SHOULD HIGH RISK AML PATIENTS UNDERGO MAINTENANCE FOLLOWING HCT?
NO

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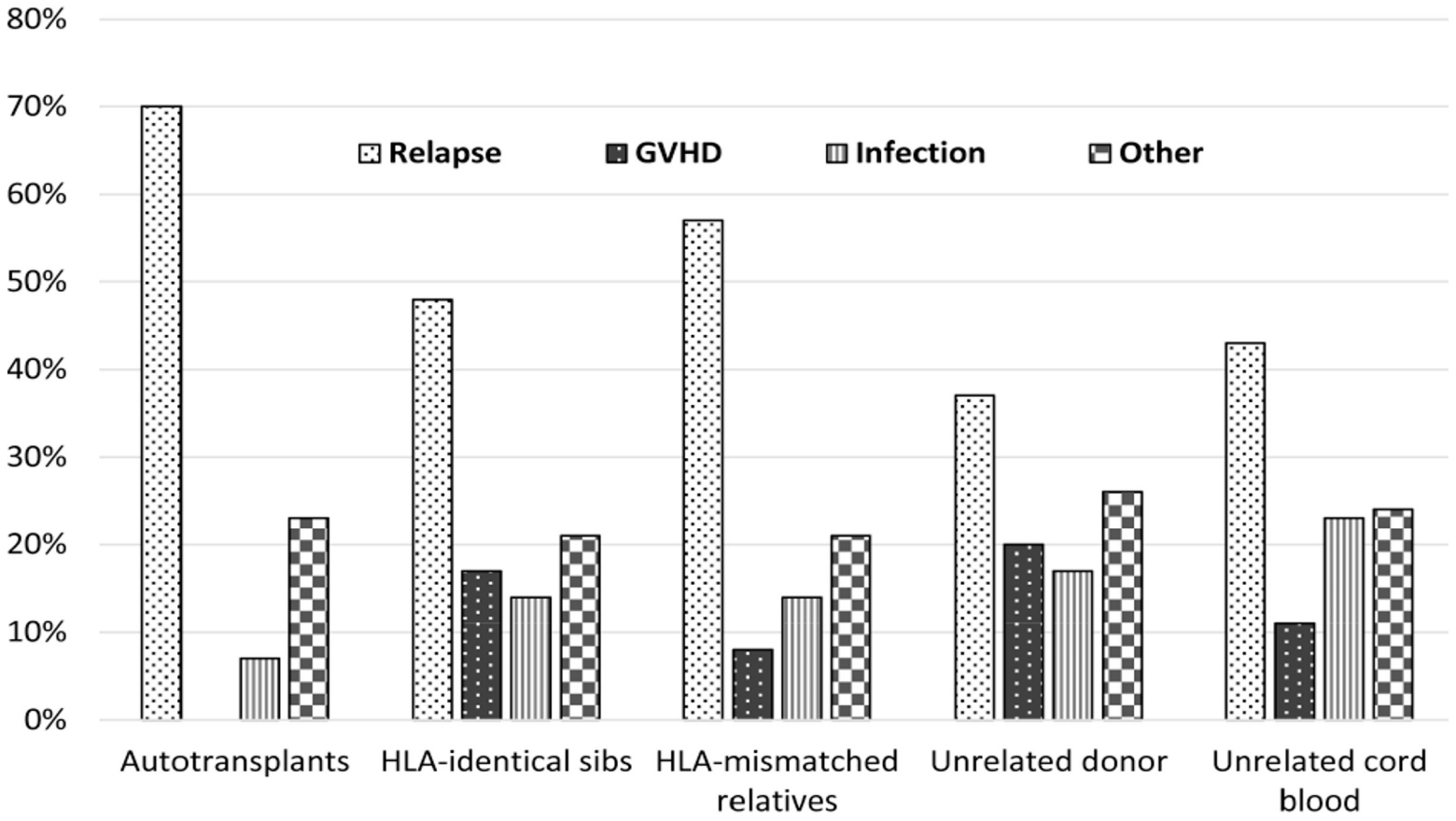
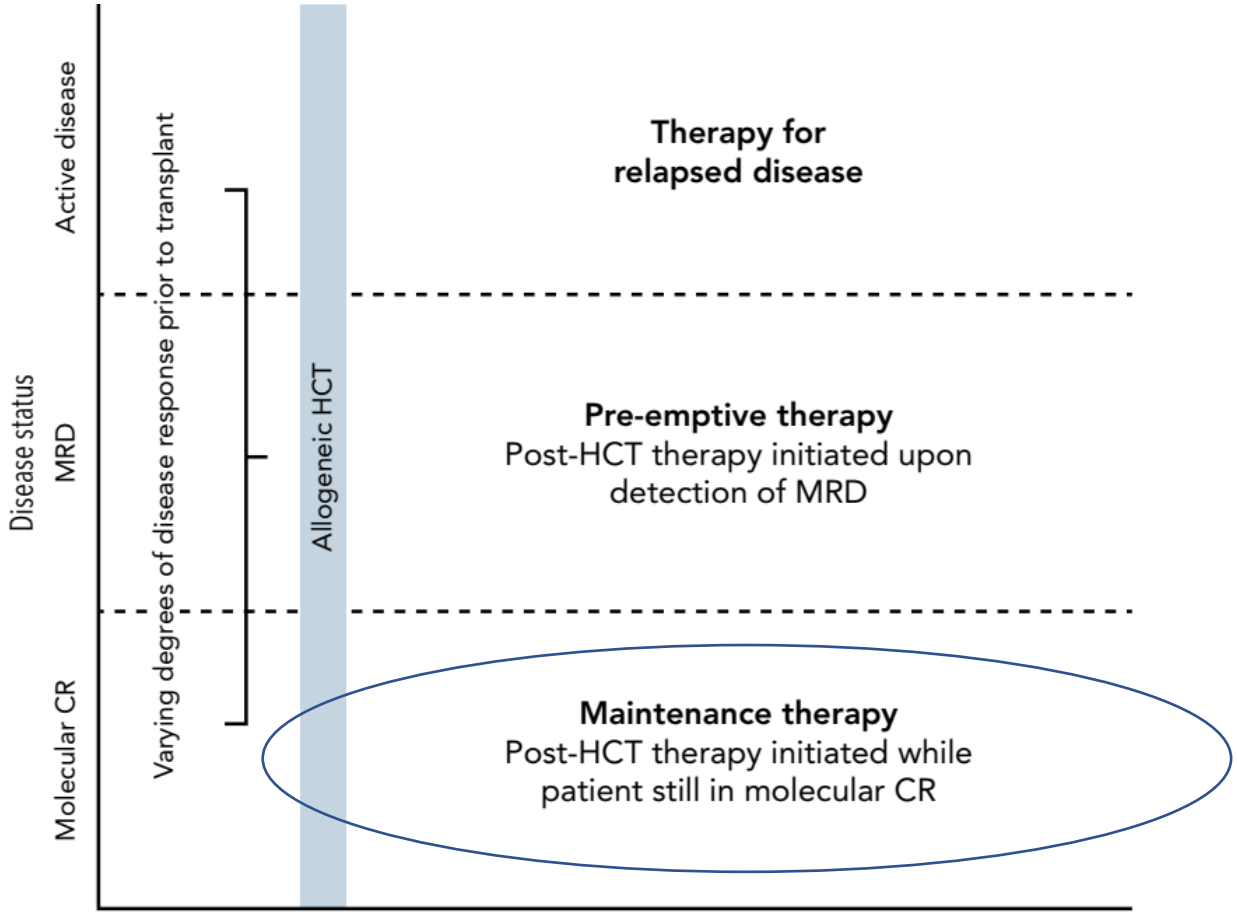
No disclosures to declare

