Klinik für Hämatologie und Stammzelltransplantation
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Strategien zur MRD-Konversion bei AML

Jahrestagung der DGHO – Basel 2024

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Disclosures

1. Employment or Leadership Position: -
2. Advisory Role or Speaker Honoraria: Pfizer, JAZZ Pharmaceuticals, BMS
3. Stock Ownership: -
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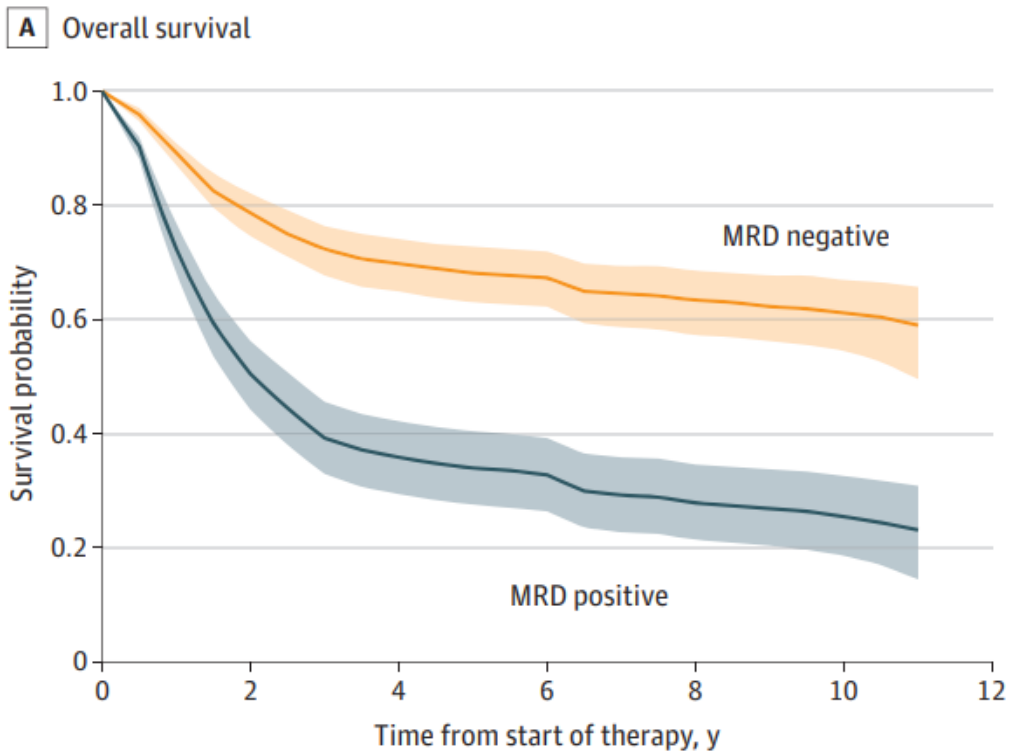
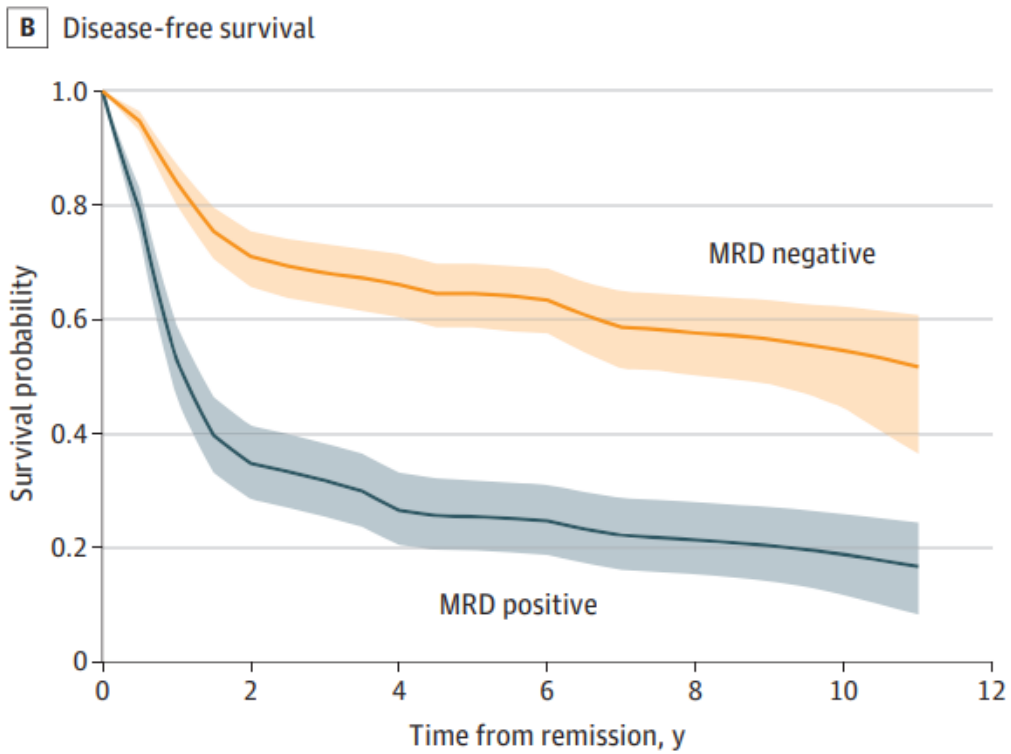
Agenda

- Background
- Strategies for MRD-Conversion during Course of Treatment
  - Intensive Chemotherapy and Targeted Therapy prior allo-SCT
  - Conditioning during allo-SCT
  - Maintenance and Pre-emptive Therapy post allo-SCT
- Conclusion I/II

Background



5-year OS: 68% MRD- vs. 34% MRD+

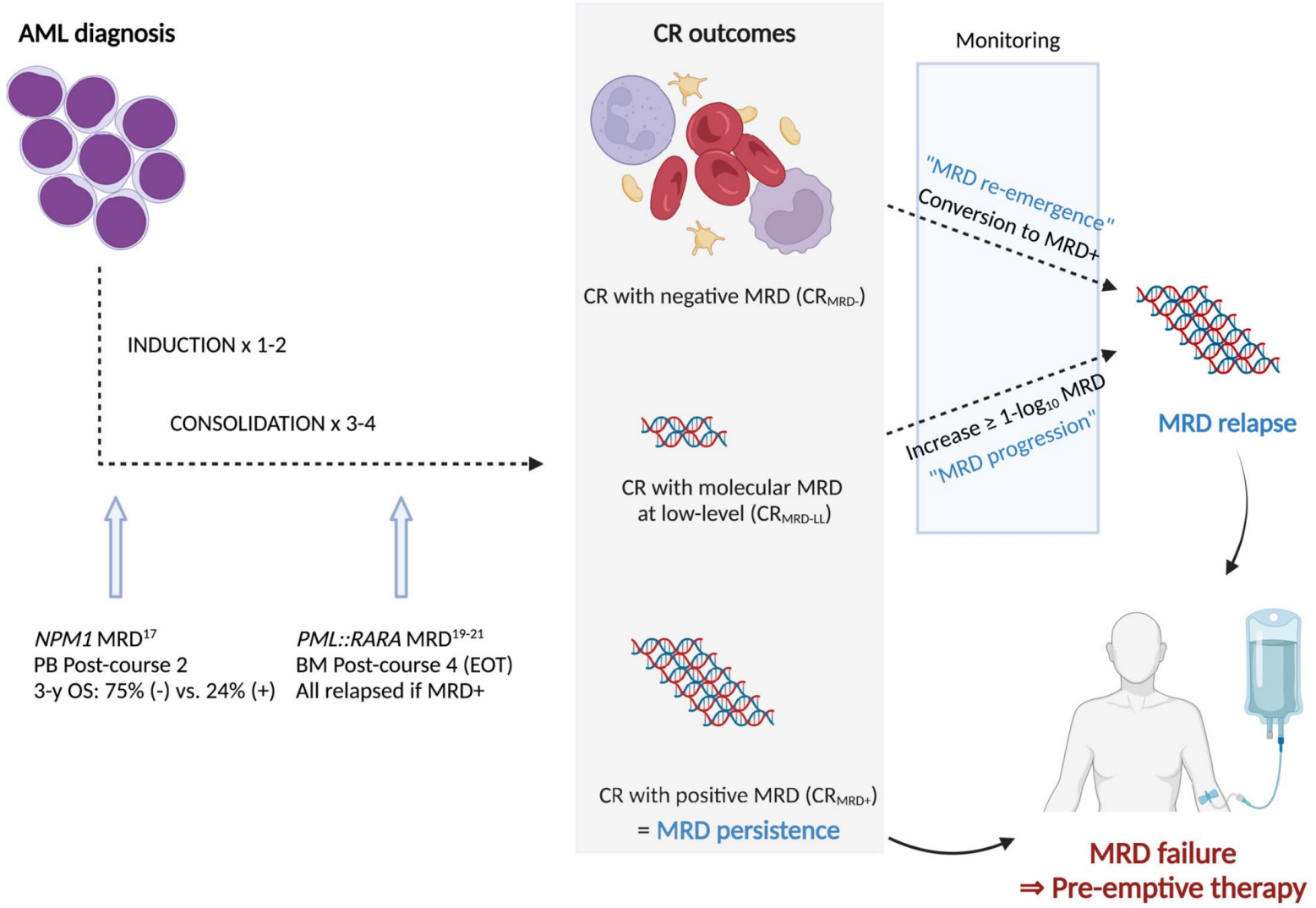


5-year DFS: 64% MRD- vs. 25% MRD+

The value of MRD negativity appears to be consistent across age groups, AML subtypes, time of MRD assessment, specimen source and MRD detection methods

Short et al. *JAMA Oncol.* 2020

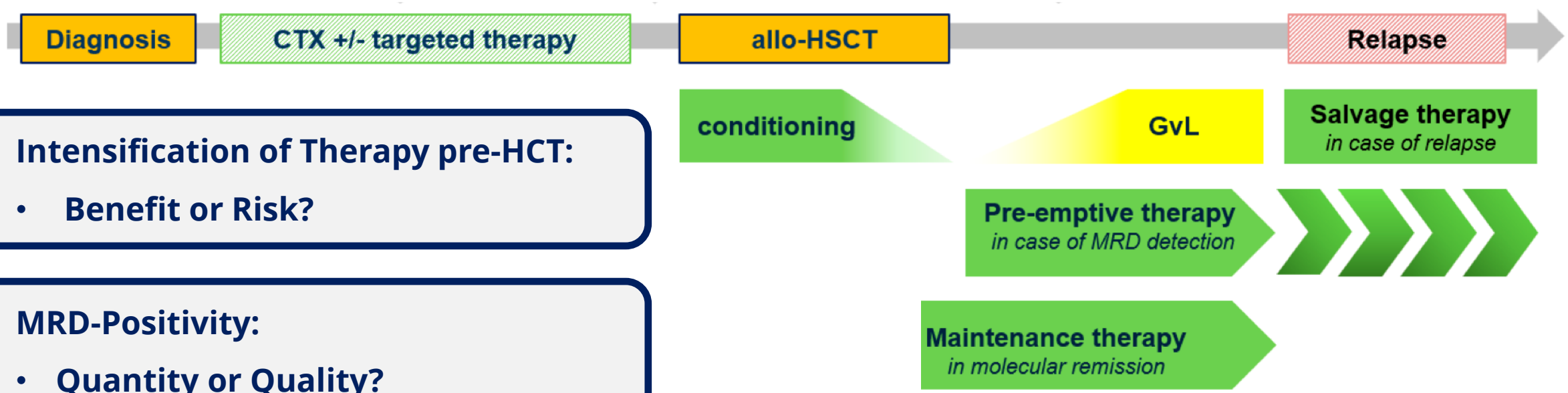
Background



Tedjaseputra, Russel and Dillon, Clin Lymphoma, Myeloma and Leukemia 2024

Strategies for MRD-Conversion during Course of Treatment

prior… **during…** **post allo-SCT**



Intensification of Therapy pre-HCT:

- **Benefit or Risk?**

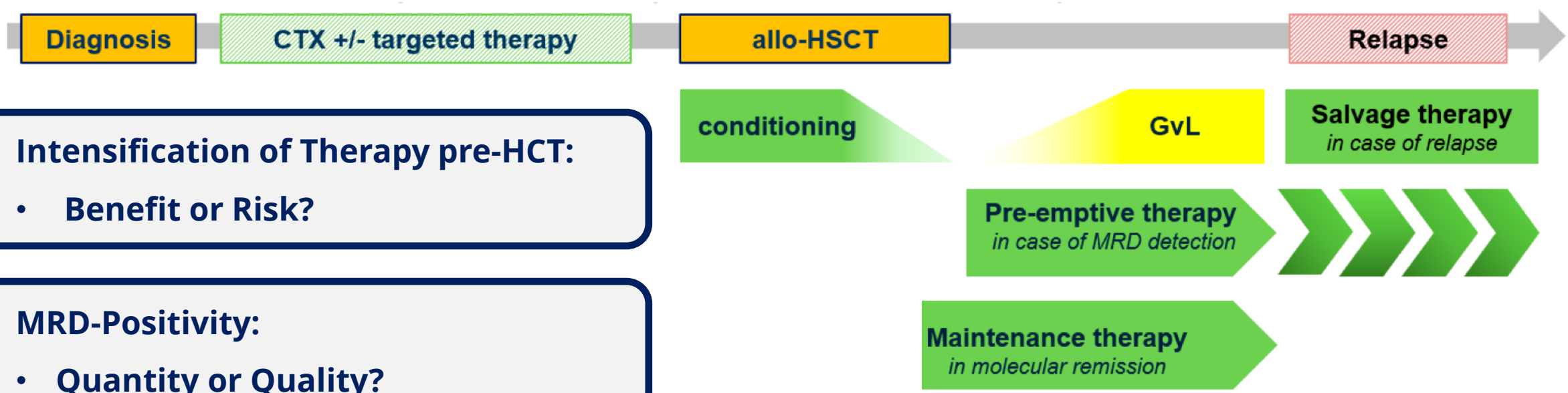
MRD-Positivity:

- **Quantity or Quality?**

Strategies for MRD-Conversion during Course of Treatment

- **FLT3-Inhibition**
- **Venetoclax & LDAC**
- **Intensive Chemotherapy**

during… **post allo-SCT**



Intensification of Therapy pre-HCT:

- **Benefit or Risk?**

MRD-Positivity:

- **Quantity or Quality?**

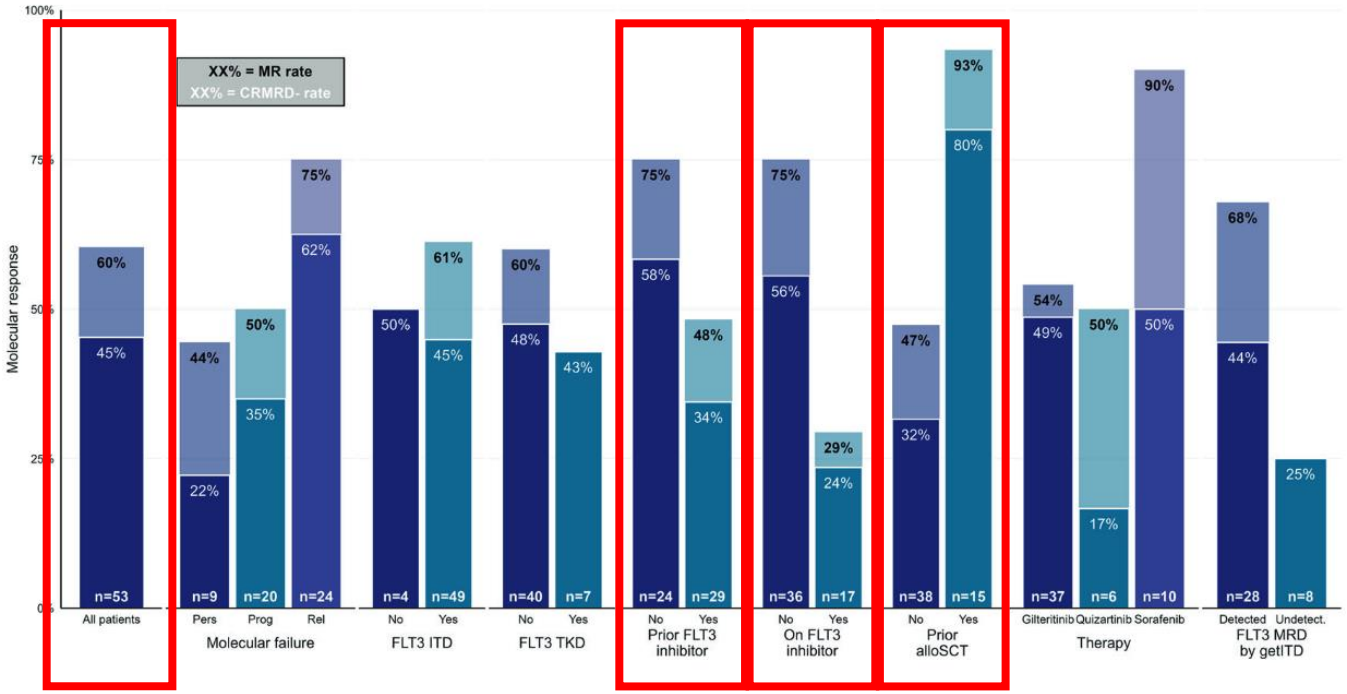
FLT3-Inhibitor based MRD-Conversion

retrospective
n=56, median age 51 yrs
part of the UK NCRI AML17 and AML19

52 FLT3-ITD, 7 FLT3-TKD, 3 both
80% NPM1, 20% FG

Treatment of molecular failure:
- **68% Gilteritinib**
- **20% Sorafenib**
- **12% Quizartinib**

