

# **ACTUALITES THERAPEUTIQUES DANS LES SMD DE HAUT RISQUE ET LAM DU SUJET AGE**

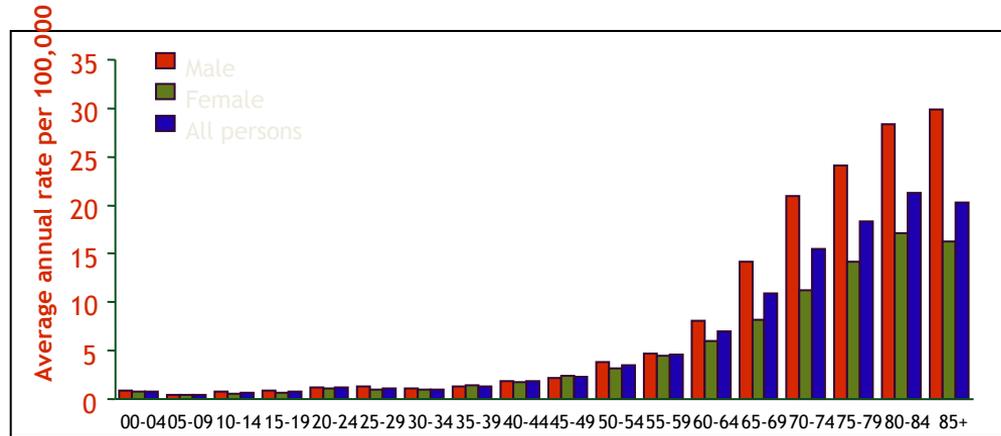
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# ACTUALITES

- Épidémiologie
- Comorbidités: patients « unfit »
- Traitements de référence
  - Chimiothérapie intensive
  - Agents déméthylants
- Nouvelles approches thérapeutiques

# INCIDENCE LAM DU SUJET AGE

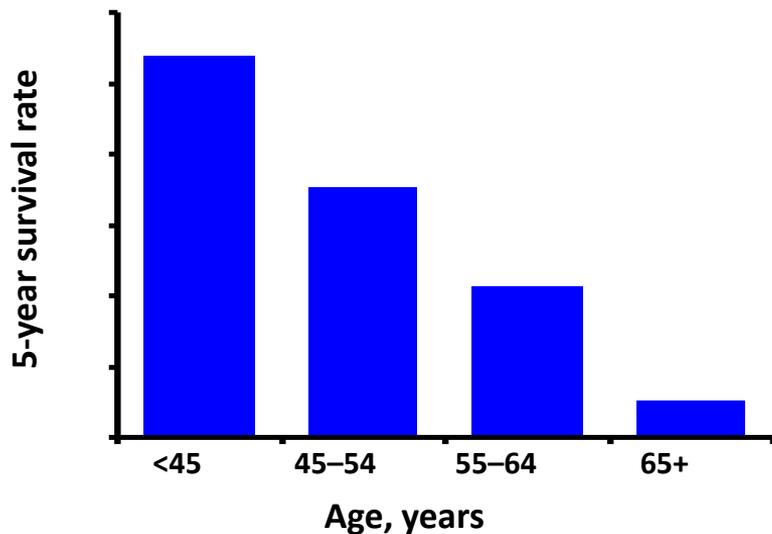
- Median age of AML is 65 years in UK (Forman, Ann Oncol, 2003)
- Age-specific incidence 17/100,000 >65 years (SEER program)
- Trend to increased incidence of elderly AML in the US between 1973-1998 (Xie, Cancer 2003)



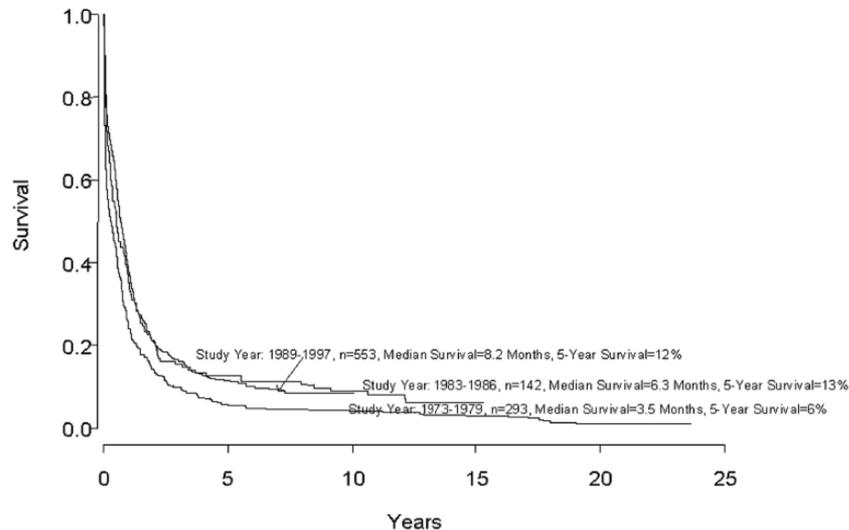
NCI SEER Program. 1995-1999.

