Therapeutische Implikationen von MRD vor und nach allogener SZT

Basel, 13.10.2024

Friedrich Stölzel
Sektion für Stammzelltransplantation und zelluläre Immuntherapie
Universitätsklinikum Schleswig-Holstein
Kiel

Offenlegung Interessenskonflikte

JAHRESTAGUNG 2024 BASEL 11.–14. Oktober

1. Anstellungsverhältnis oder Führungsposition
Universitätsklinikum Schleswig-Holstein Kiel

2. Beratungs- bzw. Gutachtertätigkeit

Astellas, medac, Servier

3. Besitz von Geschäftsanteilen, Aktien oder Fonds

4. Patent, Urheberrecht, Verkaufslizenz

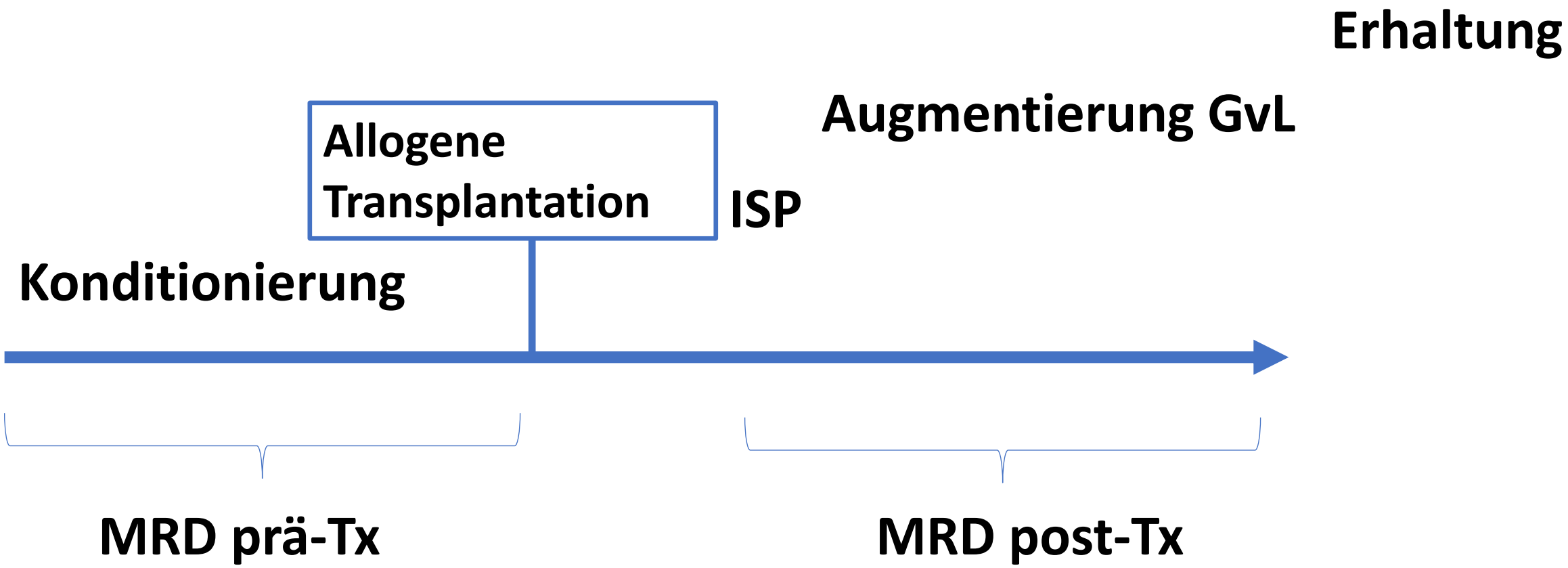
5. Honorare
Medac, Jazz

6. Finanzierung wissenschaftlicher Untersuchungen
Servier, medac

7. Andere finanzielle Beziehungen
Servier, Johnson & Johnson

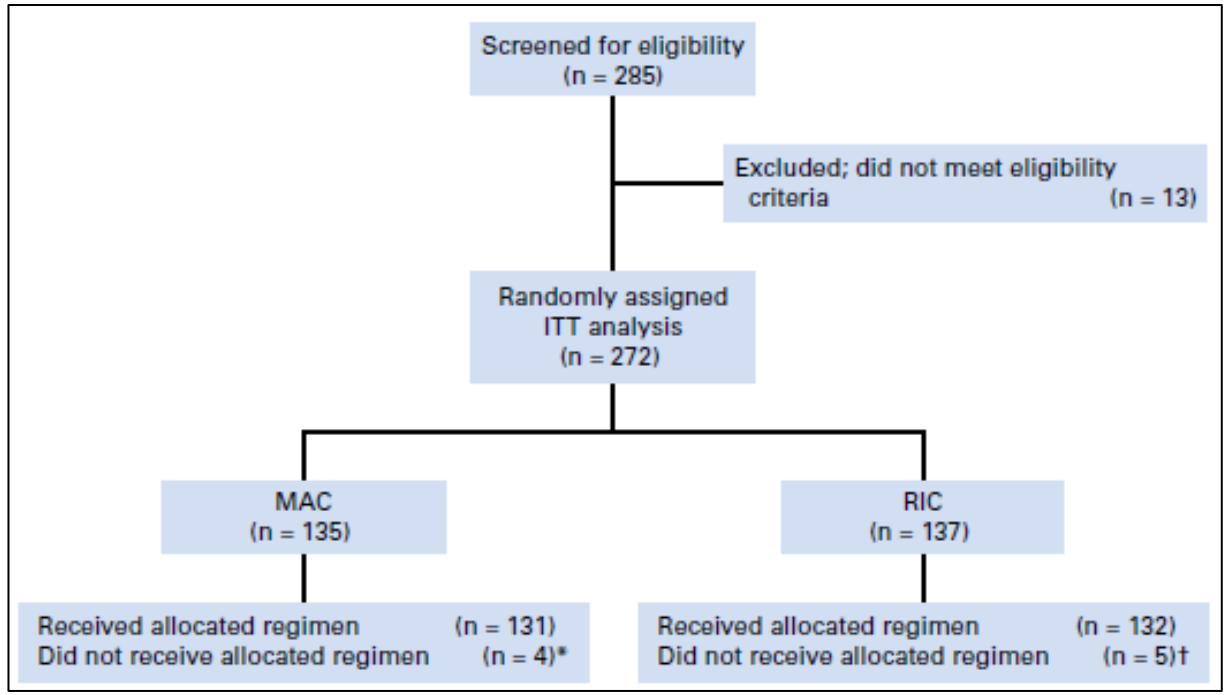
8. Immaterielle Interessenkonflikte

Agenda


Erhaltung
Augmentierung GvL
Allogene
Transplantation
ISP
Konditionierung
MRD prä-Tx
MRD post-Tx

Konditionierungsintensität

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

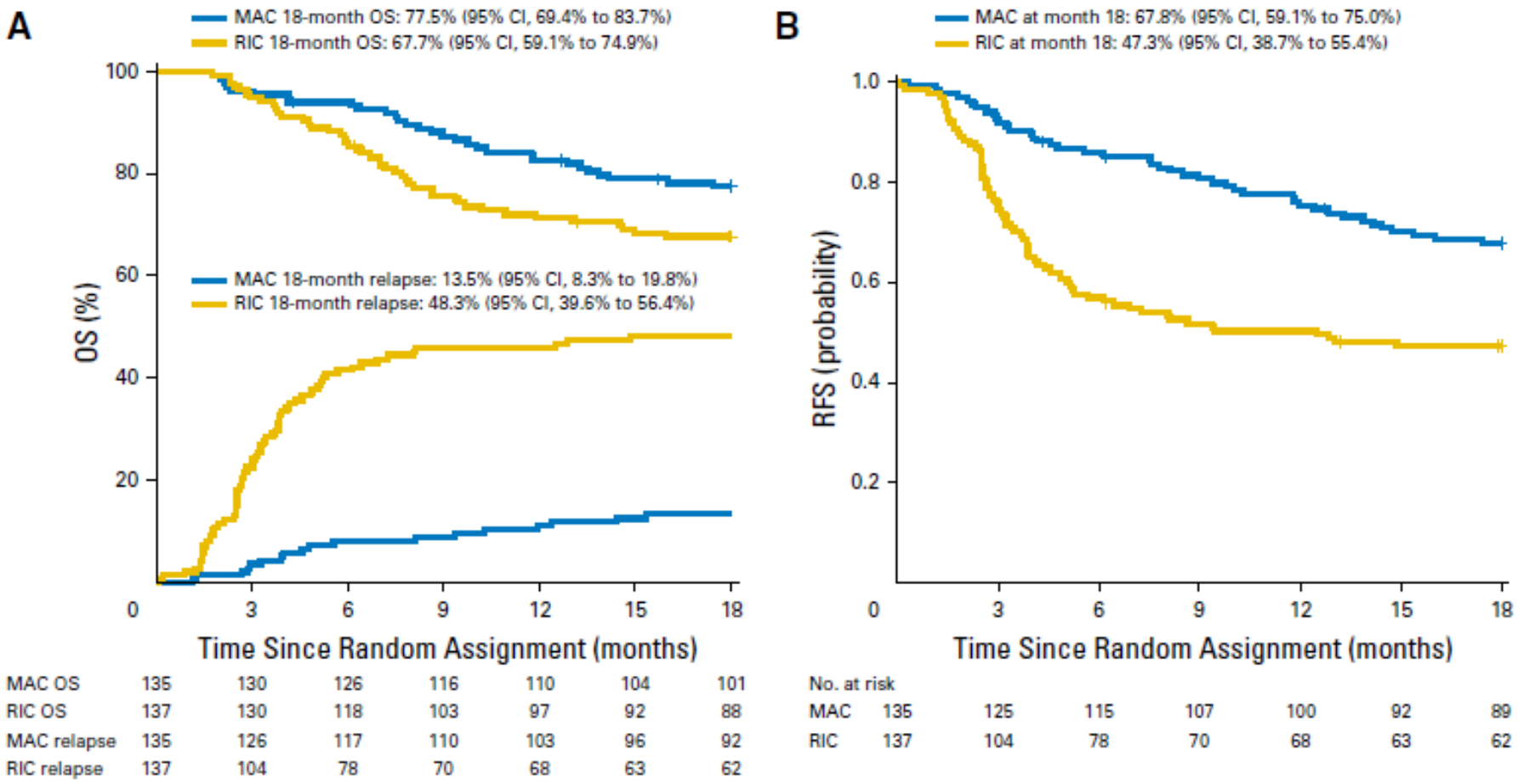


Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes

Bart L. Scott, Marcelo C. Pasquini, Brent R. Logan, Juan Wu, Steven M. Devine, David L. Porter, Richard T. Maziarz, Erica D. Warlick, Hugo F. Fernandez, Edwin P. Alyea, Mehdi Hamadani, Asad Bashey, Sergio Giralt, Nancy L. Geller, Eric Leifer, Jennifer Le-Rademacher, Adam M. Mendizabal, Mary M. Horowitz, H. Joachim Deeg, and Mitchell E. Horwitz

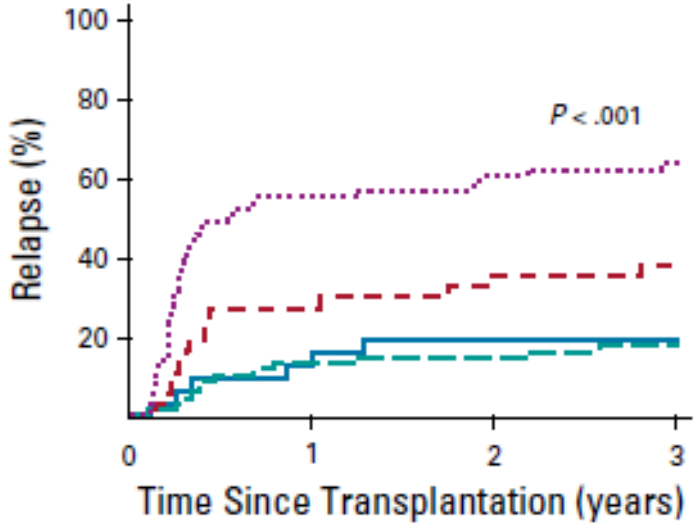
Scott et al., JCO, 2017

Konditionierungsintensität

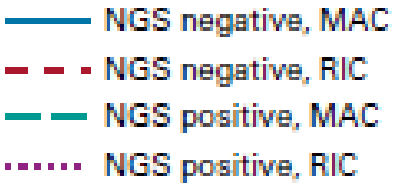


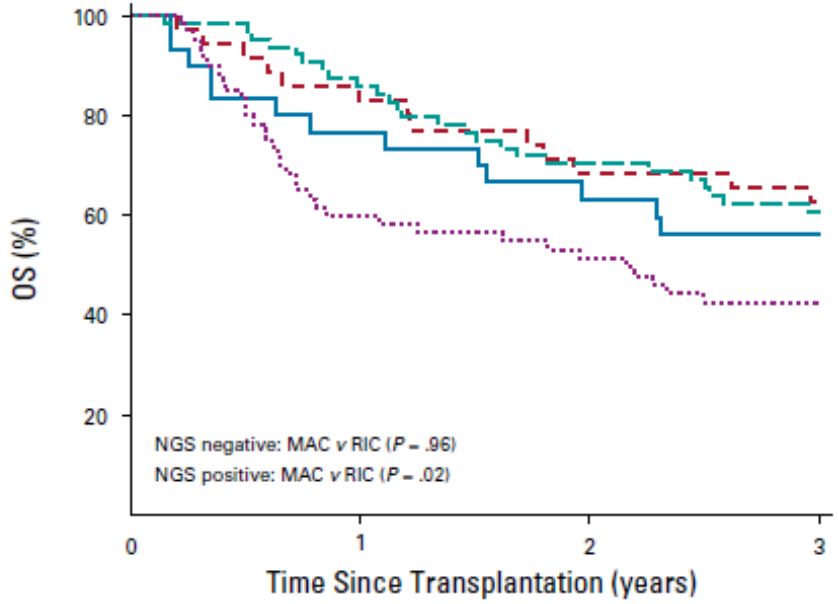
Scott et al., JCO, 2017

Konditionierungsintensität – nach MRD



No. at risk				
NGS negative				
MAC	30	21	16	15
RIC	35	24	20	18
NGS positive				
MAC	65	50	43	32
RIC	60	23	17	13





