Leucémies aiguës

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IUCT-O

Evaluation de la réponse dans les LAM

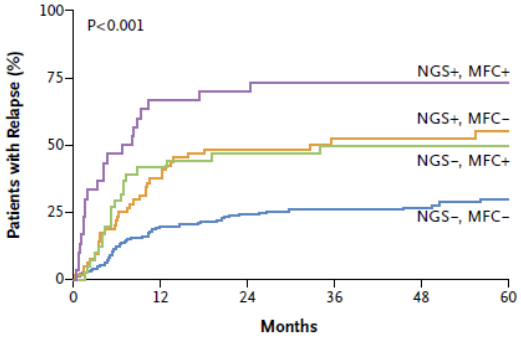
The NEW ENGLAND JOURNAL of MEDICINE

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

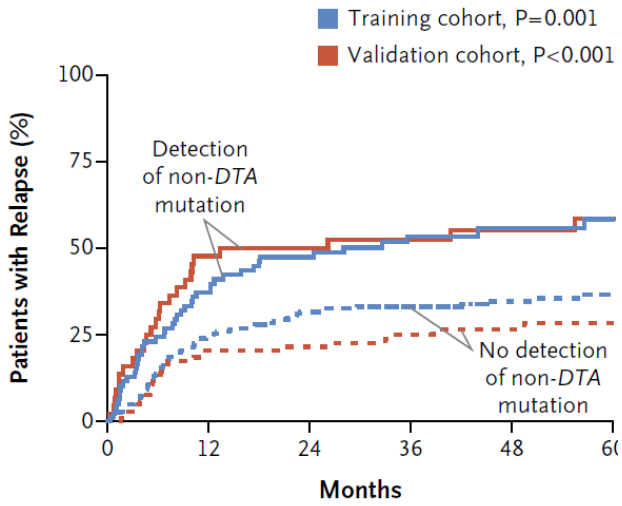
NGS/MFC



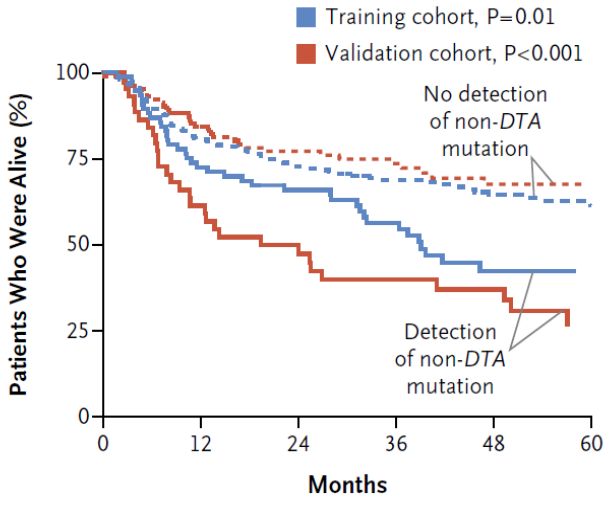
No. at Risk

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

B **Relapse among All Patients**



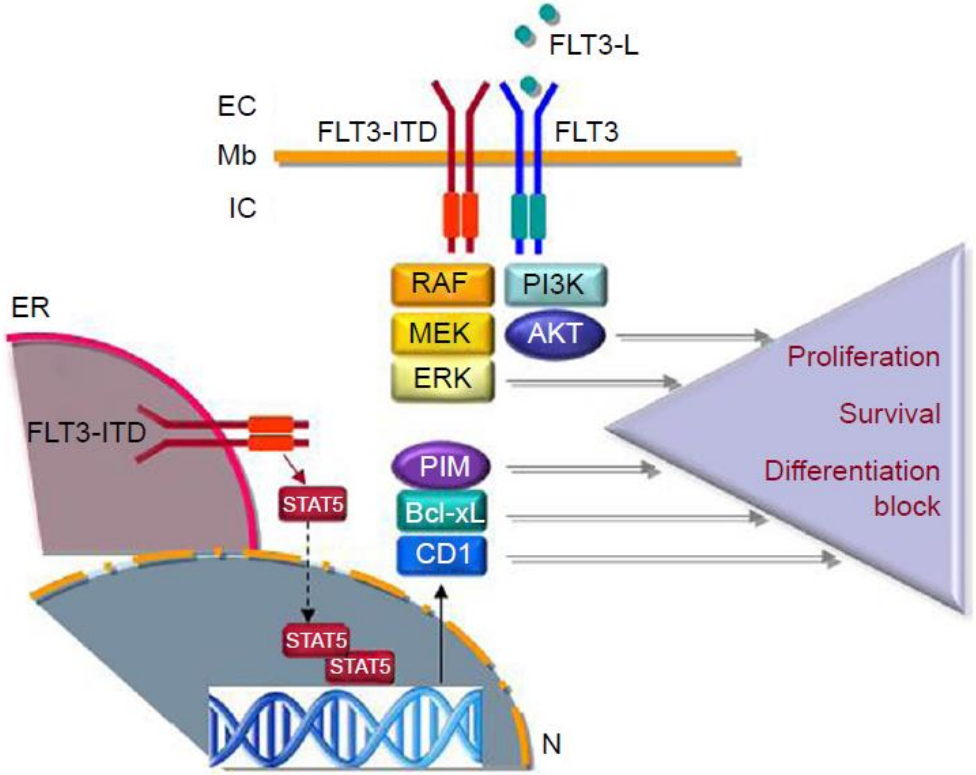
Overall Survival among All Patients



Prise en charge thérapeutique des LAM
Nouvelles cibles, nouvelles drogues

- **FLT3-ITD/FLT3-TKD: 20-30%**
