INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE
Oncopole

Hôpitaux de Toulouse

# Traitement des LAM de l'adulte jeune: Quel est le standard de traitement (produits, intensité, stratification pronostique) ?

**Christian Récher**

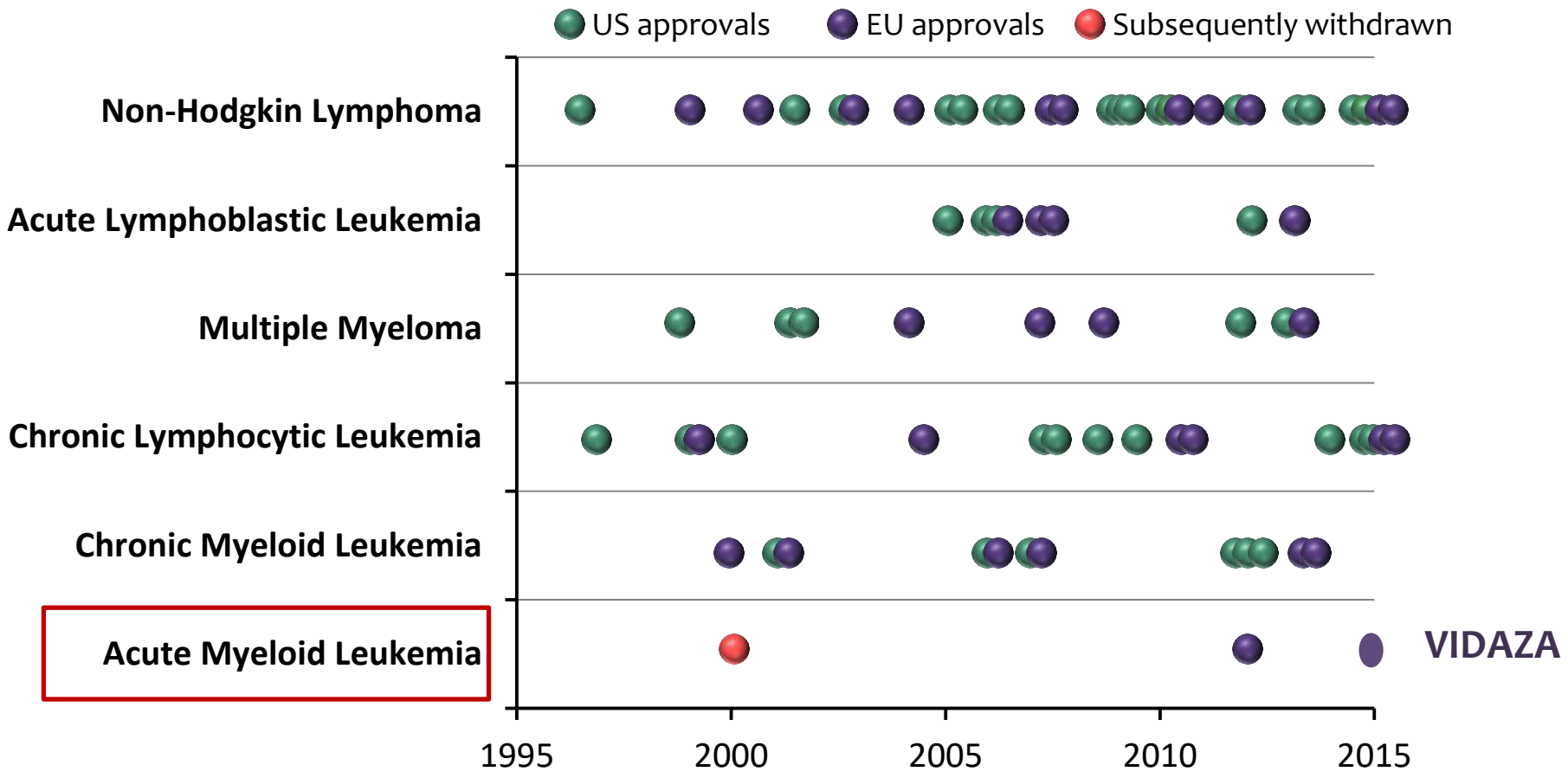
**DES Hématologie**

**18 Novembre 2016**

CRCT
Cancer Research Center of Toulouse

UNIVERSITÉ TOULOUSE III PAUL SABATIER

# Médicaments enregistrés dans les hémopathies malignes
## *LAM vs. les autres…..*




1. NCI Drug Info. http://www.cancer.gov/cancertopics/druginfo. 2. EMA Drug Approvals. http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=. 3. FDA Drug Approvals. http://www.accessdata.fda.gov/ scripts/cder/drugsatfda/index.cfm. 3. NCCN clinical practice guidelines in oncology: acute myeloid leukemia. National Comprehensive Cancer Network website. V.2.2014. http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf.

# Mme R., 42 ans

- Consulte son médecin généraliste le 11 Août 2013 pour une altération rapide de l'état général. Elle n'a pas de comorbidité. L'hémogramme montre: GB 95.7 G/L, PN neutrophiles 0.9 G/L; blastes 93%; hémoglobine 10.4 g/dl VGM 96; plaquettes 29 G/L. Elle est admise en hématologie. L'examen clinique ne retrouve pas de syndrome tumoral. Il n'y a pas de symptômes de leucostase.

- Le myélogramme montre une moelle très riche (grade 5), 91% de blastes d'allure myéloïde: LAM 1 (FAB).

- L'immunophénotypage est le suivant: CD34: 1%; CD13: 82%; CD33: 97%; CD117: 97%; HLA-DR: 84%; CD56: 0% MPO: 9%.

- Le reste du bilan ne montre pas de complication métabolique ni de CIVD.

# Question 1: quel type d'induction choisissez vous?

1. « 3+7 » (anthracycline + cytarabine)
2. Induction séquentielle
3. FLAG-Idarubicine
4. « 3+7 » + gemtuzumab ozogamycin
5. « 3+7 » + sorafenib

# Séquentiel *vs.* « 3+7 »

- Réponse

| | **3+7*** | Double ind | **Séquentiel** | 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 |

*: less salvage in DI arm

**Daunorubicine 80 mg/m²*

NEOPLASIA

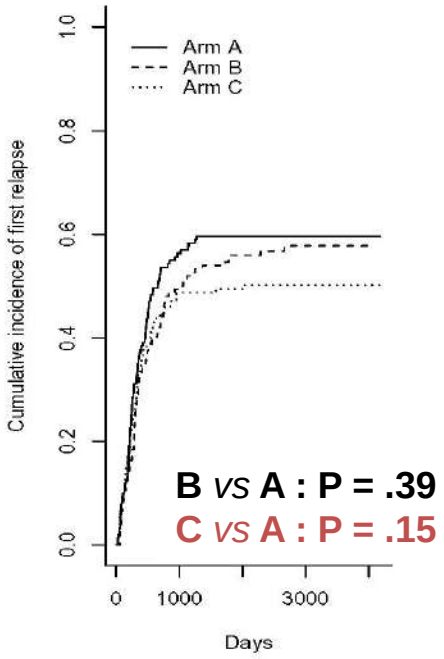
Randomized comparison of double induction and timed-sequential induction to a "3 + 7" induction in adults with AML: long-term analysis of the Acute Leukemia French Association (ALFA) 9000 study

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

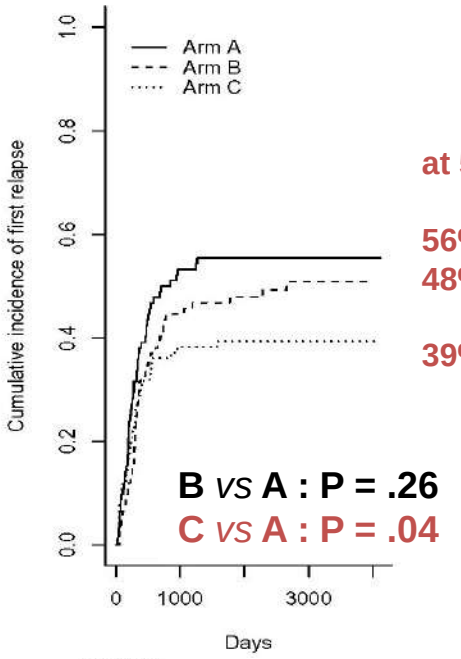
# Séquentiel *vs.* « 3+7 »

- Rechute

**N = 449 CR pts**




**N = 282 CR pts < 50y**




**at 5 years :**

**56% (46-66)**
**48% (38-58)**

**39% (29-49)**

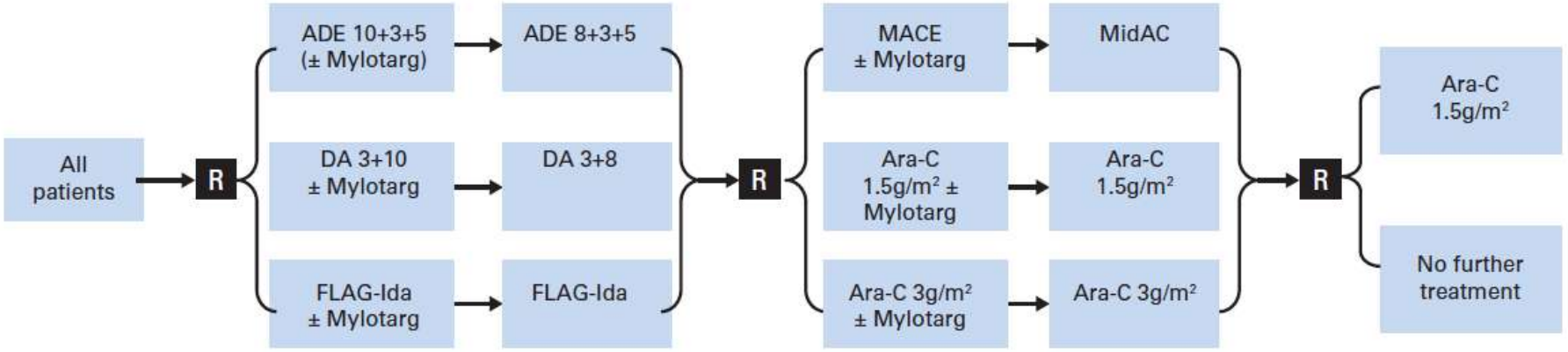
NEOPLASIA

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 Lemon, Brigitte Dupriez, Michel Renoux, Maud Janvier, Jean-Michel Micléa, Xavier Thomas, Christian Bastard, Claude Preudhomme, Francis Bauters, Laurent Degos, and Hervé Dombret

**** Pas de différence en OS***

# FLAG-ida *vs.* « 3+7 »




JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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. Jyson, Keith Wheatley, and Donald Milligan

# FLAG-ida *vs.* « 3+7 »

**Table 3.** Patient Outcomes: Induction (%)

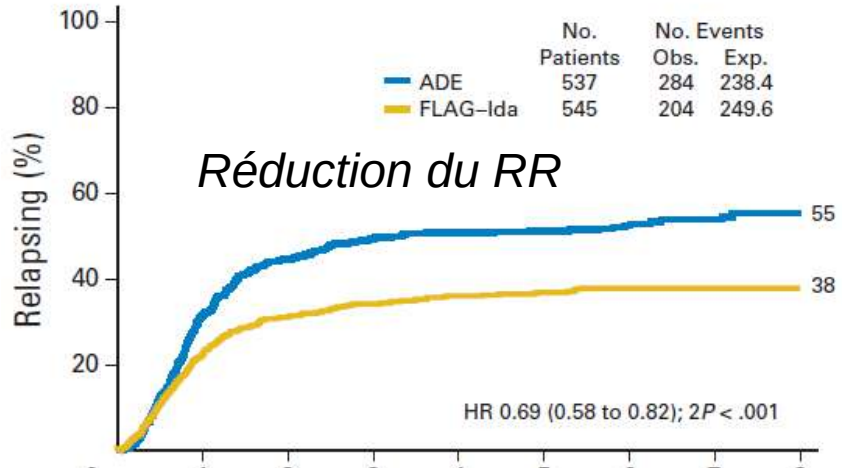
| | CR | CRi | ORR (CR + CRi) | ORR post C1 | Res Dis | Ind Death | 3 |
|---|---|---|---|---|---|---|---|
| DA | 78 | 6 | 84 | 63 | 10 | 6 | |
| ADE | 82 | 4 | 86 | 70 | 8 | 5 | |
| OR/HR | 1.24 | | 1.20 | 1.35 | 1.25 | 1.09 | |
| 95% CI | 0.99 to 1.54 | | 0.94 to 1.54 | 1.12 to 1.63 | 0.93 to 1.70 | 0.93 to 1.70 | |
| *P* | .06 | | .14 | .002 | .14 | .7 | |
| FLAG-Ida | 84 | 2 | 86 | 77 | 7 | 7 | |
| ADE | 81 | 4 | 85 | 67 | 8 | 7 | |
| OR | 0.84 | | 0.94 | 0.60 | 0.82 | 1.09 | |
| 95% CI | 0.63 to 1.13 | | 0.69 to 1.29 | 0.47 to 0.76 | 0.54 to 1.26 | 0.71 to 1.68 | |
| *P* | .2 | | .7 | < .001 | .4 | .7 | |

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

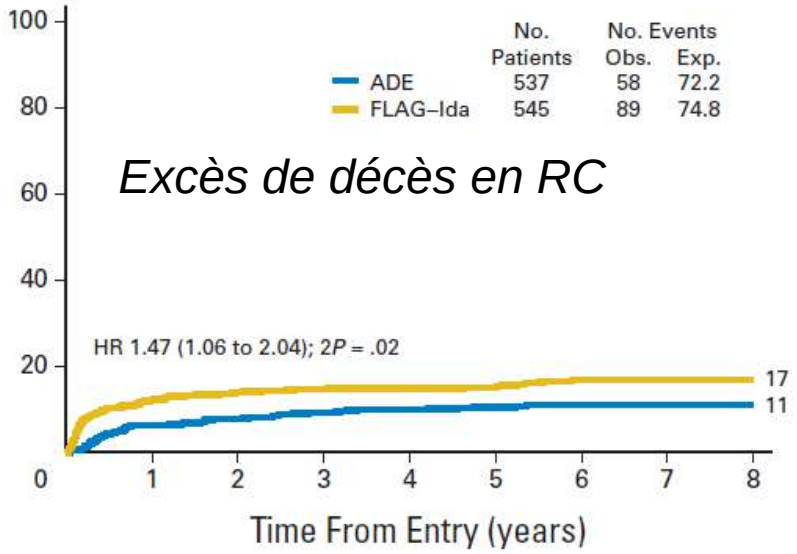
Optimization of Chemotherapy for Younger Patients With Acute Myeloid Leukemia: Results of the Medical Research Council AML15 Trial

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

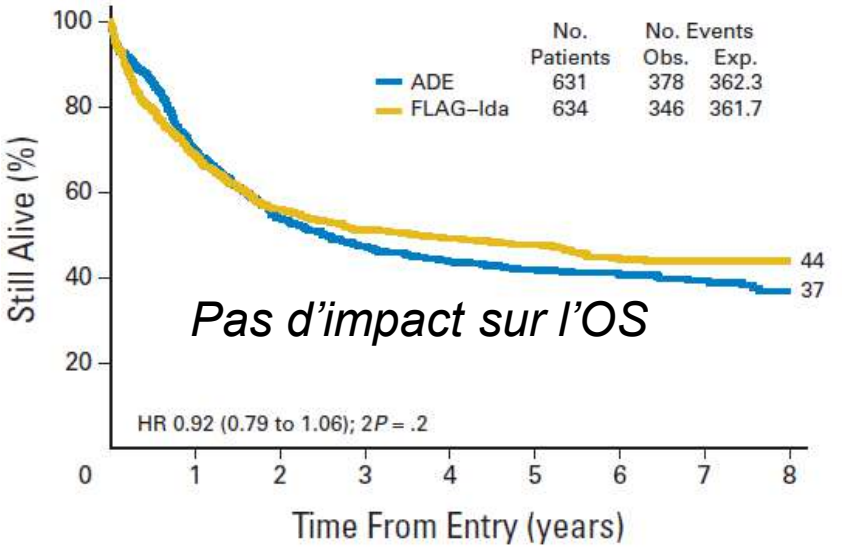
# FLAG-ida *vs.* « 3+7 »



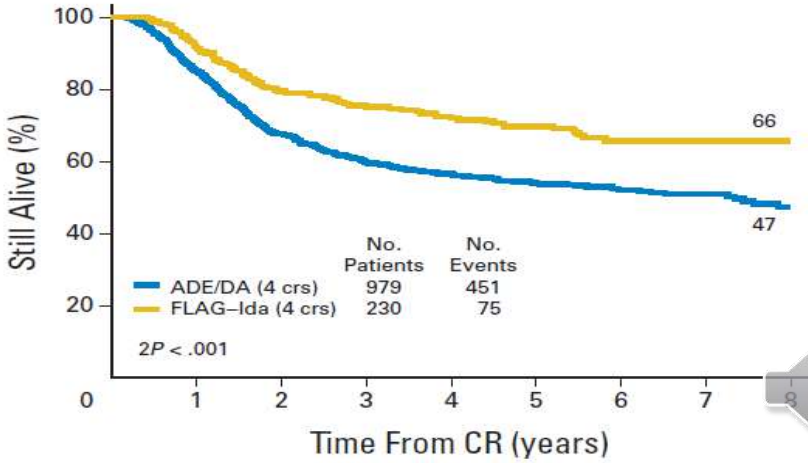

*Réduction du RR*




*Excès de décès en RC*




*Pas d'impact sur l'OS*

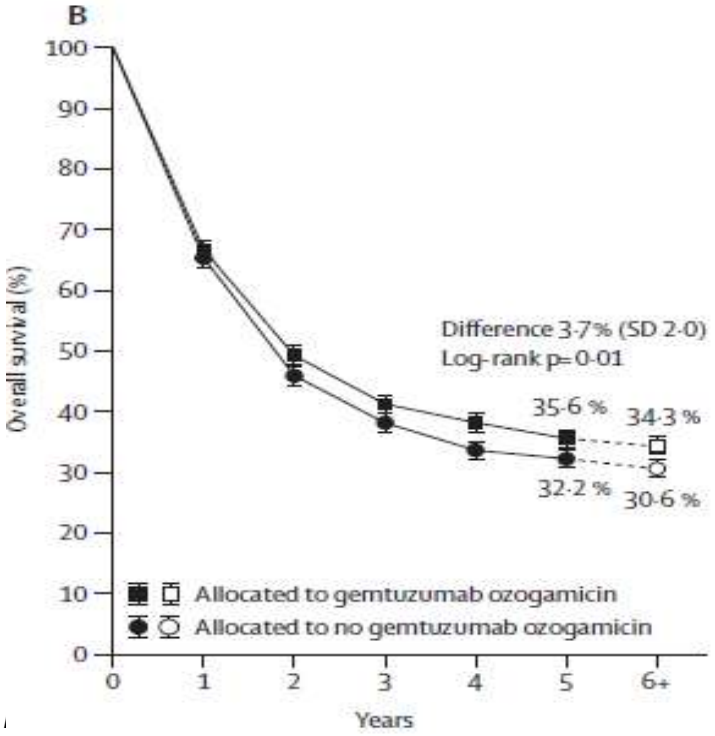


# « 3+7 » +/- gemtuzumab ozogamicin

*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

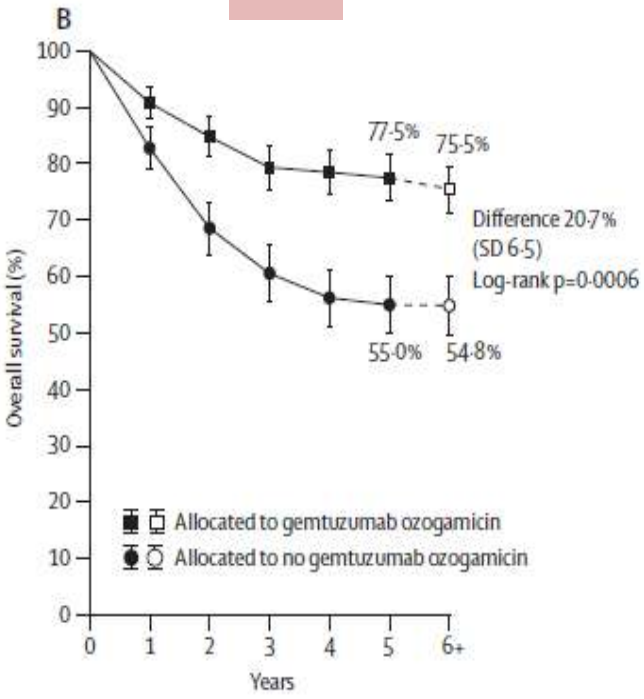



| Annual event rates | Years 1–5 | Years 6+ |
|---|---|---|
| Gemtuzumab ozogamicin | 26·7 % SD 0·8 | 3·5 % SD 0·8 |
| No gemtuzumab ozogamicin | 29·5 % SD 0·9 | 5·2 % SD 1·0 |

*MRC AML15: 3 mg/m²*
*NCRI AML16: 3 mg/m²*
*ALFA 07-01: 3 mg/m²x3*
*GOELAMS AML-IR2006: 6 mg/m²*
*SWOG 01-06: 6 mg/m²*

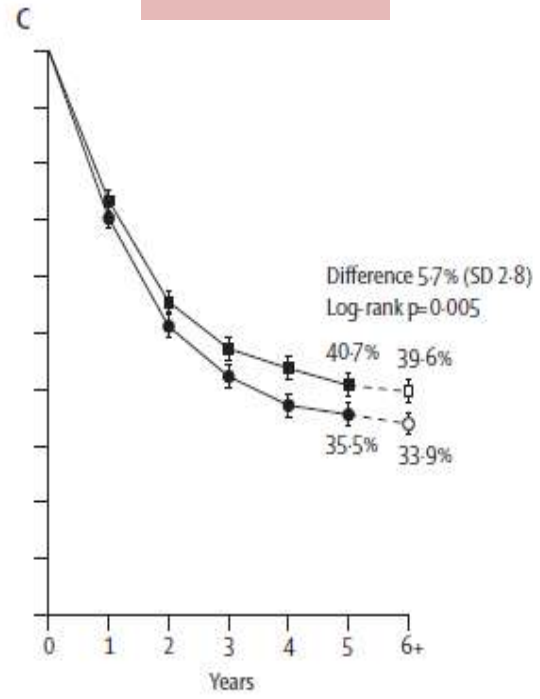
# « 3+7 » +/- GO

## CBF



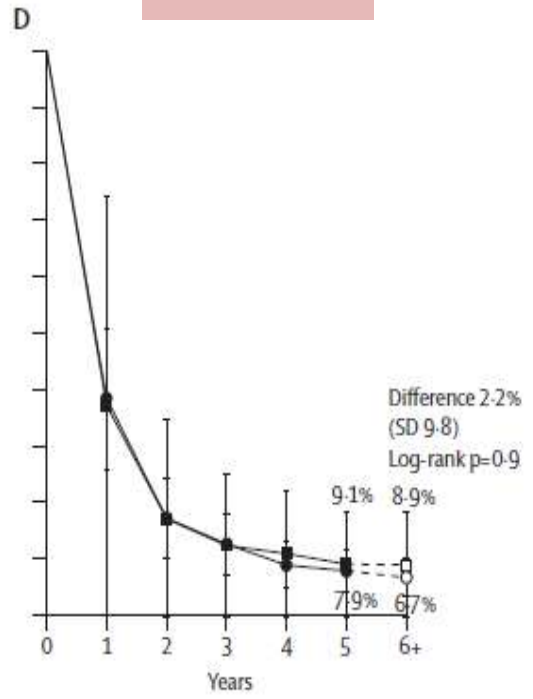

| Annual event rates | Years 1–5 | Years 6+ |
|---|---|---|
| Gemtuzumab ozogamicin | 5·8% SD 1·1 | 2·3% SD 1·3 |
| No gemtuzumab ozogamicin | 14·1% SD 1·9 | 0·0% SD 0·0 |