No. at risk				
NGS negative				
MAC	30	23	18	16
RIC	35	29	24	22
NGS positive				
MAC	65	55	45	35
RIC	60	36	29	24

Hourigan et al., JCO, 2020

Konditionierungsintensität – nach MRD

Relapse

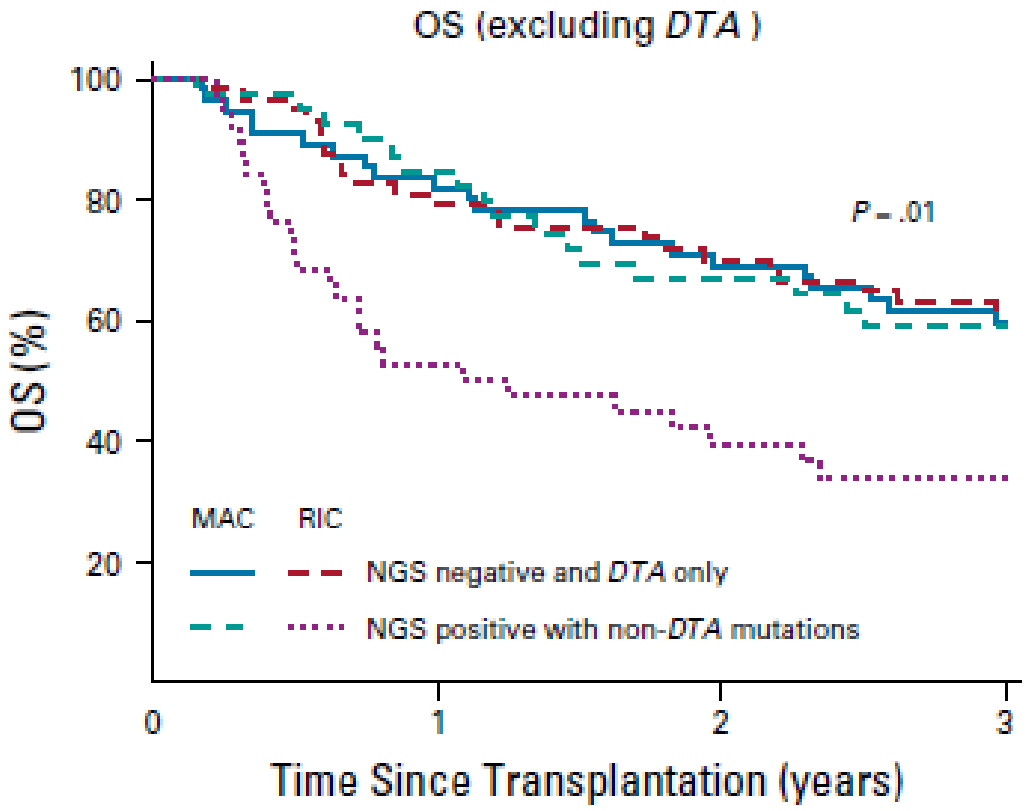
Model 2: interaction between NGS and intensity ($P = .024$)[a]					
NGS positive					
Conditioning	MAC	63	1.00	—	—
Conditioning	RIC	58	6.38	3.37 to 12.10	< .001
NGS negative					
Conditioning	MAC	30	1.00	—	—
Conditioning	RIC	34	1.78	0.72 to 4.38	.210

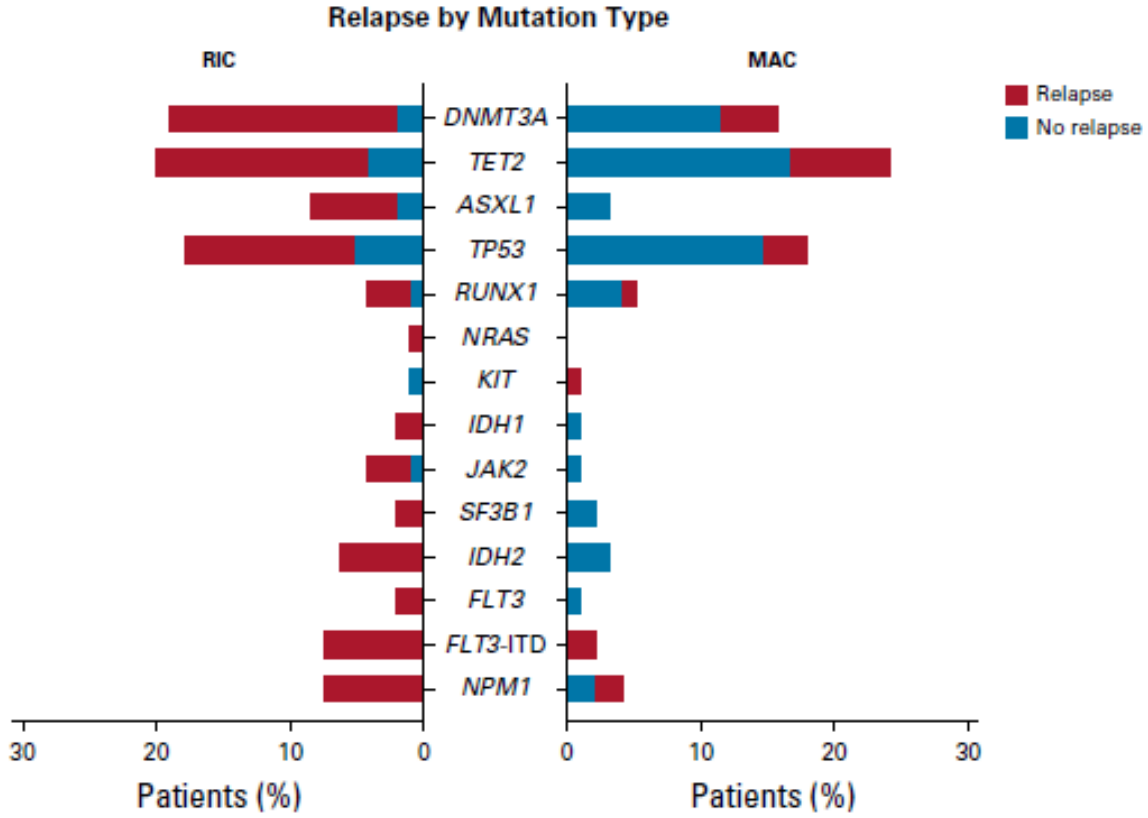
Overall Survival

Model 2: interaction between NGS and intensity ($P = .168$)[a]					
NGS positive					
Conditioning	MAC	63	1.00	—	—
Conditioning	RIC	58	1.97	1.17 to 3.30	.010
NGS negative					
Conditioning	MAC	30	1.00	—	—
Conditioning	RIC	34	1.05	0.50 to 2.18	.905

Hourigan et al., JCO, 2020

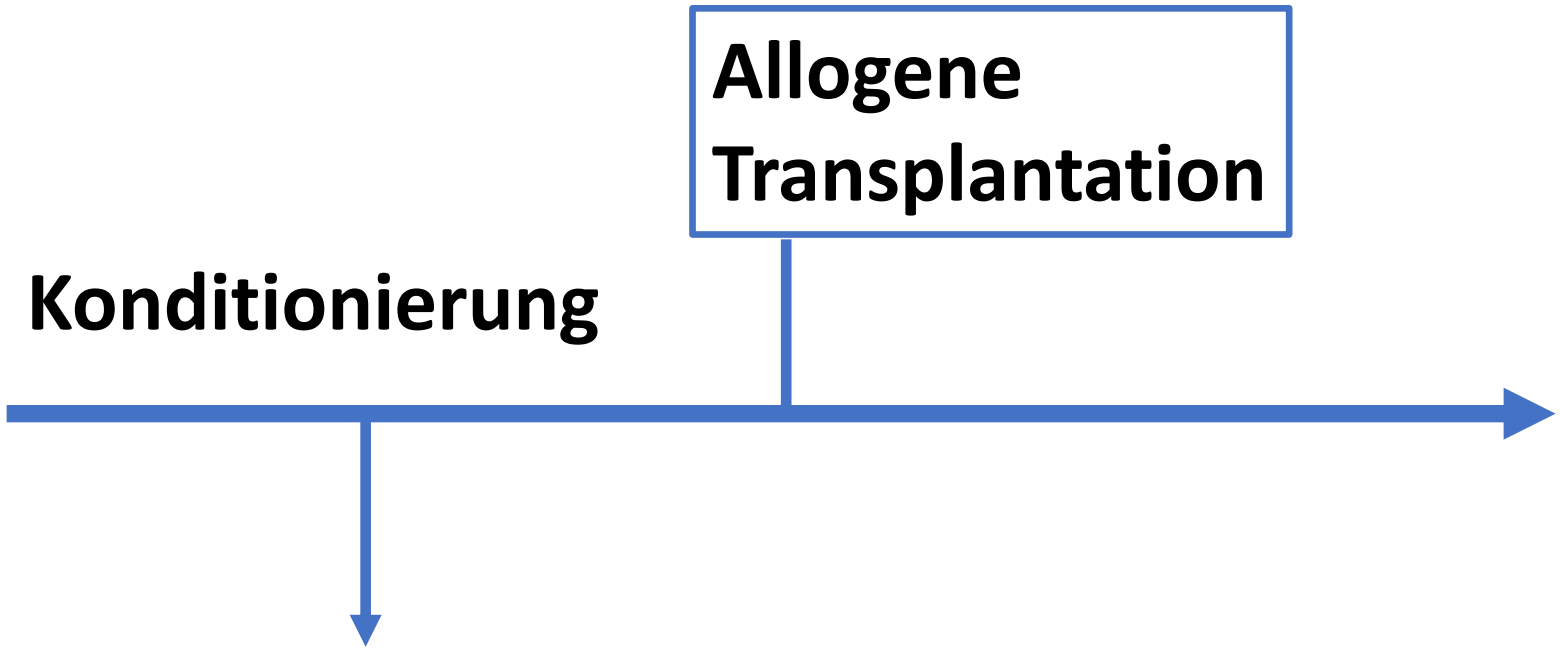
Konditionierungsintensität – nach MRD





Hourigan et al., JCO, 2020

Agenda


Allogene
Transplantation
Konditionierung
MRD prä-Tx: nur MAC vs. RIC ?

Konditionierungsintensität – nach MRD

JAMA Oncology | Brief Report

Measurable Residual *FLT3* Internal Tandem Duplication Before Allogeneic Transplant for Acute Myeloid Leukemia

Laura W. Dillon, PhD; Gege Gui, ScM; Niveditha Ravindra, MD; Georgia Andrew, BSc; Devdeep Mukherjee, PhD; Zoë C. Wong, BS; Ying Huang, PhD; Jason Gerhold, BS; Matt Holman, BSc; Julian D'Angelo, BSc; Jeffrey Miller, PhD; Jake Higgins, PhD; Jesse J. Salk, MD, PhD; Jeffery J. Auletta, MD; Firas El Chaer, MD; Steven M. Devine, MD; Antonio Martin Jimenez-Jimenez, MD; Marcos J. G. De Lima, MD; Mark R. Litzow, MD; Partow Kebriaei, MD; Wael Saber, MD; Stephen R. Spellman, MBS; Scott L. Zeger, PhD; Kristin M. Page, MD; Christopher S. Hourigan, DM, DPhil

