FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

# Gestion des rechutes moléculaires dans les LAM *NPM1* et LAM CBF

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10es Journées du FILO
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INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

CHU TOULOUSE

# Liens d'intérêt

Abbvie, Astellas, BMS-Celgene, Jazz Pharmaceuticals, Novartis, Servier

# LAM *NPM1* et LAM CBF - Classification ELN 2022

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

Modulo la MRD

Modulo la MRD

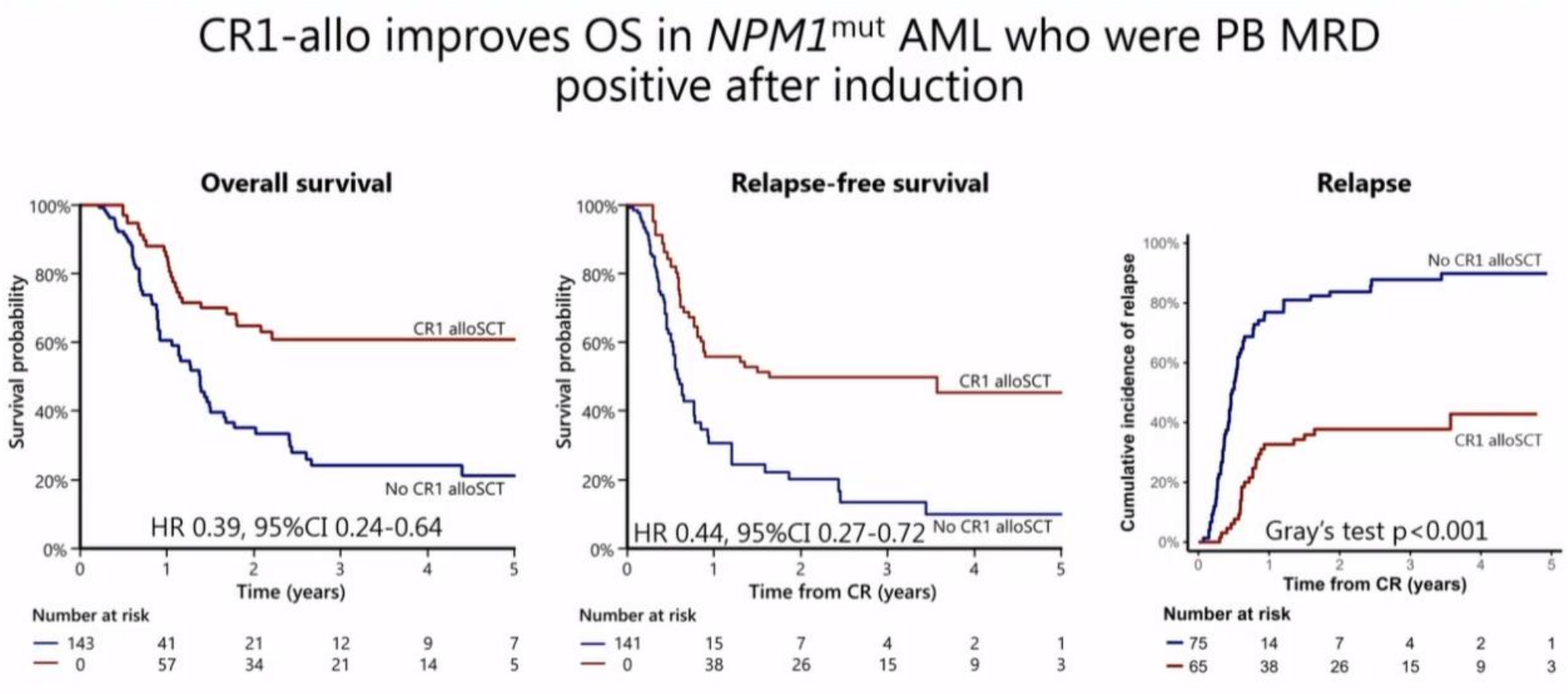
Si *NPM1*m et caryotype défavorable : risque adverse

Si concomitante d'une mutation de *NPM1,* reste du sous-groupe favorable

Döhner H, Blood 2022

# LAM *NPM1* : Traitement guidé par la MRD

Essais AML17 et AML19, n = 737 LAM *NPM1* en RC après 2 cycles, avec une MRD2 évaluable




Othman J, ASH 2023

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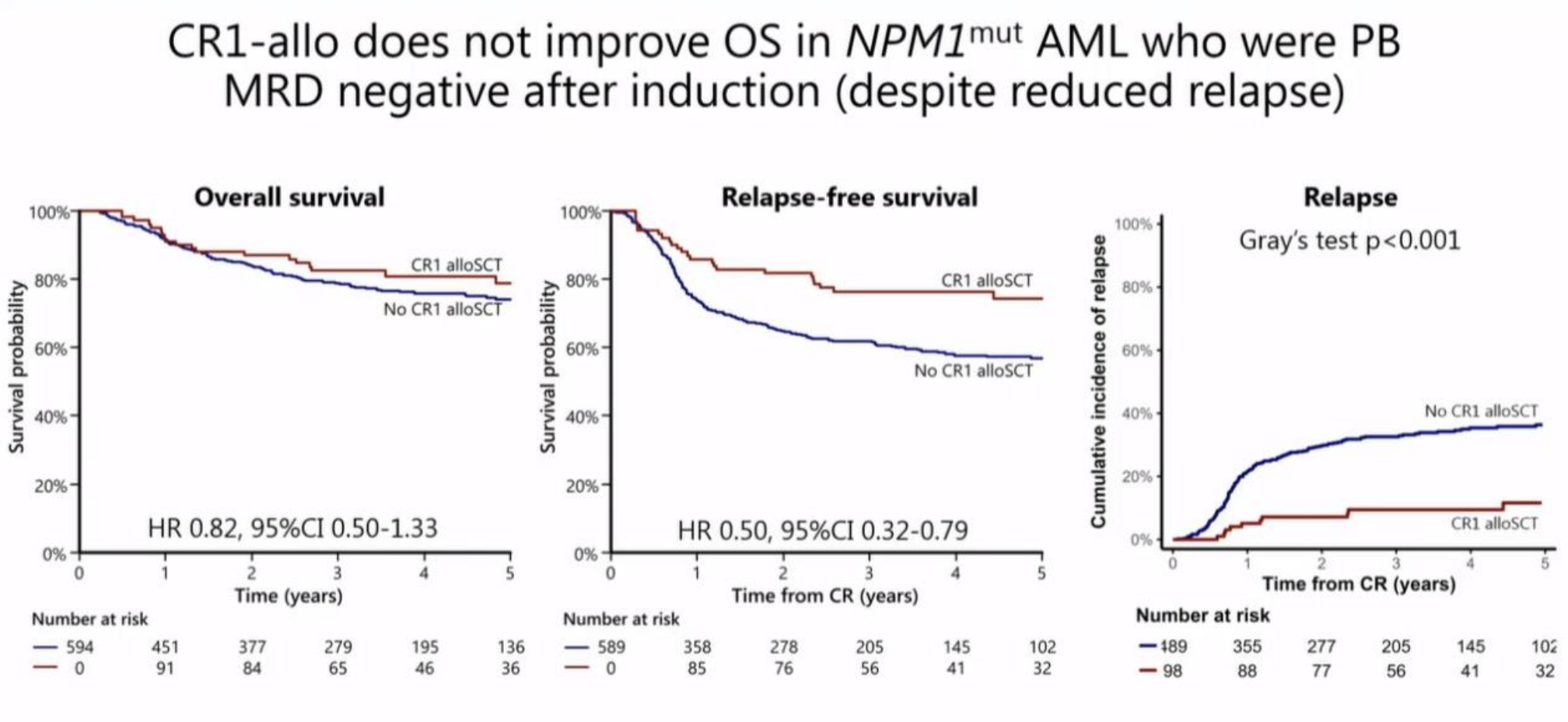
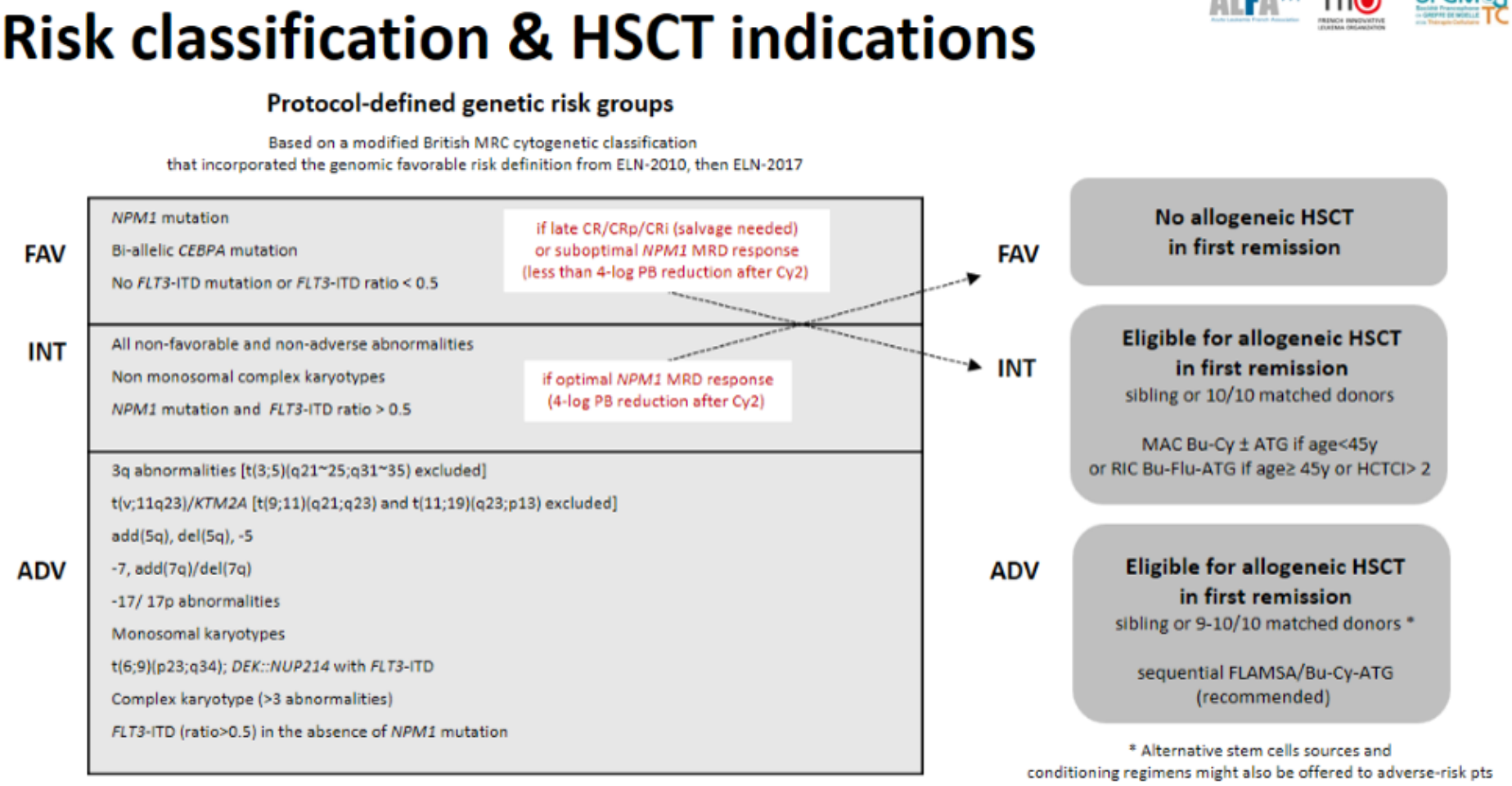



