E’ indicata una terapia di mantenimento post-trapianto nella leucemia mieloide acuta?

Le ragioni del Sì

Enrico Maffini,

Trapianto e Terapie cellulari avanzate, Istituto Seràgnoli, Bologna, IRCCS

I have No disclosures

AML relapse after allogeneic HCT

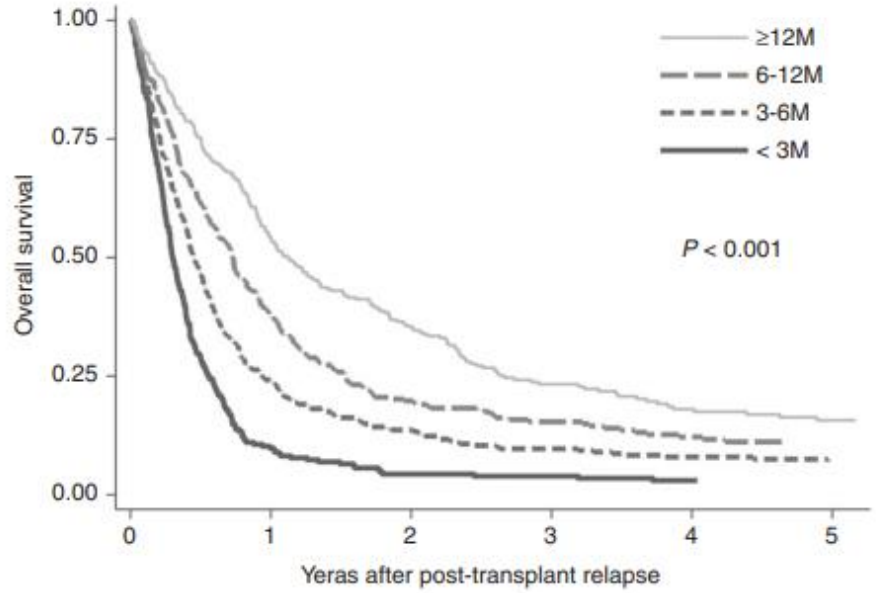
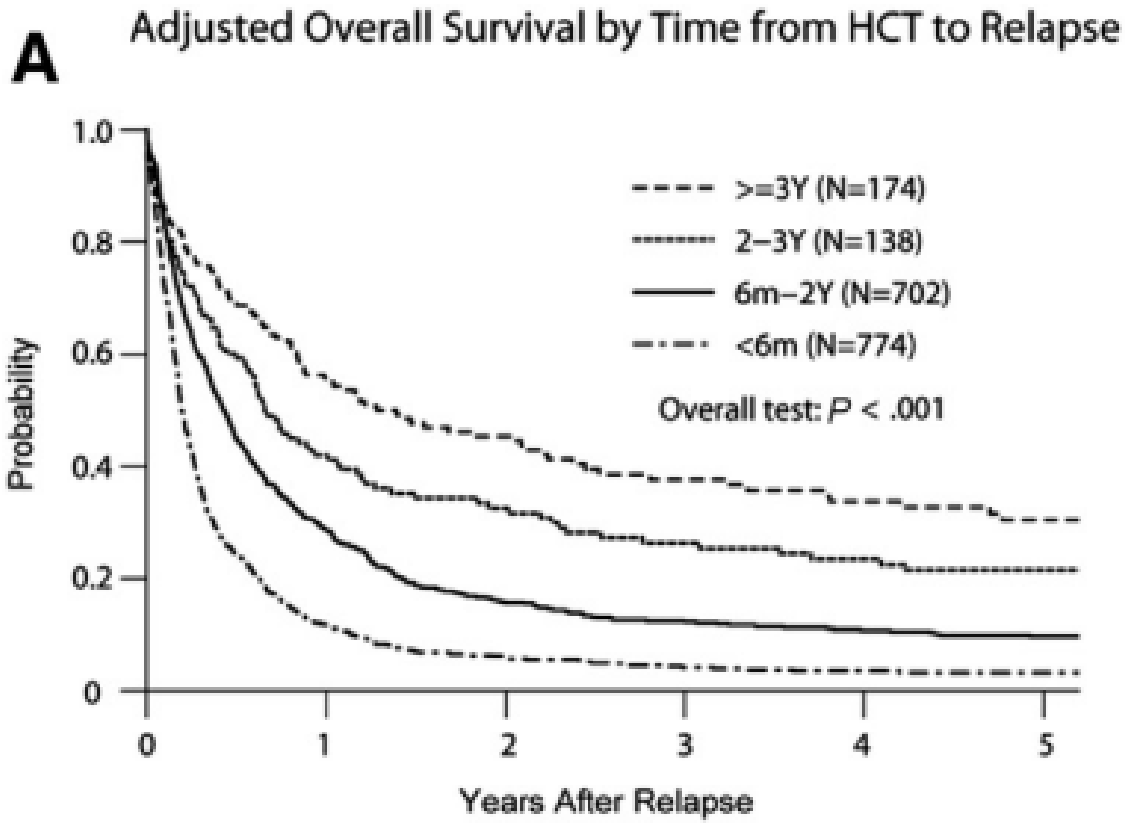


Fig. 2 Overall survival from posttransplant relapse according to the interval from transplantation to relapse. The 2-year probabilities of overall survival were 4% for patients who had suffered posttransplant relapse within 3 months ($n = 275$), 14% in 3–6 months ($n = 355$), 20% in 6–12 months ($n = 297$), and 35% after 12 months ($n = 338$).

Yanada, et al. BMT 2020



Bejanyan, et al. CIBMTR TCT 2015

Maintenance after HCT - *So Many questions, so Few answers*.

Relapse after transplant remains the leading cause of long-term failure.

Over the last decade, intense interest has emerged as to whether maintenance therapy after HCT can reduce relapse and improve post-transplant survival

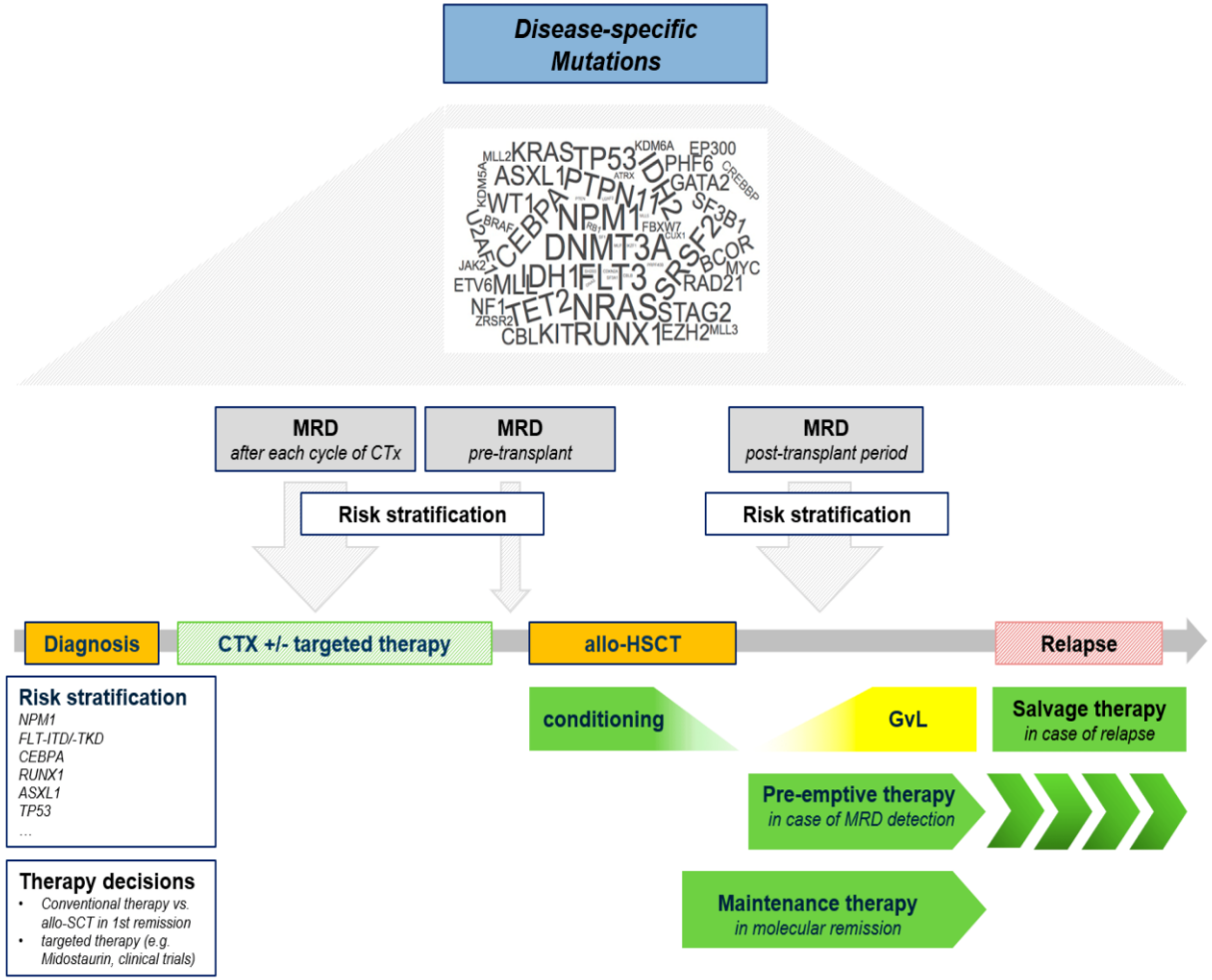
Maintenance – How?

. The choice of maintenance therapy will likely be guided by:

- patient's AML genomics, remission status and transplant eligibility.

. Designing any maintenance therapy in AML should be considered with respect to burdens of:

- additional toxicity, hospital visits and the patient's quality of life.

