

E' indicata una terapia di mantenimento nel post-trapianto?

Le ragioni del NO

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CONVEGNO EDUCAZIONALE GITMO

HOT QUESTIONS IN TRASPLANTATION AND CELLULAR THERAPIES

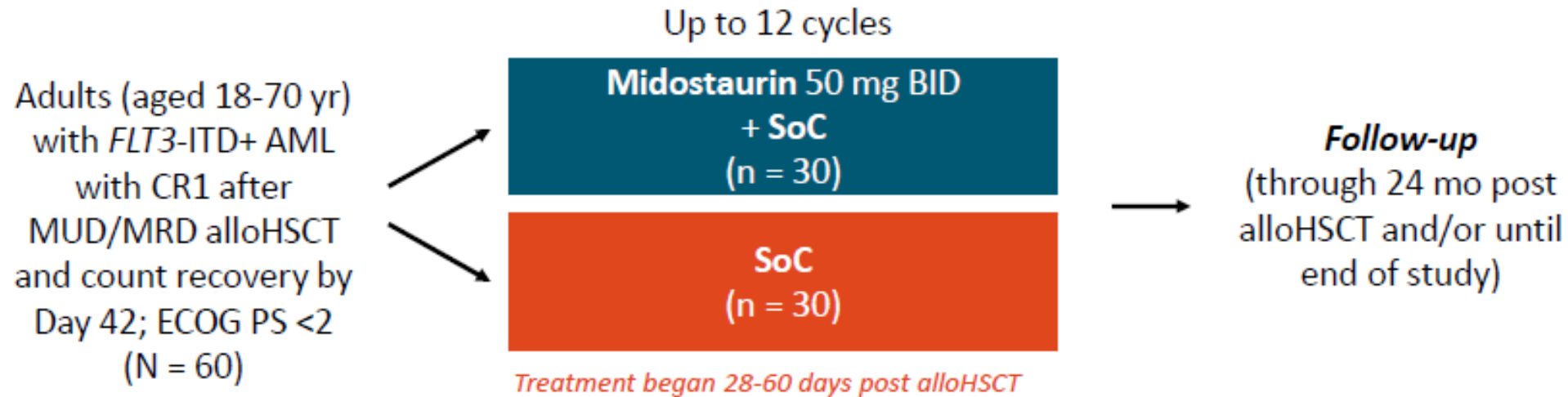
Udine

13-14 novembre 2023

Aula Polifunzionale - Ospedale di Udine

RADIUS: Midostaurin Maintenance After AlloHSCT in *FLT3*-ITD+ AML: Study Design

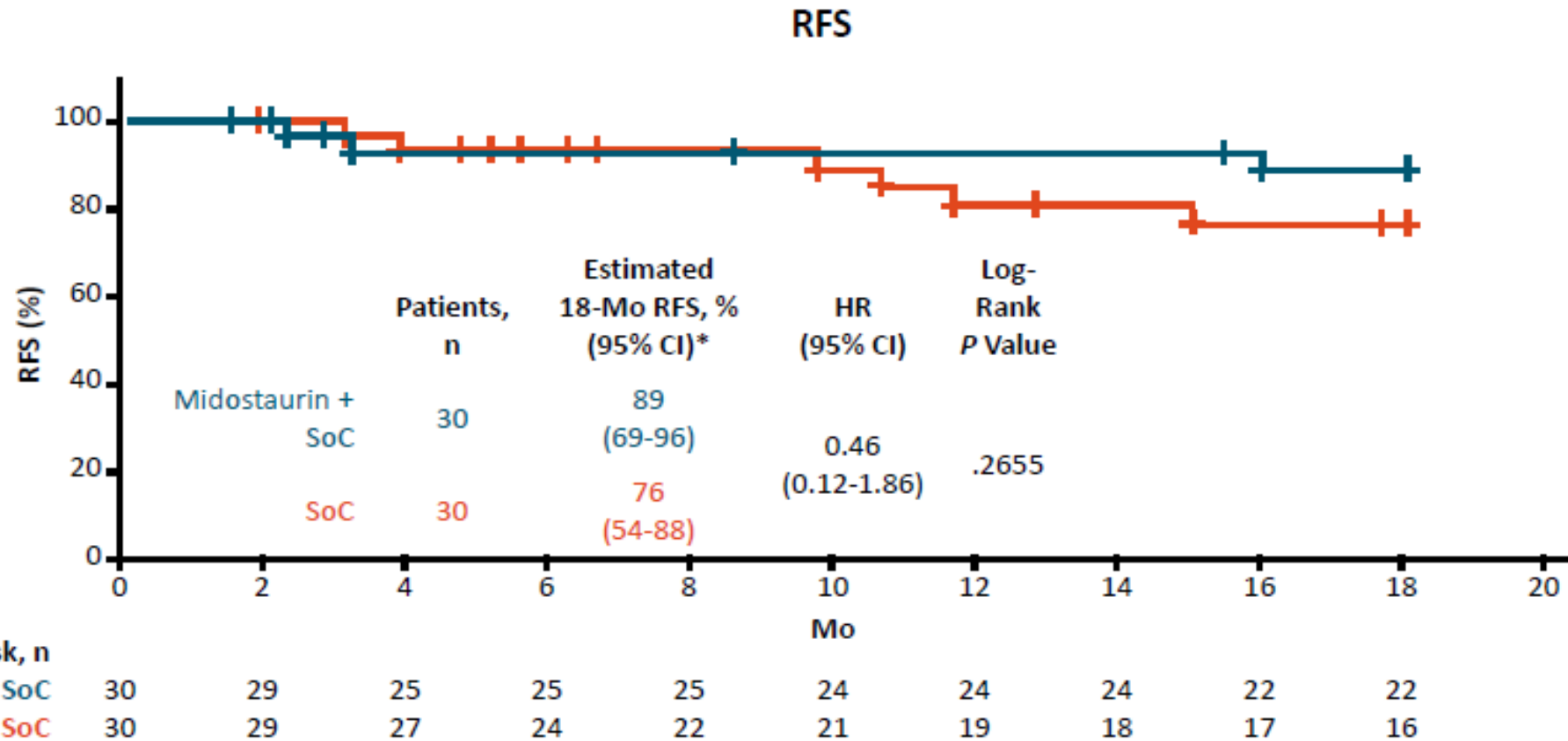
- Open-label, randomized phase II trial



- **Primary endpoint:** RFS (18 mo post alloHSCT)
- **Key secondary endpoints:** OS, RFS (24 mo post alloHSCT), safety

R. T. Maziarz et al. *BMT*, (2021) 56:1180–1189

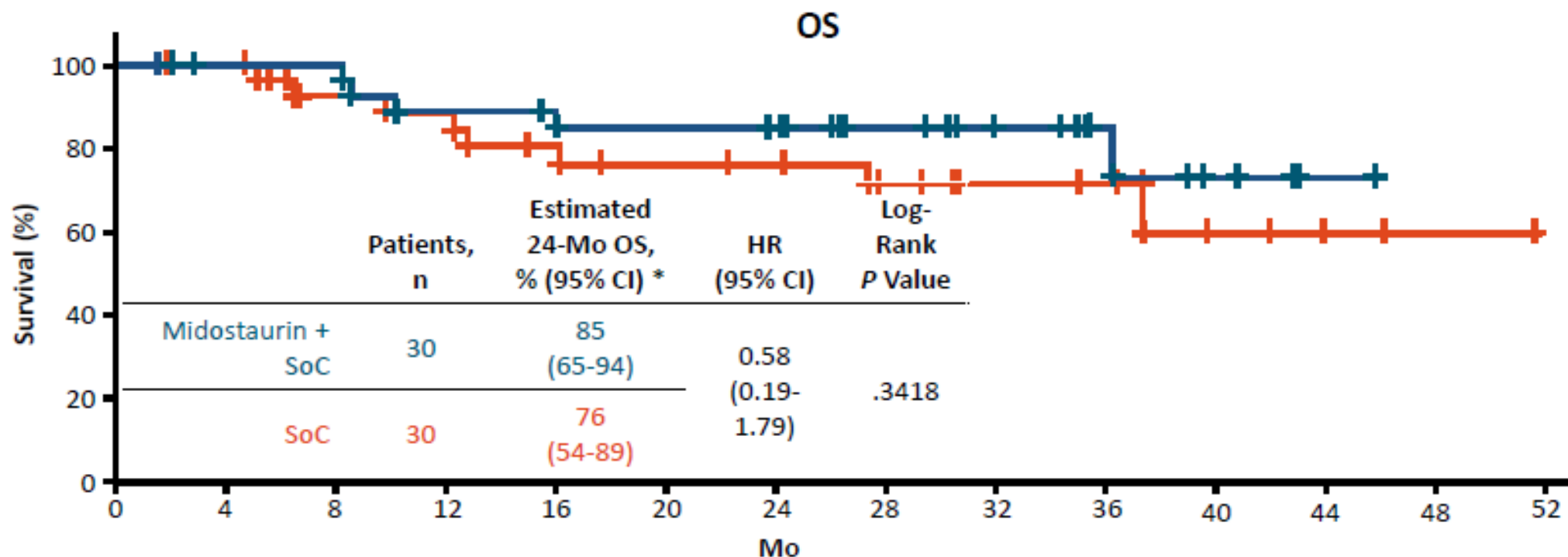
RADIUS: Relapse-Free Survival



*Median RFS was not reached.