1/3 ≥ 2 prior lines of therapy
30% prior allo-SCT, >50% prior Mido

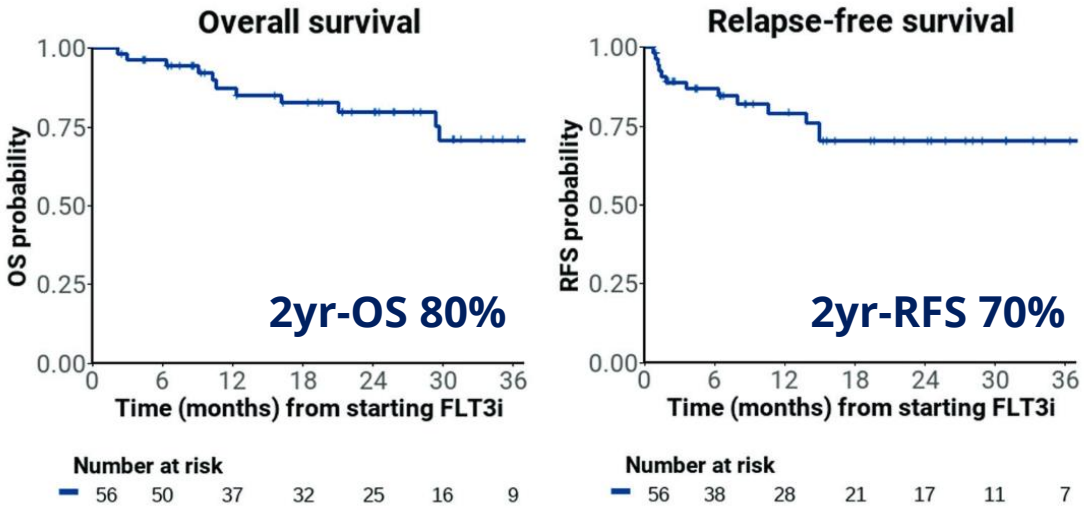


60% mol response (≥ 1 Logstufe Reduktion), 45% MRD-neg

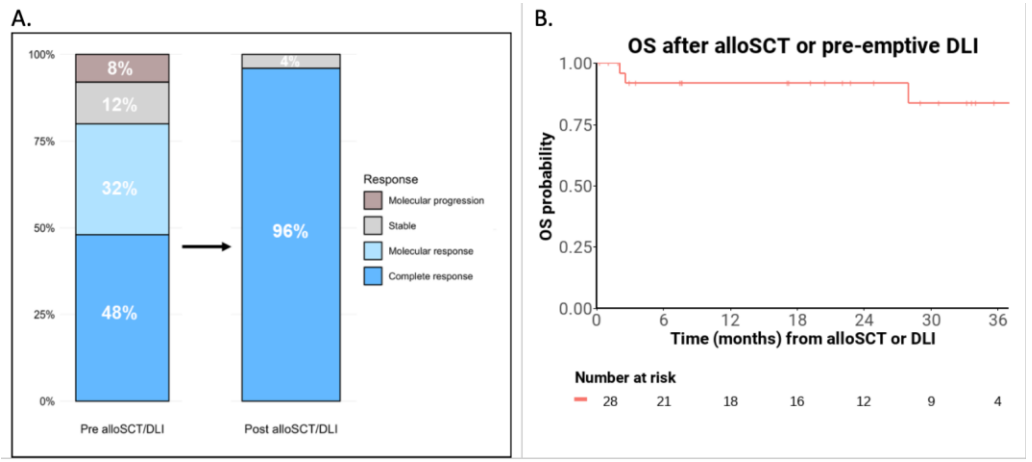
lower rate of mol response / MRD-neg. in case of:
- **prior FLT3i (48% vs. 75%)**
- **on FLT3i @mol failure (29% vs. 75%)**
- **no prior allo-SCT (47% vs. 93%)**

FLT3-Inhibitor based MRD-Conversion

median 6 cycles (range 1-43)
median Follow-Up 25 months

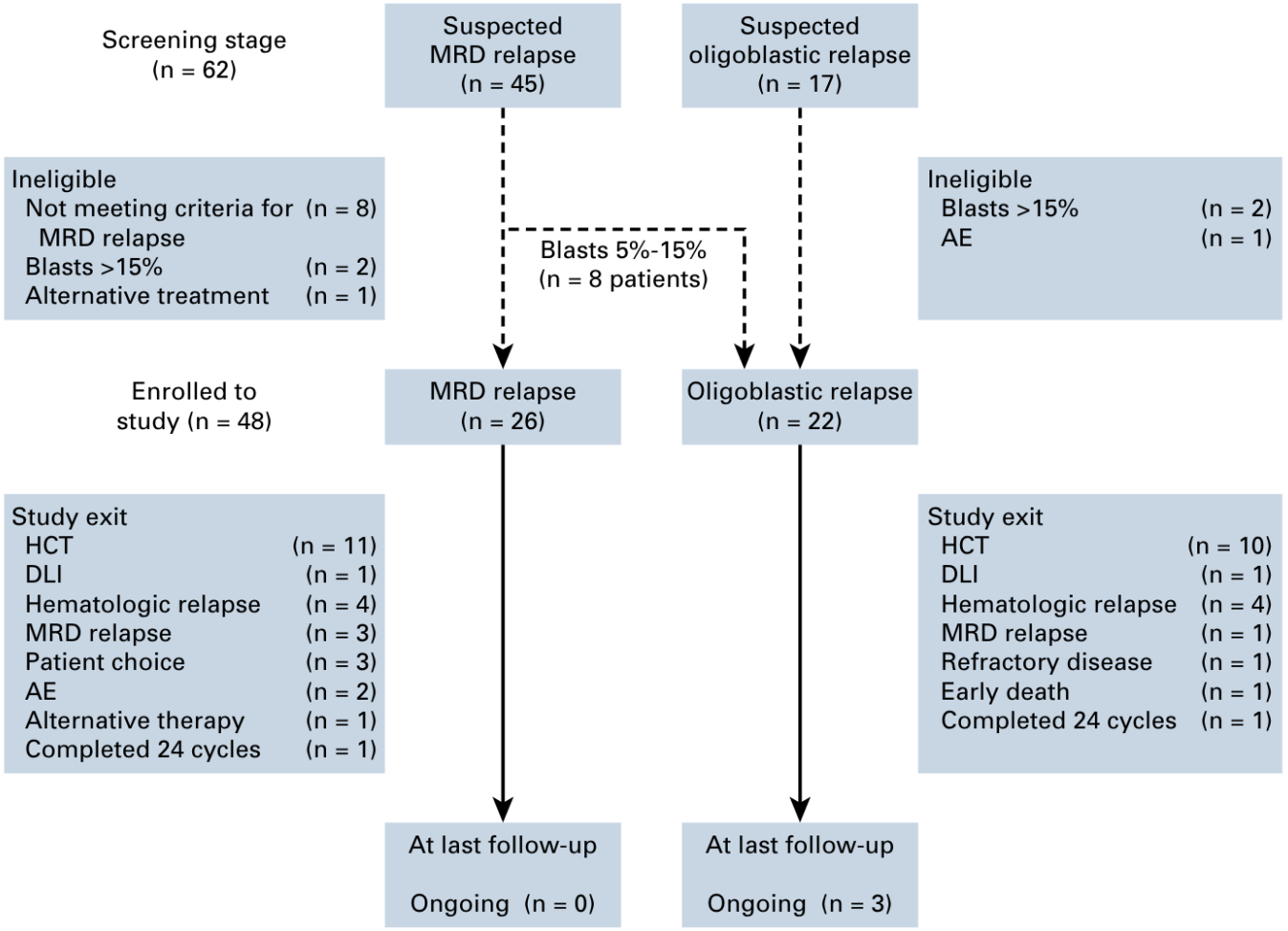


50% bridged to allo-SCT (n=22)/DLI (n=6)
after a median of 2.5 cycles



- **FLT3-ITD not stable @relapse, but lost in up to 50% of pts with prior Midostaurin**
- **FLT3-ITD MRD so far without broad applicability**
- **TKI-Resistance through Gate-Keeper Co-Mutations**

Venetoclax-based MRD-Conversion, VALDAC



Prospective Phase II
n=48, median age 67 yrs
- **26 mol. Relapse**

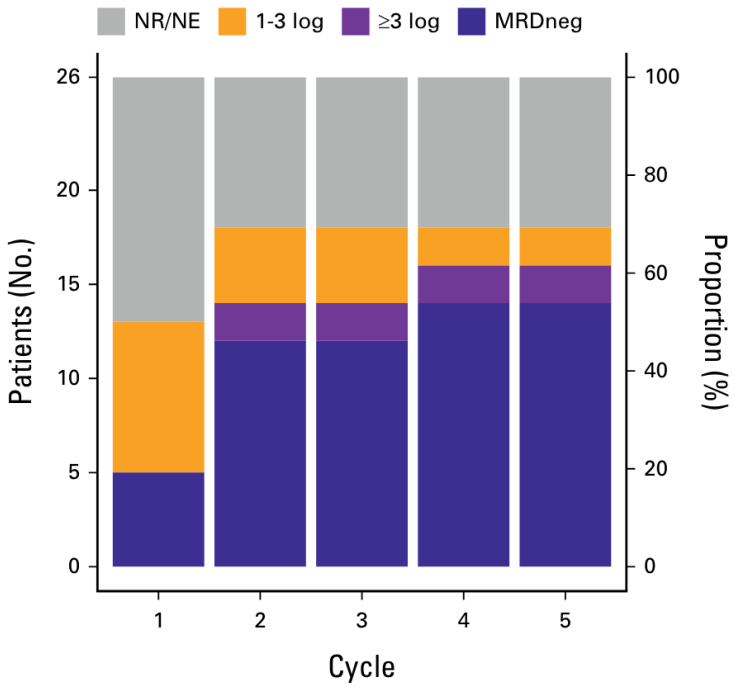
95% with prior int. CTX, median 3 cycles
n=2 with prior allo-SCT

60% NPM1, 40% FLT3-ITD, 40% IDH1/2
2/3 ELN fav risk
1/3 ELN int risk
few adv risk

Ven 600mg p.o. d1-28
LDAC 20mg/qm s.c. d1-10
up to 24 cycles, median 4

Tiong et al. JCO 2024

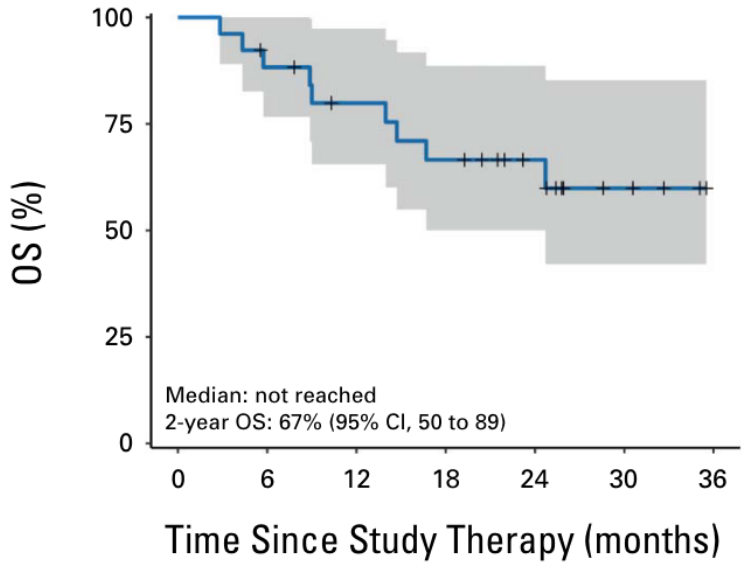
Venetoclax-based MRD-Conversion, VALDAC



69% mol response after 2 cycles

46% MRD-neg. after 2 cycles

deepening of response up to 54%

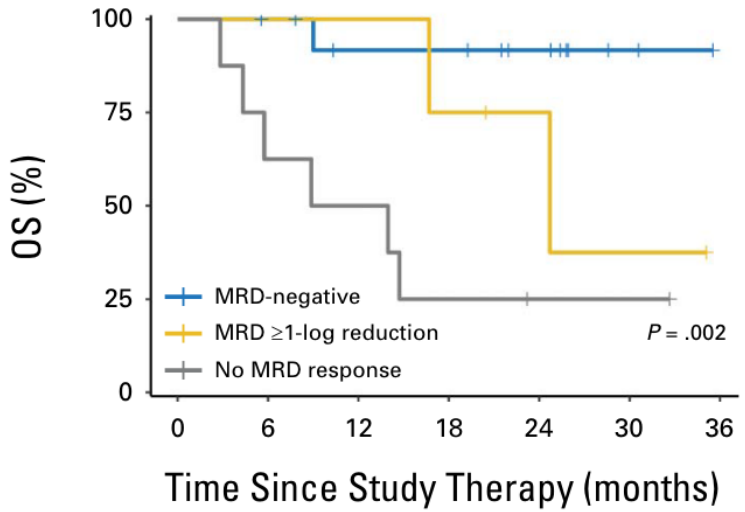


med. Follow-Up 25 months

med. OS not reached

2yr-OS 67%

d60 landmark analysis



2yr-OS:

