Leucémies aiguës myéloïdes
Stratégies d'induction chez l'adulte jeune

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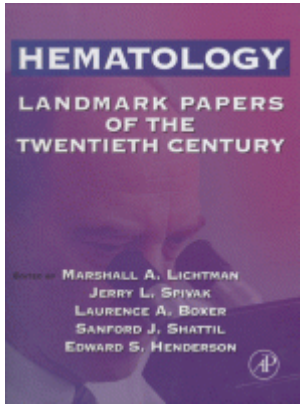
French Innovative Leukemia Organization (FILO)

Webinaire n°1 – 8 JANVIER 2021

Induction chemotherapy in AML



Commentary on and reprint of **Yates JW, Wallace HJ, Ellison RR, Holland JF, Cytosine arabinoside and daunorubicin therapy in acute nonlymphocytic leukemia, in *Cancer Chemotherapy Reports* (1973) 52:485–488**

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)
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)
• Intermediate-risk genetics	• Allogeneic HCT from matched-related or unrelated donor
	• 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), or
	• High-dose therapy and autologous HCT
• Adverse-risk genetics	• Allogeneic HCT from matched-related or unrelated donor
Older patients (>60/65 y)	
• Favorable-risk genetics	• 2-3 cycles of IDAC (500-1000 mg/m^2 IV over 3 h q12h, d1-3; or 500-1000 mg/m^2 IV over 3 h d1-5 or 6)
• Intermediate/adverse-risk genetics	• No established value of intensive consolidation therapy; consider allogeneic HCT in patients with low HCT-Comorbidity Index, or investigational therapy

The beginning of a new era in AML

2017
Midostaurine (FLT3)
CPX-351 (t-AML/MRC)
Enasidenib (IDH2)
Gemtuzumab ozogamycin (CD33)

2018
Ivosidenib (IDH1)
Gilteritinib (FLT3)
Venetoclax
Glasdegib

2020
CC-486 (azacitidine tablet)

FDA U.S. FOOD & DRUG ADMINISTRATION

Timeline of information required for decision making

Patient characteristics

Age
PS
Comorbidities
(fitness vs unfitness)

Geriatric assessment
« Cooling-off » period

Disease characteristics

Morphology
(CBF, NPM1, MRC?)
Flow cytometry
(CD33, CD34)

Conventional
cytogenetics
FISH

Targetable mutations
FLT3-ITD
FLT3-TKD
IDH1
IDH2
TP53

NGS
Myeloid gene panel

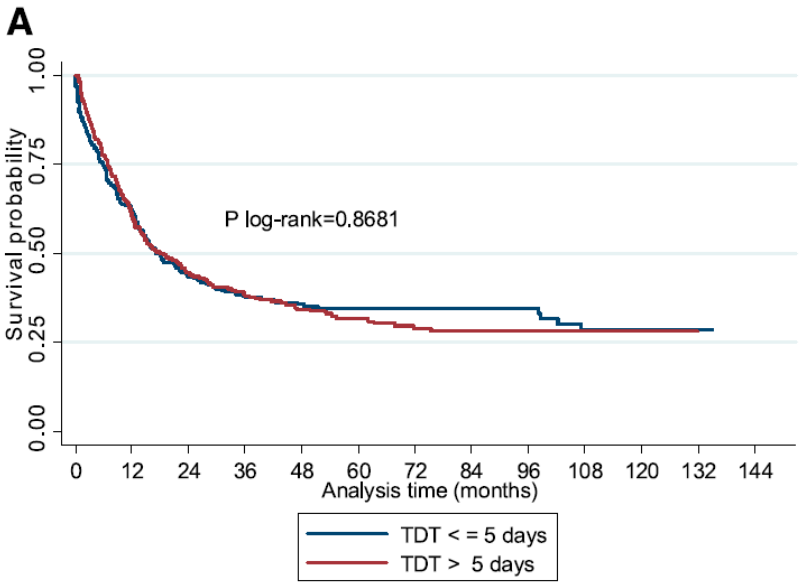
We can wait (a little while) for work-up results

blood

2013 121: 2618-2626
Prepublished online January 30, 2013;
doi:10.1182/blood-2012-09-454553

Time from diagnosis to intensive chemotherapy initiation does not adversely impact the outcome of patients with acute myeloid leukemia

Sarah Bertoli, Emilie Bérard, Françoise Huguet, Anne Huynh, Suzanne Tavitian, François Vergez, Sophie Dobbelstein, Nicole Dastugue, Véronique Mansat-De Mas, Eric Delabesse, Eliane Duchayne, Cécile Demur, Audrey Sarry, Valérie Lauwers-Cances, Guy Laurent, Michel Attal and Christian Récher

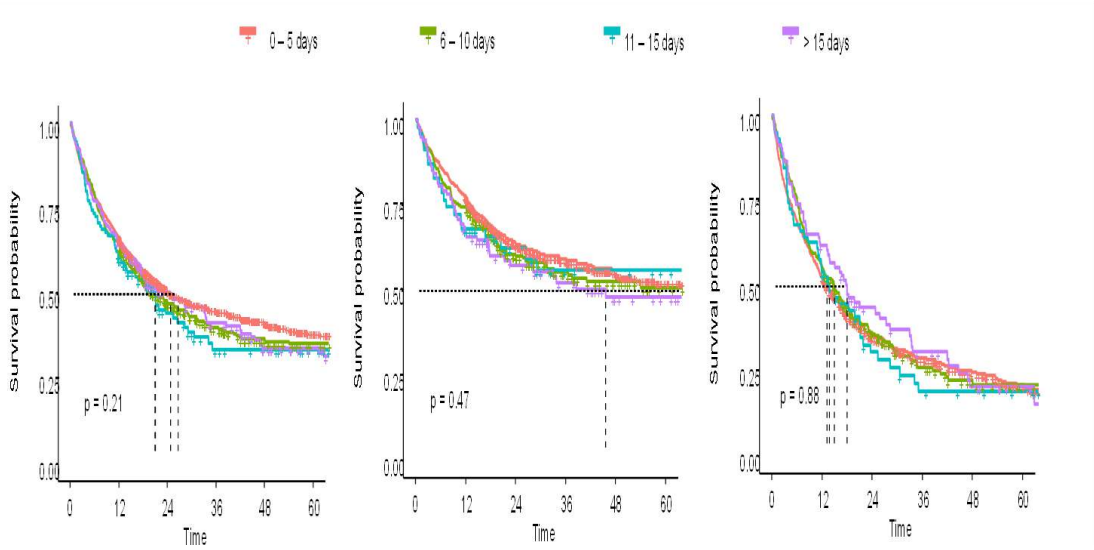


blood
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Does time from diagnosis to treatment affect the prognosis of patients with newly diagnosed acute myeloid leukemia?

Christoph Röllig,[1] Michael Kramer,[1] Christoph Schliemann,[2] Jan-Henrik Mikesch,[2] Björn Steffen,[3] Alwin Krämer,[4,5] Richard Noppeney,[6] Kerstin Schäfer-Eckart,[7] Stefan W. Krause,[8] Mathias Hänel,[9] Regina Herbst,[9] Volker Kunzmann,[10] Hermann Einsele,[10] Edgar Jost,[11] Tim H. Brümmendorf,[11] Sebastian Scholl,[12] Andreas Hochhaus,[12] Andreas Neubauer,[13] Kristina Sohlbach,[13] Lars Fransecky,[14] Martin Kaufmann,[15] Dirk Niemann,[16] Markus Schaich,[17] Norbert Frickhofen,[18] Alexander Kiani,[19] Frank Heits,[20] Ulrich Krümpelmann,[21] Ulrich Kaiser,[22] Johannes Kullmer,[23] Maxi Wass,[24] Friedrich Stölzel,[1] Malte von Bonin,[1] Jan Moritz Middeke,[1] Christian Thiede,[1] Johannes Schetelig,[1,25] Wolfgang E. Berdel,[2] Gerhard Ehninger,[1] Claudia D. Baldus,[14] Carsten Müller-Tidow,[4] Uwe Platzbecker,[26] Hubert Serve,[3] and Martin Bornhäuser[1]



Monocentric → Multicentric

Bertoli S, Blood 2013; Röllig C, Blood 2020

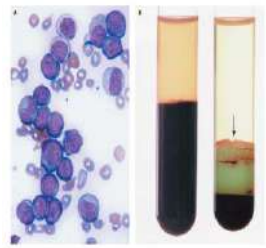
Focus on AML with hyperleukocytosis

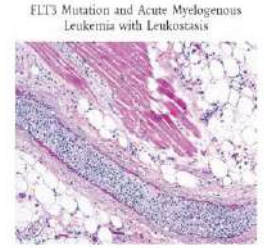
- 25% of AML have WBC > 50 G/L
- Leukostasis (lung, brain)
- Disseminated intravascular coagulation (DIC)
- Tumor lysis syndrome (TLS)

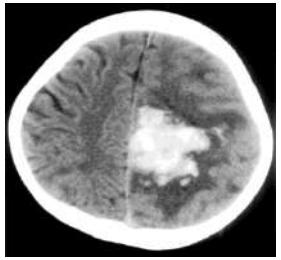
- High risk for early death

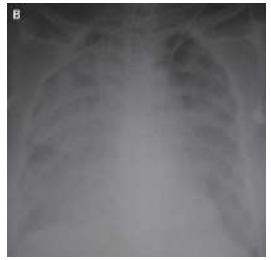
- Oncologic emergency
- Consider direct admission to ICU

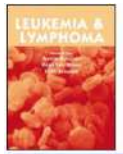
- Rapid cytoreduction (hydroxyurea, urgent induction chemotherapy, leukapheresis)
- TLS prevention: non alcaline hyperhydration, rasburicase
- DIC (platelet transfusions, fibrinogen, fresh frozen plasma)











Leukemia & Lymphoma

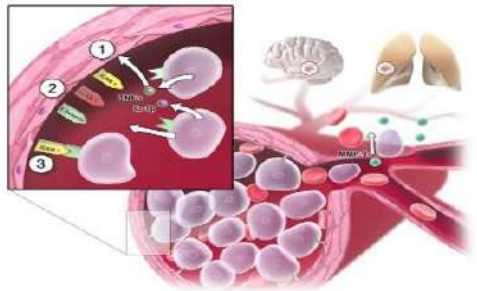
ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: http://www.tandfonline.com/loi/ilal20

Pre-treatment with oral hydroxyurea prior to intensive chemotherapy improves early survival of patients with high hyperleukocytosis in acute myeloid leukemia

Anne-Claire Mamez, Emmanuel Raffoux, Sylvie Chevret, Virginie Lemiale, Nicolas Boissel, Emmanuel Canet, Benoît Schlemmer, Hervé Dombret, Elie Azoulay & Etienne Lengliné

Rationale to use dexamethasone in hyperleukocytic AML

Mechanisms of leukostasis



DEXAMETHASONE

Downregulation of mediators of inflammation induced by leukemic blasts and endothelial cells

Reduced induction death rate?
Increased chemosensitivity?

Stucki A, Blood 2001
Rollig C, Blood 2015

Clinical experience

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Improved Outcome of Acute Promyelocytic Leukemia With High WBC Counts Over the Last 15 Years: The European APL Group Experience

All APL patients with WBCs >10 G /L received DEX 10mg/12 hours at day 1 of "3+7"+ATRA, for at least 3 days as prevention of differentiation syndrome.

Eur Respir J 2012; 39: 648–653
DOI: 10.1183/09031936.00057711

Dexamethasone in patients with acute lung injury from acute monocytic leukaemia

É. Azoulay*, E. Canet*, E. Raffoux#, E. Lengliné#, V. Lemiale*, F. Vincent*, A. de Labarthe#, A. Seguin*, N. Boissel#, H. Dombret# and B. Schlemmer*

Leukemia & Lymphoma, 2014; Early Online: 1–8
ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2014.887709

ORIGINAL ARTICLE: CLINICAL

Respiratory events at the earliest phase of acute myeloid leukemia

Anne-Sophie Moreau[1], Etienne Lengline[2], Amélie Seguin[3], Virginie Lemiale[1], Emmanuel Canet[1], Emmanuel Raffoux[2], Benoit Schlemmer[1] & Elie Azoulay[1]

Dexamethasone policy for hyperleukocytic patients in 2010

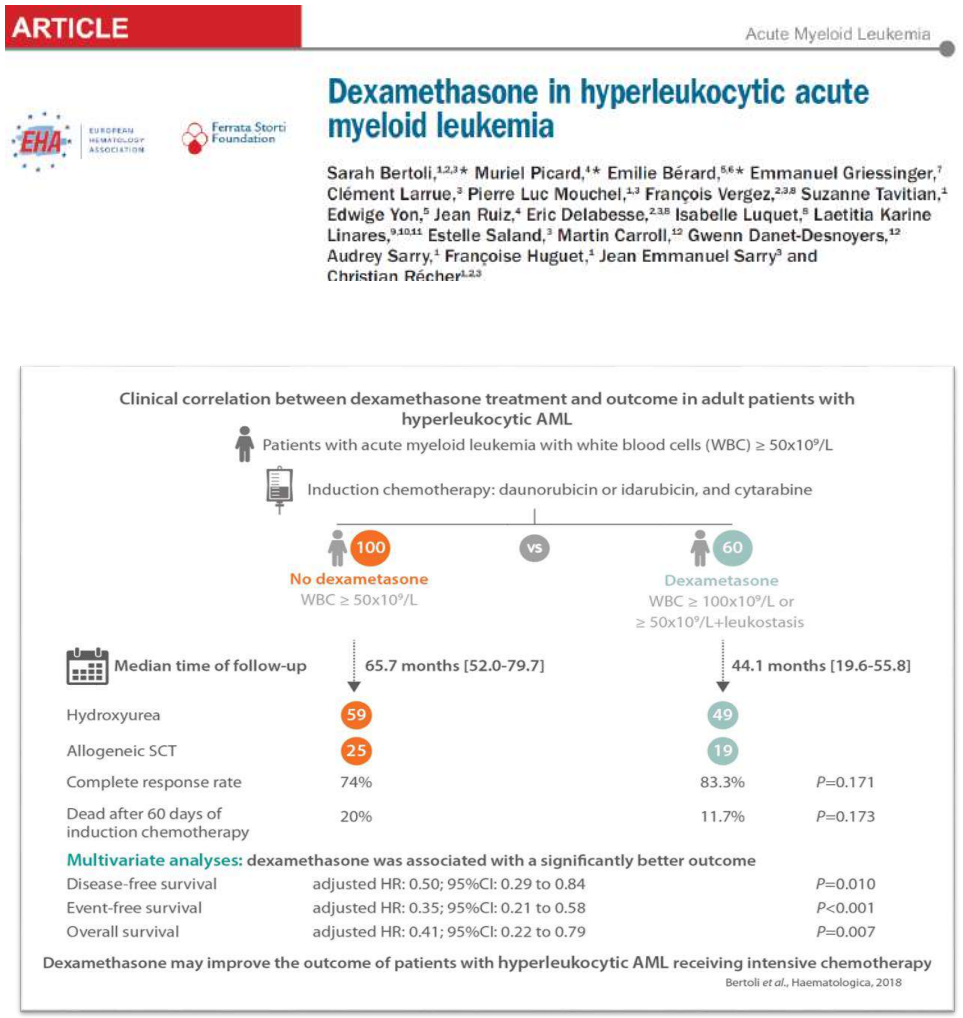
- **Patient selection:** WBC ≥ 100 x 10^9/L or 50 x 10^9/L with symptoms of leukostasis.

- **Induction chemotherapy:**
  - Daunorubicin (60-90 mg/m², 3d) or idarubicin (8 mg/m², 5d) + cytarabine 100-200 mg/m², 7 days.
  - Lomustine (200 mg/m² d1) added to idarubicin-cytarabine in most patients >60y.
  - Dexamethasone 10 mg b.i.d for 3 days systematically starting from 2010.

