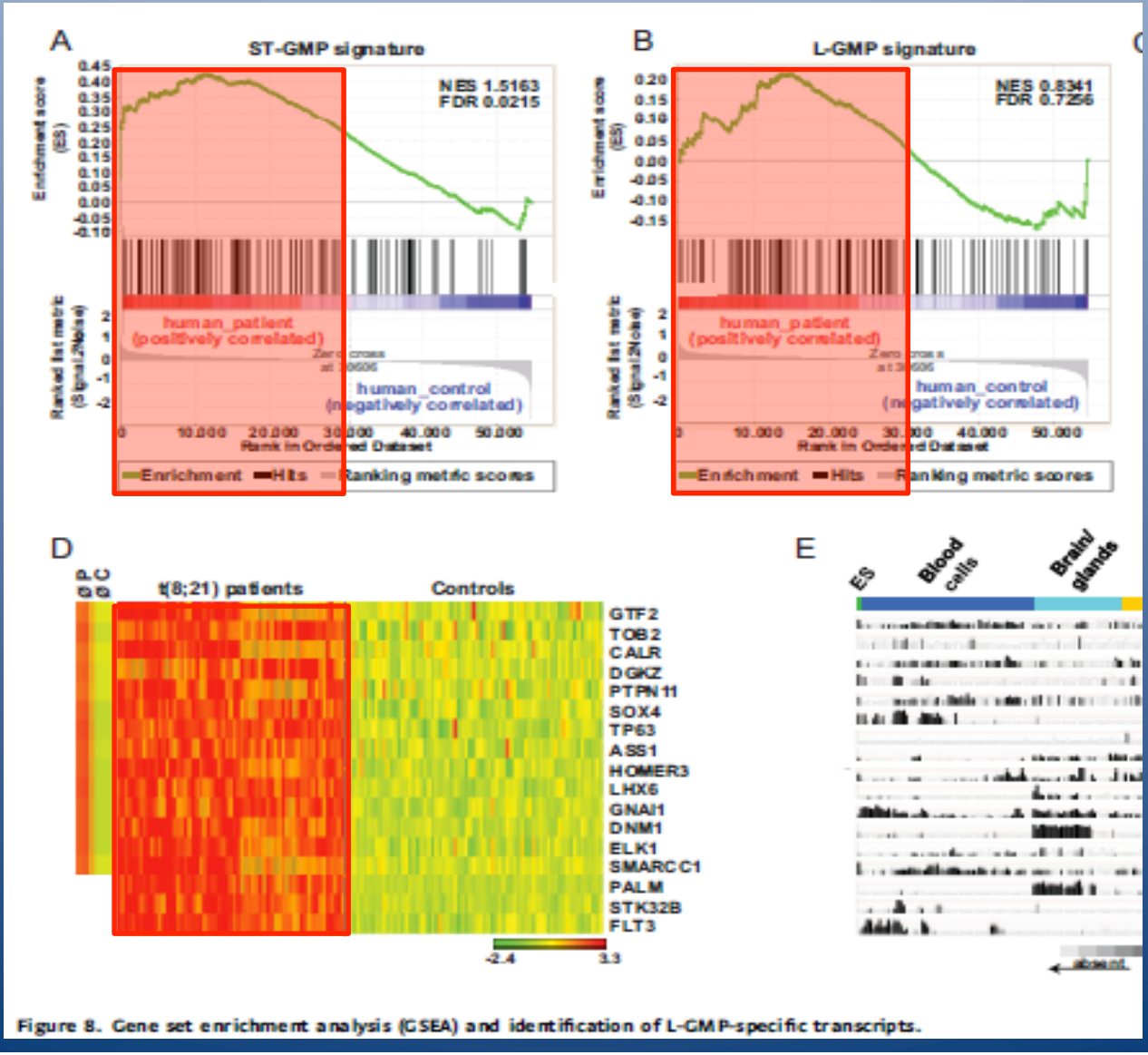
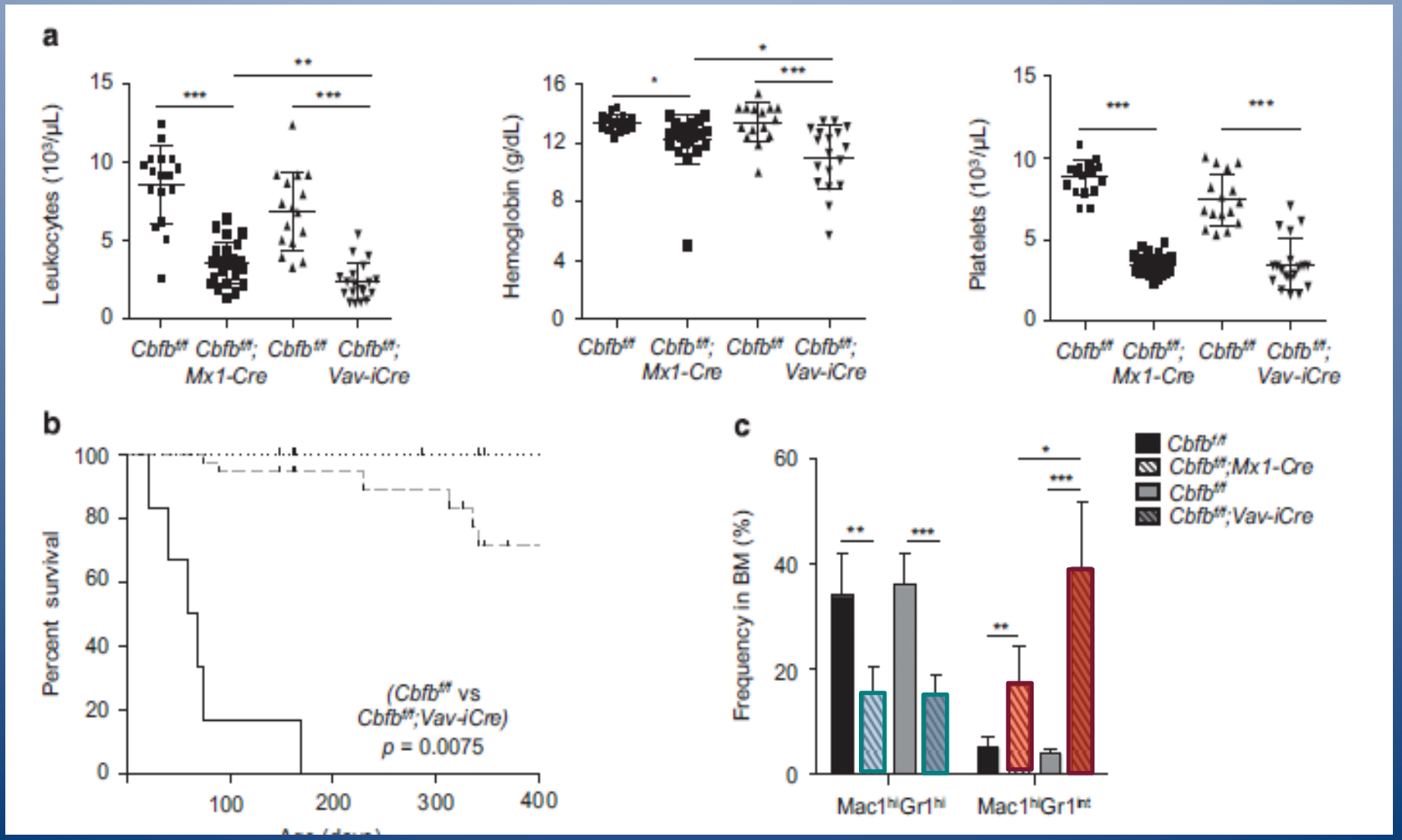


Figure 8. Gene set enrichment analysis (GSEA) and identification of L-GMP-specific transcripts.

Cbfb deficiency results in differentiation blocks and stem/progenitor cell expansion in hematopoiesis

Leukemia (2015) **29,** 753–757; doi:10.1038/leu.2014.316



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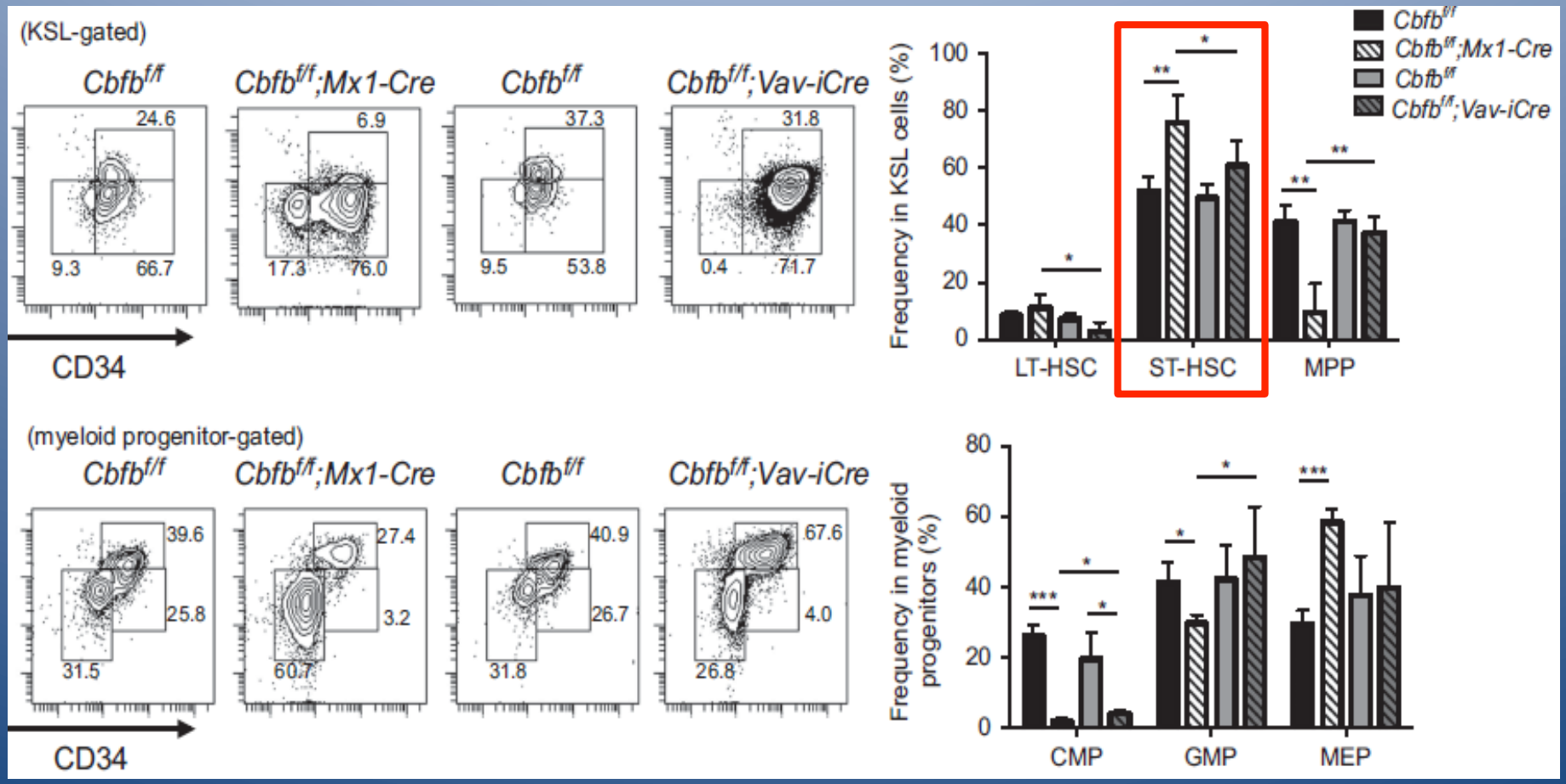


Review Article

Stem Cell Modeling of Core Binding Factor Acute Myeloid Leukemia

Federico Mosna and Michele Gottardi

Hematology, Department of Specialty Medicine, Ospedale Santa Maria di Ca' Foncello, Piazza Ospedale 1, 31100 Treviso, Italy

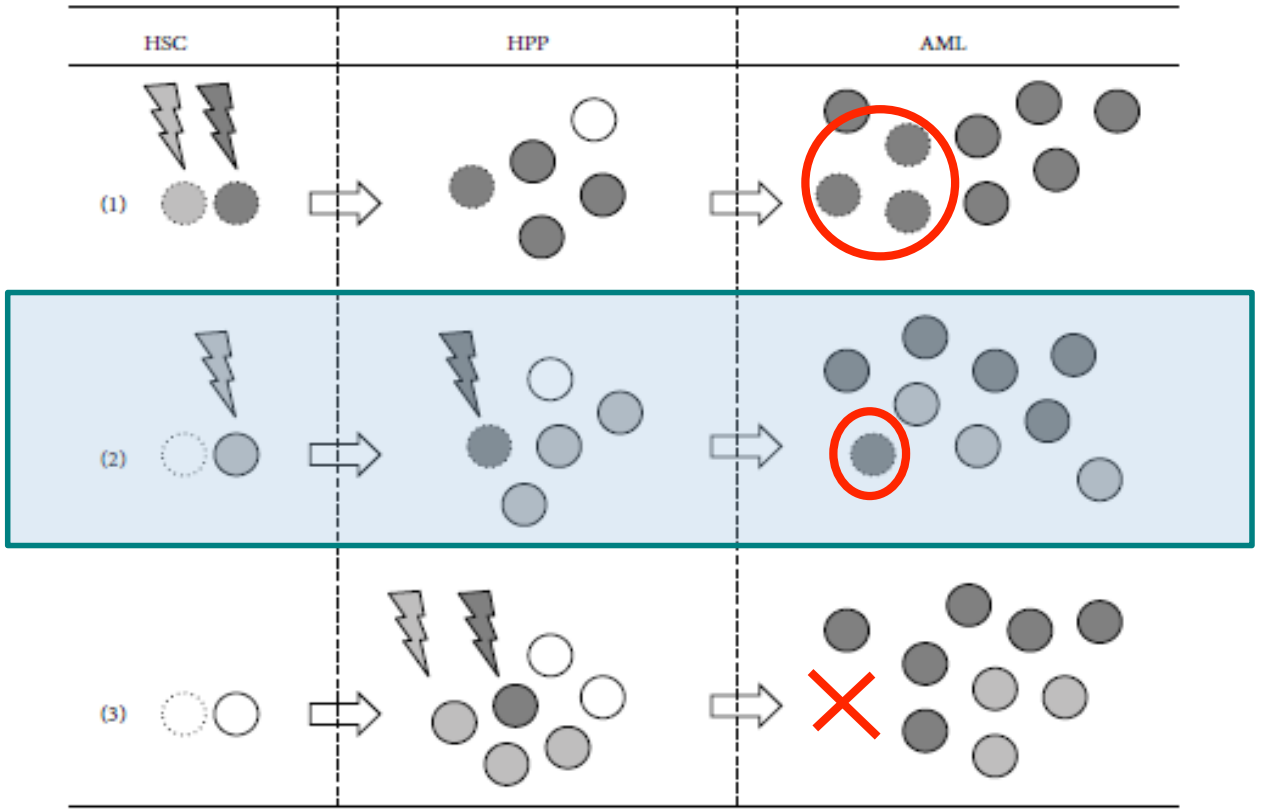


Figure 2: Proposed model for leukemogenesis. According to this model, AML arises following (at least) three different scenarios. In the first one (1) both "class-2" (represented as "light grey lightning bolts") and "class-1" ("dark grey lightning bolts") mutagenic events happen in the HSC ("white dotted circles"), thus creating a rapidly expanding clone endowed by some of the persisting physiological abilities of HSC, such as self-renewal ability (all cells with self-renewal abilities are represented as "dotted circles" in the figure). The resulting leukemia therefore contains more L-IC (represented by "grey dotted circles"), with consequences on the resistance to chemotherapy and the chance of relapse. In the second scenario (2) an initial "class-2" event gives rise to a preleukemic phase where different subclones ("light grey circles") compete one another and with residual hematopoiesis ("white circles") until the emergence of a dominant clone which benefits from self-renewal ability ("dark grey dotted circles"), conferred by an additional "class-1" mutation. This is the scenario thought to model leukemogenesis in the case of CBF AML. In the last scenario (3) leukemia arises from "class-2" and "class-1" events both happening in early committed HPP; leukemia therefore consists mainly of dysplastic HPP which are possibly more sensitive to chemotherapy and agents forcing differentiation.

In utero origin of t(8;21) *AML1-ETO* translocations in childhood acute myeloid leukemia

Joseph L. Wiemels, Zhijian Xiao, Patricia A. Buffler, Ana T. Maia, Xiaomei Ma, Brian M. Dicks, Martyn T. Smith, Luoping Zhang, James Feusner, John Wiencke, Kathy Pritchard-Jones, Helena Kempski, and Mel Greaves

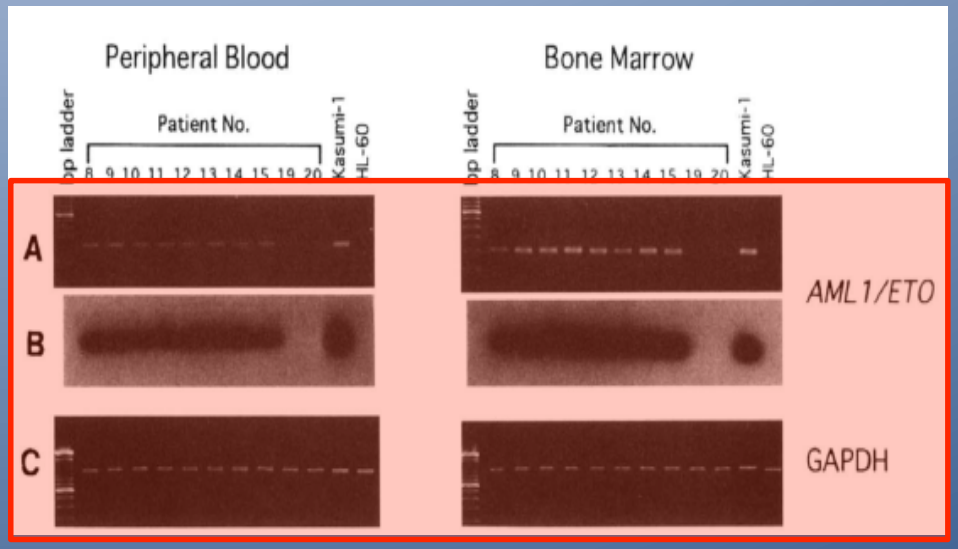
Table 2. Patient age at diagnosis and summary of backtracking *AML1-ETO* genomic fusions in childhood acute myeloid leukemia

Study no.	Age at diagnosis, y, mo	Guthrie segments tested	Guthrie segments positive	Positive or negative*
1	3, 6	12	2	+
2	3, 11	4	2	+
3	4, 11	12	0	–
4	5, 2	12	0	–
5	6, 3	4	1	+
6	7, 9	12	0	–
7	8, 7	12	0	–
8	10, 0	10	0	–
9	10, 1	12	5	+
10	12, 2	12	1	+

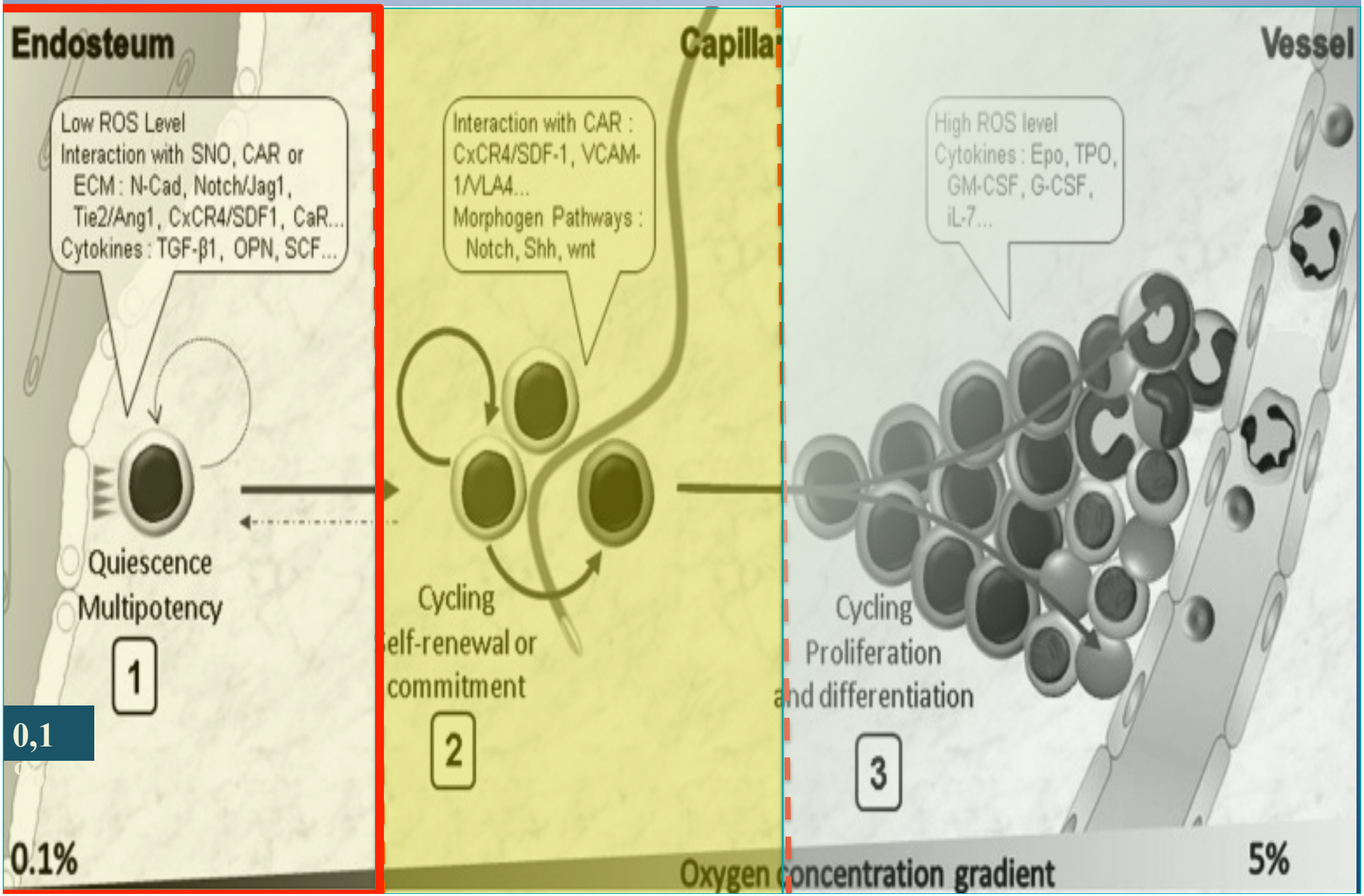
*A plus sign indicates the presence of clonotypic *AML1-ETO* in the Guthrie card; a minus sign indicates the lack of demonstrable clonotypic translocation sequence, which is indeterminate for prenatal origin.

