Leucémies aiguës myéloïdes : diagnostic, thérapies, critères d'évaluation de la réponse

Dr Sarah BERTOLI

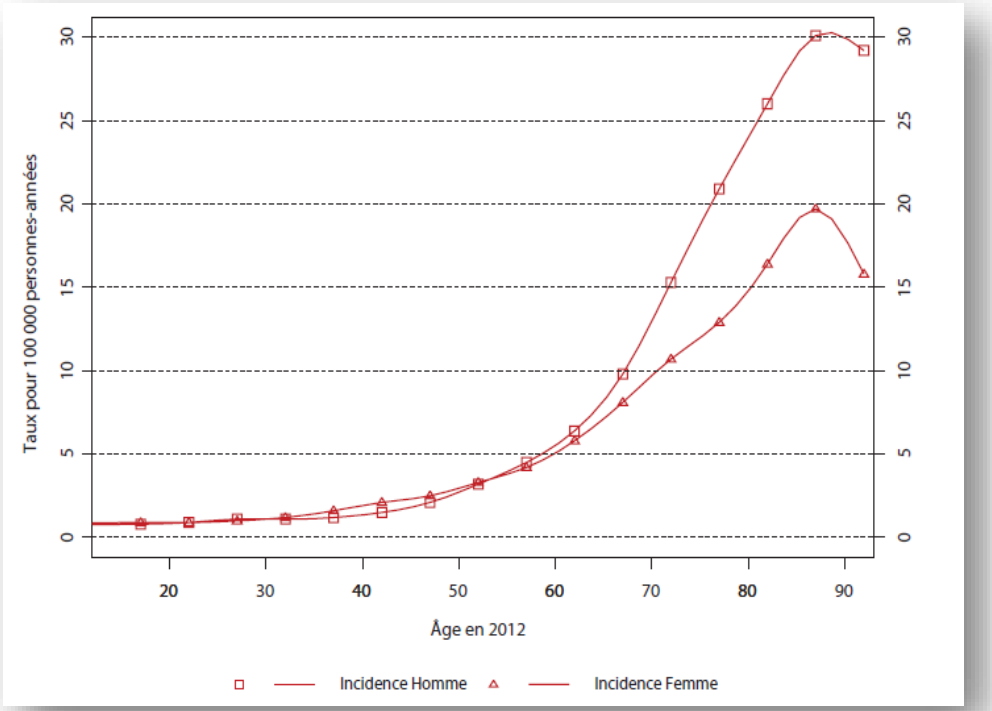
CHU de Toulouse – Institut Universitaire du Cancer de Toulouse-Oncopole

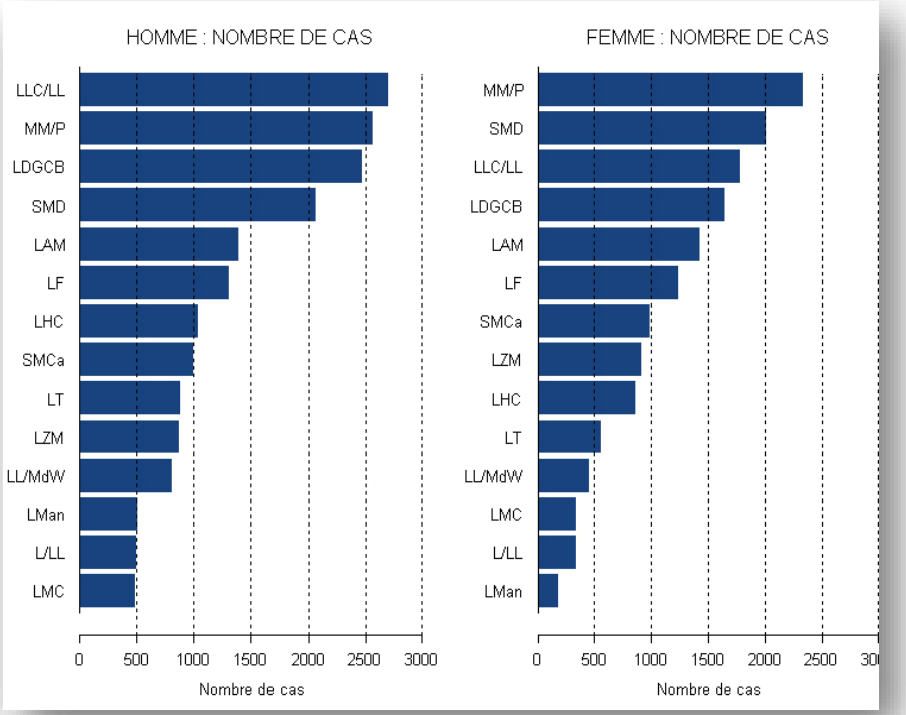
17es Rencontres de Recherche Clinique

DIJON – Palais des Congrès

23 novembre 2022

Epidémiologie





~ 3,000 nouveaux cas par an en France

Incidence liée à l'âge – médiane d'âge au diagnostic >70 ans

5e hémopathie

Diagnostic : clinique

Circonstances de découverte

Insuffisance médullaire:

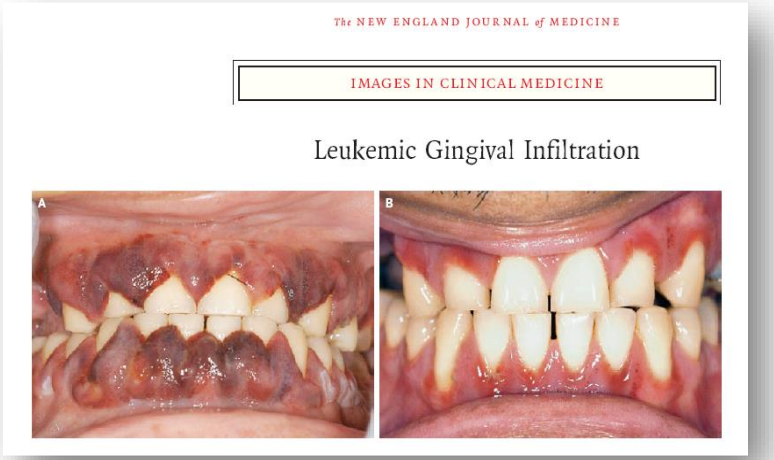
*syndrome anémique (pâleur, asthénie, dyspnée d'effort..)
*syndrome hémorragique (purpura, ecchymoses, gingivorragies, épistaxis)
*syndrome infectieux (fièvre isolée, angines, pneumopathies, choc septique…)

Syndrome tumoral:

*Hépato-splénomégalie, localisations cutanées, hypertrophie gingivale (LAM5), adénopathies (rares), pulmonaires, neurologiques
*Sarcome granulocytaire

Anomalies de la coagulation avec syndrome hémorragique majeur (CIVD des LAM3)

Surveillance d'un SMP ou MDS



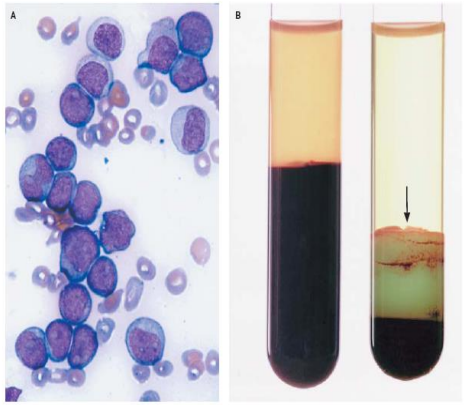
Diagnostic : clinique

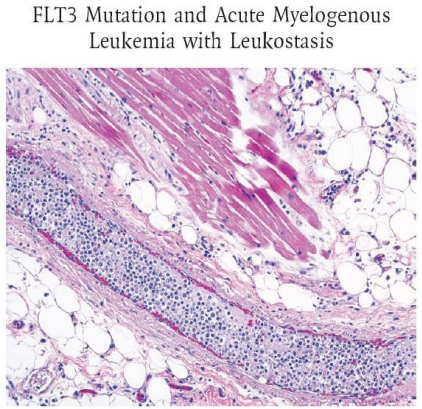
*Hyperleucocytose/leucostase

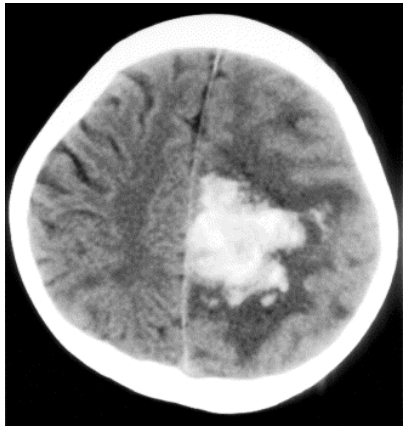
*Hémorragies (CIVD)

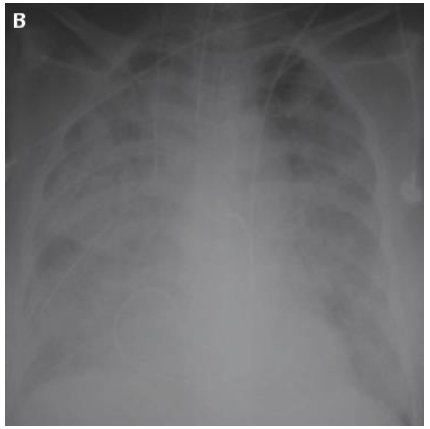
*Syndrome de lyse tumorale et troubles métaboliques

*Infection sévère









Diagnostic : biologie

Biologie « standard »

*NFS: hyperleucocytose ou pancytopénie, blastes circulants ou non, neutropénie, anémie arégénérative, thrombopénie.
*Bilan d'hémostase (CIVD) – bilan biochimique (SLT)

Cytologie

*analyse cytologique (coloration May Grünewald Giemsa MGG)
FAB
Dysplasie (uni/multilignée ; quantification)

Phénotype

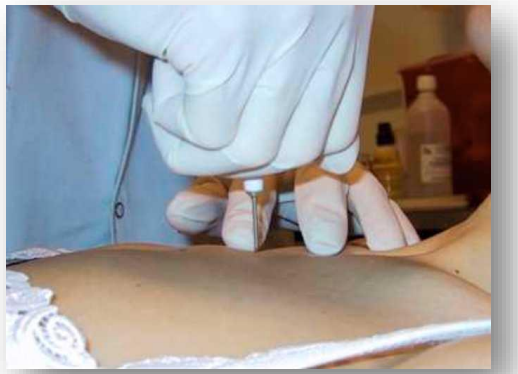
*utile ++ pour la MRD
*prédiction des mutations associées, pronostique

Analyses cytogénétiques et moléculaires

*analyse cytogénétique (caryotype, FISH: Fluorescence In Situ Hydrization (MLL, EVI1))
*biologie moléculaire (transcrits de fusion; mutations *FLT3-ITD/TKD, NPM1, CEBPA, IDH1, IDH2, DNMT3A, ASXL1)*
*NGS complet : de plus en plus

Biopsie ostéo-médullaire (rare)

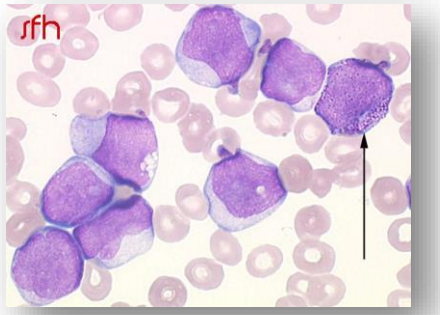
si aspiration difficile du suc médullaire (myélofibrose associée – LAM7)

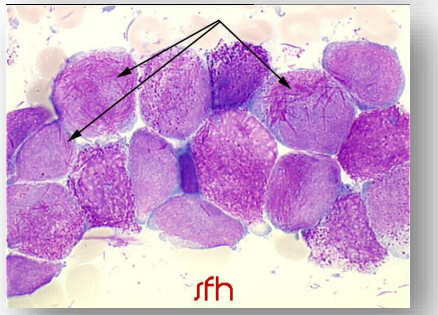


Ponction sternale
-Ligne médiane, au milieu du manubrium (1er espace intercostal)
-Contre-indications : sternotomie, radiothérapie dans le territoire.
Attention petits gabarits !
Par un interne ou un senior

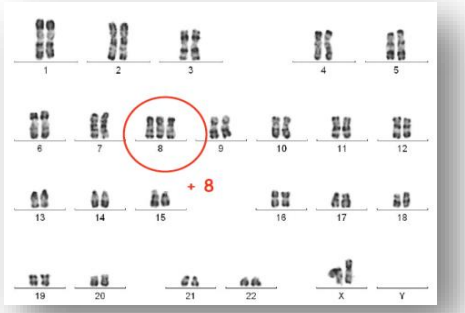
Diagnostic : biologie

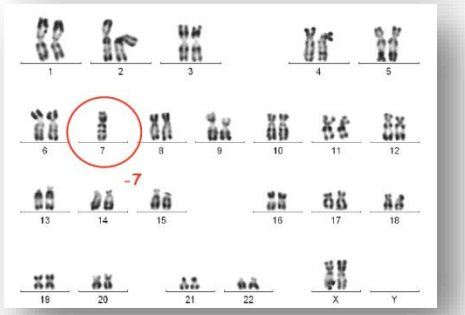
1976 → **Classification Morphologique FAB**





1985-2000 → **Cytogénétique**

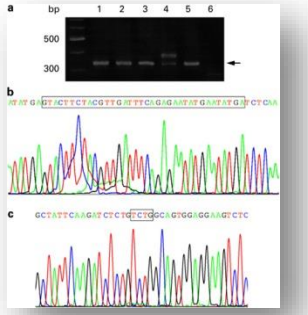




1997-2010 → **Moléculaire**

Mutations

FLT3-ITD/KIT
NPM1
CEBPA
DNMT3A/IDH1/2
WT1/MLL-PTD/RAS/AML1
PHF6/TET2/ASXL1



Séquençage du génome

NGS

Caryotype

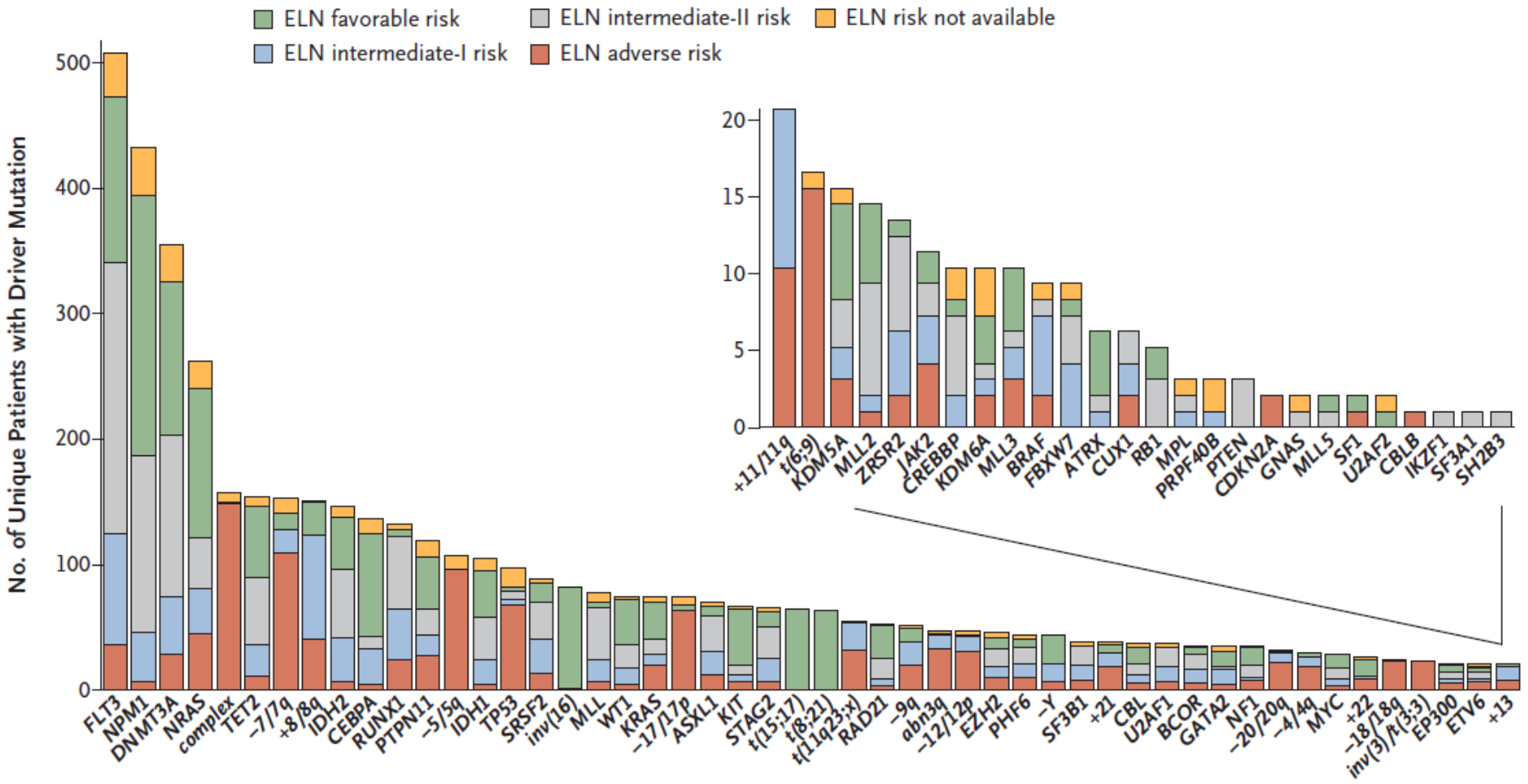
Table 4. Revised MRC prognostic classification based on multivariable analyses

Cytogenetic abnormality	Comments
Favorable	
t(15;17)(q22;q21)	
t(8;21)(q22;q22)	Irrespective of additional cytogenetic abnormalities*
inv(16)(p13q22)/t(16;16)(p13;q22)	
Intermediate	
Entities not classified as favorable or adverse	
Adverse	
abn(3q) [excluding t(3;5)(q21~25;q31~35)],	
inv(3)(q21q26)/t(3;3)(q21;q26),	
add(5q), del(5q), −5,	
−7, add(7q)/del(7q),	Excluding cases with favorable karyotype†
t(6;11)(q27;q23),	
t(10;11)(p11~13;q23),	
t(11q23) [excluding t(9;11)(p21~22;q23) and t(11;19)(q23;p13)]	
t(9;22)(q34;q11),	
−17/abn(17p),	
Complex (≥ 4 unrelated abnormalities)	

*All favorable-risk abnormalities.
†All adverse-risk abnormalities.

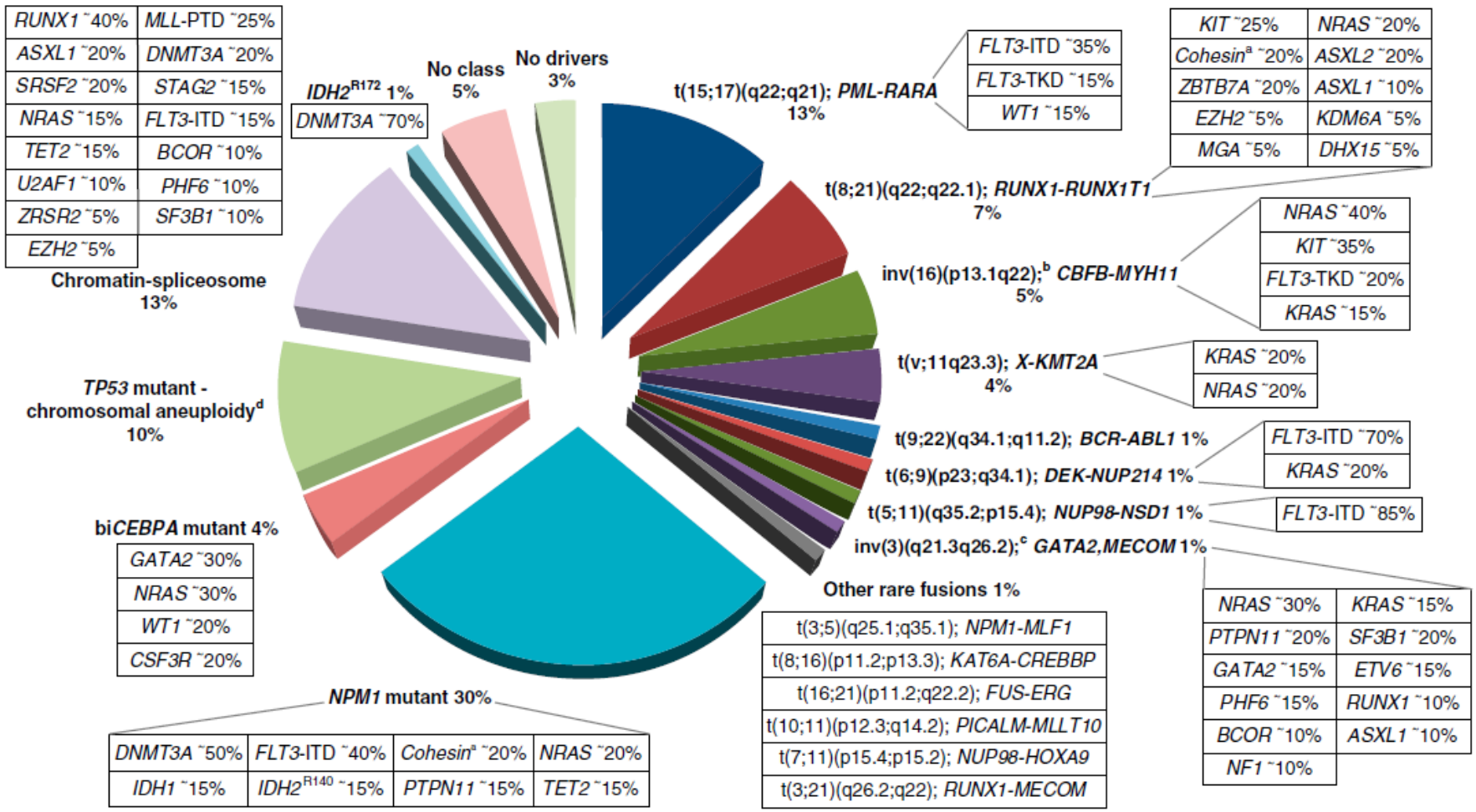
Grimwade D, Blood 2010

Biologie moléculaire



Papaemmanuil E, NEJM 2016

Biologie moléculaire



Döhner H, Blood 2017

Tests and procedures

Tests to establish the diagnosis

- Complete blood count and differential count*
- Bone marrow aspirate†
- Bone marrow trephine biopsy‡
- Immunophenotyping by flow cytometry (see Table 5)

Genetic analyses	Results preferably available within
Cytogenetics§	• 5-7 d
Screening for gene mutations required for establishing the diagnosis and to identify actionable therapeutic targets#	
• *FLT3*,¶ *IDH1*, *IDH2*	• 3-5 d
• *NPM1*	• 3-5 d
• *CEBPA*,# *DDX41*, *TP53*; *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*	• 1st cycle
Screening for gene rearrangements**	
• *PML*::*RARA*, *CBFB*::*MYH11*, *RUNX1*::*RUNX1T1*, *KMT2A* rearrangements, *BCR*::*ABL1*, other fusion genes (if available)	• 3-5 d

Additional genes recommended to test at diagnosis††

- *ANKRD26*, *BCORL1*, *BRAF*, *CBL*, *CSF3R*, *DNMT3A*, *ETV6*, *GATA2*, *JAK2*, *KIT*, *KRAS*, *NRAS*, *NF1*, *PHF6*, *PPM1D*, *PTPN11*, *RAD21*, *SETBP1*, *TET2*, *WT1*

Medical history

- Demographics and medical history‡‡
- Detailed family history[a]
- Patient bleeding history[b]
- Analysis of comorbidities

Additional tests and procedures

- Complete physical examination[c]
- Performance status (ECOG/WHO score)
- Geriatric assessment[d] (optional)
- Biochemistry, coagulation tests[e]
- Hepatitis A, B, C; HIV-1 testing; CMV, EBV, HSV, VZV
- Serum pregnancy test[f]
- Eligibility assessment for allogeneic HCT (incl. HLA-typing)[g]
- Chest x-ray, 12-lead electrocardiogram, echocardiography or MUGA (on indication)
- Computed tomography of the chest (on indication)[h]
- Lumbar puncture (on indication)[i]
- Information on oocyte and sperm cryopreservation[j]
- Biobanking[k]