# PRONOSTIC DE LA LAM DU SUJET AGE

5-year relative survival rates with respect to age in patients with AML<sup>1</sup>



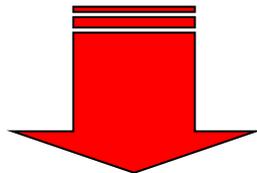
OS in patients aged >55 years (ECOG data from 1973-1997)<sup>2</sup>



1. Howlader N, et al (eds). SEER Cancer Statistics Review, 1975-2008 (2010); available at [http://seer.cancer.gov/csr/1975\\_2008/](http://seer.cancer.gov/csr/1975_2008/)
2. Appelbaum FR et al, Hematology Am Soc Hematol Educ Program 2001:62-86

## PROFIL DE LA LAM DU SUJET AGE

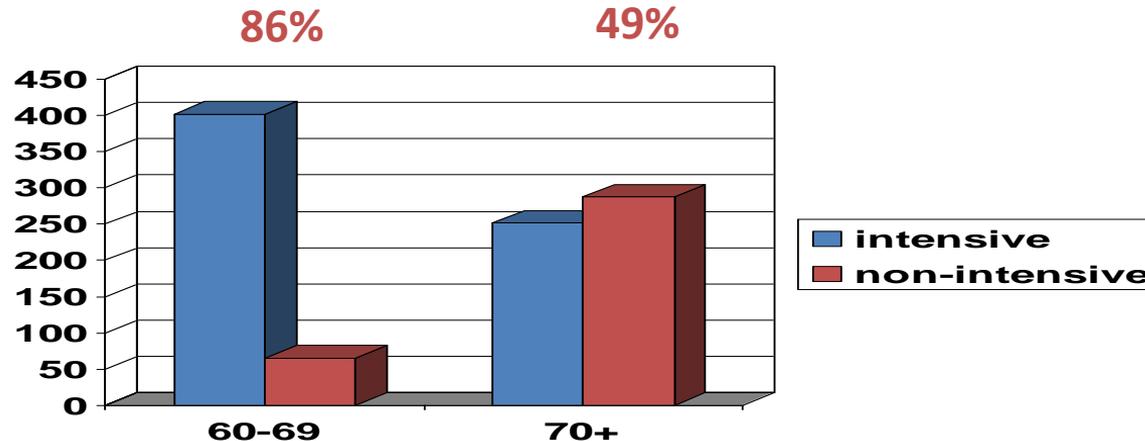
- LAM secondaires
  - >20% des cas (Appelbaum. Blood. 2006;107(9):3481-5).
- Dysplasie multilignée, leucocytose faible
  - Buchner. J Clin Oncol. 2009;27(1):61-9
- Expression CD34
  - Leith. Blood. 1997;89(9):3323-9
- Expression MDR
  - van den Heuvel-Eibrink Annals of hematology. 2007;86(5):329-37)
- Cytogénétique défavorable



# CHIMIO-RESISTANCE

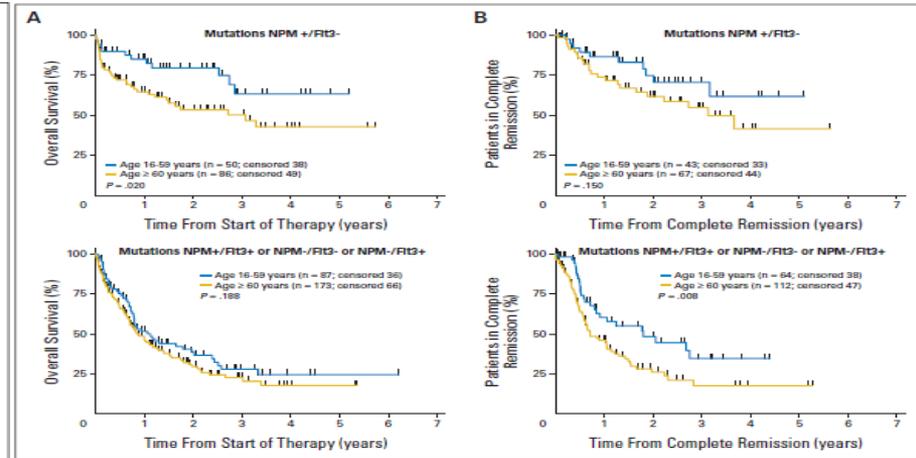
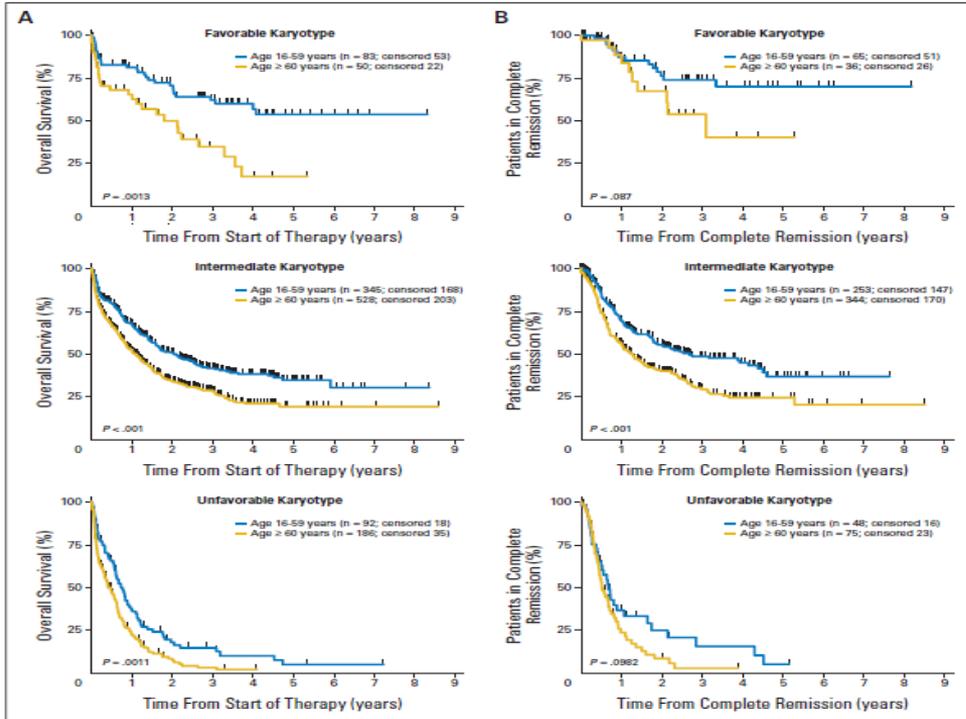
# CHOIX THERAPEUTIQUES CHEZ LE SUJET AGE

