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CLONAL HEMATOPOIESIS AND ALLOGENEIC STEM CELL TRANSPLANTATION

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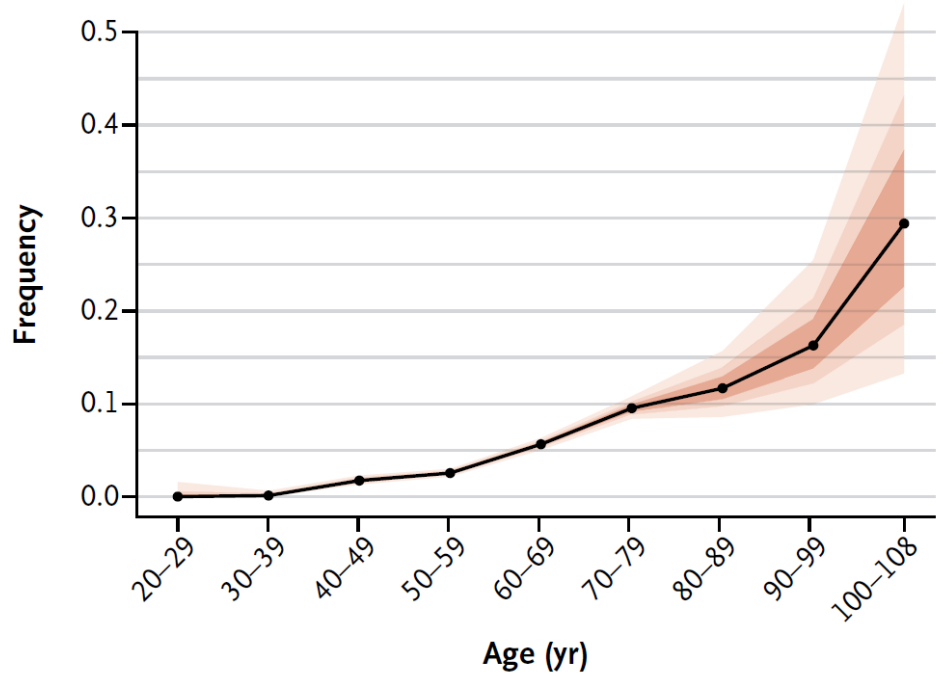
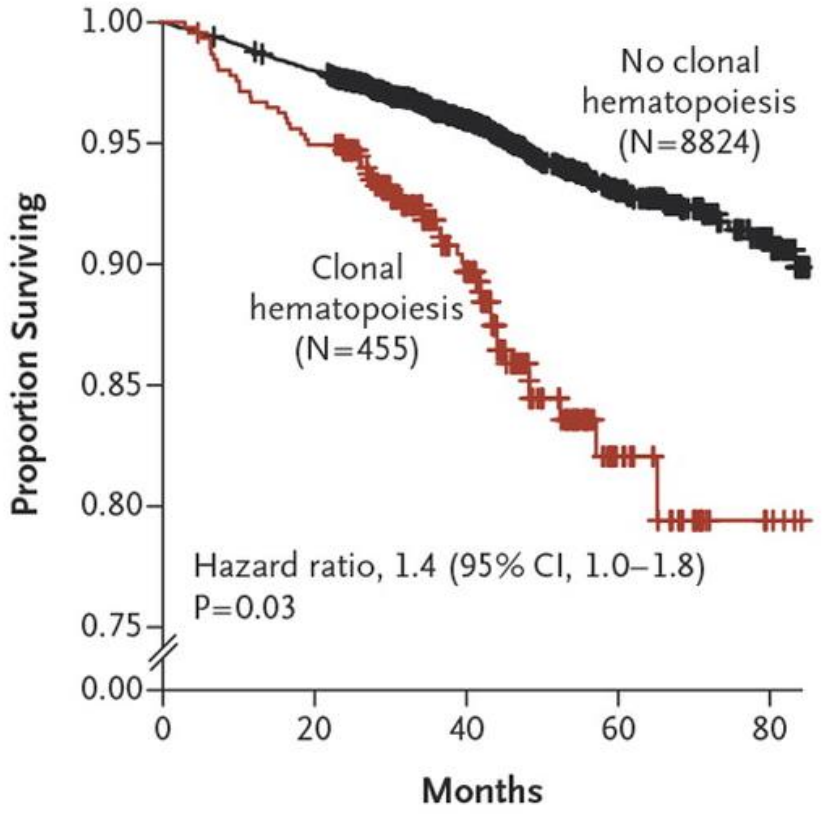
What is clonal hematopoiesis (CH)?

- "*Clonal hematopoiesis of indeterminate potential (CHIP)*":

Acquisition of somatic mutations in hematopoietic cells in the absence of cytopenias and dysplastic hematopoiesis (allele burden: VAF ≥2%).



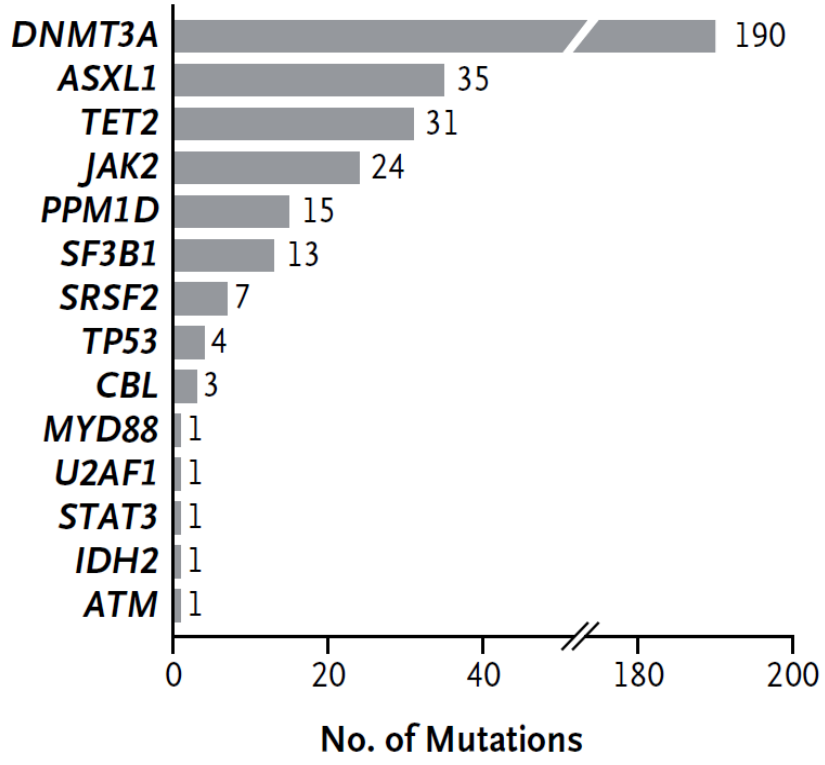
No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

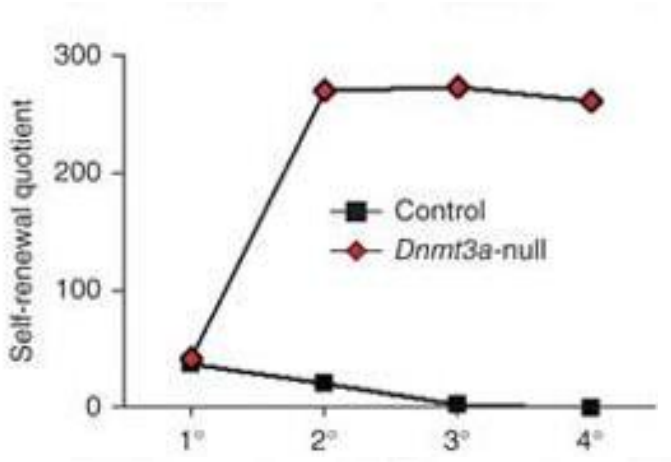


Genovese *et al*., NEJM 2014; Jaiswal *et al*, NEJM 2014; Xie et al, Nature Medicine 2014

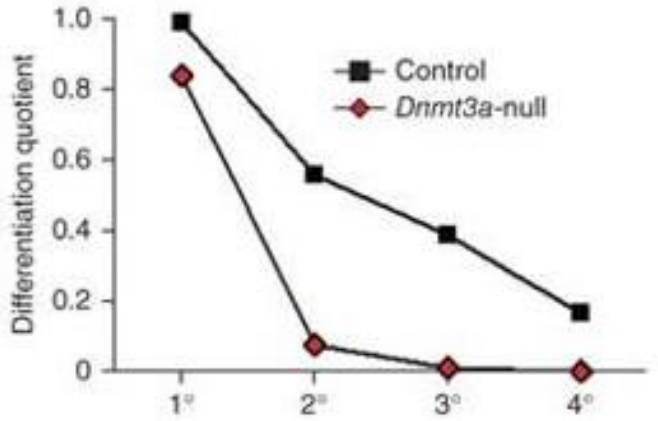
What ist clonal hematopoiesis (CH)?

- Mutations occur non-randomly in the human genome and mainly affect three epigenetic regulators of transcription (*DNMT3A, ASXL1*, and *TET2*).