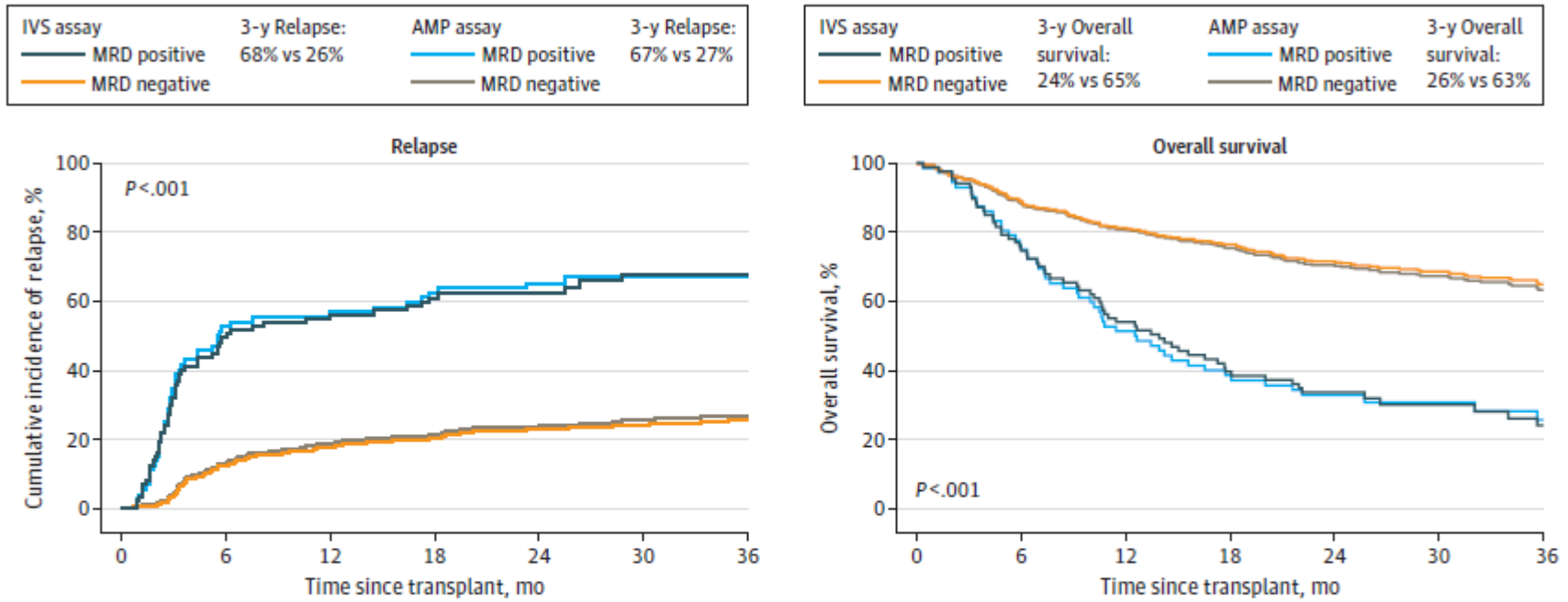
Pre-MEASURE

n = 537 AML mit *FLT3*-ITD

Dillon et al., JAMA Oncol, 2024

Konditionierungsintensität – nach MRD

B Cumulative incidence of relapse and overall survival among patients with *FLT3*-ITD variants

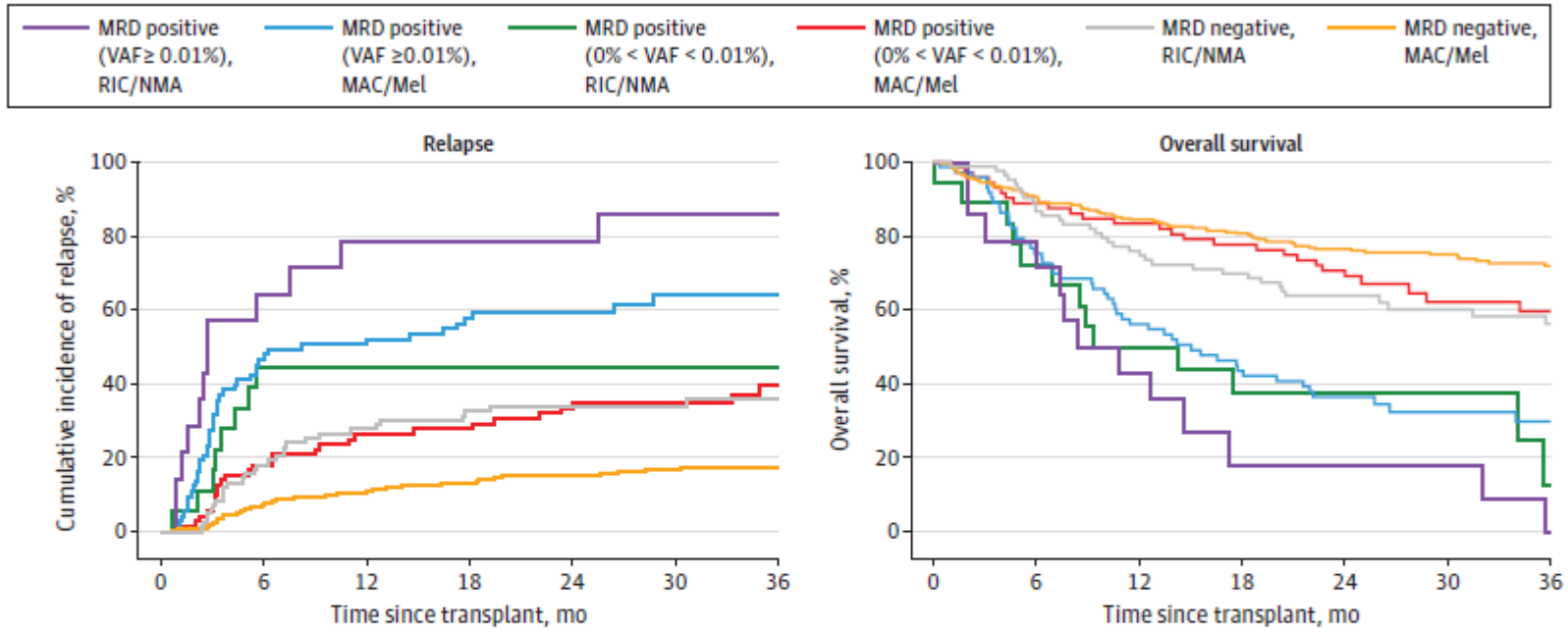


No. at risk														
IVS assay														
MRD negative	450	360	323	295	250	175	145	450	398	361	335	281	191	157
MRD positive	87	39	30	24	19	9	9	87	65	47	33	26	15	12
AMP assay														
MRD negative	465	369	329	299	253	175	145	465	409	371	341	286	194	159
MRD positive	72	30	24	20	16	9	9	72	54	37	27	21	12	10

Dillon et al., JAMA Oncol, 2024

Konditionierungsintensität – nach MRD

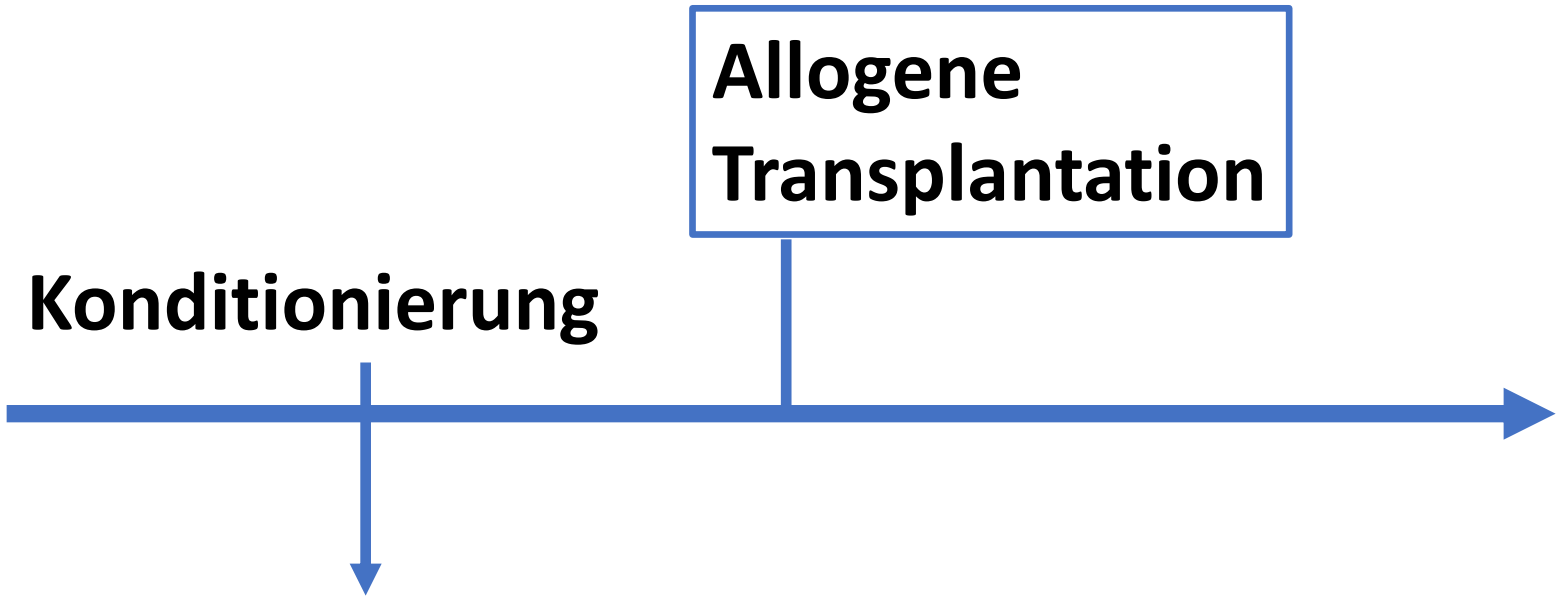
A Cumulative incidence of relapse and overall survival by VAF and conditioning regimen received among patients with *FLT3*-ITD variants



No. at risk														
MRD positive														
VAF ≥0.01%, RIC/NMA	14	4	1	1	1	0	0	14	10	6	2	2	2	0
VAF ≥0.01%, MAC/Mel	73	35	29	23	18	9	9	73	55	41	31	24	13	12
0% < VAF < 0.01%, RIC/NMA	18	6	5	4	4	1	0	18	13	9	6	6	3	1
0% < VAF < 0.001%, MAC/Mel	72	55	49	45	39	23	19	72	64	60	55	48	25	22
MRD negative														
RIC/NMA	83	65	54	47	37	28	24	83	72	63	58	45	32	26
MAC/Mel	277	234	215	199	170	123	102	277	249	229	216	182	131	108

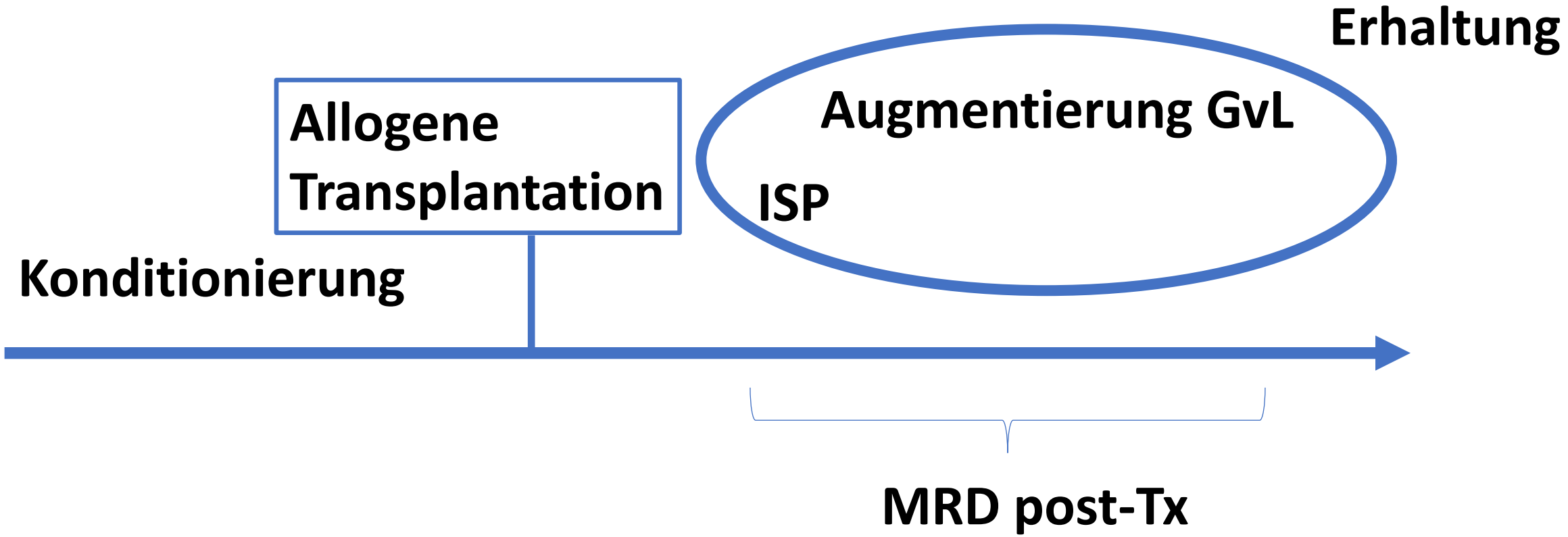
Dillon et al., JAMA Oncol, 2024

Agenda

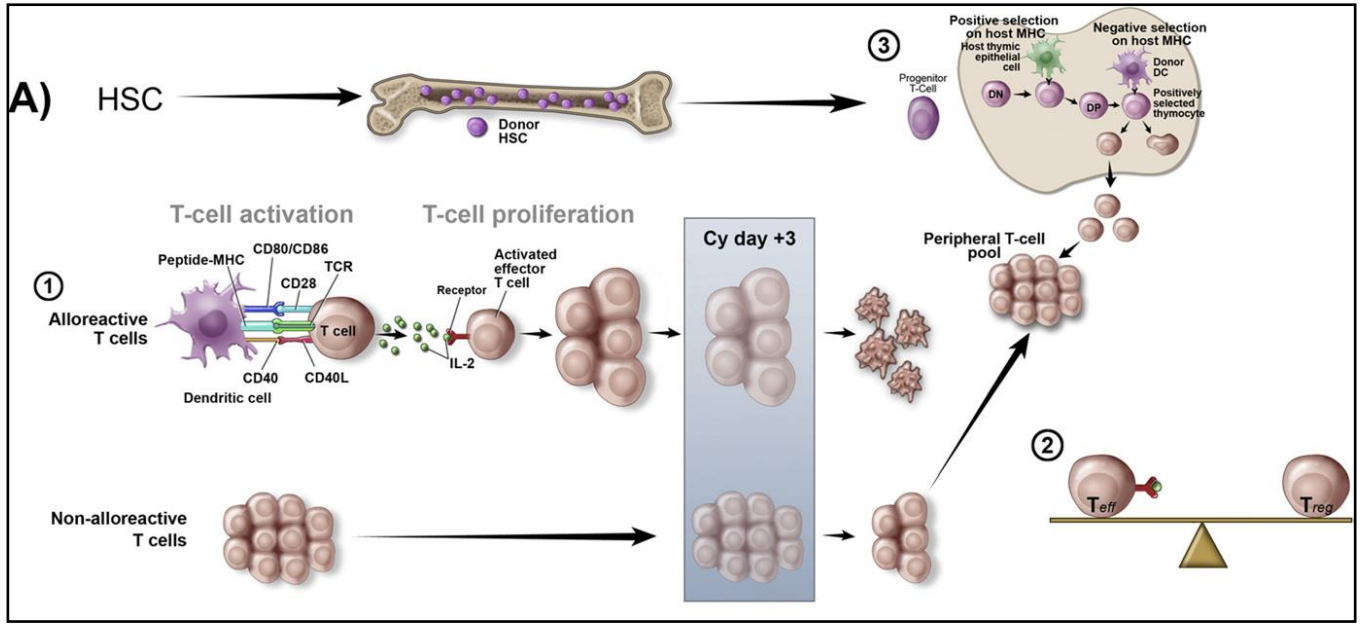


MRD prä-Tx: nur MAC vs. RIC ? ***Most likely not…***

Agenda


Erhaltung
Augmentierung GvL
ISP
Allogene Transplantation
Konditionierung
MRD post-Tx

