

44°

CONVEGNO NAZIONALE
di Studi di Medicina Trasfusionale

Rimini | Palacongressi, 3-5 maggio 2022



Attualità e prospettive del trapianto di CSE

Fabio Ciceri

Presidente, GITMO

Il sottoscritto Fabio CICERI, in qualità di Relatore
dichiara che

nell'esercizio della Sua funzione e per l'evento in oggetto, NON È in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le sue funzioni al fine di trarne vantaggio.

Programmi Trapianti (PT) GITMO

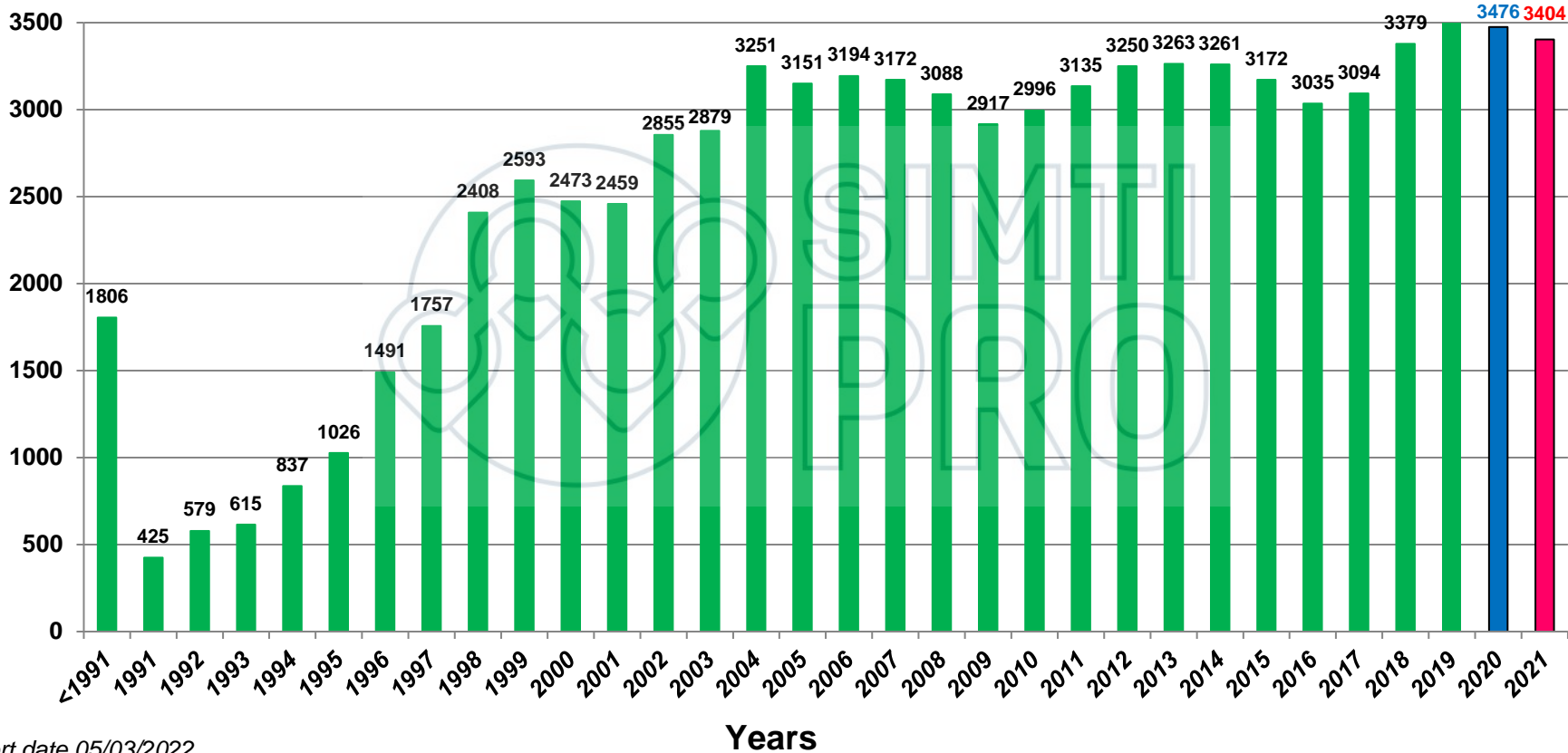
Tipologia PT	N PT
Singolo	69
Singolo Misto	4
Congiunto	10
Metropolitano	5
Totale	88

Tipologia trapianto	N PT
Autologo	88
Allogeneico familiare	61
Allogeneico MUD	59

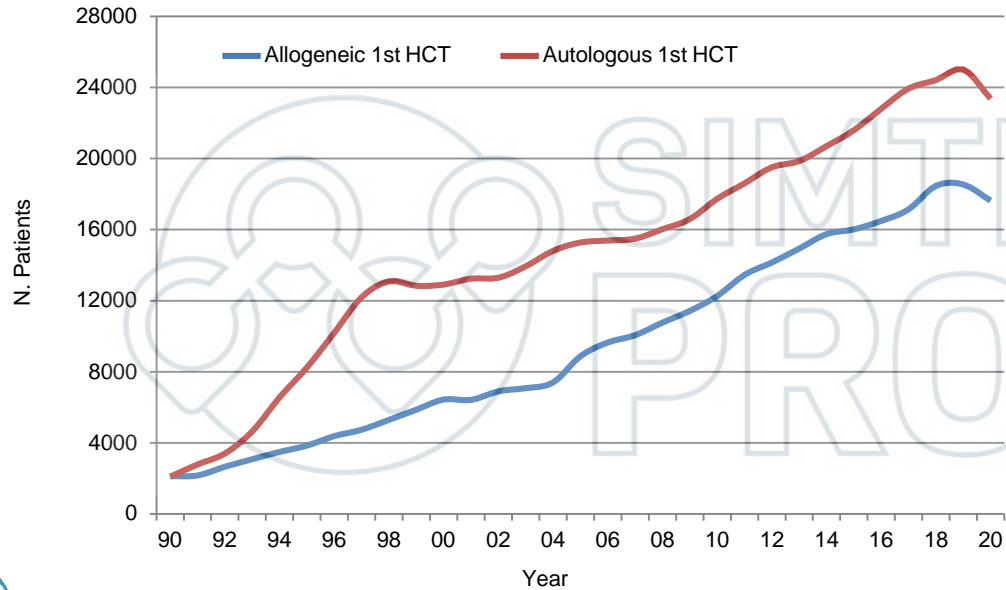
Tipologia pazienti	N PT
Adulti	62
Pediatrici	10
Misti (adulti+pediatrici)	16
Totale	88

Autologous Transplants

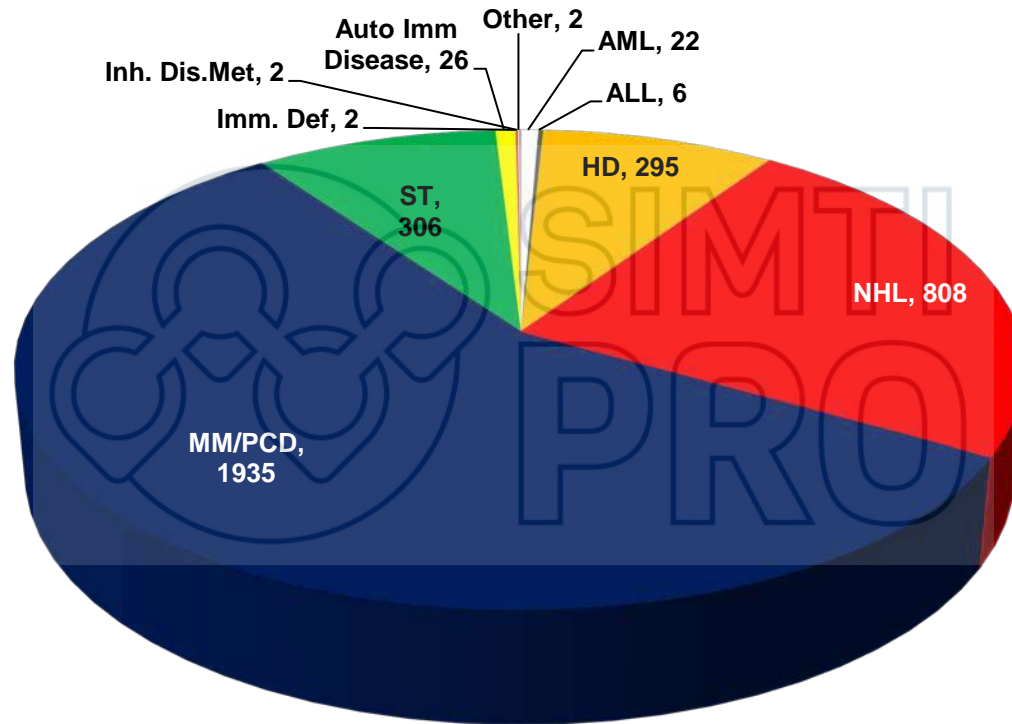
(n=80.021)



Number of patients receiving their 1st HSCT



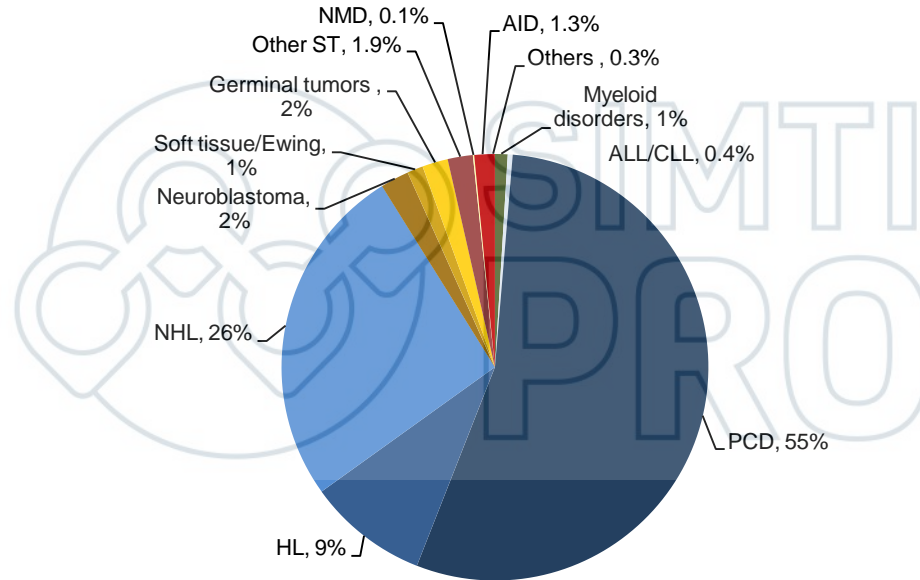
Autologous Transplants - Indications 2021