Persistence of Multipotent Progenitors Expressing *AML1/ETO* Transcripts in Long-Term Remission Patients With t(8;21) Acute Myelogenous Leukemia

By Toshihiro Miyamoto, Koji Nagafuji, Koichi Akashi, Mine Harada, Taiichi Kyo, Tomoyuki Akashi, Katsuto Takenaka, Shin-ichi Mizuno, Hisashi Gondo, Takashi Okamura, Hiroo Dohy, and Yoshiyuki Niho

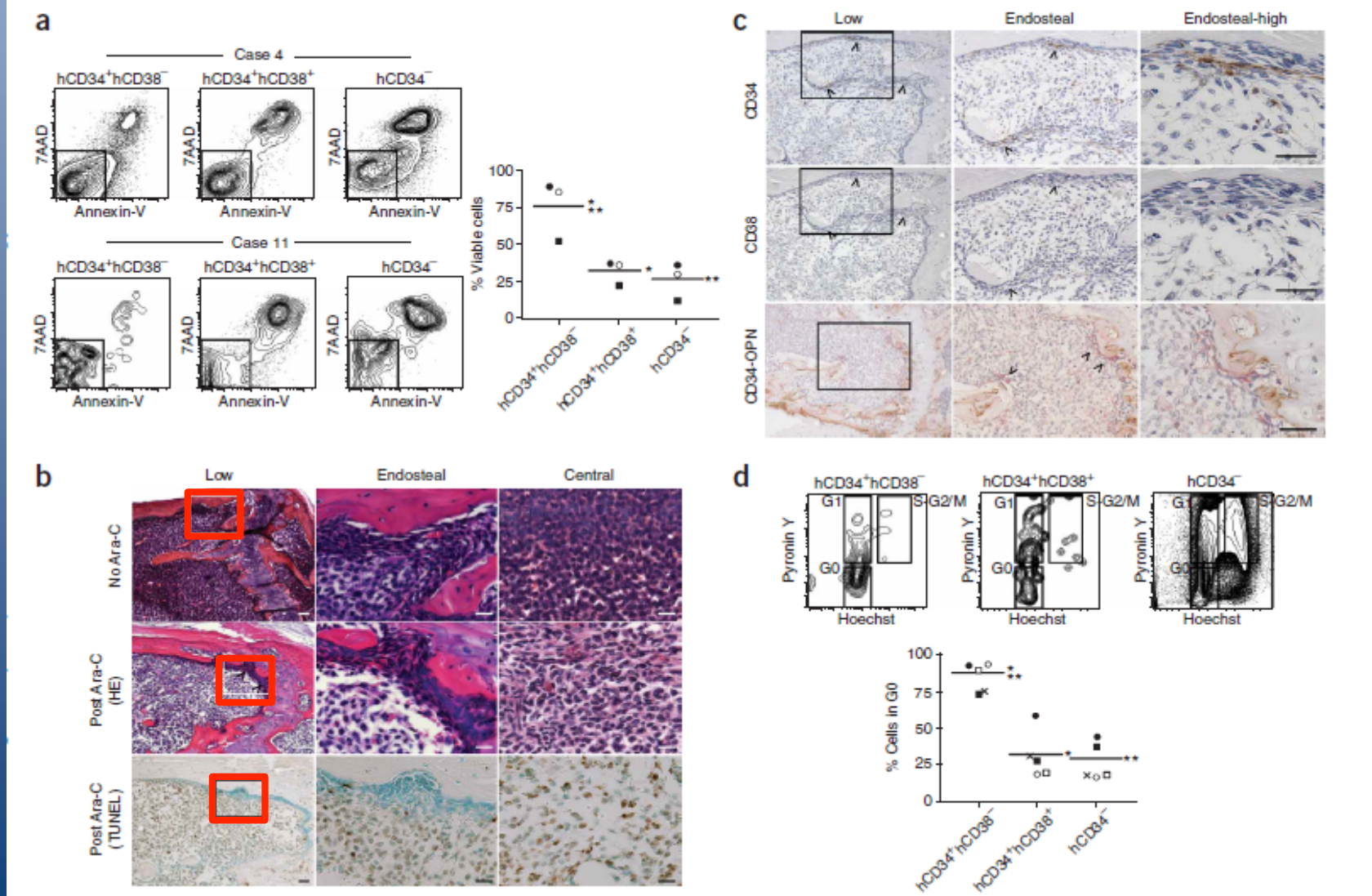


LE NICCHIE

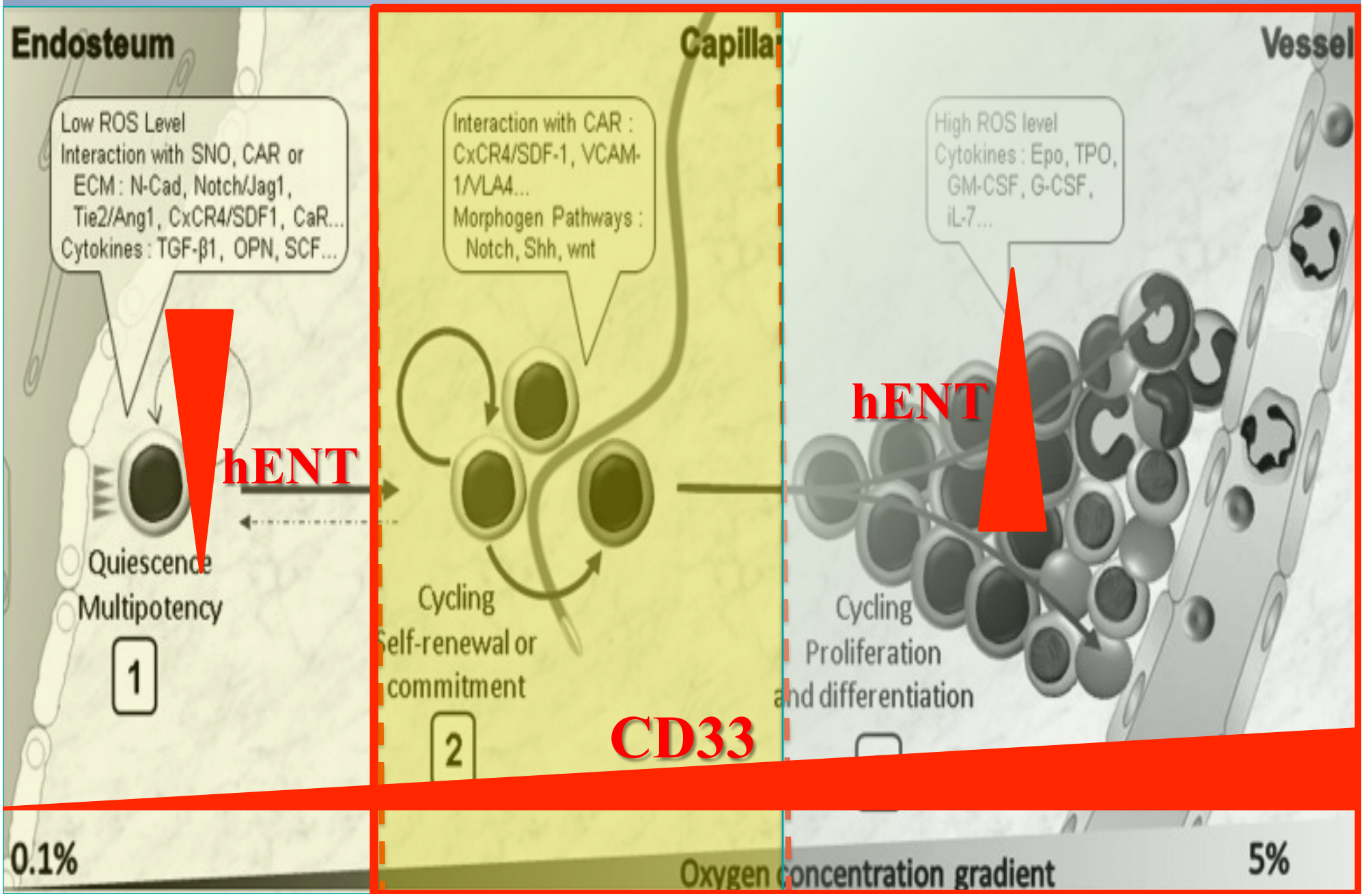

Endosteum
Capilla
Vessel
Low ROS Level
Interaction with SNO, CAR or ECM : N-Cad, Notch/Jag1, Tie2/Ang1, CxCR4/SDF1, CaR...
Cytokines : TGF-β1, OPN, SCF...
Interaction with CAR : CxCR4/SDF-1, VCAM-1/VLA4...
Morphogen Pathways : Notch, Shh, wnt
High ROS level
Cytokines : Epo, TPO, GM-CSF, G-CSF, iL-7...
Quiescence
Multipotency
1
Cycling
elf-renewal or
commitment
2
Cycling
Proliferation
and differentiation
3
0,1
0.1%
Oxygen concentration gradient
5%

Chemotherapy-resistant human AML stem cells home to and engraft within the bone-marrow endosteal region

Fumihiko Ishikawa[1,3], Shuro Yoshida[1,3], Yoriko Saito[1,5], Atsushi Hijikata[2], Hiroshi Kitamura[2], Satoshi Tanaka[6], Ryu Nakamura[7], Toru Tanaka[7], Hiroko Tomiyama[6], Noriyuki Saito[3], Mitsuhiro Fukata[3], Toshihiro Miyamoto[4], Bonnie Lyons[8], Koichi Ohshima[9], Naoyuki Uchida[10], Shuichi Taniguchi[10], Osamu Ohara[2,11], Koichi Akashi[4,12], Mine Harada[3] & Leonard D Shultz[8]



LE NICCHIE


Endosteum
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Low ROS Level
Interaction with SNO, CAR or
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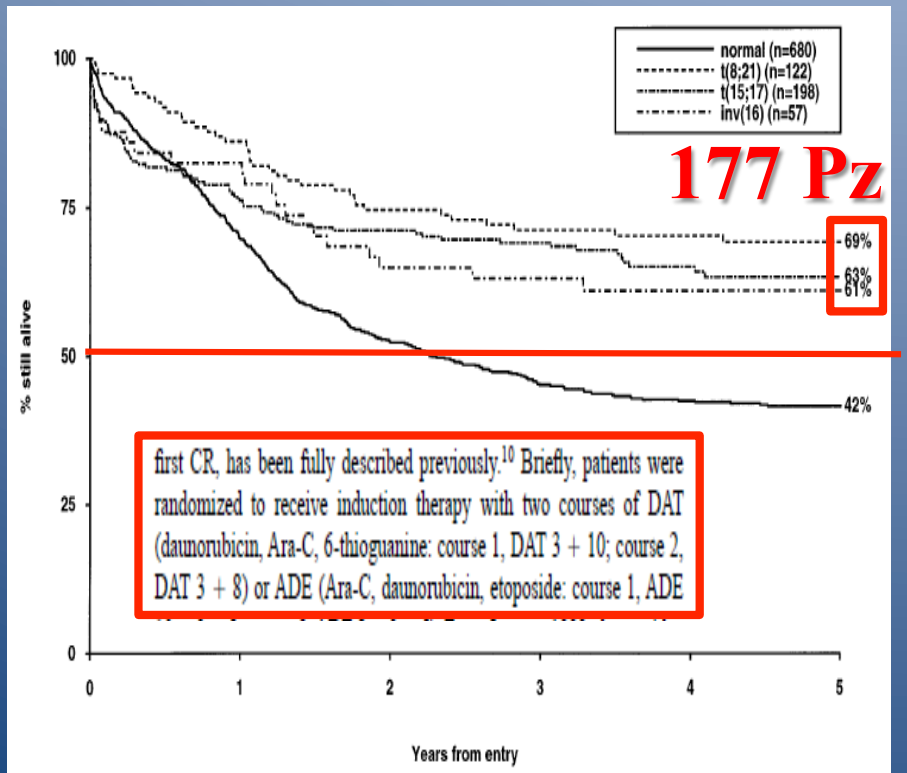
Tie2/Ang1, CxCR4/SDF1, CaR...
Cytokines : TGF-β1, OPN, SCF...
Interaction with CAR :
CxCR4/SDF-1, VCAM-
1/VLA4...
Morphogen Pathways :
Notch, Shh, wnt
High ROS level
Cytokines : Epo, TPO,
GM-CSF, G-CSF,
iL-7...
hENT
hENT
Quiescence
Multipotency
1
Cycling
Self-renewal or
commitment
2
Cycling
Proliferation
and differentiation
CD33
0.1%
Oxygen concentration gradient
5%

“Quando un uomo con la pistola incontra un uomo col fucile, quello con la pistola è un uomo morto”

The Importance of Diagnostic Cytogenetics on Outcome in AML: Analysis of 1,612 Patients Entered Into the MRC AML 10 Trial

By David Grimwade, Helen Walker, Fiona Oliver, Keith Wheatley, Christine Harrison, Georgina Harrison, John Rees, Ian Hann, Richard Stevens, Alan Burnett, and Anthony Goldstone on behalf of the Medical Research Council Adult and Children's Leukaemia Working Parties



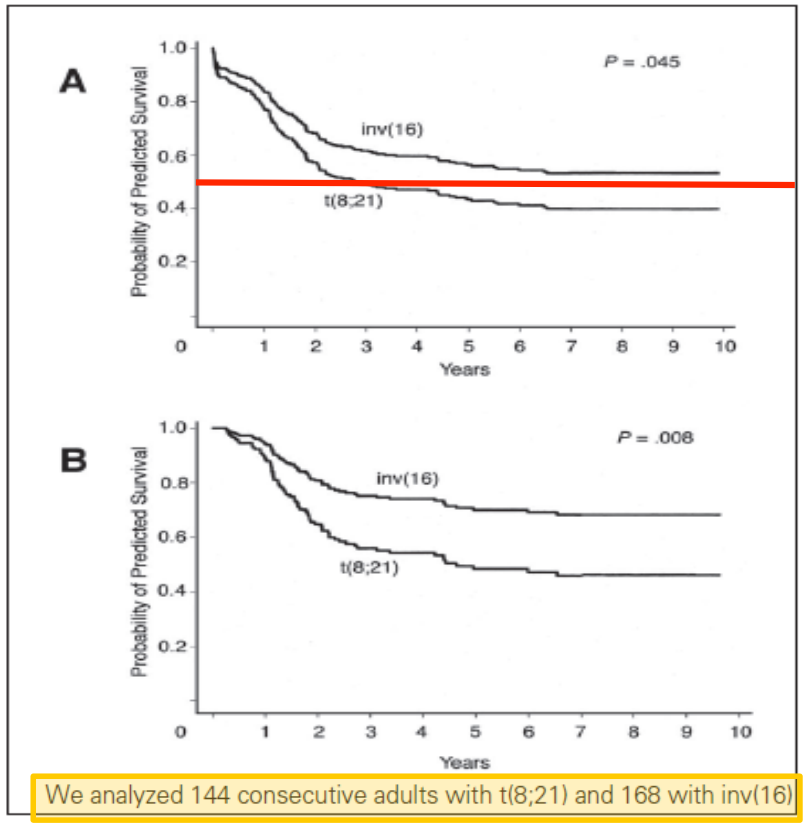
first CR, has been fully described previously.[10] Briefly, patients were randomized to receive induction therapy with two courses of DAT (daunorubicin, Ara-C, 6-thioguanine: course 1, DAT 3 + 10; course 2, DAT 3 + 8) or ADE (Ara-C, daunorubicin, etoposide: course 1, ADE

Fig 1. Overall survival of patients with favorable cytogenetic abnormalities, irrespective of the presence of additional abnormalities. The group with normal karyotype is included for comparison.

Prognostic Factors and Outcome of Core Binding Factor Acute Myeloid Leukemia Patients With t(8;21) Differ From Those of Patients With inv(16): A Cancer and Leukemia Group B Study

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Guido Marcucci, Krzysztof Mrózek, Amy S. Ruppert, Kati Maharry, Jonathan E. Kolitz, Joseph O. Moore, Robert J. Mayer, Mark J. Pettenati, Bayard L. Powell, Colin G. Edwards, Lisa J. Sterling, James W. Vardiman, Charles A. Schiffer, Andrew J. Carroll, Richard A. Larson, and Clara D. Bloomfield



We analyzed 144 consecutive adults with t(8;21) and 168 with inv(16)

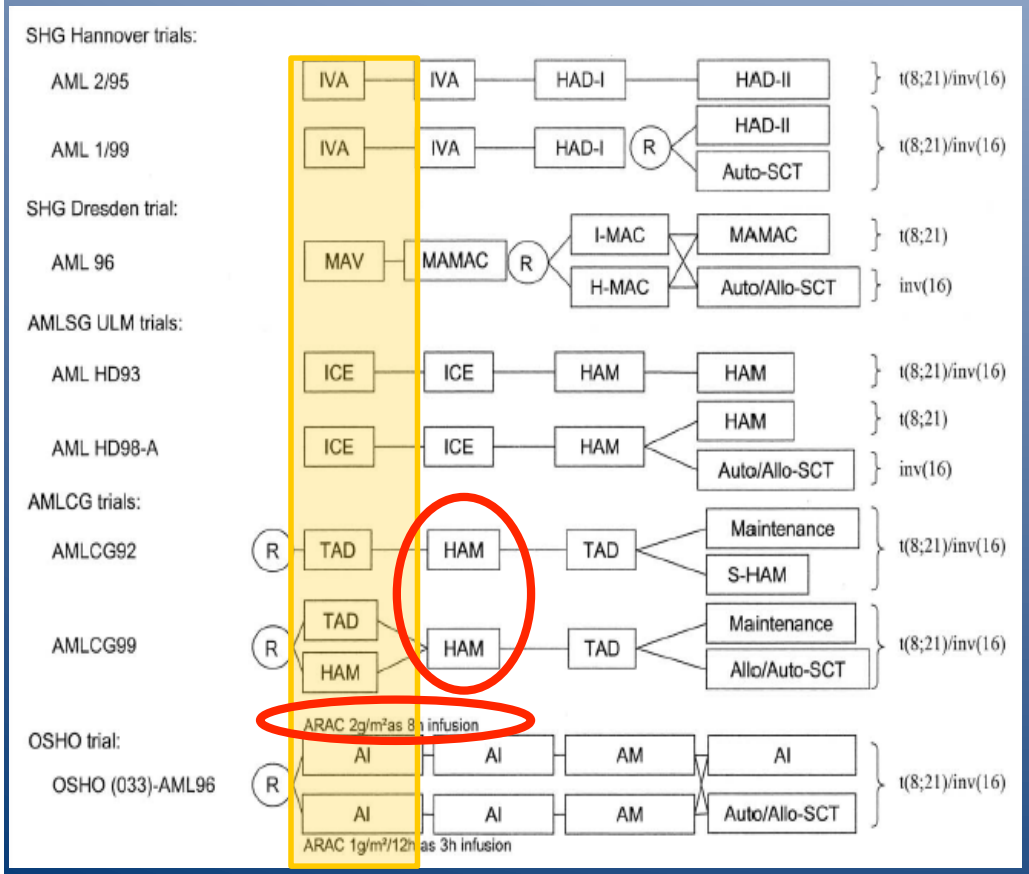
Fig 1. Comparison of overall survival of acute myeloid leukemia patients with t(8;21) and inv(16). (A) All patients. Curves adjusted for age, log[WBC], and log[platelets]. (B) Patients younger than 60 years who achieved CR and were assigned to consolidation treatment. Curves adjusted for induction, consolidation, and $\log_{WBC}$.

“Quando un uomo con la pistola incontra un uomo col fucile, quello con la pistola è un uomo morto”

Individual Patient Data–Based Meta-Analysis of Patients Aged 16 to 60 Years With Core Binding Factor Acute Myeloid Leukemia: A Survey of the German Acute Myeloid Leukemia Intergroup

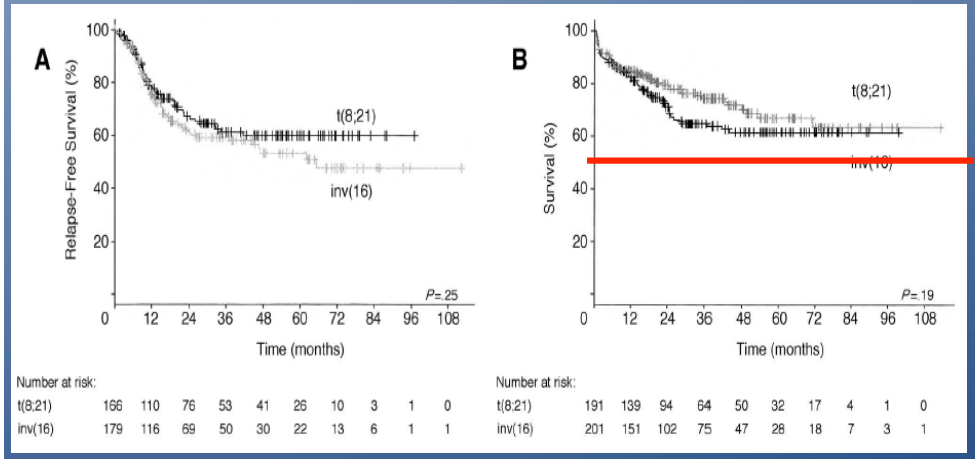
R.F. Schlenk, A. Benner, J. Krauter, T. Büchner, C. Sauerland, G. Ehninger, M. Schaich, B. Mohr, D. Niederwieser, R. Krahl, R. Pasold, K. Döhner, A. Ganser, H. Döhner, and G. Heil

VOLUME 22 · NUMBER 18 · SEPTEMBER 15 2004
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT



Patients and Methods

Individual patient data–based meta-analysis was performed on 392 adults (median age, 42 years; range, 16 to 60 years) with CBF AML (t(8;21), n = 191; inv(16), n = 201) treated between 1993 and 2002 in prospective German AML treatment trials.