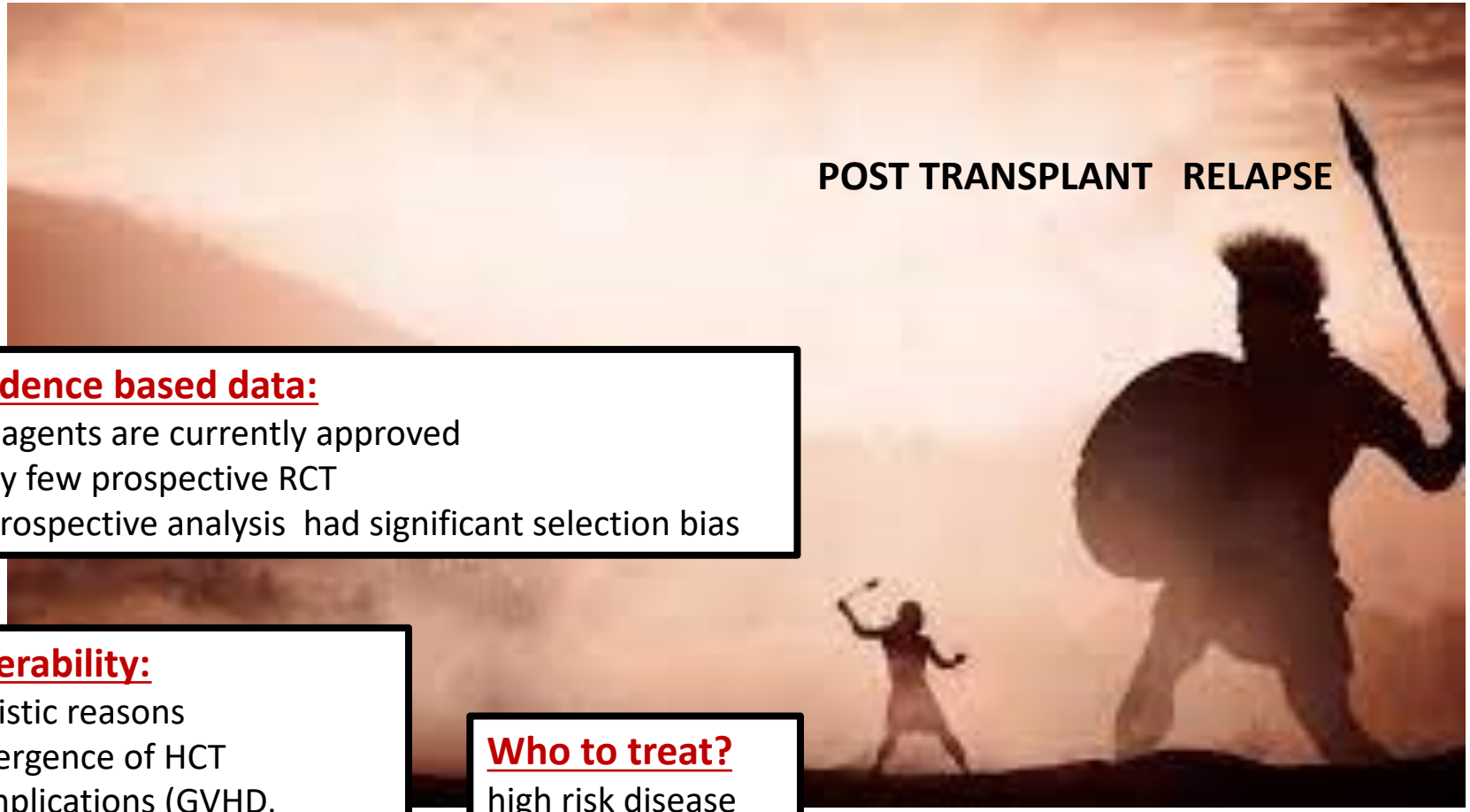


Horowitz et al. BMT 2018

Key issues of maintenance therapy



Zachariah et al. Blood 2023



Evidence based data:
No agents are currently approved
Very few prospective RCT
Retrospective analysis had significant selection bias

Tolerability:
Logistic reasons
Emergence of HCT complications (GVHD, infections)
Toxicities

Who to treat?
high risk disease
Disease status at tx
Conditioning
GVHD prophylaxis

€uros

Which drug? Which dose? How long?

Drugs interactions

FLT3 INHIBITORS

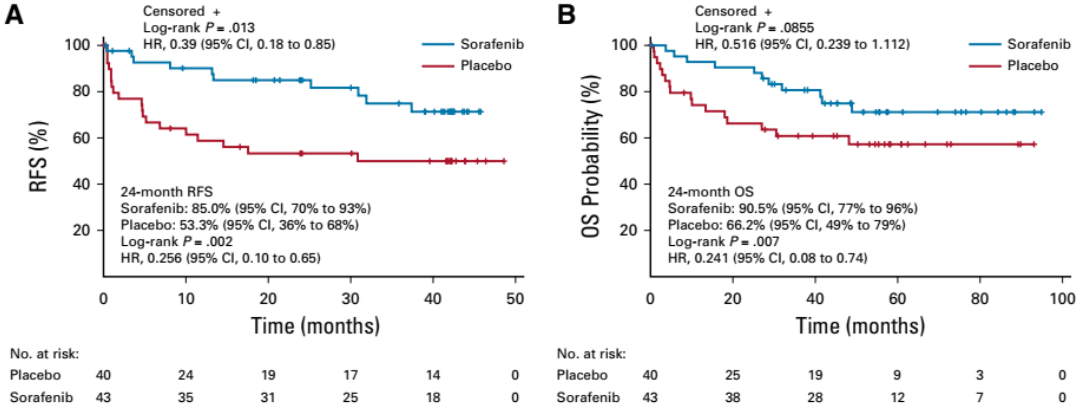
SORAFENIB

SORMAIN TRIAL

Multicenter double blind placebo controlled phase II trial in Germany and Austria

- 83 patients FLT3 AML patients: 43 sorafenib maintainance vs 40 placebo
- treatment start 60-100 days post HCT, 24 months of therapy
- Escalated dose (from 400mg/die up to 800 mg/die)

2 y RFS
85vs 53%
p=0.02



2 y OS
90 vs 66.2%
p=0.007

- drug discontinuations due of toxicities occurred in 22% of patients taking sorafenib vs 5% of placebo-treated patients
- Closed early because of poor accrual
- The majority of patients did not receive FLT3 inhibitors during induction therapy