ISP & Augmentierung GvL

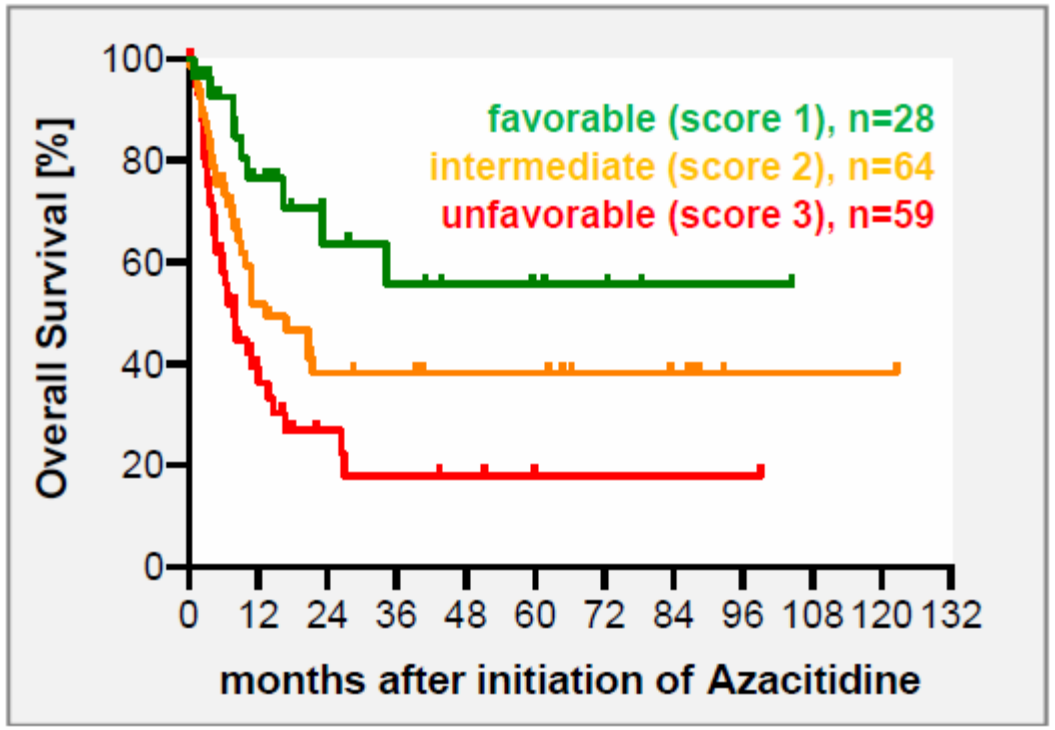


Luznik, O'Donnell & Fuchs, Semin Oncol., 2012

- PTCy 2 x 50 mg/kg
- MMF Stopp +28 bis +35

- PTCy 2 x 30 mg/kg
- ATG + PTCy
- PTCy ohne MMF

ISP & Augmentierung GvL



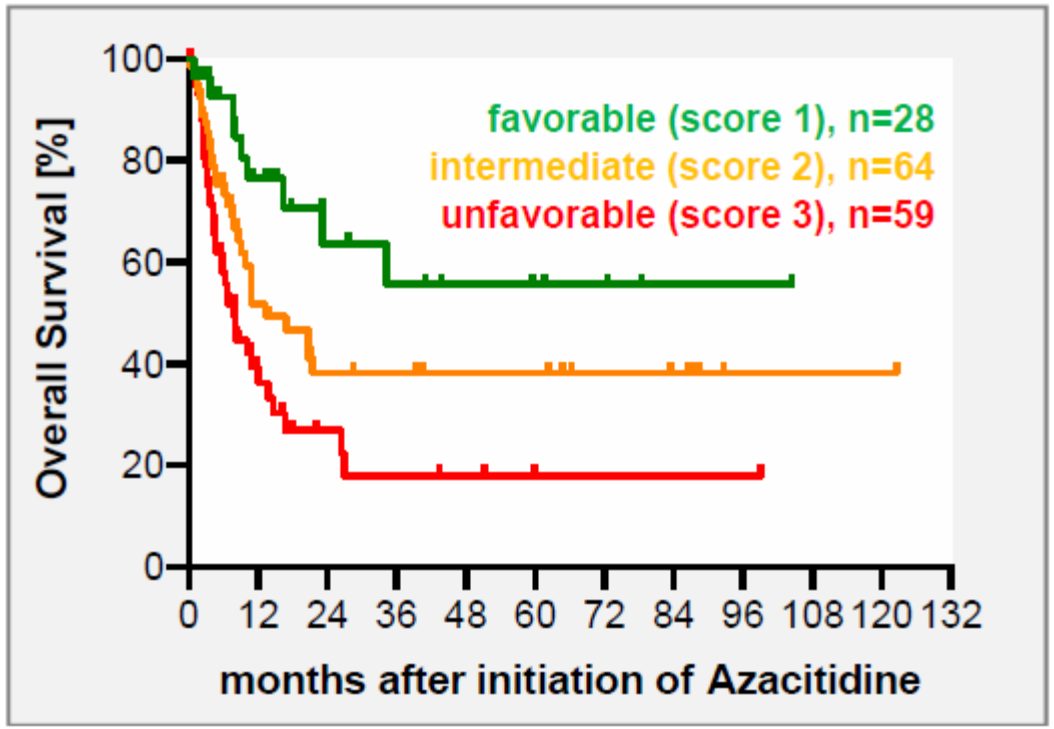
favorable vs. intermediate, $p = 0.047$

intermediate vs. unfavorable, $p = 0.038$

- APSS-R
- Aza + DLI (70%)
- Favorable (score 1) = MRD+

Rautenberg et al., Cancers, 2020

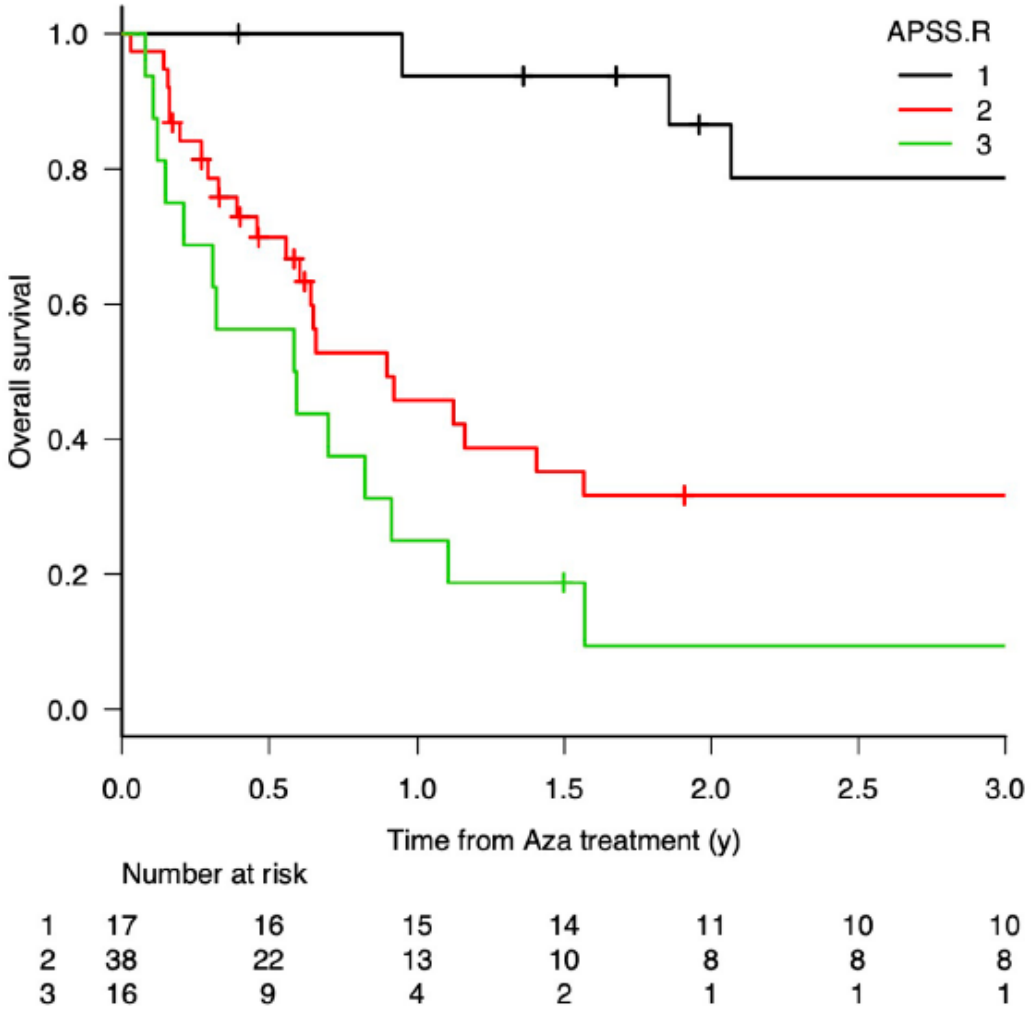
APSS-R



favorable vs. intermediate, $p = 0.047$

intermediate vs. unfavorable, $p = 0.038$

Rautenberg et al., Cancers, 2020



Liberatore et al., Ther Adv Hematol, 2022

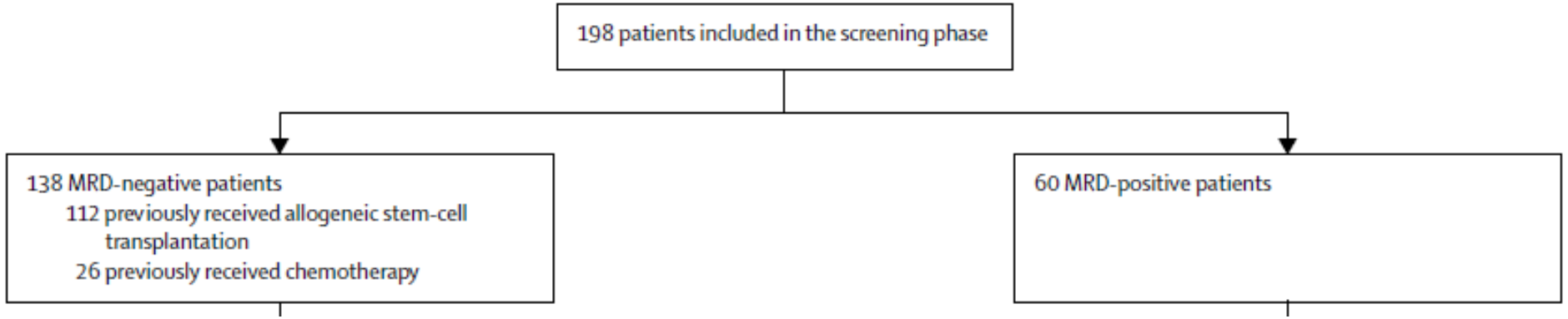
Relaza2 – Trial

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*, Christin 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**

Platzbecker et al., Lancet Oncol, 2018

Relaza2 – Trial



- **MRD during 24 months from baseline by either quantitative PCR for mutant *NPM1*, leukaemia-specific fusion genes (*DEK–NUP*214, *RUNX1–RUNX1T1*, *CBFb–MYH11*), or analysis of donor-chimaerism in flow cytometry-sorted CD34-positive cells**

- **MRD-positive patients in confirmed complete remission received azacitidine 75 mg/m2 per day subcutaneously on days 1–7 of a 29-day cycle for 24 cycles. After six cycles, MRD status was reassessed and patients with major responses (MRD negativity) were eligible for a treatment de-escalation. The primary endpoint was the proportion of patients who were relapse-free and alive 6 months after the start of pre-emptive treatment**

