Terapia della malattia in recidiva ematologica

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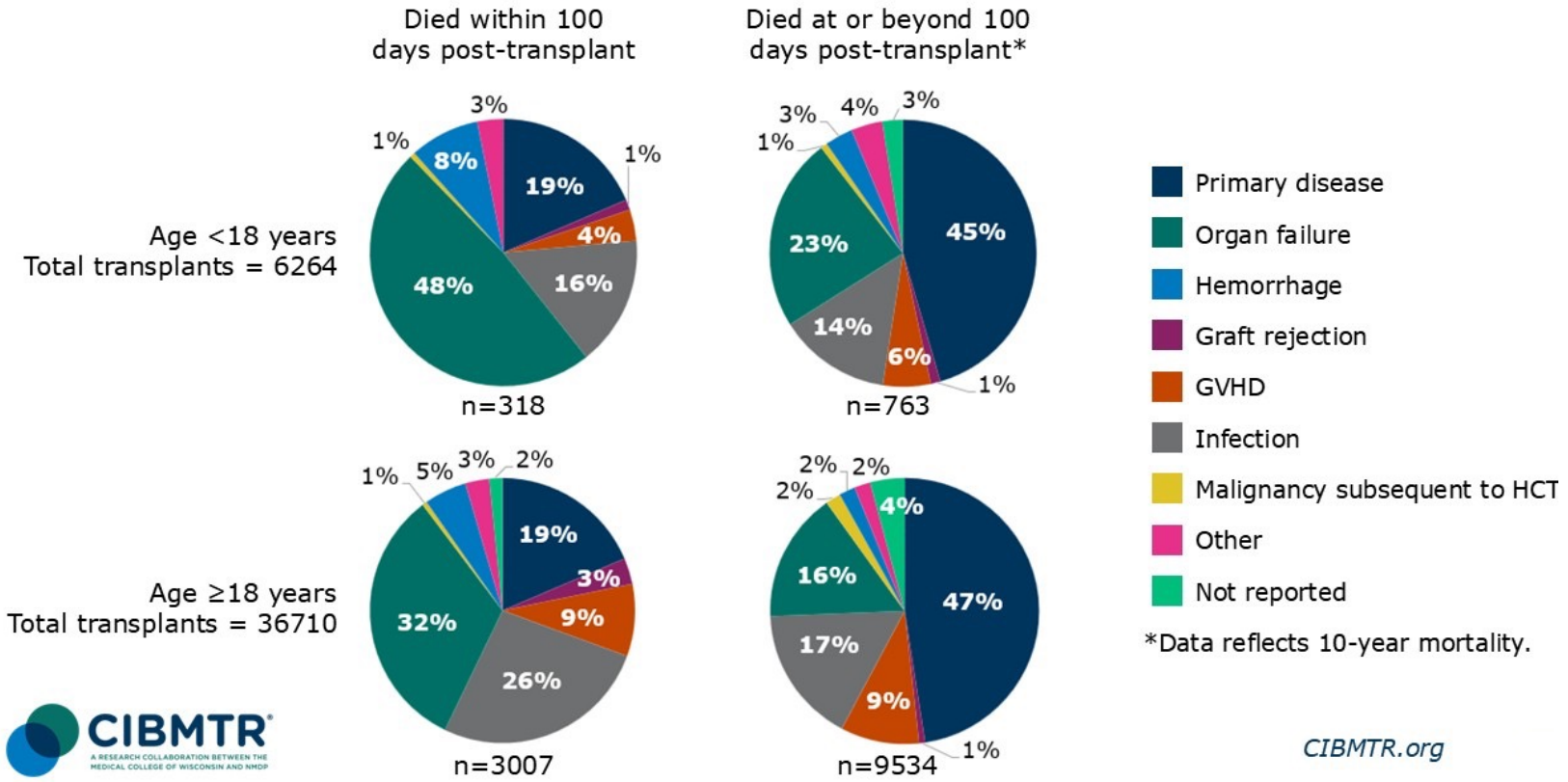
Disclosures of Patrizia Chiusolo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					x		
Therakos					x		
Astellas					x		
Novartis						x	
GSK					x		
MSD						x	
Takeda						x	
Sanofi			x				
Amgen						x	

Causes of Death after Allogeneic HCTs in the US, 2019-2023



*Data reflects 10-year mortality.

CIBMTR
A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

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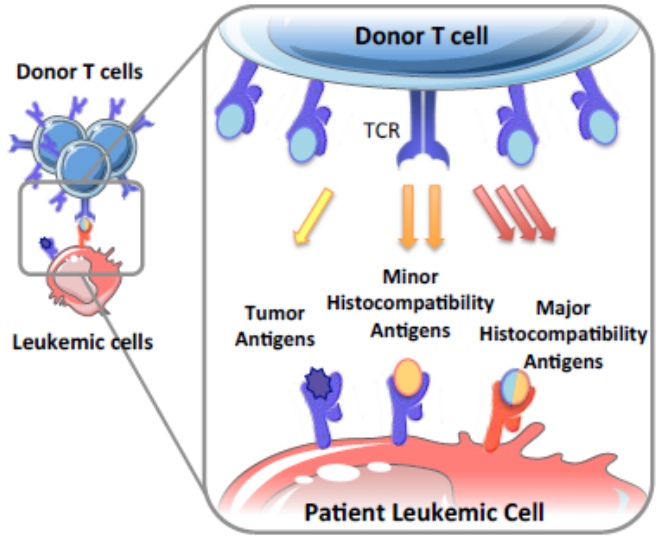


BACKGROUND

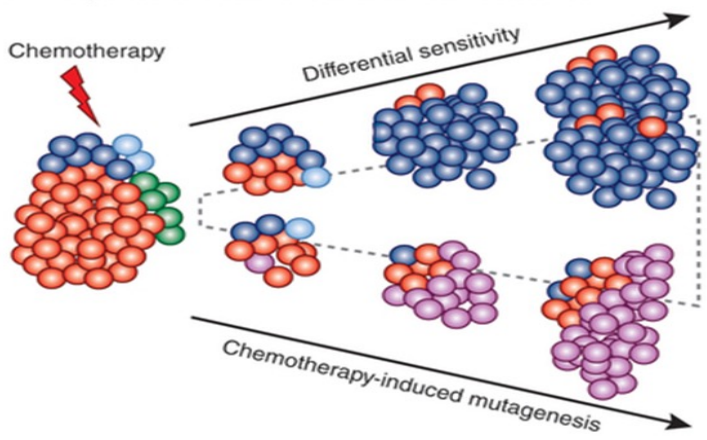
- Allogeneic HSCT is the only potentially curative therapy for myeloid malignancies.
- Disease relapse is the main cause of failure of allo-HCT, occurring in 30%–40% of patients who underwent transplant
- There is no consensus regarding optimal salvage therapy for these patients.
- Less than one-third of patients achieve remission after post-HSCT1 AML relapse.
- 1-year survival from relapse is approximately 25% with long-term survival of 10%.

Biology of relapse post AlloHSCT-1

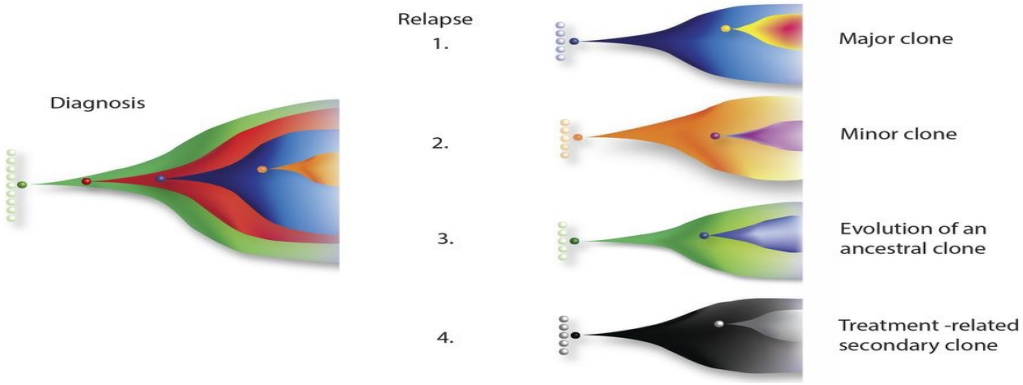
- Multiple patient-, disease-, and transplant related factors implicated in an increased risk of relapse post allo-HCT:
  - Older age
  - High-risk cytogenetics
  - Presence of FLT3, TP53, WT1 mutations
  - **Clone instability**
  - Time from achieving remission to allo-HCT
  - Absence of GVHD
  - In-vivo T-cell depletion

Craddock C et al. Journal of Internal Medicine, 2018, 283; 371–379

Leukemia is not a static condition
Relapse after alloHCT is associated with acquisition of new variants