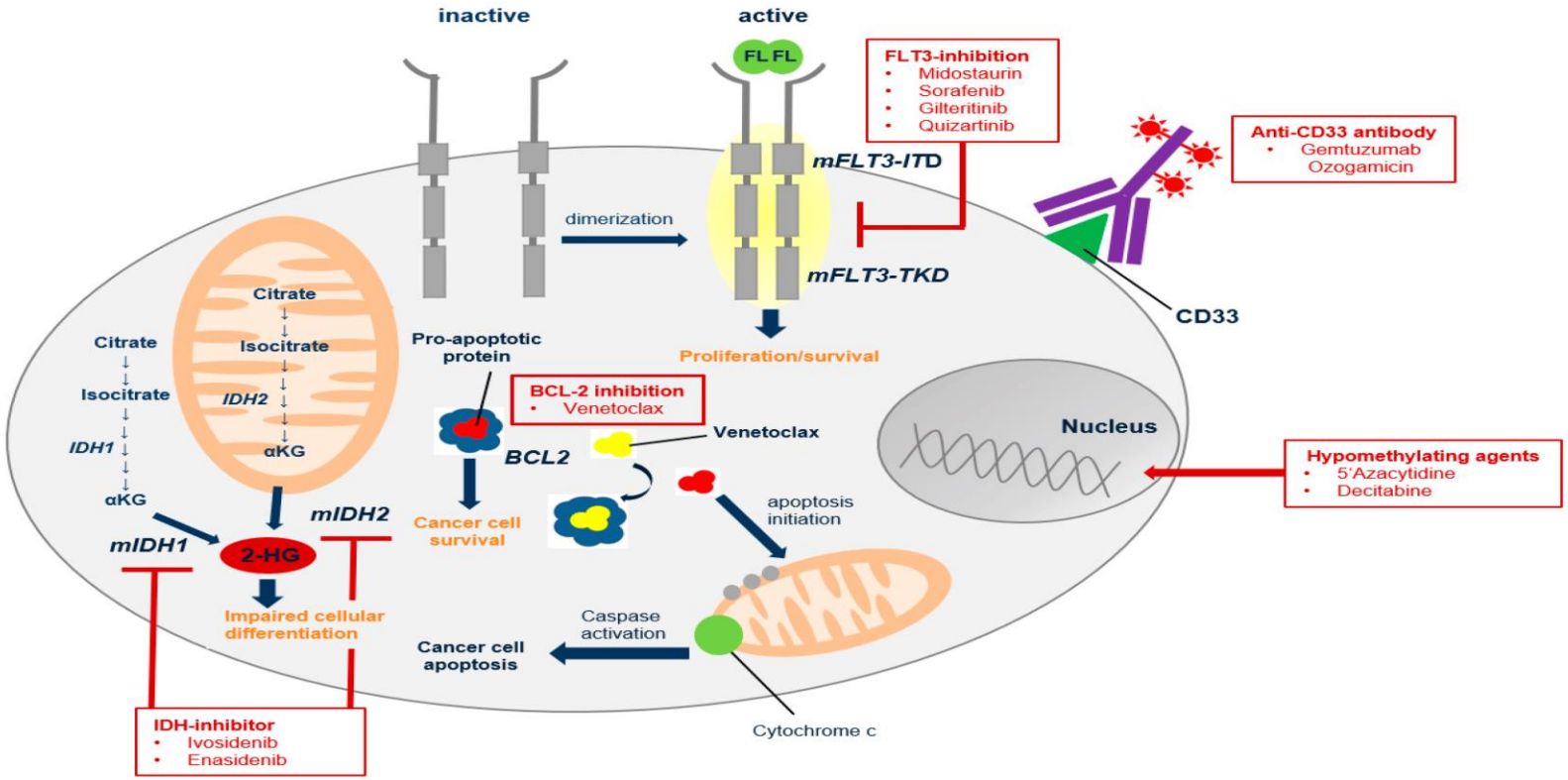


Adapted from Rautenberg, et al. IJMS, 2019

Pharmacologic interventions:

A) Non-targeted strategies

B) Targeted approaches



Adapted from Rautenberg, et al. IJMS, 2019

Non-Targeted Therapy – Hypometilators

Azacitidine

Decitabine

Pre-Emptive HMA in HCT

LEADING ARTICLE

Azacitidine for treatment of imminent relapse in MDS or AML patients after allogeneic HSCT: results of the RELAZA trial

U Platzbecker[1], M Wermke[1], J Radke[1], U Oelschlaegel[1], F Seltmann[1], A Kiani[1], I-M Klut[2], H Knoth[2], C Röllig[1], J Schetelig[1], B Mohr[1], X Graehlert[1], G Ehninger[1], M Bornhäuser[1] and C Thiede[1]

[1]Medical Clinic and Polyclinic I, University Hospital 'Carl Gustav Carus' Technical University of Dresden, Dresden, Germany and [2]Department of Pharmacy, University Hospital 'Carl Gustav Carus' Technical University of Dresden, Dresden, Germany

Measurable residual disease-guided treatment with azacitidine to prevent haematological relapse in patients with myelodysplastic syndrome and acute myeloid leukaemia (RELAZA2): an open-label, multicentre, phase 2 trial

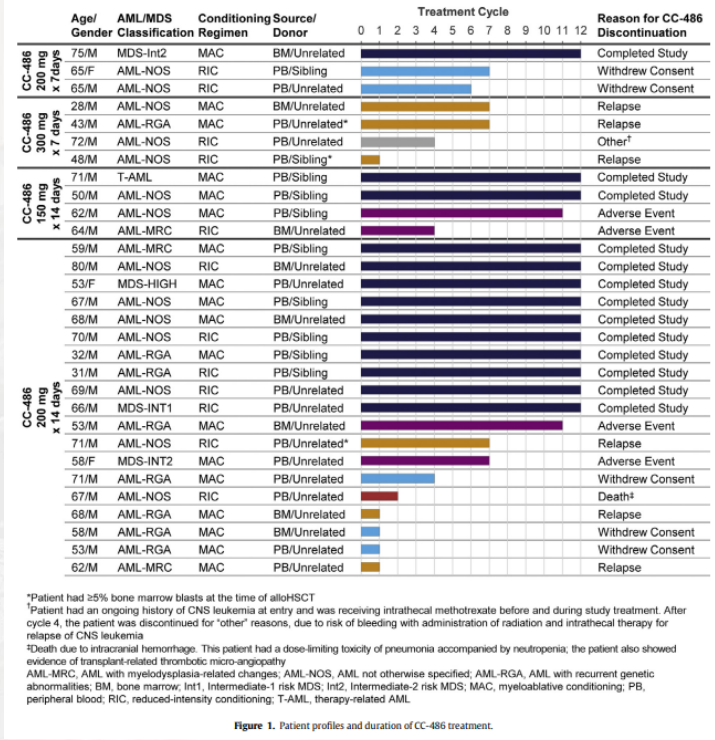
Uwe Platzbecker, Jan Moritz Middeke*, Katja Sockel*, Regina Herbst*, Dominik Wolf*, Claudia D Baldus*, Uta Oelschlägel*, Anke Mütherig*, Lars Fransecky*, Richard Noppeney*, Gesine Bug*, Katharina S Götze, Alwin Krämer*, Tilmann Bochtler*, Matthias Stelljes*, Christoph Groth*, Antje Schubert*, Marika Mende*, Friedrich Stölzel*, Christine Borkmann*, Anne Sophie Kubasch*, Malte von Bonin*, Hubert Serve*, Mathias Hänel*, Ulrich Dührsen*, Johannes Schetelig*, Christoph Röllig*, Michael Kramer*, Gerhard Ehninger*, Martin Bornhäuser*, Christian Thiede**

MRD-guided treatment with AZA
could be an effective strategy to prevent or substantially delay haematological relapse

How about Moving toward a Prophylaxis strategy?

CC-486 Maintenance after Stem Cell Transplantation in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndromes

Marcos de Lima[1*], Betul Oran[2], Richard E. Champlin[2], Esperanza B. Papadopoulos[3], Sergio A. Giralt[3], Bart L. Scott[4], Basem M. William[5], Joel Hetzer[6], Eric Laille[6], Becky Hubbell[6], Barry S. Skikne[6], Charles Craddock[7]



	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

Treatment Cycle: 0 1 2 3 4 5 6 7 8 9 10 11 12

*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

Figure 1. Patient profiles and duration of CC-486 treatment.

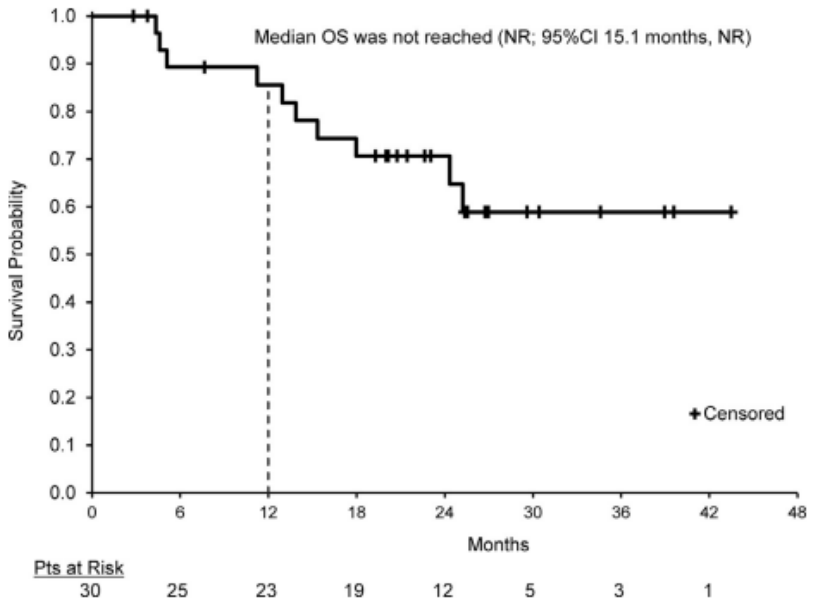


Figure 2. OS from time of alloSCT.

Tolerability and Clinical Activity of Post-Transplantation Azacitidine in Patients Allografted for Acute Myeloid Leukemia Treated on the RICAZA Trial

Charles Craddock [1,2,*], Nadira Jilani [1,2], Shamyla Siddique [1,2], Christina Yap [1,2], Josephine Khan [2], Sandeep Nagra [1], Janice Ward [1], Paul Ferguson [1,2,3], Peter Hazlewood [1,2], Richard Buka [1], Paresh Vyas [4], Oliver Goodyear [3], Eleni Tholouli [5], Charles Crawley [6], Nigel Russell [7], Jenny Byrne [7], Ram Malladi [1,2,3], John Snowden [8], Mike Dennis [9]

Table 1
Demographics of Study Population

Characteristic	Value
Diagnosis	
AML, de novo	24
AML, secondary	13
Karyotype	
Intermediate	30
Poor	7
Age, median (range), yr	60 (40-71)
Sex	
Male	21
Female	16
Disease status at time of transplantation	
CR1	24
CR2	8
First relapse	3
Primary refractory disease	2
Conditioning treatment	
Fludarabine, melphalan, alemtuzumab	34
Fludarabine, cytarabine, amsacrine	3
Donor type	
Sibling	13
Matched unrelated donor	24
CMV status (patient/donor)	
Positive/positive	14
Positive/negative	6
Negative/positive	3
Negative/negative	14
Stem cell source	
Peripheral blood	34
Bone marrow	3

CMV indicates cytomegalovirus.

Table 2
Summary of Hematological and Nonhematological Adverse Events Occurring in >10% of the Patient Population

	Grades 1-2	Grades 3-4	Total
Hematological Adverse Event			
Anemia	16	10	26
Thrombocytopenia	10	13	23
Neutropenia	3	10	13
Nonhematological Adverse Event			
Laboratory investigations — biochemistry	75	10	85
Gastrointestinal (inc. nausea, vomiting, diarrhea, constipation, anorexia)	71	2	73
Infection	35	19	54
Injection site reaction	28	0	28
Pain	21	2	23
Dermatology/skin (rash, mucositis, pruritus, shingles, dry skin, bruising, itching, peeling epidermis, skin breakdown)	21	0	21
Fatigue/lethargy	20	0	20
Pulmonary/upper respiratory (cough, dyspnea, hypoxia)	12	1	13
Neurology (headache, depression, apnea, syncope)	7	2	9
Fever	6	1	8
Cold/flu-like symptoms	8	0	8
Edema	4	0	4

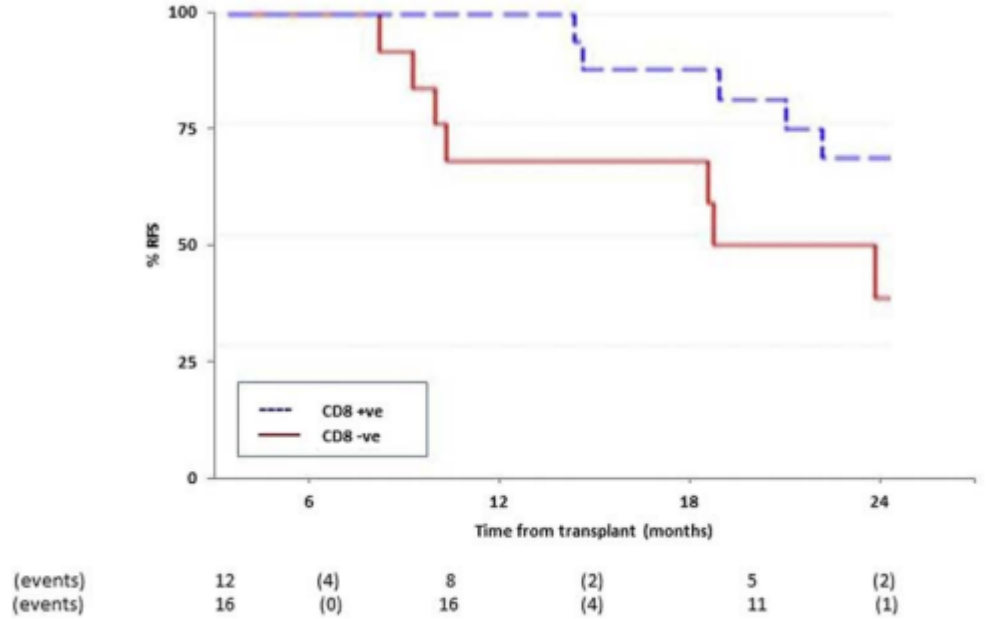


Figure 1. RFS of patients according to post-transplantation CD8$^+$ T cell response to tumor antigens.

