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ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

UNDER THE AUSPICES OF:

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GITMO

SIE - Società Italiana di Ematologia

5 may 2022

Session I – Acute Myeloid Leukemia

Is it maintenance necessary?

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Maintenance Therapy in AML

- Recent advances in therapeutics coupled with steady improvements in supportive care for patients with AML have led to improved outcomes.

- However, high rates of relapse remain a clinical dilemma, even in patients that achieve a CR with initial therapy.

- The most effective post-remission therapy in AML continues to be allo-SCT, but is not available to all patients with high-risk disease (high rates of complications, lack of suitable donors, patients' comorbidities).

Kadia T, Front Oncol 2019
Isidori A et al Front Oncol 2021
Daver N et al, Leuk 2021

Maintenance Therapy in AML

- For decades, investigators have attempted strategies of maintenance therapy to prolong both CR duration and OS in AML patients.
- These approaches have included cytotoxic chemotherapy, immunotherapy, hypomethylating agents, and targeted small molecule therapy.
- The current standard of care for most AML patients achieving a CR is **observation without maintenance** therapy.
- However, with the recent completion of the QUAZAR AML-001 clinical study and FDA approval of oral azacitidine this paradigm maybe set to change…

Kadia T, Front Oncol 2019
Isidori A et al Front Oncol 2021
Daver N et al, Leuk 2021
Wey A et al, NEJM 2021

Goal of maintenance

- The goal of maintenance therapy should be **to improve overall survival**.
- Improvements in DFS, RFS, EFS are not enough to justify the added exposure to and toxicity from anti-leukemia therapy unless they translate to gains in OS.
- With the availability of newer methods to measure MRD after achieving a CR, it is intuitive that residual disease persisting after induction/consolidation is the source of most relapses.
- It follows then, that another quantifiable goal of post remission maintenance therapy is to eradicate MRD.

Maintenance with cytotoxic chemotherapy

- Clinical trials evaluating maintenance cytotoxic chemotherapy in AML in the past have consistently failed to show a benefit in overall survival while providing occasionally seen benefit in RFS.

- 5 main randomized studies investigated maintenance chemotherapy compared with observation in CR patients with AML

Placebo-controlled, randomized studies of maintenance therapy with cytotoxic chemotherapy in AML

Trial	Patients entering maintenance randomization	Age (range)	Maintenance regimen	Follow-up	DFS/RFS/LFS	Overall Survival
Sauter et al (Lancet 1984)	74	7-65	Ara-C/Thiog alt Ara-C/Pdn vs placebo (2y)	44 months	No significant difference in DFS	No significant difference in OS
Buchner et al (JCO 1985)	145	15-78	Ara-C/Dauno alt ara-C/Thiog and Ara-C/Edx vs placebo (3y)	2.5 years	Median RFS 13mo vs 8 mo (p=0.003)	Not reported
Johnson et al (Acta Onc 1988)	32	18-74	Thiog/Eto alt CCNU vs plac	Not reported	No significant difference in DFS	No significant difference in OS
Lowemberg et al (JCO 1998)	147	60-88	LDAC vs plac	6 years	Median DFS 51 weeks vs 29 (p=0.006)	No significant difference in OS
Palva et al (Eur J Hem 1991)	108	16-59	Ara-C/Thiog vs HL IFN vs placebo	82 months	No significant difference in DFS	No significant difference in OS

Maintenance with immunotherapies

- Probably the most extensively studied approach to maintenance therapy in patients with AML has been with immunotherapy.
- AlloSCT can be considered a “type of maintenance therapy” in that grafted allogeneic T cells continuously surveille and maintain remission in responders through GVL effect.
- AlloSCT serves as a proof of concept that harnessing the immune system has the potential to cure AML.
- 7 main randomized studies investigated maintenance chemotherapy compared with observation in CR patients with AML

Placebo-controlled, randomized studies of maintenance therapy in AML with immunotherapies

Trial	Patients entering maintenance randomization	Age (range)	Maintenance regimen	Follow-up	DFS/RFS/LFS	Overall Survival
Zuhrie et al (BJC 1990)	41	Adult	BCG and irradiated alloMB vs placebo	Not reported	Median RFS 35.14 weeks vs 19.71 (p=0.039)	Median OS 96.14 vs 53 weeks (p=0.04)
Palva et al (Eur J Hem 1991)	108	16-59	Ara-C/Thiog vs HL IFN vs placebo	82 months	No differences in DFS	No differences in OS
Anguille et al (Leuk 2011)	362	44-75	IFN vs placebo	Not reported	No differences in DFS	No differences in OS
Baer et al (JCO 2008)	163	60-83	IL-2 vs placebo	Not reported	No differences in DFS	No differences in OS
Willemze et al (Blood 2011)	550	15-60	IL-2 vs placebo	3.6 years	No differences in DFS	No differences in OS
Pautas et al (JCO 2010)	161	50-70	IL-2 vs placebo	49 months	No differences in DFS	No differences in OS
Brune et al (Blood 2006)	160	18-84	Histamine dihydrochloride plus IL-2 vs placebo	47 months	36 month LFS 34% vs 24% (p=0.01)	No differences in OS