MRD-neg. 92%

MRD-red. 75%

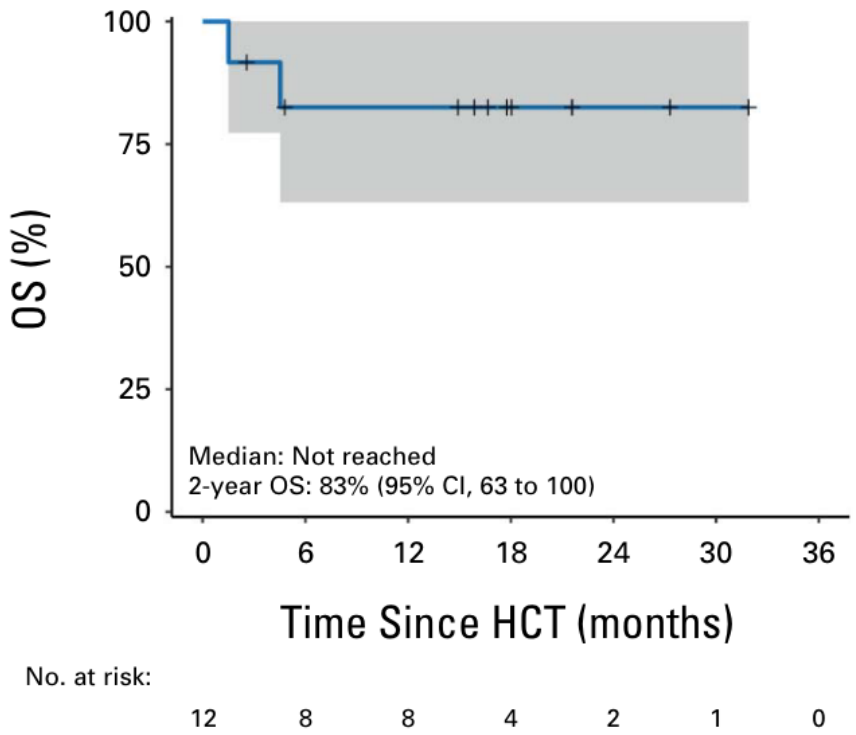
no mol resp 25%

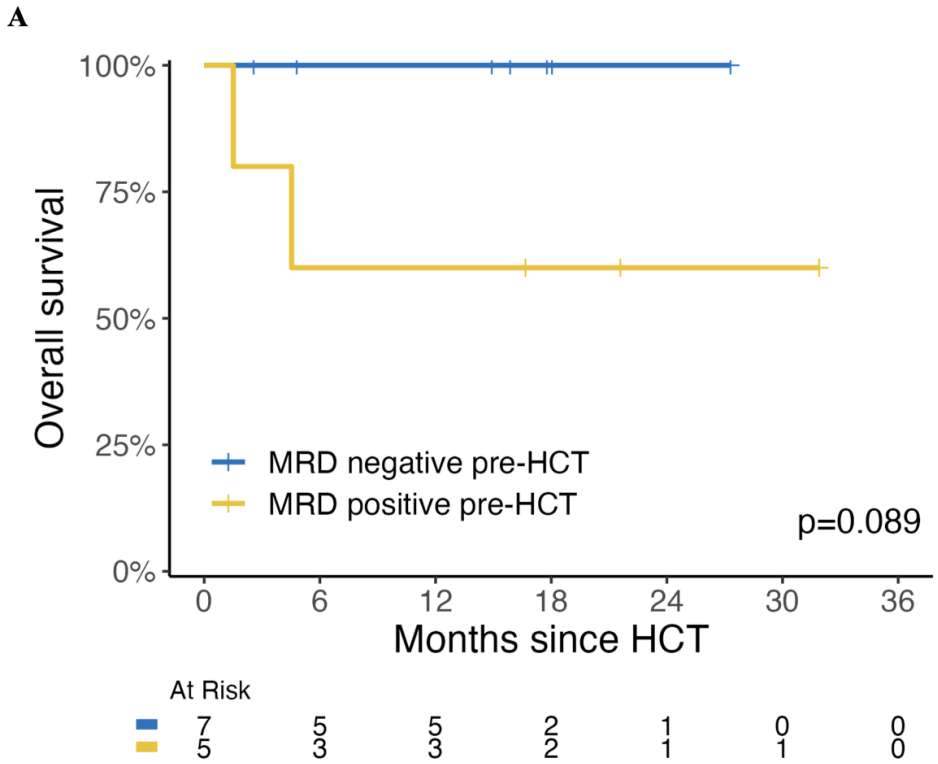
Tiong et al. JCO 2024

Venetoclax-based MRD-Conversion, VALDAC

18/26 pts with mol rel were transplant-eligible (regarding age, comorbidities, donor availability)

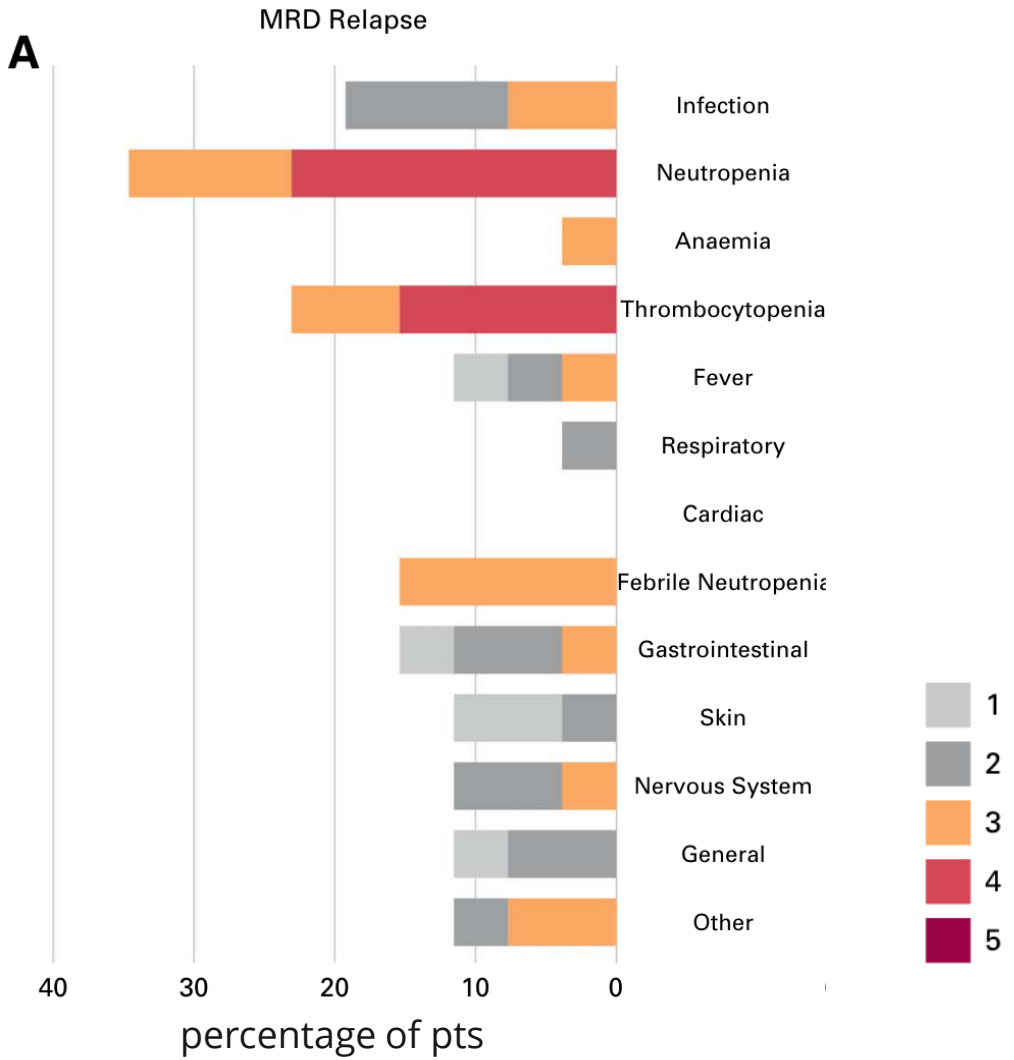
- **12/18 (67%) proceeded to allo-SCT after a median of 3.8 months**





Tiong et al. JCO 2024

Venetoclax-based MRD-Conversion, VALDAC



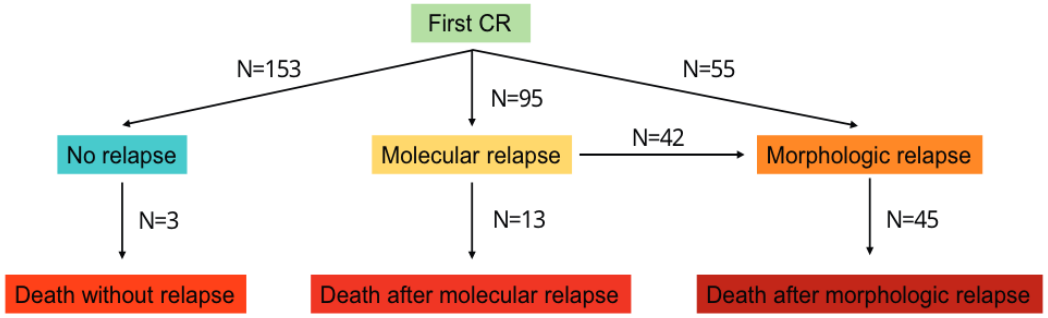
unplanned hospital admissions:

- **in 9/26 (35%) pts with mol relapse**
- **for a median of 6 days**
- **esp. within the first two cycles of therapy**
- **mainly related to infection (41%), febrile neutropenia (18%) or non-neutropenic fever (9%)**

Intensive CTX based MRD-Conversion in NPM1mut/CBF AML

retrospective
n=303 CBF or NPM1-mut AML
2010-2019
MRD monitoring in CR1 after 1st line int CTX

266 with FLT3-status:
- **40 FLT3-ITD (Ratio?)**
- **2 FLT3-TKD**



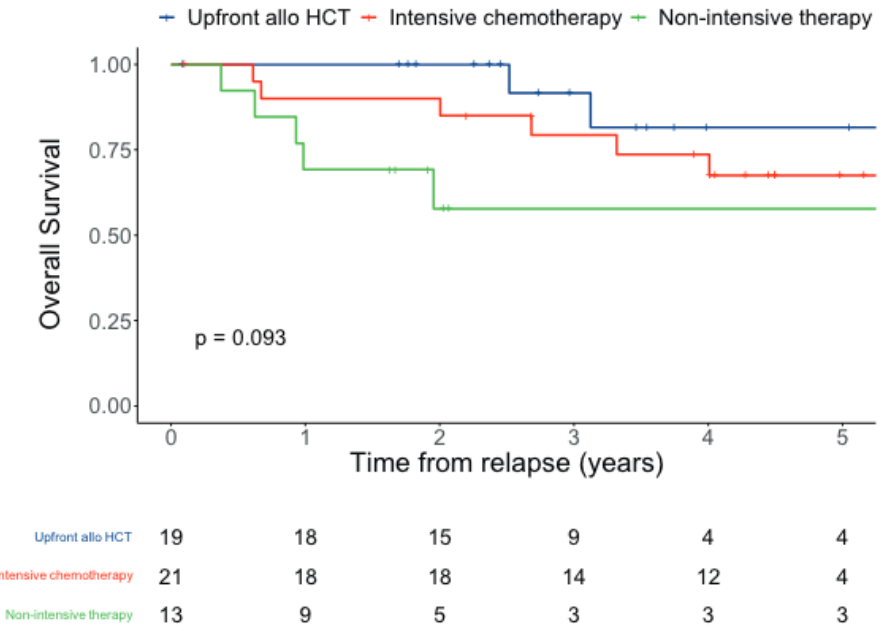
Total : 303	Molecular relapse	Morphologic relapse	Death without relapse	Death after molecular relapse	Death after morphologic relapse	No event
Diagnosis	95	55	3	0	0	150
Molecular relapse	0	42	0	13	0	40
Morphologic relapse	0	0	0	0	45	52

Characteristic	All relapses ($n = 150$)	Molecular relapse ($n = 53$)	Molecular-morphologic relapse ($n = 42$)	Upfront morphologic relapse ($n = 55$)
Time from relapse to salvage therapy (IQR), days	33 (14–64)	49 (27–75)	62 (38–132)	10 (4–22)
Type of salvage treatment, *n* (%)				
Upfront allogeneic HCT	23 (15%)	19 (36%)	2 (5%)	2 (4%)
Intensive chemotherapy	95 (63%)	21 (40%)	33 (79%)	41 (75%)
GO-containing chemotherapy	34 (23%)	10 (19%)	11 (26%)	13 (24%)
Non-intensive chemotherapy	30 (20%)	13 (25%)	5 (12%)	12 (22%)
IDH inhibitors	3 (2%)	2 (4%)	0	1 (2%)
FLT3 inhibitors	8 (5%)	2 (4%)	2 (5%)	4 (7%)
Azacitidine	3 (2%)	1 (2%)	0	2 (4%)
Azacitidine-GO	4 (3%)	4 (8%)	0	0
Azacitidine-venetoclax	5 (3%)	2 (4%)	2 (5%)	1 (2%)
GO	5 (3%)	0	1 (2%)	4 (7%)
Other	2 (1%)	2 (4%)	0	0
No treatment	2 (1%)	0	2 (5%)	0
Allogeneic HCT, *n* (%)	121 (81%)	45 (85%)	31 (74%)	45 (82%)
Sequential allogeneic HCT	29 (19%)	12 (23%)	8 (19%)	9 (16%)

Intensive CTX based MRD-Conversion in NPM1mut/CBF AML

Response to salvage therapy in CBF/NPM1-mut AML who receive preemptive treatment

Characteristic	Upfront allogeneic HCT (n=19)	Intensive chemotherapy (n=21)	Non-intensive chemotherapy (n=13)
Time from relapse to treatment (IQR), days	68 (52-105)	41 (26-54)	42 (17-65)
Age at salvage (IQR), years	52 (39-56)	41 (38-53)	48 (43-54)
Level of transcript before salvage (IQR)	1.6 (1.1-16.7)	1.4 (0.3-17.8)	6.0 (1.8-15)
Response after salvage, n (%)			
CR_{MRD-}		11 (52%)	2 (15%)
CR_{MRD-LL}		2 (10%)	0
CR_{MRD+} other than CR_{MRD-LL}		6 (29%)	5 (38%)
Allogeneic HCT, n (%)	19 (100%)	15 (71%)	11 (85%)
Level of transcript before allogeneic HCT (IQR)	1.6 (1.1-16.7)	0.003 (0.001-0.29)	2.5 (0.01-11.3)
Response after allogeneic HCT, n (%)			
CR_{MRD-}	15 (79%)	10 (67%)	5 (45%)
CR_{MRD-LL}	1 (5%)	1 (7%)	2 (18%)
CR_{MRD+} other than CR_{MRD-LL}	1 (5%)	1 (7%)	1 (9%)



Conclusion I

- **MRD-Conversion prior allo-SCT is feasible**

  - but also reasonable (risk?) and required (benefit)?

- **Well-designed prospective trials incorporating new treatment approaches**

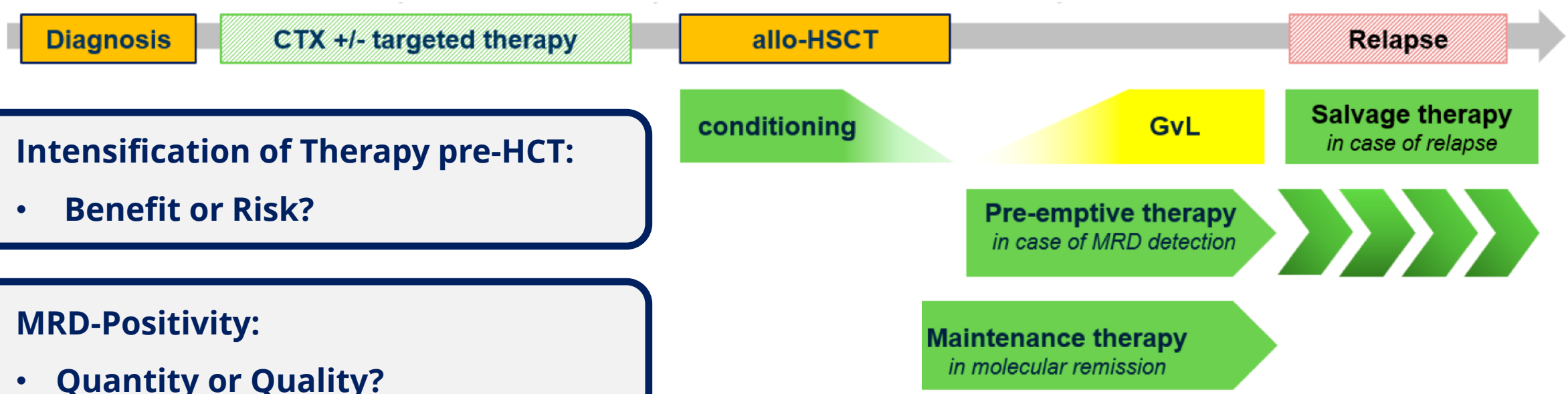
(e.g. BCL2-/Menin-Inhibition etc.) in MRD-pos disease evaluating MRD clearance compared to proceeding to allo-SCT are needed

Strategies for MRD-Conversion during Course of Treatment

- **FLT3-Inhibition**
- **Venetoclax & LDAC**
- **Intensive Chemotherapy**

Conditioning

post allo-SCT



Intensification of Therapy pre-HCT:

- **Benefit or Risk?**

MRD-Positivity:

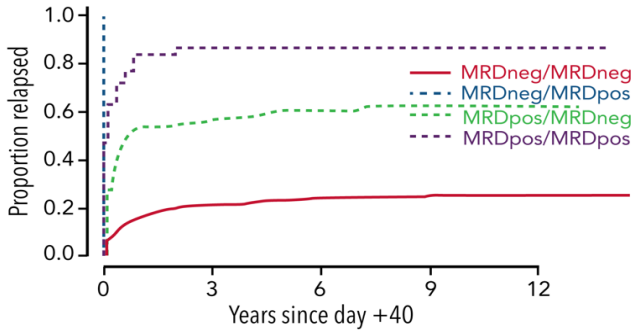
- **Quantity or Quality?**

MRD-Conversion during allo-SCT

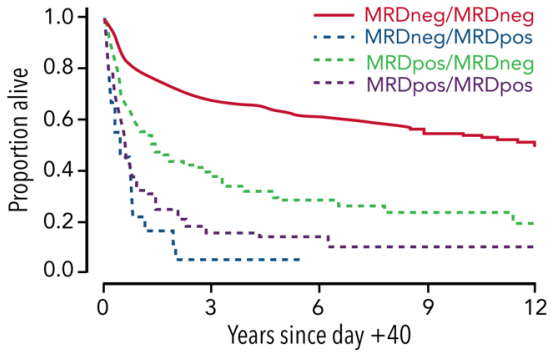
- **20-51% MRD-positive prior allo-SCT**
- **MRD-conversion with allo-SCT in 60-79%**
- **MRD conversion is associated with improved outcome (CIR, OS)**

MFC MRD n=810

CIR by MRD pre/post HSCT

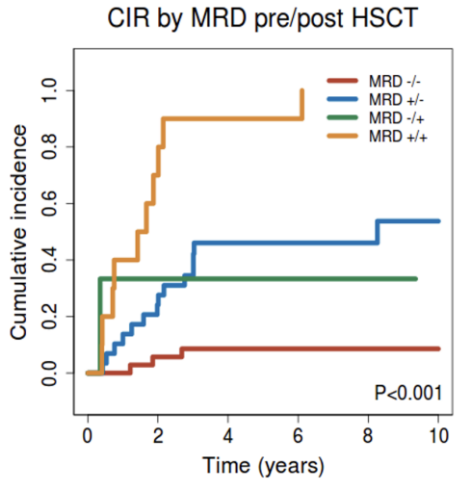


OS by MRD pre/post HSCT

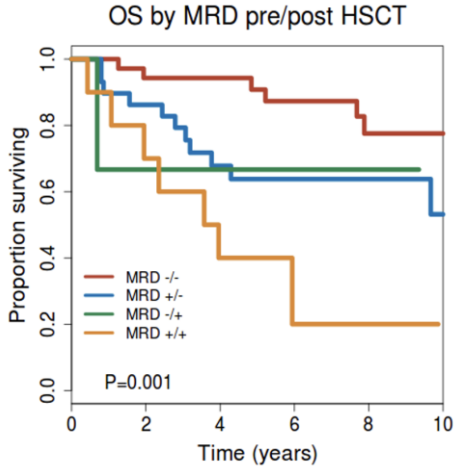


NGS MRD n=77

CIR by MRD pre/post HSCT



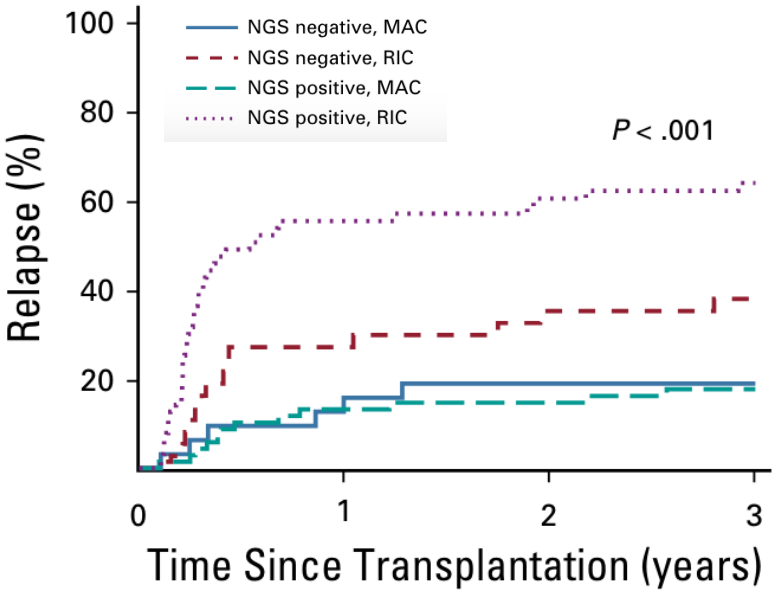
OS by MRD pre/post HSCT

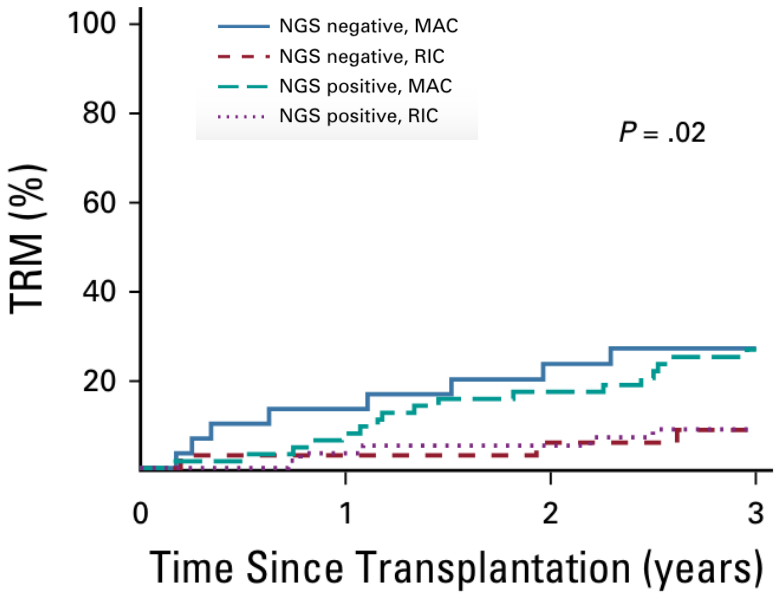


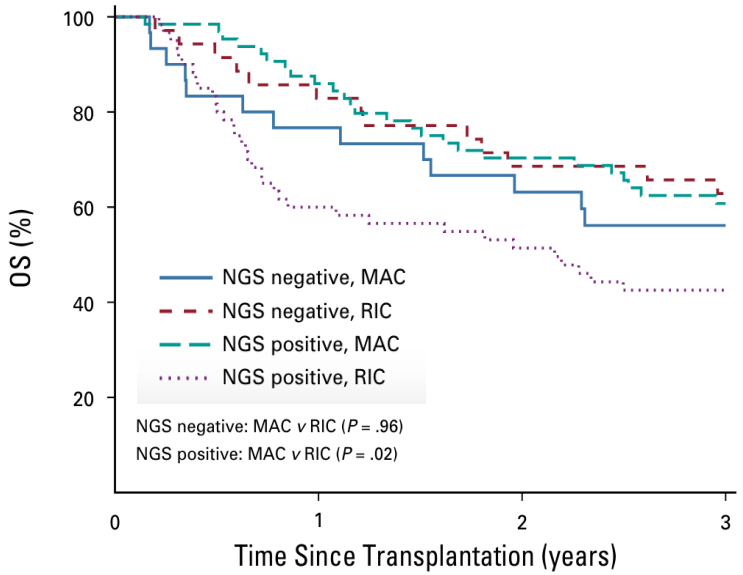
Paras et al. Blood 2022; Heuser et al. Blood Advances 2021

Pre-Transplant MRD and Conditioning (RIC vs. MAC)

- **Prospective randomized Phase III RIC vs MAC Trial (BMT CTN 0901)**
- **NGS, pB prior allo-SCT, n=190**





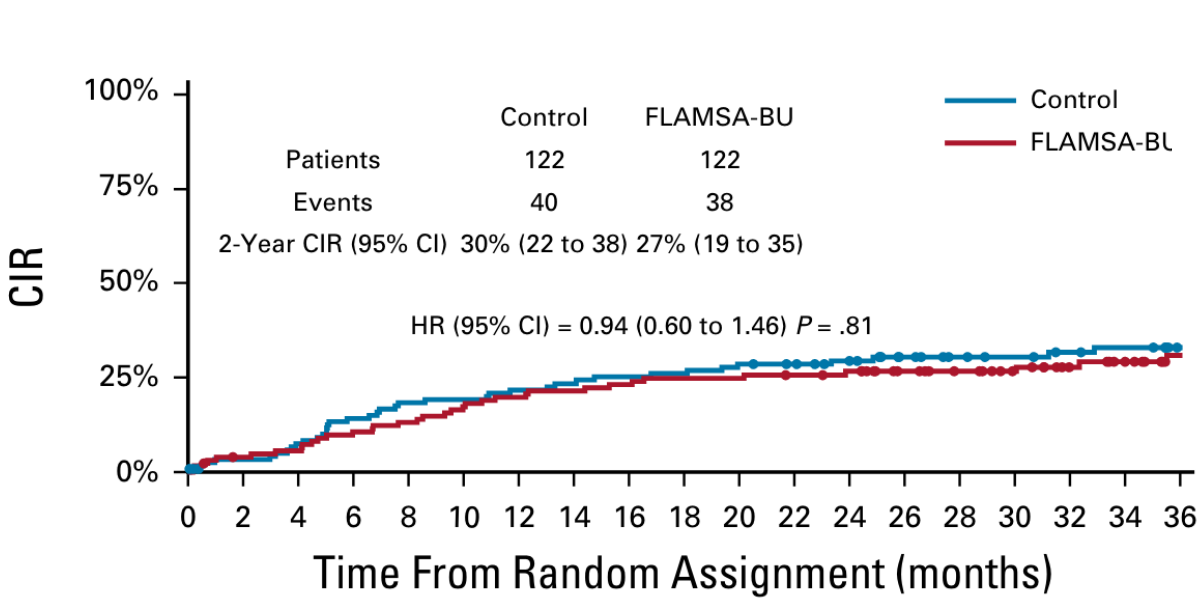


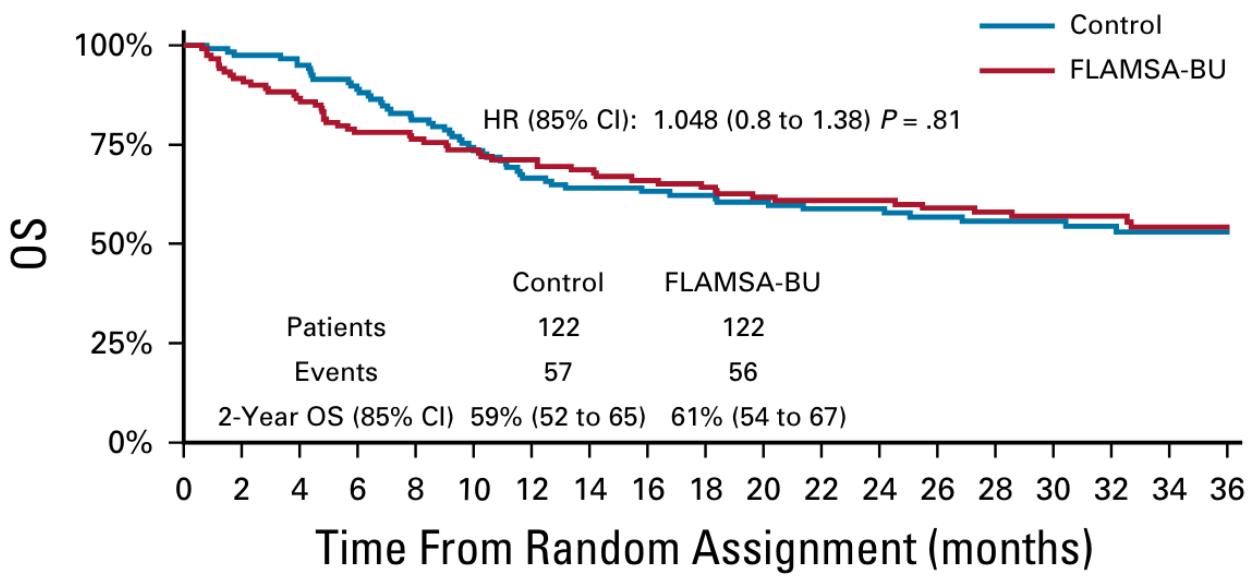
MAC reduces relapse incidence and improves OS in pre-HCT MRD-positive patients
CAVE: small numbers in MRD-negative arm, high CIR in RIC-arm, no information on MRD kinetics

Hourigan et al. JCO 2019

FLAMSA-based RIC vs. Flu-based RIC

- **Prospective randomized Phase II FIGARO (Flu-based RIC vs. FLAMSA-Bu)**
- **AML in CR1/2, primary refractory, high risk MDS**
- **MFC, BM prior allo-SCT**



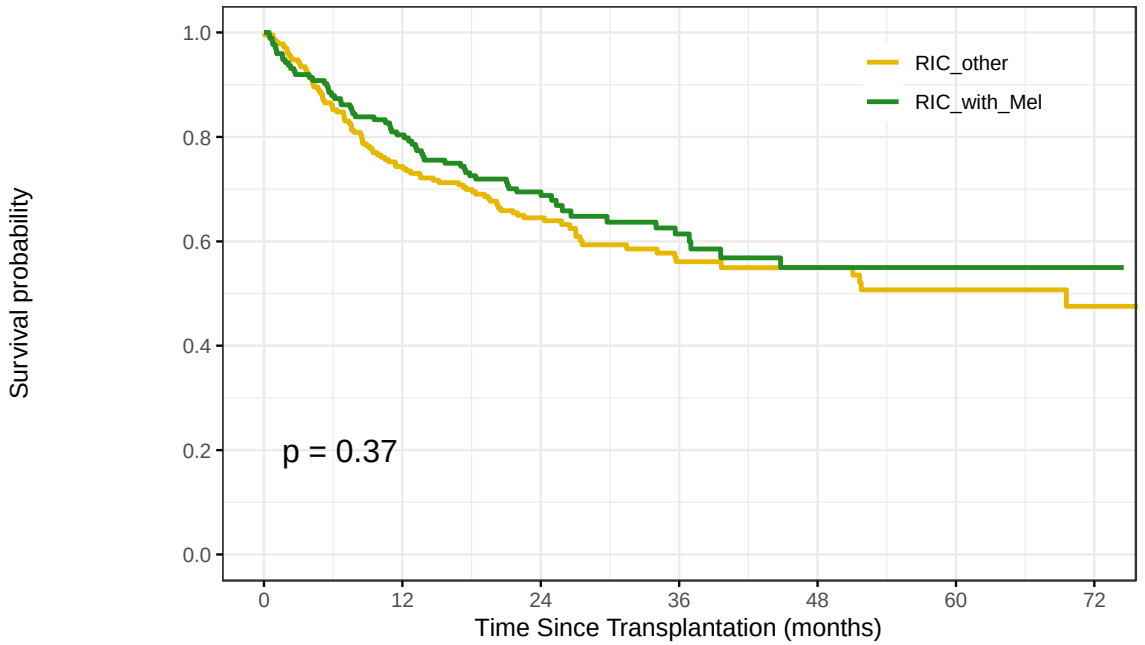


No interaction between MRD-status and conditioning intensity regarding CIR and OS
No difference in post-transplant MRD-clearance d+42 among both treatment arms