- Hydroxyurea (1.5-4 g/d).

- No leukapheresis.

- **Retrospective analysis: before (2004-2009) vs. after (2010-2015) the DEX policy (IUCT-Oncopole AML database)**



ARTICLE

Acute Myeloid Leukemia

Dexamethasone in hyperleukocytic acute myeloid leukemia

Sarah Bertoli,[1,2,3]* Muriel Picard,[4]* Emilie Bérard,[5,6]* Emmanuel Griessinger,[7] Clément Larrue,[3] Pierre Luc Mouchel,[1,3] François Vergez,[2,3,8] Suzanne Tavitian,[1] Edwige Yon,[5] Jean Ruiz,[4] Eric Delabesse,[2,3,8] Isabelle Luquet,[8] Laetitia Karine Linares,[9,10,11] Estelle Saland,[3] Martin Carroll,[12] Gwenn Danet-Desnoyers,[12] Audrey Sarry,[1] Françoise Huguet,[1] Jean Emmanuel Sarry[3] and Christian Récher[1,2,3]

Clinical correlation between dexamethasone treatment and outcome in adult patients with hyperleukocytic AML

Patients with acute myeloid leukemia with white blood cells (WBC) ≥ 50x10⁹/L

Induction chemotherapy: daunorubicin or idarubicin, and cytarabine

	100 No dexametasone WBC ≥ 50x10⁹/L	vs	60 Dexametasone WBC ≥ 100x10⁹/L or ≥ 50x10⁹/L+leukostasis	
Median time of follow-up	65.7 months [52.0-79.7]		44.1 months [19.6-55.8]	
Hydroxyurea	59		49	
Allogeneic SCT	25		19	
Complete response rate	74%		83.3%	*P*=0.171
Dead after 60 days of induction chemotherapy	20%		11.7%	*P*=0.173

Multivariate analyses: dexamethasone was associated with a significantly better outcome

Disease-free survival	adjusted HR: 0.50; 95%CI: 0.29 to 0.84	*P*=0.010
Event-free survival	adjusted HR: 0.35; 95%CI: 0.21 to 0.58	*P*<0.001
Overall survival	adjusted HR: 0.41; 95%CI: 0.22 to 0.79	*P*=0.007

Dexamethasone may improve the outcome of patients with hyperleukocytic AML receiving intensive chemotherapy

Bertoli *et al.*, Haematologica, 2018

Historique récent de la chimiothérapie des LAM (18-60 ans) en France

FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

GOELAMS Groupe Ouest-Est d'étude des Leucémies Aiguës et autres Maladies du Sang

ALFA Alfa Leukemia French Association

- **Induction conditionnelle**
  - DNR 60 mg/m² J1-3 ou IDA 8 mg/m² J1-5, cytarabine 200mg/m² J1-7 IVC
  - Si blastes J15 ≥ 5% : DNR 35 mg/m² ou IDA 8 mg/m² J17-18, cytarabine 1 g/m²/12h J17-20
- **Consolidation**
  - Mini-conso avec anthracyclines
  - HDAC avec anthracyclines
  - Autogreffe CSH

- **Induction séquentielle**
  - DNR 80 mg/m² **J1-3**, cytarabine 500 mg/m² IVC **J1-3** →Mitoxantrone 12 mg/m² **J8-9**, cytarabine 500 mg/m²/12h **J8-10**
- **Consolidation**
  - Mini-conso avec amsacrine
  - EMA (VP16-MTX-AraC séquentiel) puis HDAC

Induction séquentielle vs. « 3+7 »

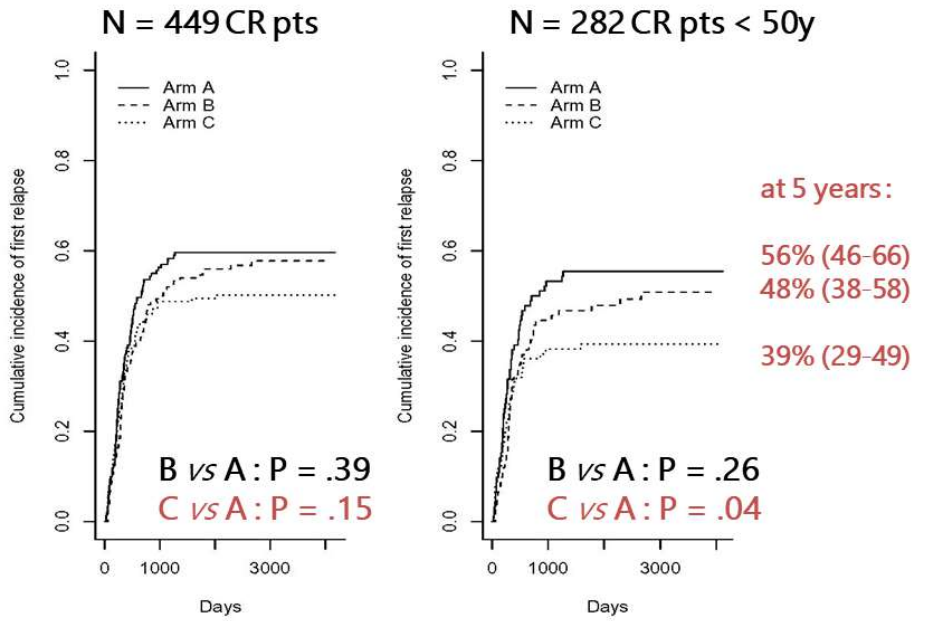
NEOPLASIA

Randomized comparison of double induction and timed-sequential induction to a "3 + 7" induction in adults with AML: long-term analysis of the Acute Leukemia French Association (ALFA) 9000 study

Sylvie Castaigne, Sylvie Chevret, Eric Archimbaud, Pierre Fenaux, Dominique Bordessoule, Hervé Tilly, Thierry de Revel, Marc Simon, Brigitte Dupriez, Michel Renoux, Maud Janvier, Jean-Michel Micléa, Xavier Thomas, Christian Bastard, Claude Preudhomme, Francis Bauters, Laurent Degos, and Hervé Dombret

	3+7	Double ind	Time Sequential	P value
N	197	198	197	
CR rate	77%	77%	74%	0.72
Neutropenia	25 days	37 days	30 days	<0.001
Severe infection	46	54	49	0.67
TRM (if age<50y)	8% (6%)	12%** (6%)	11% (7%)	0.38

NB: DNR 80 mg/m²



Castaigne et a., Blood 2004

Réduction du risque de rechute dans le sous-groupes des patients < 50 ans mais pas d'impact sur la survie globale

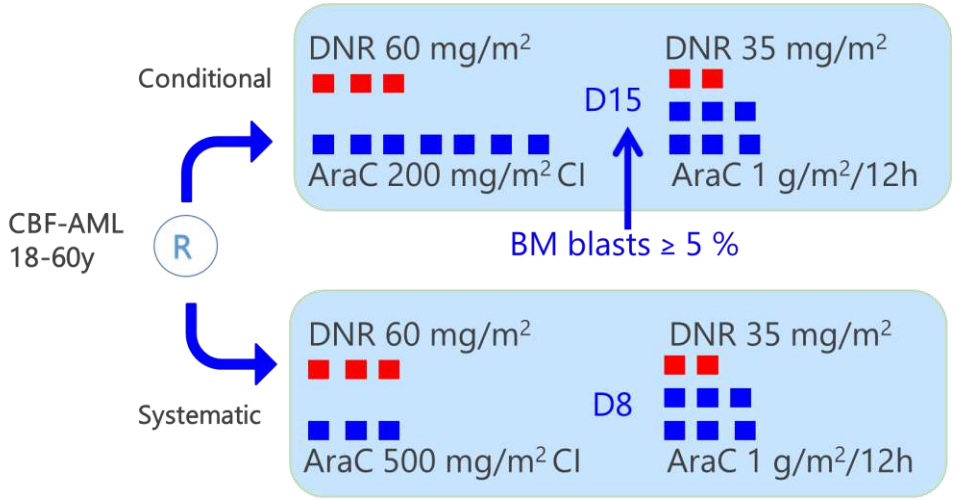
Induction séquentielle vs. conditionnelle

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

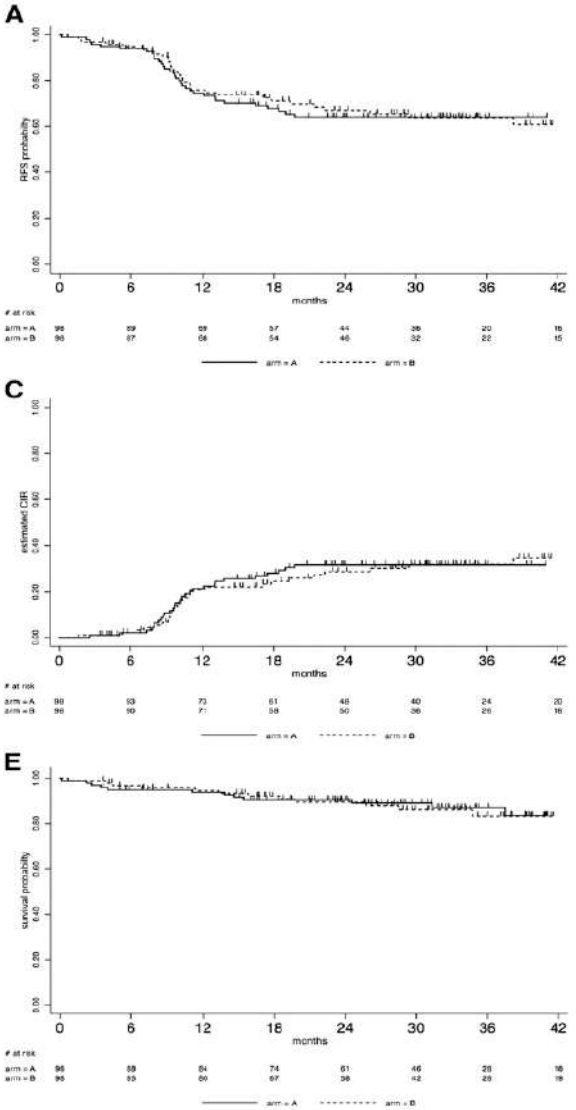
Prospective evaluation of gene mutations and minimal residual disease in patients with core binding factor acute myeloid leukemia

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



Key Points

- In adult patients with core binding factor AML, intensified induction is not associated with a better outcome in the context of intensive postremission therapy.
- Minimal residual disease, rather than *KIT* or *FLT3* gene mutations, should be used to identify core binding factor AML patients at higher risk of relapse.



Idarubicine *vs.* daunorubicine

Long-term results of a randomized phase 3 trial comparing idarubicin and daunorubicin in younger patients with acute myeloid leukaemia

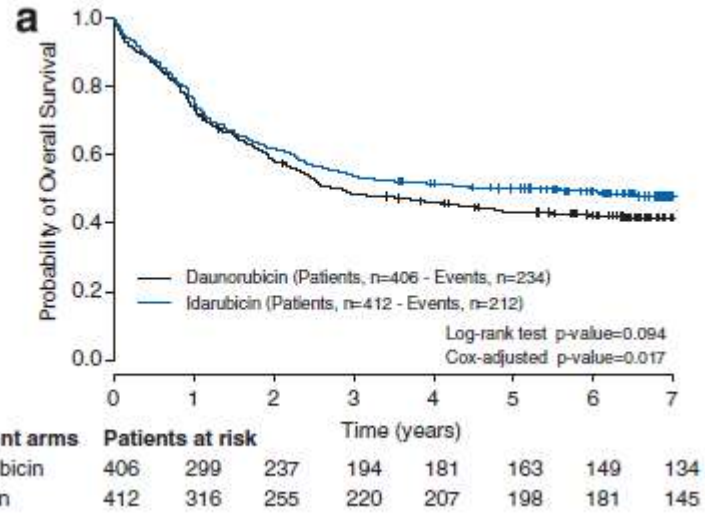
Leukemia (2014) **28,** 440–443; doi:10.1038/leu.2013.290

Récher C et al.

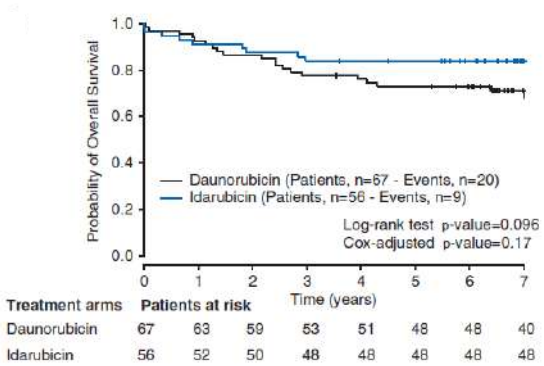
years, the Groupe Ouest-Est des Leucémies Aigues et autres Maladies du Sang (GOELAMS) conducted a phase 3 randomized

LAM-2001 trial (FILO, ex GOELAMS)

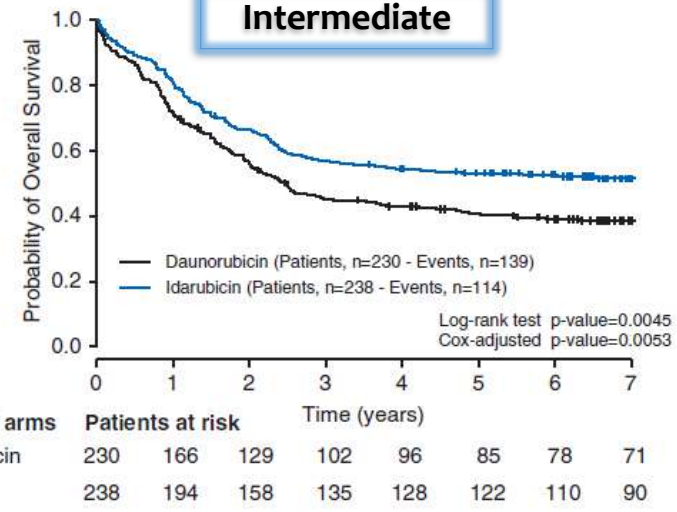
Daunorubicin : 60 mg/m² x 3d (total trial dose: 420-470 mg/m²)
vs. Idarubicin: 8 mg/m² x 5d (total trial dose: 88-104 mg/m²)
+cytarabine 200 mg/m²x7d



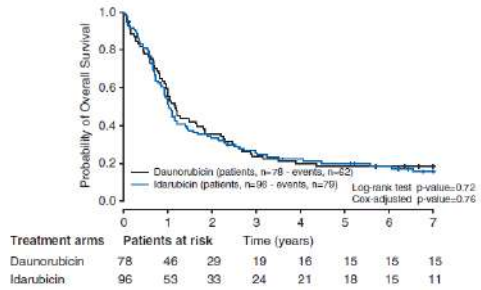
Favorable (CBF)



Intermediate



Unfavorable



Anthracycline intensification during induction

Daunorubicin 90 mg/m²x3 standard of care (<60y)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

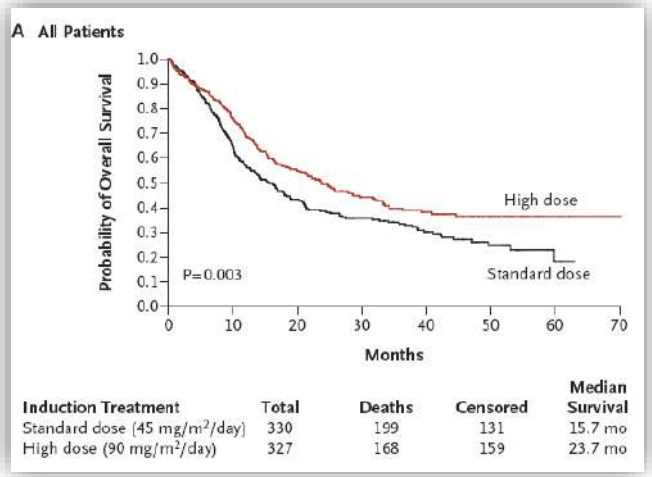
Anthracycline Dose Intensification in Acute Myeloid Leukemia

Hugo F. Fernandez, M.D., Zhuoxin Sun, Ph.D., Xiaopan Yao, Ph.D., Mark R. Litzow, M.D., Selina M. Luger, M.D., Elisabeth M. Paietta, Ph.D., Janis Racevskis, Ph.D., Gordon W. Dewald, Ph.D., Rhett P. Ketterling, M.D., John M. Bennett, M.D., Jacob M. Rowe, M.D., Hillard M. Lazarus, M.D., and Martin S. Tallman, M.D.

