
# Should high risk AML patients undergo maintenance following HSCT?

## YES

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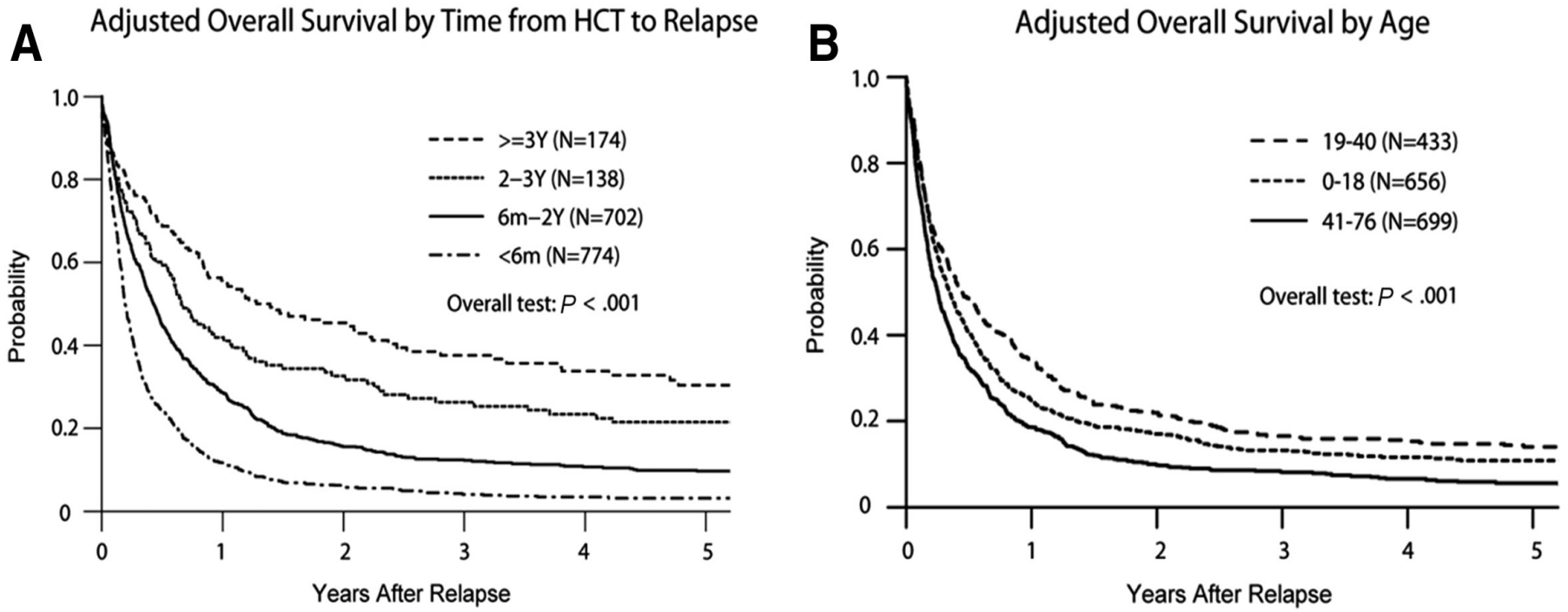
# No COI to disclose

# Why prevent relapse in AML?

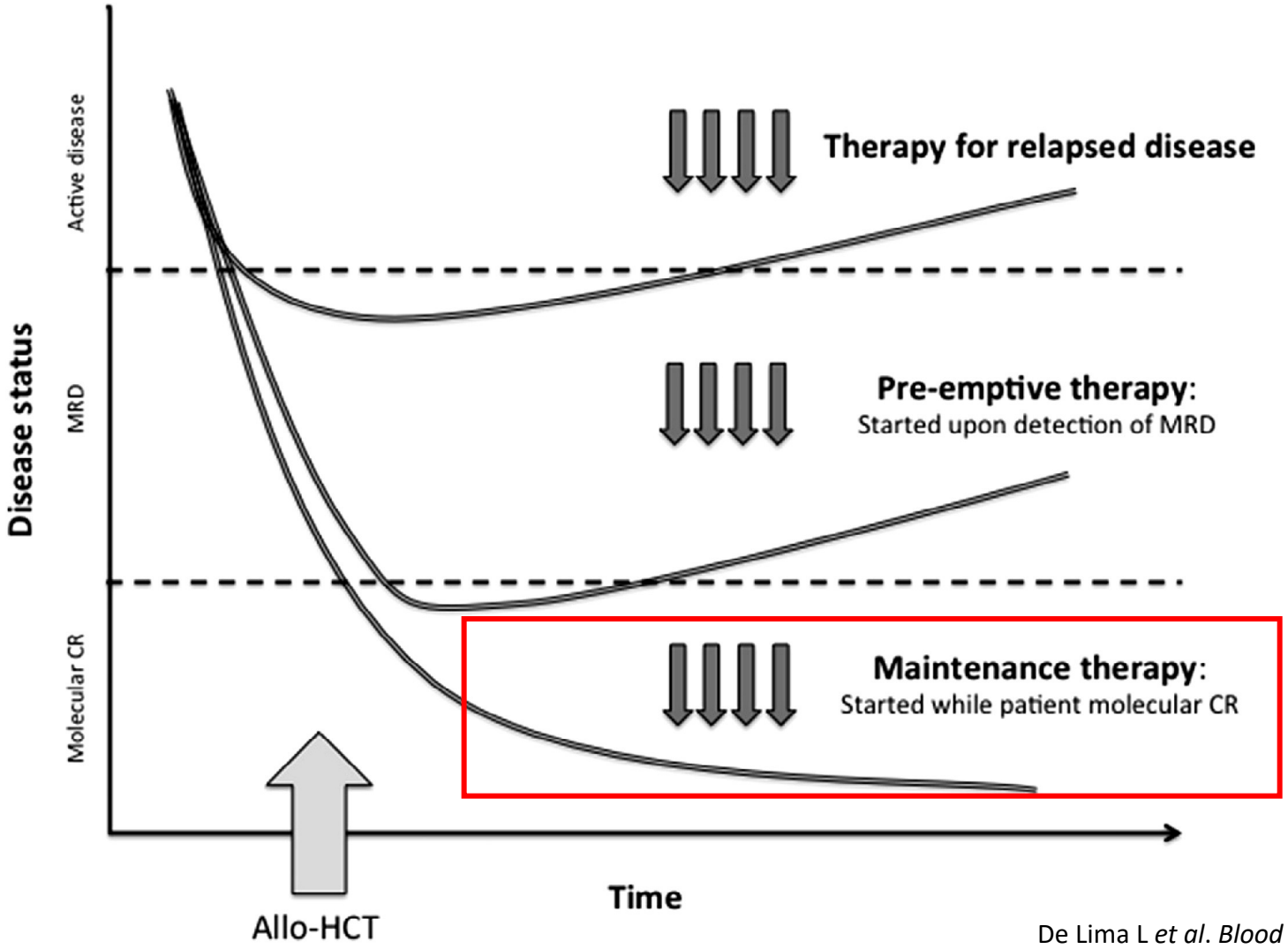
- AML relapse is the major cause of treatment failure after allografting, especially in the first 12 months after allo-HSCT
- Survival after relapse remains poor, with less than 25% of patients alive 1 year after relapse and less than 20% at 2 years
- Treatment of relapse post transplant is often suboptimal
- Treatment of relapse is not always feasible in transplanted patients




Bejanyan N *et al*. *Biol Blood Marrow Transplant* 2015

# Maintenance therapy: definition

An extended but time-limited course of treatment, that is usually less toxic, given after achievement of CR with the objective of reducing the risk of leukemic relapse.




De Lima L *et al*. *Blood Reviews* 2021

# High risk AML definition

**Table 6. 2022 European LeukemiaNet (ELN) risk classification by genetics at initial diagnosis[a]**

| Risk Category[b] | Genetic Abnormality |
|---|---|
| **Favorable** | • t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*[b,c]<br>• inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*[b,c]<br>• Mutated *NPM1*[b,d] without *FLT3*-ITD<br>• bZIP in-frame mutated *CEBPA*[e] |
| **Intermediate** | • Mutated *NPM1*[b,d] with *FLT3*-ITD<br>• Wild-type *NPM1* with *FLT3*-ITD<br>• t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[b,f]<br>• Cytogenetic and/or molecular abnormalities not classified as favorable or adverse |
| **Adverse** | • t(6;9)(p23;q34.1)/*DEK*::*NUP214*<br>• t(v;11q23.3)/*KMT2A*-rearranged[g]<br>• t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*<br>• t(8;16)(p11;p13)/*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,[h] monosomal karyotype[i]<br>• Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*[j]<br>• Mutated *TP53*[k] |

## High-risk AML in allo-HSCT to potentially consider for maintenance

- Adverse risk AML
- Relapsed/refractory AML
- Secondary AML
- CR-MRD+ AML
- *FLT3-ITD mutated AML*