“Quando un uomo con la pistola incontra un uomo col fucile, quello con la pistola è un uomo morto”

CLINICAL TRIALS AND OBSERVATIONS

Prospective evaluation of gene mutations and minimal residual disease in patients with core binding factor acute myeloid leukemia

Eric Jourdan,[1] Nicolas Boissel,[2] Sylvie Chevret,[3] Eric Delabesse,[4] Aline Renneville,[5] Pascale Cornillet,[6] Odile Blanchet,[7] Jean-Michel Cayuela,[2] Christian Recher,[4] Emmanuel Raffoux,[2] Jacques Delaunay,[8] Arnaud Pigneux,[9] Claude-Eric Bulabois,[10] Céline Berthon,[11] Cécile Pautas,[12] Norbert Vey,[13] Bruno Lioure,[14] Xavier Thomas,[15] Isabelle Luquet,[6] Christine Terré,[16] Philippe Guardiola,[17] Marie C. Béné,[18] Claude Preudhomme,[5] Norbert Ifrah,[17] and Hervé Dombret,[2] for the French AML Intergroup

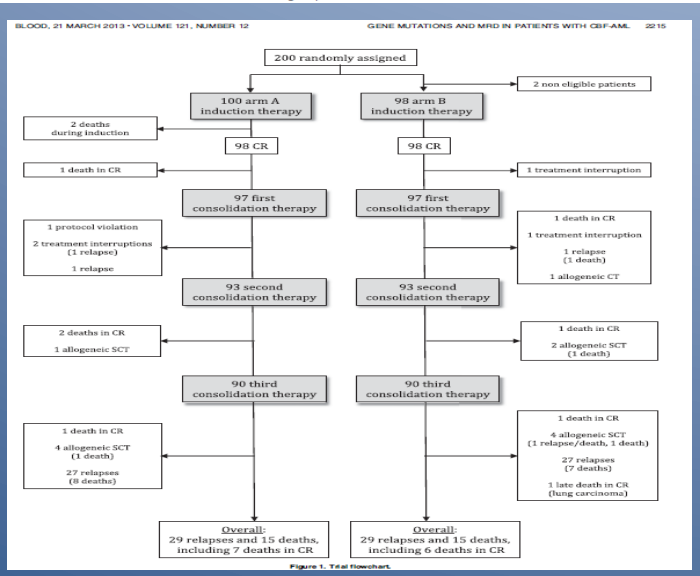
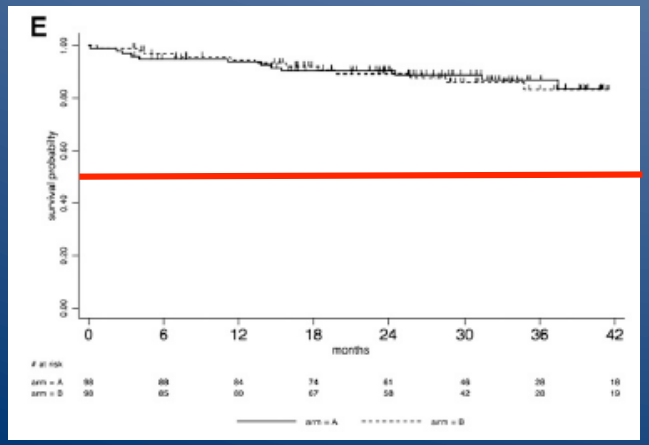


Figure 1. Trial flowchart.

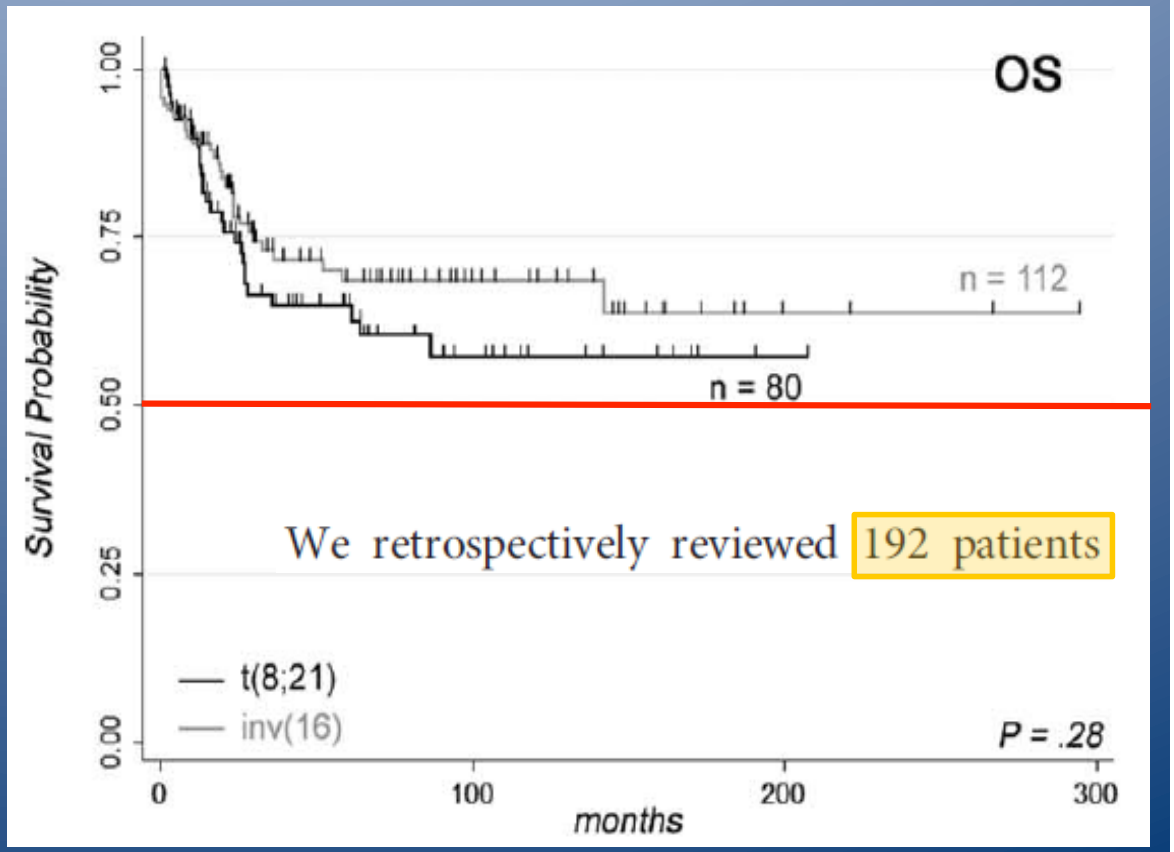


RESEARCH ARTICLE

AJH

Complex karyotype, older age, and reduced first-line dose intensity determine poor survival in core binding factor acute myeloid leukemia patients with long-term follow-up

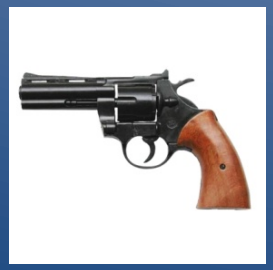
Federico Mosna,[1] Cristina Papayannidis,[2] Giovanni Martinelli,[2*] Eros Di Bona,[3] Angela Bonalumi,[4] Cristina Tecchio,[4] Anna Candoni,[5] Debora Capelli,[6] Andrea Piccin,[7] Fabio Forghieri,[8] Catia Bigazzi,[9] Giuseppe Visani,[10] Renato Zambello,[11] Lucia Zanatta,[12] Francesca Volpato,[1] Stefania Paolini,[2] Nicoletta Testoni,[2] Filippo Gherlinzoni,[1] and Michele Gottardi[1]



American Journal of Hematology, Vol. 90, No. 6, June 2015

“Quando si spara si spara, non si parla”

3 + 7
O QUALCOSA DI PIU’ IN INDUZIONE?



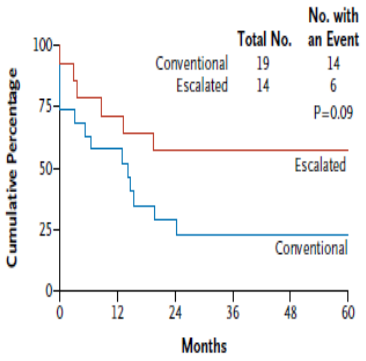
"Quando si spara si spara, non si parla"

High-Dose Daunorubicin in Older Patients with Acute Myeloid Leukemia

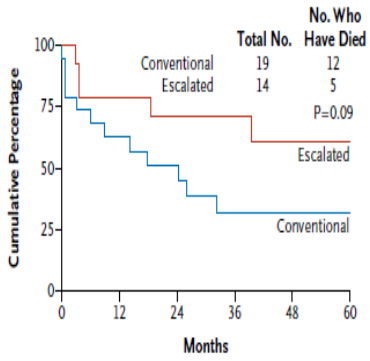
Bob Löwenberg, M.D., Gert J. Ossenkoppele, M.D., Wim van Putten, M.Sc., Harry C. Schouten, M.D., Carlos Graux, M.D., Augustin Ferrant, M.D., Pieter Sonneveld, M.D., Johan Maertens, M.D., Mojca Jongen-Lavrencic, M.D., Marie von Lilienfeld-Toal, M.D., Bart J. Biemond, M.D., Edo Vellenga, M.D., Marinus van Marwijk Kooy, M.D., Leo F. Verdonck, M.D., Joachim Beck, M.D., Hartmut Döhner, M.D., Alois Gratwohl, M.D., Thomas Pabst, M.D., and Gregor Verhoef, M.D., for the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON), German AML Study Group (AMLSG), and Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group

Variable	Conventional-Dose Group (N=411)	Escalated-Dose Group (N=402)
Favorable	19 (5)	14 (3)
t(8;21)	11 (3)	6 (1)
inv(16)/t(16;16)	8 (2)	8 (2)

G Event-free Survival, Patients with CBF Abnormalities



H Overall Survival, Patients with CBF Abnormalities



The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 24, 2009 VOL. 361 NO. 13

CLINICAL TRIALS AND OBSERVATIONS

Benefit of high-dose daunorubicin in AML induction extends across cytogenetic and molecular groups

Marlise R. Luskin,[1] Ju-Whei Lee,[2] Hugo F. Fernandez,[3] Omar Abdel-Wahab,[4,5] John M. Bennett,[6] Rhett P. Ketterling,[7] Hillard M. Lazarus,[8] Ross L. Levine,[4,5] Mark R. Litzow,[9] Elisabeth M. Paietta,[10] Jay P. Patel,[4] Janis Racevskis,[10] Jacob M. Rowe,[11] Martin S. Tallman,[5] Zhuoxin Sun,[2] and Selina M. Luger[1]

Table 1. Median OS and HRs for death by treatment (HD vs SD), according to subgroup

Subgroup	Standard dose (45 mg/m² per day) CR rate	Median OS (months) (no. of events/total)	4-year OS	High dose (90 mg/m² per day) CR rate	Median OS (months) (no. of events/total)	4-y	Multivariable* HR (95% CI)	Wald P
All patients	59%	16.6 (246/330)	31%	71%	25.4 (207/327)		0.74 (0.61, 0.89)	.001
Age								
<50 years	61%	20.7 (133/188)	35%	73%	44.7 (96/172)		0.67 (0.52, 0.88)	.004
≥50 years	56%	12.6 (113/142)	25%	68%	17.6 (111/155)		0.82 (0.63, 1.07)	.14
Cytogenetic								
Favorable	84%	39.4 (24/38)	46%	80%	NR (19/51)		0.44 (0.24, 0.82)	.01
Intermediate	56%	20.1 (101/141)	35%	77%	33.5 (71/127)		0.75 (0.55,1.03)	.08
Indeterminate	62%	14.3 (66/91)	29%	67%	21.3 (62/85)		0.89 (0.63, 1.27)	.53
Unfavorable	44%	10.2 (54/59)	14%	57%	10.6 (54/63)		0.66 (0.44, 0.98)	.04
Gene mutation								
NPM1	60%	16.9 (50/65)	29%	89%	75.9 (31/65)		0.51 (0.32, 0.81)	.005
FLT3-ITD	48%	10.1 (74/83)	17%	70%	15.2 (44/64)		0.50 (0.32, 0.77)	.002
DNMT3A	61%	14.1 (55/61)	13%	79%	16.5 (40/58)		0.67 (0.42, 1.05)	.08
MLL-PTD	56%	16.2 (16/16)	6%	60%	20.6 (10/15)		0.60 (0.24, 1.54)	.29

Table 2. Median EFS and HRs by treatment (HD vs SD), according to subgroup

Subgroup	Standard dose (45 mg/m² per day) 4-year cum rlps rate*	Median EFS (months) (no. of events/total)	4-year EFS	High dose (90 mg/m² per day) 4-y Cum Rlps Rate	Median EFS (months) (no. of events/total)	4-year EFS	Multivariable‡ HR (95% CI)	Wald P
All patients	57%	4.5 (272/330)	20%	55%	11.3 (235/327)	28%	0.70 (0.59, 0.84)	<.0001
Age								
<50 years	58%	5.0 (152/188)	20%	51%	13.9 (112/172)	36%	0.63 (0.49, 0.82)	.0004
≥50 years	54%	4.0 (120/142)	19%	58%	9.4 (123/155)	19%	0.83 (0.64, 1.08)	.16
Cytogenetic								
Favorable	54%	14.0 (25/38)	36%	39%	17.2 (28/51)	44%	0.63 (0.47, 0.84)	.002
Intermediate	56%	3.7 (116141)	20%	55%	16.1 (84/127)	33%	0.90 (0.64, 1.26)	.53
Indeterminate	59%	4.9 (74/91)	20%	69%	8.7 (69/85)	18%	0.63 (0.43, 0.93)	.02
Unfavorable	54%	0.8 (56/59)	8%	49%	4.5 (53/63)	16%		
Gene mutation								
NPM1	61%	4.0 (56/65)	18%	46%	21.0 (38/65)	41%	0.44 (0.29, 0.69)	.0003
FLT3-ITD	70%	1.9 (78/83)	8%	61%	6.8 (47/64)	23%	0.51 (0.34, 0.75)	.0007
DNMT3A	NA	4.4 (58/61)	5%	69%	9.4 (46/58)	21%	0.70 (0.46, 1.05)	.09
MLL-PTD	NA	5.2 (16/16)	0%	NA	8.7 (12/15)	20%	0.71 (0.27, 1.87)	.49

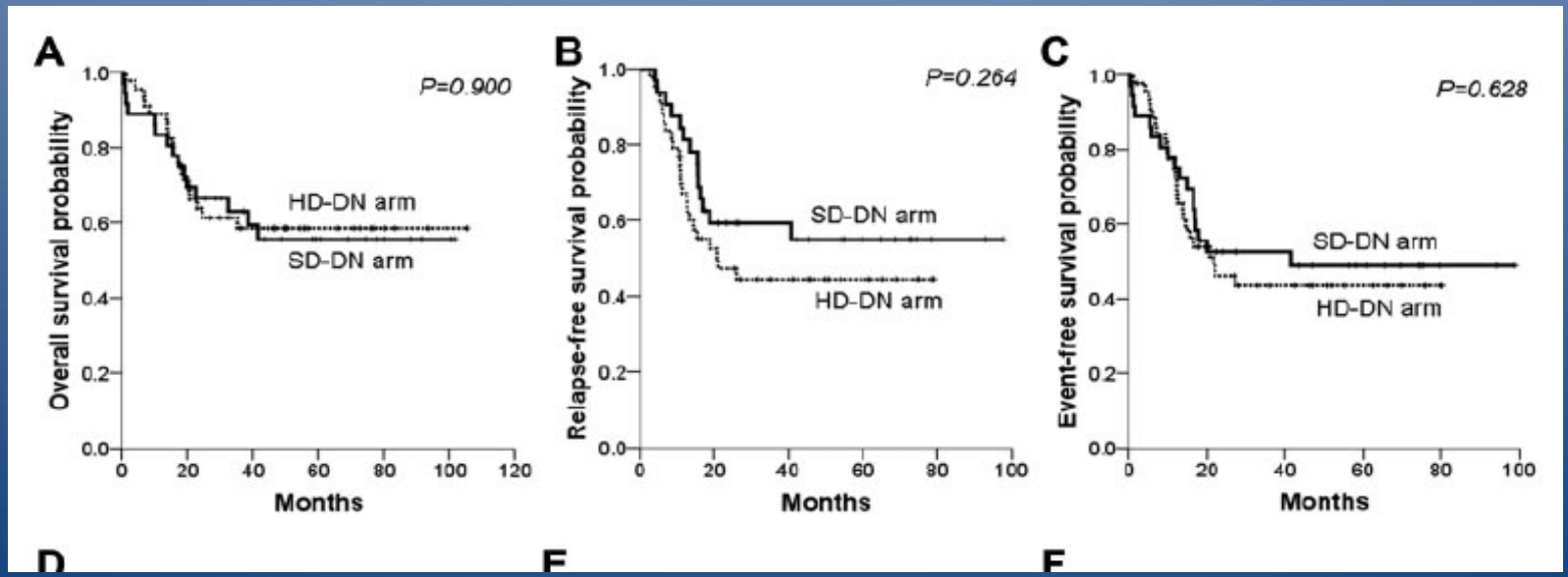
“Quando si spara si spara, non si parla”

A randomized trial comparing standard versus high-dose daunorubicin induction in patients with acute myeloid leukemia

Je-Hwan Lee,[1] Young-Don Joo,[2] Hawk Kim,[3] Sung Hwa Bae,[4] Min Kyoung Kim,[5] Dae Young Zang,[6] Jung-Lim Lee,[7] Gyeong Won Lee,[8] Jung-Hee Lee,[1] Jae-Hoo Park,[3] Dae-Young Kim,[1] Won-Sik Lee,[9] Hun Mo Ryoo,[4] Myung Soo Hyun,[5] Hyo Jung Kim,[6] Young Joo Min,[3] Yae-Eun Jang,[10] and Kyoo-Hyung Lee,[1] for the Cooperative Study Group A for Hematology

Table 1. Characteristics of eligible patients according to treatment group

	Total (n = 383), no. (%)	SD-DN arm (n = 189), no. (%)	HD-DN arm (n = 194), no. (%)	P
Cytogenetic risk group				
Good	81 (21.1)	36 (19.0)	45 (23.2)	.521
Intermediate	239 (62.4)	123 (65.1)	116 (59.8)	
Poor	57 (14.9)	26 (13.8)	31 (16.0)	
Unknown	6 (1.6)	4 (2.1)	2 (1.0)	



BLOOD, 6 OCTOBER 2011 • VOLUME 118, NUMBER 14

“Quando si spara si spara, non si parla”

A Randomized Investigation of High-Dose Versus Standard-Dose Cytosine Arabinoside With Daunorubicin in Patients With Previously Untreated Acute Myeloid Leukemia: A Southwest Oncology Group Study

By James K. Weick, Kenneth J. Kopecky, Frederick R. Appelbaum, David R. Head, Laura L. Kingsbury, Stanley P. Balcerzak, John N. Bickers, H.E. Hynes, Jeanna L. Welborn, Sheryl R. Simon, and Michael Grever

→ Non informazioni citogenetiche

CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

Double Induction Strategy for Acute Myeloid Leukemia: The Effect of High-Dose Cytarabine With Mitoxantrone Instead of Standard-Dose Cytarabine With Daunorubicin and 6-Thioguanine: A Randomized Trial by the German AML Cooperative Group

By Thomas Büchner, Wolfgang Hiddemann, Bernhard Wörmann, Helmut Löffler, Winfried Gassmann, Torsten Haferlach, Christa Fonatsch, Detlef Haase, Claudia Schoch, Dieter Hossfeld, Eva Lengfelder, Carlo Aul, Axel Heyll, Georg Maschmeyer, Wolf-Dieter Ludwig, Maria-Cristina Sauerland, and Achim Heinecke

→ Non informazioni su CBF/AML

A Randomized Study of High-Dose Cytarabine in Induction in Acute Myeloid Leukemia

By James F. Bishop, Jane P. Matthews, Graham A. Young, Jeffrey Szer, Ann Gillett, Douglas Joshua, Kenneth Bradstock, Arno Enno, Max M. Wolf, Richard Fox, Ralph Cobcroft, Richard Herrmann, Martin Van Der Weyden, Raymond M. Lowenthal, Fiona Page, O. Margaret Garson, and Surender Juneja

→ Non informazioni su CBF/AML

***Blood* Spotlight**

Sense and nonsense of high-dose cytarabine for acute myeloid leukemia

Bob Löwenberg[1]

[1]Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands

Table 1. Phase 3 studies concerned with the therapeutic value of dose-escalated cytarabine (HDAC, 2000-3000 mg/m²) regimens in AML in adults up to 60 years of age

	Reference	Study size, n	Improved outcome for HDAC	
			DFS	OS
Remission induction chemotherapy				
HDAC (3000) vs Ara-C 100*	6	301	Yes	No
HDAC (2000) vs Ara-C 200*	7	665	Yes	No
HDAC 1000/2000 vs Ara-C 200/1000*	8	840	No	No
Consolidation of complete remission				
HDAC (3000) vs Ara-C 100/400†	5	596	Yes	Yes
HDAC (3000) vs Ara-C 1000*	9	933	No	No
HDAC (2000) vs Ara-C 200*	10	781	No	No

HDAC indicates high-dose cytarabine at 2000 mg/m² or 3000 mg/m² per intravenous infusion given twice daily; and Ara-C, cytarabine at conventional dose (100, 200, 400 mg/m² per 24-hour continuous infusion) or intermediate dose (1000 mg/m² twice daily).