R. T. Maziarz et al. *BMT*, (2021) 56:1180–1189

RADIUS: Overall Survival



Patients at Risk, n		Mo													
	yr.	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Midostaurin + SoC		30	27	27	24	22	22	21	15	11	7	4	1	0	
SoC		30	29	23	22	19	17	16	13	10	9	4	2	1	

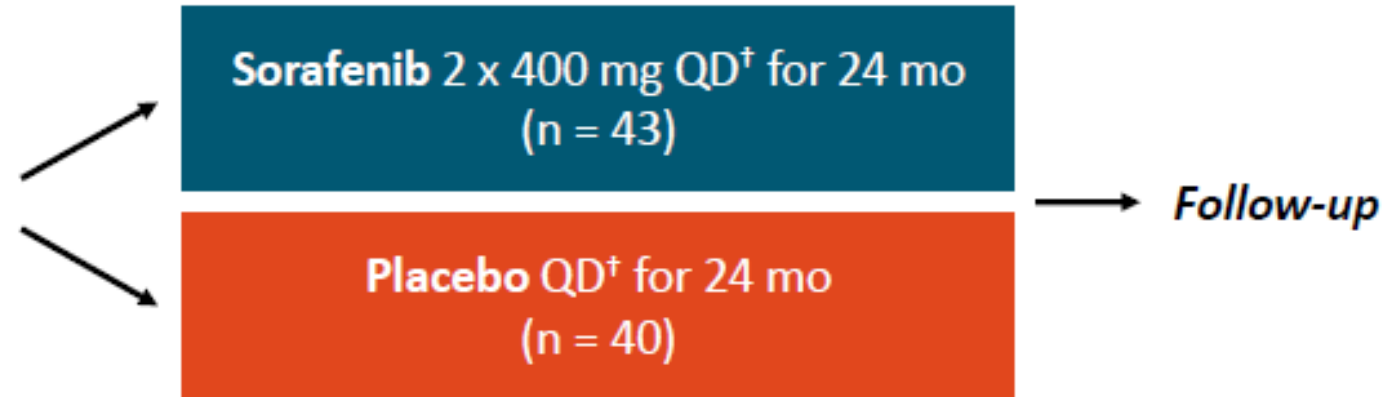
*Median OS was not reached.

R. T. Maziarz et al. *BMT*, (2021) 56:1180–1189

SORMAIN: Sorafenib Maintenance After AlloHSCT in *FLT3*-ITD AML: Study Design

- Primary analysis of international, randomized, double-blind phase II trial

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

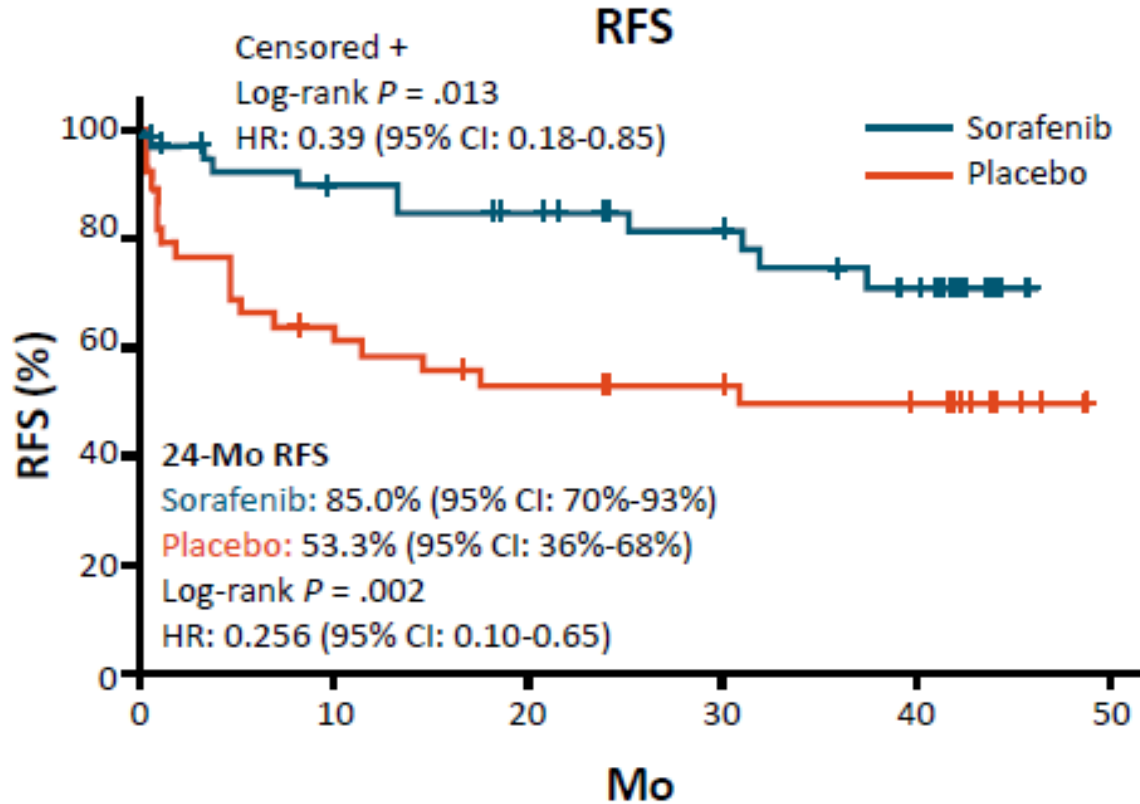


*Planned N = 184. Study ended early because of slow accrual. [†]Starting dose of 2 x 200 mg, increased every 14 days up to 2 x 400 mg as tolerated.

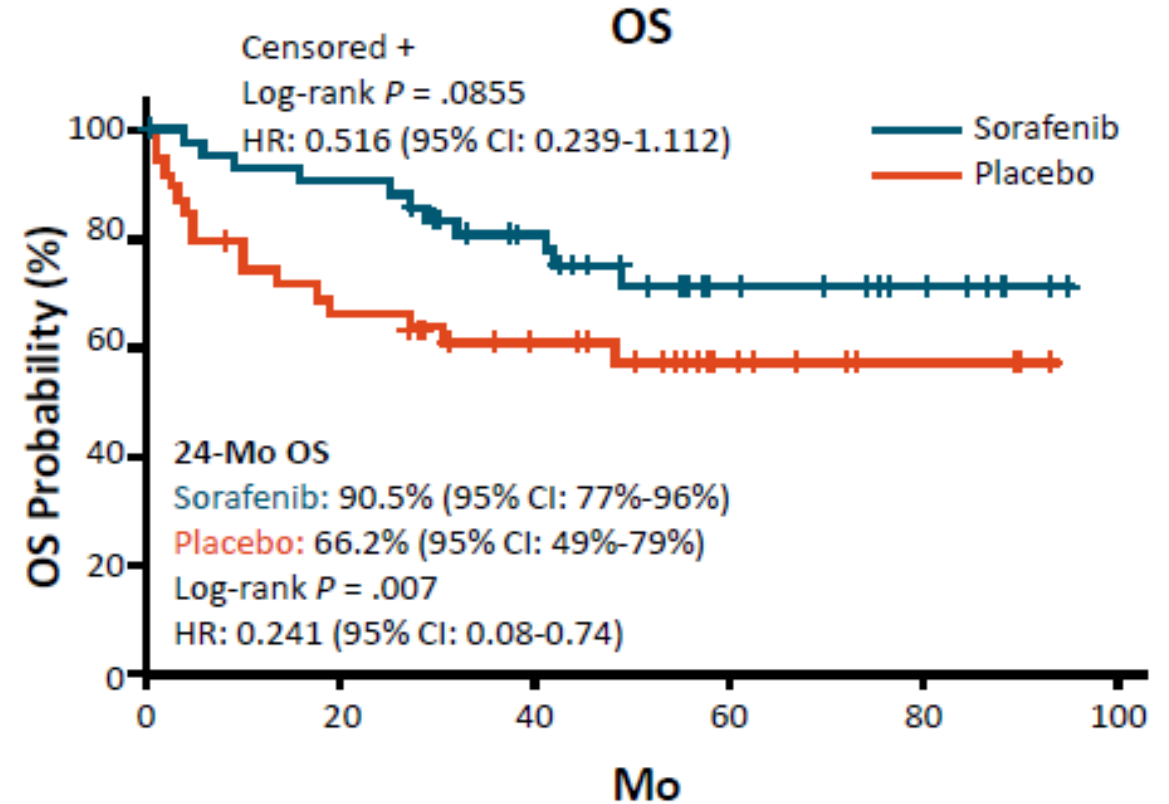
- Primary endpoint:** RFS rate, where RFS events were death from any cause or relapse of AML
- Secondary endpoints:** OS; RFS and OS in *NPM1*-mutated vs wild-type patients; RFS and OS by *FLT3*-ITD ratio; safety; biomarker analysis