Craddock et al., JCO 2020

Melphalan-based RIC

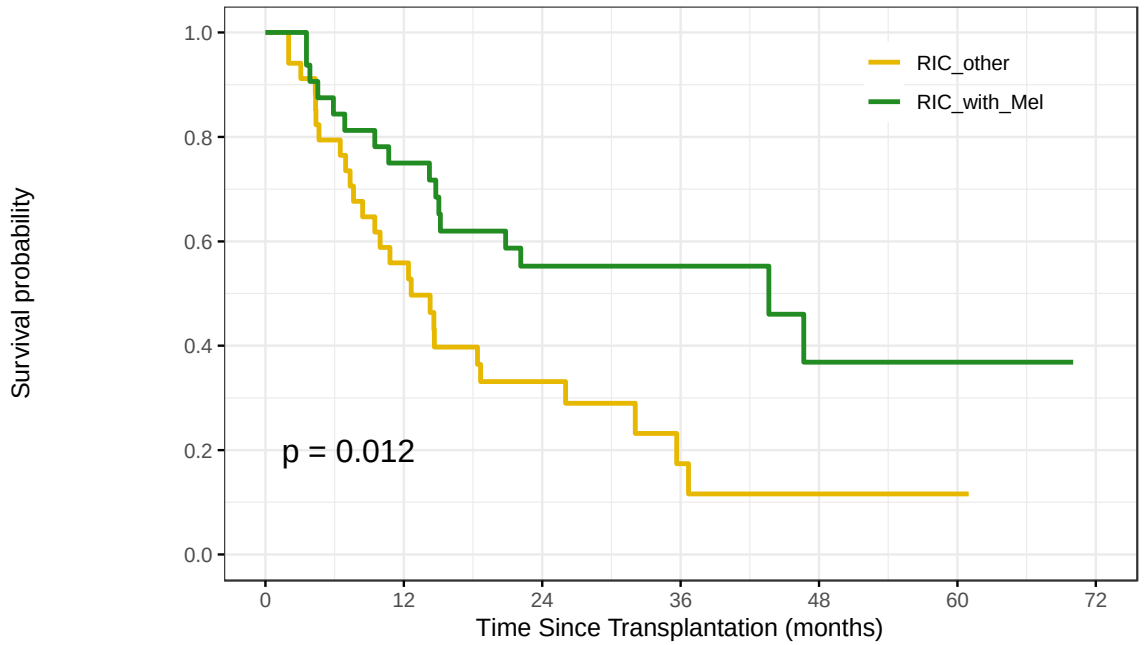
MRD negative



Number at risk

RIC_other	230	171	123	65	46	33	10
RIC_with_Mel	174	139	100	51	25	16	7

MRD positive



Number at risk

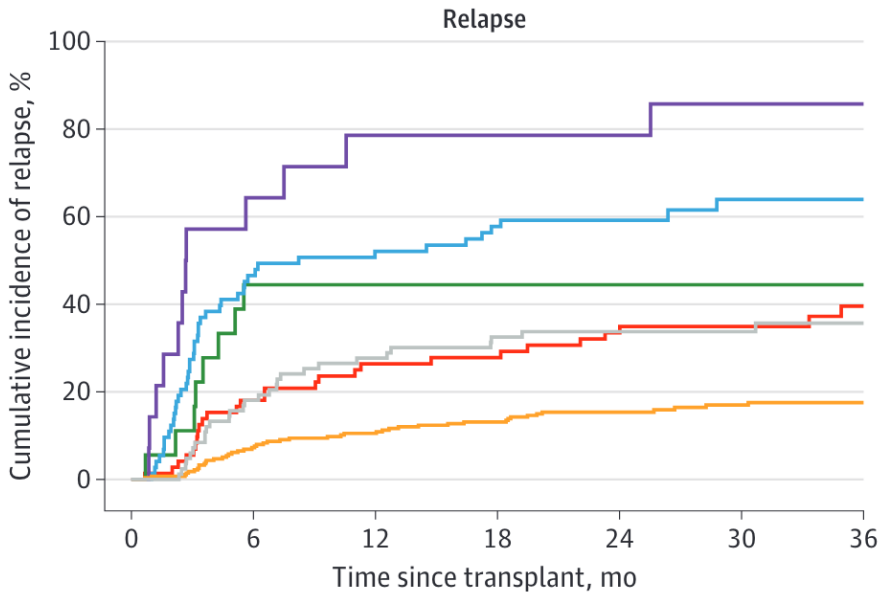
RIC_other	34	18	9	3	1	1	0
RIC_with_Mel	32	24	14	7	4	3	0

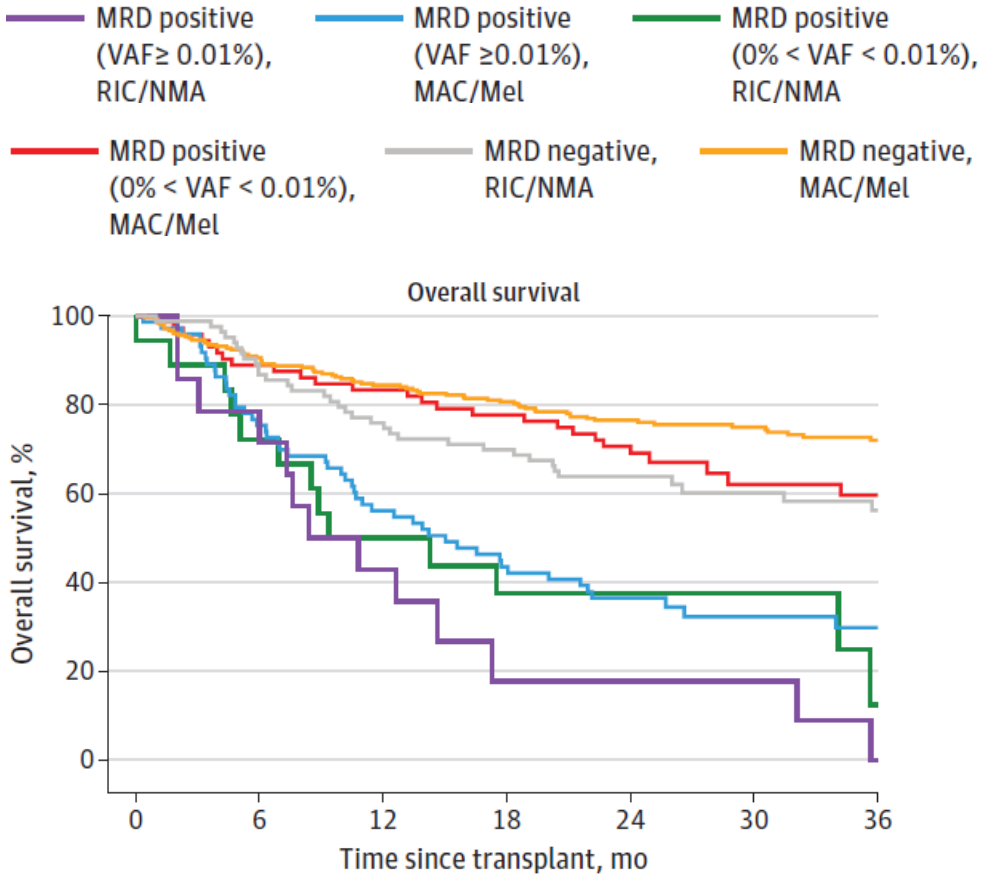
CIBMTR pre-MEASURE cohort (n=1075 pts)

Christopher HOURIGAN, *Journal of Clinical Oncology* 40, no. 16_suppl 2022:7006-7006

Melphalan-based RIC

- **Retrospective, n=537**
- **AML CR1 allografted 2013-2019**
- **FLT3-ITD NGS, pB prior allo-SCT**



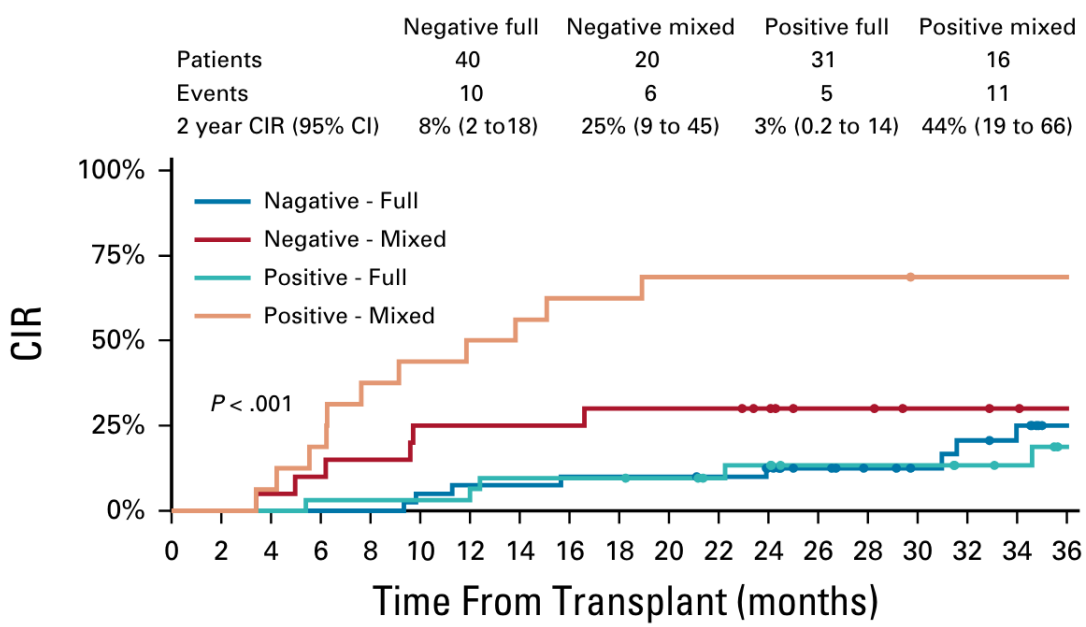


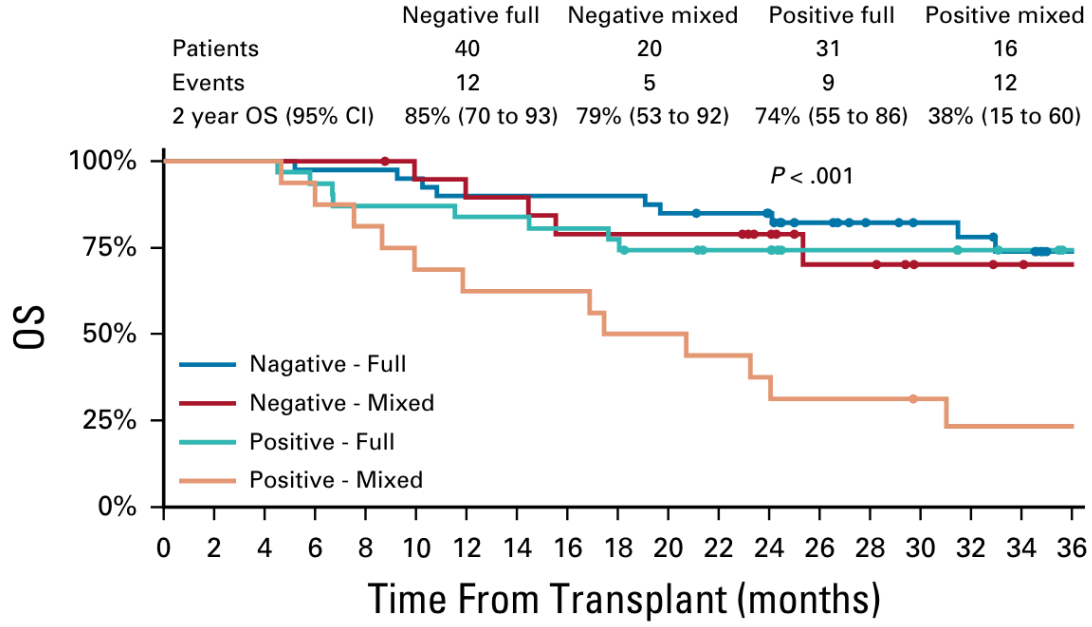
Melphalan-containing RIC may improve survival in MRD positive patients before allo-SCT

Dillon et al. JAMA Oncology 2024

Pre-Transplant MRD and Post-transplant Chimerism

- **Achievement of full donor T-cell chimerism (FDTCC) 3 months after allo-SCT is…**
  - **Independent of MRD-status and Conditioning**
  - **Associated with an improved outcome (CIR and OS) in pre-transplant MRD-positive pts**





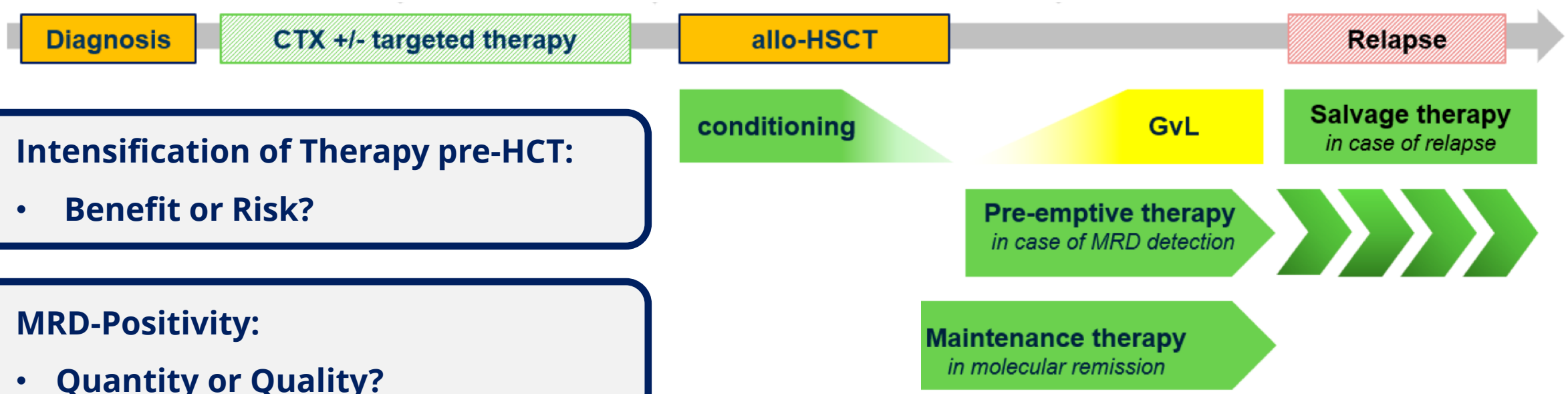
Strong and reliable GvL-effect as important approach to optimize posttransplant outcome!