Döhner H, Blood 2022

Classification ELN 2017

Table 5. 2017 ELN risk stratification by genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Ratio < 0.5

Ratio ≥ 0.5

Döhner H, Blood 2017

2022 ELN risk categorization

Döhner H, Blood 2022

Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*‡‡ • Mutated *TP53*[a]

Si *NPM1*m et caryotype défavorable : risque adverse

t(9;11) intermédiaire même si anomalie défavorable associée

Modulo les MRD (CBF et *NPM1*)
Pronostic non modifié par mut de *KIT* ou *FLT3*

Uniquement mutations *in-frame* affectant la région bZIP (mono- ou biallélique)

Disparition de la notion de ratio pour *FLT3*-ITD

Sauf *MLL*-PTD

Sauf si concomitante d'un sous-groupe favorable

*VAF au moins 10%, mono- ou bi-allélique

Critères de réponse de l'ELN

Category	Definition	Comment
Response		
CR*,†,‡	Bone marrow blasts < 5%; absence of circulating blasts; absence of extramedullary disease; ANC ≥ 1.0×10^9/L (1,000/μL); platelet count ≥ 100×10^9/L (100 000/μL)	
CRh*,†,‡	ANC ≥ 0.5×10^9/L (500/μL) and platelet count ≥ 50×10^9/L (50 000/μL), otherwise all other CR criteria met	If CRh used, CRi should only include patients not meeting the definition of CRh
CRi*,†,‡	All CR criteria except for residual neutropenia < 1.0×10^9/L (1,000/μL) or thrombocytopenia < 100×10^9/L (100 000/μL)	
MLFS	Bone marrow blasts < 5%; absence of circulating blasts; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; bone marrow spicules should be present; at least 200 cells should be enumerated in the aspirate or cellularity should be at least 10% in the biopsy. Mainly used in the context of phase 1-2 clinical trials
PR	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pre-treatment bone marrow blast percentage by at least 50%	Mainly used in the context of phase 1-2 clinical trials
No response	Patients evaluable for response but not meeting the criteria for CR, CRh, CRi, MLFS or PR are categorized as having no response prior to the response landmark. Patients failing to achieve response by the designated landmark are designated as having refractory disease	
Nonevaluable for response	Non-evaluable for response will include patients lacking an adequate bone marrow response evaluation. This category will include patients with early death, withdrawal prior to response assessment, or a technically suboptimal bone marrow sample precluding assessment	
Response (if including assessment of MRD)§		
CR, CRh, or CRi without MRD‡ (CR_{MRD-}, CRh_{MRD-} or CRi_{MRD-})	CR, CRh or CRi with MRD below a defined threshold for a genetic marker by qPCR, or by MFC. Response without MRD should be confirmed with a subsequent assessment at least 4 wk apart. The date of response without MRD is the first date in which the MRD was below the defined threshold Response with MRD detection at low-level (CR_{MRD-LL}) is included in this category of CR, CRh or CRi without MRD. CR_{MRD-LL} is currently only defined for *NPM1*-mutant and CBF-AML	Sensitivities vary by marker tested, and by method used; therefore, test used, tissue source and minimum assay sensitivity for evaluability should be reported; analyses should be done in experienced laboratories (centralized diagnostics)

Döhner H, Blood 2022

Critères de réponse de l'ELN

Treatment failure		
Refractory disease	No CR, CRh or CRi at the response landmark, ie, after 2 courses of intensive induction treatment or a defined landmark, eg, 180 d after commencing less-intensive therapy	Patients not responding to a first cycle of 7 + 3 should be considered for a regimen containing higher doses of cytarabine
Relapsed disease (after CR, CRh or CRi)	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood in at least 2 peripheral blood samples at least one week apart; or development of extramedullary disease	
Treatment failure (if including assessment of MRD)§		
MRD relapse (after CR, CRh or CRi without MRD)	1. Conversion from MRD negativity to MRD positivity, independent of method, or 2. Increase of MRD copy numbers ≥ 1 $\log_{10}$ between any two positive samples in patients with $CR_{MRD\text{-}LL}$, $CRh_{MRD\text{-}LL}$ or $CRi_{MRD\text{-}LL}$ by qPCR The result of 1. or 2. should be rapidly confirmed in a second consecutive sample from the same tissue source	Test methodology, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

Döhner H, Blood 2022

Critères de réponse : MRD

	Method	Target	Sensitivity	Applicable in % of AML	Turn-around time (days)	Limitations/ problems
Established	Multi-parameter flow cytometry (MFC)	Leukemia-associated immunophenotype (LAIP) or different from normal (DfN)	10^{-3} to 10^{-4}	85-90	2	Less sensitive, more subjective analysis
Established	Real-time quantitative PCR (RT-qPCR)	Robust data: *NPM1*, *CBFB*::*MYH11*, *RUNX1*::*RUNX1T1* Less validated: *KMT2A*::*MLLT3*, *DEK*::*NUP214*, *BCR*::*ABL1*, *WT1*	10^{-4} to 10^{-5}	40-50*	3-5	Limited applicability
Exploratory	Next-generation sequencing (NGS)†,‡	Potentially any somatic mutation†	10^{-2} to 10^{-4}	~100	5-10	Less sensitive, costly, technically challenging
Exploratory	Digital PCR (dPCR)	Specific targeted mutations	10^{-3} to 10^{-4}	~70	3-5	Specific assay necessary for every mutation, limited sensitivity

Döhner H, Blood 2022

Critères de réponse : MRD

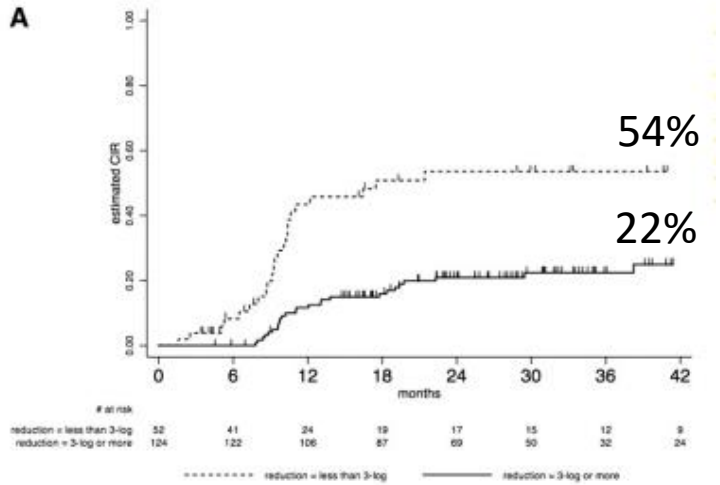
- **Quelle technique ?**
  - Cytométrie de flux : pour (presque) tous
  - Biologie moléculaire (PCR) : *NPM1, CBFB::MYH11, AML1::ETO, PML-RARA, BCR::ABL*
  - NGS : pas encore en routine
- **Pour qui ?**
  - Tout le monde ? : permet d'adapter les traitements
    - Allogreffe ?
    - Arrêt du traitement ? (AZA-VEN)
    - Traitement d'entretien ? (AZA oral)
- **Quand ?**
  - Après 1 et 2 cycles de chimiothérapie intensive : Log-réduction à la MRD2++
  - Après 2 cycles d'AZACITIDINE-VENETOCLAX
  - En suivi : fin de traitement/J100 post-allogreffe/tous les 3 mois…

Rôle de la MRD

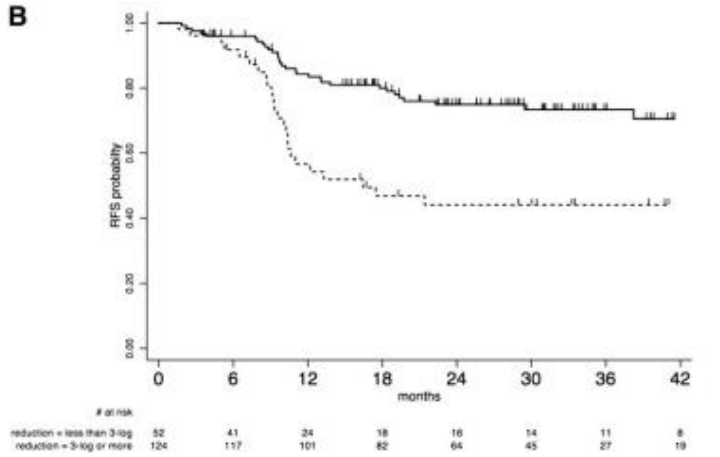
- **Identifier les patients à haut risque en RC1**
  - Chez les patients intermédiaires mais MRD+ en post-induction / consolidation
  - Détection de la rechute par MRD (avant rechute cytologique)
  - Stratégies de traitement : indication d'allogreffe

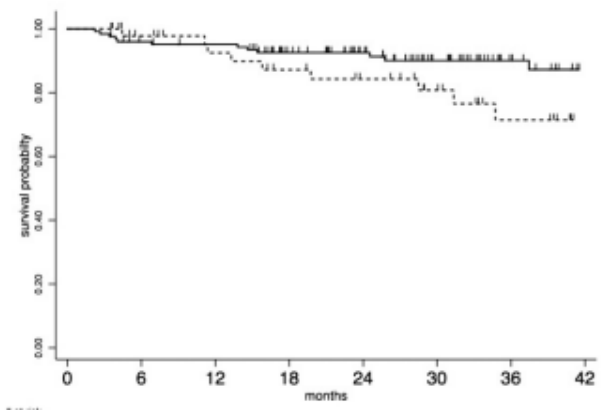
- **Influencer la stratégie dans les LAM de haut risque**
  - Moins bon pronostic si MRD persistante en pré ou post allogreffe
  - Modification du conditionnement de greffe
  - Modulation immunosuppression en post-allogreffe / DLI
  - Maintenance
  - Rattrapage si cinétique d'augmentation de la MRD rapide

Traitement intensif : rôle de la MRD dans les LAM CBF



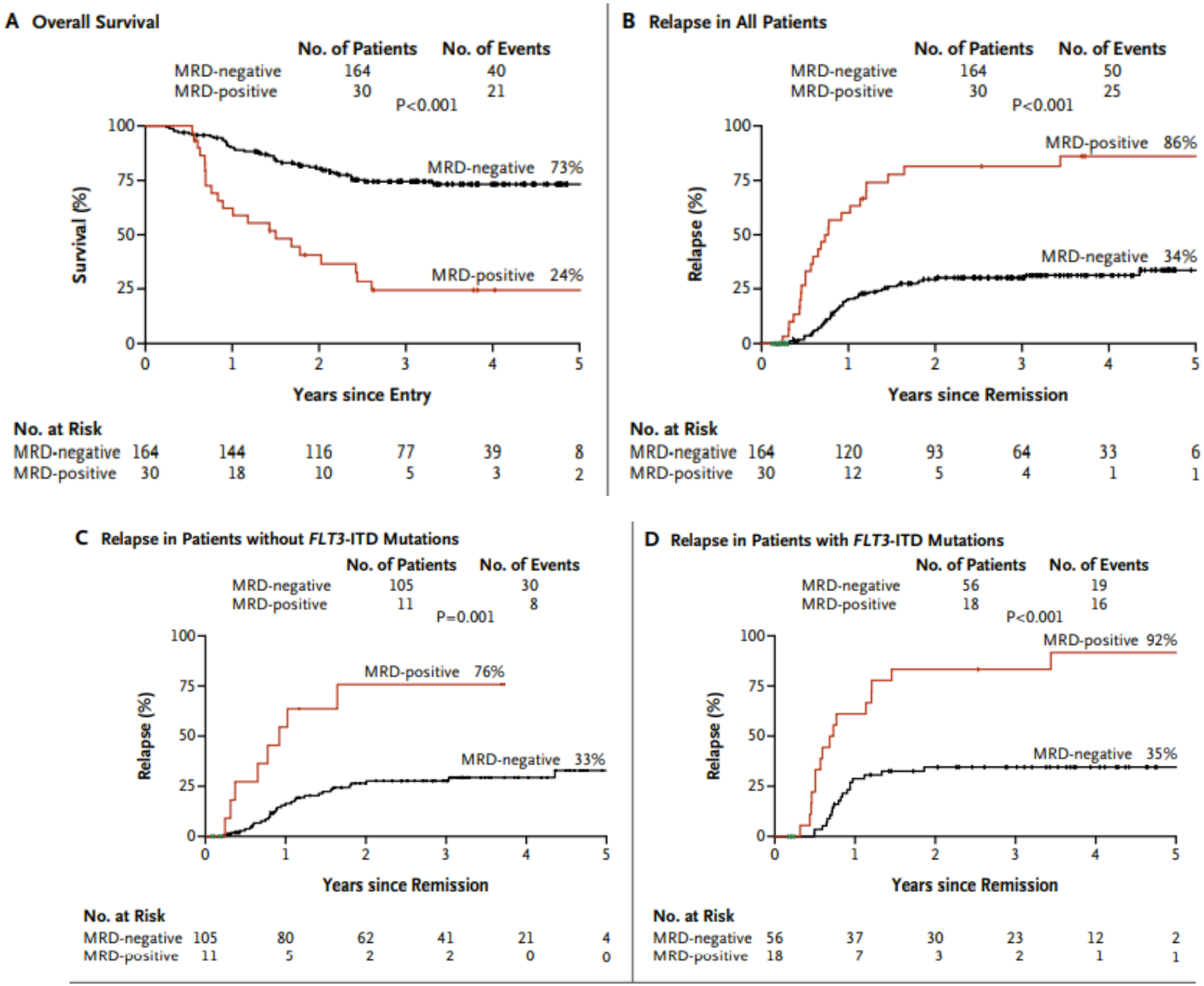
3-log MRD2 reduction





Jourdan E, Blood 2013

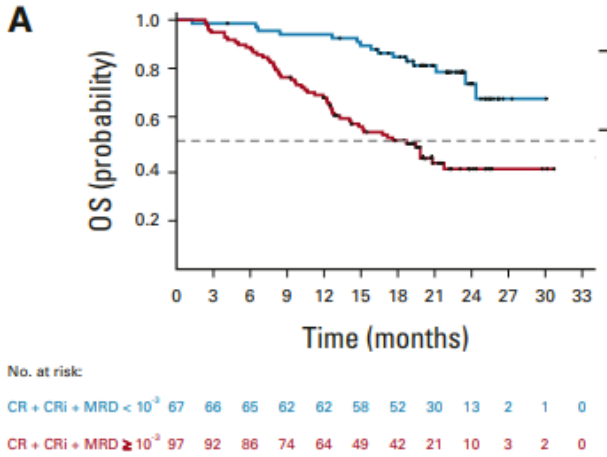
Traitement intensif : rôle de la MRD dans les LAM *NPM1*m



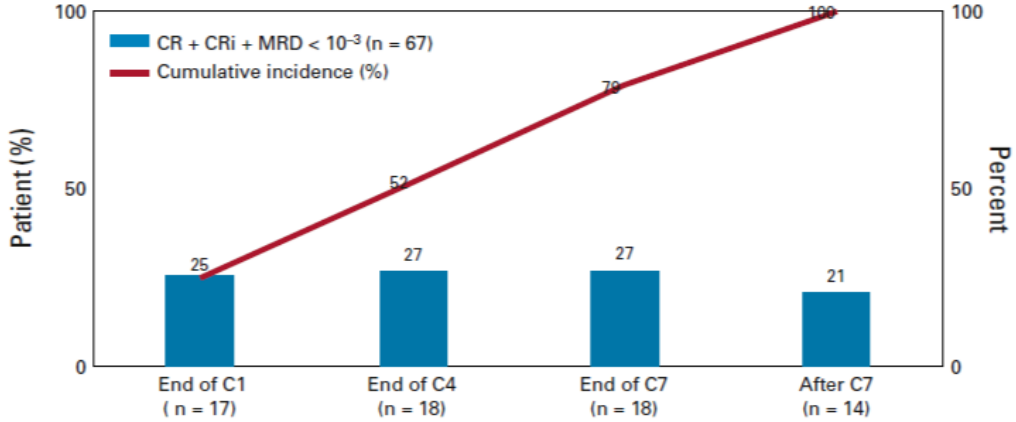
Ivey A, NEJM 2016

Traitement non intensif des LAM : rôle de la MRD au cours du traitement par Azacitidine-Venetoclax

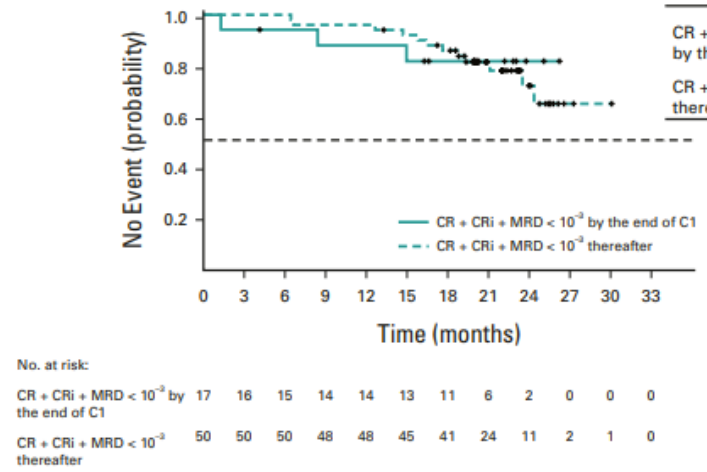
A



OS	No. of Events	12 Months, % (95% CI)	18 Months, % (95% CI)	Median OS, Months (95% CI)
CR + CRi + MRD < 10^{-3}	15	94.0 (84.7 to 97.7)	84.6 (73.3 to 91.4)	NR (24.4 to NR)
CR + CRi + MRD ≥ 10^{-3}	52	67.9 (57.6 to 76.2)	50.1 (39.6 to 59.8)	18.7 (12.9 to NR)



D



OS	No. of Events	12 Months, % (95% CI)	18 Months, % (95% CI)	Median OS, Months (95% CI)
CR + CRi + MRD < 10^{-3} by the end of cycle 1	3	87.8 (59.5 to 96.8)	81.6 (53.0 to 93.7)	NR (NR to NR)
CR + CRi + MRD < 10^{-3} thereafter	12	96.0 (84.9 to 99.0)	85.8 (72.5 to 93.0)	NR (24.4 to NR)

Pratz K, JCO 2022

Traitements de première ligne : les possibilités

INTENSITE

Traitements intensifs	Traitements « non intensifs »
3+7 CPX-351 (VYXEOS)	AZACITIDINE AZACITIDINE-VENETOCLAX AZACITIDINE-IVOSIDENIB

COMBINAISON

Cible	Thérapie ciblée
FLT3	Midostaurine (AMM), Gilteritinib (ph 3)
IDH 1/2	Ivosidenib, Enasidenib (ph 3)
Autres	Sabatolimab, Magrolimab (ph 2-3)

ALLOGREFFE

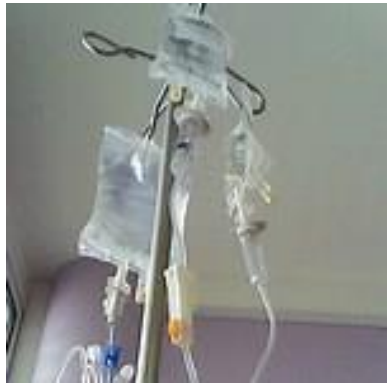
Sujets fits choix conditionnement/donneur	LAM haut risque Selon décroissance de la MRD

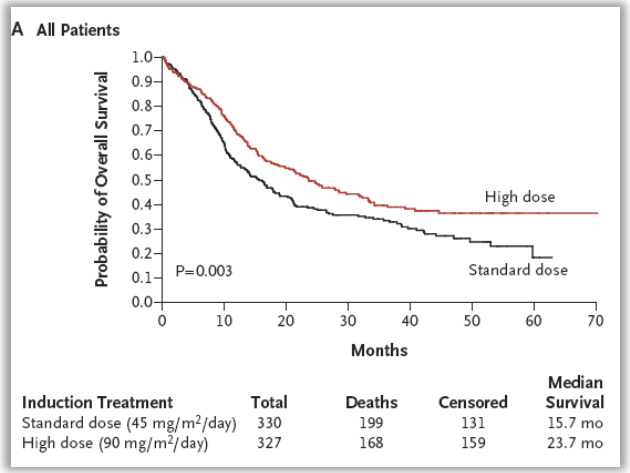
ENTRETIEN

Cible	Thérapie ciblée
AZACITIDINE orale	ONUREG
FLT3	Midostaurine (AMM), Gilteritinib (ph 3)
IDH 1/2	Ivosidenib, Enasidenib (ph 3)

Traitements de première ligne : comment choisir ?

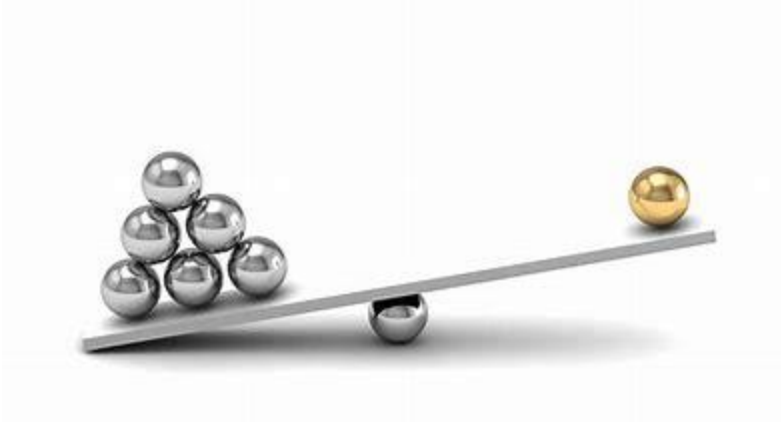
« 3+7 »



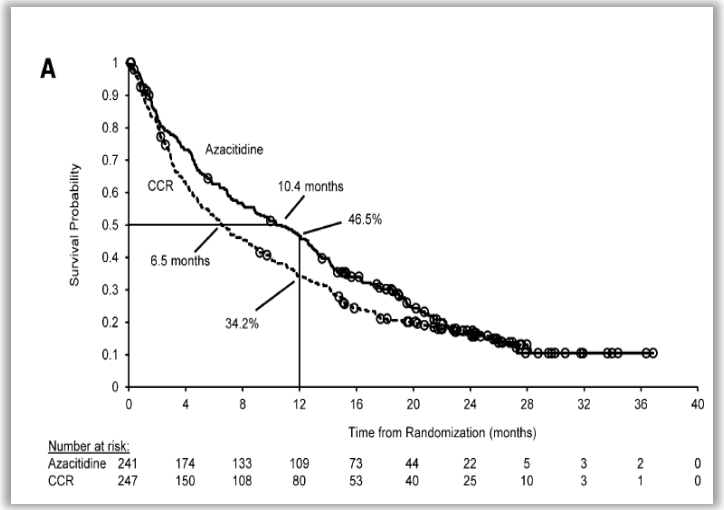


Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m²/day)	330	199	131	15.7 mo
High dose (90 mg/m²/day)	327	168	159	23.7 mo

Fernandez, NEJM 2009



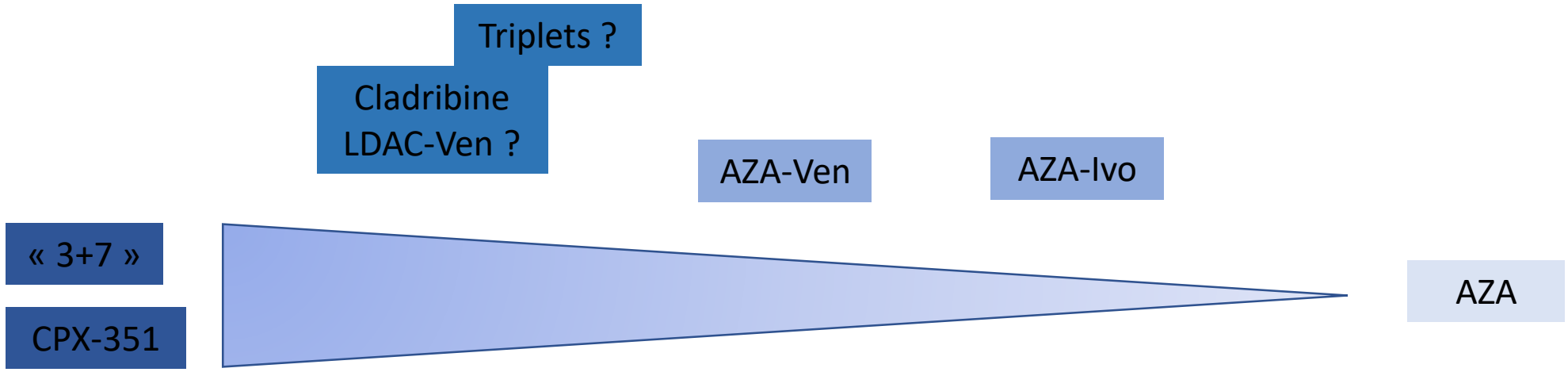
Azacitidine



AZA 75 mg/m²/jr

Dombret, Blood 2015

Traitements de première ligne : comment choisir ?



