

Acute Leukemia French Association

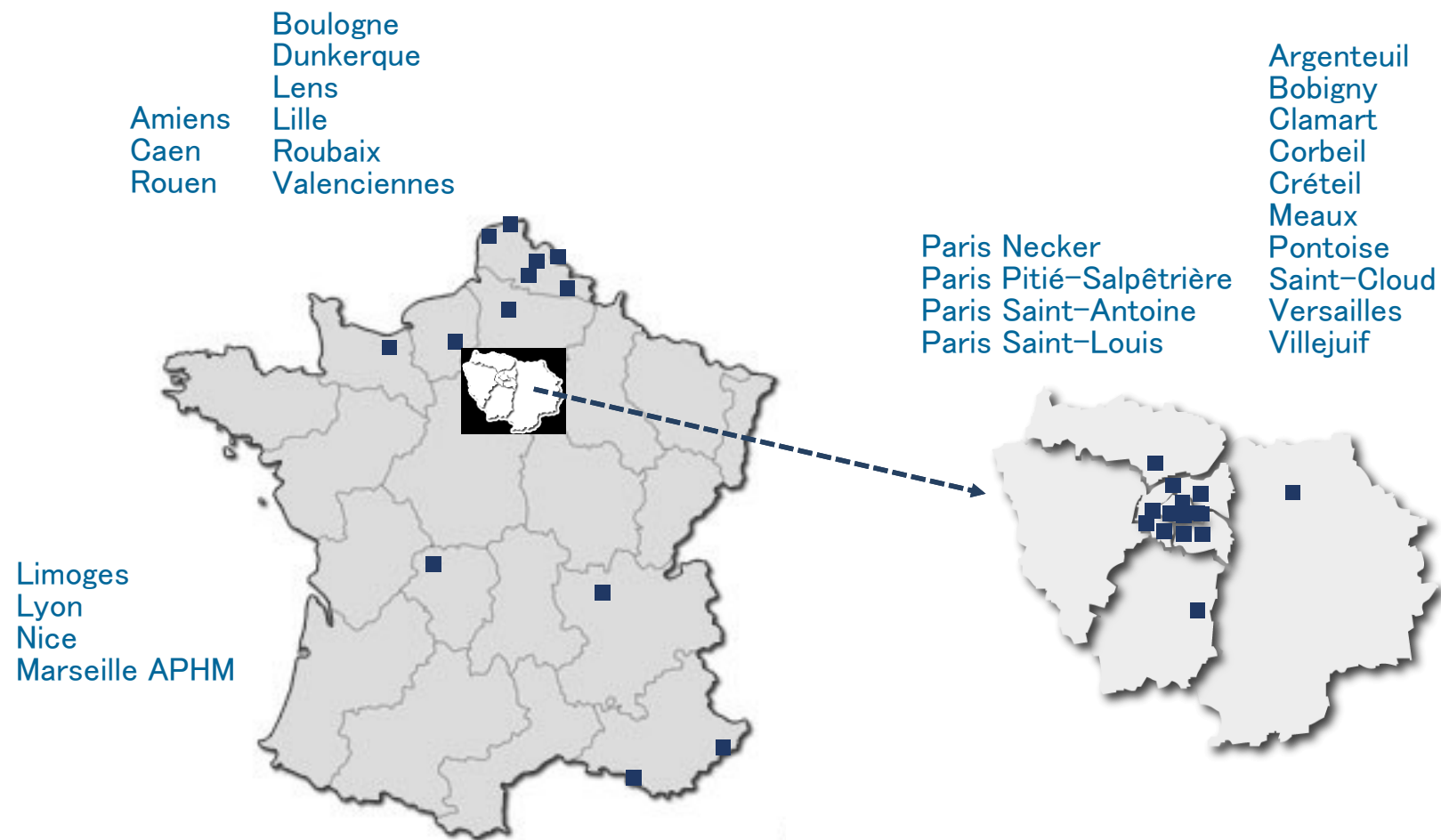
Bilan d'activité 1998-2026

Liens d'intérêt (2020-present)

Personal fees	Servier Incyte Jazz Pharma Daiichi Sankyo
Research grants	Amgen Astellas Pfizer BMS-Celgene Jazz Pharma Incyte Servier
Shareholder	La Cave de Lesconil (29740)

