Profilassi, interventi precocci e trattamento del relapse post-trapianto

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Disclosures of Marta Stanzani

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Profilassi, interventi precoci e trattamento del relapse post-trapianto

Marta Stanzani, MD, PhD

19 novembre 2022

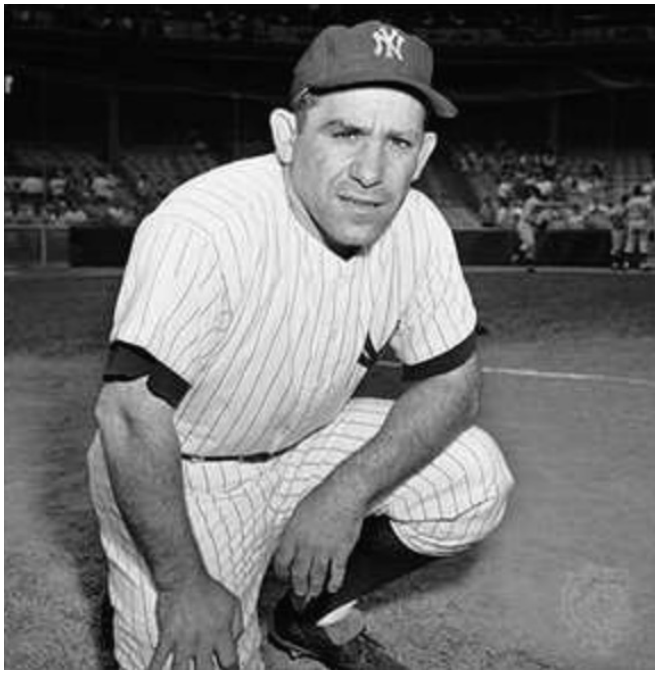
Key Points

1. Relapse prognosis and risk factors

2. Methods to detect relapse/MRD
   - Molecular methods
   - Cytofluorimetry methods
   - Chimerism

3. Clinical strategies
   - Maintenance approach
   - Preemptive approach
   - Therapeutic approach

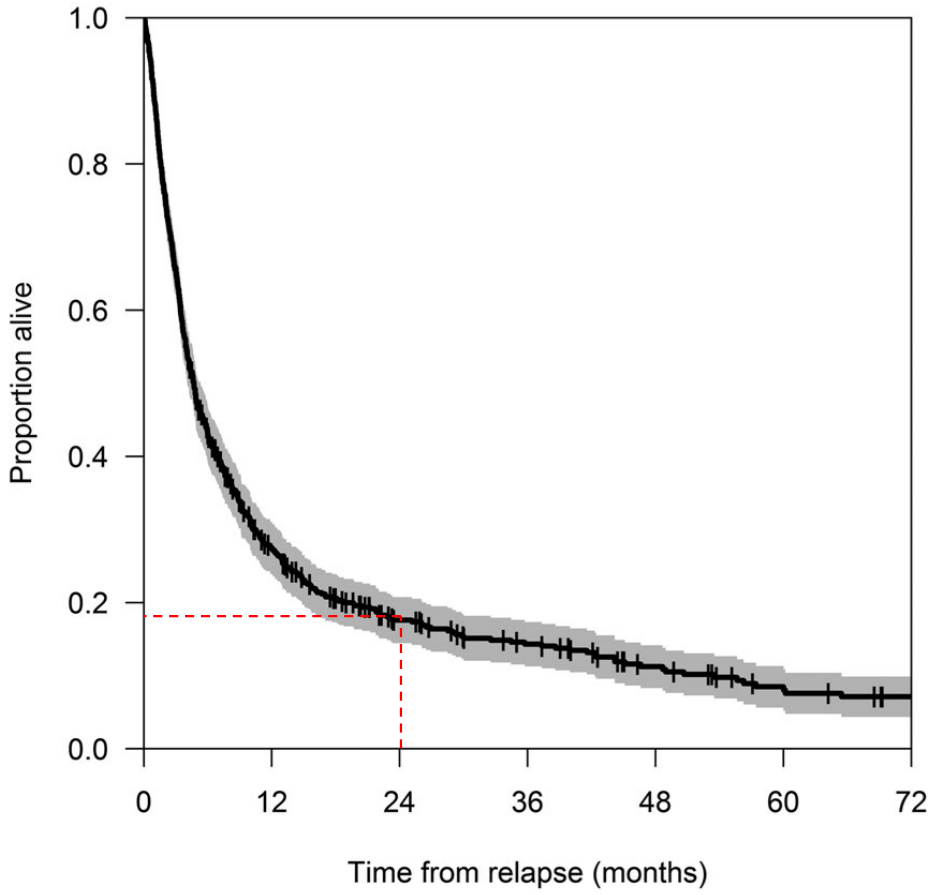
4. Therapeutic strategies
   - Cellular-Based therapies
   - Drug-Based therapies
   - Combo therapies



“It's tough to make predictions, especially about the future.”

— Yogi Berra

AML & MDS Relapse After-Transplant



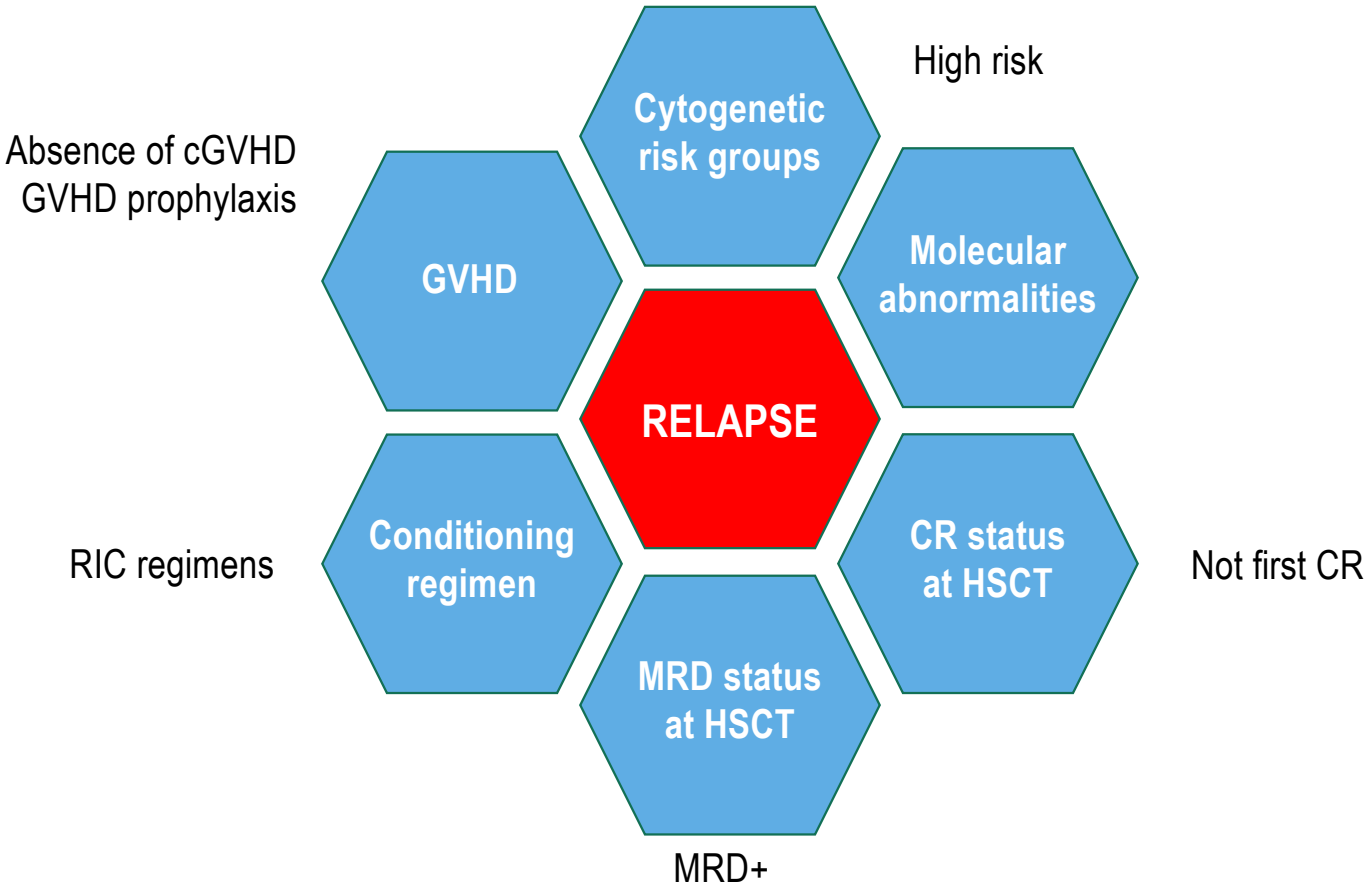
Schmid C et al. EHA. *Haematologica*. **2018**; 103(2):237-245

A Journey That Begins at Diagnosis

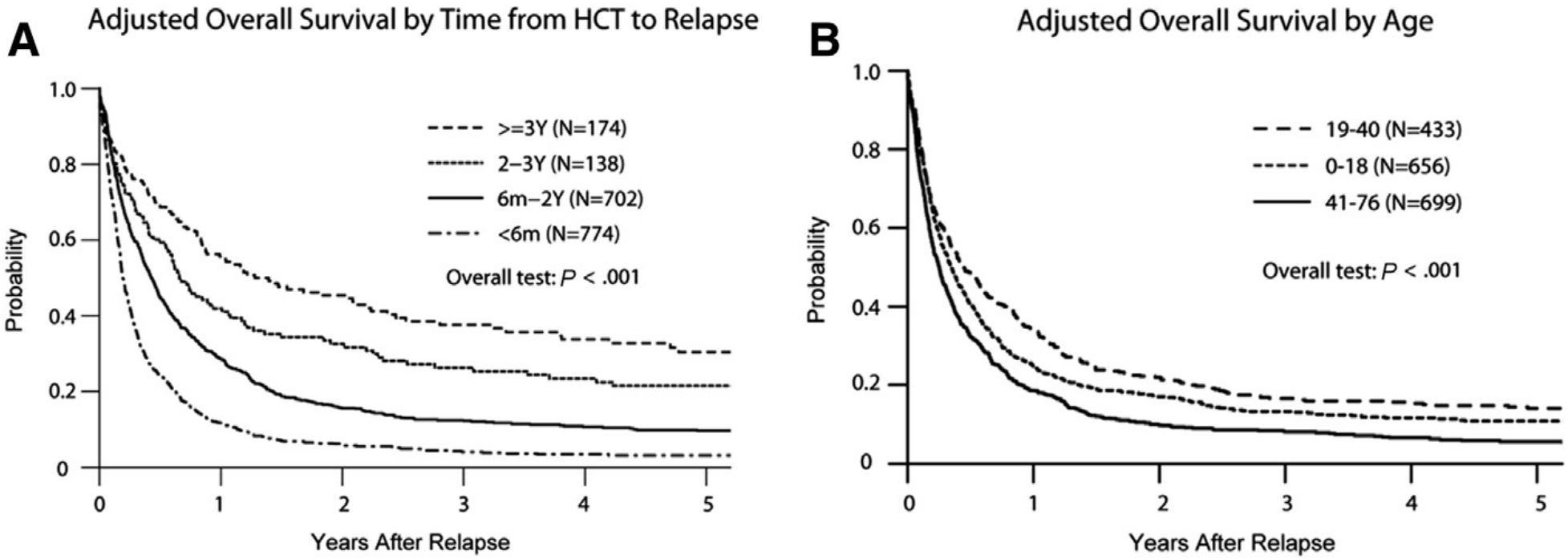
FAVORABLE	• t(8;21)(q22;q22.1); RUNX1-RUNX1T1 • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB • MYH11 Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low} Biallelic mutated CEBPA
INTERMEDIATE	• Mutated NPM1 and FLT3-ITDhigh • Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low}(without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3); MLLT3-KMT2A • Cytogenetic abnormalities not classified as favorable or adverse
ADVERSE	• t(6;9)(p23;q34.1); DEK-NUP214 • t(v;11q23.3); KMT2A rearranged • t(9;22)(q34.1;q11.2); BCR-ABL1 • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) • -5 or del(5q); 27; 217/abn(17p) • Complex karyotype, monosomal karyotype • Wild-type NPM1 and FLT3-ITD^{high} • Mutated RUNX1 • Mutated ASXL1 • Mutated TP53

Döhner H et al. 2017 ELN recommendations. *Blood*. **2017**; 129(4):424-447

Risk Factors for Relapse After Transplant

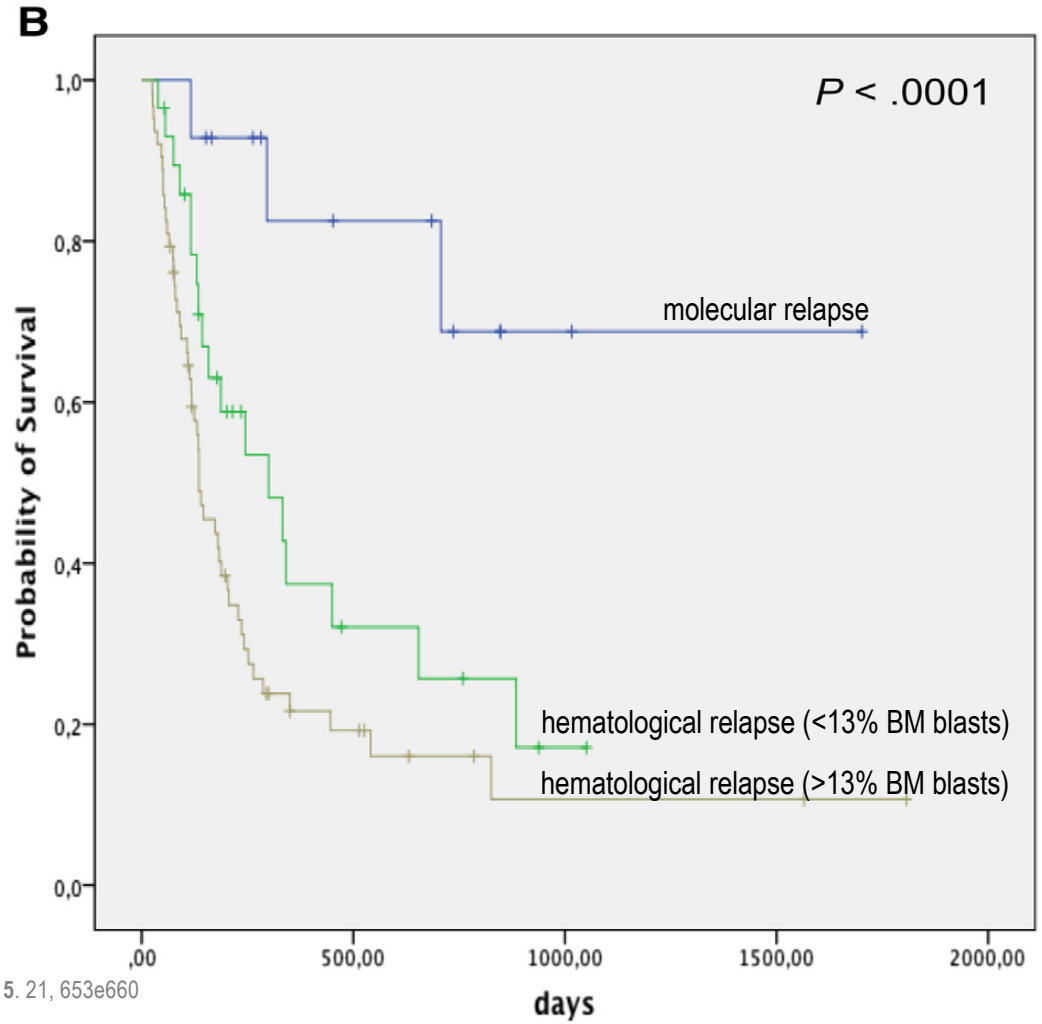


Overall Survival in Relapsed Patients After Transplant by Time to Relapse and Age