Maintenance with immunotherapies, Phase II

- Single arm nivolumab: 15 pts in CR, at high risk for relapse but ineligible for alloSCT (Reville et al, Blood Cancer J 2021), 12- and 24-month estimated OS: 60% and 53%, 2 pts MRD-negative
- A larger, randomized phase 2 study (NCT02275533) of nivolumab for MRD eradication in high-risk AML in CR is ongoing.
- Single-arm lenalidomide in patients with high-risk AML in CR1 or CR2, ineligible for SCT:
  - 28 patients, median follow-up of 22.3 mo,
  - median CR duration 18.7 months, 2-year OS 63%, surpassing historical controls (Aboudalle et al, Blood 2018)

Maintenance with hypomethylating agents

- Recent studies with HMAs have shown some promise in AML patients in CR that are not eligible for alloSCT.
- Three randomized studies have compared strategies using azacitidine maintenance with observation (AML 16, HOVON 97, QUAZAR AML-001)
- One phase II randomized study compared decitabine maintenance with observation (ECOG/ACRIN E2906)
- One randomized study compared decitabine versus «conventional care» for maintenance therapy in AML in CR was completed, but failed to show a benefit for decitabine maintenance *(Boumber et al, Leukenmia 2012).*

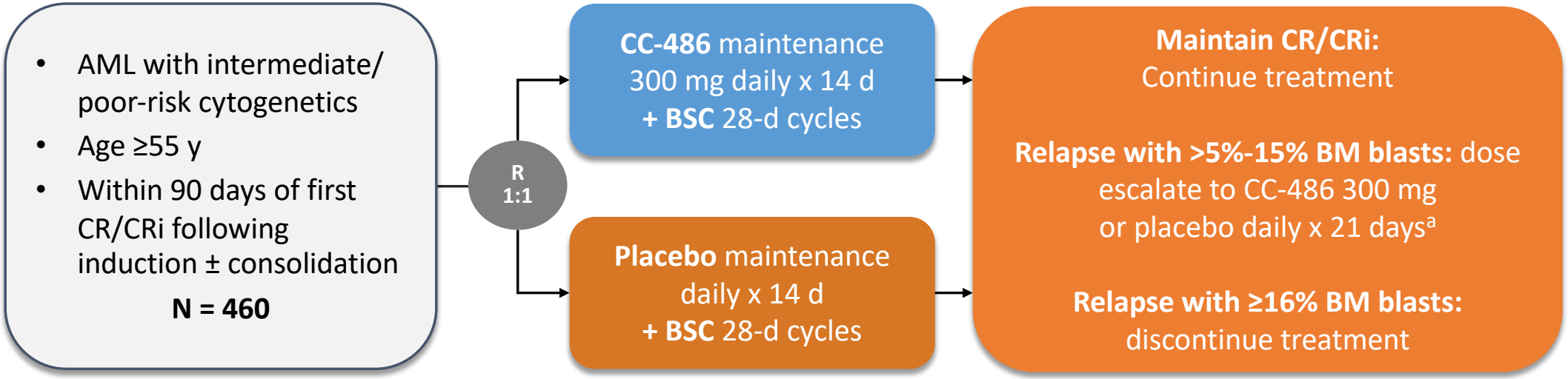
Maintenance with HMAs

Placebo-controlled, randomized studies of maintenance therapy in AML

Trial	Patients entering maintenance randomization	Age (range)	Follow-up	Maintenance regimen	DFS/RFS/LFS	Overall Survival
UK NCRI AML 16 (Burnett et al Haematologica 2015)	530	53-84	50.4 mo	AZA vs placebo	Not reported	No differences in OS
HOVON 97 (Huls et al Blood 2019)	116	60-81	41.4 mo	AZA vs placebo	Median DFS 15.9 vs 10.3 mo	No differences in OS
QUAZAR AML-001 (Wei et al NEJM 2021)	460	55-86	41.2 mo	CC-486 vs placebo	Median RFS 10.2 vs 4.8 mo (p=0.0001)	Median OS 24.7 vs 14.8 mo (p=0.0009)
ECOG ACRIN E2906 (Foran et al Blood 2019)	120	60-85	49.8 mo	Decitabine vs placebo	No differences in DFS	No differences in OS

Phase 3 QUAZAR Study (CC-486-AML-001): CC-486 as Maintenance Therapy in AML[1,2]