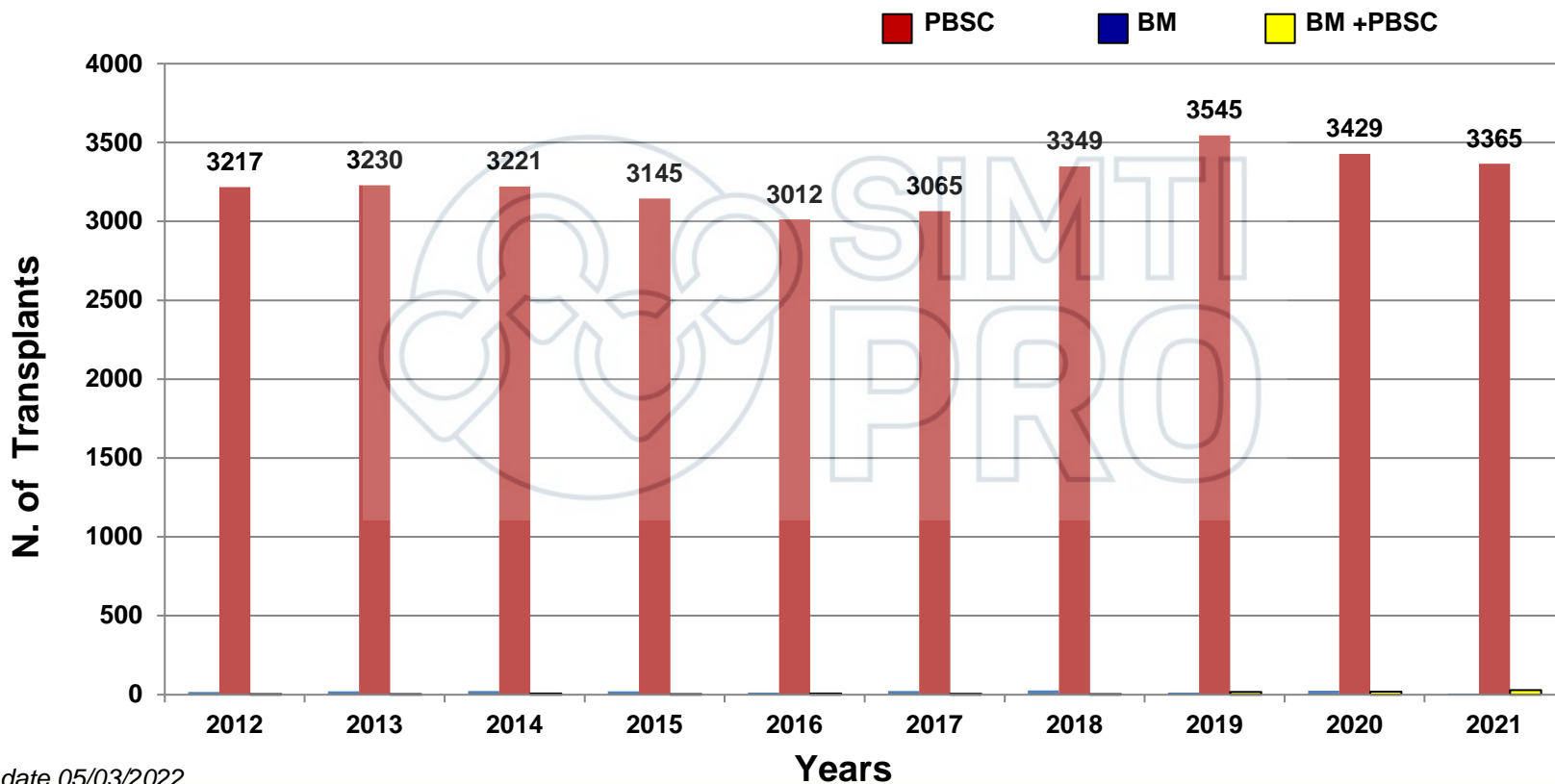
Export date 05/03/2022

DA VITA NASCE VITA: PROMUOVERE LA DONAZIONE DI CELLULE STAMINALI EMOPOIETICHE IN ITALIA

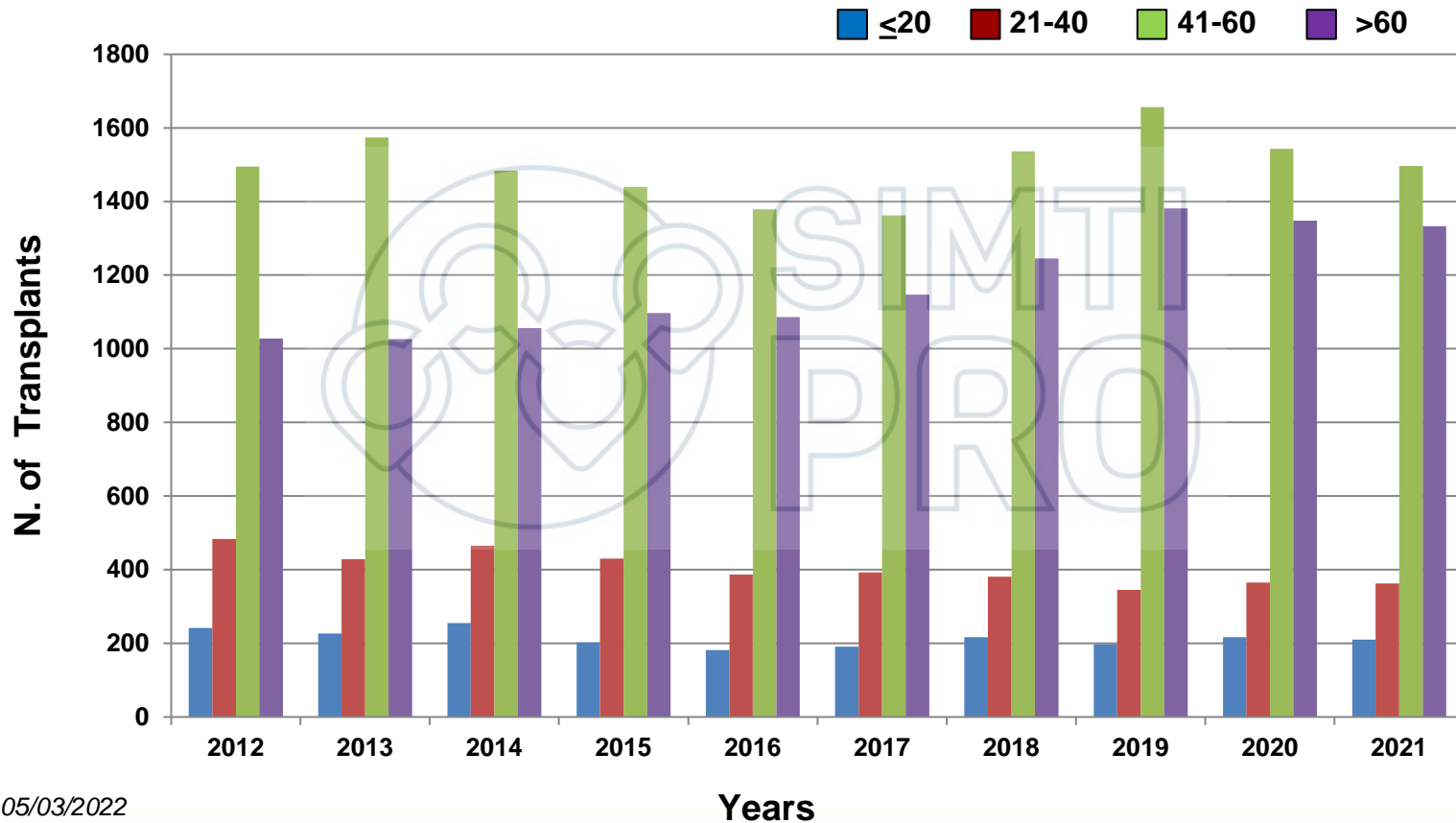
Relative proportion of disease indications for autologous HCT in Europe 2020