Burchert et al, JCO 38:2993-3002, 2020

SORMAIN: Relapse-Free and Overall Survival



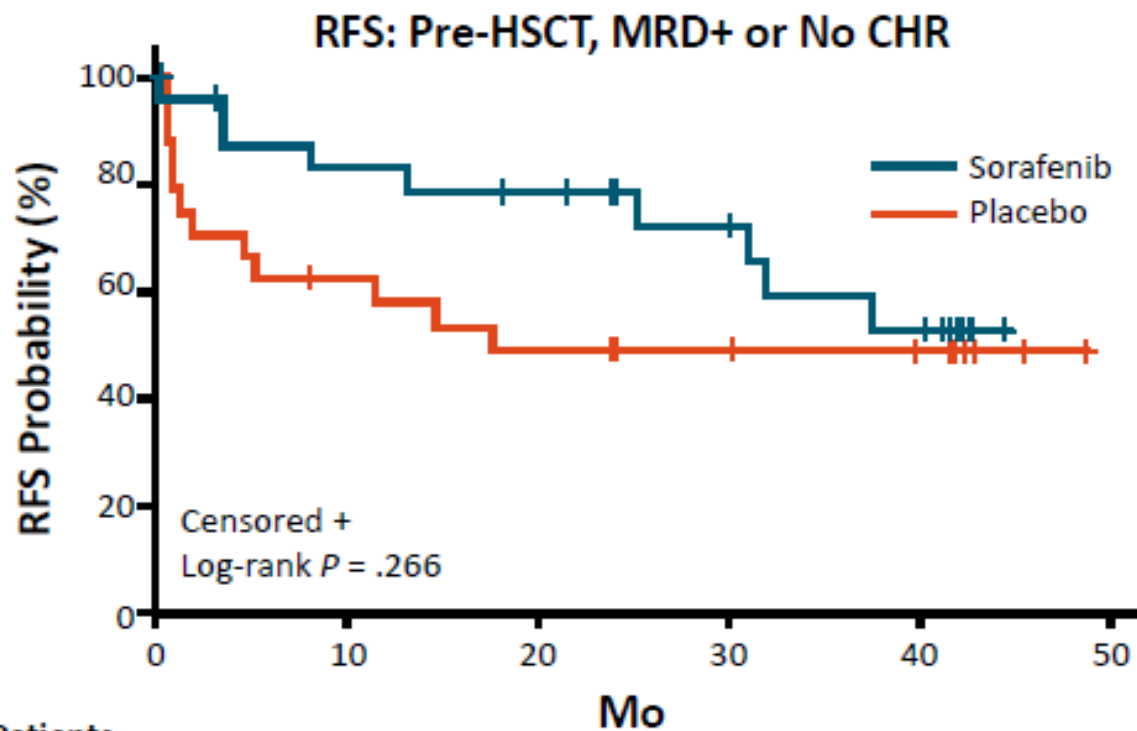
- Median f/u: 41.8 mo
- mRFS (sorafenib vs placebo): NR vs 30.9



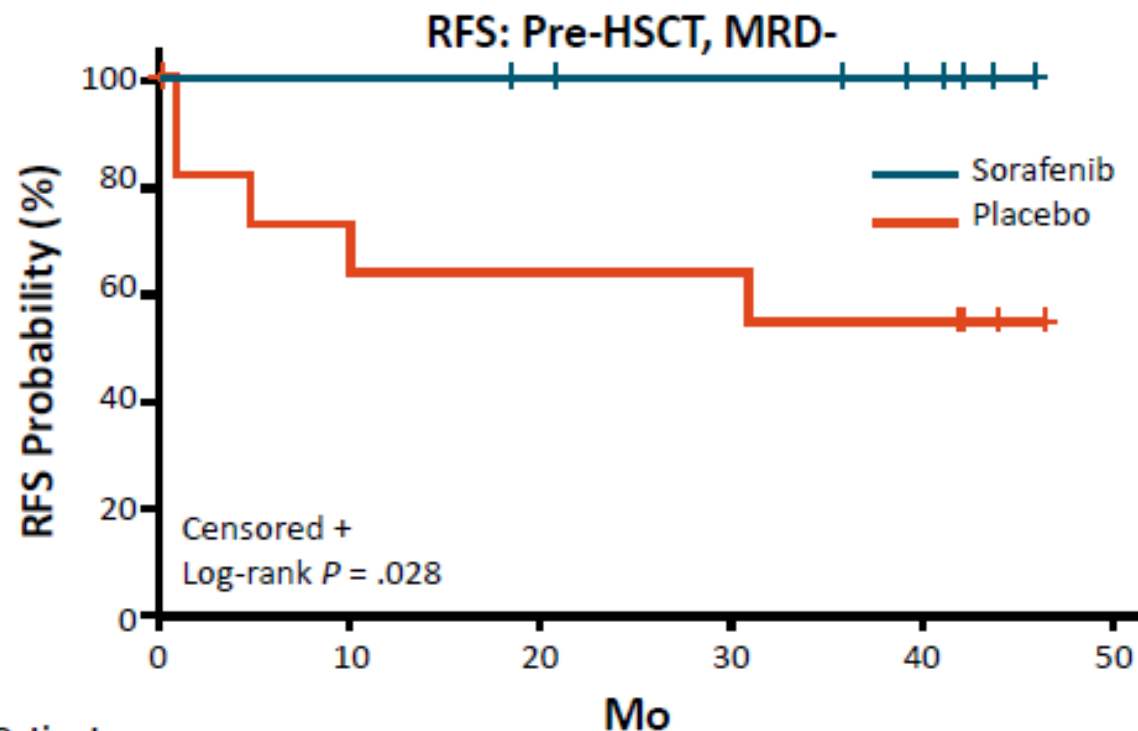
- Median f/u: 55.1 mo
- mOS NR in either treatment arm

Burchert et al, JCO 38:2993-3002, 2020

SORMAIN: RFS by Pretransplant MRD or Response



Patients at Risk, n		0	10	20	30	40	50
Placebo	24	14	11	9	7	0	0
Sorafenib	25	19	17	12	8	0	0

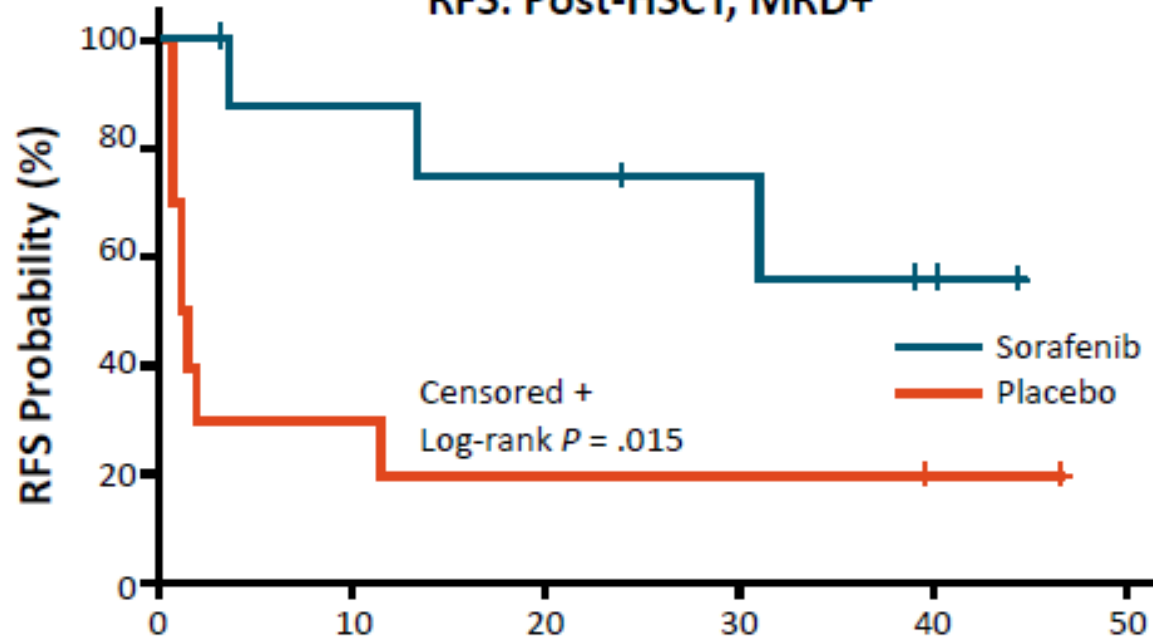


Patients at Risk, n		0	10	20	30	40	50
Placebo	12	8	7	7	6	0	0
Sorafenib	9	9	8	7	5	0	0