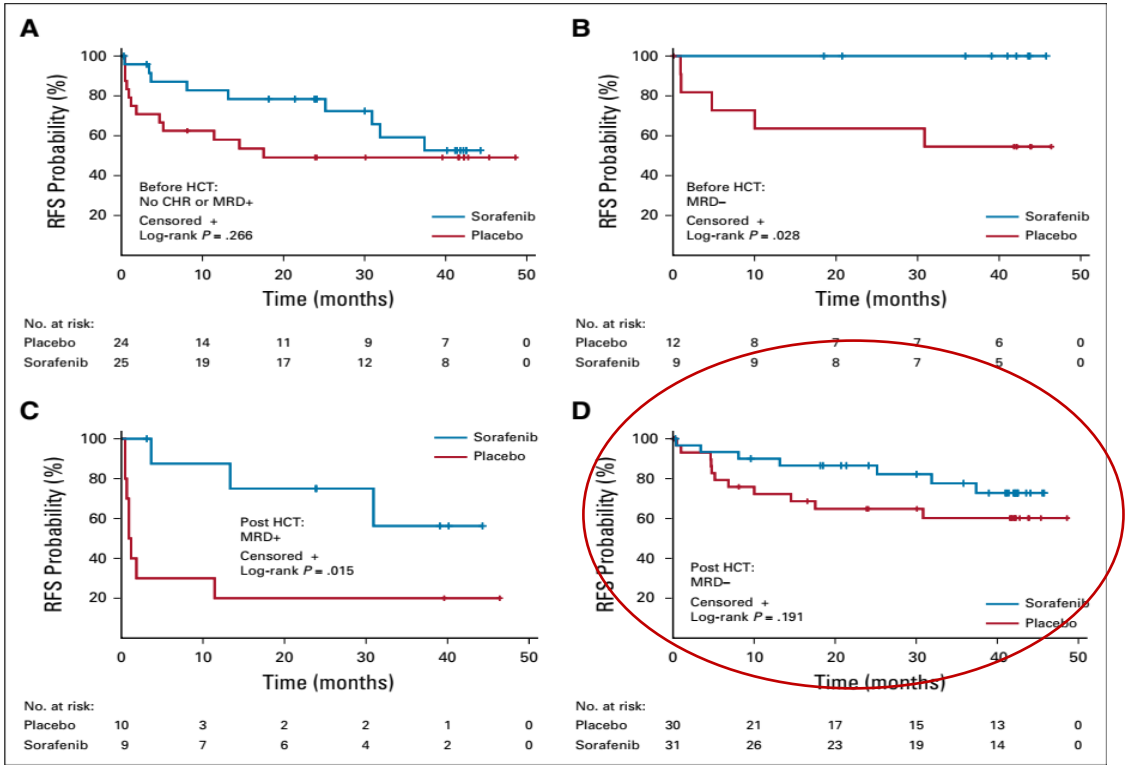
Burcheret et al. JCO 2020

SORAFENIB

SORMAIN TRIAL

NO CR
PRE HCT

MRD+
POST HCT



MRD-
PRE HCT

MRD-
POST HCT

Burcheret et al. JCO 2020

SORAFENIB

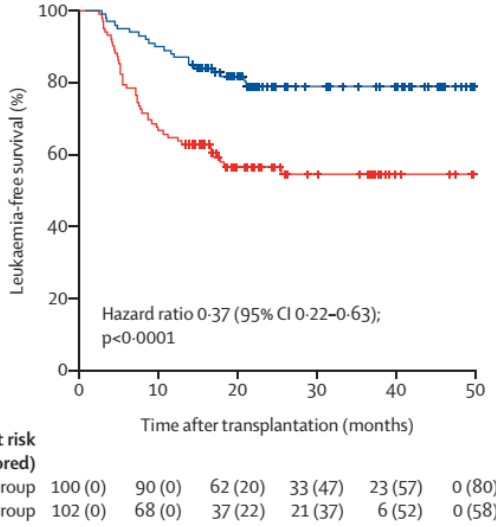
Multicenter randomized phase III trial in China

- 202 patients: 100 sorafenib vs 102 control between 2015 and 2018
- Treatment start 30-60days post HCT, Sorafenib was administered for up of 6 months
- Starting dose 400 mg twice daily

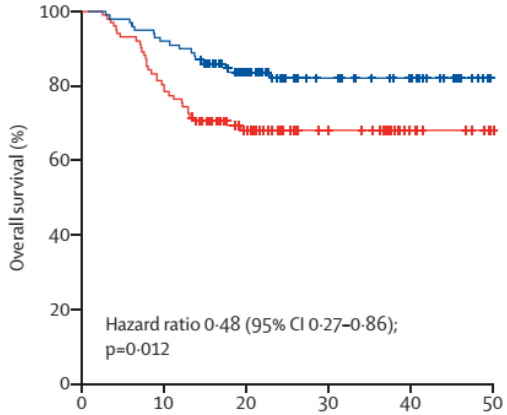
2y RFS

79 VS 57%

p<0.001



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 ımber 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)