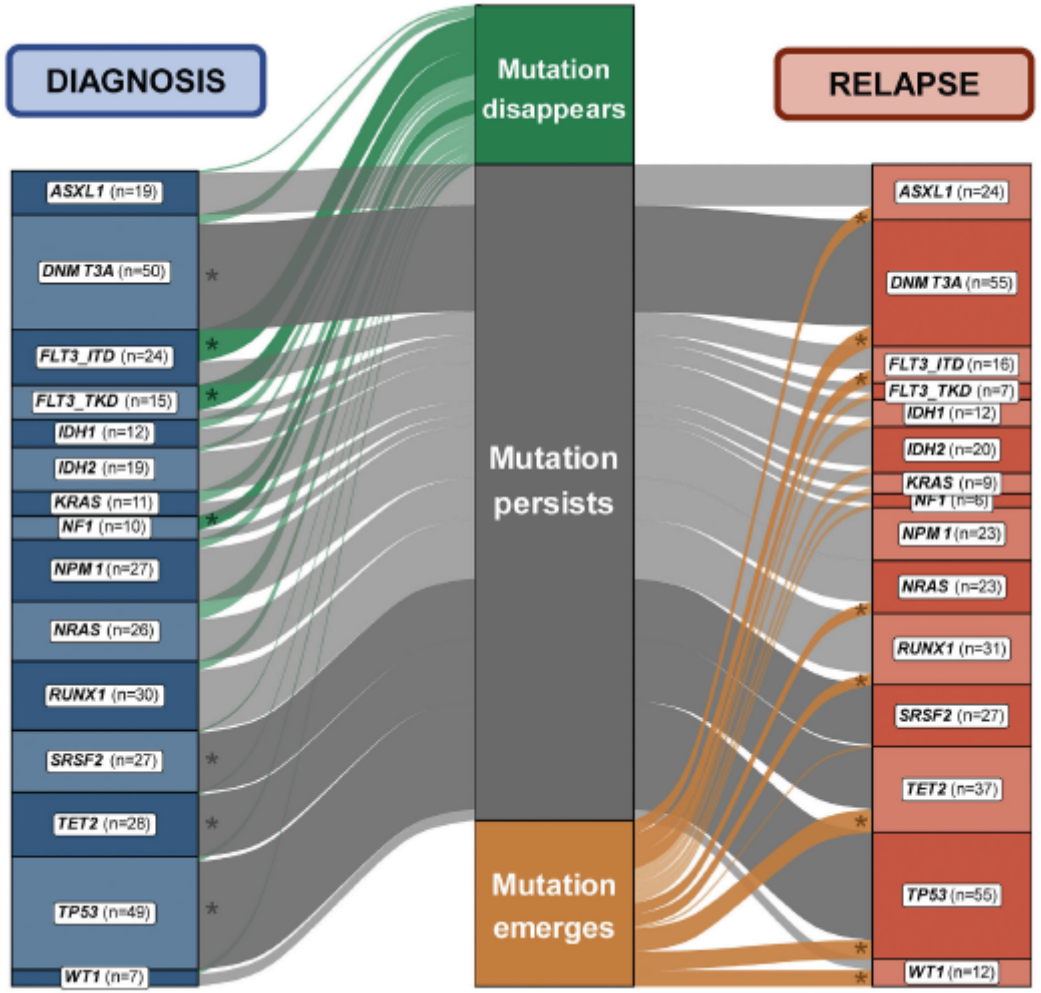


Repeating genomic analysis at relapse is necessary



Kleppe M, Levine RL. *Nat Med*. 2014;20(4):342-344.; Grimwade D, et al. *Blood*. 2016;127(1):29-41; Christopher et al. NEJM 2018

Mutation dynamics

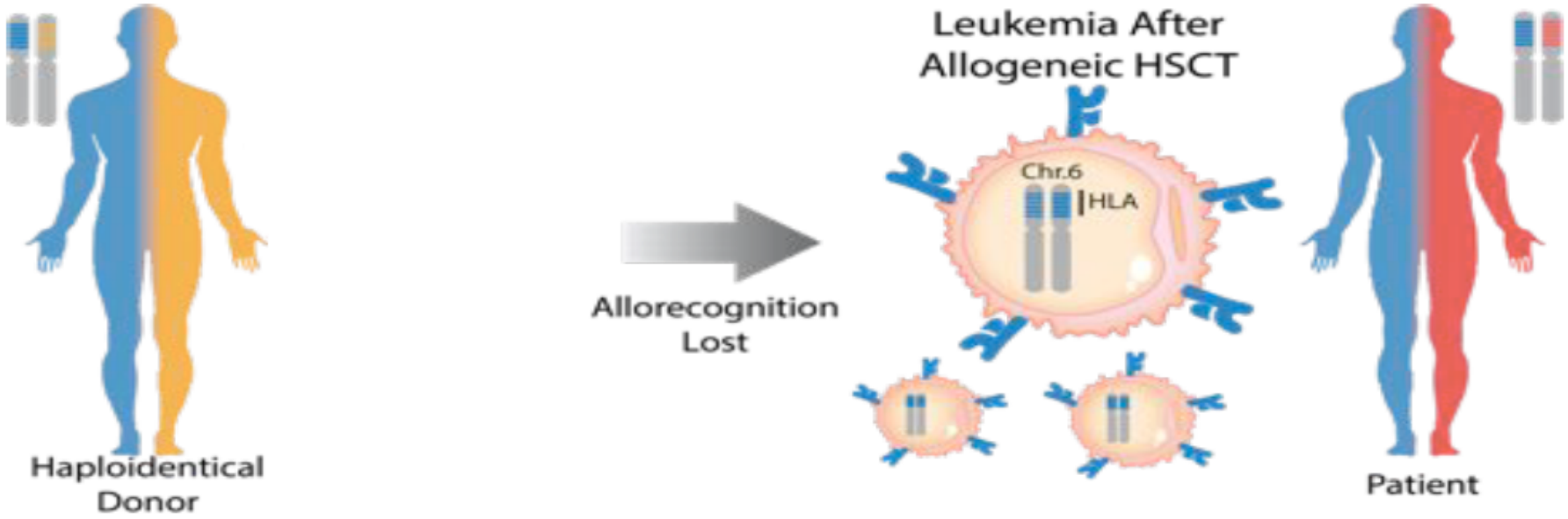


Bataller A et al. Haematologica 2024

Immune microenvironment involved

- Downregulation of MHC Class II genes
- Downregulation of NK cell targets
- **Loss of expression of an HLA haplotype**
- Increased expression of inhibitory checkpoint ligands

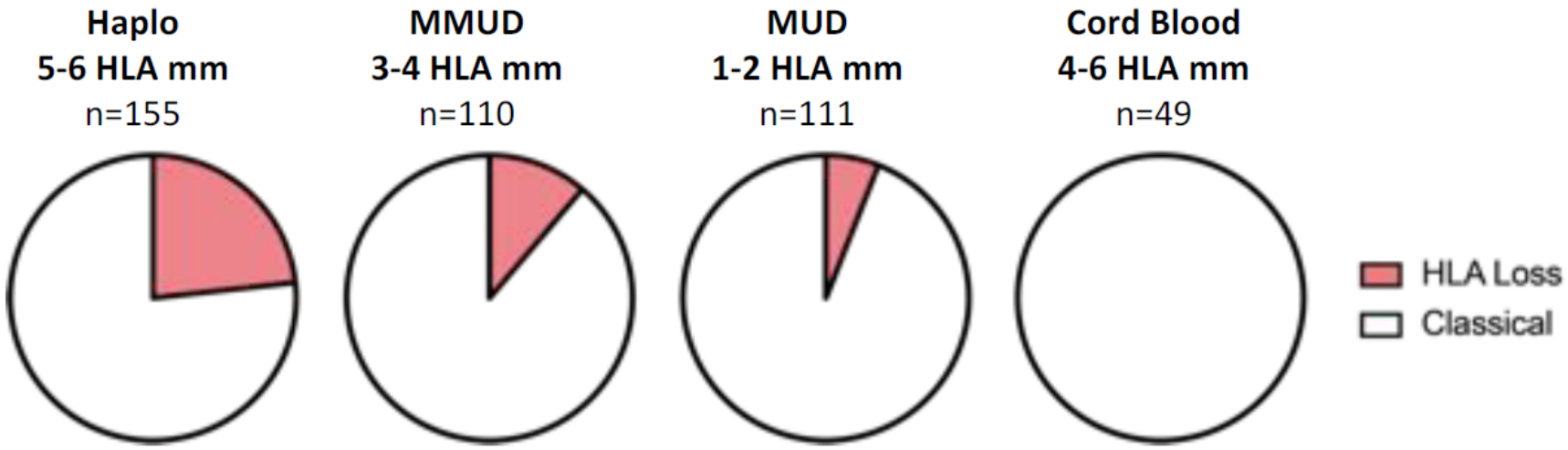
HLA loss



- Loss of the entire HLA complex (both class I and class II)
- Genomic mechanism (irreversible)
- Occurs only in leukemia cells, and rapidly becomes clonally prevalent
- Loss is counterbalanced by duplication of the other haplotype (expression level unchanged)

Vago L et al NEJM 2009
Crucitti L et al Leukemia 2015

HLA loss occurrence



HLA loss
n=38 (**24%**)

HLA loss
n=12 (**11%**)

HLA loss
n=7 (**6%**)

HLA loss
n=0 (**0%**)

Risk factors
Hyperleukocytosis at dx
Previous ALLO
Active disease at tx
PB
cGvHD

HLA loss relapses mostly occurred late after transplant (median 307 days, range 56–784)
'classical' occurred much earlier (median 88 days, range 12–579; P<0.0001).

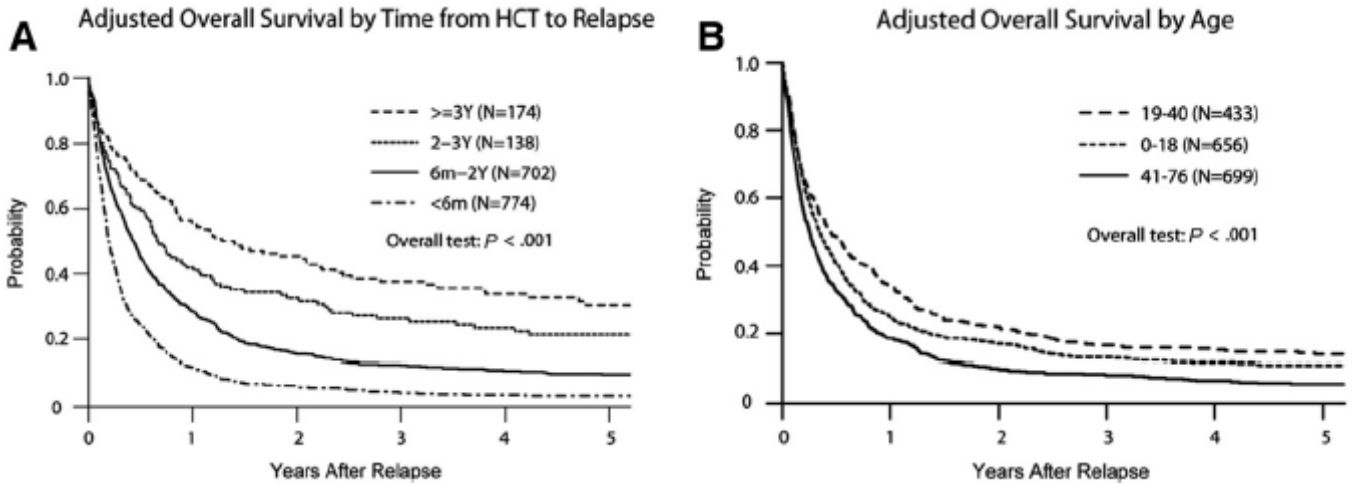
Crucitti L et al Leukemia 2015

Treatment of relapse

- **Cell-base therapy:**
  - Donor lymphocyte infusion
  - Second alloSCT
- **Pharmacologic-based Therapy:**
  - Standard CT
  - HMA+Venetoclax
  - Gilteritinib
  - Menin Inhibitors
  - IDH inhibitors