- Oral AZA formulation was assessed in the phase 3 QUAZAR study

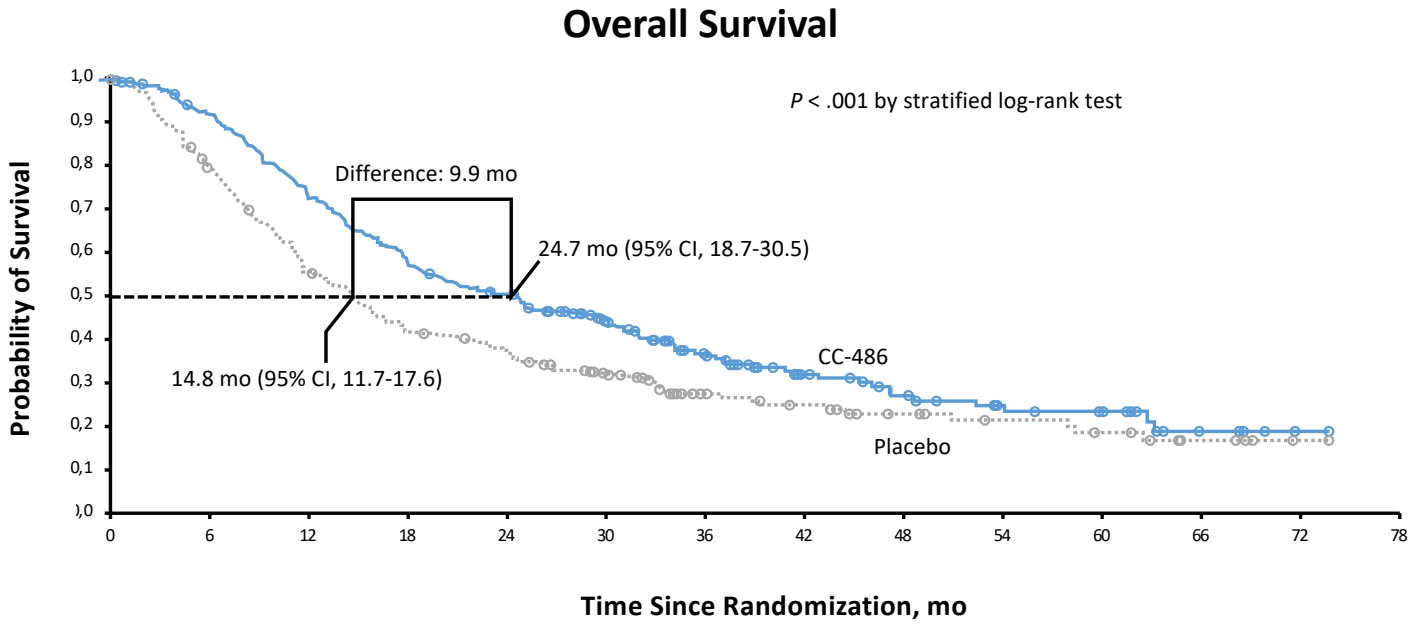


Primary endpoint: OS

[a] May also discontinue treatment based on investigator's decision.

1. https://clinicaltrials.gov/ct2/show/NCT01757535. 2. Roboz GJ et al. *Future Oncol*. 2016;12:293-302.

QUAZAR: Efficacy Outcomes Summary[1]



No. at Risk														
CC-486	238	213	168	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	127	96	82	58	34	27	19	14	11	6	1	0

Relapse-Free Survival (From Randomization)

Median RFS was
10.2 mo with CC-486 vs 4.8 for placebo

- Stratified $P < .001$

1-year RFS was 44.9% in the CC-486 arm
and 27.4% in the placebo arm

1. Wei AH et al. *N Engl J Med*. 2020;383:2526-2537.

QUAZAR: Safety Summary and Practical Points

In the QUAZAR trial, the most common AEs in both arms were grade 1/2 gastrointestinal events[1]

- GI events were predominantly noted during the first 2 treatment cycles (antiemetic prophylaxis recommended in first 2 cycles)
- Common grade 3 or 4 adverse events were neutropenia (in 41% of patients in the CC-486 group and 24% of patients in the placebo group) and thrombocytopenia (in 22% and 21%, respectively)

Based on these data, CC-486 was FDA approved for the continued treatment of patients with AML in first CR/CRi following intensive induction chemotherapy who are unable to complete intensive curative therapy[2]

1. Wei AH et al. *N Engl J Med*. 2020;383:2526-2537. 2. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-onureg-azacitidine-tablets-acute-myeloid-leukemia.

QUAZAR: Recent Prognostic Analysis (ASCO and EHA 2021)

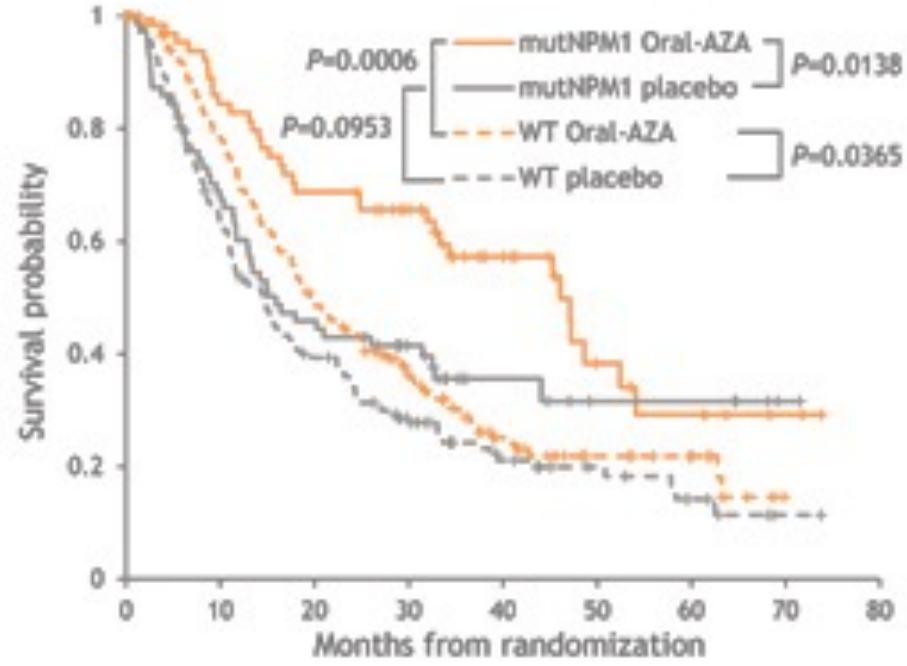
- Oral-AZA reduced the risk of death by 30% and the risk of relapse by 41% vs placebo, independent of baseline characteristics[1,2]