  - Midostaurine, quizartinib, gilteritinib, crenolanib
- **IDH1 / IDH2: 15-20%**
  - Enasidenib, ivosidenib, FT-2102
- **Haut risque, caryotype complexe, LAM secondaires: 20-25%**
  - CPX-351
- **DNA MethyTransferase: sujets âgés, non éligibles à une CTx intensive**
  - HMA: azacitidine, decitabine, guadecitabine
- **Apoptose**
  - Venetoclax
  - Idasanutlin
- **PML-RARA: 5-10%**
  - ATO-ATRA

Inhibiteurs de FLT3

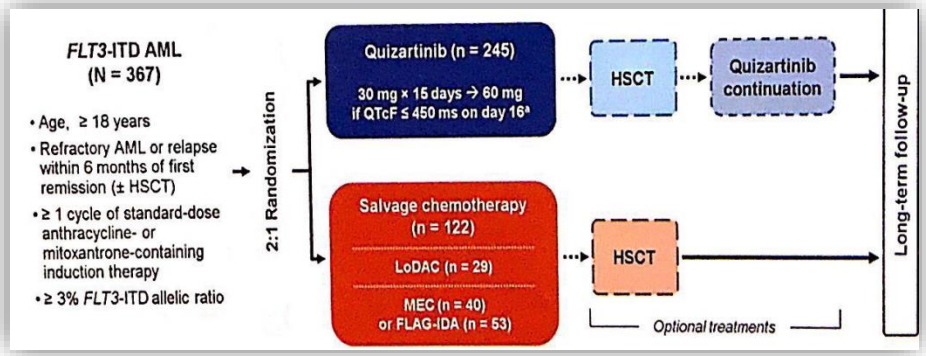


- Midostaurin
- Sorafenib
- Quizartinib
- Gilteritinib
- Crenolanib

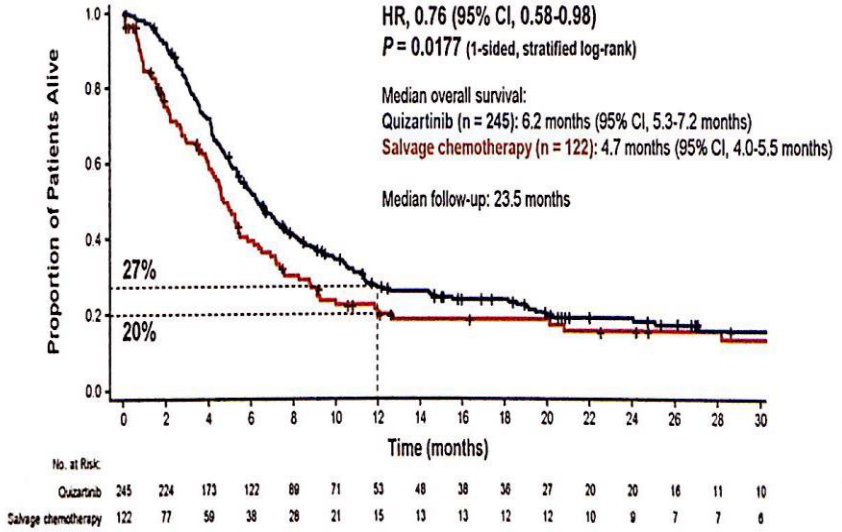
Hospital MA, OncoTargets and Therapy 2017