*In adults younger than 60-65 years.

†In adults 15-86 years of age.

“Quando si spara si spara, non si parla”

Treatment of Core-Binding-Factor in Acute Myelogenous Leukemia With Fludarabine, Cytarabine, and Granulocyte Colony-stimulating Factor Results in Improved Event-free Survival

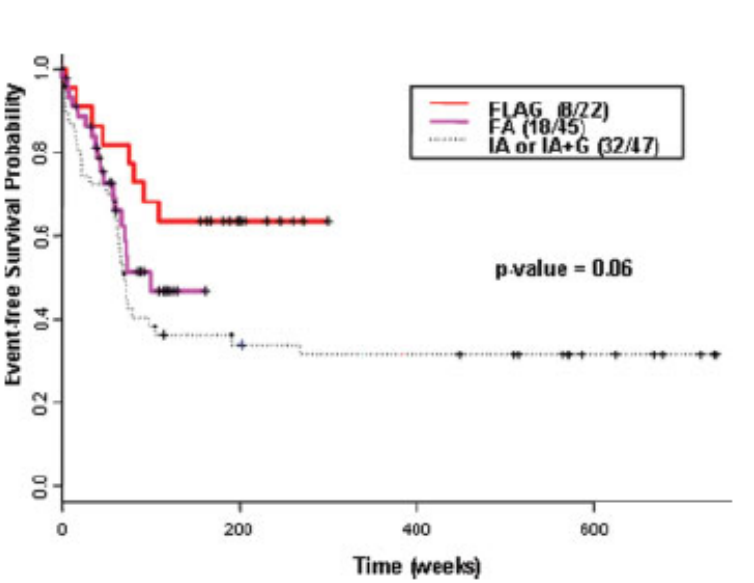
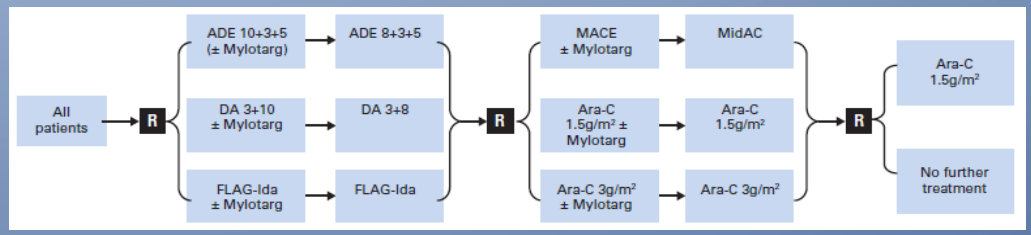


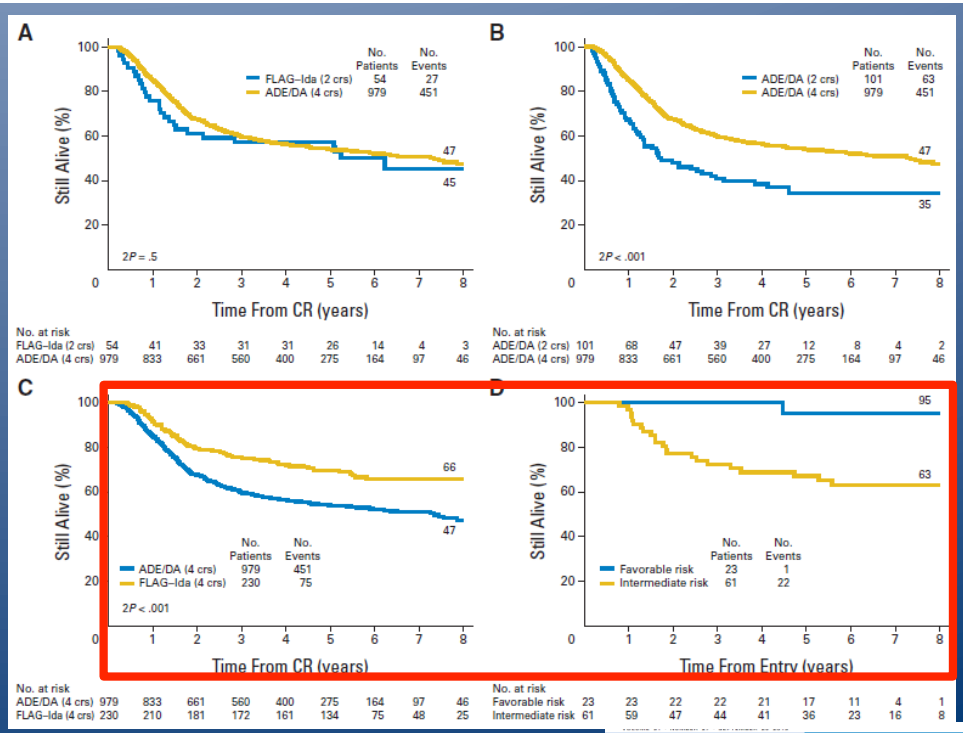
FIGURE 1. Kaplan-Meier estimates for event-free survival by treatment. P = .02 for FLAG versus IA/IAG. P = .31 for FA versus IA/IAG. P = .19 for FLAG versus FA.

Gautam Borthakur, MD[1]
Hagop Kantarjian, MD[1]
Xuemei Wang, MS[2]
William K. Plunkett Jr, PhD[3]
Varsha V. Gandhi, PhD[3]
Stefan Faderl, MD[1]
Guillermo Garcia-Manero, MD[1]
Farhad Ravandi, MD[1]
Sherry Pierce, RN[1]
Elihu H. Estey, MD[1]

Optimization of Chemotherapy for Younger Patients With Acute Myeloid Leukemia: Results of the Medical Research Council AML15 Trial

Alan K. Burnett, Nigel H. Russell, Robert K. Hills, Ann E. Hunter, Lars Kjeldsen, John Yin, Brenda E.S. Gibson, Keith Wheatley, and Donald Milligan





“Quando si spara si spara, non si parla”

Review Article

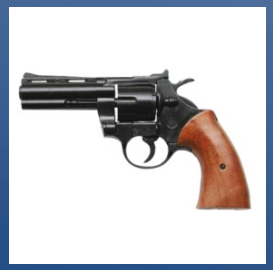
blood

Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel

Hartmut Döhner,[1] Elihu Estey,[2] David Grimwade,[3] Sergio Amadori,[4] Frederick R. Appelbaum,[2] Thomas Büchner,[5] Hervé Dombret,[6] Benjamin L. Ebert,[7] Pierre Fenaux,[8] Richard A. Larson,[9] Ross L. Levine,[10] Francesco Lo-Coco,[4] Tomoki Naoe,[11] Dietger Niederwieser,[12] Gert J. Ossenkoppele,[13] Miguel Sanz,[14] Jorge Sierra,[15] Martin S. Tallman,[10] Hwei-Fang Tien,[16] Andrew H. Wei,[17,18] Bob Löwenberg,[19] and Clara D. Bloomfield[20]

Table 8. Selected conventional care regimens for patients with AML

	Selected conventional care regimens
Patients eligible for intensive chemotherapy	
Induction therapy (all ages) (“7+3”)*,†,‡	• 3 d of an IV anthracycline: daunorubicin at least 60 mg/m^2; idarubicin 12 mg/m^2; or mitoxantrone 12 mg/m^2, and 7 d of continuous infusion cytarabine (100-200 mg/m^2)



“Vedi, il mondo si divide in due categorie: chi ha la pistola carica, e chi scava. Tu scavi”

E UNA VOLTA IN CR?

“Vedi, il mondo si divide in due categorie: chi ha la pistola carica, e chi scava. Tu scavi”

[CANCER RESEARCH 58, 4173–4179, September 15, 1998]

Frequency of Prolonged Remission Duration after High-Dose Cytarabine Intensification in Acute Myeloid Leukemia Varies by Cytogenetic Subtype[1]

Clara D. Bloomfield, David Lawrence, John C. Byrd,[2] Andrew Carroll, Mark J. Pettenati, Ramana Tantravahi, Shivanand R. Patil, Frederick R. Davey, Deborah T. Berg, Charles A. Schiffer, Diane C. Arthur, and Robert J. Mayer

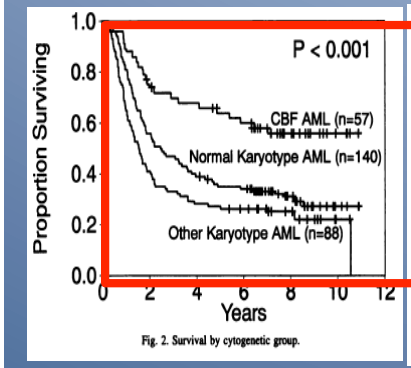


Fig. 2. Survival by cytogenetic group.

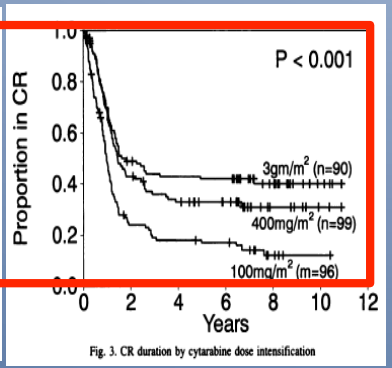
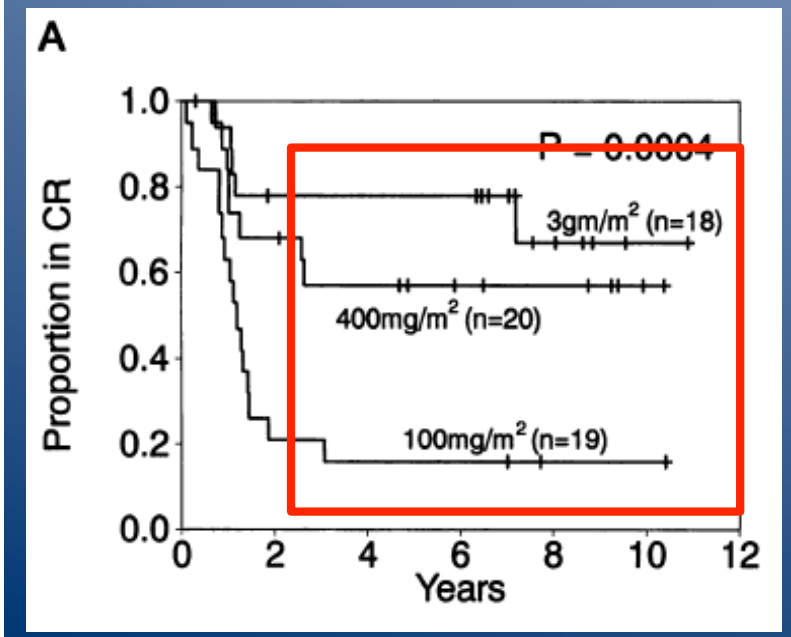
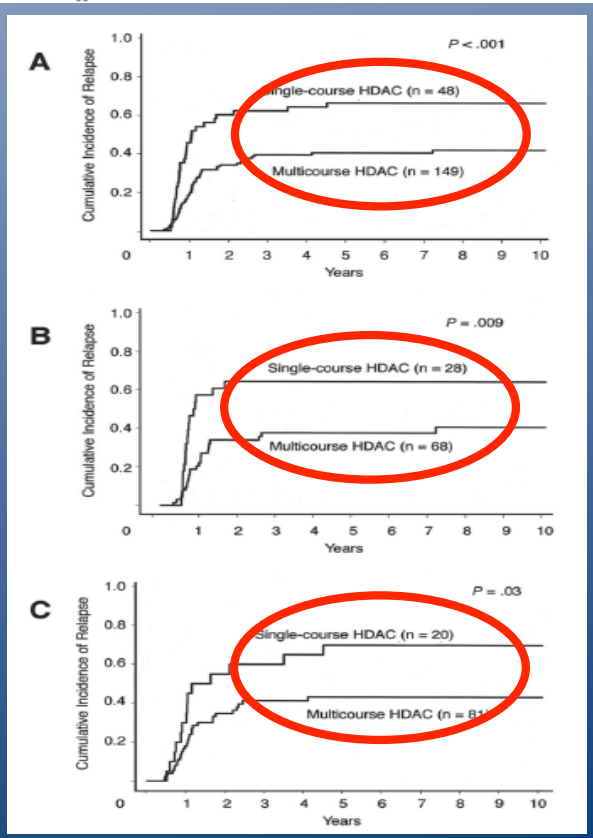


Fig. 3. CR duration by cytarabine dose intensification



Prognostic Factors and Outcome of Core Binding Factor Acute Myeloid Leukemia Patients With t(8;21) Differ From Those of Patients With inv(16): A Cancer and Leukemia Group B Study

Guido Marcucci, Krzysztof Mrózek, Amy S. Ruppert, Kati Maharry, Jonathan E. Kolitz, Joseph O. Moore, Robert J. Mayer, Mark J. Pettenati, Bayard L. Powell, Colin G. Edwards, Lisa J. Sterling, James W. Vardiman, Charles A. Schiffer, Andrew J. Carroll, Richard A. Larson, and Clara D. Bloomfield



“Vedi, il mondo si divide in due categorie: chi ha la pistola carica, e chi scava. Tu scavi”

Repetitive Cycles of High-Dose Cytarabine Benefit Patients With Acute Myeloid Leukemia and inv(16)(p13q22) or t(16;16)(p13;q22): Results from CALGB 8461

John C. Byrd, Amy S. Ruppert, Krzysztof Mrózek, Andrew J. Carroll, Colin G. Edwards, Diane C. Arthur, Mark J. Pettenati, Judith Stamberg, Prasad R.K. Koduru, Joseph O. Moore, Robert J. Mayer, Frederick R. Davey, Richard A. Larson, and Clara D. Bloomfield

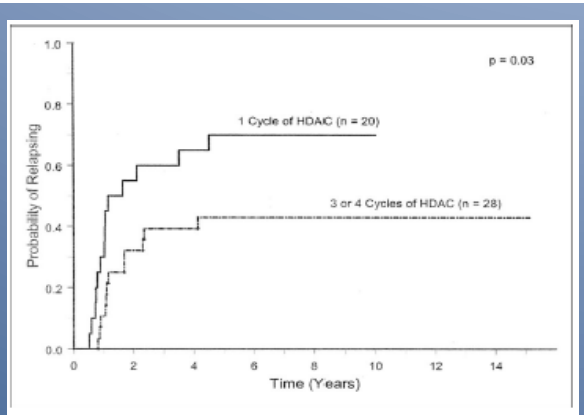


Fig 2. Cumulative incidence of relapse of inv(16)/t(16;16) patients based on assignment to treatment with 3 to 4 cycles compared with only 1 cycle of high-dose cytarabine (HDAC) consolidation therapy.

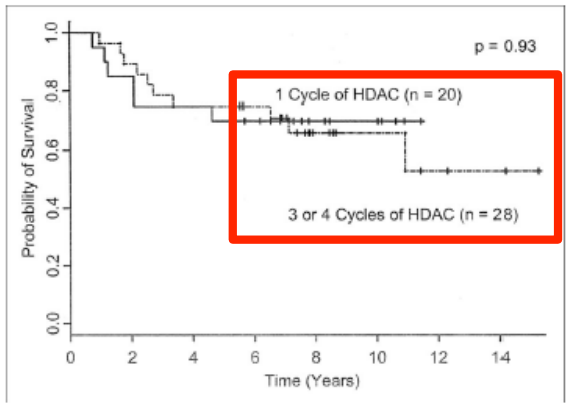


Fig 3. Overall survival of inv(16)/t(16;16) patients based on assignment to treatment with 3 to 4 cycles compared with only 1 cycle of high-dose cytarabine (HDAC) consolidation therapy.

PERGAMON

Leukemia Research 26 (2002) 539–543

Leukemia Research

www.elsevier.com/locate/leukres

High-dose cytarabine as consolidation treatment for patients with acute myeloid leukemia with t(8;21)

Salvatore Palmieri [a], Lucia Sebastio [b], Giuseppina Mele [a], Mario Annunziata [a], Silvana Annunziata [a], Carolina Copia [a], Assunta Viola [a], Mariacarla De Simone [a], Barbara Pocali [a], Ettore Mariano Schiavone [a], Felicetto Ferrara [a,*]

[a] *Division of Hematology, Cardarelli Hospital, Naples, Italy*
[b] *Medical Genetics Service, Cardarelli Hospital, Naples, Italy*

Received 15 July 2001; accepted 10 October 2001

Table 2
Therapeutic results

Complete remission	14/17 (82%)
Induction death	3/17 (18%)
Resistant	0 (0%)
CD34+ve cells successful mobilization	8/11 (73%)
Courses of HD-ARA-C (programmed/administered)	42/42 (100%)
Relapse	1[a]/14 (7%)
Median follow-up	44 months

[a] Second CR after FLAG; death from severe aGVHD after AlloBMT.

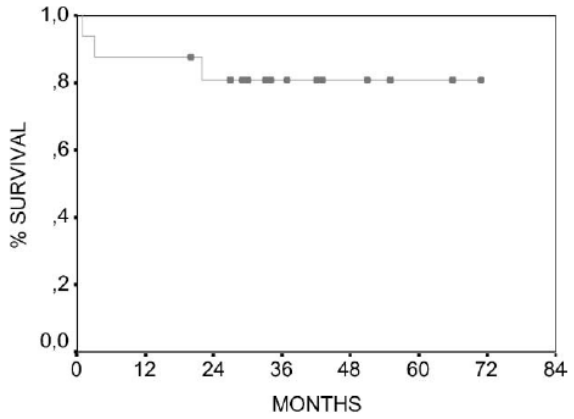


Fig. 1. Overall survival of patients with AML with t(8;21) programmed to be consolidated with high dose cytarabine ($n = 17$).

“Vedi, il mondo si divide in due categorie: chi ha la pistola carica, e chi scava. Tu scavi”

A randomized comparison of 4 courses of standard-dose multiagent chemotherapy versus 3 courses of high-dose cytarabine alone in postremission therapy for acute myeloid leukemia in adults: the JALSG AML201 Study

Shuichi Miyawaki,[1] Shigeki Ohtake,[2] Shin Fujisawa,[3] Hitoshi Kiyoi,[4] Katsuji Shinagawa,[5] Noriko Usui,[6] Toru Sakura,[1] Koichi Miyamura,[7] Chiaki Nakaseko,[8] Yasushi Miyazaki,[9] Atsushi Fujieda,[10] Tadashi Nagai,[11] Takahisa Yamane,[12] Masafumi Taniwaki,[13] Masatomo Takahashi,[14] Fumiharu Yagasaki,[15] Yukihiko Kimura,[16] Norio Asou,[17] Hisashi Sakamaki,[18] Hiroshi Handa,[19] Sumihisa Honda,[20] Kazunori Ohnishi,[21] Tomoki Naoe,[4] and Ryuzo Ohno[22]

BLOOD, 24 FEBRUARY 2011 • VOLUME 117, NUMBER 8

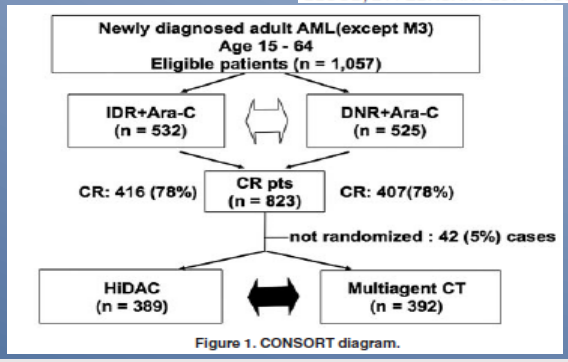


Figure 1. CONSORT diagram.

Karyotype, n		
Favorable	108	110

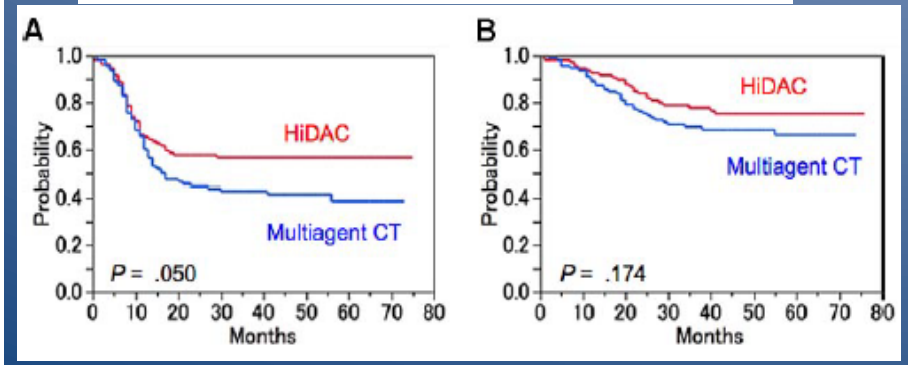


Figure 5. DFS and OS by treatment arm for the favorable cytogenetic risk group. (A) Predicted 5-year DFS was 57% for the HiDAC group (n = 108; red line) and 39% for the multiagent CT group (n = 110; blue line; *P* = .050). (B) Predicted 5-year OS was 75% for the HiDAC group (n = 108; red line) and 66% for the multiagent CT group (n = 110; blue line; *P* = .174).