These promising results needed a confirmatory phase III randomized trial

A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients

Betül Oran,[1] Marcos de Lima,[2] Guillermo Garcia-Manero,[3] Peter F. Thall,[4] Ruitao Lin,[4] Uday Popat,[1] Amin M. Alousi,[1] Chitra Hosing,[1] Sergio Giralt,[5] Gabriela Rondon,[1] Glenda Woodworth,[1] and Richard E. Champlin[1]

[1]Department of Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, TX; [2]University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH; [3]Department of Leukemia and [4]Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX; and [5]Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Azacitidine Maintenance after Allogeneic Hematopoietic Stem Cell Transplantation in High Risk AML and MDS Patients: Outcomes of a phase III Randomized Clinical Trial

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

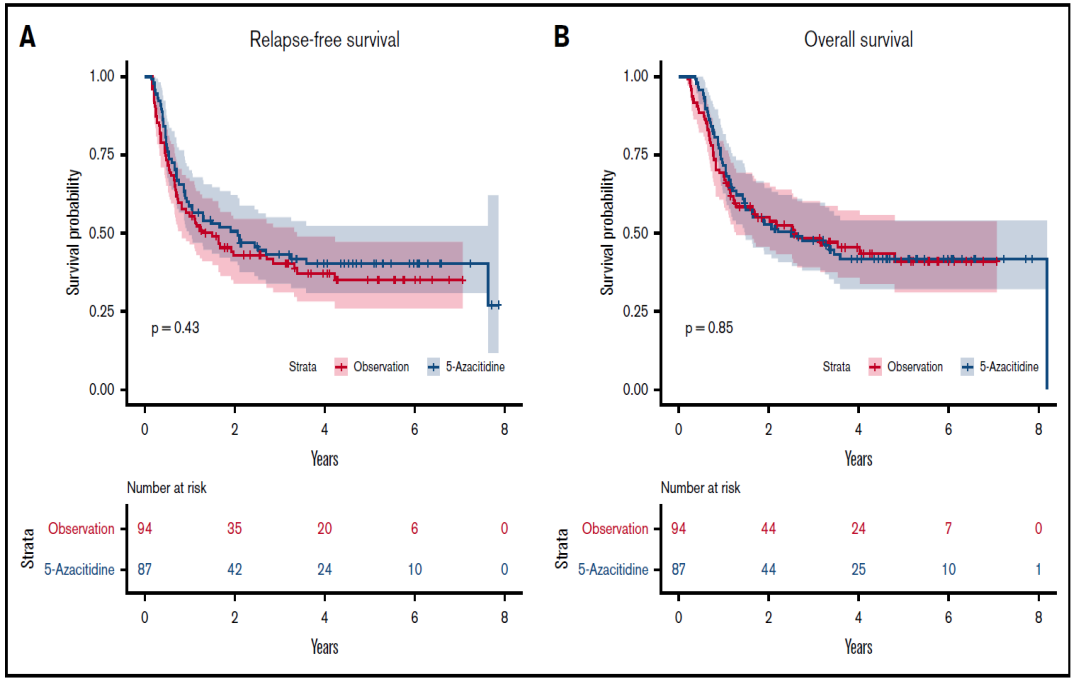
Follow up until:
Completion of 12 cycles of maintenance
Relapse/death
Discontinuation of maintenance

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.



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[1]Department of Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, TX; [2]University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH; [3]Department of Leukemia and [4]Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX; and [5]Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Primary Endpoint - RFS Failed!

- very long enrollment time (> 9 years)
- confounding bias in patients selection
- >75% screen failure rate – more patients excluded than enrolled
- only 27% patients completed the presumed schedule
- expected AZA cycles to be completed 12; effective median: 4
- low-dose AZA schedule (32mg/m2/die x 5 days)

Decitabine

original reports

Effect of rhG-CSF Combined With Decitabine Prophylaxis on Relapse of Patients With High-Risk MRD-Negative AML After HSCT: An Open-Label, Multicenter, Randomized Controlled Trial

Lei Gao, MD, PhD[1]; Yanqi Zhang, PhD[2]; Sanbin Wang, MD, PhD[3]; Peiyan Kong, MD, PhD[1]; Yi Su, MM[4]; Jiong Hu, MD[5]; Ming Jiang, MD[6]; Hai Bai, MD[7]; Tao Lang, MD[8]; Jishi Wang, MD, PhD[9]; Li Liu, MD, PhD[10]; Tonghua Yang, MD[11]; Xiaobing Huang, MD[12]; Fang Liu, MD[4]; Shifeng Lou, MD[13]; Yao Liu, MD, PhD[1]; Cheng Zhang, MD, PhD[1]; Hong Liu, MM[1]; Li Gao, MD, PhD[1]; Jia Liu, MM[1]; Lidan Zhu, MM[1]; Qin Wen, PhD[1]; Ting Chen, MM[1]; Ping Wang, MM[1]; Jun Rao, MD[1]; Min Mao, MD[8]; Cunbang Wang, MD[7]; Xianlin Duan, MD[6]; Le Luo, MD, MM, MS[3]; Xiangui Peng, MM[1]; Kaniel Cassady, PhD[14]; Jiang F. Zhong, PhD[15]; and Xi Zhang, MD, PhD[1]

- 2-year cumulative incidence of relapse in the G-Dec group was 15.0% (95% CI, 8.0% to 22.1%), vs. 38.3% (95% CI, 28.8% to 47.9%) in the non–G-Dec group (P,.01), with HR of 0.32 (95% CI, 0.18 to 0.57; P,.01).

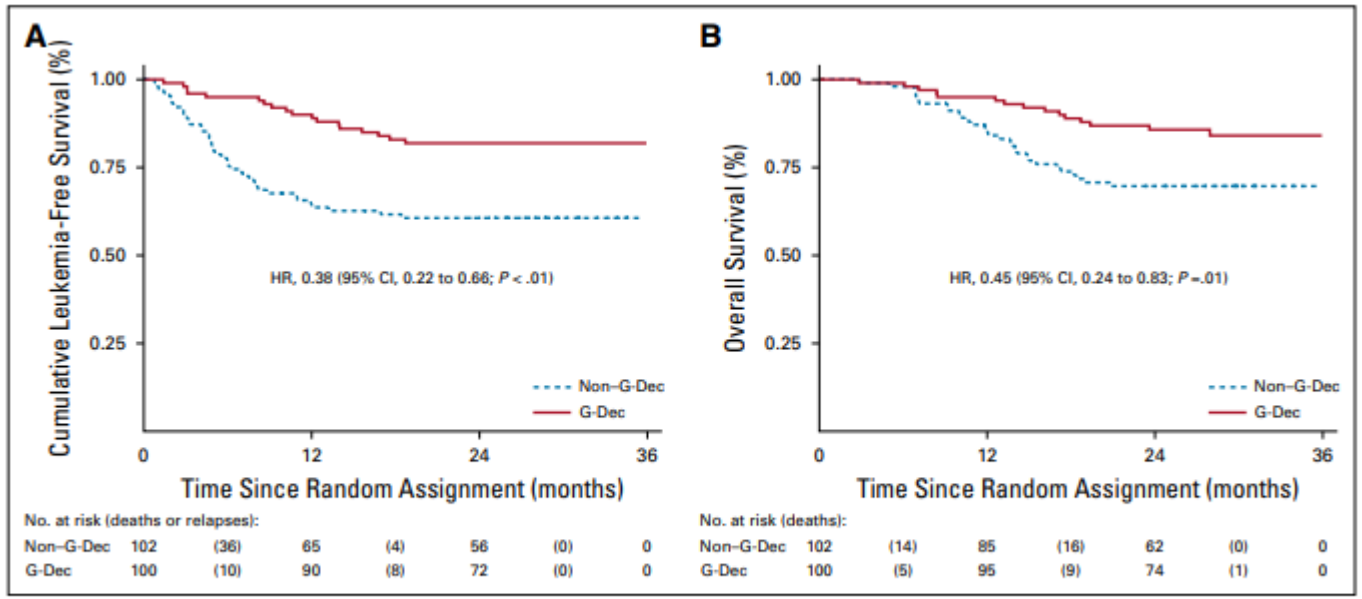
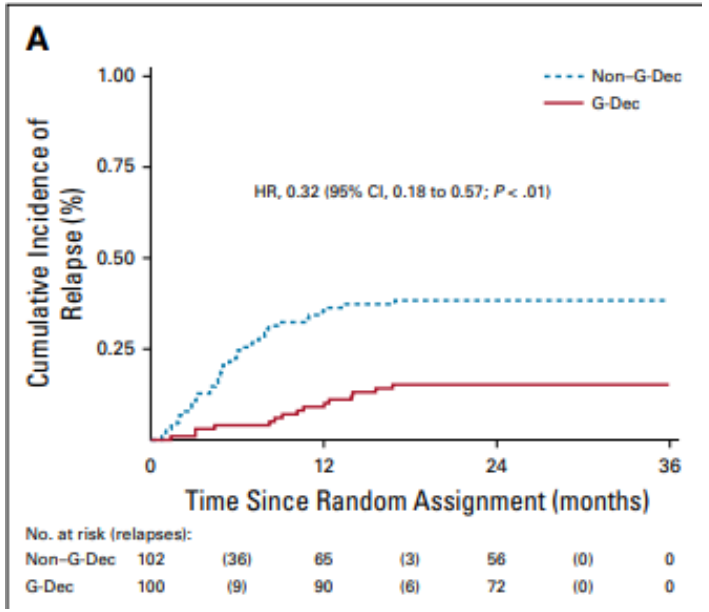


FIG 4. (A) Leukemia-free survival and (B) overall survival among the patients in the two groups. G-Dec, recombinant human granulocyte colony-stimulating factor plus decitabine; HR, hazard ratio.



HMA in HCT - considerations

- Wide applicability respect to Target-therapy BUT lack of clear Efficacy.
- No selective-clone specific pressure -> AZA may retain efficacy respect to clonal heterogeneity after HCT.
- Major toxicity -> citopenias.
- No acute or chronic GVHD rate increase.