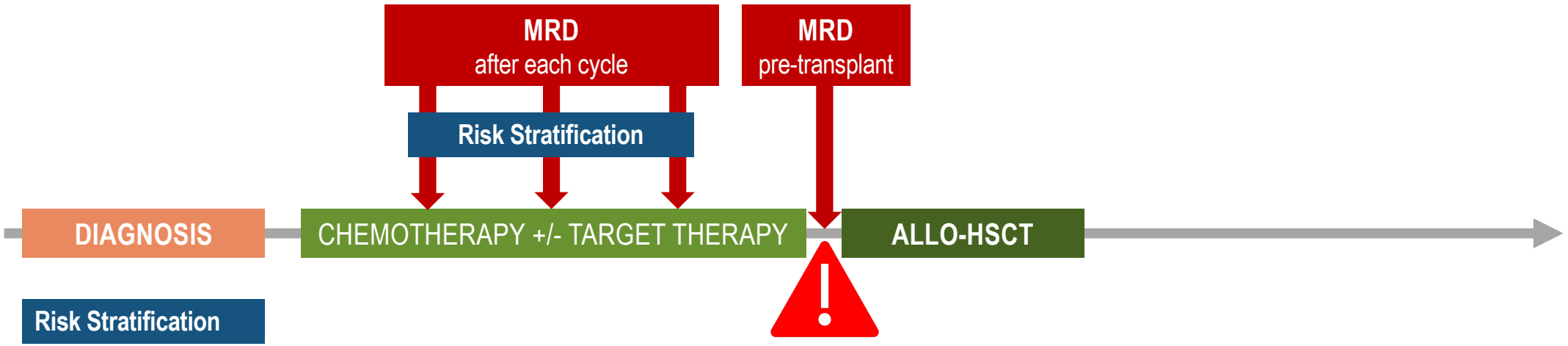


Bejanyan N et al. *Biol Blood Marrow Transplant.* **2015**. 21, 454e459

Overall Survival in Relapsed Patients After Transplant by Disease Burden



Schroeder T et al. *Biol Blood Marrow Transplant*. **2015**. 21, 653e660



Therapeutic strategy
- Target therapies
- Conventional CTH
- Allo-HSCT in 1CR

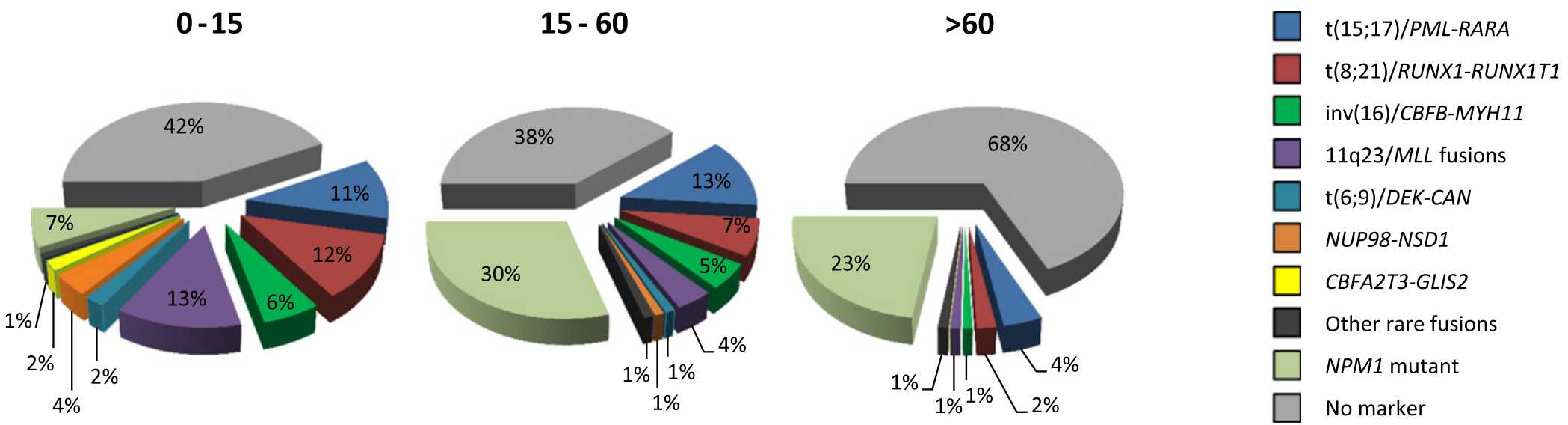
Adapted from: Rautenberg C et al. Int. J. Mol. Sci. **2019**; 20, 228

Methods to Detect MRD Before and After HSCT

	Multiparametric Flow Cytometry	Molecular Genetics ▪ Mutated Genes: NPM1, FLT3, IDH1-2 ▪ Fusion Gene Transcripts: CBF (CBFB-MYH11;RUNX1-RUNX1T1) ▪ Gene Overexpression: WT1	Chimerism (*only post-transplant*)
Methods	▪ Leukemia-Associated Immunephenotype (LAIP) ▪ Different from Normal (DfN)	▪ Quantitative PCR ▪ Digital Droplet PCR ▪ Next Generation Sequencing	▪ Deletions-Insertions (DIP-PCR) ▪ Short-Tandem-Repeats (STR-PCR) ▪ Variant-Allele-Specific quantitative PCR ▪ X-Y-FISH ▪ CD34+ cell subset analysis
Sensitivity	10^{-3} –10^{-4} (BM)	10^{-6}	10^{-2}–10^{-3} 10^{-4}–10^{-5}
Advantages	Broad applicability (90% of patients)	High sensitivity and specificity	Applicable in all patients after allo-SCT
Comments	Need for standardization	▪ Mostly restricted to select patients ▪ Need for standardizatiom	▪ Low sensitivity and specificity ▪ Not directly detecting leukemic cells

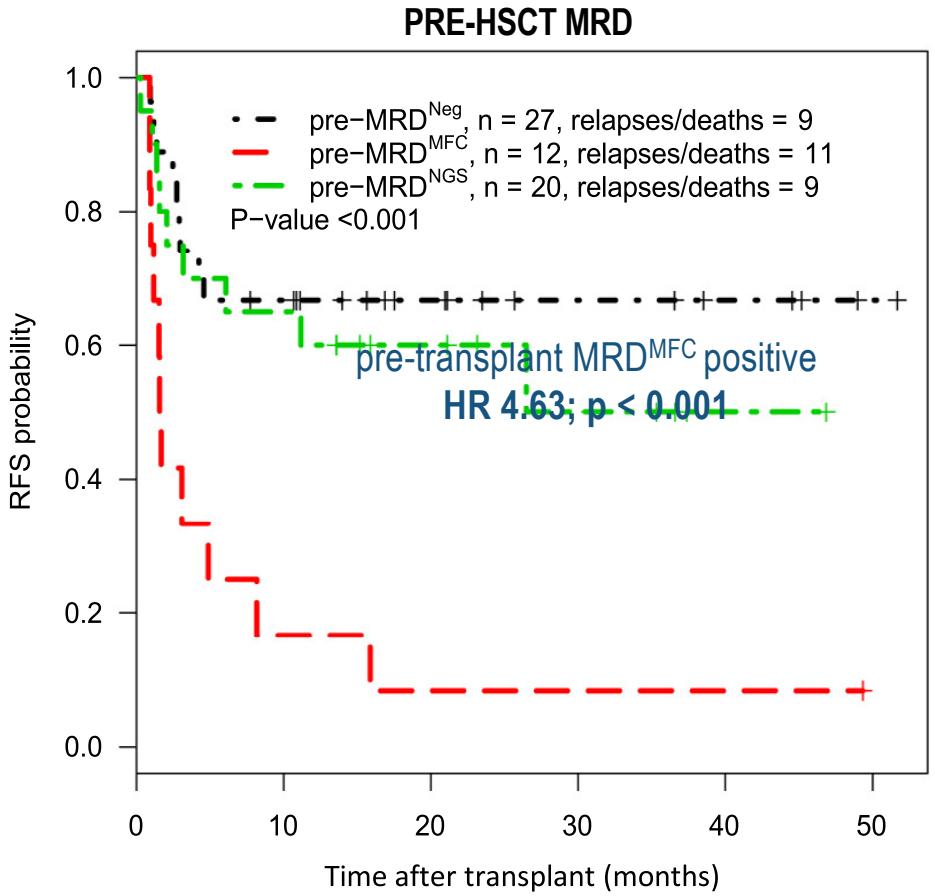
Adapted from: Rautenberg C et al. *Int. J. Mol. Sci.* **2019**; 20, 228

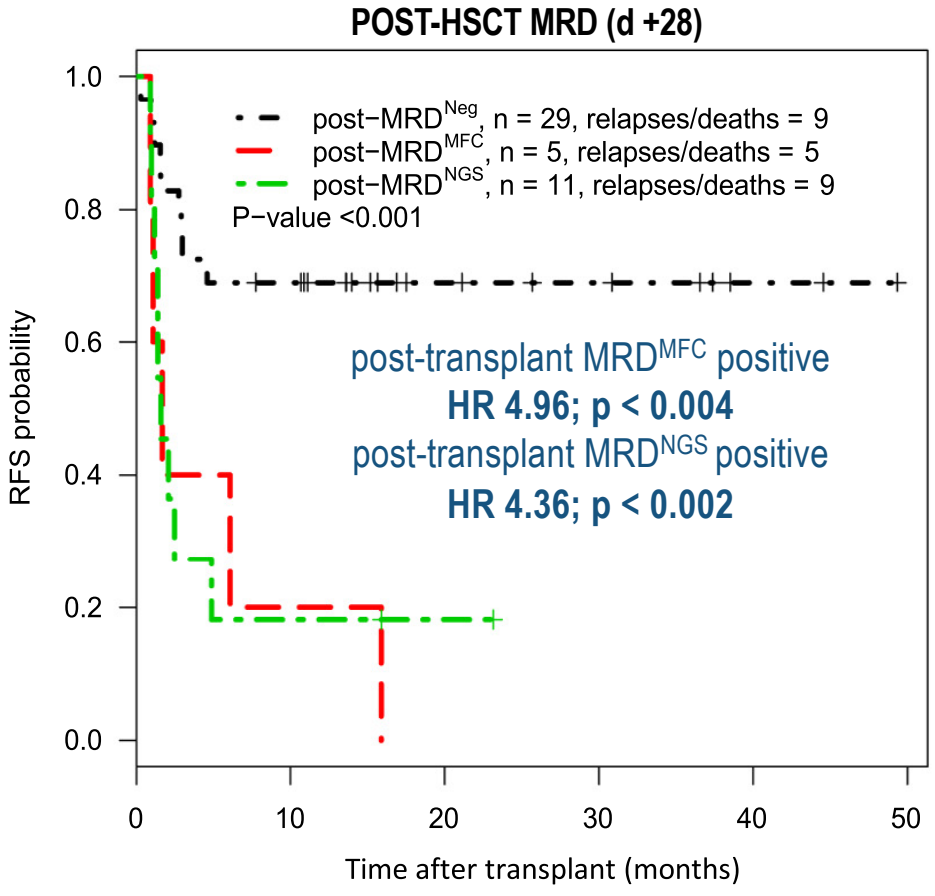
Minimal Residual Disease



Grimwade D, et al. *Blood*. **2014**; 124(23):3345-3355

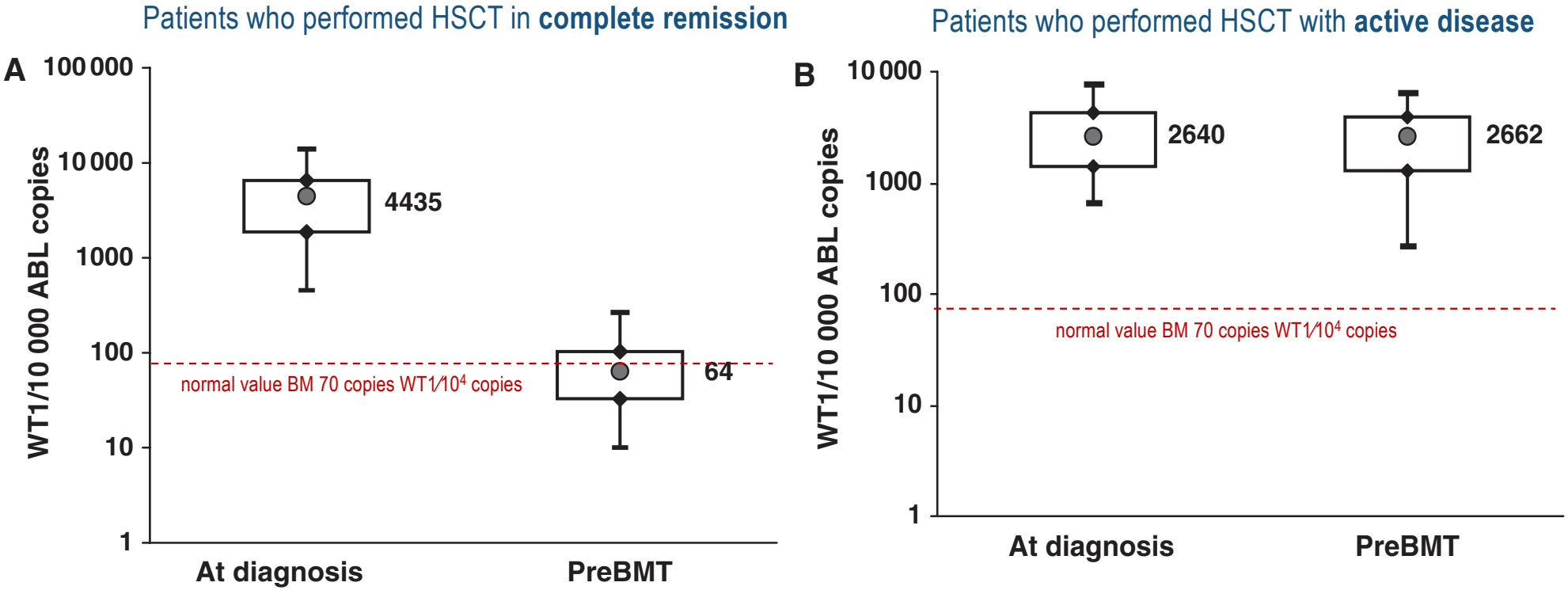
NPM1+ Pre and Post-Transplant Is the Most Important Factor for Relapse After Transplant