## Intermédiaire




| 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 |

## Défavorable

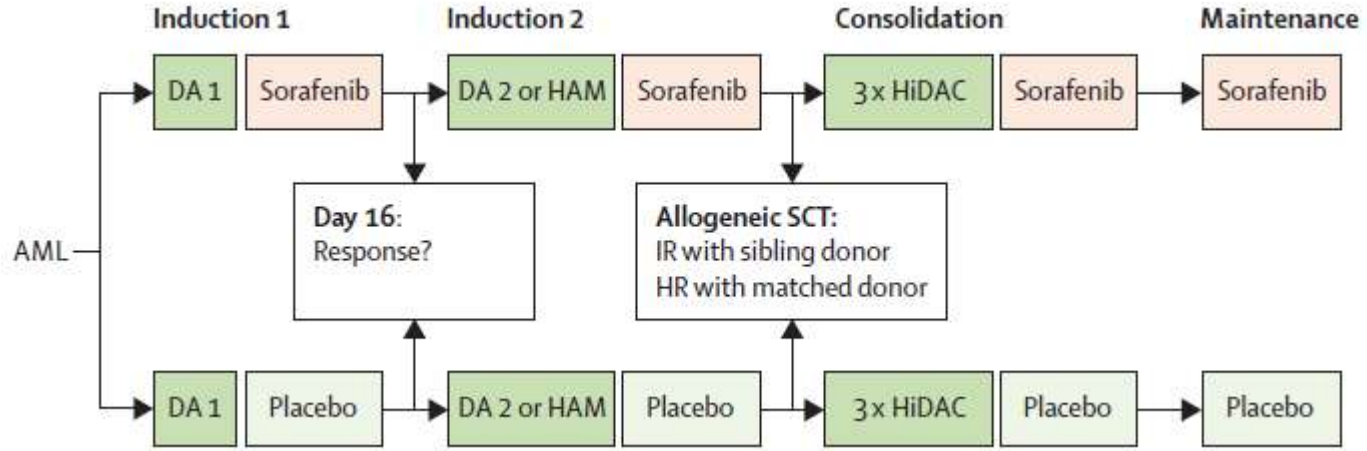



| Annual event rates | Years 1–5 | Years 6+ |
|---|---|---|
| Gemtuzumab ozogamicin | 73·8% SD 4·6 | 2·4% SD 2·4 |
| No gemtuzumab ozogamicin | 76·7% SD 4·8 | 21·1% SD 10·5 |

# « 3+7 » +/- Sorafenib

**Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukaemia (SORAML): a multicentre, phase 2, randomised controlled trial**

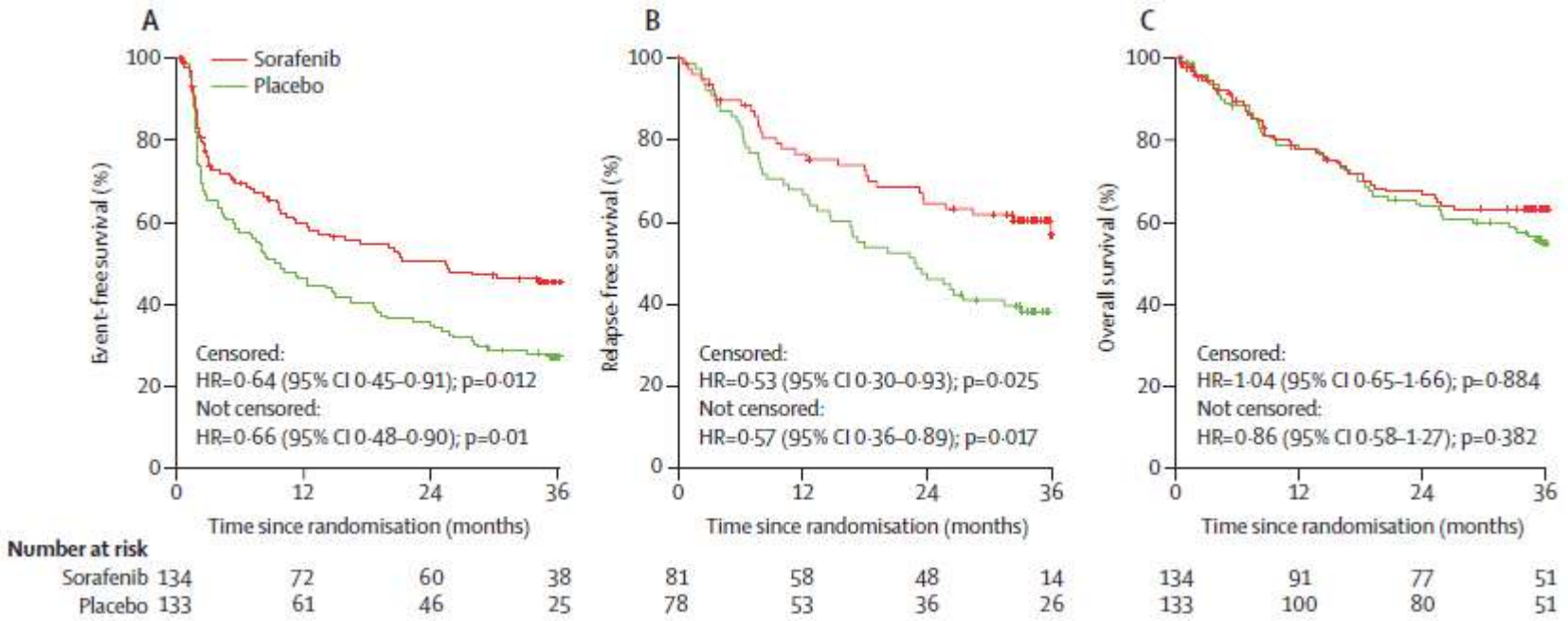
Christoph Röllig*, Hubert Serve*, Andreas Hüttmann, Richard Noppeney, Carsten Müller-Tidow, Utz Krug, Claudia D Baldus, Christian H Brandts, Volker Kunzmann, Hermann Einsele, Alwin Krämer, Kerstin Schäfer-Eckart, Andreas Neubauer, Andreas Burchert, Aristoteles Giagounidis, Stefan W Krause, Andreas Mackensen, Walter Aulitzky, Regina Herbst, Mathias Hänel, Alexander Kiani, Norbert Frickhofen, Johannes Kullmer, Ulrich Kaiser, Hartmut Link, Thomas Geer, Albert Reichle, Christian Junghanß, Roland Repp, Frank Heits, Heinz Dürk, Jana Hase, Ina-Maria Klut, Thomas Illmer, Martin Bornhäuser, Markus Schaich, Stefani Parmentier, Martin Görner, Christian Thiede, Malte von Bonin, Johannes Schetelig, Michael Kramer, Wolfgang E Berdel*, Gerhard Ehninger*, for the Study Alliance Leukaemia



# « 3+7 » +/- Sorafenib

| Outcome | Sorafenib (n=134) | Placebo (n=133) |
|---|---|---|
| Complete remission all | 81 (60%) | 78 (59%) |
| Complete remission FLT3-ITD | 13 (57%) | 12 (52%) |
| | | |
| Stem cell transplantation in 1st CR | 42 (31%) | 35 (26%) |
| Stem cell transplantation in relapse | 39 (29%) | 66 (50%) |

# « 3+7 » +/- Sorafenib



# Question 2: vous optez pour le « 3+7 » considéré comme le standard de soin: quel type d'anthracyclines choisissez-vous?

1. Daunorubicine 45 mg/m² x 3 jours
2. Daunorubicine 50 mg/m² x 5 jours
3. Daunorubicine 60 mg/m² x 3 jours
4. Daunorubicine 90 mg/m² x 3 jours
5. Idarubicine 12 mg/m² x 3 jours
6. Idarubicine 8 mg/m² x 5 jours

# Daunorubicine
# 90 mg/m² *vs.* 45 mg/m²

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Anthracycline Dose Intensification in Acute Myeloid Leukemia

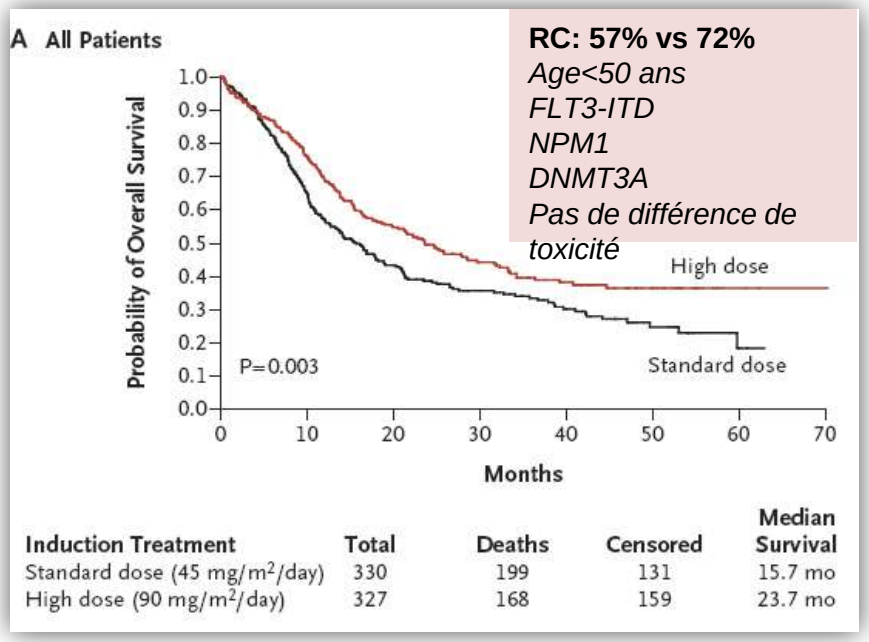
Hugo F. Fernandez, M.D., Zhuoxin Sun, Ph.D., Xiaopan Yao, Ph.D., Mark R. Litzow, M.D., Selina M. Luger, M.D., Elisabeth M. Paietta, Ph.D., Janis Racevskis, Ph.D., Gordon W. Dewald, Ph.D., Rhett P. Ketterling, M.D., John M. Bennett, M.D., Jacob M. Rowe, M.D., Hillard M. Lazarus, M.D., and Martin S. Tallman,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

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]

**DNR 90mg/m² x 3 jours**
**Ara-C IVC 100mg/m² x 7**




| 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 |

**RC: 57% vs 72%**
*Age<50 ans*
*FLT3-ITD*
*NPM1*
*DNMT3A*
*Pas de différence de toxicité*

**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.

***** *200 mg/m² en France*

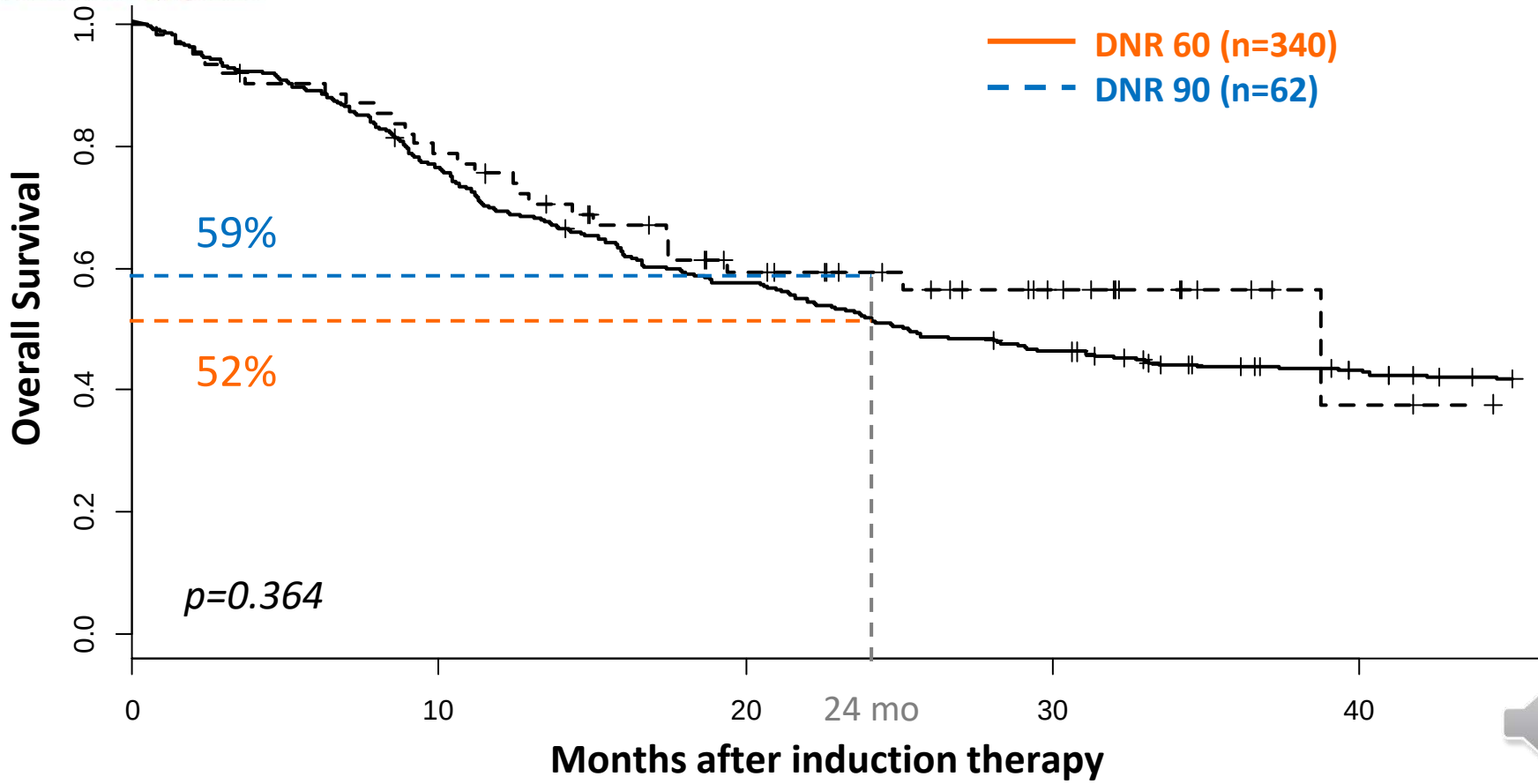
Fernandez et al, NEJM, 2009

# Daunorubicine
# 90 mg/m² *vs.* 60 mg/m²

CORRESPONDENCE

Comparison of 60 or 90 mg/m² of daunorubicin in induction therapy for acute myeloid leukemia with intermediate or unfavorable cytogenetics

*Cohorte IPC-CHU de Tou*

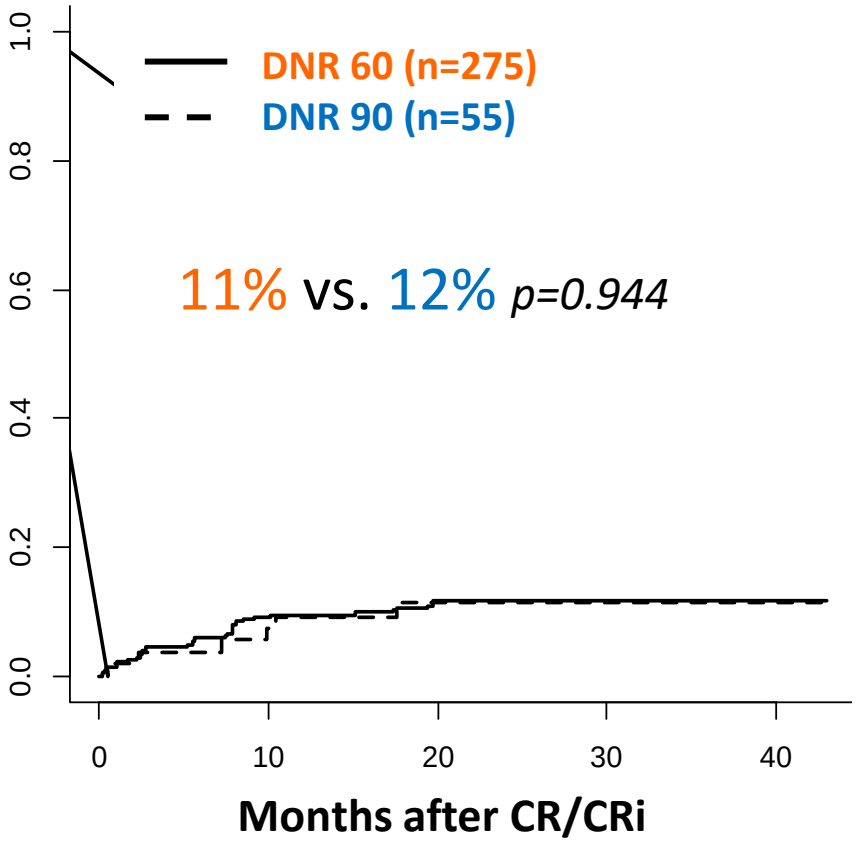



*Devillier R, AJH 20*

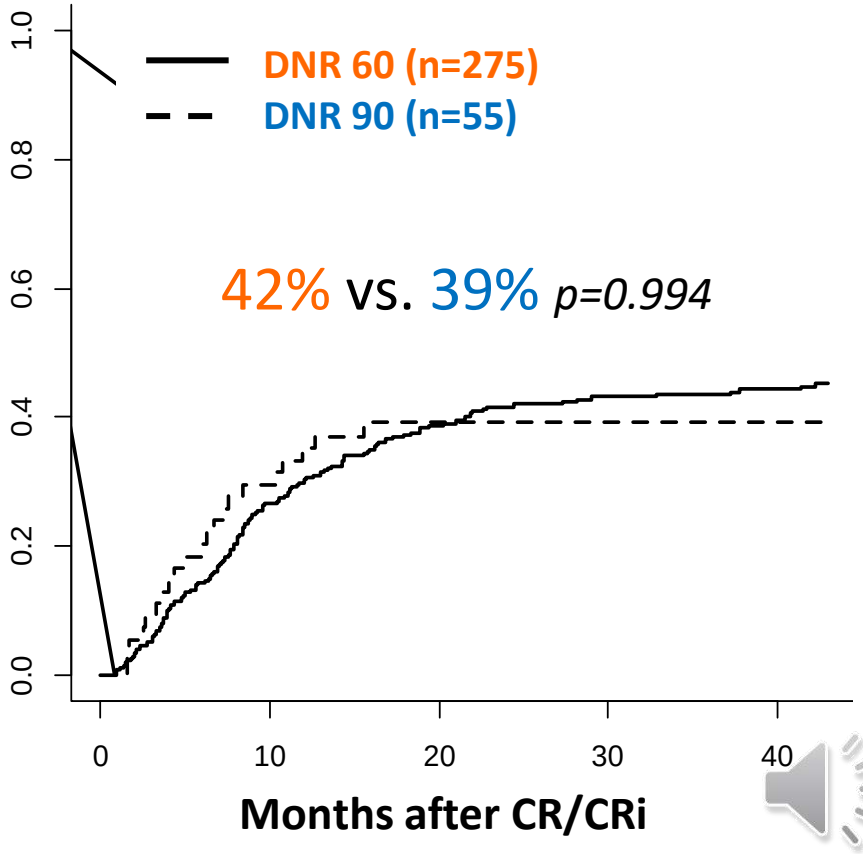
# Daunorubicine
# 90 mg/m² *vs.* 60 mg/m²

*Cohorte IPC-CHU de Tou*

Non Relapse Mortality




Relapse




*Devillier R, AJH 2014*

# Daunorubicine
# 90 mg/m² *vs.* 60 mg/m²

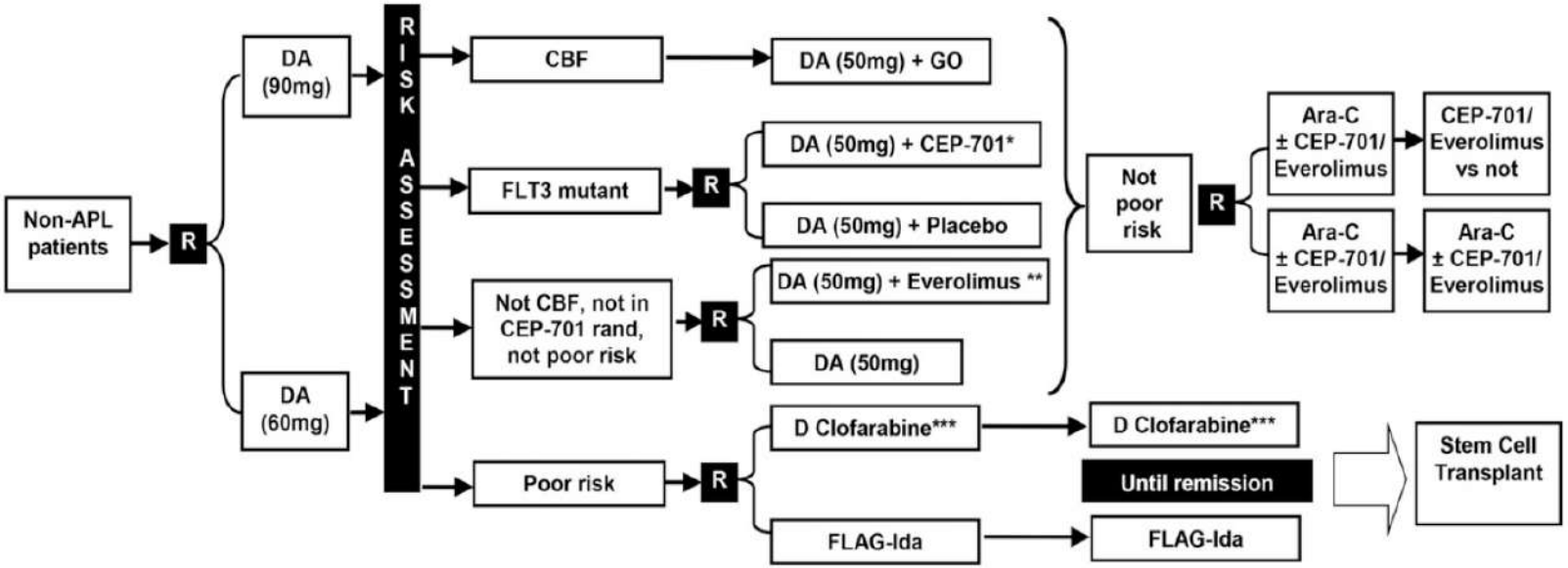
CLINICAL TRIALS AND OBSERVATIONS

CME Article

**A randomized comparison of daunorubicin 90 mg/m² vs 60 mg/m² in AML induction: results from the UK NCRI AML17 trial in 1206 patients**