HMA in HCT

- **Which categories of patients should be treated with HMA ?**
- Unfavorable cytogenetic risk according to ELN 2017/2022
- Patients with disease not in remission at the time of transplantation
- Pretransplant MRD+ patients receiving RIC conditioning
- Patients in CR>=2
- Primary induction Failure

- **What is the optimal duration of maintenance?**
- The number of cycles ranges from 6 to 12 in the studies

HMA - What's next? 1

AMADEUS: A Double-blind, Phase III, Randomised Study to Compare the Efficacy and Safety of Oral Azacitidine (CC-486) Versus Placebo in Subjects with AML or MDS as Maintenance after Allogeneic Haematopoietic Stem Cell Transplantation.

IMPACT THE UK'S STEM CELL TRANSPLANT CLINICAL TRIALS PARTNERSHIP

The randomized, double-blind, placebo-controlled phase III AMADEUS trial (NCT04173533) is currently ongoing to evaluate the efficacy of maintenance therapy with Oral-AZA in patients with MDS or AML post-HCT.

After transplant, patients receive Oral-AZA 200 mg or placebo on days 1 to 14 of each 28-day treatment cycle, for up to 12 cycles.

Patient stratification prior to randomization is based on conditioning intensity, age (< 60 or ≥ 60 y), and donor type (sibling or unrelated). The primary endpoint is RFS rate 1 year from randomization.

HMA - What's next? 2

Maintenance Therapy with Venetoclax/Azacitidine Can be Safely Given after Venetoclax/FluBu2 RIC Allogeneic Transplantation for the Treatment of High Risk MDS/AML: Results of a Phase 1 Study

Jacqueline S. Garcia, Haesook T Kim, Jennifer Brock, H. Moses Murdock, Corey S. Cutler, Daniel J. DeAngelo, Christopher J. Gibson, Mahasweta Gooptu, Vincent Ho, John Koreth, Marlise R. Luskin, Sarah Nikiforow, Rizwan Romee, Roman M Shapiro, Richard M. Stone, Martha Wadleigh, Eric S. Winer, Michela Ansuinelli, Eliza Elliot, Geoffrey Fell, Hannah Karp, Jeremy Ryan, Anthony G. Letai, Coleman Lindsley, Robert J Soiffer, Joseph H. Antin, Fiona Loschi, Jerome Ritz

NIH U.S. National Library of Medicine

ClinicalTrials.gov

ClinicalTrials.gov Identifier: NCT03613532

Part 2 post-transplant period includes therapy with azacitidine and venetoclax. Dose escalation will occur using a 10+10 approach.

- Venetoclax: 14 doses for 8-12 cycles based on level assigned
- Azacitidine: 5 doses for 8-12 cycles based on level assigned

Part 3 post-transplant period includes therapy with oral decitabine/cedazuridine and venetoclax. Dose escalation will occur using a 10+10 approach.

- Venetoclax: 14 doses for 8 cycles
- Decitabine/cedazuridine: 3 doses for 8 cycles

CLINICAL TRIALS AND OBSERVATIONS | DECEMBER 17, 2021

Adding venetoclax to fludarabine/busulfan RIC transplant for high-risk MDS and AML is feasible, safe, and active

Clinical Trials & Observations

Jacqueline S. Garcia, Haesook T. Kim, H. Moses Murdock, Corey S. Cutler, Jennifer Brock, Mahasweta Gooptu, Vincent T. Ho, John Koreth, Sarah Nikiforow, Rizwan Romee, Roman Shapiro, Fiona Loschi, Jeremy Ryan, Geoffrey Fell, Hannah Q. Karp, Fabienne Lucas, Annette S. Kim, Danielle Potter, Thelma Mashaka, Richard M. Stone, Daniel J. DeAngelo, Anthony Letai, R. Coleman Lindsley, Robert J. Soiffer, Joseph H. Ant

DANA-FARBER CANCER INSTITUTE

HMA - What's next? 3

Eprenetapopt Plus Azacitidine After Allogeneic Hematopoietic Stem-Cell Transplantation for *TP53*-Mutant Acute Myeloid Leukemia and Myelodysplastic Syndromes

Check for updates

Asmita Mishra, MD[1]; Roni Tamari, MD[2]; Amy E. DeZern, MD[3]; Michael T. Byrne, DO[4]; Mahasweta Gooptu, MD[5]; Yi-Bin Chen, MD[6]; ...

Data derived from
Mishra A, et al. *J Clin Oncol*. 2022;doi:10.1200/JCO.22.00181.

Knowledge Generated

Post-HCT maintenance with eprenetapopt plus azacitidine was well tolerated with acceptable safety. The median relapse-free survival of 12.5 months and the overall survival of 20.6 months were encouraging in this high-risk population.

Relevance

Maintenance therapy with the eprenetapopt and azacitidine combination has the potential to improve post-HCT outcomes in patients with m*TP53* AML or MDS.

Although RFS and OS both appear to be superior to historical comparisons, it bears mention that only 55 of the 84 screened patients were transplanted and only 33 were started on maintenance therapy. Further, only 13 patients ultimately completed the full planned 12 months of maintenance. Thus, the patients analyzed may well not be representative of the full cohort of TP53-mutant MDS and AML.

Pretransplant TP53 variant allele frequency did not appear to correlate with outcomes for those 33 patients who received the maintenance therapy.

Targeted Therapy – FLT3 Inhibitors

FLT3-mutant AML disease

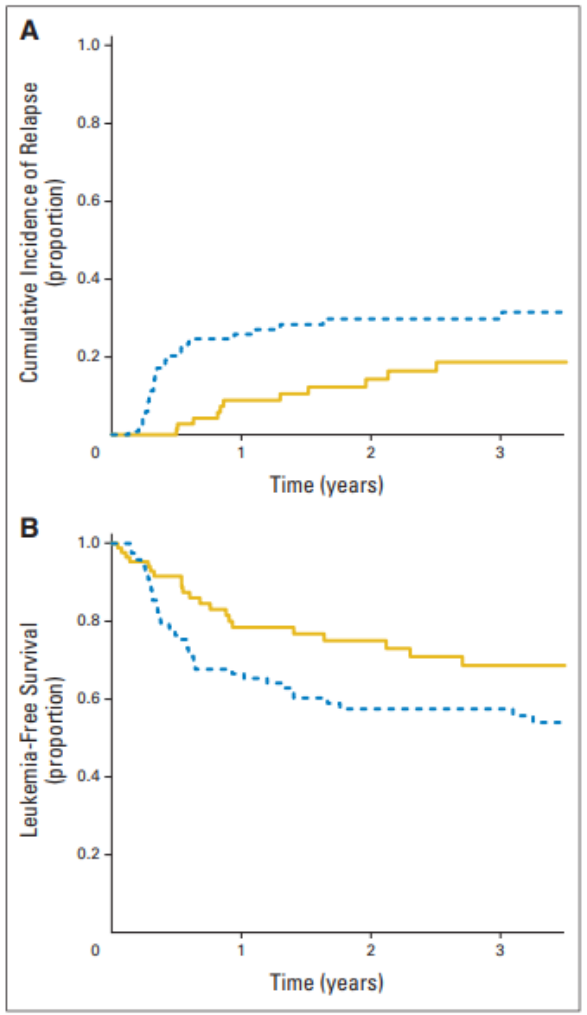
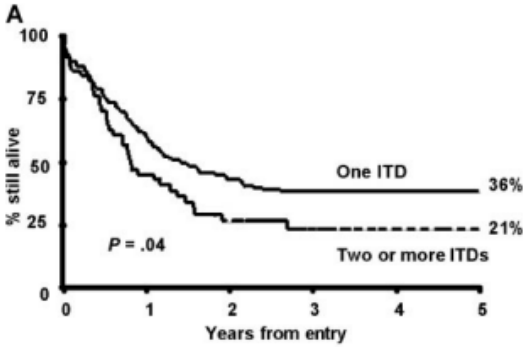


Fig 1. Outcome after allogeneic transplantation performed in first complete remission for patients with acute myeloid leukemia and normal cytogenetics according to the presence (dashed line) or absence (solid line) of internal tandem duplication of *FLT3* gene. (A) Estimated probability of 2 years of cumulative incidence of relapse; (B) leukemia-free survival after transplantation at 2 years.

Impact of FLT3 Internal Tandem Duplication on the Outcome of Related and Unrelated Hematopoietic Transplantation for Adult Acute Myeloid Leukemia in First Remission: A Retrospective Analysis

Salut Brunet, Myriam Labopin, Jordi Esteve, Jan Cornelissen, Gerard Socié, Anna P. Iori, Leo F. Verdonck, Liisa Volin, Alois Gratwohl, Jorge Sierra, Mohamad Mohty, and Vanderson Rocha



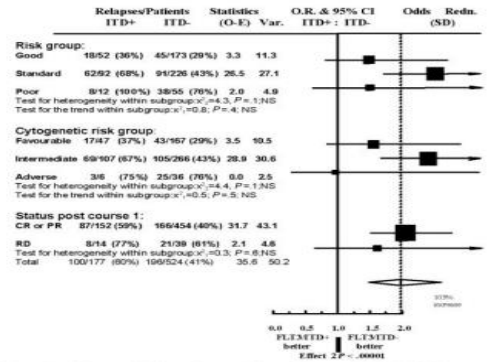
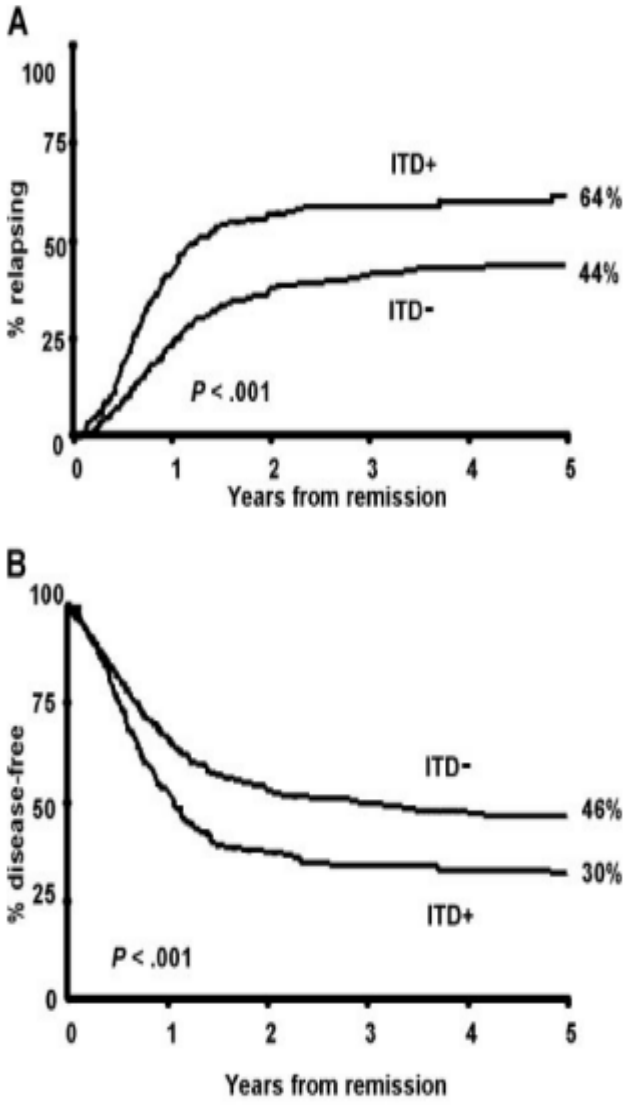


Figure 2. Relapse risk in patients with or without a FLT3/ITD. Patients are grouped according to risk category, cytogenetic risk category, or BM status after course 1 of chemotherapy.