Othman J, ASH 2023

# Traitement guidé par la MRD : Recommandations BIG-1

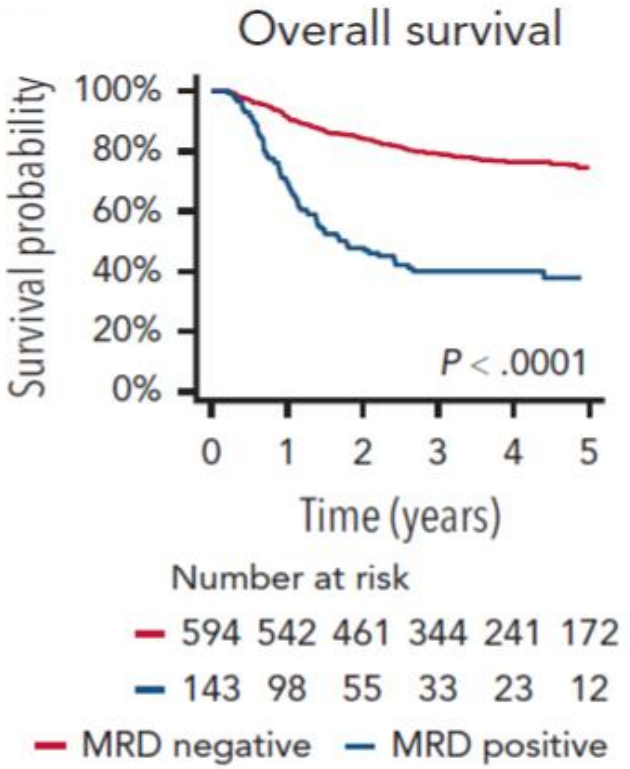


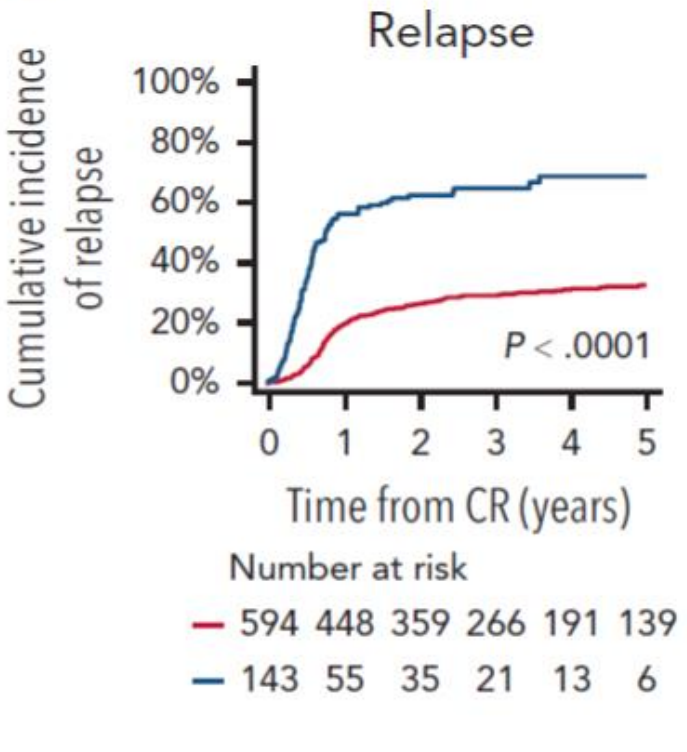

Hunault M, ASH 2023

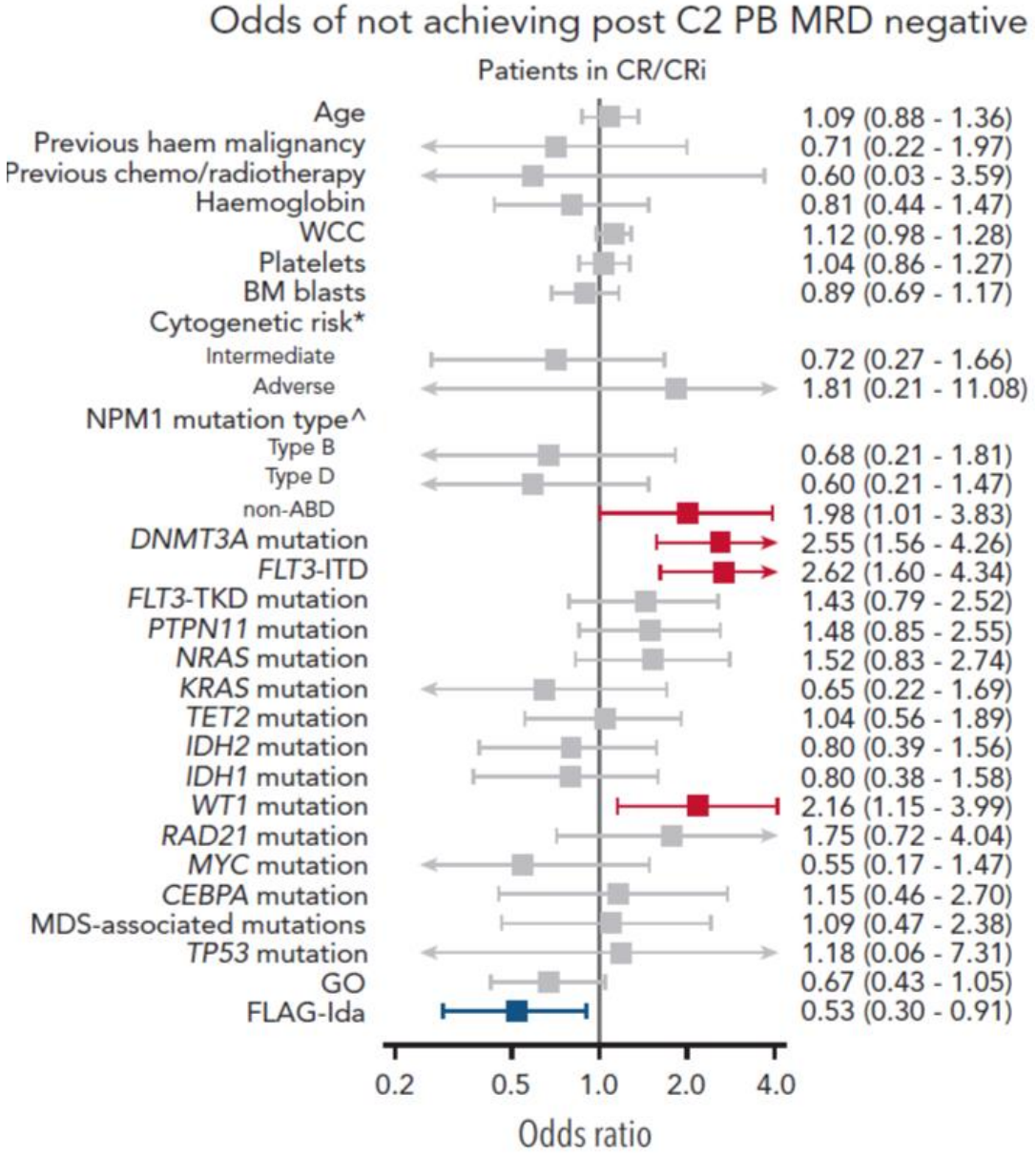
# Molecular, clinical, and therapeutic determinants of outcome in *NPM1*-mutated AML

Jad Othman,[1-3] Nicola Potter,[1] Adam Ivey,[4] Yanis Tazi,[5] Elli Papaemmanuil,[5] Jelena Jovanovic,[1] Sylvie D. Freeman,[6] Amanda Gilkes,[7] Rosemary Gale,[8] Tanya Rapoz-D'Silva,[8] Manohursingh Runglall,[1,2] Michelle Kleeman,[9] Pawan Dhami,[9] Ian Thomas,[10] Sean Johnson,[10] Joanna Canham,[10] Jamie Cavenagh,[11] Panagiotis Kottaridis,[12] Claire Arnold,[13] Hans Beier Ommen,[14] Ulrik Malthe Overgaard,[15] Mike Dennis,[16] Alan Burnett,[17] Charlotte Wilhelm-Benartzi,[10] Brian Huntly,[18] Nigel H. Russell,[2] and Richard Dillon[1,2]

Essais AML17 et AML19, n = 1357 LAM *NPM1*




Othman J, Blood 2024

CLINICAL TRIALS AND OBSERVATIONS

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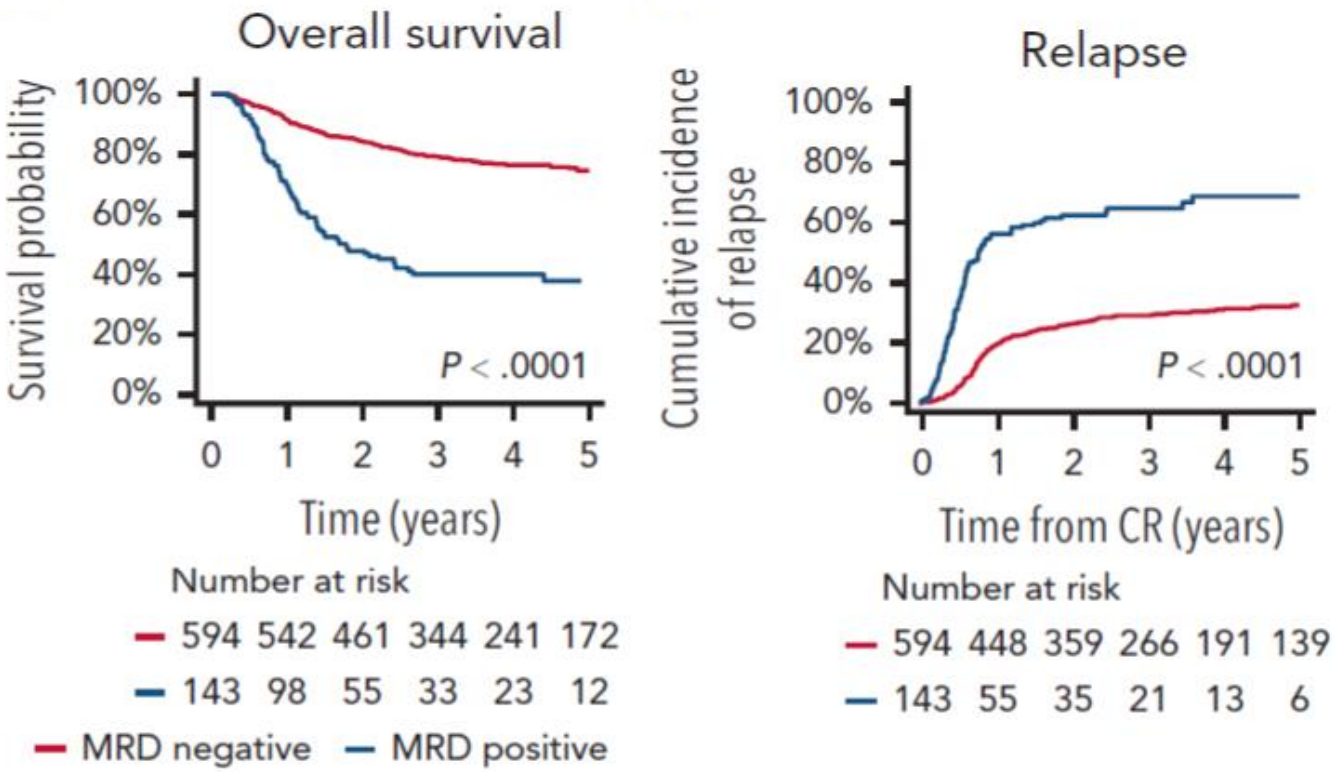
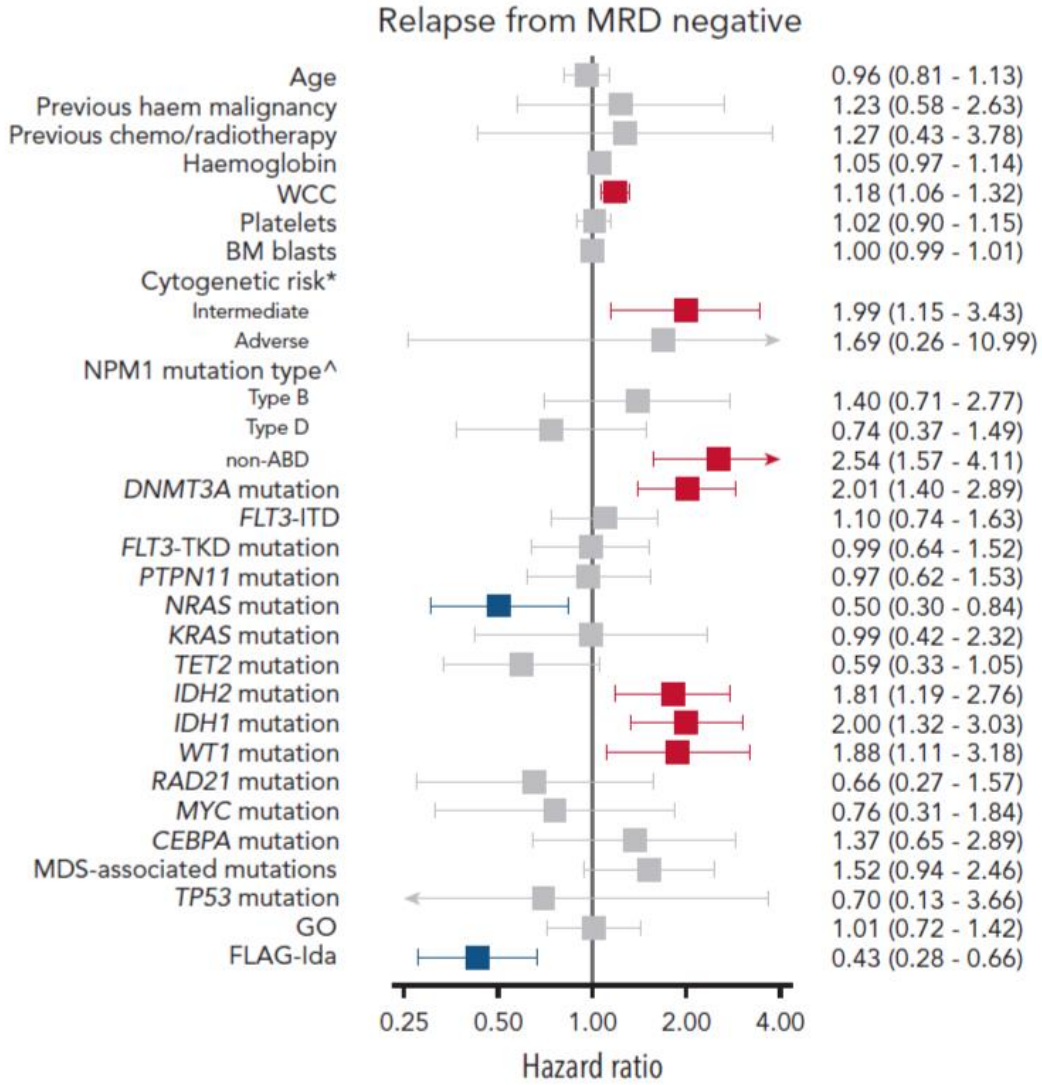
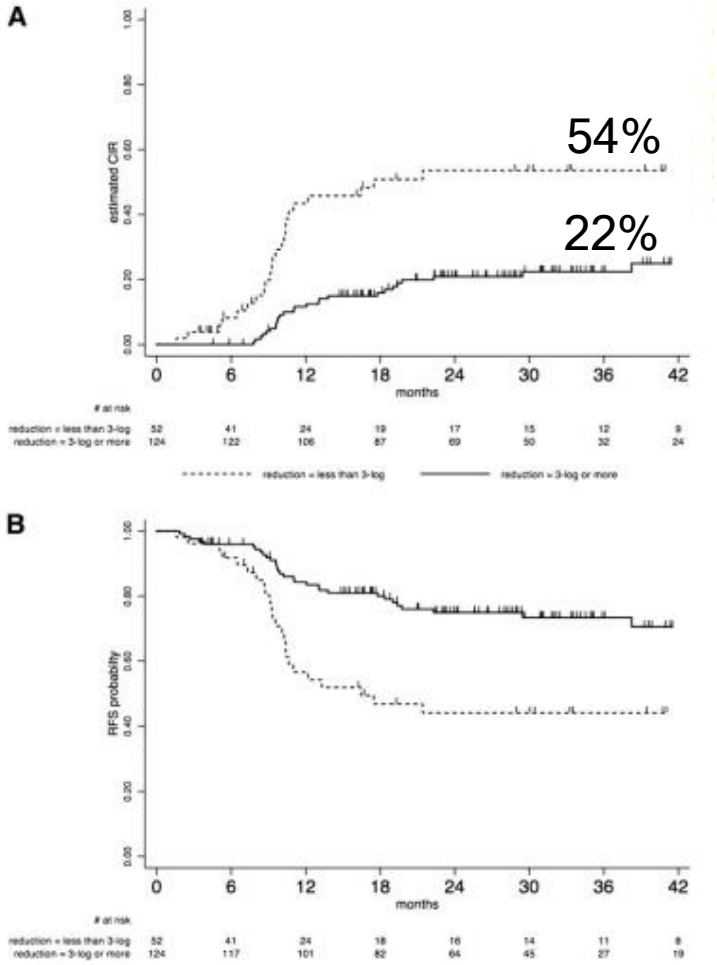