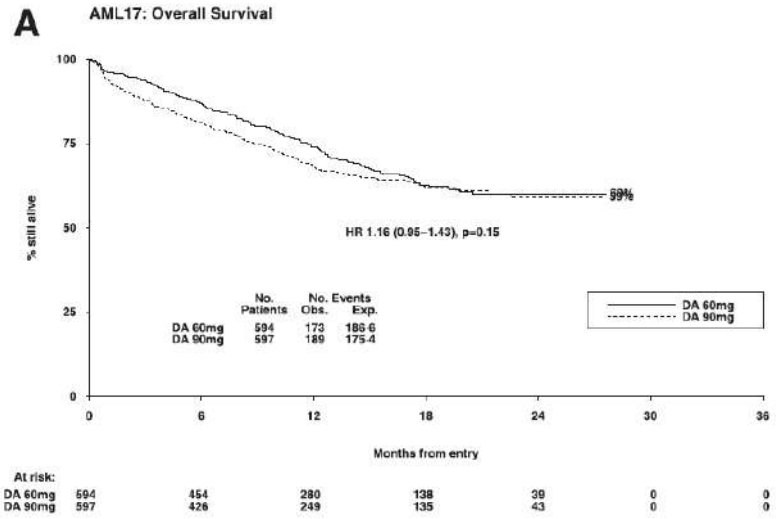
Alan K. Burnett,[1] Nigel H. Russell,[2] Robert K. Hills,[1] Jonathan Kell,[3] Jamie Cavenagh,[4] Lars Kjeldsen,[5] Mary-Frances McMullin,[6] Paul Cahalin,[7] Mike Dennis,[8] Lone Friis,[9] Ian F. Thomas,[1] Don Milligan,[10] and Richard E. Clark,[11] on behalf of the UK NCRI AML Study Group

Induction 1: Dauno 60 vs 90 J1, 3, 5 + AraC 100 mg/m² /12h J1-J10
Induction 2: Dauno 50 J1, 3, 5 + AraC 100 mg/m² /12h J1-J8



# Daunorubicine
# 90 mg/m² *vs.* 60 mg/m²

| | DA60 | DA90 | OR/HR and CI | *P* |
|---|---|---|---|---|
| CR | 75% | 73% | 1.07 (0.83-1.39) | .6 |
| CRi | 9% | 8% | | |
| CR/CRi | 84% | 81% | 1.21 (0.90-1.63) | .2 |
| Induction death | 4% | 6% | 1.63 (0.97-2.73) | .07 |
| Resistant disease | 12% | 13% | 1.04 (0.74-1.47) | .8 |
| CR/CRi post–course 1 | 66% | 68% | 0.89 (0.70-1.14) | .4 |
| 30-day mortality | 4% | 6% | 1.56 (0.94-2.61) | .09 |
| 60-day mortality | 5% | 10% | 1.98 (1.30-3.02) | .001 |
| 2-year OS | 60% | 59% | 1.16 (0.95-1.43) | .15 |
| 2-year RFS | 48% | 51% | 1.05 (0.85-1.30) | .7 |
| 2-year cumulative incidence of relapse | 43% | 39% | 1.00 (0.79-1.27) | 1.0 |
| 2-year cumulative incidence of death in CR | 8% | 10% | 1.27 (0.79-2.04) | .3 |
| 2-year OS from CR | 69% | 70% | 1.04 (0.79-1.38) | .8 |
| 2-year OS censored at SCT | 60% | 60% | 1.20 (0.96-1.51) | .11 |



# Daunorubicine
# 90 mg/m² *vs.* 60 mg/m²

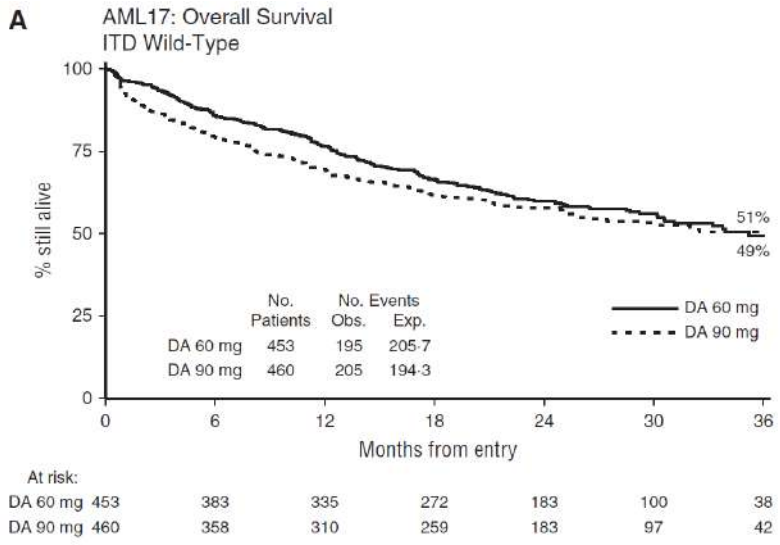
**Letters to *Blood***

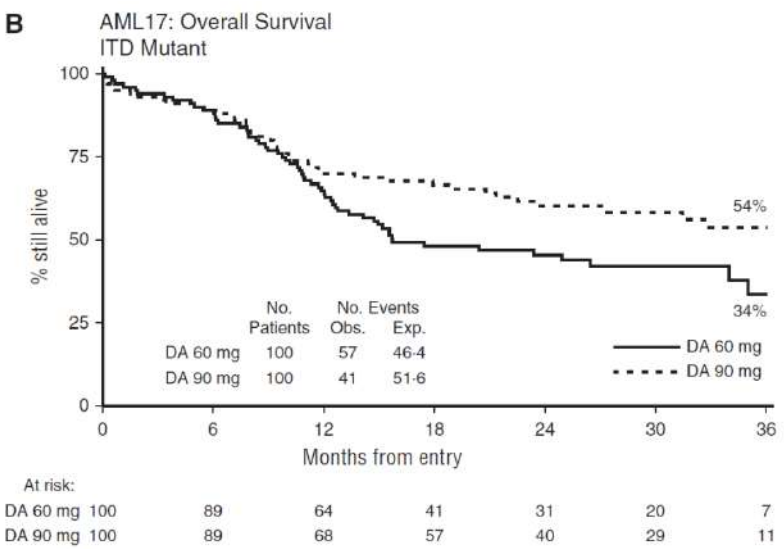
blood

To the editor:

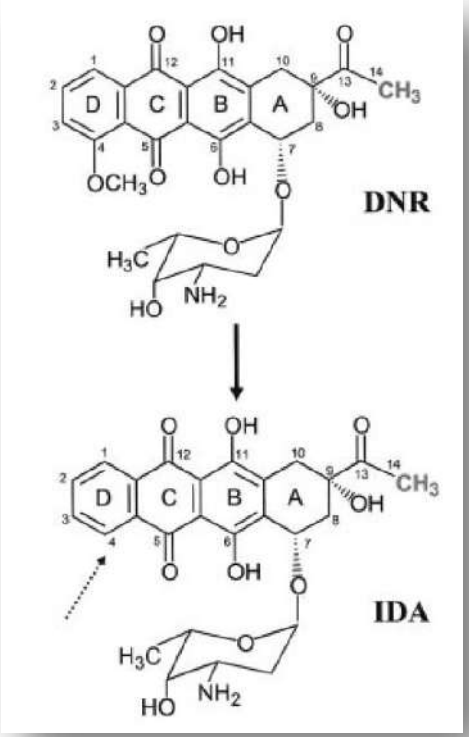
**Higher daunorubicin exposure benefits *FLT3* mutated acute myeloid leukemia**

Alan K. Burnett,[1] Nigel H. Russell,[2] and Robert K. Hills,[1] on behalf of the United Kingdom National Cancer Research Institute Acute Myeloid Leukemia Study Group



# Idarubicine




4-demethoxy-anthracycline analogue of daunorubicin

- Lipophile
- Pénétration intracellulaire
- Moins sensible au MDR
- Liaison à l'ADN plus forte
- 10 fois plus actif *in vitro*
- Actif sur lignées dauno-R
- Moins cardiotoxique?
- Métabolite: idarubicinol aussi actif que l'Ida et détecté jusqu'à 72h dans le plasma après la dernière injection

# Ida *vs.* Dauno: les années 90

**Results of a Randomized Trial Comparing Idarubicin and Cytosine Arabinoside With Daunorubicin and Cytosine Arabinoside in Adult Patients With Newly Diagnosed Acute Myelogenous Leukemia**

By Ellin Berman, Glenn Heller, JoAnne Santorsa, Susan McKenzie, Timothy Gee, Sanford Kempin, Subash Gulati, Michael Andreeff, Jonathan Kolitz, Janice Gabrilove, Lilian Reich, Klaus Mayer, Deborah Keefe, Kathleen Trainor, Alice Schluger, Darryl Penenberg, Virginia Raymond, Richard O'Reilly, Suresh Jhanwar, Charles Young, and Bayard Clarkson

**A Phase III Trial Comparing Idarubicin and Daunorubicin in Combination With Cytarabine in Acute Myelogenous Leukemia: A Southeastern Cancer Study Group Study**

By William R. Vogler, Enrique Velez-Garcia, Roy S. Weiner, Morris A. Flaum, Alfred A. Bartolucci, George A. Omura, Mirjam C. Gerber, and Phillip L.C. Banks

**Cytarabine Plus Idarubicin or Daunorubicin as Induction and Consolidation Therapy for Previously Untreated Adult Patients With Acute Myeloid Leukemia**

By Peter H. Wiernik, Phillip L.C. Banks, Delvyn C. Case Jr, Zalmen A. Arlin, Phillip O. Periman, Mary B. Todd, Paul S. Ritch, Robert E. Enck, and Alan B. Weitberg

. Review article

Treatment of acute myeloblastic leukemia in adults. The GOELAM experience*

J.L. Harousseau[1], B. Pignon[2], F. Witz[3], V. Polin[4], Z. Tellier[4], P. Hurteloup[4] and J.Y. Cahn[5]

# A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia

THE AML COLLABORATIVE GROUP*

*Received 18 May 1998; accepted for publication 3 July 1998*

| | Early induction failure (%) | | Late induction failure (%) | | Complete remission (%) | |
|---|---|---|---|---|---|---|
| Age (years) | Idarubicin | Daunorubicin | Idarubicin | Daunorubicin | Idarubicin | Daunorubicin |
| <40 | 2·2 (2/93) | 7·6 (6/78) | 11·8 (11/93) | 30·7 (24/78) | 86·0 (80/93) | 61·5 (48/78) |
| 40–59 | 14·0 (20/143) | 12·9 (22/170) | 15·4 (22/143) | 25·9 (44/170) | 70·6 (101/143) | 61·1 (104/170) |
| 60+ | 29·1 (83/285) | 23·9 (68/284) | 20·3 (58/285) | 29·9 (85/284) | 50·5 (144/285) | 46·1 (131/284) |
| All patients | 20·2 (105/521) | 18·0 (96/532) | 17·5 (91/521) | 28·8 (153/532) | 62·4 (325/521) | 53·2 (283/532) |
| | Effect: $P = 0·4$<br>Trend: $P = 0·06$ | | Effect: $P < 0·0001$<br>Trend: $P = 0·2$ | | Effect: $P = 0·002$<br>Trend: $P = 0·006$ | |

*« The induction regimens based on idarubicin achieved, in the particular circumstances of the trials reviewed here*, better remission rates and better overall survival than those based on*

* Daun ≤5

# Daunorubicine *vs.* idarubicine

blood

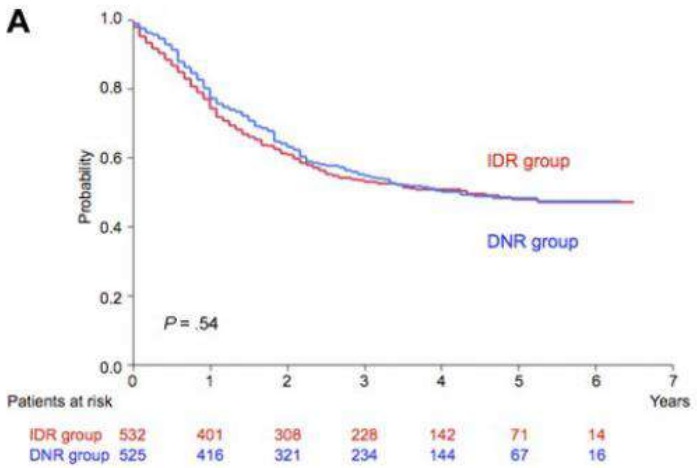
2011 117: 2358-2365
Prepublished online Aug 6, 2010;
doi:10.1182/blood-2010-03-273243

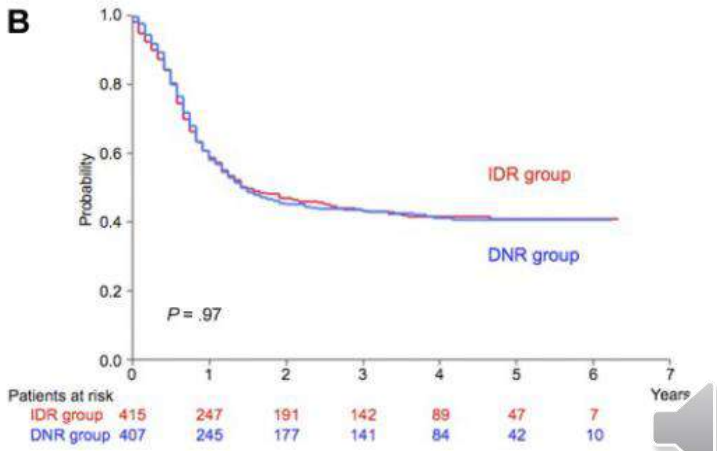
**Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study**

***Daunorubicine : 50 mg/m² x 5j***
***Ou Idarubicine: 12 mg/m² x 3j***
*+cytarabine 100 mg/m²x7*

Table 2. Results of induction therapy

| | IDR group, n (%) | DNR group, n (%) |
|---|---|---|
| Patients | 532 | 525 |
| CR | 416 (78.2) | 407 (77.5) |
| CR by 1 course | 341 (64.1) | 321 (61.1) |
| CR by 2 courses | 75 (14.1) | 86 (16.4) |
| 95% CI | 74.5-81.5 | 73.8-80.9 |



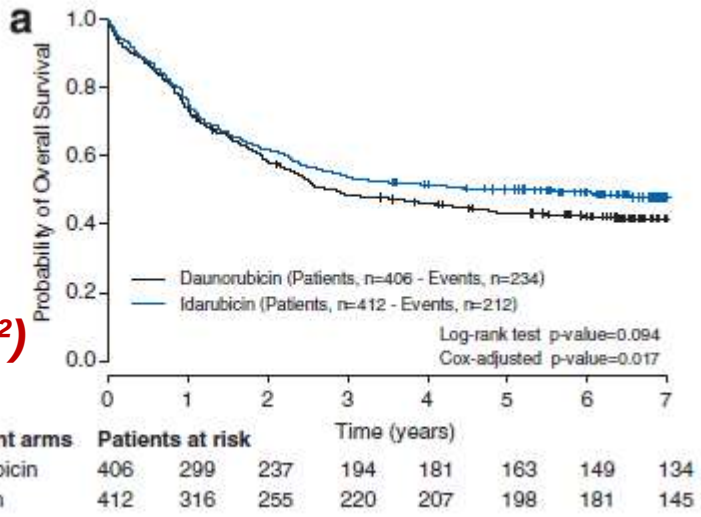
# Daunorubicine *vs.* idarubicine



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

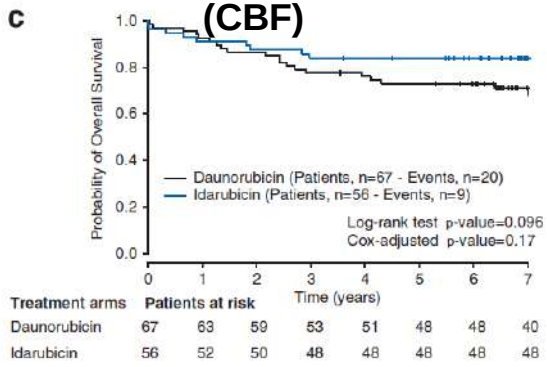
*Leukemia* (2014) **28**, 440–443; doi:10.1038/leu.2013.290

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

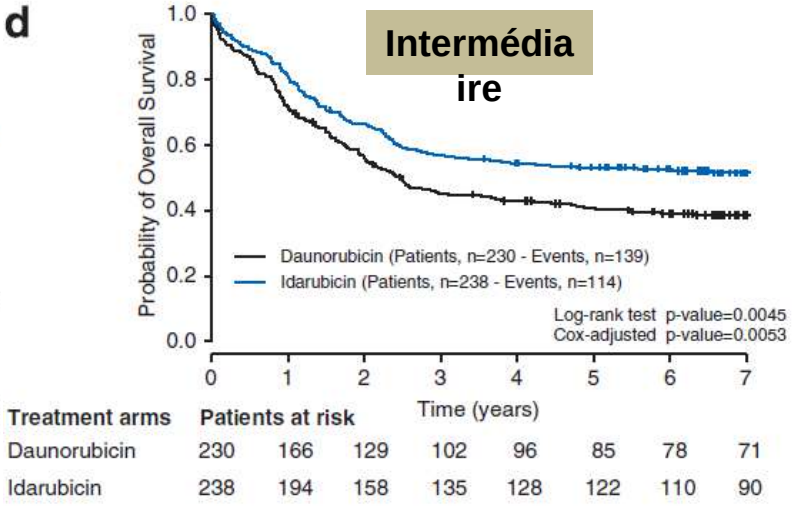



***Daunorubicine : 60 mg/m² x 3j (DT: 420-470 mg/m²)***
***Ou Idarubicine: 8 mg/m² x 5j (DT: 88-104 mg/m²)***
*+cytarabine 200 mg/m²x7*

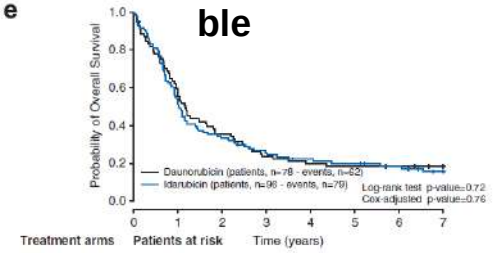
**Favorable (CBF)**



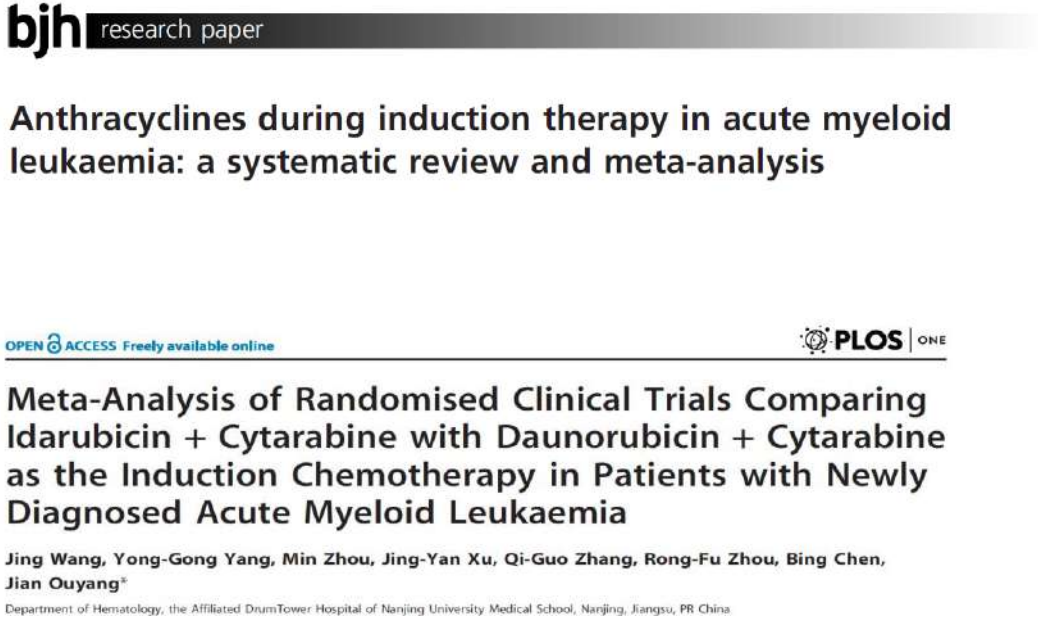

**Intermédiaire**




**Défavorable**



# Daunorubicine *vs.* idarubicine méta-analyses



bjh research paper

Anthracyclines during induction therapy in acute myeloid leukaemia: a systematic review and meta-analysis

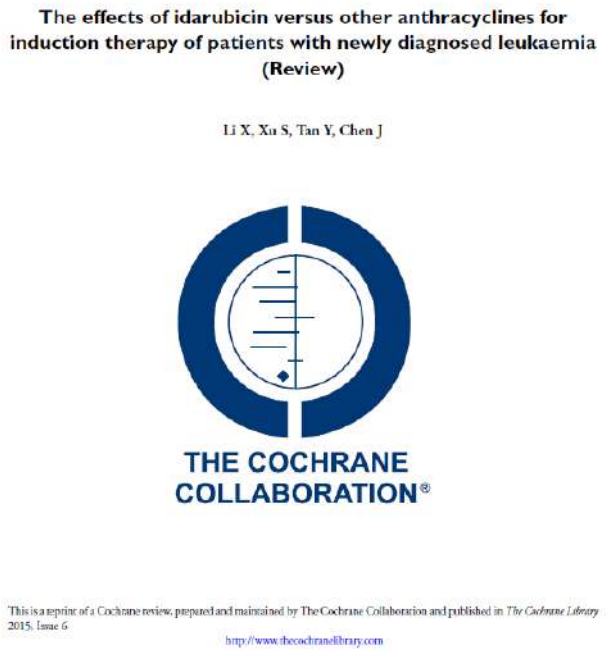
OPEN ACCESS Freely available online

PLOS ONE

Meta-Analysis of Randomised Clinical Trials Comparing Idarubicin + Cytarabine with Daunorubicin + Cytarabine as the Induction Chemotherapy in Patients with Newly Diagnosed Acute Myeloid Leukaemia

Jing Wang, Yong-Gong Yang, Min Zhou, Jing-Yan Xu, Qi-Guo Zhang, Rong-Fu Zhou, Bing Chen, Jian Ouyang*

Department of Hematology, the Affiliated DrumTower Hospital of Nanjing University Medical School, Nanjing, Jiangsu, PR China



The effects of idarubicin versus other anthracyclines for induction therapy of patients with newly diagnosed leukaemia (Review)

Li X, Xu S, Tan Y, Chen J

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 6

http://www.thecochranelibrary.com

*Compared with DNR in induction therapy of newly diagnosed AML,* ***IDA prolongs OS and DFS, increases CR rate and reduces relapse rate****, although increases the risks of death on induction therapy and grade 3/4*

Question 4: la patiente est en rémission complète après une cure. Le bilan complémentaire montre un caryotype normal et un génotype avec mutation de *NPM1* et *FLT3*-ITD (ratio 0.5).
Quel type de consolidation choisissez-vous?