The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials

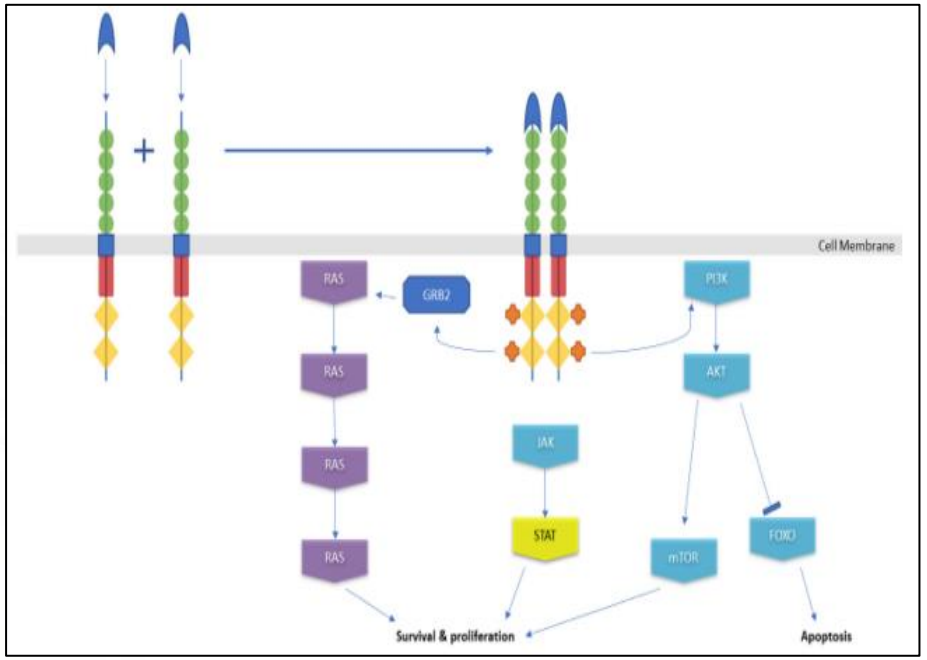
Panagiotis D. Kottaridis, Rosemary E. Gale, Marion E. Frew, Georgina Harrison, Stephen E. Langabeer, Andrea A. Belton, Helen Walker, Keith Wheatley, David T. Bowen, Alan K. Burnett, Anthony H. Goldstone, and David C. Linch

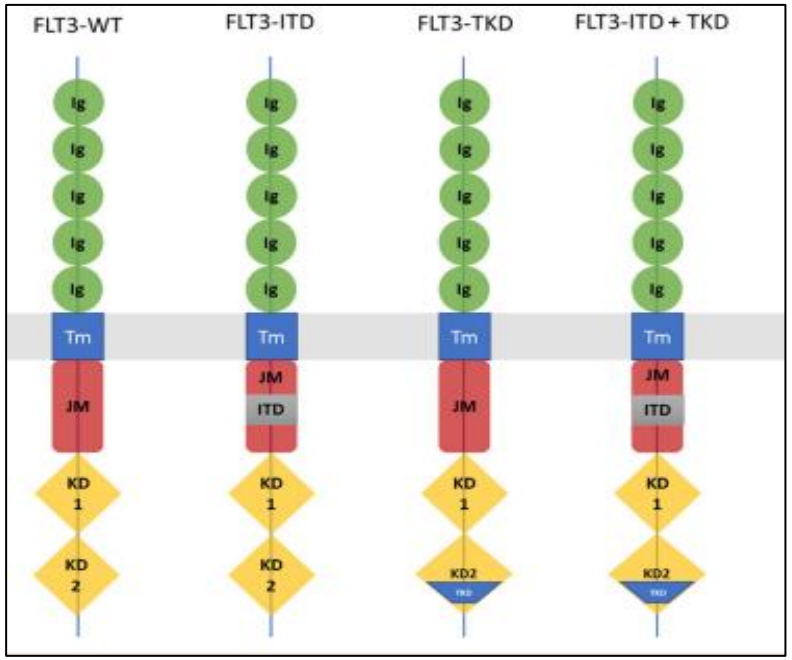


Characteristics of FMS-Like Tyrosine Kinase 3 Inhibitors

Target	Midostaurin	Gilteritinib	Sorafenib	Quizartinib	Crenolanib
FLT3-ITD	■	■	■	■	■
FLT3-TKD	■	■			■
c-KIT	■		■	■	
PDGFR-α					■
PDGFR-β	■		■		■
VEGFR-1	■		■		
VEGFR-2			■		
VEGFR-3	■				
PKC	■				
Syk	■				
Flk-1	■				
Akt	■				
PKA	■				
Fgr	■				
Src	■				
RAF			■		
RET			■	■	
AXL		■			
LTK		■			
ALK		■			
CSF1R				■	

Drug (Pre-market designation)	Inhibits *FLT ITD and/or TKD*	Gen.	Type
Midostaurin (PKC412)	ITD + TKD	1st	I
Sorafenib (DB00398)	ITD only	1st	II
Gilteritinib (ASP2215)	ITD + TKD	2nd	I
Crenolanib (CP-868-596)	ITD + TKD	2nd	I
Quizartinib (AC220)	ITD only	2nd	II





Elli D. Novatcheva et al. Clinical Lymphoma, Myeloma and Leukemia, Vol. 22, No. 3, e161–e184 (2021).

original reports

Sorafenib Maintenance After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia With *FLT3*–Internal Tandem Duplication Mutation (SORMAIN)

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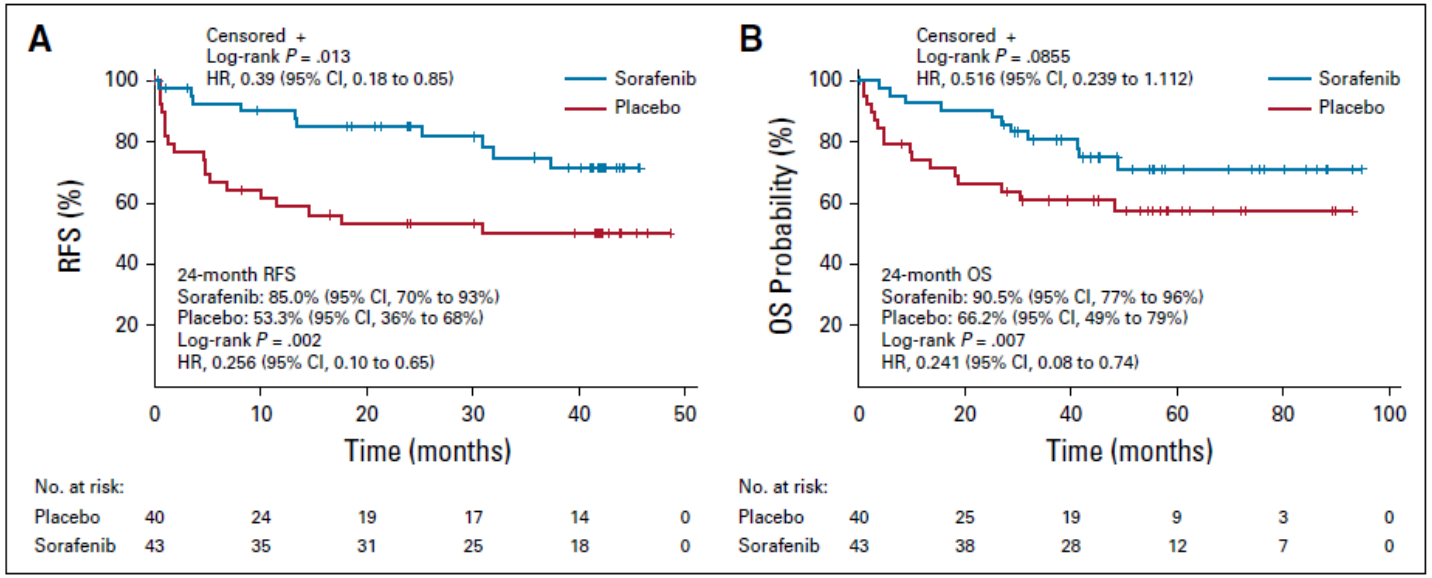