Strategies for MRD-Conversion during Course of Treatment

- **FLT3-Inhibition**
- **Venetoclax & LDAC**
- **Intensive Chemotherapy**

Conditioning

Maintenance



Intensification of Therapy pre-HCT:

- **Benefit or Risk?**

MRD-Positivity:

- **Quantity or Quality?**

Strategien zur MRD-Konversion im Behandlungsverlauf

Post-Transplant Maintenance aims at…

…Targeting LSC/Progenitor Population directly

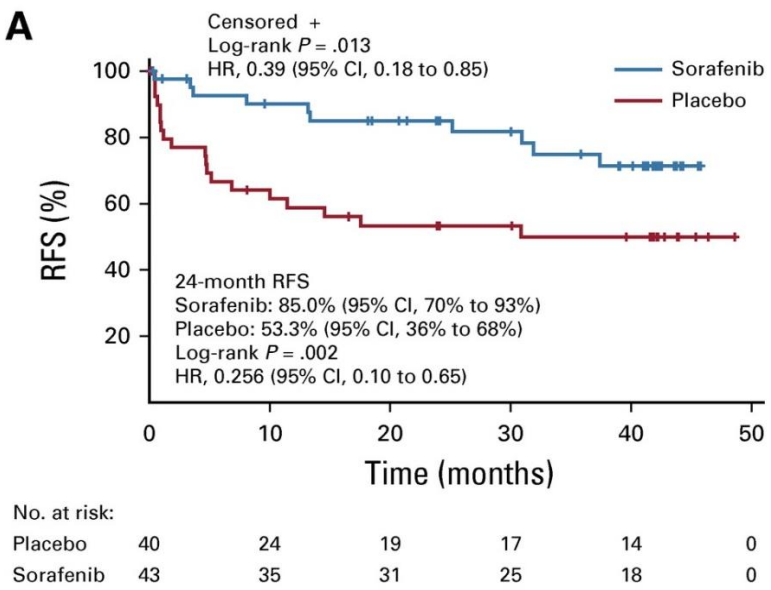
…Manipulating the kinetics of disease relapse after allo-SCT

…„Buying time“ for GvL-effect

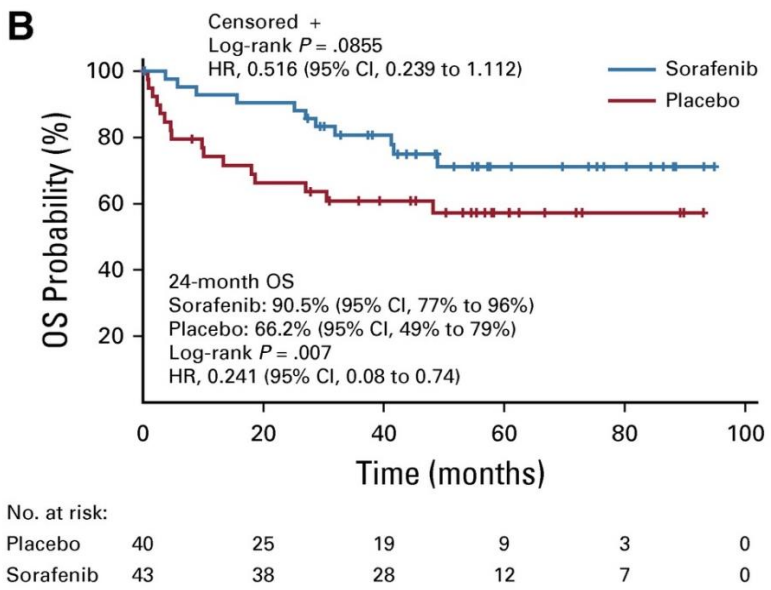
…Postponing the requirement for DLI until toxicity is reduced

Sorafenib as Maintenance for FLT3-ITD mut AML, SORMAIN

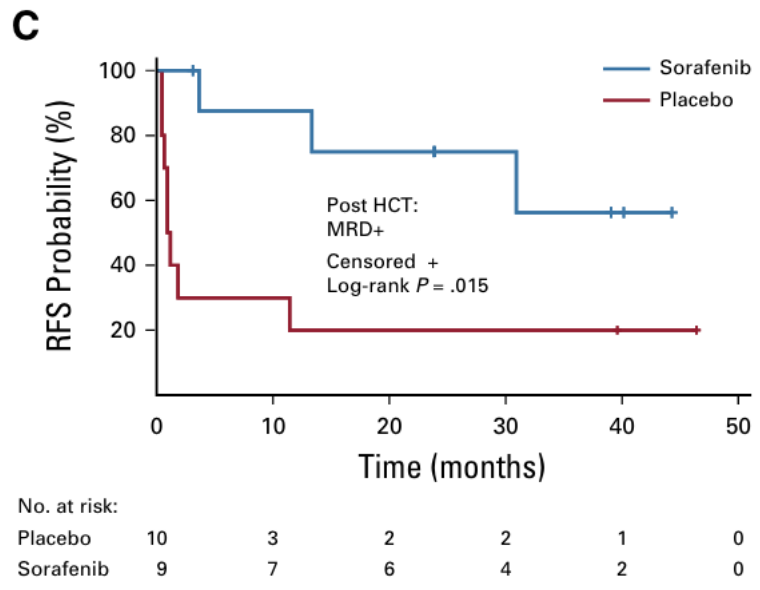
Relapse-Free Survival n=83



Overall Survival n=83



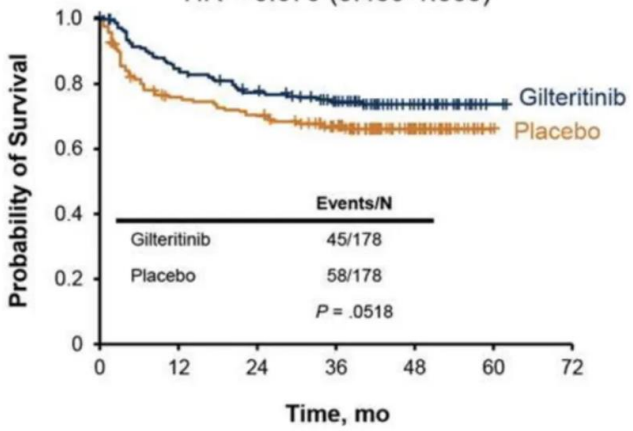
Relapse-Free Survival MRD-pos post allo-SCT n=19



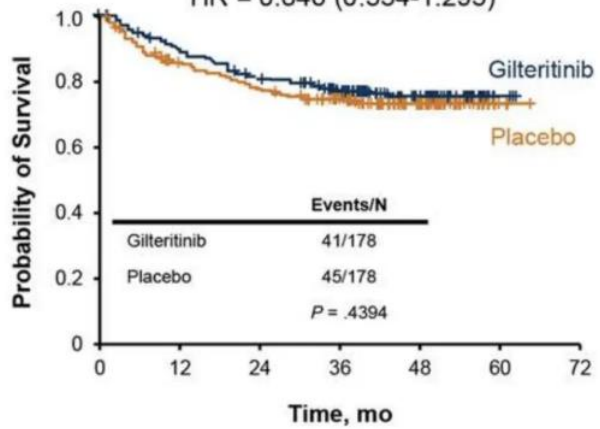
Burchert et al. JCO 2020

Gilteritinib as Maintenance for FLT3-ITD mut AML, MORPHO

Primary Objective:
RFS
HR = 0.679 (0.459-1.005)



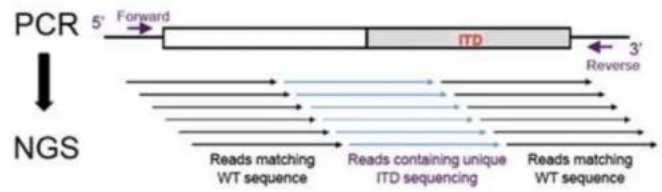
Key Secondary Objective:
OS
HR = 0.846 (0.554-1.293)



PCR-NGS Assay

- Two-step assay
- PCR of juxta-membrane region, amplicons analyzed by NGS
- Detects *FLT3*-ITD mutation with sensitivity of ~1 x 10^{-6}
- Quantitative/linear down to 1 x 10^{-4}
- *Qualitative* to LLOD at 1 x 10^{-6}
- Patient-specific "fingerprint"
- Frequently detects multiple ITDs

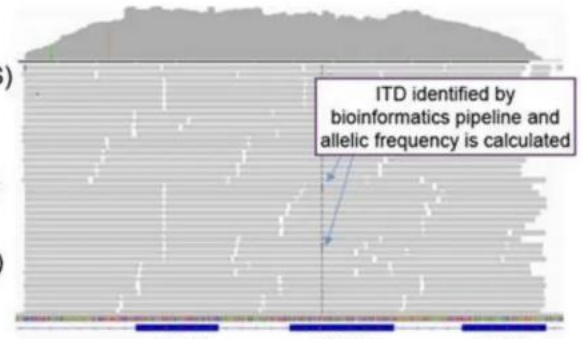
MRD Assay for *FLT3*-ITD: WT Burden



Ultra-deep sequencing of the region (Illumina SBS)

Diverse reads aligned to *FLT3* genomic sequence

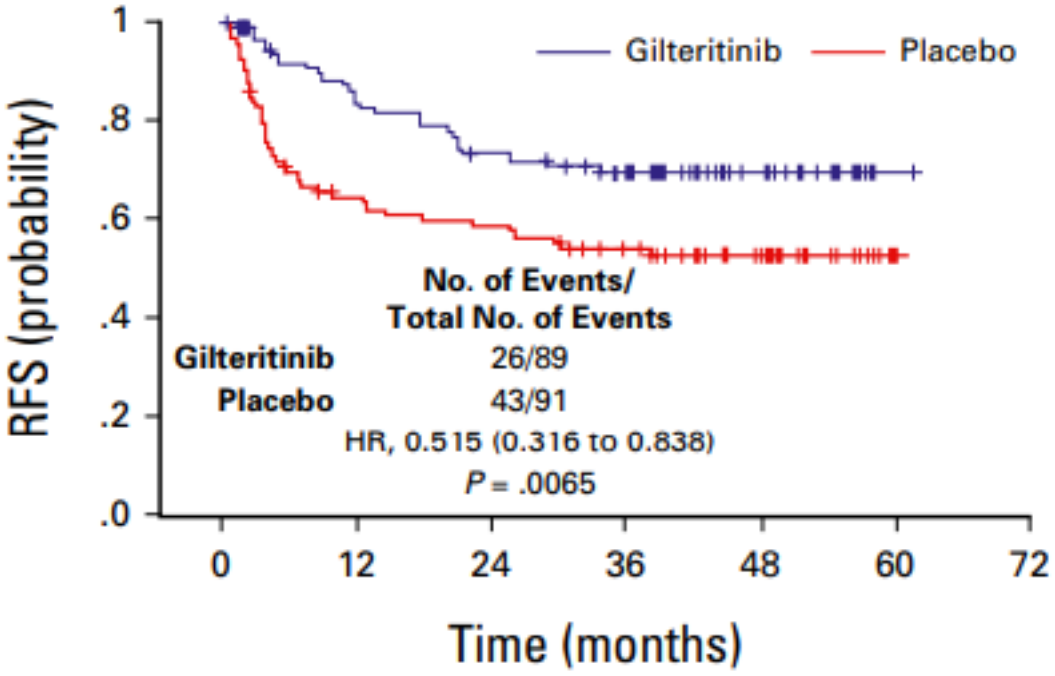
Relevant *FLT3* region (exon 14-15) targeted



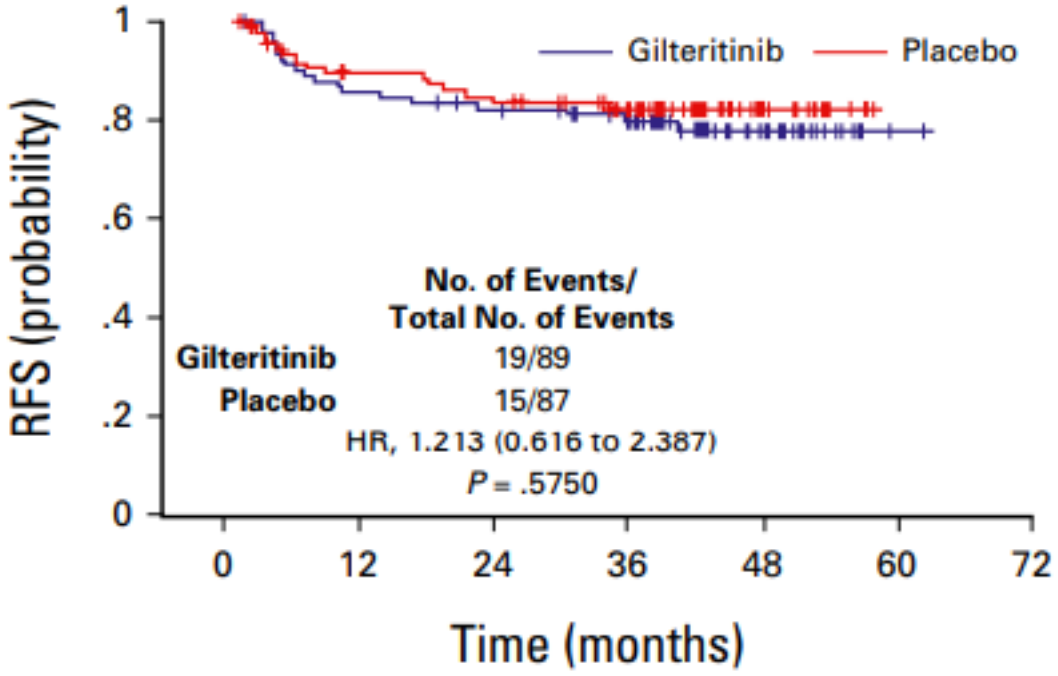
"get ITD"

Gilteritinib as Maintenance for FLT3-ITD mut AML, MORPHO

MRD-positive peri-HCT
Relapse-Free Survival



MRD-negative peri-HCT
Relapse-Free Survival



Gilteritinib seems to augment the effect of HCT:
in 71 MRD+ pts post allo-SCT, MRD was eradicated in 69% of pts on Gilteritinib vs. 44% in pts on PBO

Levis et al. JCO 2024

CC-486 as Maintenance

Phase I/II, n=30

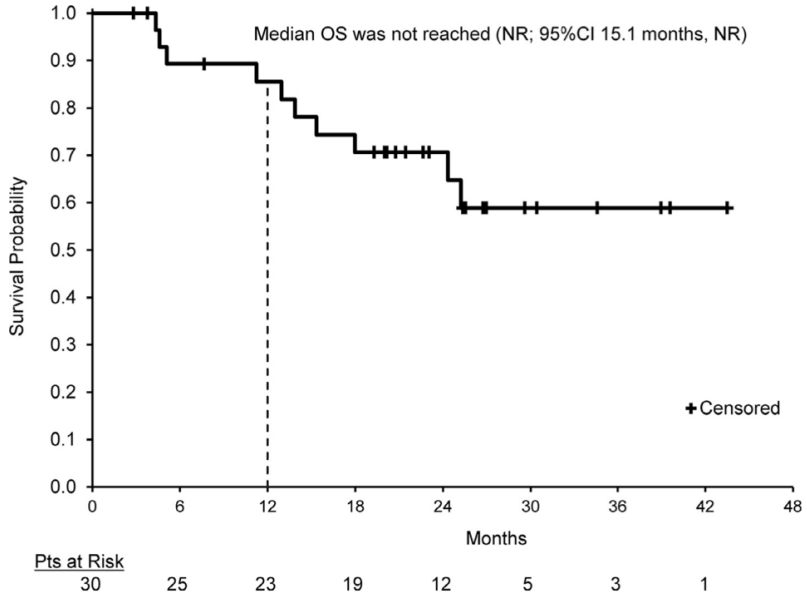
87% AML, 13% MDS
4 schedules per 28 days for 12 cycles

70% int cytogenetic risk (AML)
75% int-2/high risk IPSS (MDS)

Disease status @allo-SCT:
- 80% CR1
- 10% CR2
- 10% no CR

Time allo-SCT – CC-486 start: 82 days
Median no. of cycles: 9
- 43% pf pts completed all cycles

Median FU 19 months
1-yr OS 85%

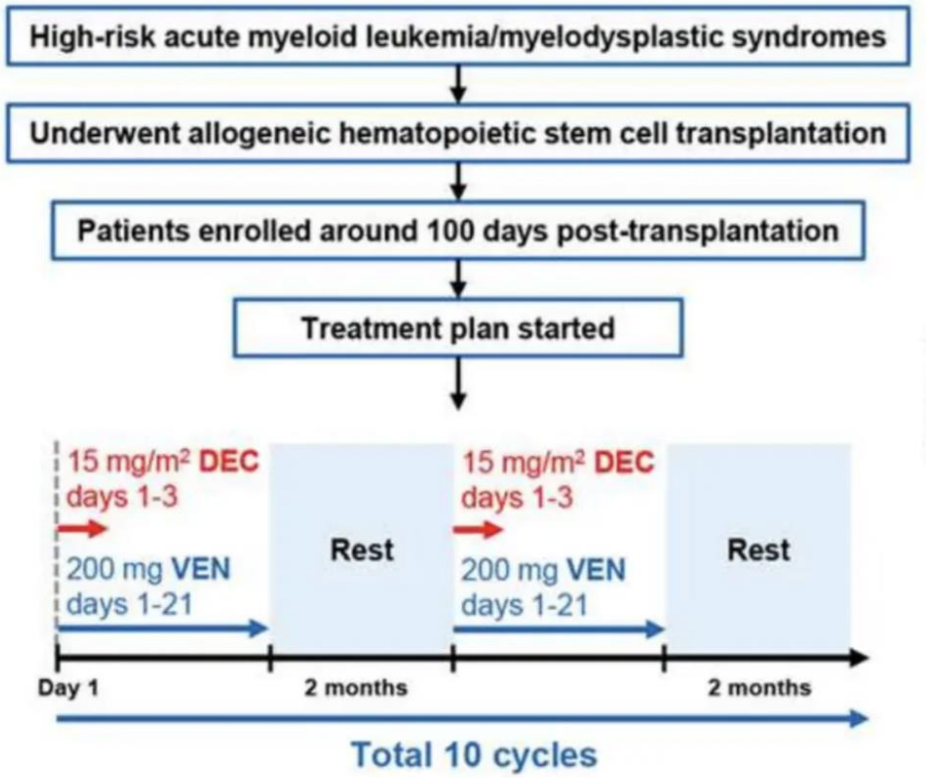


AMADEUS Trial (NCT04173533)