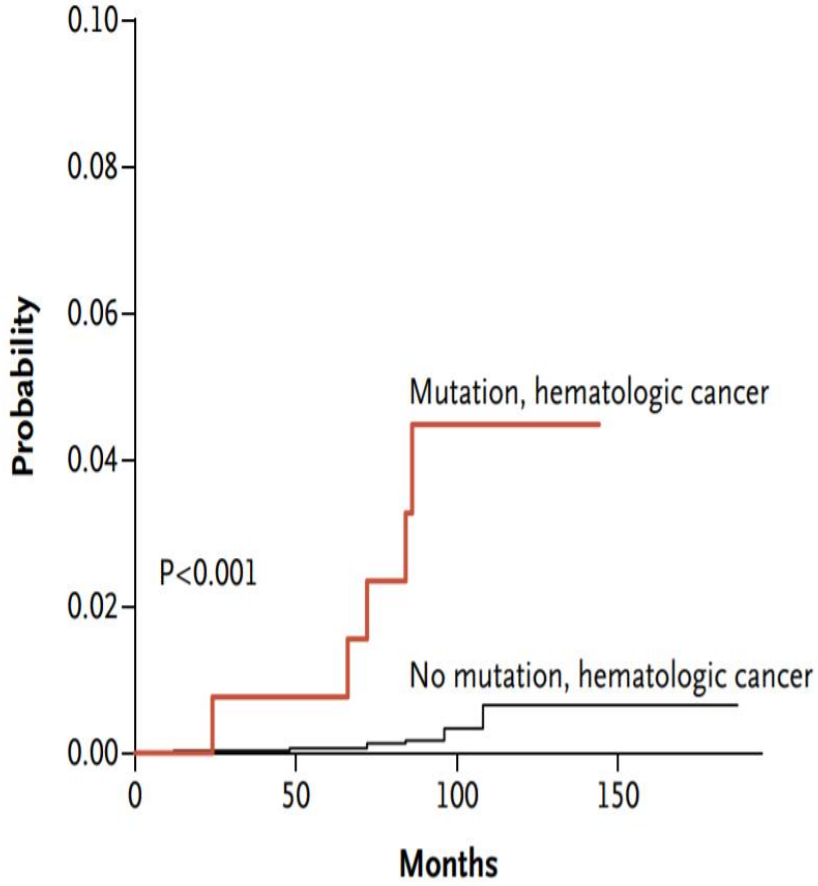
Self-renewal



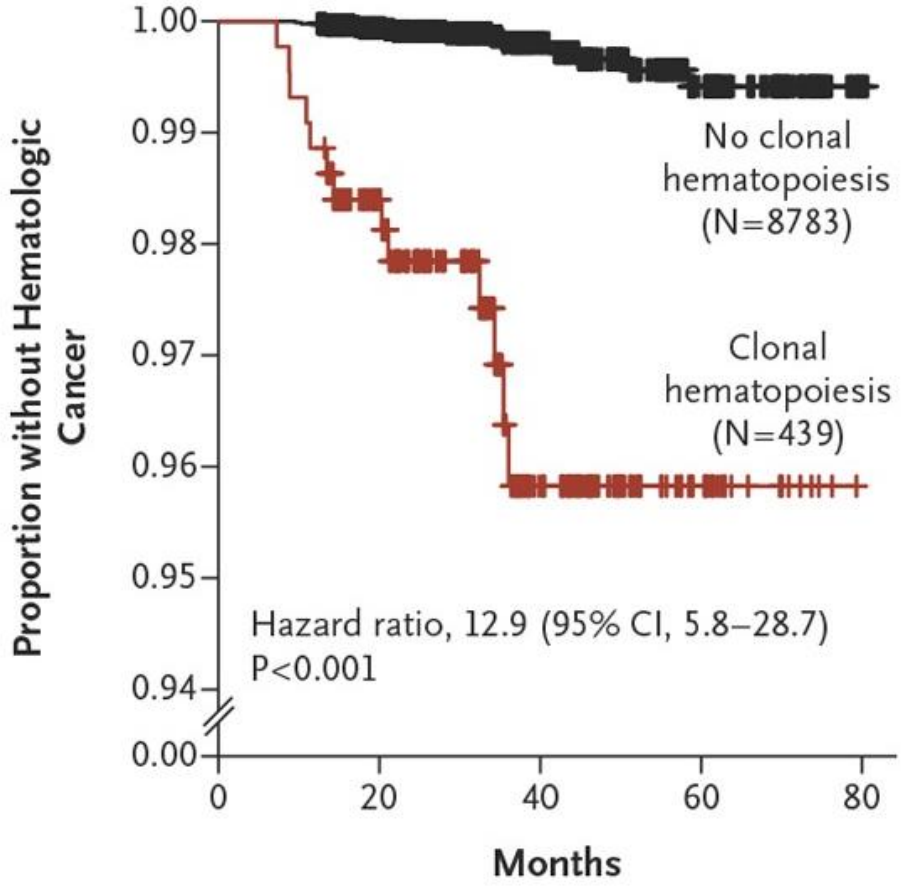
Differentiation

Genovese *et al*., NEJM 2014; Challen *et al*, Nature Genetics 2011

CH and risk for hematologic malignancies

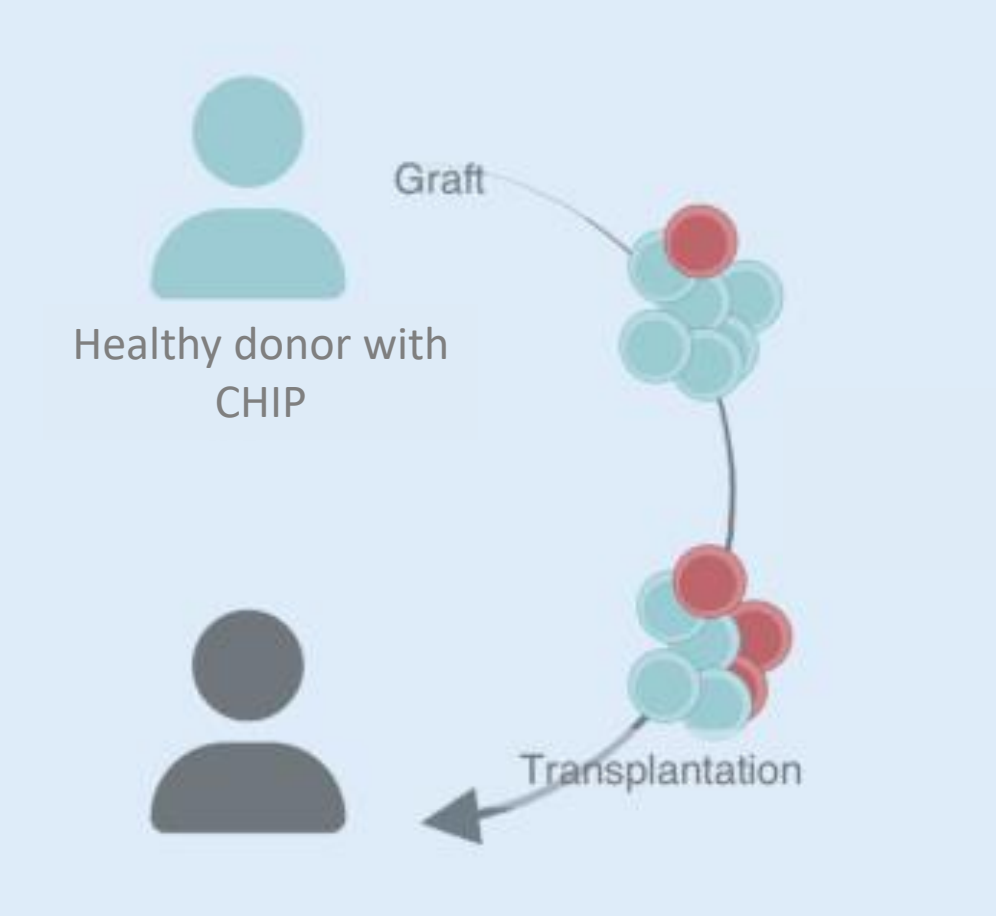


Jaiswal *et al.*, NEJM 2014



Genovese *et al.*, NEJM 2014

CH and allogeneic stem cell transplantation



Allogeneic SCT

- therapy-related myeloid neoplasms
- donor-cell leukemia (DCL)
- cardiovascular events
- disease relapse
- graft failure
- Infections
- Graft-versus-host disease (GvHD)

Modified from Teipel *et al.*, Innere Medizin 2014

Current knowledge (1)

original report

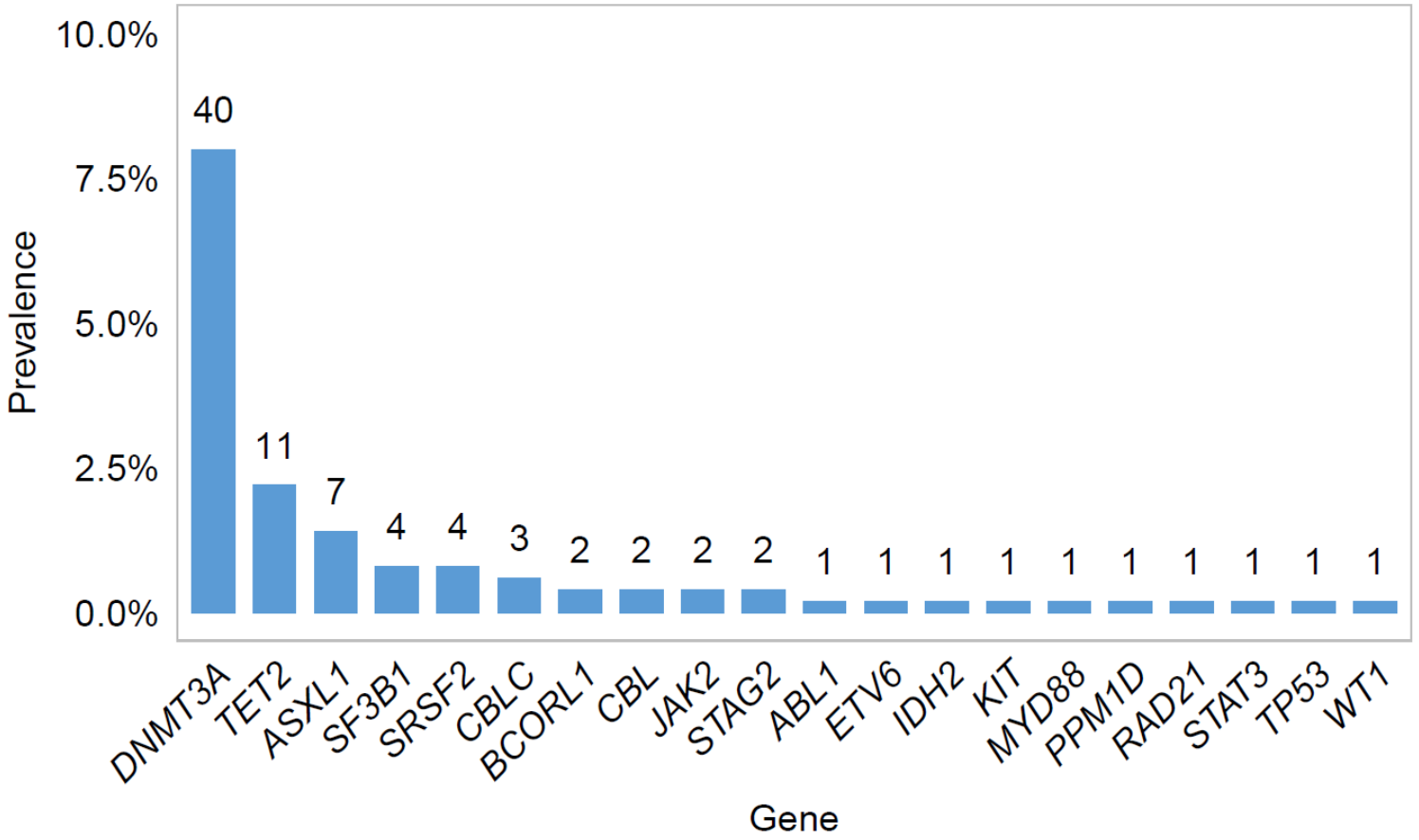
Role of Donor Clonal Hematopoiesis in Allogeneic Hematopoietic Stem-Cell Transplantation

Mareike Frick[1,2]; Willy Chan[1,2]; Christopher Maximilian Arends[1,2]; Raphael Hablesreiter[1,2]; Adriane Halik[1,2]; Michael Heuser[3]; David Michonneau[4]; Olga Blau[1,2]; Kaja Hoyer[1,2]; Friederike Christen[1,2]; Joel Galan-Sousa[1,2]; Daniel Noerenberg[1,2]; Verena Wais[5]; Michael Stadler[3]; Kenichi Yoshida[6]; Johannes Schetelig[7]; Esther Schuler[8]; Felicitas Thol[3]; Emmanuelle Clappier[9]; Maximilian Christopeit[10]; Francis Ayuk[10]; Martin Bornhäuser[7]; Igor Wolfgang Blau[1,2]; Seishi Ogawa[6]; Tomasz Zemojtel[11]; Armin Gerbitz[1,2]; Eva M. Wagner[12]; Bernd M. Spriewald[13]; Hubert Schrezenmeier[14]; Florian Kuchenbauer[5]; Guido Kobbe[8]; Markus Wiesneth[14]; Michael Koldehoff[15]; Gérard Socié[4]; Nicolaus Kroeger[10]; Lars Bullinger[1,2,16]; Christian Thiede[7,16]; and Frederik Damm[1,2,16]

Frick *et al.*, JCO 2019

CH in related elderly donors

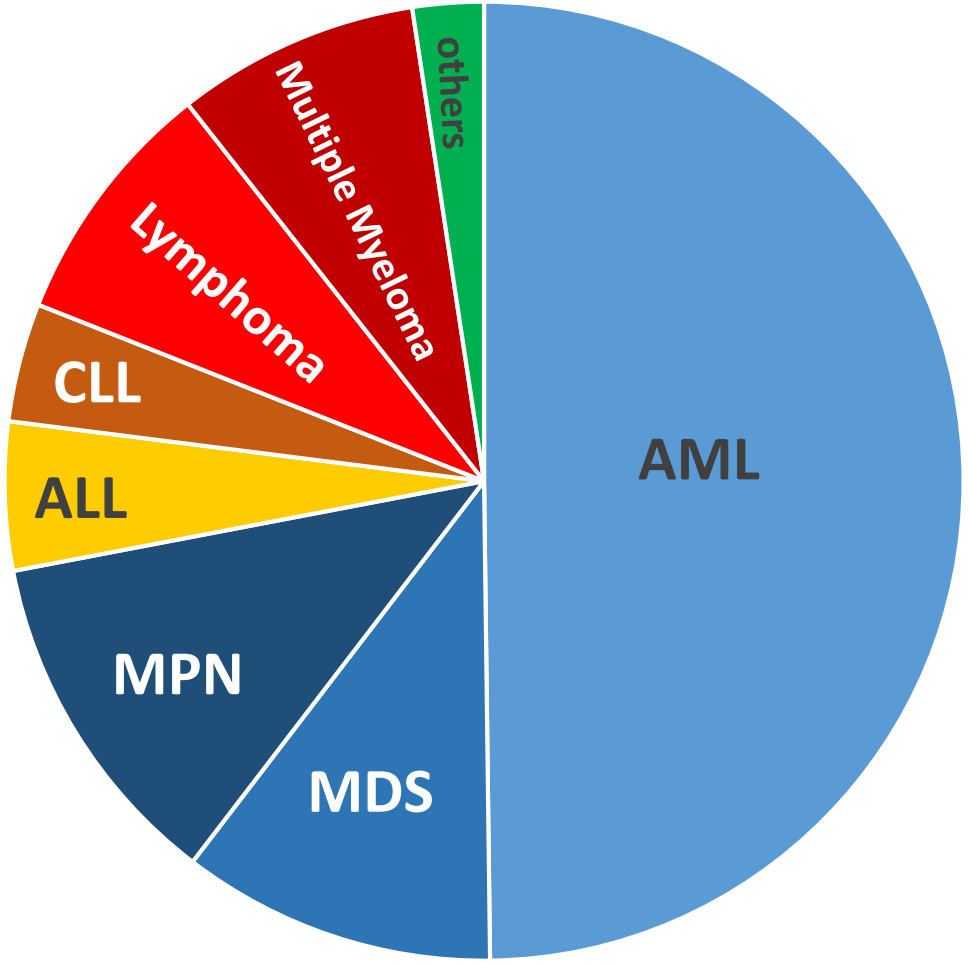
92 mutations in 500 related donors (55years) (donor-CHIP prevalence = 16%)



- Median VAF 5.9% (range 2 – 43%)
- 25 mutations in 20 donors with a VAF ≥10%
- Number of mutations/donor:
  - 1 mutation: 70 donors
  - 2 mutations: 9 donors
  - 4 mutations: 1 donor
- Frequent co-mutations:
  - *DNMT3A/DNMT3A* (n=4)
  - *DNMT3A/ASXL1* (n=3)