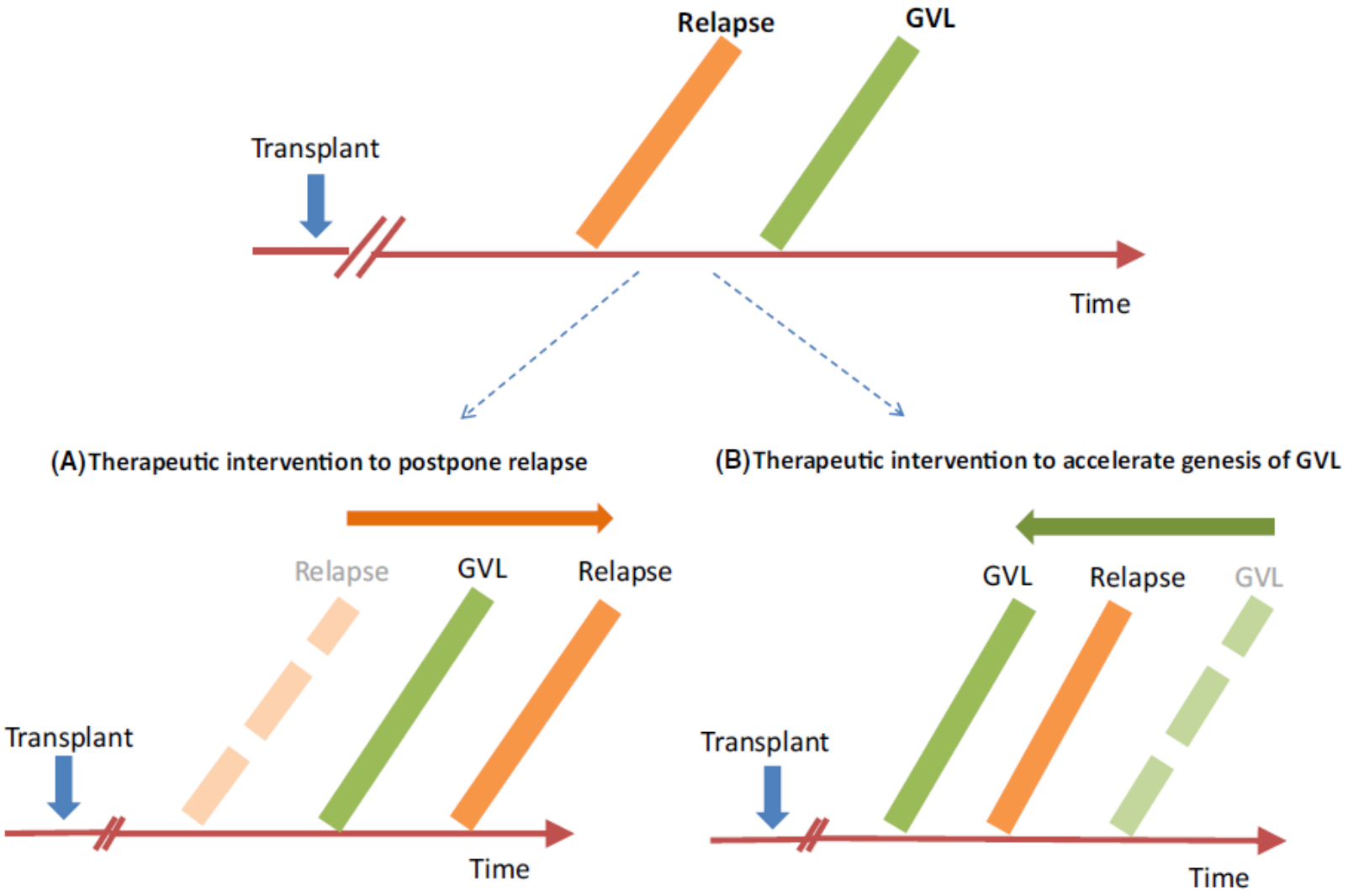
*Also consider the intensity of the conditioning regimen*

Dohner H *et al*. *Blood* 2022

# The “ideal” maintenance agent in AML

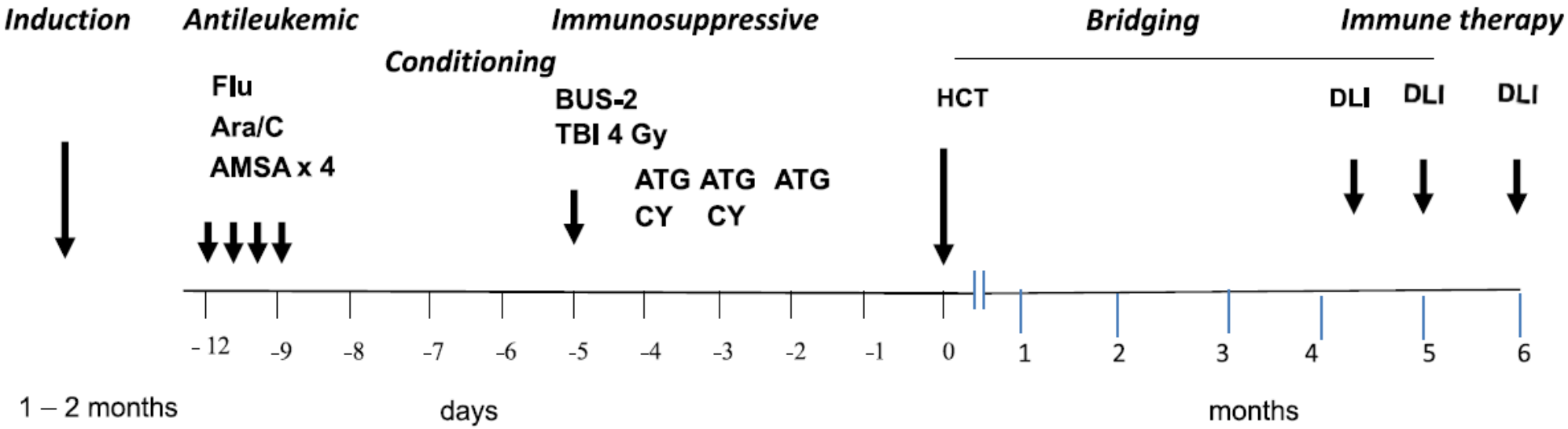
- Active against the disease, ex. targeting LSC/progenitor population.
- Not too toxic.
- Not myelotoxic (or with tolerable myelotoxicity).
- Can be given early after transplant.
- Influence donor cells favorably: GVL effect optimisation.

# Accelerate or “buy” time for the GVL effect




Loke J *et al*. *Br J Hematol* 2019

# The FLAMSA concept




**Post-transplant management**

| | |
|---|---|
| from day +49 | Taper immunosuppression |
| day +90 | Stop of immunosuppression |
| day +120 | Prophylactic/adjuvant DLI (if no GVHD) |

**Results**

n=75 high-risk AML received FLAMSA-RIC

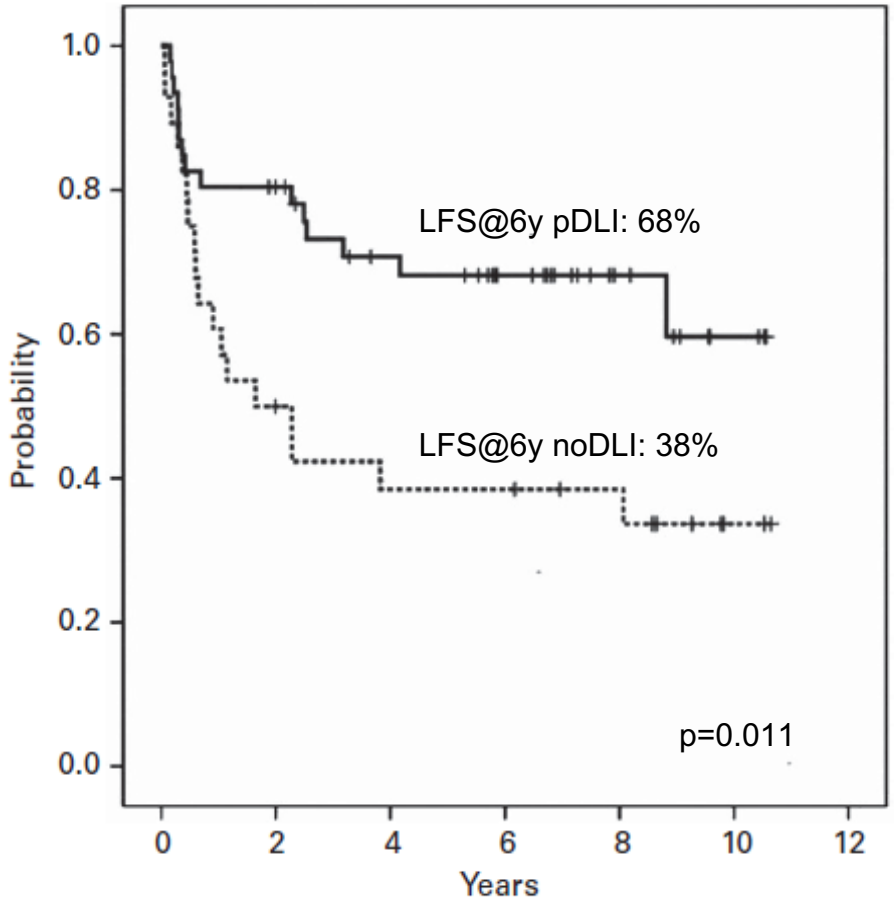
Only n=12 received pDLI

Median time to DLI1: 160 (range 120-294) days

GVHD in 4 pts

Schmid C *et al*. *Ann Hematol* 2020

# pDLI to enhance GVL effect in high-risk AML




OS@6y: pDLI 67% vs noDLI 31% (p<0.001)