Platzbecker et al., Lancet Oncol, 2018

Relaza2 – Trial

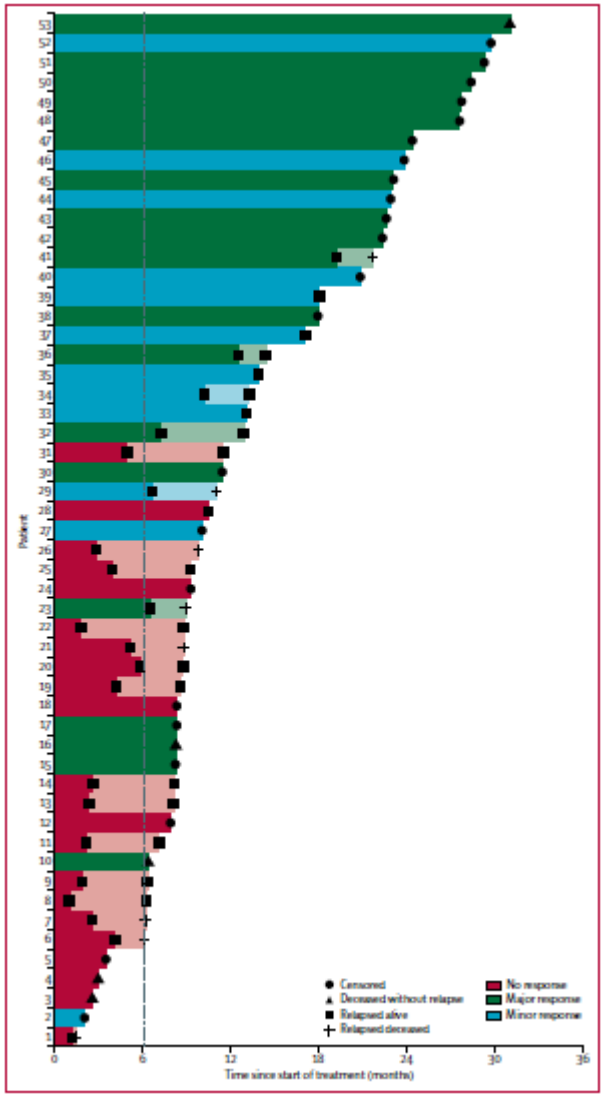
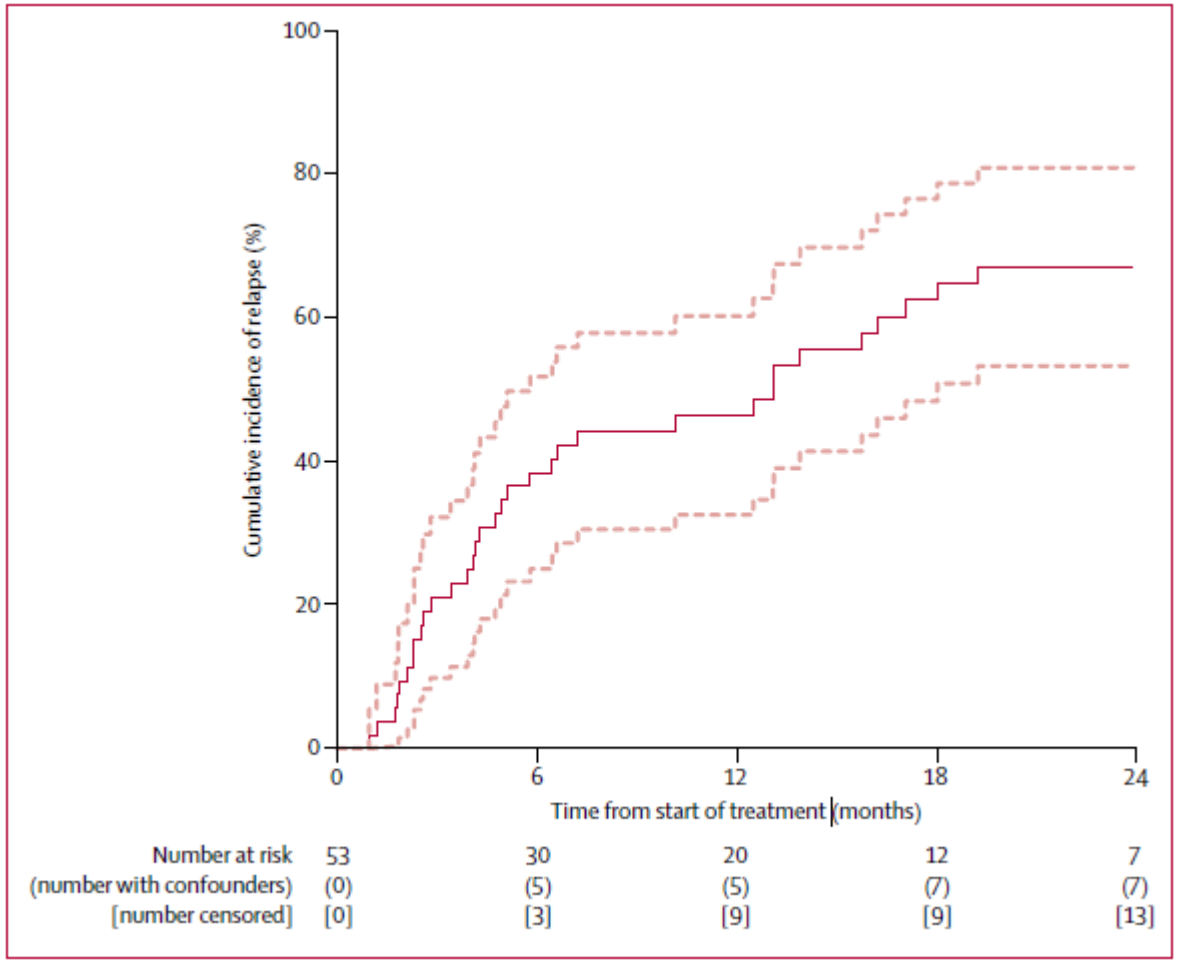


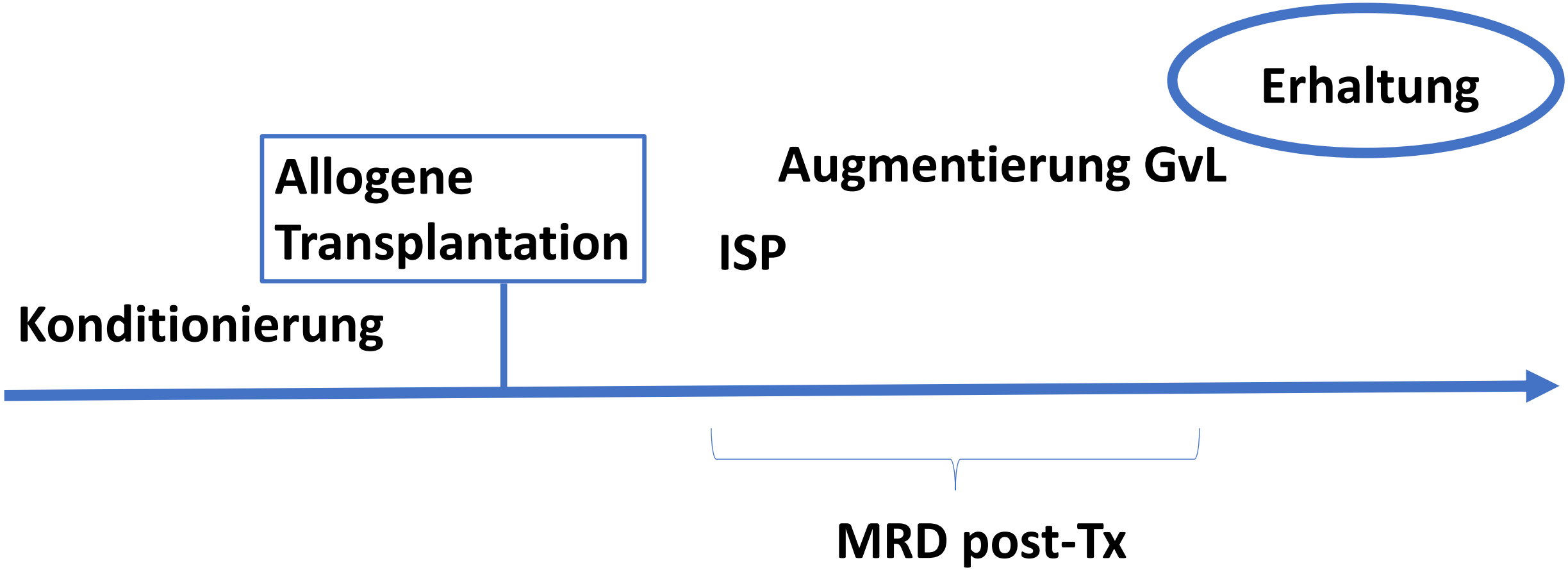
Figure 2: Response
Swimmer plot displaying all patients with MRD positivity at baseline who received study treatment.



Relapse-free survival
at 12 months
46% (95% CI 32–59)