1. Anthracycline + cytarabine à dose intermédiaire

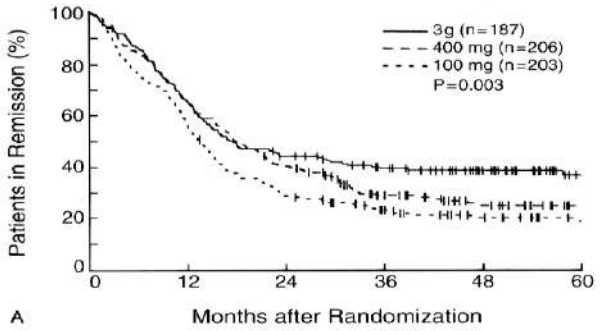
2. Cytarabine 1.5 g/m²/12h x 3 jours

3. Cytarabine 3g/m²/12h x 3 jours

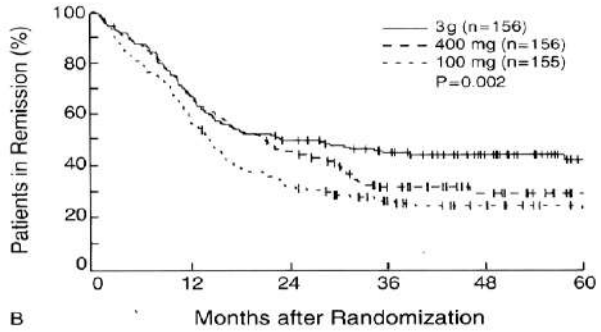
4. Schéma multi-agents avec anthracycline + cytarabine à dose standard (100-200 mg/m²) en perfusion continue

# Traitement de post-rémission

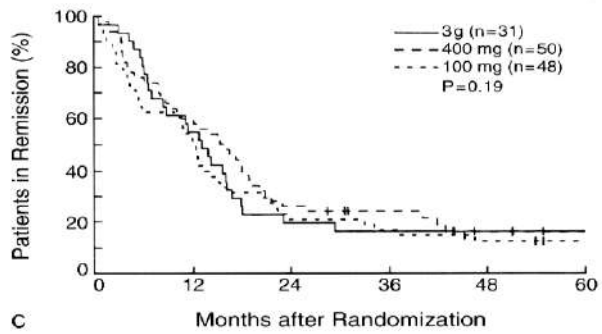
*repose sur la cytarabine*




All patients




Age ≤ 60y




Age > 60y

Mayer et al, NEJM 1994

# HiDAC: 3 ou 4 cures?

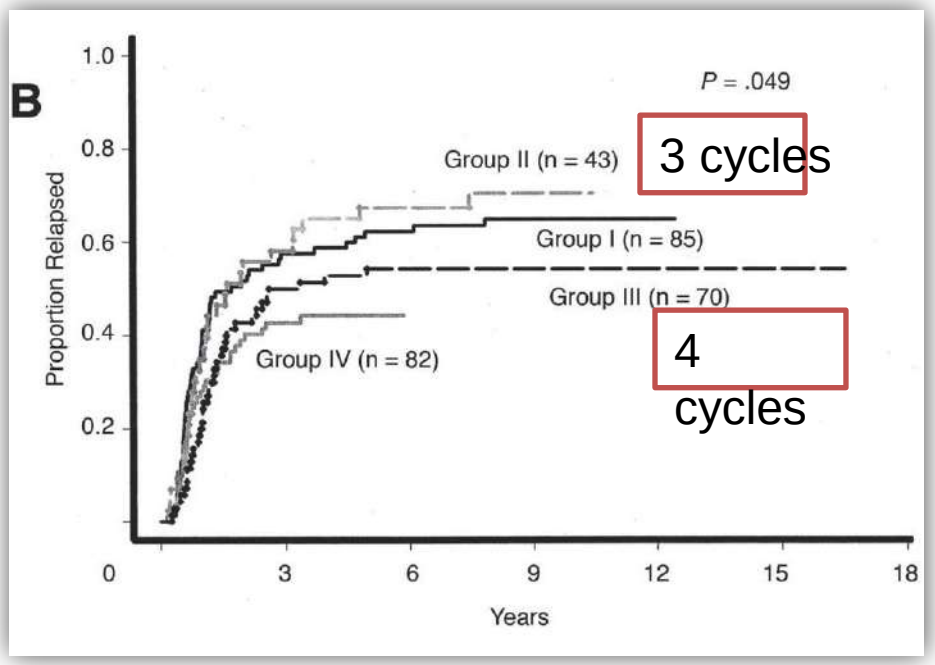
VOLUME 23 · NUMBER 3 · JANUARY 20 2005
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

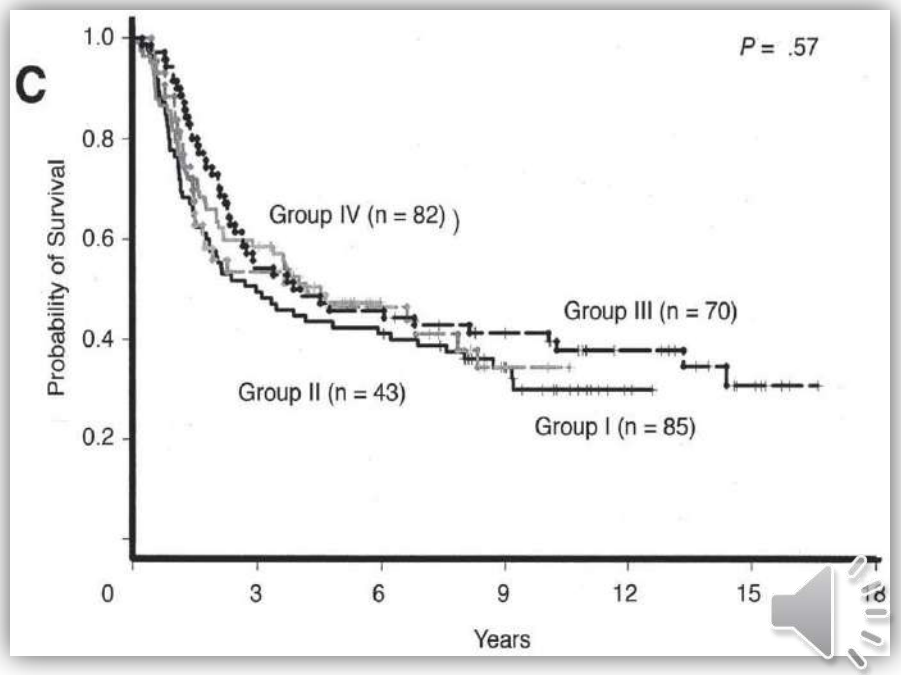
**CALGB**

Etude comparative d'essais prospectifs dans les LA

Outcome of Induction and Postremission Therapy in Younger Adults With Acute Myeloid Leukemia With Normal Karyotype: A Cancer and Leukemia Group B Study

*Sherif S. Farag, Amy S. Ruppert, Krzysztof Mrózek, Robert J. Mayer, Richard M. Stone, Andrew J. Carroll, Bayard L. Powell, Joseph O. Moore, Mark J. Pettenati, Prasad R.K. Koduru, Judith Stamberg, Maria R. Baer, AnneMarie W. Block, James W. Vardiman, Jonathan E. Kolitz, Charles A. Schiffer, Richard A. Larson, and Clara D. Bloomfield*



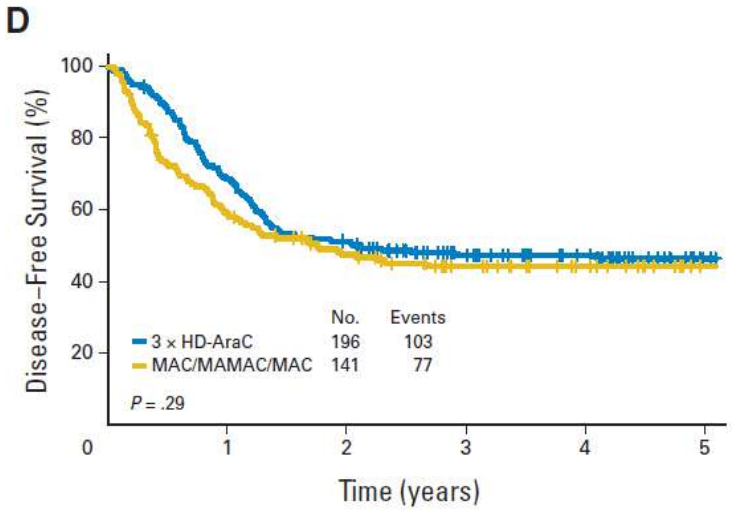

Farag, et al, JCO 2005

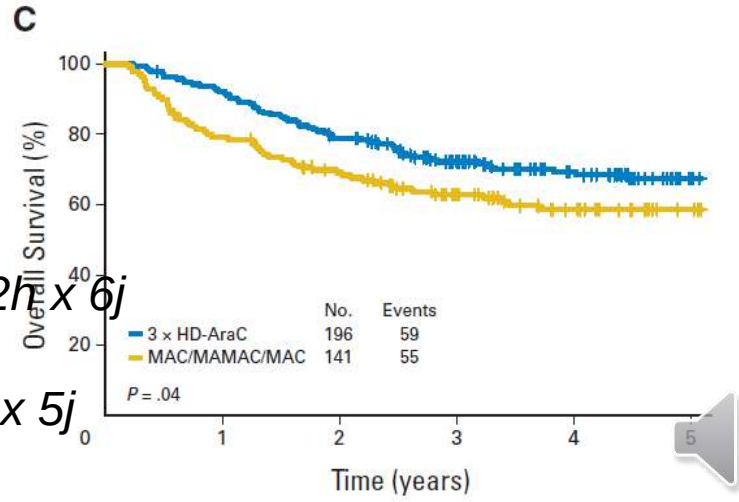
# Anthracyclines + cytarabine dose intermédiaire

VOLUME 31 · NUMBER 17 · JUNE 10 2013
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

High-Dose Cytarabine Consolidation With or Without Additional Amsacrine and Mitoxantrone in Acute Myeloid Leukemia: Results of the Prospective Randomized AML2003 Trial

*Markus Schaich, Stefani Parmentier, Michael Kramer, Thomas Illmer, Friedrich Stölzel, Christoph Röllig, Christian Thiede, Mathias Hänel, Kerstin Schäfer-Eckart, Walter Aulitzky, Hermann Einsele, Anthony D. Ho, Hubert Serve, Wolfgang E. Berdel, Jiri Mayer, Norbert Schmitz, Stefan W. Krause, Andreas Neubauer, Claudia D. Baldus, Johannes Schetelig, Martin Bornhäuser, and Gerhard Ehninger*




*Cytarabine 3g/m²/12h J1 J3 J5 x 3 cycles*
*Vs.*
*C1-C2*
*Mitoxantrone 10 mg/m² x 3j + cytarabine 1g/m²/12h x 6j*
*C3*
*Amsacrine 100 mg/m² x5j +cytarabine 1g/m²/12h x 5j*

# Anthracyclines + cytarabine dose intermédiaire

VOLUME 31 · NUMBER 17 · JUNE 10 2013
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

High-Dose Cytarabine Consolidation With or Without Additional Amsacrine and Mitoxantrone in Acute Myeloid Leukemia: Results of the Prospective Randomized AML2003 Trial

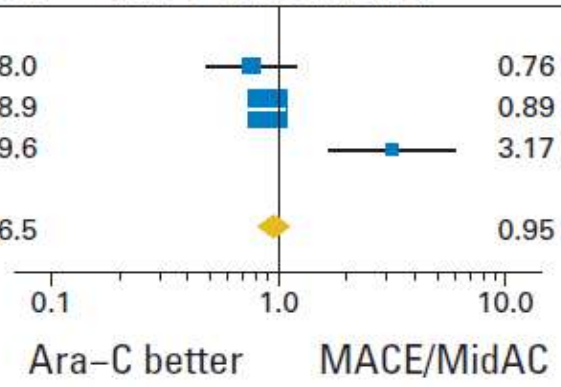
*Markus Schaich, Stefani Parmentier, Michael Kramer, Thomas Illmer, Friedrich Stölzel, Christoph Röllig, Christian Thiede, Mathias Hänel, Kerstin Schäfer-Eckart, Walter Aulitzky, Hermann Einsele, Anthony D. Ho, Hubert Serve, Wolfgang E. Berdel, Jiri Mayer, Norbert Schmitz, Stefan W. Krause, Andreas Neubauer, Claudia D. Baldus, Johannes Schetelig, Martin Bornhäuser, and Gerhard Ehninger*

*Cytarabine 3g/m²/12h J1 J3 J5 x 3 cycles*
*Vs.*

| | |
|---|---|
| MACE | Amsacrine 100 mg/m² days 1-5; cytarabine 200 mg/m² continuous days 1-5; etoposide 100 mg/m² days 1-5 |
| MidAC | Mitoxantrone 10 mg/m² daily by slow IV push on days 1-5 inclusive (5 doses), cytarabine 1.0 g/m² 12-hourly by 2-hour IV infusion on days 1-3 inclusive (6 doses) |

**A**

| | Deaths/Patients Ara–C | MACE/MidAC | Statistics (O–E) | Var. | OR & 95% CI (Ara–C MACE/MidAC) |
|---|---|---|---|---|---|
| Cytogenetic group | | | | | |
| Favorable | 32/153 | 40/153 | –5.0 | 18.0 | 0.76 (0.48 to 1.20) |
| Intermediate | 204/428 | 232/452 | –12.5 | 108.9 | 0.89 (0.74 to 1.08) |
| Adverse | 29/31 | 13/23 | 11.0 | 9.6 | 3.17 (1.68 to 5.97) |
| Total | 265/612 | 285/628 | –6.4 | 136.5 | 0.95 (0.81 to 1.13) |




Test for heterogeneity (3 groups): $\chi^2_2 = 15.2$; $P < .001$
Overall test for trend: $\chi^2_1 = 9.0$; $P = .003$

Effect $2P = 0.6$; NS

# Schéma multi-agents avec anthracyclines + cytarabine à dose standard

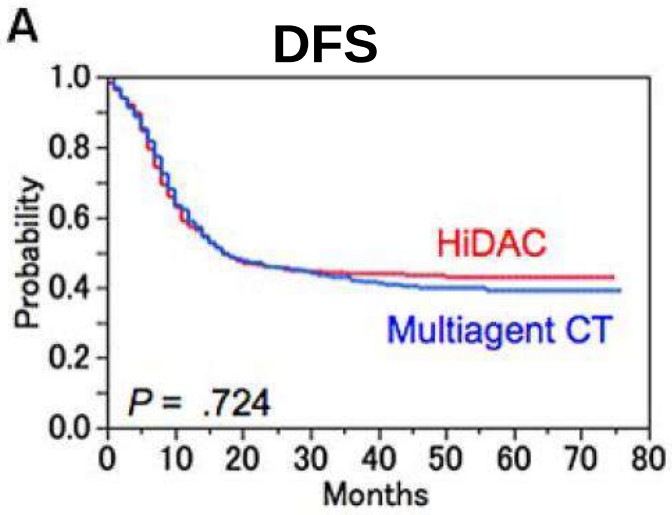
blood

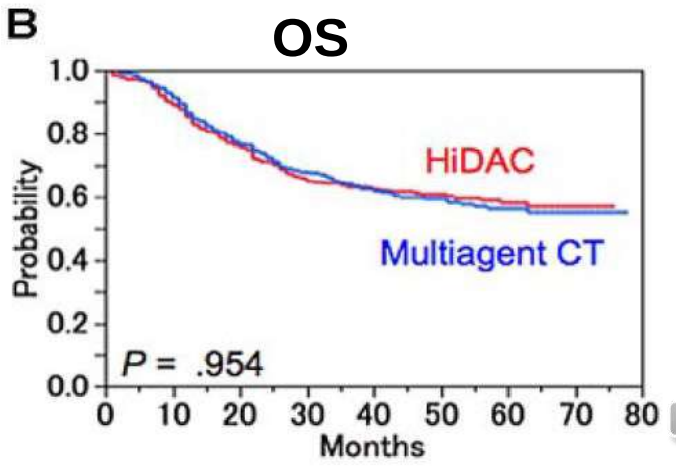
2011 117: 2366-2372
Prepublished online Dec 29, 2010;
doi:10.1182/blood-2010-07-295279

**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**

HiDAC: 2g/m$^2$/12h x 5j (3 cycles) *vs.*
Ara-C IVC 200 mg/m$^2$ x 5j + anthracycline (4 cycles

of multiagent CT consisted of mitoxantrone (7 mg/m$^2$ by 30-minute infusion for 3 days) and Ara-C (200 mg/m$^2$ by 24-hour continuous infusion for 5 days). The second consisted of DNR (50 mg/m$^2$ by 30-minute infusion for 3 days) and Ara-C (200 mg/m$^2$ by 24-hour continuous infusion for 5 days). The third consisted of aclarubicin (20 mg/m$^2$ by 30-minute infusion for 5 days) and Ara-C (200 mg/m$^2$ by 24-hour continuous infusion for 5 days). The fourth consisted of Ara-C (200 mg/m$^2$ by 24-hour continuous infusion for 5 days), etoposide (100 mg/m$^2$ by 1-hour infusion for 5 days), vincristine (0.8 mg/m$^2$ by bolus injection on day 8), and vindesine (2 mg/m$^2$ by bolus injection on day 10). Each consolidation was started as soon as



# Cytarabine 3g/m² vs. 1.5g/m²

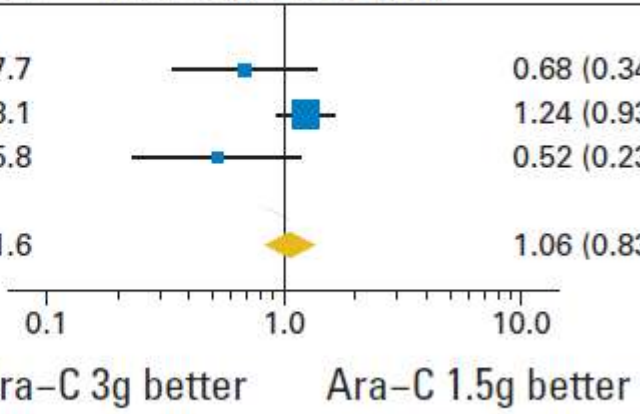
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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*

**B**

| | Deaths/Patients | | Statistics | | OR & 95% CI |
|---|---|---|---|---|---|
| | Ara–C 3g | Ara–C 1.5g | (O–E) | Var. | (Ara–C 3g Ara–C 1.5g) |
| Cytogenetic group | | | | | |
| Favorable | 13/64 | 18/66 | –3.0 | 7.7 | 0.68 (0.34 to 1.38) |
| Intermediate | 104/195 | 89/197 | 10.3 | 48.1 | 1.24 (0.93 to 1.64) |
| Adverse | 13/13 | 14/14 | –3.7 | 5.8 | 0.52 (0.23 to 1.19) |
| Total | 130/272 | 121/277 | 3.6 | 61.6 | 1.06 (0.83 to 1.36) |




Test for heterogeneity (3 groups): $\chi^2_2 = 5.5$; $P = .06$

Overall test for trend: $\chi^2_1 = 0.0$; $P = .9$; NS

Effect $2P = 0.6$; NS

# Cytarabine 3g/m² vs. dose intermédiaire



**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

| | 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.

There is no direct evidence either to suggest that any particular genetically defined subset of AML would benefit from HDAC dose levels of the drug.

The accumulated circumstantial evidence may even suggest the plausible notion that a single cycle of 1000 mg/m² cytarabine given twice daily in the treatment of AML might be sufficient.

Question 5: Après une cure de consolidation, la patiente est toujours en RC. Elle est en bon état général. Les éléments complémentaires de son dossier sont les suivants: ratio allélique: 0.5; présence d'un donneur HLA compatible phéno-identique 10/10.

1. Vous proposez une allogreffe de cellules souches hématopoïétiques.

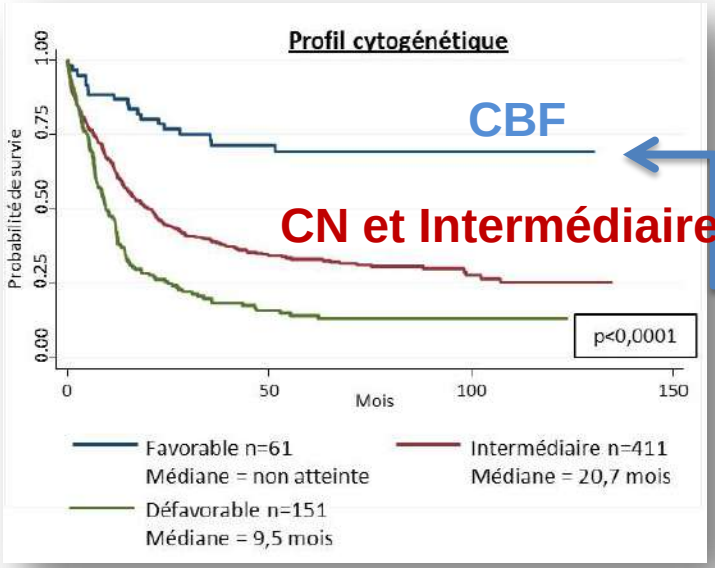
2. Vous proposez de conclure le traitement par deux cures supplémentaires de chimiothérapie de consolidation.