Frick *et al.*, JCO 2019

Recipients‘ diseases leading to allogeneic SCT



- 72.0% meyloid malignancies
- 25.6% lymphatic neoplasms
- 2.4% others

donor/recipient baseline characteristics

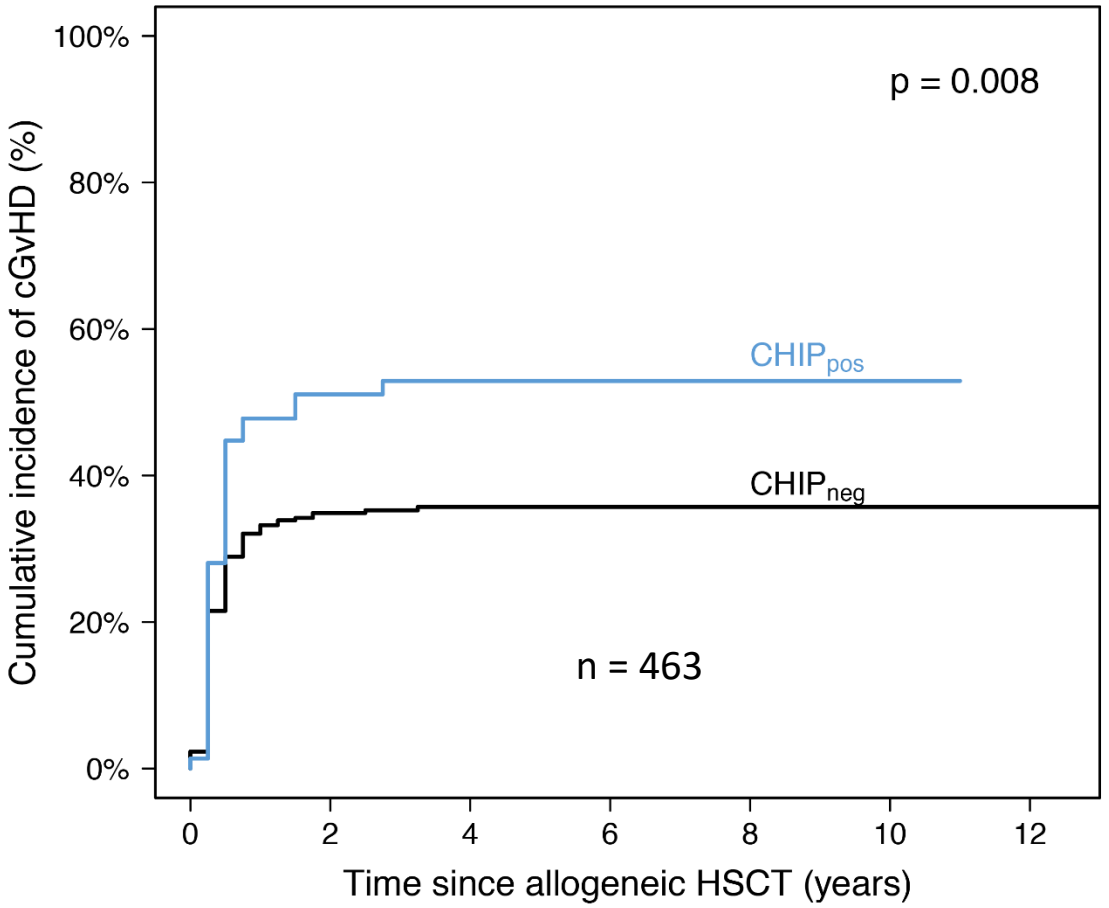
donor

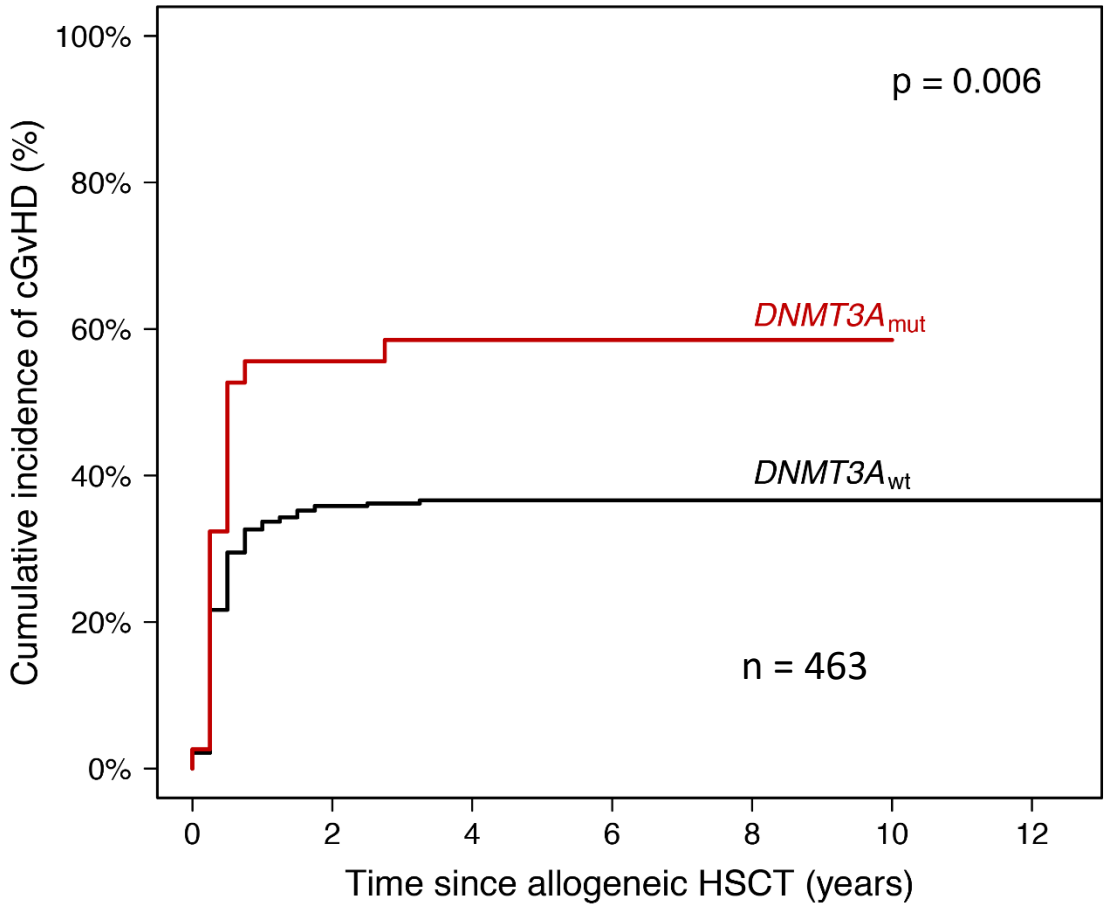
Characteristic	CHIP positive	CHIP negative	p-value
	(n= 80)	(n= 420)	
Age Donor			.388
Median (years)	65.0	63.0	
Range (years)	55 - 79	55 - 79	
Sex Donor			.646
Male - no.	39 (48.8%)	193 (46.0%)	
Female - no.	41 (51.2%)	227 (54.0%)	
Transplanted CD34+cells (x10^6/kg/body weight of recipient)			.456
Median	5.5	5.1	
Range	1.1 – 16.03	1.04 – 19.54	
Missing data	1	10	
Stem Cell Source			.524
PBSC	77 (96.3%)	397 (94.5%)	
Bone Marrow	3 (3.7%)	23 (5.5%)	

recipient

Characteristic	CHIP positive	CHIP negative	p-value
	(n= 80)	(n= 420)	
Recipient age			.762
Median (years)	60.0	61.0	
Range (years)	26 - 75	10 - 75	
Recipient sex			.647
Male - no.	50 (62.5%)	251 (59.8%)	
Female - no.	30 (37.5%)	169 (40.2%)	
Disease status at transplantation			.568
CR	28 (35.9%)	164 (39.3%)	
Non-CR	50 (64.1%)	253 (60.7%)	
Missing data	2	3	
ECOG Recipient			.326
ECOG 0/1	75 (93.8%)	372 (90.3%)	
ECOG >1	5 (6.2%)	40 (9.7%)	
Missing Data	0	8	
Conditioning Regimen			.424
MAC	13 (16.3%)	54 (12.9%)	
Non-MAC	67 (83.7%)	364 (87.1%)	
Missing data	0	2	
ATG application			.223
Yes	24 (30.0%)	156 (37.1%)	
No	56 (70.0%)	264 (62.9%)	

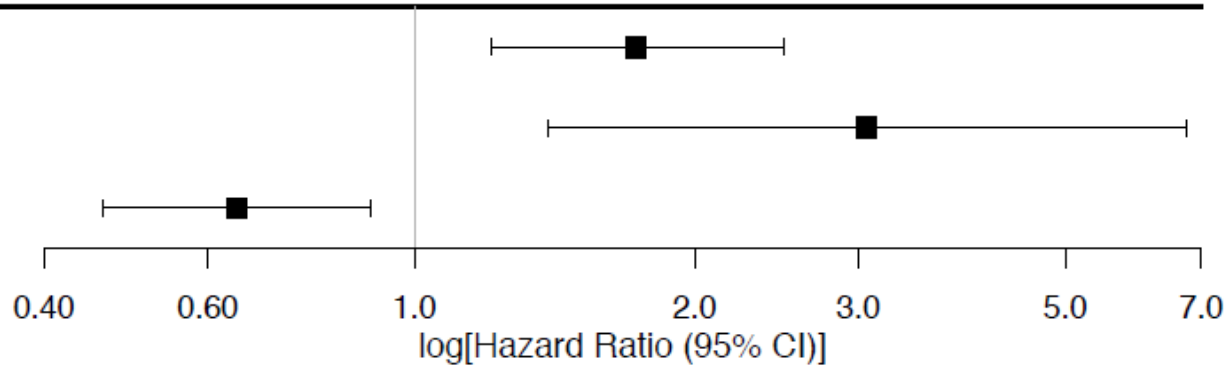
Transplantation outcome: cGvHD



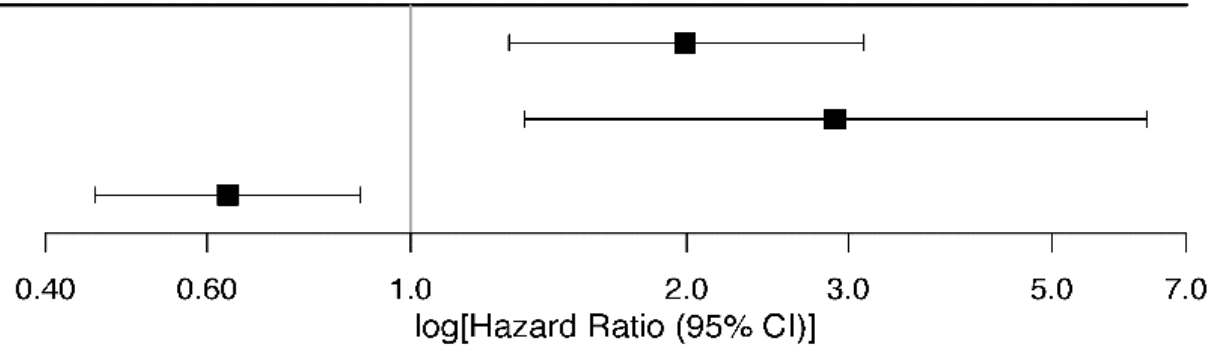


Transplantation outcome: cGvHD

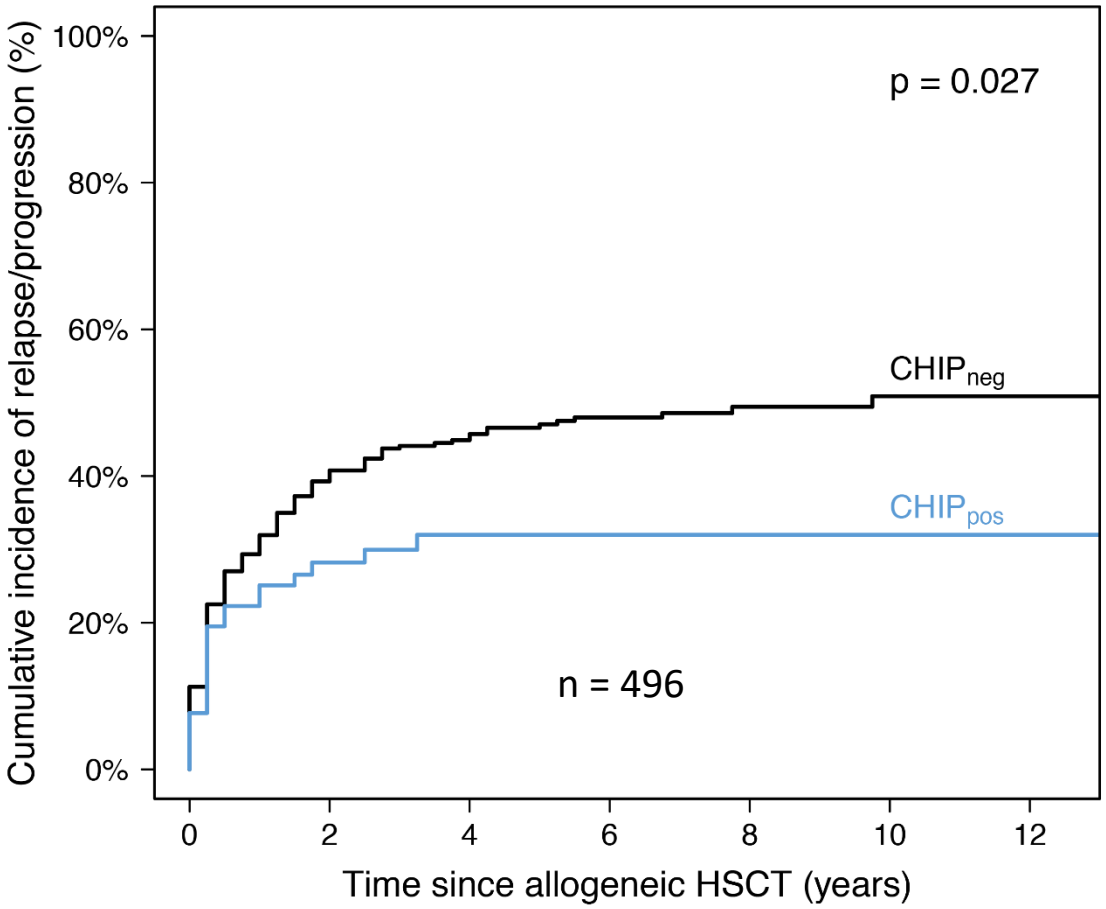
Parameter	HR	95% CI	p–value
CHIP	1.73	[1.21–2.49]	0.003
Donor age ≥ 60	3.06	[1.39–6.74]	0.006
ATG	0.65	[0.46–0.90]	0.010