Platzbecker et al., Lancet Oncol, 2018

Agenda


Erhaltung
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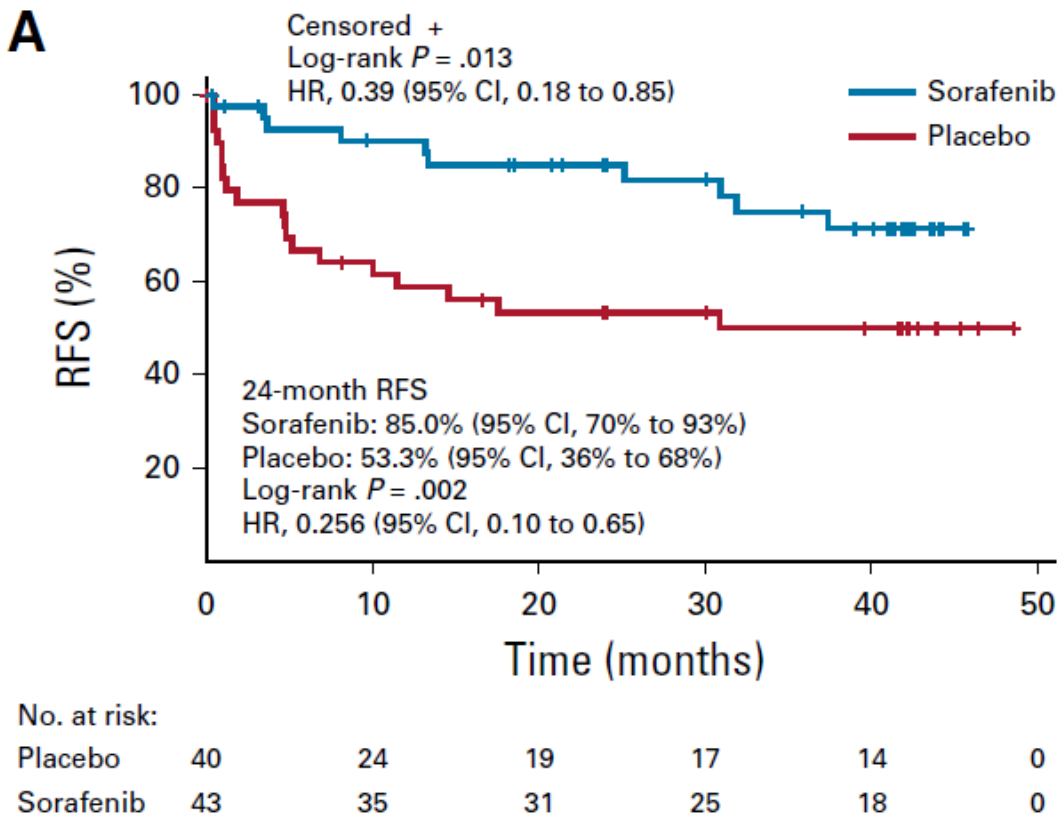
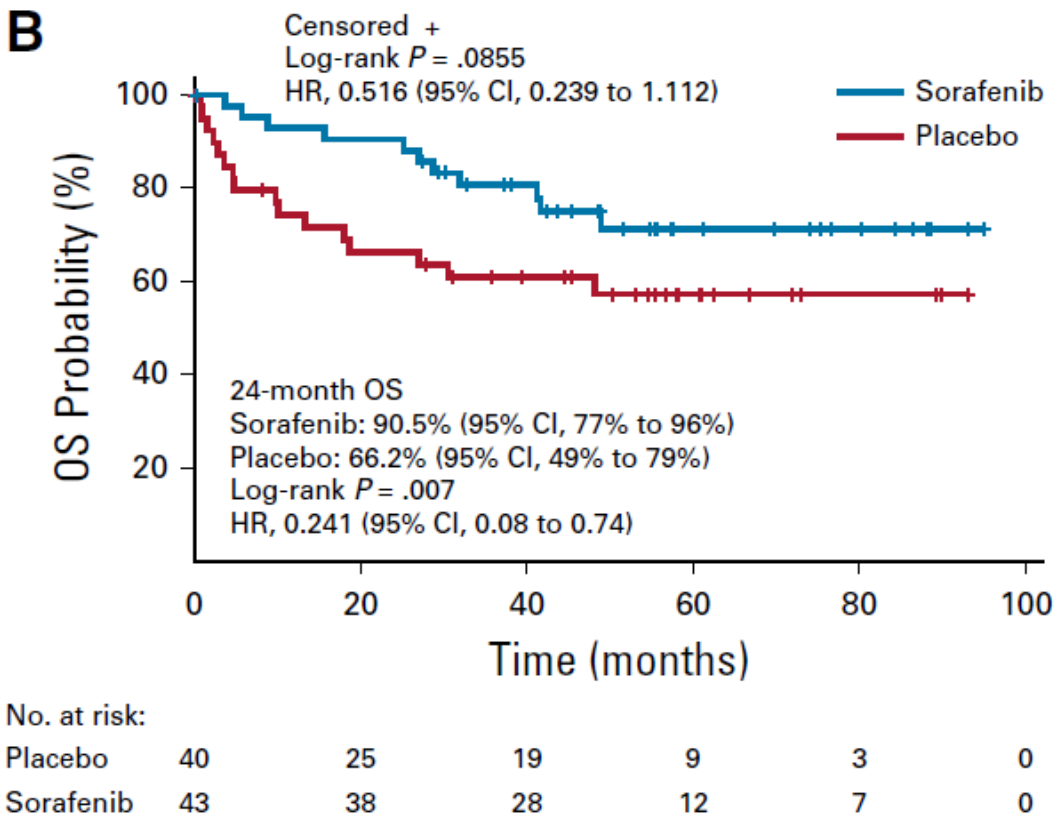
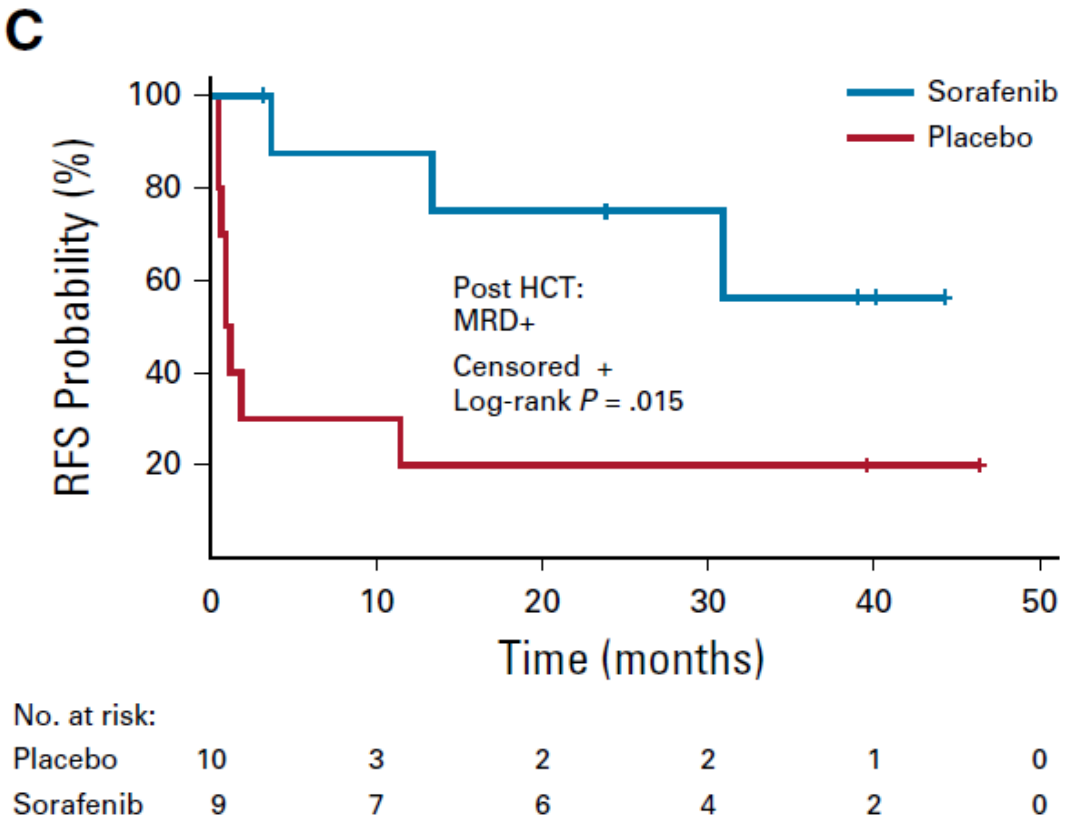
MRD post – Sormain – Trial

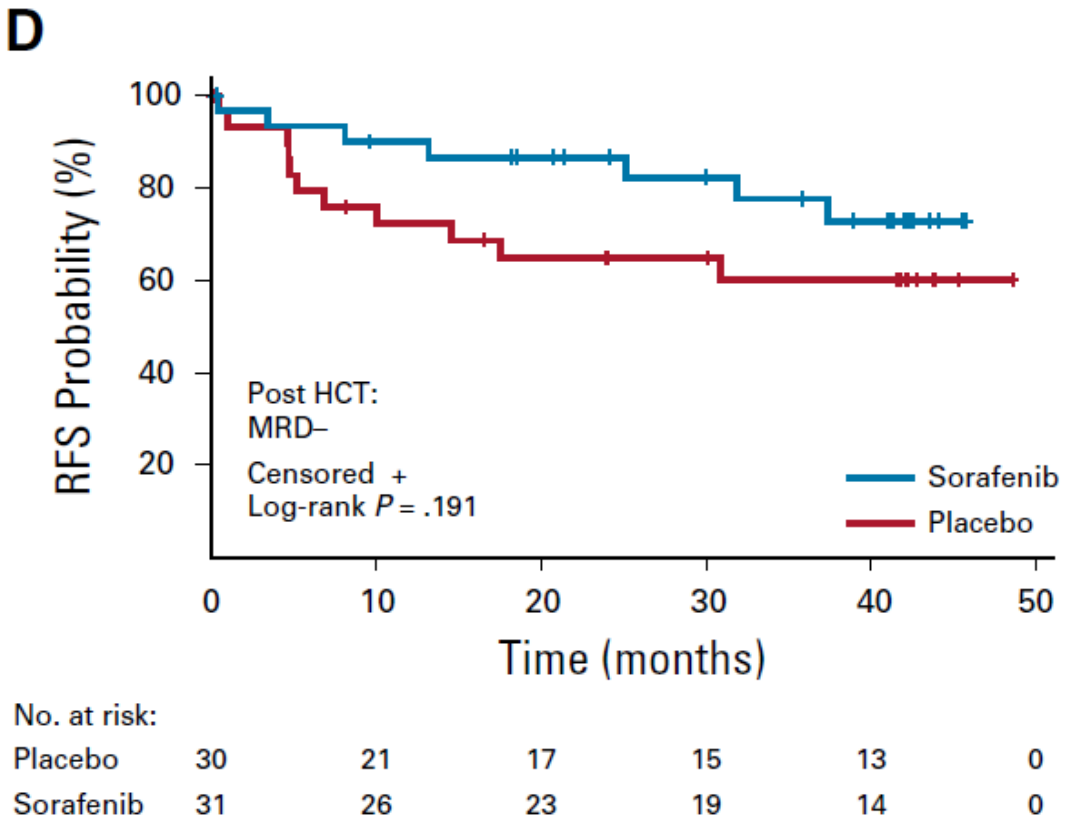




Burchert et al., JCO, 2020

MRD post – Sormain – Trial

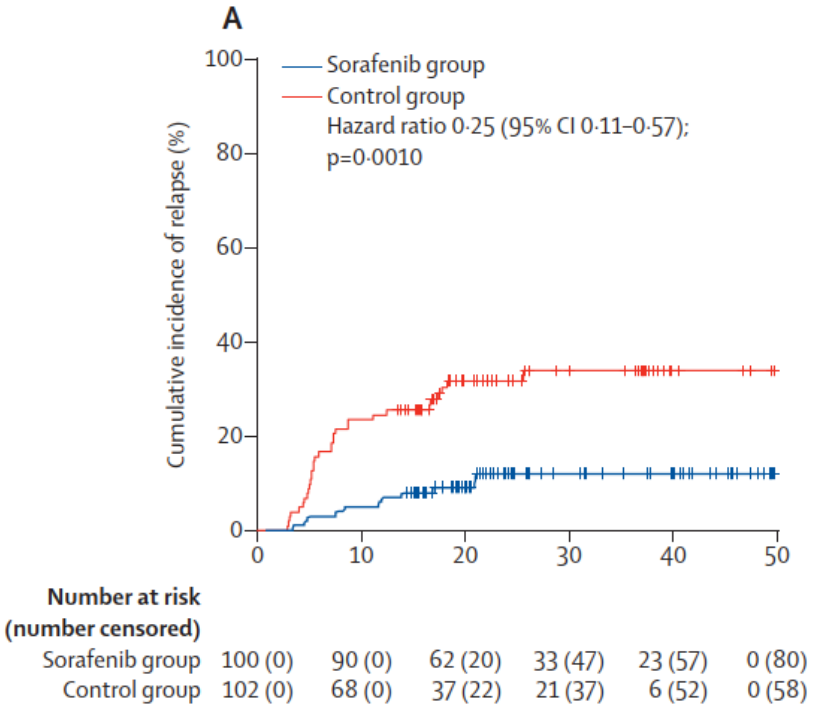


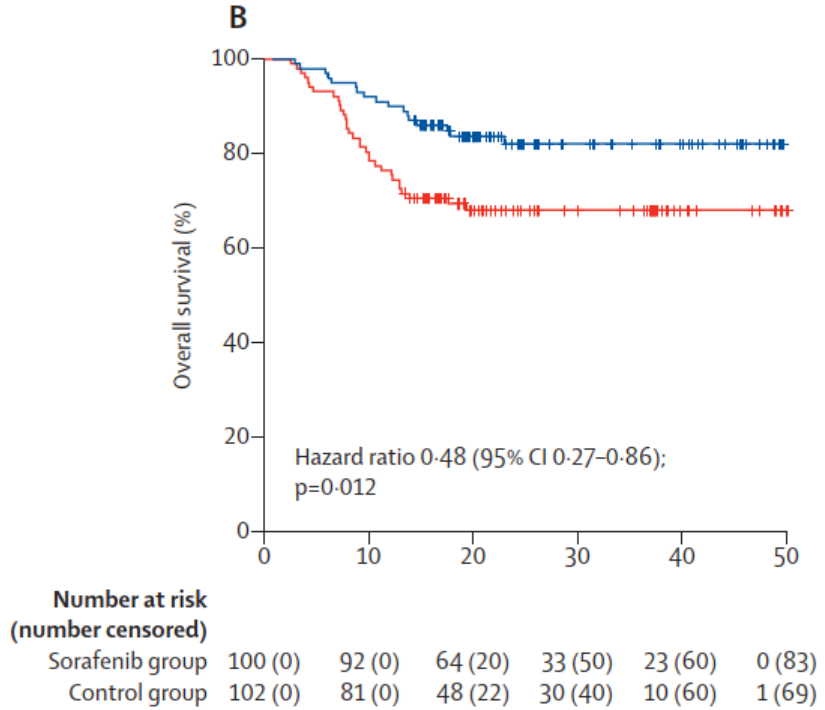


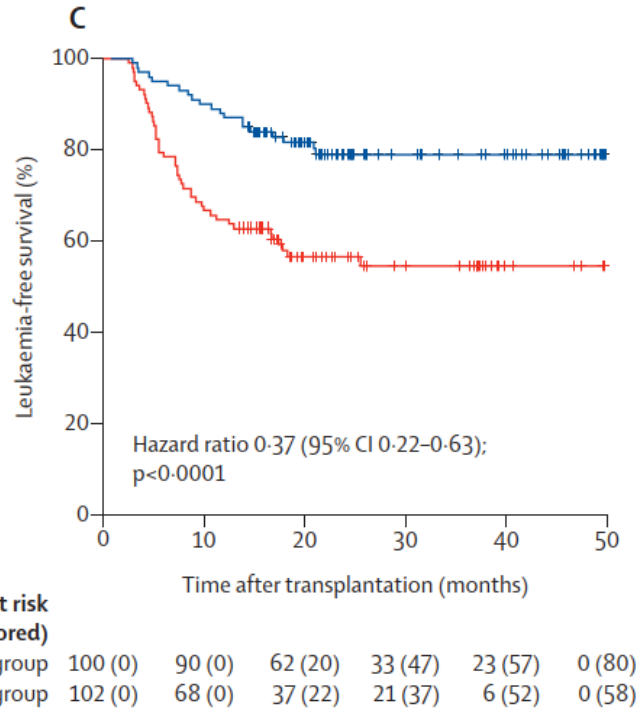
Burchert et al., JCO, 2020

MRD post – Sora maintenance – Trial

- AML, *FLT3*-ITD, n = 202
- 18 – 60 years
- 60% Sora vor Tx
- MRD/MUD/haplo
- MAC (Bu/Cy)