Autologous Transplants – Source of HSC

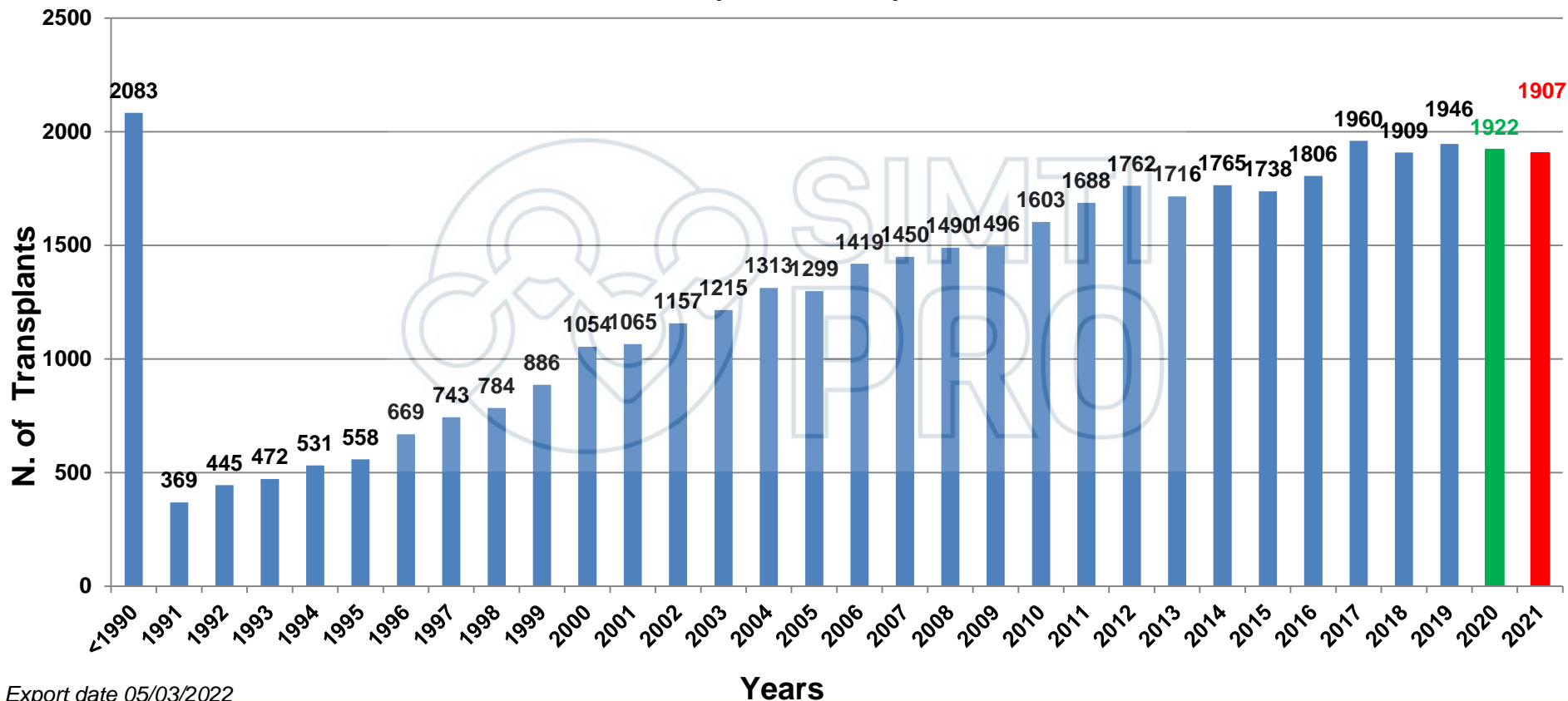


Autologous Transplants – Patient age at transplantation

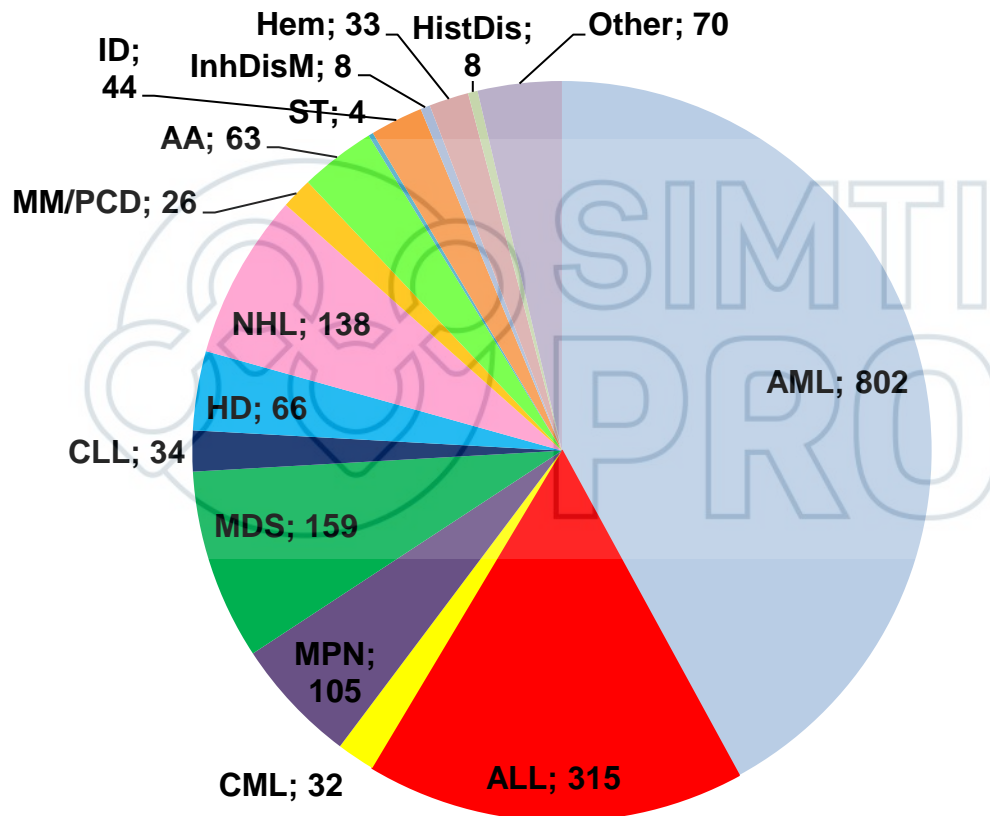


Allogeneic Transplants

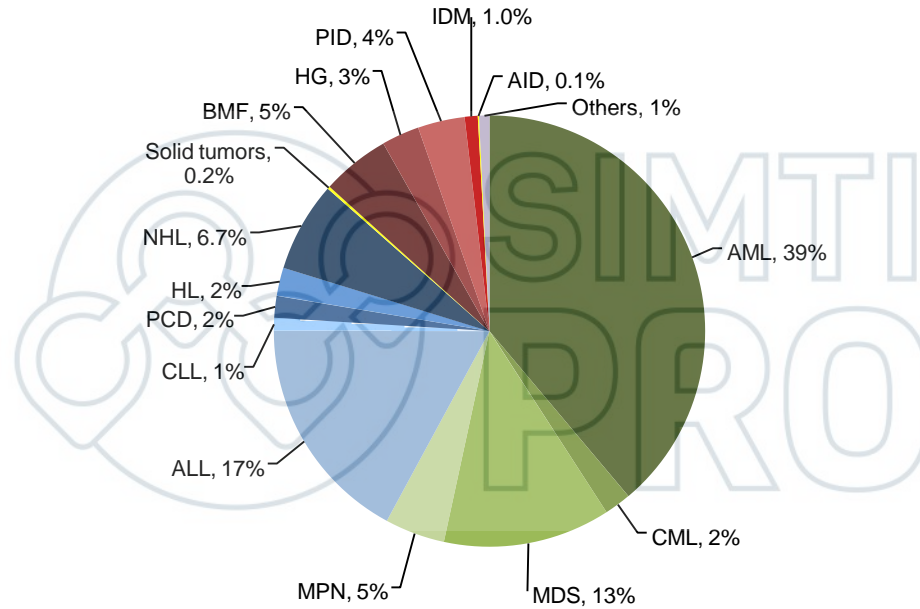
(n = 42.220)



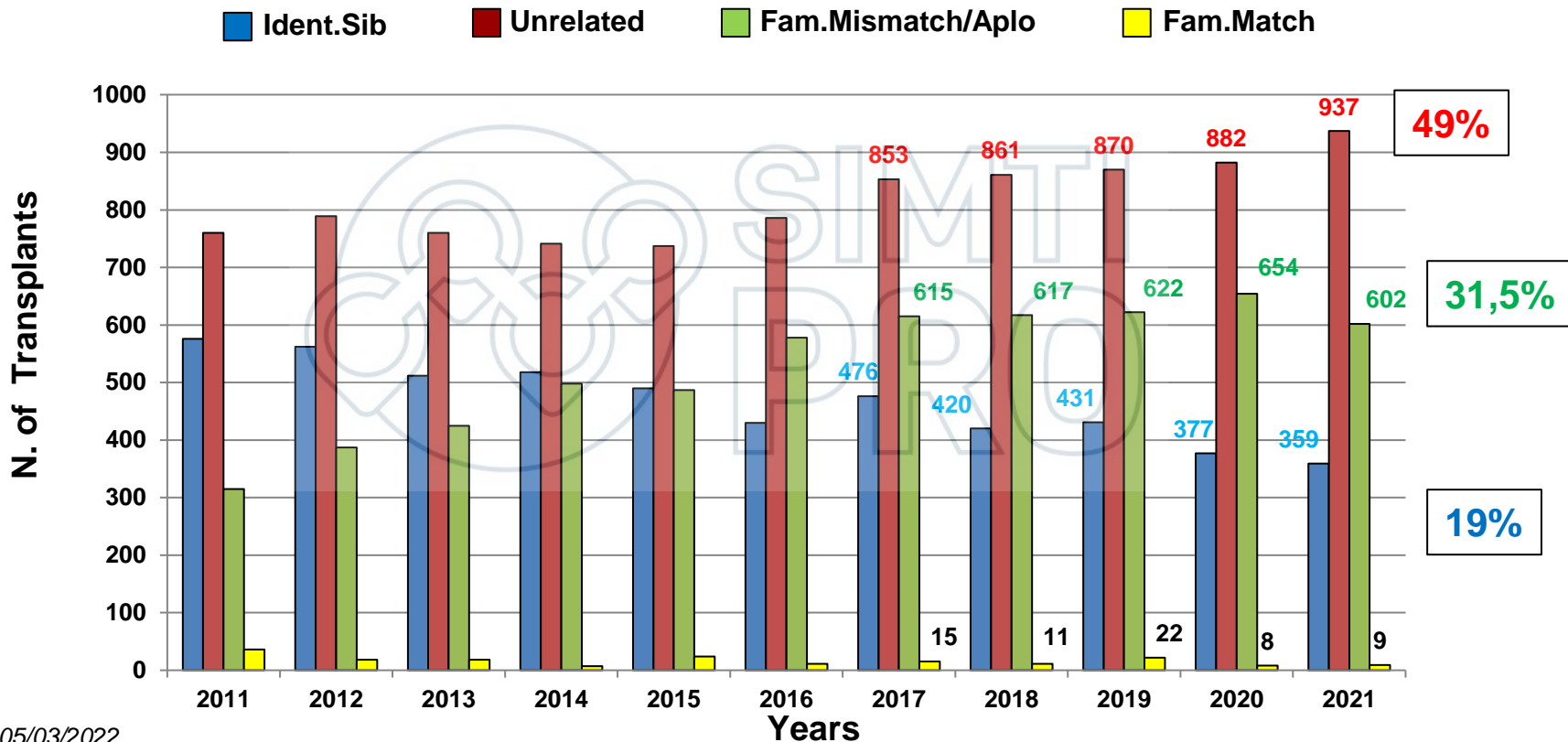
Allogeneic Transplants - Indications 2022



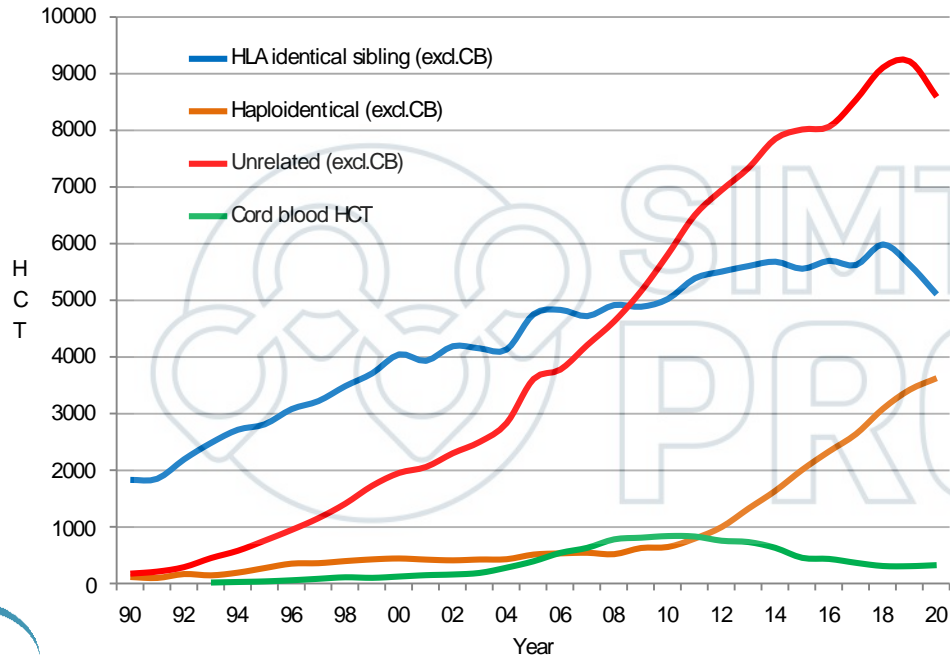
Relative proportion of disease indications for allogeneic HCT in Europe 2020