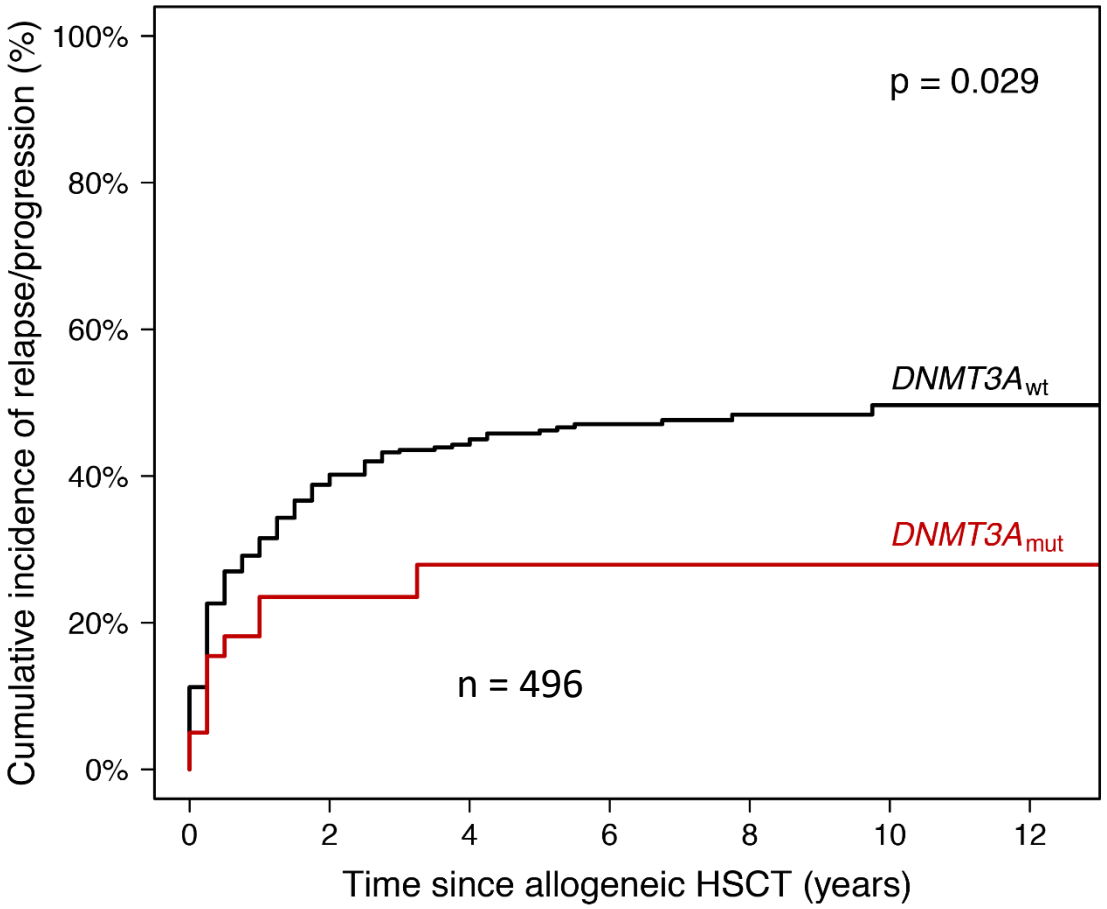


Parameter	HR	95% CI	p–value
DNMT3A	1.99	[1.28–3.12]	0.002
Donor age ≥ 60	2.90	[1.33–6.34]	0.008
ATG	0.63	[0.45–0.88]	0.007



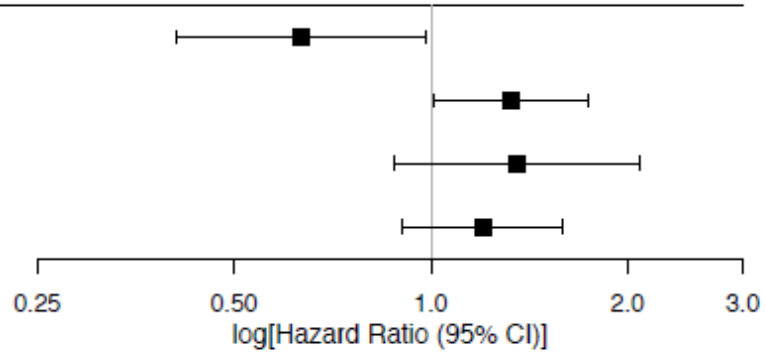
Transplantation outcome: Cumulative Incidence of Relapse/Progression (CIRP)



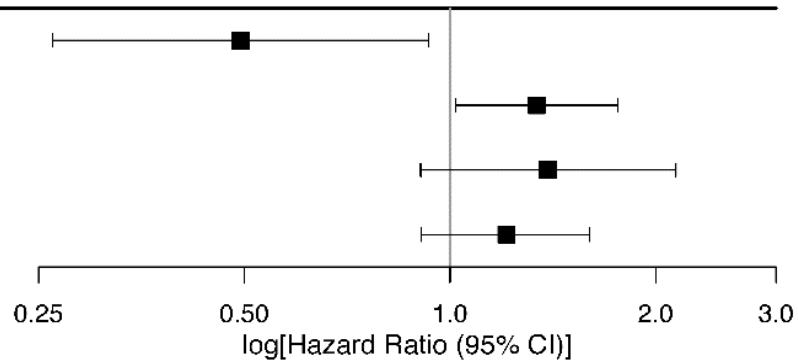


Transplantation outcome: Cumulative Incidence of Relapse/Progression (CIRP)

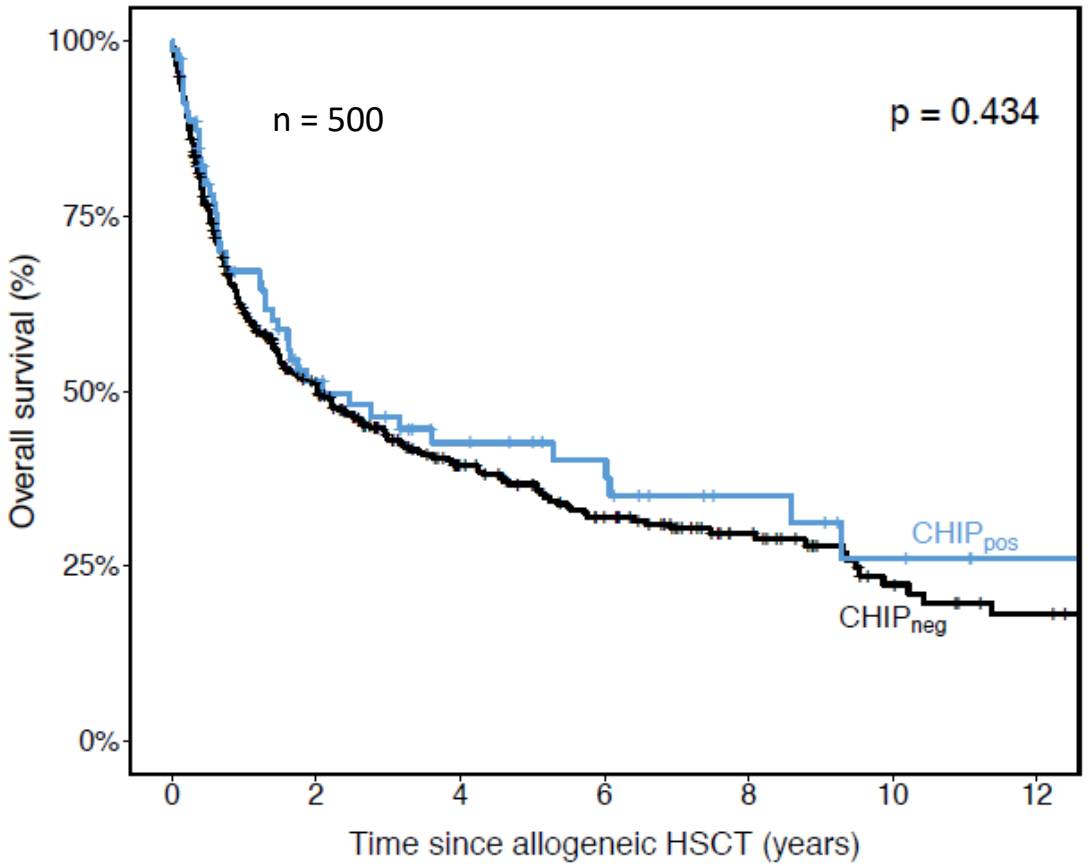
Parameter	HR	95% CI	p–value
CHIP	0.63	[0.41–0.98]	0.042
AML	1.33	[1.01–1.74]	0.043
Non–MAC conditioning regimen	1.35	[0.88–2.08]	0.170
ATG	1.20	[0.90–1.59]	0.210

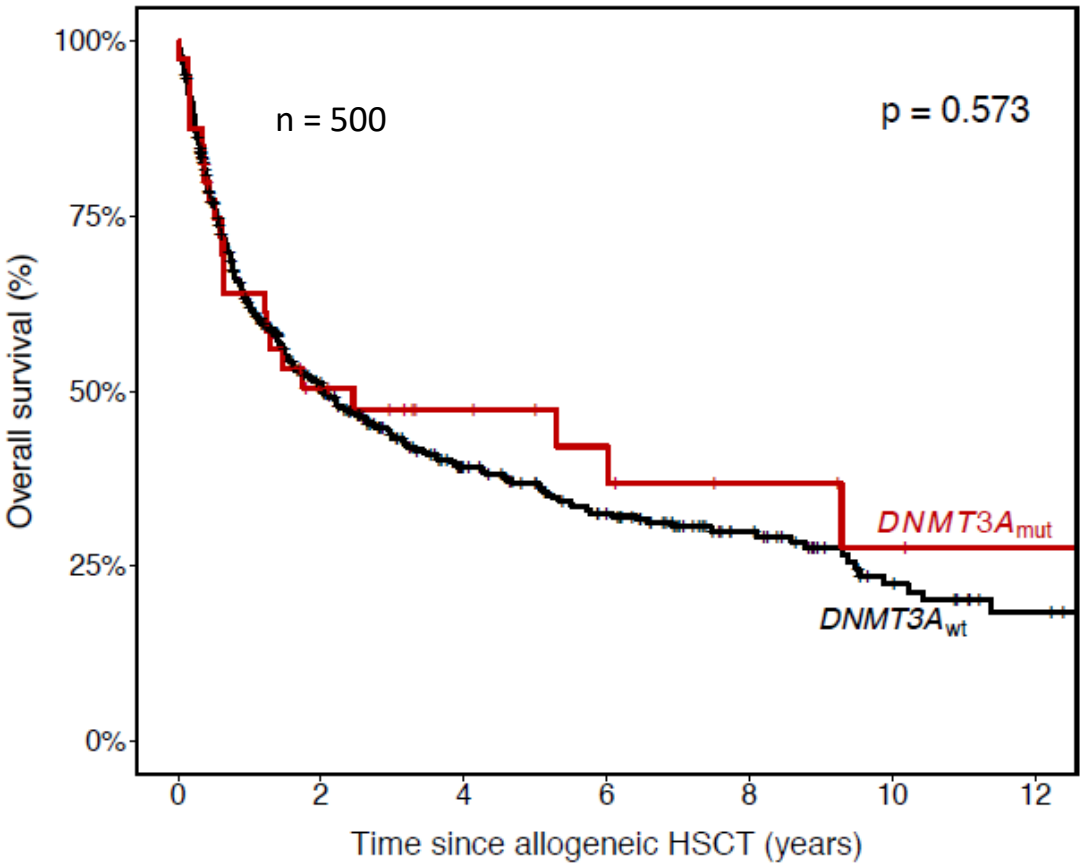


Parameter	HR	95% CI	p–value
DNMT3A	0.49	[0.26–0.93]	0.029
AML	1.34	[1.02–1.76]	0.037
Non–MAC conditioning regimen	1.39	[0.91–2.14]	0.130
ATG	1.21	[0.91–1.60]	0.200



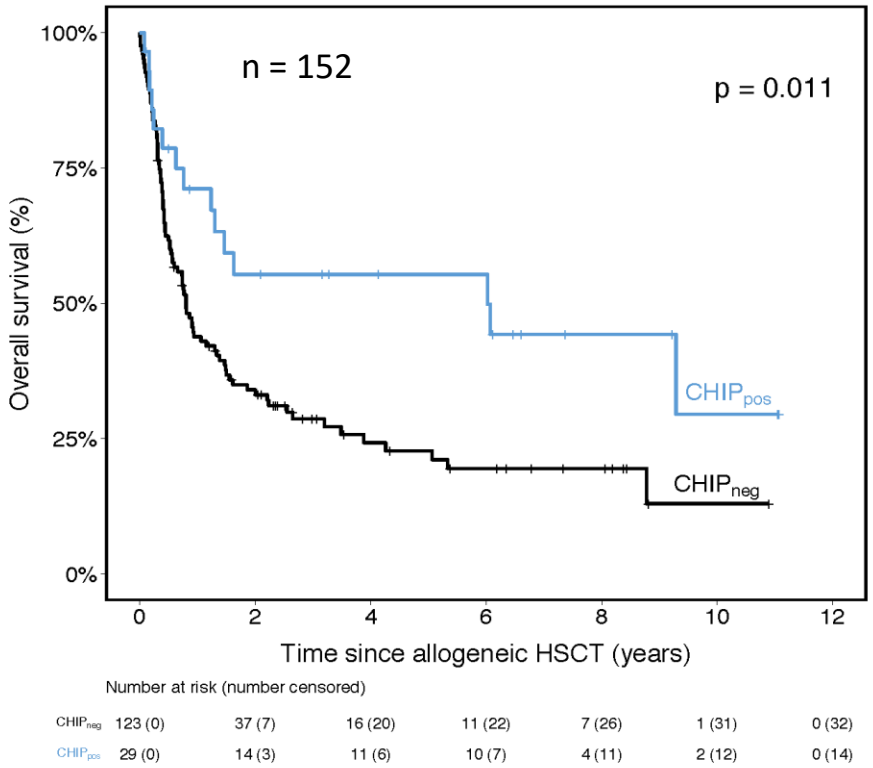
Transplantation outcome: overall survival