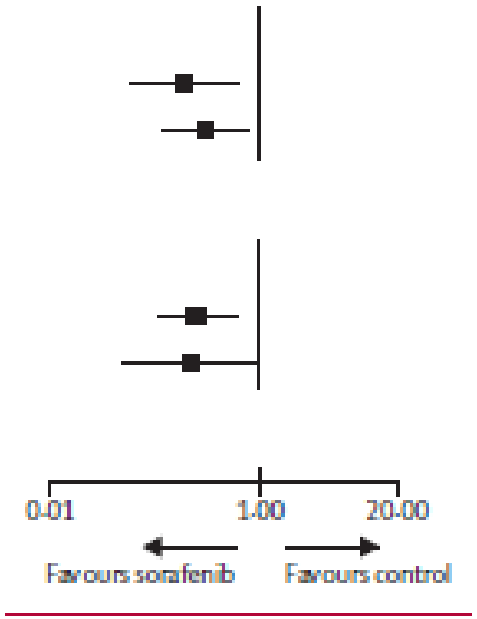




Xuan et al., Lancet Oncol. 2020

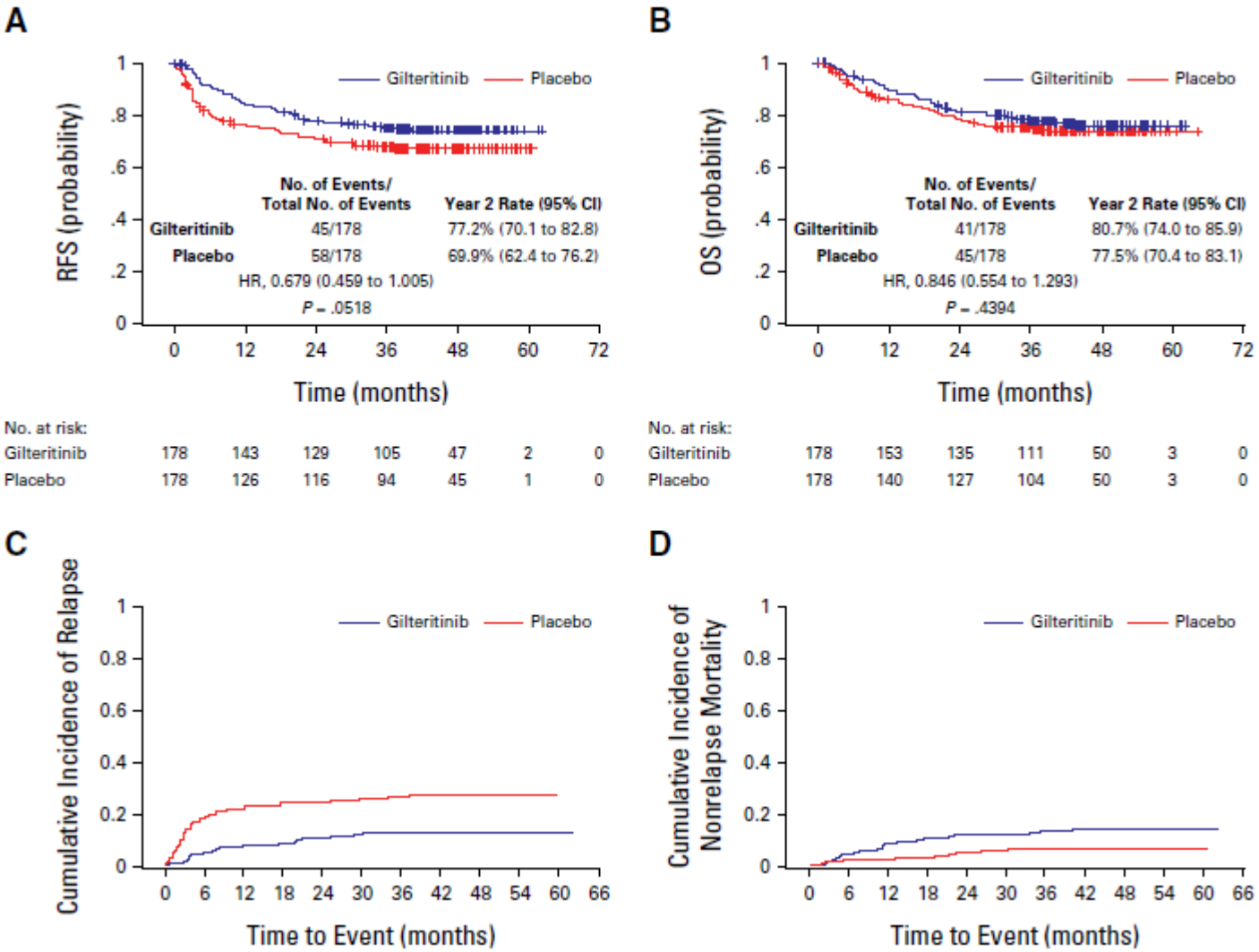
MRD post – Sora maintenance – Trial

	Sorafenib group (events, n/ patients, N)	Control group (events, n/ patients, N)	Cumulative incidence of relapse in sorafenib group at 2 years (95% CI)	Cumulative incidence of relapse in control group at 2 years (95% CI)	Hazard ratio (95% CI)
MRD at transplantation					
Negative	4/69	15/68	6·9% (2·1–15·5)	21·6% (12·4–32·5)	0·21 (0·07–0·64)
Positive	7/31	17/34	23·1% (9·9–39·5)	51·5% (32·7–67·4)	0·33 (0·14–0·79)
MRD at the time of enrolment post-transplantation					
Negative	8/91	24/91	9·8% (4·5–17·6)	26·3% (17·5–36·0)	0·28 (0·13–0·62)
Positive	3/9	8/11	33·3% (6·5–64·2)	77·3% (24·3–95·4)	0·25 (0·06–0·94)