DNR 90 mg/m² vs. 45 mg/m²x 3 d1-d3
Ara-C IVC 100 mg/m² d1-d7

If d14 >5% second induction
DNR 45 mg/m² d1-d3
Ara-C IVC 100 mg/m² d1-d7

CR rate: 72% vs 57%



Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m²/day)	330	199	131	15.7 mo
High dose (90 mg/m²/day)	327	168	159	23.7 mo

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]

Key Points

- High-dose daunorubicin benefits AML patients with favorable and intermediate cytogenetics and with *FLT3*-ITD, *NPM1*, and *DNMT3A* mutations.
- High-dose daunorubicin is required for the favorable impact of the *NPM1* mutation in AML.

Main therapeutic changes over time (real world data)

- Anthracyclines (from 2010)
  - Dose intensification during induction (DNR 90mg/m²x3d or IDA 9mg/m²x5d)
  - No longer used during consolidation
  - Reduced total dose (DNR 420 vs 270 mg/m² or IDA 88 mg vs 45mg)
- Cytarabine (consolidation)
  - Dose adaptation according to age (1.5g/m² if >50y) (Lowenberg B, Blood 2013)

- Supportive care (new antifungals)
- Dexamethasone in hyperleukocytic AML (Bertoli S, Haematologica 2018)

- Molecular stratification in CR1 (NPM1, FTL3, CEBPA) guiding indications for allo-SCT

- More allogeneic-SCT in CR1
  - 2000-2004: 30% vs 50% in 2010-2014
- No more autologous-SCT
  - 2000-2004: 30% vs 2% in 2010-2014

Bertoli S, Blood Cancer Journal, 2017

Progress with the good old chemo before the era of novel drugs

Bertoli et al. Blood Cancer Journal (2017)7:635
DOI 10.1038/s41408-017-0011-1

Blood Cancer Journal

ARTICLE Open Access

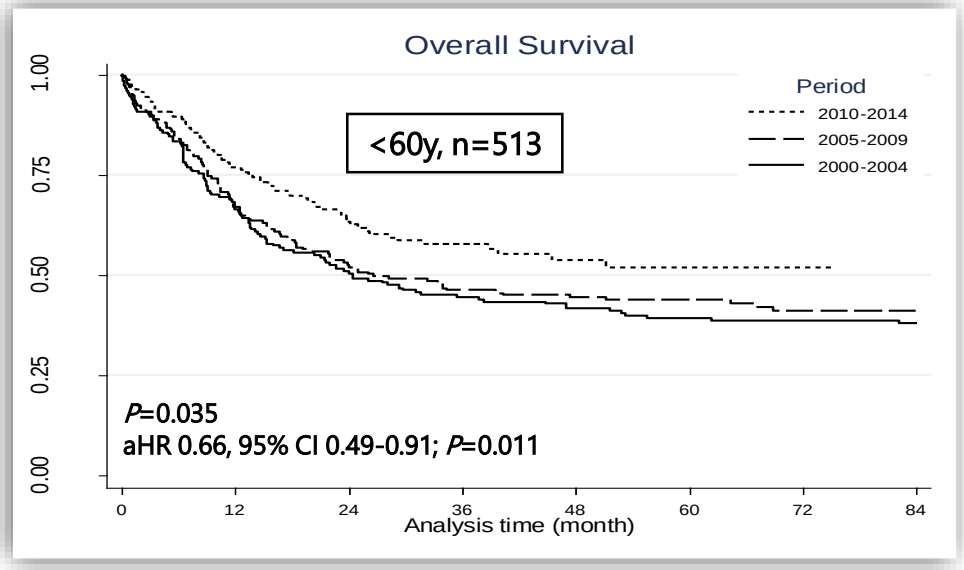
Improved outcome for AML patients over the years 2000–2014

TOULOUSE DATAML

2000-2014
N=1649 patients

- N=24 >2014
- N=28 APL (2010-)
- N=621 w/o intensive chemo

N=976 patients treated by intensive chemo
*513 patients < 60 y
*463 patients ≥ 60y



Multivariate analysis	HR	95% CI	P
2005-2009	0.94	0.72-1.24	0.676
2010-2014	0.66	0.49-0.91	0.011
Age ≥ 50y	1.27	1.00-1.62	0.057
Secondary AML	1.91	1.43-2.57	<0.001
Cytogenetic risk			
Intermediate	3.09	1.83-5.21	<0.001
Adverse	5.37	3.04-9.47	<0.001
WBC > 50 giga/L	1.58	1.18-2.10	0.002
Allo-SCT in CR1	0.66	0.49-0.89	0.006

Bertoli S, Blood Cancer Journal, 2017

Simplification of the chemo backbone in younger AML patients

(BIG-1 trial, ALFA-FILO French Intergroup)

- Induction
  - Daunorubicin 90 mg/m² d1-d3 (270 mg/m²) *vs.* idarubicin 9 mg/m² d1-d5 (45 mg/m²)
    - Midostaurin added in patients with *FLT3*-ITD/TKD
    - IDAC or HDAC as 2nd induction course if failure
- Consolidation
  - IDAC (1.5g/m²/12h x 3d) *vs.* HDAC (3g/m²/12h x 3d)
  - 3 cycles
- Allogeneic-SCT
  - After 1 IDAC/HDAC (high risk) or 2 IDAC/HDAC (intermediate risk)
  - MRD-guided

Nothing better than « 3+7 »

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Acute Myeloid Leukemia (AML): Different Treatment Strategies Versus a Common Standard Arm—Combined Prospective Analysis by the German AML Intergroup

Thomas Büchner, Richard F. Schlenk, Markus Schaich, Konstanze Döhner, Rainer Krahl, Jürgen Krauter, Gerhard Heil, Uiz Krug, Maria Cristina Sauerland, Achim Heinecke, Daniela Späth, Michael Kramer, Sebastian Scholl, Wolfgang E. Berdel, Wolfgang Hiddemann, Dieter Hoelzer, Rüdiger Hehlmann, Joerg Hasford, Verena S. Hoffmann, Hartmut Döhner, Gerhard Ehninger, Arnold Ganser, Dietger W. Niederwieser, and Markus Pfirrmann

Bras standard
Cytarabine 100 mg/m²/d (CIV), d1-7
Daunorubicin 60 mg/m², d3-5
2 cycles (C2 at d22)

VS.

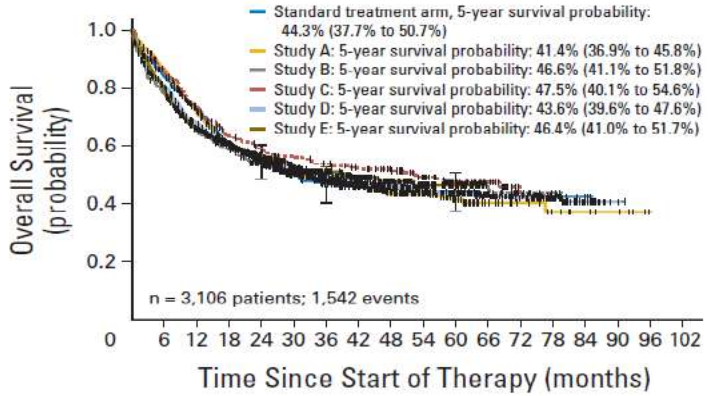
Study A
Double induction by two courses of the standard-dose cytarabine, idarubicin and etoposide (ICE)

Study B
High-dose cytarabine
(2 g/m² per day on days 1, 3, 5, and 7)

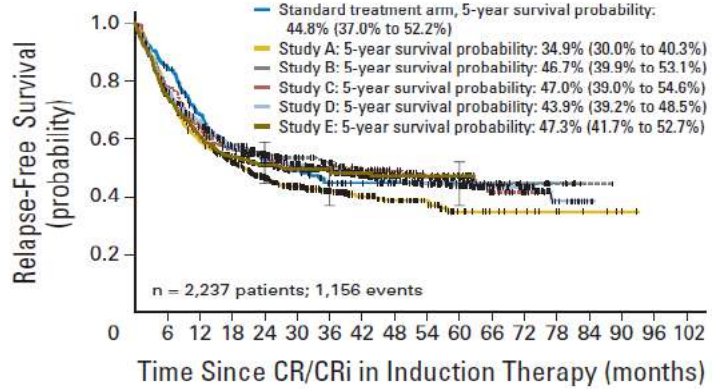
Study C
Double induction with standard-dose cytarabine combination and early consolidation by intermediate-dose cytarabine (1 g/m²/12 hours, d1-4) and daunorubicin

Study D
Thioguanine, cytarabine, and daunorubicin (TAD) and high-dose cytarabine and mitoxantrone (HAM) TAD-HAM, or HAM-HAM, with TAD based on standard-dose cytarabine (200mg/m²) and HAM based on high-dose cytarabine (3 g/m²/12h, d1-3).

Study E
Risk-adapted intensified versus a standard-intensity treatment strategy.



No. at risk							
Standard treatment arm	302	200	127	80	56	32	12
Study A	828	576	386	227	115	44	15
Study B	373	239	186	126	88	55	23
Study C	211	148	111	96	79	47	15
Study D	771	486	352	256	176	119	59
Study E	621	378	245	134	53	14	0



No. at risk							
Standard treatment arm	204	127	76	49	31	17	6
Study A	608	347	234	130	66	22	10
Study B	272	174	128	86	58	31	11
Study C	171	105	83	73	57	31	8
Study D	561	348	253	184	129	91	44
Study E	421	226	137	79	32	10	0

A third drug for high risk patients? The exemple of cladribine

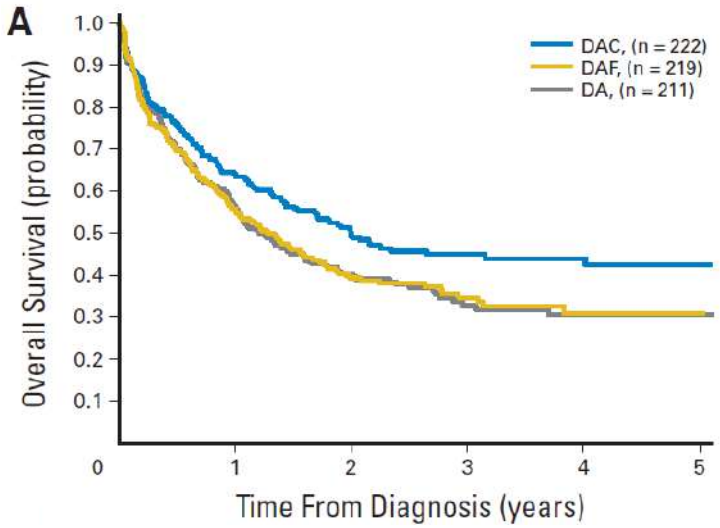
VOLUME 30 · NUMBER 20 · JULY 10 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

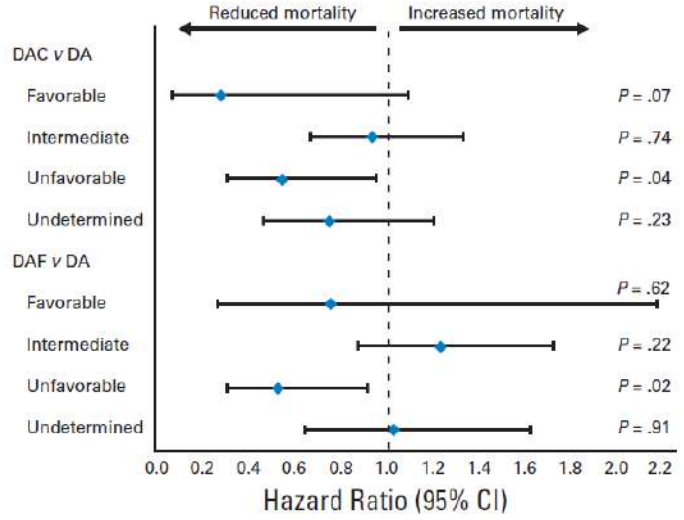
Cladribine, But Not Fludarabine, Added to Daunorubicin and Cytarabine During Induction Prolongs Survival of Patients With Acute Myeloid Leukemia: A Multicenter, Randomized Phase III Study

Jerzy Holowiecki, Sebastian Grosicki, Sebastian Giebel, Tadeusz Robak, Sławomira Kyrcz-Krzemien, Kazimierz Kuliczkowski, Aleksander B. Skotnicki, Andrzej Hellmann, Kazimierz Sulek, Anna Dmoszynska, Janusz Kloczko, Wiesław W. Jedrzejczak, Barbara Zdziarska, Krzysztof Warzocha, Krystyna Zawilska, Mieczysław Komarnicki, Marek Kielbinski, Beata Piatkowska-Jakubas, Agnieszka Wierzbowska, Malgorzata Wach, and Olga Haus

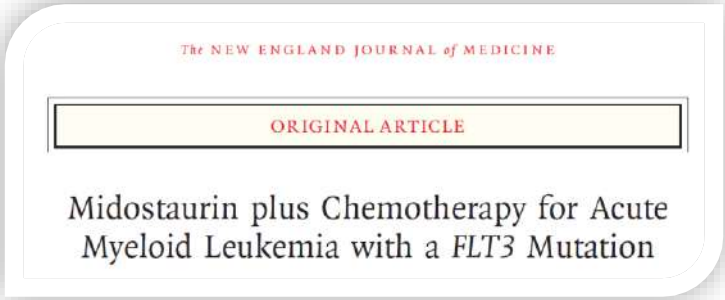
Induction
DA
DNR 60 mg/m² d1-3, AraC 200mg/m² d1-7
DAC
+Cladribine 5 mg/m² d1-5
DAF
+Fludarabine 25 mg/m² d1-5

Consolidation
AraC 1.5g/m² d1-3, mitoxantrone 10 mg/m² d3-5
AraC 2 g/m²/12h IV d1, 3, 5





Midostaurin for AML with *FLT3*-ITD/TKD mutation


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation

Arm 1:

Induction therapy

*Midostaurin 50mg oral twice daily d8-21
*Cytarabine 200mg/m² IV d1-7
*Daunorubicin 60mg/m² IV d1-3.

Consolidation therapy

*Midostaurin 50mg oral, twice daily d8-21
*Cytarabine 3,000mg/m²/12 h d1, 3, 5.
28 day cycle for up to 4 cycles.