ALFA, principales caractéristiques

- Créé en 1990 : *L. Degos, S. Castaigne, E. Archimbaud, P. Fenaux*
- Association Loi de 1901 fondée en 1998
- Réseau multidisciplinaire dédié à la recherche clinique et translationnelle dans les LAM de l'adulte
- Structures opérationnelles mutualisées ou centralisées
 - Coordination centrale (Paris Saint-Louis)
 - Revue cytogénétique centralisée (Versailles, puis Rouen)
 - Laboratoire de biologie moléculaire centralisé (Lille)
 - Biobanque centralisée (Lille)
 - Data center / unité de biostatistique indépendante privilégié (Paris Saint-Louis)
 - Laboratoires de recherche translationnelle privilégiés (Paris Saint-Louis, Lille, Gustave Roussy...)
 - Participation au réseau multicentrique français de cytométrie en flux (Flow-MRD)
- Collaboration croissante avec le FILO depuis BIG-1



- Bureau de l'association : *H. Dombret (P), C. Preudhomme (VP), P. Rousselot (VP), C. Pautas (T)*
- Conseil d'Administration : *C. Berthon, D. Penther, S. de Botton, P. Turlure, S. Chantepie, M. Heiblig, T. Cluzeau, R. Itzykson*
- Comité de pilotage scientifique : *R. Itzykson (P), J. Lambert (VP), N. Duployez (VP)*

ALFA, aspects réglementaires et RH

- Pas de promotion propre jusqu'à récemment
- Promotion ALFA prudemment introduite en 2022 pour des études rétrospectives ou observationnelles (Retro-CBF, ALFA-PPP)
- Assure des tâches de promotion déléguées
 - DRCI (AP-HP, Versailles, Lyon HCL Nice CHU, Nice CLCC)
 - HOVON-AMLSG
- Structure centrale renforcée
 - Ressources humaines :
1 coordinatrice et 4 ARC moniteurs AP-HP mis à disposition, 1 ARC moniteur, 1 chef de projet, 1 médecin coordonnateur
 - Prestataires :
1 informaticien, 1 DPO, 1 expert comptable
 - Plateforme Télémédecine (CleanWEB)
 - Plateforme informatique Adessia
 - Prestataires pour le circuit des échantillons

ALFA, périodes stratégiques

1. Double induction ? (1990-1996)

- Older AML (LDAC study)
- Older AML (IAMLSG G-CSF study)
- Younger AML (ALFA-9000 study)

H. Tilly, JCO 1990

H. Dombret, NEJM 1996

S. Castaigne, Blood 2004

2. Plus est-il mieux ? (1997-2006)

- Younger AML (ALFA-9802 study)
- Intermediate-
- Older AML (A

X. Thomas, Blood 2011

JCO 2011

Blood 2007

Pas d'autogreffe !

Pas d'étude de traitement non intensif depuis 1990 !

3. Nouveaux médica

- Younger CBF-AML (CBF-2006 ALFA-GOELAM study)
- Intermediate-age AML (ALFA-0701/MyloFrance 3 study)
- Younger AML (ALFA-0702/CLARA study)

E. Jourdan, Blood 2013

S. Castaigne, Lancet 2012

X. Thomas, JCO 2017

4. Unification des traitements (2013-2019)

- Older AML backbone (ALFA-1200)
- French younger AML backbone (BIG-1 ALFA-GOELAM study)

C. Gardin, Blood Adv. 2020

M. Hunault, NEJM Evid. 2025

5. Observatoires (2022-prés)

- Etude observationnelle prospective (ALFA-PPP)

recrute...

Double induction (9000)

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

- Age, 15-65y
- N= 592 patients with *de novo* AML (1990-1996)
- HD-DNR 7+3 *versus* TSI (d1-d8) *versus* double induction (d1-d21)
- Post-remission: allo-SCT or timed-sequential EMA
- TSI:
 - More CR in one course
 - Longer duration of neutropenia
 - Lower relapse incidence in patients aged 50y or less
 - Similar EFS and OS