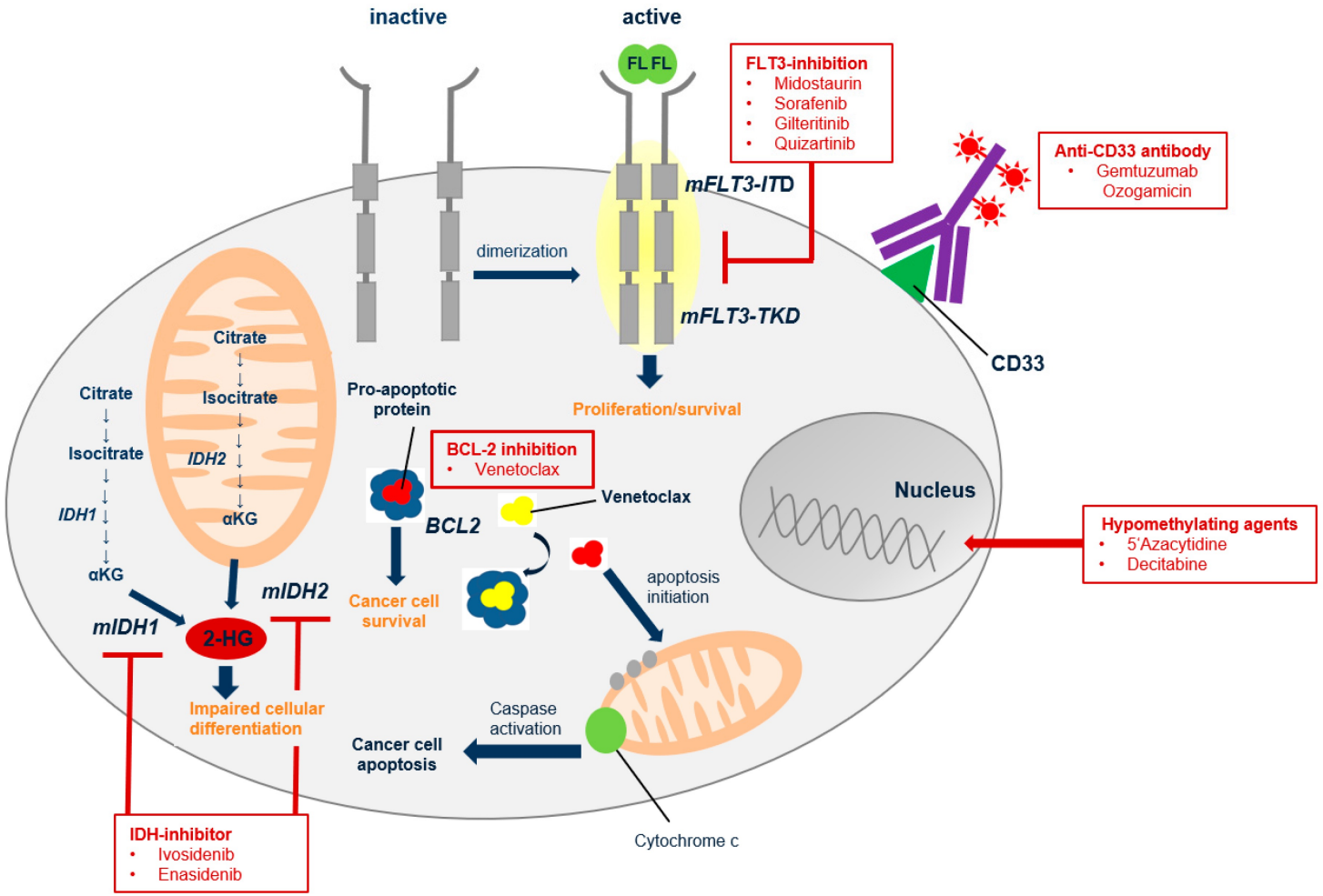
**Table 4.** Outcome of patients after aDLT

| *Variable* | N |
|---|---|
| Patients receiving aDLT | 46 |
| Alive/dead | 31/15 |
| *Acute* GvHD | |
| Grade I | 0 |
| Grade II | 3 |
| Grade III | 1 |
| *Chronic GvHD* | |
| limited | 5 |
| extended | 3 |
| *Disease status after aDLT* | |
| continuous CR | 36 |
| relapse after aDLT | 10 |
| *Treatment-related mortality* | |
| infection | 2 |
| chronic GvHD | 1 |
| secondary malignancy | 2 |

Abbreviation: aDLT = adjuvant transfusion of donor lymphocyte.

Jedlickova Z, *et al*. *Bone Marrow Transplant* 2016

# Potential targets for maintenance therapy in AML




Hypomethylating agents

FLT3 inhibitors

Histone deacethylase inhibitors

Mono (bi) clonal antibodies

Immunostimulatory agents: anti-CTLA-4, anti-PD1, anti-PDL1 (antagonistic), anti-4-1BB, anti-OX40 (agonistic)

Cells – educated or not (eg. CAR T cells)

Tumor vaccines

etc. etc.

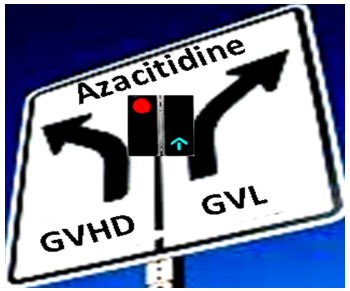
Rautenberg C *et al*. *Int J Mol Sci* 2019

# Hypomethylating agents as maintenance agents after allo-HSCT

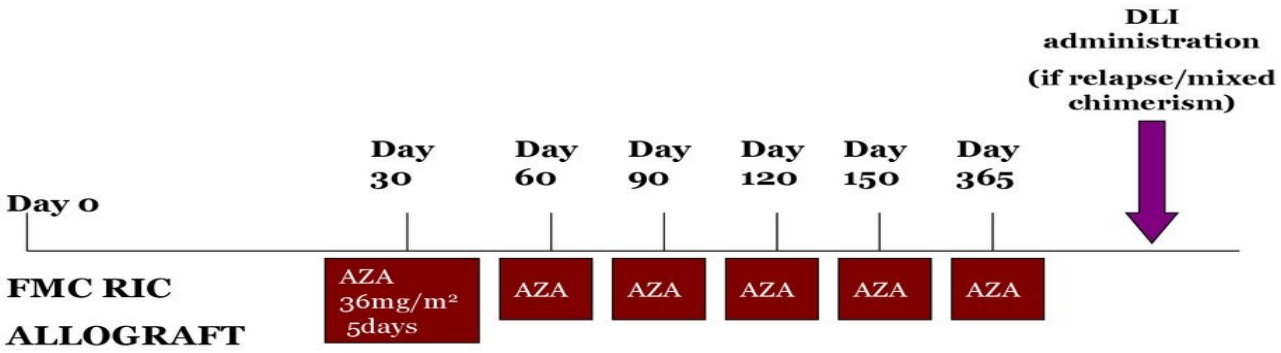
# Hypomethylating agents: potential effects

- Increased expression of tumor-associated antigens (Roman-Gomez et al., 2007)
- Increased expression of KIR ligands on hematopoietic cells (Liu et al., 2009)
- Recovery of reduced expression of HLA class I, II and III antigens on tumor cells (Campoli & Ferrone, 2008; Pinto et al., 1984)
- Increased expression of known Minor antigens (Hambach et al., 2009)
- Increased FoxP3 expression and $T_{reg}$ generation and CD8+ T-cell response induction (Polansky et al., 2008; Choi et al. 2010; Sanchez-Abarca et al. 2010; Goodyear et al. Blood 2011)