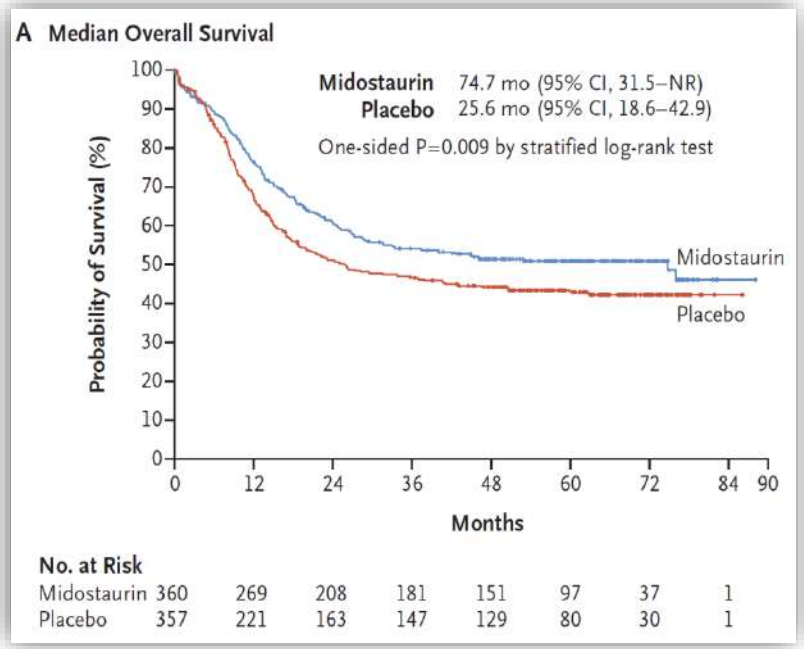
Continuation therapy

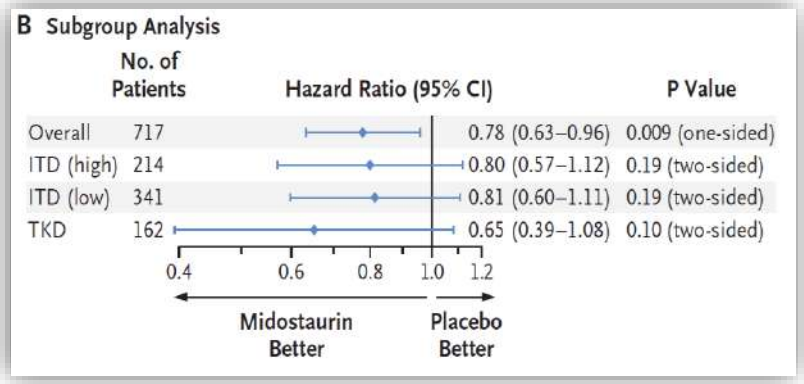
*Midostaurin 50mg oral, twice daily (twelve 28-day cycle).

Arm 2: Placebo

N=717 patients

TKD: 22.6%
ITD low: 47.6%
ITD high: 22.8%

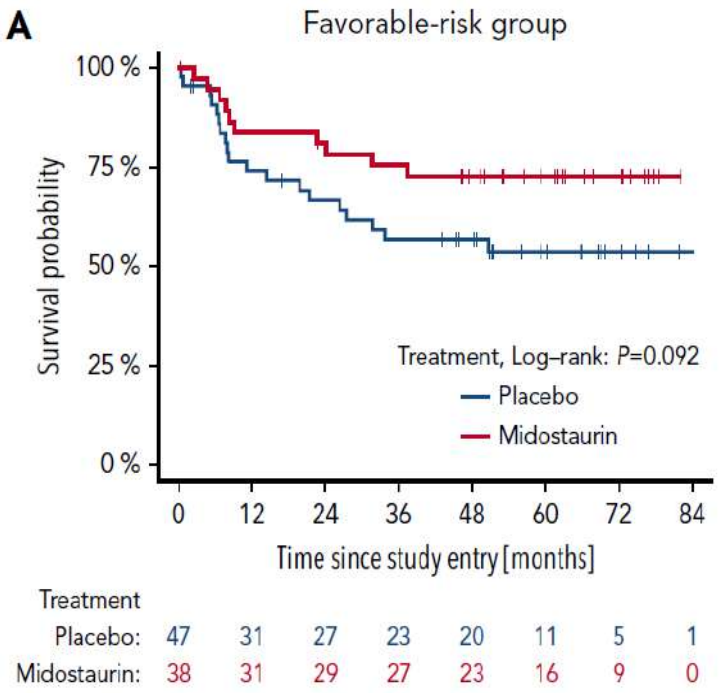




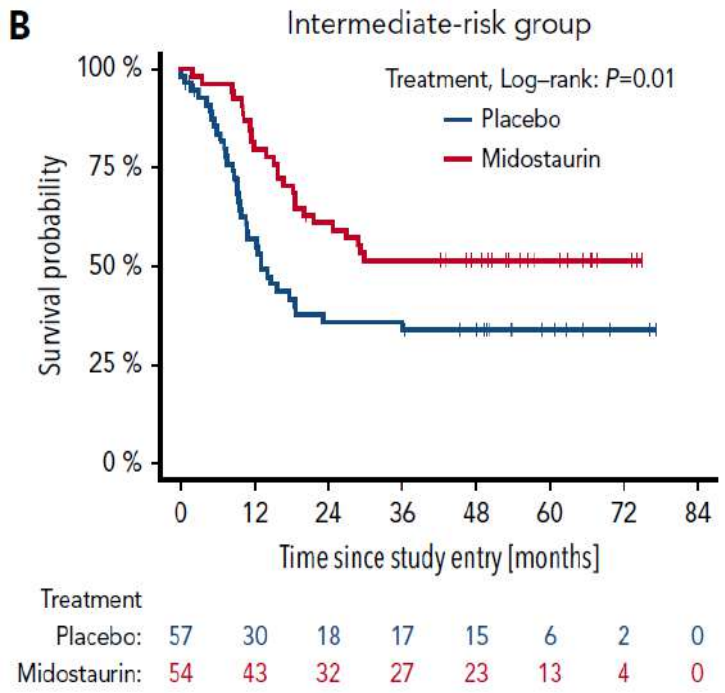
Stone R, NEJM 2017

Beneficial effect of midostaurin in *FLT3*-ITD AML across all 3 ELN risk groups

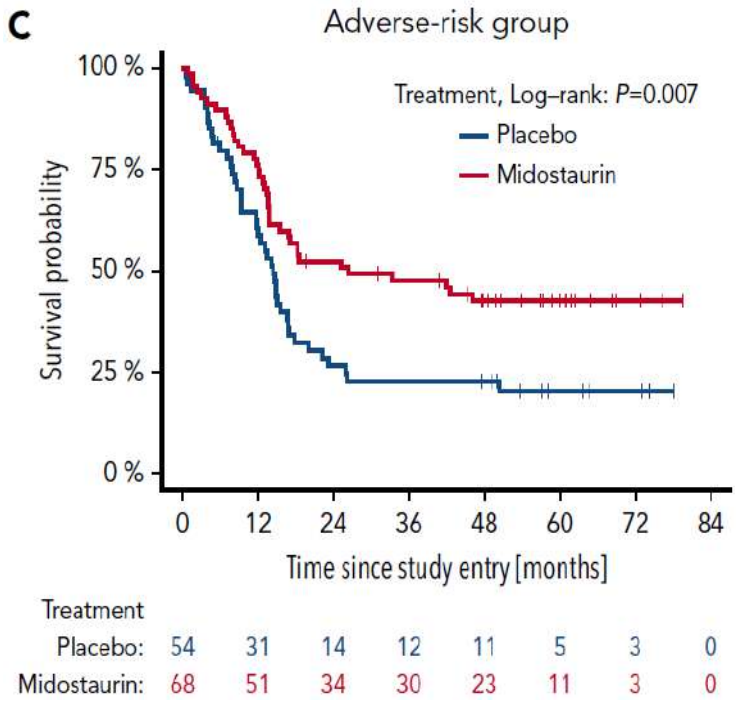
*Subgroup analysis of the RATIFY trial according to the **4 NPM1/FLT3-ITD** genotypes, considering the FLT3-ITD AR (low, 0.05-0.5; high, > 0.5), n=427*



NPM1mut/FLT3-ITDlow



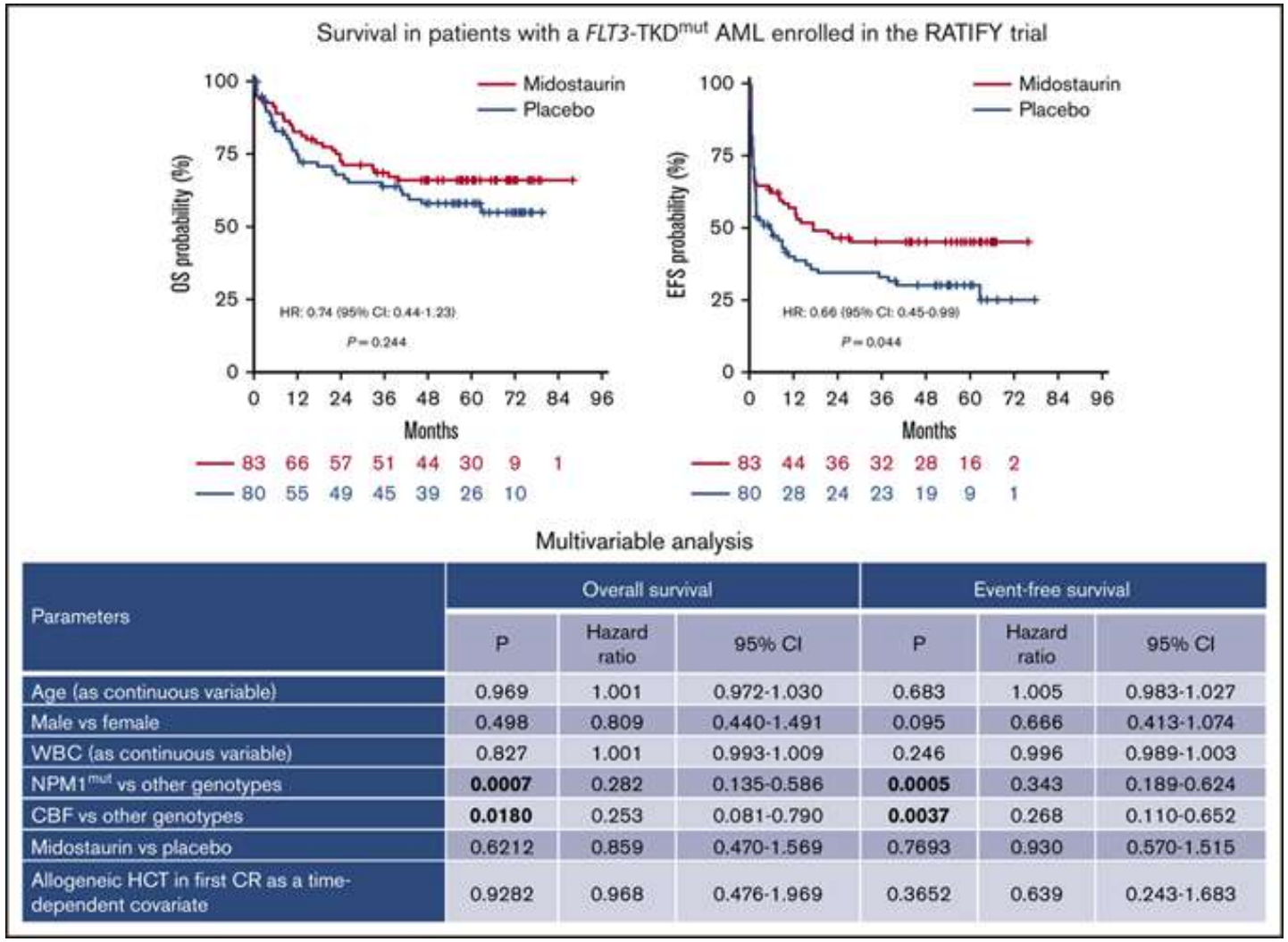
NPM1mut/FLT3-ITD high
NPM1wt/FLT3-ITD low



NPM1wt/FLT3-ITD high

Döhner K, Blood 2020

Beneficial effect of midostaurin in *FLT3*-TKD AML



Multivariable analysis

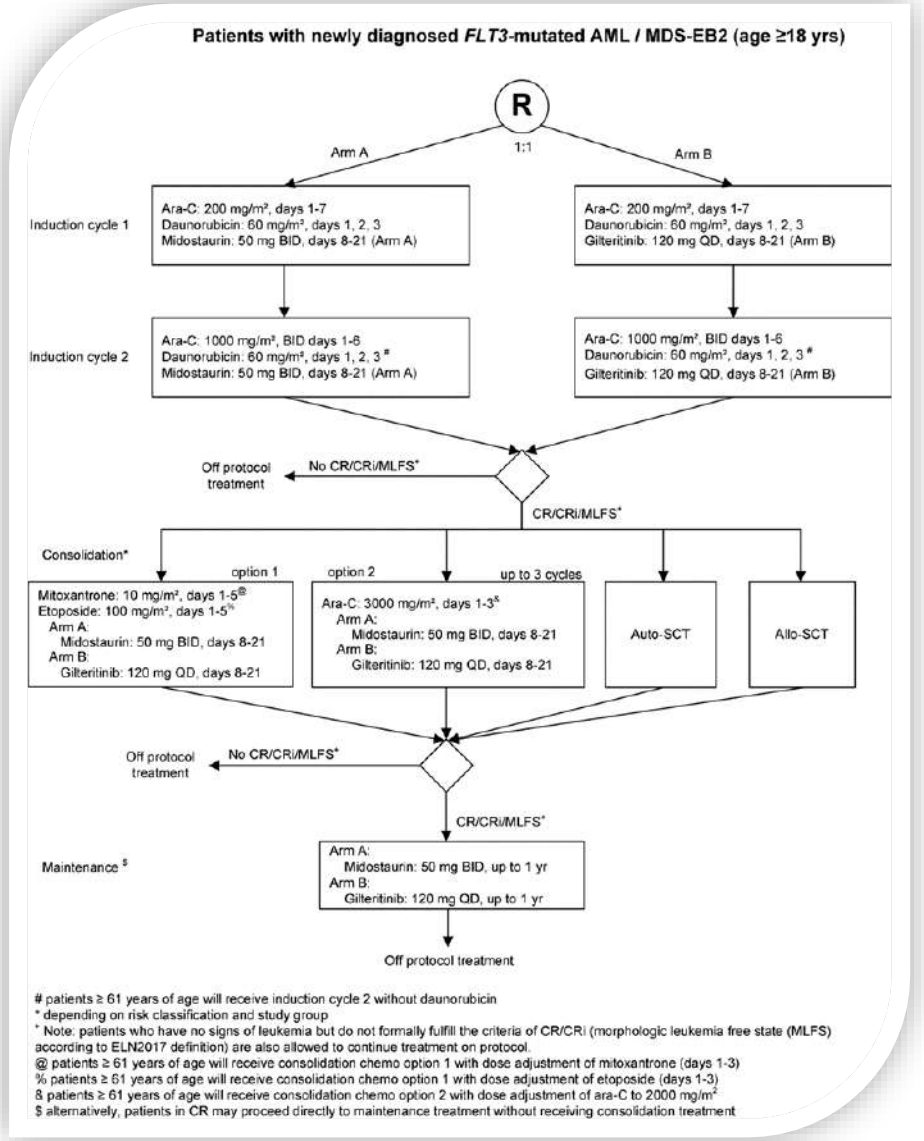
Parameters	Overall survival			Event-free survival		
	P	Hazard ratio	95% CI	P	Hazard ratio	95% CI
Age (as continuous variable)	0.969	1.001	0.972-1.030	0.683	1.005	0.983-1.027
Male vs female	0.498	0.809	0.440-1.491	0.095	0.666	0.413-1.074
WBC (as continuous variable)	0.827	1.001	0.993-1.009	0.246	0.996	0.989-1.003
NPM1^{mut} vs other genotypes	**0.0007**	0.282	0.135-0.586	**0.0005**	0.343	0.189-0.624
CBF vs other genotypes	**0.0180**	0.253	0.081-0.790	**0.0037**	0.268	0.110-0.652
Midostaurin vs placebo	0.6212	0.859	0.470-1.569	0.7693	0.930	0.570-1.515
Allogeneic HCT in first CR as a time-dependent covariate	0.9282	0.968	0.476-1.969	0.3652	0.639	0.243-1.683