Xuan et al., Lancet Oncol. 2020

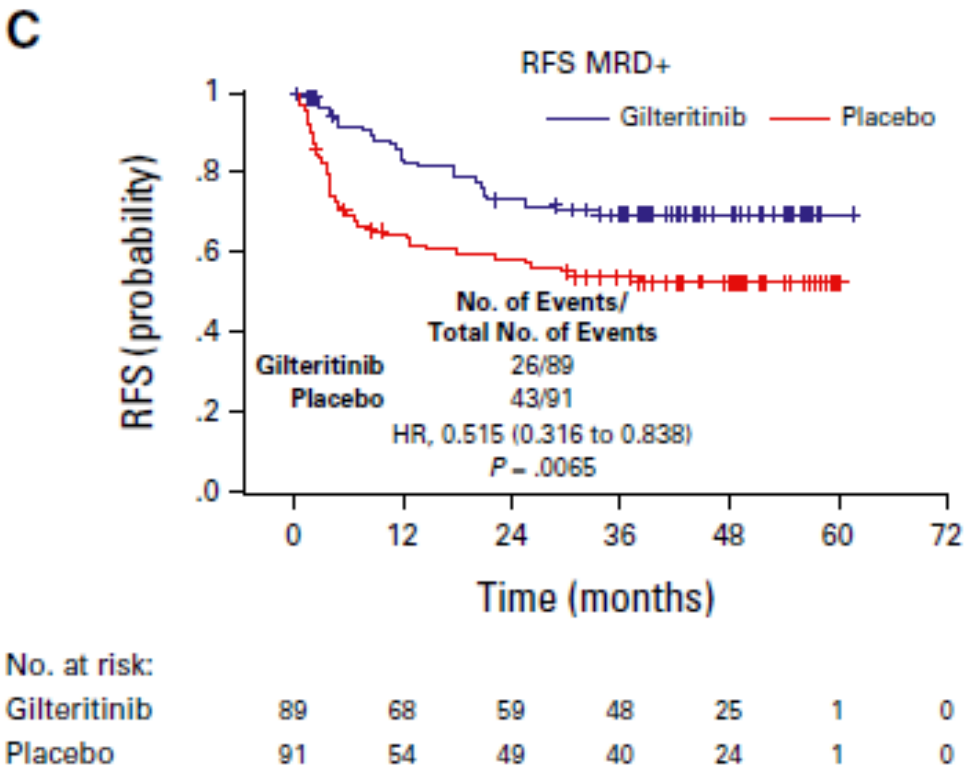
MRD post – Morpho – Trial

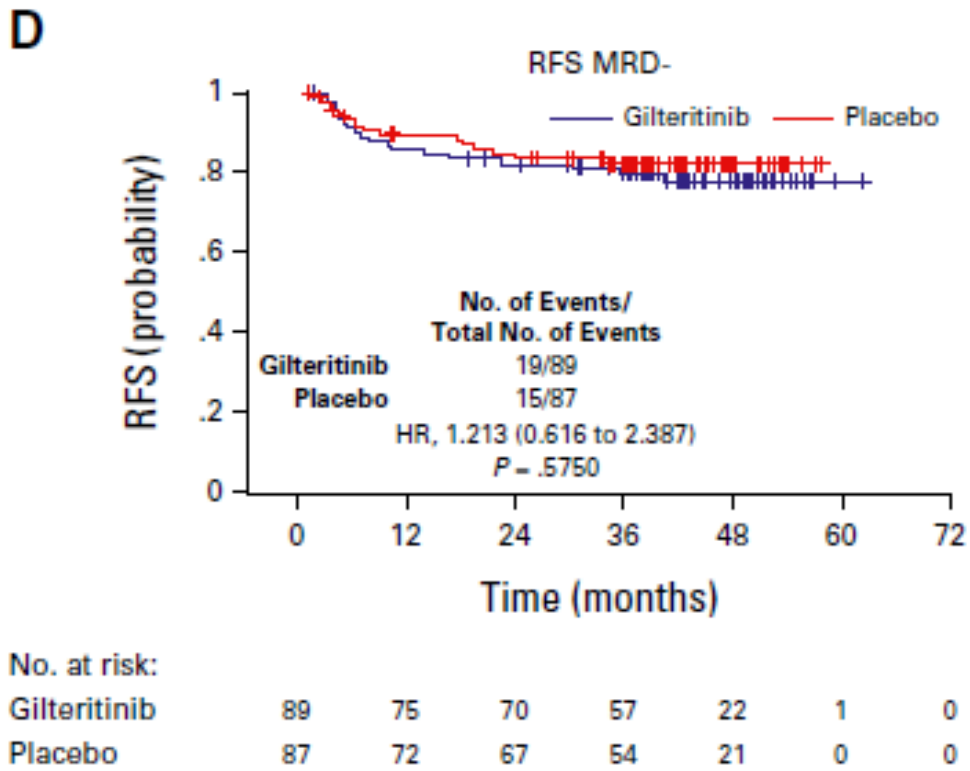


- AML, *FLT3*-ITD, n = 356
- 18 – 78 years
- MRD/MUD/MMUD/haplo/CB

Levis et al., JCO, 2024

MRD post – Morpho – Trial





Levis et al., JCO, 2024

DRST Analysis

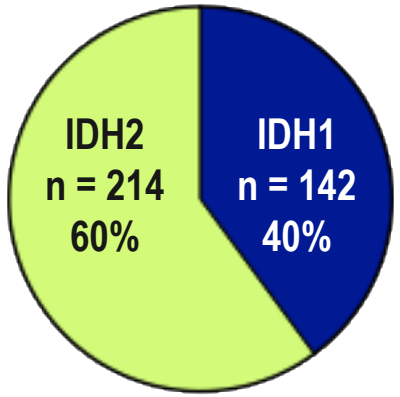
AML with IDH1 or IDH2 mutation

First allo-SCT 2014-2021

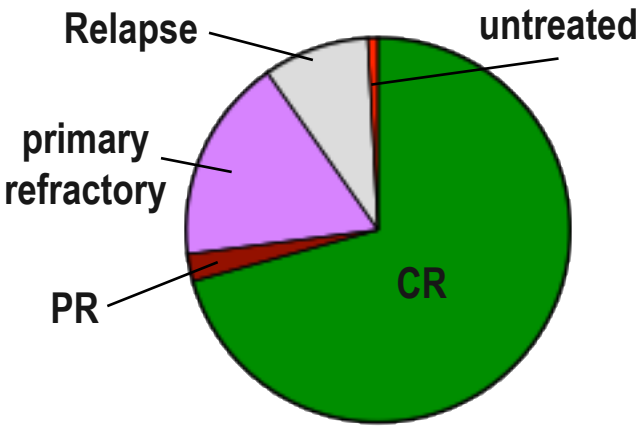
Follow-up > 6 months

Total n = 356

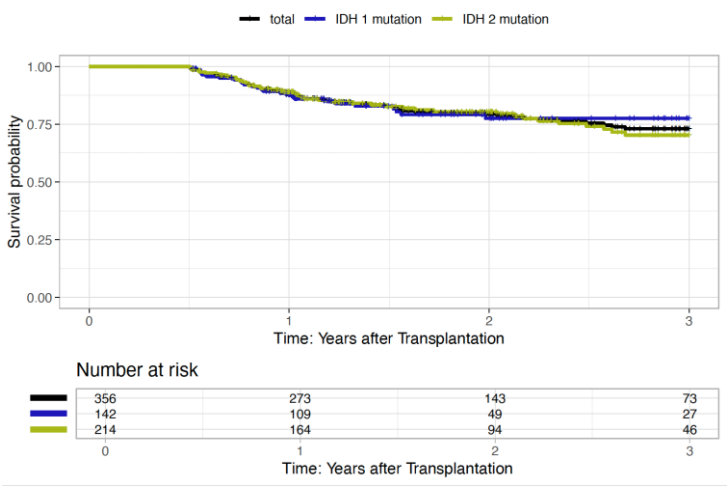
Distribution of IDH mutations



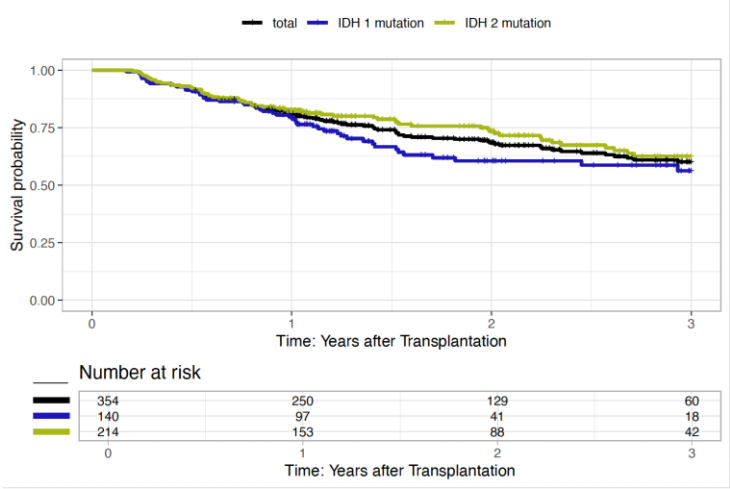
Remission status at transplant



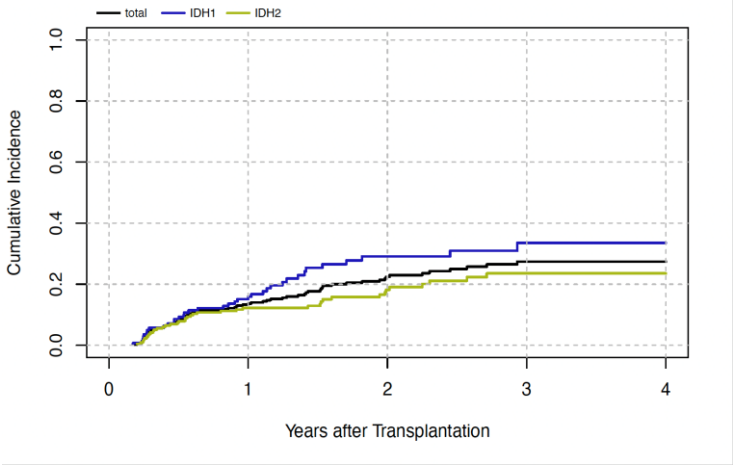
Overall Survival



Event-free Survival



Relapse Incidence

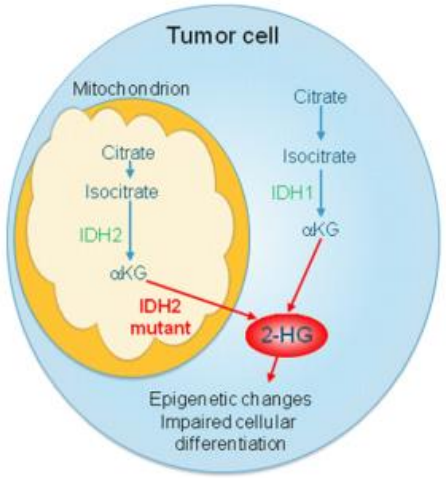


Key Findings

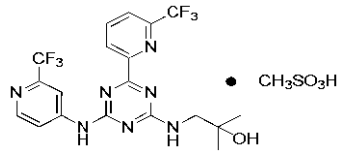
- Despite a relapse rate of 27% 3-year OS of 73% was promising
- Different biological behavior of *IDH1* and *IDH2* mutations with higher relapse risk (34% vs. 24%) and lower EFS in *IDH1*-mutated patients
- Active disease was the strongest risk factor for adverse outcome

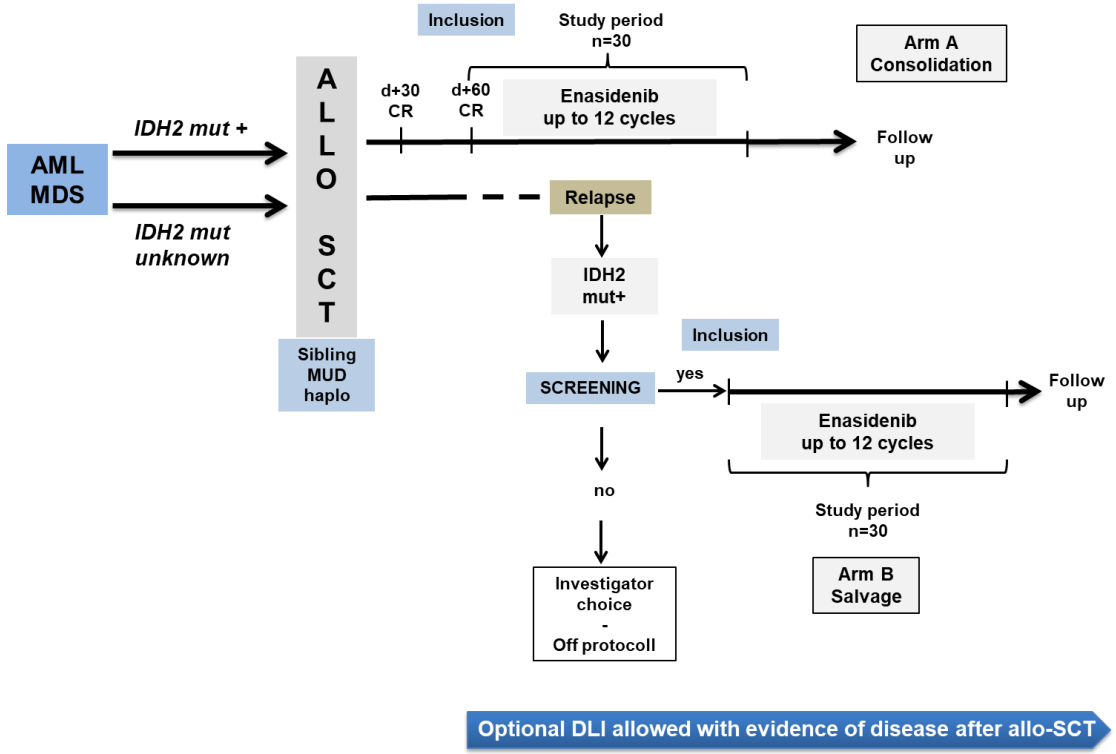
Courtesy of Rautenberg & Schroeder, under review

IDH2-Post-Allo-Trial – Genotype-specific Maintenance



ENASIDENIB





Trial type: Multi-center, open-label, non-randomized, 2 single arms

Patients number: n=60, start Q1/2020

Primary Endpoint: Safety (Adverse Events, GvHD, Hospitalization)

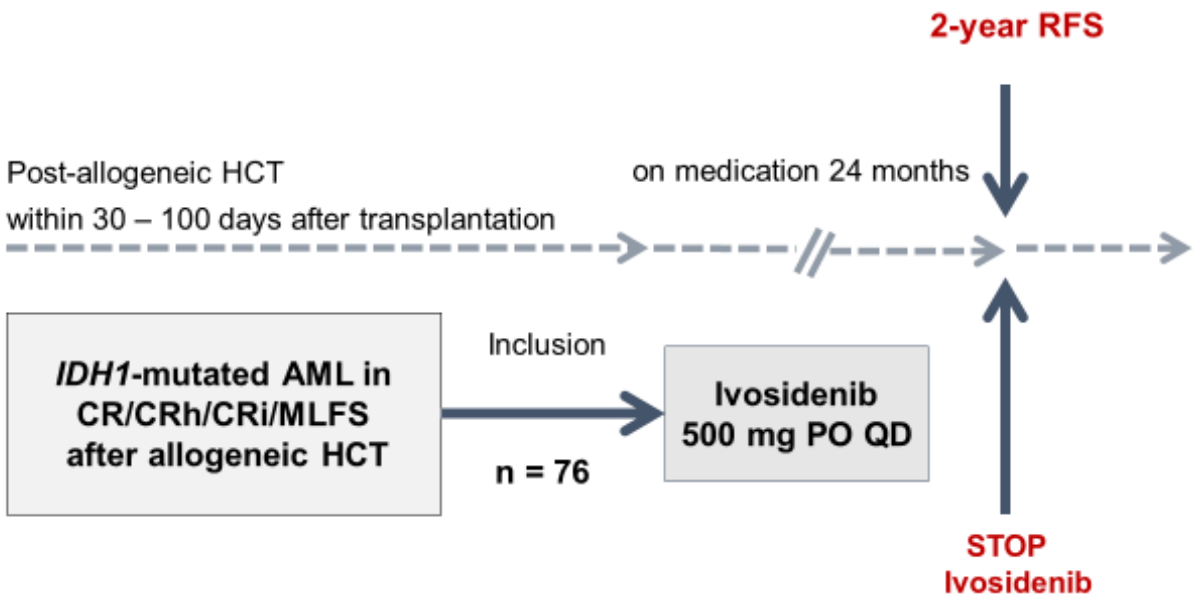
Secondary Endpoint: Efficacy (Response, Duration of response, Overall Survival)

PIs: Schroeder & Kobbe

PIVOT

PIVOT Trial

Prospective Evaluation of Ivosidenib post allogeneic Transplantation



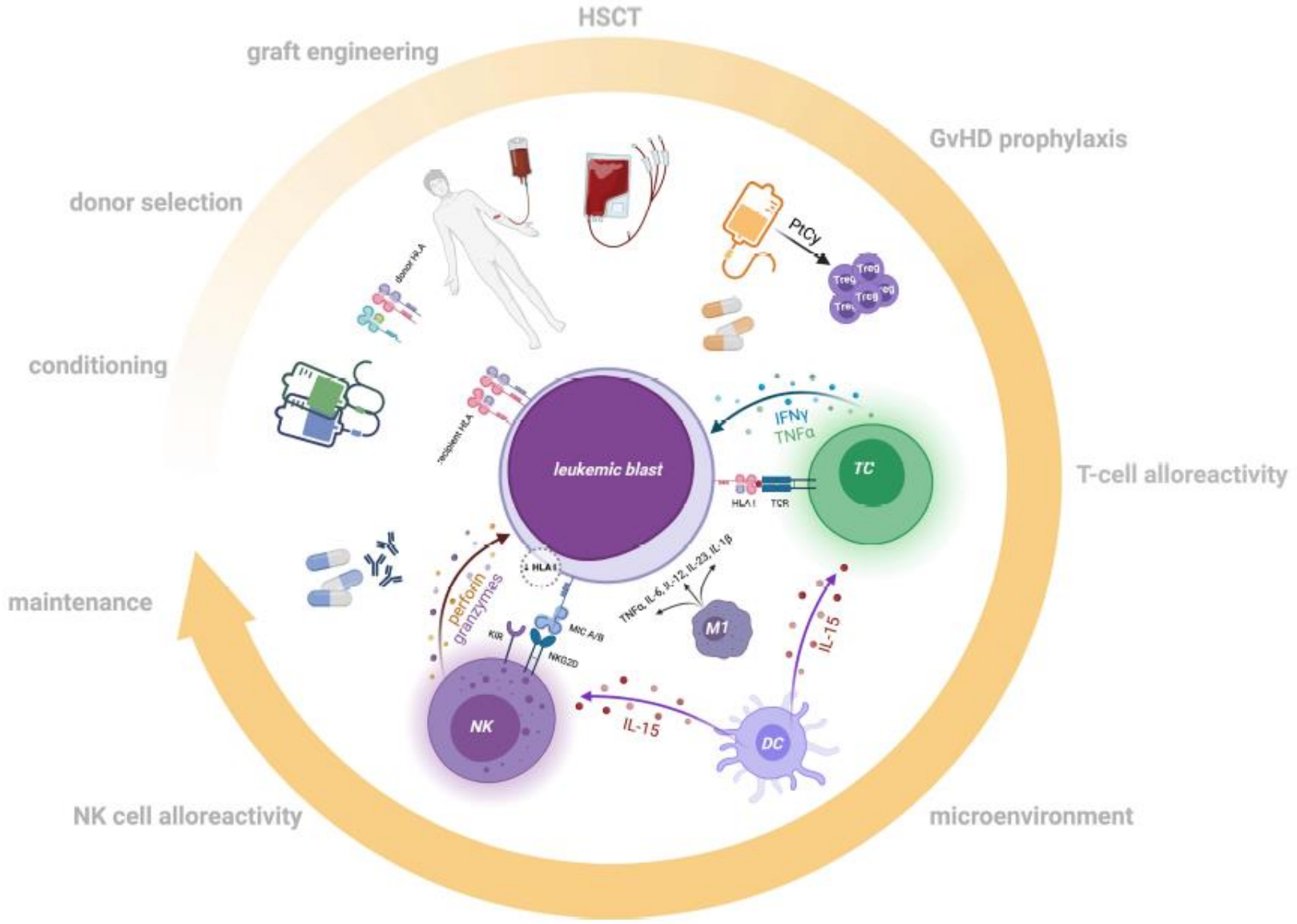
- prospective, open-label, multicenter phase-II trial single-arm study; following A'Hern design assuming complete observations (minimum follow-up of 2 years) :

  n = 69 patients + drop-out rate 10% resulting to a

  total of **n = 76** patients

- RFS 50% after 2 years (in CR1: ~60% 2 years (Duchmann *et al.*, Blood 2021; Kunadt *et al.*, 2022 J Hematol Oncol)
- Assumption: + 15% with ivosidenib, 18 months treatment
- Countries: Germany, Czech Republic (SAL/AMLCG, KTS)
- Centers: n = 20

Weitere Schaltstellen der Modulation



Kunadt & Stölzel,
Cancer Manag Res., 2021

Vielen Dank für Ihre Aufmerksamkeit

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