Survival of Patients with Acute Myeloid Leukemia Relapsing after Allogeneic Hematopoietic Cell Transplantation: A Center for International Blood and Marrow Transplant Research Study

1788 AML patients relapsing after alloHCT (1990 to 2010)
during first or second complete remission (CR)



Survival for all patients was 23% at 1 year after relapse

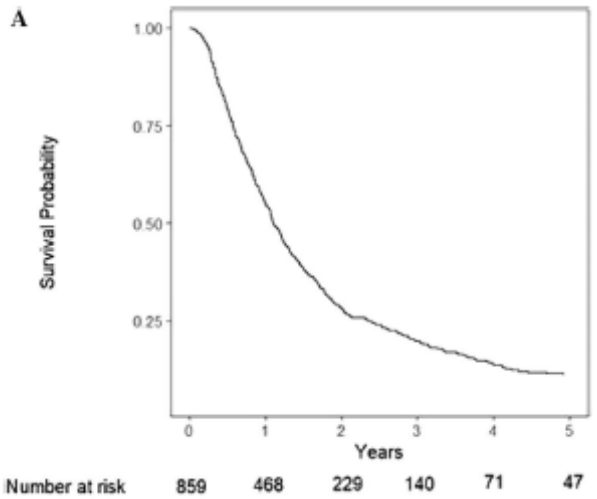
Time from HCT to Relapse	DLI			Second HCT		
	n	Survival ≥1 Year after Relapse n (%)	*P* Value*	n	Survival ≥1 Year after Relapse n (%)	*P* Value*
<6 mo	90	12 (13)	<.001	110	35 (32)	<.001
6 mo-2 yr	81	28 (35)		167	92 (55)	
2-3 yr	14	7 (50)		37	23 (62)	
≥3 yr	17	10 (59)		55	32 (58)	
Median (range)	7 (1-177)†	13 (2-106)		12 (1-150)‡	14 (2-78)	

Survival after DLI and Second HCT

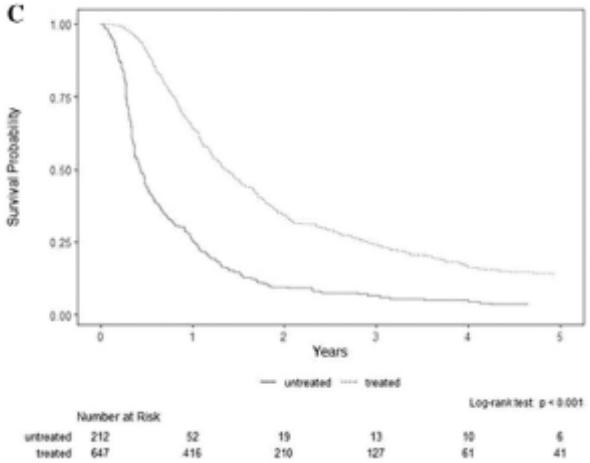
N. Bejanyan et al. / Biol Blood Marrow Transplant 21 (2015) 454–459

Outcome of Patients With Acute Myeloid Leukemias or Myelodysplastic Syndromes After Relapsing From Allogeneic Stem Cell Transplantation: The GITMO AML/MDS-Relapse Registry Study

859 pts (2015-2021)
768 AML/91 MDS
507/859 (59%) received the transplant in first CR



1-year OS = 55%
2-year OS = 28%



Treated: 1-year OS = 64%
2-year OS = 34%
Untreated: 1-year OS = 25%
2-year OS = 10%

MVA

Increased risk of RM:
the age at transplant was the only factor independently associated with an increased risk (HR 1.01)

Reduced risk:
-relapse occurring at least 12 months from transplant (HR 0.38)

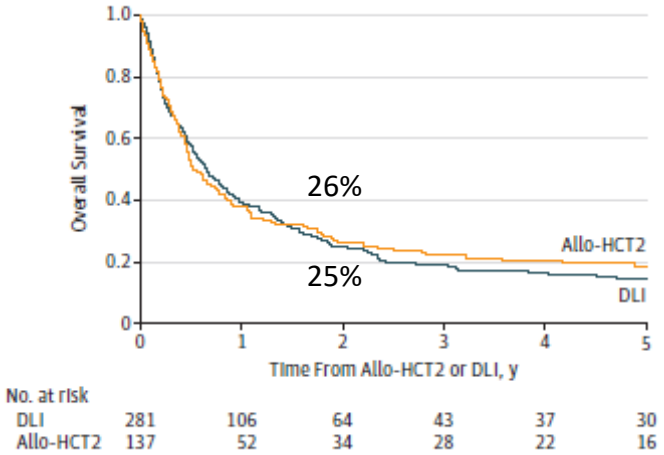
-disease relapsing with MRD positivity and/or molecular mixed chimerism (HR 0.47)

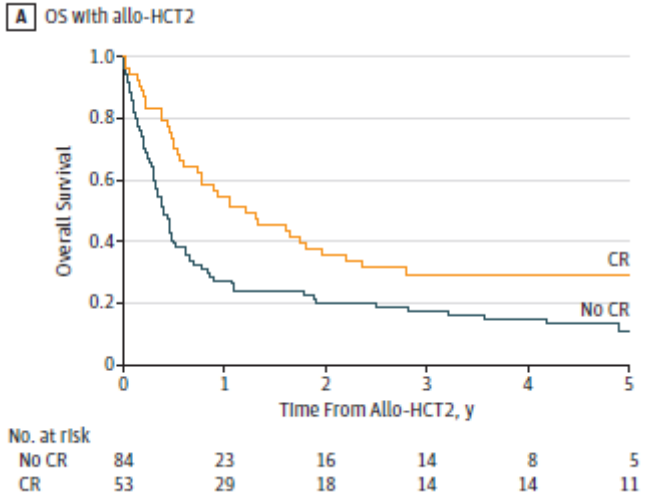
-disease in CR at allo-SCT (HR 0.59)

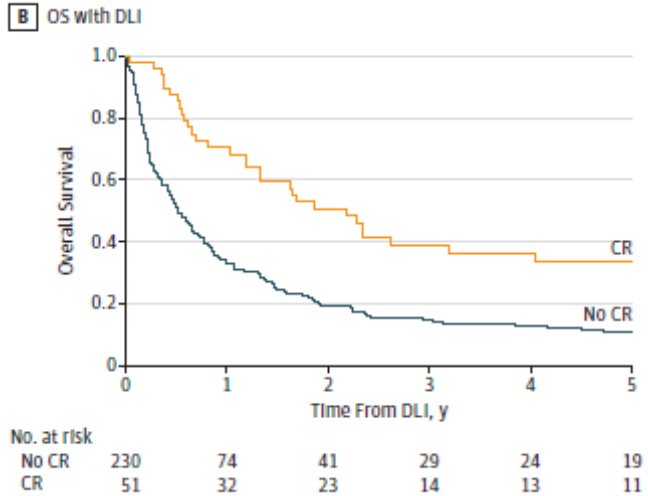
-post-relapse therapy based on HMA±venetoclax (HR 0.56)

Malagola M et al. *American Journal of Hematology,* 2025; 100:1902–1905

A retrospective registry study from the ALWP of EBMT
418 adults who received an allo-HCT2 (n = 137) or DLI (n = 281) for postallograft-relapsed AML



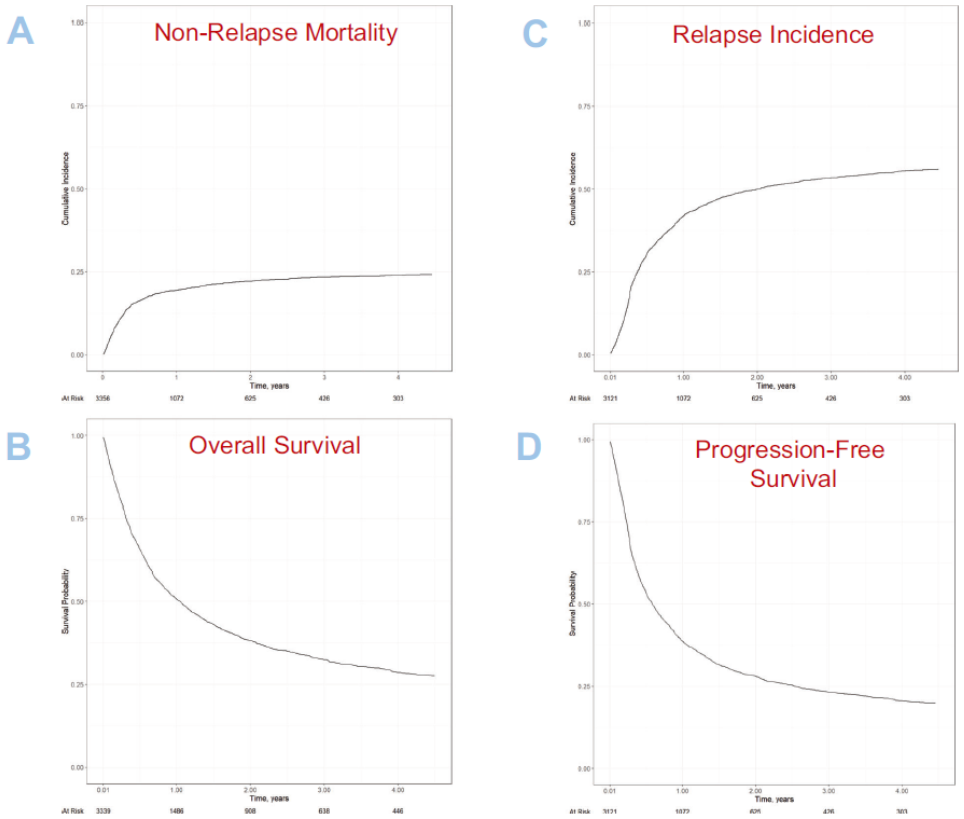




Kharfan-Dabaja et al.. JAMA Oncol, 2018

How risky is a second allogeneic stem cell transplantation?