Qui n’est pas éligible à la chimiothérapie intensive ?

- **Critères d’inéligibilité à la chimiothérapie du protocole VIALE-A :**

  - **AGE ≥ 75 ans***

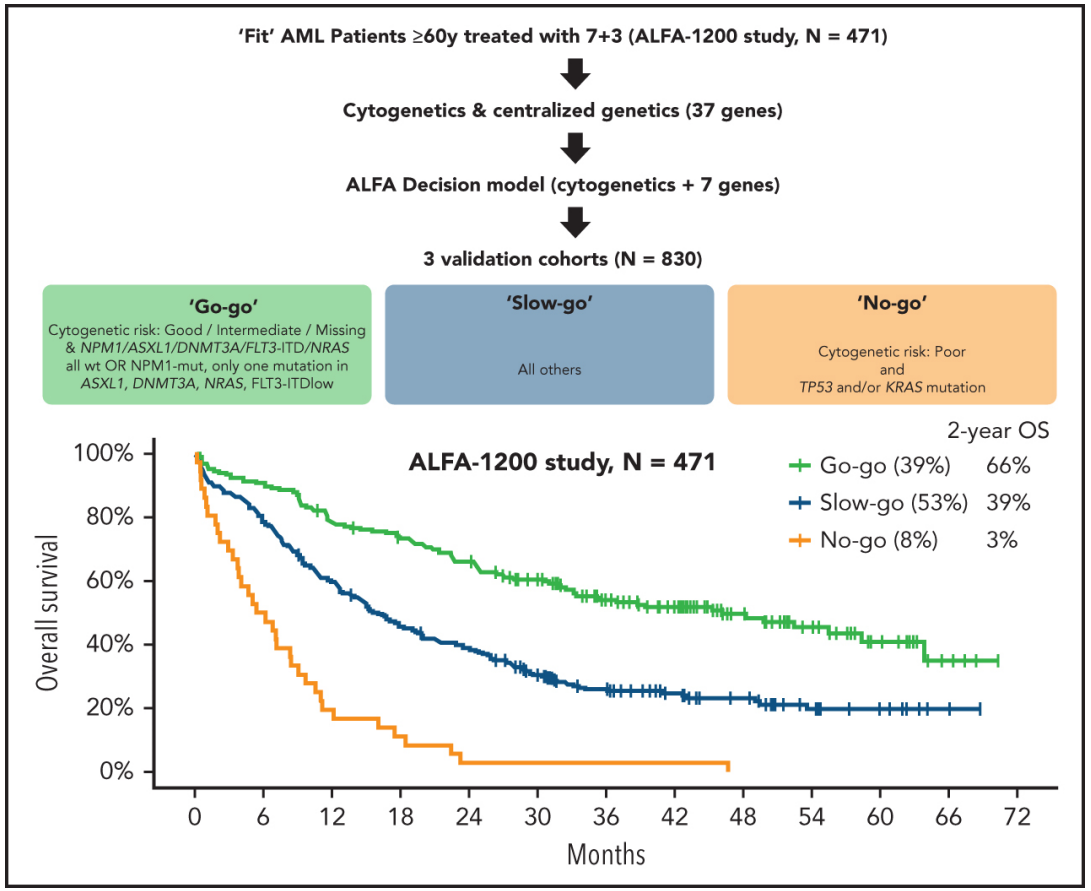
  OU

  - **≥ 18 à 74 ans** avec au moins une comorbidité parmi :
    - o ECOG Performance Status 2-3
    - o Antécédent d’insuffisance cardiaque nécessitant un traitement ou fraction d’éjection ≤ 50% ou angor chronique stable
    - o DLCO ≤ 65% ou VEMS ≤ 65%;
    - o Clairance de la créatinine entre ≥30 mL/min et < 45 ml/min;
    - o Bilirubine totale > 1.5 to ≤ 3.0 × ULN;
    - o Une autre comorbidité rendant le patient inéligible à la chimiothérapie intensive

  **l’ECOG doit alors être 0-2*

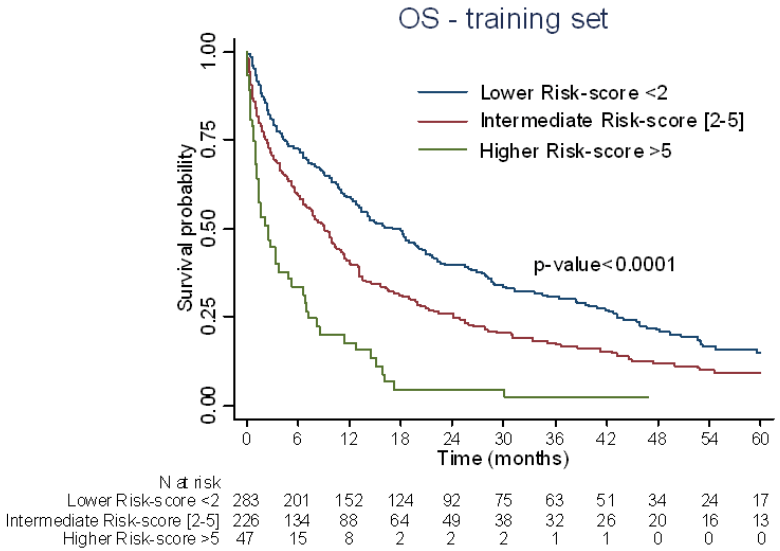
DiNardo C, NEJM 2020

Scores pronostiques



Itzykson R, Blood 2021

European Scoring System ≥70
1199 patients 3 registres européens, CTI

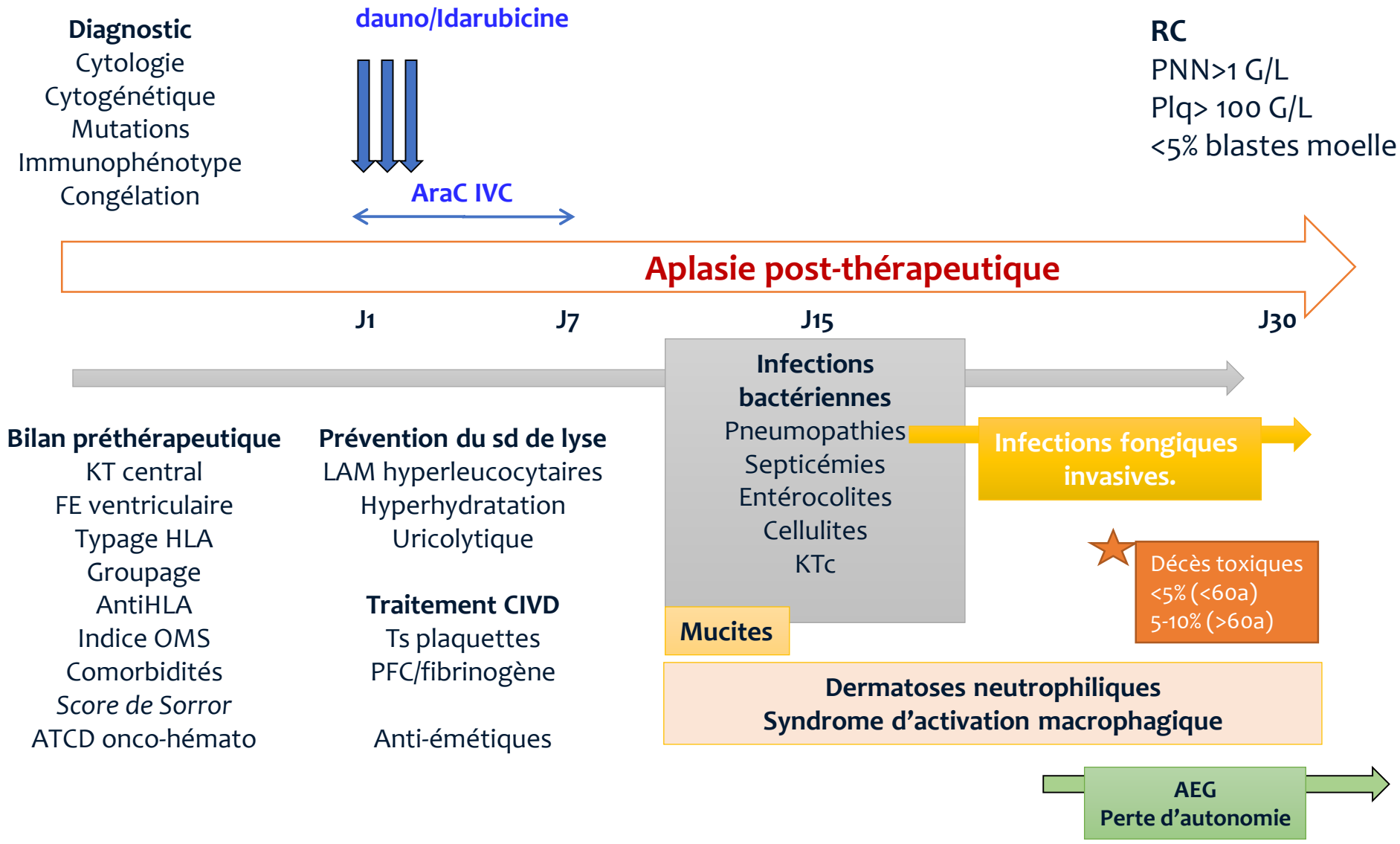


Age, performance status, statut secondaire, leucocytose, risque cytogénétique, mutations *NPM1* et *FLT3*-ITD

Bérard E, Blood Cancer Journal 2022

Chimiothérapie intensive

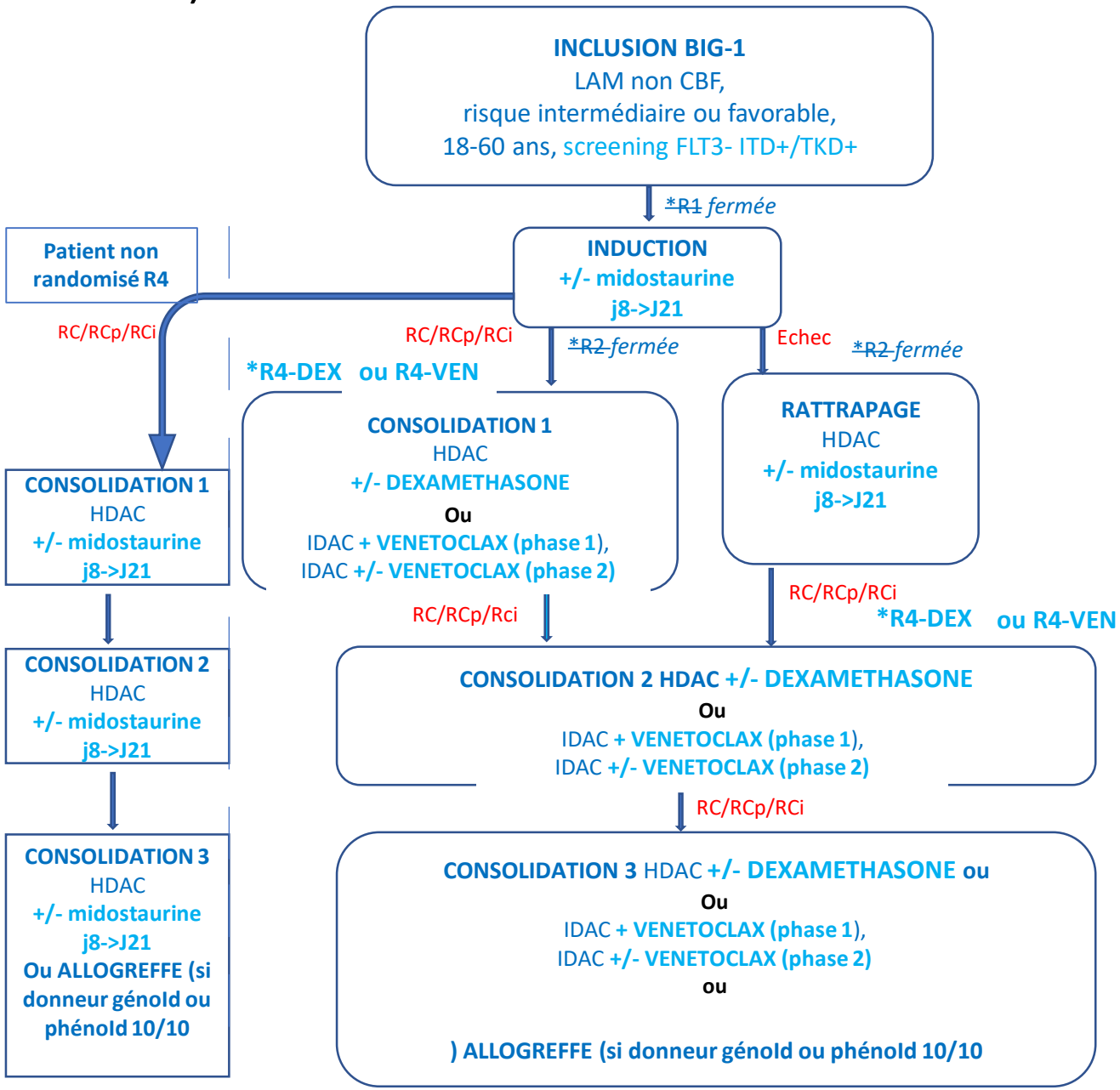
l'induction: un cap difficile



Essai BIG-1 (2015-)
Intergroupe français des LAM (ALFA/FILO)

- R1 Induction : daunorubicine (270 mg/m²) vs idarubicine (45 mg/m²)
  - Objectif: OS à 3 ans, 45 vs 55%, 1018 patients FERME : IDARUBICINE (FILO) - DNR (ALFA)
- R2 post induction : cytarabine haute dose (HDAC) vs. intermédiaire (IDAC) FERME
  - 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 FERME
  - 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 rémission
  - Phase 2
  - IDAC ou HDAC vs. IDAC ou HDAC + X
  - Objectif: survie sans leucémie à 18 mois: 55 à 75%, 200 patients
  - HDAC + DEXAMETHASONE ; IDAC + VOSAROXINE ; IDAC + VENETOCLAX
- Allogreffe adaptée au risque génétique et à la MRD2
- + MIDOSTAURINE

Essai BIG-1 (2015-)



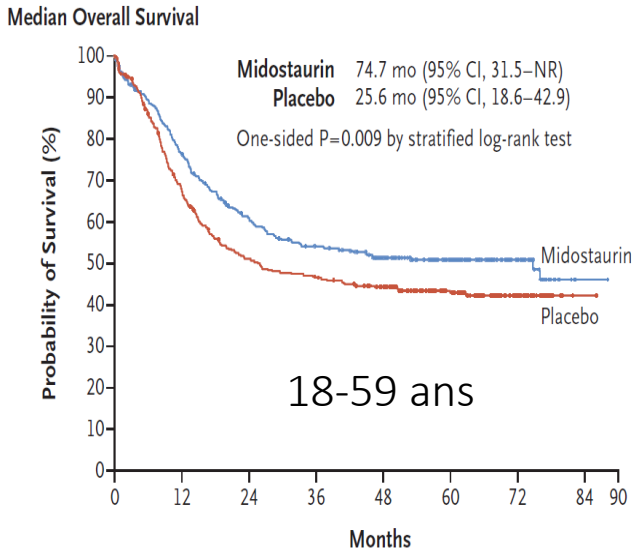
Midostaurine : Essai RATIFY

Registre MIDOLA

ORIGINAL ARTICLE

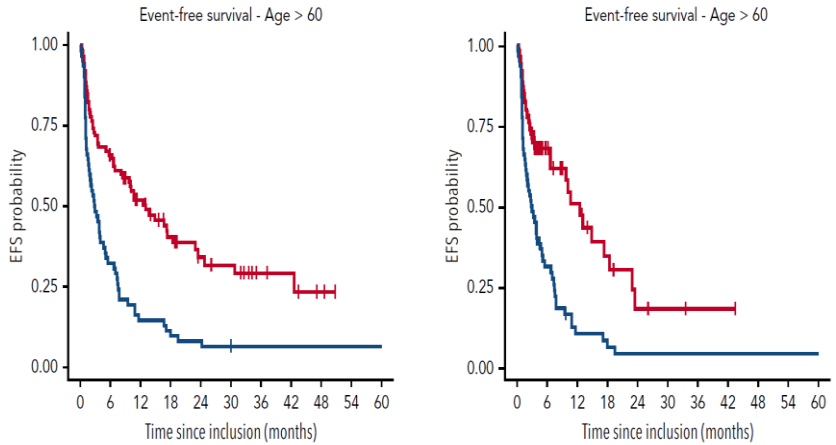
Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation

R.M. Stone, S.J. Mandrekar, B.L. Sanford, K. Laumann, S. Geyer, C.D. Bloomfield, C. Thiede, T.W. Prior, K. Döhner, G. Marcucci, F. Lo-Coco, R.B. Klisovic, A. Wei, J. Sierra, M.A. Sanz, J.M. Brandwein, T. de Witte, D. Niederwieser, F.R. Appelbaum, B.C. Medeiros, M.S. Tallman, J. Krauter, R.F. Schlenk, A. Ganser, H. Serve, G. Ehninger, S. Amadori, R.A. Larson, and H. Döhner



Stone, NEJM 2017 - Schlenk, Blood 2019

1ère ligne > 60



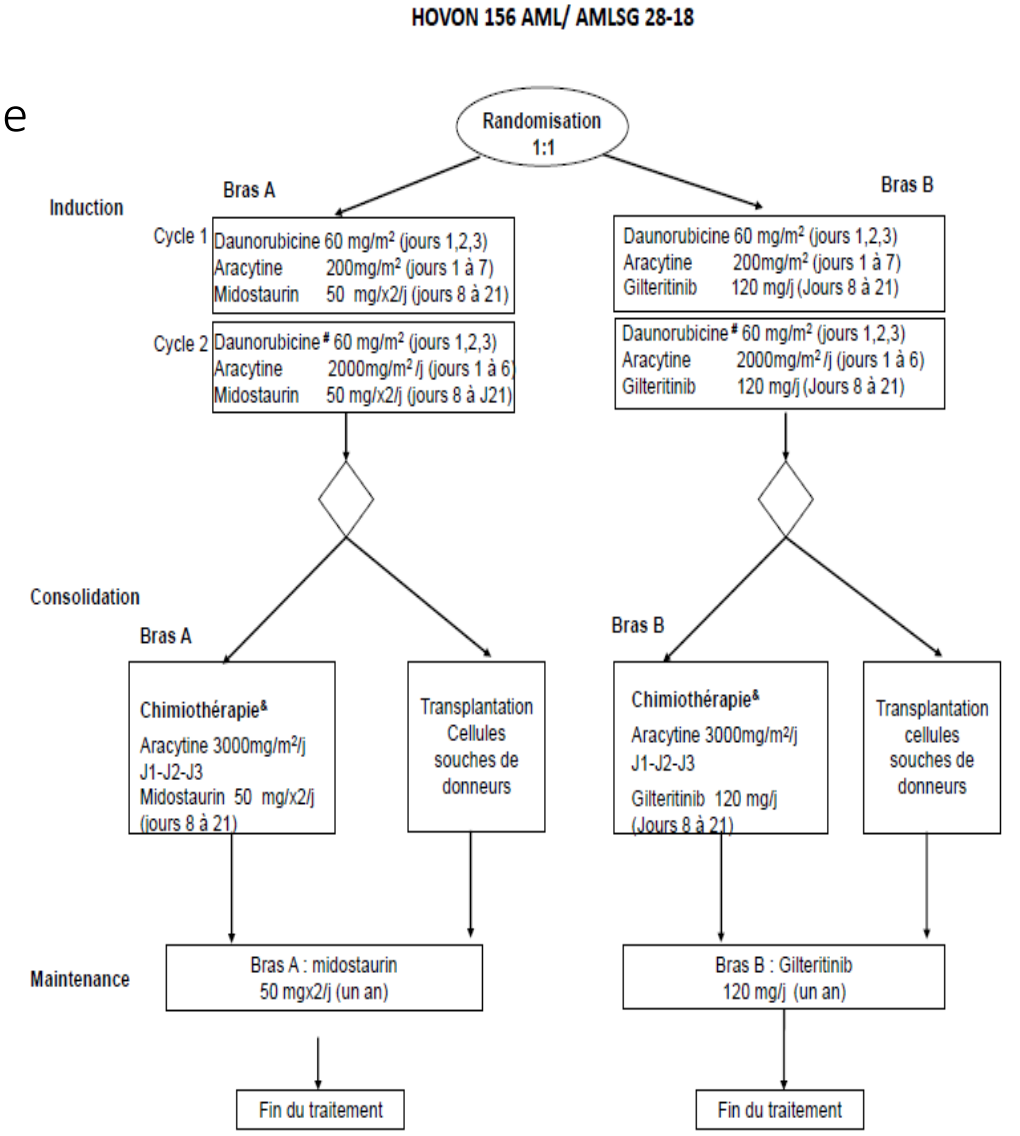
	All patients (n = 97)
Months, median (range)	9 (1-13)
Early termination, n (%)	
Total	60 (61.8)
Death	1 (1.7)
IC/patients' wish	11 (18.3)
Midostaurin toxicity	28 (46.6)
Other reasons*	7 (11.7)
Relapse	13 (21.7)

AMM : 50 mgx2/jr J8-J21 en induction, consolidation + maintenance en continu 12 mois
LAM FLT3-ITD et FLT3-TKD

Essai HOVON-156

Inhibiteur de FLT3 + chimiothérapie intensive en première ligne

- Essai de phase 3
- LAM ou SMD-EB2, ≥ 18 ans
- **HOVON 156 AML**
  - «3+7» + Midostaurine ou «3+7» + Gilteritinib



Les patients âgés de 61 ans ou plus ne recevront pas de daunorubicine pendant le cycle 2 en raison du risque accru d'effets secondaires

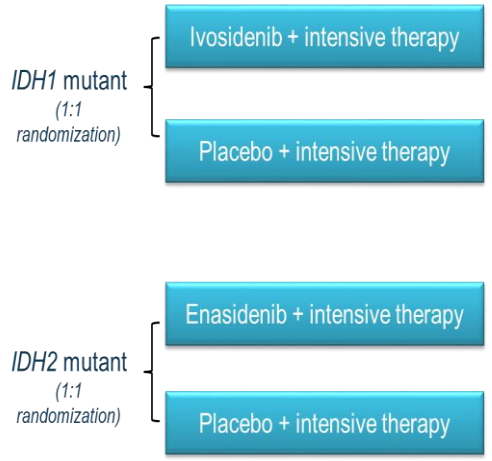
& Pour les patients âgés de 61 ans et plus, la posologie de l'aracytine sera réduite à 2000 mg/m²/j