Independently Predicted OS and RFS Outcomes:	Did Not Influence OS or RFS:
✓Cytogenetic risk at diagnosis ✓MRD status at baseline ✓Age (3% increased risk of death with each additional year of age)	✓CR vs CRi response after induction ✓No consolidation vs 2 consolidation cycles

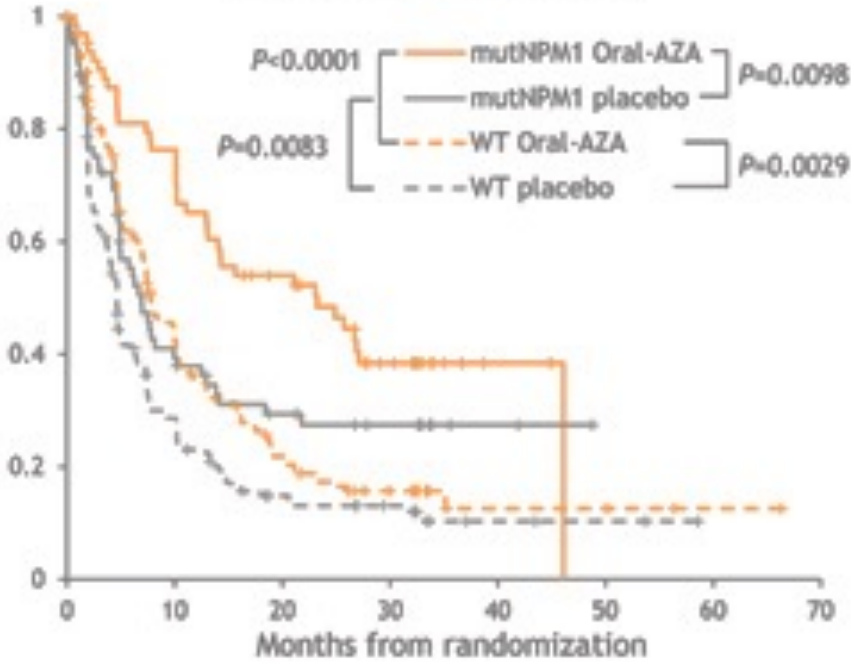
1. Roboz G et al. ASCO 2021. Abstract 7014. 2. Roboz G et al. EHA 2021. Abstract EP428.

Extended OS Benefit With Oral AZA for Patients With *NPM1*-Mutated AML[1]

Overall Survival



Relapse-Free Survival



OS benefit of more than 2.5 years vs placebo (OS for all pts in QUAZAR AML-001 was lengthened by 9.9 months with oral-AZA

Suggests that *NPM1*-mutation status is prognostically favorable overall and independently predictive of increased OS with oral-AZA

1. Dohner H et al. EHA 2021. Abstract S131.

Maintenance with targeted therapies

FLT3-TKI maintenance outside the context of allo-SCT

- 3 trials randomized and placebo-controlled trials (RATIFY, SORAML, and *NCT00373373*) combining FLT3-TKIs with intensive CHT/HMAs included a TKI maintenance therapy after first-line chemotherapy/TKI induction and consolidation.
- In all three trials, TKI maintenance was discontinued once patients underwent HCT.
- A *post hoc* efficacy analysis of the midostaurin-maintenance phase in the RATIFY trial suggested that midostaurin maintenance might not further reduce the probability of relapse, even though RATIFY was not designed to test this.
- In the SORAML study, Sorafenib improved RFS with no impact on OS