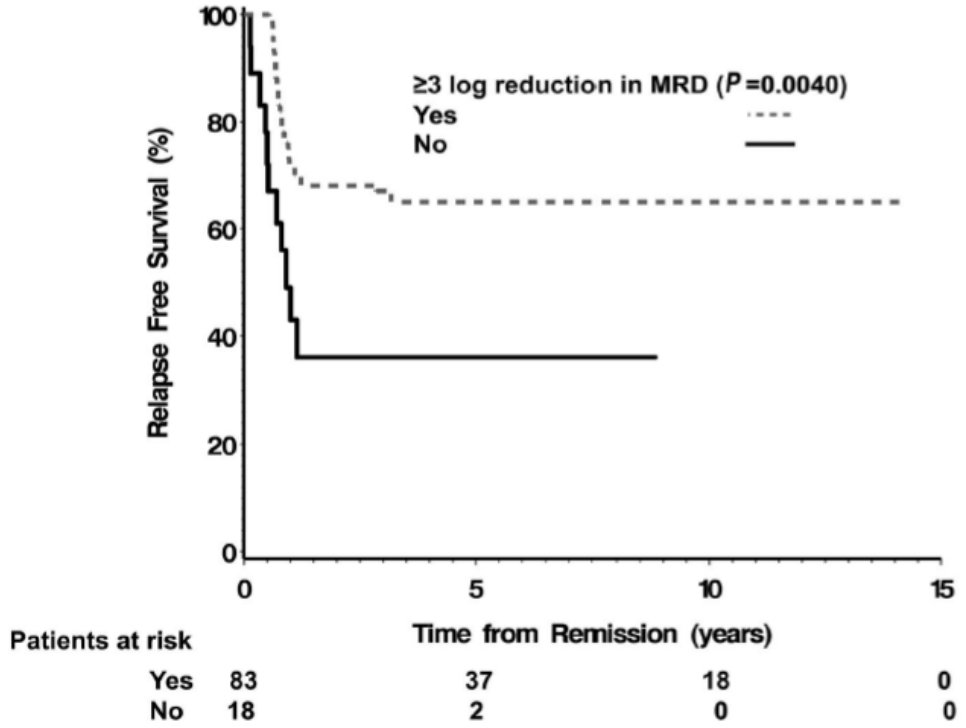




Othman J, Blood 2024

# LAM CBF : Traitement guidé par la MRD




3-log MRD2 reduction




Jourdan E, Blood 2013

Puckrin R, Haematologica 2020

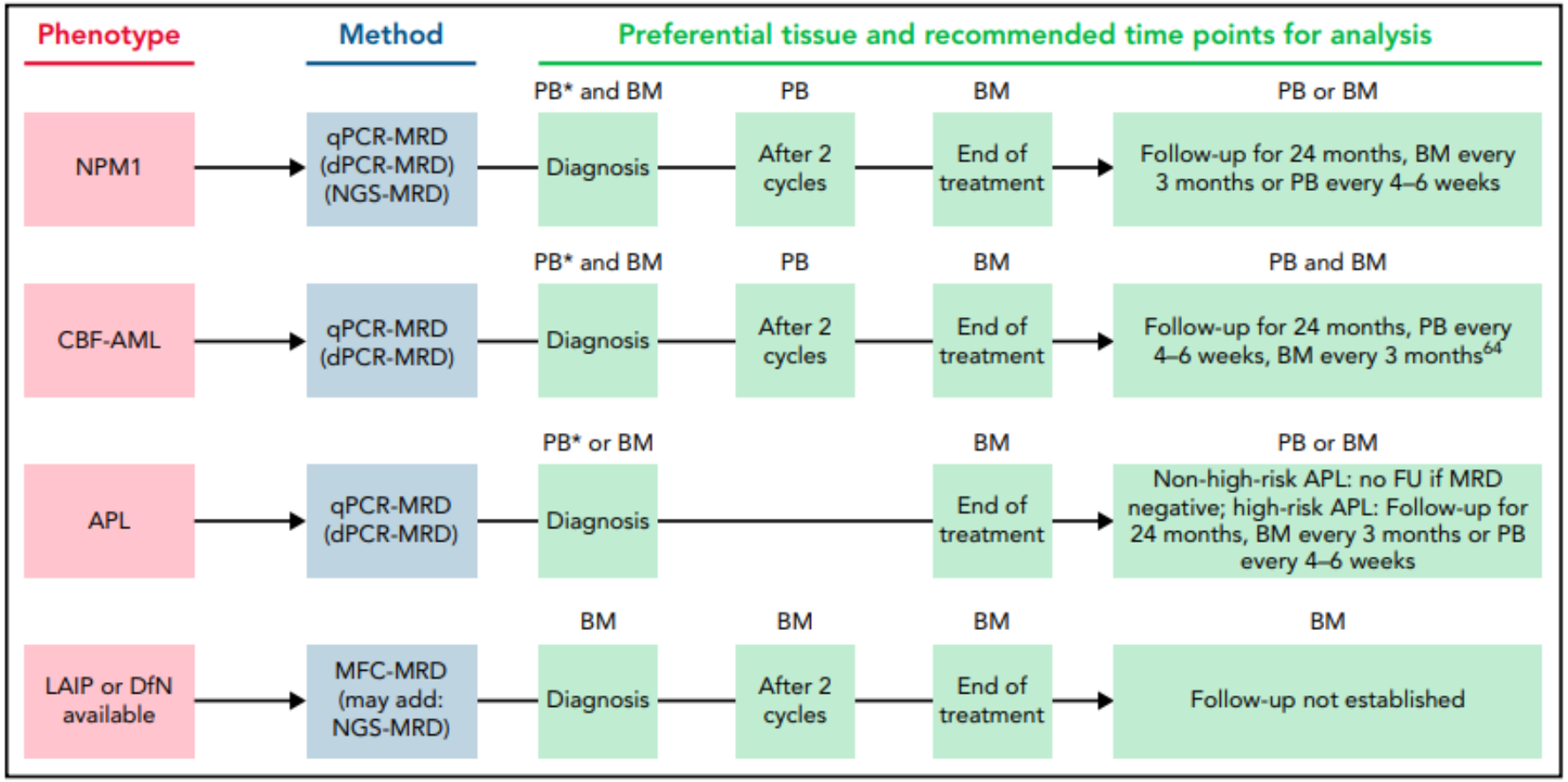
# Monitoring de la MRD : Recommandations ELN 2022

## Rôles du monitoring de la MRD :

- Fournir une **méthodologie quantitative** pour établir un statut de rémission plus profond
- **Affiner l'évaluation du risque de rechute post-rémission**
- **Identifier la rechute imminente pour permettre une intervention précoce**
- **Surrogate endpoint** pour accélérer le développement et l'enregistrement de médicaments

Döhner H, Blood 2022

# Suivi de la MRD : Recommandations de l'ELN MRD Working Party




Heuser M, Blood 2021

# Définition de la rechute moléculaire

Une notion récente : apparue dans les recommandations ELN 2017 puis plus clairement dans les recommandations de l'ELN 2022

**CR, CRh, or CRi with MRD relapse** For patients initially achieving CR, CRh, or CRi without MRD, the term CR, CRh, or CRi with MRD relapse may be applied if there is evidence of MRD relapse as defined by ELN criteria (Table 8).[67]

| Category | Definition | Comment |
|---|---|---|
| **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<br>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<br><br>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) |