Phase 3: quizartinib vs. standard
LAM FLT3-ITD R/R: Quantum-R

Cortes J, EHA 2018



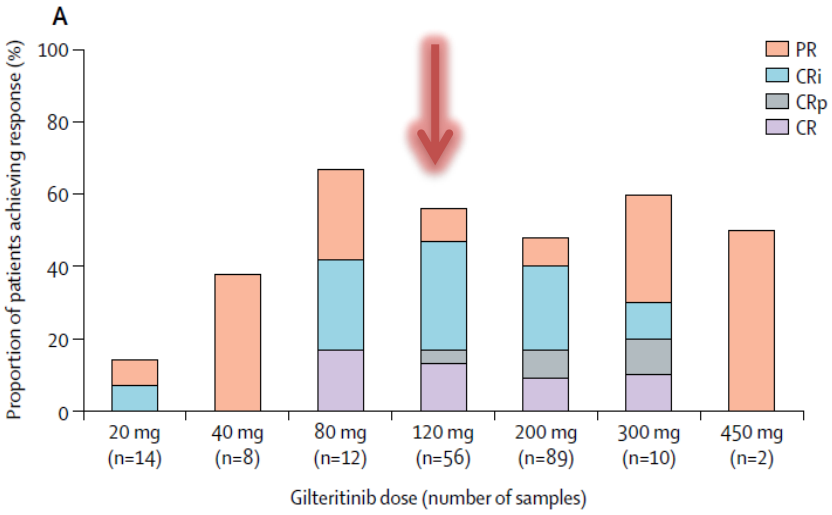
Characteristic	Percentage (95% CI)	
	Quizartinib n = 245	Salvage Chemotherapy n = 122
Best response		
CRc[a]	48 (42-55)	27 (19-36)
CR	4 (2-7)	1 (0-5)
CRp	4 (2-7)	0 (0-3)
CRi	40 (34-47)	26 (19-35)
PR	21 (16-27)	3 (1-8)
ORR (CRc + PR)	69 (63-75)	30 (22-39)
No response	25 (20-31)	37 (28-46)
Nonevaluable	5 (3-9)	33 (25-42)



*Myélosuppression (KIT)
*Prolongation QTc (dose dpdt)
*Interactions médicamenteuses

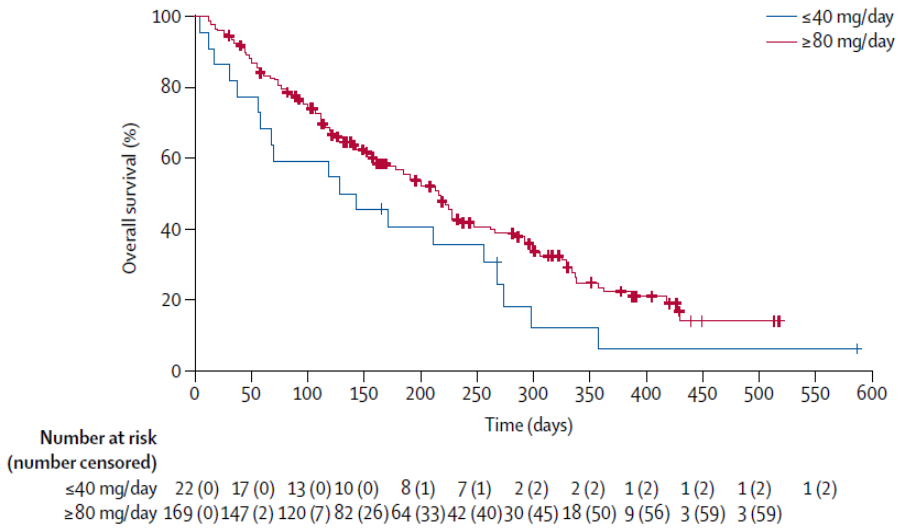
Gilteritinib phase 1/2

RC+RCp+RCi : 41%



Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1–2 study

Alexander E Perl*, Jessica K Altman*, Jorge Cortes, Catherine Smith, Mark Litzow, Maria R Baer, David Claxton, Harry P Erba, Stan Gill, Stuart Goldberg, Joseph G Jurcic, Richard A Larson, Chaofeng Liu, Ellen Ritchie, Gary Schiller, Alexander I Spira, Stephen A Strickland, Raoul Tibes, Celalettin Ustun, Eunice S Wang, Robert Stuart, Christoph Röllig, Andreas Neubauer, Giovanni Martinelli, Erkut Bahceci, Mark Levis



Phases 3

* LAM R/R FLT3-ITD ou TKD+, monothérapie vs. CT, maintenance post greffe
* FLT3-ITD+ ou TKD+ en RC1, maintenance post chimio vs. placebo
* FLT3-ITD+ ou TKD+ en RC1, maintenance post allo vs. placebo