Burchert et al, JCO 38:2993-3002, 2020

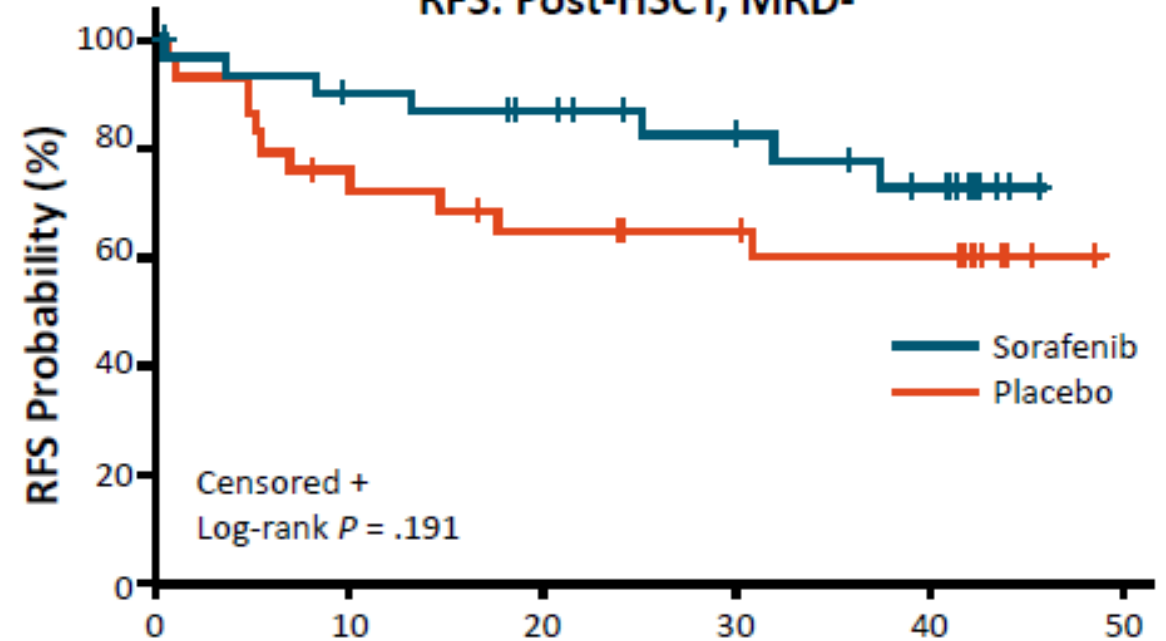
SORMAIN: RFS by Posttransplant MRD Status

RFS: Post-HSCT, MRD+



	0	10	20	30	40	50
Patients at Risk, n						
Placebo	10	3	2	2	1	0
Sorafenib	9	7	6	4	2	0

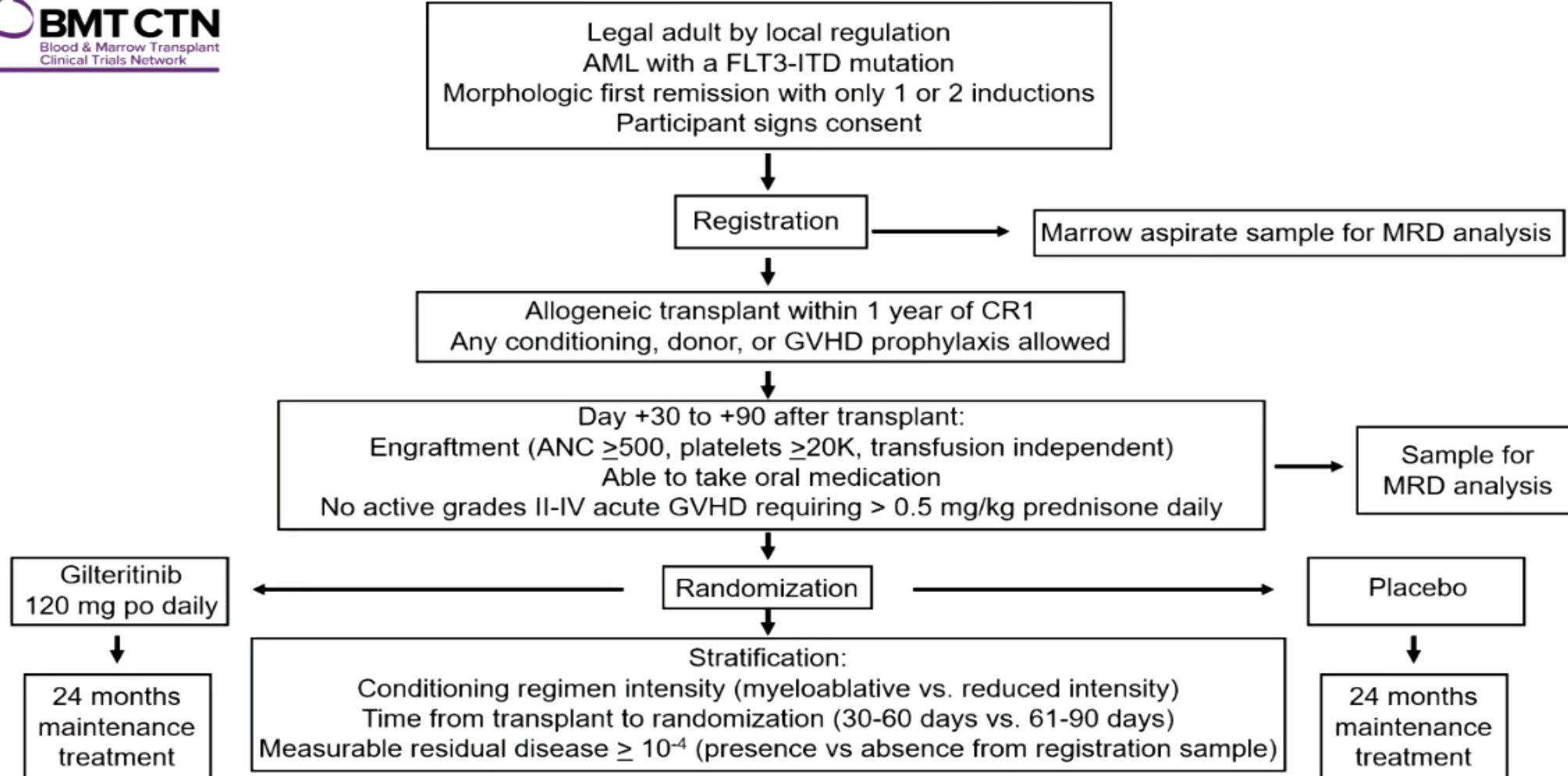
RFS: Post-HSCT, MRD-



	0	10	20	30	40	50
Patients at Risk, n						
Placebo	30	21	17	15	13	0
Sorafenib	31	26	23	19	14	0