Voso MT, Blood 2020

Gilteritinib vs. midostaurin in *FLT3*-mut AML

A phase 3, multicenter, open-label, randomized, study of gilteritinib versus midostaurin in combination with induction and consolidation therapy followed by one year maintenance in patients with newly diagnosed Acute Myeloid Leukemia (AML) or Myelodysplastic syndromes with excess blasts-2 (MDS-EB2) with FLT3 mutations eligible for intensive chemotherapy

HOVON 156 AML / AMLSG 28-18



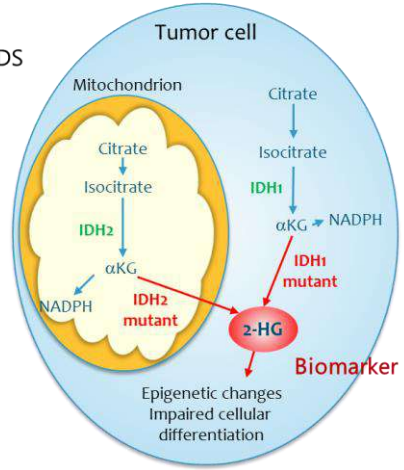
Other phase 3 trials

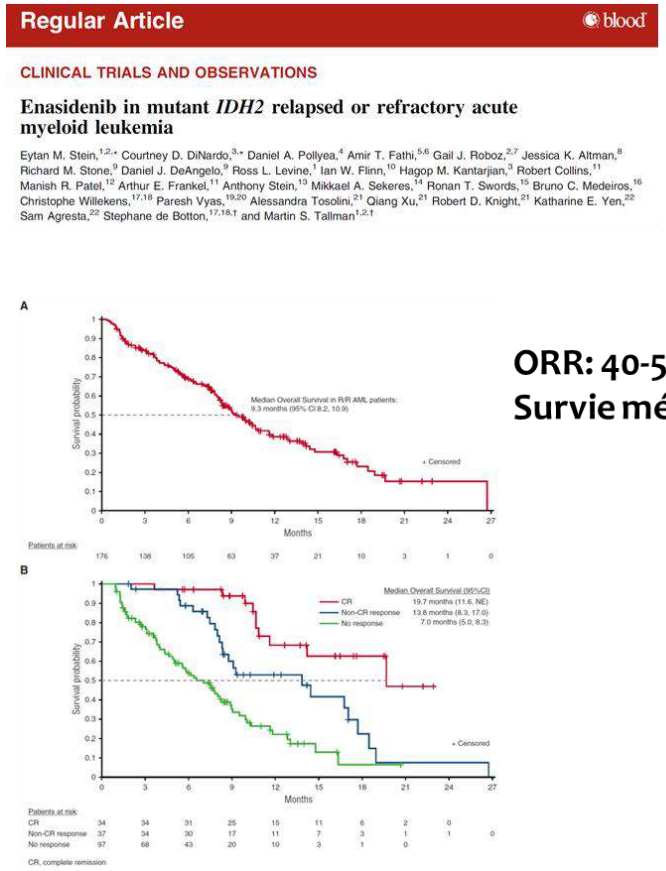
* QuANTUM-First NCT02668653
Induction, consolidation and maintenance with **quizartinib** vs placebo

* ARO-0212 NCT03258931
Crenolanib versus midostaurin in combination induction and consolidation therapy

IDH1 (ivosidenib) or IDH2 (enasidenib) inhibitors in R/R AML

- Isocitrate dehydrogenase (IDH) is a critical enzyme of the citric acid cycle
- IDH mutations occur in a spectrum of solid and hematologic tumors
  - IDH1 mutations: 6–10% of AML and 3% of MDS
  - IDH2 mutations: 9–13% of AML and 3–6% of MDS
- IDH1/2 mutations confer a gain-of-function:
  - production of **2-hydroxyglutarate (2-HG)**
  - Biomarker (Janin, JCO 2013)
- 2-HG drives multiple oncogenic processes:
  - increased histone and DNA methylation
  - impaired cellular differentiation




Regular Article

blood

CLINICAL TRIALS AND OBSERVATIONS

Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia

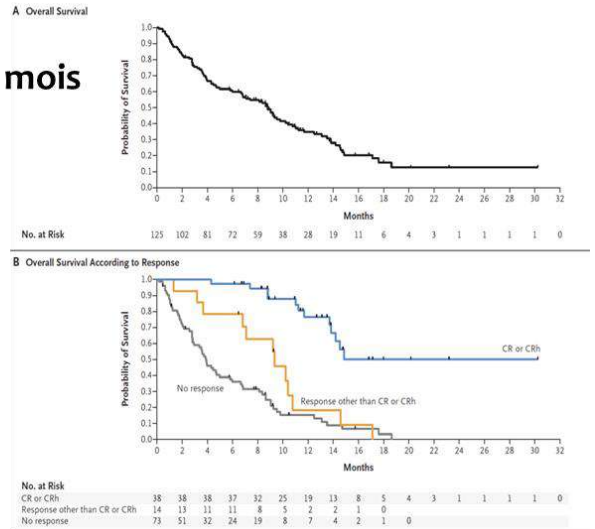
Eytan M. Stein,[1,2,*] Courtney D. DiNardo,[3,*] Daniel A. Pollyea,[4] Amir T. Fathi,[5,6] Gail J. Roboz,[2,7] Jessica K. Altman,[8] Richard M. Stone,[9] Daniel J. DeAngelo,[9] Ross L. Levine,[1] Ian W. Flinn,[10] Hagop M. Kantarjian,[3] Robert Collins,[11] Manish R. Patel,[12] Arthur E. Frankel,[11] Anthony Stein,[13] Mikkael A. Sekeres,[14] Ronan T. Swords,[15] Bruno C. Medeiros,[16] Christophe Willekens,[17,18] Paresh Vyas,[19,20] Alessandra Tosolini,[21] Qiang Xu,[21] Robert D. Knight,[21] Katharine E. Yen,[22] Sam Agresta,[22] Stephane de Botton,[17,18,†] and Martin S. Tallman[1,2,†]

ORR: 40-50%
Survie médiane: 9 mois

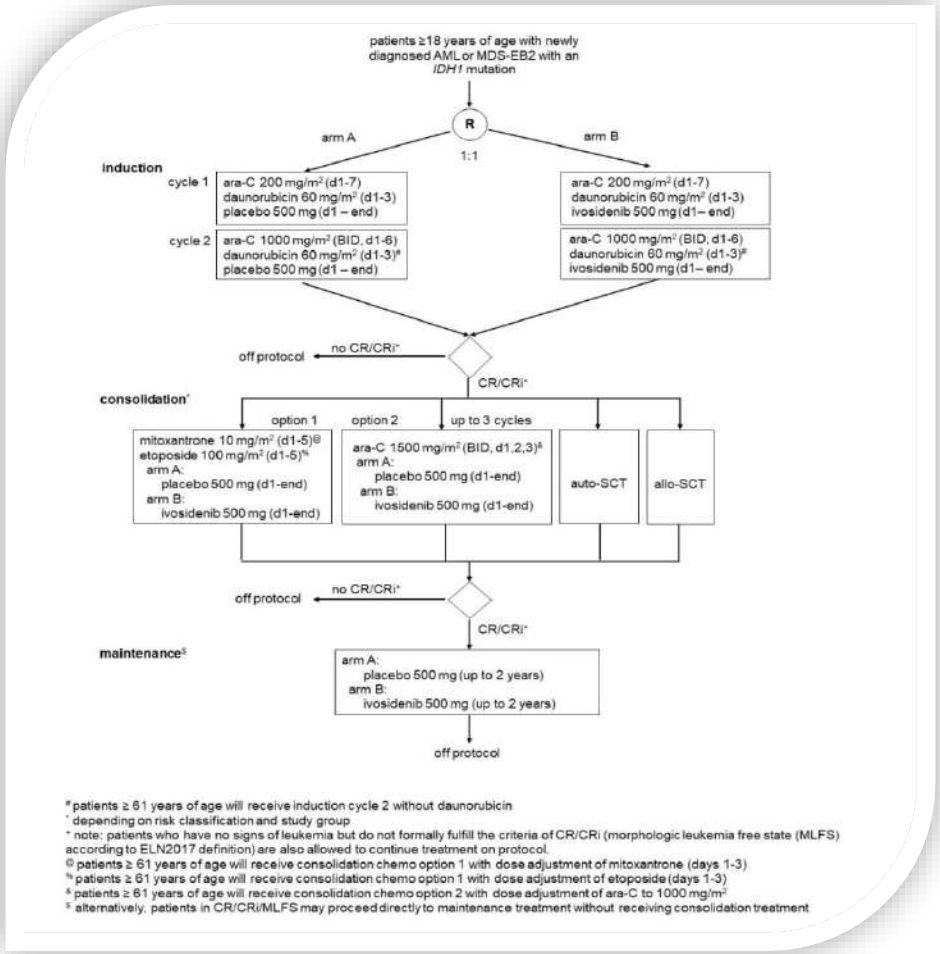
ORIGINAL ARTICLE

Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML

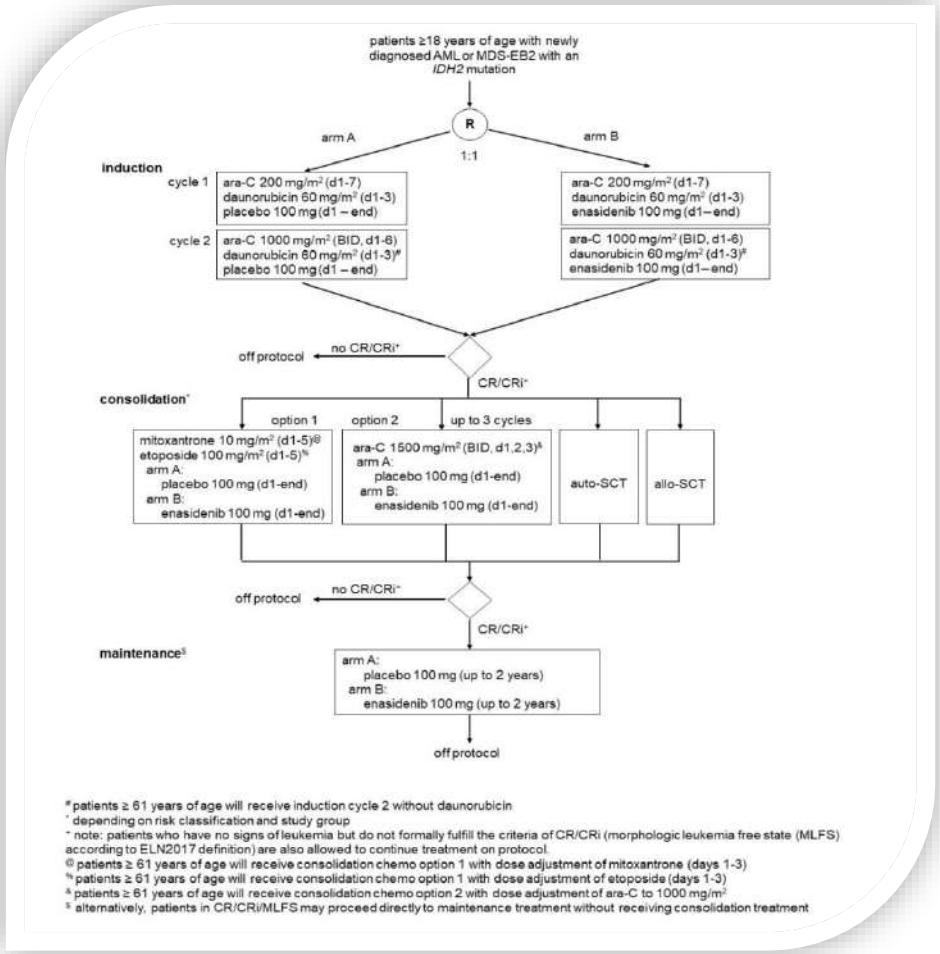
C.D. DiNardo, E.M. Stein, S. de Botton, G.J. Roboz, J.K. Altman, A.S. Mims, R. Swords, R.H. Collins, G.N. Mannis, D.A. Pollyea, W. Donnellan, A.T. Fathi, A. Pigneux, H.P. Erba, G.T. Prince, A.S. Stein, G.L. Uy, J.M. Foran, E. Traer, R.K. Stuart, M.L. Arellano, J.L. Slack, M.A. Sekeres, C. Willekens, S. Choe, H. Wang, V. Zhang, K.E. Yen, S.M. Kapsalis, H. Yang, D. Dai, B. Fan, M. Goldwasser, H. Liu, S. Agresta, B. Wu, E.C. Attar, M.S. Tallman, R.M. Stone, and H.M. Kantarjian



HOVON150/AMLSG 29-18 IDH1/2 AML



patients ≥ 61 years of age will receive induction cycle 2 without daunorubicin
* depending on risk classification and study group
* note: patients who have no signs of leukemia but do not formally fulfill the criteria of CR/CRi (morphologic leukemia free state (MLFS) according to ELN2017 definition) are also allowed to continue treatment on protocol.
@ patients ≥ 61 years of age will receive consolidation chemo option 1 with dose adjustment of mitoxantrone (days 1-3)
% patients ≥ 61 years of age will receive consolidation chemo option 1 with dose adjustment of etoposide (days 1-3)
& patients ≥ 61 years of age will receive consolidation chemo option 2 with dose adjustment of ara-C to 1000 mg/m²
$ alternatively, patients in CR/CRi/MLFS may proceed directly to maintenance treatment without receiving consolidation treatment



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Addition of Gemtuzumab ozogamycin (GO) to « 3+7 »

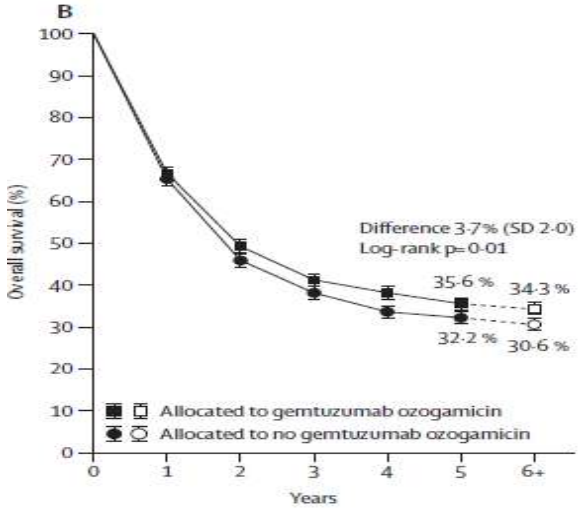
Lancet Oncol 2014

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

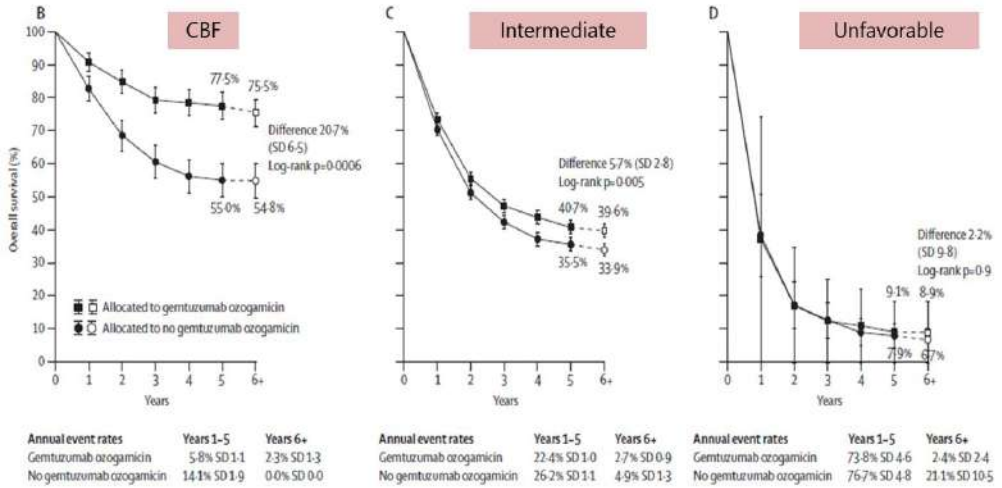
Robert K Hills, Sylvie Castaigne, Frederick R Appelbaum, Jacques Delaunay, Stephen Petersdorf, Megan Othus, Elihu H Estey, Hervé Dombret, Sylvie Chevret, Norbert Ifrah, Jean-Yves Cahn, Christian Récher, Lucy Chilton, Anthony V Moorman, Alan K Burnett