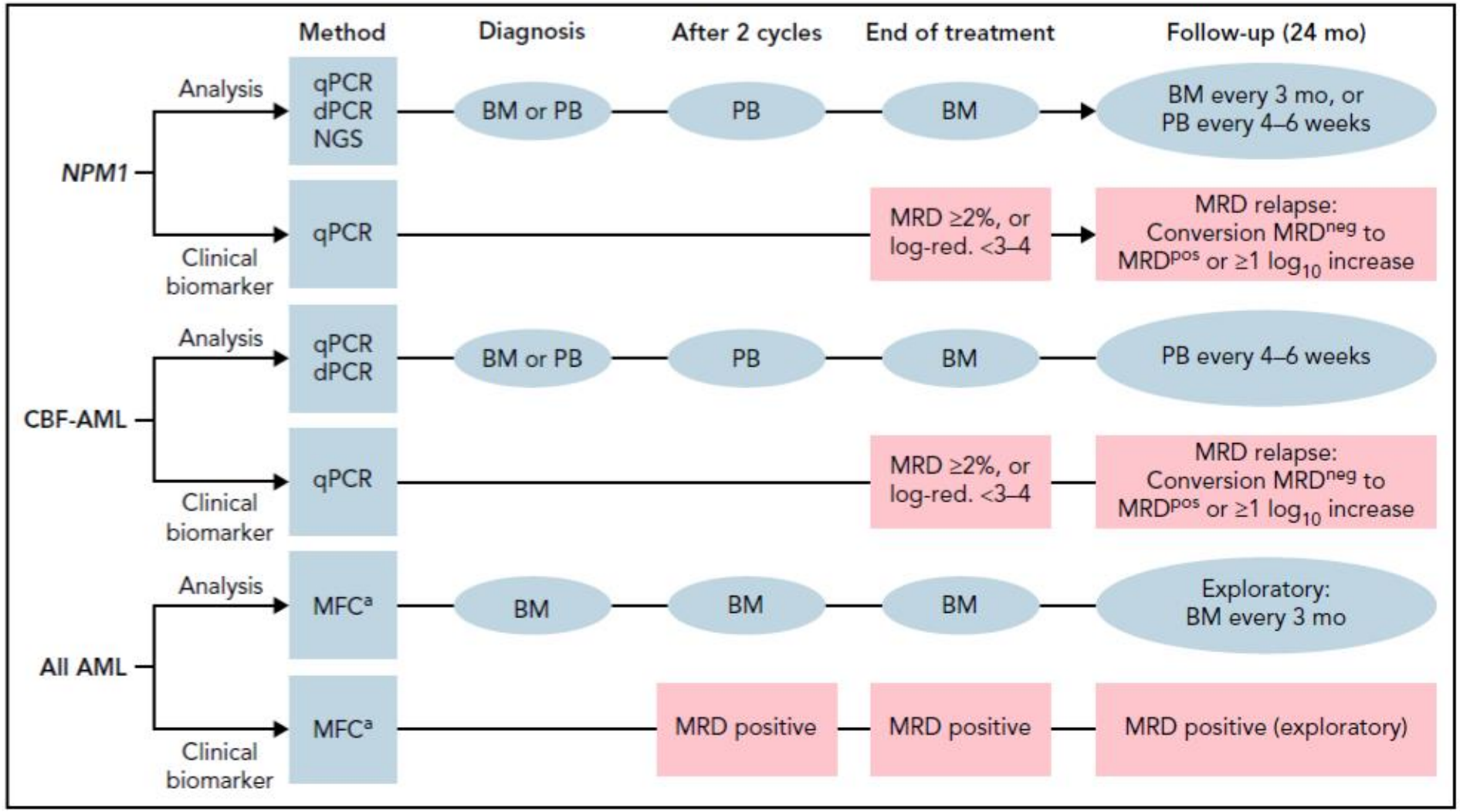
Döhner H, Blood 2022

# Définition de la rechute moléculaire ; et autres endpoints

| | |
|---|---|
| **If including assessment of MRD relapse** | |
| $EFS_{MRD†}$ | Measured from day 1 of randomization or day 1 of registration in non-randomized trials to the date of failure to achieve CR, CRh or CRi by a defined landmark (eg, after two cycles of intensive chemotherapy or 180 d for non-intensive therapy), hematologic relapse, MRD relapse (for patients achieving CR, CRh or CRi without MRD) or death from any cause |
| $RFS_{MRD†}$ | Measured from the date of achievement of a remission (CR, CRh, or CRi) until the date of hematologic relapse, MRD relapse, or death from any cause |
| $CIR_{MRD†}$ | Measured from the date of achievement of a remission (CR, CRh or CRi) until the date of hematologic relapse, or molecular MRD relapse; patients who died without relapse are counted as a competing cause of failure |
| $CID_{MRD}$ | Measured from the date of achievement of a remission (CR, CRh, or CRi) to death without prior relapse; morphologic or molecular MRD relapse is considered as competing risk |

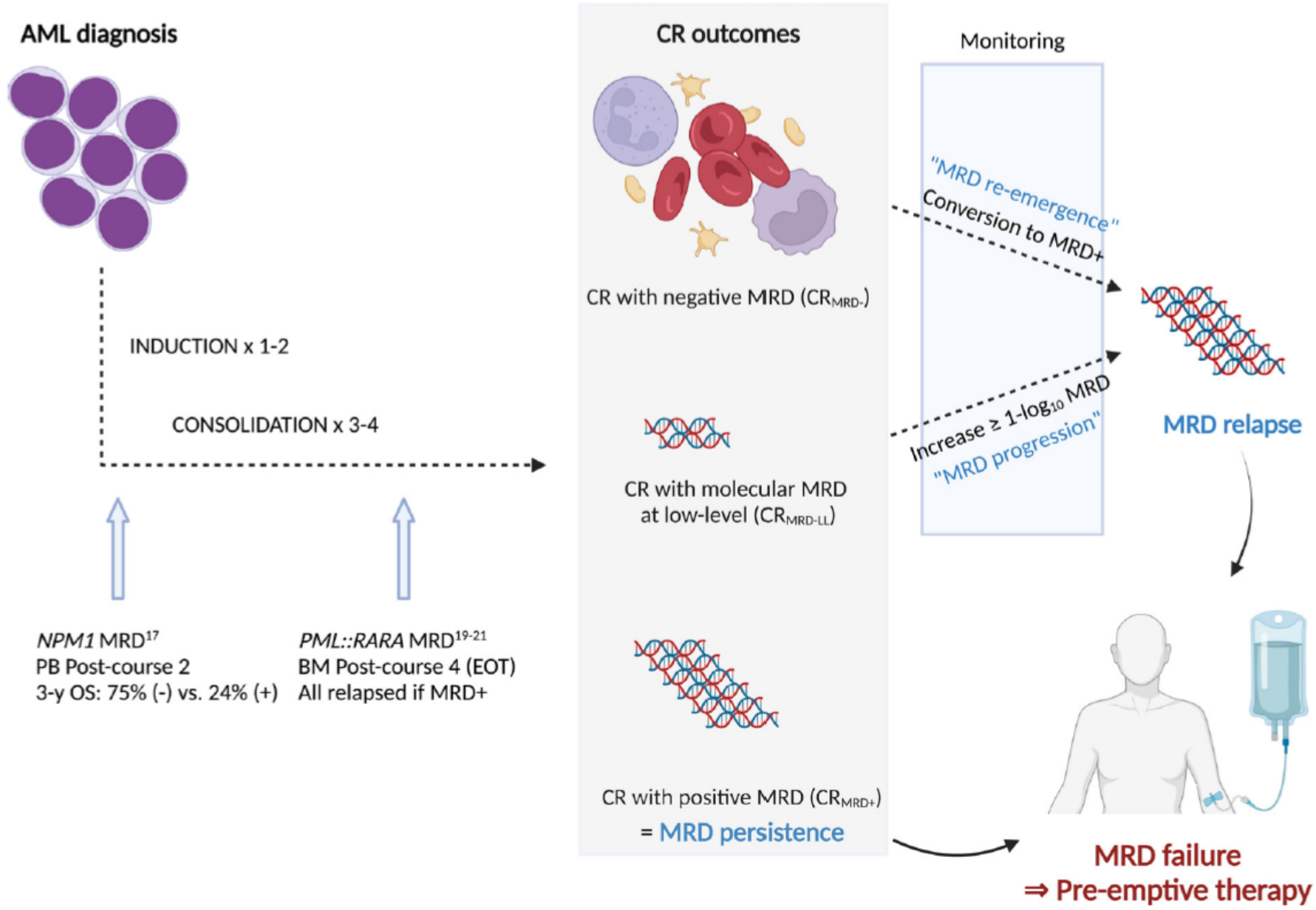
Döhner H, Blood 2022

# Définition de la rechute moléculaire ; et de l'échec moléculaire




Döhner H, Blood 2022

*Timepoints for treatment modification based on a clinical relevant biomarker




Tedjaseputra A, Clin Lymph Myel Leuk 2024

# Rechutes moléculaires

LAM CBF ou *NPM1*m, 2010-2019

RC1 après chimio intensive, sans allogreffe

Au moins un suivi MRD après la 1ere ligne

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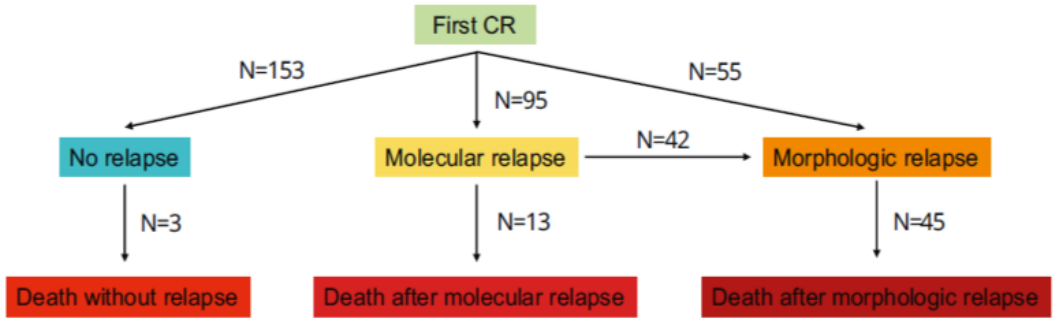
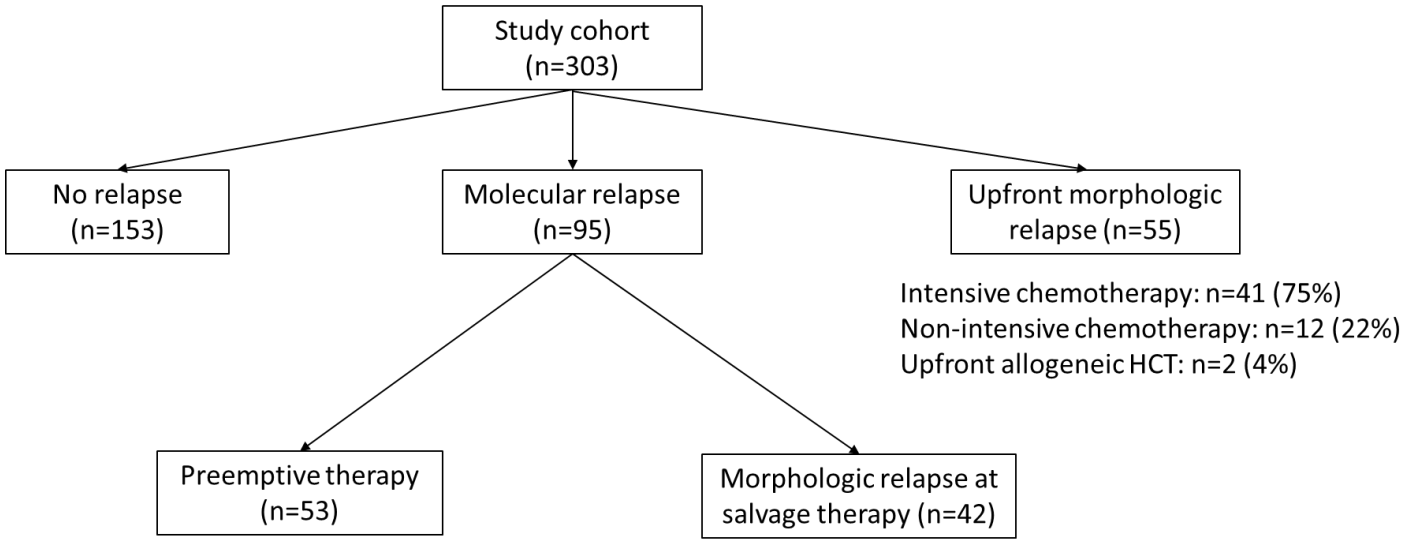
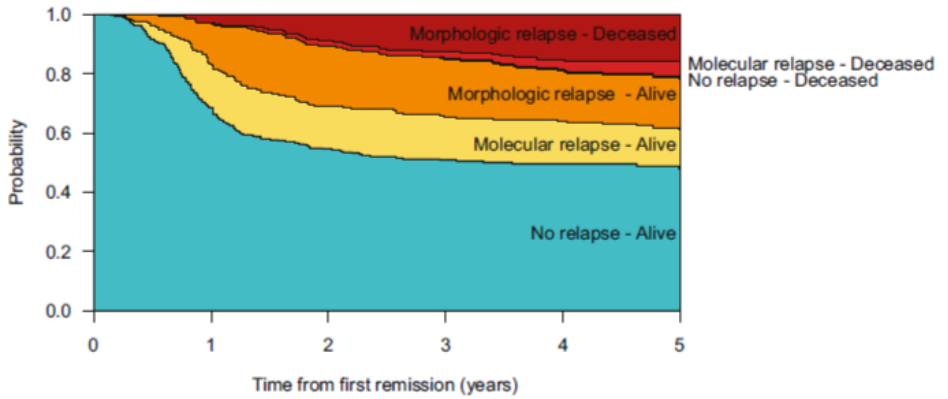



| Total : 303 | Molecular relapse | Morphologic relapse | Death without relapse | Death after molecular relapse | Death after morphologic relapse | No event |
|---|---|---|---|---|---|---|
| Diagnosis | 95 | 55 | 3 | 0 | 0 | 150 |
| Molecular relapse | 0 | 42 | 0 | 13 | 0 | 40 |
| Morphologic relapse | 0 | 0 | 0 | 0 | 45 | 52 |