* **LAM FLT3-ITD ou TKD+ en 1ere ligne: 3+7+gilteritinib vs. 3+7+midostaurine**

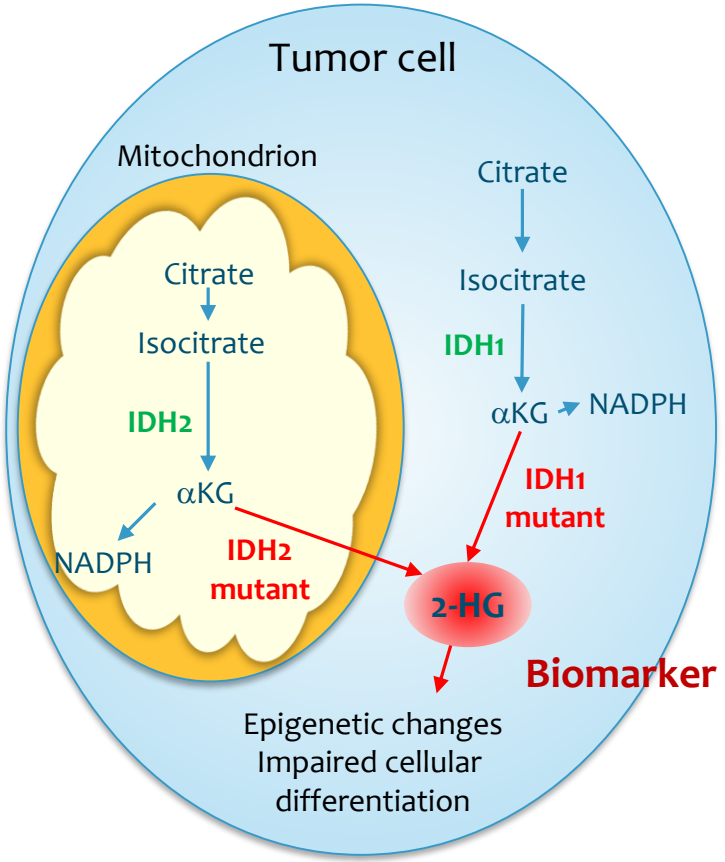
Inhibiteurs des IDH1 (ivosidenib) et IDH2 (enasidenib)

* 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



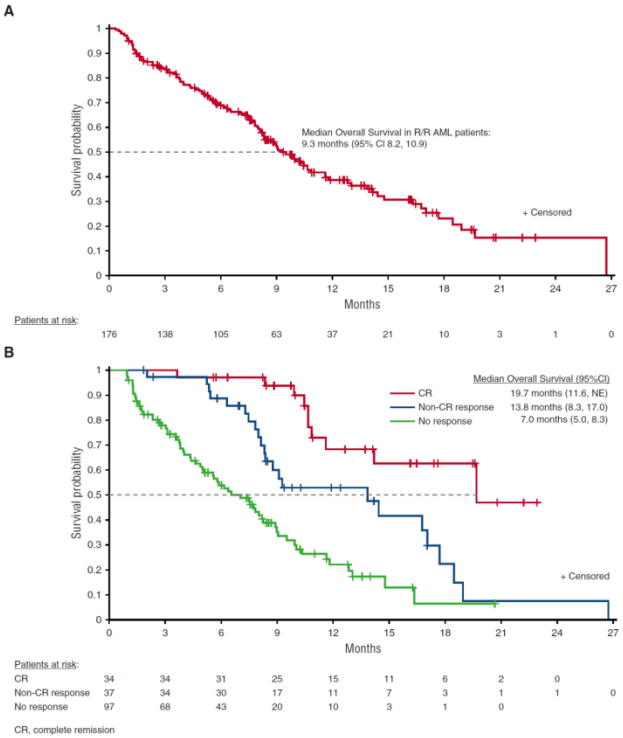
Inhibiteurs des IDH1 (ivosidenib) et IDH2 (enasidenib)

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,†]