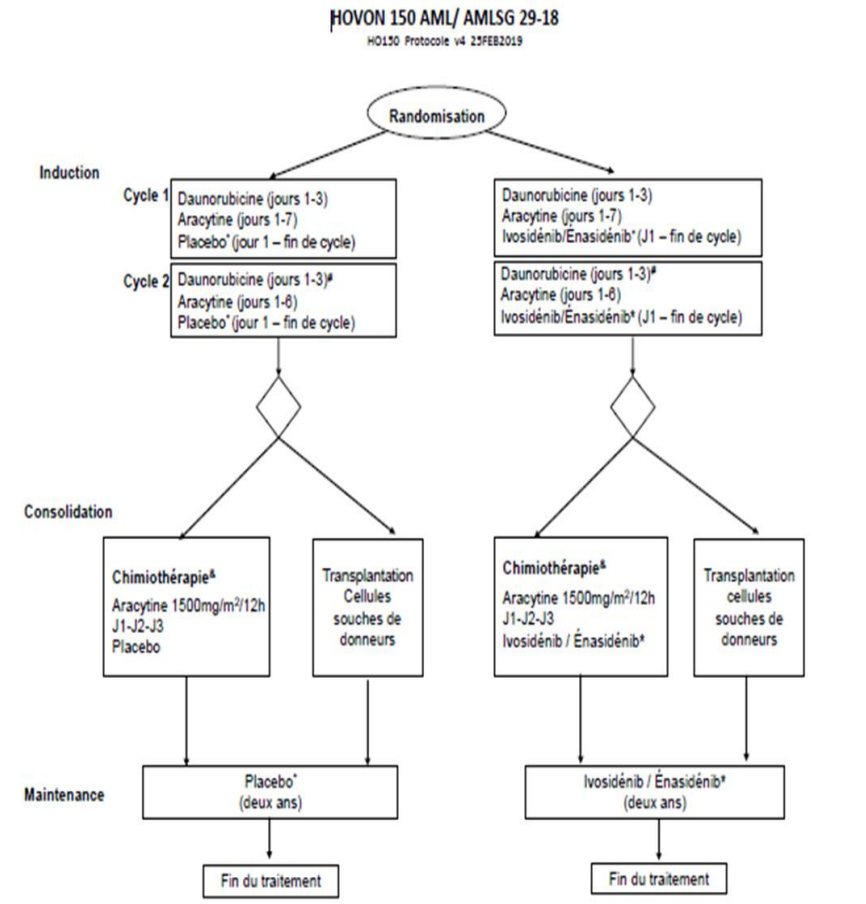
Flowchart FRANCE Bras AraC V1 septembre 2019 basé sur protocole HO156 Version 03 01/07/2019

Essai HOVON-150

Inhibiteur d'IDH1/2 + chimiothérapie intensive en première ligne

- Essai de phase 3
- LAM ou SMD-EB2, ≥ 18 ans
- **HOVON 150 AML/ AMLSG 29-18**
  - IDH1: «3+7» + Ivosidenib/placebo
  - IDH2: «3+7» + Enasidenib/placebo





* Les patients présentant une mutation *IDH1* reçoivent un placebo ou de l'ivosidénib ; les patients présentant une mutation *IDH2* reçoivent un placebo ou de l'énasidénib

Les patients âgés de 61 ans ou plus ne recevront pas de daunorubicine pendant le cycle 2 en raison du risque accru d'effets secondaires

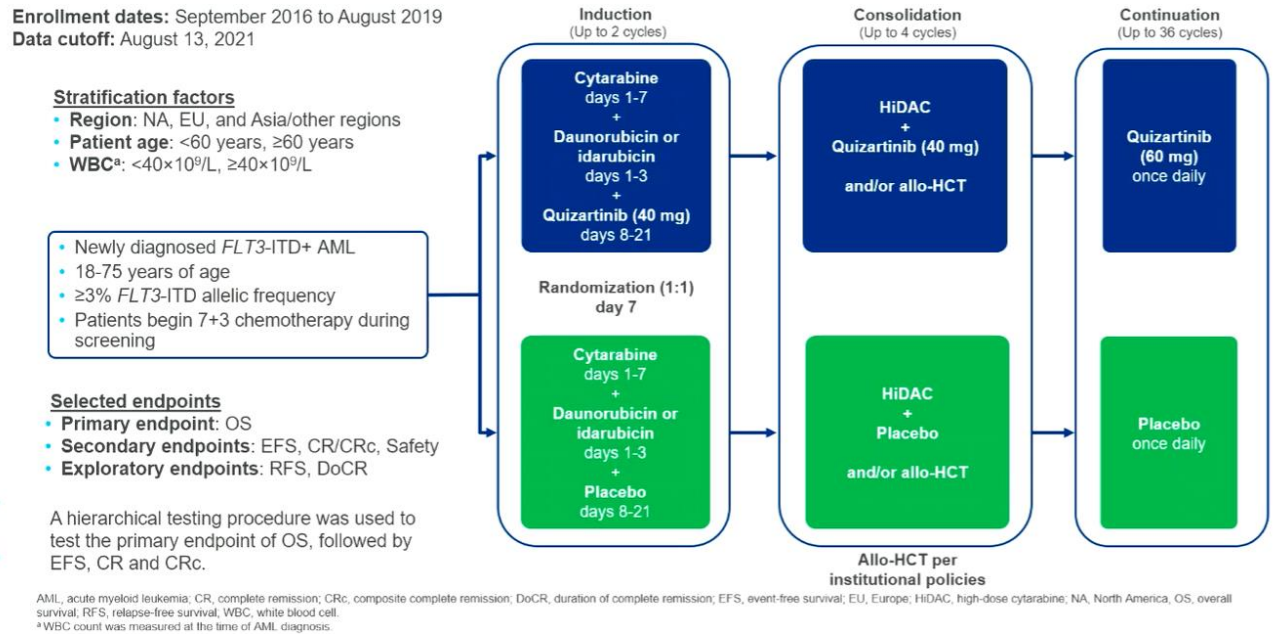
& Pour les patients âgés de 61 ans et plus, la posologie de l'aracytine sera réduite à 1000 mg/m²/12h

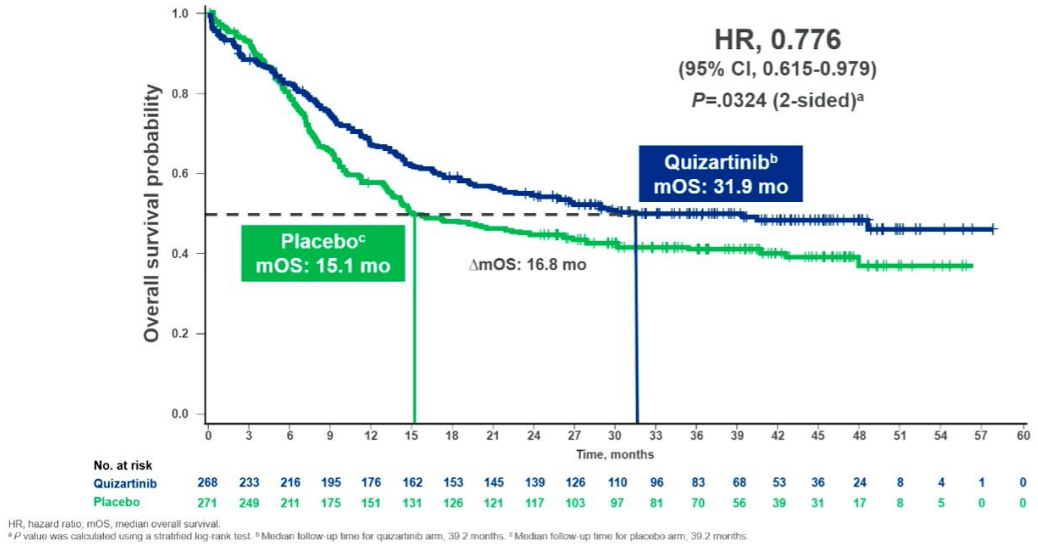
Quizartinib en 1ere ligne : Essai Quantum-First

- **Mutations *FLT3*-ITD uniquement**
- 3+7 + Quizartinib vs. 3+7 + Placebo

- CRc : 71.6% vs. 64.9%
- Durée de réponse : 38,6 vs. 12,4 mois
- Survie globale médiane : 31,9 mois vs. 15,1 mois
  - HR 0,776 ; P=0,0324

- Enregistrement ?

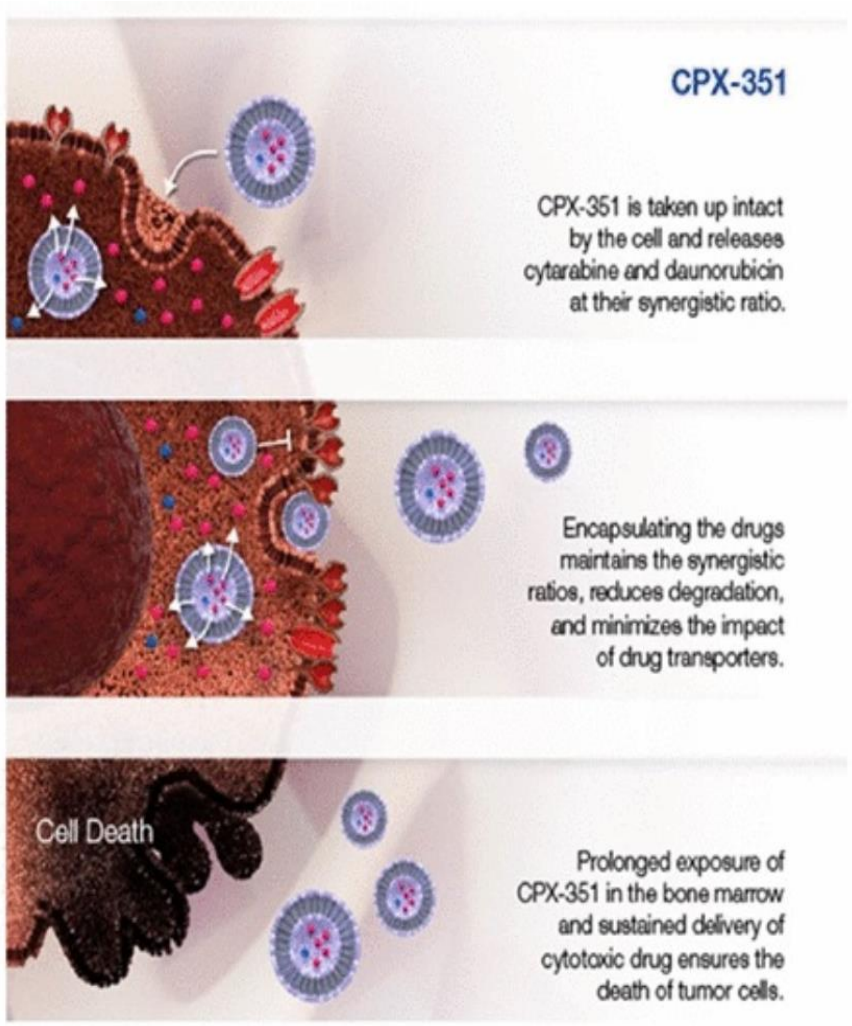




Erba H, EHA 2022

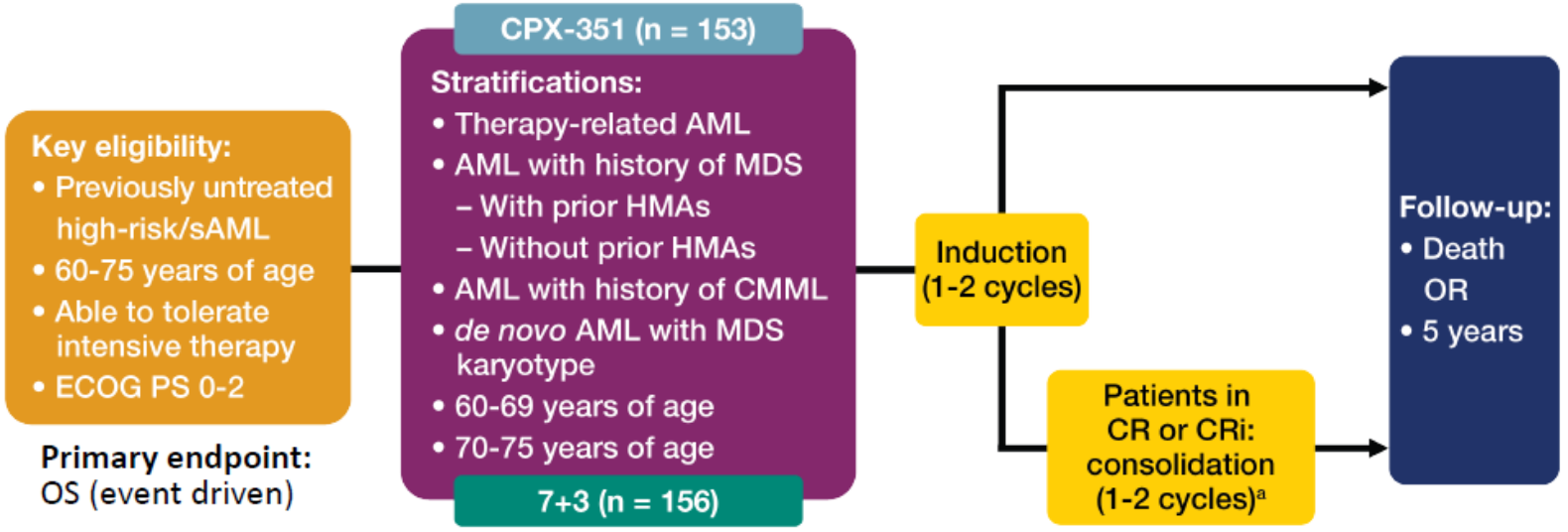
Une alternative au 3+7 : CPX-351

Composé bilamellaire liposomal
Ratio daunorubicine/Cytarabine 1:5



CPX-351 : Phase III –Etude 301

Étude de phase III de supériorité, randomisée menée en ouvert chez des patients atteints d'une LAM de mauvais pronostic* non traitée
N=309



[a]Patients with documented CR or CRi were eligible for consolidation if they had left ventricular ejection fraction of ≥50%, ECOG PS of 0-2, absolute neutrophil count recovered to >500/µL, and platelet count recovered to >50,000/µL. CR was defined as having bone marrow blasts <5%, absence of blasts with Auer rods, absence of extramedullary disease, absolute neutrophil count ≥1.0 × 10^9/L, platelet count ≥100 × 10^9/L, and independence from red cell transfusions; CRi was defined as having all CR criteria except residual neutropenia (<1.0 × 10^9/L) or thrombocytopenia (<100 × 10^9/L).

CPX-351[b]
Administered as a 90-minute infusion

Induction: 100 units/m² on Days 1, 3, and 5 (Days 1 and 3 for 2nd induction)
Consolidation: 65 units/m² on Days 1 and 3

7+3
Cytarabine + daunorubicin

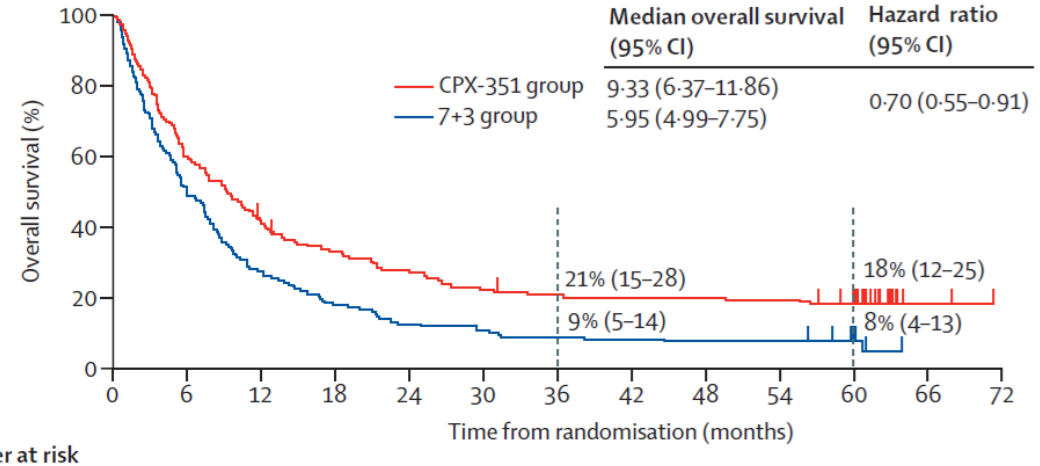
Cytarabine 100 mg/m²/day continuous infusion + daunorubicin 60 mg/m²/day
Induction: 7+3 schedule (5+2 for 2nd induction)
Consolidation: 5+2 schedule

[b]1 unit = 0.44 mg daunorubicin + 1 mg cytarabine.

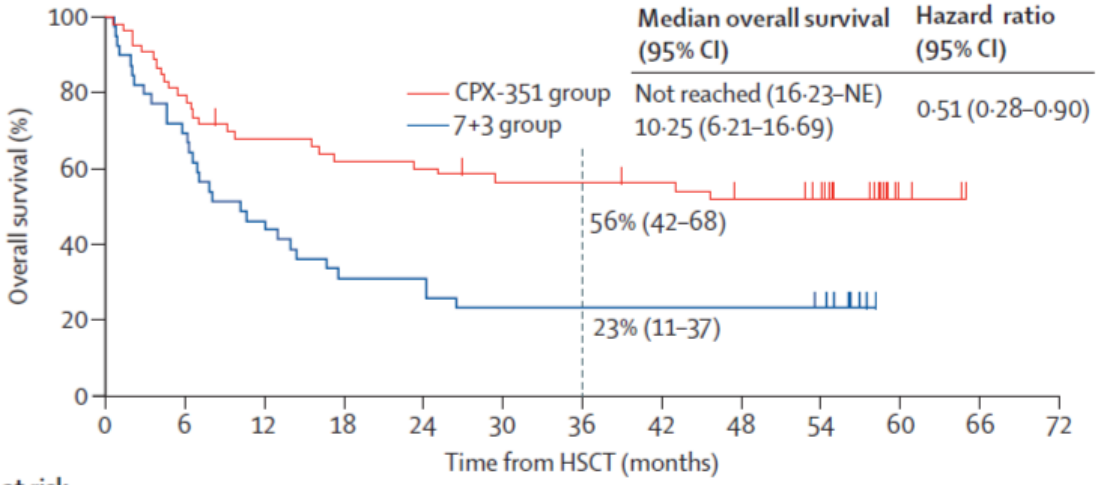
Lancet JE, Lancet Hematol 2021

***LAM secondaire (secondaire à un traitement (LAM-t) ou à un SMD ou à une LMMC transformée en LAM) ou LAM de novo avec un caryotype de type SMD.**

CPX-351 : Phase III-Etude 301 : actualisation à 5 ans



Number at risk (number censored)													
CPX-351 group	153	92	62	49	40	33	30	29	29	28	22	2	0
	(0)	(0)	(1)	(2)	(2)	(2)	(3)	(3)	(3)	(3)	(7)	(27)	(29)
7+3 group	156	77	43	28	20	17	14	13	12	12	5	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(7)	(11)	(11)



Number at risk (number censored)													
CPX-351 group	53	42	35	32	31	28	28	27	24	21	6	0	0
	(0)	(0)	(1)	(1)	(1)	(2)	(2)	(3)	(4)	(7)	(22)	(28)	(28)
7+3 group	39	27	18	12	12	9	9	9	9	8	0	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(9)	(9)	(9)

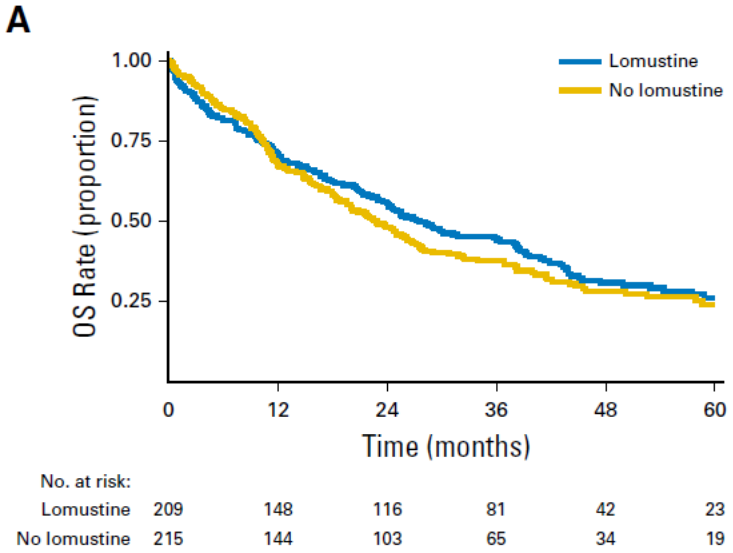
Lancet JE, Lancet Hematol 2021

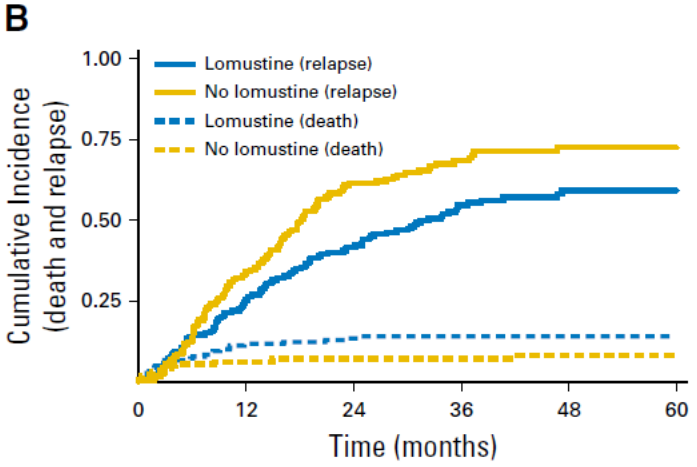
Traitement intensif du sujet âgé

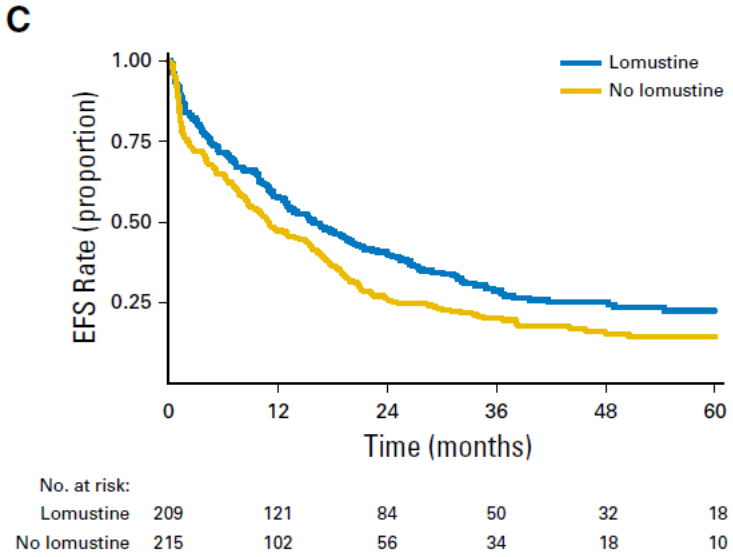
- Essais récents du FILO :
  - LAMSA-2007
  - DEXAML-02
  - EPAG

Chimiothérapie intensive du sujet âgé : LAMSA-2007

Idarubicine 8mg/m² x5 + **Cytarabine** 100 mg/m² x7 + **Lomustine (CCNU)** 200 mg/m² x1







En pratique :
Utile en induction : améliore EFS
Toxique en consolidation

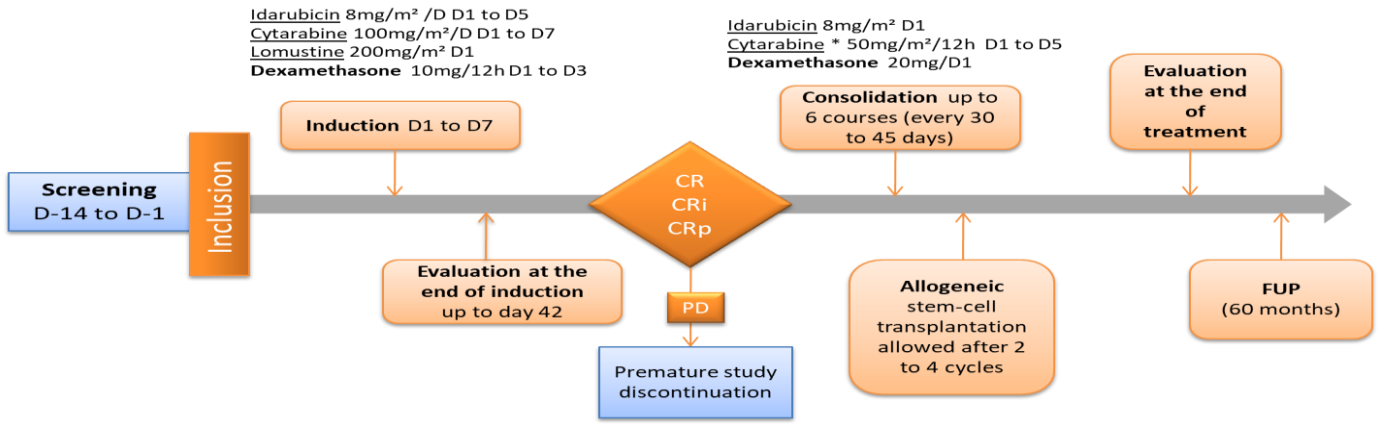
FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

Pigneux A, JCO, 2018

Chimiothérapie intensive du sujet âgé : DEXAML-02

Etude de phase 2 évaluant l'addition de la dexaméthasone à la chimiothérapie d'induction et de consolidation chez les sujets âgés traités pour une LAM nouvellement diagnostiquée

- **> 60 ans**
- LAM de novo selon la classification OMS 2016 ou LAM liée à un traitement anti-cancéreux
- Risque cytogénétique favorable ou intermédiaire selon la classification MRC 2010.
- ECOG < 3
- SORROR < 3 hors antécédents carcinologiques



•NB1: the addition of midostaurin (50 mg orally twice daily, on days 8 through 21) in patients with FLT3-ITD or FLT3-TKD mutations is allowed according to standard recommendations of the product.