Orvain C et al., Leukemia 2024

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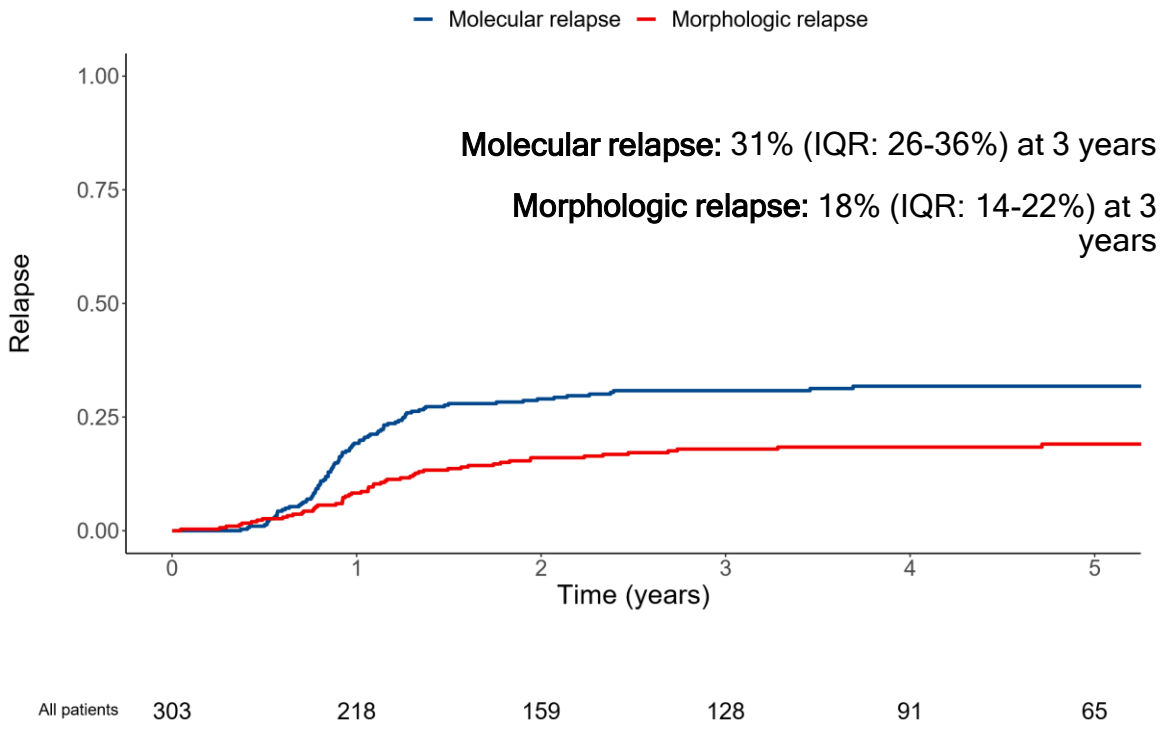
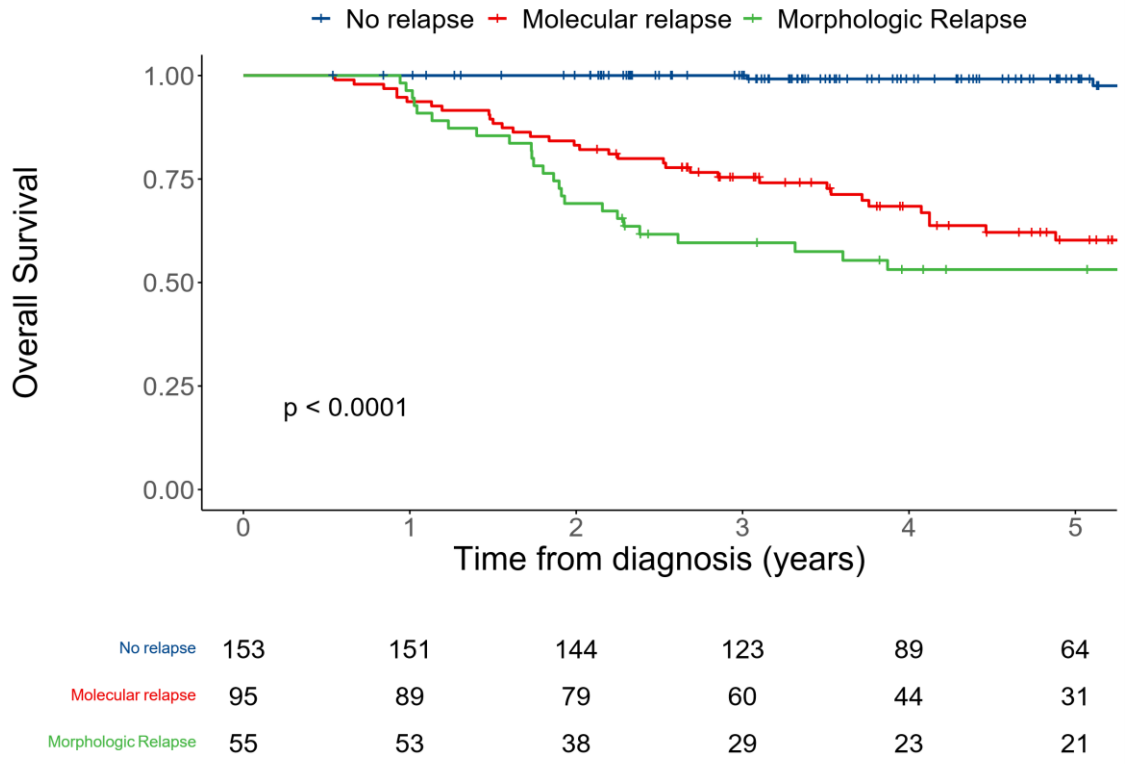



**Molecular relapse:** 31% (IQR: 26-36%) at 3 years

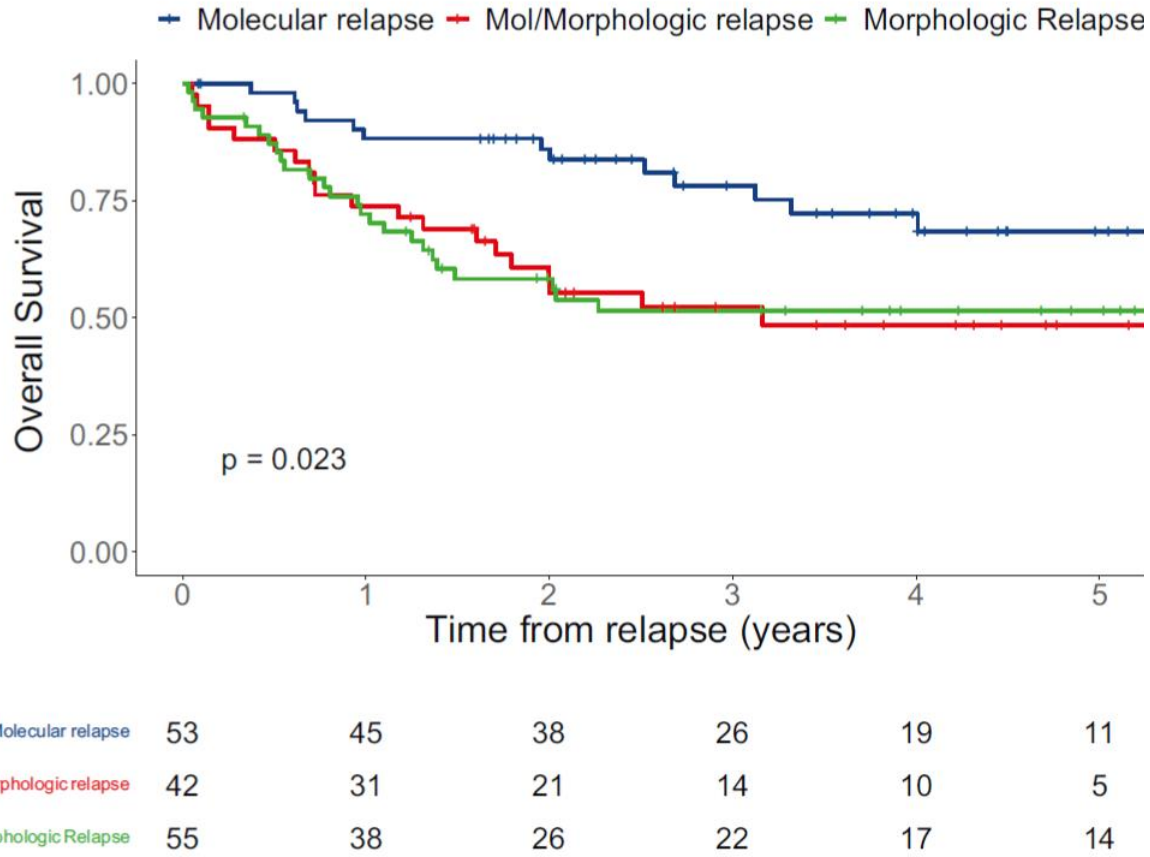
**Morphologic relapse:** 18% (IQR: 14-22%) at 3 years

3-year OS:
- No relapse: 100%
- Molecular relapse: 75%
- Upfront morphologic relapse: 60%

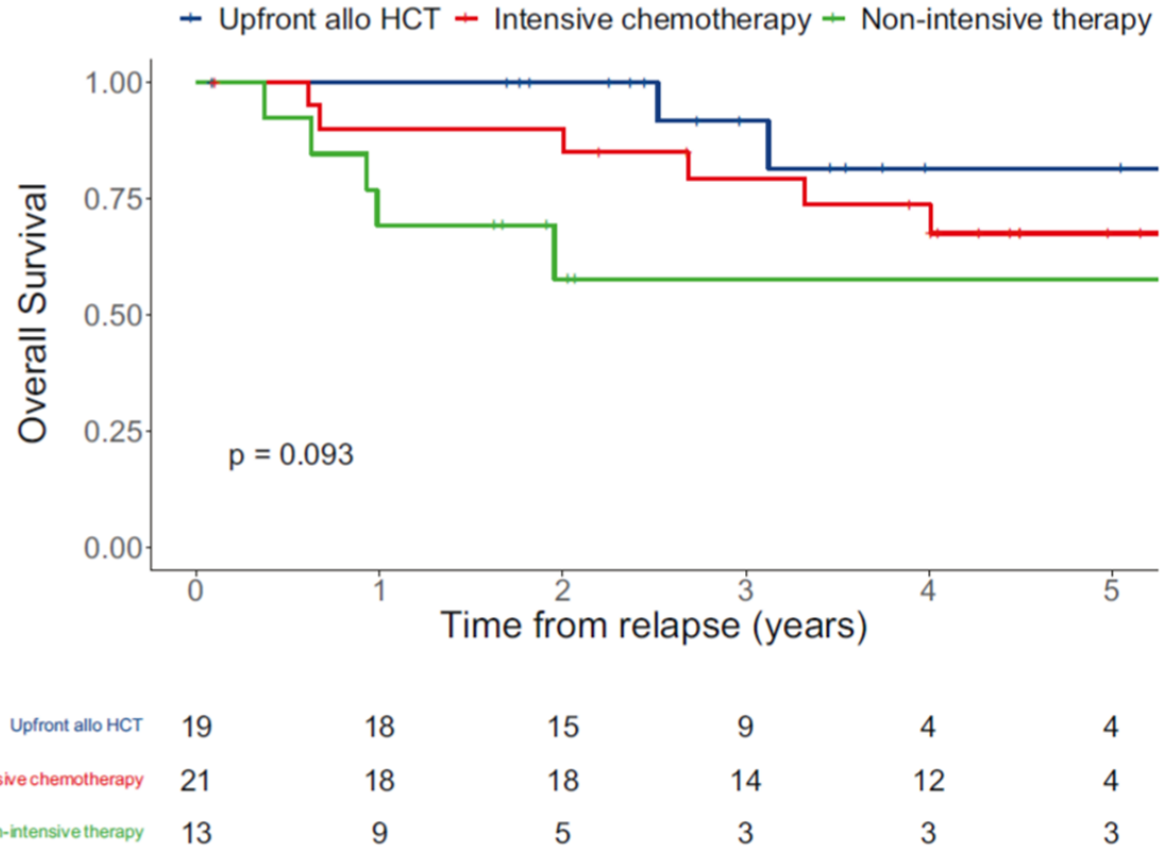



Orvain C et al., Leukemia 2024

# Rechutes moléculaires




| | | | | | | |
|---|---|---|---|---|---|---|
| Molecular relapse | 53 | 45 | 38 | 26 | 19 | 11 |
| Mol/Morphologic relapse | 42 | 31 | 21 | 14 | 10 | 5 |
| Morphologic Relapse | 55 | 38 | 26 | 22 | 17 | 14 |




| | | | | | | |
|---|---|---|---|---|---|---|
| Upfront allo HCT | 19 | 18 | 15 | 9 | 4 | 4 |
| Intensive chemotherapy | 21 | 18 | 18 | 14 | 12 | 4 |
| Non-intensive therapy | 13 | 9 | 5 | 3 | 3 | 3 |