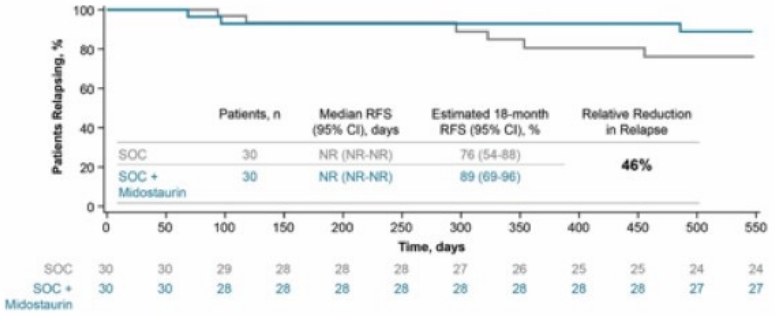
Maintenance after allo-SCT

- AML relapse after alloSCT remains a major concern, with 40% of patients relapsing with a very dismal prognosis.
- Goal in this setting: maintaining remission to allow time for or to cooperate with the GVL effect to eradicate residual leukemic cells.
- Several drugs tested or under exploration in HR AML
  - AZA in HR AML/MDS: no benefit in RFS/OS (*Oran et al, Blood Adv 2020*)
  - LENAMAINT: early discontinuation due to high rate of GVHD
  - Phase III AMADEUS (CC-486) (NCT 04173533)
  - Ven + AZA (NCT 04128501

Post-Allogeneic SCT Maintenance Therapy With Midostaurin RADIUS Trial

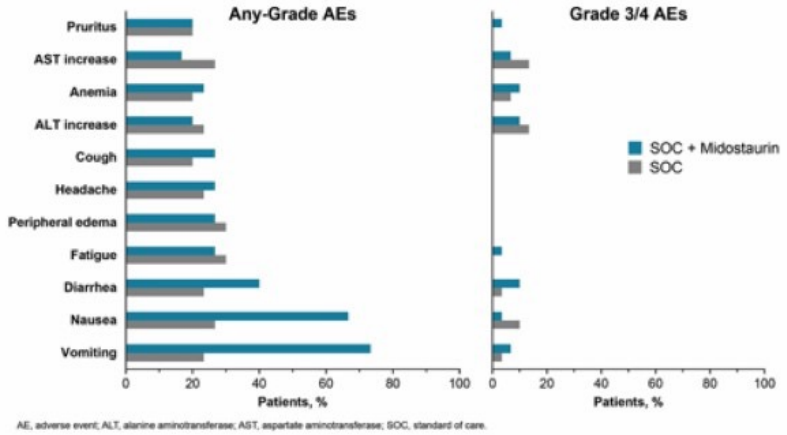
- 60 patients
  - *FLT3*-ITD-positive, AlloSCT in first CR, hem recovery
    - Midostaurin n = 30, SOC n = 30
    - 12 cycles (M n = 16; SOC n = 14)
    - Median exposure to M: 10.5 months
- 18-month RFS
  - M arm: 89%
  - SOC arm: 76%
- AEs
  - GvHD: M arm 73%; SOC arm 70%
  - Serious AEs: M arm 30%; SOC arm 57%
    - Diarrhea, nausea, vomiting, pyrexia

Figure 1: Kaplan-Meier Plot for Relapse-Free Survival at 18 Months After alloHSCT[a]



alloHSCT, allogeneic hematopoietic stem cell transplant; NR, not reached; RFS, relapse-free survival; SOC, standard of care.
[a]RFS was defined as the time from transplant to relapse or death due to the disease.

Figure 2: Any-Grade and Grade 3/4 AEs (occurring in ≥20% of patients overall)

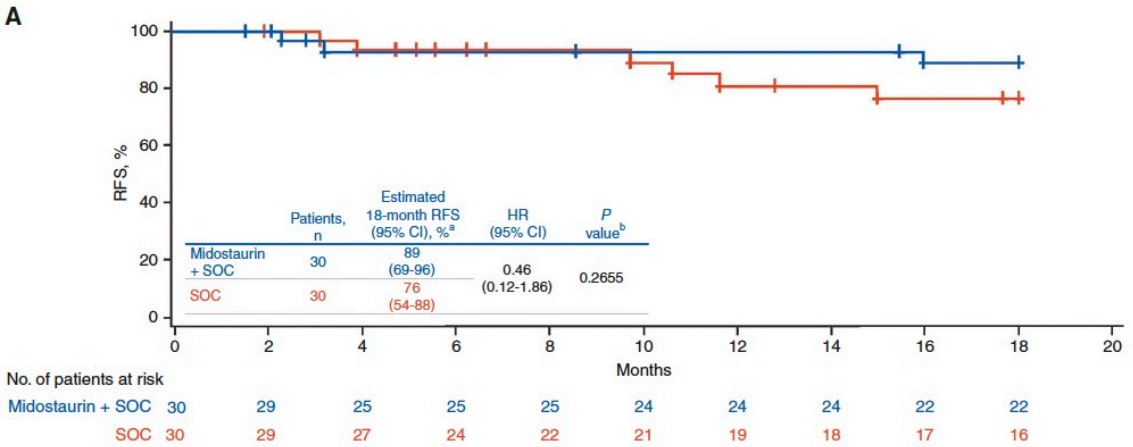


AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOC, standard of care.