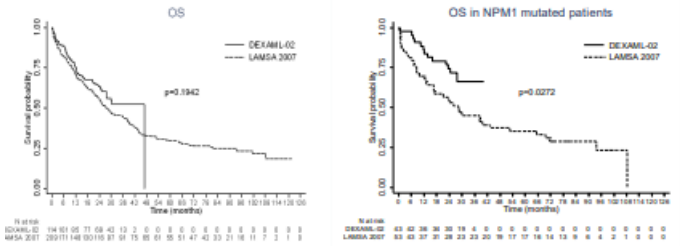
•NB2 : patients with CBF-AML could receive 2-3 cycles of intermediate doses of cytarabine (IDAC) instead of 6 cycles of mini-consolidations according to investigator choice:

Response	All patients - n (%)	NPM1 mut - n (%)
CR	77 (67.5)	38 (88.4)
CRi	7 (6.1)	2 (4.7)
CRp	11 (9.7)	1 (2.3)
CR/CRi/CRp	**95 (83.3)**	41 (95.4)
Refractory	14 (12.3)	1 (2.3)
Toxic death	5 (4.4)	1 (2.3)

	DEXAML-02	LAM-SA 2017*
Median FU (months, IQR)	32 (28.2-35.5)	86.7 (78.1-88.9)
Median OS (months, IQR)	**47.0 (11.9-47.0)**	**27.6 (10.2-81.5)**
1-y OS (95%CI)	74.5% (65.5-81.6)	70.8% (64.1-76.5)
2y-OS	63.1% (53.5-71.2)	55.5% (48.5-61.9)
3-y OS	52.2 (42.2-61.3)	44.4% (37.6-51.0)
5y-OS	-	29.4% (23.3-35.8)

5. Outcome (vs. LAM-SA 2017 trial): *NPM1* mutated patients

	DEXAML-02 (n=43)	LAM-SA 2017 (n=53)
Median OS (months, IQR)	**NR (23.4-NR)**	**28.2 (8.3-93.6)**
1-y OS (95%CI)	83.7% (68.9-91.9)	69.8% (55.5-80.3)
2y-OS	74.4% (58.6-84.9)	52.8% (38.7-65.2)
3-y OS	66.4 (49.8-78.6)	45.1% (31.4-57.8)
5y-OS	-	35.2% (22.5-48.0)

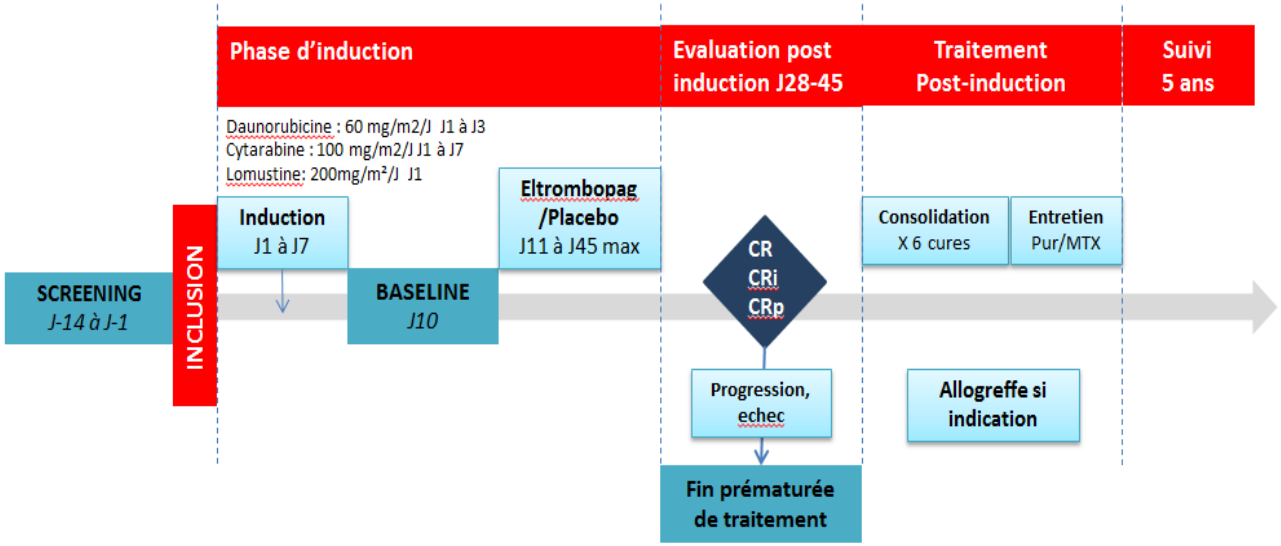


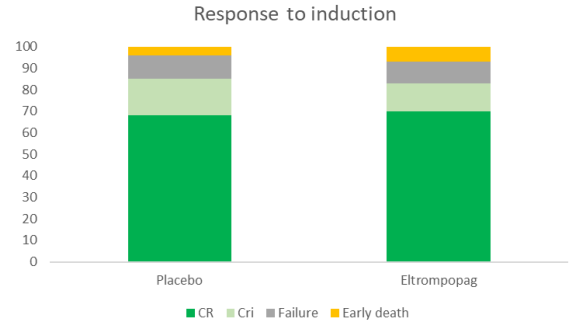
Récher C, ASH 2022

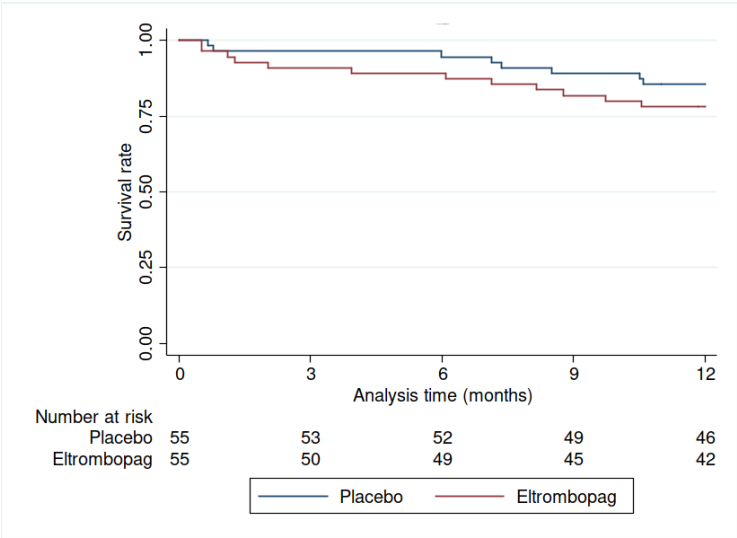
Chimiothérapie intensive du sujet âgé : EPAG

Etude de phase II randomisée en double aveugle contre placebo de l'effet d'Eltrombopag associé à la chimiothérapie d'induction, chez des patients âgés atteints de LAM

- **≥ 60 ans**
- LAM de novo ou LAM liée à un traitement anti-cancéreux (sauf M7)
- Risque cytogénétique favorable ou intermédiaire selon la classification MRC 2010.
- ECOG < 3
- SORROR < 3 hors antécédents carcinologiques







En post induction :
- 6 cures de mini-consolidation par Dauno 60 mg/m2/J , J1 + Cytarabine 50mg/m²/x2/J, J1-J5
- Entretien Purinethol-Methotrexate

The number of platelet transfusions was significantly reduced in the eltrombopag group 9.76± 5.38 vs 12.56 ± 9.69, p = 0.063

Pigneux A, ASH 2022

Essai LAMSA 2020

- Induction

  Idarubicine 8 mg/m² x5 + Cytarabine 100 mg/m² x7 + Lomustine (CCNU) 200 mg/m² x1

- Si RC :
  - **Randomisation :**
    - Mini-consolidation 1+5 Idarubicine-Cytarabine S/C
    - Cytarabine S/C – Venetoclax 600 mg/jr

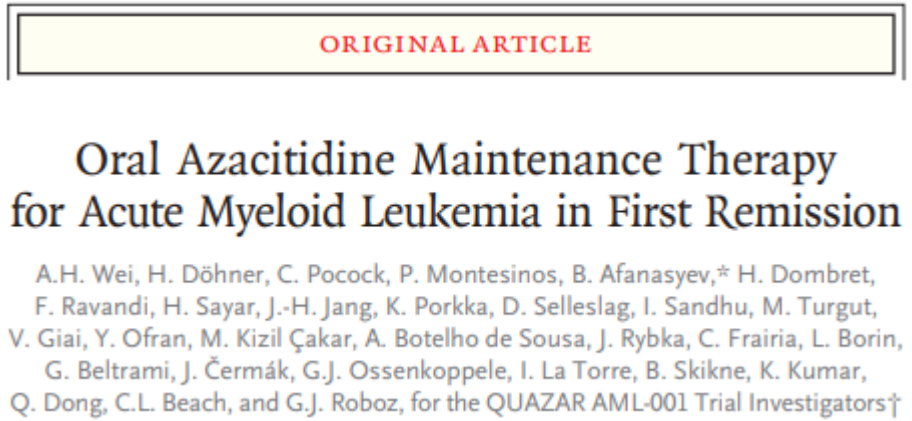
- LAM à caryotype favorable ou intermédiaire

Après la chimiothérapie : Traitement de maintenance

- **Inhibiteurs de FLT3** :
  - Sorafenib (SORMAIN)
  - Midostaurine (AMM, selon RATIFY)
  - Gilteritinib (HOVON 156)

- **Inhibiteurs d'IDH1/2** (HOVON 150)

- **AZACITIDINE Orale (ONUREG)** : essai QUAZAR


ORIGINAL ARTICLE

Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission

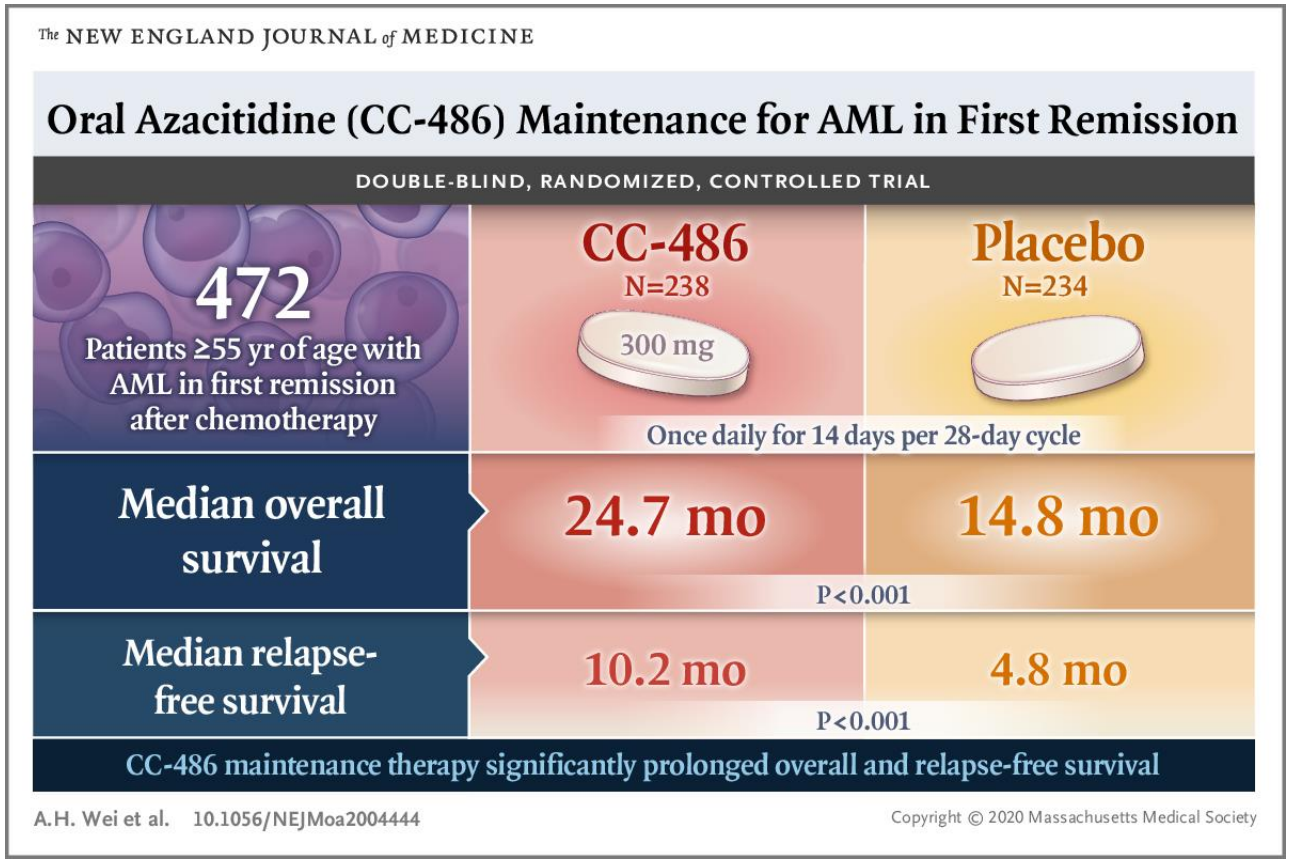
A.H. Wei, H. Döhner, C. Pocock, P. Montesinos, B. Afanasyev,* H. Dombret, F. Ravandi, H. Sayar, J.-H. Jang, K. Porkka, D. Selleslag, I. Sandhu, M. Turgut, V. Giai, Y. Ofran, M. Kizil Çakar, A. Botelho de Sousa, J. Rybka, C. Frairia, L. Borin, G. Beltrami, J. Čermák, G.J. Ossenkoppele, I. La Torre, B. Skikne, K. Kumar, Q. Dong, C.L. Beach, and G.J. Roboz, for the QUAZAR AML-001 Trial Investigators†

Wei A, NEJM 2021

AZACITIDINE orale : Onureg
Essai QUAZAR

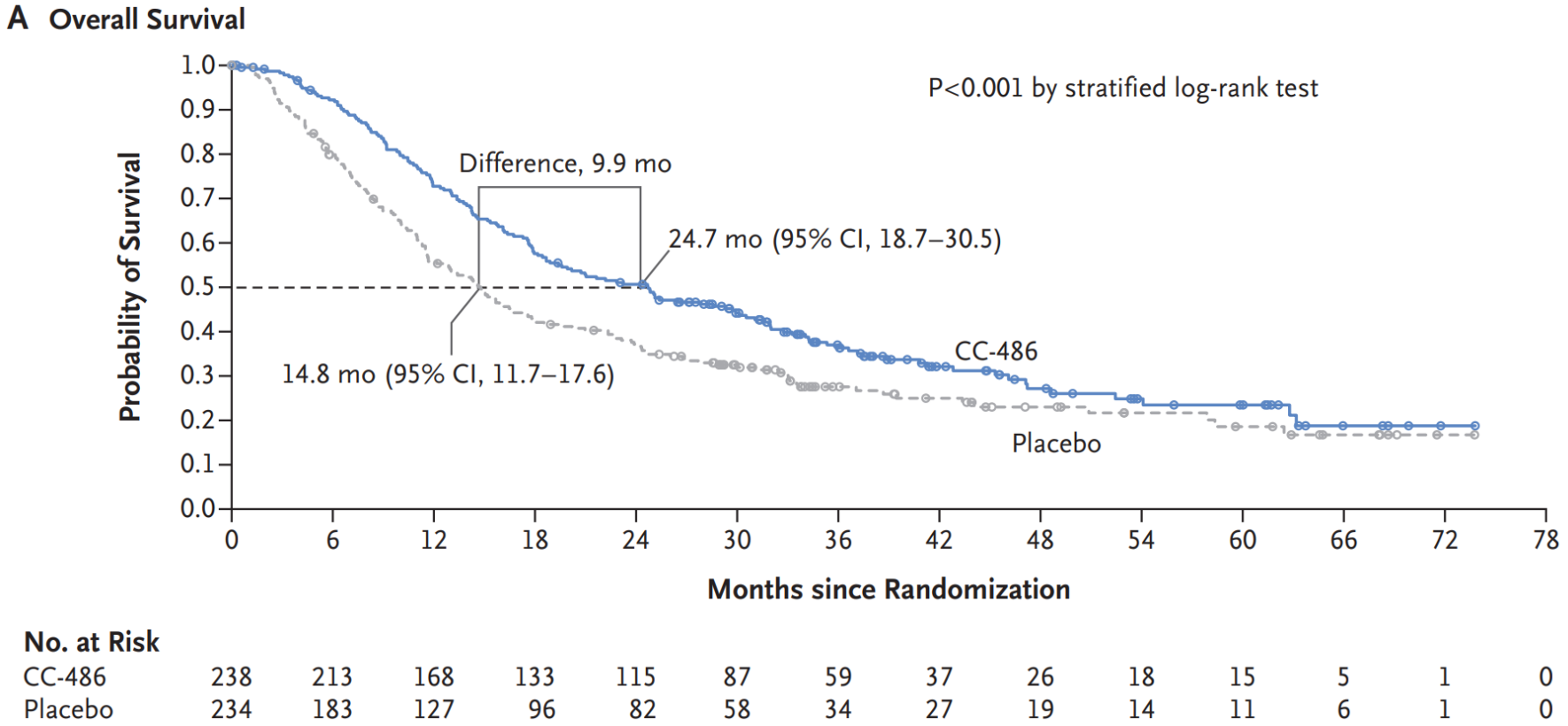
Phase 3 ≥ 55 ans ND AML in CR1

Patients aged ≥ 55 with de novo or secondary AML in first CR/CRi with IC; ECOG PS 0-3; intermediate or poor risk cytogenetics; ineligible for HSCT; adequate BM recovery



Wei A, NEJM 2021

AZACITIDINE orale : Onureg
Essai QUAZAR



* Approved for maintenance (or continued) treatment in pts in CR/CRi after intensive chemotherapy who cannot complete further curative treatment (incl. allogeneic HCT)

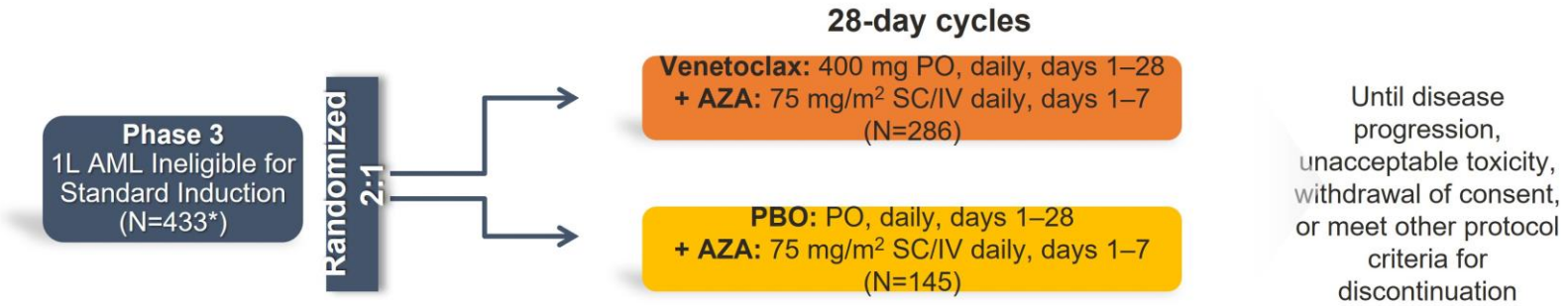
Data gaps: First, data regarding the role of oral azacitidine in younger populations or patients with core-binding factor AML are lacking; Second, there was considerable variability in therapy prior to selection for maintenance, ie, 45% of patients had received one consolidation cycle, 31% two cycles, and 20% not any consolidation.