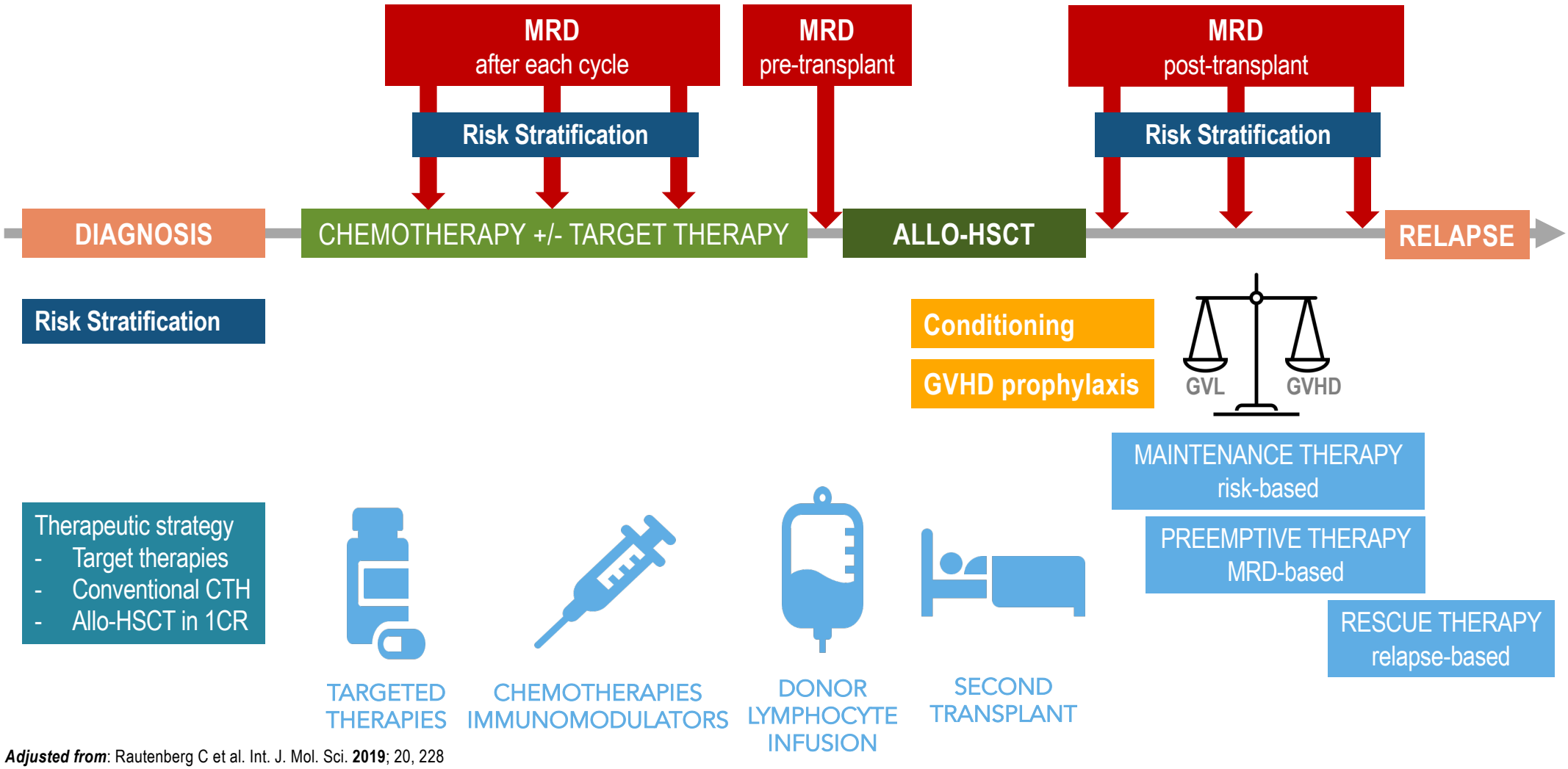
Zhou Y et al. Biol Blood Marrow Transplant. **2018**. 24, 1615–1620

WT1 Gene Expression After Transplant is for monitoring MDR in AML



Candoni A et al. Europ. J. Haematol. **2009**. 82, 61-68

Interventions in High-Risk Patients



Adjusted from: Rautenberg C et al. Int. J. Mol. Sci. **2019**; 20, 228

Strategy for Relapse Prevention

IMPROVED CONDITIONING REGIMENS
- Incorporating drugs with strong antileukemia activity

EARLY WITHDRAWAL OF IMMUNOSUPPRESSION
- High risk of GVHD may offset reduced relapse risk

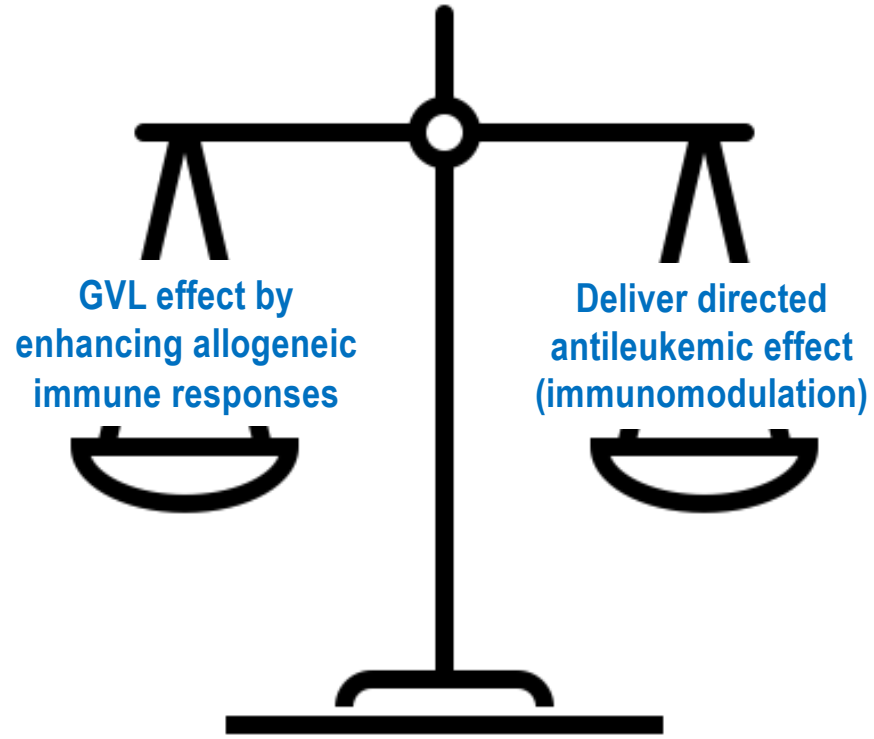
MAINTENANCE
- Relapse risk defined by pre-transplantation parameters
- Ideal maintenance agent:
  - Documented activity against the disease
  - Acceptable non-hematologic toxicity (will be tolerated early after transplant)
  - Acceptable myelotoxicity (will not interfere with engraftment)
  - Minimal drug interactions
  - Will not inhibit GVT
  - Will not worsen GVHD

PREEMPTIVE TREATMENT
- Monitoring for MRD
- Intervention based on detection of MRD

Prevention Approach

- ✓ To reduce the risk of relapse in HR patients
- ✓ Choose agents have proven efficacy in other settings
- ✓ Prospective Phase II and III clinical trials after transplant are limited:
  - competing risk (cytopenias, organ toxicity, infections, GVHD)
  - side effects (more difficult to predict in the post-transplant immunological environment)
  - difficult recruitment

Cellular-Based versus Drug-Based Strategies



Biol Blood Marrow Transplant 23 (2017) 938–944

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Allogeneic: Adult

Donor Lymphocyte Infusion for Relapsed Hematological Malignancies after Unrelated Allogeneic Bone Marrow Transplantation Facilitated by the Japan Marrow Donor Program

Toshihiro Miyamoto [1,*], Takahiro Fukuda [2], Marie Nakashima [3], Tomoko Henzan [4], Shinsuke Kusakabe [5], Naoki Kobayashi [6], Junichi Sugita [7], Takeshi Mori [8], Mineo Kurokawa [9], Shin-ichiro Mori [10] for the Medical Committee of Japan Marrow Donor Program, Japanese Data Center for Hematopoietic Cell Transplantation

Retrospective, Mixed Diseases, 414 patients

Outcome on 100 Days after UDLI

Disease Status at UDLI		Numbers of DLI*			Infused CD3+ Cells, $\times 10^7$/kg†			Response at 100 Days after DLI			
		1	2	≥3	First DLI	Second DLI	Total	CR	PR	NR	NE
Molecular/ cytogenetic relapse	65							37 (57%)	6 (9%)	16 (25%)	
DLI alone	40	25	7	8	1.0 (.03-15.6)	1.79 (.33-15.6)	2.54 (.05-24.8)	20 (50%)	3 (7%)	12 (30%)	5
Combination with UDLI	25	12	5	8	1.0 (.1-4.47)	1.72 (.5-6.0)	2.97 (.10-11.0)	17 (68%)	3 (12%)	4 (16%)	1
Hematological relapse	349							69 (20%)	28 (8%)	216 (62%)	
DLI alone	108	49	39	20	1.0 (.05-11.1)	2.31 (.05-11.0)	4.0 (.05-18.18)	22 (20%)	10 (9%)	66 (61%)	10
Combination with UDLI	241	133	65	43	1.0 (.04-17.0)	2.0 (.05-10.0)	3.74 (.1-43.03)	47 (20%)	18 (7%)	150 (62%)	26
Total	414	219 (54%)	116 (28%)	79 (19%)	1.0 (.03-17.0)	1.72 (.05-15.6)	3.51 (.05-43.03)	106 (26%)	34 (8%)	232 (56%)	42 (10%)

Multivariate Analysis of Risk Factors for Complete Response

Predictors	Multivariate HR (95% CI)	*P*
Patient age		
Sex mismatch		
Year of UD-BMT <2007 versus >2007		
Disease status at relapse	***.190 (.0934-.429)***	***<.001***
Molecular/cytogenetic versus hematological relapse		
Interval, BMT to relapse		
Interval, BMT to UDLI	.999 (.999-1.00)	.062
Acute GVHD after BMT		
Chronic GVHD after BMT		
Occurrence of GVHD after UDLI	***.543 (.319-.922)***	***.024***
Severity of GVHD after UDLI		
Grade I-II versus none	.527 (.236-1.180)	.118
Grade III-IV versus none		
DLI alone versus DLI + chemotherapy		
No. of the first infused CD3+ cells		
Total no. of infused CD3+ cells		
No. of UDLI infusions		
UDLI for CML versus other diseases	***4.980 (1.540-16.100)***	***.007***

GVHD after UDLI

GVHD*	n	Response after UDLI			
		CR	PR	NR	NE
None	276 (67%)	64 (23%)	16 (6%)	173 (63%)	23
Grade I	29 (7%)	8 (28%)	5 (17%)	13 (45%)	3
Grade II	41 (10%)	17 (41%)	4 (10%)	16 (39%)	4
Grade III	27 (6%)	8 (30%)	5 (18%)	12 (44%)	2
Grade IV	26 (6%)	9 (38%)	4 (15%)	9 (35%)	4
NE	15			9	6
Total	414	106 (26%)	34 (8%)	232 (56%)	42 (10%)

* Occurrence of GVHD was significantly associated with CR ($P = .017$).

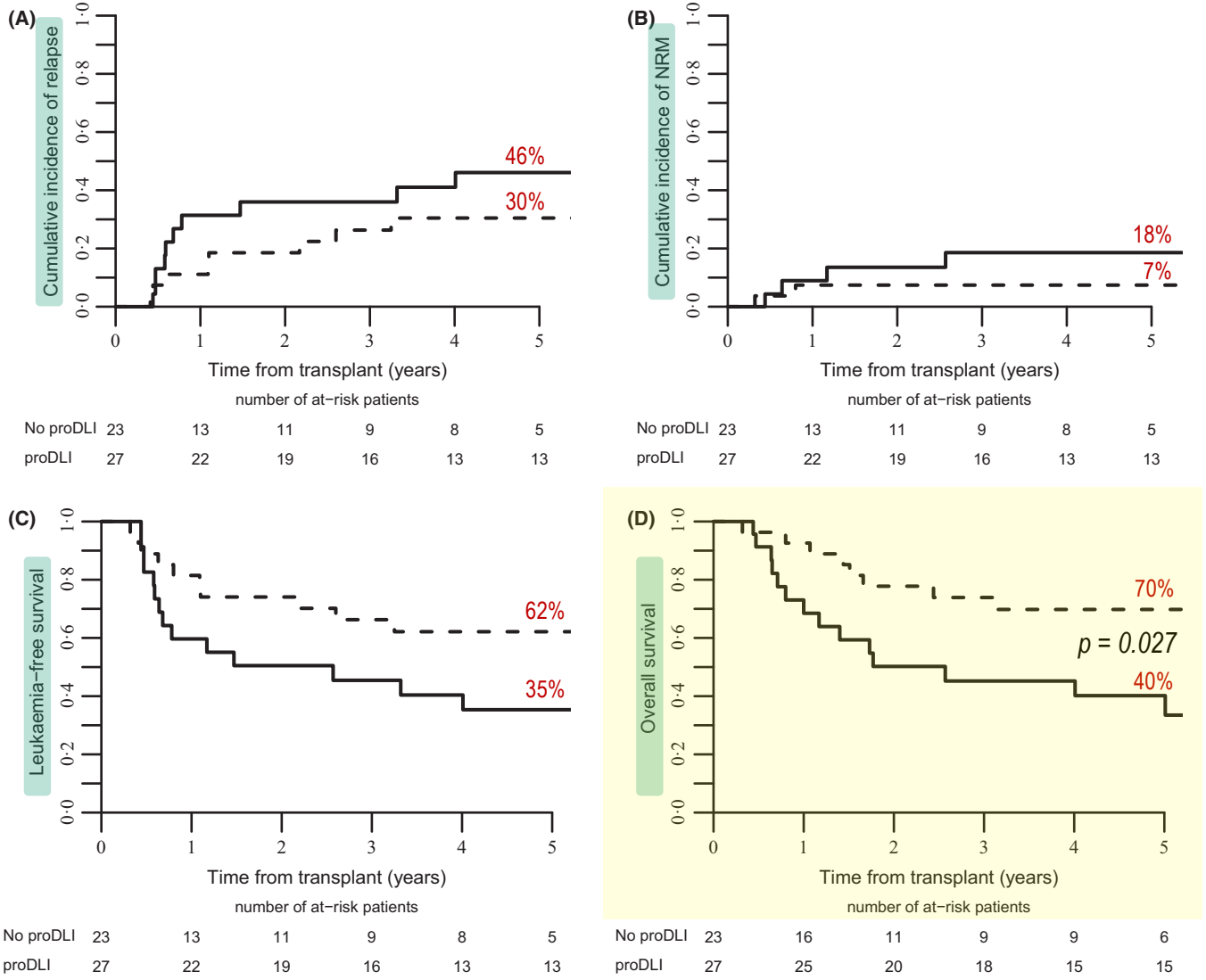
bjh short report

Prophylactic donor lymphocyte infusion after allogeneic stem cell transplantation in acute leukaemia – a matched pair analysis by the Acute Leukaemia Working Party of EBMT