CLINICAL TRIALS AND OBSERVATIONS

Complex karyotype, older age, and reduced first-line dose intensity determine poor survival in core binding factor acute myeloid leukemia patients with long-term follow-up

Federico Mosna,[1] Cristina Papayannidis,[2] Giovanni Martinelli,[2]* Eros Di Bona,[3] Angela Bonalumi,[4] Cristina Tecchio,[4] Anna Candoni,[5] Debora Capelli,[6] Andrea Piccin,[7] Fabio Forghieri,[8] Catia Bigazzi,[9] Giuseppe Visani,[10] Renato Zambello,[11] Lucia Zanatta,[12] Francesca Volpato,[1] Stefania Paolini,[2] Nicoletta Testoni,[2] Filippo Gherlinzoni,[1] and Michele Gottardi[1]

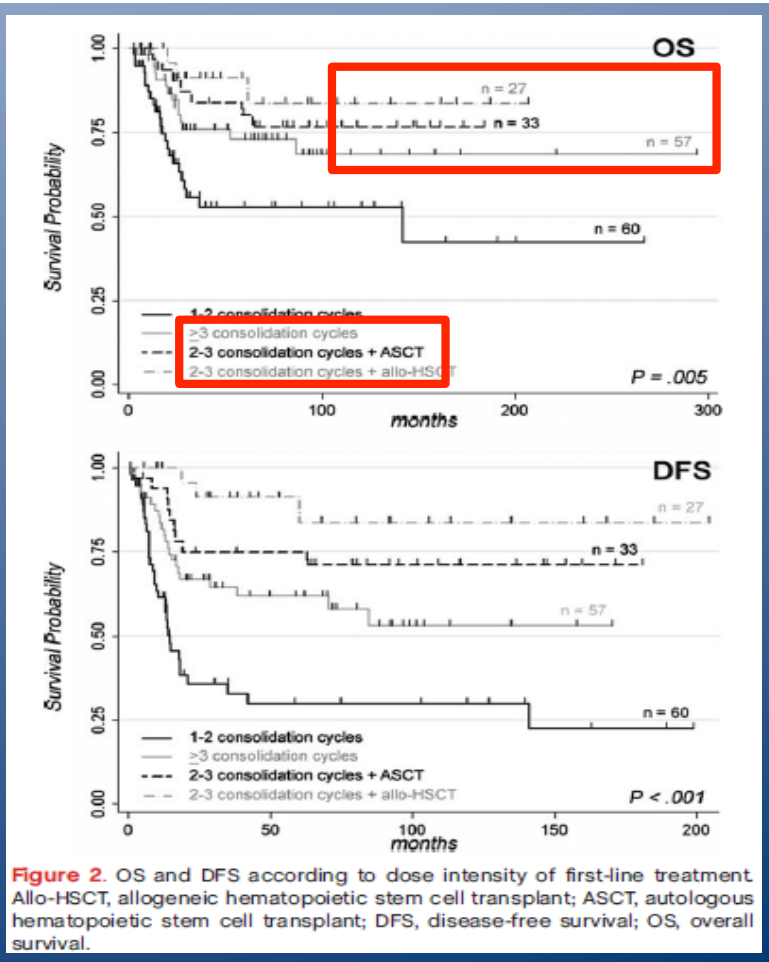


Figure 2. OS and DFS according to dose intensity of first-line treatment Allo-HSCT, allogeneic hematopoietic stem cell transplant; ASCT, autologous hematopoietic stem cell transplant; DFS, disease-free survival; OS, overall survival.

“Vedi, il mondo si divide in due categorie: chi ha la pistola carica, e chi scava. Tu scavi”

The value of allogeneic bone marrow transplant in patients with acute myeloid leukaemia at differing risk of relapse: results of the UK MRC AML 10 trial

Alan K. Burnett,[1] Keith Wheatley,[2] Anthony H. Goldstone,[3] Richard F. Stevens,[4] Ian M. Hann,[5] John H. K. Rees[6] and Georgina Harrison[7] on behalf of the Medical Research Council Adult and Paediatric Working Parties [1]*Department of Haematology, University of Wales College of Medicine, Cardiff,*

Subgroup	Deaths/Patients[1] Donor	No donor	Statistics (O-E)	Var.	O.R. & 95% CI (Donor : No donor)	Odds Redn. (SD)
Cytogenetic risk group:						
t(15;17)	11/46 (75%)	28/98 (72%)	-1·6	8·5		17% (31); p = 0·6
t(8;21)/inv(16)	18/49 (63%)	22/92 (77%)	5·4	8·6		47% (47); p = 0·07
Intermediate	107/239 (54%)	276/493 (44%)	-21·3	85·2		22% (10); p = 0·02
Adverse	18/21 (14%)	49/67 (27%)	3·1	11·5		31% (34); p = 0·4
Unknown	32/64 (50%)	64/118 (45%)	-2·0	21·9		9% (20); p = 0·7

B

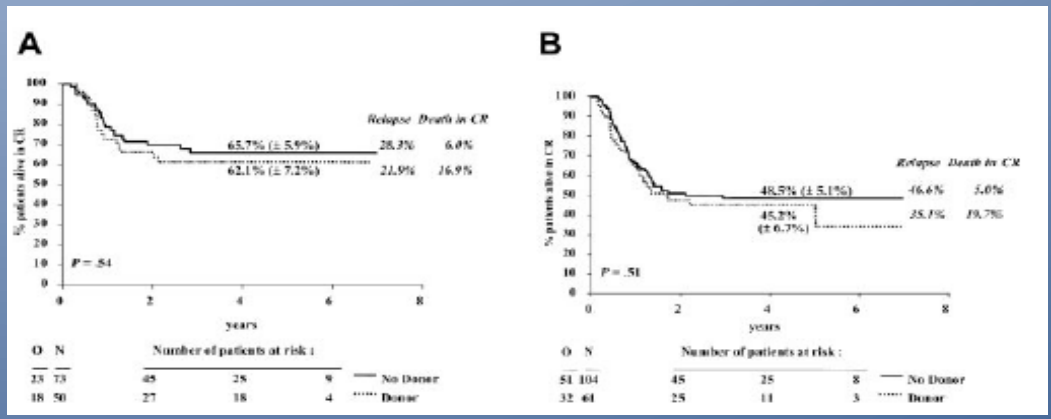
Subgroup	Relapses/Patients[1] Donor	No donor	Statistics (O-E)	Var.	O.R. & 95% CI (Donor : No donor)	Odds Redn. (SD)
Cytogenetic risk group:						
t(15;17)	9/46 (22%)	41/98 (43%)	-7·7	11·0		50% (22); p = 0·02
t(8;21)/inv(16)	12/49 (30%)	25/92 (29%)	0·5	7·9		6% (37); p = 0·9
Intermediate	75/239 (36%)	252/493 (56%)	-39·0	74·1		41% (9); p < 0·0001
Adverse	14/21 (80%)	48/67 (75%)	-1·6	11·6		13% (28); p = 0·6
Unknown	20/64 (36%)	54/118 (51%)	-7·3	17·2		35% (20); p = 0·08

Subgroup	Deaths/Patients[1] Donor	None	Statistics (O-E)	Var.	O.R. & 95% CI (Donor : None)	Odds Redn. (SD)
Cytogenetic risk group:						
t(15;17)	8/46 (20%)	7/98 (9%)	3·0	3·3		-143% (88); p = 0·1
t(8;21)/inv(16)	11/49 (24%)	6/92 (7%)	5·4	3·7		330% (117); p = 0·00
Intermediate	42/239 (21%)	49/493 (13%)	10·7	20·5		-69% (29); p = 0·02
Adverse	4/21 (27%)	3/67 (6%)	2·2	1·4		386% (209); p = 0·07
Unknown	14/64 (27%)	15/118 (16%)	3·5	6·7		-68% (51); p = 0·2

Received 13 December 2001; accepted for publication 18 March 2002

Allogeneic compared with autologous stem cell transplantation in the treatment of patients younger than 46 years with acute myeloid leukemia (AML) in first complete remission (CR1): an intention-to-treat analysis of the EORTC/GIMEMA AML-10 trial

Stefan Suciu, Franco Mandelli, Theo de Witte, Robert Zittoun, Eugenio Gallo, Boris Labar, Gennaro De Rosa, Amine Belhabri, Rosario Giustolisi, Richard Delarue, Vincenzo Liso, Salvatore Mirto, Giuseppe Leone, Jean-Henri Bourhis, Giuseppe Fioritoni, Ulrich Jehn, Sergio Amadori, Paola Fazi, Anne Hagemeijer, and Roel Willemze, for the EORTC and GIMEMA Leukemia Groups



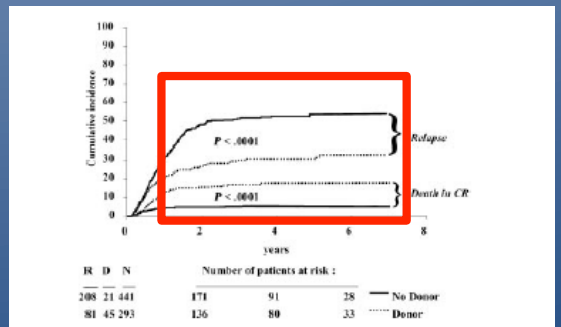


Figure 2. Cumulative incidence of relapse and cumulative incidence of death in complete remission according to donor availability. N indicates number of patients; R, observed number of relapses; D, observed number of deaths in first CR. *P* is determined by the Gray test.

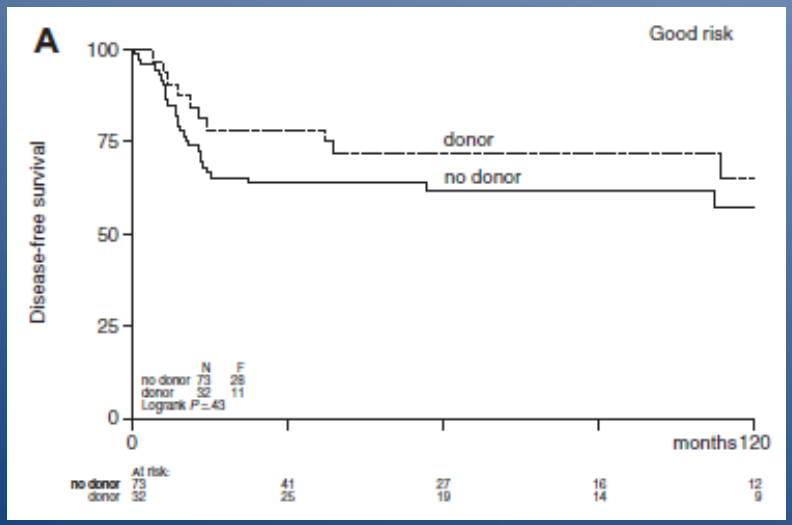
“Vedi, il mondo si divide in due categorie: chi ha la pistola carica, e chi scava. Tu scavi”

Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom?

Jan J. Cornelissen,[1] Wim L. J. van Putten,[1] Leo F. Verdonck,[2] Matthias Theobald,[3] Emanuel Jacky,[4] Simon M. G. Daenen,[5] Marinus van Marwijk Kooy,[6] Pierre Wijermans,[7] Harry Schouten,[8] Peter C. Huijgens,[9] Hans van der Lelie,[10] Martin Fey,[11] Augustin Ferrant,[12] Johan Maertens,[13] Alois Gratwohl,[14] and Bob Lowenberg[1]

Table 1. Risk group classification

Group	Definition
Good	t(8;21) *and* WBC count ≤ 20 × 10⁹/L *and* no additional unfavorable cytogenetic abnormalities; inv/del(16) *and* no additional unfavorable cytogenetic abnormalities
Intermediate	Patients not assigned to good or poor-risk groups
Poor	Unfavorable cytogenetics: complex karyotypes (≥3); del(5q)/−5; del(7q)/−7; abn(3q); t(6;9)/t(9;22); abn(11q23); and late CR*



ADVANCES IN ACUTE MYELOID LEUKEMIA

Review Series

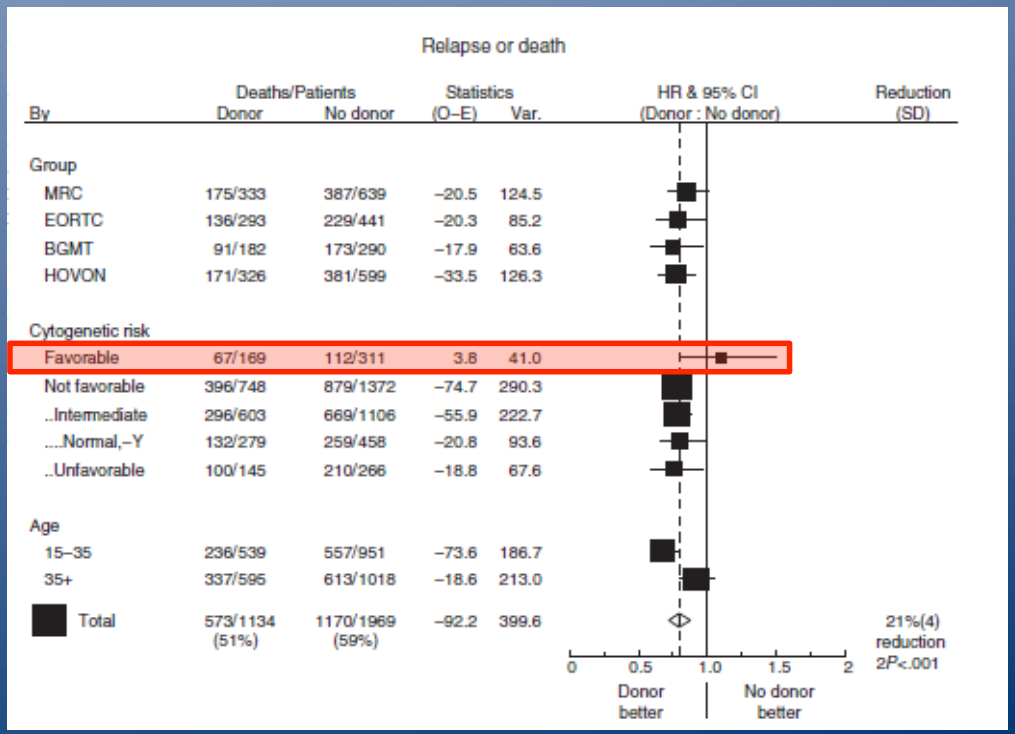
Hematopoietic stem cell transplantation for patients with AML in first complete remission

Jan J. Cornelissen[1] and Didier Blaise[2]

[1]Department of Hematology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands; and [2]Département d'Hématologie, Programme de Transplantation et de Thérapie Cellulaire, Centre de Recherche en Cancérologie de Marseille, Institut Paoli Calmettes, Marseille, France

Table 1. Recommendation for alloHSCT in AML CR1 based on integrated risk profiles

AML risk group‡	AML risk assessment criteria at diagnosis	MRD after cycle 2	Risk of relapse following consolidation approach: Chemotherapy or autoHSCT (%)	Risk of relapse following consolidation approach: AlloHSCT (%)	Prognostic scores for NRM that indicate alloHSCT as preferred consolidation: EBMT score[52]	Prognostic scores for NRM that indicate alloHSCT as preferred consolidation: HCT-CI score[53]	Prognostic scores for NRM that indicate alloHSCT as preferred consolidation: NRM risk (%)
Good	–t(8;21) or *AML1-ETO*, WBC <20	Positive or negative	35-40	15-20	NA (≤1)	NA (<1)	10-15



"Vedi, il mondo si divide in due categorie: chi ha la pistola carica, e chi scava. Tu scavi"

Review Article blood

Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel

Hartmut Döhner,[1] Elihu Estey,[2] David Grimwade,[3] Sergio Amadori,[4] Frederick R. Appelbaum,[2] Thomas Büchner,[5] Hervé Dombret,[6] Benjamin L. Ebert,[7] Pierre Fenaux,[8] Richard A. Larson,[9] Ross L. Levine,[10] Francesco Lo-Coco,[4] Tomoki Naoe,[11] Dietger Niederwieser,[12] Gert J. Ossenkoppele,[13] Miguel Sanz,[14] Jorge Sierra,[15] Martin S. Tallman,[10] Hwei-Fang Tien,[16] Andrew H. Wei,[17,18] Bob Löwenberg,[19] and Clara D. Bloomfield[20]

Consolidation therapy‡,§	
Younger patients (18-60/65 y)	
• Favorable-risk genetics	• 2-4 cycles of IDAC (1000-1500 mg/m^2 IV over 3 h q12h, d1-3; or 1000-1500 mg/m^2 IV over 3 h d1-5 or 6)

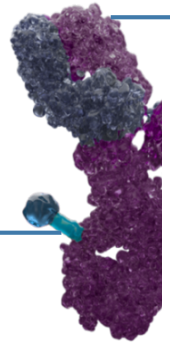
§Results from assessment of MRD should be taken into account for selecting the appropriate consolidation therapy.

“Sei: numero perfetto.
Non è tre il numero perfetto?
Sì, ma io ho sei colpi qui dentro.”

MIGLIORARE LA MIRA PER UNA MAGGIORE INTENSIFICAZIONE ?

"Sei: numero perfetto.
Non è tre il numero perfetto?
Sì, ma io ho sei colpi qui dentro."

MYLOTARG

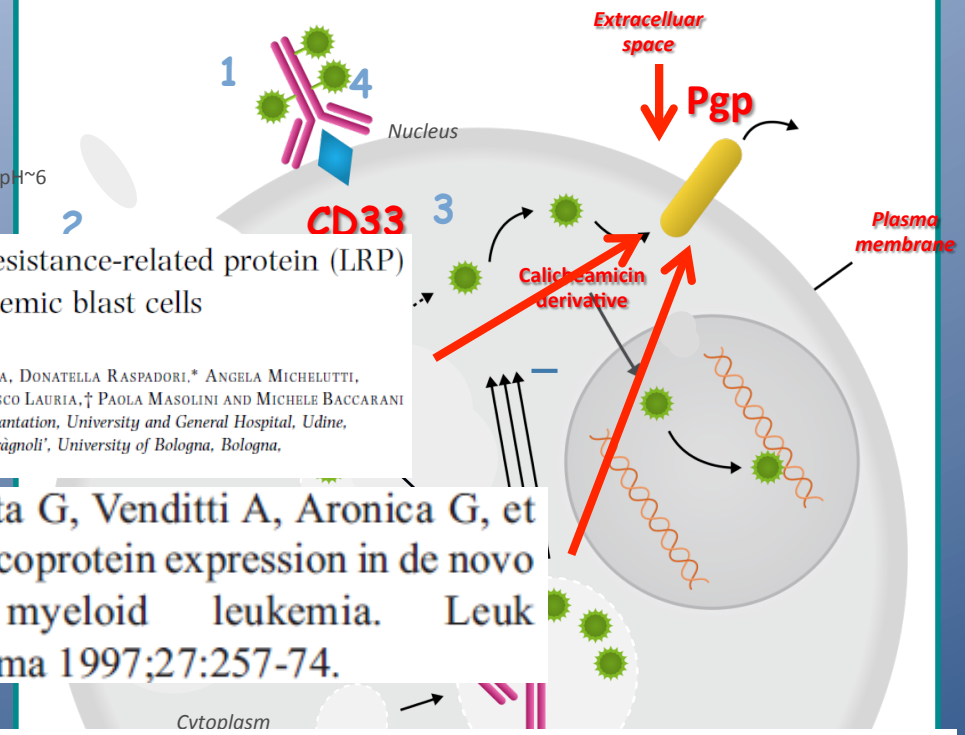


P-glycoprotein (PGP) and lung resistance-related protein (LRP) expression and function in leukaemic blast cells

MARIAGRAZIA MICHIELI, DANIELA DAMIANI, ANNA ERMACORA, DONATELLA RASPADORI,* ANGELA MICHELUTTI, STEFANIA GRIMAZ, RENATO FANIN, DOMENICO RUSSO, FRANCESCO LAURIA,† PAOLA MASOLINI AND MICHELE BACCARANI
*Division of Haematology, Department of Bone Marrow Transplantation, University and General Hospital, Udine, *Institute of Haematology and Medical Oncology 'L. and A. Seràgnoli', University of Bologna, Bologna, and †Chair of Haematology, University of Siena, Siena, Italy*

Del Poeta G, Venditti A, Aronica G, et al. P-glycoprotein expression in de novo acute myeloid leukemia. Leuk Lymphoma 1997;27:257-74.