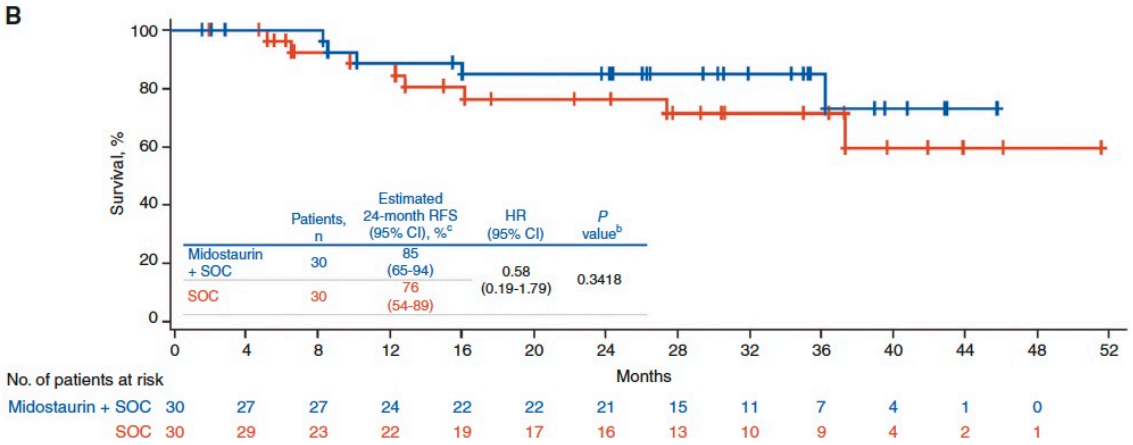
Maziarz RT, et al. *Blood*. 2018. Abstract 662.

RADIUS TRIAL Outcomes after allo-SCT

RFS@18 mo
P=0.2



OS@24 mo
P=0.3

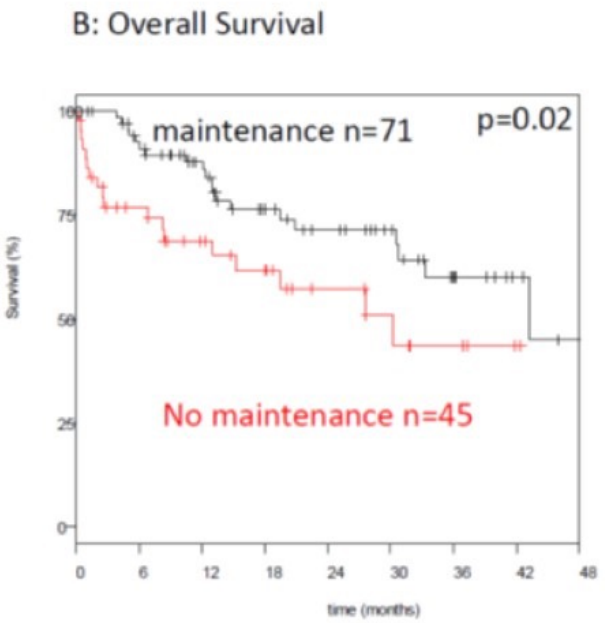


Mariarz R et al, BMT 2021

Post-Allogeneic SCT Maintenance With Midostaurin AMLSG 16-10

- AMLSG 16-10: 284 patients (ITD only)
- AlloHCT in CR1: n = 134 (47%)
- Maintenance in 75 patients (56%)
- Median time post-allo: day 71
- Toxicity
  - GI toxicity: 70%
  - Infections: 51%
  - Blood count: 46%
- Median duration of maintenance: 9 months