↑ **GVL**



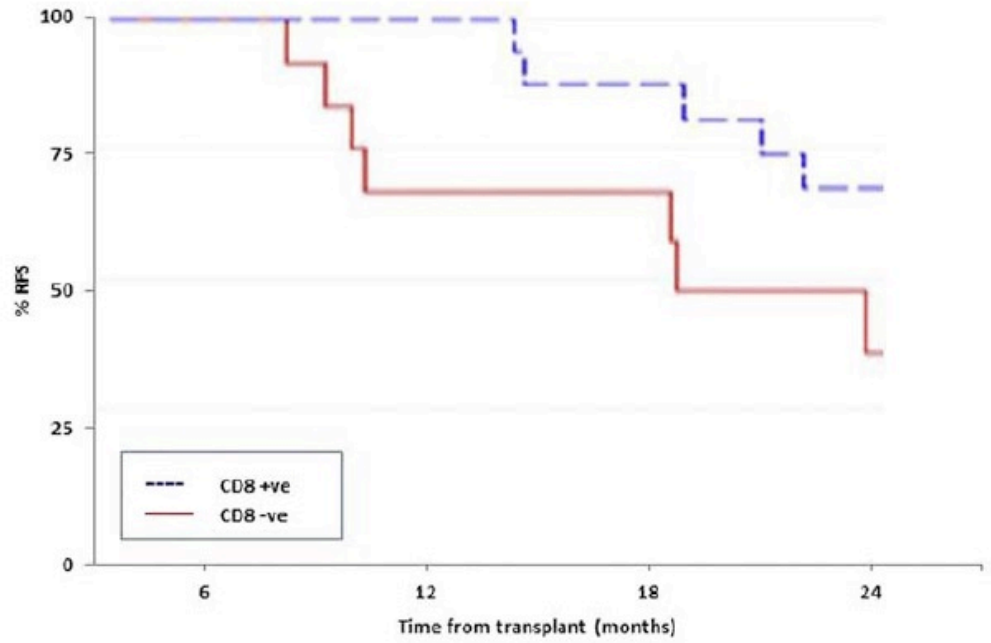
# RICAZA trial




Commence AZA 36 mg/m² on Day +42 if ANC >0.5, Plt >50
AZA discontinued at 12/12 post SCT

- Decreased relapse and improved OS in pts developing a CD8+ specific T cell response post-transplant

- Aza in 37 pts at a median of 55 days after RIC-allo-HSCT
- 32 pts completed at least 3 cycles and 16 at least 10 cycles
- 4 pts developed limited cGVHD; no extensive cGVHD




Craddock C et al, *Biol Blood Transplant* 2016

# Azacitidine vs placebo as maintenance: a randomized study

Screening period:
Days 40-100 after alogeneic transplant.

Patient population:
High risk AML/MDS
CMML
Aged 18-75
CR after allo-HSCT

R
1:1

5-azacitidine 32mg/m2/dayX5

observation

Follow up until:
Completion of 12 cycles of maintenance
Relapse/death
Discontinuation of maintenance

Population:
187 enrolled and randomized:
94 observation
93 5-azacitidine
87 started the 5-azacitidine maintenance
Median number of cycles=4

Statistics:
Primary outcome: RFS
Secondary outcomes: OS, aGvHD and toxicity

| Efficacy endpoint | 5-azacitidine, n=87 | Observation, n=94 | HR, 95%CI, p |
|---|---|---|---|
| RFS | 2.07 yr | 1.28 yr | 0.77, 0.51-1.14, 0.19 |
| OS | 2.52 yr | 3.56 yr | 0.84, 0.56-1.28, 0.43 |

Conclusion:
- 5-azacitidine given as 32 mg/m2/dayX5 did not lead to improved RFS or OS.
- There was no safety concern.

Oran B et al, *Blood Adv* 2020

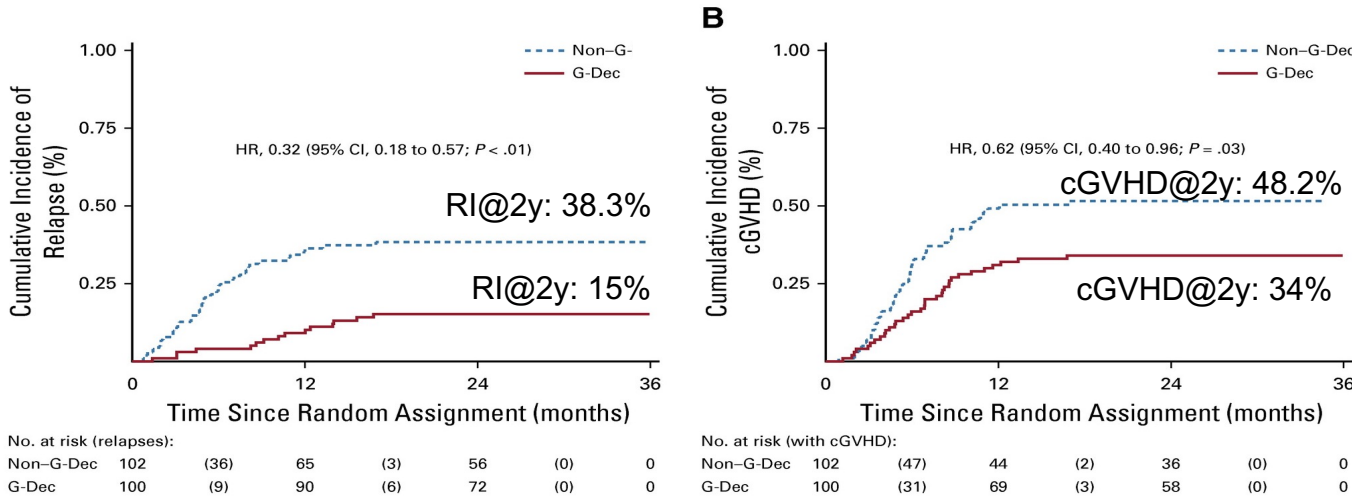
# Azacitidine vs placebo as maintenance: potential study biases

- **Lack of comprehensive genomic risk classification and integrated MRD assessments**
- Some patients with detectable MRD not considered for the study but received Aza outside clinical trial
- Slow accrual: 7.5 years were needed to enroll 187 high-risk AML/MDS patients, and the study was closed due to slow accrual
- Screening failure in 41% of cases.
- 32 mg/m$^2$: is this the correct dose?
- Only 17.7% patients receiving RIC

Oran B et al, *Blood Adv* 2020
El Chaer F et al. *Blood Adv* 2020

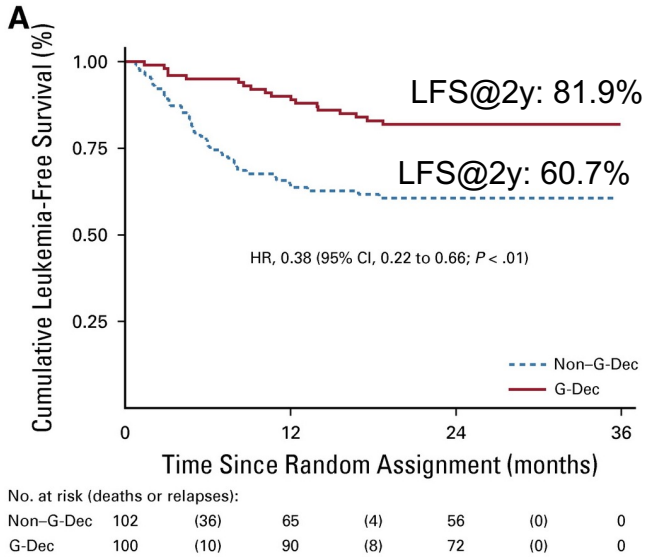
# Maintenance with Decitabine+rhGCSF vs no treatment

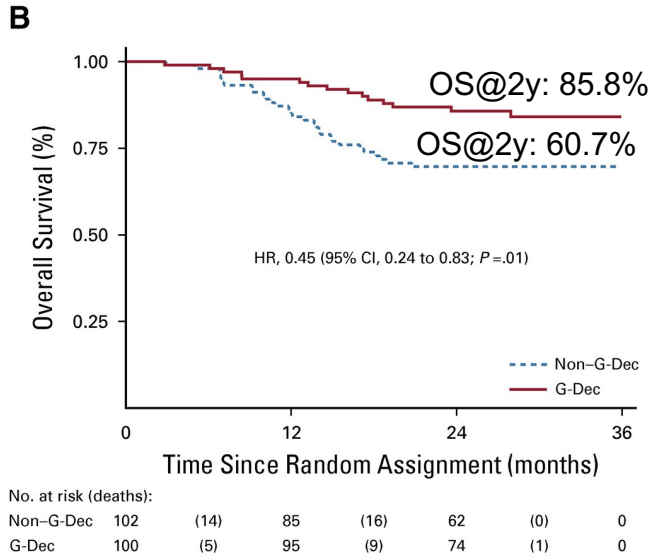
- Stratification according to MRD before allo-HSCT
- Inclusion criteria (among others):
  - AML with poor genetic abnormalities, primary refractory AML, relapsed AML, or secondary AML.
  - CR and minimal residual disease (MRD) negative.
- Primary endpoint: CIR