- 2657 AML patients >65 years, Medicare database<sup>1</sup>
  - Chemotherapy in 30% of patients
  - Menzin et al. Arch Intern Med. 2002 Jul 22;162(14):1597-603
- British MRC database<sup>2</sup>
  - 38% patients aged >60 years received intensive chemotherapy
  - Taylor PR et al. Leukemia. 1995 Feb;9(2):231-7.



Treatment choices in 1001 elderly patients  
IPC database (n=1911 AML)

# PRONOSTIC PEJORATIF DANS TOUS LES SOUS GROUPES



# EVALUATION DES COMORBIDITES

	Giles BJH 2007	Etienne Cancer 2007	Malfuson Hematol. 2008	Harb Cancer 2009	Savic Leuk Res 2011
No of patients	177	133	416	92	100
Median age (range)	70 (60-89)	73 (70-85)	72 (65-85)	83 (80-96)	69 (61-85)
HCT-CI					
0	22%	68%	25%	8%	29%
1-2	30%	29%	70%	33%	32%
≥3	48%	4%	5%	59%	39%
Prognostic value	CR/ED/OS	CR	OS	NA	ED/CR/OS

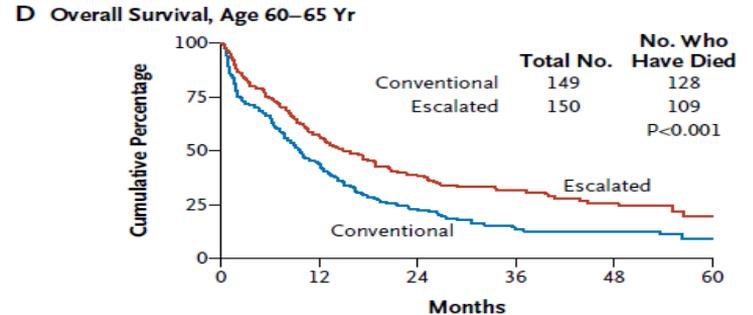
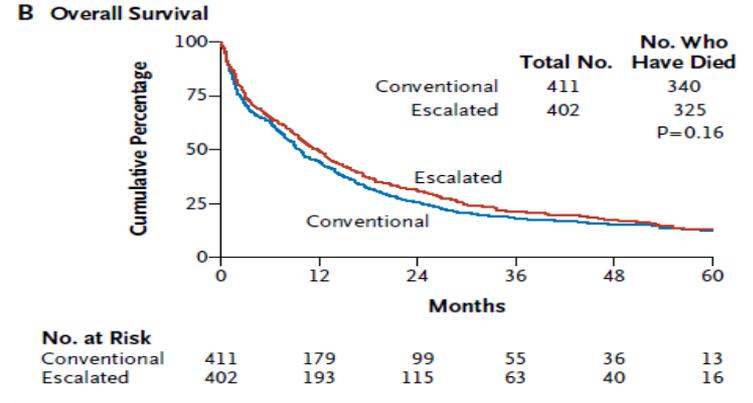
- 25% to 30% of the patients had no comorbidity (score=0)
- Cardiac disease was the most frequent comorbidity
- HCT-CI was shown to be independent from both age and performans status (Malfuson, Haematol. 2008)

# EVALUATION DU STATUT FONCTIONNEL

- IADL (Wedding U, JCRCO 2006;132(10):665-71)
  - 63 patients aged 19-85 years (median 61.1); 50 received induction Cx
  - impairment of IADL, Karnofsky, PS and unfavourable cytogenetics significantly predicted survival by multivariate analysis
  - age was not an independent predictor of OS
- Comprehensive Geriatric Assessment (Klepin HD, JAGS 2011;59(10):1837-46)
  - Prospective study of 54 elderly AML patients (median age 70 years) for whom intensive treatment with chemotherapy was planned
  - 63% of participants had impairments of more than one functional domains