HR = 2.51

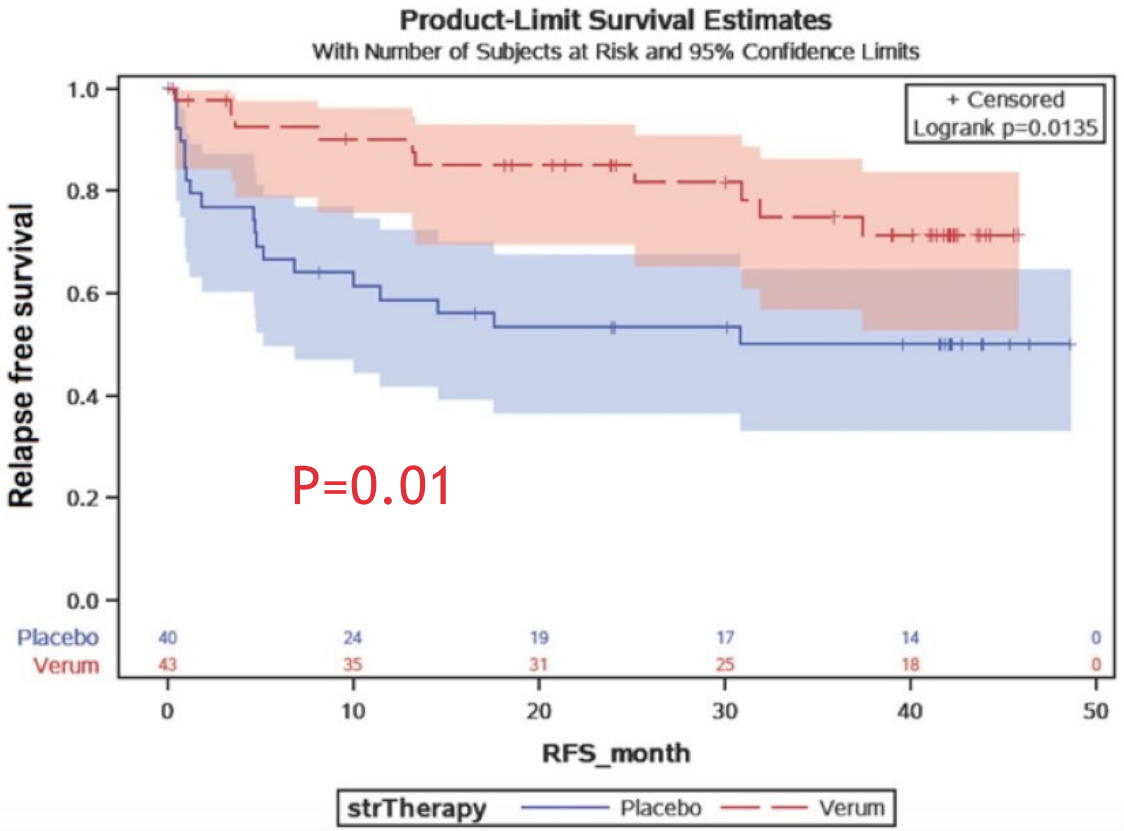


HR = 2.64

Schlenk RF, et al. *Blood*. 2019;133:840-851.

Post-Allogeneic SCT Maintenance Therapy With Sorafenib SORMAIN Trial (EudraCT 2010-018539-16)

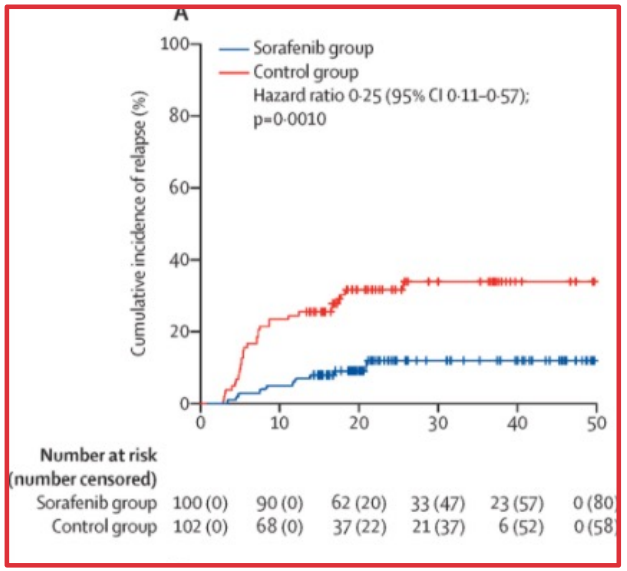
- 83 patients randomized (10-y period)
- Sorafenib or placebo: day 30 to day 100 post allo
- 2-y RFS
  - Placebo: 53.3 %
  - Sorafenib 85.0%
- AEs
  - aGvHD grade ≥ 2: 18% placebo, 24% sorafenib



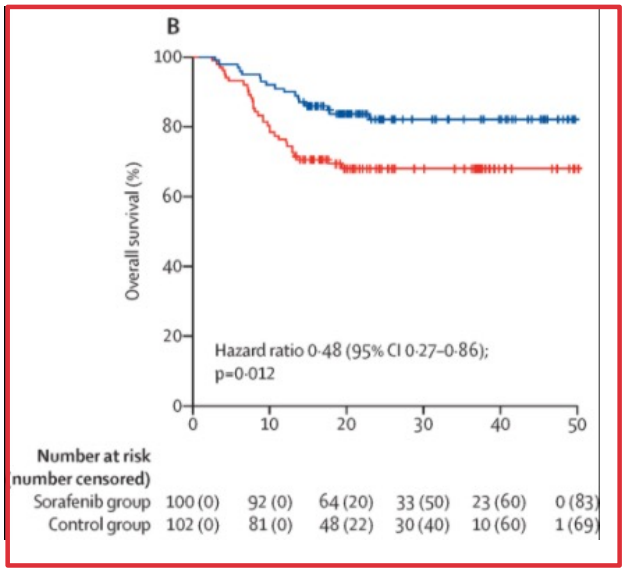
Burchet A, et al. *Blood*. 2018;132:661.

Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial.