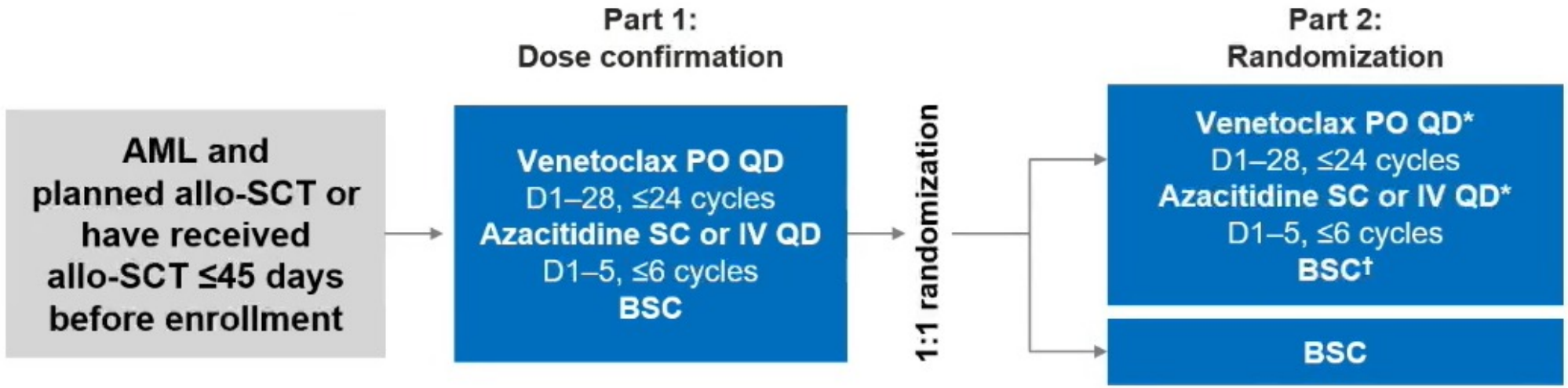





Gao L *et al. J Clin Oncol* 2020

# What about combination strategies?




**Key inclusion criteria**

- Diagnosed with AML by WHO 2016 criteria
- Planned or have received allo-SCT ≤45 days before enrollment
- Blast % <10% in BM before transplant and <5% after
- Blast count in PB: 0
- Part 1: ≥18 years old
- Part 2: ≥12 years old

**Primary endpoints:**

- DLTs (Part 1)
- RFS (Part 2)

**Secondary endpoints (Part 2):**

- OS
- GvHD-free RFS
- QoL
- GvHD rate
- MRD $<10^{-3}$

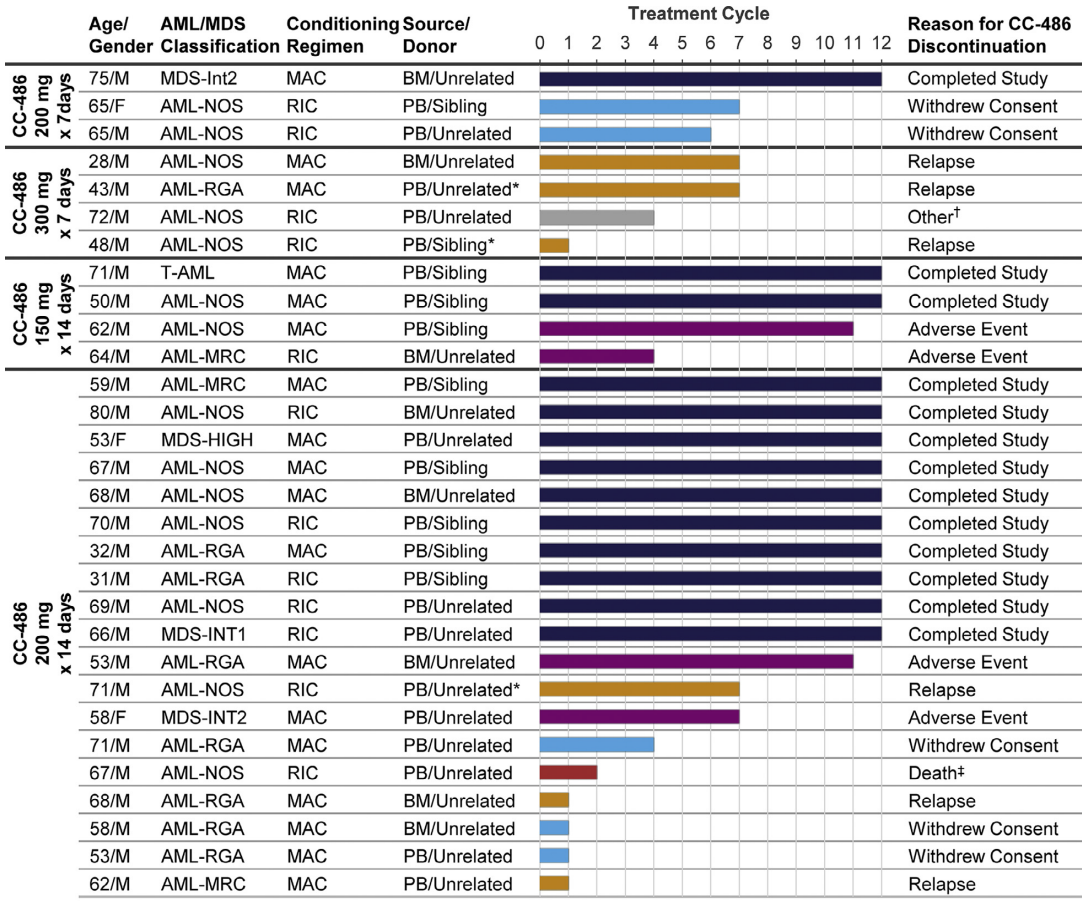
# CC-486 as maintenance after allo-HSCT: a phase 1/2 study

- CC-486 after 42-84 days from allo-HSCT in adults undergoing allo-HSCT for AML or MDS
- Endpoints: safety and efficacy; MTD
- Treatment period: 2013-2015

Results:

- N=31
- Acceptable safety profile (mainly GI and hematologic tox)

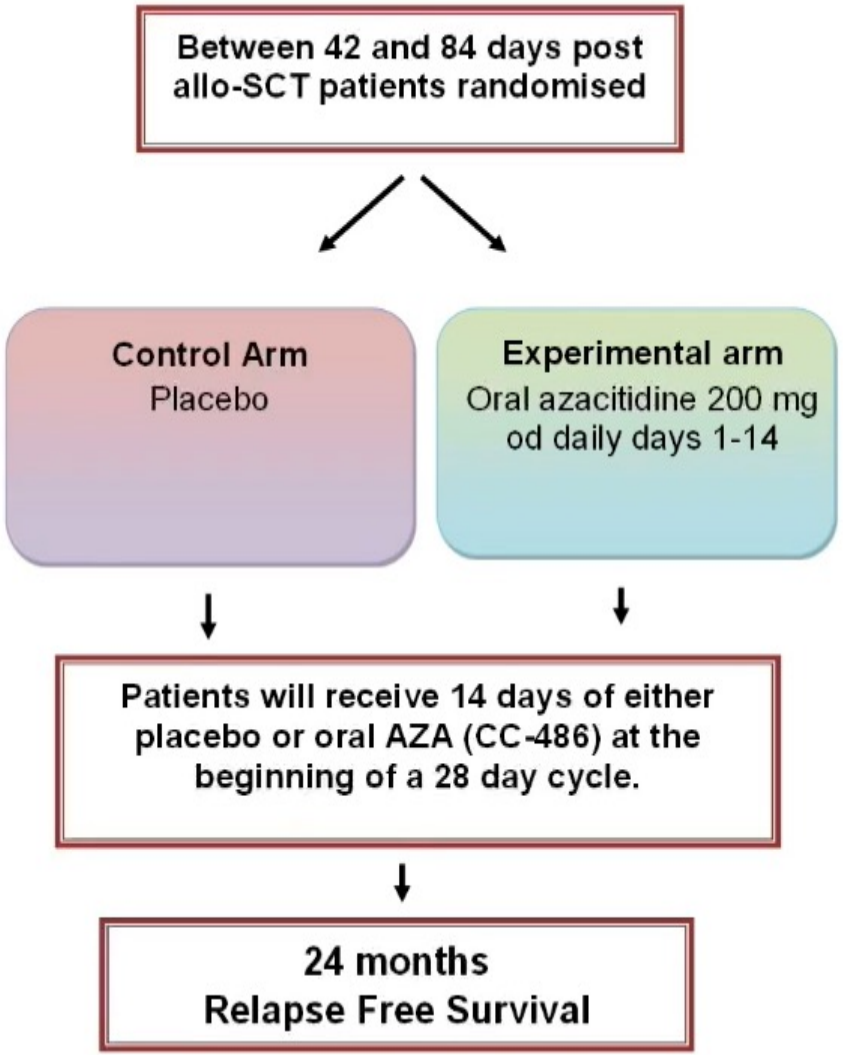
| | Age/ Gender | AML/MDS Classification | Conditioning Regimen | Source/ Donor | Reason for CC-486 Discontinuation |
|---|---|---|---|---|---|
| CC-486 200 mg x 7days | 75/M | MDS-Int2 | MAC | BM/Unrelated | Completed Study |
| | 65/F | AML-NOS | RIC | PB/Sibling | Withdrew Consent |
| | 65/M | AML-NOS | RIC | PB/Unrelated | Withdrew Consent |
| CC-486 300 mg x 7 days | 28/M | AML-NOS | MAC | BM/Unrelated | Relapse |
| | 43/M | AML-RGA | MAC | PB/Unrelated* | Relapse |
| | 72/M | AML-NOS | RIC | PB/Unrelated | Other† |
| | 48/M | AML-NOS | RIC | PB/Sibling* | Relapse |
| CC-486 150 mg x 14 days | 71/M | T-AML | MAC | PB/Sibling | Completed Study |
| | 50/M | AML-NOS | MAC | PB/Sibling | Completed Study |
| | 62/M | AML-NOS | MAC | PB/Sibling | Adverse Event |
| | 64/M | AML-MRC | RIC | BM/Unrelated | Adverse Event |
| CC-486 200 mg x 14 days | 59/M | AML-MRC | MAC | PB/Sibling | Completed Study |
| | 80/M | AML-NOS | RIC | BM/Unrelated | Completed Study |
| | 53/F | MDS-HIGH | MAC | PB/Unrelated | Completed Study |
| | 67/M | AML-NOS | MAC | PB/Sibling | Completed Study |
| | 68/M | AML-NOS | MAC | BM/Unrelated | Completed Study |
| | 70/M | AML-NOS | RIC | PB/Sibling | Completed Study |
| | 32/M | AML-RGA | MAC | PB/Sibling | Completed Study |
| | 31/M | AML-RGA | RIC | PB/Sibling | Completed Study |
| | 69/M | AML-NOS | RIC | PB/Unrelated | Completed Study |
| | 66/M | MDS-INT1 | RIC | PB/Unrelated | Completed Study |
| | 53/M | AML-RGA | MAC | BM/Unrelated | Adverse Event |
| | 71/M | AML-NOS | RIC | PB/Unrelated* | Relapse |
| | 58/F | MDS-INT2 | MAC | PB/Unrelated | Adverse Event |
| | 71/M | AML-RGA | MAC | PB/Unrelated | Withdrew Consent |
| | 67/M | AML-NOS | RIC | PB/Unrelated | Death‡ |
| | 68/M | AML-RGA | MAC | BM/Unrelated | Relapse |
| | 58/M | AML-RGA | MAC | BM/Unrelated | Withdrew Consent |
| | 53/M | AML-RGA | MAC | PB/Unrelated | Withdrew Consent |
| | 62/M | AML-MRC | MAC | PB/Unrelated | Relapse |