MRC AML15: 3 mg/m²
NCRI AML16: 3 mg/m²
ALFA 07-01: 3 mg/m²x3 (FDA/EMA approved)
GOELAMS AML-IR2006: 6 mg/m²
SWOG 01-06: 6 mg/m²

Addition of GO:
* no ↑ CR rate: OR 0.91; P=0.3
* did not increase mortality: OR 1.13; P=0.4
* improved survival: OR 0.89; P=0.01
* reduced relapse: OR 0.81; P=0.001
* improved survival: OR 0.90; P=0.01
* highly significant survival benefit for favorable risk (OR 0.47; P=0.006)



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	26·7 % SD 0·8	3·5 % SD 0·8
No gemtuzumab ozogamicin	29·5 % SD 0·9	5·2 % SD 1·0

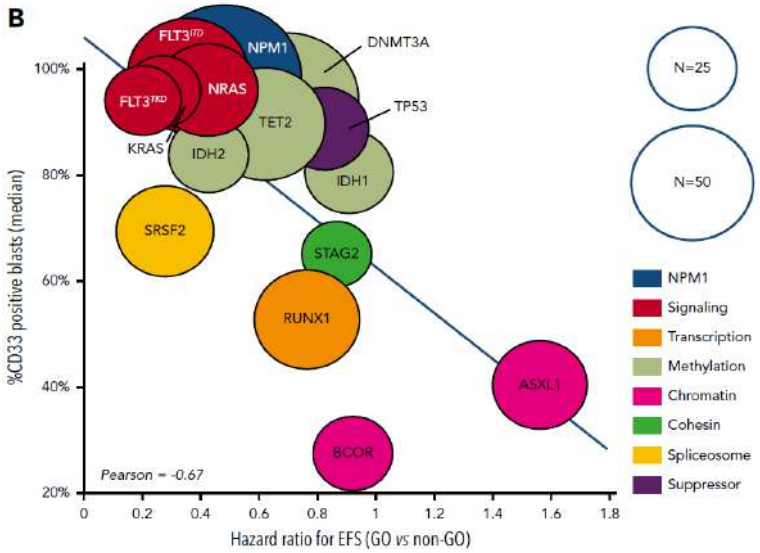


Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

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

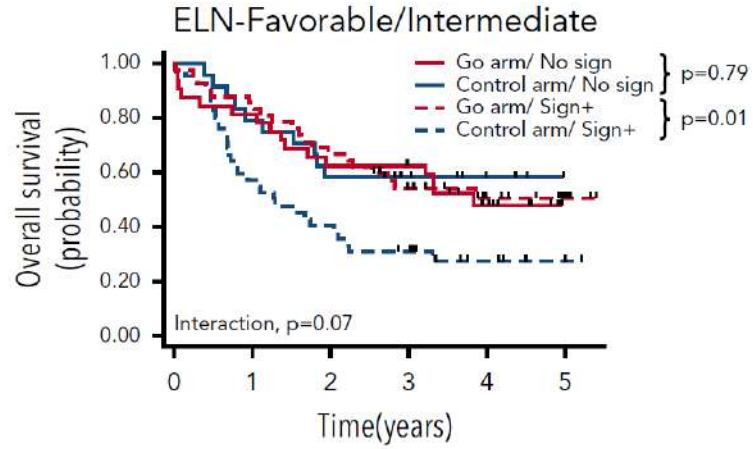
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

Mutational profile and GO benefit (ALFA-0701, 50-70y)

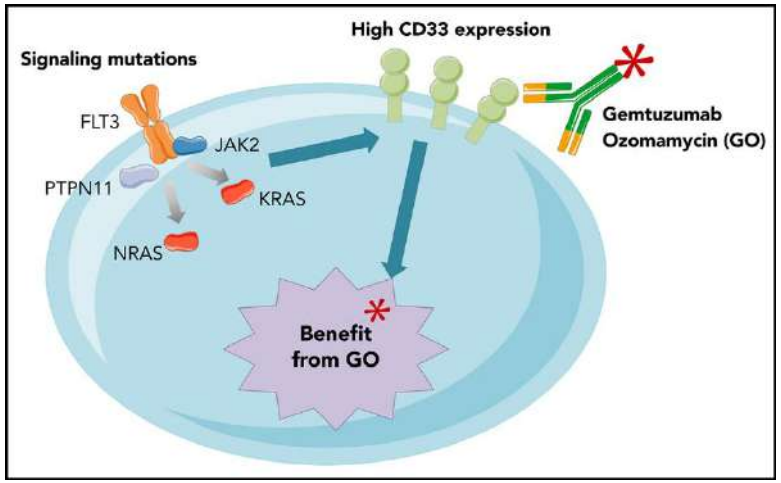


KEY POINTS

- **The benefit of GO in non-CBF AML patients with favorable or intermediate ELN 2017 risk is restricted to those with signaling mutations.**
- **Higher CD33 expression levels on non-CBF AML blasts correlate with the presence of activating signaling mutations.**



Number at risk						
Control arm/No sign	24	19	14	7	3	0
Control arm/Sign+	42	24	17	12	5	1
Go arm/No sign	32	26	20	19	10	0
Go arm/Sign+	42	36	28	18	11	4



Fournier E, Blood 2020

GO in AML with *NPM1* mutation

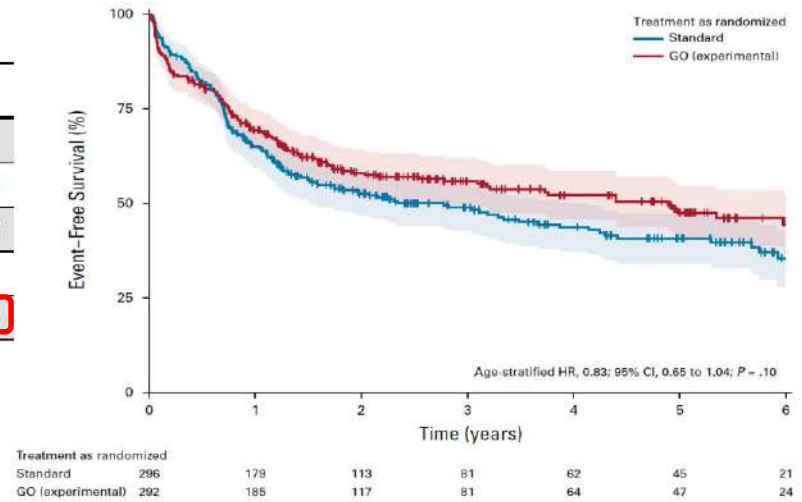
original reports

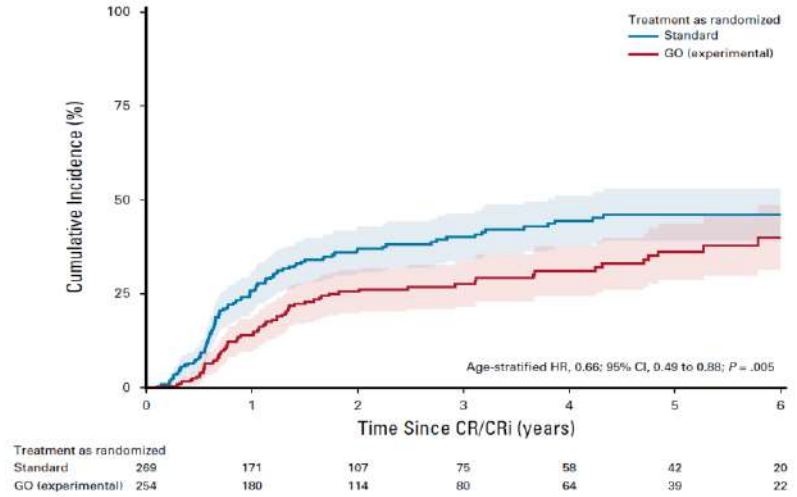
Gemtuzumab Ozogamicin in *NPM1*-Mutated Acute Myeloid Leukemia: Early Results From the Prospective Randomized AMLSG 09-09 Phase III Study

Richard F. Schlenk, MD[1-3]; Peter Paschka, MD[1]; Julia Krzykalla, MSc[4]; Daniela Weber, MSc[1]; Silke Kapp-Schwoerer, MD[1]; Verena I. Gaidzik, MD[1]; Claudia Leis, BSc[1]; Walter Fiedler, MD[5]; Thomas Kindler, MD[6]; Thomas Schroeder, MD[7]; Karin Mayer, MD[8]; Michael Lübbert, MD[9]; Mohammed Wattad, MD[10]; Katharina Götze, MD[11]; Heinz A. Horst, MD, PhD[12]; Elisabeth Koller, MD[13]; Gerald Wulf, MD[14]; Jan Schleicher, MD[15]; Martin Bentz, MD[16]; Richard Greil, MD[17]; Bernd Hertenstein, MD, PhD[18]; Jürgen Krauter, MD[19]; Uwe Martens, MD[20]; David Nachbaur, MD[21]; Maisun Abu Samra, MD[22]; Michael Girschikofsky, MD[23]; Nadezda Basara, MD, DSc[24]; Axel Benner, Dipl-Stat[4]; Felicitas Thol, MD[25]; Michael Heuser, MD[25]; Arnold Ganser, MD[25]; Konstanze Döhner, MD[1]; and Hartmut Döhner, MD[1]

TABLE A1. Response to Induction Therapy

Response	No. of Patients (%)	
	Standard Arm	GO Arm
All patients[a]	296	292
CR	163 (55.1)	134 (45.9)
CRi	100 (33.8)	116 (39.7)
RD	16 (5.4)	12 (4.1)
Deaths	17 (5.7)	30 (10.3)





Induction therapy (2 cycles of ICE+ATRA +/- GO)

*GO, 3 mg/m^2 d1

*Idarubicin 12 mg/m^2 IV d1, 3, and 5
[in cycle 2 and for patients > 60y, reduced to d1 and 3]

*Cytarabine 100 mg/m^2 continuously IV d1-7

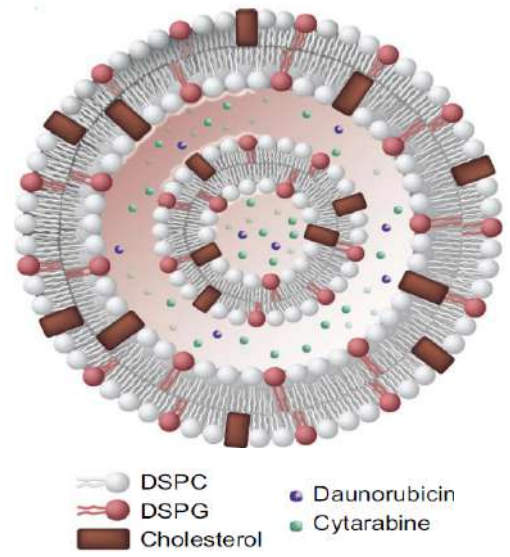
*Etoposide 100 mg/m^2 IV on days 1 to 3
[in cycle 2 and for patients>60y, reduced to d1 and 3]

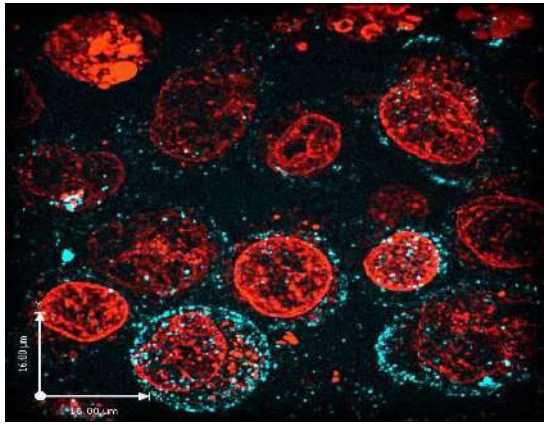
*ATRA (45 mg/m^{2}orally [PO] on d6 to 8 and 15 mg/m^2 PO on d9 to 21

Consolidation therapy

*HDAC/IDAC (>60y) + ATRA (3 cycles)
*GO 3 mg/m^2, d1 of consolidation 1

CPX-351: a new way to deliver intensive chemotherapy

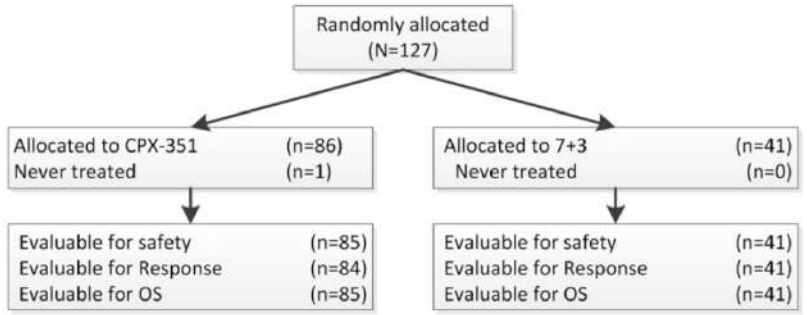




- Dual-drug liposomal encapsulation of cytarabine and daunorubicin
- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- Maximally synergistic and minimally antagonistic anti leukemia activity *in vitro*
- Prolonged drug exposure
- Accumulates in BM with preferential uptake by leukemia cells

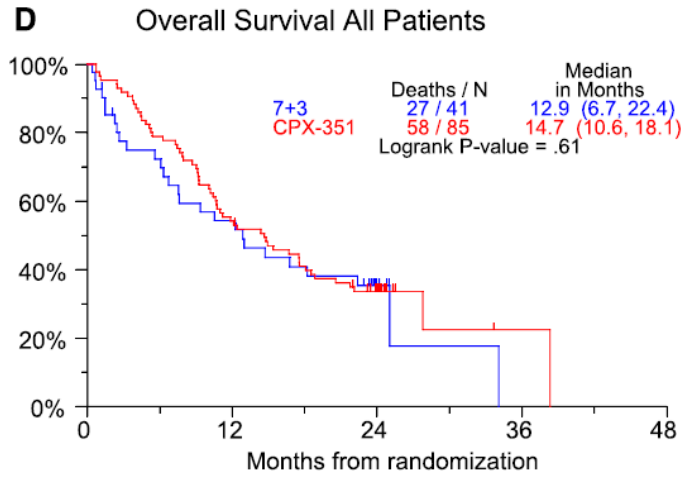
Lim, W. S., Leuk Res, 2010
Mayer L, International Journal of Nanomedicine 2019