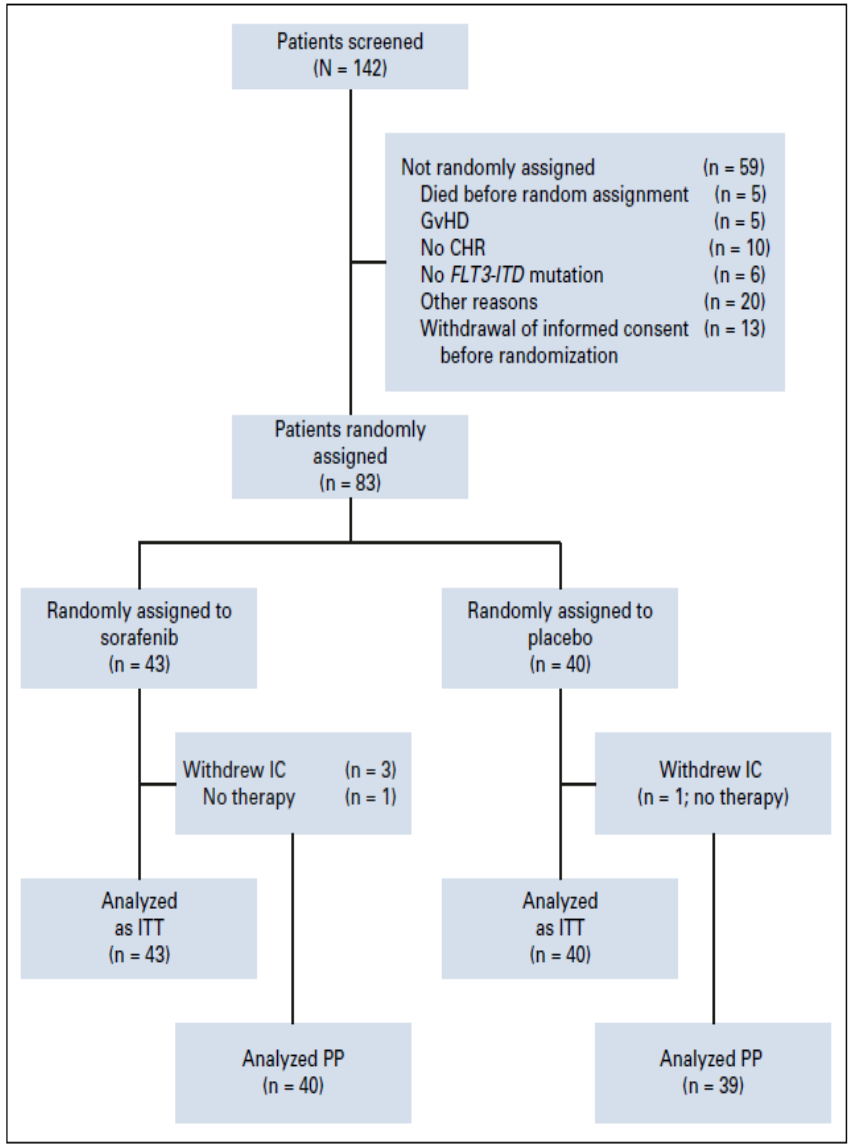

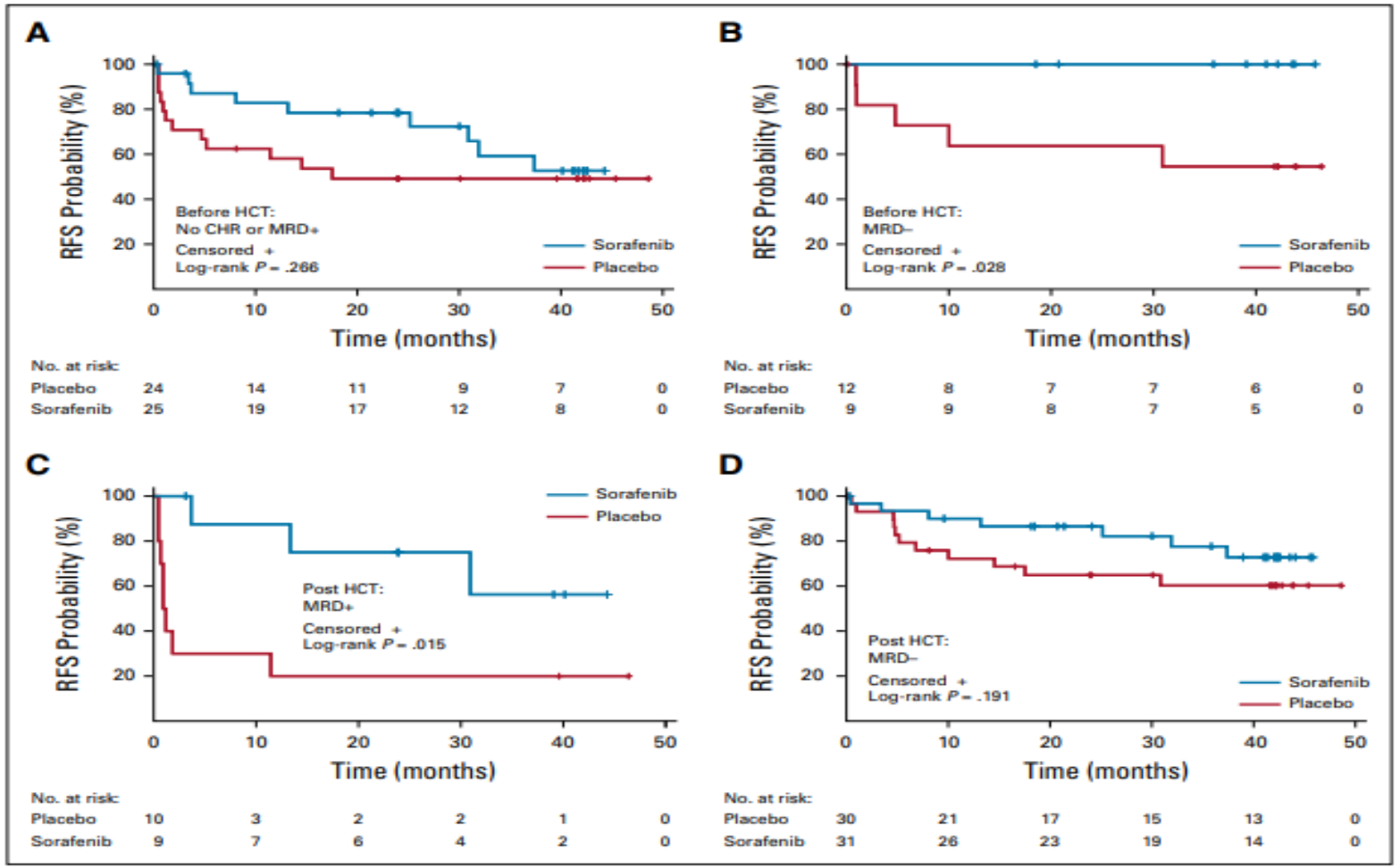

FIG 3. Distribution of relapse-free survival (RFS) in the sorafenib and placebo treatment groups by minimal residual disease level pre– and post–stem cell transplantation. (A) Kaplan-Meier curves for RFS probabilities in non–complete hematologic remission (CHR) patients or CHR patients with detectable minimal residual disease (MRD; no CHR or MRD+) versus (B) undetectable MRD (MRD−) before hematopoietic stem cell transplantation (HCT). MRD was defined as detectable nucleophosmin 1 mutations (*NPM1*^{mut}) mRNA, or, in *NPM1* wild type acute myeloid leukemia, FMS-like tyrosine kinase 3–internal tandem duplication mRNA. (C) Kaplan-Meier curves for RFS probabilities in the sorafenib group and the placebo group with detectable MRD (MRD+) or (D) undetectable MRD (MRD−) post-HCT at the time of randomization. Tick marks indicate censoring of data. Survival differences were assessed using log-rank tests.

- MRD-negative patients before HCT derived the strongest benefit from sorafenib maintenance.
- The benefit from sorafenib was relevant in the MRD+ post-HCT cohort, which had a statistically significantly better RFS with sorafenib than with placebo.

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

Li Xuan, Yu Wang*, Fen Huang*, Zhiping Fan*, Yajing Xu, Jing Sun, Na Xu, Lan Deng, Xudong Li, Xinquan Liang, Xiaodan Luo, Pengcheng Shi, Hui Liu, Zhixiang Wang, Ling Jiang, Chunzi Yu, Xuan Zhou, Ren Lin, Yan Chen, Sanfang Tu, Xiaojun Huang, Qifa Liu*

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Summary

Background Findings of retrospective studies suggest that sorafenib maintenance post-transplantation might reduce relapse in patients with *FLT3* internal tandem duplication (*FLT3*-ITD) acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation. We investigated the efficacy and tolerability of sorafenib maintenance post-transplantation in this population.

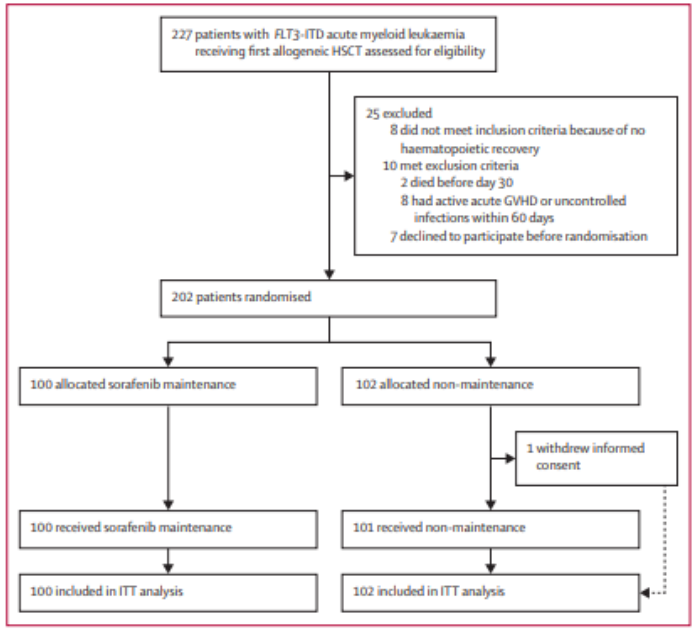
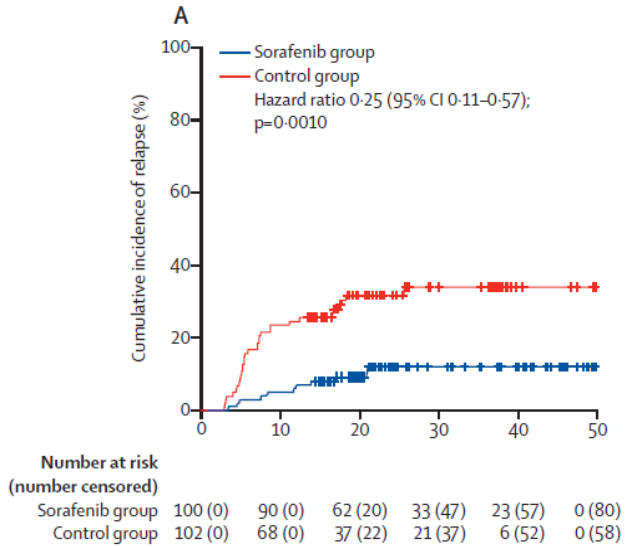


Figure 1: Trial profile
FLT3-ITD=*FLT3* internal tandem duplication. GVHD=graft-versus-host disease. HSCT=haematopoietic stem-cell transplant. ITT=intention to treat.



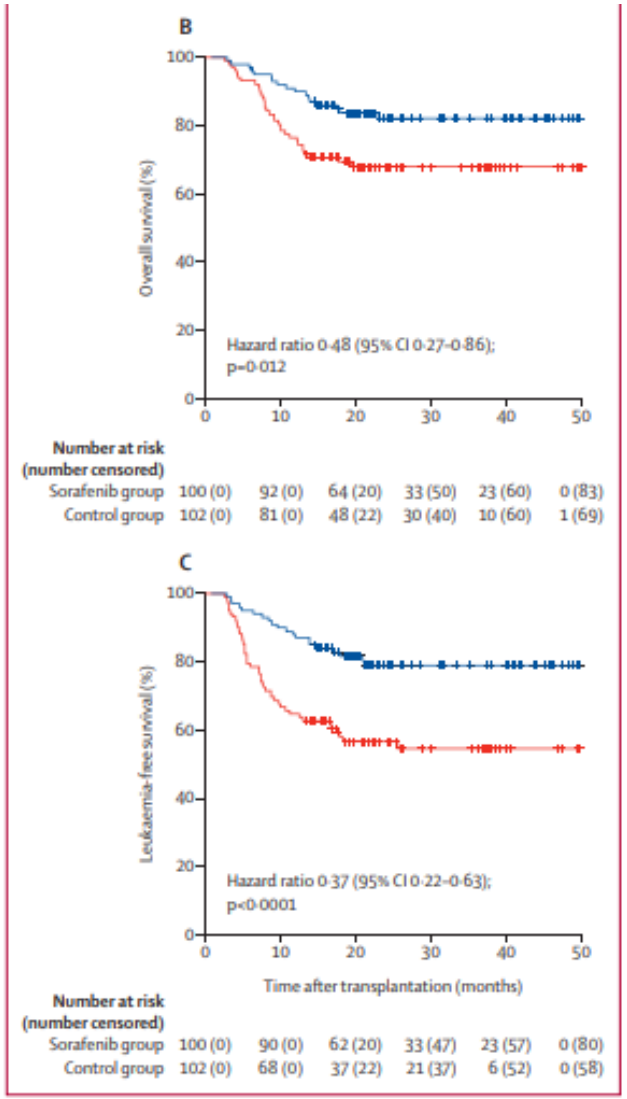


Figure 2: Cumulative incidence of leukaemia relapse (A), overall survival (B), and leukaemia-free survival (C)

Sorafenib maintenance after allogeneic haemopoietic stem-cell transplantation in patients with *FLT3*-ITD acute myeloid leukaemia: long-term follow-up of an open-label, multicentre, randomised, phase 3 trial

Prof Li Xuan, MD * • Prof Yu Wang, MD * • Kaibo Yang, MD * • Ruoyang Shao, MD * • Fen Huang, MD * • Zhiping Fan, MD • et al. Show all authors • Show footnotes

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THE LANCET
Haematology

Extended follow-up showed (median FU 60.4 months):

. improved OS: 72% [95% CI 62·1-79·7] vs 55·9% [45·7-64·9]; p=0·011),

. better LFS: 70% [60·0-78·0] vs 49% [39·0-58·3]; 0·47, 0·30-0·73; p=0·0007),

. better GRFS (58% [47·7-67·0] vs 39.2% [29·8-48·5]; 0·56, 0·38-0·83; p=0·0030),

. lower cumulative incidence of Relapse (15·0% [8·8-22·7] vs 36·3% [27·0-45·6]; 0·33, 0·18-0·60; p=0·0003)

. no increase in NRM (15·0% [8·8-22·7] vs 14·7% [8·6-22·3]; 0·79, 0·39-1·62; p=0·98)

Clinical practice recommendation on hematopoietic stem cell transplantation for acute myeloid leukemia patients with *FLT3*-internal tandem duplication: a position statement from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Ali Bazarbachi,[1,2] Gesine Bug,[3] Frederic Baron,[4] Eolia Brissot,[5] Fabio Ciceri,[6] Iman Abou Dalle,[1] Hartmut Döhner,[7] Jordi Esteve,[8] Yngvar Floisand,[9,10] Sebastian

Ferrata Storti Foundation

Haematologica 2020
Volume 105(6):1507-1516

Post-transplant maintenance

Post-transplant systemic maintenance therapy with a FLT3 inhibitor for patients who underwent allo-SCT for *FLT3*-ITD AML is recommended (except for patients with active acute GvHD).