MYLOTARG



MOLECULAR AND CELLULAR BIOLOGY, June 1998, p. 3604–3611 Vol. 18, No. 6
0270-7306/98/$04.00+0

The MYND Motif Is Required for Repression of Basal Transcription from the Multidrug Resistance 1 Promoter by the t(8;21) Fusion Protein

BART LUTTERBACH,[1] DAXI SUN,[2] JOHN SCHUETZ,[2] AND SCOTT W. HIEBERT[1]*
Department of Biochemistry and the Vanderbilt Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee 37027,[1] and Department of Pharmaceutical Science, St. Jude Children's Research Hospital, Memphis, Tennessee 38105[2]

Received 2 December 1997/Returned for modification 20 February 1998/Accepted 24 March 1998

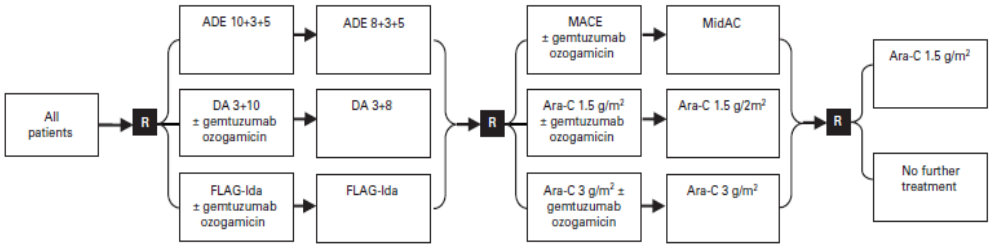
1. **MYLOTARG binds to CD33 antigens on leukaemi**
2. **Once bound, the MYLOTARG/CD33 complex is in**
3. **Calicheamicin is released from the antibody–dru**
4. **Calicheamicin causes double-strand DNA breaks**

ADC, antibo
Ricart AD. *Clin Cancer* 2011;17:6417–6427

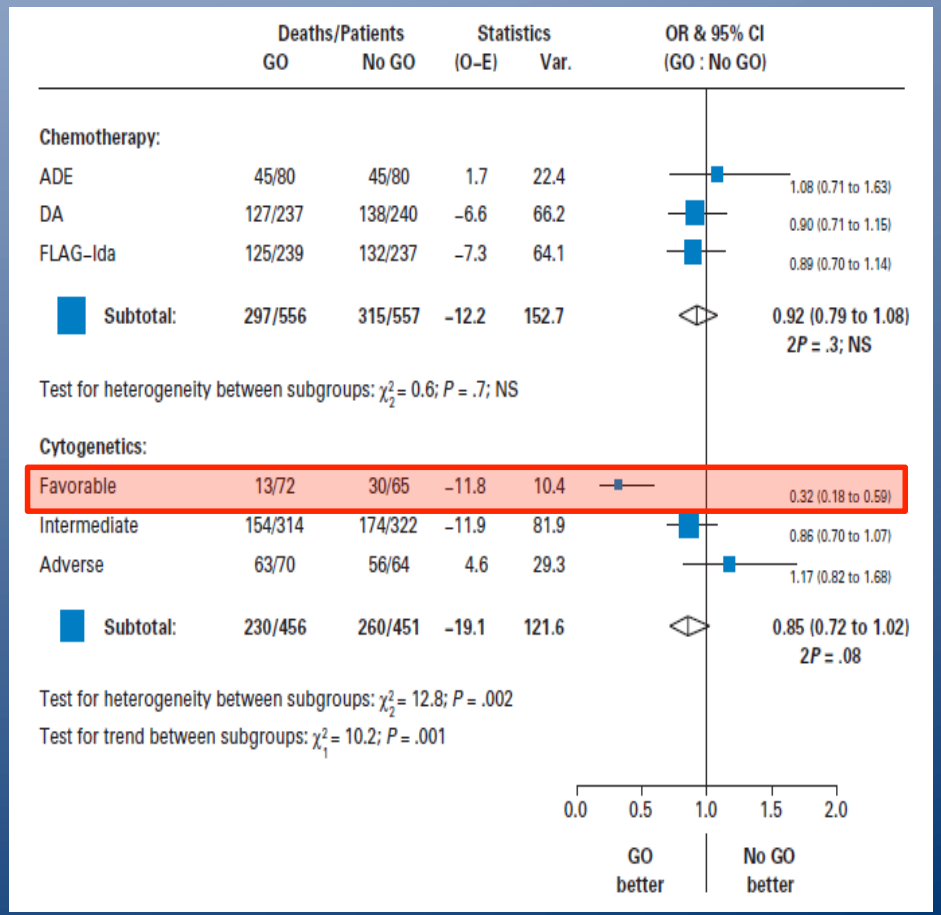
“Sei: numero perfetto.
Non è tre il numero perfetto?
Sì, ma io ho sei colpi qui dentro.”

Identification of Patients With Acute Myeloblastic Leukemia Who Benefit From the Addition of Gemtuzumab Ozogamicin: Results of the MRC AML15 Trial

Alan K. Burnett, Robert K. Hills, Donald Milligan, Lars Kjeldsen, Jonathan Kell, Nigel H. Russell, John A.L. Yin, Ann Hunter, Anthony H. Goldstone, and Keith Wheatley



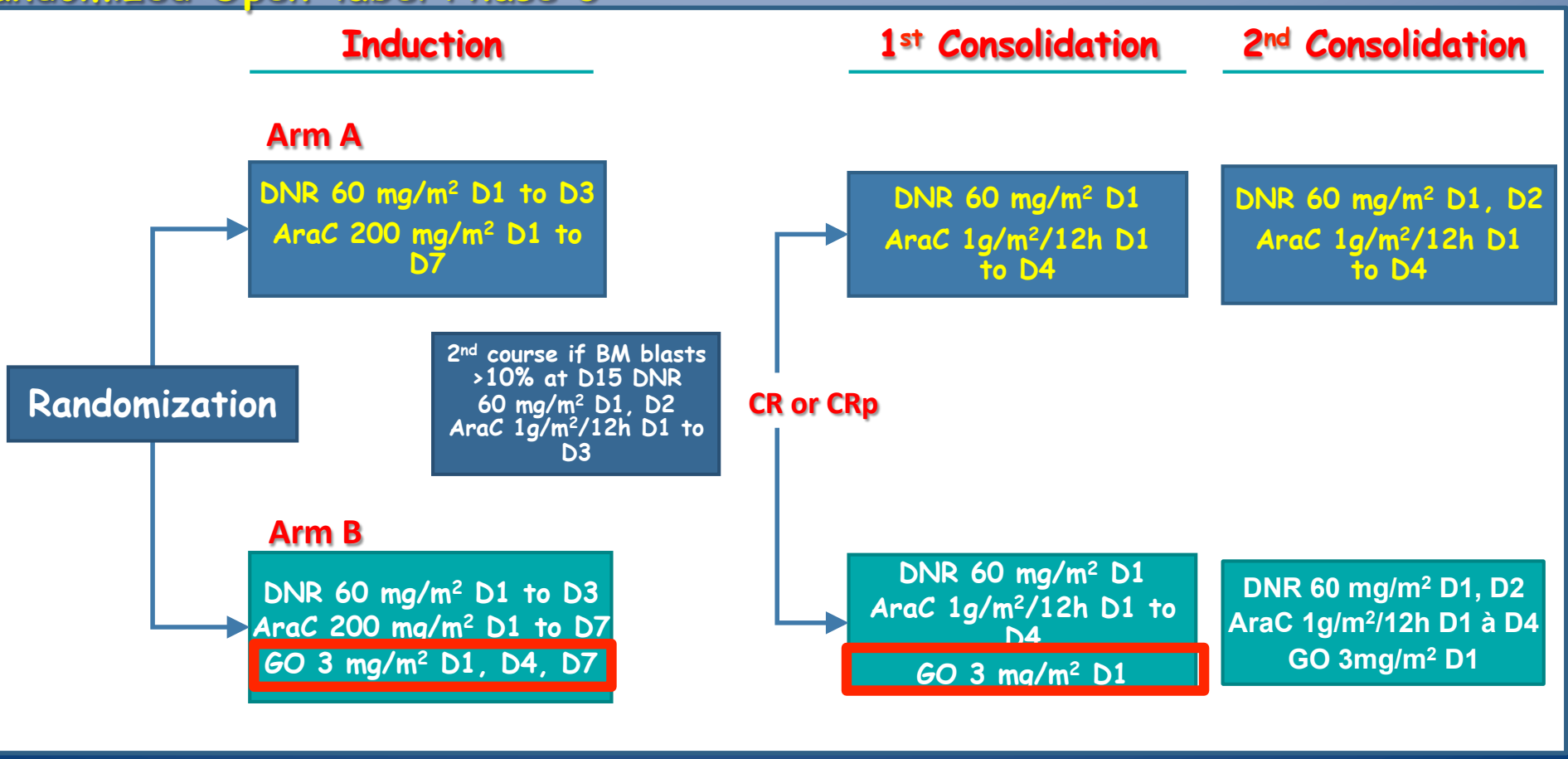
DA 3+10	daunorubicin 50 mg/m² d1,3,5; cytarabine 100 mg/m² d1-10 every 12h
DA 3+8	daunorubicin 50 mg/m² d1,3,5; cytarabine 100 mg/m² d1-8 every 12h
ADE 10+3+5	daunorubicin 50 mg/m² d1,3,5; cytarabine 100 mg/m² d1-10 every 12h; etoposide 100 mg/m² d1-5
ADE 8+3+5	daunorubicin 50 mg/m² d1,3,5; cytarabine 100 mg/m² d1-8 every 12h; etoposide 100 mg/m² d1-5
Gemtuzumab ozogamicin	gemtuzumab ozogamicin 3 mg/m² d1
MACE	amsacrine 100 mg/m² d1-5; cytarabine 200 mg/m² continuous d1-5; etoposide 100 mg/m² d1-5
MidAC	mitozantrone 10 mg/m² daily by slow IV push on d1-5 inclusive (5 doses), cytosine arabinoside 1.0 mg/m² 12-hourly by 2h IV infusion on d1-3 inclusive (6 doses)
FLAG-Ida	fluduarabine 30 mg/m² IV d2-6 inclusive, cytosine arabinoside 2 g/m² over 4h starting after fluduarabine on d2-6, G-CSF (lenograstin 263 µg (1 vial) SC daily d1-7
High-dose Ara-C (1.5 g/m²)	Ara-C 1.5 g/m² d1 given IV over 4h 12 hourly on d1,3,5 (6 doses)
High-dose Ara-C (3.0 g/m²)	Ara-C 3.0 g/m² d1 given IV over 4h 12 hourly on d1,3,5 (6 doses)



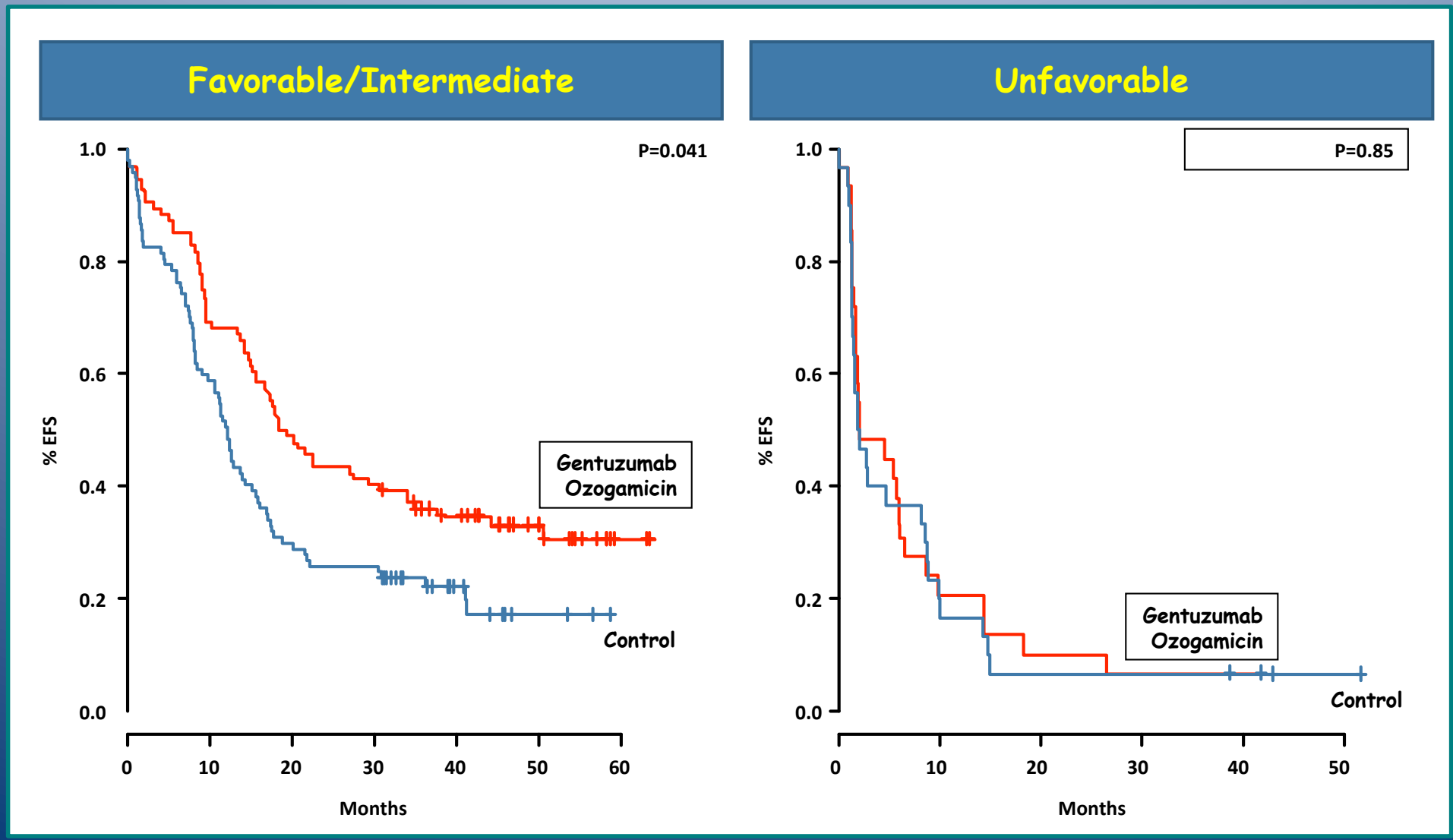
"Sei: numero perfetto.
Non è tre il numero perfetto?
Sì, ma io ho sei colpi qui dentro."

ALFA-0701: Study Design

Randomized Open-label Phase 3



ALFA-0701: Event-Free Survival by Cytogenetic Status (Final Analyses)



Hills et al. (2014) Meta-Analysis

Objective

- **Meta-Analysis of individual patient data from 5 trials in adults in which gemtuzumab ozogamicin was given in combination with standard induction chemotherapy**
  - **Does gemtuzumab ozogamicin provide overall benefit with acceptable early mortality?**
  - **What is the optimum dose and dosing schedule?**

Articles

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

Summary

Background Gemtuzumab ozogamicin was the first example of antibody-directed chemotherapy in cancer, and was developed for acute myeloid leukaemia. However, randomised trials in which it was combined with standard induction chemotherapy in adults have produced conflicting results. We did a meta-analysis of individual patient data to assess the efficacy of adding gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia.

Methods We searched PubMed for reports of randomised controlled trials published in any language up to May 1, 2013, that included an assessment of gemtuzumab ozogamicin given to adults (aged 15 years and older) in conjunction with the first course of intensive induction chemotherapy for acute myeloid leukaemia (excluding acute promyelocytic leukaemia) compared with chemotherapy alone. Published data were supplemented with additional data obtained by contacting individual trialists. The primary endpoint of interest was overall survival. We used standard meta-analytic techniques, with an assumption-free (or fixed-effect) method. We also did exploratory stratified analyses to investigate whether any baseline features predicted a greater or lesser benefit from gemtuzumab ozogamicin.

Findings We obtained data from five randomised controlled trials (3325 patients); all trials were centrally randomised and open label, with overall survival as the primary endpoint. The addition of gemtuzumab ozogamicin did not increase the proportion of patients achieving complete remission with or without complete peripheral count recovery (odds ratio [OR] 0·91, 95% CI 0·77–1·07; p=0·3). However, the addition of gemtuzumab ozogamicin significantly reduced the risk of relapse (OR 0·81, 0·73–0·90; p=0·0001), and improved overall survival at 5 years (OR 0·90, 0·82–0·98; p=0·01). At 6 years, the absolute survival benefit was especially apparent in patients with favourable cytogenetic characteristics (20·7%; OR 0·47, 0·31–0·73; p=0·0006), but was also seen in those with intermediate characteristics (5·7%; OR 0·84, 0·75–0·95; p=0·005). Patients with adverse cytogenetic characteristics did not benefit (2·2%; OR 0·99, 0·83–1·18; p=0·9). Doses of 3 mg/m² were associated with fewer early deaths than doses of 6 mg/m², with equal efficacy.

Interpretation Gemtuzumab ozogamicin can be safely added to conventional induction therapy and provides a significant survival benefit for patients without adverse cytogenetic characteristics. These data suggest that the use of gemtuzumab ozogamicin should be reassessed and its licence status might need to be reviewed.

Funding None.

Introduction

Very few treatments for acute myeloid leukaemia have gained regulatory approval. One of the few successes was the immunoconjugate drug gemtuzumab ozogamicin (Pfizer, New York, NY, USA), which gained approval in the USA in 2000 (with a dosing schedule of 9 mg/m² on days 1 and 15 of induction chemotherapy) on the basis of data from a non-randomised, phase 2 study done in 142 patients with relapsed disease.[1,2] The label restricted approval to "older patients with relapse who were not suitable for intensive treatment".[1] A confirmatory randomised trial was required for full approval.

Gemtuzumab ozogamicin was approved in Japan for the same patient population and with the same dosing schedule; however, when combined with frequently used chemotherapy regimens, this schedule resulted in prohibitive toxic effects.[3] Results from a dose-finding study[4] in which gemtuzumab ozogamicin was combined with frequently used induction and consolidation chemotherapy regimens provided evidence that a single, lower dose of 3 mg/m² was safe and apparently effective. That study was the prelude to a randomised trial[5] in which gemtuzumab ozogamicin was added to different courses of chemotherapy. Feasibility was established in combination with the first and third courses of chemotherapy. On the basis of these data, two large trials were done in which a gemtuzumab ozogamicin dose of 3 mg/m² was added to induction chemotherapy in younger patients

Lancet Oncol 2014

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See Online for podcast interview with Robert K Hills

School of Medicine, Cardiff University, Cardiff, UK (R K Hills DPhil, Prof A K Burnett MD); Centre Hospitalier de Versailles, Université de Versailles Saint Quentin, Le Chesnay, France (Prof S Castaigne MD, S Chevret PhD); Fred Hutchinson Cancer Research Center, Seattle, WA, USA (Prof F R Appelbaum MD, S Petersdorf MD, M Othus PhD, Prof E H Estey MD); Service D'Hematologie Clinique, CHU Hotel Dieu, Nantes, France (J Delaunay MD); Hôpital Saint-Louis, University Paris Diderot, Paris, France (Prof H Dombret MD); Service des Maladies du Sang and Inserm U892/CNRS6299, CHU d'Angers, Angers, France (Prof N Ifrah MD); Department of Haematology, University Hospital, Grenoble, France (Prof J-Y Cahn MD); Centre Hospitalier Universitaire de Toulouse, Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France (Prof C Récher MD); and Leukaemia Research Cytogenetics Group, Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, UK (L Chilton PhD, Prof A V Moorman PhD)

Correspondence to: Prof Alan K Burnett, School of Medicine, Cardiff University, Cardiff CF14 1XW, UK BurnettAK@cardiff.ac.uk

Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

Hills Meta-Analysis: Studies Included

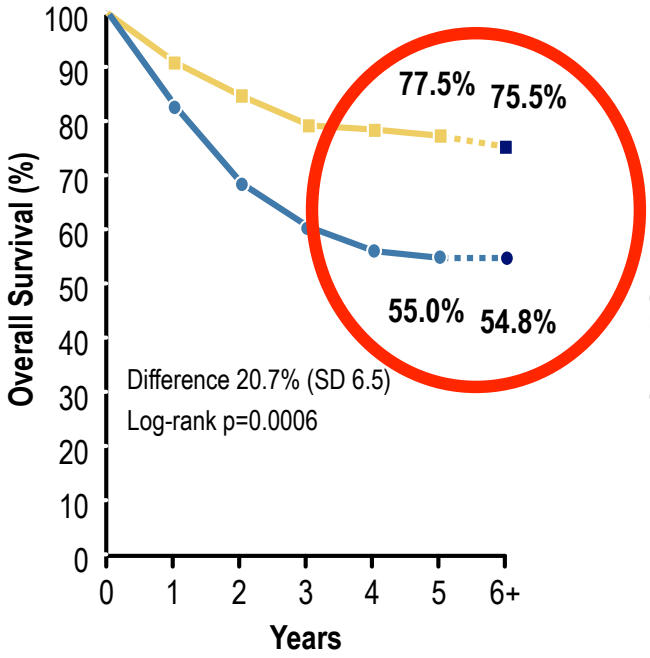
Trial	No. Patients	Eligibility Criteria	Median Age in Years (Range)	Chemotherapy	Dose and Schedule of GO	Median Follow-up for Survival
ALFA-0701 (Castaigne et al, 2012)	278	*de novo* AML; aged 50-70 years	62 (50-70)	DA (3+7)	3 mg/m² on days 1, 4, and 7 of chemotherapy, up to 5 mg per dose	24.1 months (IQR 15.7-32.8)
MRC AML15 (Burnett et al, 2011)	1,099	AML, either *de novo* or secondary; mostly aged <60 years	50 (15-71)	DA (3+10, then 3+8), ADE (3+10+5, then 3+8+5), or FLAG-Ida	3 mg/m² on day 1 of chemotherapy	86.0 months (IQR 76.6-99.4)
NCRI AML16 (Burnett et al, 2012)	1,115	AML, either *de novo* or secondary, or high-risk MDS; mostly aged ≥60 years	67 (51-84)	DA (3+10, then 3+8) or daunorubicin (days 1, 3, and 5) plus clofarabine (days 1-5)	3 mg/m² on day 1 of chemotherapy	45.5 months (IQR 34.3-57.6)
SWOG S0106 (Petersdorf et al, 2013)	595	*de novo* AML; aged 18-60 years	47 (18-60)	DA (3+7) plus G-CSF or GM-CSF	6 mg/m² on day 4 of chemotherapy	55.2 months (IQR 46.0-66.3)
GOELAMS AML 2006 IR (Delaunay et al, 2011)	238	*de novo* AML, aged 18-60 years	50.5 (18-60)	DA (3+7)	6 mg/m² on day 4 of chemotherapy	39.3 months (IQR 29.1-44.4)

GO = gemtuzumab ozogamicin; AML = acute myelocytic leukemia; DA = daunorubicin plus cytarabine; ADE = daunorubicin, cytarabine, and etoposide; FLAG-Ida = fludarabine, cytarabine, G-CSF, and idarubicin; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IQR = interquartile range; IR = immediate release; MDS = myelodysplastic syndrome; MRC = Medical Research Council; NCRI = National Cancer Research Institute; SWOG = Southwest Oncology Group.

Hills RK, et al. *Lancet Oncol*. 2014;15:986-996.