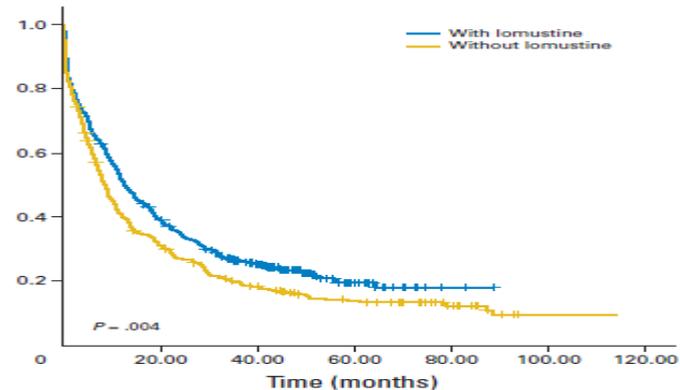
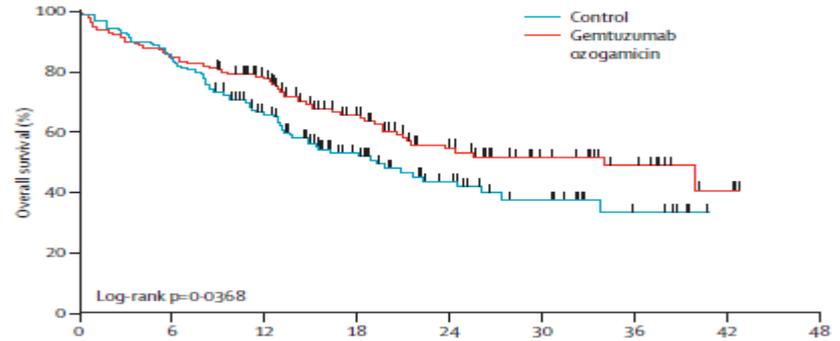
# CHIMIOThERAPIE INTENSIVE

- 3+7 reste le standard
  - DNR 90 oui mais chez « jeunes-vieux »  
(Lowenberg, N Engl J Med 2009;361:1235-48)



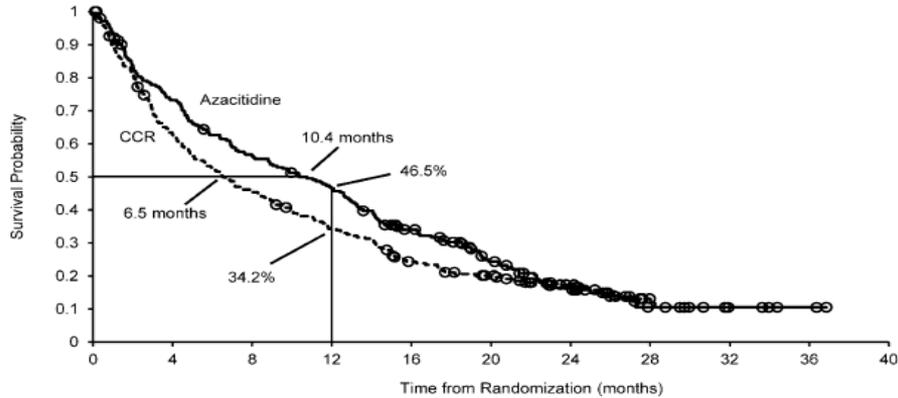
# CHIMIOThERAPIE INTENSIVE: 3<sup>e</sup> DROGUE?

- Addition of fractionnated GO improves OS (Castaigne Lancet 2012)
- Addition of lomustine in a meta-analysis of 3 GOELAMS trials (Pigneux, JCO 2011)
- FLT3-inhibitors? SAL phase 3 in elderly patients (Serve, JCO 2013)
  - Similar OS, EFS
  - Inferior CR rates and higher induction deaths in the sorafenib arm