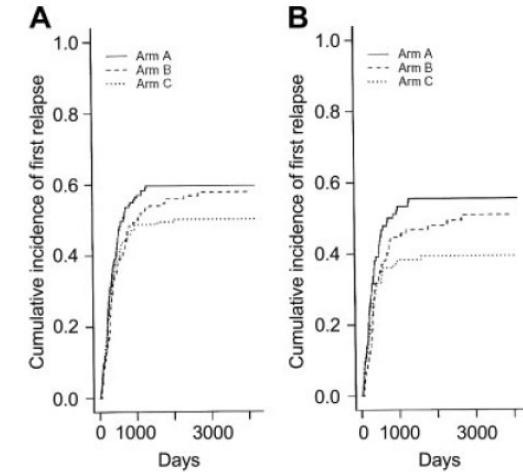


Figure 3. Relapse-free interval (cumulative incidence of relapse as first event) according to the 3 randomization arms. Panel A shows relapse-free interval in the 449 CR patients ($P = .39$ and $.15$ when arms B and C were compared to arm A, respectively, using the Gray test) (Table 3); and panel B, in the 282 CR patients younger than 50 ($P = .26$ and $.038$ when arms B and C were compared to arm A, respectively, using the Gray test) (Table 5).

Similar EFS and OS

S. Castaigne et al, Blood 2004

TS consolidation (9802)

Comparison of high-dose cytarabine and timed-sequential chemotherapy as consolidation for younger adults with AML in first remission: the ALFA-9802 study

Xavier Thomas,¹ Mohamed Elhamri,¹ Emmanuel Raffoux,² Aline Renneville,³ Cécile Pautas,⁴ Stéphane de Botton,⁵ Thierry de Revel,⁶ Oumedaly Reman,⁷ Christine Terré,⁸ Claude Gardin,⁹ Youcef Chelghoum,¹ Nicolas Boissel,² Bruno Quesnel,³ Yosr Hicheri,⁴ Jean-Henri Bourhis,⁵ Pierre Fenaux,⁹ Claude Preudhomme,³ Mauricette Michallet,¹ Sylvie Castaigne,⁸ and Hervé Dombret²

- Age, 15-50y
- N= 459 patients with *de novo* AML (1999-2006)
- TSI (d1-d8) ± GM-CSF priming (ind. & conso.)
- Post-remission: allo-SCT or HDAC (CALGB) *versus* EMA
- HDAC consolidation:
 - Similar overall RFS (41% vs 35% at 5 years)
 - Longer DFS in intermediate-risk (49% vs 29%) or CN-AML (48% vs 31%)
- GM-CSF priming:
 - Longer EFS in intermediate-risk patients (57% vs 35% at 5 years; P=0.04)

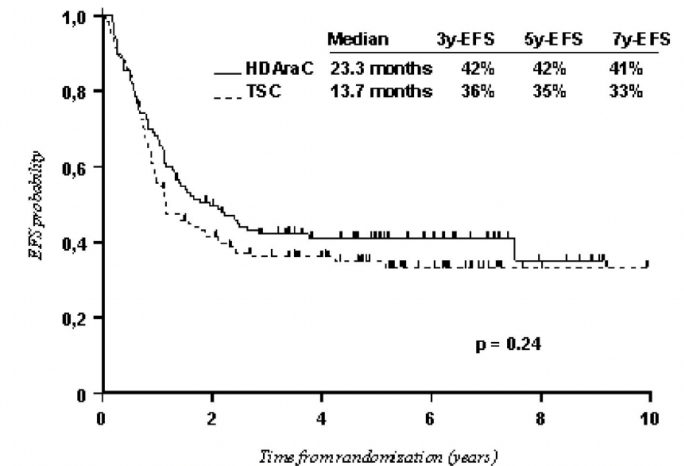


Figure 3. Comparison between the P1 arm (HD AraC consolidation) and the P2 arm (TSC consolidation; 237 patients).

Similar RFS

X. Thomas et al. Blood 2011

Higher IDA doses (9801)

Randomized Study of Intensified Anthracycline Doses for Induction and Recombinant Interleukin-2 for Maintenance in Patients With Acute Myeloid Leukemia Age 50 to 70 Years: Results of the ALFA-9801 Study

Cecile Pautas, Fatiha Merabet, Xavier Thomas, Emmanuel Raffoux, Claude Gardin, Selim Corm, Jean-Henri Bourhis, Oumedy Reman, Pascal Turlure, Nathalie Contentin, Thierry de Revel, Philippe Rousselot, Claude Preudhomme, Dominique Bordessoule, Pierre Fenaux, Christine Terré, Mauricette Michallet, Hervé Dombret, Sylvie Chevret, and Sylvie Castaigne