3356 second alloSCTs performed 2011–21



The current standard of care is to base second alloSCT decisions on the most important factors:

(a) extent and aggressiveness of relapsed disease, including the presence of extramedullary involvement and cytogenetic/molecular risk factors;

(b) patient's overall health, organ function, and ability to tolerate conditioning regimens;

(c) the duration between the first transplant and relapse;

(d) availability of suitable donors;

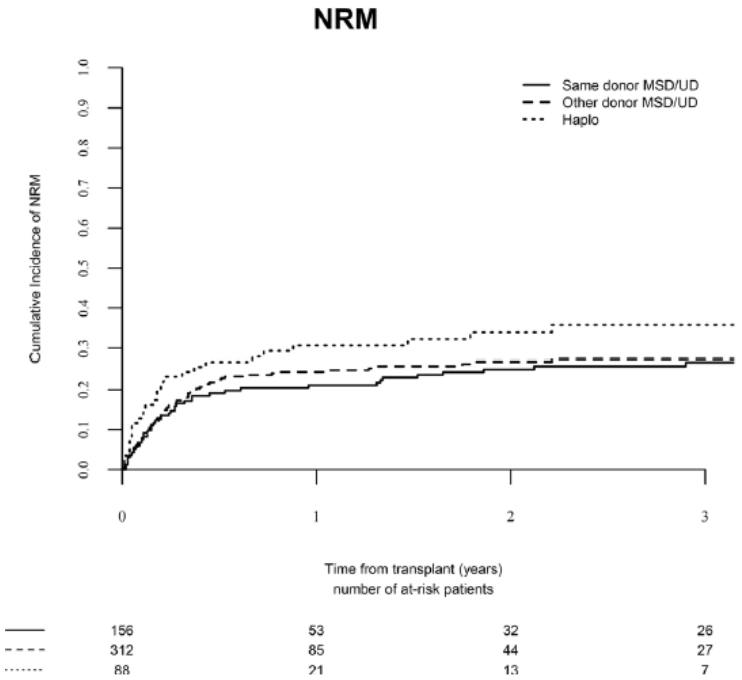
(e) pre-existing comorbidities as well as prior transplant-related toxicities.

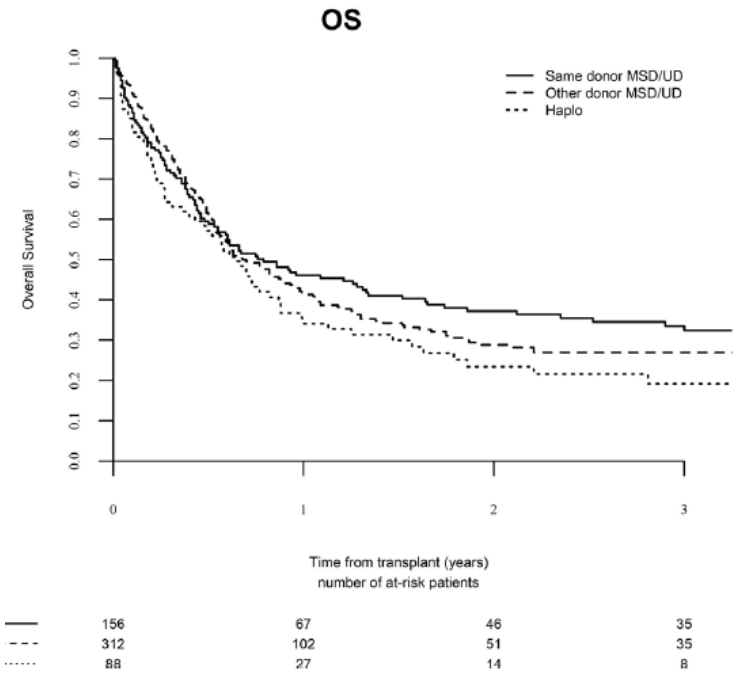
At 2 years after second alloSCT **NRM** 22%, **relapse incidence** 50%, **overall survival** 38%, and **progression-free survival** 28%.

Penack O et al Leukemia (2024) 38:1799–1807

Donor selection for a second allogeneic stem cell transplantation

556 SCT2

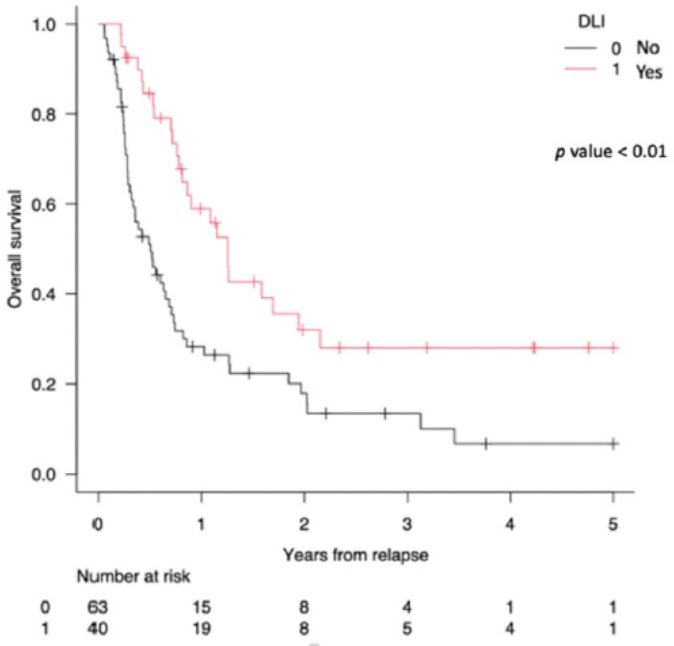


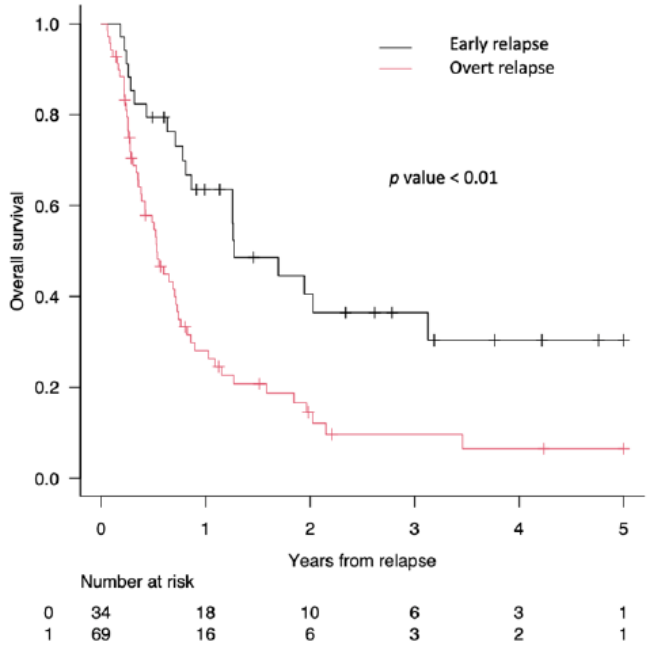


No better GVL with a second haplo-donor, and since a second haplo-identical transplant was associated with more NRM, outcome was inferior

Shimoni et al. Blood Cancer Journal (2019)9 :88

Donor Lymphocyte Infusion in the Treatment of Post-Transplant Relapse of Acute Myeloid Leukemias and Myelodysplastic Syndromes Significantly Improves Overall Survival: A French–Italian Experience of 134 Patients





January 2015 to December 2021, a total of 553 AML/MDS

134 relapsed after allo-SCT (24.2%) and 103 (18.6%) were subsequently treated.

-overt relapse (69/103 patients—67%)

-early relapse, which included patients with molecular/cytogenetic relapse and/or with mixed chimerism (34/103 patients—33%).

New drugs such as HMA, venetoclax, or FLT3 inhibitors likely enable to reduce the leukemic burden and achieve remission, which can be further consolidated with subsequent DLI infusions.

Cancers **2024**, 16, 1278

Conventional therapy

Authors	Regimens	Subsequent DLI/2nd Transplant	Relapse within 6 months of Prior Transplant	Median Age	N	% CR	ORR	OS
Responses Assessed after Chemotherapy Alone								
Koren-Michowitz et al.	Ara-C + GO	25%/13%	81%	53 (31-63)	16	31%	60%	25% at 1 year
Devillier et al.	HiDAC +/- GO +/- Anthracycline	8%/25%	42%	42	24	71%		33% at 1 year
Schmid et al.	Ara-C + Anthracycline +/-Other, HiDAC +/-Other, Anthracycline + Other	0%/0%	>50%[#]	56 (18-76)[#]	47	27%		4.4% at 2 years
Sauer et al.	HiDAC +/- Anthracycline OR ICE	0%	>50%[$]	52 (17-73)[$]	16	13%		34.4% at 1 year
Responses Assessed after Chemotherapy and DLI								
Motabi et al.	FLAG, FLAG-Ida, FLAG-IM, CLAG, CLAM, MEC, 7+3	56%/7%	58%	52 (18-70)	73	40%	51%	32% at 1 year
Levine et al.*	7+3 (Dauno 30) or Other	100%/3%	55%	42 (2-59)	65	42%		19% at 2 years
Sauer et al.	HiDAC +/- Anthracycline OR ICE	100%	>50%[$]	52 (17-73)[$]	31	48%		29% at 1 year

*[#]Median age and time to relapse reflect the full cohort of 776 patients with post-transplant relapse. [$]Median age and time to relapse reflect the full cohort of 108 patients with post-tramsplant relapse. *Study includes 4 patients with CML and 11 with MDS.*

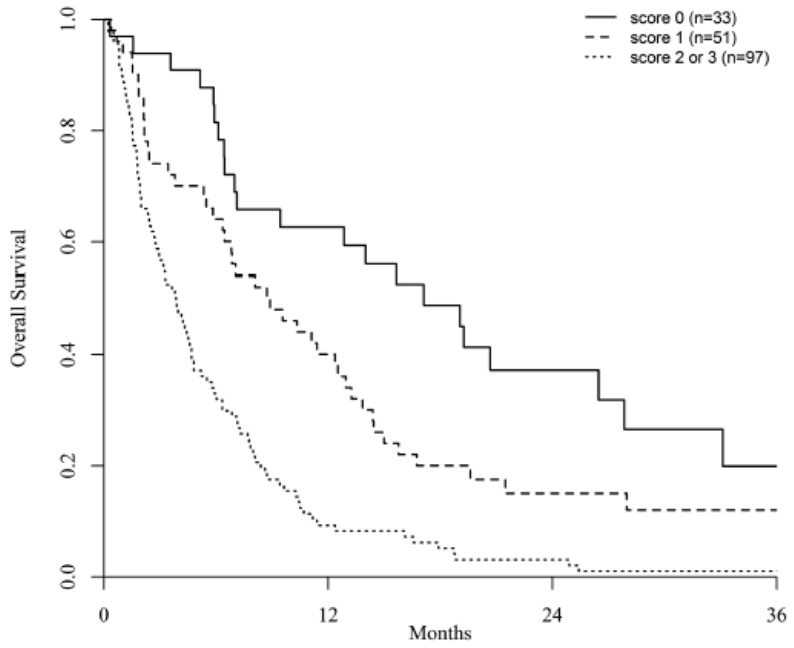
Unsatisfactory median survival rates compared to NRM of 20%