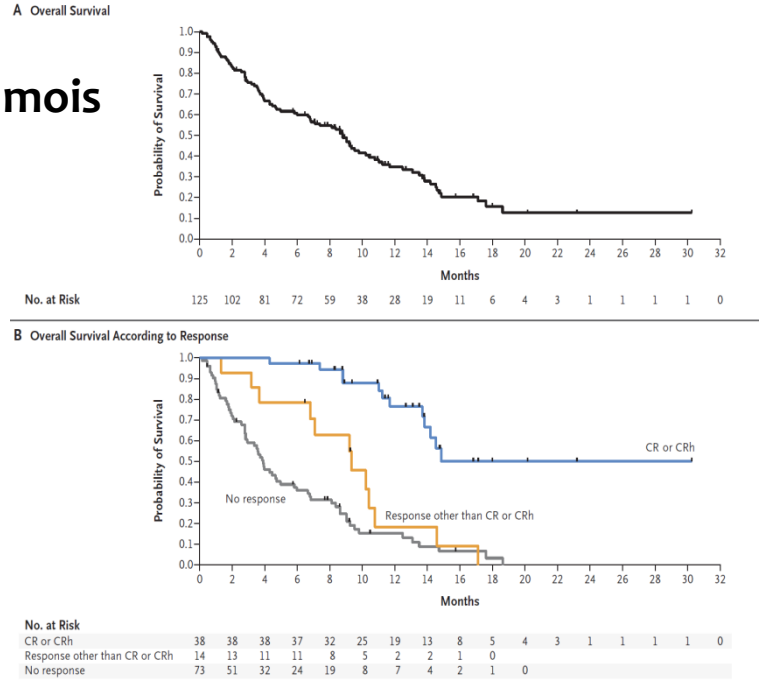
ORR: 40-50%

Survie médiane: 9 mois

ORIGINAL ARTICLE

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

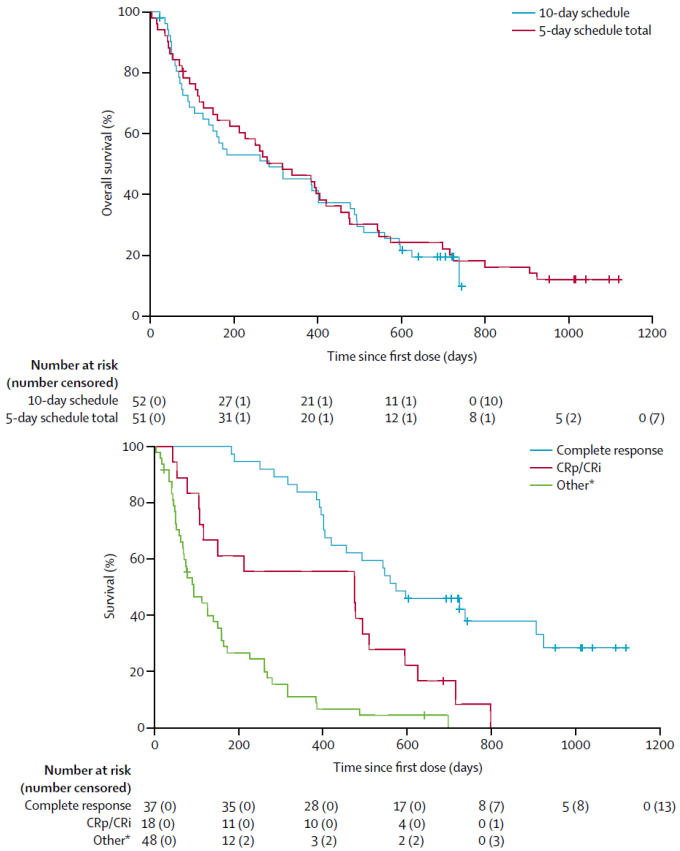
C.D. DiNardo, E.M. Stein, S. de Botton, G.J. Roboz, J.K. Altman, A.S. Mims, R. Swords, R.H. Collins, G.N. Mannis, D.A. Pollyea, W. Donnellan, A.T. Fathi, A. Pigneux, H.P. Erba, G.T. Prince, A.S. Stein, G.L. Uy, J.M. Foran, E. Traer, R.K. Stuart, M.L. Arellano, J.L. Slack, M.A. Sekeres, C. Willekens, 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



Guadecitabine en première ligne (phase 1/2)

Guadecitabine (SGI-110) in treatment-naive patients with acute myeloid leukaemia: phase 2 results from a multicentre, randomised, phase 1/2 trial

Hagop M Kantarjian*, Gail J Roboz*, Patricia L Kropf, Karen W L Yee, Casey L O'Connell, Raoul Tibes, Katherine J Walsh, Nikolai A Podoltsev, Elizabeth A Griffiths, Elias Jabbour, Guillermo Garcia-Manero, David Rizzieri, Wendy Stock, Michael R Savona, Todd L Rosenblat, Jesus G Berdeja, Farhad Ravandi, Edwin P Rock, Yong Hao, Mohammad Azab, Jean-Pierre J Issa



	5-day schedule		10-day schedule
	60 mg/m² (n=24)	90 mg/m² (n=27)	60 mg/m² (n=52)
Composite complete response*	13 (54%; 32·8–74·4)	16 (59%; 38·8–77·6)	26 (50%; 35·8–64·2)
Complete response	9 (38%)	11 (41%)	17 (33%)
Complete response with incomplete neutrophil recovery regardless of platelets	4 (17%)	3 (11%)	4 (8%)
Complete response with incomplete platelet recovery	0	2 (7%)	5 (10%)
Partial response	1 (4%)	1 (4%)	1 (2%)
Non-responder	10 (42%)	10 (37%)	25 (48%)
Not assessable	0	0	0

Responses were based on the International Working Group response criteria for acute myeloid leukaemia.[16] Data are n (%, 95% CI) or n (%). *Complete response, complete response with incomplete neutrophil recovery regardless of platelets, or complete response with incomplete platelet recovery.