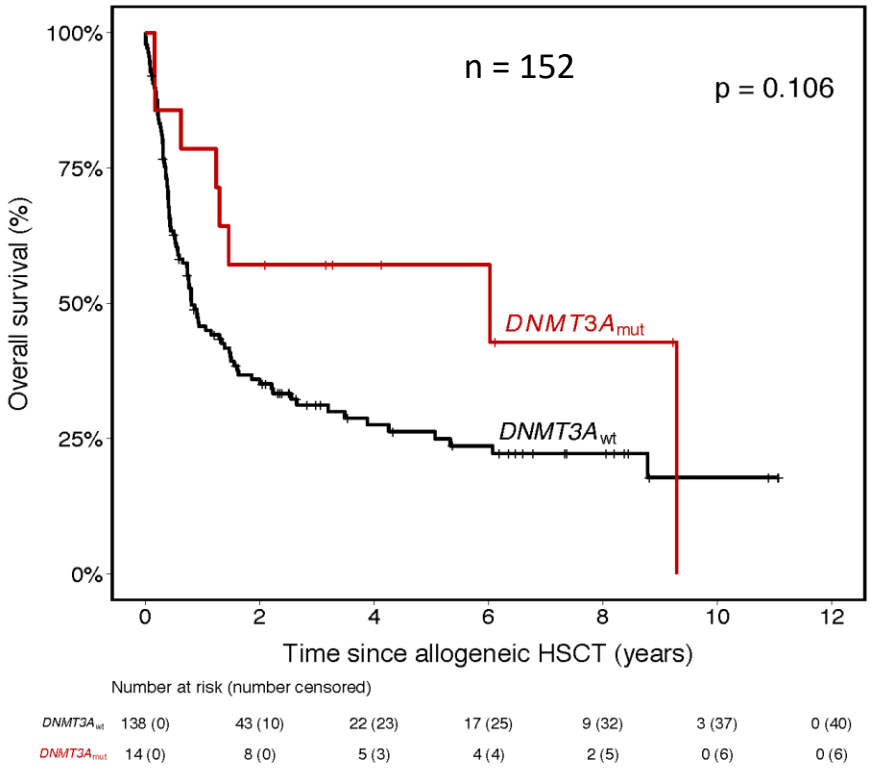




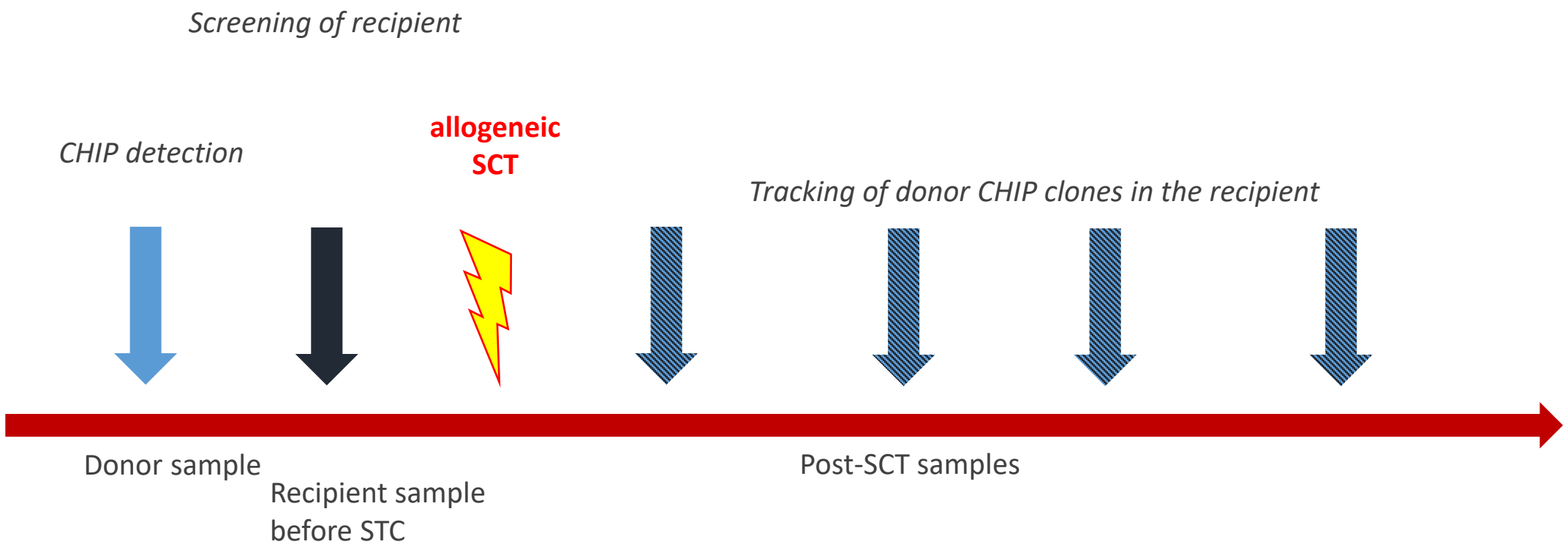
Donor CHIP/*DNMT3A* mutation status has no impact on recipients‘ overall survival

Transplantations-Outcome: Gesamtüberleben AML/MDS in non-CR



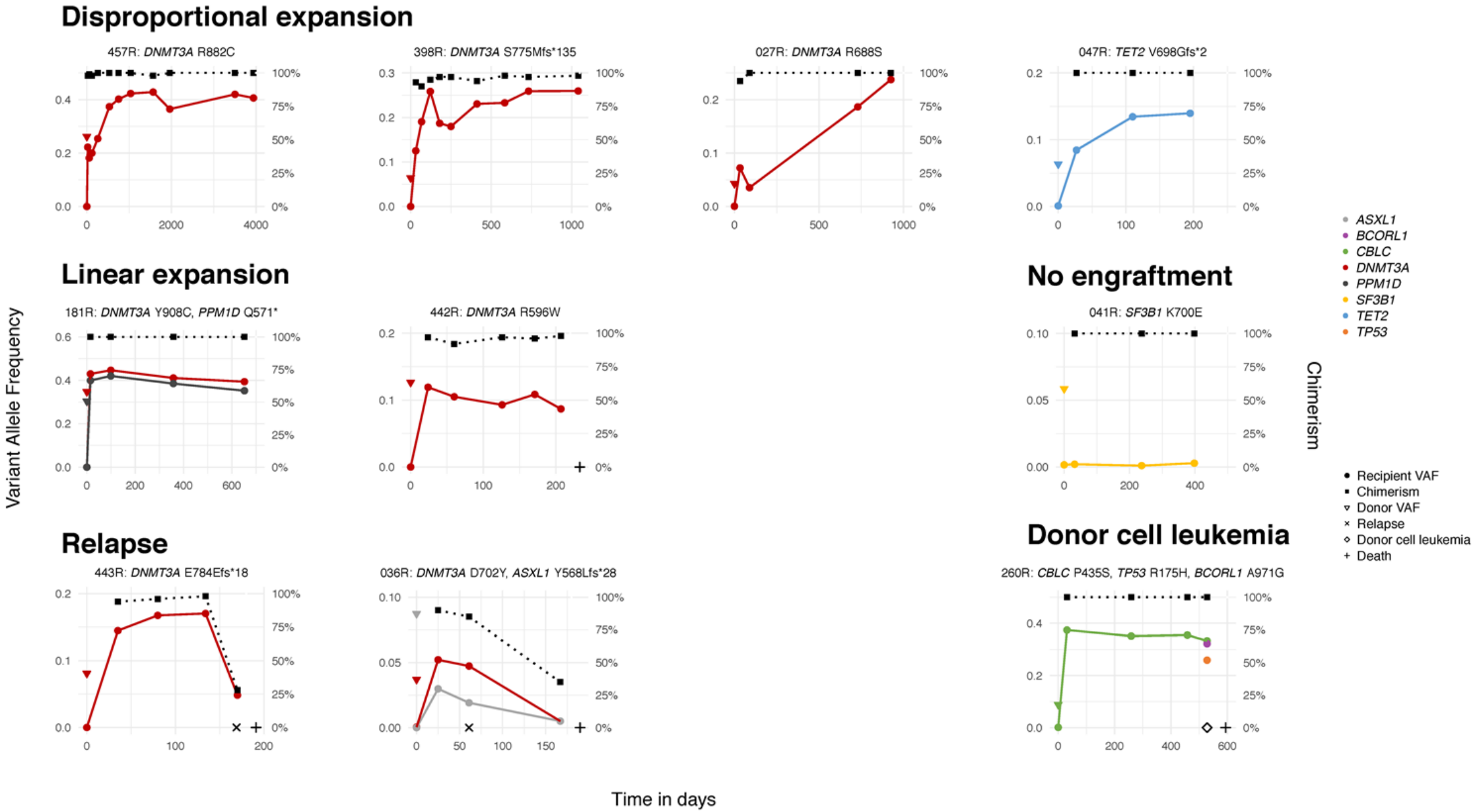


Clonal dynamics of transplanted CHIP clones

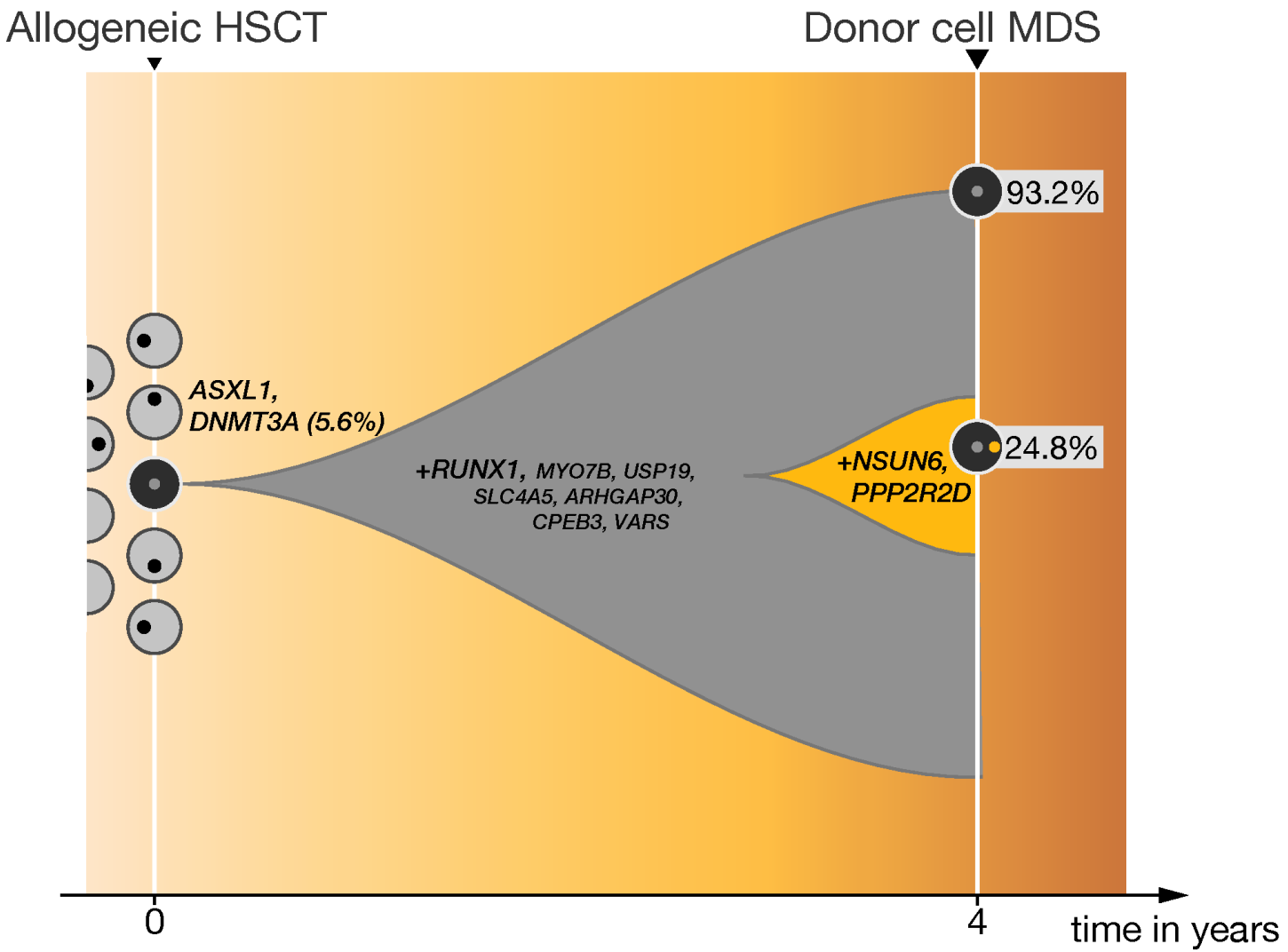


→ Serielle Analysen von 25 CHIP-Mutationen in 22 Empfängern

Dynamics of transplanted CHIP clones



CH and donor-derived MDS/AML



Frick *et al.*, JCO 2019

Summary

- donor-CHIP is associated with chronic GvHD
- donor-CHIP is associated with a reduced risk for relapse/progression
- donor-CHIP appears safe in the context of allogeneic SCT
- donor-CHIP clones frequently show disproportional expansion

Current knowledge (2)