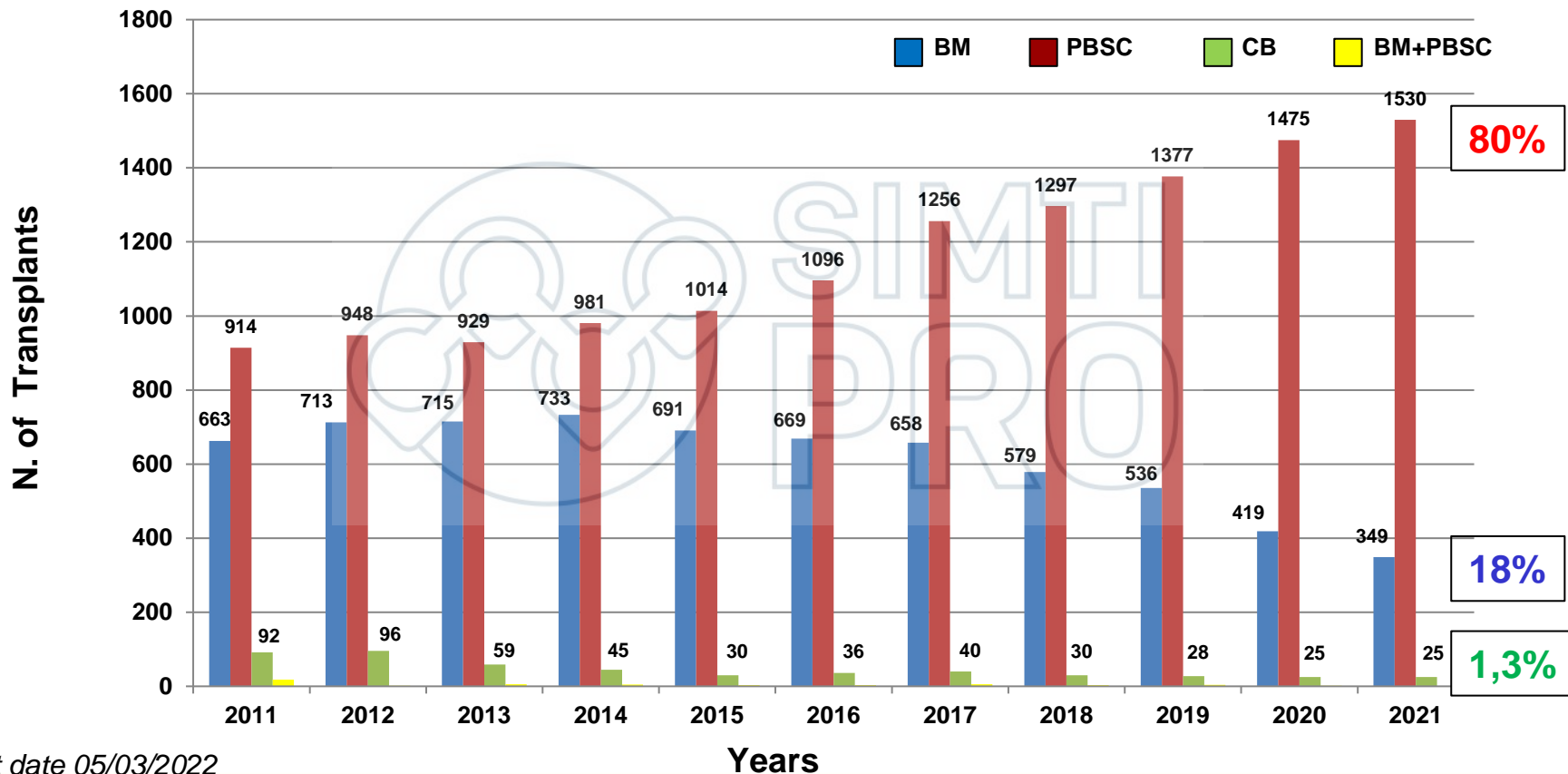
Allogeneic Transplants – Donor type



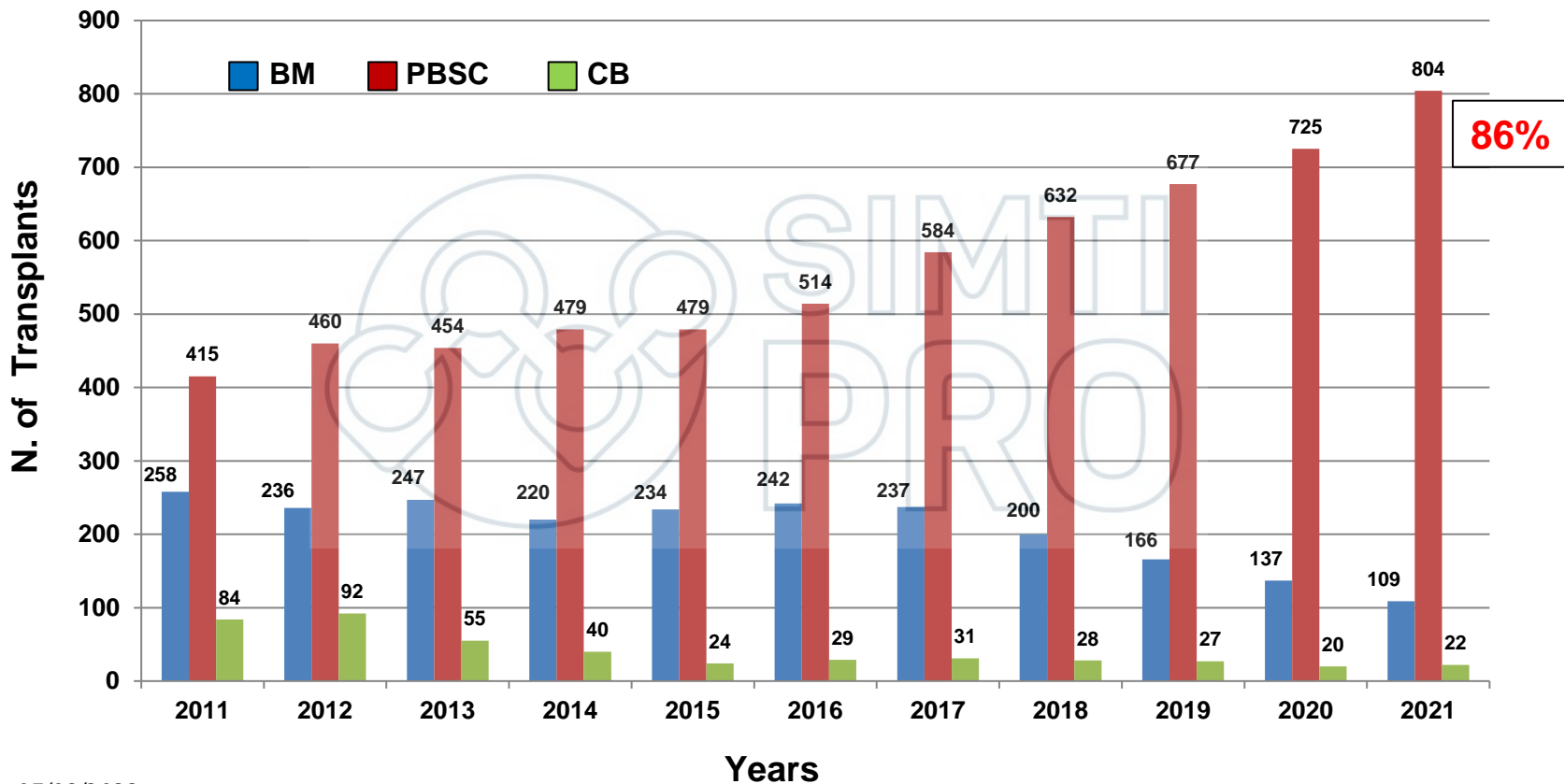
Change of donor type from 1990 to 2020



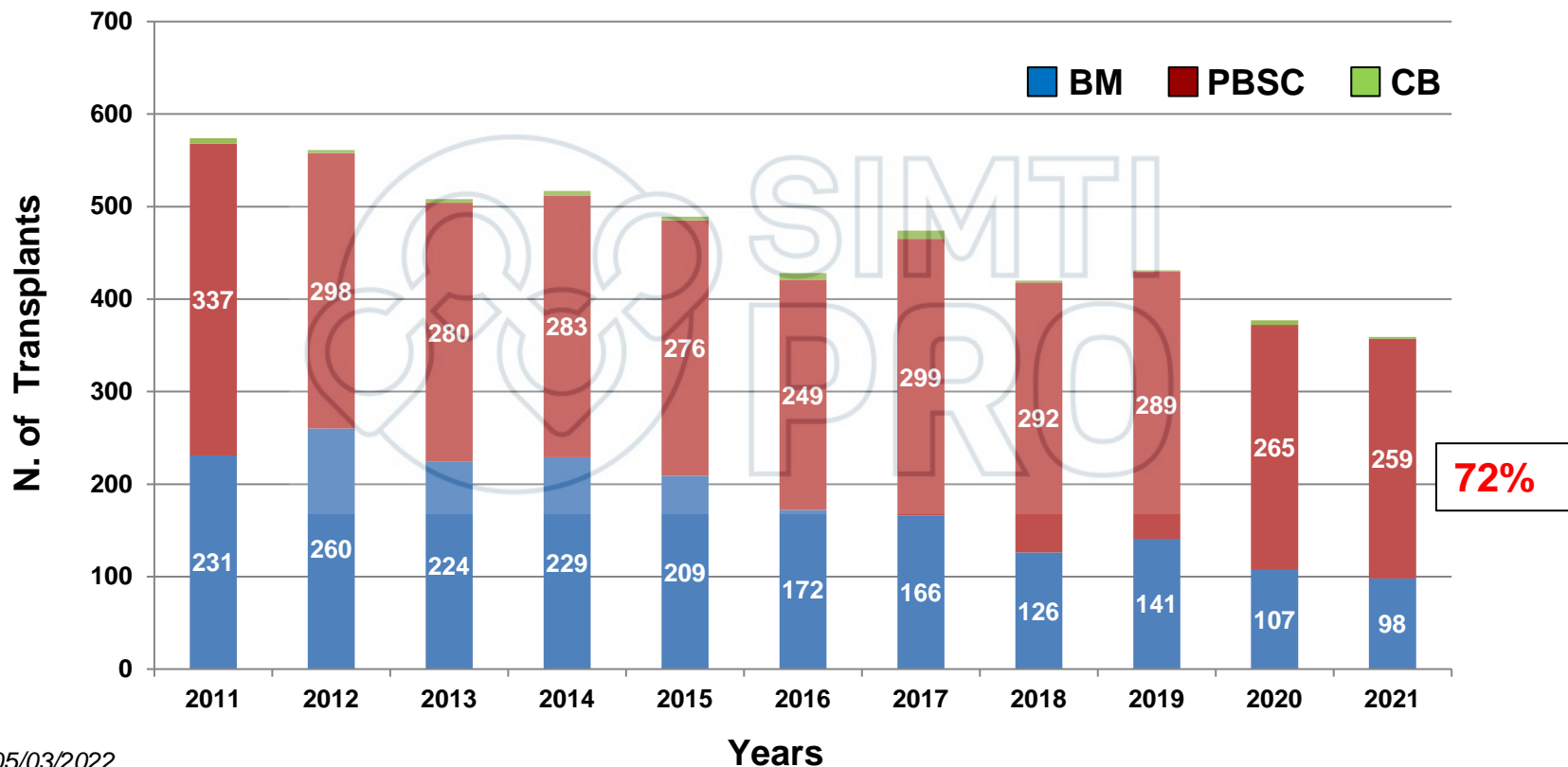
Allogeneic Transplants – Source of HSC



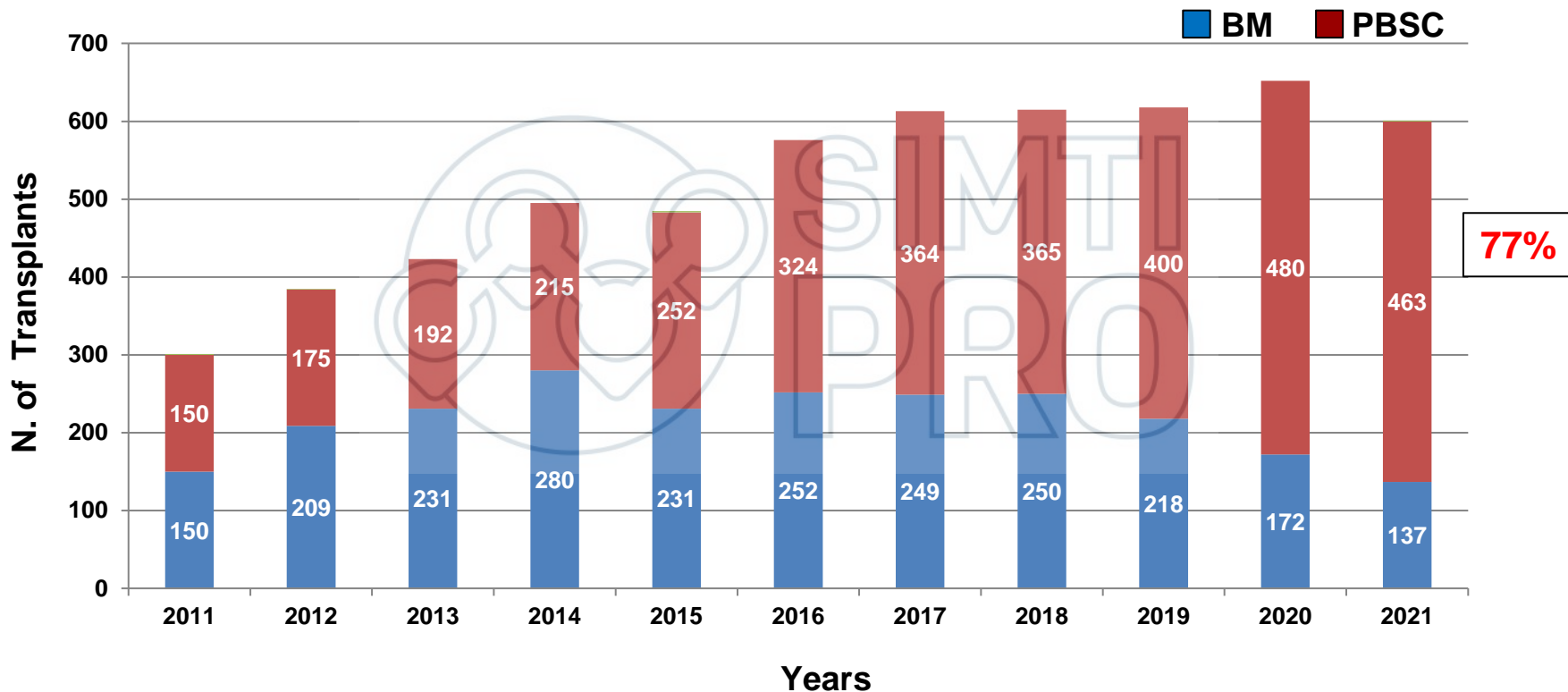
Allogeneic Transplants: Unrelated Donor and Source of HSC