Wei A, NEJM 2021

Traitement non intensif : AZACITIDINE-VENETOCLAX

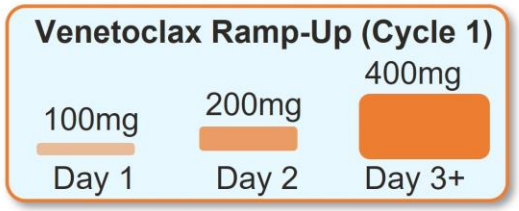
Viale-a
Venetoclax Trial in AML with Azacitdine

VIALE-A (NCT02993523) – Phase 3 randomized, double-blind study of VEN + AZA vs PBO + AZA in treatment-naïve patients with AML who are ineligible for standard induction therapy



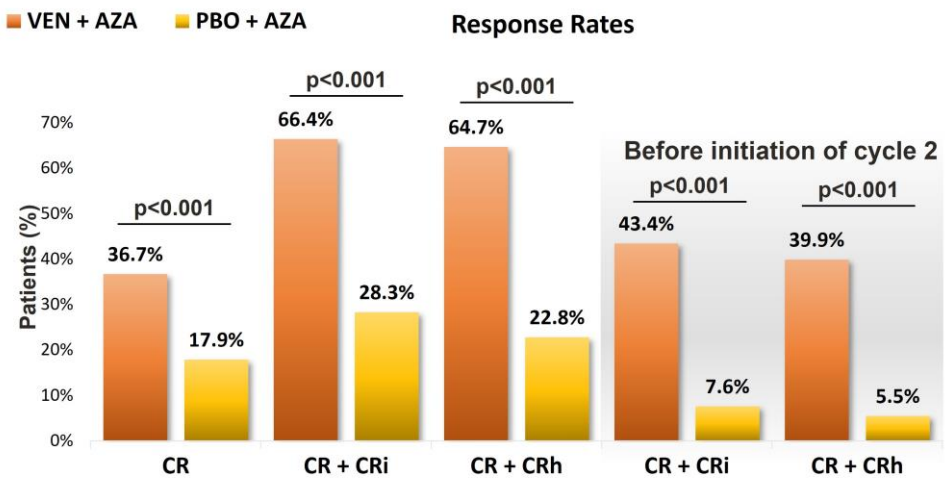
Key inclusion criteria
- Ineligible for standard induction therapy
- ≥75 years
- ≥18 years with comorbidities

Key exclusion criteria
- Prior HMA treatment for MDS
- APL or favorable risk cytogenetics
- Active CNS involvement with AML
- Prior MPN



DiNardo C, NEJM 2020

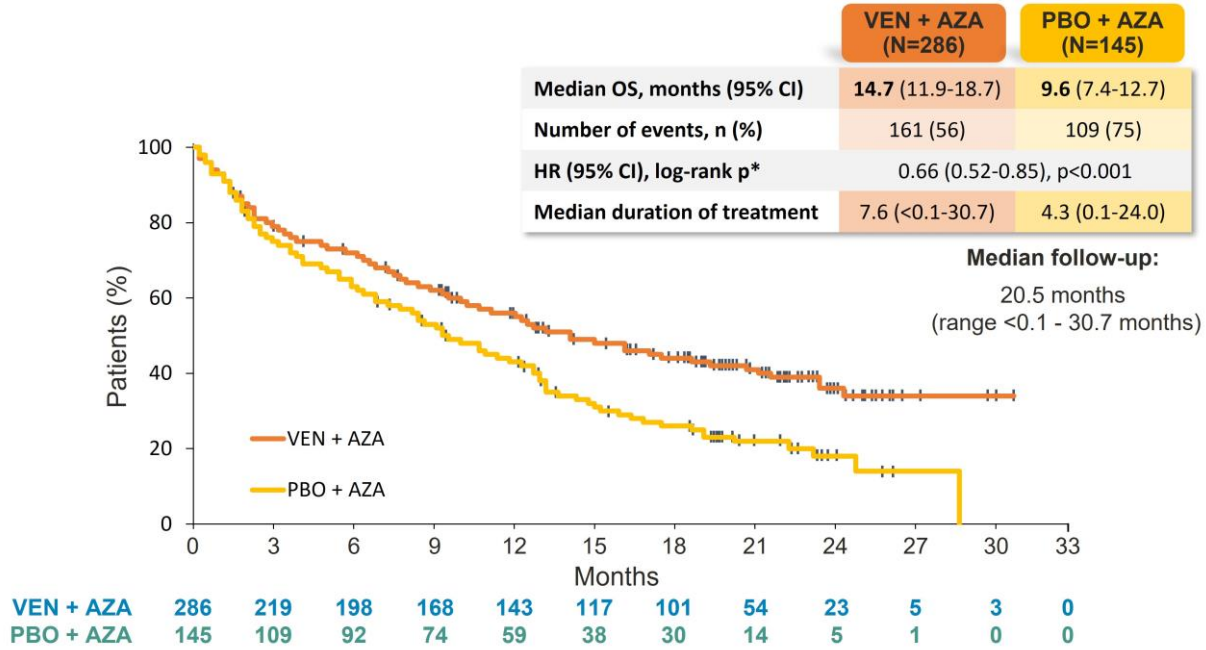
Traitement non intensif : AZACITIDINE-VENETOCLAX



In patients with CR + CRi, MRD negativity occurred in:

- **23.4%** receiving VEN + AZA vs
- **7.6%** receiving PBO + AZA

Median months (range)	VEN + AZA (N=286)	PBO + AZA (N=145)
Time to first response (CR or CRi)	1.3 (0.6-9.9)	2.8 (0.8-13.2)
Time to first response (CR or CRh)	1.0 (0.6-14.3)	2.6 (0.8-13.2)



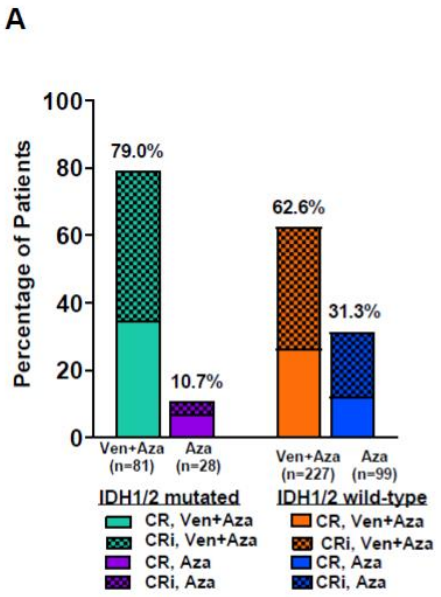
	VEN + AZA (N=286)	PBO + AZA (N=145)
Median OS, months (95% CI)	**14.7** (11.9-18.7)	**9.6** (7.4-12.7)
Number of events, n (%)	161 (56)	109 (75)
HR (95% CI), log-rank p*	0.66 (0.52-0.85), p<0.001	
Median duration of treatment	7.6 (<0.1-30.7)	4.3 (0.1-24.0)

Median follow-up:
20.5 months
(range <0.1 - 30.7 months)

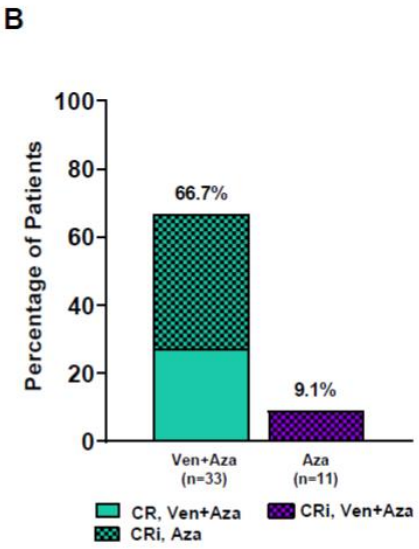
DiNardo C, NEJM 2020

Azacitidine-Venetoclax : **mutations d'*IDH1/2***

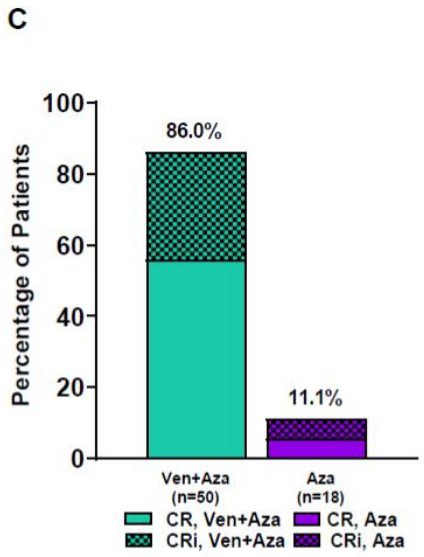
IDH1/2m



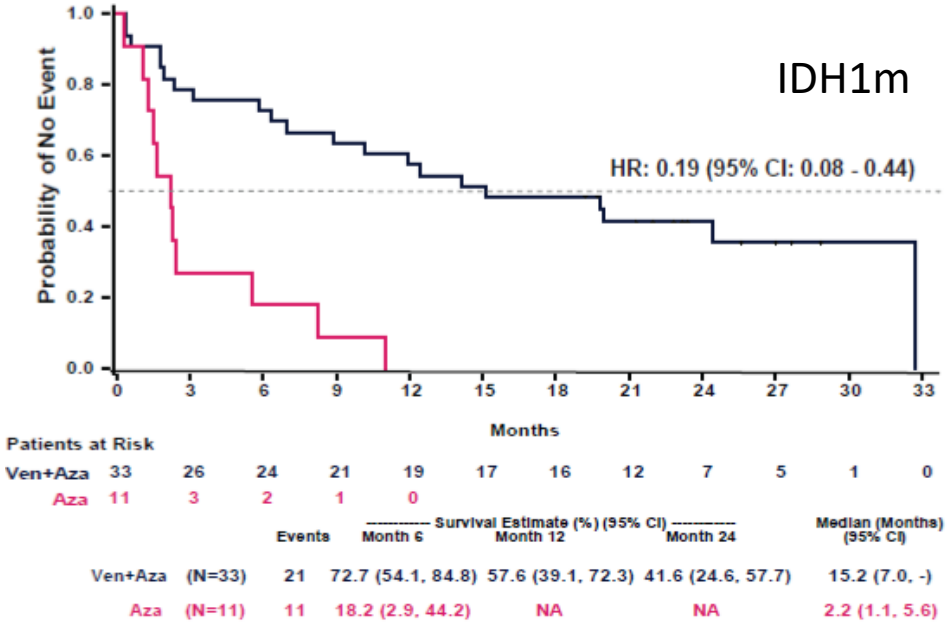
IDH1m



IDH2m



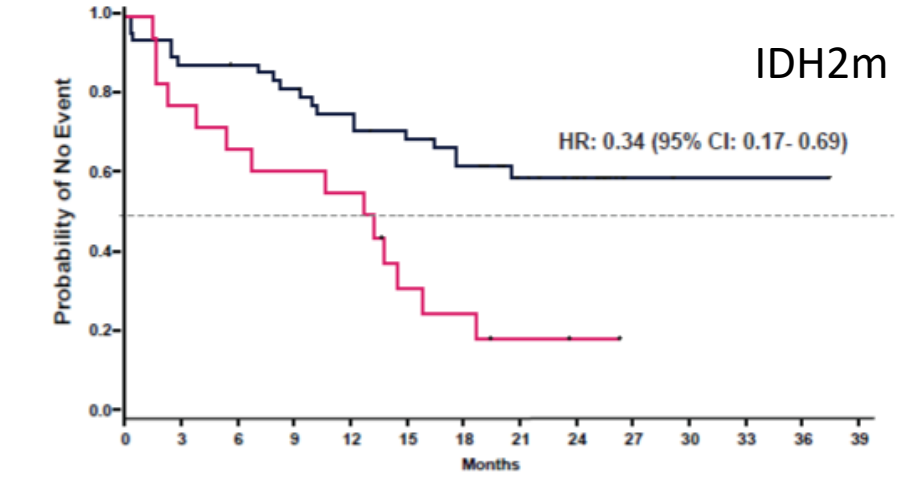
IDH1m



Patients at Risk													
Ven+Aza	33	26	24	21	19	17	16	12	7	5	1	0
Aza	11	3	2	1	0							

		Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) (95% CI)
Ven+Aza	(N=33)	21	72.7 (54.1, 84.8)	57.6 (39.1, 72.3)	41.6 (24.6, 57.7)	15.2 (7.0, -)
Aza	(N=11)	11	18.2 (2.9, 44.2)	NA	NA	2.2 (1.1, 5.6)

IDH2m

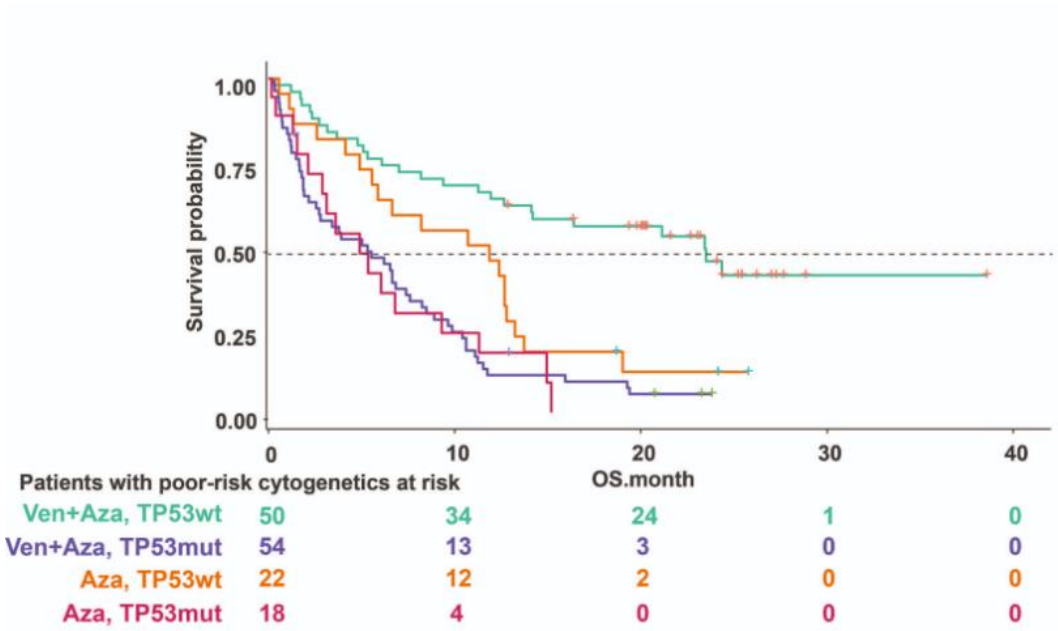


Patients at Risk													
Ven+Aza	50	44	43	40	36	32	28	19	14	2	1	1	1	0
Aza	18	14	12	11	10	5	4	2	1	0				

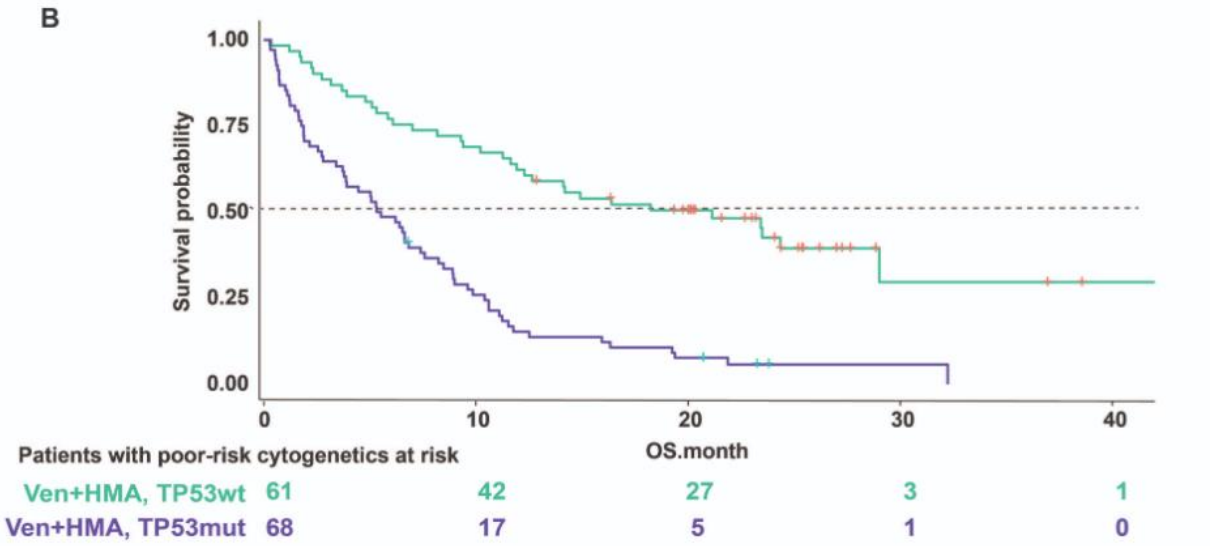
		Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) (95% CI)
Ven Aza	(N=50)	19	88.0 (75.2, 94.4)	75.6 (61.0, 85.3)	59.5 (43.9, 72.2)	- (17.6, -)
Aza	(N=18)	14	66.7 (40.4, 83.4)	55.6 (30.5, 74.8)	19.0 (4.8, 40.3)	13.0 (3.8, 15.8)

Pollyea A, Clin Cancer Res 2022

Azacitidine-Venetoclax : **mutations de *TP53***



Overall survival among patients with poor-risk cytogenetics and TP53 status in venetoclax and azacitidine versus azacitidine groups



Overall survival among patients with poor-risk cytogenetics and TP53 status in venetoclax and hypomethylating agent group

Pollyea A, ASH 2021

Traitement non intensif : AZACITIDINE-VENETOCLAX et 3^{e} molécule

- Pevonedistat (anti-NEDD8)
- Cusatuzumab (anti-CD70)
- Sabatolimab (anti-TIM3) : essai STIMULUS
- Magrolimab (anti-CD47) : essais ENHANCE-3 et 2

Sabatolimab (MBG453)

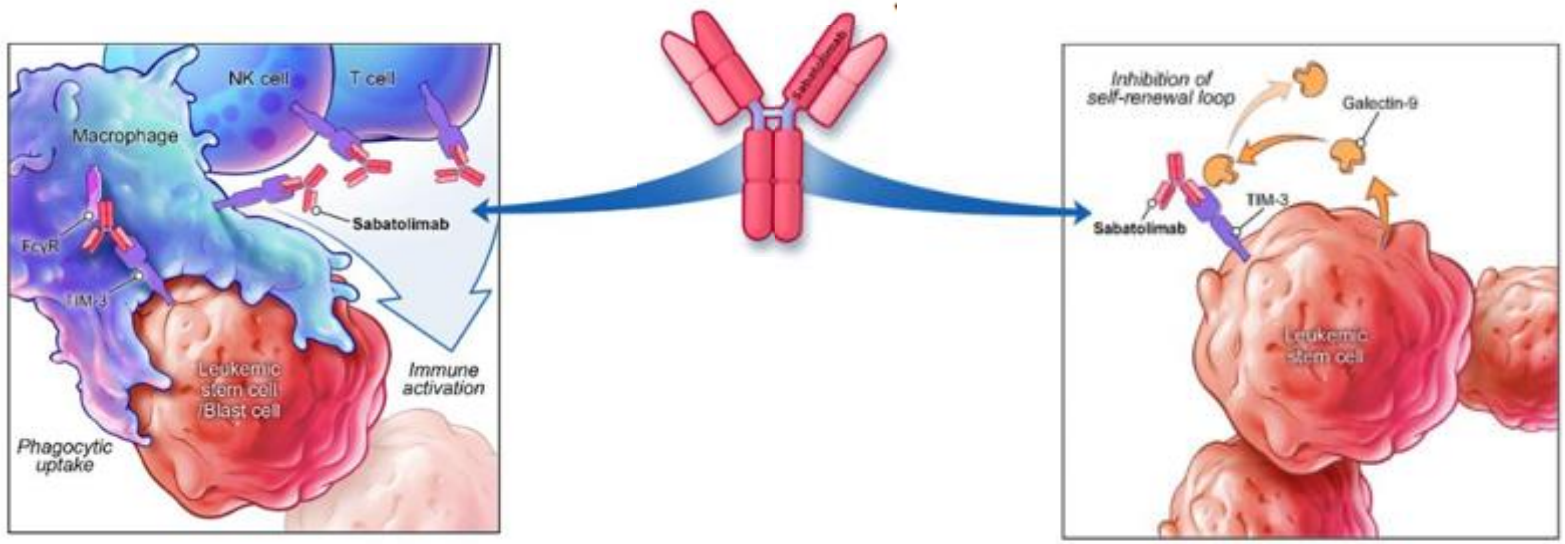
Anticorps anti-TIM3 ciblant à la fois les cellules immunitaires et les CSL/blastes: activité immuno-myéloïde

Cible les cellules immunitaires

- Se lie à TIM3 sur les cellules effectrices de l'immunité **relançant l'immunité**[1,2]
- Augmente **la phagocytose**, facilitant l 'élimination des CSL et blastes[1-4]

Cible les cellules leucémiques

- Cible directement les **CSLs** via une liaison à haute affinité avec TIM3[2]
- Le blocage de TIM3 sur les CSL pourrait **inhiber leur auto-renouvellement** induit par la boucle TIM3/galectine9 [1,2]



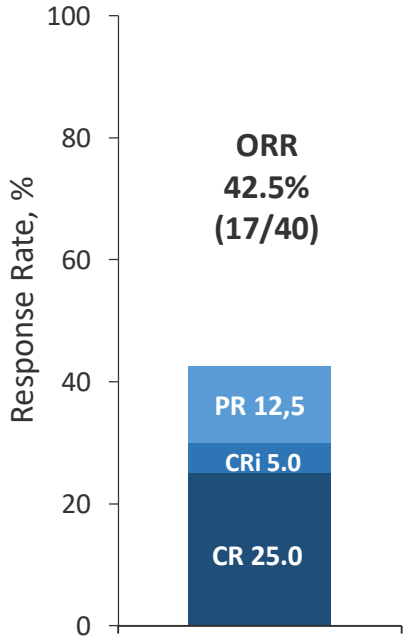
1. Acharya N et al. J Immunother Cancer 2020;8(1):e000911
2. Sabatos-Peyton C et al. SITC 2020 Abstract 439
3. Borate U et al. HemaSphere 2020;4(suppl1):abstract S185AACR 2016. Oral presentation;
4. Borate U et al.EHA2020 Oral presentation

FcγR Fc gamma recepteur; CSL cellules souches leucémiques; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

Sabatolimab + HMA demonstrates durable clinical responses in ND-AML

Response Rate

(evaluable patients[a])

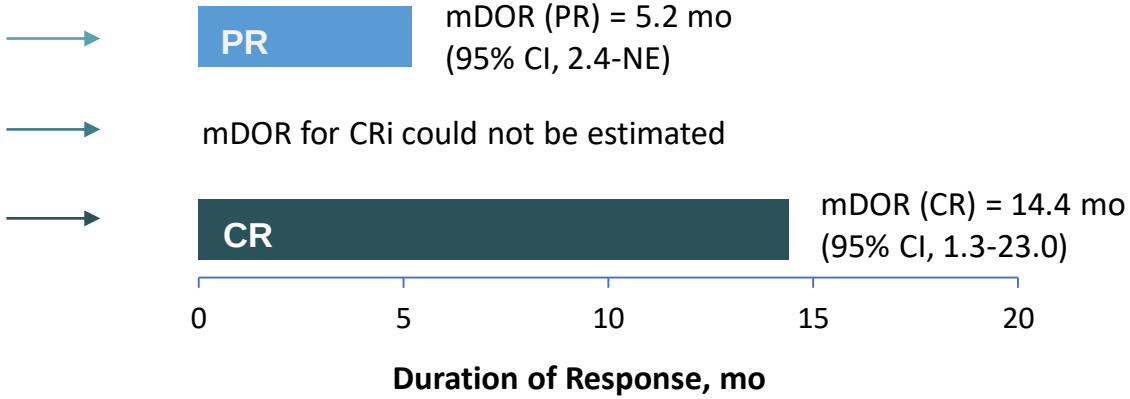


Durability Assessments

12.6 mo — Median DOR [CR / CRi / PR] (95% CI, 5.2-18.0)

26.8% — Estimated 12-mo PFS rate (95% CI, 14.2%-41.0%)

Median Duration of Response (mDOR) by response category



[a]Evaluable patients, including patients with a valid baseline and at least 1 postbaseline bone marrow assessment or if they had disease progression or disease-related death prior to the first marrow assessment.

CRi, complete remission with incomplete hematologic recovery.

Brunner, ASH21, oral communication, abstract 244.

Part 1 Stimulus-AML1, C12201 (EHA 2022): Patient disposition and AE regardless of treatment

Poster P582

Amer M. Zeidan, MBBS
amer.zeidan@yale.edu

First Results of a Phase II Study (STIMULUS-AML1) Investigating Sabatolimab + Azacitidine + Venetoclax in Patients With Newly Diagnosed Acute Myeloid Leukemia

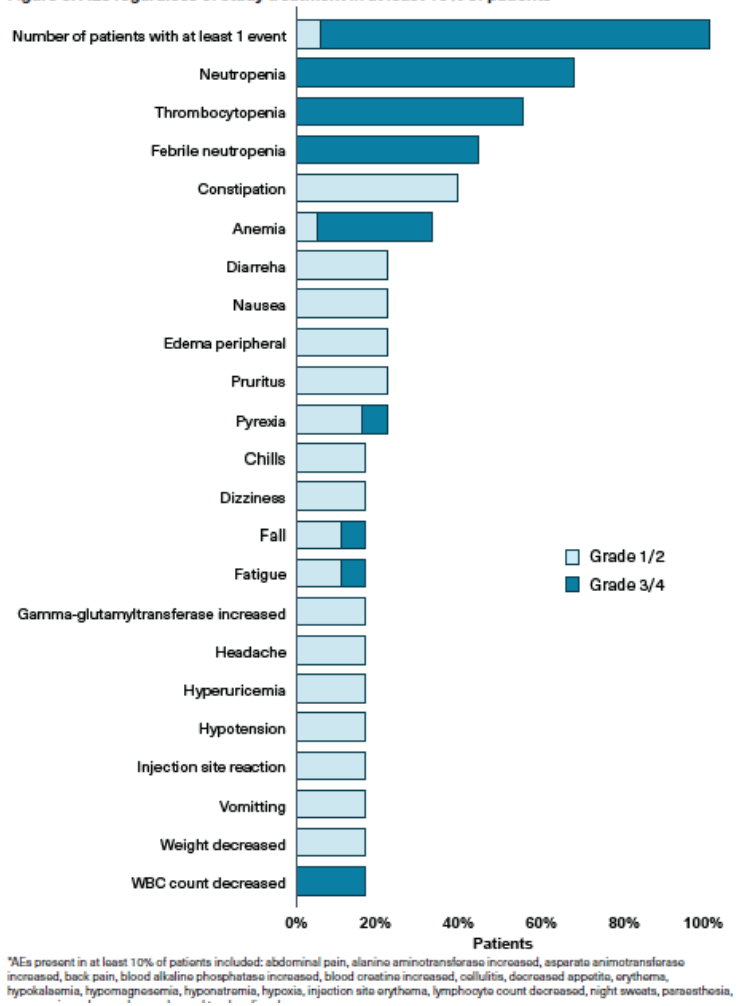
Amer M. Zeidan,[1] Jörg Westermann,[2] Tibor Kovacsovics,[3] Sarit Assouline,[4] Andre C. Schuh,[5] Hee-Je Kim,[6] Gabriela Rodriguez Macias,[7] David Sanford,[8] Marlise R. Luskin,[9] Eytan M. Stein,[10] Kamel Malek,[11] Jiaying Lyu,[12] Mario Stegert,[11] Jordi Esteve[13]

Table 2. Patient Disposition

Characteristic	Cohort 1 400 mg sabatolimab + AZA + VEN (n=5)	Cohort 2 800 mg sabatolimab + AZA + VEN (n=13)	All Patients (N=18)
Treatment ongoing,[a] n (%)	1 (20.0)	8 (61.6)	9 (50.0)
Discontinued from treatment, n (%)	4 (80.0)	5 (38.5)	9 (50.0)
Reason for discontinuation, n (%)			
Adverse event	1 (20.0)	2 (15.4)	3 (16.7)
HSCT Planned	1 (20.0)	1 (7.7)	2 (11.1)
Physician decision	0	1 (7.7)	1 (5.6)
Progressive disease	2 (40.0)	1 (7.7)	3 (16.7)

[a]Ongoing at time of data cutoff on September 6, 2021.
HSCT, hematopoietic stem cell transplant.