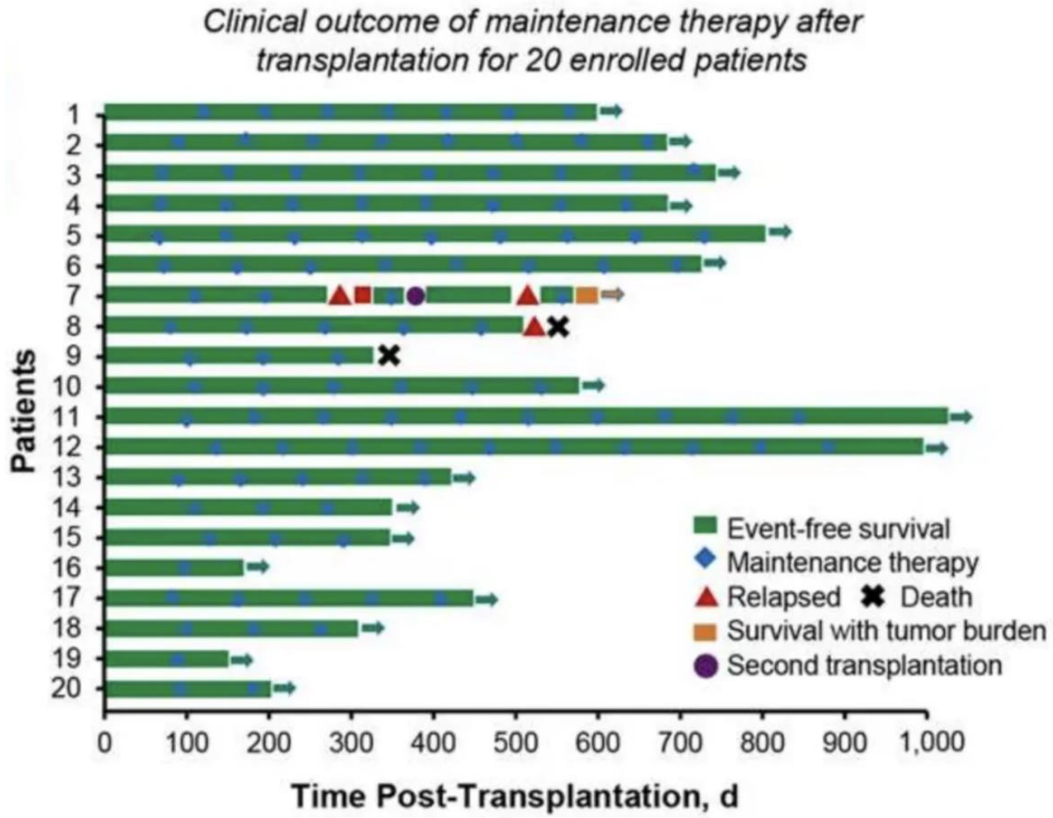
Oral-AZA vs. PBO

De Lima et al. BBMT 2018

Low Dose Decitabine/Ven Maintenance



n=20



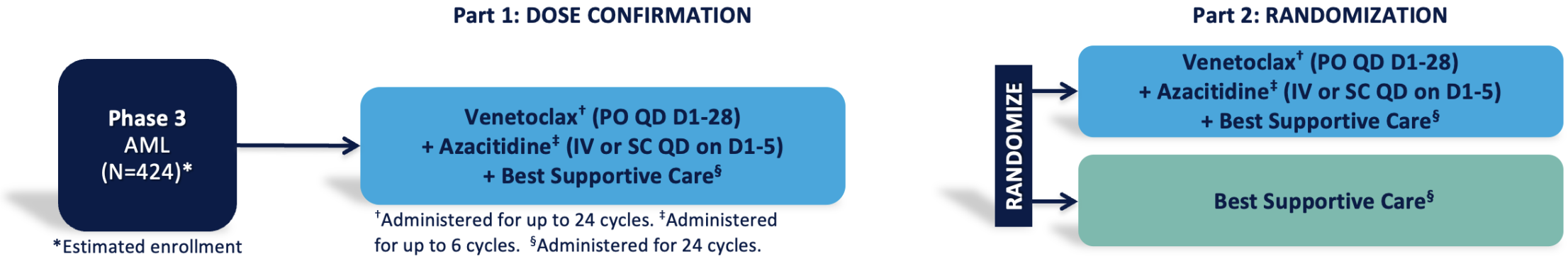
Grade II/III hematologic AE in 50%/20% of pts

2yr OS: 85%
2yr RFS: 84%

2yr CIR: 15%
2yr NRM: 6%

Wei et al. Cancer Science 2021

Azacitidine s.c./Ven Maintenance, VIALE-T (NCT04161885)



Key Eligibility:

- Patients with AML ≥ 12 yrs old
- BM blasts <10% before and <5% after allo-SCT
- ANC ≥ 1000 mcL
- Platelet count ≥ 50000 mcL

N = ca. 400

Endpoints:

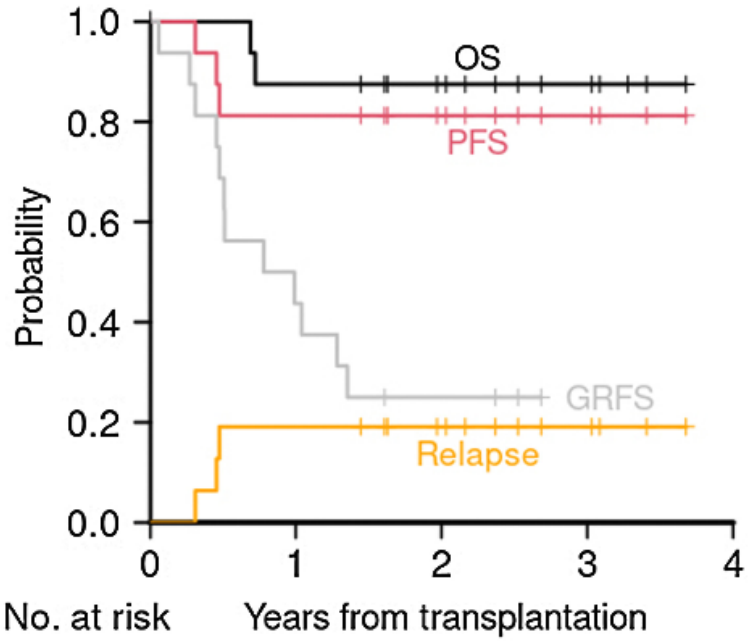
- Primary:
  - Part 1: DLTs
  - Part 2: RFS
- Secondary:
  - Part 2: OS, GFRS, GvHD Rate

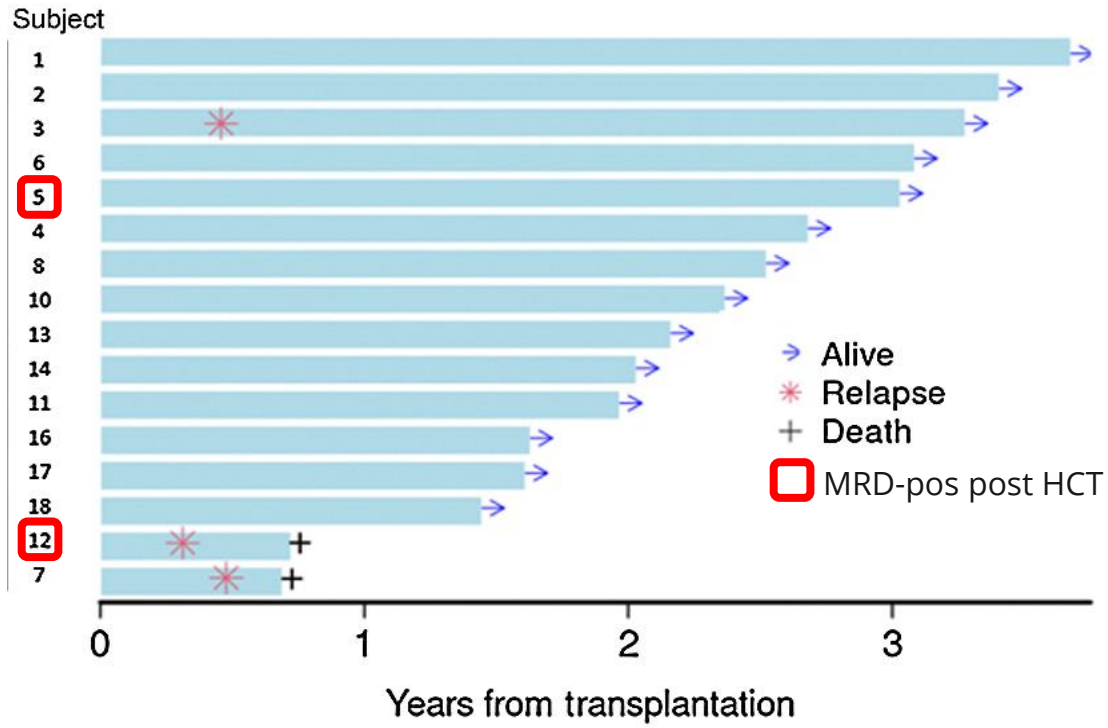
Adapted from Heuser M, et al. P669. EBMT 2023

Maintenance for IDH1 mut AML

Ivosidenib, Phase I, n=18

44% had received allo-SCT for R/R
33% with prior exposure to IDH-inhibitor
75% int, 25% adv cytogenetic risk
60% RIC, 40% MAC





Post-Tx MRD available 11/18

- MRD+ n=2 → 1 relapse
- MRD- n=9 → 2 relapses

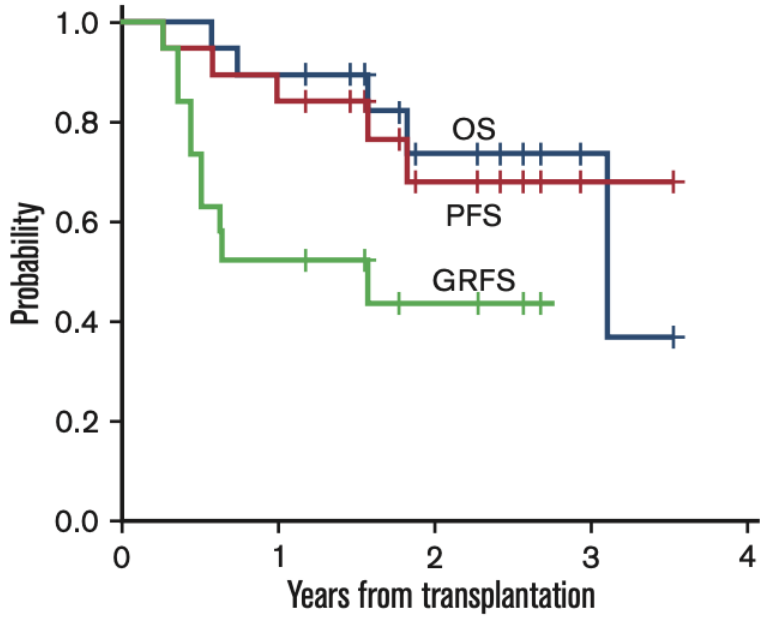
PIVOT Trial

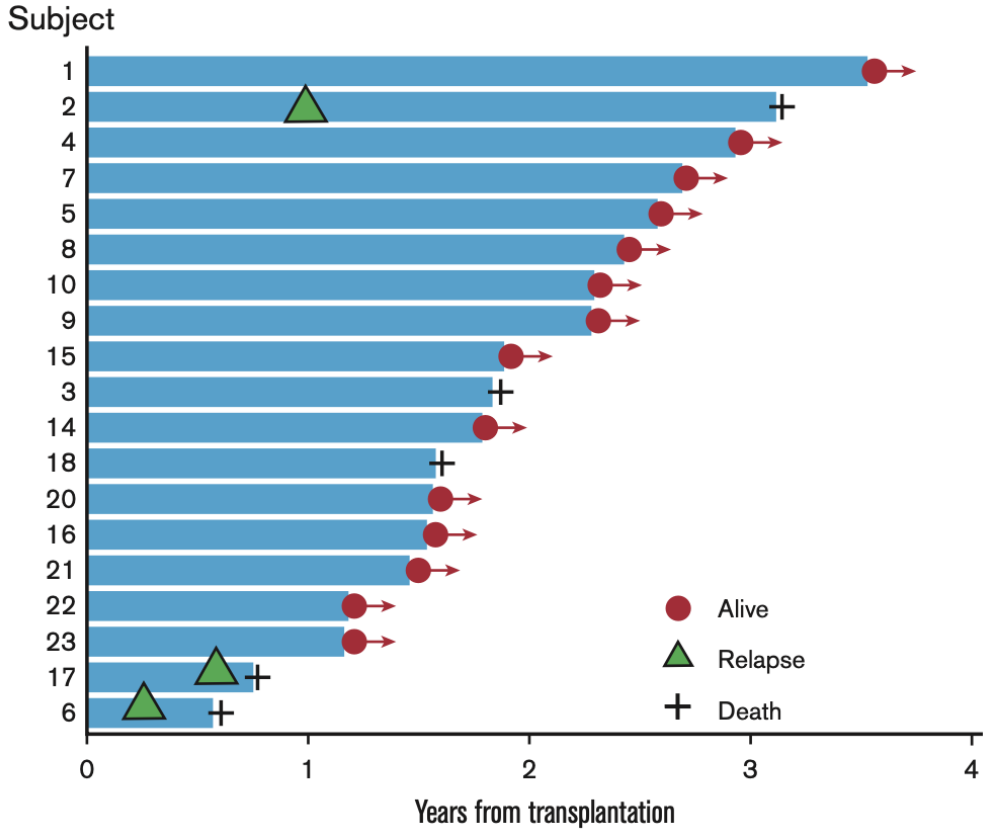
Fathi et al. Clinical Cancer Research 2023

Maintenance for IDH2 mut AML

Enasidenib, Phase I, n=19

20% had received allo-SCT for R/R
50% with prior exposure to IDH-inhibitor
80% int, 20% adv cytogenetic risk
80% RIC, 20% MAC





Post-Tx MRD available 14/19

- MRD+ n=6 → 1 relapse
- MRD- n=8 → 1 relapse

IDH2-Post-Allo Trial

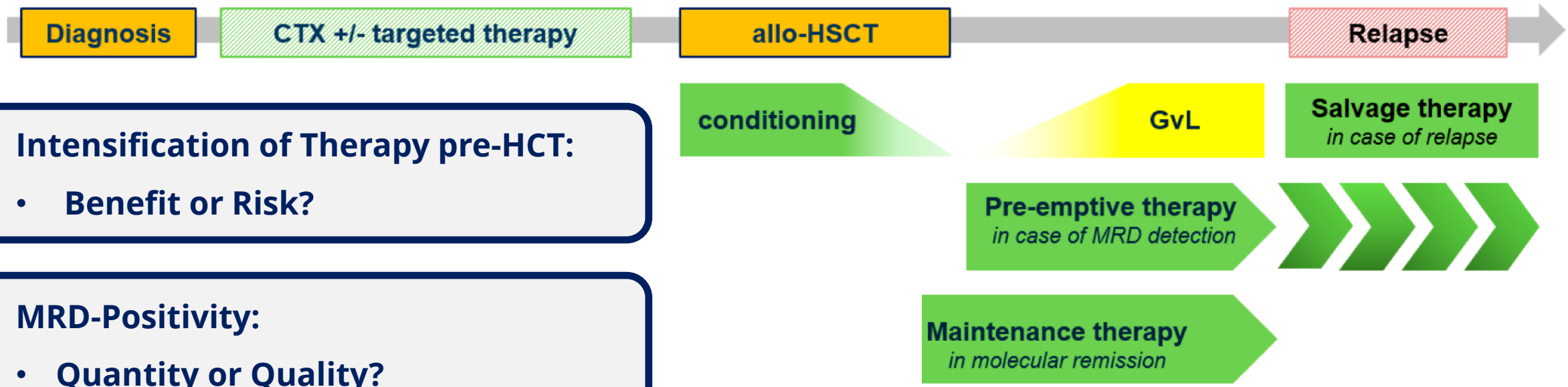
Strategies for MRD-Conversion during Course of Treatment

- **FLT3-Inhibition**
- **Venetoclax & LDAC**
- **Intensive Chemotherapy**

Conditioning

Maintenance

Pre-emptive Therapy



Intensification of Therapy pre-HCT:

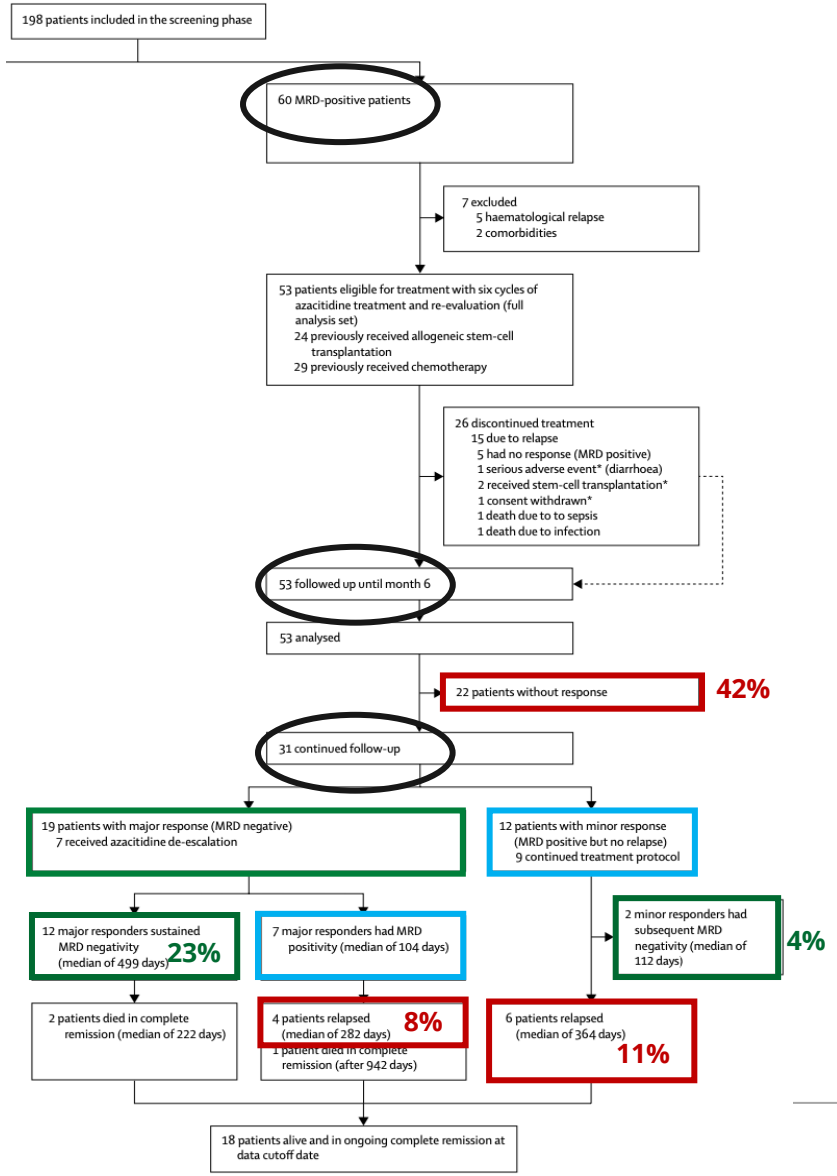
- **Benefit or Risk?**

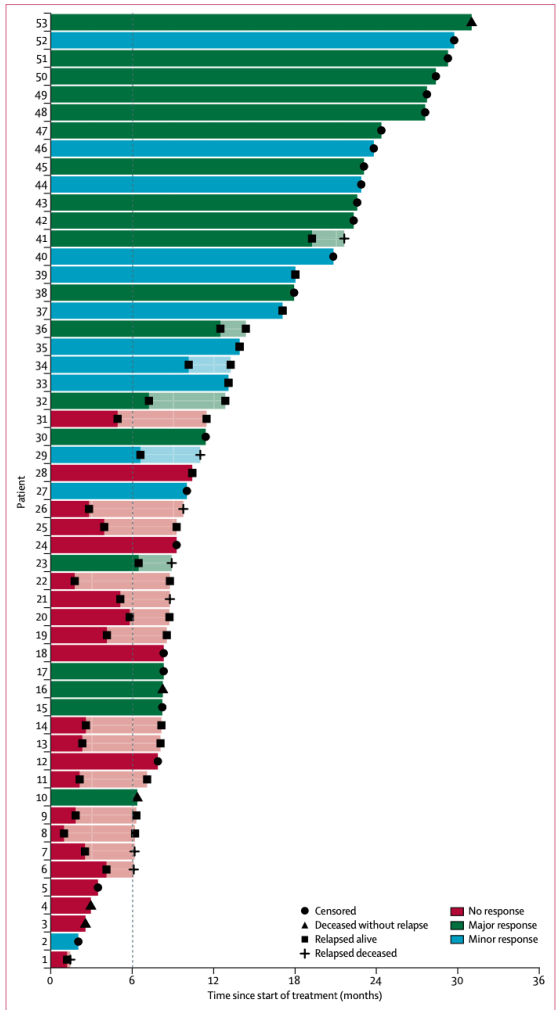
MRD-Positivity:

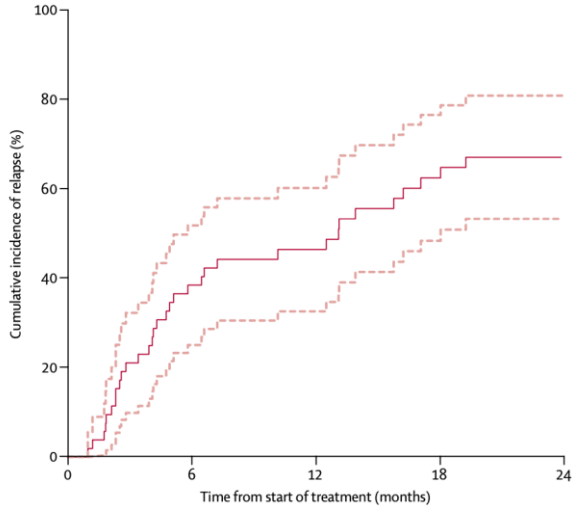
- **Quantity or Quality?**

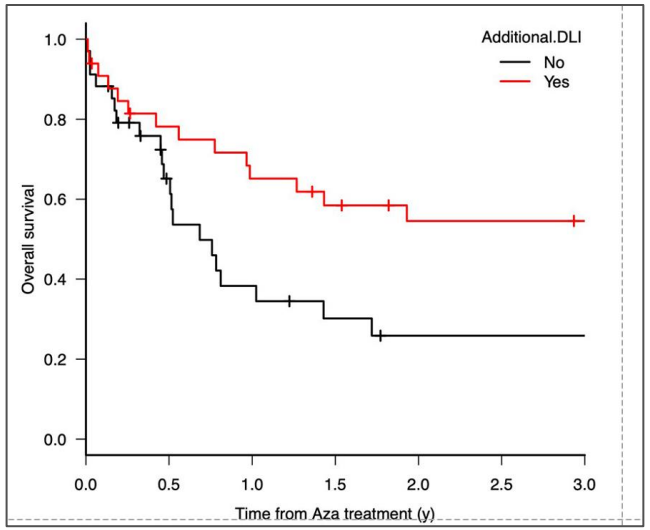
Adaptiert nach Rautenberg et al. IJMS 2019

Pre-emptive Therapie with HMA – RELAZA2









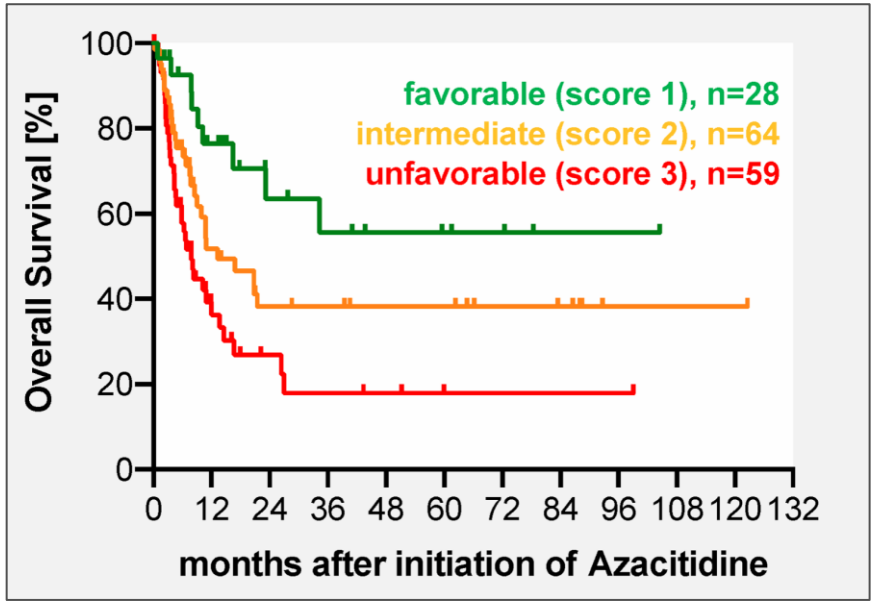
Pre-emptive Therapie with HMA & DLI

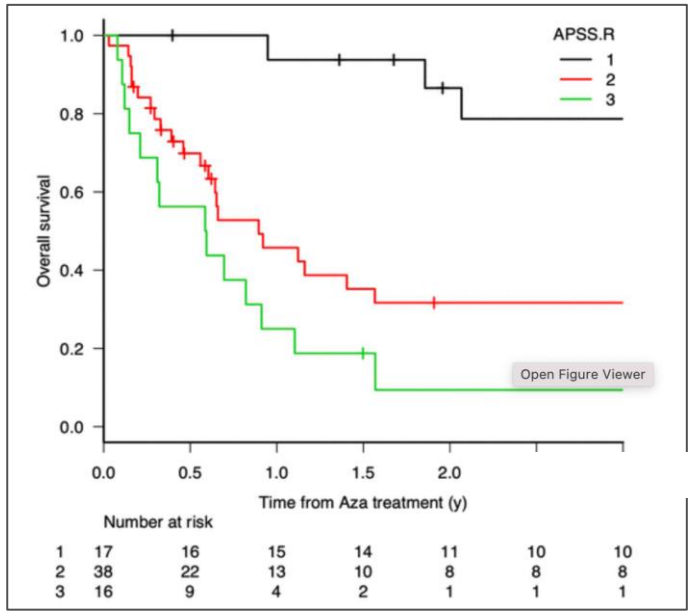
Type of relapse:

- **Molecular 1 point**
- **Hematologic 2 points**

Time to relapse:

- **> 6 months 0 points**
- **< 6 months 1 point**





Risk Score/Group	Response Rate (CR) after Azacitidine	2-y OS Rate after Azacitidine [±SEM]
1 (n = 28)	71%	64% ± 11%
2 (n = 64)	39%	38% ± 8%
3 (n = 59)	29%	27% ± 7%
	$p = 0.0007$	$p = 0.0012$

n=71
44% molecular relapse

Rautenberg et al. Cancers 2020; Liberatore et al. Therapeutic advances in hematology 2022

Conclusion II

- **MRD-Conversion achieved with allo-SCT in up to 79% of Patients!**
- **Optimal Conditioning Intensity remains to be elucidated, but a MAC can be offered whenever clinical feasible especially in MRD-pos pts and also Mel-based RIC appears to be an option**
- **Maintenance Concepts can successfully target MRD peri-transplant, but „All-Comer“ concepts are awaited eagerly**
- **For Post-transplant molecular relapse HMA & DLI remains standard of care**

Thank you very much for your attention

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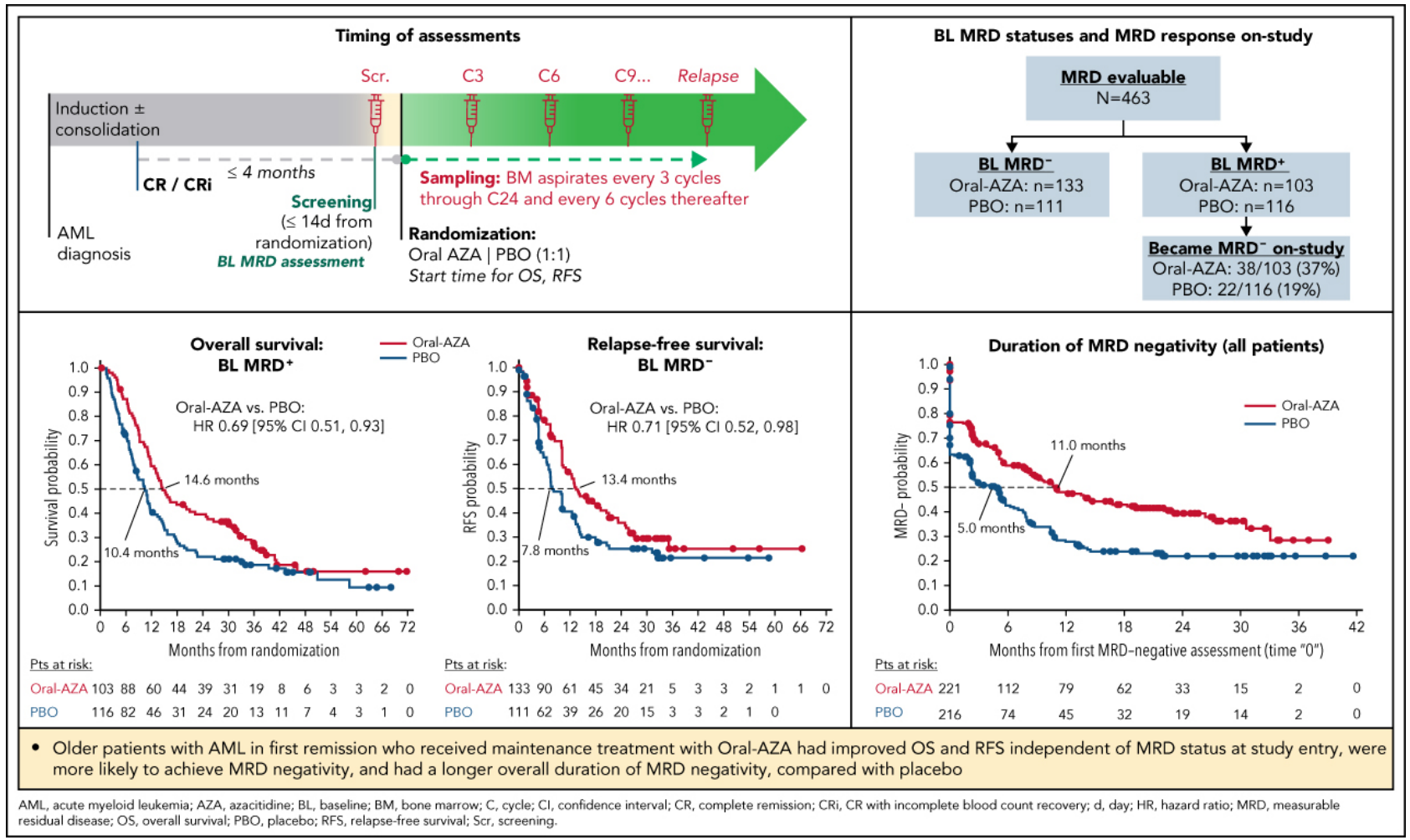
QUAZAR



- Older patients with AML in first remission who received maintenance treatment with Oral-AZA had improved OS and RFS independent of MRD status at study entry, were more likely to achieve MRD negativity, and had a longer overall duration of MRD negativity, compared with placebo

AML, acute myeloid leukemia; AZA, azacitidine; BL, baseline; BM, bone marrow; C, cycle; CI, confidence interval; CR, complete remission; CRi, CR with incomplete blood count recovery; d, day; HR, hazard ratio; MRD, measurable residual disease; OS, overall survival; PBO, placebo; RFS, relapse-free survival; Scr, screening.

How effective is chemotherapy in relapsed/refractory AML?

	CR/CRi/CRh in R/R AML	60-day mortality
FLAG-IDA venetoclax[1]	67%	3%
GO[2]	30%	8%
Venetoclax + HMA/LDAC[3]	33%	n.d.

1 DiNardo et al. J Clin Oncol. 2021;39:2768-2778

2 Sievers et al. J Clin Oncol. 2001;19:3244-54