*Patient had ≥5% bone marrow blasts at the time of alloHSCT
†Patient had an ongoing history of CNS leukemia at entry and was receiving intrathecal methotrexate before and during study treatment. After cycle 4, the patient was discontinued for "other" reasons, due to risk of bleeding with administration of radiation and intrathecal therapy for relapse of CNS leukemia
‡Death due to intracranial hemorrhage. This patient had a dose-limiting toxicity of pneumonia accompanied by neutropenia; the patient also showed evidence of transplant-related thrombotic micro-angiopathy
AML-MRC, AML with myelodysplasia-related changes; AML-NOS, AML not otherwise specified; AML-RGA, AML with recurrent genetic abnormalities; BM, bone marrow; Int1, Intermediate-1 risk MDS; Int2, Intermediate-2 risk MDS; MAC, myeloablative conditioning; PB, peripheral blood; RIC, reduced-intensity conditioning; T-AML, therapy-related AML

De Lima M *et al*. *Biol Blood Marrow Transplant* 2018

# AMADEUS: post-transplant maintenance with CC-486




**Inclusion criteria (among others):**

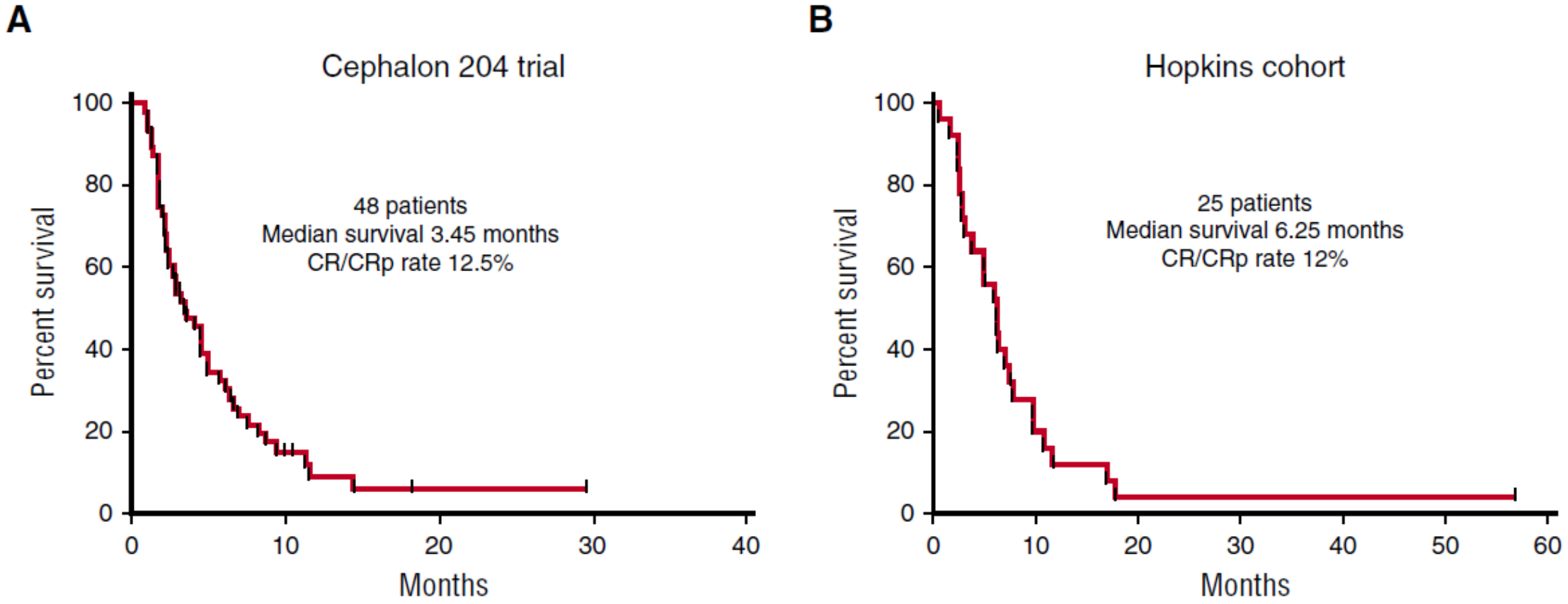
Patients with a diagnosis of any of the below:

- AML (CR1 or CR2) according to World Health Organization (WHO) classification;
- Secondary AML (defined as previous history of MDS, antecedent hematological disease or chemotherapy exposure; CR1 or CR2); or
- Advanced or high risk MDS with an IPSS-R of ≥3.5 (intermediate 3.5 or higher) including intermediate or high risk chronic myelomonocytic leukaemia (CMML) (e.g. CPSS int-2 or high risk) (as per IPSS-R)
- undergoing allo-SCT using myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) preparative regimens, and with either peripheral blood or bone marrow as the source of hematopoietic stem cells.

NCT04173533

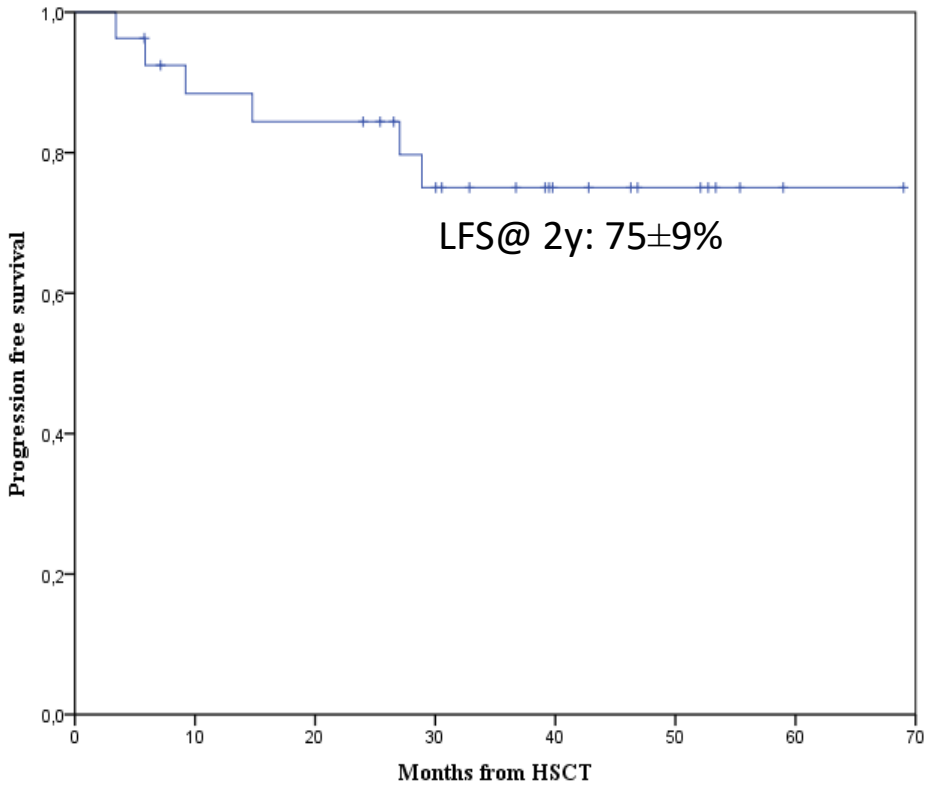
# FLT3-inhibitors as maintenance agents after allo-HSCT