Table 2: Proportion of patients who achieved a response

Sous-cutanée
60 mg/kg 5 jours, J1=J28

Phases 3 GUADECITABINE

HMA

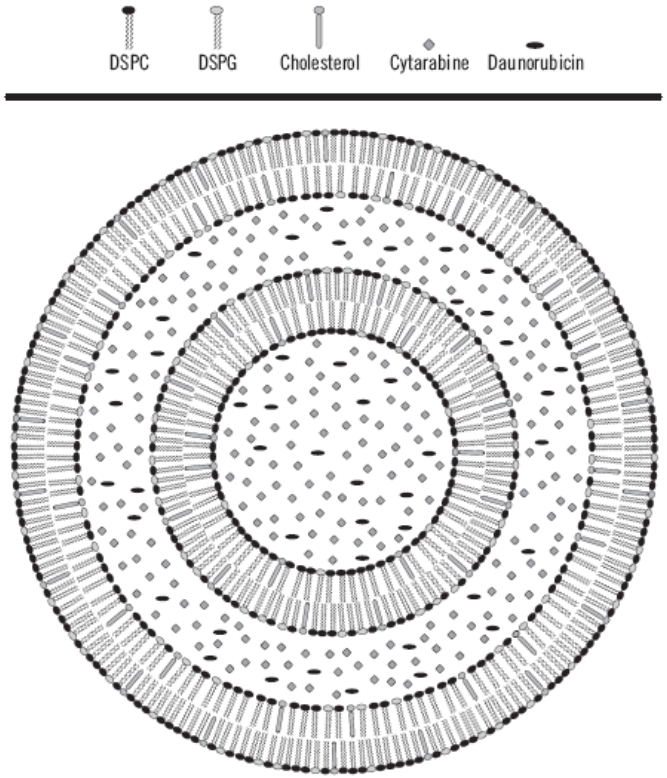
STRAL-1
Treatment Naive AML

Première ligne, fermé: **pas de différence**

STRAL-2
Relapsed/Refractory AML

LAM R/R, **arrêtée après analyse intérimaire et excès de décès infectieux**

CPX-351 (Vyxeos®)

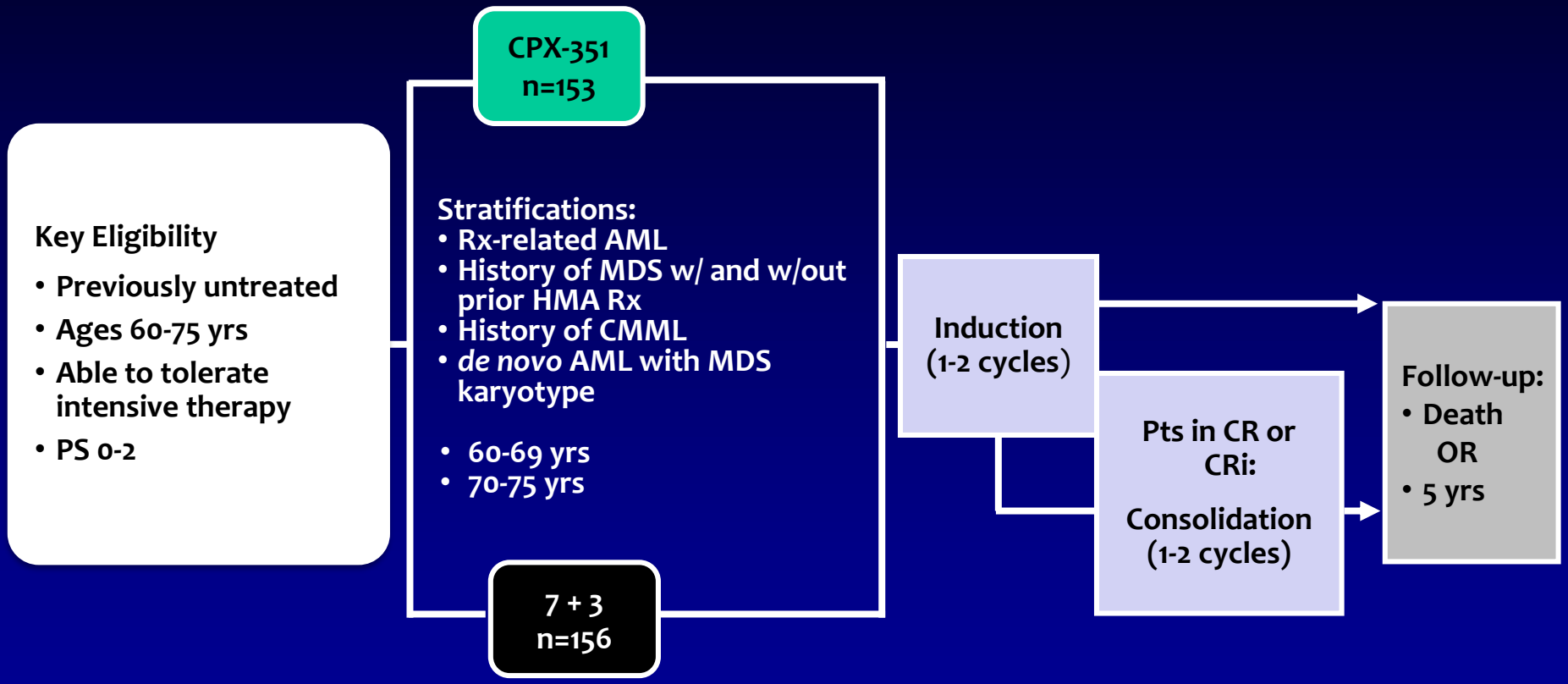


- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- Maximally synergistic ratio in cell lines
- Accumulates in BM with preferential uptake by leukemia cells