3. Vous proposez une allogreffe uniquement si la maladie résiduelle NPM1 est positive.

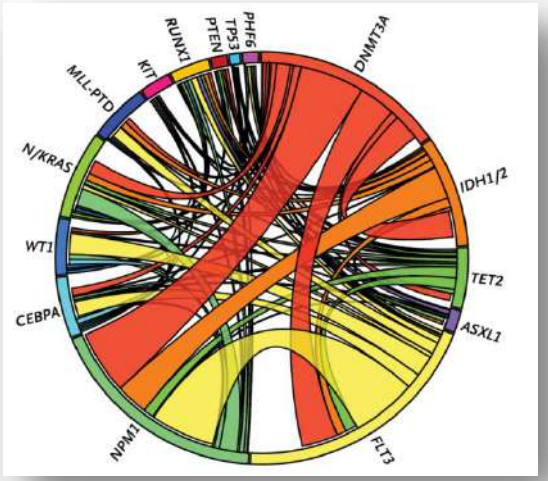
# Essai BIG-1

- **R1 Induction : daunorubicine (270 mg/m²) vs idarubicine (45 mg/m²)**
  - Objectif: OS à 3 ans, 45 vs 55%, 1018 patients
- **R2 post induction : cytarabine haute dose (HDAC) vs. intermédiaire (IDAC)**
  - Objectif: non infériorité (<8%, HR,1.25), 3100 patients
  - Analyse intermédiaire à 18, 36 et 56 mois
- **R3 allogreffe : prévention de la GvH aiguë**
  - MAC (<45 ans et Sorror <2): Ciclo-MTX vs. Ciclo-AMp
  - RIC (≥45 ans ou Sorror>2): Ciclo vs. Ciclo-Amp
  - Objectif: réduction de 15%; MAC 60 vs. 45% (346 pts); RIC 50 vs. 35% (326 pts)
  - Analyse intermédiaire à 200 et 400 patients
- **R4 post remission**
  - Phase 2
  - IDAC ou HDAC vs. IDAC ou HDAC + X
  - Objectif: survie sans leucémie à 18 mois: 55 à 75%, 200 patients

# Impact des mutations au sein des sous-groupes cytogénétiques




| Gene | Overall Frequency (%) |
|---|---|
| *FLT3* (ITD, TKD) | 37 (30, 7) |
| *NPM1* | 29 |
| *DNMT3A* | 23 |
| *NRAS* | 10 |
| *CEBPA* | 9 |
| *TET2* | 8 |
| *WT1* | 8 |
| *IDH2* | 8 |
| *IDH1* | 7 |
| *KIT* | 6 |
| *RUNX1* | 5 |
| *MLL-PTD* | 5 |
| *ASXL1* | 3 |
| *PHF6* | 3 |
| *KRAS* | 2 |
| *PTEN* | 2 |
| *TP53* | 2 |
| *HRAS* | 0 |
| *EZH2* | 0 |




CHU de Toulouse
2000-2009: 643 patients
CTx intensive

**Les trois qualités d'un marqueur moléculaire**

* Impact pronostique clair * Impact thérapeutique *
Marqueur de maladie résiduelle

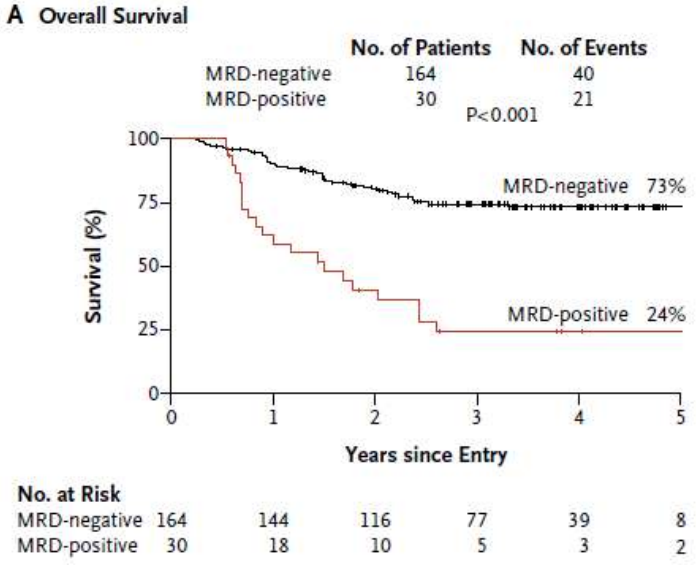
# Impact du contexte mutationnel et de la maladie résiduelle

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

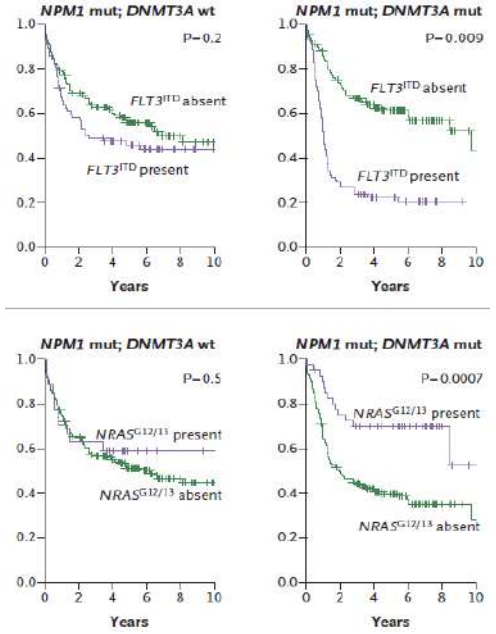



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2016 VOL. 374 NO. 23

## Genomic Classification and Prognosis in Acute Myeloid Leukemia

Elli Papaemmanuil, Ph.D., Moritz Gerstung, Ph.D., Lars Bullinger, M.D., Verena I. Gaidzik, M.D., Peter Paschka, M.D., Nicola D. Roberts, B.Sc., Nicola E. Potter, Ph.D., Michael Heuser, M.D., Felicitas Thol, M.D., Niccolo Bolli, M.D., Ph.D., Gunes Gundem, Ph.D., Peter Van Loo, Ph.D., Inigo Martincorena, Ph.D., Peter Ganly, B.M., B.Ch., Ph.D., Laura Mudie, B.Sc., Stuart McLaren, B.Sc., Sarah O'Meara, B.Sc., Keiran Raine, M.Sc., David R. Jones, M.Sc., Jon W. Teague, B.Sc., Adam P. Butler, B.Sc., Mel F. Greaves, Ph.D., Arnold Ganser, M.D., Konstanze Döhner, M.D., Richard F. Schlenk, M.D., Hartmut Döhner, M.D., and Peter J. Campbell, M.B., Ch.B., Ph.D.



# Classification ELN 2016
## *interprétation des essais cliniques*

| Risk Category[a] | Genetic Lesion |
|---|---|
| **Favorable** | t(8;21)(q22;q22); *RUNX1-RUNX1T1*<br>inv(16)(p13.1q22); *CBFB-MYH11*<br>Mutated *NPM1* without *FLT3*-ITD[b] (normal karyotype)<br>Biallelic mutated *CEBPA* |
| **Intermediate-I** | Mutated *NPM1* and *FLT3*-ITD[b] (normal karyotype)<br>Wild type *NPM1* and *FLT3*-ITD[b] (normal karyotype)<br>Wild type *NPM1* without *FLT3*-ITD (normal karyotype) |
| **Intermediate-II** | t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*<br>Cytogenetic abnormalities not classified as favorable or adverse |
| **Adverse** | t(6;9)(p23;q34.1); *DEK-NUP214*<br>t(v;11q23); *KMT2A* rearranged<br>t(9;22)(q34.1;q11.2); *BCR-ABL1*<br>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*<br>Complex karyotype (≥3), -5 or del(5q); -7; -17/abn(17p)<br>**Mutated *RUNX1*[c]**<br>**Mutated *ASXL1*[c]**<br>**Mutated *TP53*[d]** |

[a] Prognostic impact of a marker is treatment-dependent and may change with new therapies
[b] Prognostic impact of *FLT3*-ITD dependent on mutant to wildtype ITD allelic ratio
[c] These mutations should not be used as adverse prognostic marker if they co-occur with favorable-risk AML subtypes
[d] *TP53* mutations frequently occur in AML with complex karyotype; in this context they portend a particularly poor prognosis

# Classification du BIG-1
## *indications des allogreffes en RC1*

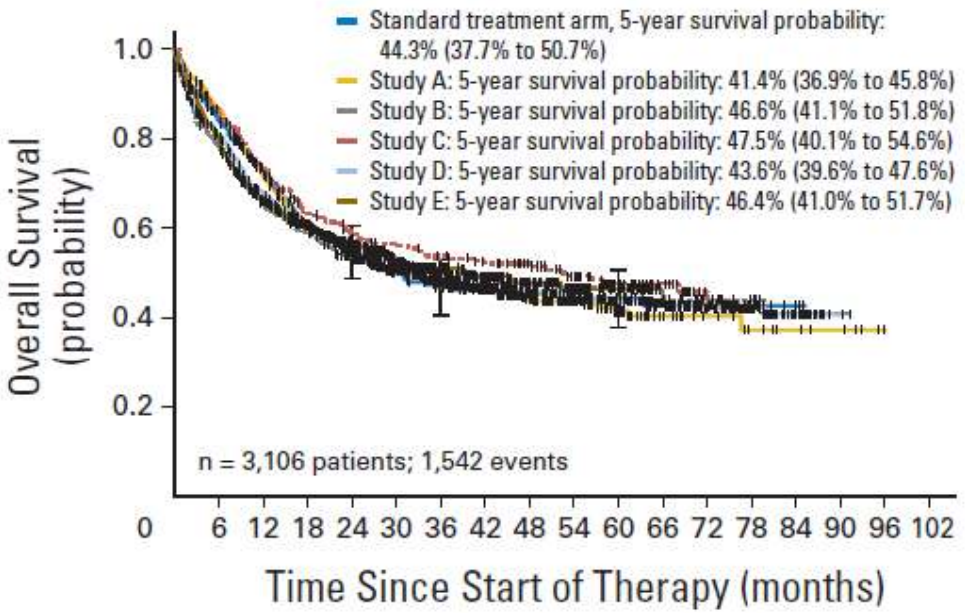
| **Classification** | **Caractéristiques** | **Survie globale** | **Allogreffe/ type donneur/conditionnement** |
|---|---|---|---|
| Risque favorable* | Caryotype normal **et** mutation *NPM1* **et** absence de mutation *FLT3*-ITD ou ratio *FLT3*-ITD < 0.10 **et** MRD2 pour *NPM1* < *1 %*<br>Caryotype normal **et** mutation *CEBPA* « bi-allélique » **et** absence de mutation *FLT3*-ITD ou ratio *FLT3*-ITD < 0.10<br>Une seule cure pour obtenir la première RC* | 60-70 % | Allogreffe : non |
| Risque intermédiaire** | Tous les autres<br>t(3;5)(q21~25;q31~35)<br>t(9;11)(p21~22;q23)<br>t(11;19)(q23;p13)<br>t(6;9)(p23;q34) isolée (en l'absence de *FLT3*-ITD)<br>Caryotypes complexes non monosomiques | 25-40 % | Allogreffe : oui<br>Type de donneur:<br>HLA génoidentique<br>HLA phénoidentique 10/10<br>Conditionnement:<br>MAC ou RIC selon âge et score de Sorror |
| Risque défavorable*** | Anomalie 3q [excluant t(3;5)(q21~25;q31~35)]<br>inv(3)(q21q26.2) ou t(3;3)(q21;q26.2)<br>t(6;11)(q27;q23)<br>t(10;11)(p11~13;q23)<br>t(11q23) sauf t(9;11)(p21~22;q23) et t(11;19)(q23;p13)<br>add(5q), del(5q), -5<br>-7, add(7q)/del(7q)<br>-17/anomalie 17p<br>Caryotype monosomique<br>t(6;9)(p23;q34) et mutation *FLT3-ITD* | 10-15 % | Allogreffe : oui<br>Type de donneur :<br>HLA génoidentique<br>HLA phénoidentique 10/10 ou 9/10<br>Conditionnement : FLAMSA RIC<br><br>Hors BIG-1 :<br>Sang de cordon<br>HLA haplo-identique |

# Hétérogénéité thérapeutique
## *Existe-t-il un traitement standard?*

**Induction 1:**
Ara-C 100 mg/m² J1-J7
ivc
Daunorubicine 60 mg/m²
J3, 4, 5

**Induction 2 à J22:**
Ara-C 100 mg/m² J1-J7
ivc
Daunorubicine 60 mg/m²
J3, 4, 5

**Post-rémission:**
Ara-C 3g/m²/12h J1, 3, 5
3 cycles



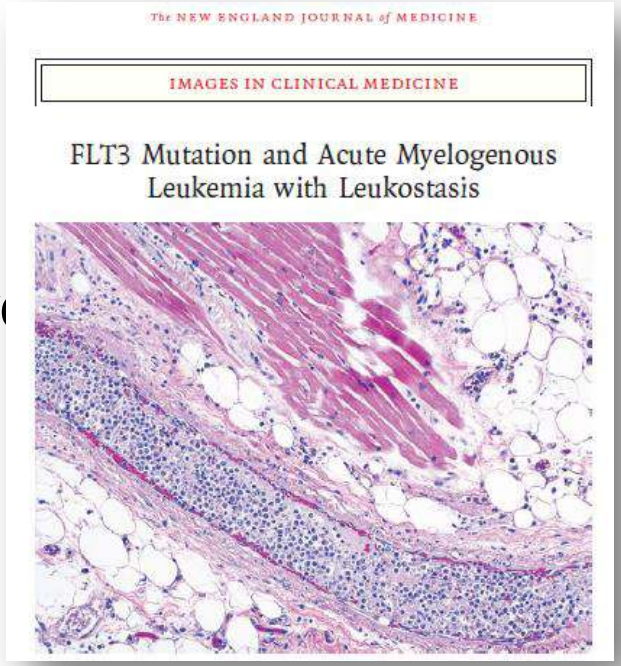

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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, Utz 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*

# *FLT3*-ITD

- De novo
- Hyperleucocytose
- ↑ % de blastes sanguins et médullair
- Caryotype normal (65-70%)
- Association aux mutations de NPM1



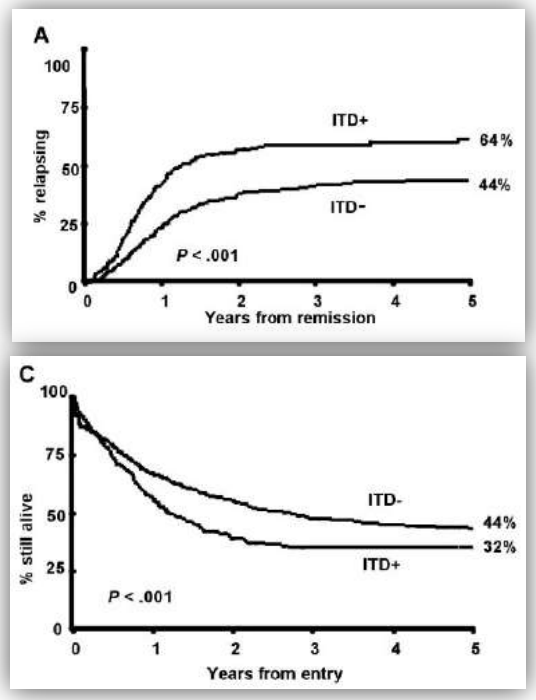

- Rechute:
  - perte de la mutation ou émergence d'un autre mutant FLT3-ITD
  - 88% des patients présentent la même mutation qu'au diagnostic
  - Ratio ITD/wt ↑: perte de l'allèle sauvage, disomie uniparentale (UPD13q)

# Pronostic

CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

## The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials

Panagiotis D. Kottaridis, Rosemary E. Gale, Marion E. Frew, Georgina Harrison, Stephen E. Langabeer, Andrea A. Belton, Helen Walker, Keith Wheatley, David T. Bowen, Alan K. Burnett, Anthony H. Goldstone, and David C. Linch

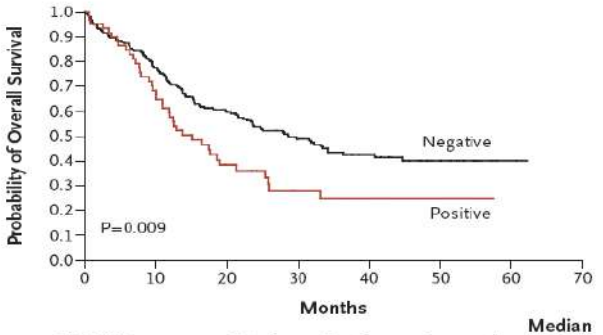



The NEW ENGLAND JOURNAL of MEDICINE

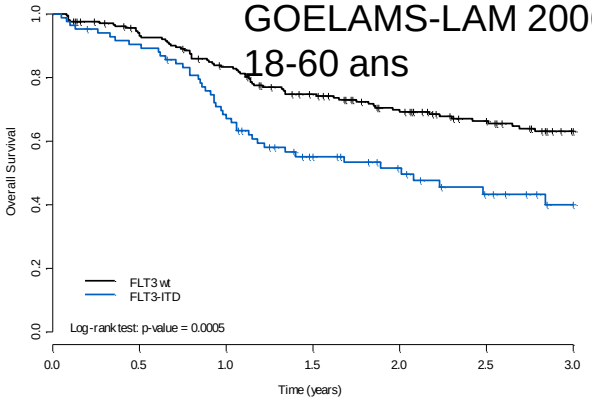
ORIGINAL ARTICLE

## 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.




| *FLT3*-ITD | Total | Deaths | Censored | Median Survival |
|---|---|---|---|---|
| Negative | 241 | 116 | 125 | 28.6 mo |
| Positive | 64 | 39 | 25 | 15.2 mo |

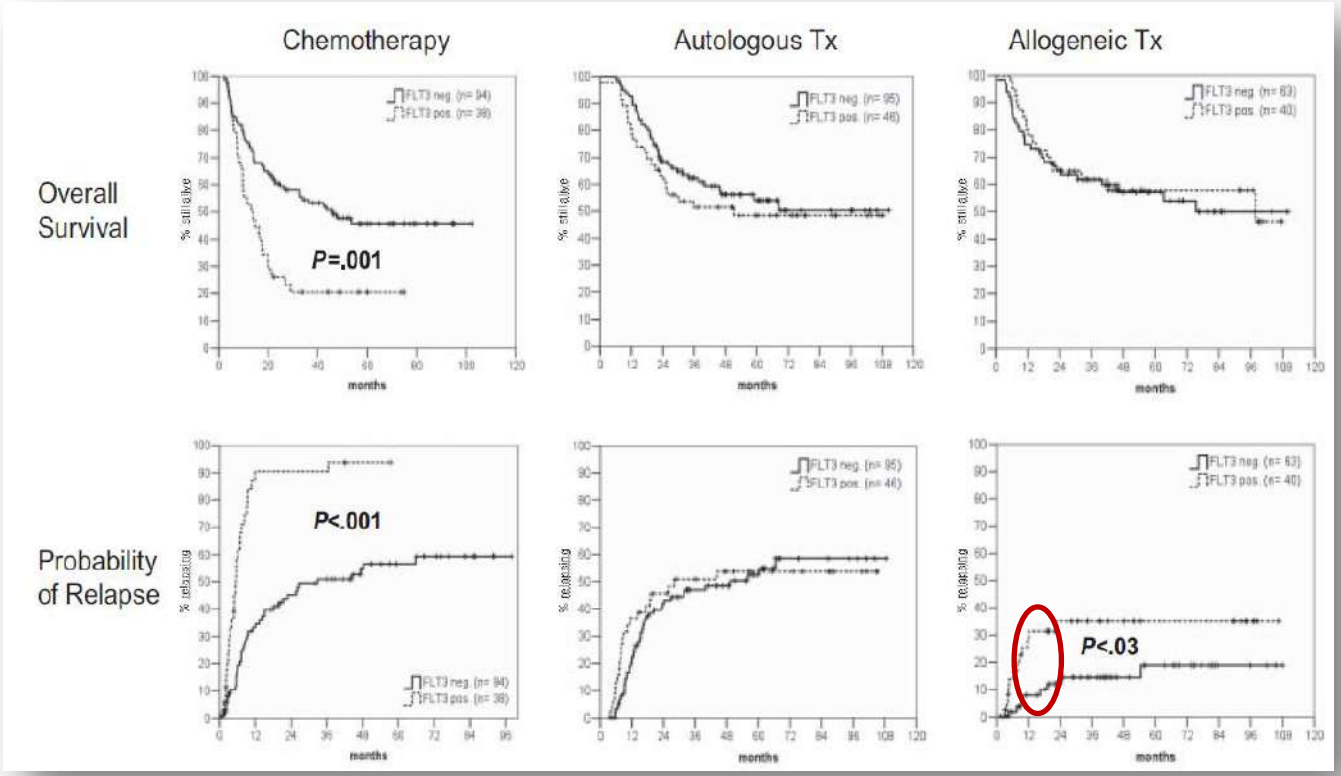



GOELAMS-LAM 2006 IR 18-60 ans

- Pas d'impact sur la RC
- Risque de rechute précoce ++

Kottaridis, Blood 2001

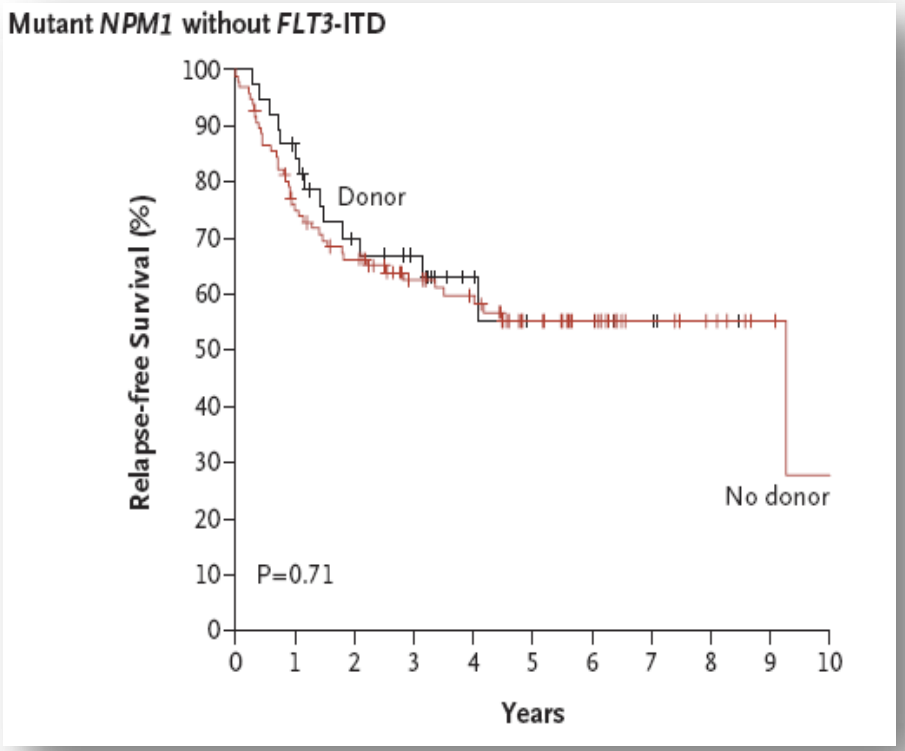
# *FLT3*-ITD et traitement de post-rémission
# Intérêt de l'allogreffe?