Christoph Schmid,[1] Myriam Labopin,[2] Nicolaas Schaap,[3] Hendrik Veelken,[4] Michael Schleuning,[5] Michael Stadler,[6] Juergen Finke,[7] Erin Hurst,[8] Frederic Baron,[9] Olle Ringden,[10] Gesine Bug,[11] Didier Blaise,[12] Johanna Tischer,[13] Adrian Bloor,[14] Jordi Esteve,[15] Sebastian Giebel,[16] Bipin Savani,[17] Norbert-Claude Gorin,[18] Fabio Ciceri,[19] Mohamad Mohty,[20,*] Arnon Nagler[21,*] and on behalf of the EBMT Acute Leukaemia Working Party

British Journal of Haematology, 2019, **184,** 782–787

5-year Outcome in HR Patients



Median 2 infusions
3 x 10^6/kg within
1 year from HSCT

Cumulative Incidence

aGVHD III-IV°	4.5%
cGVHD	28%

Schmid C et al. *British Journal of Haematology*, **2019**, 184, 782–787

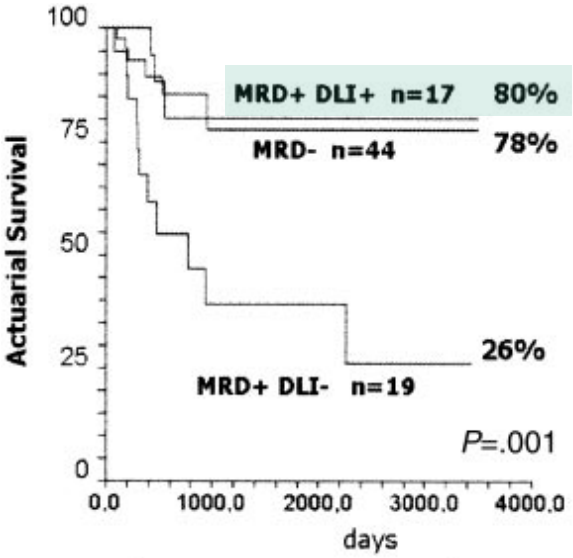
BLOOD, 1 JUNE 2007 • VOLUME 109, NUMBER 11

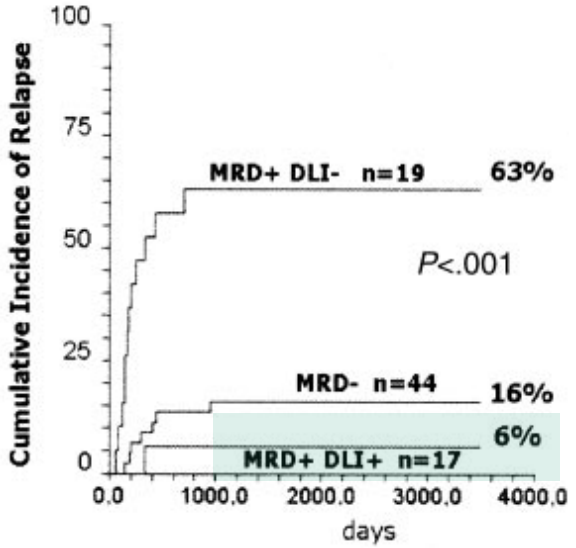
To the editor:

Donor lymphocyte infusions for the treatment of minimal residual disease in acute leukemia

Alida Dominietto, Sarah Pozzi, Maurizio Miglino, Flavio Albarracin, Giovanna Piaggio, Francesca Bertolotti, Raffaella Grasso, Simona Zupo, Anna Maria Raiola, Marco Gobbi, Francesco Frassoni, and Andrea Bacigalupo

80 patients
- 44 ALL — IgH VDJ-PCR, TCR-gene rearrangment
- 36 AML — WT1





Dominietto A et al. *Blood*, **2007**, 109, 5063-5064

VOLUME 31 · NUMBER 26 · SEPTEMBER 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Second Allograft for Hematologic Relapse of Acute Leukemia After First Allogeneic Stem-Cell Transplantation From Related and Unrelated Donors: The Role of Donor Change

Maximilian Christopeit, Oliver Kuss, Jürgen Finke, Ulrike Bacher, Dietrich Wilhelm Beelen, Martin Bornhäuser, Rainer Schwerdtfeger, Wolfgang Andreas Bethge, Nadezda Basara, Martin Gramatzki, Johanna Tischer, Hans-Jochem Kolb, Lutz Uharek, Ralf G. Meyer, Donald Bunjes, Christof Scheid, Hans Martin, Dietger Niederwieser, Nicolaus Kröger, Hartmut Bertz, Hubert Schrezenmeier, and Christoph Schmid

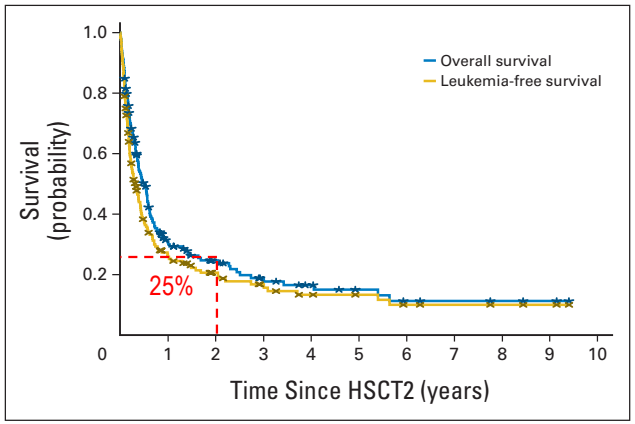


Fig 1. Probabilities of overall survival and leukemia-free survival for the entire cohort (N = 179) were 31% ± 4% and 26% ± 4%, respectively, at 1 year and 25% ± 4% and 21% ± 3%, respectively, at 2 years from second hematopoietic stem-cell transplantation (HSCT2).

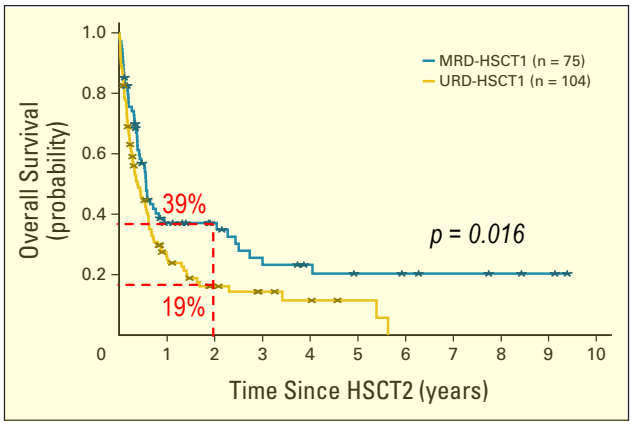


Fig 2. Overall survival from second hematopoietic stem-cell transplantation (HSCT2) in patients after first hematopoietic stem-cell transplantation (HSCT1) from matched related donor (MRD) and from unrelated donor (URD; hazard ratio, 1.53; 95% CI, 1.08 to 2.18; *P* = .016).

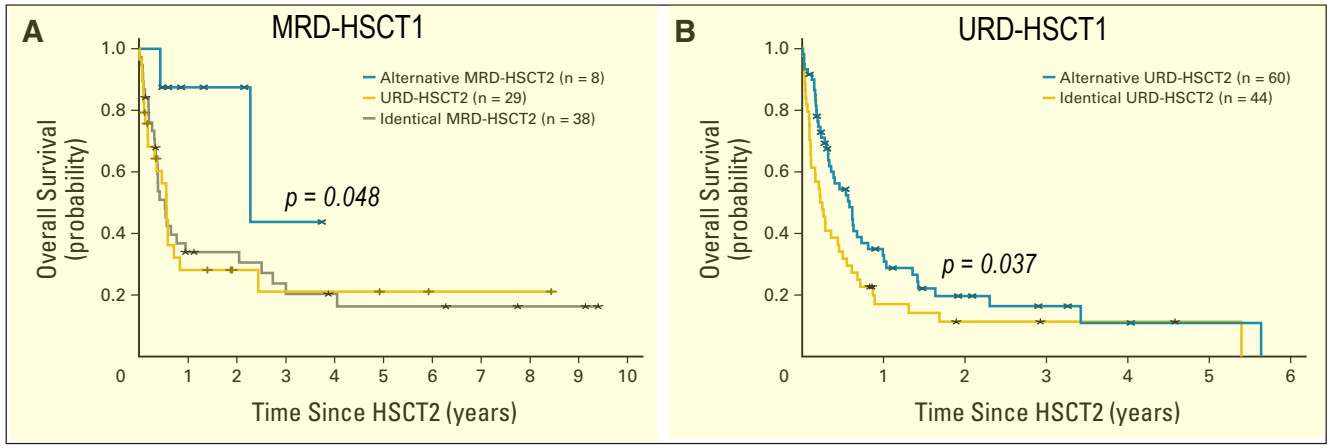
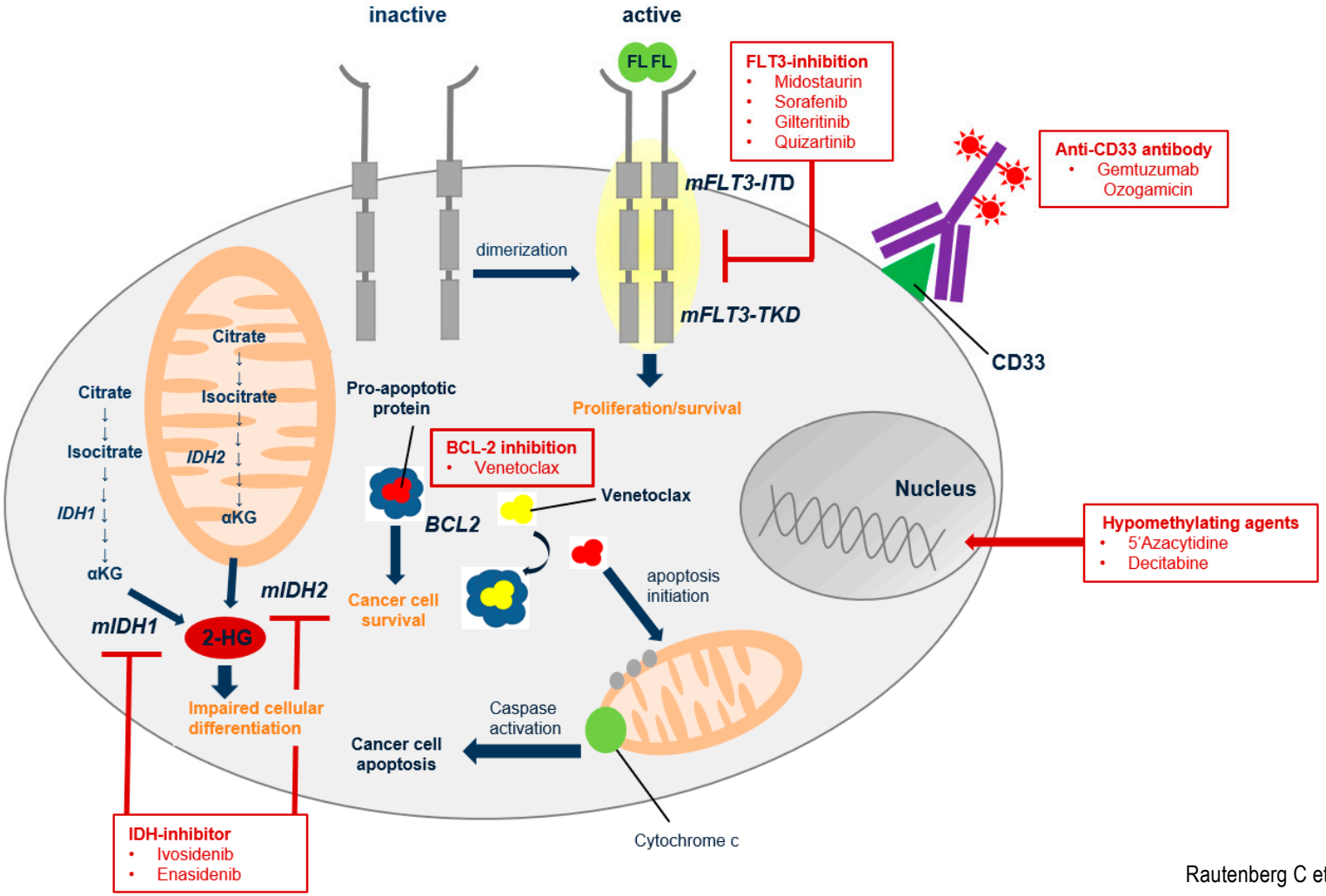


Fig 3. The role of donor at second hematopoietic stem-cell transplantation (HSCT2) was analyzed separately in cohorts with relapsed acute leukemia after related and unrelated first allogeneic hematopoietic stem-cell transplantation (HSCT1). (A) After related HSCT1 (n = 75), identical outcome was observed after using the same matched related donor (MRD) or changing to an unrelated donor (URD) for HSCT2 (hazard ratio [HR], 1.02; 95% CI, 0.77 to 1.36; *P* = .891). In contrast, overall survival (OS) was superior in eight patients receiving HSCT2 from another MRD (HR, 4.17; 95% CI, 1.01 to 17.18; *P* = .048). (B) After relapse from an unrelated HSCT1 (n = 104), change to another URD resulted in improved OS from HSCT2 compared with HSCT2 from the same URD (HR, 0.63; 95% CI, 0.41 to 0.97; *P* = .037).

Drug-Based Therapies

- ✓ DLI, second HSCT and chemotherapy achieve long-term outcomes in only 5% of cases
- ✓ The best therapeutic potency is applied in the context of CR after transplant: MAINTENANCE
- ✓ The optimal duration of maintenance therapies is unclear:
  - 12 months
  - 24 months
- ✓ Are targeted maintenance therapies applied to all novel agents approved in AML (FLT3-inhibitors, BCL-2 inhibitor, IDH1/2 inhibitor)?