2 y OS

82 vs 68%

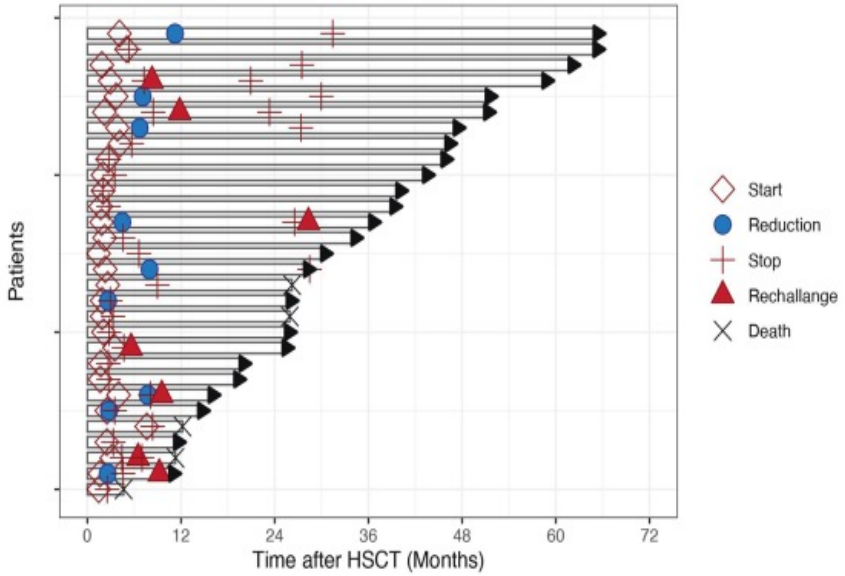
p=0.012

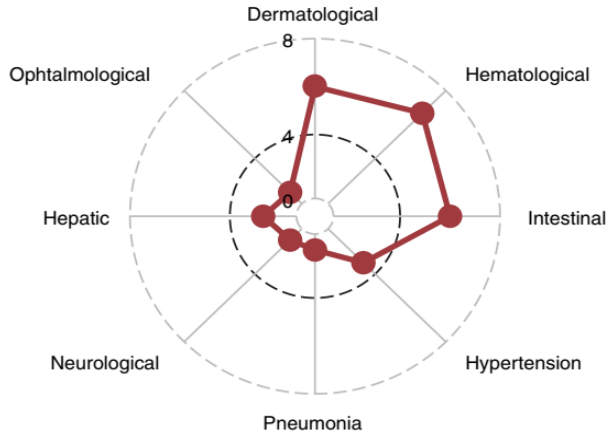
- 59 of 100 patients required dose reduction(42), interruption (12) or discontinuation(5) due to adverse effect
- 25% of both groups received FLT 3 inhibitors pre transplant
- few data on impact of MRD on outcomes
- Non blinded and no placebo controlled which might carry high risk of bias on the part of both patient and doctor in favor of investigational arm

Xuan L et al Lancet Oncology 2020

SORAFENIB

Real world experience of sorafenib maintainance after allo-HCTfor FLT3-ITD AML reveal high rates of toxicity related treatment interruption





30 FLT3-ITD AML patients between 2017-2020:

- Sorafenib was administered at 200 mg tw/d for the first week and then 400 mgtw/d
- 87% experienced toxicities leading to dose reduction (n=9) or direct interruption (n=17).
- Average time on sorafenib was 125 days (range 1-765).
- Most common toxicities were skin,gastrointestinal, and hematologic
- Overall, 60% of the entire cohort definitively discontinued sorafenib because of toxicities

Morin S et al Frontiers in Oncology 2023

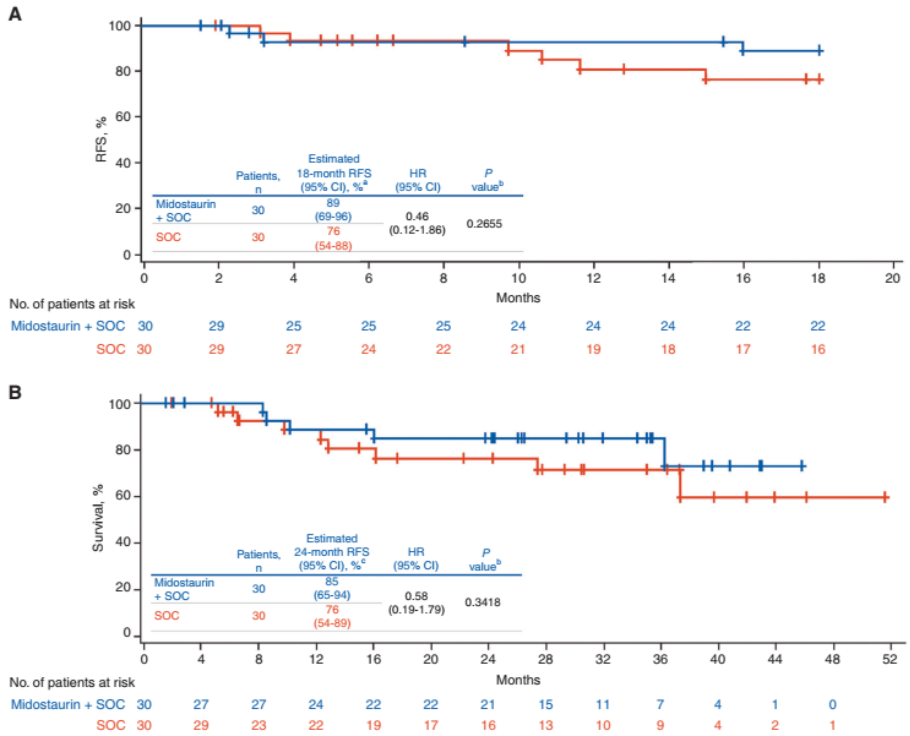
MIDOSTAURIN

RADIUS TRIAL

A Phase 2 Randomized Trial Investigating Standard of Care ± Midostaurin after Allogeneic Stem Cell Transplant in *FLT3*-ITD-Mutated AML

- 60 FLT3 AML who received alloHCT in first complete remission were randomized (30/arm) to receive SOC with or without midostaurin(50 mg twice daily) for 12 months
- 30 completed all cycles (midostaurin + SOC, n = 16; SOC, n = 14)
- Rates of graft-vs-host disease were similar between both arms (midostaurin + SOC, 70%; SOC, 73%)