Feldman E, et al. JCO, 2011

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

HR MRC



- **Primary Endpoint:** Overall survival

Lancet. JCO 34: abst 7000; 2016

CPX-351 vs 3+7

HR MRC

CPX-351 1 unit = 1 mg cytarabine + 0.44 mg daunorubicin		7 + 3	
First Induction	• 100 units/m² • Days 1, 3 and 5	First Induction	Cytarabine: 100 mg/m² x 7 d Daunorubicin: 60 mg/m² x 3 d
Re-induction	• 100 units/m² • Days 1 and 3	Re-induction	Cytarabine: 100 mg/m² x 5 d Daunorubicin: 60 mg/m² x 2 d
Consolidation	• 65 units/m² • Days 1 and 3	Consolidation	Cytarabine: 100 mg/m² x 5 d Daunorubicin: 60 mg/m² x 2 d

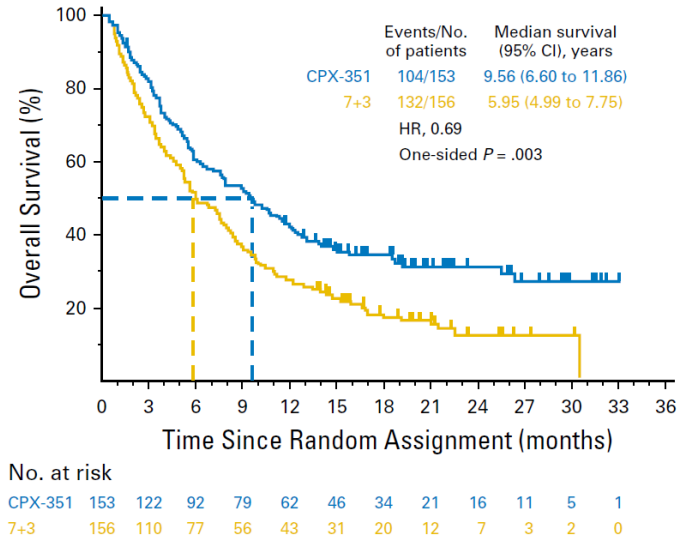
Lancet. JCO 34: abst 7000; 2016

JOURNAL OF CLINICAL ONCOLOGY RAPID COMMUNICATION

CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia

Jeffrey E. Lancet, Geoffrey L. Uy, Jorge E. Cortes, Laura F. Newell, Tara L. Lin, Ellen K. Ritchie, Robert K. Stuart, Stephen A. Strickland, Donna Hogge, Scott R. Solomon, Richard M. Stone, Dale L. Bixby, Jonathan E. Kolitz, Gary J. Schiller, Matthew J. Wieduwilt, Daniel H. Ryan, Antje Hoering, Kamalika Banerjee, Michael Chiarella, Arthur C. Louie, and Bruno C. Medeiros

A



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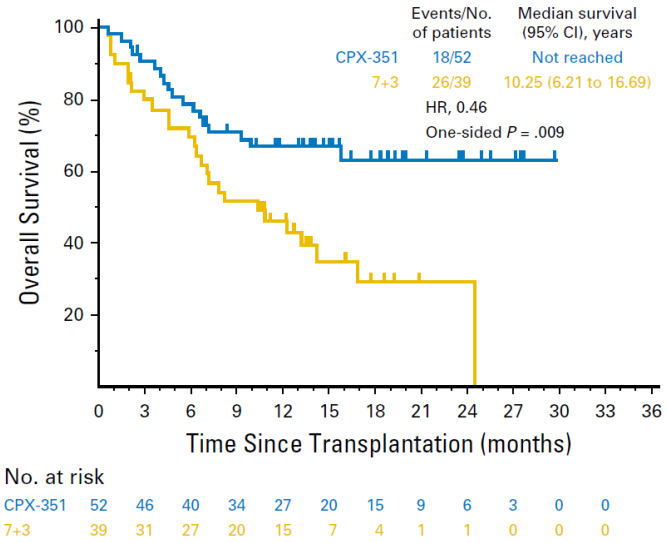
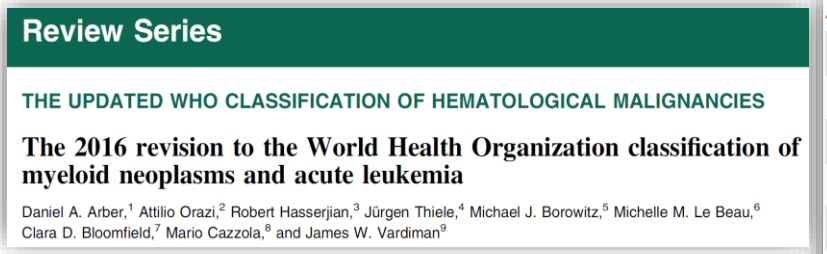


Indications VYXEOS: t-AML / AML-MRC



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]

- Définition:
  - Dysplasie ≥ 50% des cellules dans au moins 2 sur les 3 lignées myéloïdes (sauf si mutations NPM1 ou CEBPA^{dm})
  - Antécédent de syndrome myélodysplasique
  - Anomalies chromosomiques des SMD (sauf del9q)