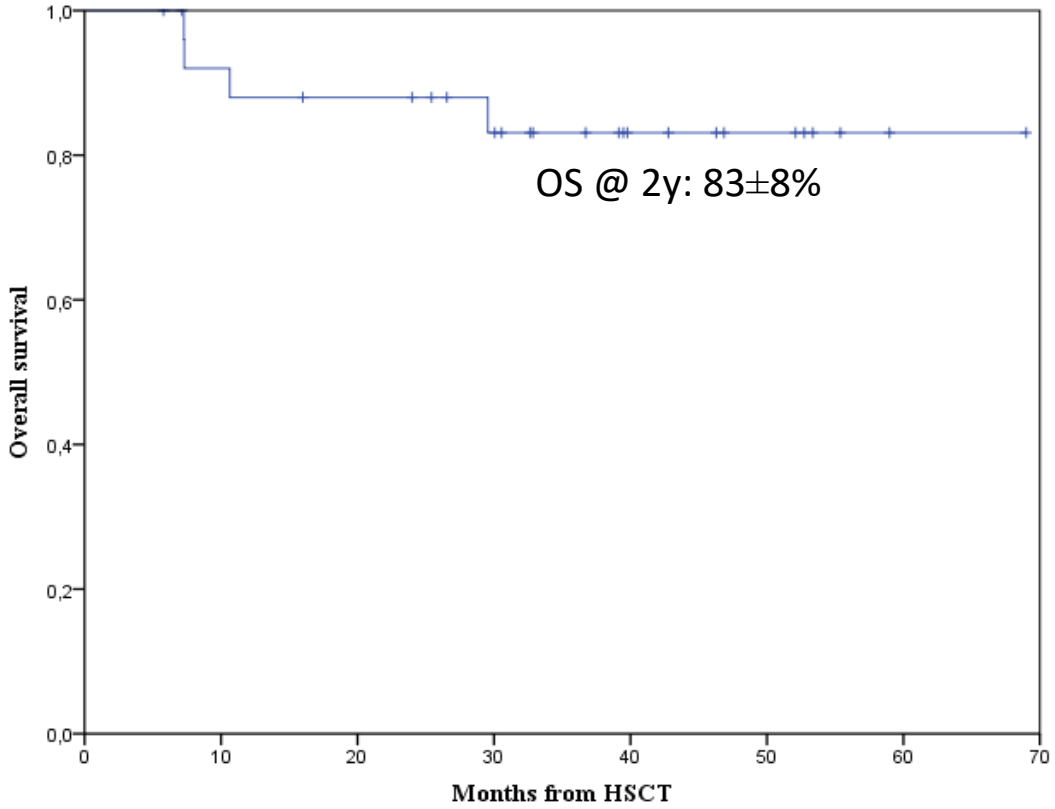
# FLT3-ITD positive relapsing AML has a dismal prognosis




Pratz KW *et al*. *Blood 2017*

# Prophylactic sorafenib after allo-HSCT




N=27

Median follow up 33 months (range 6-69)

Battipaglia G. et al. Cancer 2017

Battipaglia G. et al. Clinical Lymphoma Myeloma and Leukemia 2019

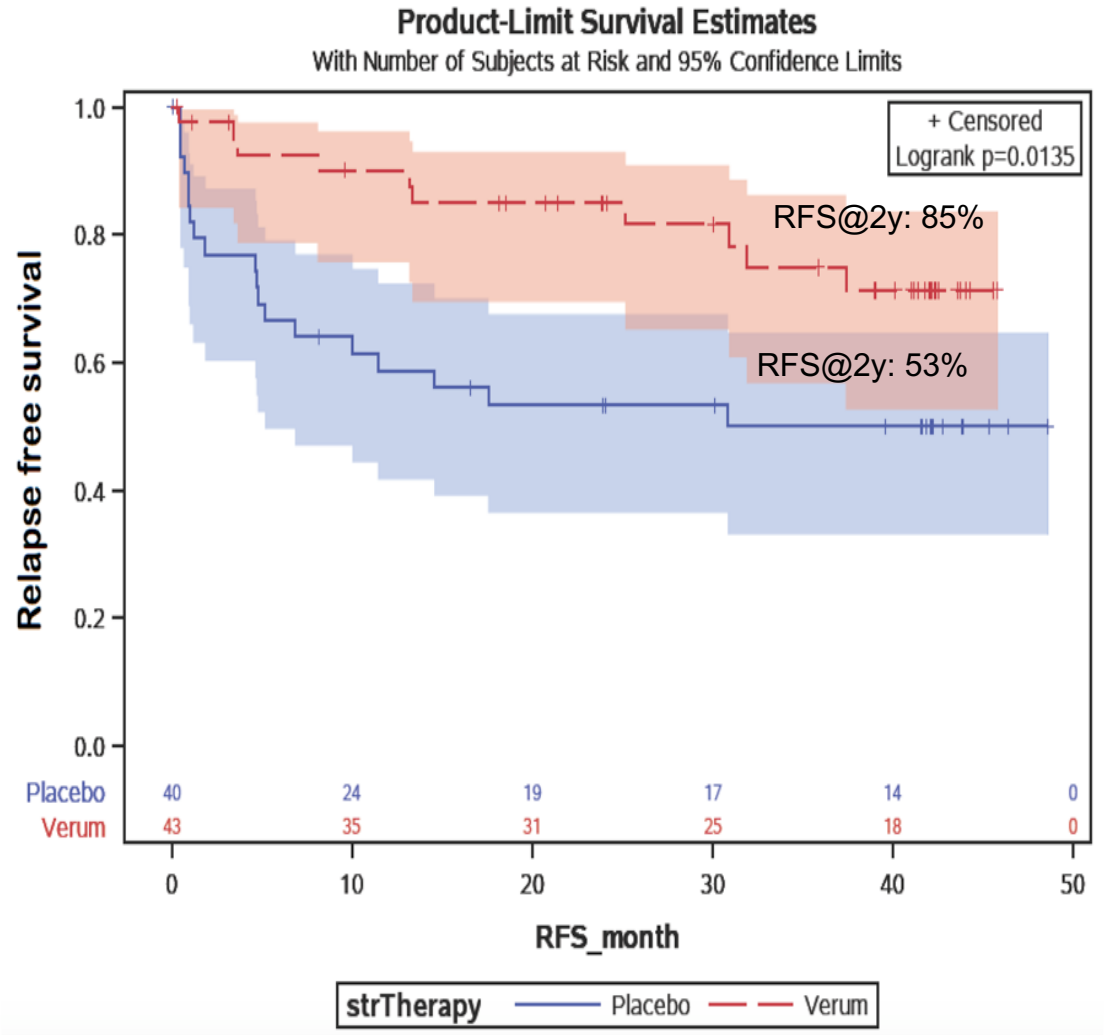
# SORMAIN trial

Patients with *FLT3*-ITD AML who underwent alloSCT; within 60-100 days post transplant, in complete hematologic response with BM blasts < 5% and normal PB, ECOG PS 0/1, no GvHD grade 2-4
(N = 83)

R

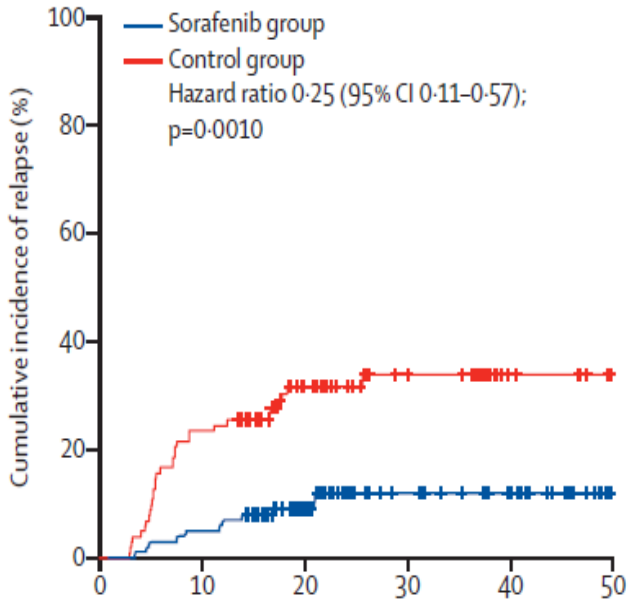
**Sorafenib**
2 x 400 mg once daily for 24 mos
(n = 43)