Les patients ayant reçu un **traitement pré-emptif** avaient une TRM significativement diminuée par rapport aux patients traités pour une rechute morphologique

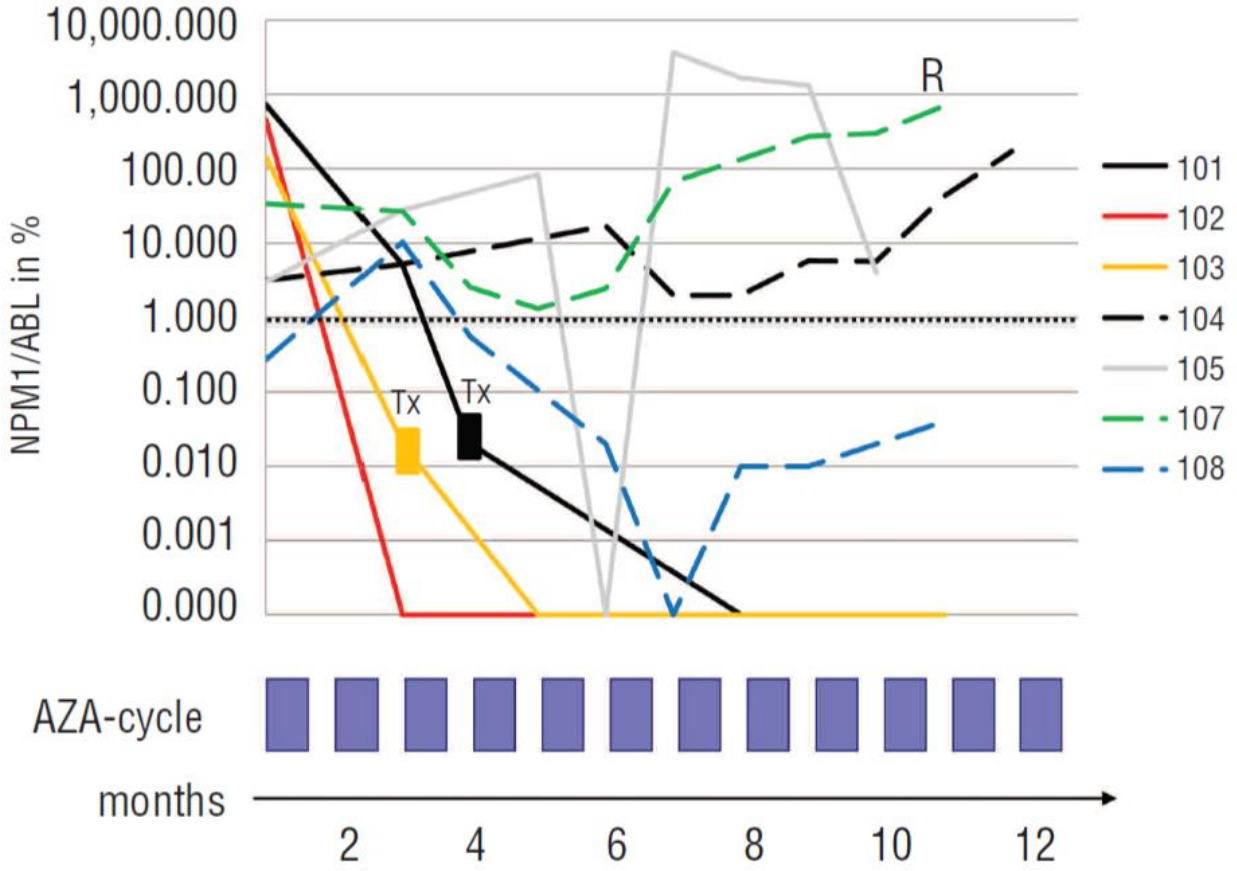
Orvain C et al., Leukemia 2024

# Traitement pré-emptif non intensif Azacitidine pour les échecs moléculaires

N=10 LAM *NPM1*
Caryotype normal, *FLT3*-ITD (N=3)
RC1 ou RC2 après chimiothérapie intensive +/- allo
3 MRD persistantes / 7 rechutes moléculaires

Médiane 5 cycles (2-12)
Neutropénie gr 3/4 : 80%
Thrombopénie gr 3/4 : 40%

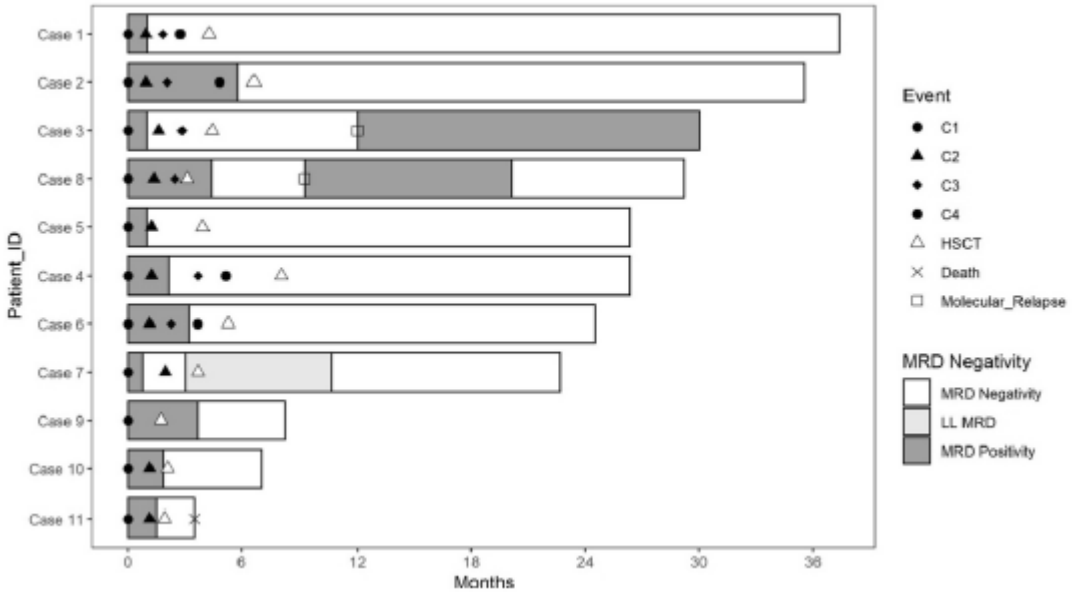
Réponse moléculaire (diminution ≥ 1 Log) : 70%
Réponse après 3-5 cycles
Réponses temporaires
Follow-up 10 mois : 3 rechutes hématologiques




Sockel K, Haematologica 2011

# Azacitidine + Venetoc pour les échecs moléc

- Molecular failure
- Analyse rétrospective de 11 patients *NPM1* MRD-positive
  - 9 rechutes moléculaires
  - 2 RC MRDpos (MRD persistence)
- Nombre médian de 2 cycles (1-4)
- RC MRDneg : 9/11 (81,8%)
- 11/11 AlloHSCT
- Avec un FU de 26 mois :
  - 10/11 patients en vie (91%) (1 NRM)
  - 9/10 RC MRDneg



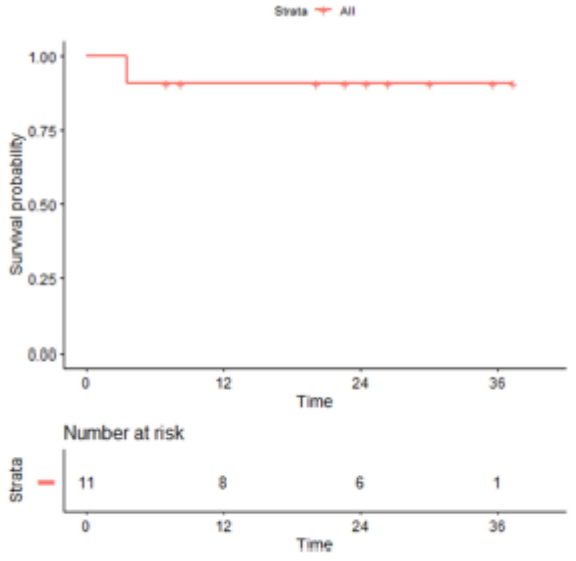




FIGURE 2 Overall survival.

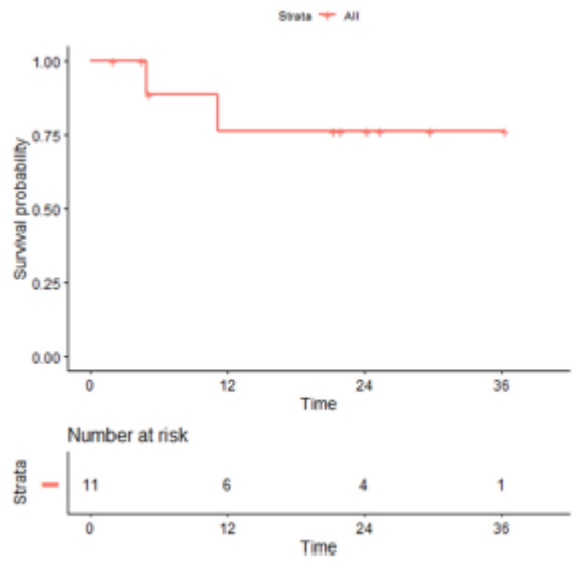
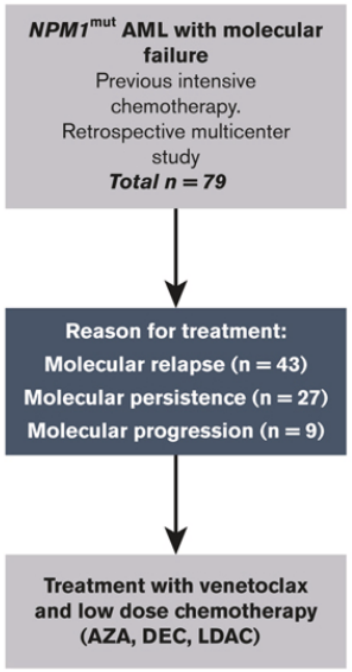


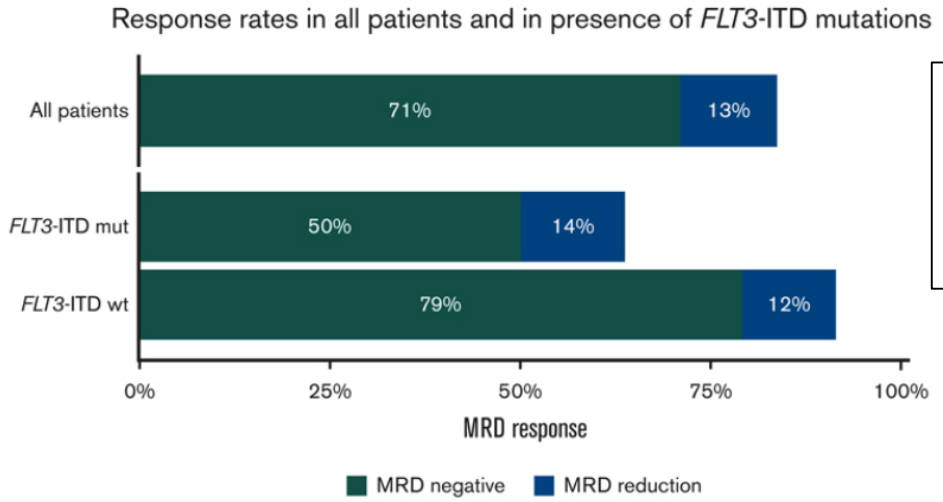

FIGURE 3 Molecular relapse free survival.