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

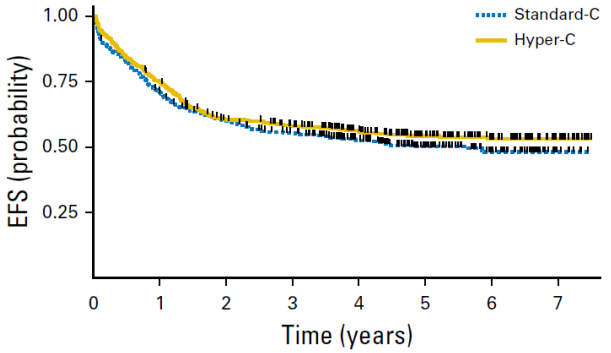
LAL non-Ph+

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Intensified Therapy of Acute Lymphoblastic Leukemia in Adults: Report of the Randomized GRAALL-2005 Clinical Trial

Françoise Huguet, Sylvie Chevret, Thibaut Leguay, Xavier Thomas, Nicolas Boissel, Martine Escoffre-Barbe, Patrice Chevallier, Mathilde Hunault, Norbert Vey, Caroline Bonmati, Stéphane Lepretre, Jean-Pierre Marolleau, Thomas Pabst, Philippe Rousselot, Agnès Buzyn, Jean-Yves Cahn, Véronique Lhéritier, Marie C. Béné, Vahid Asnafi, Eric Delabesse, Elizabeth Macintyre, Yves Chalandon, Norbert Ifrah, and Hervé Dombret, for the Group of Research on Adult ALL (GRAALL)

A



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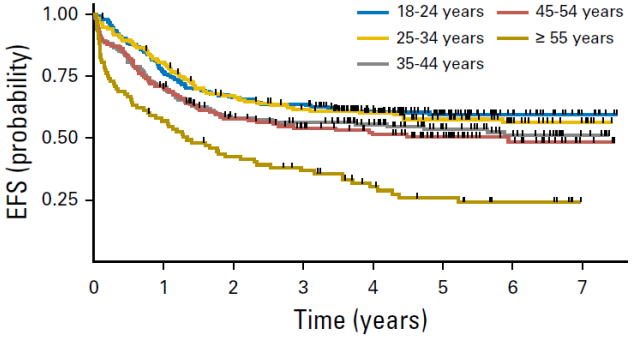
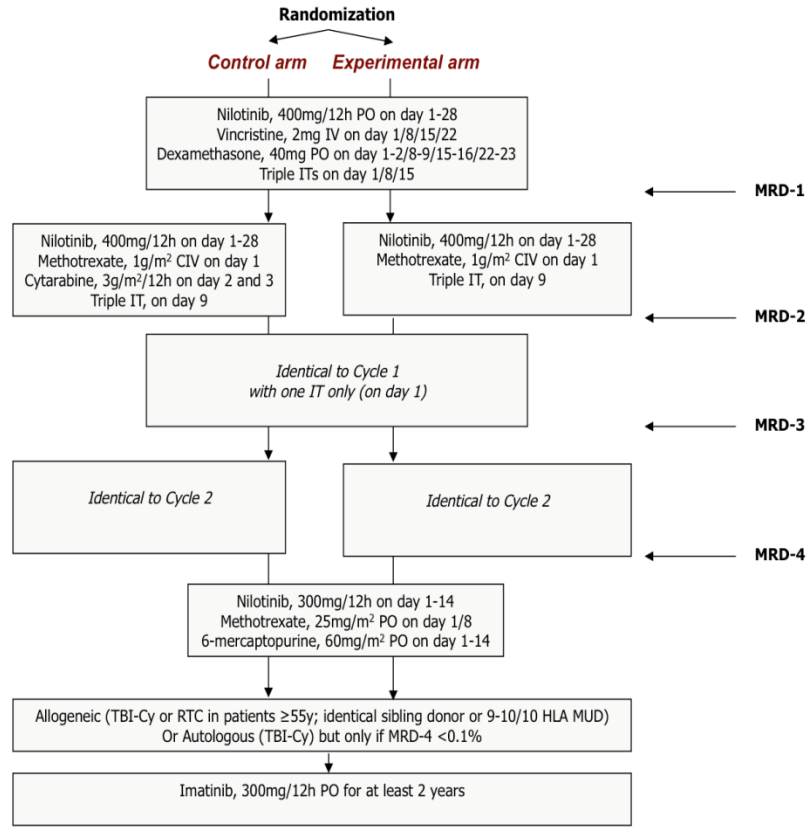


Nilotinib combined with lower-intensity chemotherapy for front-line treatment of younger adults with Ph-positive acute lymphoblastic leukemia (ALL): interim analysis of the GRAAPH-2014 trial

Figure 1



- 60 patients (18-59 ans)
- RC: 98% après C1 (1 décès toxique)
- MMolR (*BCR-ABL1/ABL1* ratio <0.1%): 43/54 patients (80%) après le cycle 2 and 38/41 patients (93%) après cycle 4.
- AlloSCT (n=31), Auto-SCT (n=13)
- A un an:
  - PFS 84.5% (95% CI, 75.0-95.2)
  - **OS: 95.9%** (95% CI, 90.3-100)