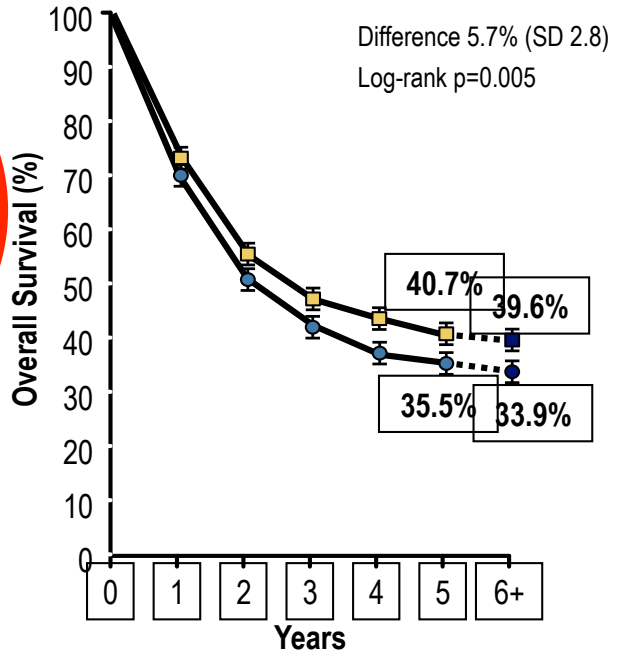
Hills Meta-Analysis: Overall Survival by Cytogenetic Status

Favorable



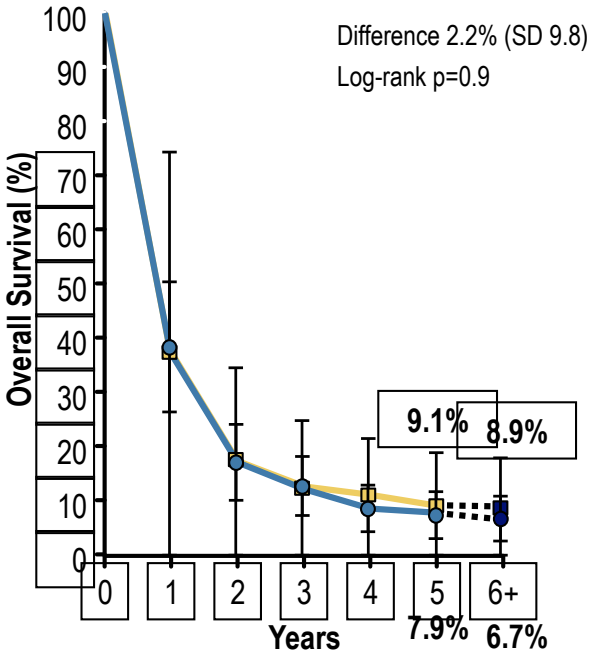
Annual Event Rates	Years 1-5	Years 6+
Gemutuzumab ozogamicin	5.8% SD 1.1	2.3% SD 1.3
No-gemutuzumab ozogamicin	14.1% SD 1.9	0.0% SD 0.0

Intermediate



Annual Event Rates	Years 1-5	Years 6+
Gemutuzumab ozogamicin	22.4% SD 1.0	2.7% SD 0.9
No-gemutuzumab ozogamicin	26.2% SD 1.1	4.9% SD 1.3

Adverse



Annual Event Rates	Years 1-5	Years 6+
Gemutuzumab ozogamicin	73.8% SD 4.6	2.4% SD 0.8
No-gemutuzumab ozogamicin	76.7% SD 4.8	21.1% SD 10.5

Hills RK, et al. *Lancet Oncol*. 2014;15:986-996.

“Sei: numero perfetto.
Non è tre il numero perfetto?
Sì, ma io ho sei colpi qui dentro.”

Clinical and experimental efficacy of gemtuzumab ozogamicin in core binding factor acute myeloid leukemia

Michele Gottardi,[1] Federico Mosna,[1]
Sergio de Angeli,[2]
Cristina Papayannidis,[3] Anna Candoni,[4]
Marino Clavio,[5] Cristina Tecchio,[6]
Andrea Piccin,[7]
Marta Campo dell’Orto,[8]
Fabio Benedetti,[6] Giovanni Martinelli,[3]
Filippo Gherlinzoni[1]

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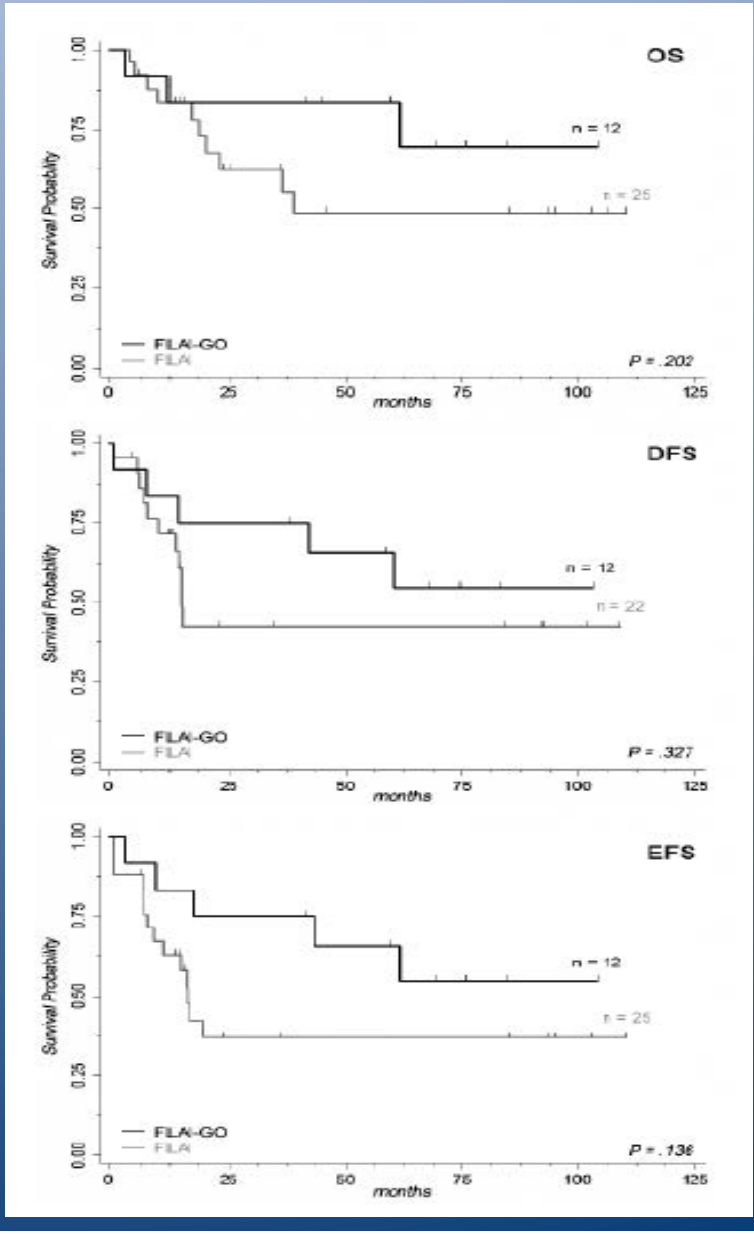


**“Il buono: Gli speroni!
Il brutto: Gli speroni si dividono in due categorie, quelli che passano dalla porta, e quelli che passano dalla finestra”**

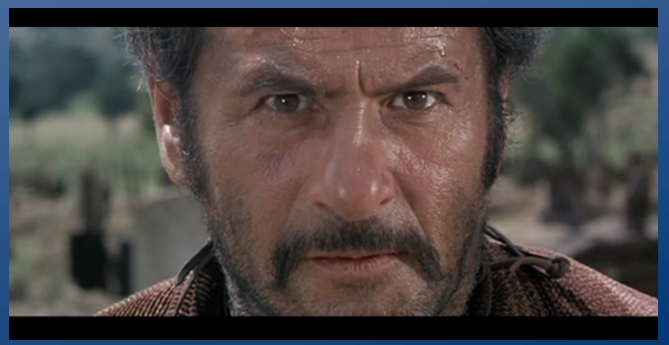
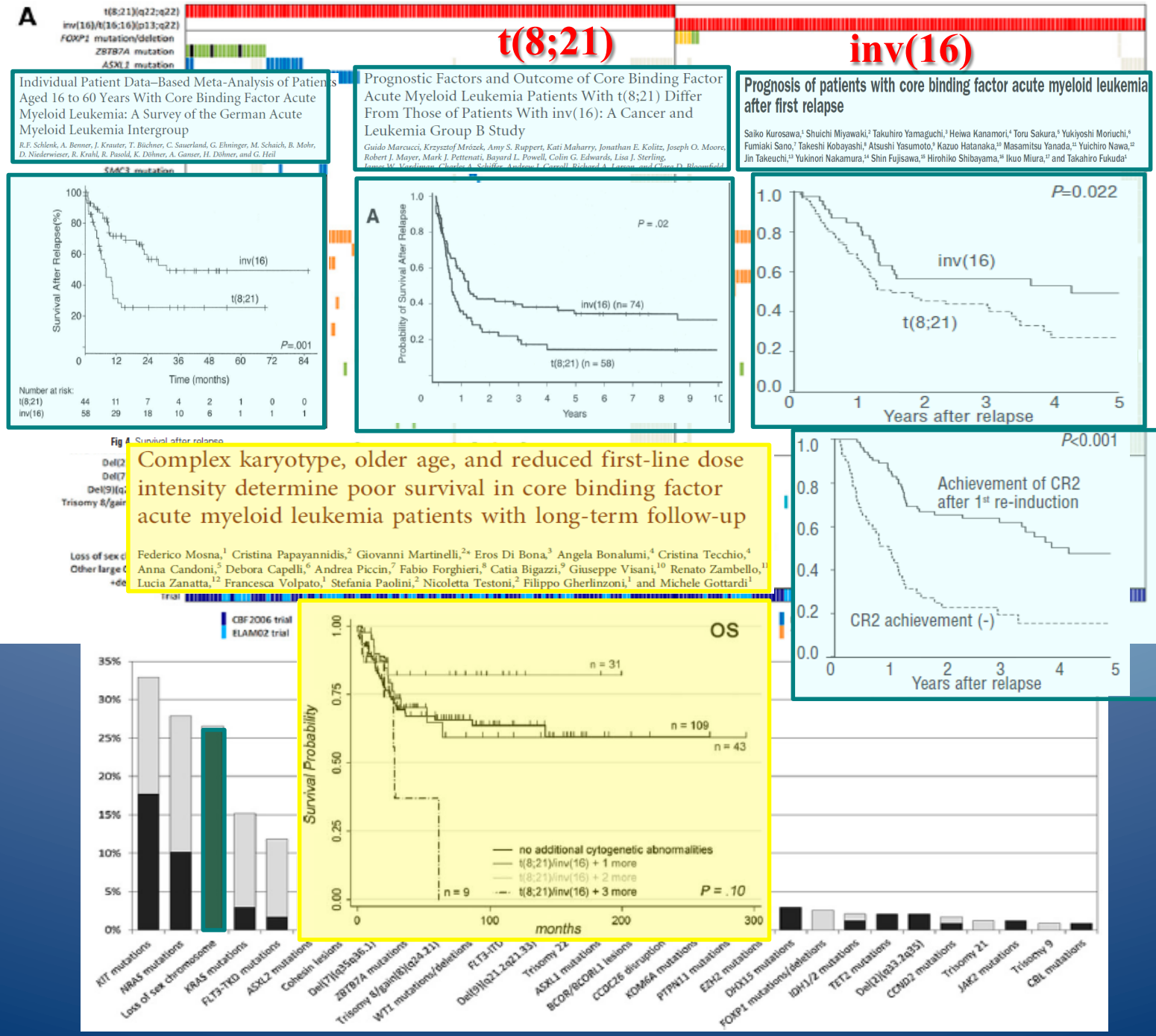


FIGURE 1. (A) Genetic Landscape and (B) Alterations Frequencies in Core-Binding Factor Acute Myeloid Leukemia (Adult CBF-2006 and Pediatric ELAM-02 Trials)



ClinicalTrials.gov Search Results 11/17/2018

1	Midostaurin Associated With Standard Chemotherapy in Patients With Core-binding Factor Leukemia
2	Dasatinib in Combination With Chemotherapy for Relapsed or Refractory Core Binding Factor Acute Myeloid Leukemia
4	Combination Chemotherapy and Dasatinib in Treating Patients With Newly Diagnosed Acute Myeloid Leukemia
5	Randomized Phase III Study of Intensive Chemotherapy With or Without Dasatinib (Sprycel™)
7	Study to Assess Dasatinib in Patients With Core Binding Factors Acute Myelogenous Leukemia
8	Dasatinib (Sprycel™) in Patients With Newly Diagnosed Core Binding Factor (CBF) Acute Myeloid Leukemia (AML)
11	Genome Wide SNP Array-based Approach to Detect Micro-cytogenetic Lesions and KIT Mutation to Improve Treatment Outcomes in Patients With Core-binding Factor Positive Acute Myeloid Leukemia

TK

Prognostic impact of *c-KIT* mut
an Italian retrospective study

Roberto Cairoli, Alessandro Beghini, Giovanni Grillo,
Patrizia Colapietro, Michele Nichelatti, Laura Pezzetti,
Mario Lazzarino, Francesco Rodeghiero, Giovanni Pi

KIT-D816 mutations in *AML1-*
event-free and overall survival

Susanne Schnittger, Tobias M. Kohl, Torsten Haferlac

ORIGINAL ARTICLE

Incidence and prognostic impact
factor acute myeloid leukemia (

N Boissel[1], H Leroy[2], B Brethon[3], N Philippe[2],
B Quesnel[4], A Baruchel[3], G Leverger[5], H Dombret[1] and C Preudhomme[2], for the Acute Leukemia French Association (ALFA)
and the Leucémies Aiguës Myéloblastiques de l'Enfant (LAME) Cooperative Groups

ORIGINAL ARTICLE

High number of additional genetic lesions in acute myeloid leukemia with t(8;21)/*RUNX1-RUNX1T1*: frequency and impact on clinical outcome

M-T Krauth[1,2], C Eder[1], T Alpermann[1], U Bacher[1], N Nadarajah[1], W Kern[1], C Haferlach[1], T Haferlach[1] and S Schnittger[1]

ORIGINAL ARTICLE

The importance of relative mutant level for evaluating impact on outcome of *KIT*, *FLT3* and *CBL* mutations in core-binding factor acute myeloid leukemia

C Allen[1], RK Hills[2], K Lamb[1], C Evans[1], S Tinsley[1], R Sellar[1], M O'Brien[3], JL Yin[3], AK Burnett[2], DC Linch[1] and RE Gale[1]

FLT3 tyrosine kinase domain mutations are biologically distinct from and have a significantly more favorable prognosis than FLT3 internal tandem duplications in patients with acute myeloid leukemia

Adam J. Mead,[1] David C. Linch,[1] Robert K. Hills,[2] Keith Wheatley,[3] Alan K. Burnett,[2] and Rosemary E. Gale[1]

[1]Department of Haematology, Royal Free and University College Medical School, London, United Kingdom; [2]Department of Haematology, School of Medicine, Cardiff University, Cardiff, United Kingdom; and [3]Clinical Trials Unit, University of Birmingham, Birmingham, United Kingdom, on behalf of the National Cancer Research Institute (NCRI) Adult Leukaemia Working Party, United Kingdom

yeloid leukemia
id leukemia
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Adding dasatinib to intensive treatment in core-binding factor acute myeloid leukemia—results of the AMLSG 11-08 trial

Peter Paschka[1] · Richard F Schlenk[1] · Daniela Weber[1] · Axel Benner[2] · Lars Bullinger[1] · Michael Heuser[3] · Verena I Gaidzik[1] · Felicitas Thol[3] · Mridul Agrawal[1] · Veronica Teleanu[1] · Michael Lübbert[4] · Walter Fiedler[5] · Markus Radsak[6] · Jürgen Krauter[7] · Heinz-A. Horst[8] · Richard Greil[9] · Karin Mayer[10] · Andrea Kündgen[11] · Uwe Martens[12] · Gerhard Heil[13] · Helmut R Salih[14] · Bernd Hertenstein[15] · Carsten Schwänen[16] · Gerald Wulf[17] · Elisabeth Lange[18] · Michael Pfreundschuh[19] · Mark Ringhoffer[20] · Michael Girschikofsky[21] · Thomas Heinicke[22] · Doris Kraemer[23] · Gudrun Göhring[24] · Arnold Ganser[3] · Konstanze Döhner[1] · Hartmut Döhner[1]

Marcucci G, Geyer S, Zhao J, Caroll AJ, Bucci D, Uy GL et al. Adding *KIT* inhibitor dasatinib (DAS) to chemotherapy overcomes the negative impact of *KIT* mutation/over-expression in core binding factor (CBF) acute myeloid leukemia (AML): results from CALGB 10801 (Alliance). Blood. 2014;124:8.

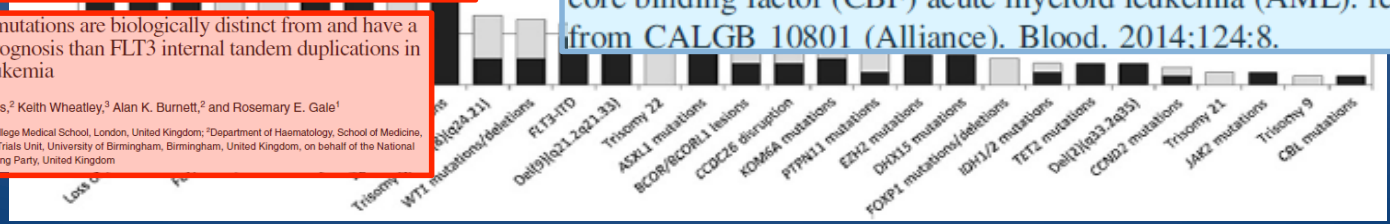
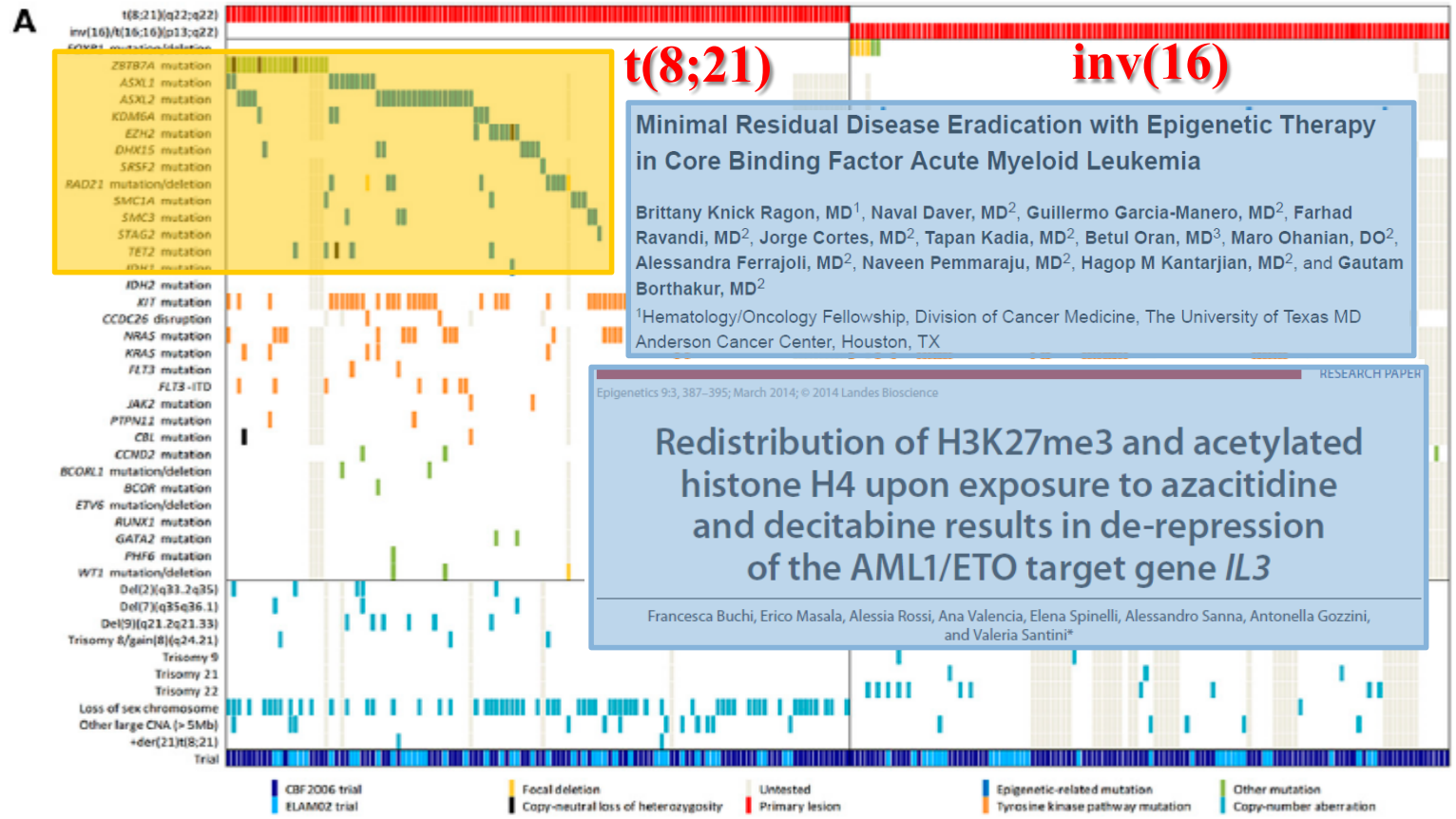


FIGURE 1. (A) Genetic Landscape and (B) Alterations Frequencies in Core-Binding Factor Acute Myeloid Leukemia (Adult CBF-2006 and Pediatric ELAM-02 Trials)



Minimal Residual Disease Eradication with Epigenetic Therapy in Core Binding Factor Acute Myeloid Leukemia

Brittany Knick Ragon, MD[1], Naval Daver, MD[2], Guillermo Garcia-Manero, MD[2], Farhad Ravandi, MD[2], Jorge Cortes, MD[2], Tapan Kadia, MD[2], Betul Oran, MD[3], Maro Ohanian, DO[2], Alessandra Ferrajoli, MD[2], Naveen Pemmaraju, MD[2], Hagop M Kantarjian, MD[2], and Gautam Borthakur, MD[2]

[1]Hematology/Oncology Fellowship, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

RESEARCH PAPER

Epigenetics 9:3, 387–395; March 2014; © 2014 Landes Bioscience

Redistribution of H3K27me3 and acetylated histone H4 upon exposure to azacitidine and decitabine results in de-repression of the AML1/ETO target gene *IL3*

Francesca Buchi, Erico Masala, Alessia Rossi, Ana Valencia, Elena Spinelli, Alessandro Sanna, Antonella Gozzini, and Valeria Santini*

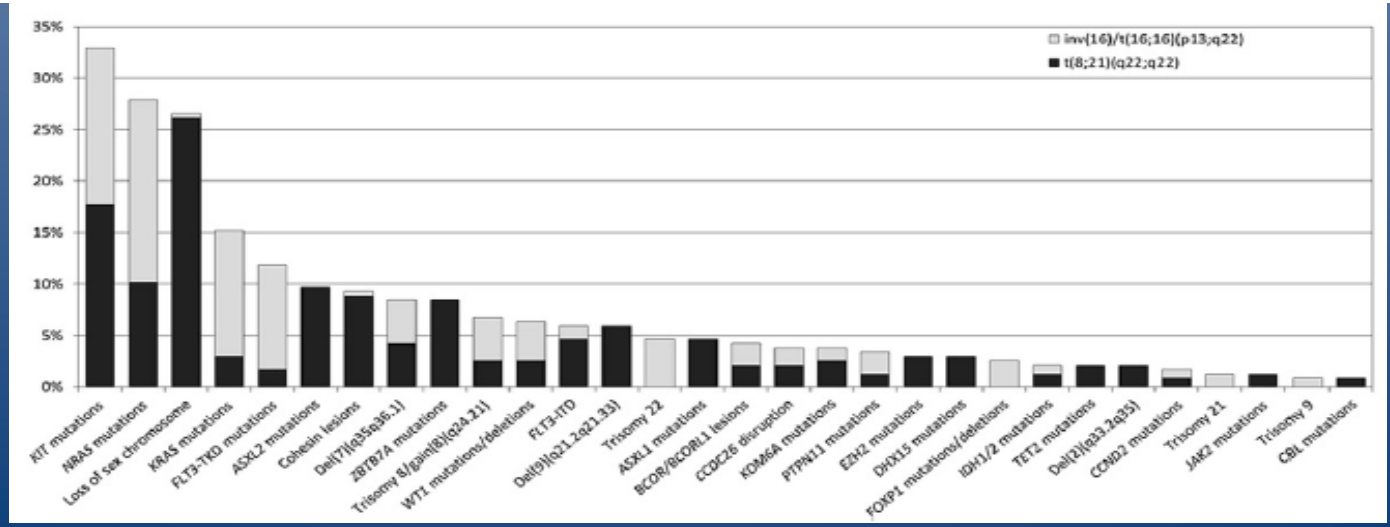



FIGURE 1. (A) Genetic Landscape and (B) Alterations Frequencies in Core-Binding Factor Acute
WARNING
significantly more favorable prognosis than FLT3 internal tandem duplications in
patients with acute myeloid leukemia
Adam J. Mead,[1] David C. Linch,[1] Robert K. Hills,[2] Keith Wheatley,[3] Alan K. Burnett,[2] and Rosemary E. Gale[1]
months
100
200
300
Trisomy 21
JAK2 mutations
Trisomy 9
CBL mutations

Journal of *Clinical Medicine*

MDPI

Review

Minimal Residual Disease in Acute Myeloid Leukemia: Still a Work in Progress?