Targeted-Therapy Based Strategies



Rautenberg C et al. Int. J. Mol. Sci. 2019; 20, 228

Original Article

Maintenance Therapy With Low-Dose Azacitidine After Allogeneic Hematopoietic Stem Cell Transplantation for Recurrent Acute Myelogenous Leukemia or Myelodysplastic Syndrome

A Dose and Schedule Finding Study

Marcos de Lima, MD[1]; Sergio Giralt, MD[1]; Peter F. Thall, PhD[2]; Leandro de Padua Silva, MD[1]; Roy B. Jones, MD[1]; Krishna Komanduri, MD[3]; Thomas M. Braun, PhD[4]; Hoang Q. Nguyen, PhD[2]; Richard Champlin, MD[1]; and Guillermo Garcia-Manero, MD[5]

Cancer 2010;116:5420–31

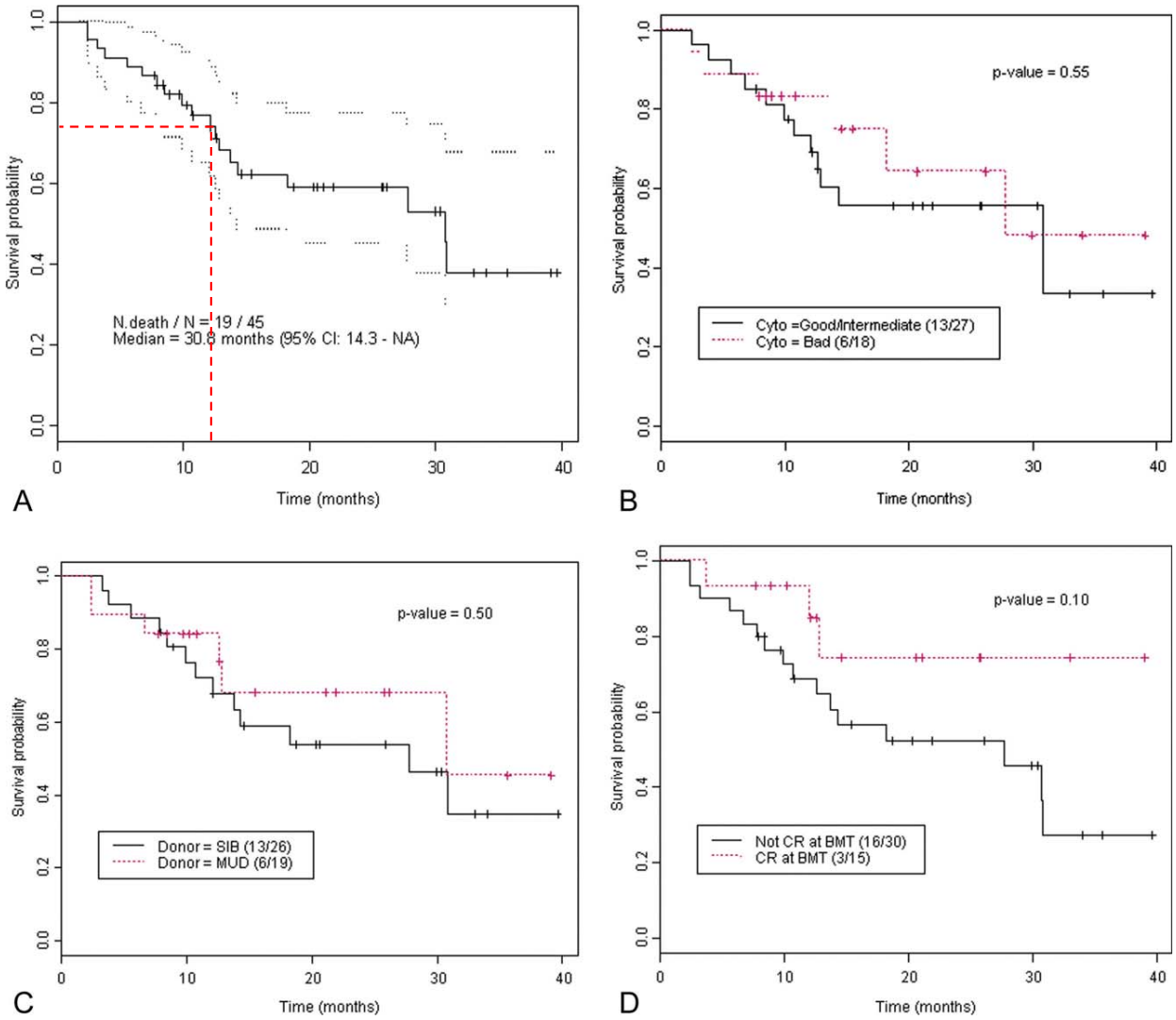


Figure 1. Kaplan-Meier estimates of overall survival (n = 45) are shown for (A) all patients, (B) patients by cytogenetics risk group, (C) patients by donor type, and (D) patients by remission status at the time of transplantation. There was no significant difference noted among the subgroups for any of the 3 variables (log-rank *P* values of .55, .50, and .10, respectively). CI indicates confidence interval; NA, not available; Cyto, cytogenetics; SIB, sibling; MUD, matched unrelated donor; CR, complete remission; BMT, bone marrow transplantation.

32 mg/mq for 5 days
(25 days rest) for 4 cycles

aGVHD
II° 27%
III° 9%
cGVHD 37%
Thrombocytopenia I-III° 20%
Neutropenia I-II° 15%

De Lima M et al. *Cancer*, 2010, 116, 5420-5431

10 NOVEMBER 2020 • VOLUME 4, NUMBER 21

REGULAR ARTICLE

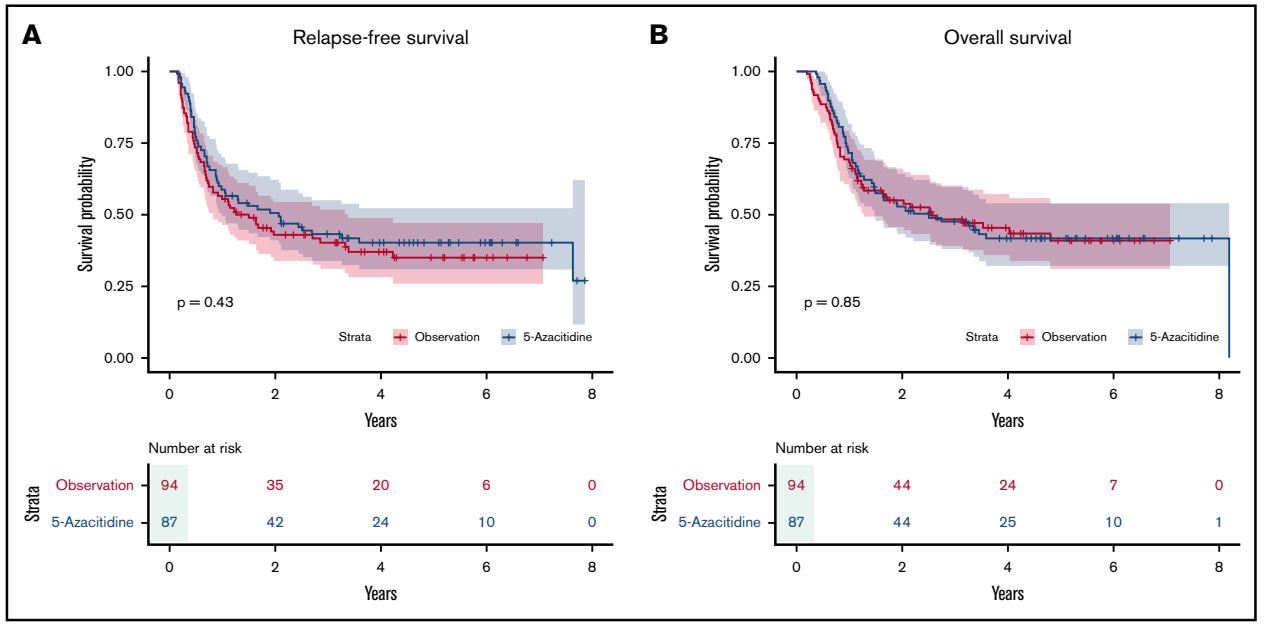
blood advances

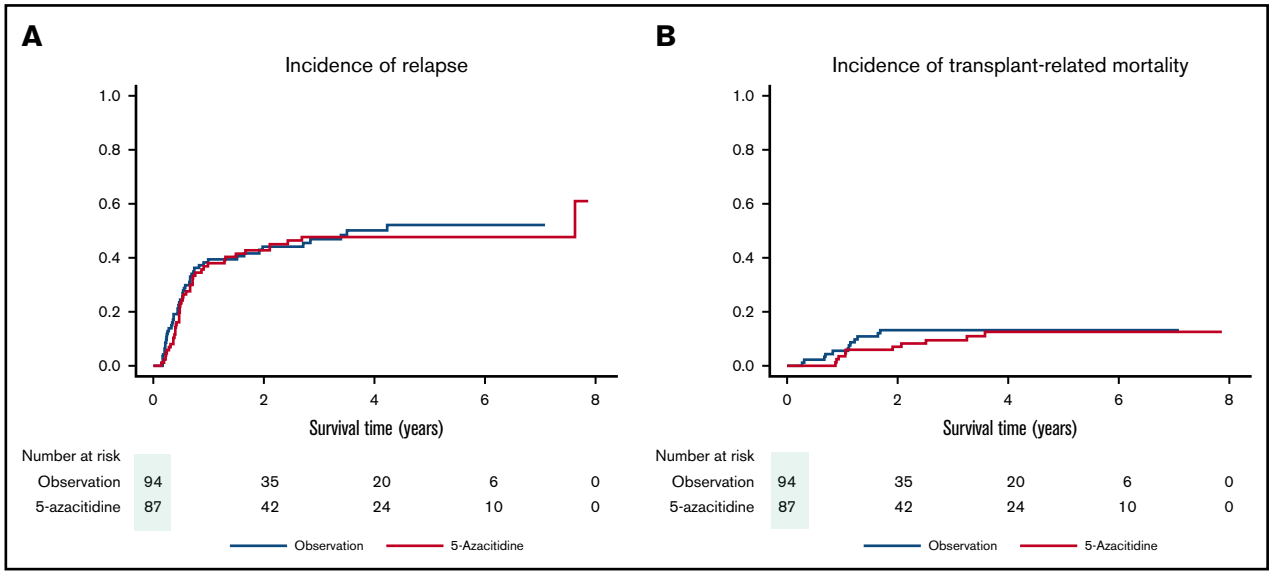
A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients

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

32 mg/mq for 5 days every 28 days for 12 cycles





Oran B et al. *Blood Adv*, 2020, 4, 5580-5588

Table 4. Summary of grade 3, 4, and 5 AEs

	Azacitidine arm*		Observation arm	
AE	**Any grade (no. of events), n = 302**	**Grade 3-5 (no. of events)†**	**Any grade (no. of events, n = 215**	**Grade 3-5 (no. of events)**
Hematologic	143	58	5	5
Thrombocytopenia	119	29	1	1
Poor graft function	33	29	2	2
Nonhematologic	159	33	210	56
Infection	42	13	52	19
Gastrointestinal	41	0	44	12
Hepatic	17	9	19	5
Pulmonary	7	4	8	6
Skin	27	2	32	5

GVHD	Azacitidine arm	Observation arm
Acute (+100) II-IV°	25.5%	29%
Acute (+100) III-IV°	4%	2%
Chronic (1-year incidence)	26%	31%

Biol Blood Marrow Transplant 24 (2018) 2017–2024

Biology of Blood and Marrow Transplantation

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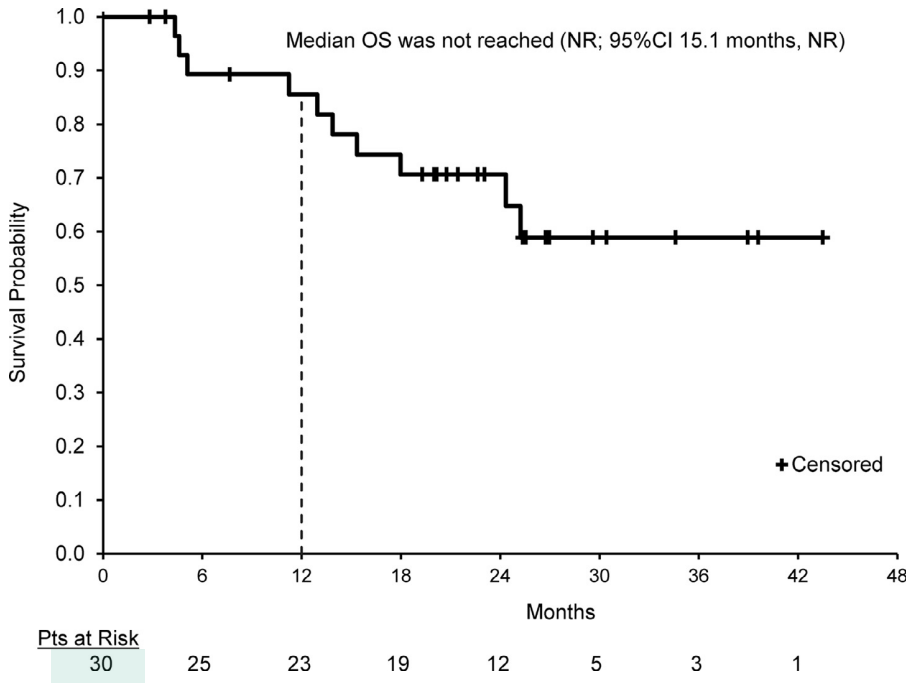
CC-486 Maintenance after Stem Cell Transplantation in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndromes

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]

Phase I/II Dose-Finding - Prospectic Study

200 mg/day for 14 days

(28-day cycle) max 12 cycles



Most Common (≥5% of All Patients) Grades 3-4

AE	Total (N = 30)
Patients with ≥1 grade 3-4 TEAE	22 (73)
Hematologic	
Lymphopenia	6 (20)
Neutropenia	5 (17)
Anemia	4 (13)
Thrombocytopenia	3 (10)
gastrointestinal	
Diarrhea	6 (20)
Vomiting	5 (17)
Nausea	4 (13)
GI GVHD*	3 (10)
Abdominal pain	2 (7)
Other	
Device-related infection	2 (7)
Dehydration	2 (7)
Pneumonia	2 (7)

Severe Chronic GVHD 10%

De Lima M et al. Biol Blood Marrow Transplant, 2018, 24, 2017-2024 (ClinicalTrials.gov NCT01835587)