**Placebo**
once daily for 24 mos
(n = 40)

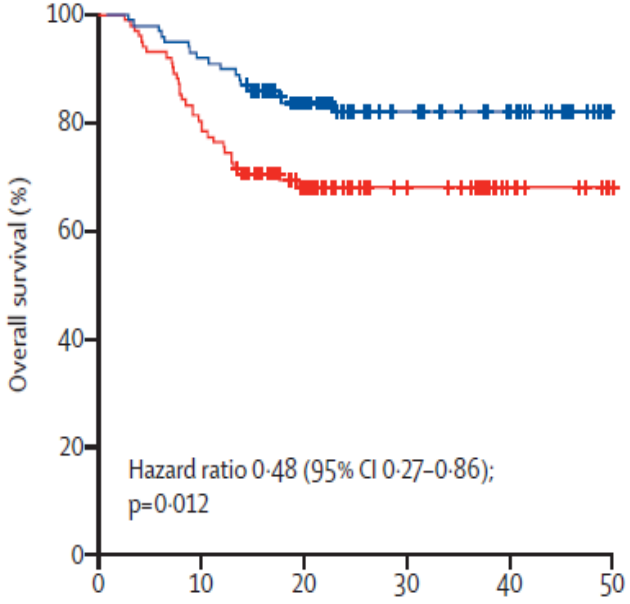



Burchert A, et al., J Clin Oncol 2020

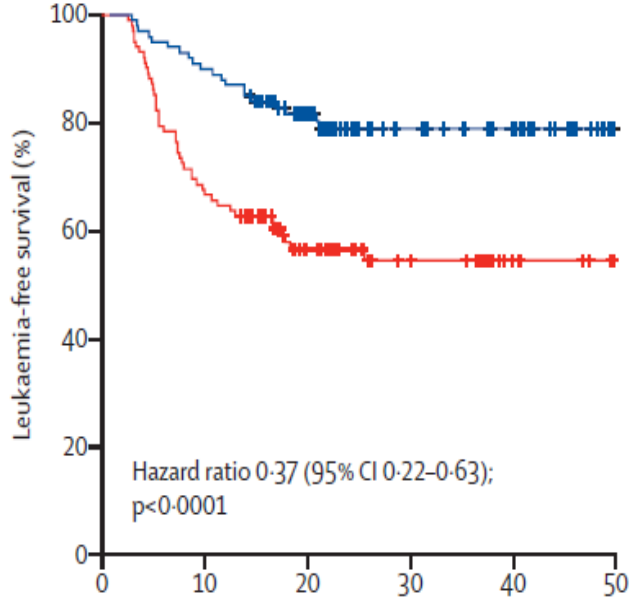
# The Chinese experience




| Number at risk (number censored) | | | | | | |
|---|---|---|---|---|---|---|
| Sorafenib group | 100 (0) | 90 (0) | 62 (20) | 33 (47) | 23 (57) | 0 (80) |
| Control group | 102 (0) | 68 (0) | 37 (22) | 21 (37) | 6 (52) | 0 (58) |




| Number at risk (number censored) | | | | | | |
|---|---|---|---|---|---|---|
| Sorafenib group | 100 (0) | 92 (0) | 64 (20) | 33 (50) | 23 (60) | 0 (83) |
| Control group | 102 (0) | 81 (0) | 48 (22) | 30 (40) | 10 (60) | 1 (69) |




| Number at risk (number censored) | | | | | | |
|---|---|---|---|---|---|---|
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| Control group | 102 (0) | 68 (0) | 37 (22) | 21 (37) | 6 (52) | 0 (58) |

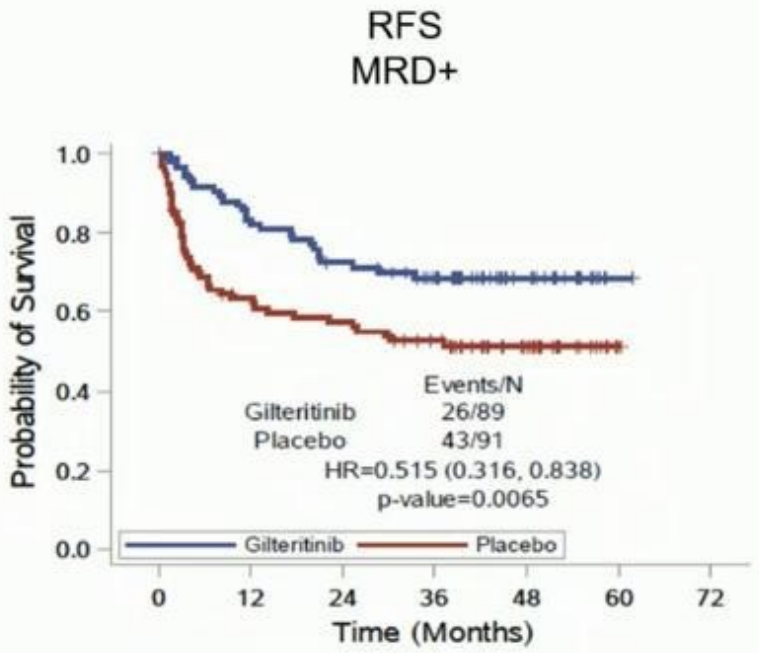
Xuan L et al, Lancet Oncol 2020

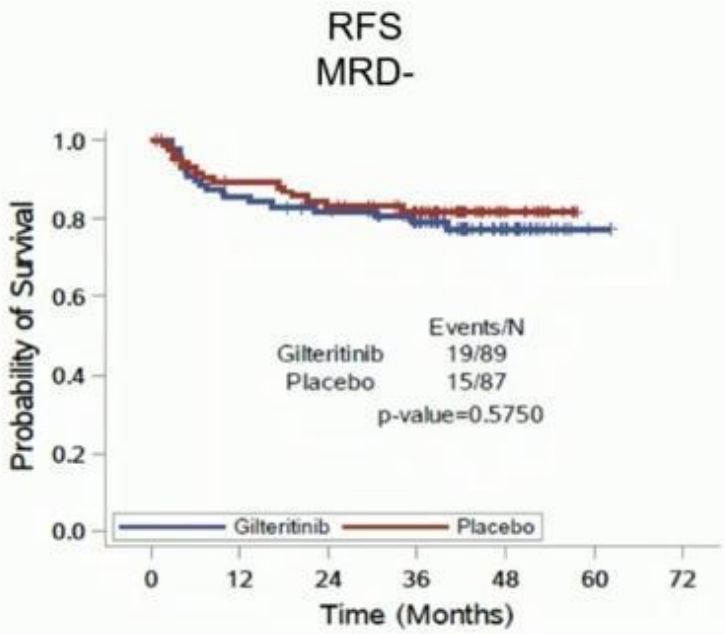
# EBMT position paper on FLT3 inhibitors after allo-HSCT

| | |
|---|---|
| **Indication for allo-HSCT in *FLT3*-mutated AML** | • In general, all patients with FLT3-ITD should be considered for allo-HSCT in CR1 if feasible with the following exception<br>• Patients with *FLT3*-ITD who belong to the ELN favourable risk group (low allelic ratio <0.5 with concomitant *NPM1* mutation) and who achieve MRD negativity, in whom the transplant indication is controversial |
| **Modalities of allo-HSCT** | • Donor selection according to EBMT general guidelines<br>• In vivo T-cell depletion decreases the risk of chronic GVHD without an apparent increase in the risk of relapse and is an option<br>• The choice of conditioning regimen has no direct link with *FLT3* mutation and should be adapted to other individual risk factors |
| **Post-transplant maintenance** | • There is **an unmet need for approved maintenance therapy for patients who undergo allo-HSCT for *FLT3*-ITD AML**<br>• In the absence of an appropriate RCT, **sorafenib could be considered**, but the role of other FLT3 inhibitors warrants investigation<br>• Ongoing studies will determine whether FLT3 inhibitors will become additional alternatives in this setting |

Bazarbachi A, et al. Haematologica. 2020

# Gilteritinib maintenance: the MORPHO study




Levis M et al. EHA 2023

# Conclusions

- Allo-HSCT is no longer the last step of a treatment plan in AML
- Emerging concept of a comprehensive treatment package incorporating new drugs and novel cellular and immune therapies pre and post allo-HSCT
- Lots of candidate agents but largest experience with hypomethylating agents and FLT3-inhibitors
- Preliminary data show feasibility and efficacy of maintenance agents in favorably preventing disease relapse
- Many unanswered questions remain:
  - Patients selection
  - Type of maintenance agent to use
  - Timing Dose
  - Duration (arbitrary duration of 1 to 2 years in trial, but in the real-life setting, the decision to discontinue maintenance when safe and efficacious is challenging)
- pending results from ongoing clinical trials should better elucidate the benefits of targeted agents in the maintenance setting.

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# GRAZIE PER L'ATTENZIONE