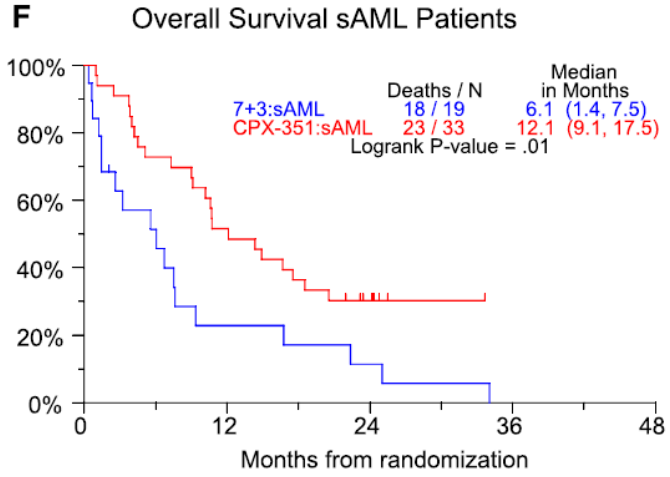
Phase 2 trial of CPX-351 vs 3+7 in older adults with untreated AML



Key Points

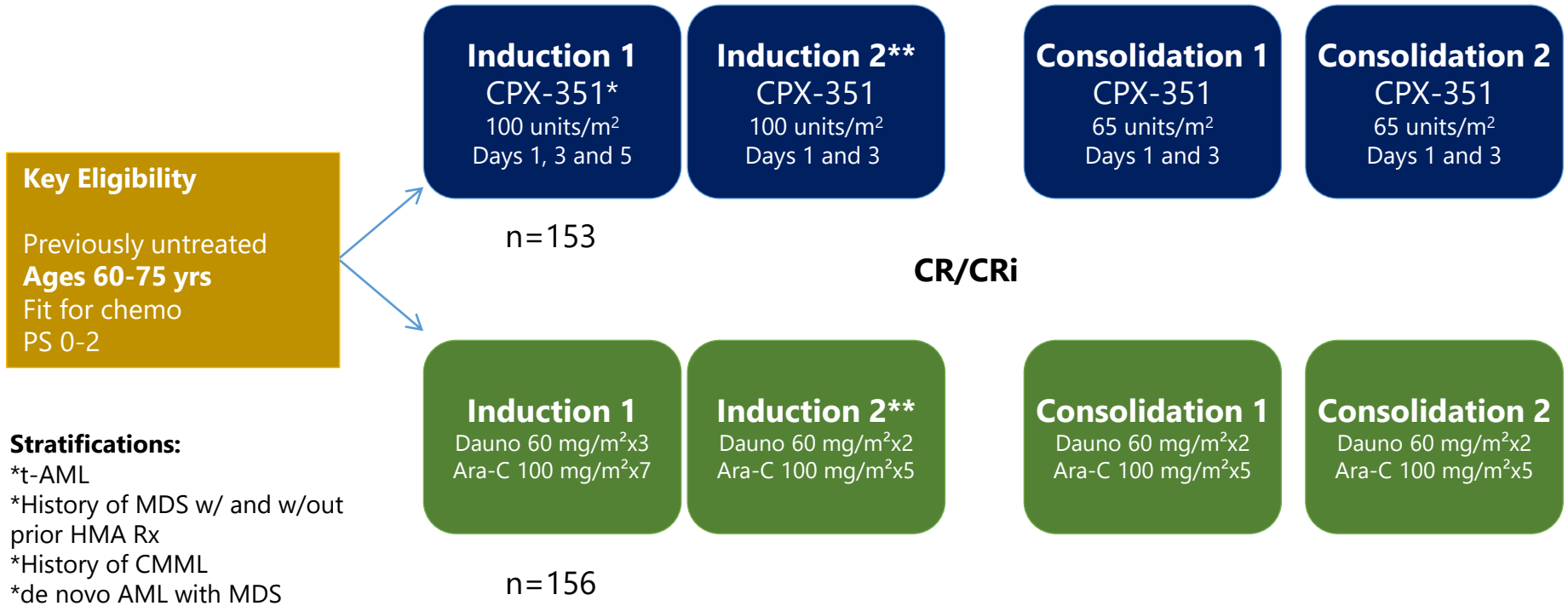
- First-line CPX-351 vs 7+3 control in newly diagnosed AML improves 60-day mortality, remission rate, and OS (HR = 0.46, *P* = .01) in sAML subset.





Lancet JE, Blood 2014

Phase 3 Study of CPX-351 vs Standard Induction in Older Patients with Newly Diagnosed High-Risk AML



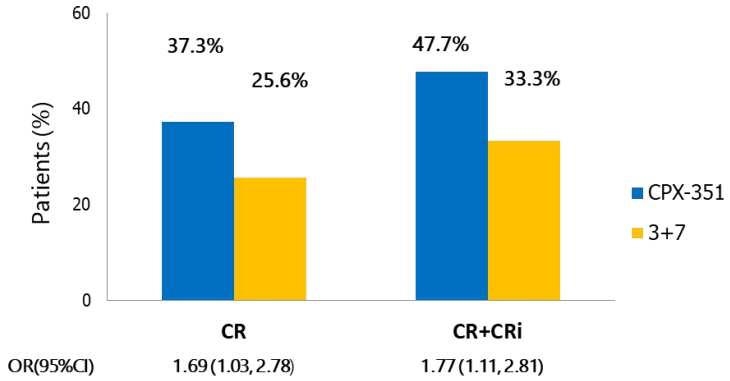
Stratifications:
*t-AML
*History of MDS w/ and w/out prior HMA Rx
*History of CMML
*de novo AML with MDS karyotype
*60-69 yrs
*70-75 yrs

*1 unit = 1 mg cytarabine + 0.44 mg daunorubicin
** if residual BM blasts at d14
Allogeneic-HCT was performed at the discretion of the treating physician.

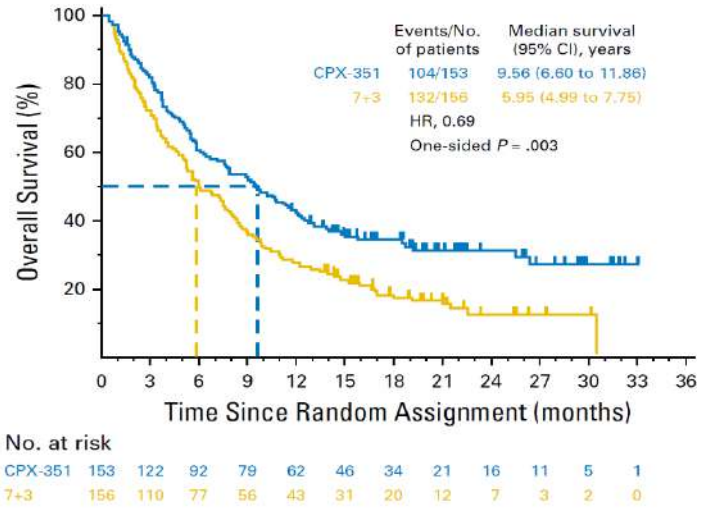
Lancet JE, JCO 2018

CPX-351 improves response rate and OS in High-Risk AML patients selected for intensive CTx

Response



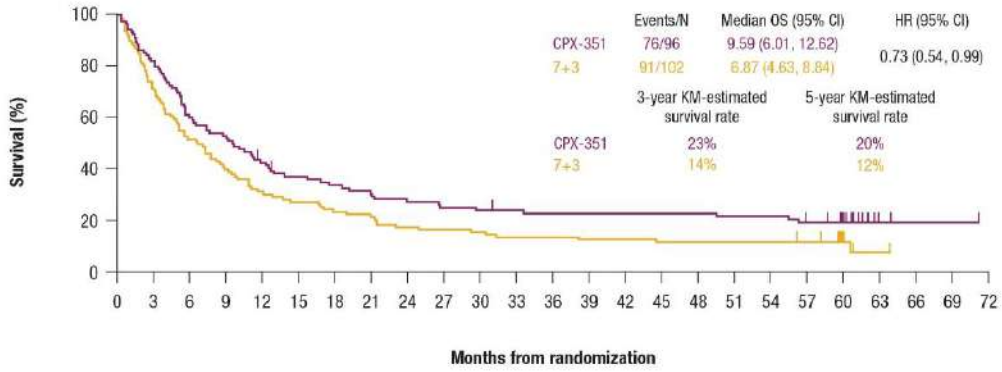
Overall survival



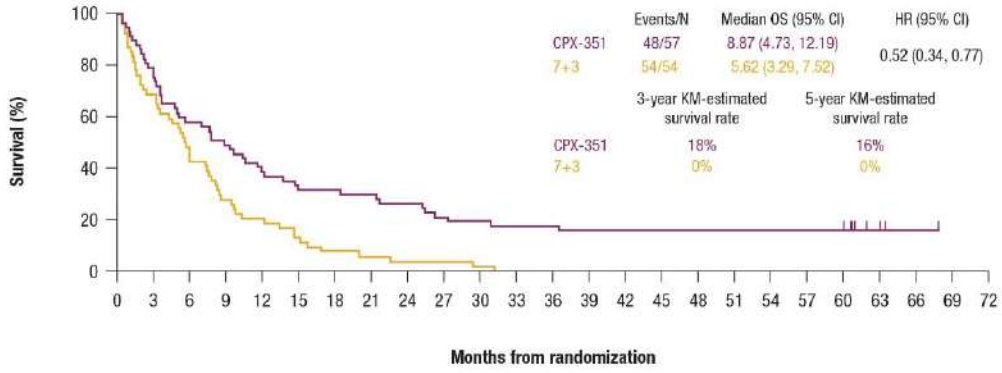
Lancet JE, JCO 2018

Figure 2. OS by Age Subgroup

A. Ages 60 to 69 Years



B. Ages 70 to 75 Years



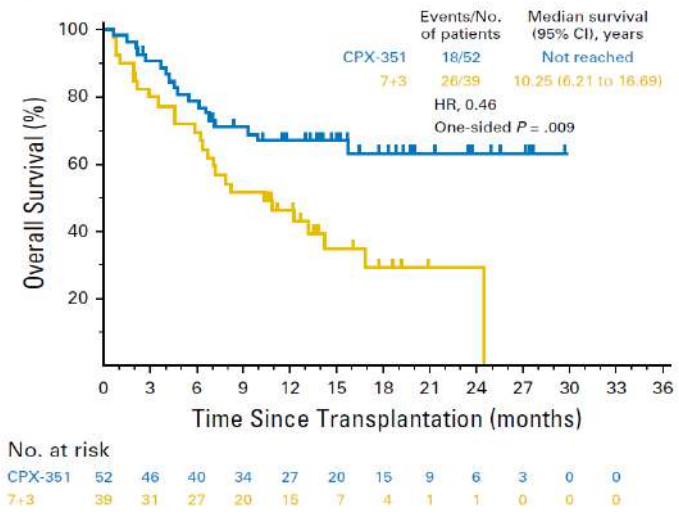
Five-Year Final Results
Lancet JE, ASH 2020

Landmark survival analysis from SCT

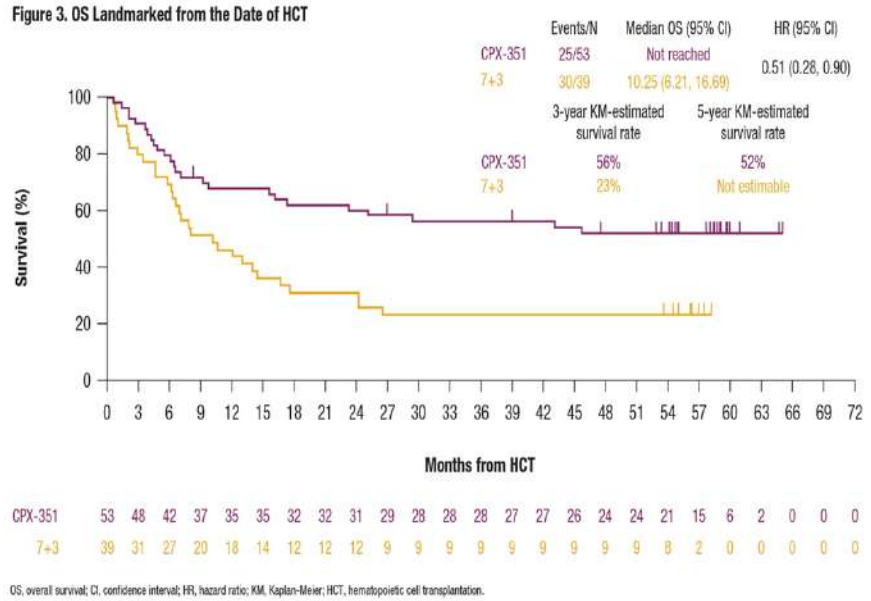
29.4% of 309 patients underwent allogeneic-HCT

* 34% of 153 in the CPX-351 arm
* 25% of 156 in the 7+3 arm

(*P* = .098)

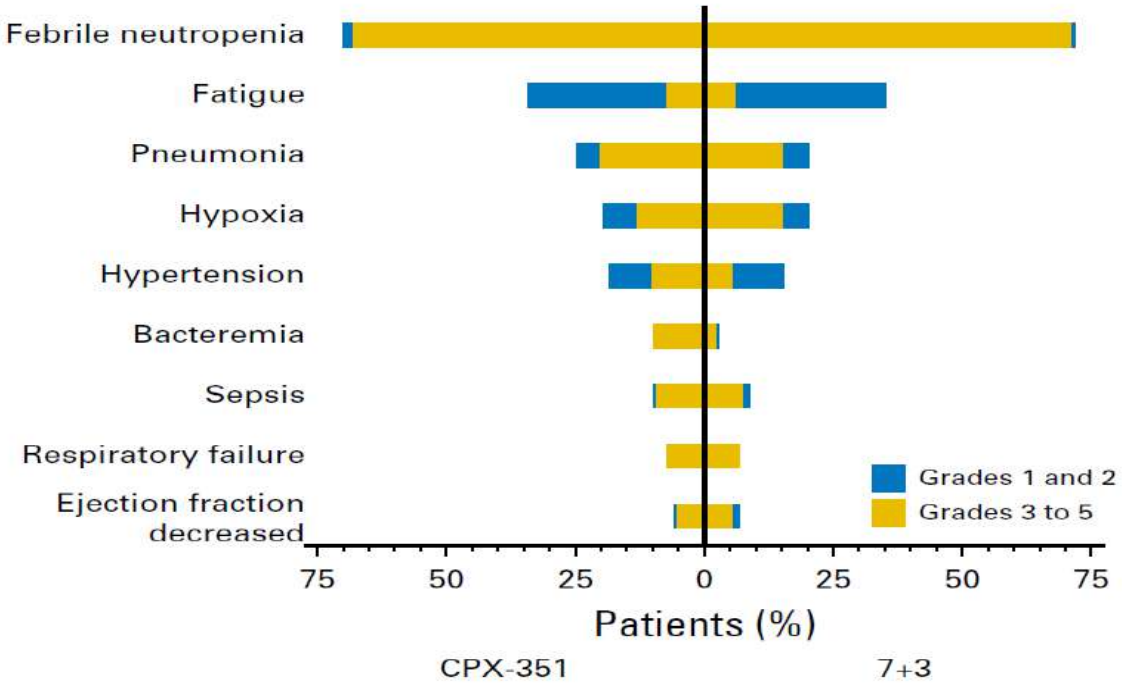


Lancet JE, JCO 2018



Five-Year Final Results
Lancet JE, ASH 2020

Safety of CPX-351: a more favorable toxicity profile



	CPX-351	3+7
ANC> 0.5 Median (days)	35	29
Platelets>50 Median (days)	36.5	29
Day-30 death	5.9%	10.6%
Day-60 death	13.7%	21.2%