Biol Blood Marrow Transplant 21 (2015) 653–660

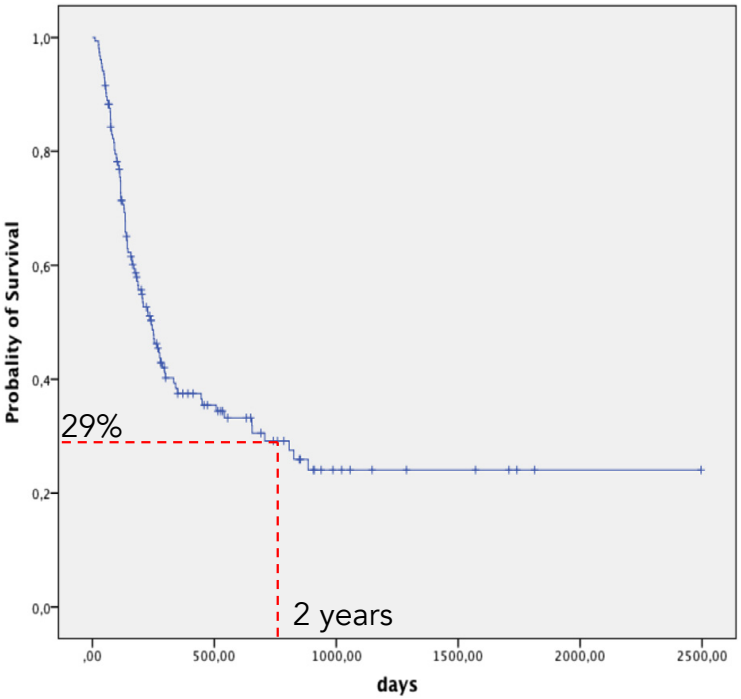
Biology of Blood and Marrow Transplantation

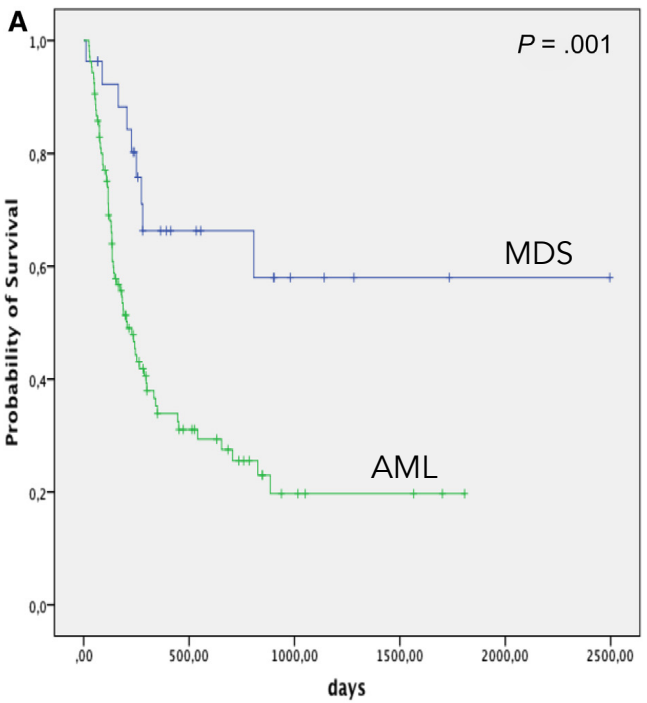
journal homepage: www.bbmt.org

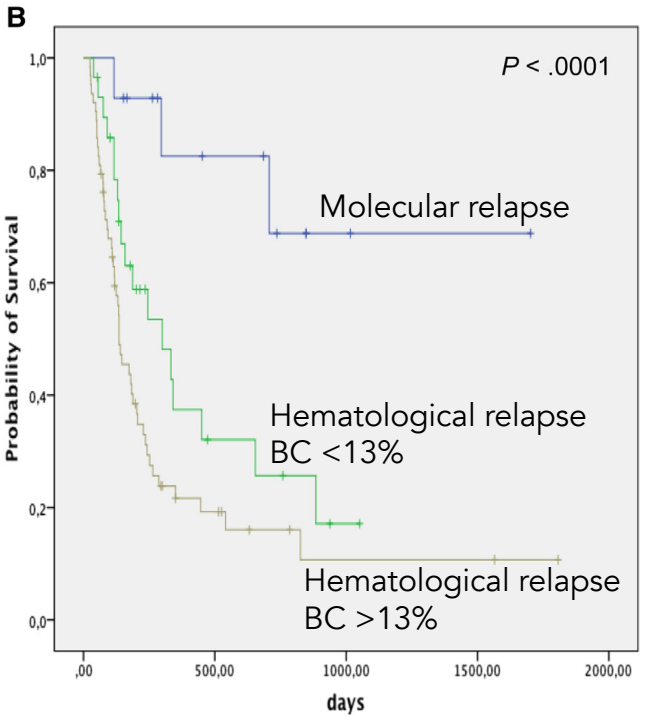
Treatment of Acute Myeloid Leukemia or Myelodysplastic Syndrome Relapse after Allogeneic Stem Cell Transplantation with Azacitidine and Donor Lymphocyte Infusions—A Retrospective Multicenter Analysis from the German Cooperative Transplant Study Group

Thomas Schroeder [1,*], Elena Rachlis [1], Gesine Bug [2], Matthias Stelljes [3], Stefan Klein [4], Nina Kristin Steckel [5], Dominik Wolf [6], Mark Ringhoffer [7], Akos Czibere [1], Kathrin Nachtkamp [1], Ariane Dienst [1], Mustafa Kondakci [1], Michael Stadler [8], Uwe Platzbecker [9], Lutz Uharek [10], Thomas Luft [11], Roland Fenk [1], Ulrich Germing [1], Martin Bornhäuser [9], Nicolaus Kröger [12], Dietrich W. Beelen [5], Rainer Haas [1], Guido Kobbe [1]

Overall survival after treatment with Aza and DLI in 154 patients







aGVHD 23% (1/3 III-IV°)
cGVHD 27% (majority limited)

Schroeder T et al. *Biol Blood Marrow Transplant*. 2015. 21, 653e660

First-Generation FLT3 Inhibitors

Drug	No.	Schedule	Strategy	Endpoint	Main results	References
SORAFENIB	22	28-day cycles 400mgx2 for 12 cycles from d45-d120	maintenance	Tollerability and feasibility	1-year PFS 85% 2-year DFS 58% 1-year OS 95%	*Chen YB*, Phase I, **2014**
	26	28-day cycles 400mgx2 or 200mgx2 for 12 cycles from d45-d120	maintenance	Primary End Point RFS Secondary End Point OS	2-year PFS 82% vs 53% 2-year OS 81% vs 61%	*Battipaglia G*, retrospective, randomized **2017**
	44	28-day cycles 200mgx2→400mgx2 (24 months) from d30-d120	maintenance	Primary End Point individualize sorafenib dose	2-year OS 76%, 2-year EFS 74% 3-year OS 76%, 3-year EFS 64% 4-year OS 57%, 4-year EFS 64%	Pratz KW, Prospectic **2020**
	202	28-day cycles 400mgx2 until +180 from d30-d60	maintenance	Primary End Point RFS Secondary End Point OS	1-year RFS 7 vs 24.5% 2-year RFS 13 vs 31% OS better	*Xuan L*, Phase III, prospective, randomised, double-blind, **2020**
	83	28-day cycles 400mgx2 for 24 months from d60-d100	maintenance	Primary End Point RFS Secondary End Point OS	Reduction relapse and death risk	*Burchert A*, **SORMAIN trial**, Phase II, prospective, randomised, open-label **2020**
MIDOSTAURIN	75	28-day cycles 50mgx2 for 9-10 months from d31-d100	maintenance	Primary End Point EFS Secondary End Point OS	2-year EFS 37.7% 2-year OS 51%	*Shlenk RF*, Phase II, prospectic, multicentric **2019**
	60	28-day cycles 50mgx2 for 12 months from d28-d60	maintenance	Primary End Point RFS Secondary End Point OS	No benefit	*Maziarz RT*, RADIUS trial, Phase II, prospective, randomised, open-label **2021**

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Pratz KW et al. *Biol. Blood Marrow Transplant.* ***2020*** 26, 300–306
Xuan L, et al *Lancet Oncol.* ***2020***;21(9):1201- 1212
Burchert A, et al. *J Clin Oncol.* **2020**;38(26):2993-3002
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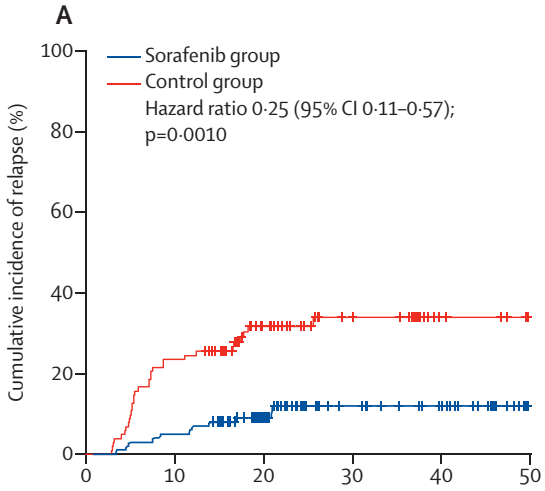
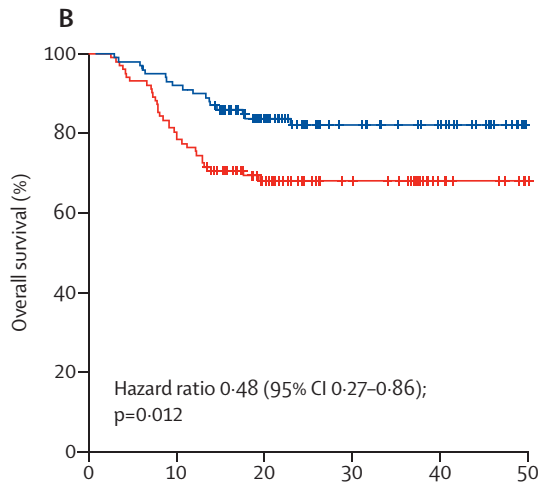
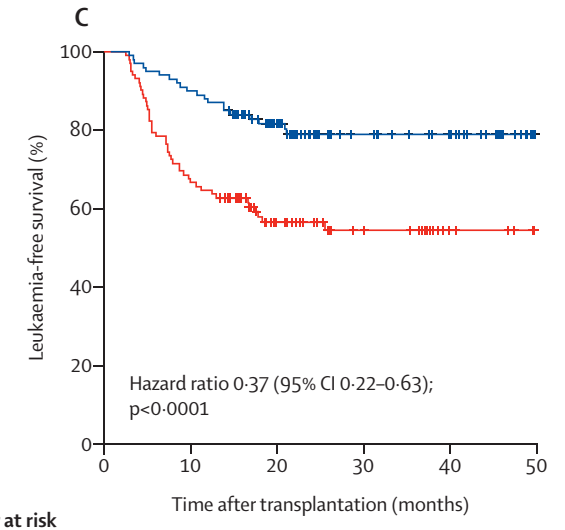
Maziarz, RT et al. *Bone Marrow Transplant.* **2021**, 1180–1189



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 (number 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)



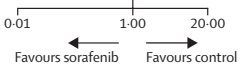
Number at risk (number censored)						
Sorafenib group	100 (0)	90 (0)	62 (20)	33 (47)	23 (57)	0 (80)
Control group	102 (0)	68 (0)	37 (22)	21 (37)	6 (52)	0 (58)

Table 3: Adverse events irrespective of causality

	Sorafenib group (n=100)			Control group (n=102)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Haematological*	..	12 (12%)	3 (3%)	..	5 (5%)	2 (2%)
Platelets decreased	..	10 (10%)	3 (3%)	..	4 (4%)	2 (2%)
Neutrophils decreased	..	7 (7%)	2 (2%)	..	3 (3%)	1 (1%)
Skin†	20 (20%)	6 (6%)	1 (1%)	9 (9%)	1 (1%)	0
Gastrointestinal†	25 (25%)	11 (11%)	0	20 (20%)	8 (8%)	0
Hepatobiliary or pancreatic†	16 (16%)	5 (5%)	0	17 (17%)	6 (6%)	0
Cardiac	14 (14%)	0	0	12 (12%)	1 (1%)	0
Renal or genitourinary	23 (23%)	4 (4%)	0	25 (25%)	5 (5%)	0
Vascular	6 (6%)	1 (1%)	0	5 (5%)	1 (1%)	0
Infections‡	8 (8%)	21 (21%)	4 (4%)	9 (9%)	19 (19%)	5 (5%)
Acute GVHD	8 (8%)	18 (18%)	5 (5%)	6 (6%)	15 (15%)	6 (6%)
Chronic GVHD§	5 (5%)	15 (15%)	3 (3%)	5 (5%)	13 (13%)	4 (4%)
Secondary malignant disease¶	..	0	2 (2%)	..	0	2 (2%)

Xuan, L. et al. Lancet Oncol. 21, 1201–1212 (**2020**)

	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)
Gender					
Male	7/50	16/52	15·0% (6·4–27·0)	30·1% (17·8–43·4)	0·35 (0·15–0·86)
Female	4/50	16/50	8·8% (2·7–19·6)	33·2% (20·2–46·7)	0·21 (0·07–0·62)
Patient age, years*					
≥35	4/50	18/49	8·0% (2·5–17·7)	38·7% (24·4–52·7)	0·17 (0·06–0·50)
<35	7/50	14/53	16·1% (6·8–28·9)	25·1% (14·2–37·7)	0·45 (0·18–1·11)
White blood cell count at diagnosis*					
≥64×10^9 per L	5/46	16/55	11·2% (4·0–22·5)	30·0% (18·2–42·7)	0·31 (0·11–0·85)
<64×10^9 per L	6/54	16/47	13·1% (5·1–25·0)	33·9% (20·1–48·2)	0·26 (0·10–0·66)
Cytogenetic risk					
Low	0/6	0/4	0·0% (0·0–0·0)	0·0% (0·0–0·0)	NA
Intermediate	8/80	27/85	11·1% (5·0–19·7)	31·5% (21·7–41·8)	0·26 (0·12–0·57)
High	1/7	1/5	14·3% (0·5–49·6)	26·7% (0·2–75·1)	0·71 (0·04–11·32)
Unknown	2/7	4/8	28·6% (2·9–64·1)	50·0% (12·5–79·4)	0·54 (0·10–2·96)
***NPM1* mutation**					
Without	7/71	22/76	10·6% (4·6–19·6)	28·6% (18·7–39·4)	0·28 (0·12–0·66)
Concomitant	4/29	10/26	15·1% (4·5–31·7)	41·3% (20·4–61·2)	0·26 (0·08–0·84)
Sorafenib pretransplantation					
No use	6/41	19/45	15·3% (6·1–28·4)	43·9% (28·4–58·2)	0·23 (0·09–0·59)
Use	5/59	13/57	9·5% (3·3–19·6)	21·7% (11·8–33·5)	0·34 (0·12–0·96)
Disease status at transplantation					
CR1	8/79	20/84	11·5% (5·2–20·4)	24·0% (15·1–34·0)	0·35 (0·15–0·80)
≥CR2	3/21	12/18	14·3% (3·4–32·7)	66·7% (38·5–84·2)	0·13 (0·04–0·48)
CRc status at transplantation					
CRp or CRi	4/27	11/23	15·2% (4·6–31·5)	47·8% (26·2–66·6)	0·23 (0·07–0·74)
CR	7/73	21/79	10·8% (4·6–20·0)	26·7% (17·1–37·3)	0·29 (0·12–0·69)
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)
Transplant modality					
MSD	2/44	13/39	5·6% (0·9–17·1)	31·0% (17·2–45·9)	0·11 (0·03–0·50)
MUD	1/8	1/6	12·5% (0·5–44·8)	16·7% (0·5–54·9)	0·66 (0·04–10·53)
HID	8/48	18/57	17·5% (8·0–30·0)	33·6% (21·1–46·6)	0·42 (0·18–0·96)
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)
Acute GVHD					
No	4/56	23/60	7·3% (2·3–16·2)	37·7% (25·1–50·1)	0·14 (0·05–0·41)
Yes	7/44	9/42	17·7% (7·5–31·5)	23·0% (11·1–37·4)	0·65 (0·24–1·76)
Chronic GVHD†					
No	8/52	20/54	16·9% (7·6–29·3)	35·1% (21·9–48·5)	0·35 (0·15–0·77)
Yes	3/47	12/45	6·8% (1·7–17·0)	27·3% (15·0–41·1)	0·21 (0·06–0·74)
All patients	**11/100**	**32/102**	**11·9% (6·2–19·6)**	**31·6% (22·6–41·1)**	**0·29 (0·15–0·58)**