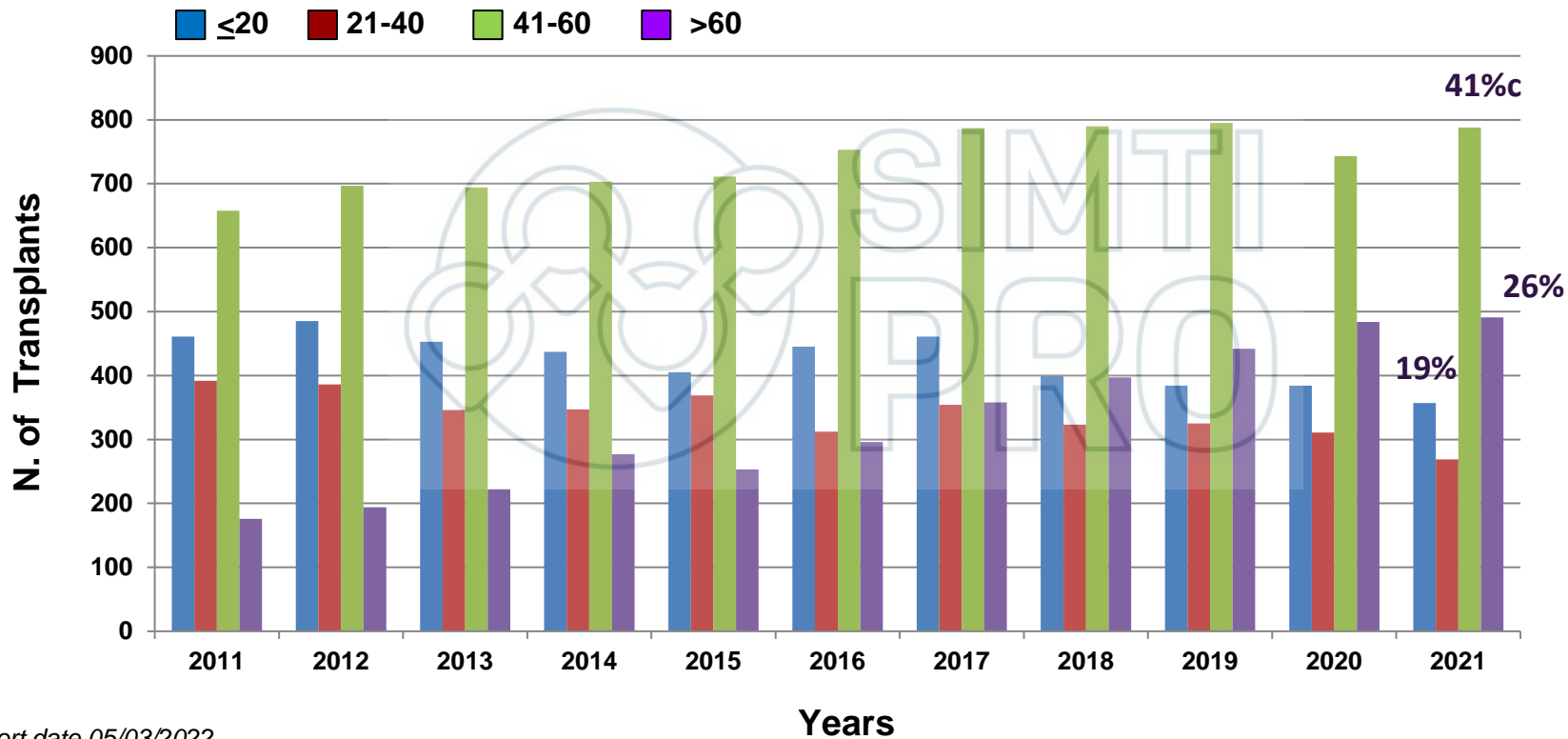
Allogeneic Transplants: HLA Identical Sibling Donor and Source of HSC



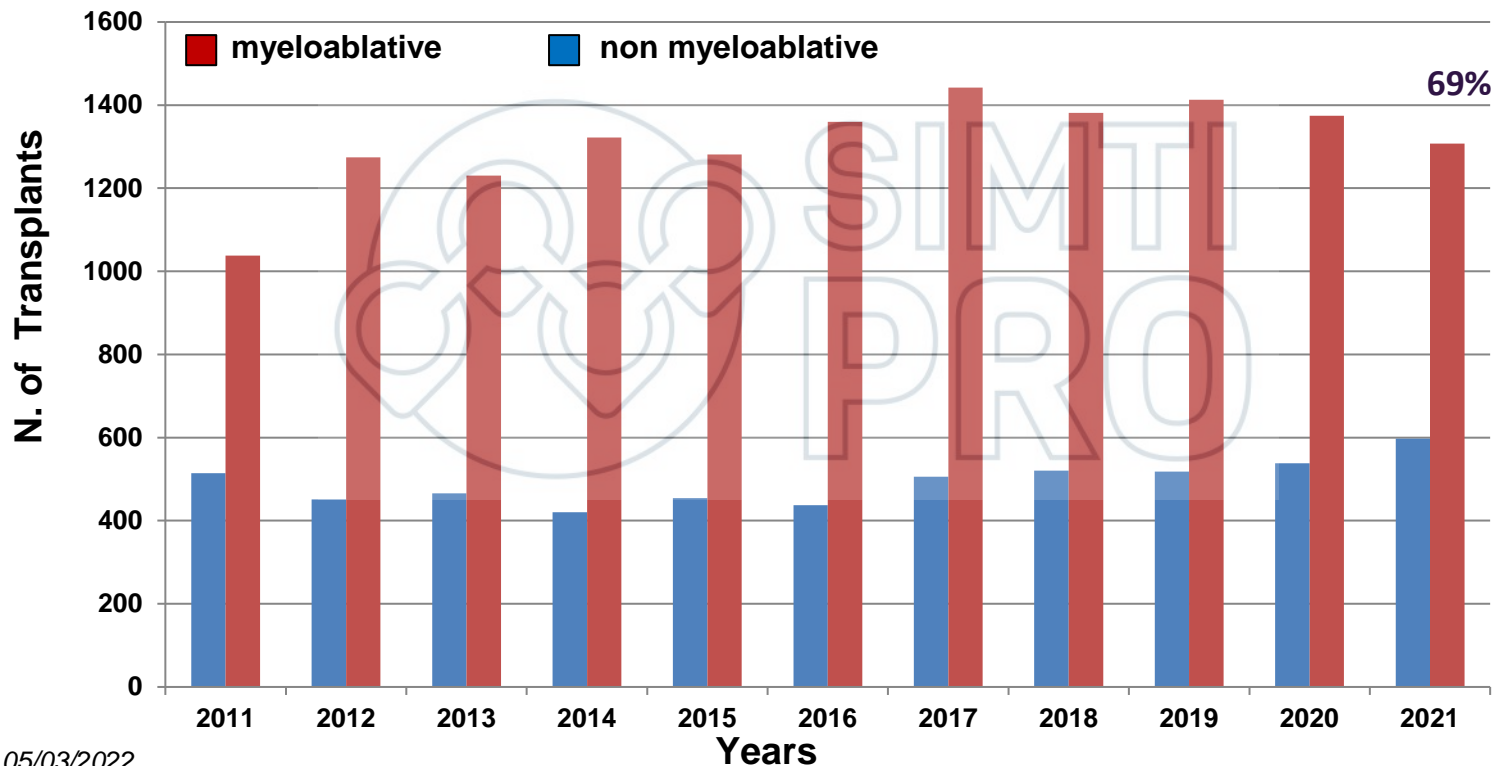
Allogeneic Transplants: Haplo/Fam.Mism.Donor and Source of HSC



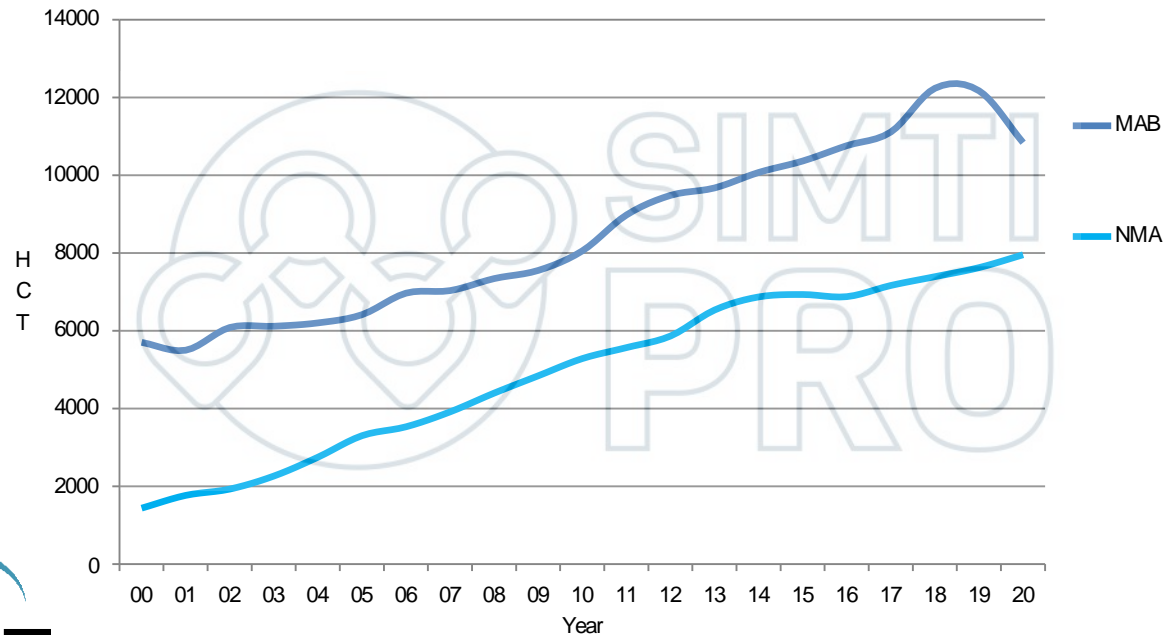
Allogeneic Transplants – Patient age at transplantation



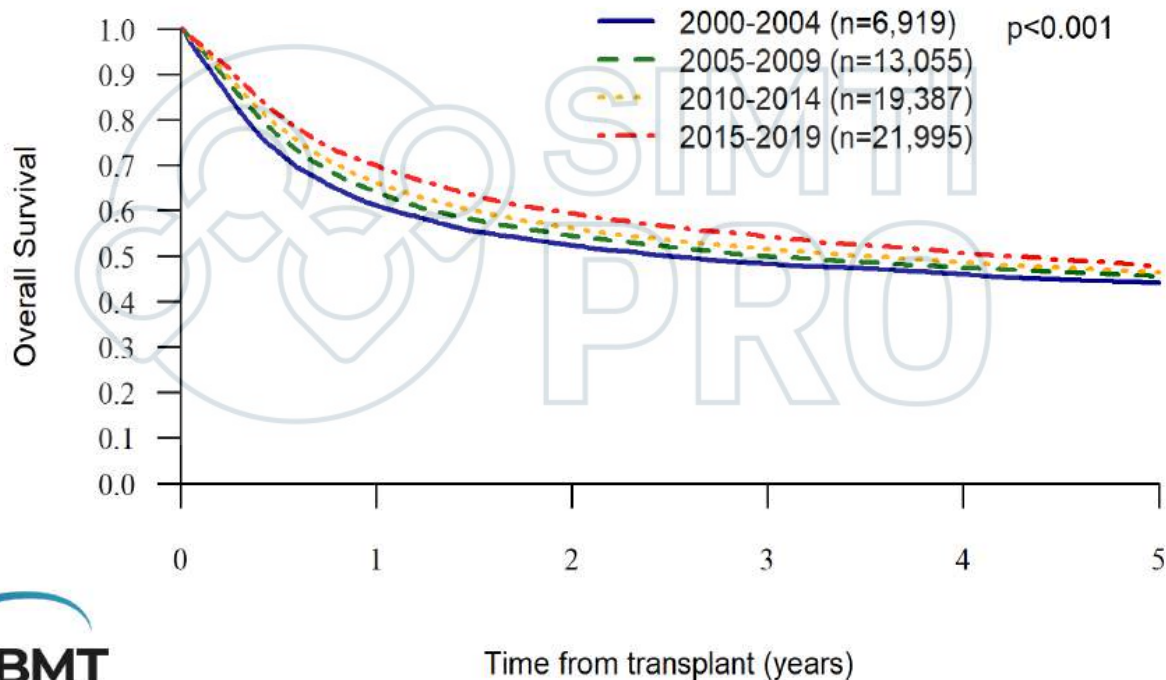
Allogeneic Transplants – Conditioning regimens