Figure 3. AEs regardless of study treatment in at least 15% of patients*



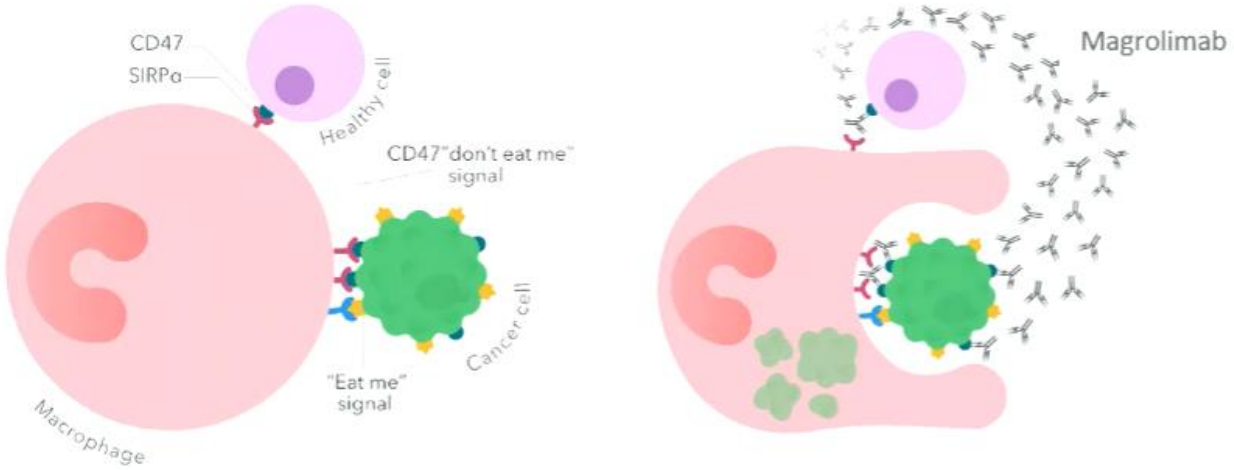
*AEs present in at least 10% of patients included: abdominal pain, alanine aminotransferase increased, aspartate aminotransferase increased, back pain, blood alkaline phosphatase increased, blood creatine increased, cellulitis, decreased appetite, erythema, hypokalaemia, hypomagnesemia, hyponatremia, hypoxia, injection site erythema, lymphocyte count decreased, night sweats, paraesthesia,

https://clinicaltrials.gov/ct2/show/NCT04150029

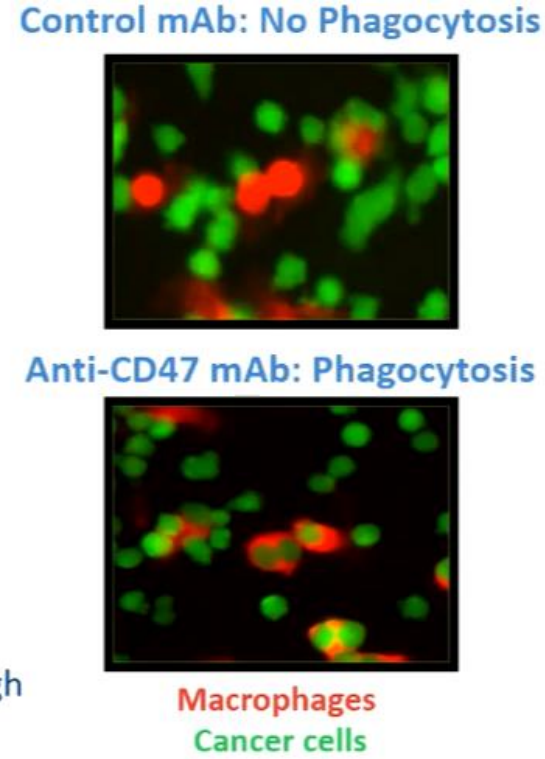
Zeidan et al. EHA2022; abstract P582

Magrolimab

Anticorps monoclonal anti-CD47



- CD47 is a "don't eat me" signal that is overexpressed in multiple cancers, including AML, leading to macrophage immune evasion.[1,2]
- Magrolimab, an IgG4 anti-CD47 monoclonal antibody, eliminates tumor cells through macrophage phagocytosis.[1]

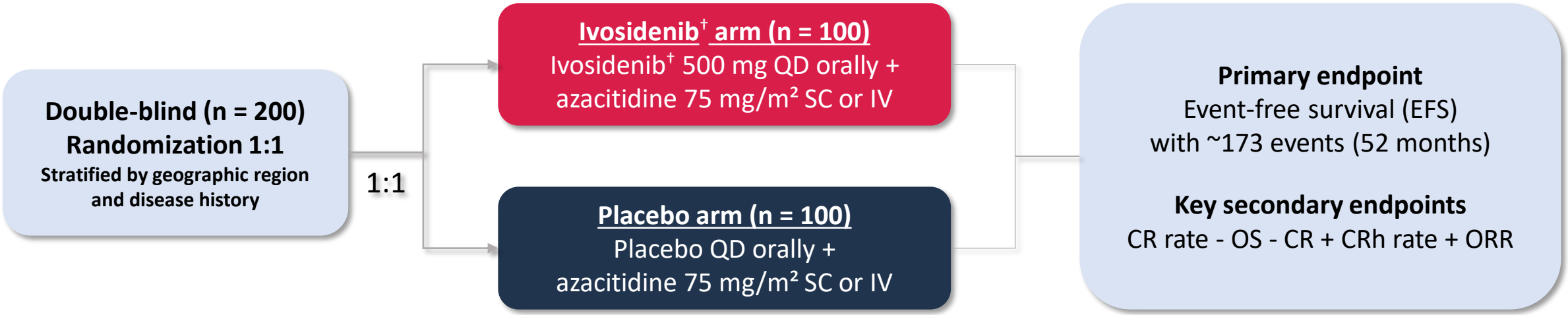


Daver N, EHA 2022

Azacitidine-Magrolimab +/-Venetoclax

- Résultats du triplet (MD Anderson)
  - LAM 1L, quelles que soient les caractéristiques moléculaires
  - ORR >90%
- Essai ENHANCE-2 :
  - LAM 1L, TP53m
  - Azacitidine-Venetoclax ou « 3+7 » vs. Azacitidine-Magrolimab
- Essai ENHANCE-3 :
  - LAM 1L unFIT, quelles que soient les caractéristiques moléculaires
  - Azacitidine-Venetoclax + Magrolimab vs. Placebo

Traitement non intensif : AZACITIDINE-Ivosidenib



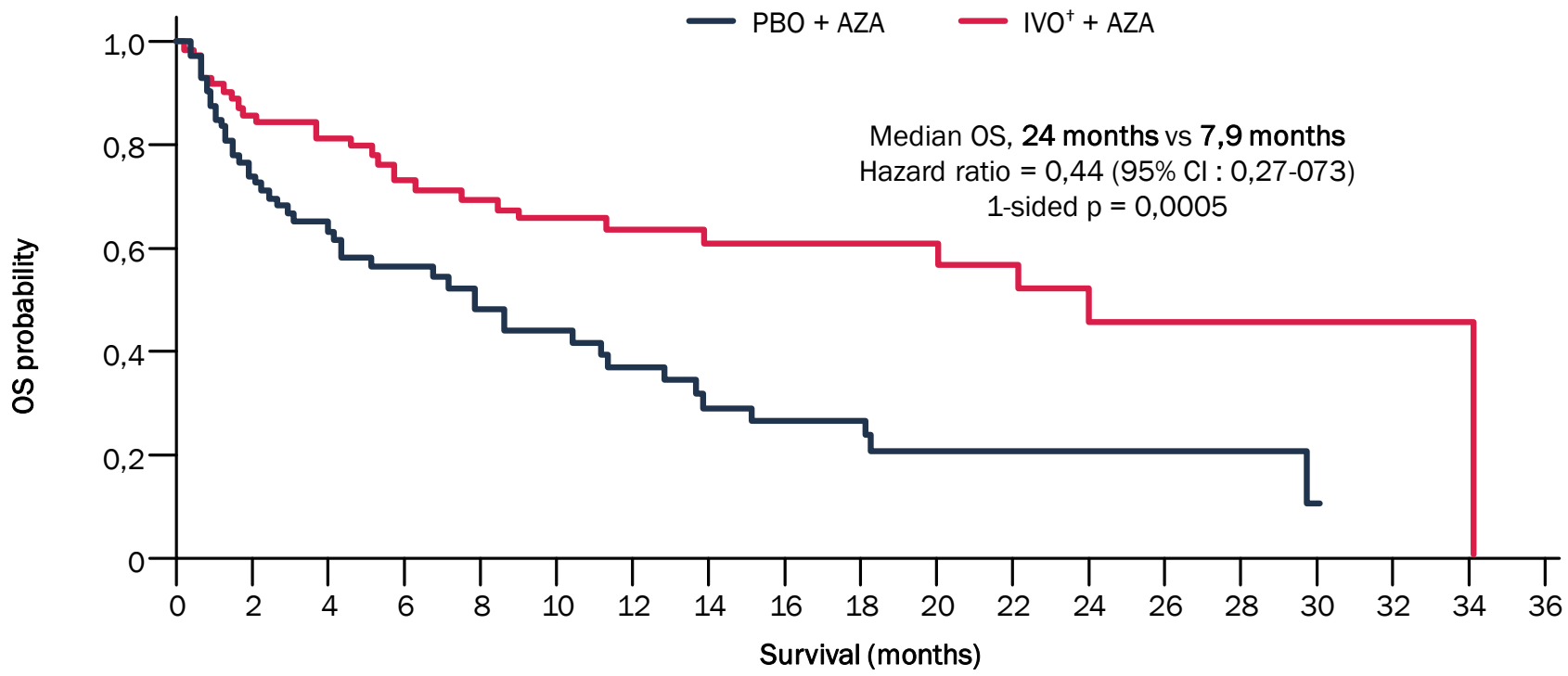
Montesinos P, NEJM 2022

Azacitidine-Ivosidenib

Response rate	IVO† + AZA (n = 72)		PBO + AZA (n = 74)
CR rate, n (%) [95% CI]	34 (47,2) [35,3-59,3]		11 (14,9) [7,7-25,0]
Odds ratio (95% CI); 1-sided p value		4,8 (2,2-10,5) ; p < 0,0001	
Median duration of CR (95% CI), months	NE (13,0-NE)		11,2 (3,2-NE)
Median time to CR (range), months	4,3 (1,7-9,2)		3,8 (1,9-8,5)
CR + CRh rate, n (%) [95% CI]	38 (52,8) [40,7-64,7]		13 (17,6) [9,7-28,2]
Odds ratio (95% CI); 1-sided p value		5,0 (2,3-10,8) ; p < 0,0001	
Median duration of CR (95% CI), months	NE (13,0 - NE)		9,2 (5,8-NE)
Median time to CR (range), months	4,0 (1,7-8,6)		3,9 (1,9-7,2)
ORR rate, n (%) [95% CI]	45 (62,5) [50,3-73,6]		14 (18,9) [10,7-29,7]
Odds ratio (95% CI); 1-sided p value		7,2 (3,3-15,4) ; p < 0,0001	
Median duration of CR (95% CI), months	22,1 (13,0-NE)		9,2 (6,6-14,1)
Median time to CR (range), months	2,1 (1,7-7,5)		3,7 (1,9-9,4)

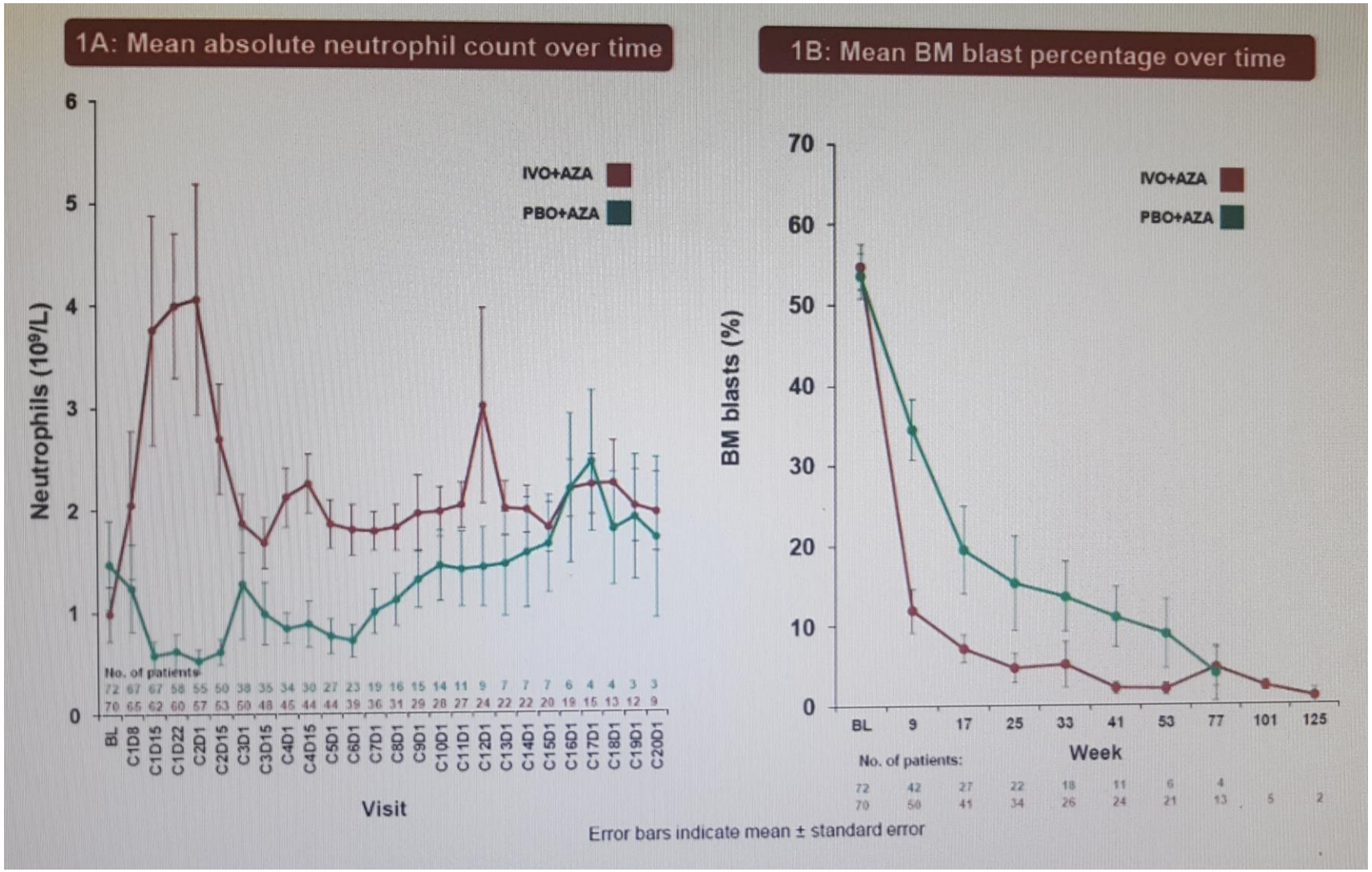
Montesinos P, NEJM 2022

Azacitidine-Ivosidenib



Montesinos P, NEJM 2022

Azacitidine-Ivosidenib



Döhner H, EHA 2022

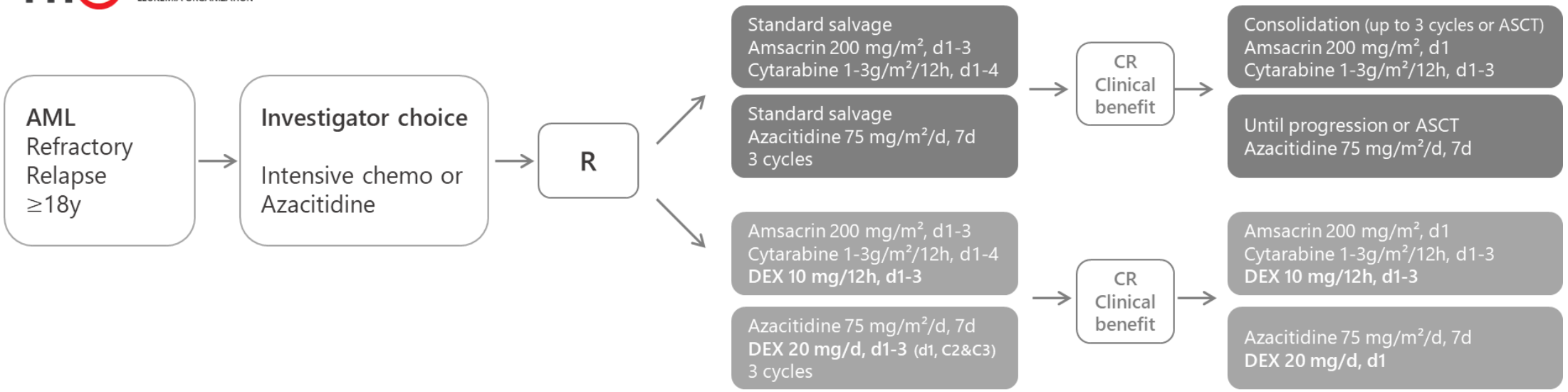
Traitement de rattrapage ou rechute :
Chimiothérapie ou Azacitidine +/- Dexaméthasone : DEXAML-03

GROUPEMENT INTERREGIONAL DE RECHERCHE CLINIQUE ET D'INNOVATION
SUD-OUEST OUTRE-MER HOSPITALIER

PROGRAMME HOSPITALIER DE RECHERCHE CLINIQUE INTERREGIONAL 2017

DEXAML-03

FRENCH INNOVATIVE LEUKEMIA ORGANIZATION



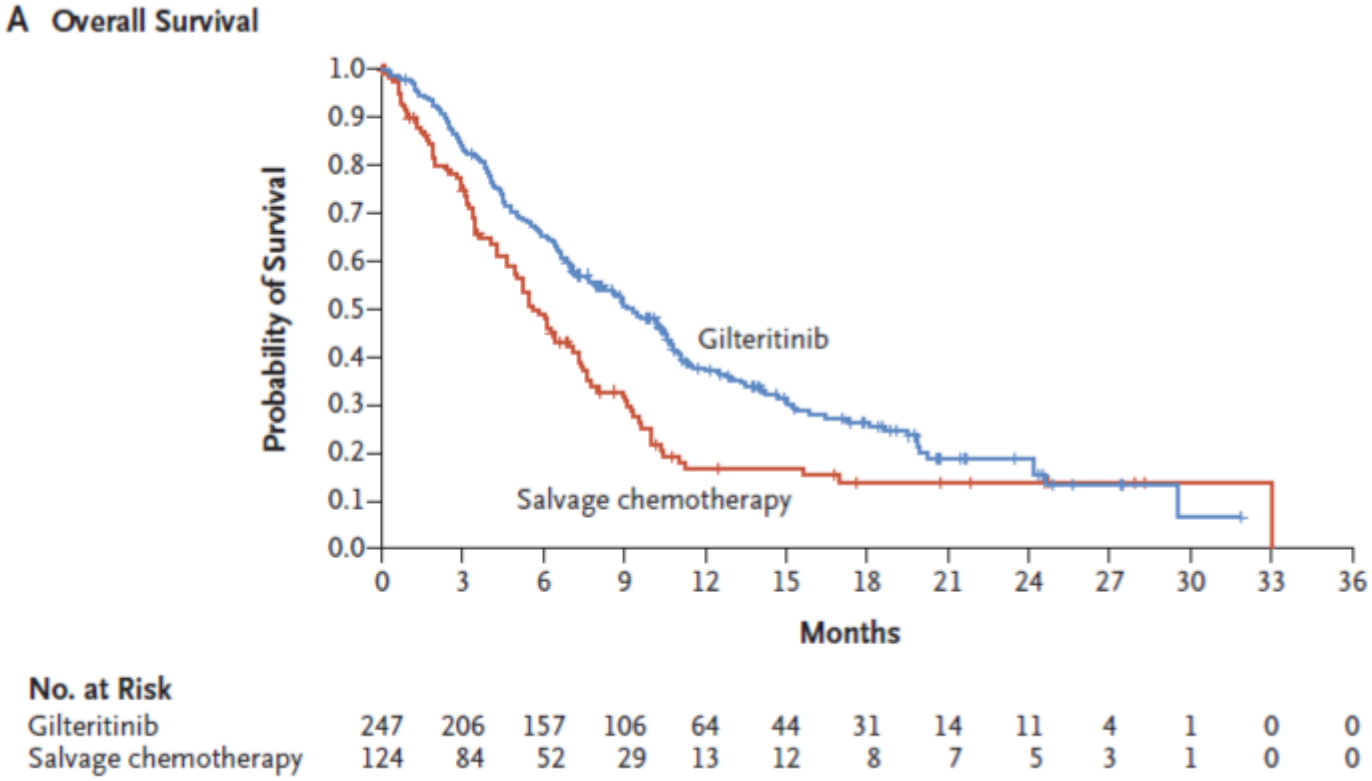
Traitement de rattrapage ou rechute : Gilteritinib en monothérapie : essai ADMIRAL

Table 2. Antileukemic Responses (Intention-to-Treat Population).*

Variable	Gilteritinib (N=247)	Salvage Chemotherapy (N=124)	Hazard Ratio or Risk Difference (95% CI)†
Median overall survival (95% CI) — mo	9.3 (7.7–10.7)	5.6 (4.7–7.3)	0.64 (0.49–0.83)
Median event-free survival (95% CI) — mo	2.8 (1.4–3.7)	0.7 (0.2–NE)	0.79 (0.58–1.09)
Response — no. (%)			
Complete remission	52 (21.1)	13 (10.5)	10.6 (2.8–18.4)
Complete remission or complete remission with partial hematologic recovery	84 (34.0)	19 (15.3)	18.6 (9.8–27.4)
Complete remission with partial hematologic recovery	32 (13.0)	6 (4.8)	ND
Complete remission with incomplete hematologic recovery	63 (25.5)	14 (11.3)	ND
Complete remission with incomplete platelet recovery	19 (7.7)	0	ND
Partial remission	33 (13.4)	5 (4.0)	ND
No response	66 (26.7)	43 (34.7)	ND
Composite complete remission‡	134 (54.3)	27 (21.8)	32.5 (22.3–42.6)
Overall response	167 (67.6)	32 (25.8)	
Median duration of remission (95% CI) — mo§	11.0 (4.6–NE)	NE (NE–NE)	NE
Time to composite complete remission — mo	2.3±1.9	1.3±0.5	NA
Median leukemia-free survival (95% CI) — mo	4.4 (3.6–5.2)	6.7 (2.1–8.5)	NE