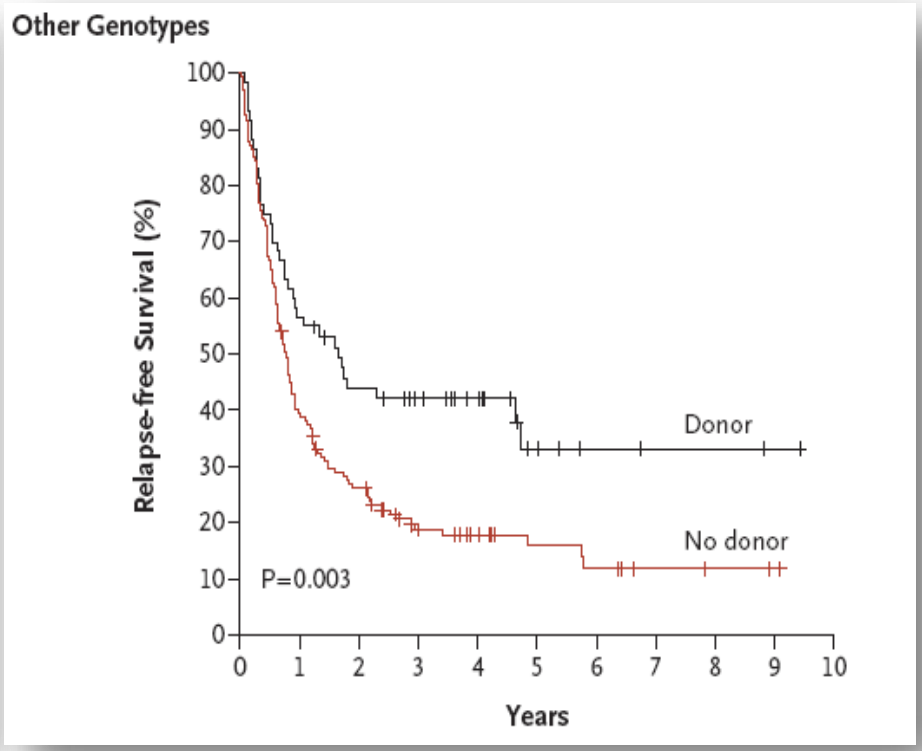



≈30% de rechute post-allo

Gale, Blood 2005; Bornhauser, Blood 2007; Brunet, Curren

# *FLT3*-ITD et post-rémission
# Intérêt de l'allogreffe?

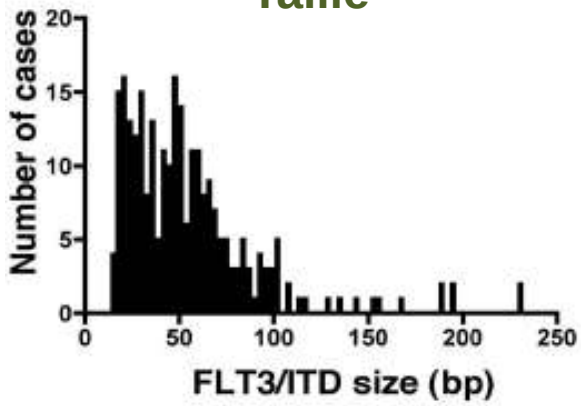


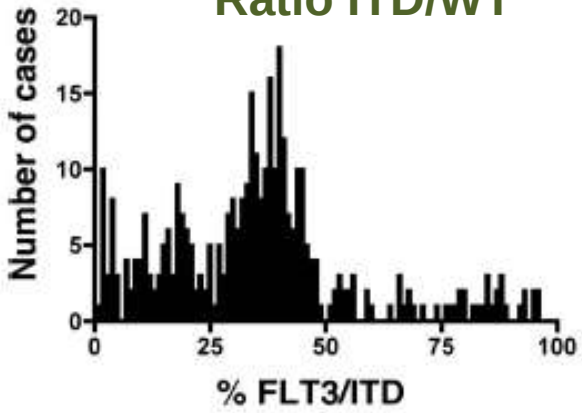

Schlenk F, NEJM 2

# Hétérogénéité des mutations *FLT3*-ITD

## Taille



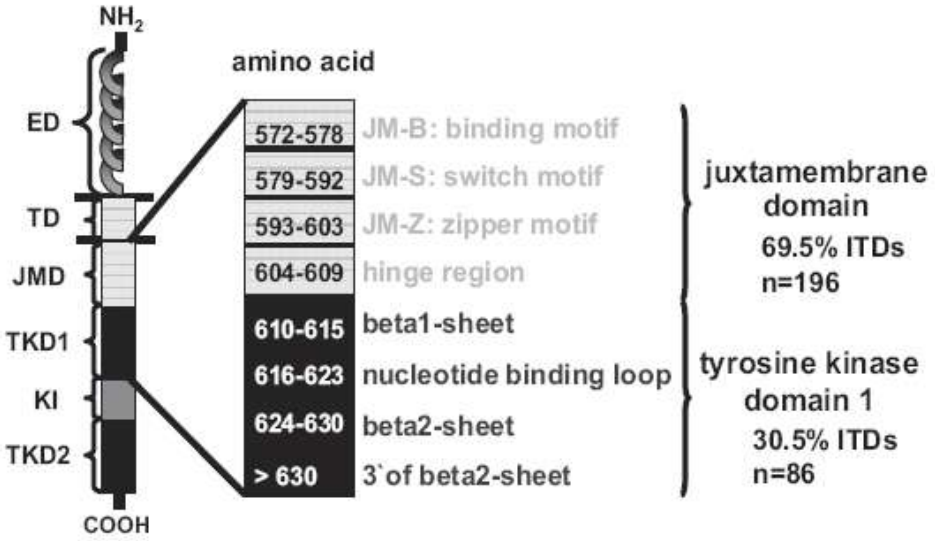

## Ratio ITD/WT




## Nombre de mutations/patients

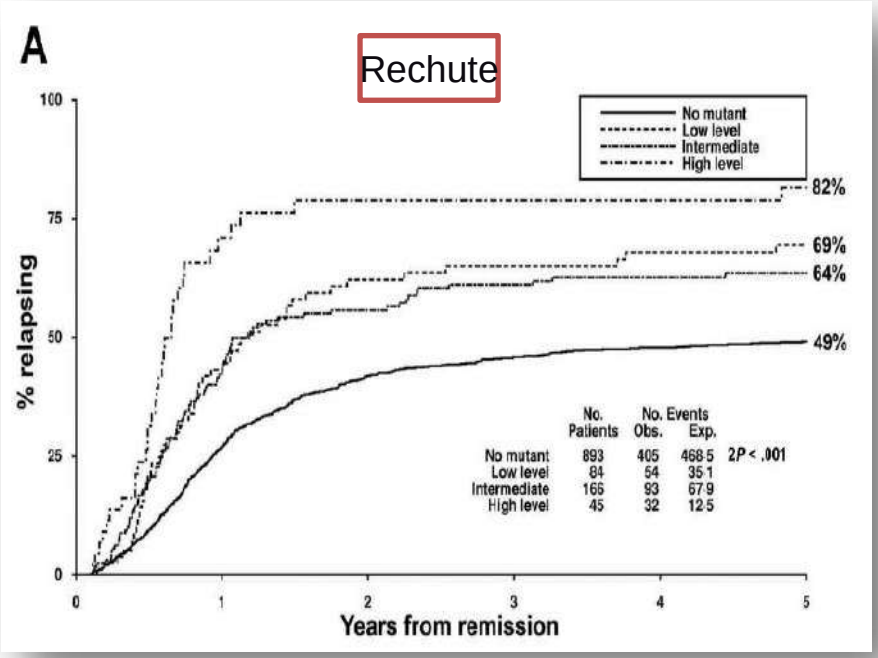
- 1 mutant (73%)
- 2 mutants (21%)
- 3 mutants (5%)
- 4 mutants (1%)

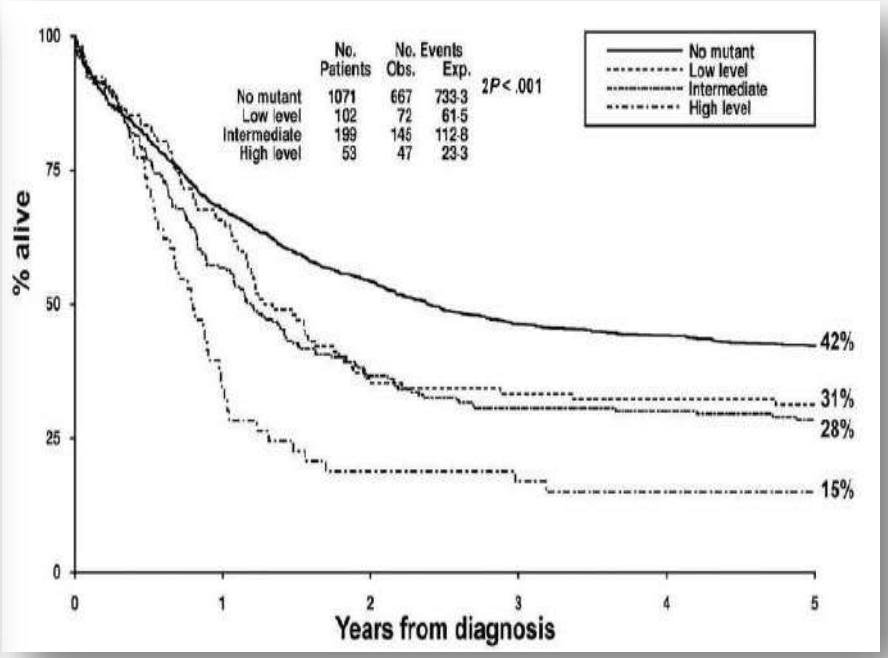
## Localisation de l'insertion




Gale R, Blood 2008; Kayser S,

# Ratio *ITD*/wt




Gale R, Blood, 2

# Influence du ratio *ITD*/wt sur la réponse à l'induction

MYELOID NEOPLASIA

**Differential impact of allelic ratio and insertion site in *FLT3*-ITD–positive AML with respect to allogeneic transplantation**

Richard F. Schlenk,[1] Sabine Kayser,[1] Lars Bullinger,[1] Guido Kobbe,[2] Jochen Casper,[3] Mark Ringhoffer,[4] Gerhard Held,[5] Peter Brossart,[6] Michael Lübbert,[7] Helmut R. Salih,[8] Thomas Kindler,[9] Heinz A. Horst,[10] Gerald Wulf,[11] David Nachbaur,[12] Katharina Götze,[13] Alexander Lamparter,[1] Peter Paschka,[1] Verena I. Gaidzik,[1] Veronica Teleanu,[1] Daniela Späth,[1] Axel Benner,[14] Jürgen Krauter,[15] Arnold Ganser,[15] Hartmut Döhner,[1] and Konstanze Döhner,[1] for the German-Austrian AML Study Group

| Outcome | Distribution of *FLT3*-ITD AR intervals, no. (%) | | | | |
|---|---|---|---|---|---|
| | First (n = 81) | Second (n = 80) | Third (n = 81) | Fourth (n = 81) | *P* value |
| CR | 66 (81.5) | 63 (79.8) | 56 (69.1) | 46 (57.5) | .003 |
| RD | 11 | 12 (15.2) | 17 (21.0) | 30 (37.5) | .001 |
| ED | 4 (4.9) | 4 (5.0) | 8 (9.9) | 4 (5.0) | .53 |

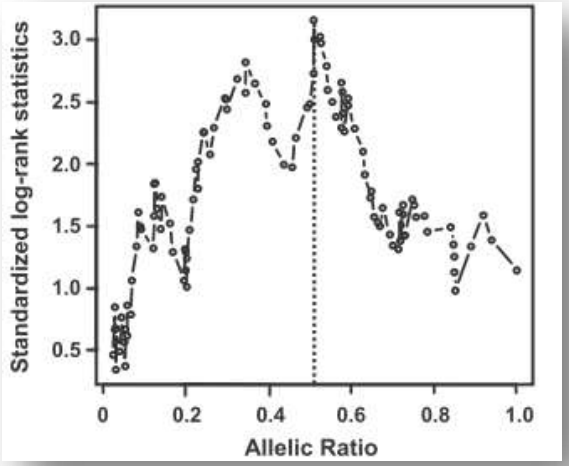
≥ Introduction rapide d'ITK à l'induction ?

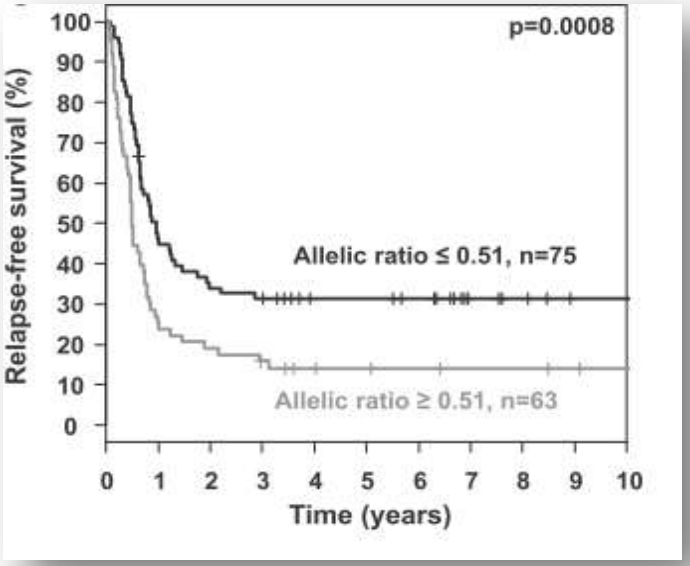
** Taille et nombre d'ITD également associés à la RC*

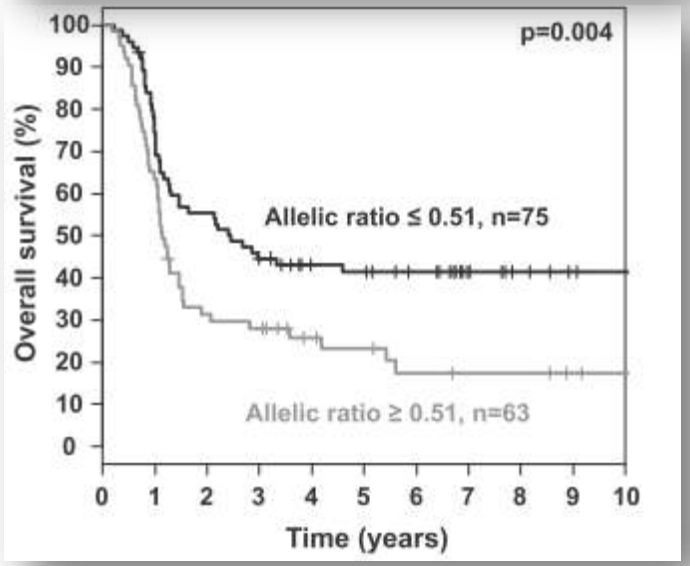
Schlenk, Blood 201

# Influence du ratio *ITD*/wt sur la survie
## Expérience du AMLSG

Patients non allogreffés




Schlenk, Blood 201

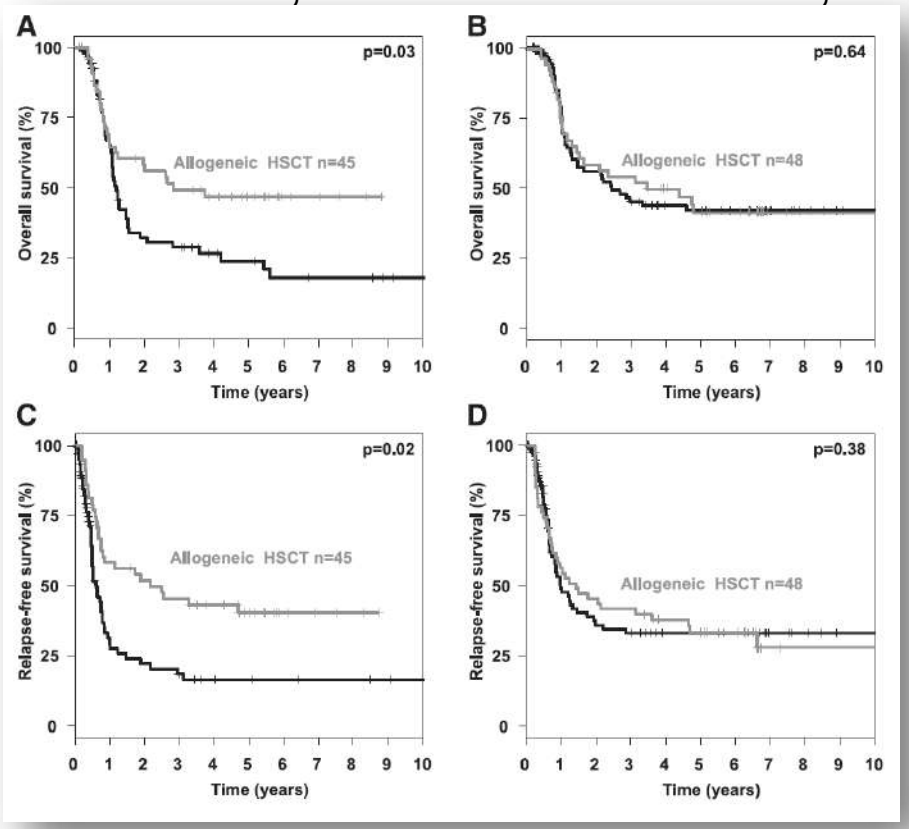
# Ratio *ITD*/wt et allogreffe
## AMLSG

MYELOID NEOPLASIA

**Differential impact of allelic ratio and insertion site in *FLT3*-ITD–positive AML with respect to allogeneic transplantation**

Richard F. Schlenk,[1] Sabine Kayser,[1] Lars Bullinger,[1] Guido Kobbe,[2] Jochen Casper,[3] Mark Ringhoffer,[4] Gerhard Held,[5] Peter Brossart,[6] Michael Lübbert,[7] Helmut R. Salih,[8] Thomas Kindler,[9] Heinz A. Horst,[10] Gerald Wulf,[11] David Nachbaur,[12] Katharina Götze,[13] Alexander Lamparter,[1] Peter Paschka,[1] Verena I. Gaidzik,[1] Veronica Teleanu,[1] Daniela Späth,[1] Axel Benner,[14] Jürgen Krauter,[15] Arnold Ganser,[15] Hartmut Döhner,[1] and Konstanze Döhner,[1] for the German-Austrian AML Study Group

ITD/wt >0,51 | ITD/wt <0,51




Allogreffe à réserver pour les patients avec ratio >0.5?

Schlenk, Blood 201

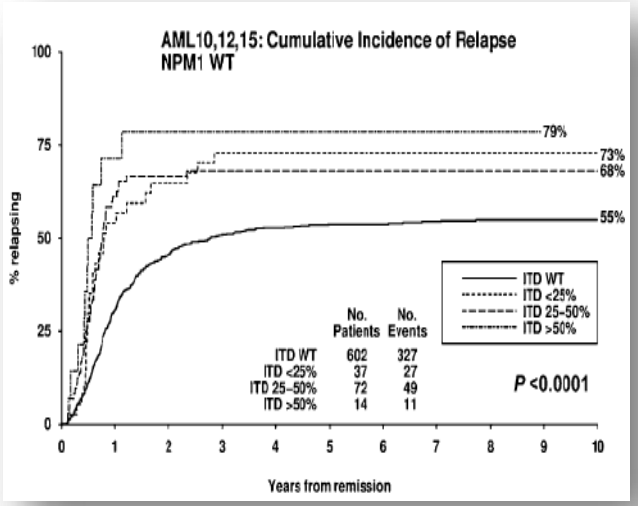
# Ratio *ITD*/wt et allogreffe
## Expérience du MRC

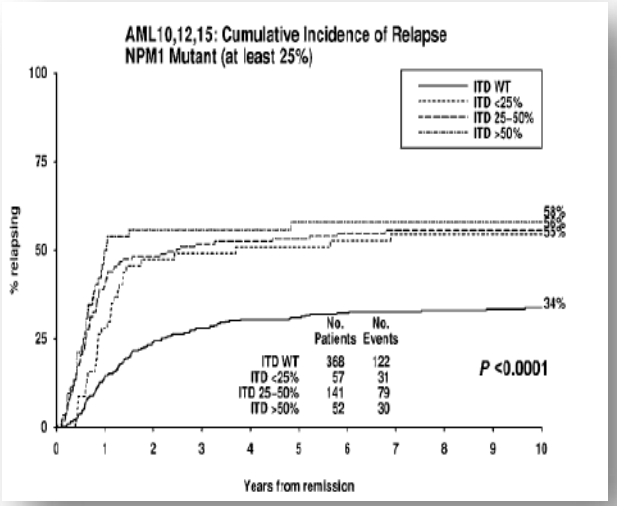
MYELOID NEOPLASIA

**Impact of *FLT3*$^{ITD}$ mutant allele level on relapse risk in intermediate-risk acute myeloid leukemia**

David C. Linch,[1] Robert K. Hills,[2] Alan K. Burnett,[2] Asim Khwaja,[1] and Rosemary E. Gale[1]

[1]Department of Haematology, University College London Cancer Institute, London, United Kingdom; and [2]Department of Haematology, Cardiff University School of Medicine, Cardiff, United Kingdom



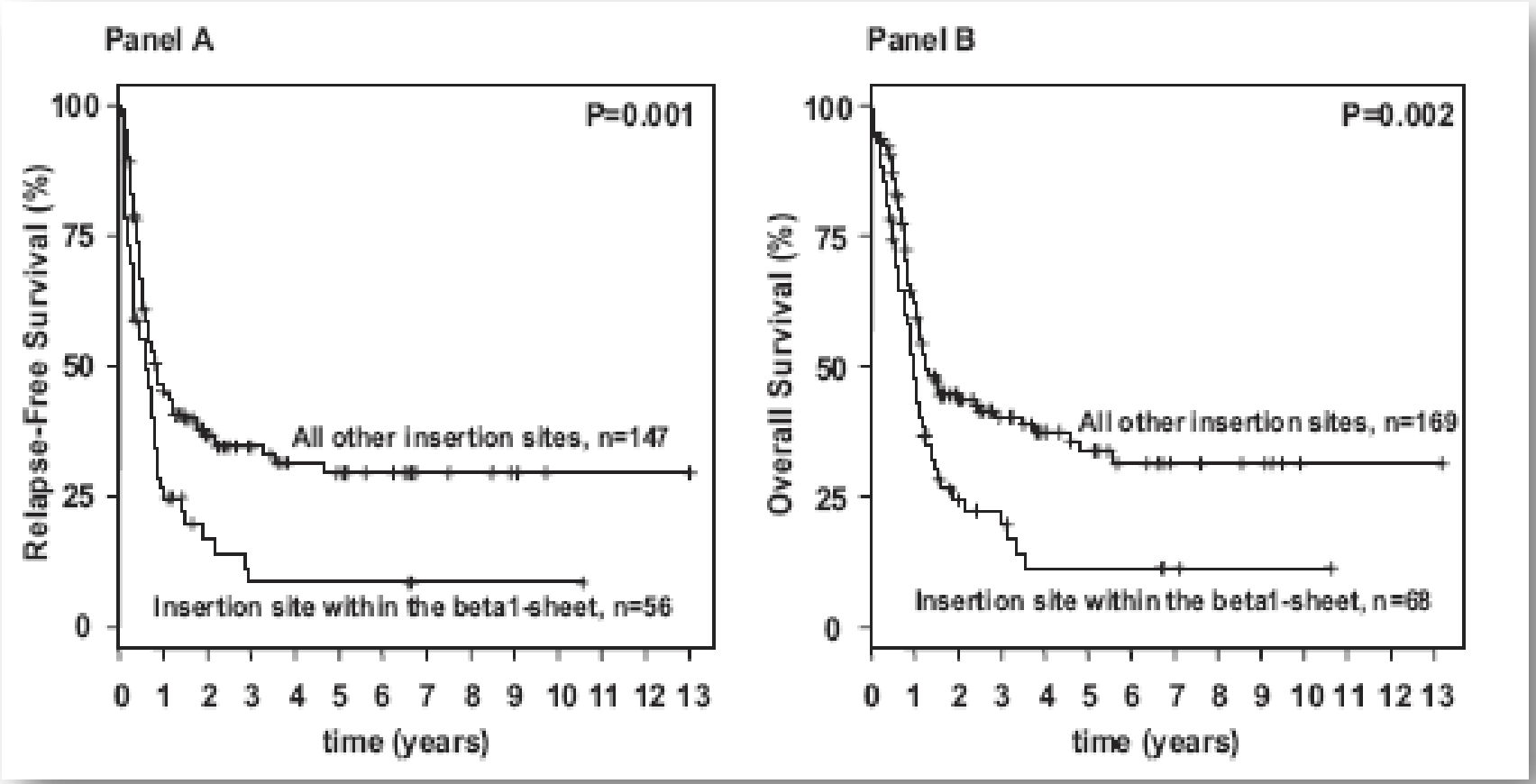




### Key Points

- In cases with intermediate-risk *NPM1*$^{MUT}$ AML, there are only minor differences in relapse risk according to *FLT3*$^{ITD}$ level.
- When considering allogeneic transplantation in first remission, *NPM1*$^{MUT}$ cases with low-level *FLT3*$^{ITD}$ should not be considered as good risk.