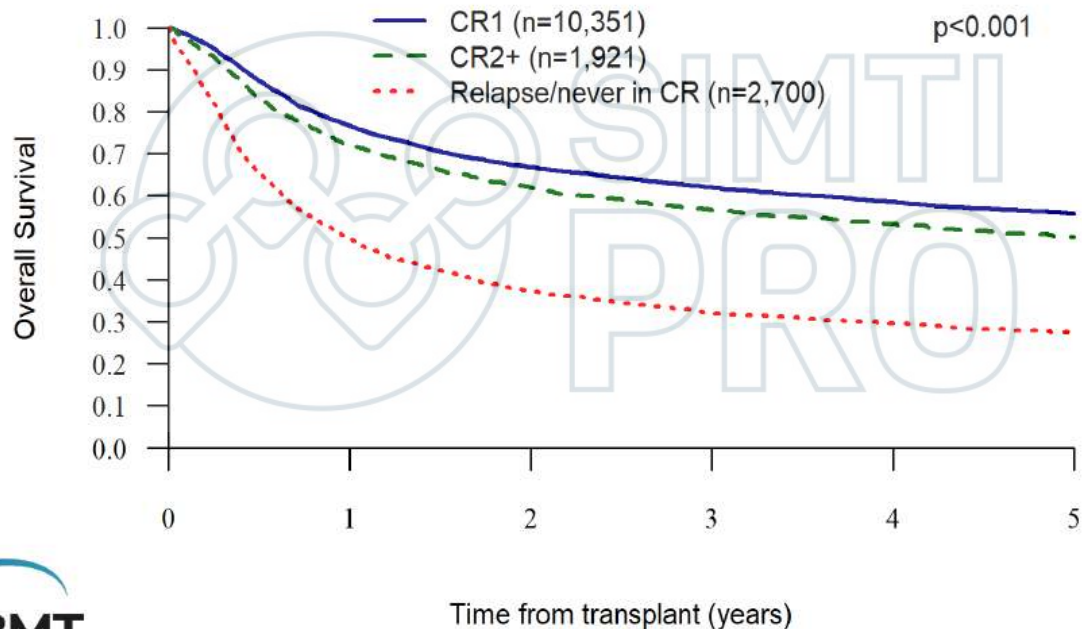
Change in the numbers of MAB versus NMA HCT in Europe 2020



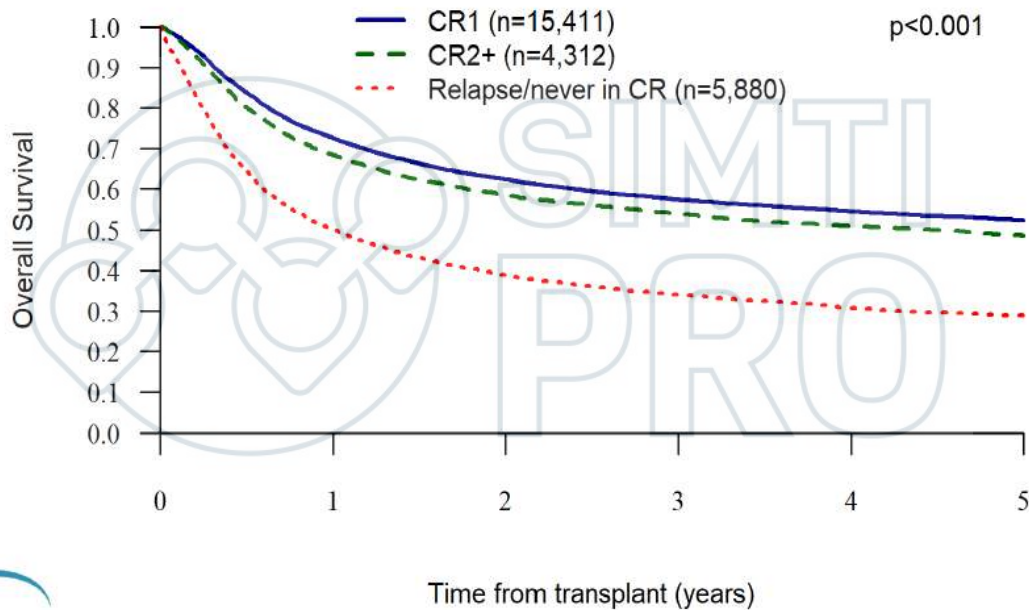
Trends in Survival after Allogeneic HCT for Acute Myelogenous Leukemia (AML), Age ≥ 18 y, 2000-2019



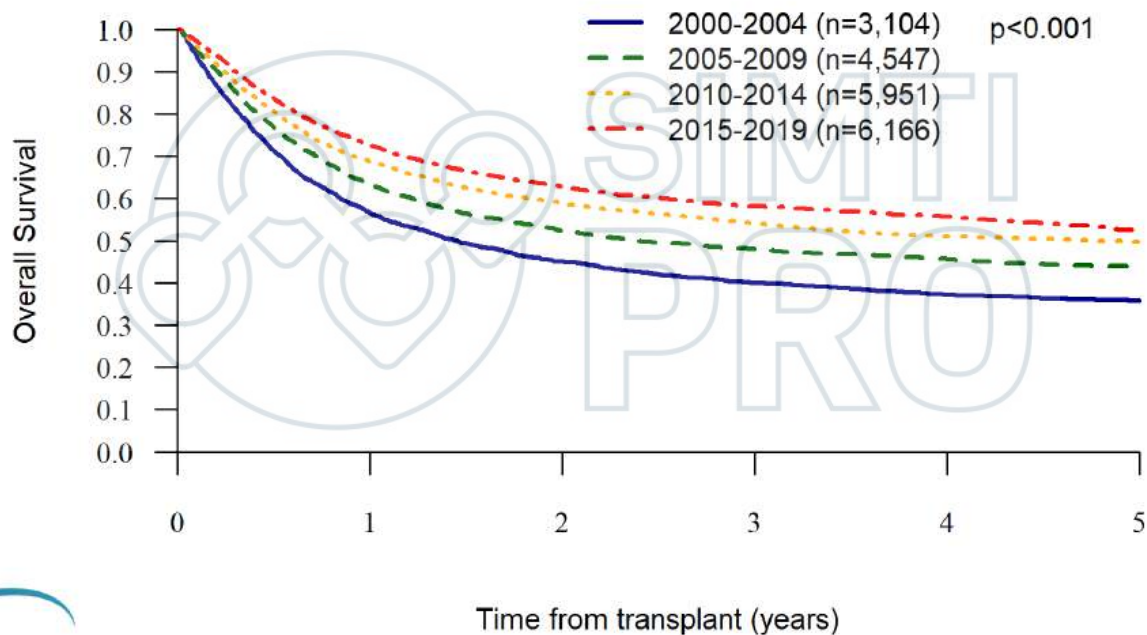
Survival after Matched Related Donor HCT for Acute Myelogenous Leukemia (AML), Age ≥ 18 y, 2009-2019



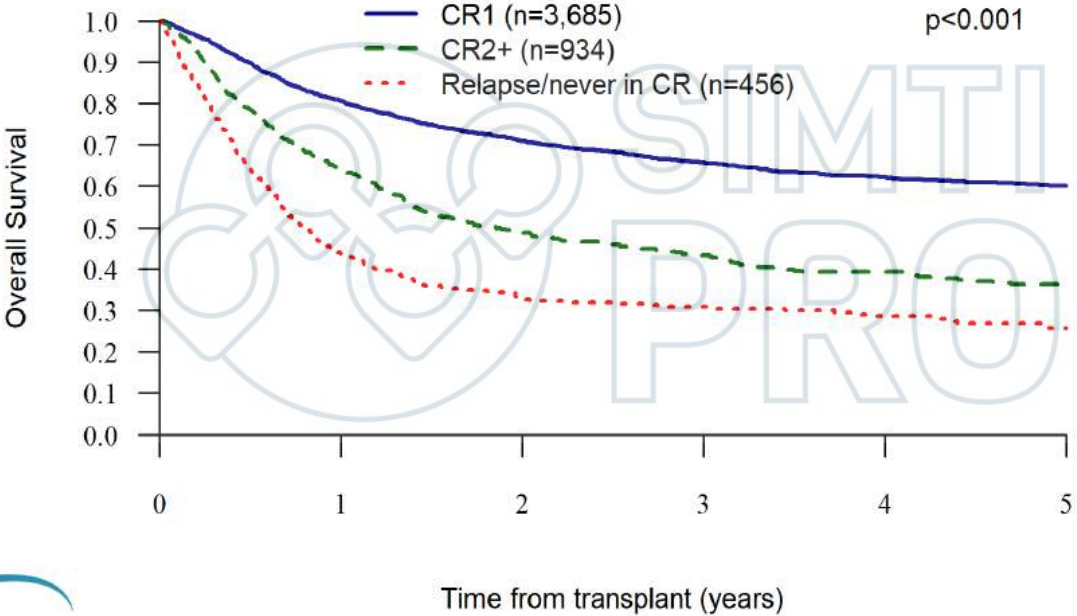
Survival after Unrelated Donor HCT for Acute Myelogenous Leukemia (AML), Age ≥ 18 y, 2009-2019



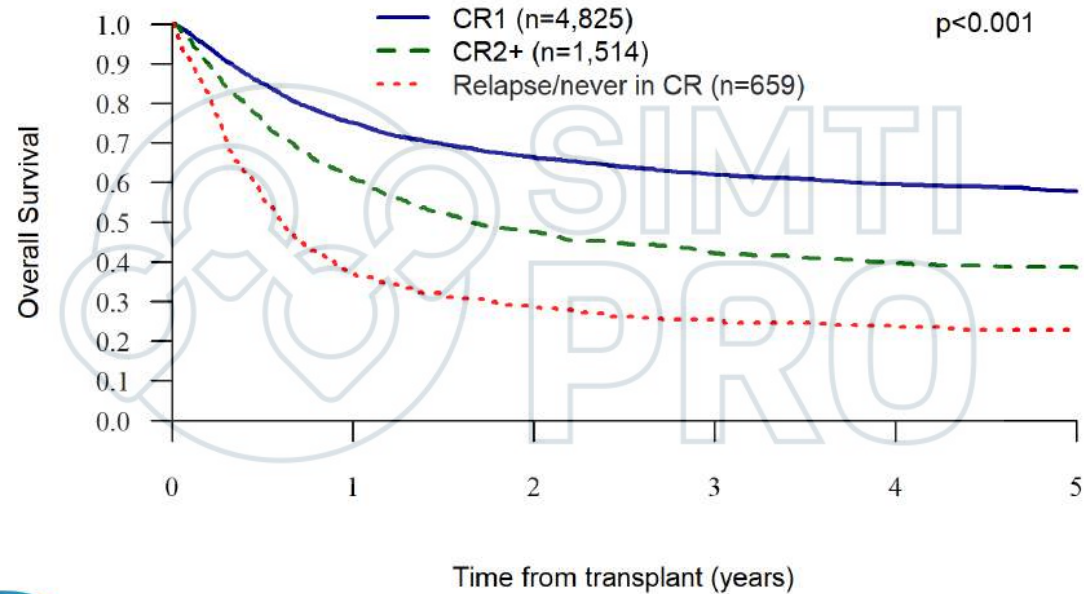
Trends in Survival after Allogeneic HCT for Acute Lymphoblastic Leukemia (ALL), Age ≥ 18 y, 2000-2019