- Age, 50-70y
- N= 592 patients with *de novo* AML (1999-2006)
- SD-IDA *versus* HD-DNR *versus* HD-IDA 7+3 induction
- Post-remission: allo-SCT or two ID-AraC based consolidation
- rIL-2 *versus* no maintenance
- HD-DNR:
 - Lower CR rate (especially after 1st course)
 - Similar relapse incidence, EFS, OS
- rIL-2 maintenance:
 - No effect

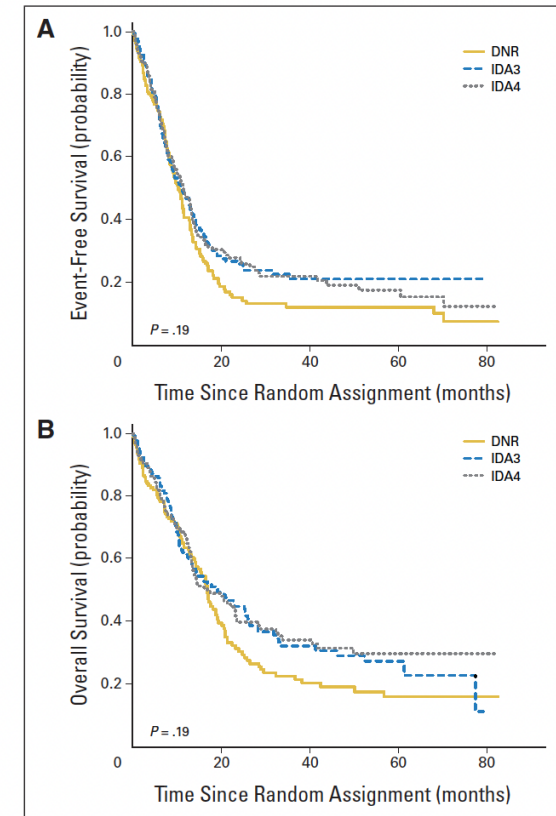


Fig 2. (A) Event-free survival (EFS) and (B) overall survival (OS) according to the three front-line randomization arms (daunorubicin [DNR] at 80 mg/m²/d × 3 days, idarubicin [IDA3] at 12 mg/m²/d × 3 days, idarubicin [IDA4] at 12 mg/m²/d × 4 days). At 4 years, EFS was estimated at 12% (95% CI, 8% to 20%), 21% (95% CI, 15% to 30%), and 22% (95% CI, 16% to 31%) in the DNR, IDA3, and IDA4 arms, respectively (*P* = .19). At 4 years, OS was estimated at 23% (95% CI, 16% to 32%), 32% (95% CI, 25% to 42%), and 34% (95% CI, 27% to 44%) in the DNR, IDA3, and IDA4 arms, respectively (*P* = .19).

Similar EFS and OS

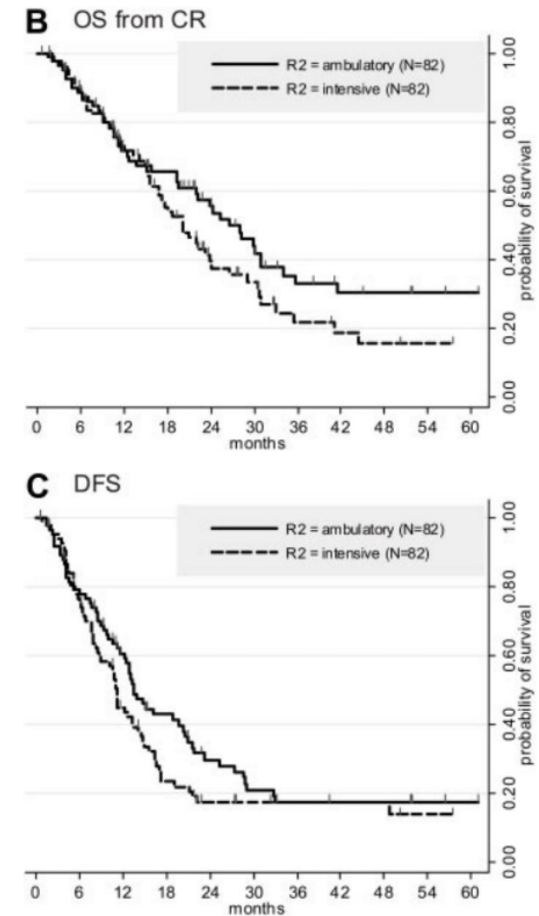
C. Pautas et al. JCO 2010

Mini-consolidations (9803)

Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial

Claude Gardin,¹ Pascal Turlure,² Thierry Fagot,³ Xavier Thomas,⁴ Christine Terre,⁵ Nathalie Contentin,⁶ Emmanuel Raffoux,⁷ Stephane de Botton,⁸ Cecile Pautas,⁹ Oumedaly Reman,¹⁰ Jean-Henri Bourhis,¹¹ Pierre Fenaux,¹ Sylvie Castaigne,⁵ Mauricette Michallet,⁴ Claude Preudhomme,⁸ Thierry de Revel,³ Dominique Bordessoule,² and Herve Dombret,⁷ for the Acute Leukemia French Association (ALFA)

- Age, 65y+
- N= 416 patients with *de novo* or post-MDS AML (1990-1996)
- **SD-IDA versus SD-DNR 7+4** induction followed by G-CSF
- Post-remission: 1 intensive (2nd induction) vs 6 **ambulatory** conso.
- IDA:
 - More CR in one course
 - Similar survival
- Ambulatory post-remission Tx:
 - Significant trend for longer OS



Longer OS from CR

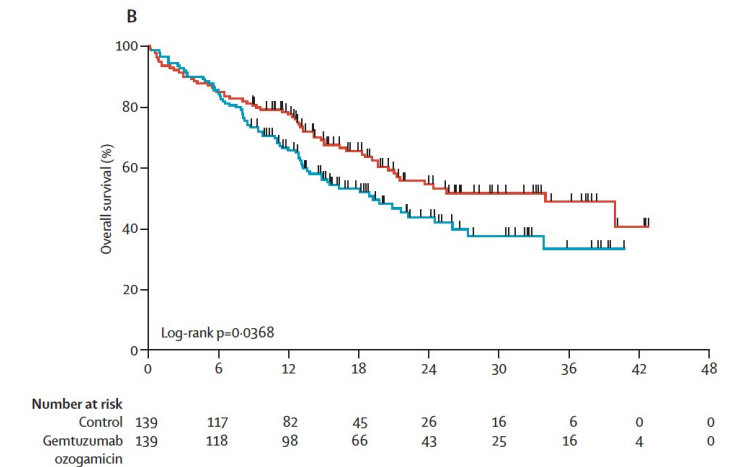
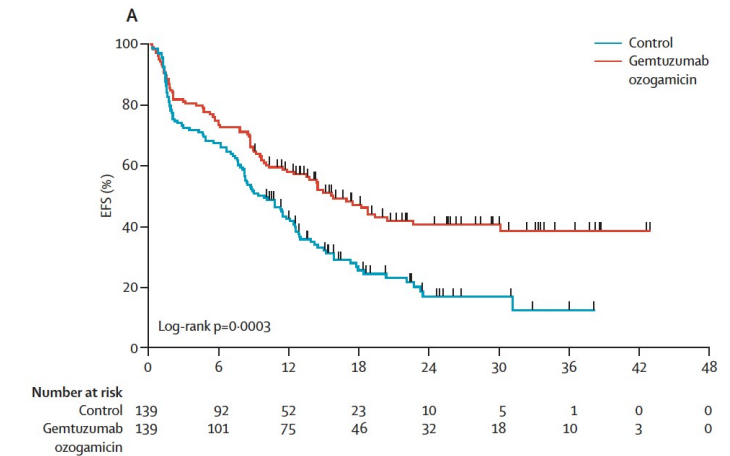
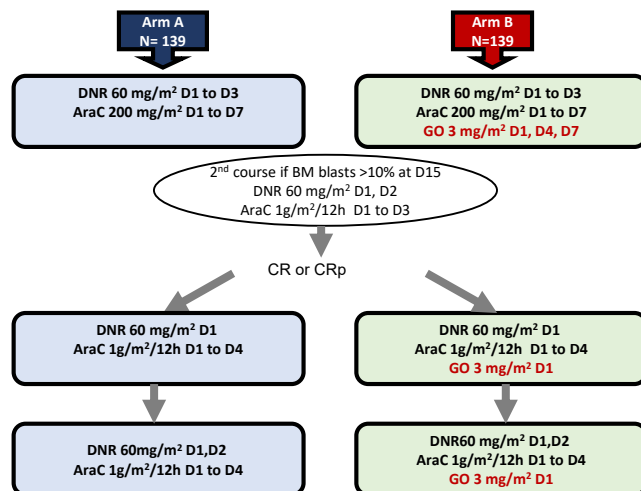
C. Gardin et al. Blood 2007