Linch, Blood

# Site d'insertion de l'ITD (TKD1)




Kayser S, Blood,

# Site d'insertion de l'ITD (TKD1)

MYELOID NEOPLASIA

**Differential impact of allelic ratio and insertion site in *FLT3*-ITD–positive AML with respect to allogeneic transplantation**

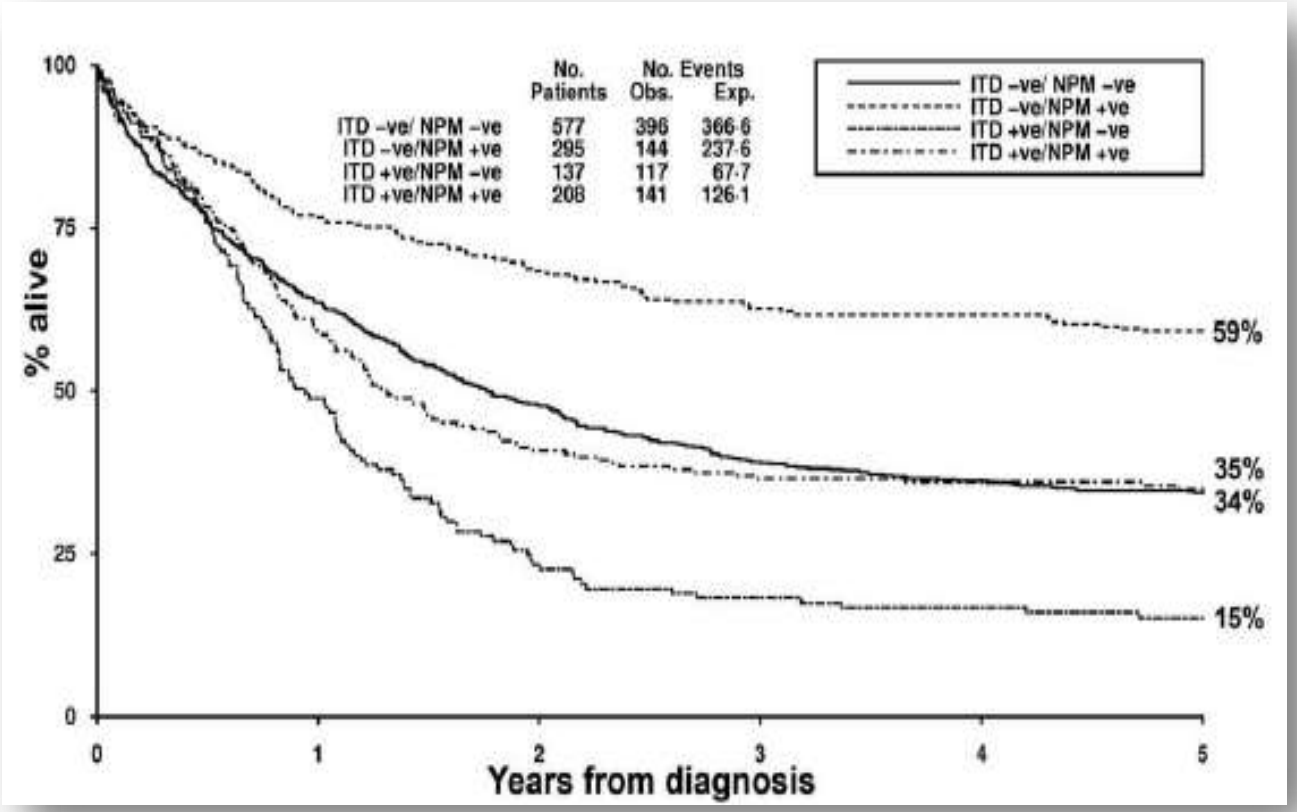
Richard F. Schlenk,[1] Sabine Kayser,[1] Lars Bullinger,[1] Guido Kobbe,[2] Jochen Casper,[3] Mark Ringhoffer,[4] Gerhard Held,[5] Peter Brossart,[6] Michael Lübbert,[7] Helmut R. Salih,[8] Thomas Kindler,[9] Heinz A. Horst,[10] Gerald Wulf,[11] David Nachbaur,[12] Katharina Götze,[13] Alexander Lamparter,[1] Peter Paschka,[1] Verena I. Gaidzik,[1] Veronica Teleanu,[1] Daniela Späth,[1] Axel Benner,[14] Jürgen Krauter,[15] Arnold Ganser,[15] Hartmut Döhner,[1] and Konstanze Döhner,[1] for the German-Austrian AML Study Group

| Outcome | Distribution of *FLT3*-ITD AR intervals, no. (%) First (n = 81) | Second (n = 80) | Third (n = 81) | Fourth (n = 81) | *P* value |
|---|---|---|---|---|---|
| CR | 66 (81.5) | 63 (79.8) | 56 (69.1) | 46 (57.5) | .003 |
| RD | 11 | 12 (15.2) | 17 (21.0) | 30 (37.5) | .001 |
| ED | 4 (4.9) | 4 (5.0) | 8 (9.9) | 4 (5.0) | .53 |
| OS (median), years | 2.19 | 2.15 | 1.20 | 0.90 | .0006 |
| RFS (median), years | 1.08 | 1.42 | 0.76 | 0.67 | .26 |
| EFS (median), years | 0.75 | 0.81 | 0.49 | 0.25 | .001 |
| **IS in the JMD** | | | | | |
| CR | 29 (91) | 35 (85) | 37 (69) | 22 (56) | .002 |
| No. missing | 28 | 8 | **5** | 12 | |
| RD | 2 (6) | 4 (10) | 13 (24) | 14 (36) | .004 |
| No. missing | 6 | 0 | 0 | 7 | |
| ED | 1 (3) | 2 (5) | 4 (7) | 3 (8) | .87 |
| No. missing | **1** | **0** | 0 | 0 | |
| **IS in the TKD1** | | | | | |
| CR | 9 (64.3) | 20 (66.7) | 14 (64) | 12 (54.5) | .84 |
| No. missing | 28 | 8 | 5 | 12 | |
| RD | 3 (21.4) | 8 (26.7) | 4 (18) | 9 (41) | .39 |
| No. missing | 6 | 0 | 0 | 7 | |
| ED | 2 (14.3) | 2 (6.7) | 4 (18) | 1 (4.5) | .41 |
| No. missing | 1 | 0 | 0 | 0 | |

| Outcome | IS in JMD (%) | IS in TKD1 (%) | *P* value |
|---|---|---|---|
| **CTX/autoHSCT** | 75 | 28 | .056 |
| (no. of patients) | | | |
| CIR after 3 years (SE) | 67 (3.0) | 86 (5.0) | .89 |
| CID after 3 years (SE) | 6.7 (1.0) | 7.1 (3.0) | .31 |
| OS after 3 years (95% CI) | 38 (28-50) | 29 (16-51) | |
| **Allogeneic HSCT** | 48 | 27 | .10 |
| **(no. of patients)** | | | |
| CIR after 3 years (SE) | 29 (4.0) | 49 (1.0) | .72 |
| CID after 3 years (SE) | 21 (4.0) | 23 (7.0) | .12 |
| OS after 3 years (95% CI) | 55 (43-72) | 36 (22-60) | |

Schlenk, Blood 201

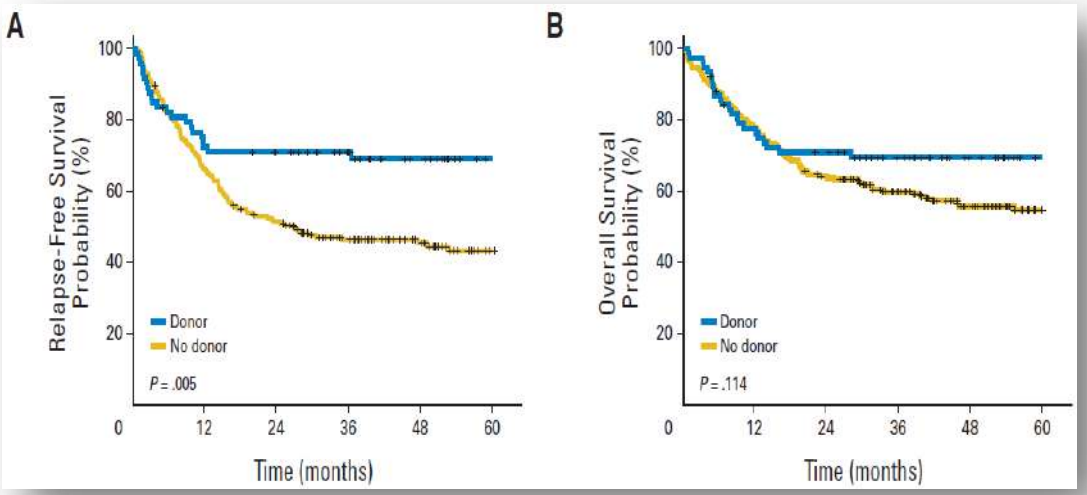
# NPM1 mitige le mauvais pronostic de *FLT3*-ITD …et vice versa




Gale R,Blood 2

# Allogreffe et NPM1
## SAL-AML 2003

NPM1+

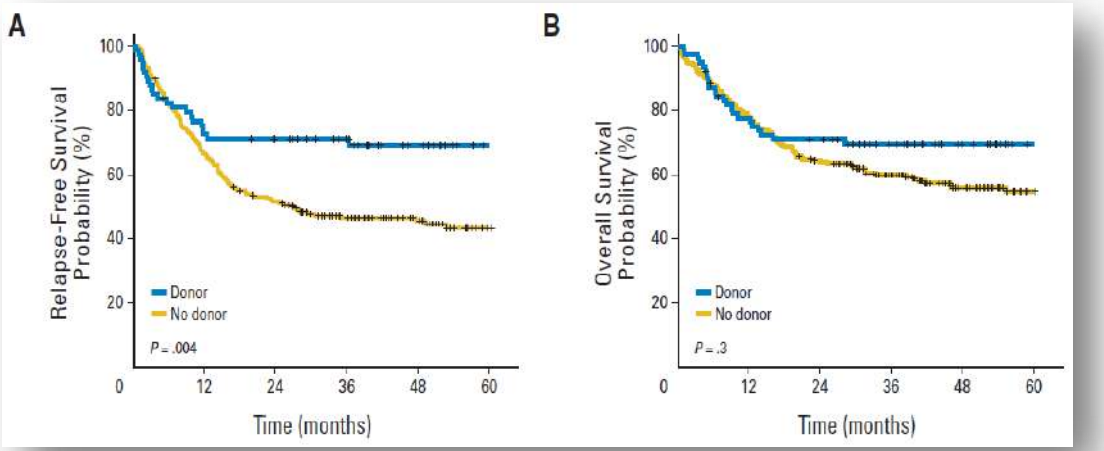



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Allogeneic Stem-Cell Transplantation in Patients With *NPM1*-Mutated Acute Myeloid Leukemia: Results From a Prospective Donor Versus No-Donor Analysis of Patients After Upfront HLA Typing Within the SAL-AML 2003 Trial

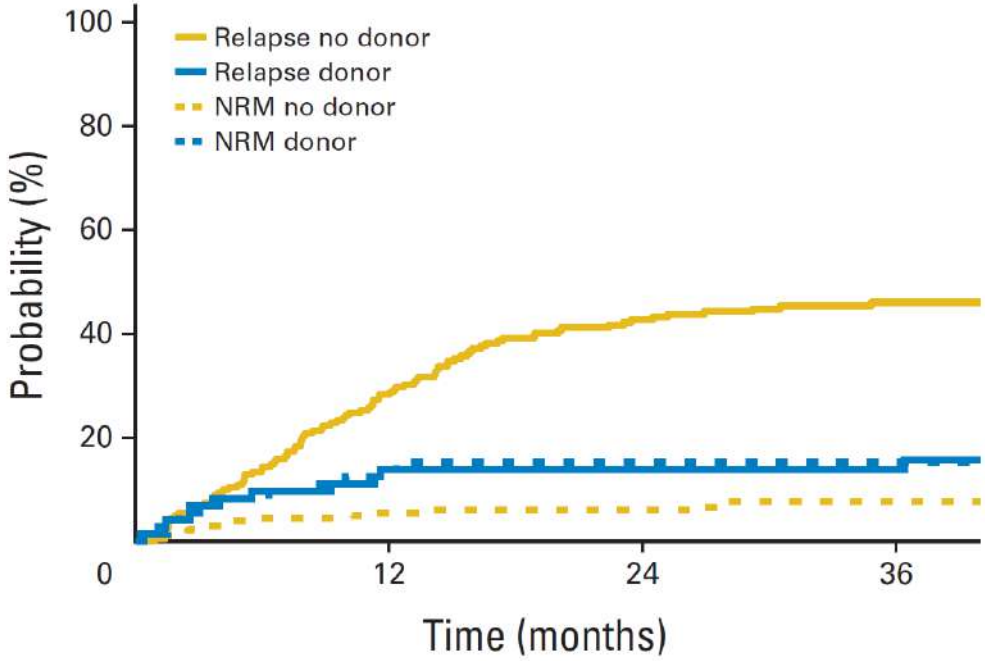
*Christoph Röllig, Martin Bornhäuser, Michael Kramer, Christian Thiede, Anthony D. Ho, Alwin Krämer, Kerstin Schäfer-Eckart, Hannes Wandt, Mathias Hänel, Hermann Einsele, Walter E. Aulitzky, Norbert Schmitz, Wolfgang E. Berdel, Matthias Stelljes, Carsten Müller-Tidow, Utz Krug, Uwe Platzbecker, Marun Wermke, Claudia D. Baldus, Stefan W. Krause, Friedrich Stölzel, Malte von Bonin, Markus Schaich, Hubert Serve, Johannes Schetelig, and Gerhard Ehninger*

CN
NPM1+/FLT3-ITD-




Rollig, JCO

# Allogreffe et NPM1
## SAL-AML 2003




| No. at risk | | | | |
|---|---|---|---|---|
| Donor | 73 | 52 | 48 | 39 |
| No donor | 203 | 134 | 101 | 72 |

| | | | |
|---|---|---|---|
| Relapse no donor | 28% (CI, 22 to 34) | 43% (CI, 36 to 50) | 46% (CI, 39 to 53) |
| Relapse donor | 14% (CI, 6 to 22) | 14% (CI, 6 to 22) | 14% (CI, 6 to 22) |
| NRM no donor | 5% (CI, 2 to 9) | 6% (CI, 3 to 9) | 8% (CI, 4 to 11) |
| NRM donor | 14% (CI, 6 to 22) | 14% (CI, 7 to 24) | 15% (CI, 7 to 24) |

# Maladie résiduelle
# AMLSG

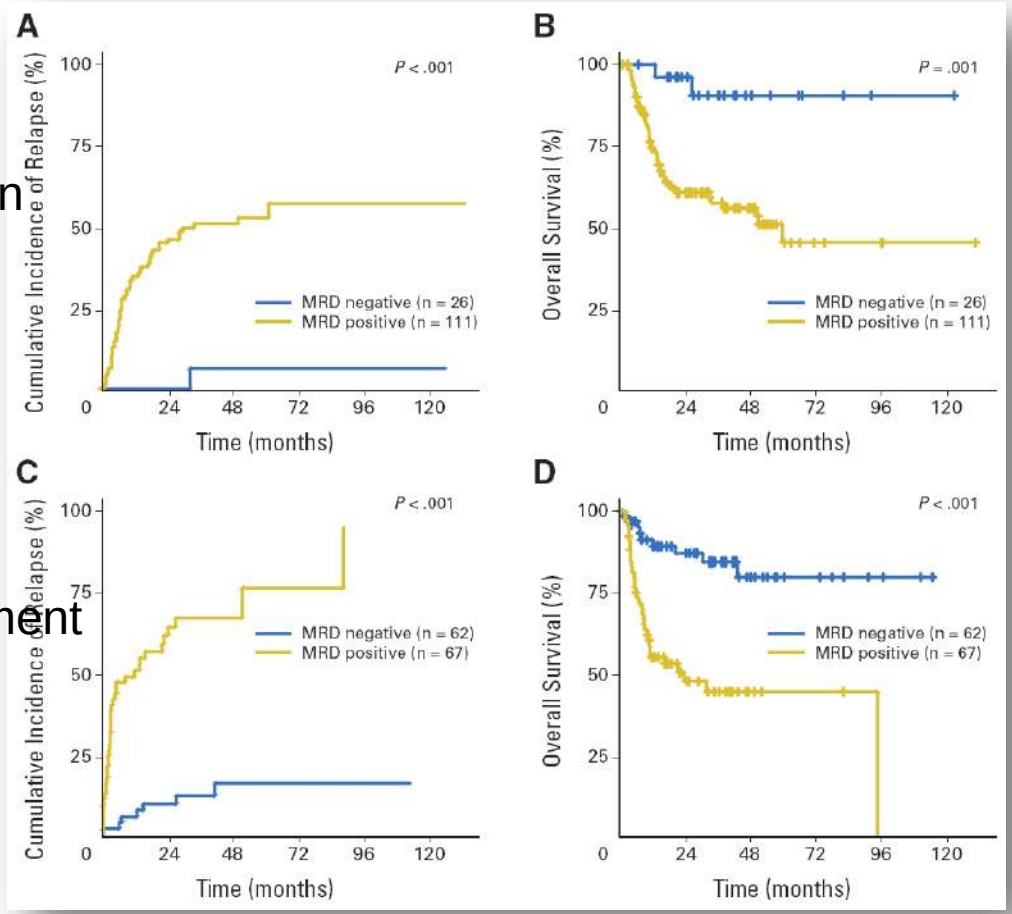
Monitoring of Minimal Residual Disease in *NPM1*-Mutated Acute Myeloid Leukemia: A Study From the German-Austrian Acute Myeloid Leukemia Study Group

*Jan Krönke, Richard F. Schlenk, Kat-Ole Jensen, Florian Tschurtz, Andrea Corbacioglu, Verena I. Gaidzik, Peter Paschka, Shiva Onken, Karina Eiwen, Marianne Habdank, Daniela Spath, Michael Lübbert, Mohammed Wasad, Thomas Kindler, Helmut R. Salih, Gerhard Held, David Nachbaur, Marie von Lilienfeld-Toal, Ulrich Germing, Detlef Haase, Hans-Gunther Mergenthaler, Jürgen Krauter, Arnold Ganser, Gudrun Göhring, Brigitte Schlegelberger, Hartmut Döhner, and Konstanze Döhner*

Post induction
(2 cycles)

*245 LAM-NPM1c*
*18-60 ans*
*Essais AMLSG 07-04 et AML HD98A*
*Suivi en RT-PCR quantitative* ***(moelle)***
*MRD- (>3 log)*