In the absence of an appropriate clinical trial, sorafenib could be considered as the preferred option, but the role of other FLT3 inhibitors warrants investigation.

Maintenance treatment should be initiated as soon as possible after disease evaluation, including MRD assessment, especially in patients with MRD-positive AML before or after allo-SCT, provided there is adequate hematologic reconstitution.

The recommended post-transplant maintenance is sorafenib at a dose of 400 mg/day in two divided doses. Patients with MRD-positive disease may receive 800 mg/day in two divided doses, to be adapted according to tolerance. Sorafenib should be transiently discontinued in the case of GvHD requiring systemic treatment with corticosteroids, but may be cautiously resumed once remission of GvHD is documented.

Ongoing studies will determine whether midostaurin, gilteritinib or other FLT3 inhibitors will become additional alternatives in this setting.

Maintenance therapy duration is not firmly established, but a minimum of 2 years is recommended, depending on tolerance.

Any role for TKIs other than Sorafenib?

MYELOID NEOPLASIA

Midostaurin added to chemotherapy and continued single-agent maintenance therapy in acute myeloid leukemia with *FLT3*-ITD

Richard F. Schlenk,[1-3] Daniela Weber,[1] Walter Fiedler,[4] Helmut R. Salih,[5] Gerald Wulf,[6] Hans Salwender,[7] Thomas Schroeder,[8] Thomas Kindler,[9] Michael Lübbert,[10] Dominik Wolf,[11] Jörg Westermann,[12] Doris Kraemer,[13] Katharina S. Götze,[14] Heinz-August Horst,[15] Jürgen Krauter,[16] Michael Girschikofsky,[17] Mark Ringhoffer,[18] Thomas Südhoff,[19] Gerhard Held,[20] Hans-Günter Derigs,[21] Roland Schroers,[22] Richard Greil,[23] Martin Grießhammer,[24] Elisabeth Lange,[25] Alexander Burchardt,[26] Uwe Martens,[27] Bernd Hertenstein,[28] Lore Marretta,[29] Michael Heuser,[16] Felicitas Thol,[16] Verena I. Gaidzik,[1] Wolfgang Herr,[9] Julia Krzykalla,[30] Axel Benner,[30] Konstanze Döhner,[1] Arnold Ganser,[16] Peter Paschka,[1] and Hartmut Döhner,[1] on behalf of the German-Austrian AML Study Group

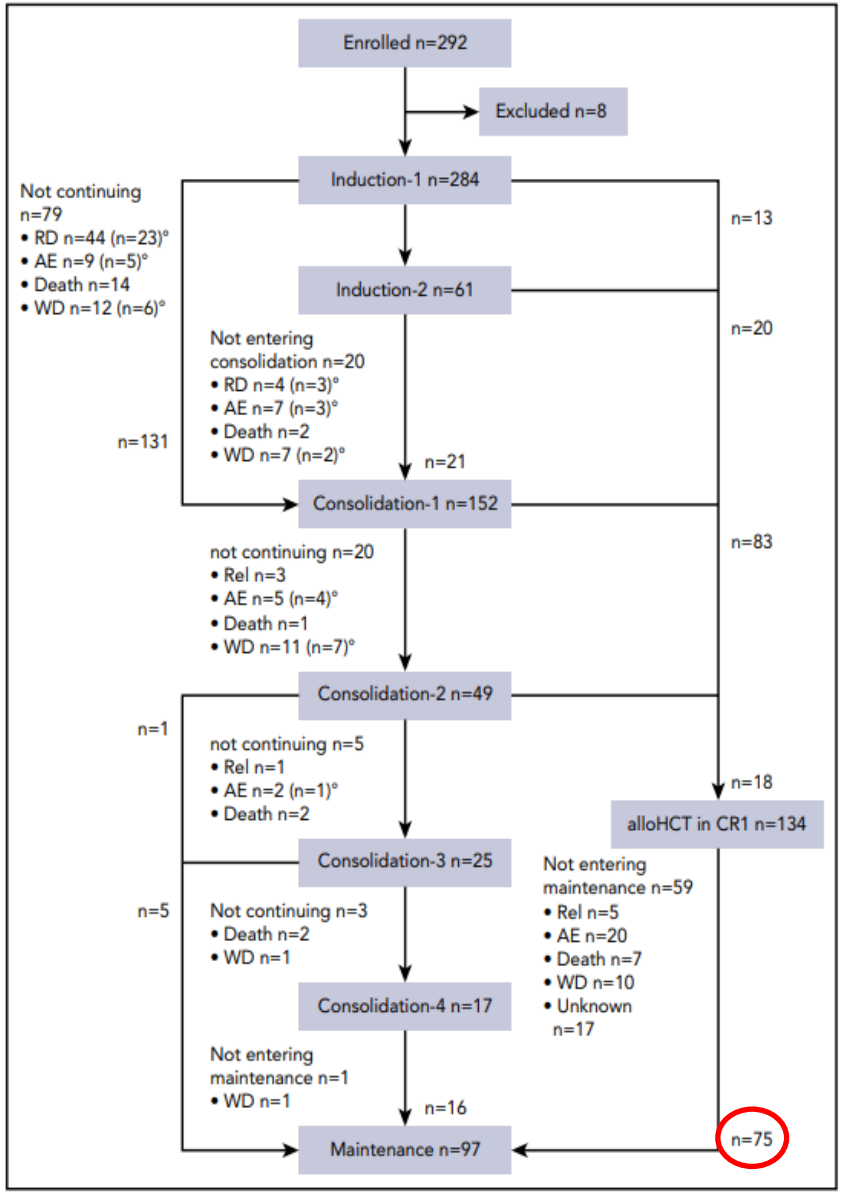
Maintenance therapy Midostaurin maintenance was intended in all patients either after alloHCT or after HiDAC. Midostaurin was given orally in a dose of 50 mg twice daily for 365 days. After consolidation, therapy with HiDAC midostaurin was continued after the last applied cycle. After alloHCT, midostaurin was started at the earliest 30 days and at the latest 100 days after transplantation.

Phase II, hypothesis generating trial

- In a landmark analysis including patients who received HCT and remained event-free in the first 100 days, those who received midostaurin maintenance had improved EFS and OS compared to those who did not (p = 0.004 and p = 0.01, respectively).

- Compared to historical controls from 5 AMLSG prospective trials, EFS was significantly higher in patients treated with midostaurin maintenance

- Maintenance was given for a median duration of nine months (range: 1–13 months), because of adverse events, including GI toxicity (80%), infections (56%), and cytopenias (52%).



Schlenk RF, et al. Blood 2019

Bone Marrow Transplantation (2021) 56:1180–1189
https://doi.org/10.1038/s41409-020-01153-1

EBMT

ARTICLE

Midostaurin after allogeneic stem cell transplant in patients with *FLT3*-internal tandem duplication-positive acute myeloid leukemia

Richard T. Maziarz[1] · Mark Levis[2] · Mrinal M. Patnaik[3] · Bart L. Scott[4] · Sanjay R. Mohan[5] · Abhinav Deol[6] · Scott D. Rowley[7] · Dennis D. H. Kim[8] · Daniela Hernandez[2] · Trivikram Rajkhowa[2] · Kelly Haines[9] · Gaetano Bonifacio[9] · Patrice Rine[9] · Das Purkayastha[9] · Hugo F. Fernandez[10]

Nello studio RADIUS, randomizzato SOC vs SOC+ midostaurina (50 mg x 2/die) x 12 mesi post trapianto:

- Trend di <RI,
- RFS a 18 mesi (primary end-point)
  89% (69–96%) mido vs 76% (54–88%) SOC (HR, 0.46 [95% CI, 0.12–1.86]; P = 0.27),
- scarsa numerosità del campione
- RFS inaspettatamente alta del gruppo di controllo.

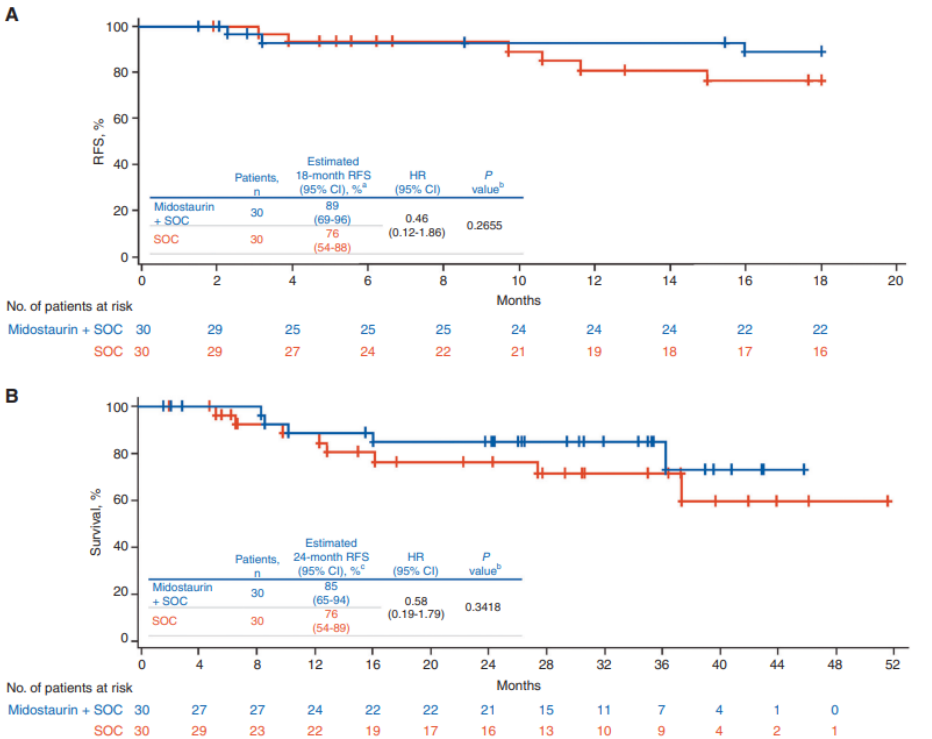


Fig. 2 Outcomes after alloHSCT. Kaplan–Meier curves of **A** RFS by treatment arm at 18 months after undergoing alloHSCT and **B** OS by treatment arm at 24 months after undergoing alloHSCT. Blue, midostaurin + SOC; red, SOC. Tick marks indicate censoring of data. alloHSCT allogeneic hematopoietic stem cell transplant, HR hazard ratio, OS overall survival, RFS relapse-free survival, SOC standard of care. [a]Median RFS was not reached. [b]Log-rank *P* value. [c]Median OS was not reached.

blood

732.CLINICAL ALLOGENEIC TRANSPLANTATION: RESULTS | NOVEMBER 13, 2019

BMT CTN Protocol 1506: A Phase 3 Trial of Gilteritinib As Maintenance Therapy after Allogeneic Hematopoietic Stem Cell Transplantation in Patients with *FLT3*-ITD$^+$ AML

Mark J. Levis, MD,[1] Mehdi Hamadani, MD,[2] Brent R. Logan,[*,3] Matt Rosales,[*,4] David Delgado,[*,4] Erkut Bahceci,[4] Steven Devine, MD,[5] Mary M. Horowitz,[6] Yi-Bin Chen[7]

BMT-CTN 1506/Morpho:
346 post-transplant FLT3-ITD AML patients

173 patients Placebo ? 173 patients Gilteritinib

Is there a benefit to FLT3 inhibition post-transplant?