GO (0701)

Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study

Sylvie Castaigne, Cécile Pautas, Christine Terré, Emmanuel Raffoux, Dominique Bordessoule, Jean-Noel Bastie, Olivier Legrand, Xavier Thomas, Pascal Turlure, Oumedy Reman, Thierry de Revel, Lauris Gastaud, Noémie de Gunzburg, Nathalie Contentin, Estelle Henry, Jean-Pierre Marolleau, Ahmad Aljijakli, Philippe Rousselot, Pierre Fenaux, Claude Preudhomme, Sylvie Chevret, Hervé Dombret, for the Acute Leukemia French Association

- Age, 50-70y
- N= 278 patients with *de novo* AML (2008-2010)



Longer EFS and OS

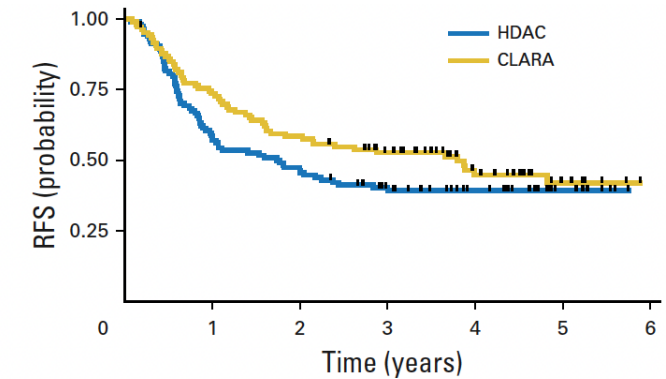
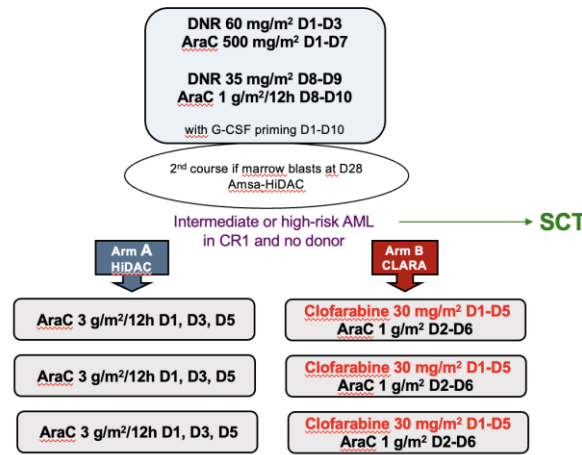
S. Castaigne et al. Lancet 2012

Clofarabine (0702)

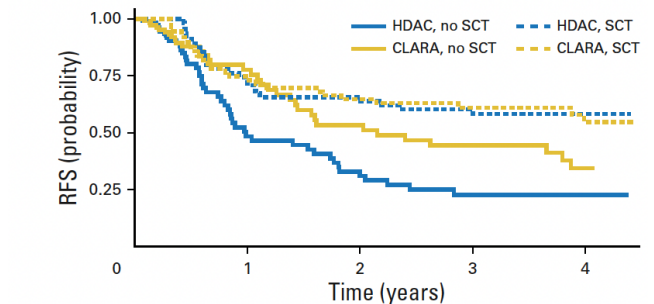
Randomized Phase II Study of Clofarabine-Based Consolidation for Younger Adults With Acute Myeloid Leukemia in First Remission

Xavier Thomas, Stéphane de Botton, Sylvie Chevret, Denis Caillot, Emmanuel Raffoux, Emilie Lemasle, Jean-Pierre Marolleau, Céline Berthon, Arnaud Pigneux, Norbert Vey, Oumedaly Reman, Marc Simon, Christian Recher, Jean-Yves Cahn, Olivier Hermine, Sylvie Castaigne, Karine Celli-Lebras, Norbert Ifrah, Claude Preudhomme, Christine Terré, and Hervé Dombret