ARTICLE

Check for updates

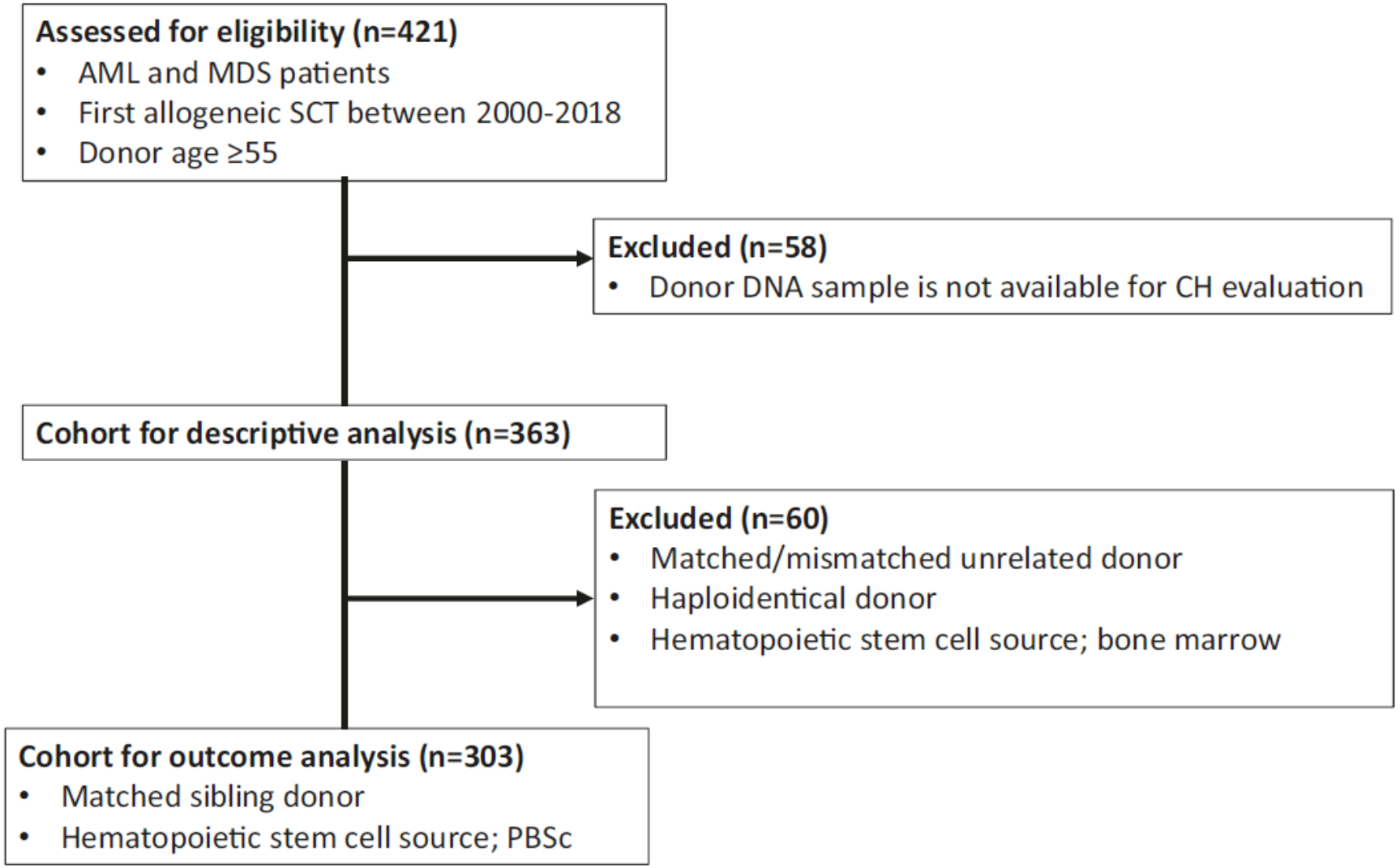
Stem Cell Transplantation

Donor clonal hematopoiesis increases risk of acute graft versus host disease after matched sibling transplantation

Betül Oran[1]✉, Richard E. Champlin[1], Feng Wang[2], Tomoyuki Tanaka[2], Rima M. Saliba[1], Gheath Al-Atrash[1], Guillermo Garcia-Manero[3], Hagop Kantarjian[3], Kai Cao[4], Elizabeth J. Shpall[1], Amin M. Alousi[1], Rohtesh S. Mehta[1], Uday Popat[1], Andy Futreal[2] and Koichi Takahashi[2,3]✉

Oran *et al*., Leukemia 2022

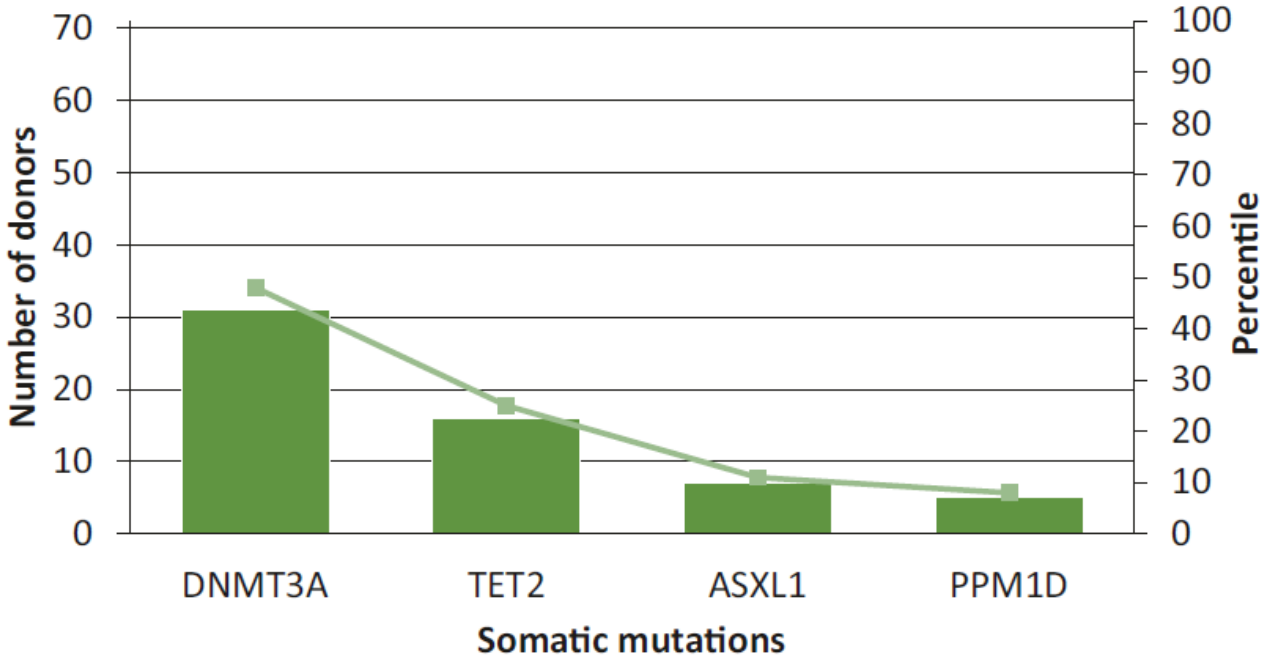
The MD Anderson cohort

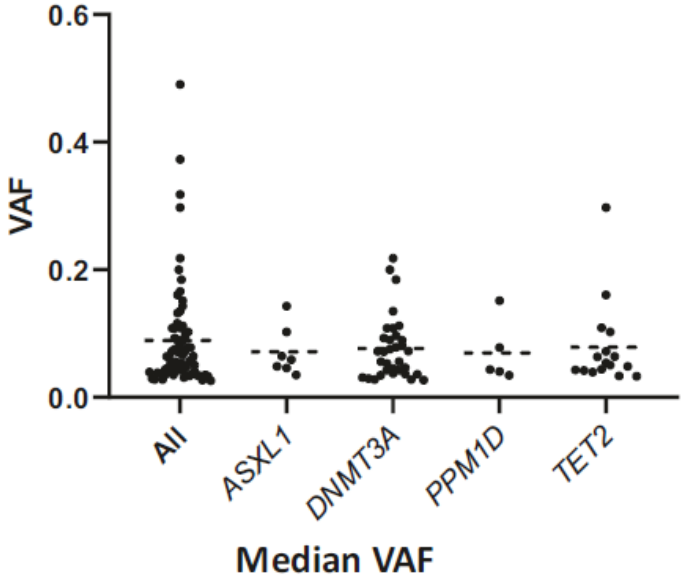


Oran *et al.*, Leukemia 2022

The MD Anderson cohort

CH mutations in 65 out of 363 donors (donor-CHIP prevalence = 18%)





Oran *et al.*, Leukemia 2022

The MD Anderson cohort

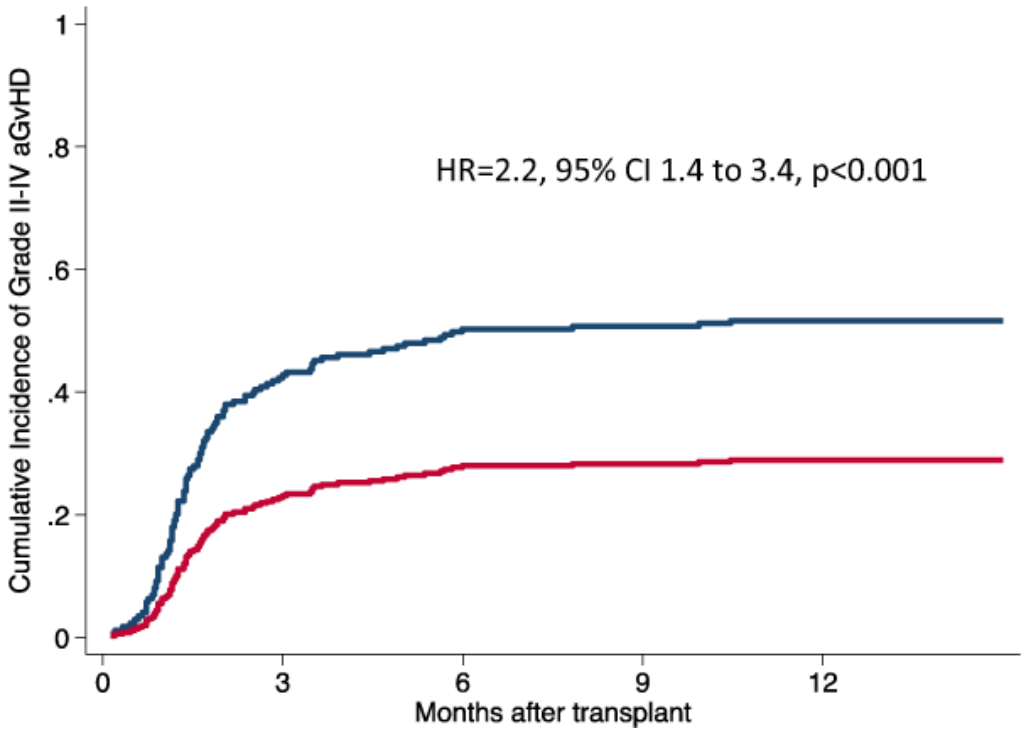
Characteristics	CH-positive donors, $n = 53$	CH-negative donors, $n = 250$	p
Donor age, median, range	63 (55–78)	61 (55–77)	0.05
Donor sex, female	24 (45%)	138 (55%)	0.2
Patient age, median, range	63 (50–72)	61 (37–77)	0.4
Recipient sex, female	16 (30%)	101 (40%)	0.2
Female donor/male recipient	15 (28%)	79 (32%)	0.6
Diagnosis			0.5
AML	40 (75%)	178 (71%)	
MDS	13 (25%)	72 (29%)	
Cytogenetic risk groups			0.7
Bad	19 (36%)	90 (36%)	
Intermediate	25 (47%)	127 (51%)	
Good	9 (17%)	30 (12%)	
Undetermined	0	3 (1%)	
Disease status at HSCT			0.3
CR1/CR2	24 (45%)	93 (37%)	
Beyond CR2/active disease	29 (55%)	157 (63%)	

Characteristics	CH-positive donors, $n = 53$	CH-negative donors, $n = 250$	p
Conditioning intensity			0.9
Reduced intensity conditioning	24 (45%)	114 (46%)	
Myeloablative conditioning	29 (55%)	136 (54%)	
GvHD prophylaxis			0.5
Tacrolimus and MTX	48 (91%)	231 (92%)	
Tacrolimus alone or with MMF	0	2 (1%)	
Cyclophosphamide and tacrolimus ± MMF	5 (9%)	14 (6%)	
Cyclophosphamide	0	3 (1%)	
HCT-CI, median, range	3 (0–8)	3 (0–11)	0.1
HCT-CI >3	20 (38%)	89 (36%)	0.8
Transplantation year			
2002–2008	11 (21%)	81 (32%)	
2009–2012	13 (24%)	73 (29%)	
2013–2018	29 (55%)	96 (38%)	0.03