Sartor C, BJH 2023

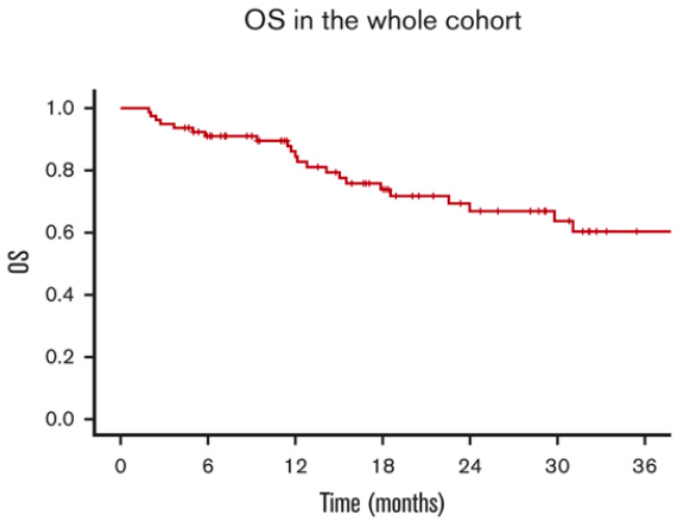
# Venetoclax + chimiothérapie non intensive pour les échecs moléculaires

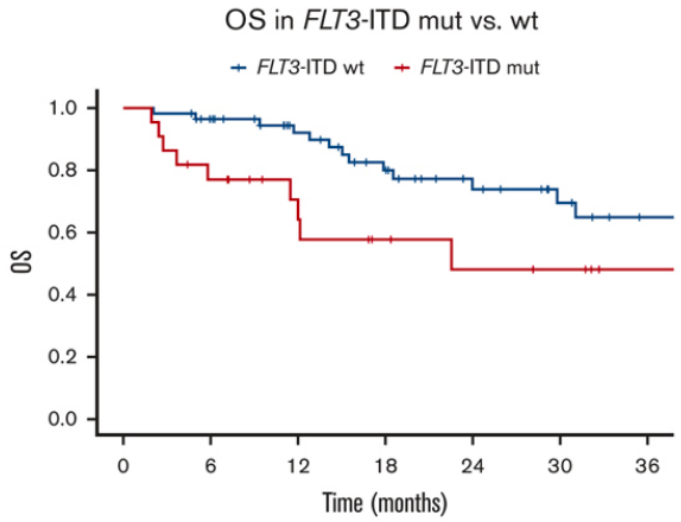



Azacitidine, N=44 (56%)
LDAC, N=34 (43%)
Decitabine, N=1
Médiane 3 cycles (1-




**Réponse moléculaire (réduction ≥1 log) : 84%**
**MRD négative : 71%**
Réponse 64% si *FLT3*-ITD vs. 91% si WT
23% d'hospitalisations, pas de décès toxique



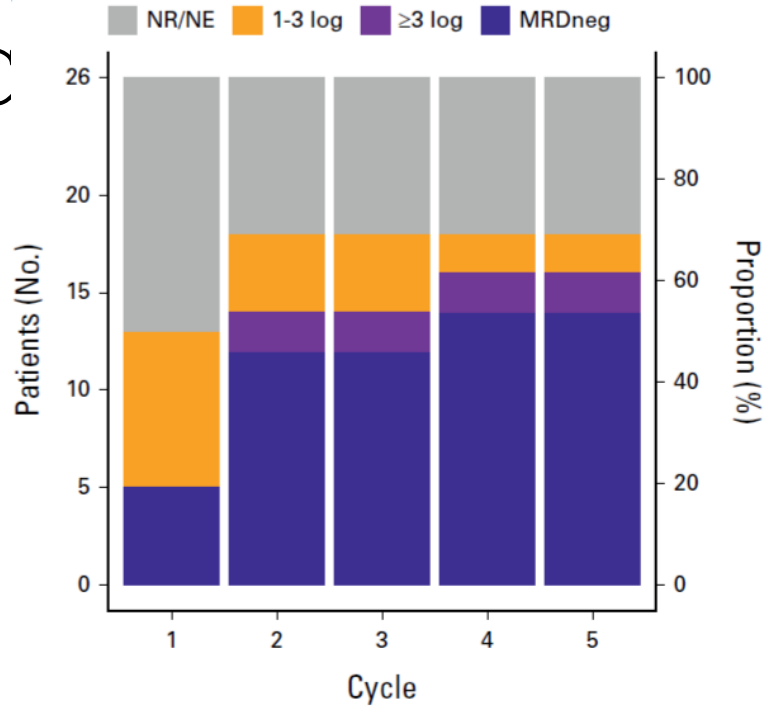

**<u>Cohorte entière</u>** :
OS à 2 ans = 67%
EFS à 2 ans = 45%

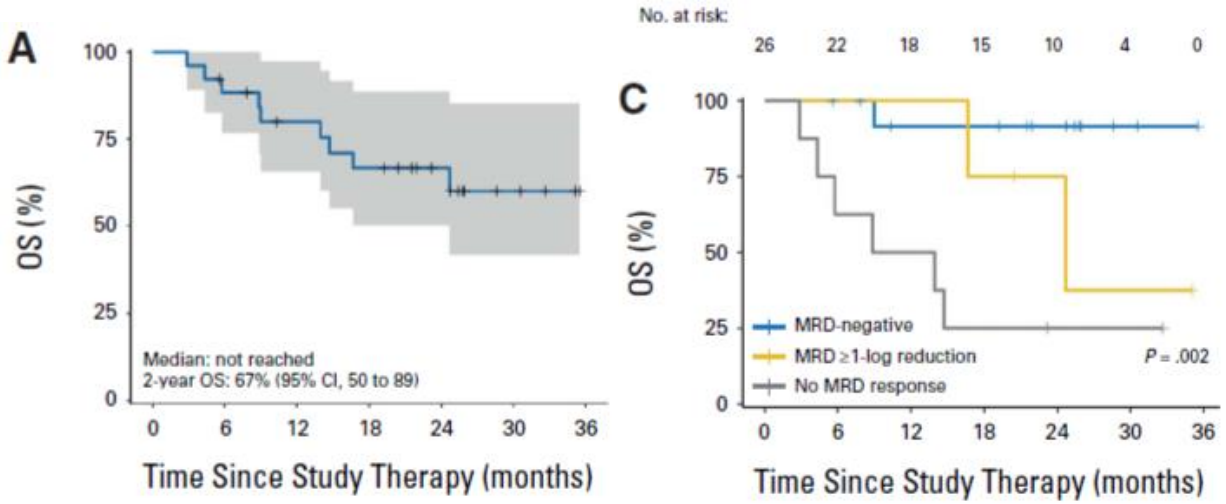
-Bridge to alloHSCT : N=41
-Sans alloHSCT : N=38
18 MRD-, 10 mois ttt en méd,
EFS à 2 ans = 67%,
$RFS_{MRD}$ à 2 ans de la fin du ttt : 62%

Jimenez-Chillon C, Blood Adv 2024

# Venetoclax + LDAC (VALDAC) Phase 2 prospective

- Rechute moléculaire ou oligoblastique (5-15% blastes) après chimio intensive (94%)
- LDAC 10 jours, Venetoclax 600 mg/jr
- 26 rechutes moléculaires
  - 77% NPM1, 8% CBF, 4% MLL
  - Médiane 4 cycles (17% ≥12 cycles)
  - Toxicité inférieure à cohorte oligoblastique
    - Anémie grade ≥3 : 4% (vs. 32%)
    - Infections 8% (vs. 36%)
    - Neutropénie grade 4 : 23% (vs. 32%)
    - Thrombopénie grade 4 : 15% (vs. 27%)
- Au cycle 2 :
  - Réponse ≥ 1 log : 69%
  - MRD négative : 46%
- OS à 2 ans : 67% ; OS médiane non atteinte
- $EFS_{MRD}$ à 2 ans : 53%



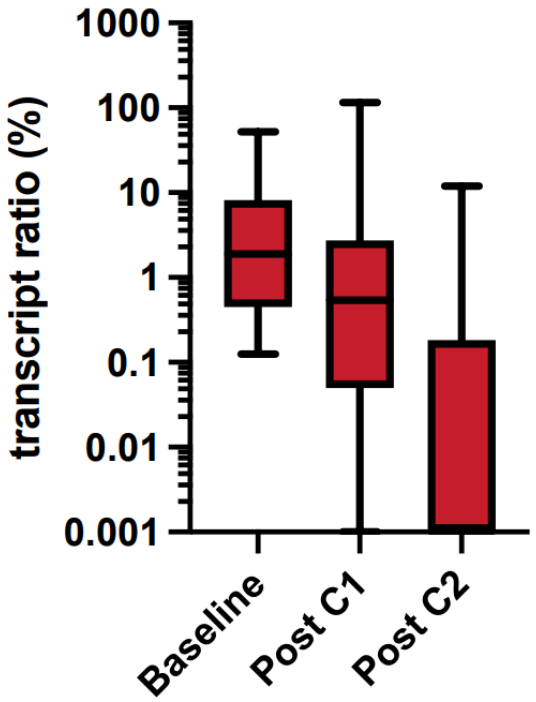

Tiong IS, JCO 2024

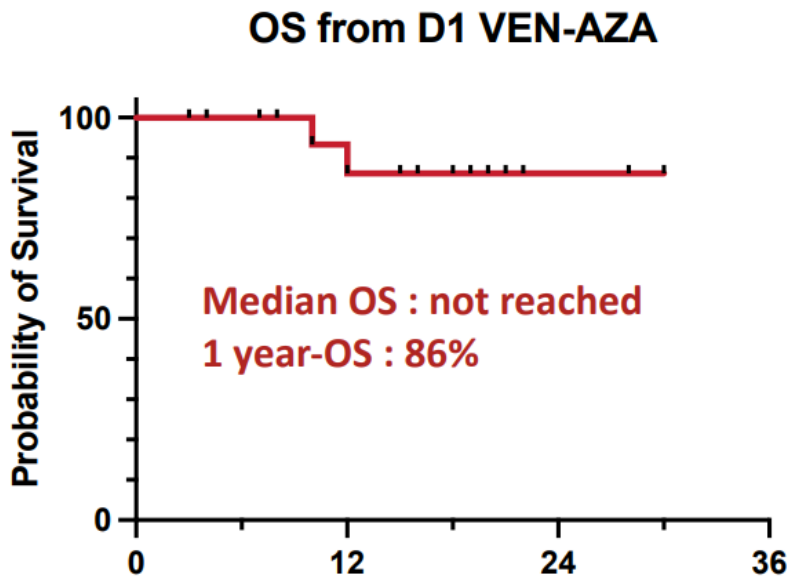
# Azacitidine-Venetoclax pour les rechu moléculaires

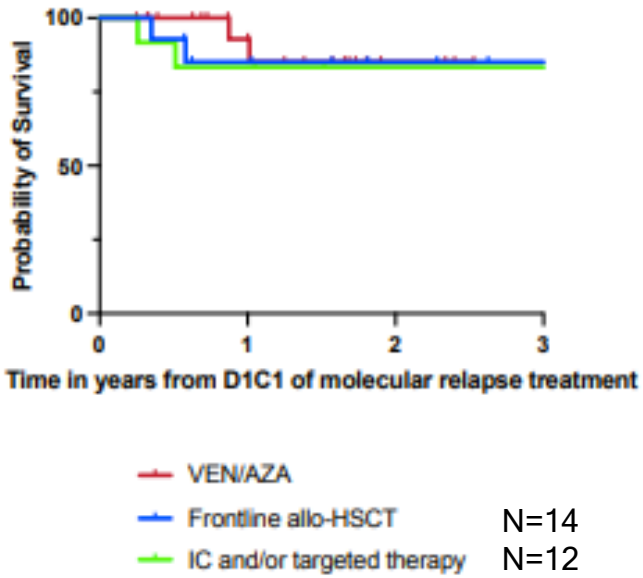
| | N = 22 |
|---|---|
| Median age (y) | 55 (27-71) |
| Sex M/F | 8 (36%) / 14 (64%) |
| LAM de novo | 21 (95%) |
| WBC at diagnosis (G/L) | 68 (2.3-339) |
| *NPM1 mutations* | 20 (90%) |
| *CBFB::MYH11* | 2 (10%) |
| FLT3 mutations<br>*ITD*<br>*TKD* | 13<br>9<br>4 |
| DNMT3A | 9 |
| Others mutations° | 15 |
| Cytogenetic risk<br>*Favorable*<br>*Intermediate* | <br>2<br>20 |
| 2022 ELN risk classification<br>*Favorable*<br>*Intermediate* | <br>9<br>11 |
| Induction chemo "3+7" | 22 (100%) |
| Post remission therapy with 3 cycles of IDAC/HDAC | 20 (90%)* |
| Negative MRD or LL-MRD in BM$ after consolidation | 19 (86%) |
| Median time between CR1 and molecular failure (months) | 9.5 (1-50) |
| Median time between molecular relapse and d1C1 VEN/AZA | 51 |