Does the detection of a FLT3/ITD mutation by a validated, sensitive MRD assay predict relapse?

Does a potent FLT3 inhibitor prevent relapse when the MRD assay detects a FLT3/ITD mutation?

- The study **failed** to reach its primary end point for RFS
- Gilteritinib resulted in 32% reduction in the risk of relapse vs placebo (HR, 0.679; 95% CI, 0.459-1.005; p= .0518),
- The 2-year RFS rates were 77.2% with gilteritinib vs 69.9% with placebo

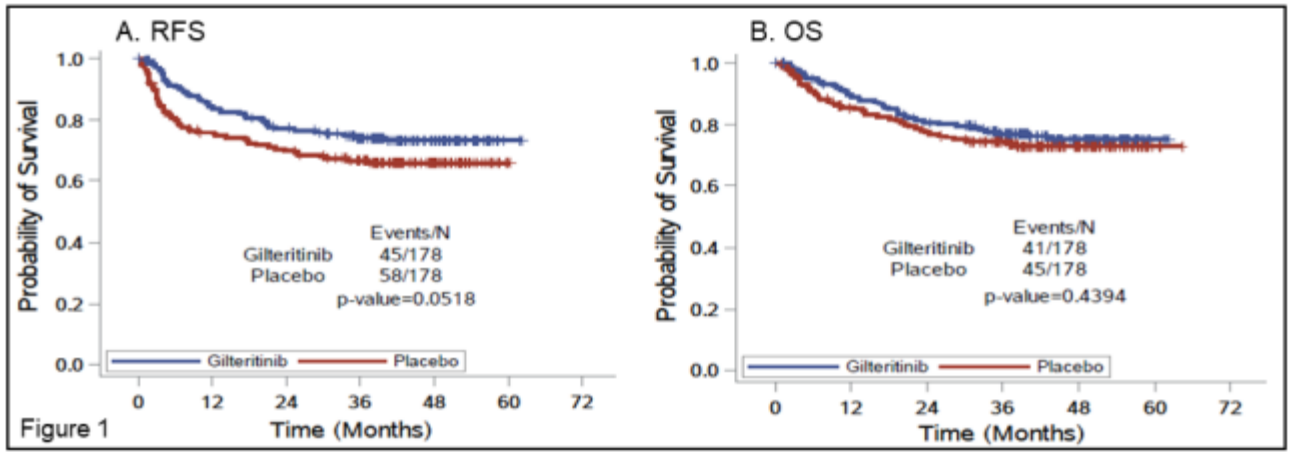


Figure 1

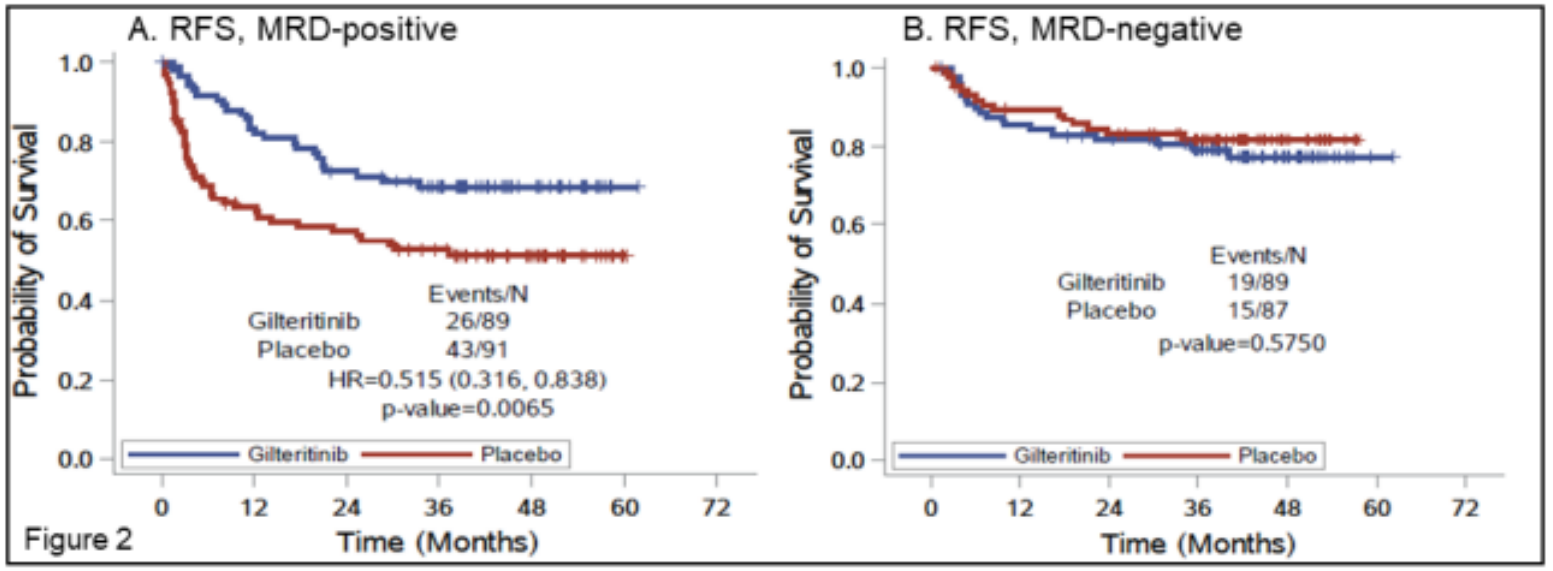


Figure 2

- Gilteritinib appears to have a benefit for the 50% of patients with detectable MRD pre- or post-transplant vs. those without detectable MRD.

- In pre-specified subgroup analysis, the effect of gilteritinib was more pronounced in pts with detectable MRD (HR=0.515, 95% CI:0.316, 0.838, p = 0.0065) than in pts without detectable MRD (HR=1.213, 95% CI: 0.616, 2.387, p = 0.575

Mark J Levis. EHA 2023 Abs

Quizartinib versus salvage chemotherapy in relapsed or refractory *FLT3*-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial

Jorge E Cortes, Samer Khaled, Giovanni Martinelli, Alexander E Perl, Siddhartha Ganguly, Nigel Russell, Alwin Krämer, Hervé Dombret, Donna Hogge, Brian A Jonas, Anskar Yu-Hung Leung, Priyanka Mehta, Pau Montesinos, Markus Radsak, Simona Sica, Meena Arunachalam, Melissa Holmes, Ken Kobayashi, Ruth Namuyinga, Nanxiang Ge, Antoine Yver, Yufen Zhang, Mark J Levis

78 received allogeneic HSCT*
49 resumed treatment after HSCT
15 ongoing post-HSCT treatment
34 discontinued treatment
17 relapse
10 adverse events
3 inadequate response or progressive disease
1 lost to follow-up
1 withdrew consent, permitted follow-up
2 other

At data cutoff (Feb 22, 2018)
21 ongoing treatment (initial or post-HSCT)
45 in follow-up for overall survival

- Patients who underwent HCT in composite CR and received quizartinib maintenance had better OS than those who did not received (n=31 *vs*. 11; median OS: 27 *vs*. 5.4 months.
- Detailed data on post-HSCT maintenance from the QuANTUM-R trial are pending

Quizartinib plus chemotherapy in newly diagnosed patients with *FLT3*-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial

Harry P Erba, Pau Montesinos, Hee-Je Kim, Elżbieta Patkowska, Radovan Vrhovac, Pavel Žák, Po-Nan Wang, Tsvetomir Mitov, James Hanyok, Yasser Mostafa Kamel, Jaime E Connolly Rohrbach, Li Liu, Aziz Benzohra, Arnaud Lesegretain, Jorge Cortes, Alexander E Perl, Mikkael A Sekeres, Hervé Dombret, Sergio Amadori, Jianxiang Wang, Mark J Levis, Richard F Schlenk, on behalf of the QuANTUM-First Study Group

- 40% of patients had 60-75 years
- Planned maintenance duration: 3 years
- 98 patients in the Quizartinib group and 89 in the control group received HCT
- median OS was 31·9 months (95% CI 21·0–not estimable) for quizartinib versus 15·1 months (13·2–26·2) for placebo (hazard ratio 0·78, 95% CI 0·62–0·98, p=0·032).
- OS censored for patients receiving allogeneic HCT
- the effect of HCT on OS with Quizartinib will be published elsewhere

FLT3 Inhibitors - considerations

- Is still Sorafenib the best TKI for post-CHT maintenance?
  There are no direct comparison between Sorafenib vs Midostaurine/Gilteritinib.

- What is the optimal duration of maintenance?
  Maintenance duration differs in different studies from 6 (Xuan et al.) to 12, to 24 months (Sormain).

- What is the efficacy of maintenance in patients who received FLT3 inhibitors prior to HCT?
  Unknown

- Is there a selective pressure and escape clones if too long maintenance duration?
  Of the 43 patients who relapsed, five of 11 assigned sorafenib and 17 of 32 allocated control had FLT3- ITD mutations

- Does short-maintenance increase relapses risk?
  RFS events might be preventable by longer maintenance duration (Sormain).

- Limited analysis of the impact of MRD on outcomes and its interaction with the use of TKI maintenance.

Which FLT3 inhibitor to choose post-HCT?

The decision will definitely be based on:

- Drug availability
- Tolerability
- MRD status pre-and post-transplant
- *FLT3* mutation type

IDH Inhibitors - considerations

- Ivosidenib & Enasidenib both inhibit R-2-hydroxyglutarate and can restore normal myeloid differentiation.

- In multicenter phase 1/2 studies, these agents have demonstrated favorable toxicity profiles and ability to induce remissions in relapsed/refractory and newly diagnosed AML.

- Ivosidenib and enasidenib have received regulatory approval from the US FDA for the treatment of IDH1- and IDH2-mutated AML.

- Several trials are ongoing to test IDH inhibition efficiency at preventing AML relapse (NCT03515512; NCT03728335; NCT04522895; NCT03564821).

Conclusions

- Fewer than 5% of transplant patients are currently recruited to prospective practice informing trials.
- Data from *post-hoc* and retrospective analysis with any maintenance approach need to be studied carefully.
- Patients with the highest risk disease (GvHD, cytopenia) are not able to receive the maintenance agent after HCT
- At long last, we need to accelerate recruitment to trials and looking how these new therapies can transform outcomes.