Clinical activity of azacitidine

181 patients relapsed after alloHSC for AML (n=116) or MDS (n=65)

Factors determining 2-year OS after azacitidine treatment

	P	HR	95% CI inf	sup
Interval SCT-relapse < 6 mo (Ref)			1.00	
6-12 mo *vs.* <6 mo	0.001	0.51	0.35	0.76
>12 mo *vs.* <6 mo	$<10^{-4}$	0.29	0.19	0.44
Blasts in BM at relapse >median	0.012	1.53	1.10	2.14



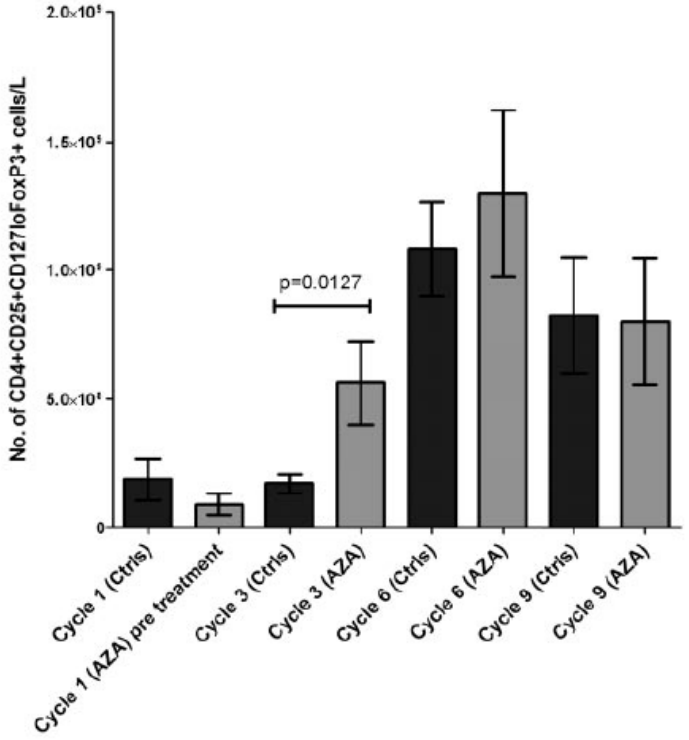
In patients who achieved CR, the 2-year overall survival was 48% *versus* 12% for the whole population
The concurrent administration of DLI did not improve either response rates or OS

Craddock C et al. Haematologica 2016; 101(7):879-883

Aza augments a GVL effect without a concomitant increase in GVHD

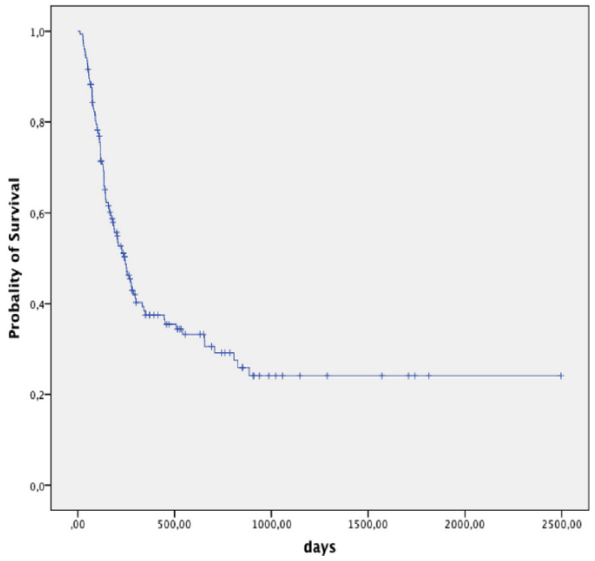
Increased number of **Tregs** within the first 3 months after transplantation compared with a control population (*P* .0127).

AZA induced a cytotoxic **CD8 T-cell response** to several tumor Ags, including WT1.

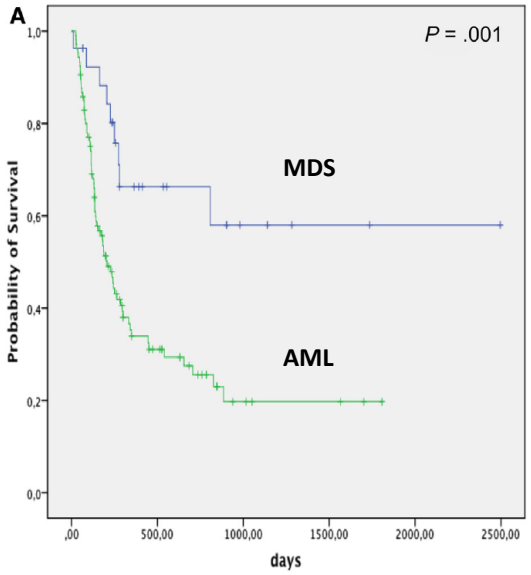


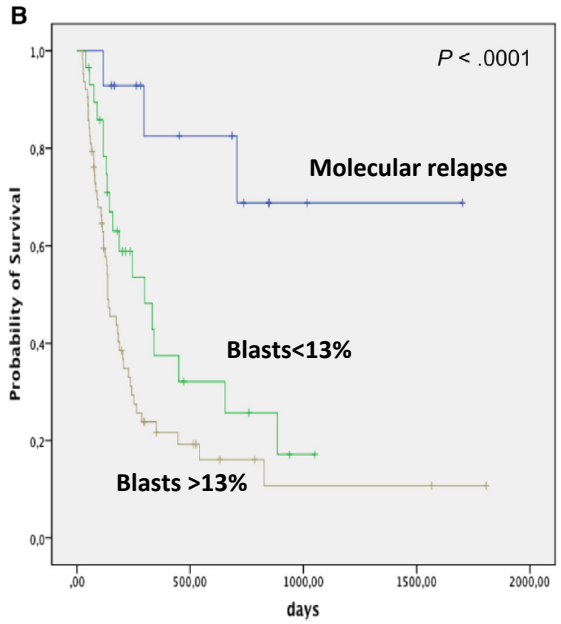
Goodyear OC et al. Blood 2012

HMA and DLI



OS was 29% (4%) at 2 years



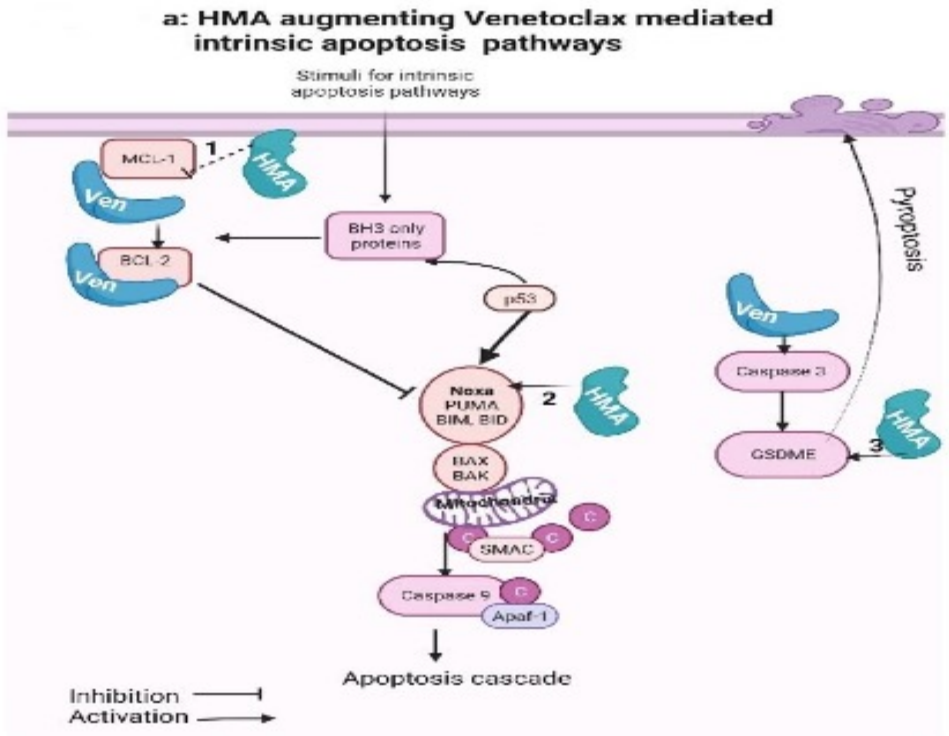


Similar results with decitabine

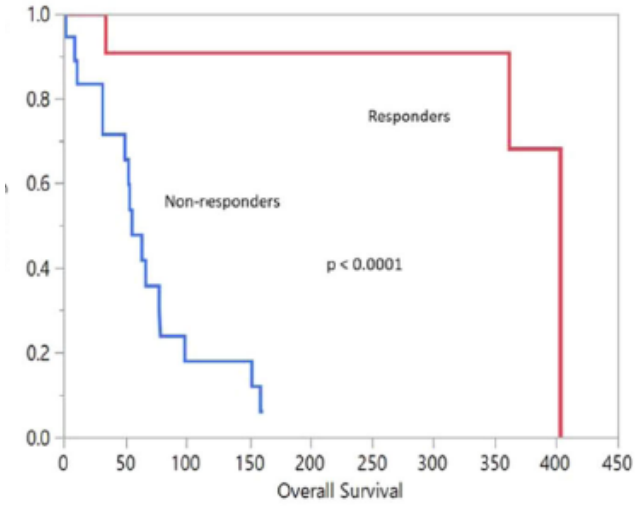
Predictive factors of response (OS) were:
-type of relapse: mol vs hem
-primary diagnosis of MDS,
-lower leukemic burden in BM at relapse

T. Schroeder et al. / Biol Blood Marrow Transplant 21 (2015) 653e660

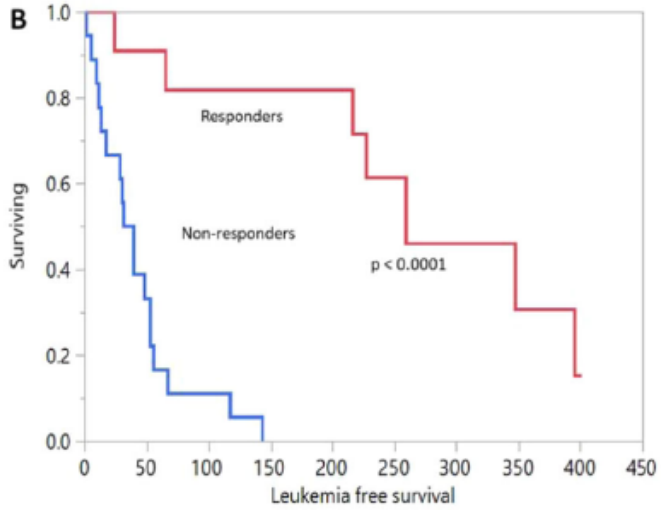
Salvage use of venetoclax-based therapy



OS



LFS



The overall response rate was 38% (n=11) with eight patients (28%) achieving complete remission (CR/CRi) and one a partial remission (PR) and two patients had a reduction in blast count.
Four of 12 patients (33%) with TP53 mutation responded, 3 achieved CR and one patient had PR.