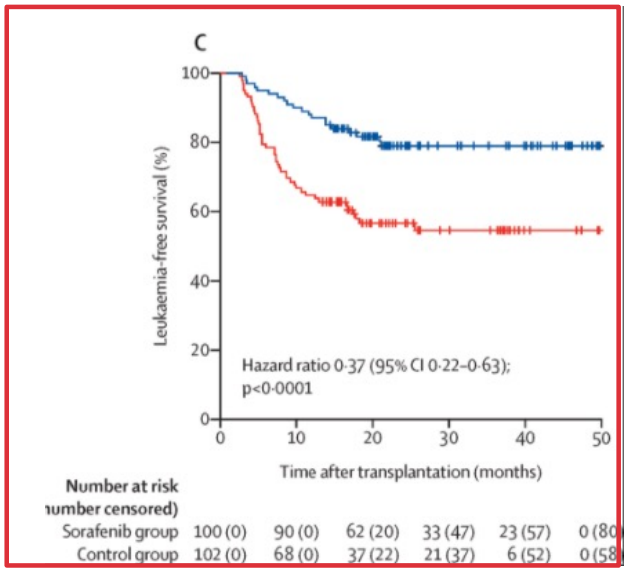
Relapse incidence



OVERALL SURVIVAL



LFS



- Median follow-up was 21.3 after allo-SCT
- 2-year cumulative incidence of relapse: 11.9% (S) and 31.6% (C), (HR, 0.29; 95% CI, 0.15-0.58; *P* <.0001).
- 2-year OS 82.1% (S) vs. 68.0% (C) (HR 0.48, 95%CI: 0.27-0.86; P=0.012)

Xuan L et al, Lancet Oncol 2020

FLT-3 TKIs maintenance and allo-SCT

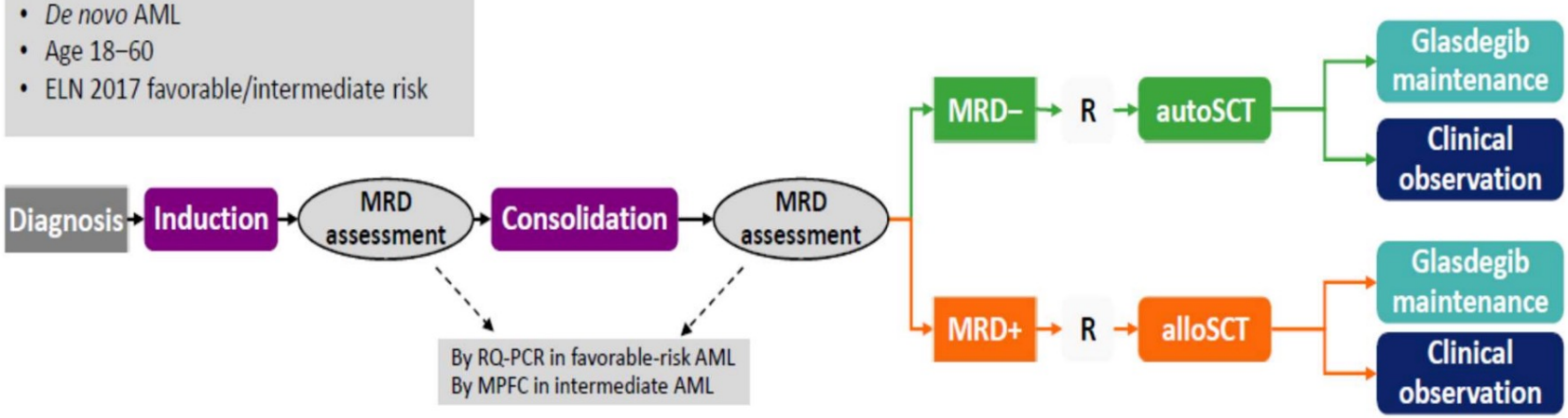
- SORMAIN data and the phase III results from Xuan et al. establish TKI maintenance treatment post HCT as a novel and efficacious therapy.
- Data from these two trials reveal an unprecedented therapeutic potency of an FLT3-kinase inhibitor if applied in the context of CR after HCT.
- In such a context, FLT3-inhibition could maintain CR in the vast majority of patients, who would otherwise relapse… BUT…
- Sorafenib is a multi-targeted TKI and that its efficacy in AML can be also FLT3-ITD independent, as evidenced by the SORAML trial, which treated mainly FLT3-ITD AML patients.

In conclusion, is maintenance *necessary* in AML?

- The biggest advance in AML maintenance currently has been the approval of CC-486, demonstrating improvement in both RFS and OS for patients in CR1 that are ineligible for alloSCT.
- SORMAIN data and the phase III results from Xuan et al. established TKI maintenance treatment post HCT as a novel and efficacious therapy.
- The continued development of better molecularly and immunologically targeted agents may allow for safer treatment and improved outcomes.
- When discussing maintenance therapy in AML going forward, it will be important to clarify the role of post induction consolidation.

GIMEMA AML1819 Trial

- *De novo* AML
- Age 18–60
- ELN 2017 favorable/intermediate risk



Two co-primary endpoints:

1. % MRD-negative after consolidation treatment
2. Disease-free survival in patients randomized to glasdegib maintenance or clinical observation

Induction	Consolidation	Maintenance post-transplant
• GO: 3 mg/m^2 D1, 4, 7*	• GO: 3 mg/m^2 D1*	• Glasdegib 100 mg/day, orally, for up to 1 year or until toxicity/relapse
• Daunorubicin : 60 mg/m^2 D1–3	• Daunorubicin : 50 mg/m^2 D4–6	
• Ara-C: 200 mg/m^2 D1–7	• Ara-C: 500 mg/m^2 BID, D1–6	

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

* Flat dose capped at 5 mg.

Questions?

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