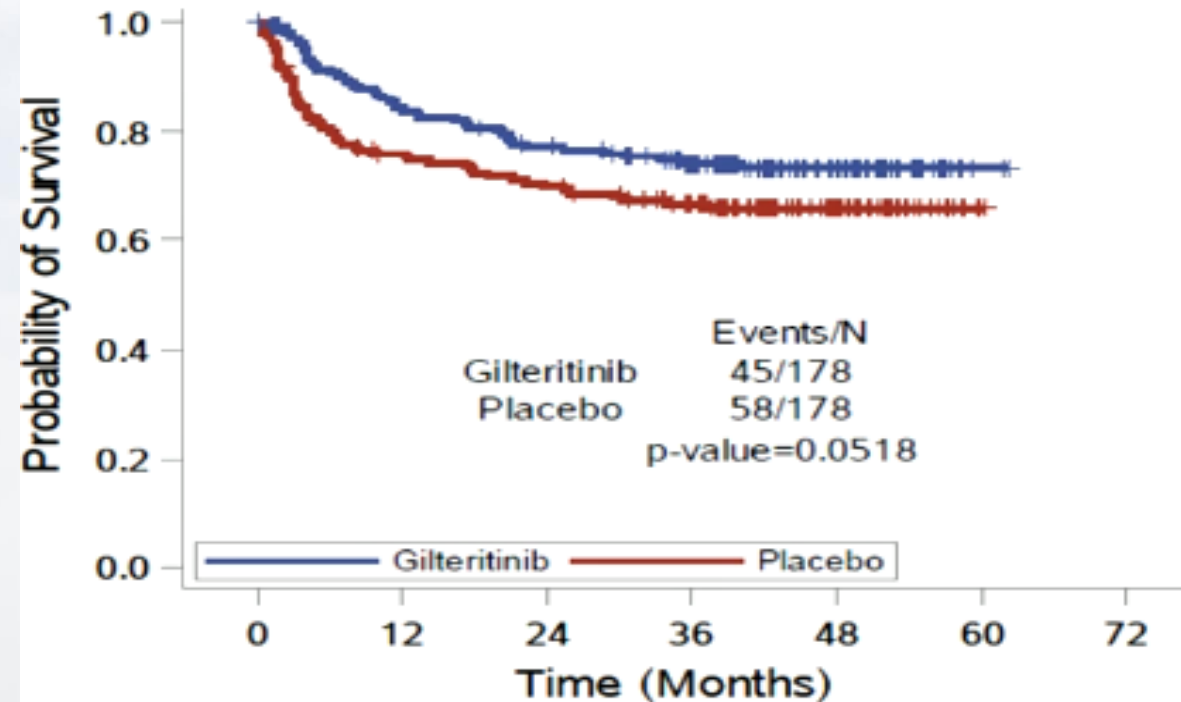
Burchert et al, JCO 38:2993-3002, 2020

BMT-CTN 1506 (MORPHO): Study Design

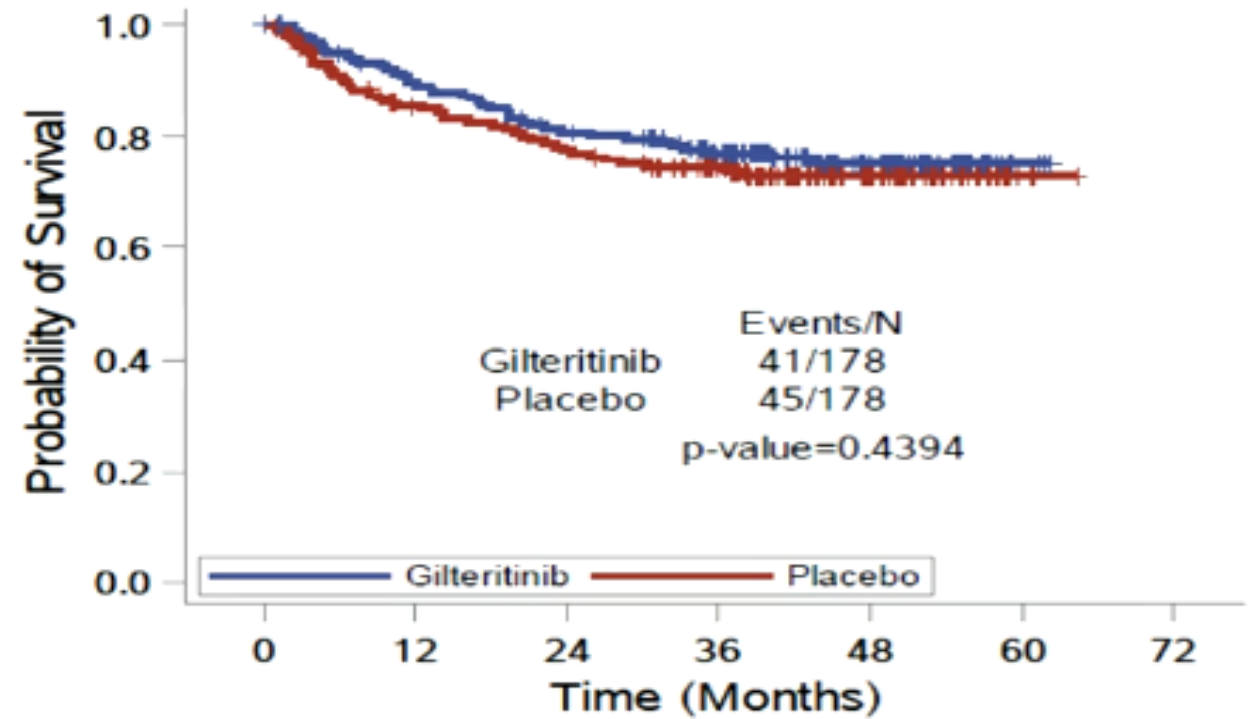


BMT-CTN 1506 (MORPHO): Efficacy Outcome

Primary objective:
Relapse-free survival
HR = 0.679 (0.459-1.005)
 $P = 0.0518$

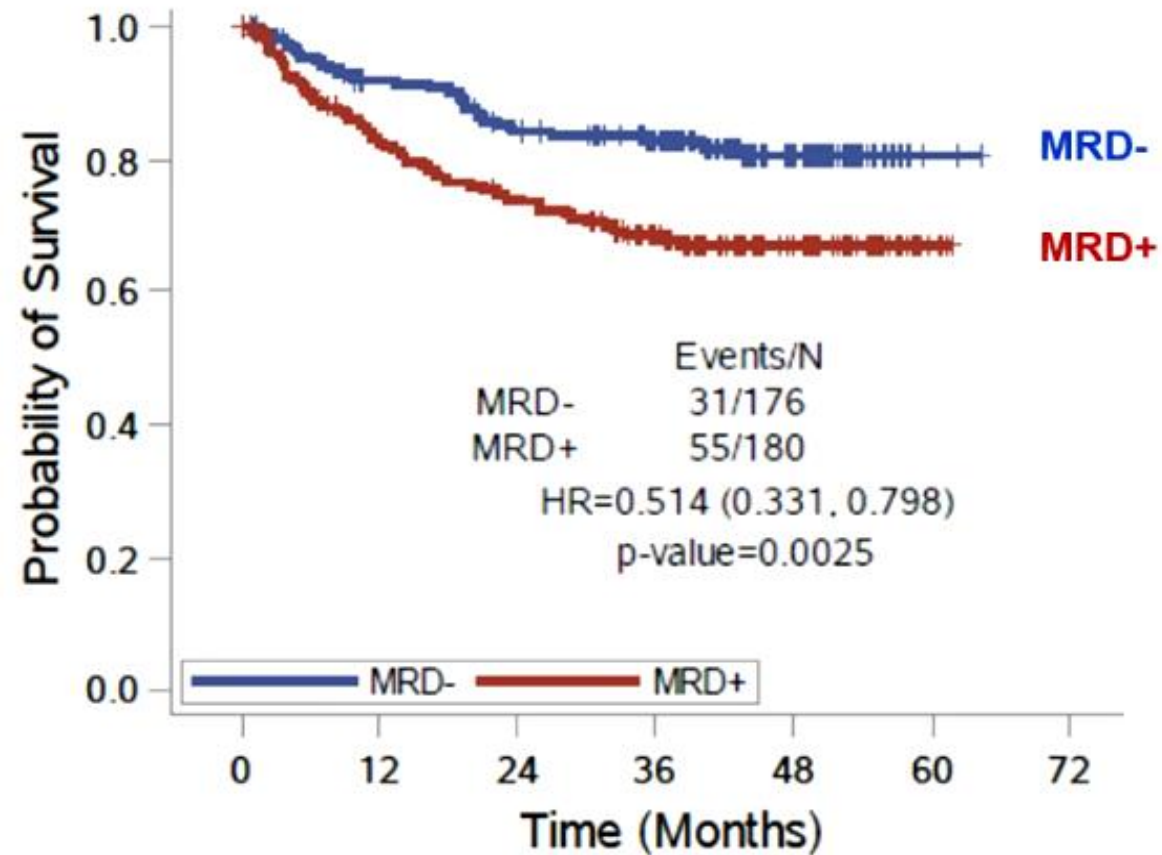


Key secondary objective:
Overall survival
HR = 0.846 (0.554-1.293)
 $P = 0.4394$



Levis M. et al, EHA 2023 LB2711

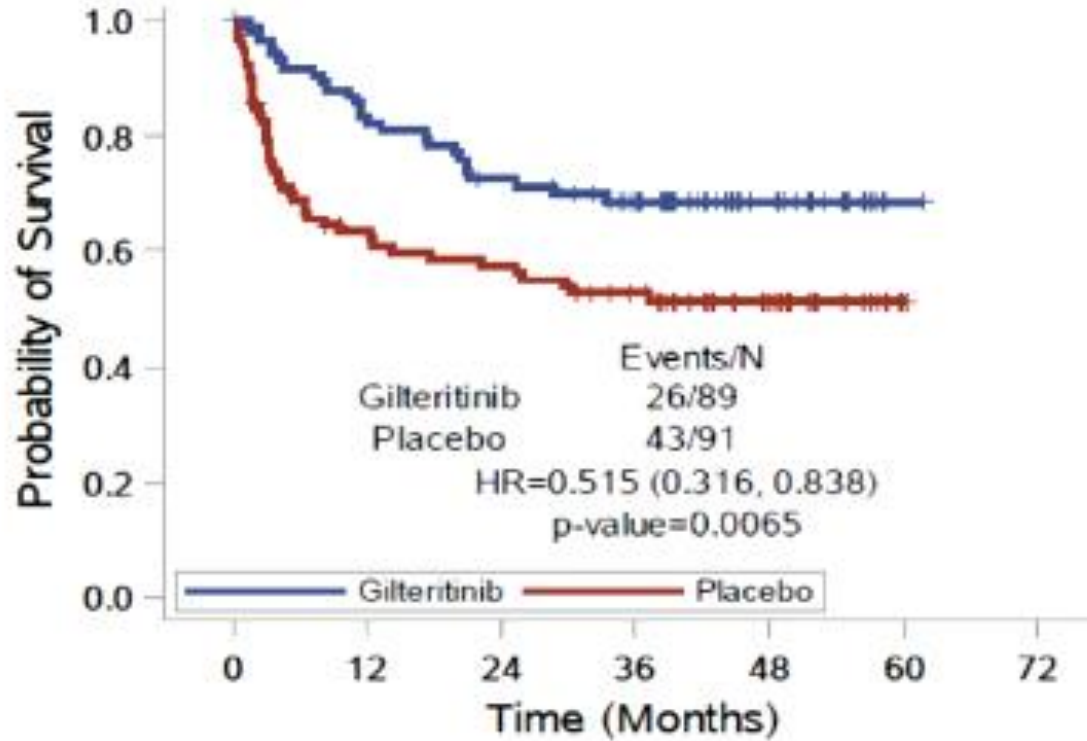
Effect of MRD6 on OS overall, irrespective of treatment arm MRD6 at registration (pre-HCT) or randomization (post-HCT)