Xuan, L. et al. Lancet Oncol. 21, 1201–1212 (**2020**)

First-Generation FLT3 Inhibitors

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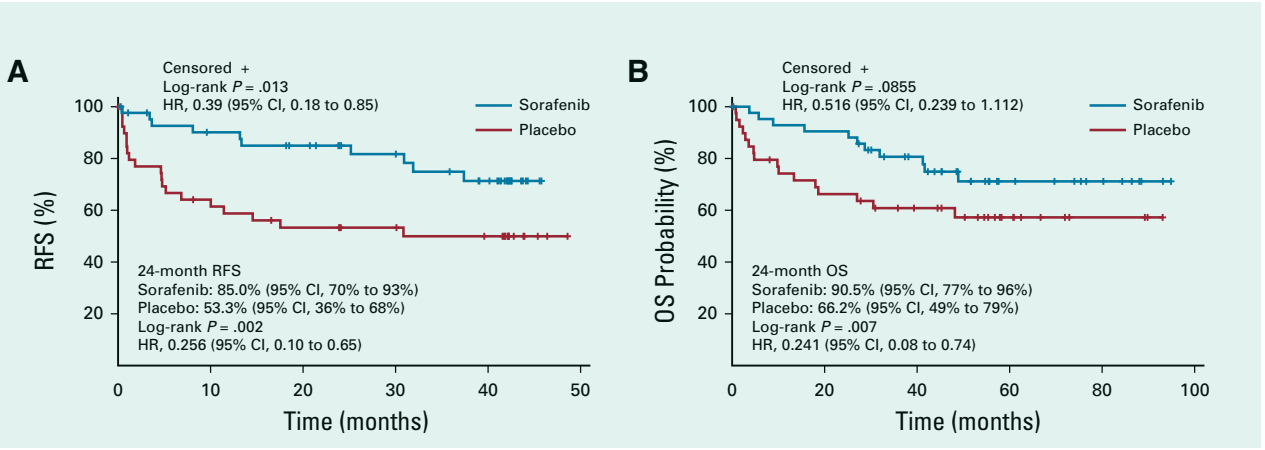
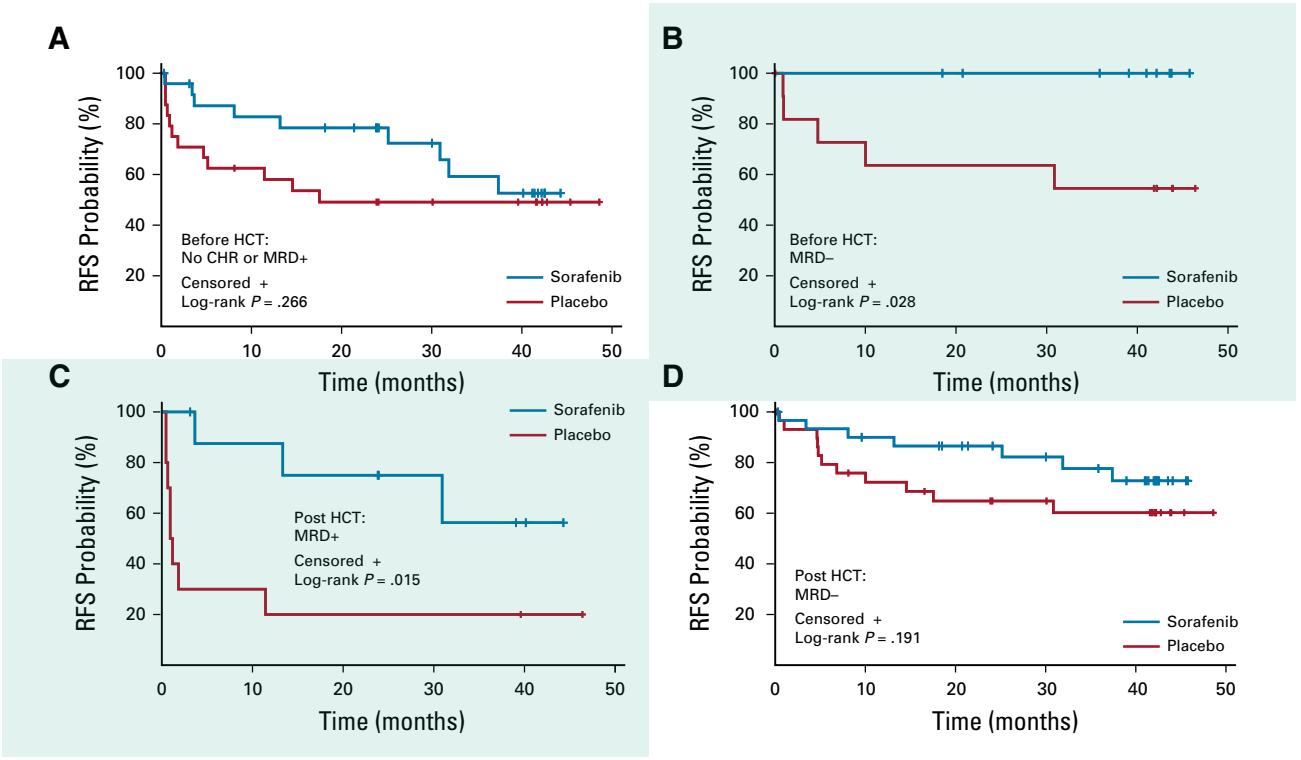


83 patients

- 43 sorafenib
- 40 placebo



Burchert A, et al. *J Clin Oncol*. **2020**;38(26):2993-3002

TABLE 3. Incidence of AE (safety population)

	Sorafenib (n = 42[a])		Placebo (n = 39[a])	
Grade 3 and 4 AE Type	**All**	**Drug Related**	**All**	**Drug Related**
Neutropenia	1 (2.4)	1 (2.4)	1 (2.6)	1 (2.6)
Thrombocytopenia	2 (4.8)	0	1 (2.6)	0
Liver toxicity: ALT, AST increased	2 (4.8)	0	2 (5.1)	2 (5.1)
GI toxicity (vomiting, nausea, diarrhea)	6 (14.3)	2 (4.8)	6 (15.4)	3 (7.7)
Skin toxicity	5 (11.9)	2 (4.8)	1 (2.6)	1 (2.6)
Infections	11 (26.2)	1 (2.4)	9 (23.1)	2 (5.1)
Overall GvHD rate	32 (76.8)	—	23 (59.8)	—
aGvHD (grade ≥ 2)	10 (24)		7 (18.2)	
cGvHD (mild/moderate)	18 (42.9)	—	14 (35.9)	—
cGvHD (severe)	8 (19.2)	—	4 (10.4)	—
Cardiotoxicity and renal insufficiency	4 (9.5)	1 (2.4)	1 (2.6)	0
Electrolyte alterations	6 (14.3)	3 (7.1)	1 (2.6)	0
Other	33 (78.6)	8 (19.1)	22 (56.4)	4 (10.3)

First Generation FLT3 Inhibitors

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Schlenk, R.F et al. *Blood* **2019**; 133, 840–851
Maziarz, RT et al. *Bone Marrow Transplant.* **2021**, 1180–1189

Table 4. Toxicities grade 3 or above, according to MedRA category coding occurring at least once during maintenance therapy

	All patients (n = 97), n (%)	After alloHCT (n = 75), n (%)	After HiDAC (n = 22), n (%)	*P*
Gastrointestinal	68 (70)	60 (80)	8 (36)	.0001
Infection Febrile neutropenia	49 (51) 14 (14)	42 (56) 10 (13)	7 (32) 4 (18)	.06 .73
Blood/marrow	46 (47)	39 (52)	1 (5)	<.0001
Pain	37 (38)	34 (45)	3 (14)	<.0001
Constitutional	35 (36)	29 (39)	6 (27)	.45
Allergy/immunology	33 (34)	32 (43)	1 (5)	.006
Metabolic/laboratory	37 (38)	35 (47)	2 (9)	.15
Dermatological	29 (30)	27 (36)	2 (9)	.02
Neurologic	24 (25)	20 (27)	4 (18)	.58
Renal/genitourinary	23 (24)	23 (31)		.001
Pulmonary/upper respiratory	16 (16)	15 (20)	1 (5)	.11
Musculoskeletal/soft tissue	13 (13)	11 (15)	2 (9)	.73
Ocular/visual	13 (13)	12 (16)	1 (5)	.29
Cardiac general	13 (13)	11 (15)	2 (9)	.72
Hemorrhage/bleeding	7 (7)	7 (9)		.34
Auditory/ear	7 (7)	7 (9)		.34
Cardiac arrhythmia	5 (5)	2 (3)	3 (14)	.07
Hepatobiliary/pancreas	4 (4)	4 (5)		.57
Secondary malignancy	2 (2)	2 (3)		.99
Other	18 (19)	16 (21)	2 (9)	.35

Schlenk, R. F. et al. Blood 133, 840–851 (2019)

First Generation FLT3 Inhibitors

Drug	No.	Schedule	Strategy	Endpoint	Main results	References
SORAFENIB	22	28-day cycles 400mgx2 for 12 cycles from d45-d120	maintenance	Tollerability and feasibility	1-year PFS 85% 2-year DFS 58% 1-year OS 95%	*Chen YB*, Phase I, **2014**
	26	28-day cycles 400mgx2 or 200mgx2 for 12 cycles from d45-d120	maintenance	Primary End Point RFS Secondary End Point OS	2-year PFS 82% vs 53% 2-year OS 81% vs 61%	*Battipaglia G*, retrospective, randomized **2017**
	44	28-day cycles 200mgx2→400mgx2 (24 months) from d30-d120	maintenance	Primary End Point individualize sorafenib dose	2-year OS 76%, 2-year EFS 74% 3-year OS 76%, 3-year EFS 64% 4-year OS 57%, 4-year EFS 64%	Pratz KW, Prospectic **2020**
	202	28-day cycles 400mgx2 until +180 from d30-d60	maintenance	Primary End Point RFS Secondary End Point OS	1-year RFS 7 vs 24.5% 2-year RFS 13 vs 31% OS better	*Xuan L*, Phase III, prospective, randomised, double-blind, **2020**
	83	28-day cycles 400mgx2 for 24 months from d60-d100	maintenance	Primary End Point RFS Secondary End Point OS	Reduction relapse and death risk	*Burchert A*, **SORMAIN trial**, Phase II, prospective, randomised, open-label **2020**
MIDOSTAURIN	75	28-day cycles 50mgx2 for 9-10 months from d31-d100	maintenance	Primary End Point EFS Secondary End Point OS	2-year EFS 37.7% 2-year OS 51%	*Shlenk RF*, Phase II, prospectic, multicentric **2019**
	60	28-day cycles 50mgx2 for 12 months from d28-d60	maintenance	Primary End Point RFS Secondary End Point OS	No benefit	*Maziarz RT*, RADIUS trial, Phase II, prospective, randomised, open-label **2021**

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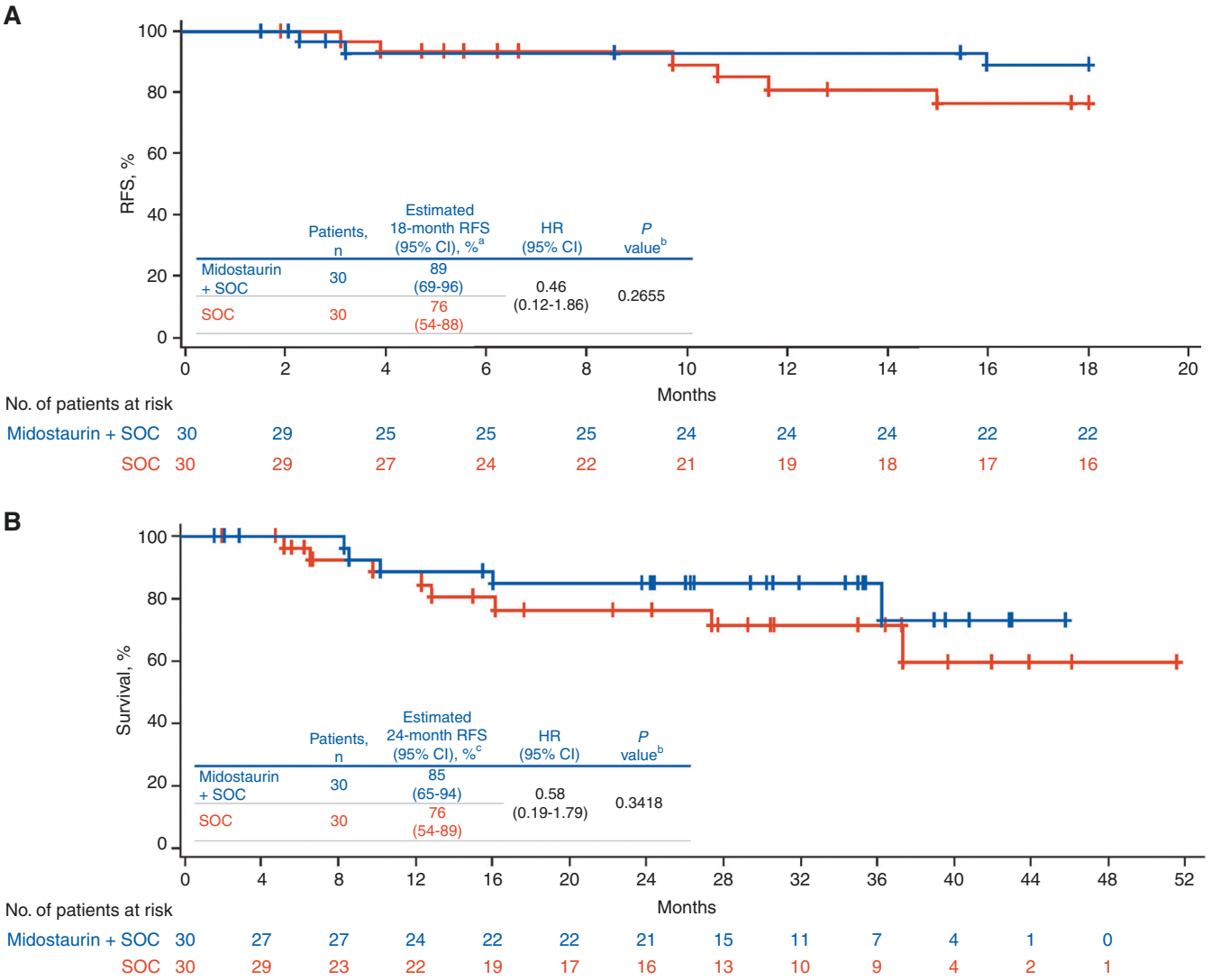

A
100
80
60
40
20
0
RFS, %
Patients, n
Estimated 18-month RFS (95% CI), %[a]
HR (95% CI)
P value[b]
Midostaurin + SOC
30
89 (69-96)
0.46 (0.12-1.86)
0.2655
SOC
30
76 (54-88)
0
2
4
6
8
10
12
14
16
18
20
Months
No. of patients at risk
Midostaurin + SOC 30 29 25 25 25 24 24 24 22 22
SOC 30 29 27 24 22 21 19 18 17 16
B
100
80
60
40
20
0
Survival, %
Patients, n
Estimated 24-month RFS (95% CI), %[c]
HR (95% CI)
P value[b]
Midostaurin + SOC
30
85 (65-94)
0.58 (0.19-1.79)
0.3418
SOC
30
76 (54-89)
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Months
No. of patients at risk
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

Table 2 Most common AEs (occurring in ≥15% of patients).