18 m RFS 89% M vs 76% SOC p=0.22



Maziarz RT et al S et al BMT 2021

FLT 3 INHIBITORS

- **GILTERITINIB (Morpho trial NCT02997202)**

full data pending, 356 FLT3AML patients in CR after induction

Recent press communication (march 9 2023) declared that gilteritinib vs placebo for 2 y post transplant failed to meet the primary endpoint of RFS benefit in the gilteritinib arm

Since RFS was not statistically significant as the primary analysis, the study including follow-up, will be stopped as per the study protocol

- **CRENOLANIB, QUIZARTINIB** ongoing

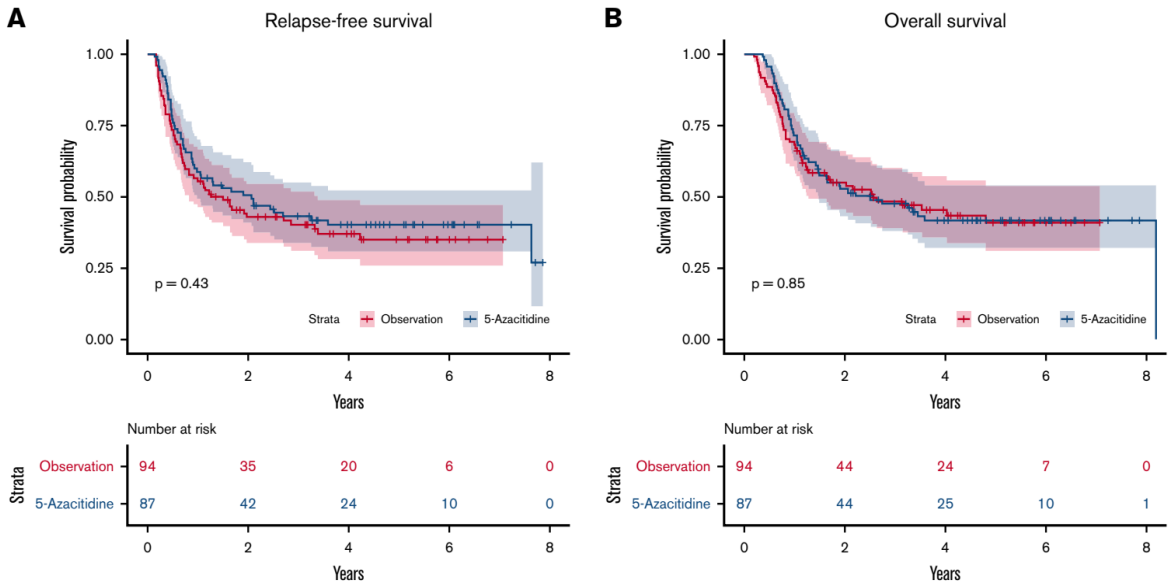
Open questions:

- Which inhibitor is more safe and effective in the post transplant setting?
- Others molecular or cytogenetic mutations and FLTallelic ratio can impact on the choice to start maintainance treatment?
- Can we aggravate the genomic instability and facilitate clonal escape?
- Post transplant MRD measurements can identify the appropriate subgroup that truly benefit from post allo-HCT?

HYPOMETILATING AGENTS

5-AZACITIDINE

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



- 187 High risk AML or MDS between 2011 and 2017, 93 aza vs 94 control arm in RC post tx
- High risk: cr 5,7 abnormalities, flt3, complex caryotype, high risk MDS (IPSS) therapy related, bipheotypic
- 12 months aza 32mg/m2 sc for 5 days every 4 w
- Median time to first cycle 54 dys Post transplant
- Median number of cycles given was 4
- No increased toxicity in treatment arm

Oran B et al al. Blood advances 2020

HYPOMETHYLATING AGENTS

Open questions:

- Which patients could benefit from hypomethilating agents?
- Oral formulations under investigation in post transplant setting (NCT04173533)
- combination with other agents (gentuzumab, venetoclax) are under investigation

IDH INHIBITHORS

IDH-1 and IDH-2 INHIBITORS

Multiple ongoing phase 1 and 2 trials are investigatig the use of IDH inhibitors as maintainance therapy post HCT