Perl A, NEJM 2019

Gilteritinib en monothérapie : ADMIRAL



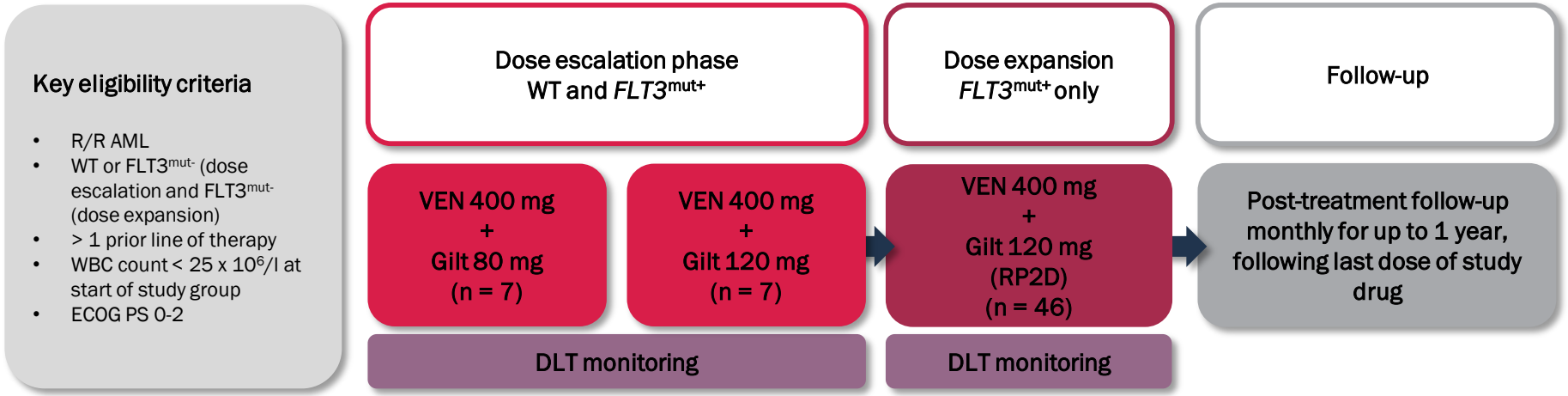
	Median Overall Survival (95% CI) *mo*
Gilteritinib	9.3 (7.7–10.7)
Salvage Chemotherapy	5.6 (4.7–7.3)

Hazard ratio for death, 0.64 (95% CI, 0.49–0.83)
P<0.001

Perl A, NEJM 2019

Registre ELEGANCE
PY DUMAS, Leukemia 2022

Phase 1 : association Venetoclax + Gilteritinib

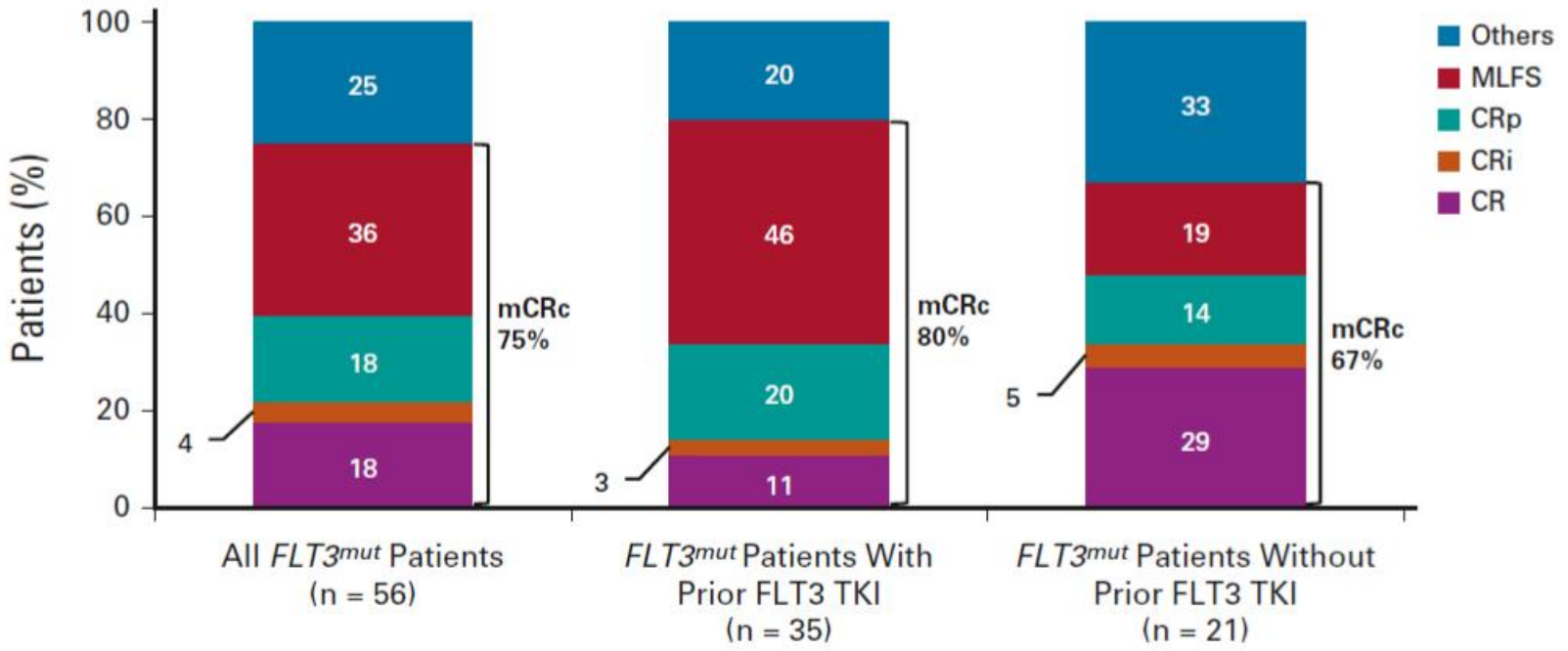


Primary endpoints	Secondary endpoints	Exploratory endpoints
• mCRc : CR + CRp + CRi + MLFS	• CR + CRh • DoR of mCRc	• OS in *FLT3*mut+ subgroups • Allelic burden of *FLT3* mutations

- Safety data are reported for all RP2D patients (WT or FLT3^{mut+}) from both escalation and expansion cohorts (n = 54 ; 2 WT [escalation], 52 FLT3mut+ [6 escalation; 46 expansion)
- Efficacy data are reported for all evaluable RP2D FLT3^{mut+} patients from both escalation and expansion cohorts (n = 51)

Naval Daver. Venetoclax in Combination with Gilteritinib Demonstrates Molecular Clearance of FLT3 mutation in Relapsed/Refractory FLT3-Mutated Acute Myeloid Leukemia. ASH 2021. Abstract #691

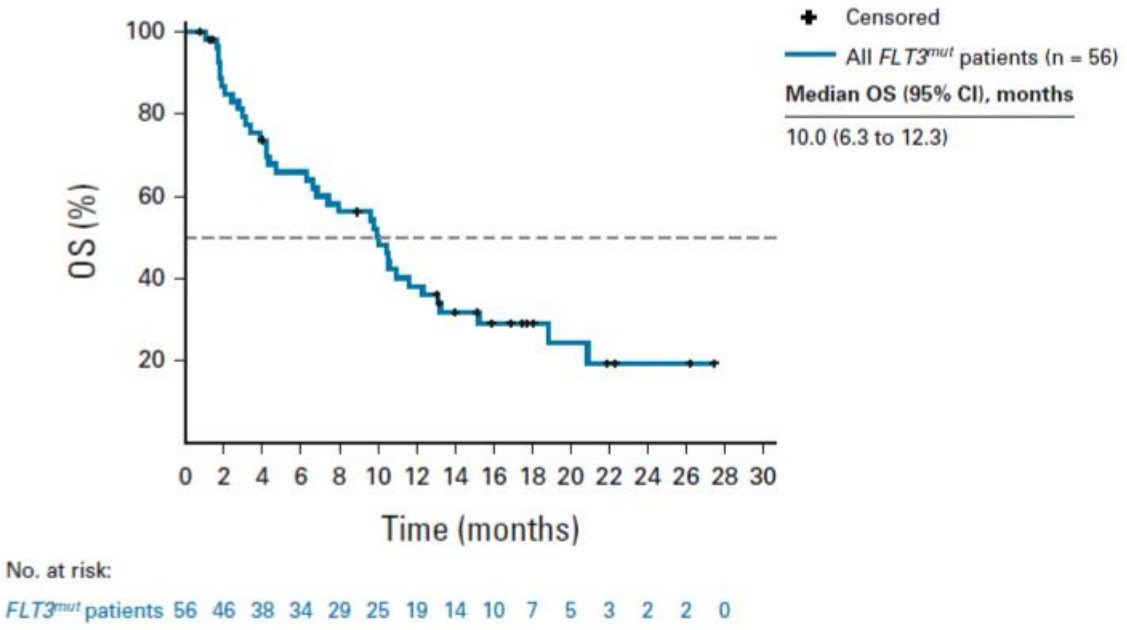
Réponses

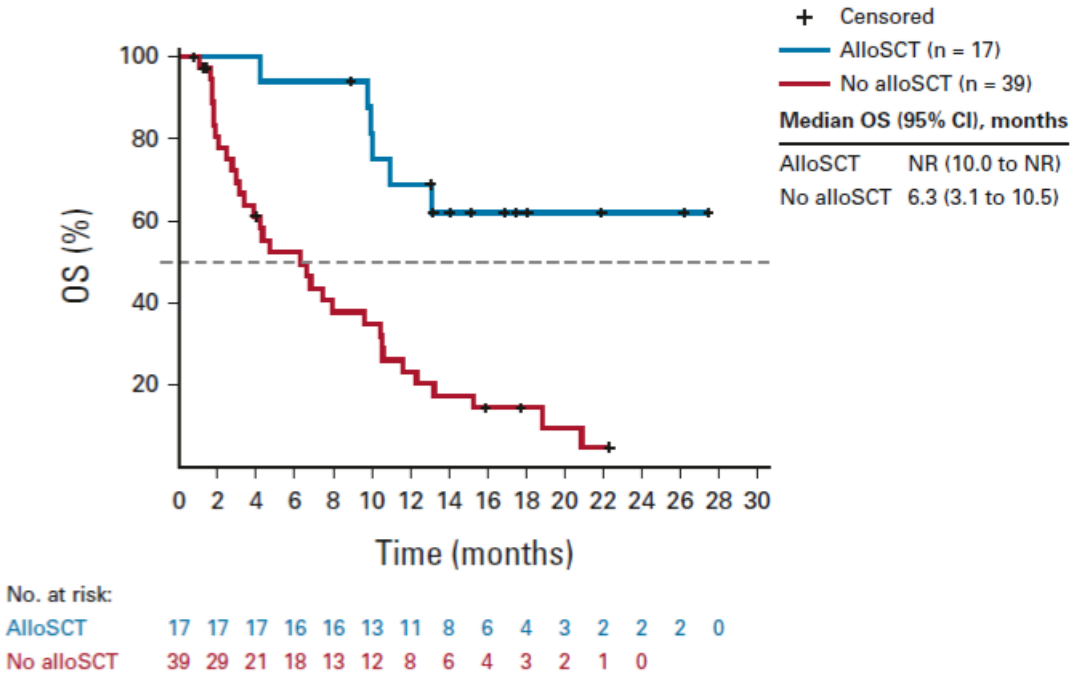


vs. 54.3% dans ADMIRAL
Durée de réponse : 4.9 mois
Réponse obtenue en 0.9 mois

Daver N, JCO 2022

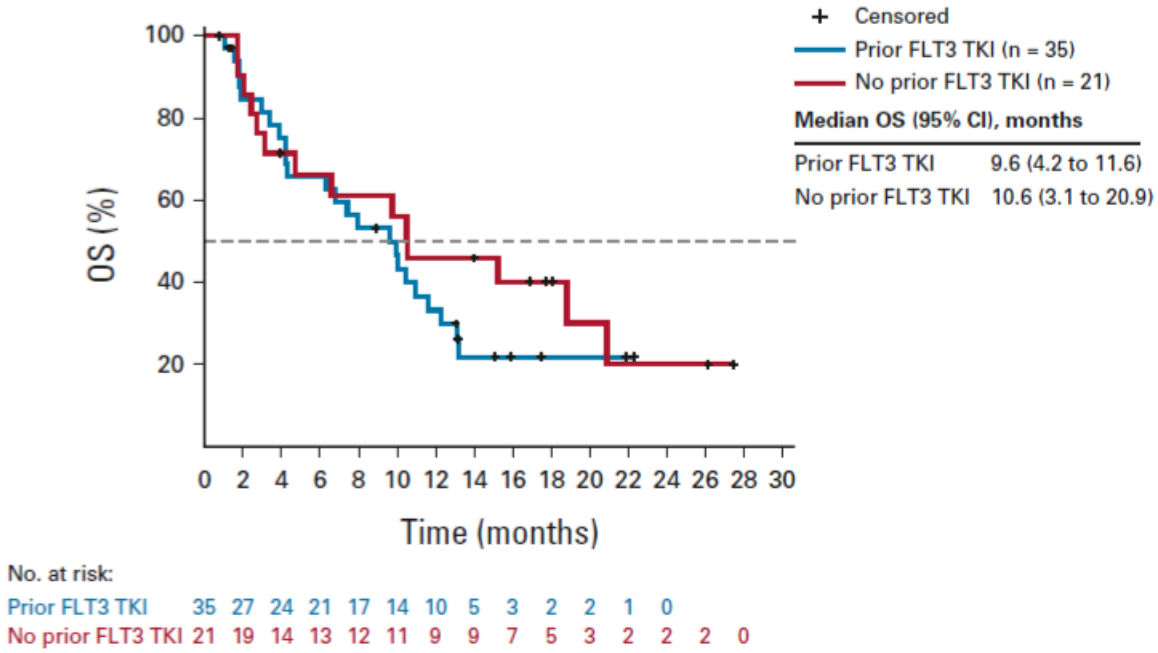
Survie





Daver N, JCO 2022

Survie



- Patients préalablement exposés au Venetoclax (n = 10)
  - Taux de mCRc : 60 %
  - Median OS : 6,7 months (95% CI : 1,7 – 10,6)

Daver N, JCO 2022

Triplet Azacitidine-Venetoclax-Gilteritinib

- Relapsed/refractory FLT3-mutated * AML or high-risk MDS or CMML
  or
- Newly diagnosed FLT3-mutated* AML unfit for intensive chemotherapy

Induction

Azacitidine
75 mg/m² IV/SC on D1-7

Venetoclax#
D1-28 (bone marrow on D14)%

Gilteritinib
80-120 mg on D1-28

Consolidation
(up to 24 cycles)

Azacitidine
75 mg/m² IV/SC on D1-5

Venetoclax
400 mg on D1-7

Gilteritinib
80-120 mg on D1-28

* FLT3-ITD or FLT3 D835 mutations allowed

Venetoclax ramp-up during cycle 1 : 100 mg on D1, 200 mg on D2, 400 mg on D3+

% If < 5 % blasts or insufficient on C1D14, venetoclax held (both cohorts) and gilteritinib held (frontline only)

- **Primary endpoint:** MTD of gilteritinib in combination (phase I), CR/Cri rate (phase II)
- **Secondary endpoints:** CR rate, MRD negativity rate, duration of response, OS, safety

Nicholas J. Short. A Triplet Combination of Azacitidine, Venetoclax and Gilteritinib for Patients with FLT3-Mutated Acute Myeloid Leukemia: Results from a Phase I/II Study. ASH 2021. Abstract #696

Triplet Azacitidine-Venetoclax-Gilteritinib : réponses

Response, n/N (%)	Frontline (n = 14)	R/R (n = 16)
mCRc (CR/Cri/MLFS)	**14 (100)**	**11 (69)**
CR	13 (93)	3 (19)
CRi	0	2 (13)
MLFS	1 (7)	6 (37)
PR*	0	1 (6)
No response	**0**	**4 (25)**
Early death	0	0

* PR in 1 patient with extramedullary-only disease (assessed by PET scan)

Nicholas J. Short. ASH 2021. Abstract #696

Autres traitements

- Inhibiteurs d'IDH
  - IDH1 : ivosidenib (ATU en monothérapie en R/R)
  - IDH2 : enasidenib (non accessible)
  - IDH1 : olutasidenib (essai FT-2102)
  - IDH1/2 : LOXO (phase 1)

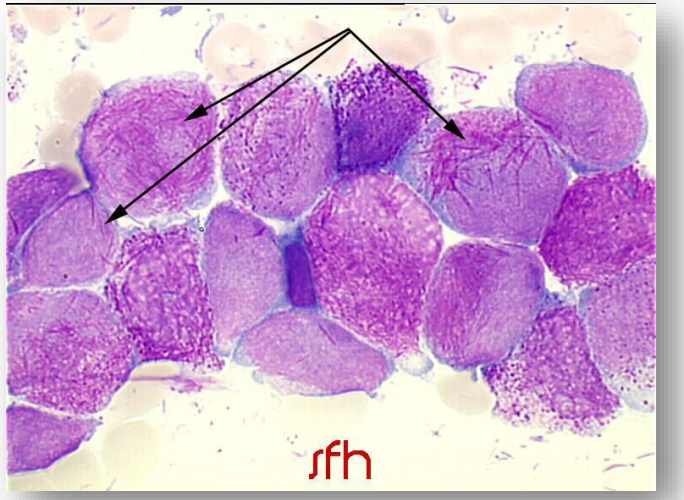
- Inhibiteur de Menin-MLL

- Immunomodulateur CC-90009

- Anticorps monoclonal anti-SIRPα
- Anticorps monoclonal anti-CD71 : INA-03
- Anticorps bispécifique : l'après Flotetuzumab

- CAR-T anti-CLL1

Leucémie aiguë promyélocytaire (LAM3) : une LAM à part



Urgence diagnostique et thérapeutique

Cytopénies + syndrome hémorragique +/- hyperleucocytose
CIVD : complications précoces

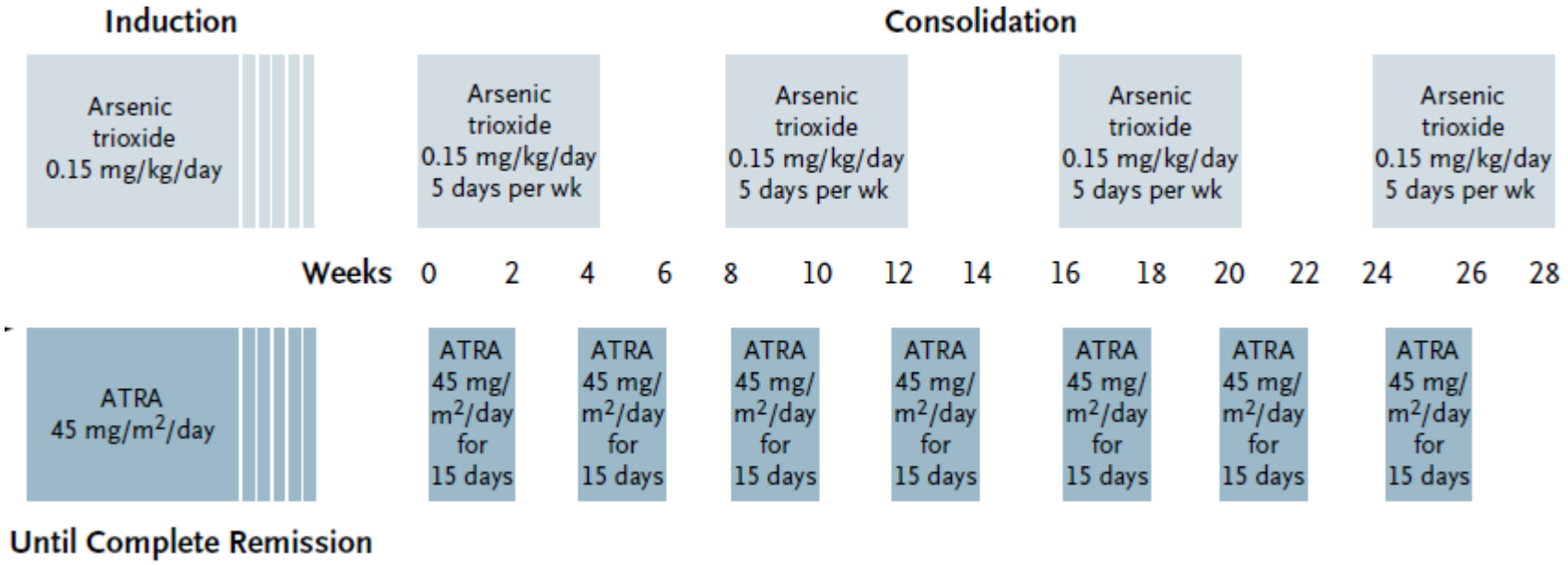
Confirmation au myélogramme et caryotype : t(15;17)

Traitements :
ATRA VESANOID 45 mg/m²/jr en 2 prises PO à débuter en urgence
Trioxyde d'Arsenic +/- chimio
Prise en charge de la CIVD +++

Guérison : 95 %

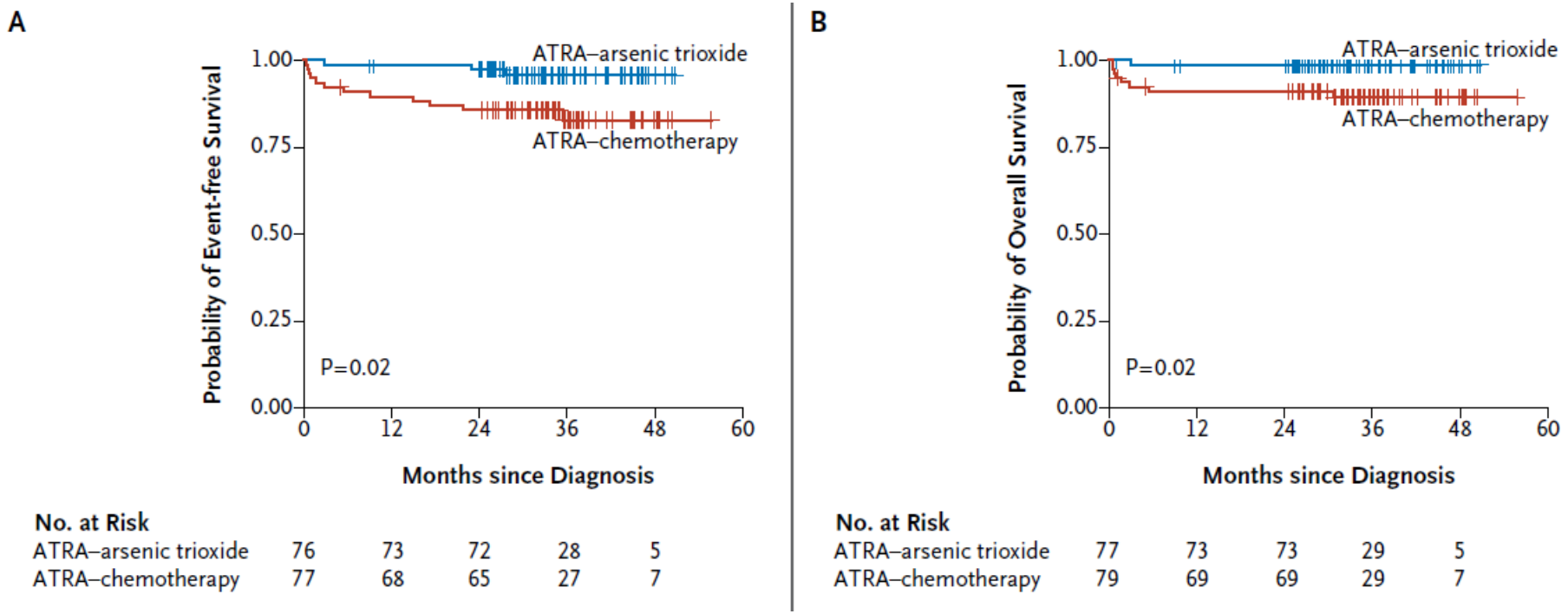
Leucémie aiguë promyélocytaire (LAM3) : traitement

- Risque faible/intermédiaire : leucocytes < 10 G/L
  - Induction :
    - ATRA 45 mg/m² J1-RC
    - Trioxyde d'arsenic 0.15 mg/kg/jr J1-30
  - Consolidations x4
    - ATRA 45 mg/m² J1-14/28
    - Trioxyde d'arsenic 0.15 mg/kg/jr J1-J28



F Lo Coco, NEJM 2013

Leucémie aiguë promyélocytaire (LAM3) : traitement



- Effets secondaires :
  - ATRA : sd de différenciation, céphalées (HTIC), sécheresse cutanéo-muqueuse
  - Neuropathie, hépatotoxicité
- Haut risque : leucocytes > 10 G/L : idarubicine
- Suivi MRD *PML::RARA* : de moins en moins….

F Lo Coco, NEJM 2013