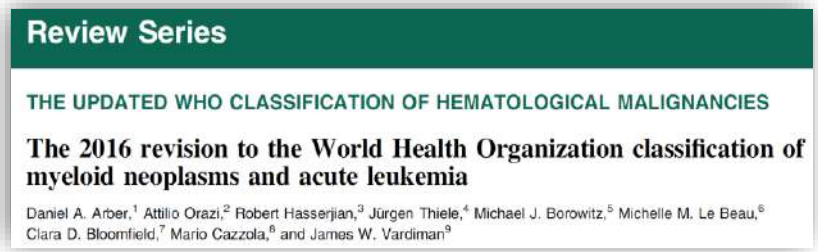
Lower rate of adverse events per patient-year with CPX-351

Also seen in phase II trials (first line and relapse)
Lancet JE Blood 2014; Cortes J, Cancer 2015

Lancet JE, JCO 2018

CPX-351 for patients with therapy-related AML or AML with myelodysplasia-related changes

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis



Review Series

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

Daniel A. Arber,[1] Attilio Orazi,[2] Robert Hasserjian,[3] Jürgen Thiele,[4] Michael J. Borowitz,[5] Michelle M. Le Beau,[6] Clara D. Bloomfield,[7] Mario Cazzola,[8] and James W. Vardiman[9]

- **AML MRC if:**
  - * Multilineage dysplasia : ≥ 50% dysplastic cells in at least 2 cell lines (unless NPM1 or CEBPA^{dm} mutations)
  - * History of MDS
  - * MDS-related cytogenetic abnormalities (unless del9q)

Cytogenetic abnormalities
Complex karyotype (3 or more abnormalities)
Unbalanced abnormalities
−7/del(7q)
del(5q)/t(5q)
i(17q)/t(17p)
−13/del(13q)
del(11q)
del(12p)/t(12p)
idic(X)(q13)
Balanced abnormalities
t(11;16)(q23.3;p13.3)
t(3;21)(q26.2;q22.1)
t(1;3)(p36.3;q21.2)
t(2;11)(p21;q23.3)
t(5;12)(q32;p13.2)
t(5;7)(q32;q11.2)
t(5;17)(q32;p13.2)
t(5;10)(q32;q21.2)
t(3;5)(q25.3;q35.1)

AML with myelodysplasia-related changes

Seymour et al. BMC Cancer (2017) 17:852
DOI 10.1186/s12885-017-3803-6

BMC Cancer

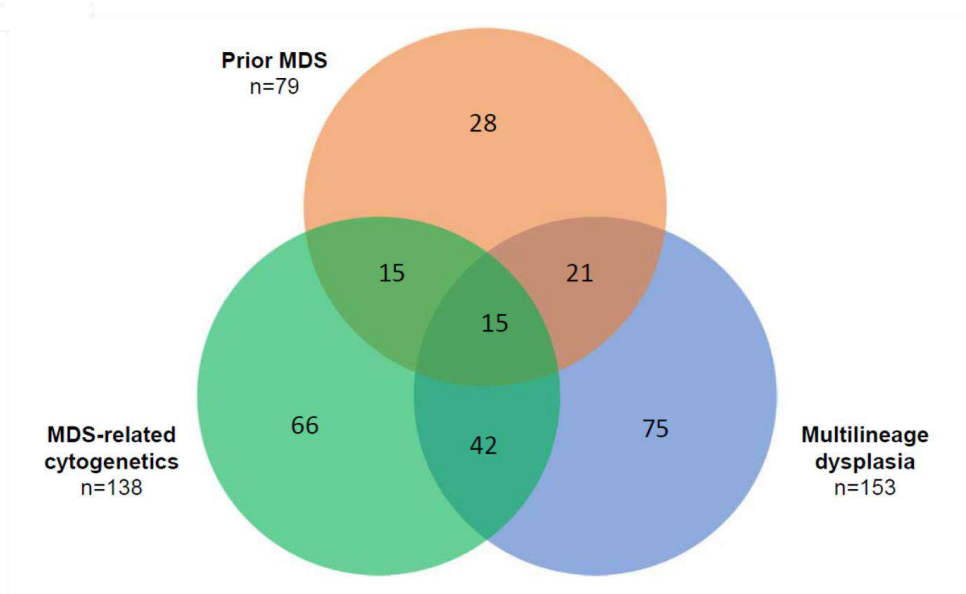
RESEARCH ARTICLE Open Access

Azacitidine improves clinical outcomes in older patients with acute myeloid leukaemia with myelodysplasia-related changes compared with conventional care regimens

John F. Seymour[1,2*], Hartmut Döhner[3], Aleksandra Butrym[4], Agnieszka Wierzbowska[5], Dominik Selleslag[6], Jun Ho Jang[7], Rajat Kumar[8], James Cavenagh[9], Andre C. Schuh[10], Anna Candoni[11], Christian Récher[12], Irwindeep Sandhu[13], Teresa Bernal del Castillo[14], Haifa Kathrin Al-Ali[15], Jose Falantes[16], Richard M. Stone[17], Mark D. Minden[10], Jerry Weaver[18], Steve Songer[18], C. L. Beach[18] and Hervé Dombret[19]

Local assessment

Central review



Response criteria and evaluation of minimal/measurable residual disease

- Complete blood count + bone marrow aspiration (ELN2017, Döhner H, Blood 2017)
  - CR / CRi / MLFS / PR (+ CRh)
  - CR without minimal residual disease: CR_{MRD-}
- MRD by molecular biology (BM/blood, RT-qPCR) (Schuurhuis GJ, Blood 2018)
  - *CBFB-MYH11A*
  - *RUNX1-RUNX1T1*
  - *NPM1*
- MRD by flow cytometry (Schuurhuis GJ, Blood 2018)
  - LAIP/Different from normal
  - Leukemic stem cells
- MRD by NGS (M. Jongen-Lavrencic, NEJM 2018)
  - non-DTA mutations (*DNMT3A, TET2, ASXL1*)

Minimal/measurable disease

a tool to better assess response and stratify treatment

The NEW ENGLAND JOURNAL of MEDICINE

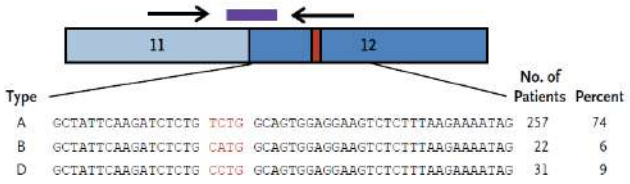
ORIGINAL ARTICLE

Assessment of Minimal Residual Disease in Standard-Risk AML

A. Ivey, R.K. Hills, M.A. Simpson, J.V. Jovanovic, A. Gilkes, A. Grech, Y. Patel, N. Bhudia, H. Farah, J. Mason, K. Wall, S. Akiki, M. Griffiths, E. Solomon, F. McCaughan, D.C. Linch, R.E. Gale, P. Vyas, S.D. Freeman, N. Russell, A.K. Burnett, and D. Grimwade, for the UK National Cancer Research Institute AML Working Group

NPM1 mutational transcript

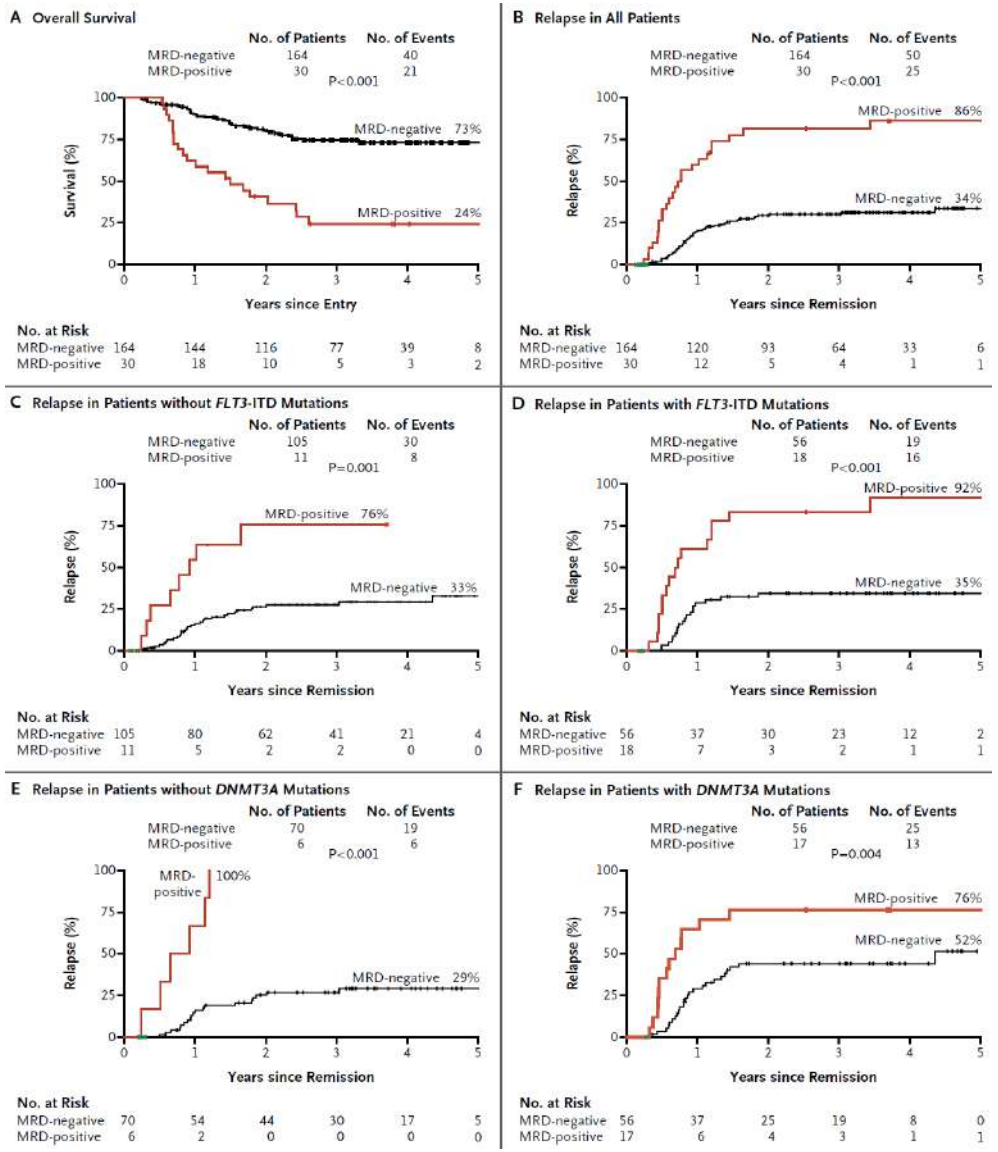
Reverse-transcriptase quantitative polymerase-chain-reaction (RT-qPCR)



Type		No. of Patients	Percent
A	GCTATTCAAGATCTCTG TCTG GCAGTGGAGGAAGTCTCTTTAAGAAAATAG	257	74
B	GCTATTCAAGATCTCTG CATG GCAGTGGAGGAAGTCTCTTTAAGAAAATAG	22	6
D	GCTATTCAAGATCTCTG CCTG GCAGTGGAGGAAGTCTCTTTAAGAAAATAG	31	9

*Blood (and/or bone marrow)
*After 2 cycles of intensive chemo

Same message for AML with *RUNX1-RUNX1T1* or *CBFB-MYH11* (CBF-AML)



Minimal/measurable disease
a tool to better assess response and stratify treatment

The NEW ENGLAND JOURNAL of MEDICINE

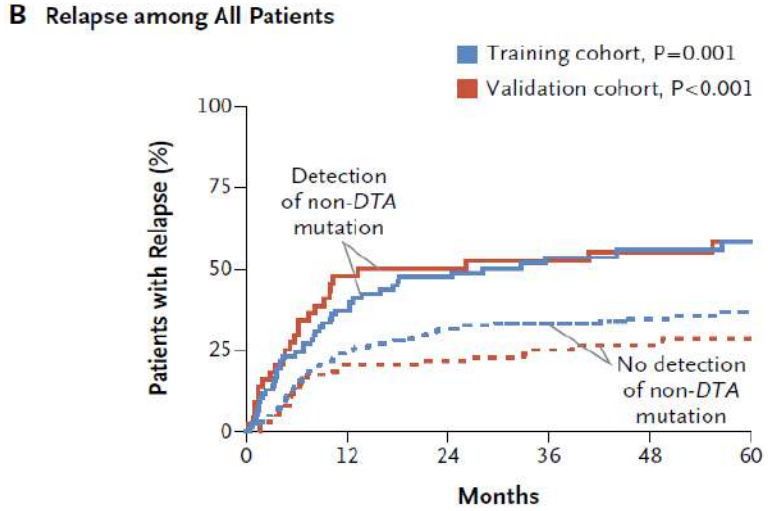
ORIGINAL ARTICLE

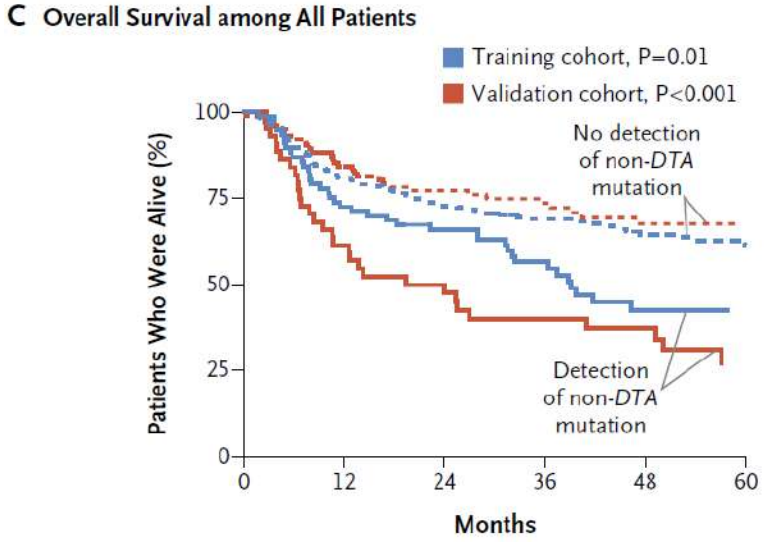
Molecular Minimal Residual Disease in Acute Myeloid Leukemia

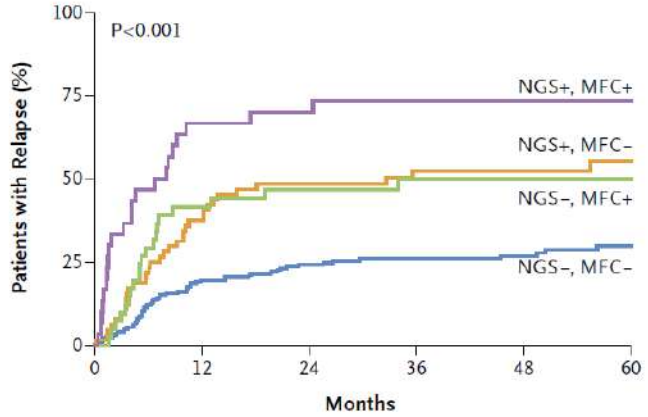
M. Jongen-Lavrencic, T. Grob, D. Hanekamp, F.G. Kavelaars, A. al Hinai, A. Zeilemaker, C.A.J. Erpelinck-Verschueren, P.L. Gradowska, R. Meijer, J. Cloos, B.J. Biemond, C. Graux, M. van Marwijk Kooy, M.G. Manz, T. Pabst, J.R. Passweg, V. Havelange, G.J. Ossenkoppele, M.A. Sanders, G.J. Schuurhuis, B. Löwenberg, and P.J.M. Valk

*Targeted next-generation sequencing
*Flow cytometry

*Bone marrow
*After 2 cycles of intensive chemo







No. at Risk						
NGS+, MFC+	30	8	7	5	4	4
NGS−, MFC+	41	22	18	14	11	7
NGS+, MFC−	64	39	30	22	15	11
NGS−, MFC−	205	153	130	101	69	42

Modern approach to AML treatment in 2020