Survival after Matched Related Donor HCT for Acute Lymphoblastic Leukemia (ALL), Age $\geq 18y$, 2009-2019



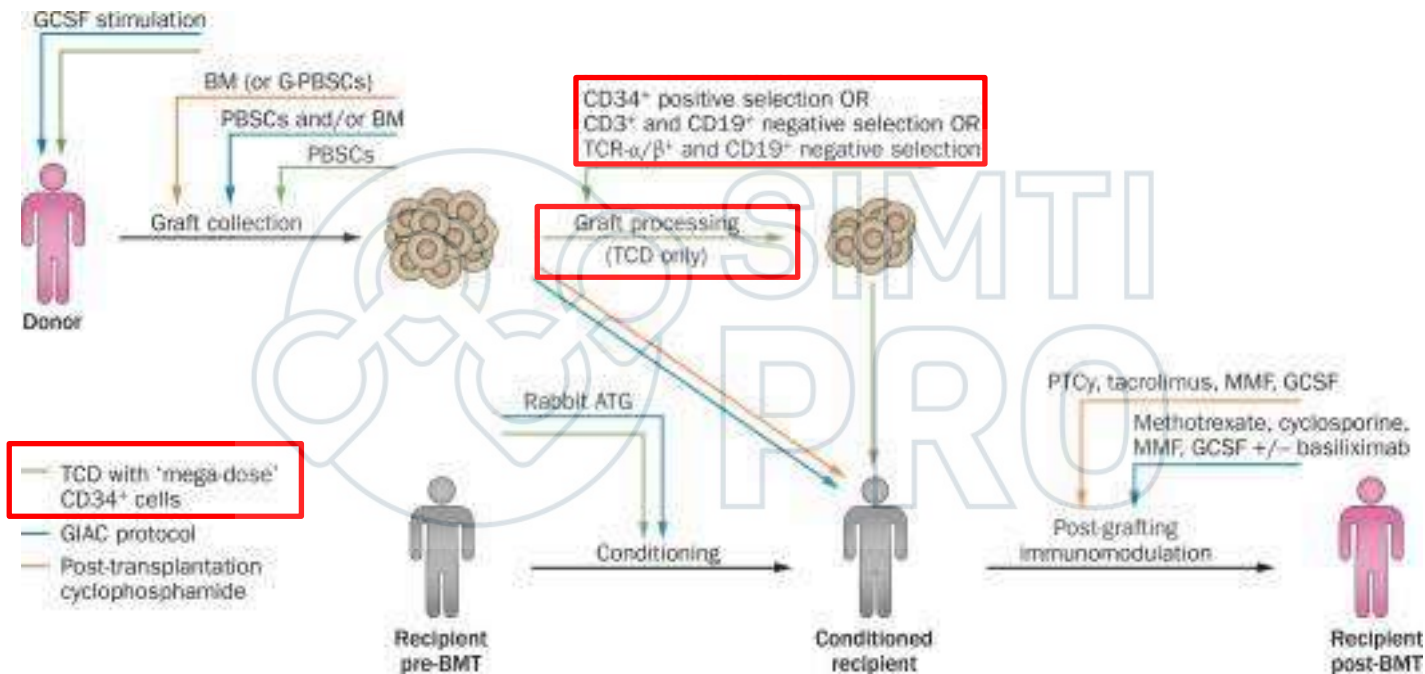
Survival after Unrelated Donor HCT for Acute Lymphoblastic Leukemia (ALL), Age ≥ 18 y, 2009-2019



Trends	AML		ALL	
	2 years	5 years	2 years	5 years
2000-2004	52.3% [51.1-53.4]	44.1% [42.9-45.3]	45% [43.2-46.7]	35.8% [34-37.5]
2005-2009	54.4% [53.5-55.3]	45.6% [44.7-46.5]	52.4% [50.8-53.9]	43.8% [42.3-45.3]
2010-2014	56.1% [55.4-56.8]	46.4% [45.6-47.2]	58.9% [57.5-60.2]	49.7% [48.2-51.1]
2015-2019	59.4% [58.6-60.1]	47.7% [46.7-48.7]	62.8% [61.5-64.2]	52.5% [50.6-54.3]
P value	0.001	0.001	0.001	0.001

2y OS	AML MSD 2009-2019	AML UD 2009-2019	ALL MSD 2009-2019	ALL UD 2009-2019
CR1	66.8% [65.8-67.8]	62.4% [61.6-63.2]	71% [69.3-72.6]	66.4% [64.9-67.8]
CR2+	61.9% [59.4-64.2]	58.5% [56.9-60.1]	48.7% [44.9-52.4]	47.5% [44.7-50.2]
advanced	37.3% [35.3-39.3]	38.8% [37.5-40.2]	33% [28.3-37.7]	28.5% [24.8-32.2]
P value	0.001	0.001	0.001	0.001

Ex vivo TCD Haploidentical platforms



Haploidentical Transplants Platforms

Non T cell depleted

- **John Hopkins PTCy**

RIC or MAC BM with post CY

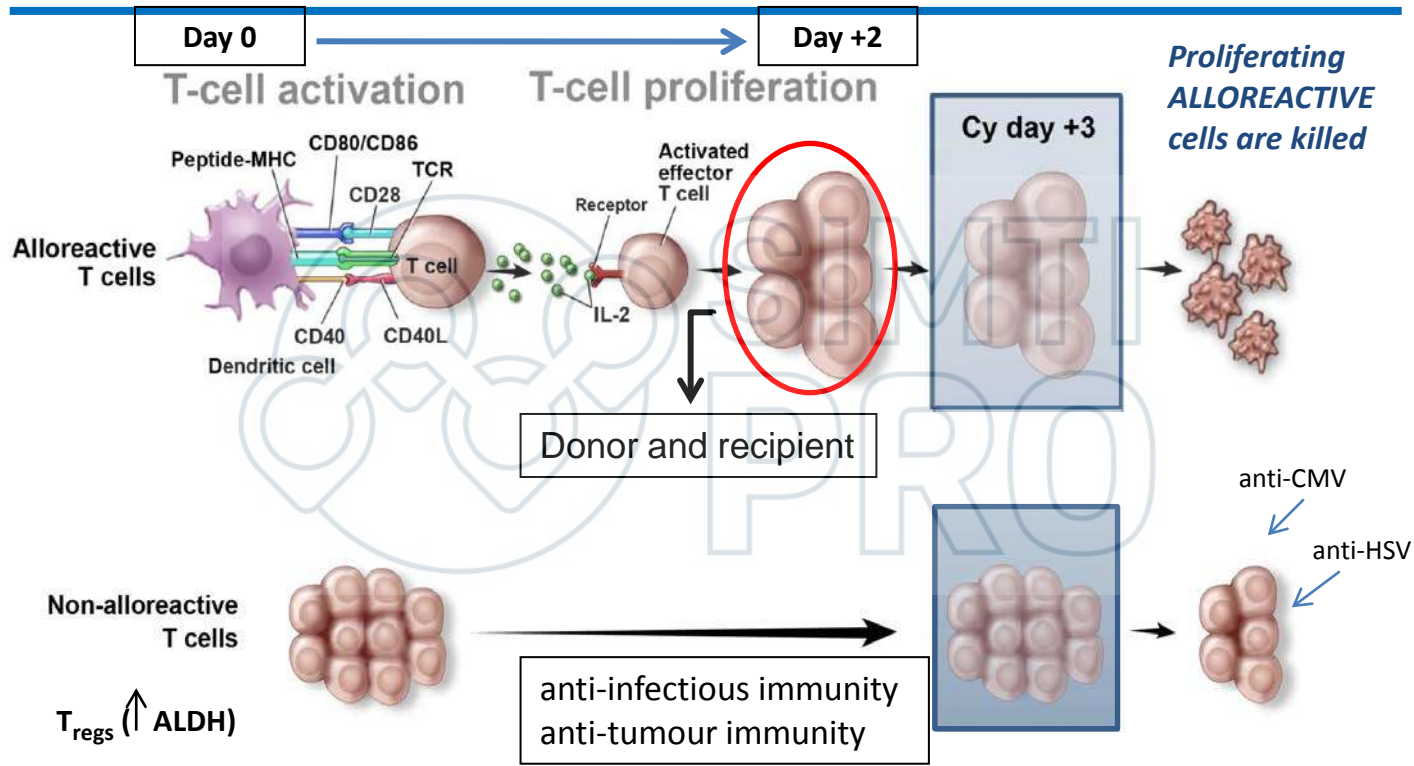
- **GIAC approach / Italian**

Mobilized GSF primed BM with high number of
IST drugs (TBF- BM- ATG + MTX + CSA +MMF
+Basiliximab)

- **Rapamycine based**

TreoFlu PBSC+MMF+Rapamycine + ATG/PTCy

Selective allopepletion with PT/Cy



Lymphs show heterogeneous ALDH1 expression
Most T cells, esp. those proliferating, express low levels of ALDH1 and are sensitive to Cy

Memory T cells, like other 'stem'-like cells, express high levels and are resistant to Cy

Kanakry, et al. *Sci Transl Med* 2013,
Luznik and Fuchs. *Immunol Res* 2010.

**Non-proliferating
non-alloreactive
cells are spared**

PTCY Transplant Related Complications

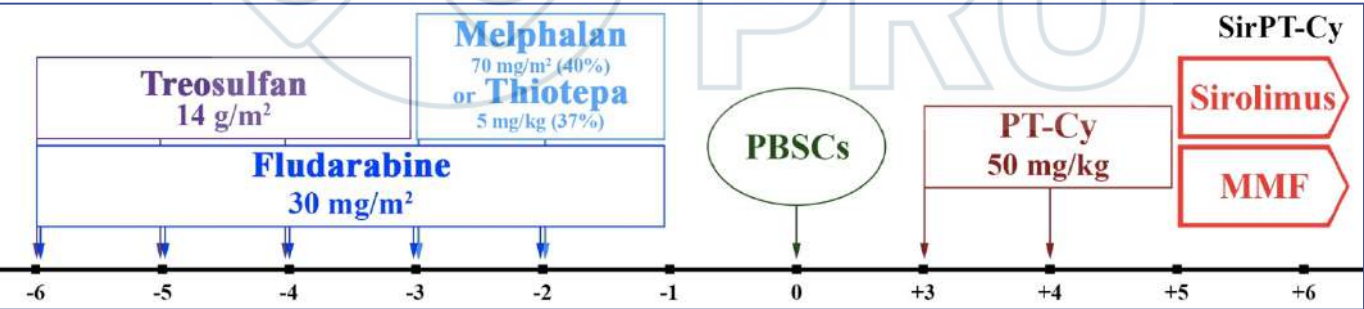
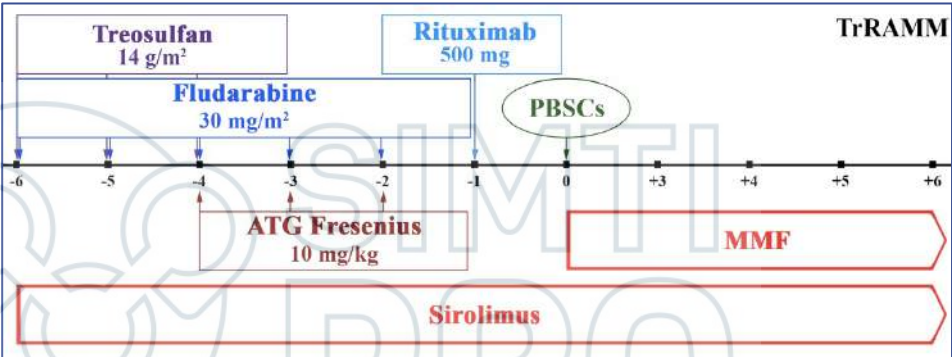
- **VOD** Incidence not higher than other allogeneic platforms, 0-9%
- **Hemorrhagic cystitis** 9%-75% Develops peri/post-engraftment
 - Increased incidences with myeloablative conditioning, addition of ATG, tacro vs CSA
 - Cumbersome but not life threatening problem
- **Infections**

Historically, lower incidence than T cell depletion platforms CMV reactivation: 6-75%

 - Viral: no increased incidence of significant/life-limiting infections
 - Fungal: 0-12%

Haplo-HSCT and Sirolimus GvHD prophylaxis

We firstly explored the association of **sirolimus and ATG** (*Peccatori et al, Leukemia, 2014*), later followed by **sirolimus with PT-Cy** (*Cieri et al, BBMT 2015*) as GvHD strategy. Herein, we describe long-term outcomes.