AE, *n* (%)	Midostaurin + SOC ($n = 30$)		SOC ($n = 30$)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Vomiting	7 (23)	1 (3)	22 (73)	2 (7)
Nausea	8 (27)	3 (10)	20 (67)	1 (3)
Diarrhea	7 (23)	1 (3)	12 (40)	3 (10)
Fatigue	9 (30)	0	8 (27)	1 (3)
Peripheral edema	9 (30)	0	8 (27)	0
Headache	7 (23)	0	8 (27)	0
Cough	6 (20)	0	8 (27)	0
ALT increased	7 (23)	4 (13)	6 (20)	3 (10)
Anemia	6 (20)	2 (7)	7 (23)	3 (10)
AST increased	8 (27)	4 (13)	5 (17)	2 (7)
Pruritus	6 (20)	0	7 (23)	3 (10)
Dry eye	6 (20)	0	5 (17)	0
Pyrexia	5 (17)	1 (3)	4 (20)	0
Rash	6 (20)	0	6 (17)	0
Tremor	4 (13)	0	7 (23)	0
Dyspnea	7 (23)	1 (3)	3 (10)	0
Insomnia	6 (20)	0	4 (13)	0
Neutrophil count decreased	3 (10)	2 (7)	7 (23)	4 (13)
Arthralgia	6 (20)	1 (3)	3 (10)	0
Dizziness	6 (20)	0	3 (10)	0
Hypertension	6 (20)	4 (13)	3 (10)	0
Upper respiratory tract infection	6 (20)	0	3 (10)	0

Table 4 Incidence of GVHD.

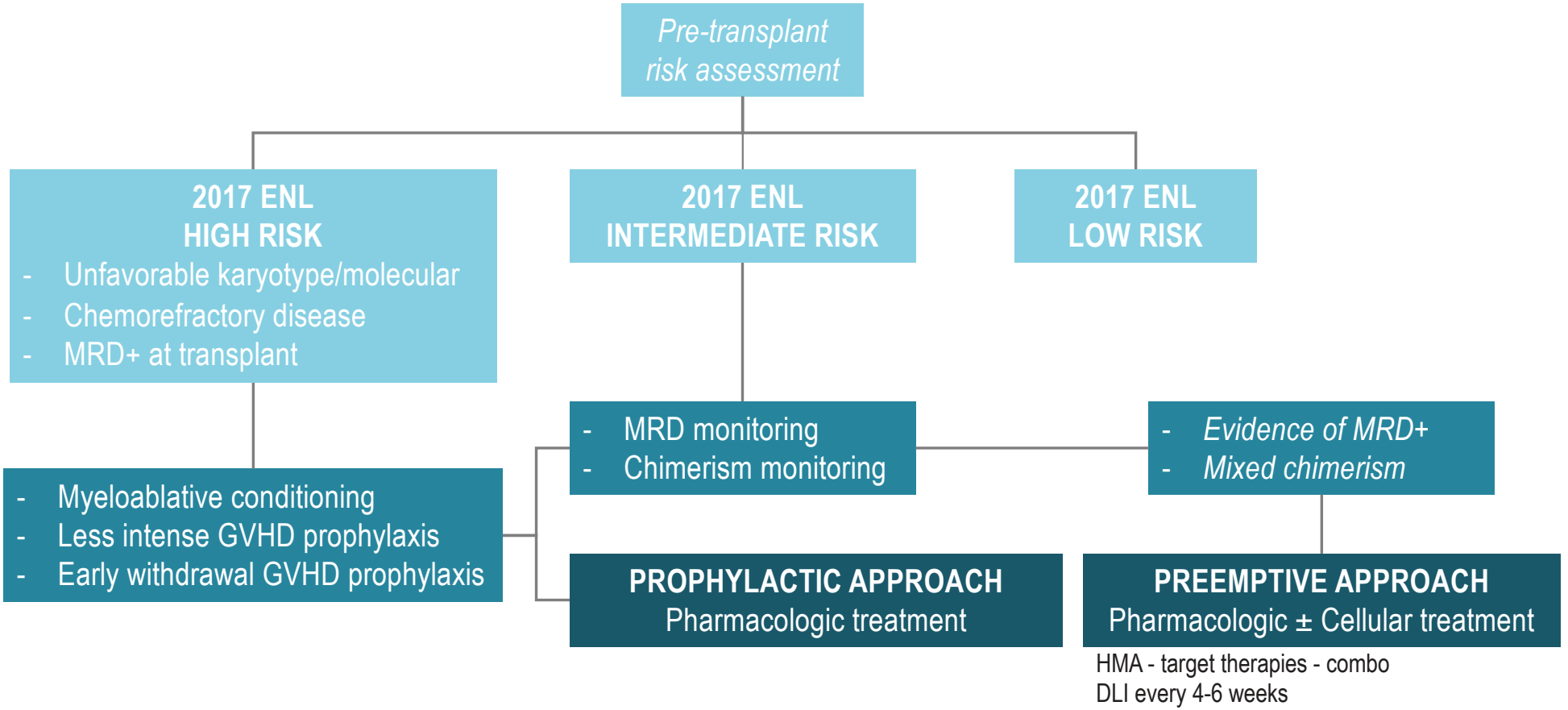
GVHD, *n* (%)[a]	Midostaurin + SOC ($n = 30$)	SOC ($n = 30$)
Acute	15 (50)	16 (53)
Grade I	7 (23)	4 (13)
Grade II	8 (27)	10 (33)
Grade III	0	2 (7)
Grade IV	0	0
Chronic	9 (30)	10 (33)
Mild	2 (7)	5 (17)
Moderate	5 (17)	4 (13)
Severe	2 (7)	1 (3)

Second Generation FLT3 Inihbitors

Drug	No.	Schedule	Strategy	Endpoint	Main results	References
GILTERITINIB	346	120 mg/day for 12 months from d60-d90	maintenance	Primary End Point RFS Secondary End Point OS	Result expected in 2025	**MORPHO Trial**, Phase III, randomized, double-blind
	768	for 24 months	maintenance	Primary End Point RFS Secondary End Point OS and CR rate	Result expected in 2023	**HOVON/AML-SG Trial**, Phase III, randomized (gliteritinib vs. midostaurin)
QUIZARTINIB	539	120 mg/day for 36 months		Primary End Point EFS Secondary End Point OS	Result expected in 2022	**QUANTUM FIRST Trial**, Phase III, randomized, double-blind
CRENOLANIB	48	100 mg TID from d30-d90 for 24 months	maintenance	Primary End Point PFS Secondary End Point OS and DFS	Result expected in 2022	Phase II, open-label, uncontrolled
	510	100 mg TID for 12 months	maintenance	Primary End Point EFS Secondary End Point OS	Result expected in 2025	Phase III, randomized (crenolanib vs. midostaurin)

Drug Class/ Intervention	Description	Duration of maintenance therapy	Status	Clinical Trial Identifier
Gilteritinib	Phase 3 double-blind, placebo RCT in FLT3-ITD AML	Up to 2 years maintenance	Completed accrual, 356 participants	NCT02997202 (BMT-CTN 1506)
Quizartinib	Phase 3, double-blind, placebo RCT (upfront and as maintenance) in FLT3-ITD AML	36 months of treatment	Completed accrual, 539 participants	NCT02668653 (QUANTUM-First)
Crenolanib	Phase 2, open label/single arm in FLT3+ AML	Up to 2 years maintenance	Completed accrual, 48 participants	NCT02400255
Enasidenib	Phase 1, open label in AML/MDS/CMML	Up to 12 months	Completed accrual w/initial results, 16 participants	NCT03515512
Ivosidenib	Phase 1 open label in AML/MDS/CMML	Up to 12 months	Completed accrual, 18 participants, initial results expected in late 2022	NCT03564821
Oral azacitidine	Phase 3, double-blind, placebo RCT in AML/MDS	Up to 12 months	Recruiting, estimated enrollment 324 participants	NCT04173533
Oral decitabine/ cedazuridine	Phase 1, open label in MDS/CMML	Up to 2 years	Recruiting, estimated enrollment 22 participants	NCT04980404
Azacitidine + Venetoclax	Phase 1, open label in high risk AML/MDS/MPN overlap	Up to 12 months	Recruiting, estimated enrollment 68 participants	NCT03613532
Azacitidine + Venetoclax	Phase 2, open label trial in AML and other hematologic malignancies	Up to 12 months	Recruiting, estimated enrollment 125 participants	NCT04128501
Azacitidine + Venetoclax	Phase 3, open label RCT in AML	Up to 24 months	Recruiting, estimated enrollment 424 participants	NCT04161885 (VIALE-T)
Azacitidine + eprenetapopt	Phase 2, open label trial in TP3 mutated AML/ MDS	Up to 12 months	Completed recruitment, 33 participants	NCT03931291
Panobinostat	Phase 3, open label RCT in AML/MDS	Unclear but at least 1 year	Completed recruitment, 52 participants	NCT04326764
DC/AML fusion cell vaccine	Phase 1 – 2 vaccines, 3 weeks apart, +/- decitabine	2 vaccines	Recruiting, estimated enrollment 45 participants	NCT03679650

Interventional Flow Chart



Conclusions

- ✓ Relapse remains the leading cause of transplant failure
- ✓ High interest on maintenance/preemptive approach after transplant
- ✓ Most promising data support the use of FLT3 inhibitors
- ✓ Other promising agents needs clinical trials
- ✓ In the next years will be avaiable results on Gilteritinib, IDH Inhibitors, oral Azacitidin, Venetoclax, Panobinostat and Cellular Therapies
- ✓ Ongoing clinical trial are evaluating double and triple-combo (HMA+Venetoclax+IDH inhibitors or HMA+Venetoclax+FLT3 inhibitors)

“90% of what we hold true in cancer research and clinical care, will be obsolete in 10 years”

Emil Freireich, MD
A “founding father” of modern chemotherapy for leukemia
University of Texas M.D. Anderson Cancer Center

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Venetoclax in Combination with Gilteritinib in Patients with Relapsed/Refractory Acute Myeloid Leukemia: A Phase 1b Study

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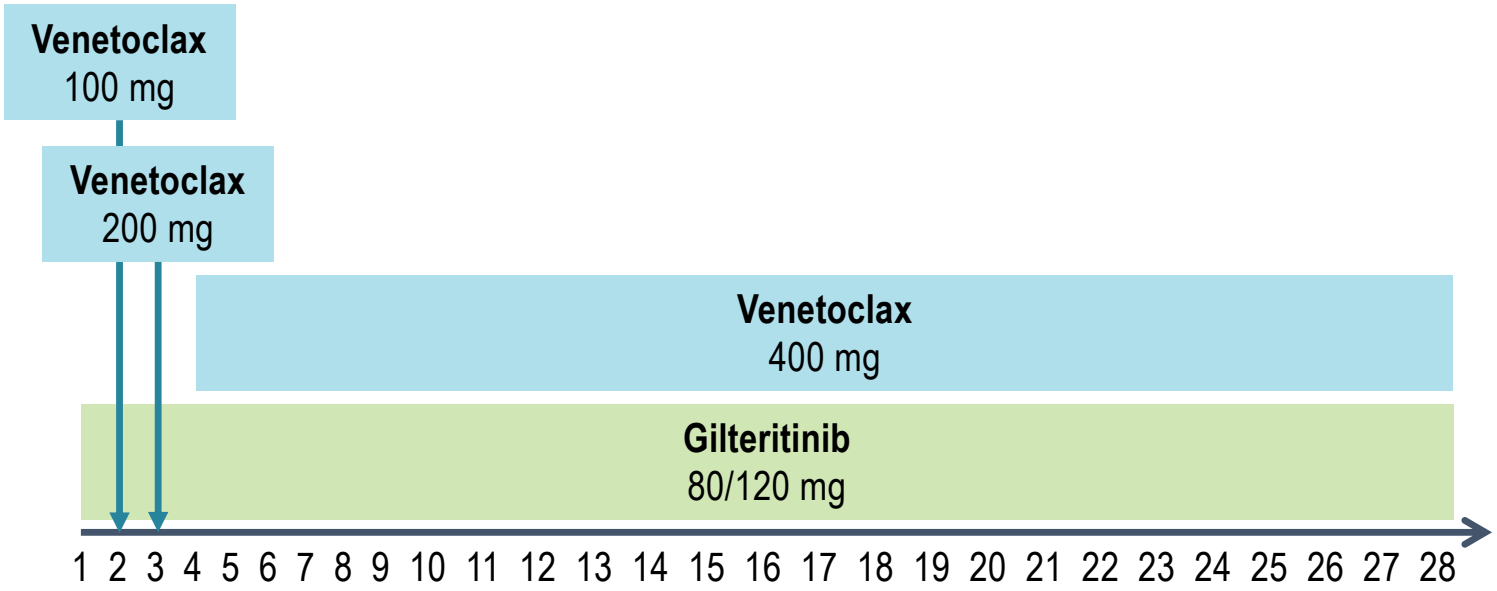

Response	No. (%)
CR	5 (50%)
PR	4 (40%)
RD	1 (10%)
Mortality <30 days	0

Perl A et al. *Blood*. **2019** 134 (Supplement 1) : 3910