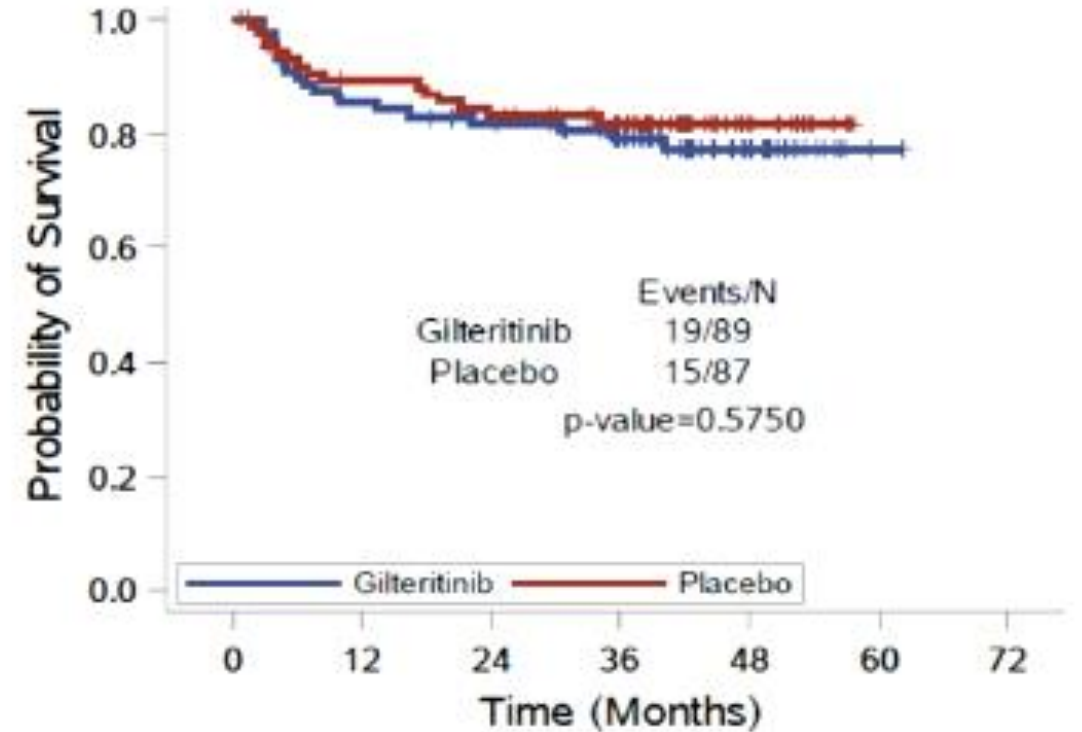
Levis M. et al, EHA 2023 LB2711

Effect of detectable MRD6 on RFS by study arm

RFS
MRD+



RFS
MRD-

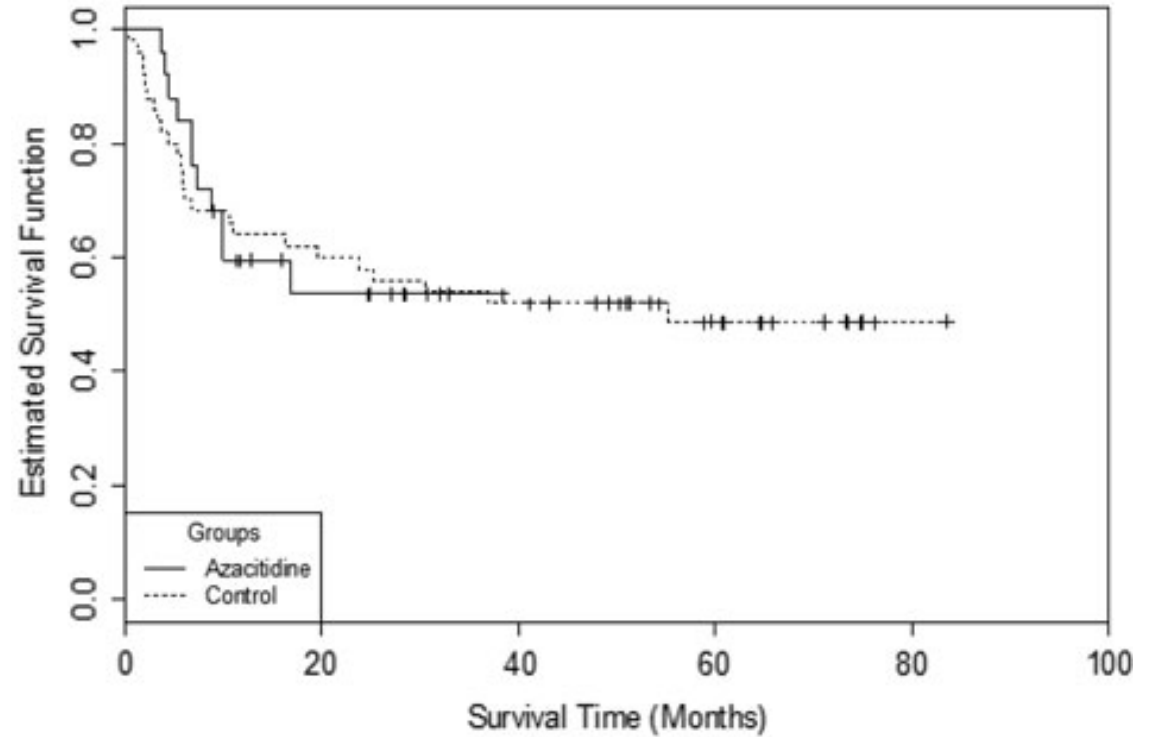
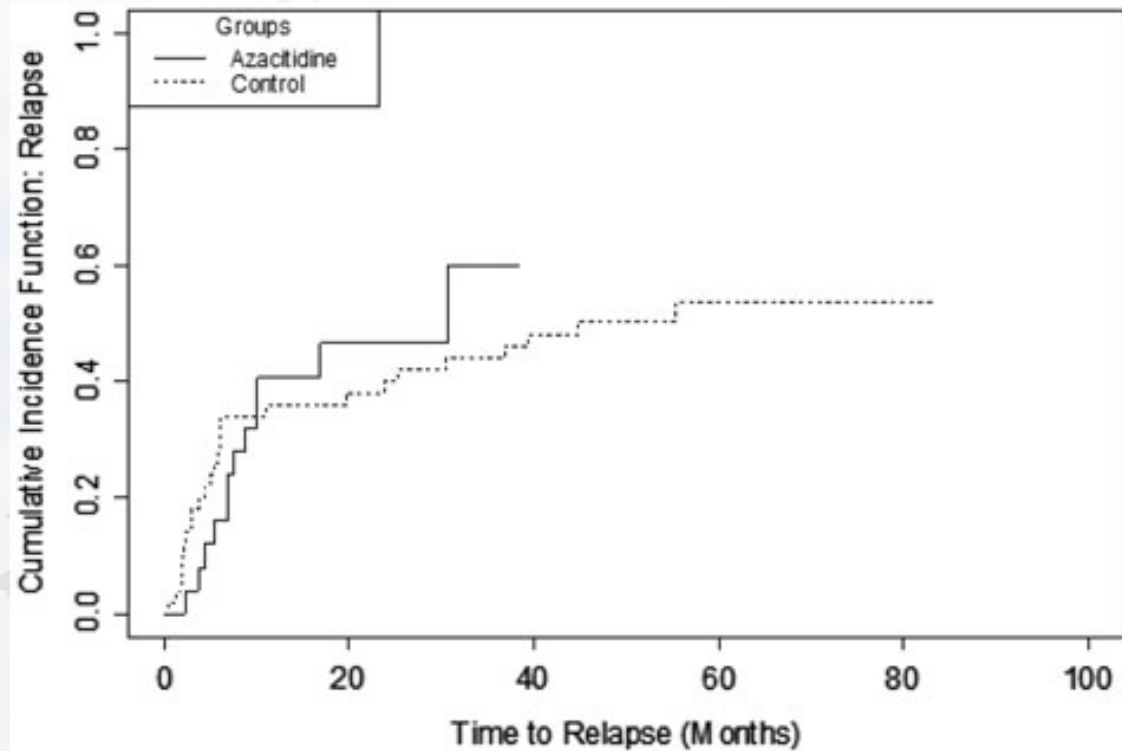