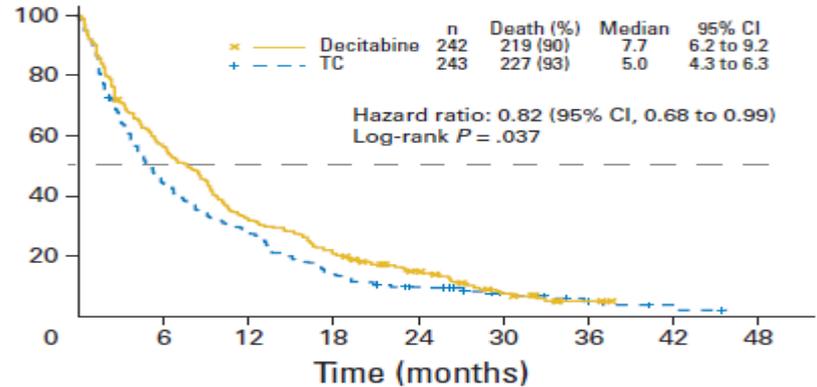


# AGENTS DEMETHYLANTS

- AMM EMEA (mais pas FDA) pour azacitidine et decitabine chez sujet âgé unfit



Dombret , Blood 2015



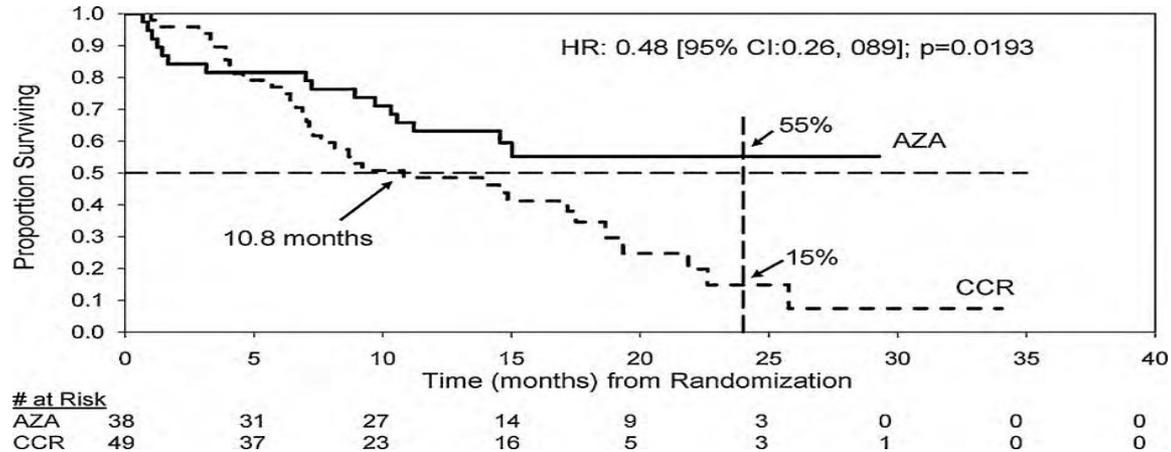
Kantarjian, JCO 2012

# SMD

- Maladie du sujet âgé
- Traitement standard pour les SMD de haut-risque: HMA
  - Azacytidine en Europe
  - Azacytidine-Decitabine aux US
- Résultats identique chez les patients les plus âgés
- Nombreuses études d'association mais pas d'amélioration (notamment HDACi)

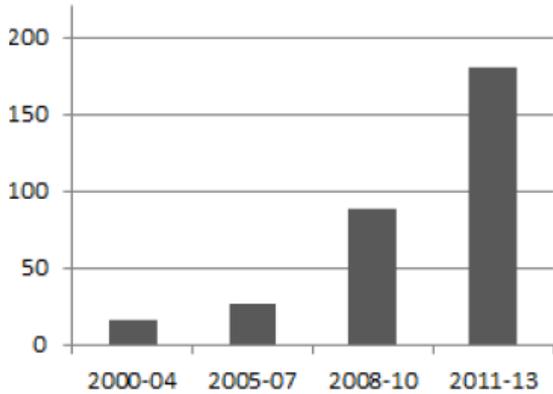
# AZACYTIDINE ET SMD SUJET AGE (AZA-001)

- Sub-analysis of 87 patients >75 years in AZA-001 trial
- AZA : 38 patients, CCR 49 patients
- 70% BSC arm selected by investigator
- Median age 78 years

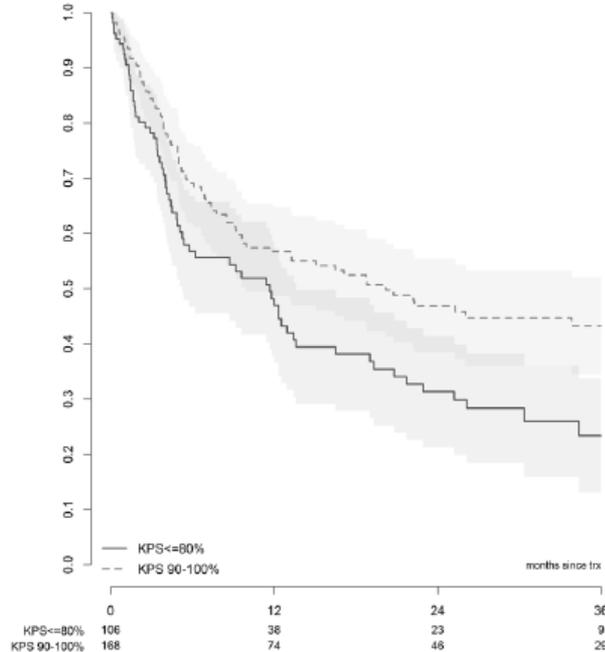


# ALLOGREFFE ET SMD SUJET AGE

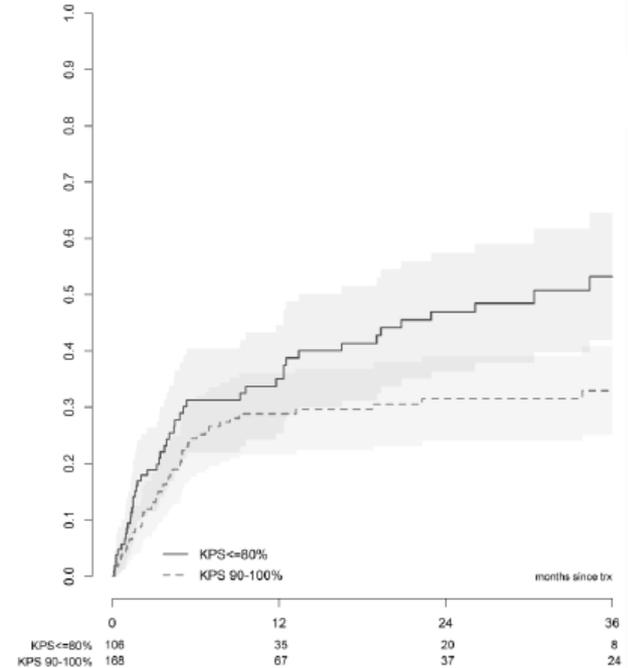
EBMT  
 313 pts  
 MDS >70 y  
 2000-2013