Joshi et al. Blood Cancer Journal (2021) 11:49

HMA+VEN: setting post HSCT

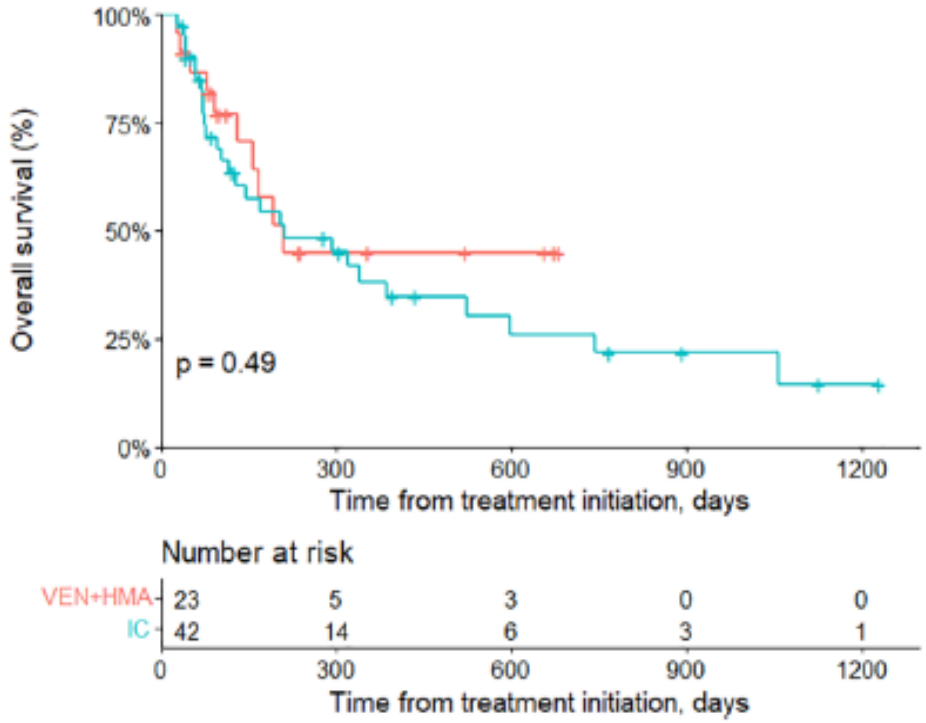
Combination efficacy:

- Byrne et al. AJH 2020: 21 pts, first study on VEN post-HSCT
- Zhao et al. Ann Hematol 2022: VEN+AZA+DLI → **ORR 53%, OS 14 mo**
- Schuler et al. Ann Hematol 2021: german multicenter study, **ORR 30-50%**

.

Comparison with intensive chemoterapy:

- Chen et al. Front Oncol 2023: Similar OS with significantly less toxicity



Venetoclax plus hypomethylating agents as first salvage therapy for myeloid malignancies relapsing after allogeneic HSCT

Study Design:

- Retrospective multicenter study
- 9 italian centers
- Median F-U: 8 months
- Period: 2022-2024

91 pts relapsed post-alloHSCT

Inclusion criteria:

- AML/MDS
- >= 18 yo
- First line treatment for relapse HMA-Venetoclax

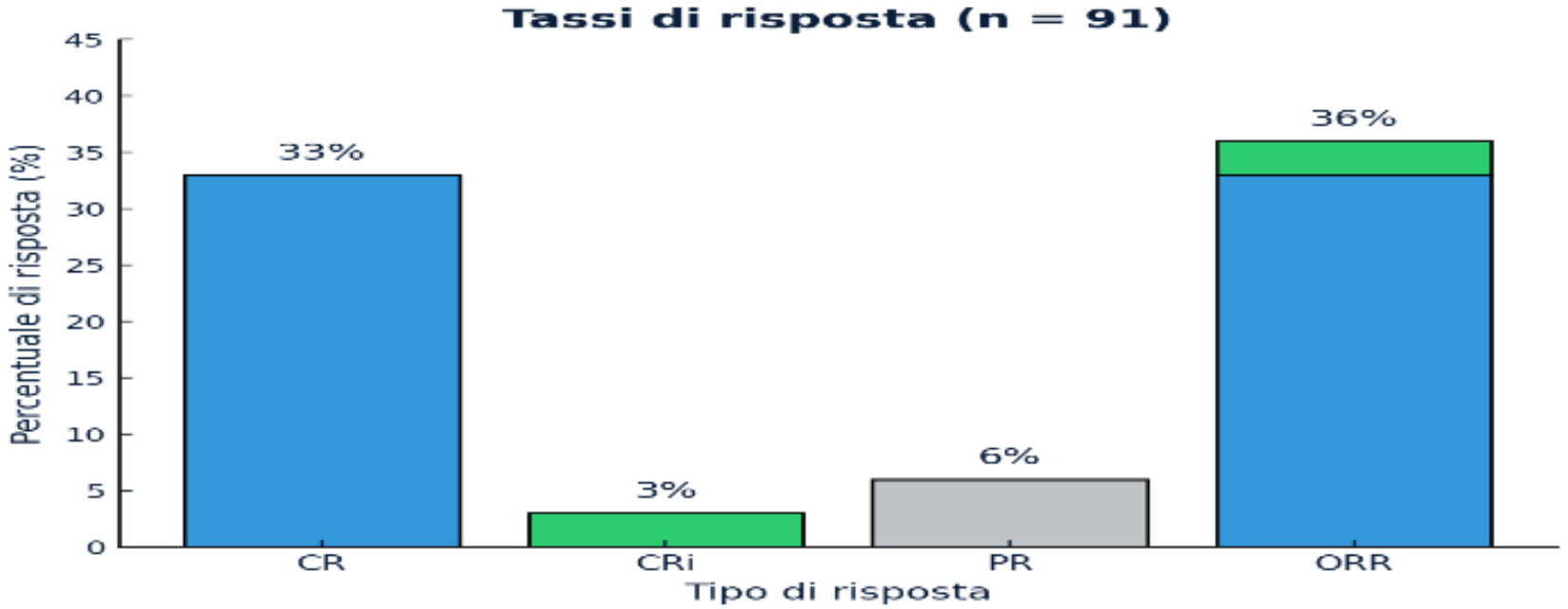
Parameter	Value
Total number of patients	91
Median follow-up (range)	8 months (1–34)
Sex (M/F)	50 / 41
Median age (range)	69 years (24–74)
Diagnosis	AML 83 (92%); MDS 7 (8%); CMML 1 (1%)
High-risk disease	48 (52%)
Pre-HSCT MRD status	Negative 59 (64%); Positive 32 (36%)
Conditioning regimen	MAC 22 (24%); RIC 69 (76%)
Donor type	MUD 38 (42%); MRD 18 (20%); Haplo 25 (27%); MMUD 9 (10%); Cord 1 (1%)
Stem cell source	PBSC 76 (84%); BM 14 (15%); Cord 1 (1%)
GVHD prophylaxis	ATG 35 (38%); ptCY 56 (62%)
Incidence of aGVHD	41 (45%)
Grade of aGVHD	I 31 (34%); II 8 (9%); III 2 (2%)
Time to relapse (range)	14 months (2–137)

Chiusolo P, Malagola M et al. BMT 2025

Results: clinical response

Response evaluation:

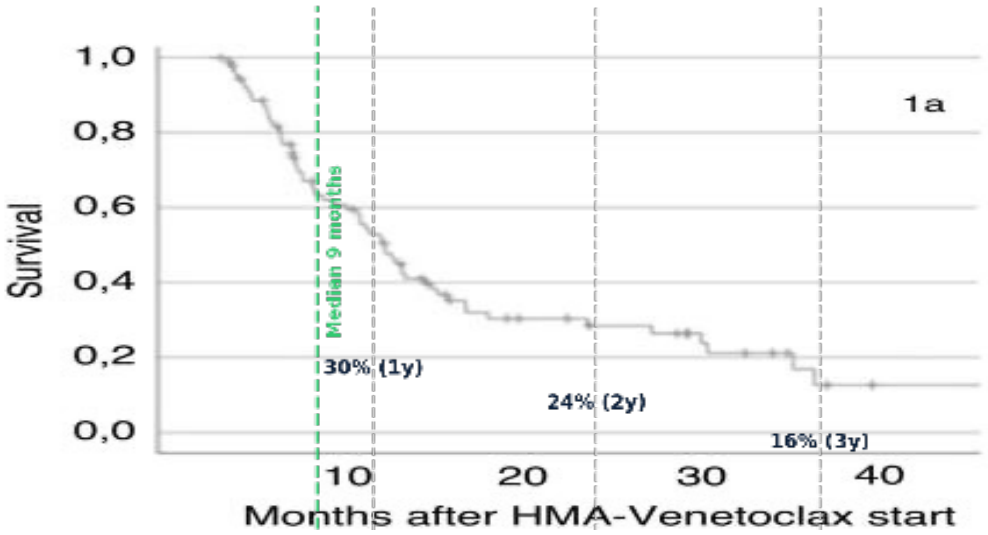
- ELN 2017/2022 Criteria (CR,CRi,PR,MLFS)
- MRD: qPCR or multiparametric Flow Cytometry
- **Evaluation after 2 cycles, media cycles administered 4 (range 1-27)**