Levis M. et al, EHA 2023 LB2711

Select Ongoing Trials in Posttransplant Maintenance

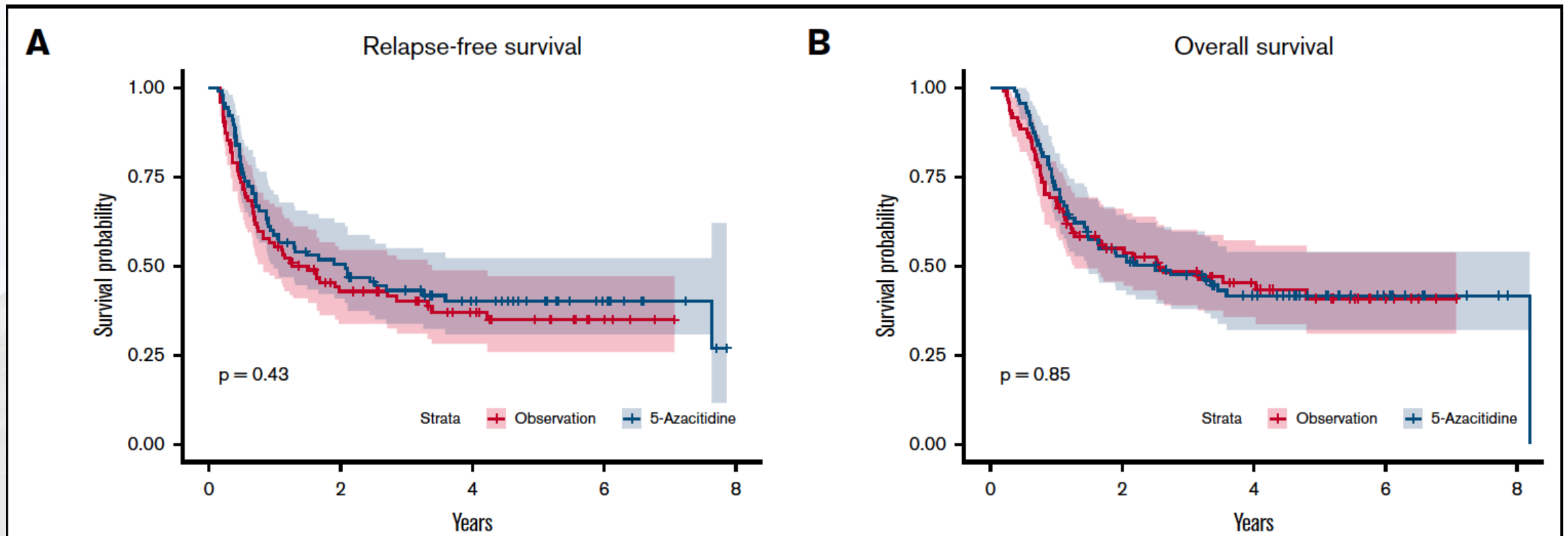
Trial	Phase	N	Agents	Patient Population	Primary Endpoint(s)	Status
FLT3 Inhibitors						
MORPHO NCT02997202	III	356	Gilteritinib vs placebo	FLT3-ITD+ AML (CR1)	RFS	Active, not recruiting
NCT02400255	II	48	Crenolanib	FLT3-ITD+ or FLT3-D835+ AML	PFS	Unknown
IDH Inhibitors						
NCT03515512	I	23	Enasidenib	IDH2-mutated AML or MDS	MTD, DLT	Active, not recruiting
NCT03564821	I	18	Ivosidenib	IDH1-mutated AML or MDS	MTD	Active, not recruiting
HMA s						
AMADEUS NCT04173533	III	324	Oral azacitidine vs placebo	AML (CR1 or CR2), secondary AML or advanced or high-risk MDS (IPSS-R ≥ 3.5)	RFS	Recruiting
VIALE-T NCT04161885	III	424	Venetoclax + azacitidine + BSC vs BSC	AML (<5% BM blast after alloSCT)	DLT, RFS	Recruiting
NCT01995578	II	32	Low dose azacitidine	De novo MDS, AML, secondary MDS/AML	Relapse rate	Active, not recruiting
NCT04128501	II	125	Azacitidine + venetoclax	AML, T-cell leukemia, and mixed phenotype acute leukemia	RFS	Recruiting

AZA Maintenance after HSCT



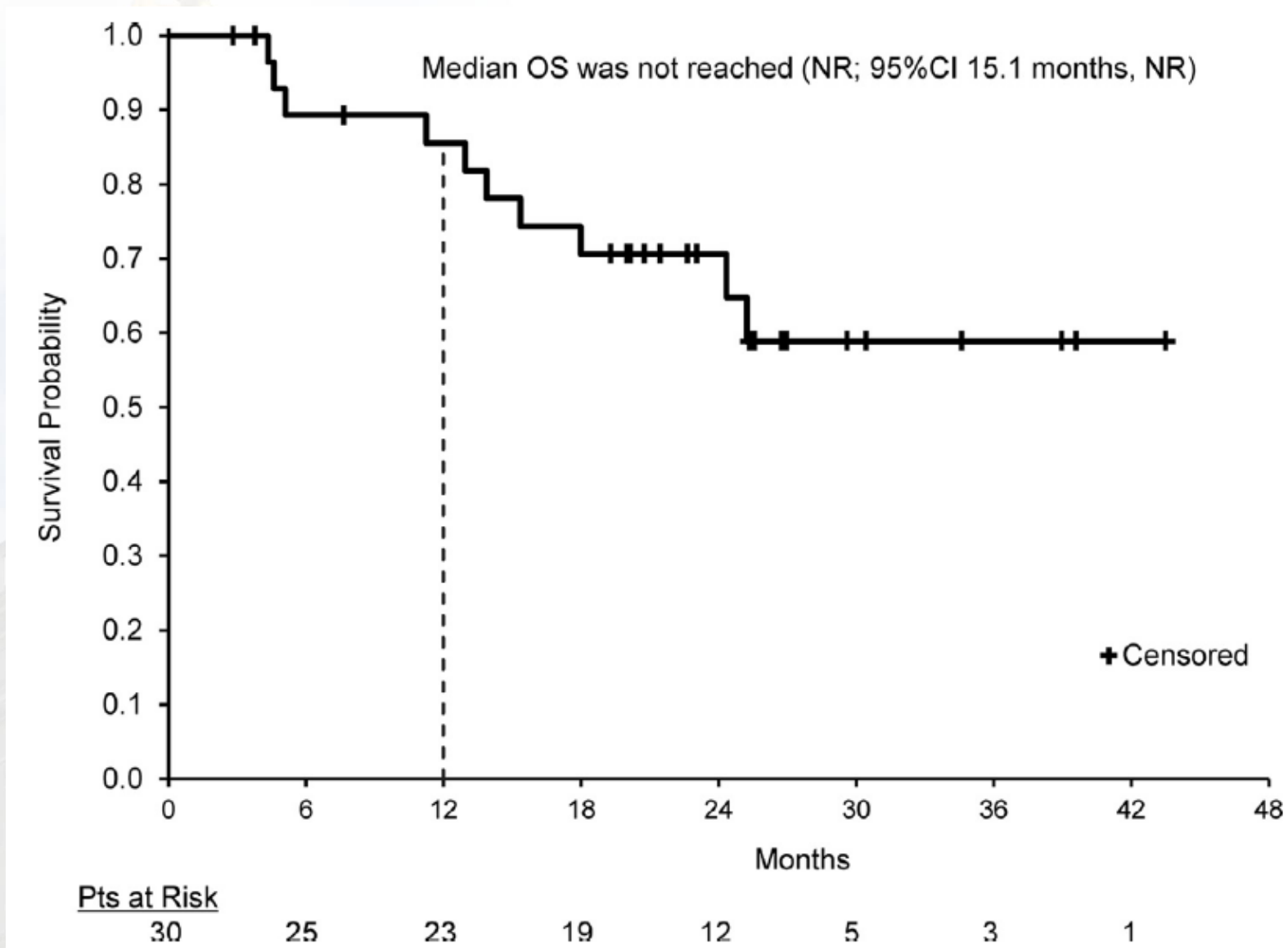
Maples KT et al; *Leuk & Lymphoma*, 2018

AZA Maintenance after HSCT



Oran et al; Blood Advances, 2020

CC-486 Maintenance after HSCT

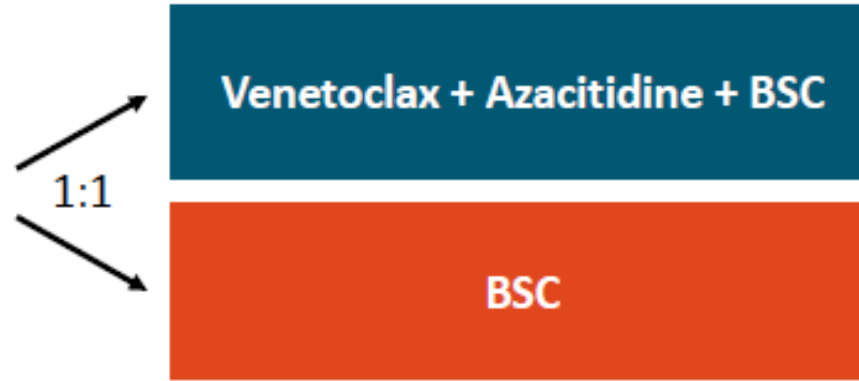


Biol Blood Marrow Transplant 24(2018)2017-2024

VIALE-T: Venetoclax Plus Azacitidine After AlloSCT

- Randomized, open-label phase III trial

Patients with AML (≥ 12 yr of age) who plan or have received an alloSCT within the past 45 days* (N = 400)