A – OS by Karnofsky status

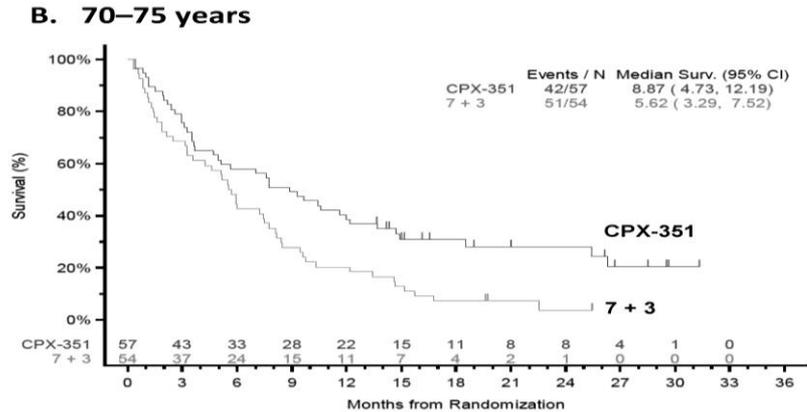
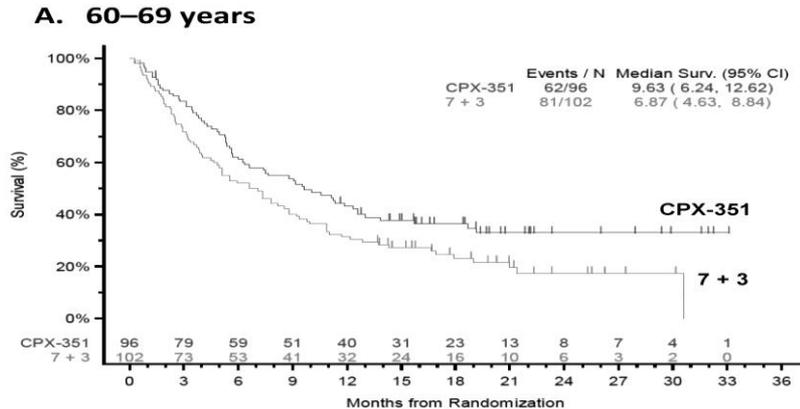


B – NRM by Karnofsky status



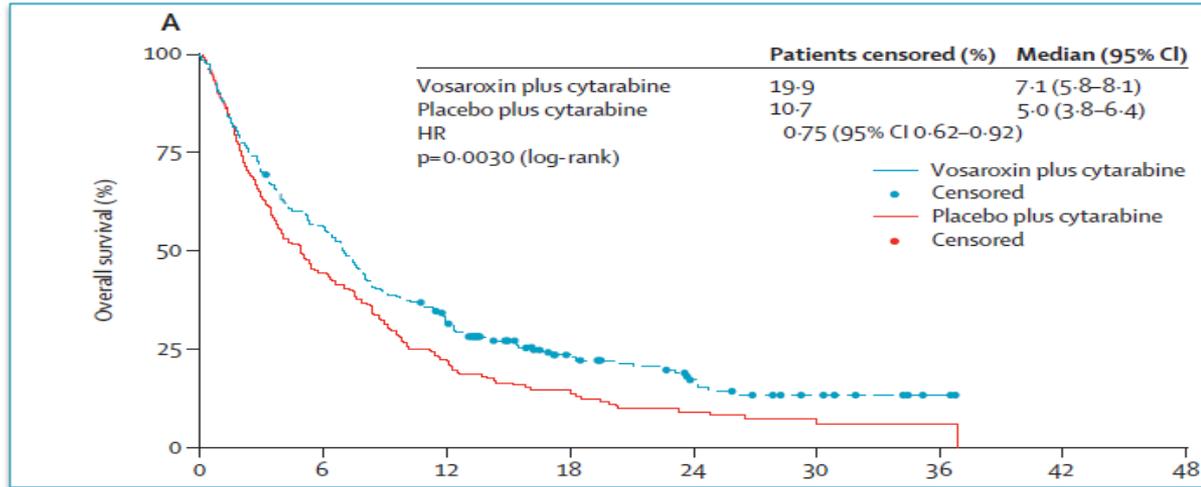
# NOUVELLES CHIMIOTHERAPIES: CPX-351

- CPX-351 (Vyxeos) is a liposomal formulation of cytarabine and daunorubicin encapsulated at a 5:1 molar ratio
- Eligibility: age 60 to 75 years and secondary AML
- 153 patients randomized to the CPX-351 arm and 156 to the 7+3 arm



# NOUVELLES CHIMIOTHERAPIES: VOSAROXIN

451 patients aged >60 yrs



**Vosaroxin-AraC is associated with OS improvement in elderly R/R AML: a sub-analysis of the VALOR trial**

## NOUVELLES MOLECULES: AcMo

- SGN33A
- Anti CD123 (études en cours, pas de résultats publiés)
  - Talacozumab
  - Bispécifiques (MGD006)
- Immune checkpoint inhibiteurs
  - Nivolumab