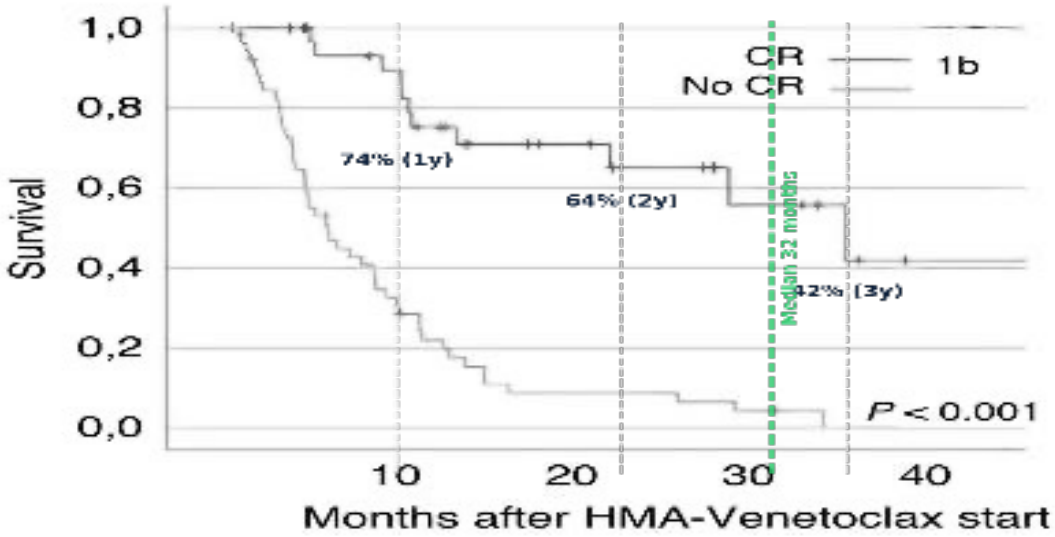


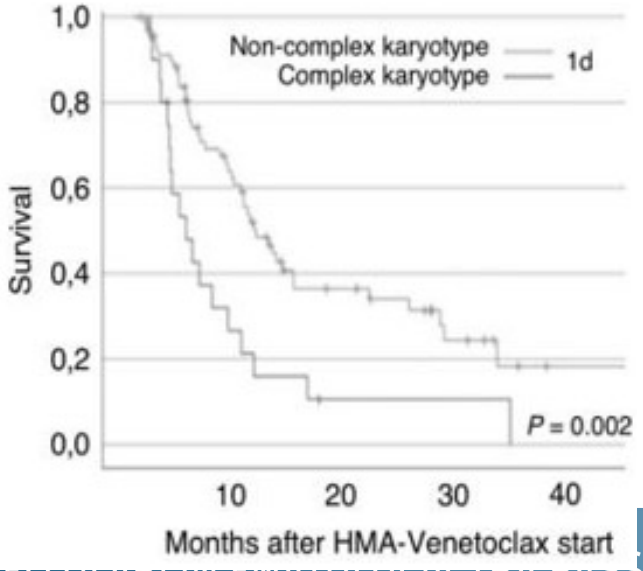
MRD neg >50% of CR pts

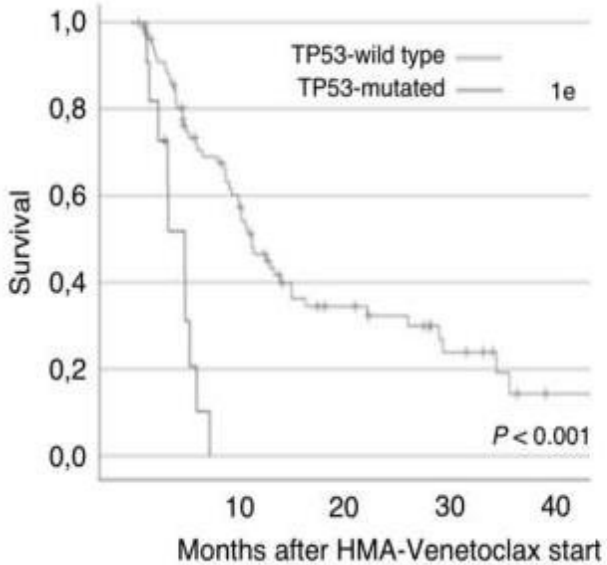
Chiusolo P, Malagola M et al. BMT 2025

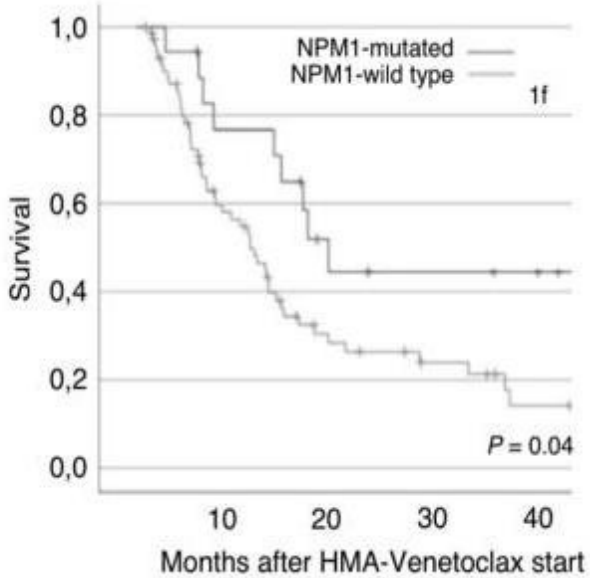
Results


1a
Survival
1,0
0,8
0,6
0,4
0,2
0,0
Median 9 months
30% (1y)
24% (2y)
16% (3y)
10
20
30
40
Months after HMA-Venetoclax start


1b
CR
No CR
Survival
1,0
0,8
0,6
0,4
0,2
0,0
74% (1y)
64% (2y)
Median 32 months
42% (3y)
P < 0.001
10
20
30
40
Months after HMA-Venetoclax start


1d
Non-complex karyotype
Complex karyotype
Survival
1,0
0,8
0,6
0,4
0,2
0,0
P = 0.002
10
20
30
40
Months after HMA-Venetoclax start


1e
TP53-wild type
TP53-mutated
Survival
1,0
0,8
0,6
0,4
0,2
0,0
P < 0.001
10
20
30
40
Months after HMA-Venetoclax start

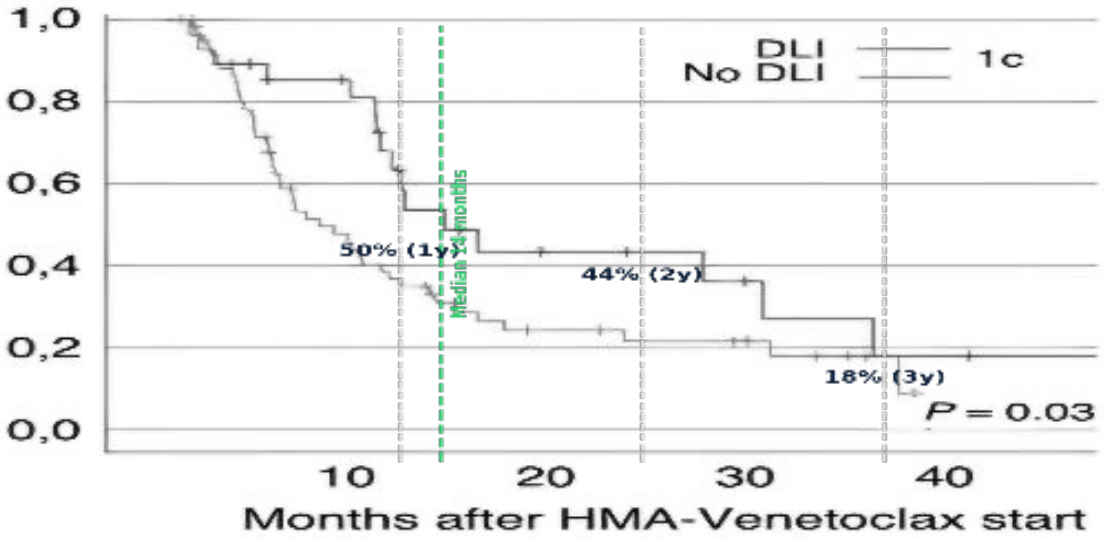

1f
NPM1-mutated
NPM1-wild type
Survival
1,0
0,8
0,6
0,4
0,2
0,0
P = 0.04
10
20
30
40
Months after HMA-Venetoclax start

Results: impact of DLI

- **28 pts (31%)** received DLI
- **Median dose**: 2x 10^6 CD3+/Kg (range 1-6)

Safety profile:
- **aGVHD: 25%** (mostly grado I)
- **No severe cGvHD**

IMPACT on OS:
- **mOS with DLI:** 14 months vs 8 months



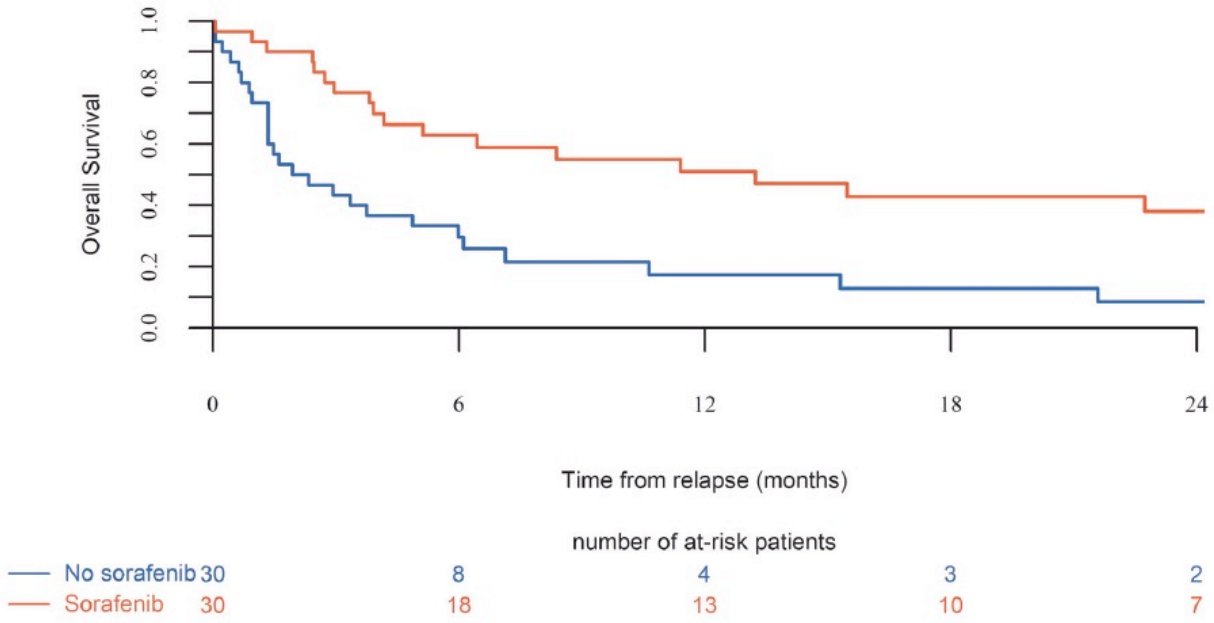
Sinergy between direct cytotoxicity (HMA-VEN) and adoptive immunotherapy (DLI)