Federico Mosna [1,*], Debora Capelli [2] and Michele Gottardi [3]

Molecular Markers	Frequency (% of All)	Occurrence in Leukemogenesis	Predictive Power for Clinical Relapse	Technique
Fusion products				
RUNX1/RUNX1T1	7–10%	Early	Very good	RT-qPCR
CBFB/MYH11	5–8%	Early	Very good	RT-qPCR

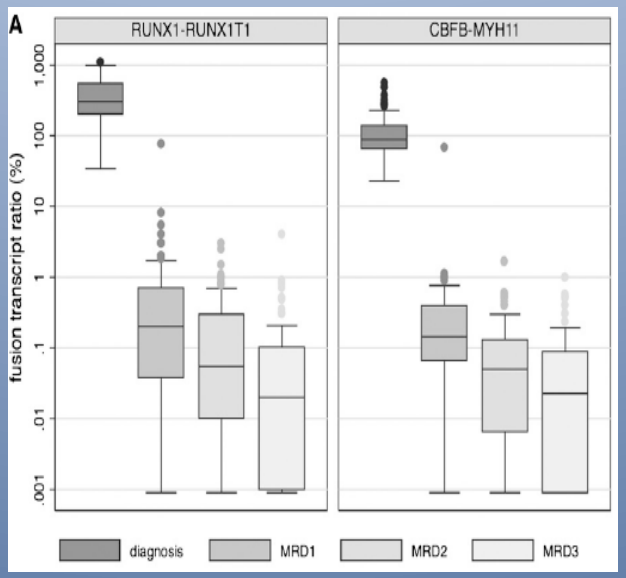
Table 2. Major ongoing clinical trials on Minimal Residual Disease in Acute Myeloid Leukemia in adults.

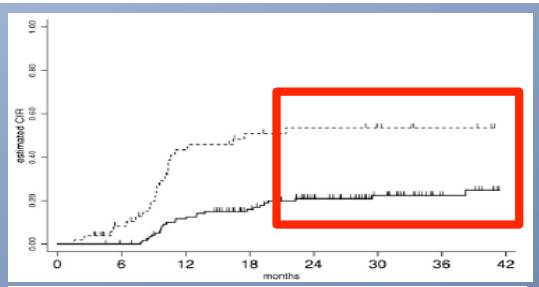
Trial	Nation	ID	MRD-Related Endpoints	Type	Age Limits
MRC *AML 17*	UK	ISRCTN55675535	Assess the prognostic value of minimal residual disease monitoring (randomization: monitoring vs. not monitoring)	Phase 3	<60 years
MRC *AML 19*	UK	ISRCTN31682779	Assess the prognostic value of minimal residual disease monitoring (randomization: monitoring vs. not monitoring)	Phase 3	18-60 years
MRC *AML 18*	UK	ISRCTN78449203	Treatment intensification in MRD+ patients after the first cycle, chemotherapy randomization	Phase 3	>60 years
GIMEMA *AML1310*	Italy	NCT01452646	MRD stratification of intermediate-risk karyotype; risk-adapted, MRD-directed therapy (autoSCT vs. SCT) after first consolidation	Phase 2	18-60 years
CETLAM *AML-03*	Spain	NCT01723657	MRD stratification of intermediate-risk karyotype; risk-adapted, MRD-directed therapy (autoSCT vs. SCT) after first consolidation	Phase 2	18-70 years
PETHEMA *LMA10*	Spain	NCT01296178	Risk-adapted, MRD-directed therapy(study arms not provided)	Phase 3	<65 years
PETHEMA	Spain	NCT00390715	Prospective study on the prognostic value of baseline cytogenetics and MRD monitoring	Observational (prospective)	<65 years
Nanfang Hospital of Southern Medical University, Guangzhou	China	NCT02870777	MRD-directed therapy for low- and intermediate-risk AML. Front-line allo-HSCT intensification is programmed for MRD+ patients	Phase 3	18-60 years
Rochester University	USA	NCT01311258	Identification by MPFC, among all MRD cells, of the clones eventually responsible for clinical relapse (LIC)	Observational (prospective)	>18 years
Az. Ospedaliera Città della Salute e della Scienza Torino	Italy	NCT02714790	Assess the prognostic role of MRD defined as BM expression of WT1	Observational (retrospective)	>18 years
Medical College of Wisconsin	USA	NCT02349178	Estimating the efficacy of Clofarabine, Cyclophosphamide and Etoposide in eliminating MRD in AML patients, otherwise in clinical remission, before allo-HSCT	Phase 2	<40 years
Technische Universitat of Dresden RELAZA2	Germany	EudraCT 2010-022388-37	5-Azacitidinetreatment of patients with MDS or AML with significant residual disease or an increase of MRD	Phase 2	>18 years
Ulm University	Germany	NCT01770158	Maintenance Therapy with Histamine Dihydrochloride and Interleukin-2 in AML MRD+ patients post consolidation therapy	Observational (prospective)	>18 years
Washington University	USA	NCT00863434	Clofarabine and Cytarabine in treating MRD+ (by MPFC) AML patients	Phase 2	18-75 years
Singapore General Hospital	Singapore	NCT00394381	Autologous Cytokine-induced Killer cell adoptive immunotherapy for MRD+ patients post autologous HSCT	Phase 1/2	12-75 years
Institute of Hematology & BloodDisease Hospital, Tianjin	China	NCT03021395	Efficacy of maintenance Decitabine (after consolidation chemotherapy) in clearing MRD in patients in clinical remission	Phase 1/2	14-55 years

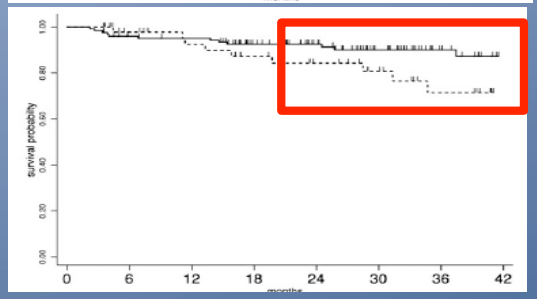
CLINICAL TRIALS AND OBSERVATIONS

Prospective evaluation of gene mutations and minimal residual disease in patients with core binding factor acute myeloid leukemia

Eric Jourdan,[1] Nicolas Boissel,[2] Sylvie Chevret,[3] Eric Delabesse,[4] Aline Renneville,[5] Pascale Cornillet,[6] Odile Blanchet,[7] Jean-Michel Cayuela,[2] Christian Recher,[4] Emmanuel Raffoux,[2] Jacques Delaunay,[8] Arnaud Pigneux,[9] Claude-Eric Bulabois,[10] Céline Berthon,[11] Cécile Pautas,[12] Norbert Vey,[13] Bruno Lioure,[14] Xavier Thomas,[15] Isabelle Luquet,[6] Christine Terré,[16] Philippe Guardiola,[17] Marie C. Béné,[18] Claude Preudhomme,[5] Norbert Ifrah,[17] and Hervé Dombret,[2] for the French AML Intergroup



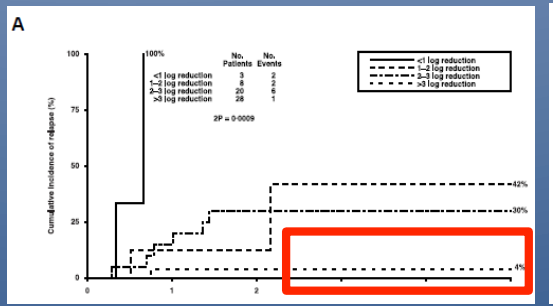


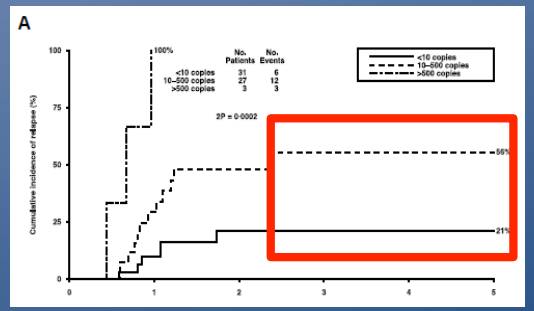


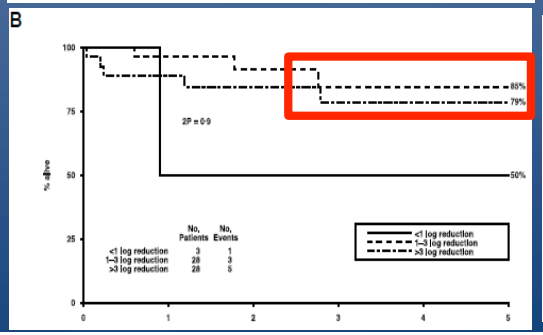
Minimal residual disease monitoring by quantitative RT-PCR in core binding factor AML allows risk stratification and predicts relapse: results of the United Kingdom MRC AML-15 trial

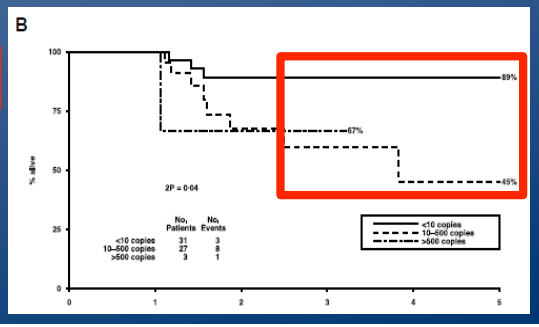
John A. Liu Yin,[1] Michelle A. O'Brien,[1] Robert K. Hills,[2] Sarah B. Daly,[1] Keith Wheatley,[3] and Alan K. Burnett[2]

[1]Department of Haematology, Manchester Royal Infirmary, Manchester, United Kingdom; [2]Department of Haematology, Cardiff University School of Medicine, Cardiff, United Kingdom; and [3]Clinical Trials Unit, University of Birmingham, Birmingham, United Kingdom









Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party

Gerrit J. Schuurhuis,[1] Michael Heuser,[2,*] Sylvie Freeman,[3,*] Marie-Christine Béné,[4] Francesco Buccisano,[5] Jacqueline Cloos,[1,6] David Grimwade,[7] Torsten Haferlach,[8] Robert K. Hills,[9] Christopher S. Hourigan,[10] Jeffrey L. Jorgensen,[11] Wolfgang Kern,[8] Francis Lacombe,[12] Luca Maurillo,[5] Claude Preudhomme,[13] Bert A. van der Reijden,[14] Christian Thiede,[15] Adriano Venditti,[5] Paresh Vyas,[16] Brent L. Wood,[17,18] Roland B. Walter,[17,19] Konstanze Döhner,[20,†] Gail J. Roboz,[21,†] and Gert J. Ossenkoppele[1]

Table 3. ELN recommendations for MRD assessment

	Recommendations
Flow cytometry	
1	Use the following markers in an MRD panel: CD7, CD11b, CD13, CD15, CD19, CD33, CD34, CD45, CD56, CD117, HLA-DR (backbone: CD45, CD34, CD117, CD13, CD33, forward scatter/sideward scatter)
5	We define molecular progression in patients with molecular persistence as an increase of MRD copy numbers ≥1 log10 between any 2 positive samples. Absolute copy numbers should be reported in addition to the fold increase to enable the clinician to make his/her own judgments.
6	We define molecular relapse as an increase of the MRD level of ≥1 log10 between 2 positive samples in a patient who was previously tested negative.
	The conversion of negative to positive MRD in PB or BM should be confirmed 4 wk after the initial sample collection in a second sample from both BM and PB. If MRD increases in the follow-up samples ≥1 log10, molecular relapse should be diagnosed.
2	MRD monitoring should be considered part of the standard of care for AML patients. Monitoring beyond 2 y of follow-up should be based on the relapse risk of the patient and decided individually. Patients with mutant NPM1, RUNX1-RUNX1T1, CBFB-MYH11, or PML-RARA should have molecular assessment of residual disease at informative clinical time points.
	During follow-up of patients with PML-RARA, RUNX1-RUNX1T1, CBFB-MYH11, mutated NPM1, and other molecular markers, we recommend molecular MRD assessment every 3 mo for 24 mo after the end of treatment in BM and in PB. Alternatively, PB may be assessed every 4-6 wk.
9	Patients with CBF AML should have an initial assessment of MRD after 2 cycles of chemotherapy, followed by serial measurements every 3 mo for at least the first 2 y after the end of treatment.

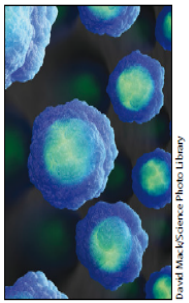
OPEN QUESTIONS

Renaissance of autologous stem cell transplantation for AML?

After intensive induction chemotherapy, 70–80% of young adult patients with newly diagnosed acute myeloid leukaemia (AML) achieve complete remission (CR); however, without additional treatment, most will relapse within a few months. Accordingly, the aim of post-remission treatment (PRT) is to eradicate residual disease, which persists after induction and is not detectable at examination of the bone marrow morphology.[1]

Three strategies are used to prevent relapse in patients with AML in first CR, including intensive chemoth
dose cyt

depends on two main factors—expected risk of relapse as determined by cytogenetic and molecular characteristics of leukaemic cells and expected morbidity and mortality associated with a specific option, according to age and comorbidities.[2] Sufficient evidence is available to suggest that allogeneic stem cell transplantation should not be used to treat patients in first CR who have favourable cytogenetics—ie, AML with t(8;21) translocation or inversion on chromosome 16, also known as core binding factor AML (CBF AML). Among the large group of patients who have a distinct prognostic
adults with AML and



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Acute Myeloid Leukemia With Translocation (8;21) or Inversion (16) in Elderly Patients Treated With Conventional Chemotherapy: A Collaborative Study of the French CBF-AML Intergroup

Thomas Prébet, Nicolas Boissel, Sarah Reutenauer, Xavier Thomas, Jacques Delaunay, Jean-Yves Cahn, Arnaud Pigneux, Bruno Quesnel, Francis Witz, Sylvain Thépot, Valérie Ugo, Christine Terre, Christian Recher, Emmanuelle Tavernier, Mathilde Hunault, Benjamin Esterni, Sylvie Castaigne, François Guilhot, Hervé Dombret, and Norbert Vey

Study design

Diagnosis:

De novo AML, Low-risk/Int-risk, 18-60 yrs

Induction

GO* 3mg/m2, D 1,4,7

DNR 60mg/m2, D 1-3

ARAC 200mg/m2, D 1-7

MRD assessment

By PCR in LR-AML

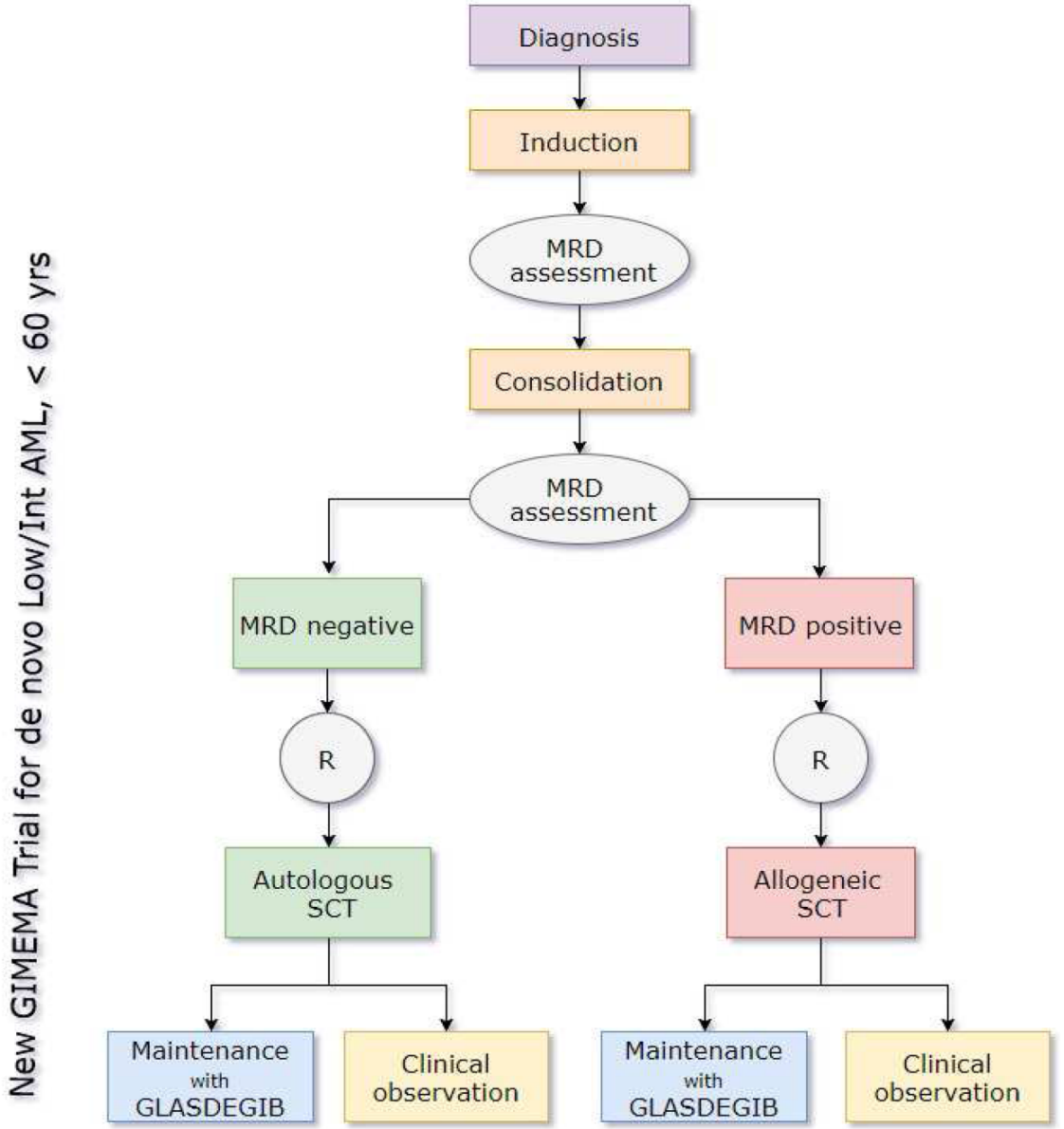
By flow in IR-AML

Consolidation

GO* 3mg/m2, D 1

DNR 50mg/m2, D 4-6

ARAC 500mg/m2/q12 hrs, D 1-6



“Le domande non sono mai indiscrete. Le risposte a volte lo sono”

1) La biologia delle CBF/AML ci invita all’intensificazione della terapia di prima linea

2) Gentuzumab-Ozogamicin si propone come la più importante “novità” per puntare a questo obiettivo

3) La biologia delle CBF/AML ci offre comunque bersagli per una possibile associazione con “target therapy”

4) La complessa biologia delle CBF/AML ci imporrà l’utilizzo sempre maggiore della MRD per una “tailored therapy” (mantenimento? alloSCT?)

5) Buono si ma dalla personalità complessa. Ancora molto da scoprire e cosa di meglio dei clinical trials?


E…..
GRAZIE DELL'ATTENZIONE