Fin de traitement




Krönke J, JCO 2010

# Maladie résiduelle
## MRC

***ASH 2014:***

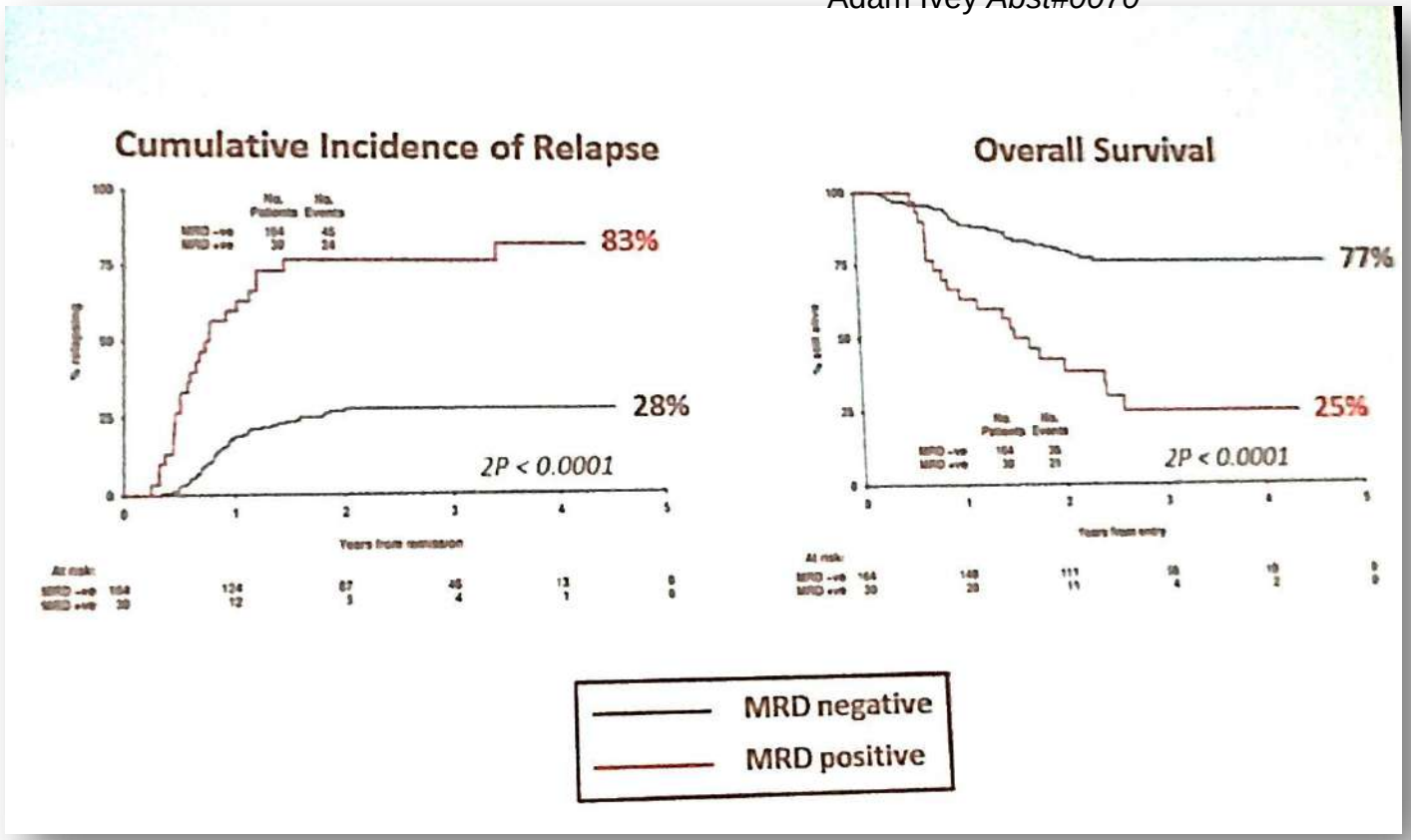
*Essai UK NCRI AML17:*

*341 patients avec mutation NPM1*

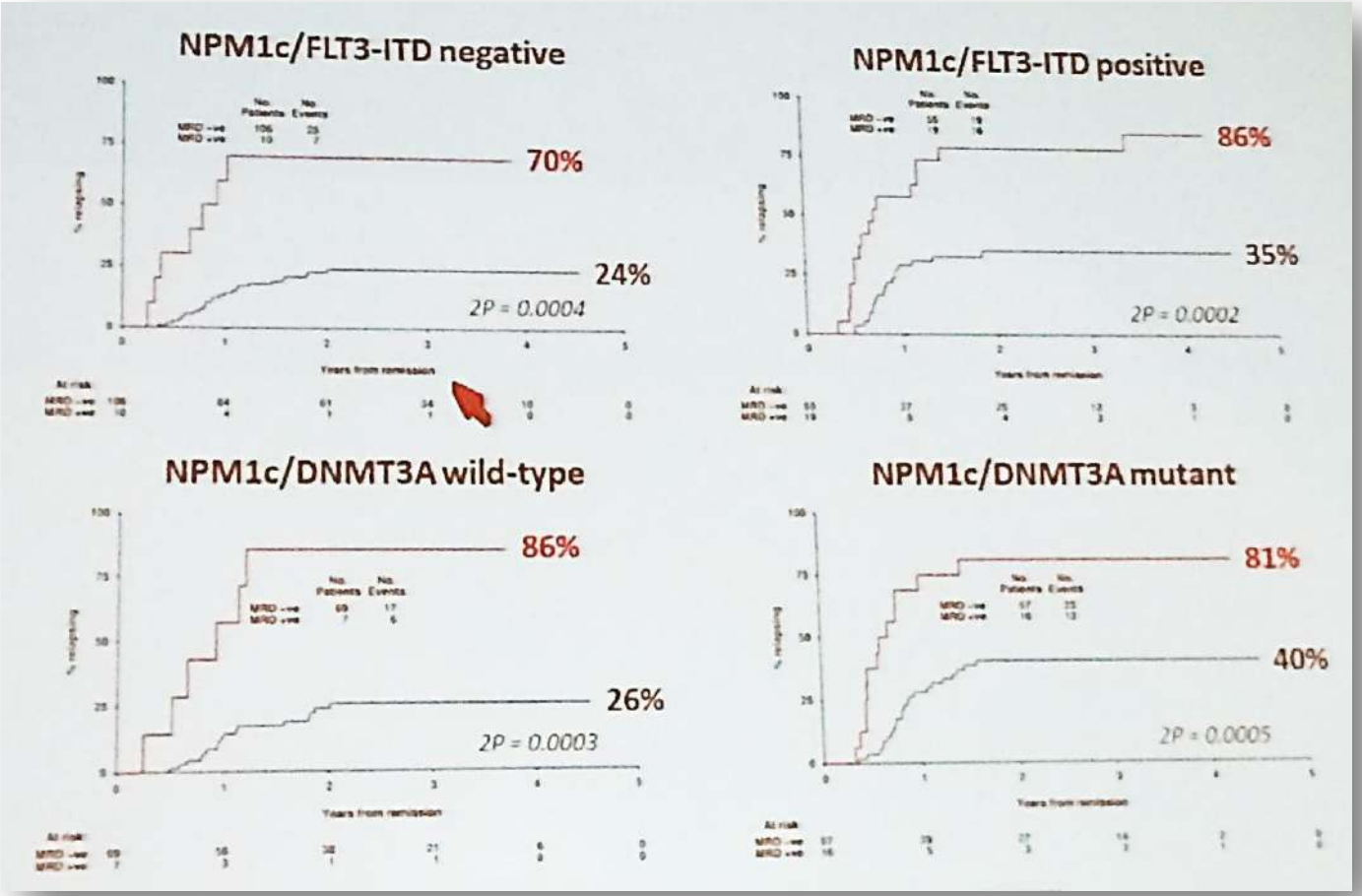
*MRD **dans le sang** après deux cures d'induction*

***Molecular Detection of Minimal Residual Disease Provides the Most Powerful Independent Prognostic Factor Irrespective of Clonal Architecture in Nucleophosmin (NPM1) Mutant Acute Myeloid Leukemia***

Adam Ivey *Abst#0070*



# MRD NPM1 indépendante de FLT3-ITD et DNMT3A



Question 6: 4 mois après l'allogreffe, la patiente rechute: GB 59 G/L, blastes 81%; hémoglobine 12.1 g/dl; plaquettes 44 G/L. Le myélogramme montre 81% de blastes, le caryotype est toujours normal; CD34 27% CD33 99%; mutation FLT3-ITD avec ratio ITD/wt =1 (perte de l'allèle sauvage) et NPM1. Que proposez-vous?

- 1. Un essai thérapeutique
- 2. Sorafenib
- 3. Une chimiothérapie de rattrapage comportant du mylotarg
- 4. Des soins palliatifs

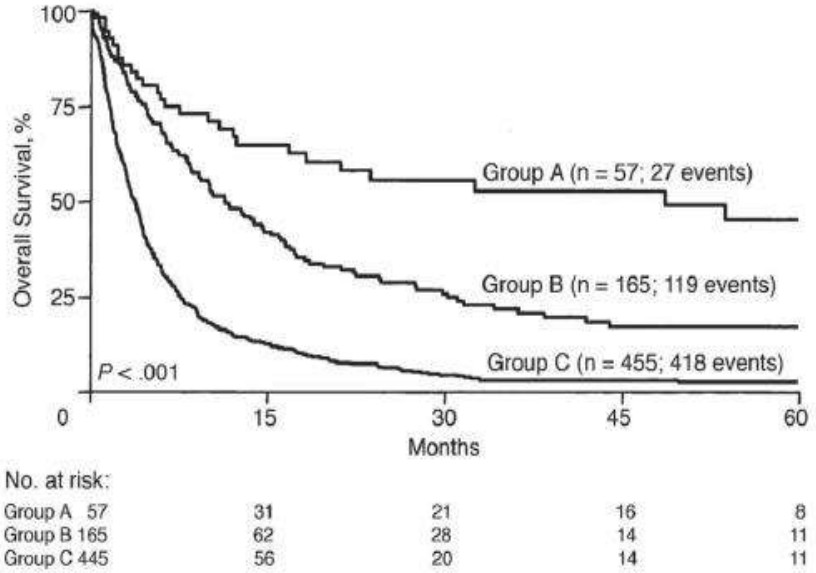
# Pronostic à la rechute

## Prognostic Index for Adult Patients With Acute Myeloid Leukemia in First Relapse

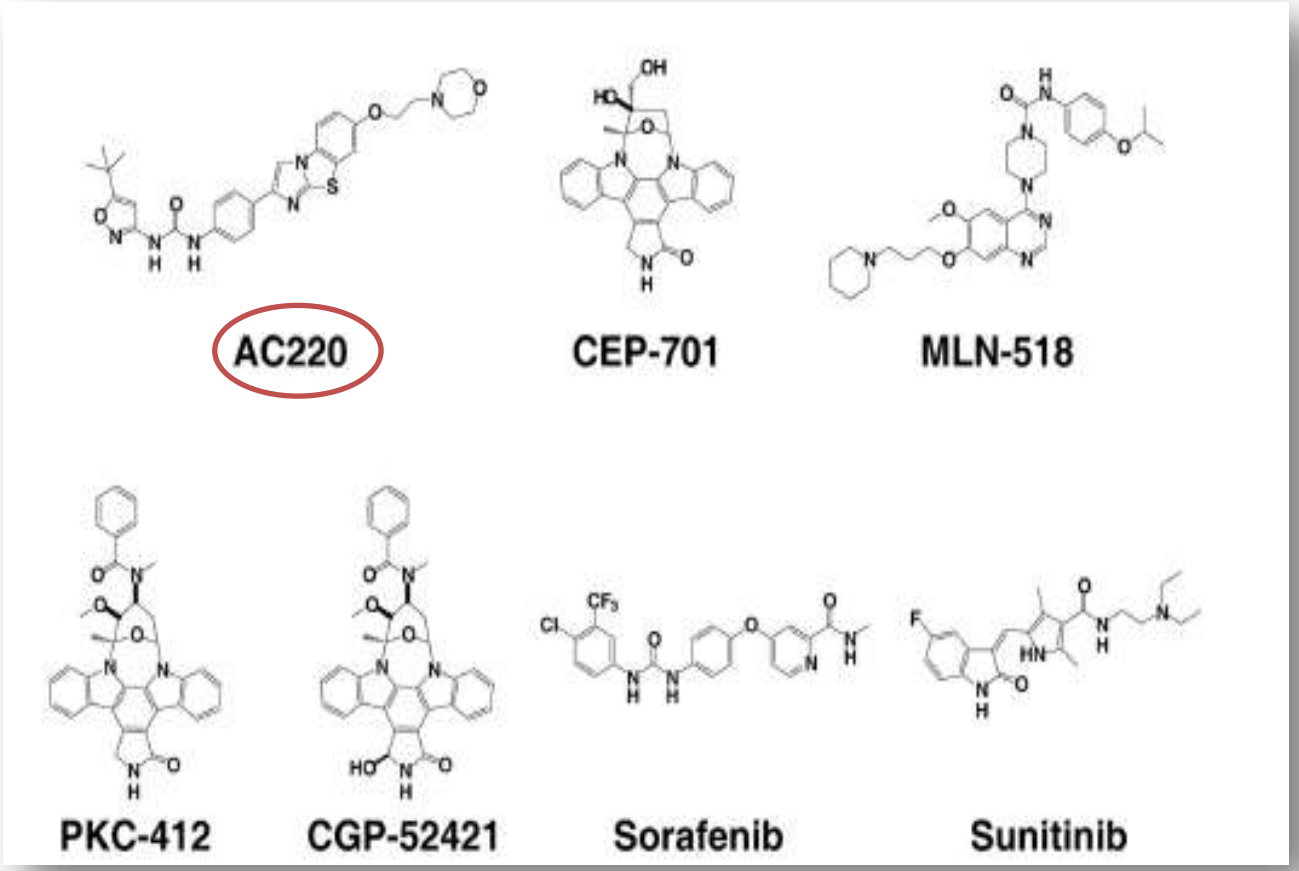
*Dimitri A. Breems, Wim L.J. Van Putten, Peter C. Huijgens, Gert J. Ossenkoppele, Gregor E.G. Verhoef, Leo F. Verdonck, Edo Vellenga, Georgine E. De Greef, Emanuel Jacky, Johannes Van der Lelie, Marc A. Boogaerts, and Bob Löwenberg*

**Table 4.** Simplified Prognostic Score (0-14 points) for Acute Myeloid Leukemia at First Relapse

| Prognostic Factor | Coefficient | Points |
|---|---|---|
| RFI, relapse-free interval from first complete remission, months | | |
| > 18 | 0 | 0 |
| 7-18 | 0.69 | 3 |
| ≤ 6 | 1.28 | 5 |
| CYT, cytogenetics at diagnosis | | |
| t(16;16) or inv(16)* | 0 | 0 |
| t(8;21)* | 0.68 | 3 |
| Other† | 1.19 | 5 |
| AGE, age at first relapse, years | | |
| ≤ 35 | 0 | 0 |
| 36-45 | 0.21 | 1 |
| > 45 | 0.47 | 2 |
| SCT, stem-cell transplantation before first relapse | | |
| No SCT | 0 | 0 |
| Previous SCT (autologous or allogeneic) | 0.49 | 2 |



# Inhibiteurs de FLT3




Zarrinkar P, Blood 2

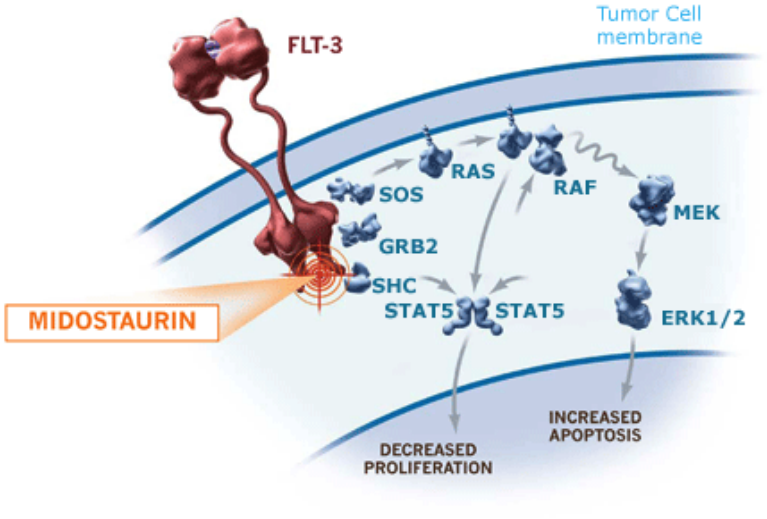
# Inhibiteurs de FLT3 en monothérapie

**Table 2. Summary of clinical trials using FLT3-TKI as single agent**

| TKI | Trial (FLT3 status) | Dosage (MTD) | Best response | Duration of response | Side effects/DLT |
|---|---|---|---|---|---|
| Midostaurin (PKC412) | Phase 2[49] (FLT3 mut only) | Oral, 75 mg, 3×/d | Blasts BM < 50%: 6/20<br>Blasts PB < 50%: 14/20 | 72-330 d | Nausea, pulmonary events |
| Lestaurtinib (CEP-701) | Phase1/2[51] (FLT3 mut only)<br>Phase 2[52] (FLT3 mut + wt, age > 70 y) | Oral, 60 mg 2×/d<br>Oral, 60-80 mg 2×/d | Blasts PB < 50%: 5/14<br>Blasts PB < 50%: FLT3-mut: 3/5<br>FLT3-wt: 5/22 | 2 wk-3 mo<br>2 wk-9 mo | Nausea, emesis, diarrhea |
| Sorafinib (BAY 43-9006) | Phase 1[54] (FLT3 mut + wt) | Oral 400 mg BID (range: 200-400 mg 2×/d) | Blast response in PB: FLT3-ITD: 6/6, FLT3-wt: 3/7, FLT3-TKD: 0/3 | ND | Pleural effusion, nausea, vomiting, rash |
| Semaxanib (SU5416) | Phase 2[57] (FLT3 mut + wt)<br>Phase 2[59] (AML, FLT3 ND) | Intravenous, 145 mg/m² 2×/wk<br>Intravenous, 145 mg/m² 2×/wk | PR: 2/33, HI: 1/33<br>Blasts PB and BM < 50%: 7/25 with 1 MR | 3-3.5 mo<br>1.6 mo (1-5 mo) | Fatigue, headache, bone pain |
| Sunitinib (SU11248) | Phase 1[61] (FLT3 mut + wt) | Oral, 50 mg 1×/d | Blasts PB and BM <50%: FLT3-ITD: 4/4 (1 HI) FLT3-wt: 2/7 | 4-16 wk | Hypertension (DLT), fatigue, edema |
| Tandutinib (MLN-518) | Phase 1[62] (FLT3 mut + wt)<br>Phase 2[63] (FLT3-ITD only) | Oral, 50-700 mg 2×/d<br>Oral, 525mg 2×/d | NA<br>6/18 responder: blast decrease in PB and BM | NA<br>1-3 mo | Muscular weakness, fatigue, nausea, vomiting |
| KW-2449 | Phase 1[64] (FLT3 mut + wt) | Oral, 500 mg 2×/d | Blasts PB and BM < 50% in 26% | ND | Vomiting, nausea, fatigue |
| AC220 | Phase 1[67] (FLT3 mut + wt) | Oral, 200 mg 1×/d (range: 12-300 mg/d) | CR: 12% PR: 18% FLT3-ITD: 56% FLT3-wt: 19% | 14 wk | QTc prolongation (DLT), peripheral edema, GI events |

Kindler T, Blood 20

# PKC-412 (midostaurin)
# Phase III internationale CALGB 10603 (RATIFY)




**Arm 1:**

*Induction therapy*

*Midostaurin 50mg oral twice daily on days 8-21
*Cytarabine 200mg/m2 IV on days 1-7
*Daunorubicin 60mg/m2 IV on days 1-3.

*Consolidation therapy*

*Midostaurin 50mg oral, twice daily on days 8-21
*Cytarabine 3,000mg/m2 IV over 3 hours every 12 hours on days 1, 3, and 5.
Both as part of a 28 day cycle for up to 4 cycles.

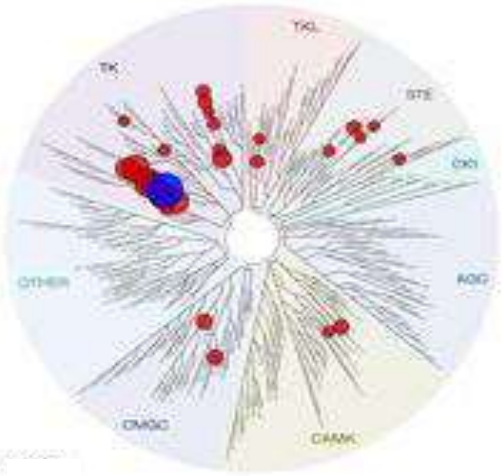
*Continuation therapy*

*Midostaurin 50mg oral, twice daily on days 1-14 as part of a 28 day cycle.

**Arm 2:** Placebo

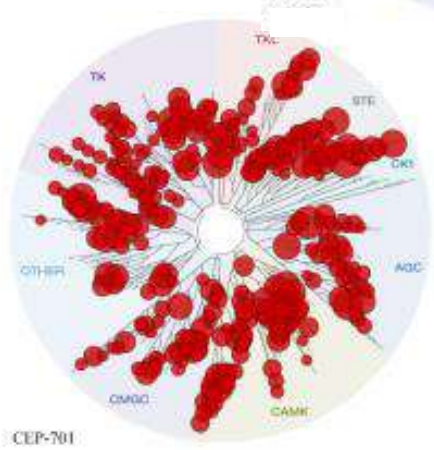
# Inhibiteurs de FLT3: AC220: le plus prometteur?

Quizartinib

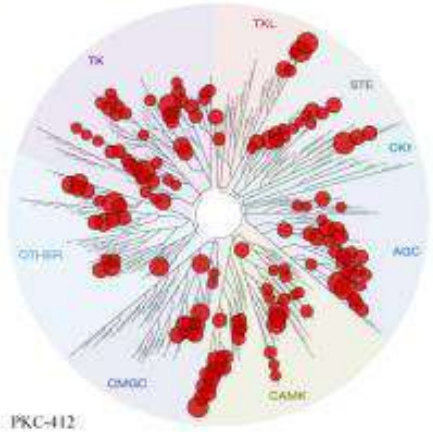



**Quizartinib (AC220)**

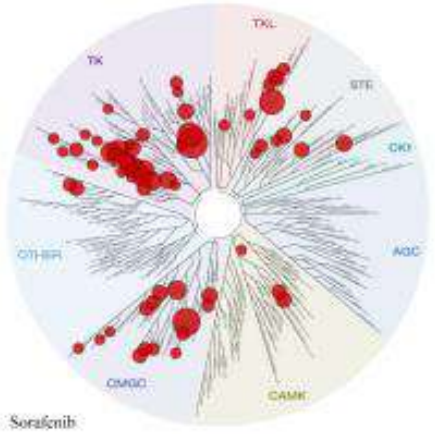
| $IC_{50}$ cellular assays | $IC_{50}$ nM (Medium) | $IC_{50}$ nM (Plasma) |
|---|---|---|
| Lestaurtinib | 2 | 700 |
| Midostaurin | 12 | 1,000 |
| Sorafinib | 0.9 | 265 |
| Quizartinib | 0.6 | 18 |




**Lestaurtinib (CEP-701)**



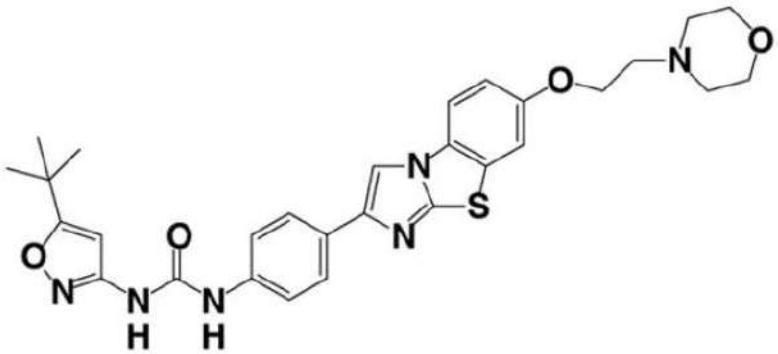

**Midostaurin (PKC-412)**




**Sorafenib**

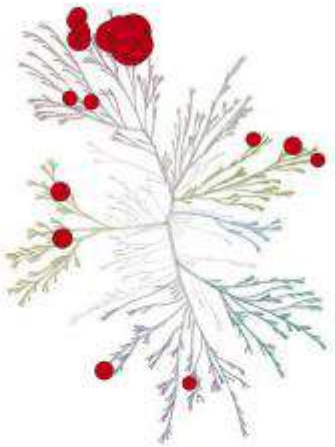
Pratz et al. Blood 2010;115(7):1425-

# AC220 (quizartinib)




**AC220**

**AC220**



| Target | Kd (nM) |
|---|---|
| FLT3 | 1.6 |
| KIT | 5 |
| PDGFR | 10 |
| CSF1R | 10 |
| RET | 10 |

# Quizartinib: phase 2

| | CRc (%) | NR (%) |
|---|---|---|
| **Best Response to Prior Therapy** | | |
| Prior CR (N=172) | 50 | 18 |
| No prior CR (N=74) | 50 | 13 |
| **Prior Allo-HSCT** | | |
| No prior HSCT (N=207) | 50 | 20 |
| Prior HSCT (N=41) | 51 | 7 |
| **Cytogenetic Risk Group*** | | |
| Good (N=1) | 100 (1/1) | 0 |
| Intermediate (N=108) | 56 | 14 |
| Poor (N=23) | 39 | 26 |
| Unknown (N=116) | 47 | 20 |
| **ITD Ratio** | | |
| >10 – 25% (N=54) | 41 | 19 |
| >25 – 50% (N=116) | 47 | 21 |
| >50% (N=78) | 62 | 13 |

# Sorafenib post-allogreffe

Leukemia (2012) **26**, 2353–2359

www.nature.com/leu

**ORIGINAL ARTICLE**

## High activity of sorafenib in FLT3-ITD-positive acute myeloid leukemia synergizes with allo-immune effects to induce sustained responses

SK Metzelder[1], T Schroeder[2], A Finck[3], S Scholl[4], M Fey[5], K Götze[6], YC Linn[7], M Kröger[8], A Reiter[9], HR Salih[10], T Heinicke[11], R Stuhlmann[12], L Müller[13], A Giagounidis[14], RG Meyer[15], W Brugger[16], M Vöhringer[17], P Dreger[18], M Mori[19,20], N Basara[21], K Schäfer-Eckart[22], B Schultheis[23], C Baldus[24], A Neubauer[1] and A Burchert[1]