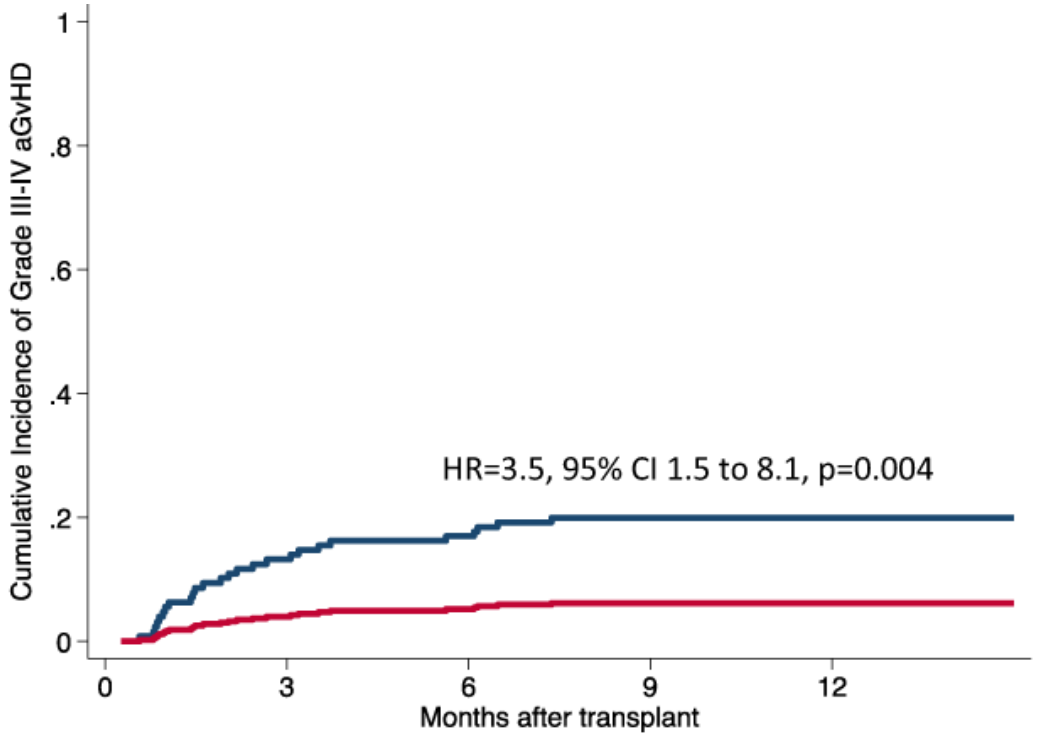
Oran *et al.*, Leukemia 2022

The MD Anderson cohort: aGvHD

donor >55 und <65 Jahre

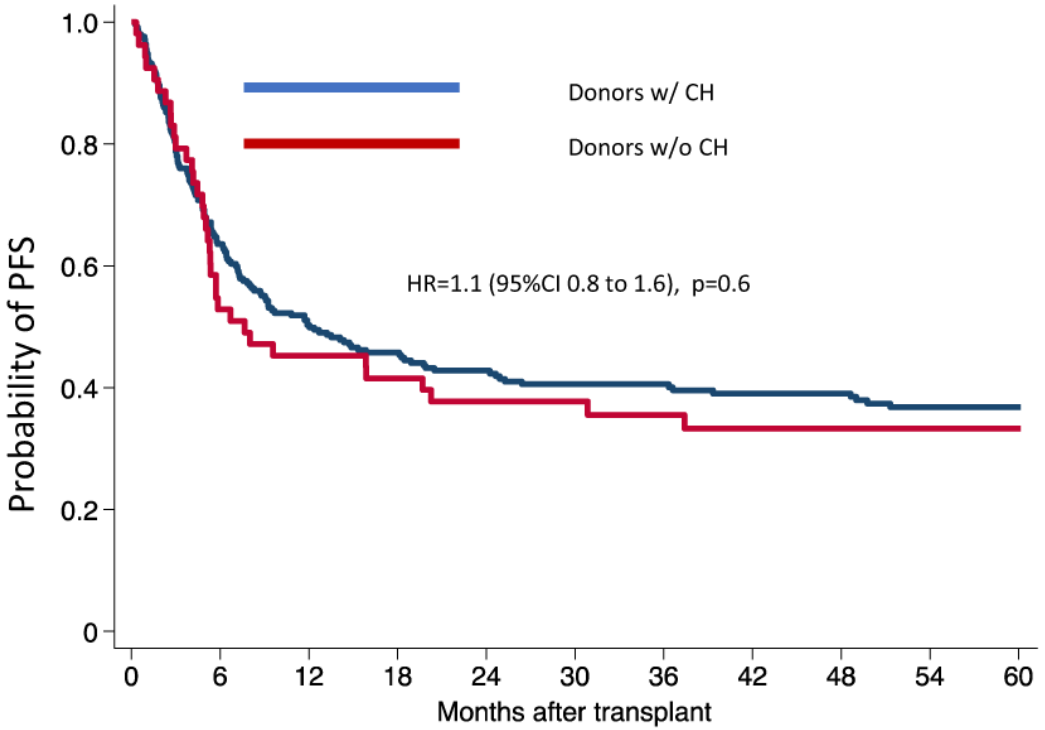


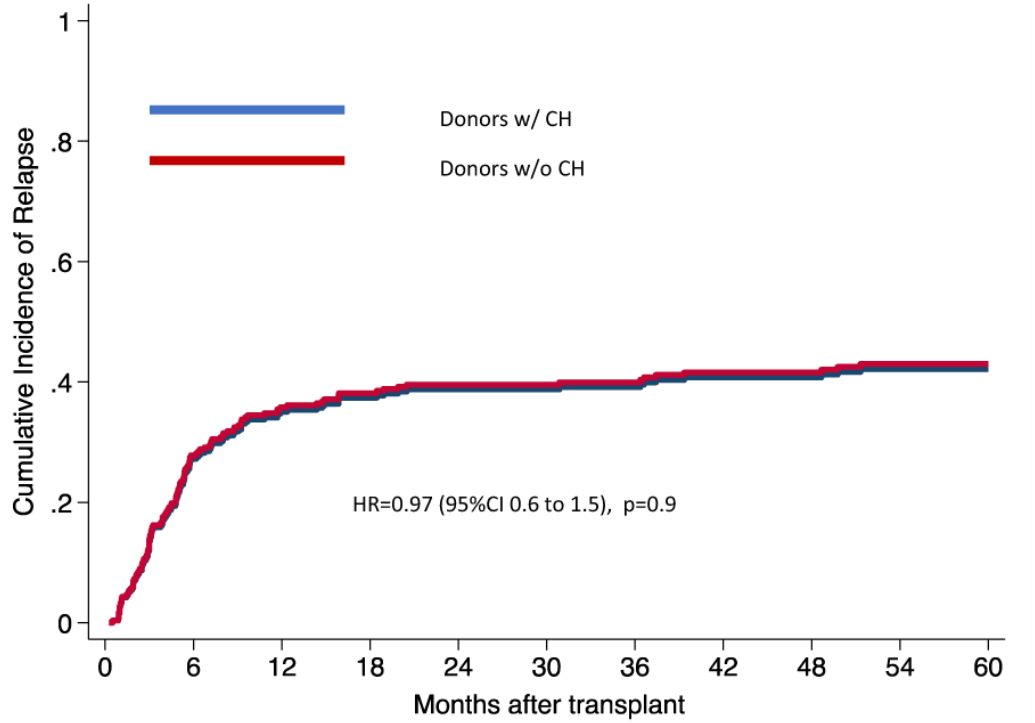
donor > 65 Jahre



Oran *et al.*, Leukemia 2022

The MD Anderson cohort: PFS and CIR





Oran *et al.*, Leukemia 2022

Current knowledge (3)

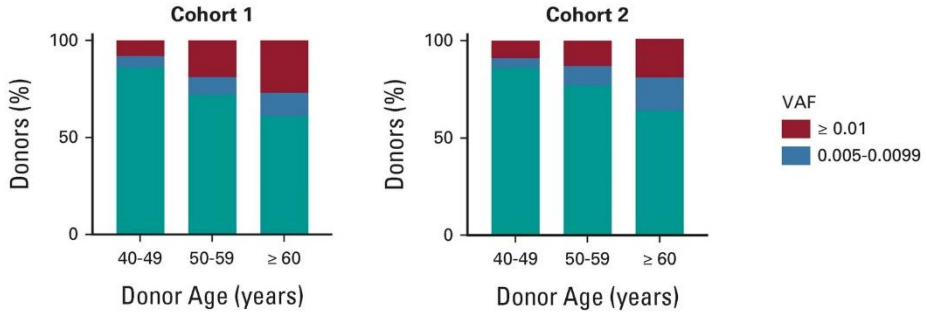
original reports

Donor Clonal Hematopoiesis and Recipient Outcomes After Transplantation

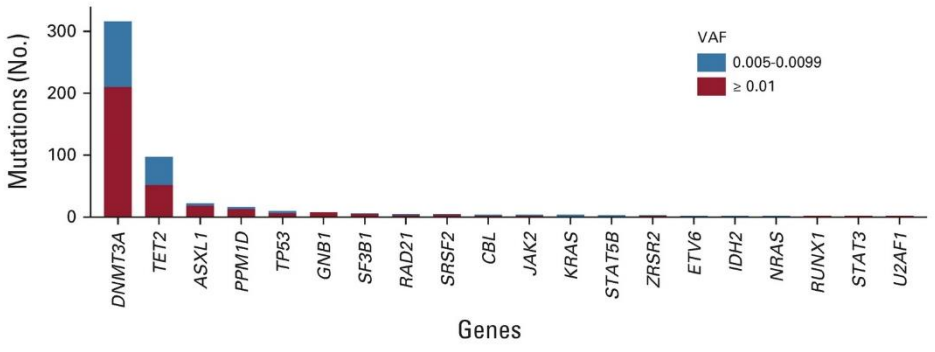
Christopher J. Gibson, MD[1]; Haesook T. Kim, PhD[2]; Lin Zhao, MD[3,4]; H. Moses Murdock, MD[5]; Bryan Hambley, MD[3]; Alana Ogata, PhD[6,7]; Rafael Madero-Marroquin, MD[3]; Shiyu Wang, BS[3]; Lisa Green, MA[8]; Mark Fleharty, PhD[8]; Tyler Dougan, BS[6,7]; Chi-An Cheng, PhD[6,7]; Brendan Blumenstiel, BS[8]; Carrie Cibulskis, BS[8]; Junko Tsuji, PhD[8]; Madeleine Duran, BS[9]; Christopher D. Gocke, MD[3,10]; Joseph H. Antin, MD[1]; Sarah Nikiforow, MD, PhD[1]; Amy E. DeZern, MD[3]; Yi-Bin Chen, MD[11]; Vincent T. Ho, MD[1]; Richard J. Jones, MD[3]; Niall J. Lennon, PhD[8]; David R. Walt, PhD[6,7]; Jerome Ritz, MD[1]; Robert J. Soiffer, MD[1]; Lukasz P. Gondek, MD, PhD[3]; and R. Coleman Lindsley, MD, PhD[1]

Gibson *et al.*, JCO 2022

Dana-Farber Cancer Institute / John Hopkins University cohorts



	Cohort 1			Cohort 2		
	40-49	50-59	≥ 60	40-49	50-59	≥ 60
VAF 0.005-0.0099	22	36	27	16	26	19
VAF ≥ 0.01	40	58	31	22	51	40
No CH	455	296	95	246	175	72



	DNMT3A	TET2	ASXL1	PPM1D	TP53	GNB1	SF3B1	RAD21	SRSF2	CBL	JAK2	KRAS	STAT5B	ZRSR2	ETV6	IDH2	NRAS	RUNX1	STAT3	U2AF1
VAF 0.005-0.0099	100	45	4	3	4	0	1	2	1	2	2	3	2	1	2	2	2	0	0	0
VAF ≥ 0.01	202	51	18	11	5	8	5	3	4	2	2	1	1	2	1	1	0	2	2	2

501 mutations in 1727 donors:

324 with a VAF ≥ 0.01
77 with a VAF ≥ 0.005-0.0099

Gibson *et al.*, JCO 2022

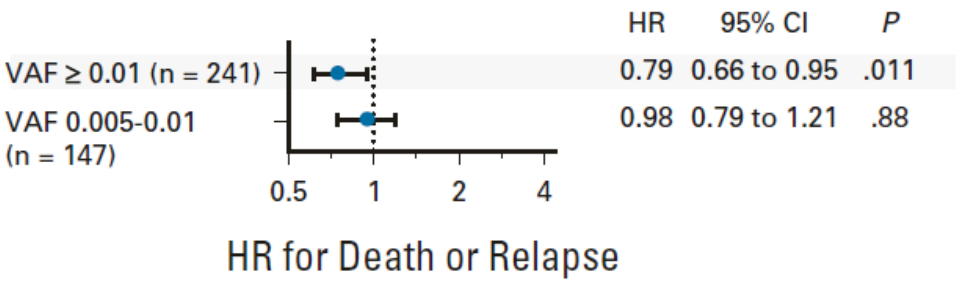
Dana-Farber Cancer Institute / John Hopkins University cohorts