# VADASTUXIMAB TARLINE (SGN-CD33A)

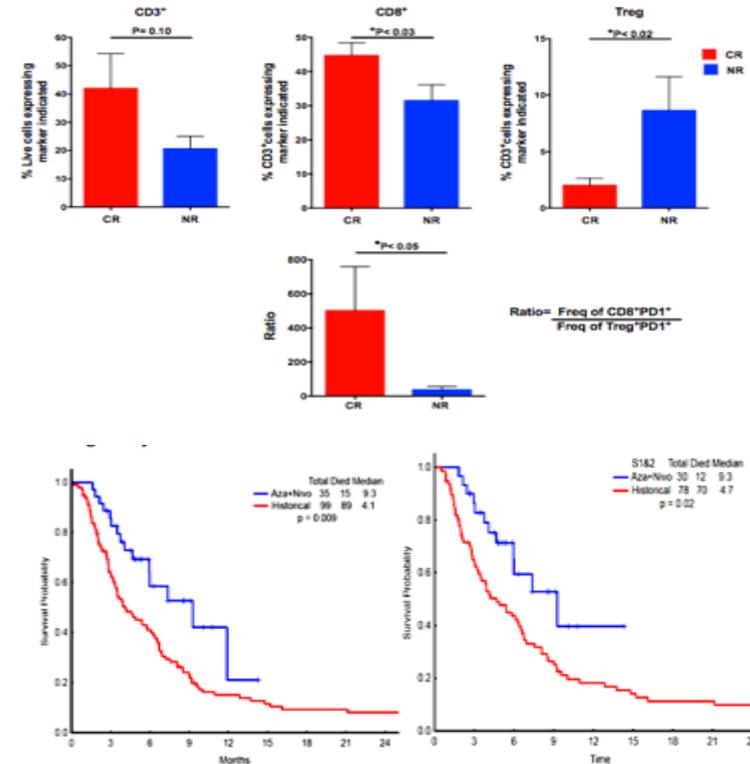
- Vadastuximab Talirine Monotherapy in Older Patients with Treatment Naive CD33-Positive AML (Dale L. Bixby et al. Abs 590, ASH 2016):
  - N=26 pts
  - 30- and 60-day mortality rates = 0% and 15%.
  - CR= 23% Cri=31% MLFS= 19%
  - Tox: myelosuppression
- Vadastuximab Talirine Plus Hypomethylating Agents in Frontline Older Patients with AML (Amir T. Fathi et al., Abs 591 ASH 2016):
  - 53 patients (age 75 years; range, 60-87)
  - 33A: 10 mcg/kg, IV every 4 weeks on the last day of HMA
  - 17 of 36 responders (47%) achieved **MRD negativity** by flow cytometry

	33A+ HMA <sup>a</sup>	HMA Alone (historical references)
CR rate	43%	14.8–19.5% <sup>b</sup>
CRi rate	31%	2.1–8.3% <sup>b</sup>
CR+CRi rate	73%	17.8–27.8% <sup>b</sup>
CR+CRi rate (adverse cytogenetic risk subgroup)	83%	24% <sup>c</sup>
CR+CRi rate (underlying myelodysplasia subgroup)	73%	26.7% <sup>d</sup>
Time to remission	2 cycles	4–6 cycles <sup>b</sup>
30-day mortality rate	2%	6.6–9% <sup>b</sup>
60-day mortality rate	8%	16.2–19.7% <sup>b</sup>

# NIVOLUMAB ET AZACYTIDINE POUR LAM EN RECHUTE

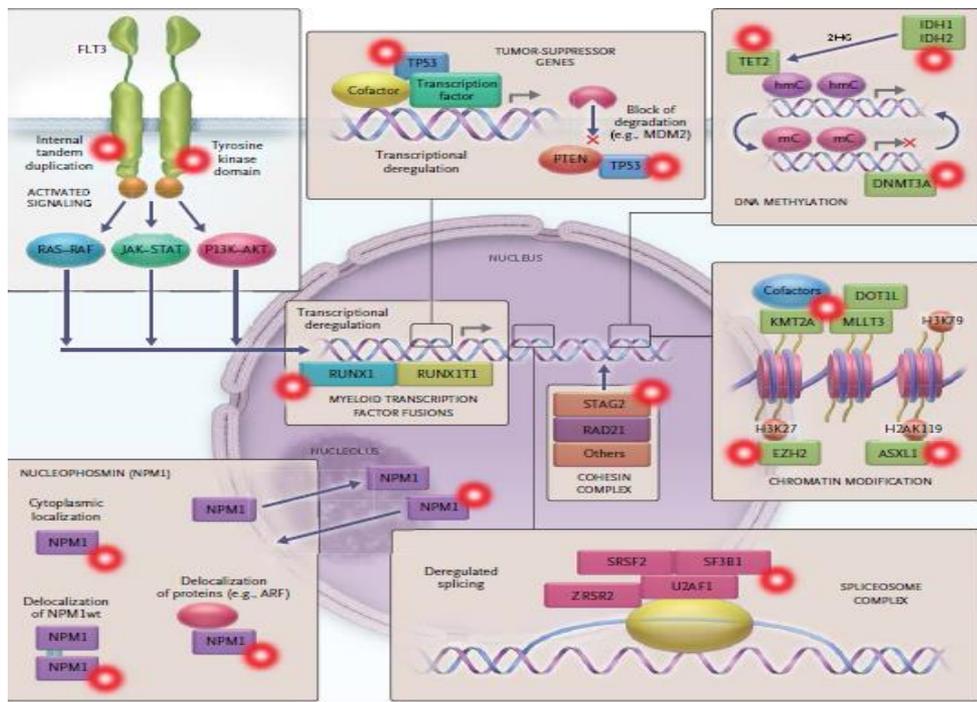
- Treatment:
  - AZA 75mg/m<sup>2</sup> Days 1-7 with nivolumab 3mg/kg on Day 1 and 14. Courses were repeated approximately every 4-5
- 51 pts with a median age of 69 years (range, 45 – 90)
- Efficacy:
  - 35 pts are evaluable for response:
  - CR/CRi: 6 (18%)
  - HI: 5 (15%)
- Tolerance
  - 4- and 8-wk mortality were 0 and 6%
  - Grade 3/4 and Grade 2 immune mediated toxicities were observed in 7 (14%) and 6 (12%)