- Age, 18-59y
- N= 713 patients with *de novo* AML (2009-2013)
- **SD-IDA** versus SD-DNR 7+4 induction
- Post-remission: CLARA vs HDAC
 - Similar RFS
 - Longer RFS if no HSCT



No. at risk							
HDAC	114	65	53	39	27	13	4
CLARA	107	78	62	49	26	12	5



No. at risk					
HDAC, no SCT	114	25	16	9	6
HDAC, SCT	0	40	37	30	21
CLARA, no SCT	107	35	24	19	9
CLARA, SCT	0	43	38	30	17

Longer RFS if no HSCT

X. Thomas et al. JCO 2017

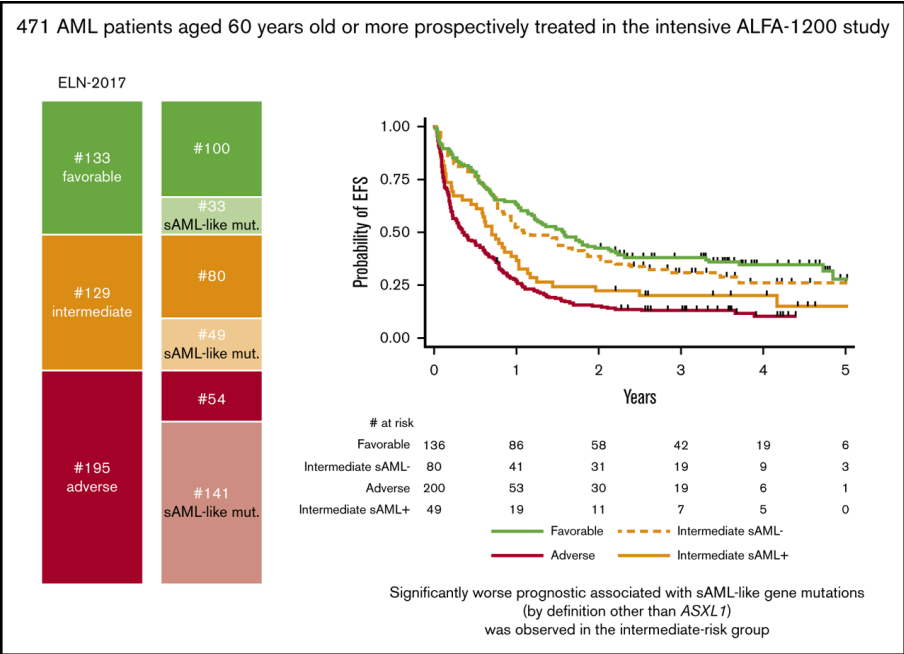
Older fit backbone (1200)

- Age, 60y+
- N= 509 patients with *de novo* or post-MDS AML (2012-2016)

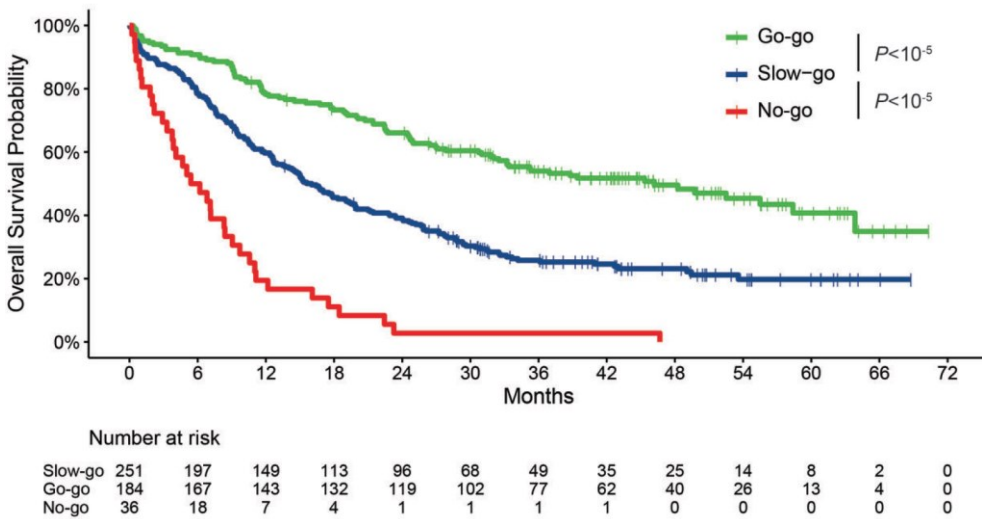
Secondary AML-like gene mutations

sAML-like genes:

ASXL1
SRSF2
STAG2
BCOR
U2AF1
EZH2
SF3B1
ZRSR2



Genetic Go/no-Go for intensive CTx



Validated in three independent cohorts: HDF, SAL and AMLSG
Recently revalidated by the MDACC (Abbas HA et al. Blood Adv. 2023)

C. Gardin et al. Blood Adv. 2020

R. Itzykson et al. Blood 2021

ALFA, nouvelles méthodologies

- Analyse de la greffe allogénique en temps-dépendant
MA. Hospital et al. Bone Marrow Transplant. 2012 Nov;47(11):1436-41

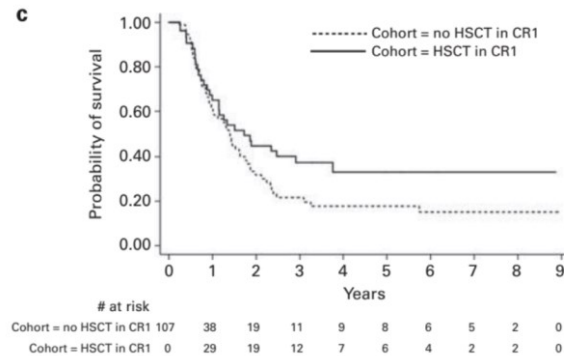
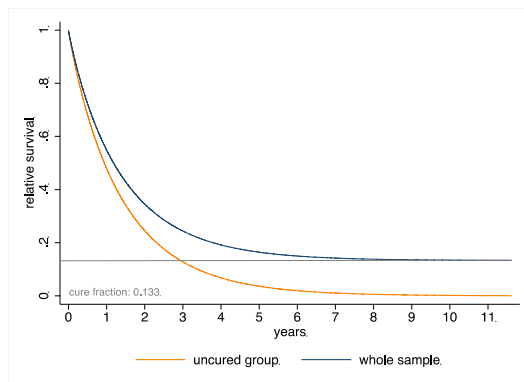


Table 4. Multivariate analyses for CIR, RFS and OS from CR: HSCT evaluated as time-dependent covariate (N = 97 CR1 patients who started the first planned post-remission chemotherapy cycle)

Variable	CIR			RFS			OS from CR		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age	1.01	0.99-1.04	0.29	1.02	0.99-1.04	0.17	1.01	0.99-1.04	0.35
Trial	0.94	0.68-1.28	0.68	0.93	0.69-1.24	0.61	0.94	0.70-1.26	0.66
Salvage for CR	1.65	0.84-3.25	0.15	1.53	0.82-2.86	0.19	1.66	0.88-3.14	0.12
HDAC-based randomization	0.96	0.50-1.86	0.91	0.99	0.52-1.90	0.97	0.77	0.40-1.51	0.45
HSCT	0.29	0.15-0.56	< 0.001	0.57	0.32-1.03	0.065	0.53	0.30-0.95	0.03

Abbreviation: CIR = cumulative incidence of relapse; HDAC = high-dose AraC; HSCT = hematopoietic SCT; RFS = relapse-free survival. The model included the following covariates: trial, need for salvage, age as a continuous variable and post-CR treatment as two dummy variables (HSCT as time-dependent variable; HDAC-based randomization).

- Analyse de la survie à long terme par le cure model
C. Gardin et al. JCO 2012;31:321-327



- Overall cure rate, 13.3%
- Covariate impacting the cure rate in multivariate analysis:
 - Age
 - IDA
 - 9.8% with DNR
 - 16.6% with IDA
 - Favorable genetics
- Covariate impacting OS of uncured patients only:
 - WBC
 - PS
 - Adverse cytogenetics

ALFA, nos fiertés !

1. Organisation multicentrique de la biologie
2. Enregistrement du Mylotarg®
3. Participations aux recommandations internationales (diagnostic, traitements, réponses...)
 - Panels d'experts de l'European LeukemiaNet (ELN) : AML, MRD
 - Recommandations du National Comprehensive Cancer Network US (NCCN)
 - Panel d'experts de l'Organisation Mondiale de la Santé (WHO)
 - Panel d'experts de l'International Consensus Classification (ICC)

La recherche clinique est bien plus que des essais thérapeutiques