N=22
Rechutes moléculaires après chimio intensive, pas d'alloHSCT en RC1
90% LAM *NPM1*m
Après 2 cycles : 10 MRD négatives, 11 MRD low level (<2%)

20 alloHSCT : 1 progression moléculaire ; tous en RC morphologique




Higué J, ASH 2023

# Azacitidine-Venetoclax pour les rechutes moléculaires

## Abstract ASH 2024

FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

- 72 patients de 10 centres FILO (2019-2024)
- LAM *NPM1*m (N=68) ou CBF (N=4), au moins 1 cycle d'AZA-Ven pour une rechute moléculaire selon les critères ELN après chimio intensive

- Après 2 cycles : 49% MRD négative et 33% MRD low-level (<2%)
- 73% allogreffe

- Follow-up : 20 mois
- Survie globale à 1 an : 82%

- Chez les patients allogreffés : survie globale à 1 an : 84% ; MRD négative ou low-level : 91%

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# Azacitidine-Venetoclax pour les rechutes moléculaires

**Phase 2 italienne non randomisée** (NCT04867928) :

- LAM *NPM1* en rechute moléculaire ou progression moléculaire
- AZA-VEN (400 mg/jr 28 jours) comme bridge to transplant
- MRD évaluée après chaque cycle
- AlloHSCT dès que MRD négative ou après 6 cycles quelle que soit la MRD

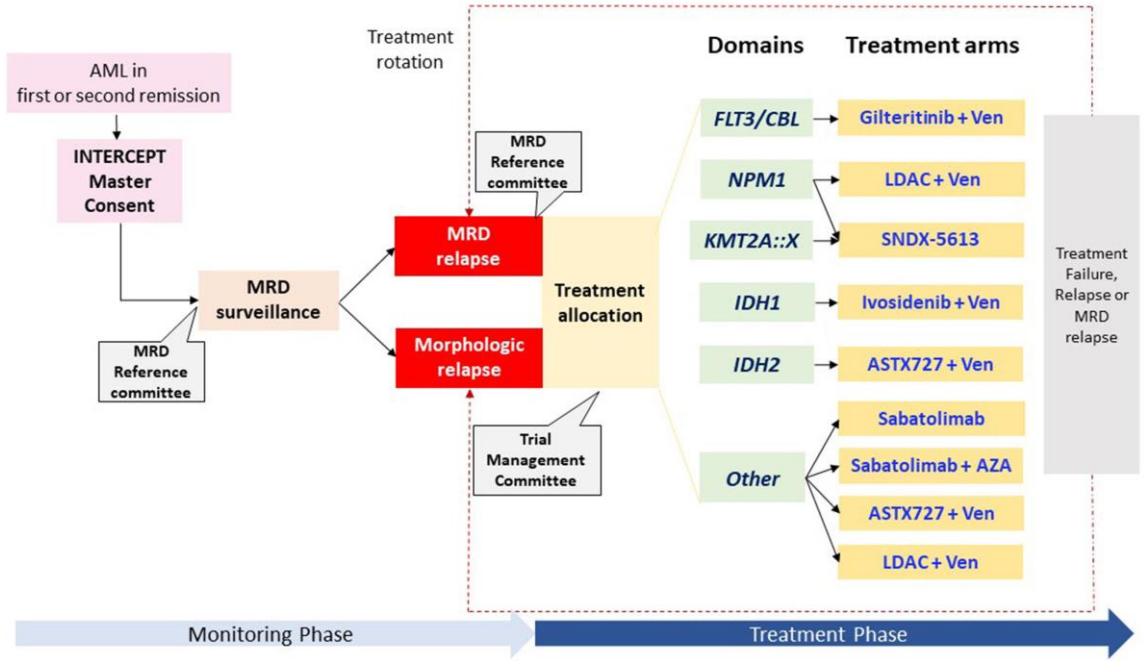
# Autres pistes

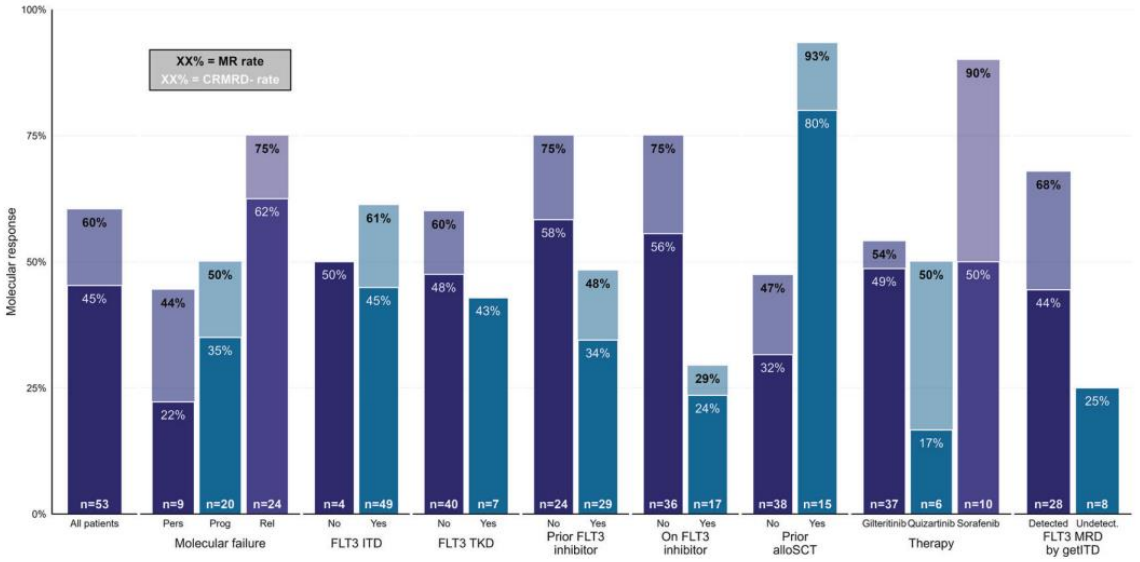
- **iMenin/MLL :**
  - Bleximenib : ALE-1001
  - Revumenib + Venetoclax (NCT06284486 ; MD Anderson, recrutement non débuté)

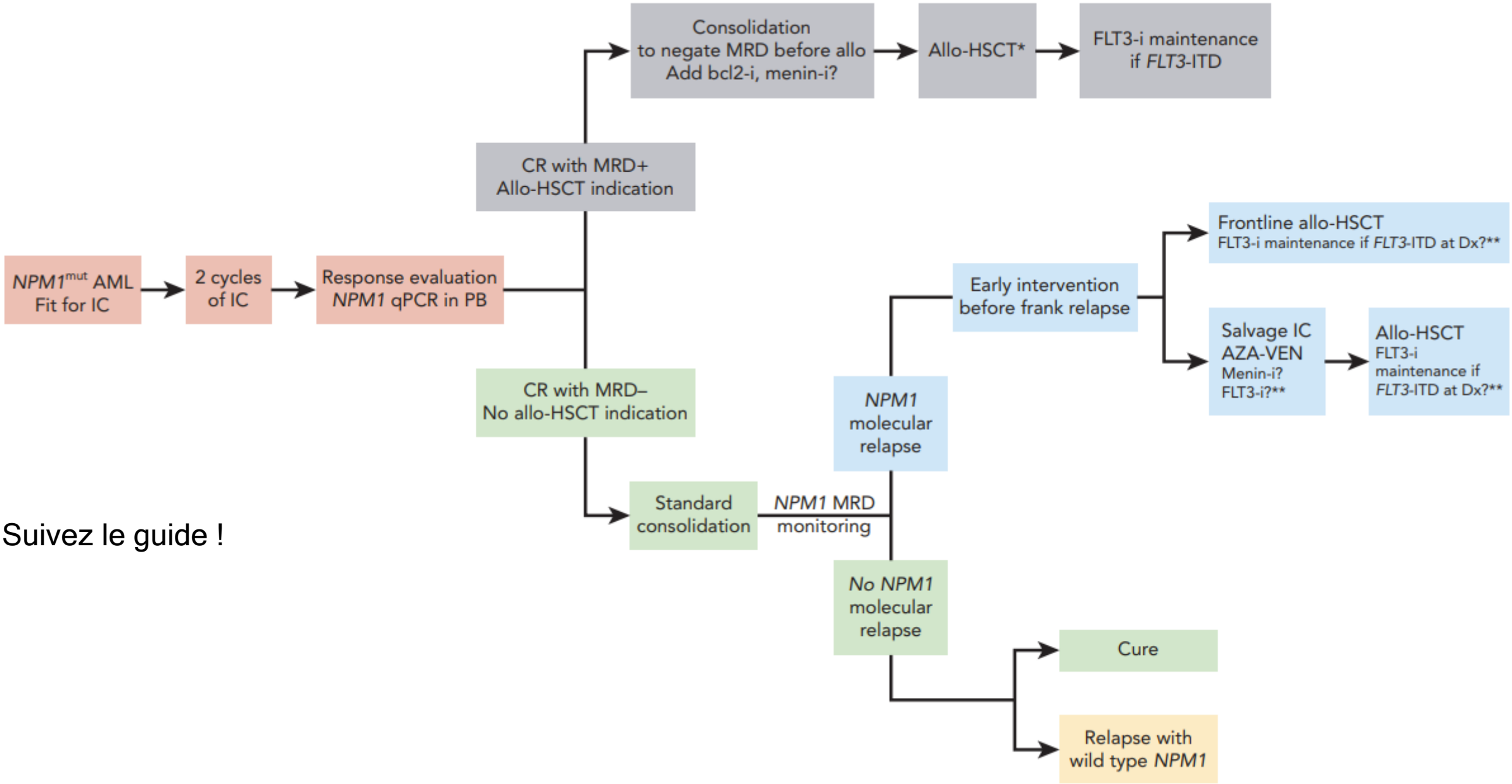
- **Essais en cours** :
  - AMLM26 INTERCEPT (ALLG)
  - MyeloMATCH : umbrella trial (NCCI)
    - ERASE : Persistent low level AML avant allo
      - Randomisation chimio (différents schémas) vs. AZA Ven

- **iFLT3** (Othman J, Leukemia 2023) :
  - N=56 molecular failure, 52 *FLT3*-ITD
  - La moitié exposée à midostaurine
  - Gilteritinib (n = 38), Quizartinib (n = 7), Sorafenib (n = 11)
  - 60% réponse moléculaire, 45% MRDneg
  - 22 bridges to alloHSCT
  - 2-year overall survival : 80%
  - 2-year molecular event-free survival 56%

Figure 1. ALLG AMLM26 INTERCEPT trial schema






Suivez le guide !

Récher C, Blood 2024

# Perspectives

- **Timing du suivi :**
  - Toutes les 4-6 semaines plutôt que tous les 3 mois ?
  - 75% des rechutes de LAM CBF ne sont pas détectées par un suivi moléculaire/3 mois (Puckrin R, Haematologica 2020)
- **Patients à risque** :
  - Patients MRDpos dans le sang et la moelle en cours/en fin de traitement intensif : traitement de rattrapage immédiat ? Monitoring serré de la MRD ?
  - Type transcrit *NPM1*, co-mutations, etc
- **Nouveaux traitements** : iMenin/MLL, iFLT3
- **Détection des co-mutations** avec techniques plus sensibles en cas de rechute moléculaire (FLT3, IDH)
- **Nouvelles stratégies de suivi** : MRD CMF ; MRD CMF dans le sang ?