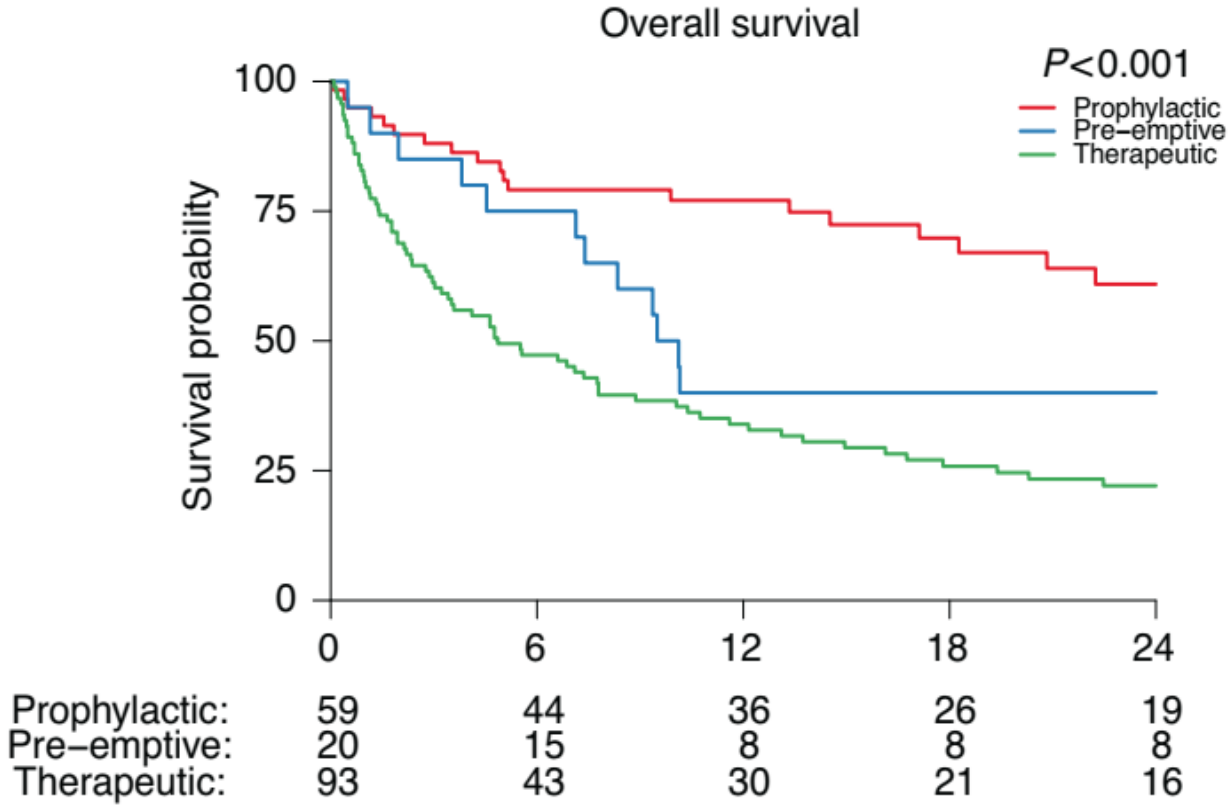
Ivosidenib and enasidenib are recently approved target agents

They are well tolerated and could teoretically be used as a maintanance for patients whose leukeima carries these mutations

- Ivosidenib (IDH-1 inhibitor): NCT03564821, NCT03839771
- Enasidenib (IDH-2 inhibitor): NCT03515512, NCT037288335, NCT04522895, NCT03839771

- Observations from these studies will estabish the toxicity profile and clinical outcome in post transplant setting
- Few data on impact of IDH mutation of relapse
- No evidence to support the use at this point!

DONOR LYMPHOCYTE INFUSION



Santoro et al. BMT 2023

PREREQUISITES FOR DLI

- Absence of tissue damages and inflammatory conditions
- ≥ 3 months from HCT
- NO GVHD (usually after >4 weeks without immunosuppression)
- NO ongoing infections

FURTHER FACTORS THAT MAY INFLUENCE TIMING AND DOSING

- History of prior GVHD
- Applied conditioning (RIC)
- Sensitivty of the underlying disease to GVL effect and of disease risk
- Use of fresh or frozen inocula
- Application to G-CSF prior to collection

Prophylactic DLI

Research in the field is characterized by a multitude of different approaches, that have mostly been studied retrospectively or in single-arm trials (different diseases, doses, timing, treatment associated..)

Disease/MRD Marker	First Author (No. of patients[a])	Applied Strategy	Cell Doses at DLI 1 × 10^6/kg	Timing of PreDLI	Results and Remarks
Prophylactic DLI					
High-risk AML and MDS	Jedlickova (46)[118]	Unmodified DLI	1	Median days, +160	Relapse rate, 22% *v* 53% in matched controls; 7-year OS, 67% *v* 31% among controls
AML/ALL after IV Campath-based conditioning	Liga (7)[110]	Unmodified DLI	Not reported	Median days, +162 (8-426)	Low GVHD rates, no relapse, 2 deaths (infection, GVHD)
AML/MDS/ALL after RIC	Kumar (18)[119]	Ex vivo costimulated T cells	10	Median days, +20	6-year follow-up flow GVHD rates: OS, 28%; LFS, 22%; relapse as cause of death, 77%
ALL, after MAC (Campath in the bag)	Eefting (14)[120]	Unmodified DLI	MFD, 3 MUD, 1.5	Median days, +185 (108-659)	50 follow-up, low GVHD rates; CIR, 16%; 2-year OS, 68%
High-risk AML, in part under IS	Legrand (22)[121]	Unmodified DLI	0.1-10	Median days, +130	2-year relapse rate, 22%; 2-year PFS, 75%; CI of GVHD, 37%; NRM, 0%
Intermediate and high risk AML/ALL	Schmid (89)[30]	Unmodified DLI	MFD, 1; MUD, 0.5	Median days, + 163	Improved OS (70% *v* 40% in matched controls) in high-risk AML; no benefit for intermediate-risk AML and ALL