Figure 2: Pretherapy T-cell subsets and T-reg activation status in bone marrow aspirate



# CIBLES ET NOUVELLES MOLECULES

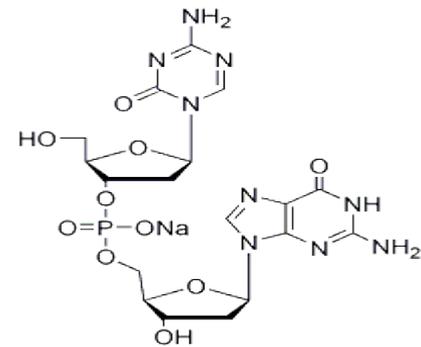
## Mutated genes



## Dysregulated pathways

- Signaling/cell cycle
  - RAS
  - PIM kinases
  - PI3K/AKT
  - CDK4-6
  - PLK
- Apoptosis
  - BCL2
  - MDM2
- LSC compartment

## NOUVEAU DEMETHYLANT: SGI 110



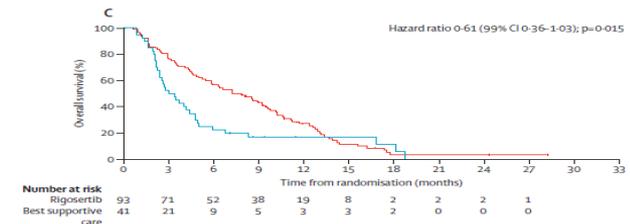
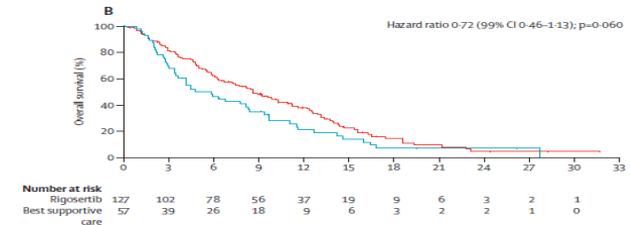
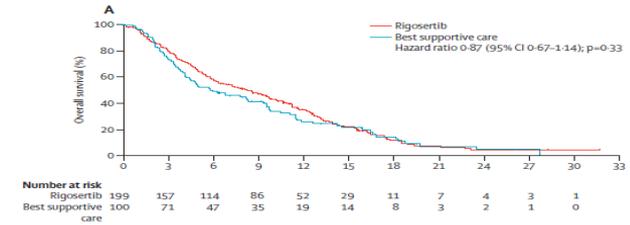
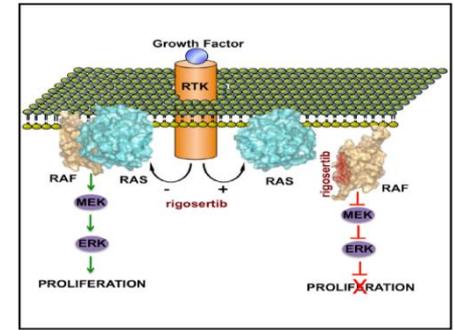
- Decitabine analog with optimized PK/PD developed by ASTEX / OTSUKA
- Phase II in AML data showed interesting results in elderly unfit patients (ORR 42%)
- HMA resistant MDS patients: 21% CR+ mCR
- Current phase II GFM and US trials
- Current phase III AML first line unfit

## INHIBITEURS IDH1 ET 2

- Fréquence : 3.6 to 12% (Patnaik et al., Leukemia 2011)
- AG120:
  - ORR: 27/78 (AML)
- AG221
  - Clinical activity in AML: ORR 79/209 (38%) (Stein ASH 2016)
- Combo with HMA ongoing

# RIGOSERTIB: INHIBITEUR MULTI KINASE

- Multi Hit Kinase inhibitor
  - PLK-1 pathway inhibitor
  - PI3-Kinase inhibitor
  - RAS inhibitor (Cell 2016)
- Phase 3 in Higher-risk MDS after AZA failure
  - 299 pts
  - ORR\*\* ≈25%
  - OS= 8.2 months vs 5.8 m (BSC) p=0.22
  - OS=8.5m vs 4.7m for primary failure
- Study 04-30: A Phase III, Randomized, Controlled Study of Rigosertib versus Physician's Choice of Treatment in Patients with MDS after Failure of a Hypomethylating Agent



## TAKE HOME MESSAGES

- Problème actuel et à venir
- Définition « unfit »: évaluation collégiale avec gériatre
- Médecine personnalisée: NGS
- Essais thérapeutiques++