Chiusolo P, Malagola M et al. BMT 2025

Tracking druggable mutations

FLT3

Sorafenib



Bazarbachi A et al. Haematologica 2019; 104:e399

Gilteritinib

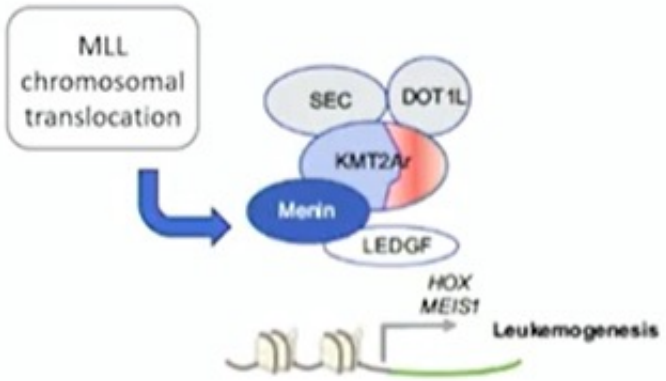
Parameter	Gilteritinib	Salvage Chemotherapy	
Median Overall Survival			**Hazard Ratio (95% CI)**
High-intensity chemotherapy	10.5 months	6.9 months	0.663 (0.471, 0.932)
Low-intensity chemotherapy	6.4 months	4.7 months	0.563 (0.378, 0.839)
Received prior HSCT	8.3 months	4.0 months	0.480 (0.274, 0.840)
Did not receive prior HSCT	9.6 months	6.0 months	0.684 (0.511, 0.917)
CR Rate, no. (%)			**Risk Difference (%) (95% CI)**
High-intensity chemotherapy	37/149 (24.8)	12/75 (16.0)	8.8 (−3.0, 20.6)
Low-intensity chemotherapy	15/98 (15.3)	1/49 (2.0)	13.3 (3.6, 22.9)
Received prior HSCT	17/48 (35.4)	3/26 (11.5)	23.9 (2.6, 45.1)
Did not receive prior HSCT	35/199 (17.6)	10/98 (10.2)	7.4 (−1.4, 16.1)
Before on-study HSCT	34/247 (13.8)	13/124 (10.5)	3.3 (−4.0, 10.5)
CR/CRh Rate, no. (%)			**Risk Difference (%) (95% CI)**
Before on-study HSCT	65/247 (26.3)	19/124 (15.3)	10.9 (2.4, 19.5)

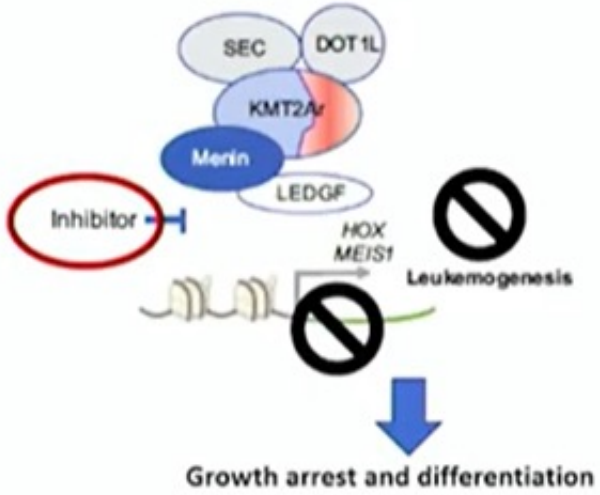
Pearl AE et alNEJM 381;18

Tracking druggable mutations

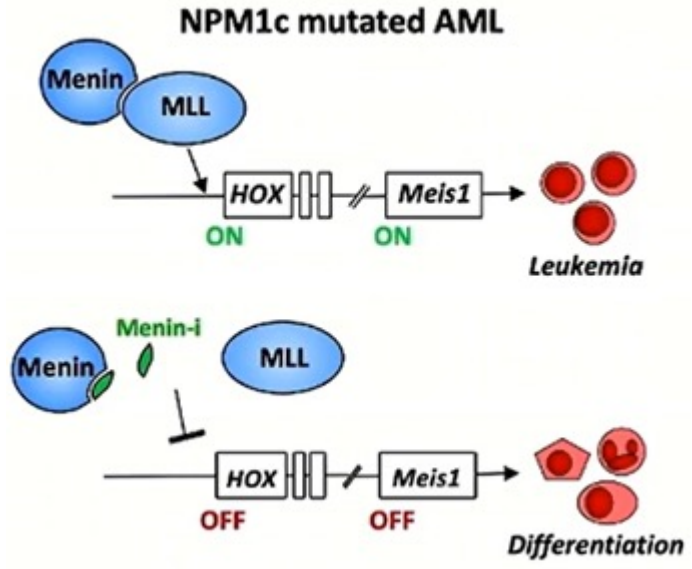
KMT2Ar and NPM1

Menin is an essential oncogenic cofactor for leukemogenesis driven by r-*KMT2A*





Modified from Issa GC et al, Leukemia 2021



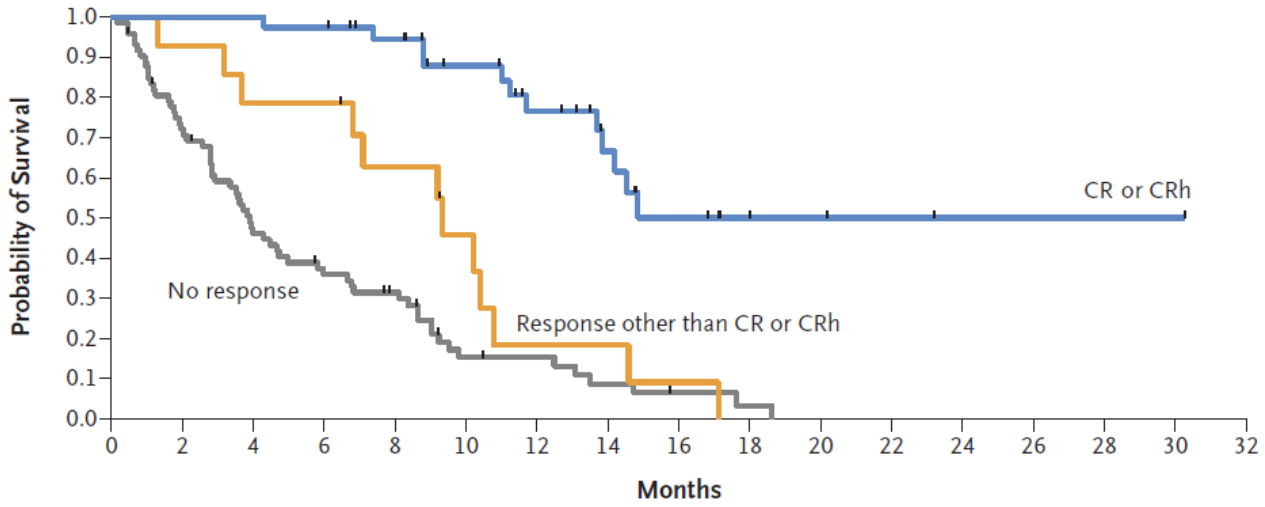
Ongoing trial in AML R/R:
Enzomenib
Ziftomenib

Uckelmann et al. Science 2020

Tracking druggable mutations

IDH1/2

IVOSIDENIB in R/R AML



Overall Survival According to Response

Trials included a limited number of patients with relapse after transplant.

Few ongoing trials on IDH inhibitors for *IDH*-mutant AML patients relapsed following allo-HSCT.

Ideal agent for **maintenance** post-transplant.

Di Nardo CD et al N Engl J Med 2018;378:2386-98.

Cell-based therapy	
Donor lymphocyte infusion	√Most effective in certain conditions, including low tumor burden and loss of chimerism or MRD √Favorable prognostic factors: •Use of an RIC/non-myeloablative conditioning regimen •Longer time from transplant to relapse √Poor prognostic factors: •Age greater than 41 years •Unfavorable karyotype •Mismatched unrelated donor •GVHD at time of relapse
Second hematopoietic stem cell transplant	√Prospective trials needed to better describe their role √Available data including patients who have survived until the intervention and who were younger than the majority of patients who relapse after the first √Favorable prognostic factors: •More than 6 months between the first transplant and relapse •Matched related donor at the first transplant
Pharmacologic-based therapy	
Isocitrate dehydrogenase (IDH) inhibitors	√Promising results in the setting of relapsed/refractory AML √Ongoing trials for IDH-mutant AML patients who relapsed following allo-HSCT
Hypomethylating agents	√Anti-leukemic activity through DNA hypomethylation √Immune modulatory activity that enhances the activity of regulatory T cells and cytotoxic T cells √Regulating GVHD while maintaining the beneficial GVL effect √The optimal dose used is 32 mg/m2 for 5 days every 28 days
Venetoclax	√Role in targeting leukemia cells with an acceptable toxicity profile √Venetoclax combination therapy: similar anti-leukemia effect yet a better toxicity profile than FLAG-idarubicin √Reduction and/or interruption of dosing may be warranted in some cases of neutropenia
FLT3 and menin inhibitors	

Modified by Kreidieh F et al. International Journal of Hematology (2022) 116:330–340

Summary

- Treatment options for post-transplant relapse are often dictated by how ‘fit’ the patient is.
- Defining the molecular profile is essential; NGS should be considered for relapsed bone marrow specimens prior to initiation of salvage therapy.
- DLI remains a powerful example of adoptive immunotherapy and an established salvage and prophylactic option post-transplant.
- Prospective trials are needed to better describe the role of second allo-HSCT.
- Even in the context of post-transplant relapse with adverse mutations, VEN-based therapy is capable of inducing CR and improving survival in responding patients.
- A common challenge with VEN-based therapy is identifying the appropriate dose and cycle duration due to hematological toxicity.
- When applying data from available studies on R/R AML, caution should be used, especially with regard to the treatment received in the frontline setting and the residual toxicity.