Characteristic	All	No CH	CH	UV *P*	MV *P*
Full cohort	**1,727 (100)**	**1,339 (77.5)**	**388 (22.5)**		
DFCI	1,060 (61.3)	846 (63.2)	214 (55.2)	.005	NA
JHU	667 (38.7)	493 (36.8)	174 (44.8)		
Recipient age, years, median (range)	55 (0.5-78)	54 (0.5-78)	56 (6-76)	.45	—
Recipient sex				.64	—
Female	700 (40.5)	547 (40.8)	153 (39.4)		
Male	1,027 (59.5)	792 (59.2)	235 (60.6)		
Donor sex				.13	—
Female	813 (47.1)	617 (46.1)	196 (50.5)		
Male	908 (52.6)	717 (53.5)	191 (49.2)		
Unknown	6 (0.3)	5 (0.4)	1 (0.3)		
Donor age, years, median (range)	51 (40-80)	49 (40-71)	56 (40-80)	< .001	< .001
Related donors	53 (40-80)	52 (40-71)	57 (40-80)		
Unrelated donors	46 (40-60)	45 (40-60)	46 (40-59)		
Disease				.33	
Lymphoid	718 (41.6)	501 (41.4)	151 (42.3)		
NHL	319 (18.5)	243 (18.1)	76 (19.6)		
ALL	149 (8.6)	116 (8.6)	33 (8.5)		
Chronic lymphocytic leukemia	116 (6.7)	92 (6.9)	24 (6.2)		
Hodgkin lymphoma	68 (3.9)	50 (3.7)	18 (4.7)		
Multiple myeloma	66 (3.8)	53 (4)	13 (3.4)		
Myeloid	929 (53.8)	718 (53.6)	211 (54.3)		
AML	609 (35.3)	455 (34.1)	154 (39.7)		
MDS	189 (10.9)	154 (11.5)	35 (9)		
Chronic myeloid leukemia	63 (3.6)	55 (4.1)	8 (2.1)		
MPN	36 (2.1)	26 (1.9)	10 (2.6)		
MDS/MPN overlap	32 (1.9)	28 (2.1)	4 (1)		
Others	80 (4.6)	67 (5)	13 (3.4)		
RBC disorder	48 (2.8)	40 (3)	8 (2.1)		
Other disease	19 (1.1)	16 (1.2)	3 (0.8)		
Other leukemia	13 (0.8)	11 (0.8)	2 (0.5)		
HCT-CI				.59	—
0	576 (33.7)	450 (33.6)	126 (32.4)		
1-2	548 (31.7)	415 (31)	133 (34.3)		
≥ 3	585 (34.2)	458 (34.2)	127 (32.7)		
Unknown	18 (1)	16 (1.2)	2 (0.5)		
Median (range)	1 (0-12)	1 (0-10)	1 (0-12)		
Graft source				.06	.98
BM	703 (40.7)	526 (39.3)	177 (45.6)		
BM and PBSC	2 (0.1)	2 (0.1)	0		
PBSC	1,022 (59.2)	811 (60.6)	211 (54.4)		
Conditioning intensity				.23	—
Myeloablative	632 (36.6)	500 (37.3)	132 (34)		
TBI-based	323 (51.1)	275 (55)	48 (36.4)		
Nonmyeloablative	1,094 (63.3)	838 (62.3)	256 (66)		
TBI-based	482 (44.1)	356 (42.5)	126 (49.2)		
Unknown	1 (0.1)	1			
Donor type				< .0001	.51
Haploidentical	454 (26.3)	333 (24.8)	121 (31.2)		
Mismatched, related	38 (2.2)	30 (2.2)	8 (2.1)		
Mismatched, unrelated	71 (4.1)	58 (4.3)	13 (3.3)		
Matched, related	889 (51.5)	674 (50.3)	215 (55.4)		
Matched, unrelated	273 (15.8)	242 (18.1)	31 (8)		
Syngeneic	2 (0.1)	2			
GVHD prophylaxis				.003	.66
PTCy	671 (38.9)	495 (37)	176 (45.4)		
Other regimens	1,056 (61.1)	844 (63)	212 (54.6)		

Gibson *et al.*, JCO 2022

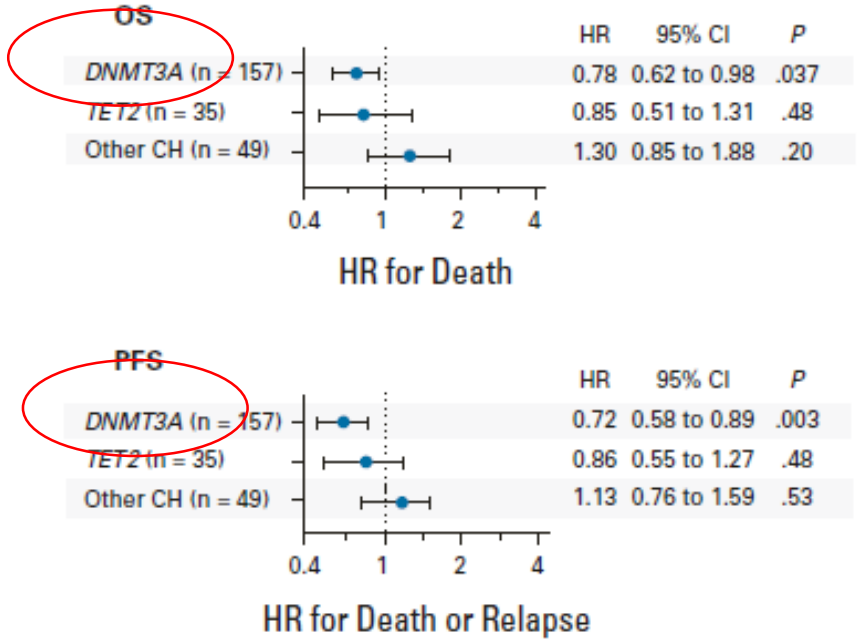
Dana-Farber Cancer Institute / John Hopkins University cohorts

PFS



n = 1727

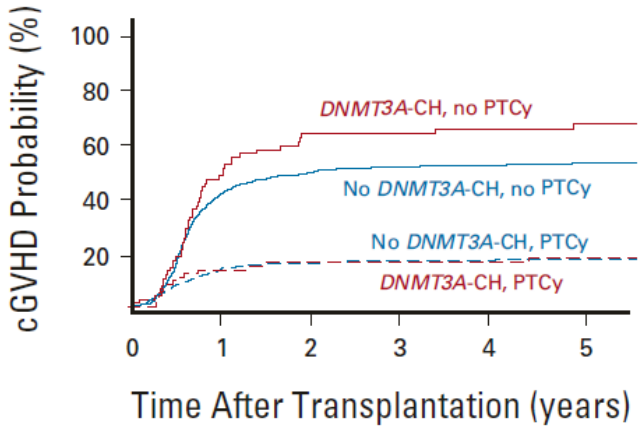
PFS und OS



Gibson *et al.*, JCO 2022

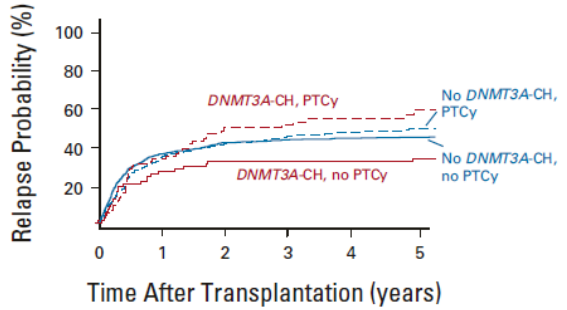
Dana-Farber Cancer Institute / John Hopkins University cohorts

cGvHD und *DNMT3A*

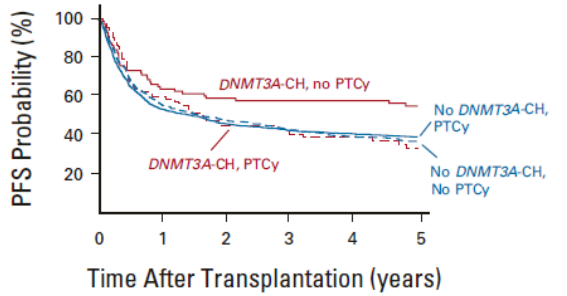


No. at risk:						
CH group, GVHD prophylaxis	0	1	2	3	4	5
No *DNMT3A*, No PTCy	977	227	130	105	90	75
DNMT3A, No PTCy	79	20	9	9	6	5
No *DNMT3A*, PTCy	593	278	207	160	125	82
DNMT3A, PTCy	78	39	29	24	19	12

DNMT3A und PTCy

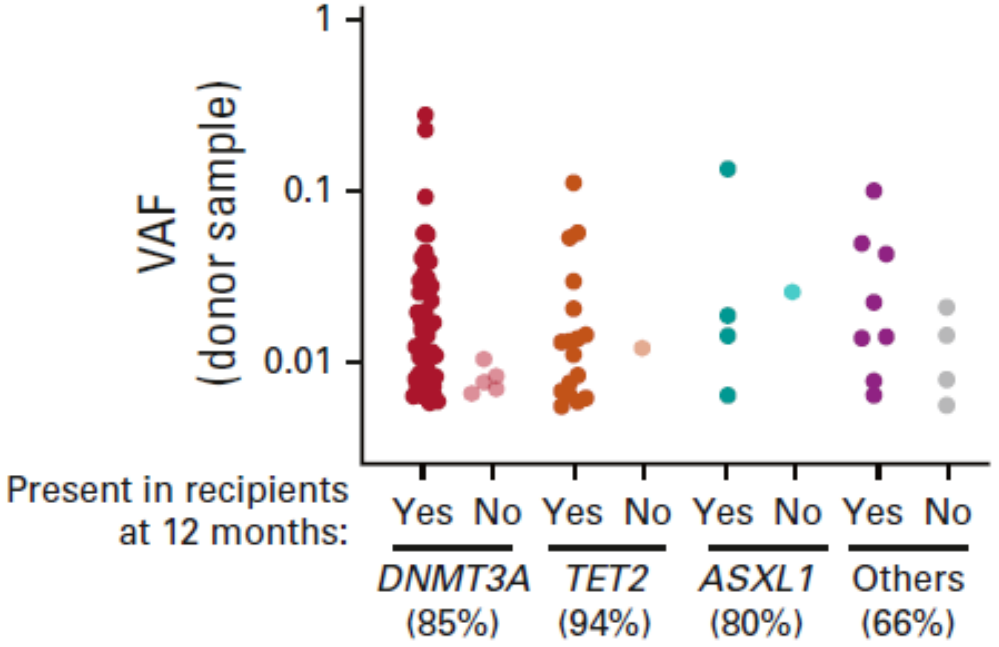


No. at risk:						
CH group, GVHD prophylaxis	0	1	2	3	4	5
No *DNMT3A*, No PTCy	977	227	130	105	90	75
DNMT3A, No PTCy	79	20	9	9	6	5
No *DNMT3A*, PTCy	593	278	207	160	125	82
DNMT3A, PTCy	78	39	29	24	19	12



No. at risk:						
CH group, GVHD prophylaxis	0	1	2	3	4	5
No *DNMT3A*, No PTCy	977	501	420	384	345	298
DNMT3A, No PTCy	79	47	42	41	37	34
No *DNMT3A*, PTCy	593	324	252	201	161	107
DNMT3A, PTCy	78	46	35	29	24	15

Dana-Farber Cancer Institute / John Hopkins University cohorts



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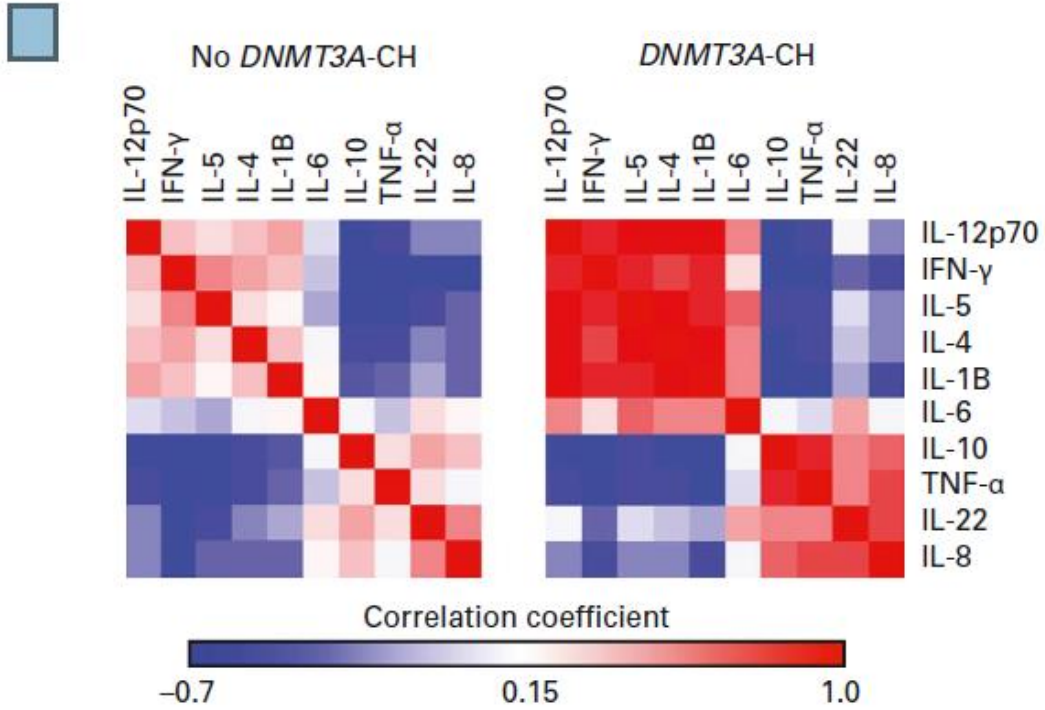

n = 262

Gibson *et al.*, JCO 2022

Summary

	Frick et al. JCO 2019	Oran et al. Leukemia 2022	Gibson et al. JCO 2022
	n=500 related donors >55y	n=303 related donors >55y	n=1727 donors > 40y (54% related; 46% unrelated)
GvHD	cGVHD ↑↑	aGVHD ↑↑	cGVHD ↑↑
CIR	↑ all CHIP carriers ↑↑ *DNMT3A* carriers	↔	↑↑ *DNMT3A* carriers
PFS	↔	↔	↑ all CH carriers ↑↑ *DNMT3A* carriers
OS	↔ ↑ in AML/MDS non-CR Patienten	↔	↑ *DNMT3A* carriers
DCL	↑	↔	↑

CR: Complete Remission; GVHD: Graft vs Host Disease; CIR: Cumulative Incidence of Relapse; PFS: Progression-free Survival; OS: Overall Survival; DCL: Donor Cell Leukemia

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B Chapuy
A Eggert
M Endres
U Keller
J Krönke
IK Na
O Penack
S Stintzing

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N Ishaque
L Ludwig
S Mathas
B Sawitzki

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G Kobbe, U Germing, **Düsseldorf**
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A Ganser, F Thol, M Heuser, **Hannover**
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DKTK Deutsches Konsortium für Translationale Krebsforschung

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