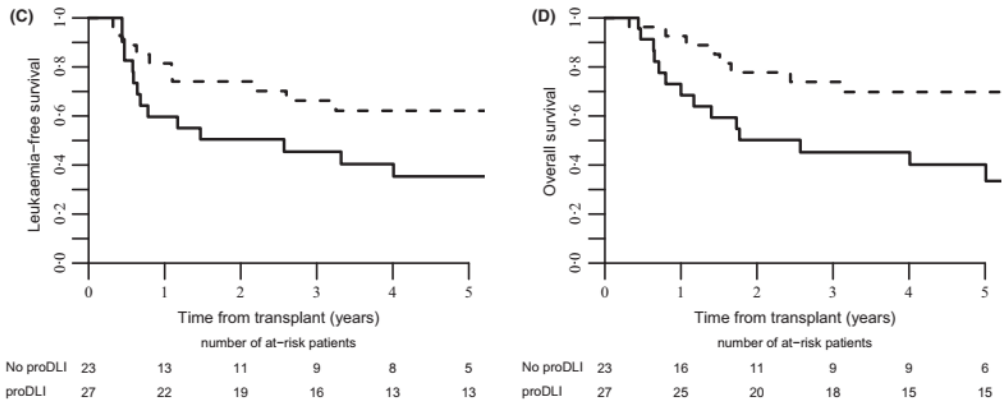
Schmidt et al. JCO 2021

PROPHYLACTIC DLI

EBMT-ALWP registry based matched pair analysis

103 proDLI (ALL-AML) CR,MRD-, complete chimera
98 matched pairs (Extensive matching wirh control selected from the registry 13827)

	Controls	proDLI recipients	p-value	HR (95%CI)
Entire population				
Ri	33.3% [23.3-43.6]	29.5% [20.3-39.3]	0.67	0.891 [0.525-1.513]
NRM	6.1% [2.2-12.8]	9.2% [4.3-16.5]	0.94	0.963 [0.347-2.675]
LFS	60.6% [49.9-71.2]	61.3% [51.1-71.5]	0.68	0.906 [0.566-1.450]
OS	64.6% [54.1-75]	68% [58.1-77.8]	0.51	0.847 [0.516-1.391]
Acute GvHD II-IV	5.6% [2.1-11.8]	8.7% [2.4-10.7]	0.86	0.89 [0.251-3.146]
Chronic GvHD	24.6% [16-34.2]	28.2% [19.2-37.9]	0.74	1.101 [0.616-1.967]



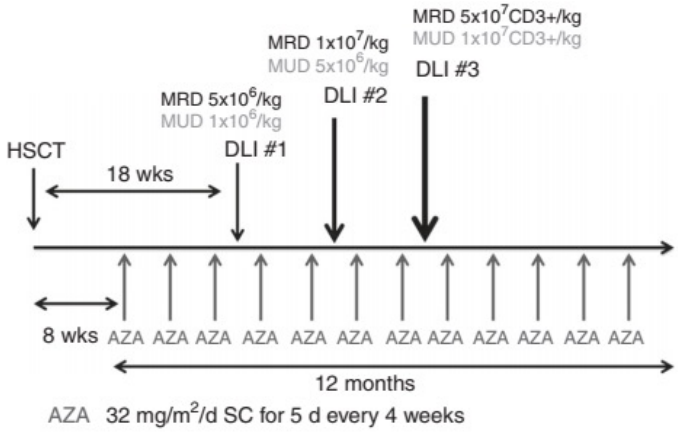
Sub group analysis
HIGH risk AML (n=52)
Defined by CYTOGENETICS

Schmid et al. BRJ haematol 2019

Pro-DLI + drugs

Prospective phase II study prophylactic AZA+DLI following SCT for high risk AML/MDS

- 20 AML/10 MDS, median age 60 (61 pt preincluded in the trial)
- 50% unfavorable karyotype, Tx mostly in CR, 16% refractory
- 60% RIC



	relapse	NRM	PFS	OS
AZA-DLI patients	27.6% [12.8–44.6]	6.9% [1.2–20.1]	65.5% [48.2–82.8]	65.5% [48.2–82.8]
Control patients	41.9% [28.9–54.4]	6.9% [2.2–15.5]	51.1% [38.2–64.1]	63.3% [50.8–75.8]
P value	0.21	0.62	0.17	0.46

NRM non-relapse mortatity, *PFS* progression-free survival, *OS* overall survival

Guillaume et al. BMT 2018

Considerations on prophylactic DLI

- RCT still missing (NCT02856464 ongoing)
- standardization of DLI and its clinical use is challenging
- More innovative immunotherapy-specific approaches such as selected/expanded leukemia specific antigens DLI, Engineered T cells are promising approach that need to be validated

Conclusions

- We have to do everything in our power to prevent relapse, but we must approach the problem methodically (AML genetics, prior transplant exposure, toxicities, patient's clinical profile and desire)
- To date very few prospective randomized clinical trials have been conducted and no pharmacological agents are currently approved in post transplant maintenance
- We must oppose the widespread adoption of maintenance therapy after allo-HCT in the absence of an understanding of who will benefit, as this will impede progress toward improving future outcomes for our patients
- If possible patients should be enrolled in randomized clinical trials

Thank you for the attention