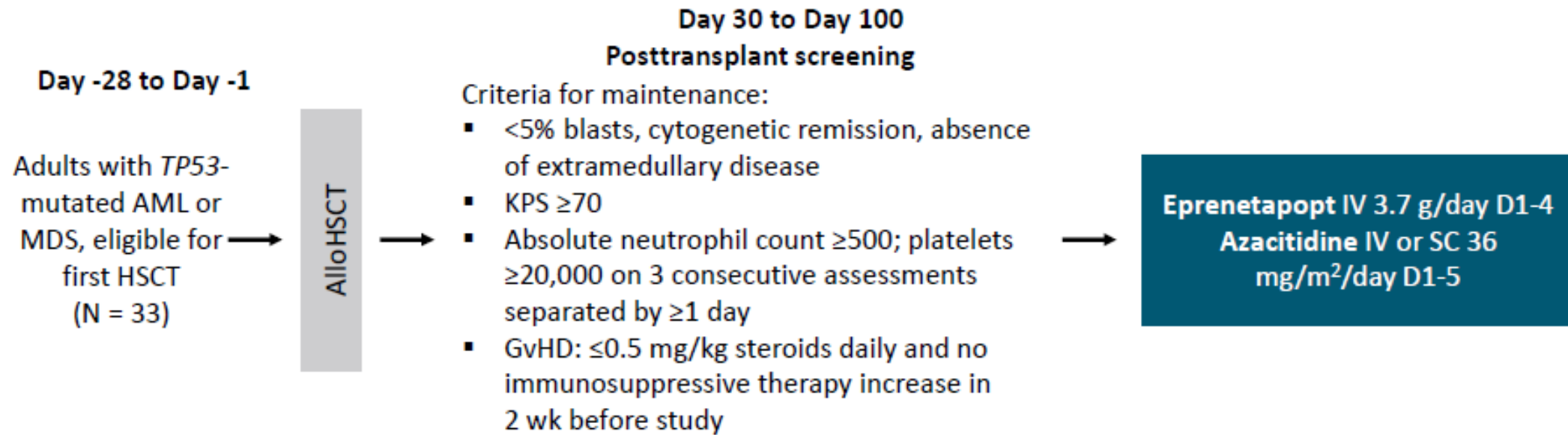
*BM blasts $< 10\%$ prior to transplant conditioning and $< 5\%$ BM blasts post transplant; ANC $\geq 1000 \mu\text{L}$ and platelet count $\geq 50,000$

- **Primary endpoint:** RFS, DLT
- **Key secondary endpoints:** OS, GRFS, GvHD rate, MRD response rate

Craddock. EHA 2022. Abstr P561. NCT04161885.

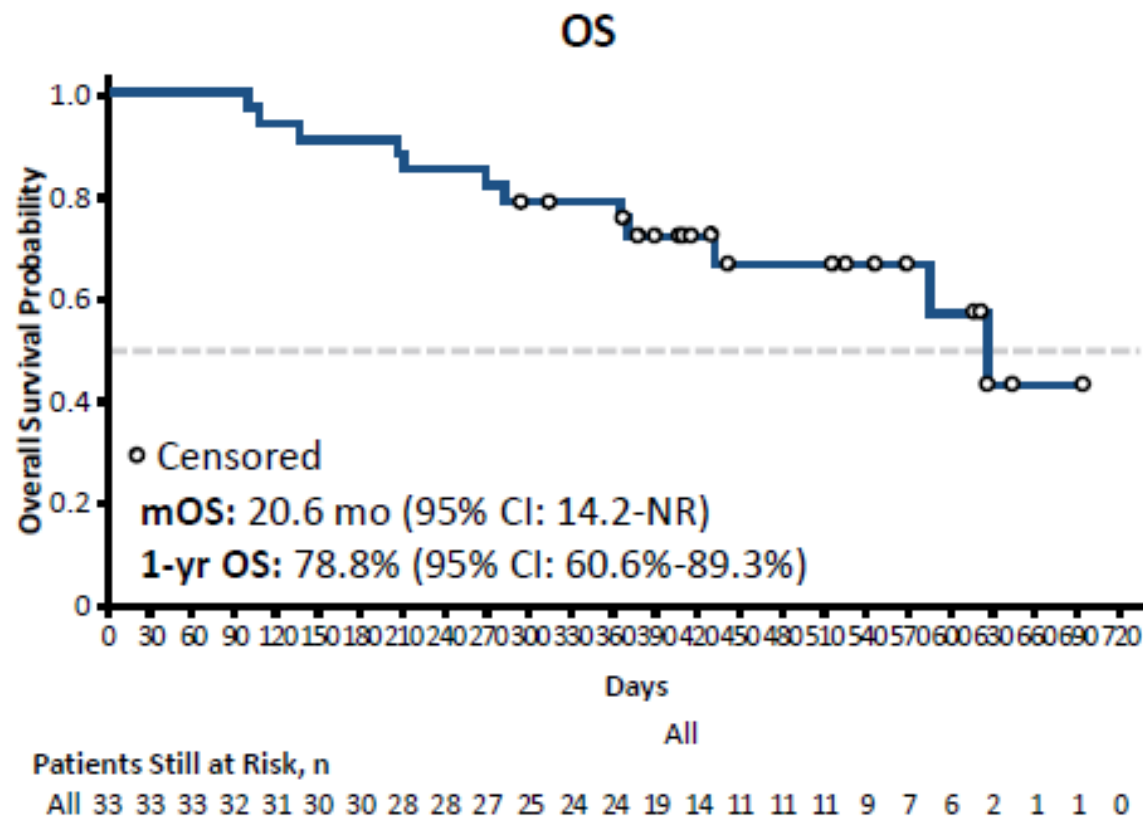
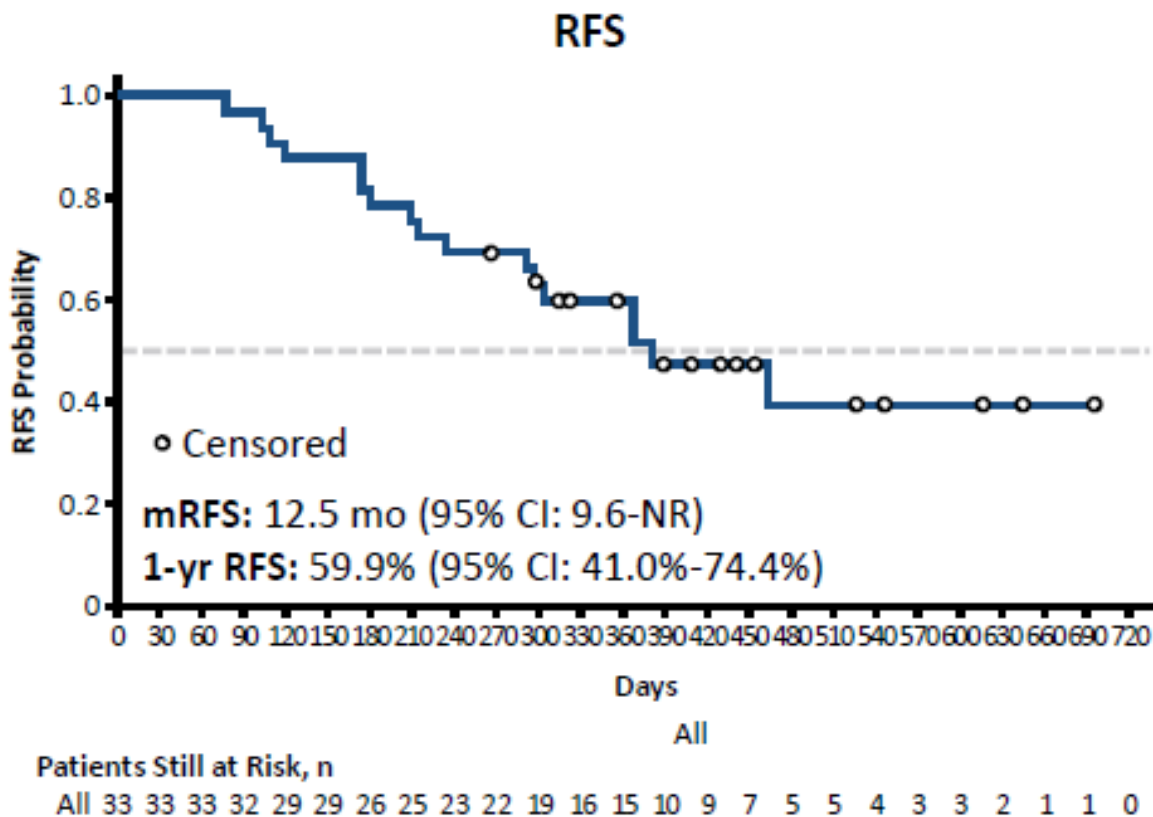
TP53 Stabilizer Eprenetapopt (APR-246) + Azacitidine Maintenance After AlloHSCT in TP53-Mutated AML

- Open-label phase II trial



- Primary endpoints: RFS, safety

Eprenetapopt (APR-246) + Azacitidine Maintenance After AlloHSCT in *TP53*-Mutated AML: Survival



Mishra. JCO. 2022;40:3985

Maintenance therapy vs observation

- Controversial data supporting post-HSCT FLT3 inhibition
 - ✓ Choice of the inhibitor
 - ✓ Role of MRD
- Length of maintenance
- QoL
- Safety
- Further studies needed to generate more robust data