Patient and Disease Characteristics

	ATG (n=203)	PTCy (n=151)	p-value
Patient age y, median (range)	46 (14-71)	50 (15-78)	0,013
Type of diagnosis, n (%)			0,54
Myeloid diseases			
AML	105 (52%)	92 (61%)	
MDS	17 (8%)	10 (7%)	
MPN	11 (5%)	5 (3%)	
Lymphoid diseases			
NHL & HL	31 (16%)	24 (16%)	
ALL	32 (16%)	19 (12%)	
MM	2 (1%)	1 (1%)	
Other diseases	5 (2%)	0	
Time from diagnosis to HSCT, median (range)	414 d (18-38933)	346 d (28-4548)	0,06
Previous allo-HSCT, n (%)	53 (26%)	38 (25%)	0,84
Disease status at HSCT, n (%)			0,26
CR1	30 (15%)	31 (21%)	
CR>1	39 (19%)	32 (21%)	
Active disease	134 (66%)	88 (58%)	
R-DRI at HSCT, n (%)			0,84
Low-intermediate	64 (32%)	52 (35%)	
High	84 (41%)	64 (42%)	
Very high	51 (25%)	35 (23%)	
Not applicable	4 (2%)	0	
HCT-CI score, median (range)	2 (0-8)	2 (0-9)	0,06

Between October 2007 and March 2017, a total of **354 adult patients** received an haploidentical HSCT for high-risk hematological malignancies.

Year of transplantation (median):

- ◆ ATG Group: 2010 (2007-2015),
- ◆ PT-Cy Group: 2015 (2012-2017).

Median follow-up:

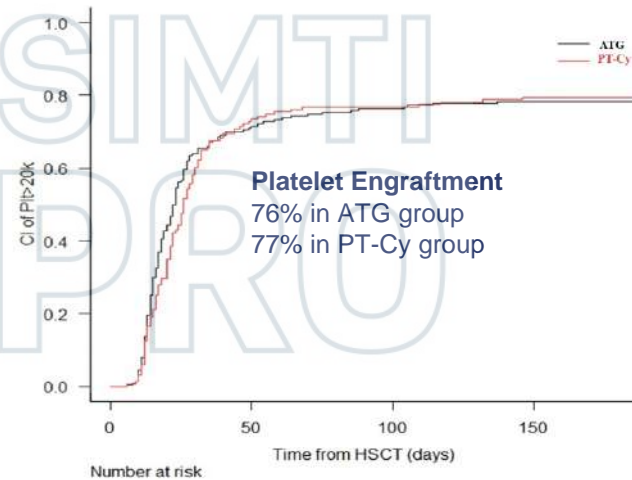
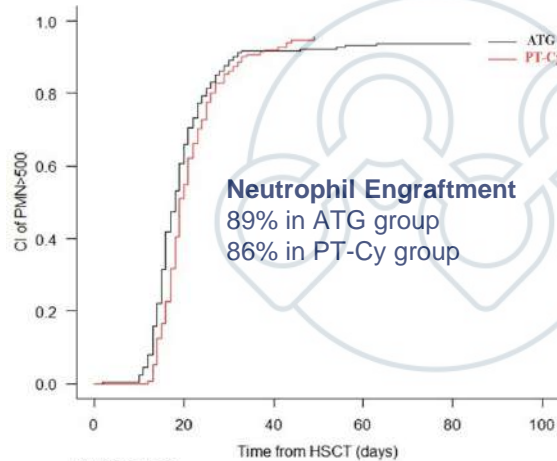
- ◆ ATG group: 75 m (12-127),
- ◆ PT-Cy group: 26 m (3-68).

Transplant Characteristics

	ATG (n=203)	PTCy (n=151)	p-value
Donor age , median (range)	38 (19-70)	37 (16-70)	0,77
Female donor/male recipient , n (%)	59 (29%)	32 (21%)	0,09
Host/donor CMV serostatus , n(%)			0,96
pos/pos	126 (62%)	96 (64%)	
pos/neg	47 (23%)	36 (24%)	
neg/pos	15 (7%)	9 (6%)	
neg/neg	10 (5%)	8 (5%)	
not available	5 (3%)	2 (1%)	
Conditioning intensity , n (%)			<0,001
RIC	115 (57%)	28 (19%)	
MAC	88 (43%)	123 (81%)	
Conditioning regimen , n (%)			<0,001
Treo-Flu	113 (56%)	23 (15%)	
Treo-Flu-TBI	76 (37%)	3 (2%)	
Treo-Flu-Mel	0	60 (40%)	
Treo-Thio-Flu	3 (1%)	56 (37%)	
Other	14 (6%)	9 (6%)	
Stem cell source , n (%)			0,43
BM	2 (1%)	3 (2%)	
PB	201 (99%)	148 (98%)	
Infused CD34+x10⁶/Kg , median (range)	7 (5-9)	6 (5-8)	0,005
Infused CD3+x10⁵/Kg , median (range)	1770 (175-4300)	2037 (857-4825)	0,012

Engraftment

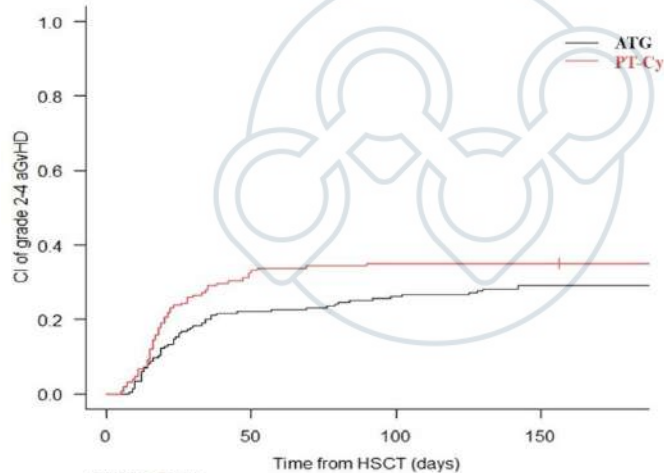
The majority of patients reached the engraftment within 30 days after HSCT.



Acute GvHD

CI of grades II-IV aGvHD

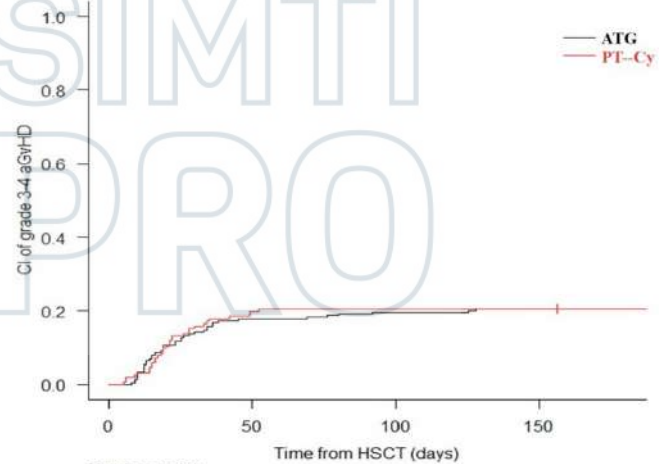
- ◇ 26% at 100 days in ATG
- ◇ 35% at 100 days in PT-Cy



	Number at risk			
	0	50	100	150
ATG	203	121	101	83
PT-Cy	151	81	67	61

CI of grades III-IV aGvHD

- ◇ 20% at 100 days in ATG
- ◇ 20% at 100 days in PT-Cy

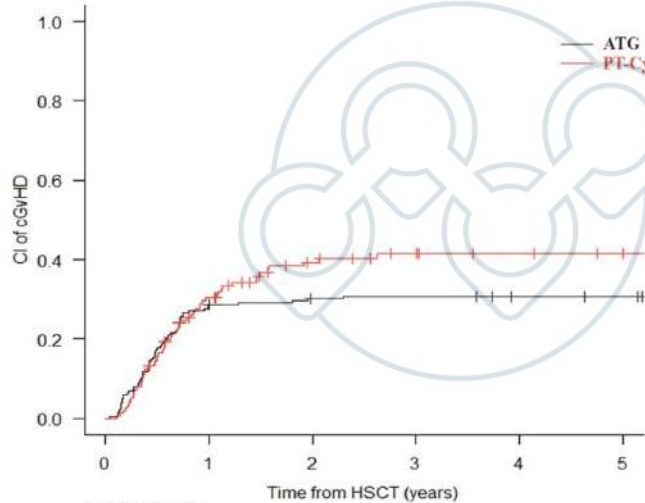


	Number at risk			
	0	50	100	150
ATG	203	130	111	97
PT-Cy	151	100	88	79

Chronic GvHD

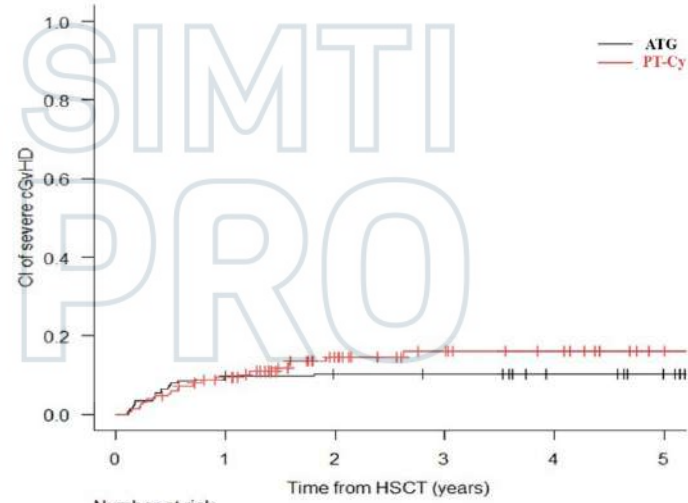
CI of overall cGvHD

- ◇ 31% at 3 years in ATG
- ◇ 42% at 3 years in PT-Cy



CI of severe cGvHD

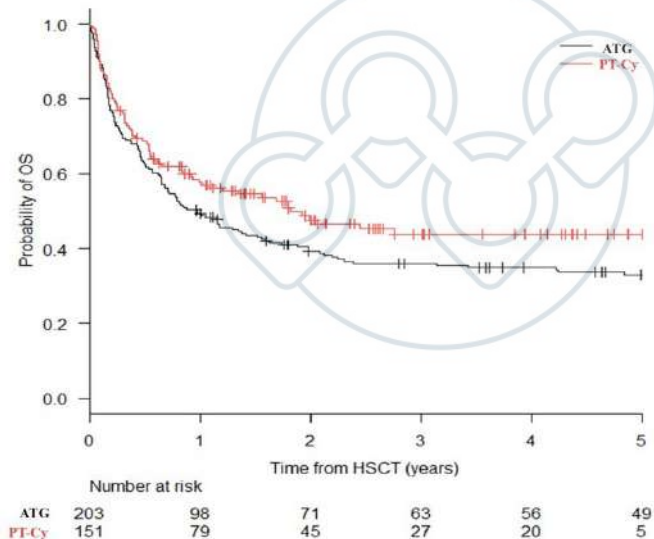
- ◇ 10% at 3 years in ATG
- ◇ 16% at 3 years in PT-Cy



Overall survival, Progression-free Survival

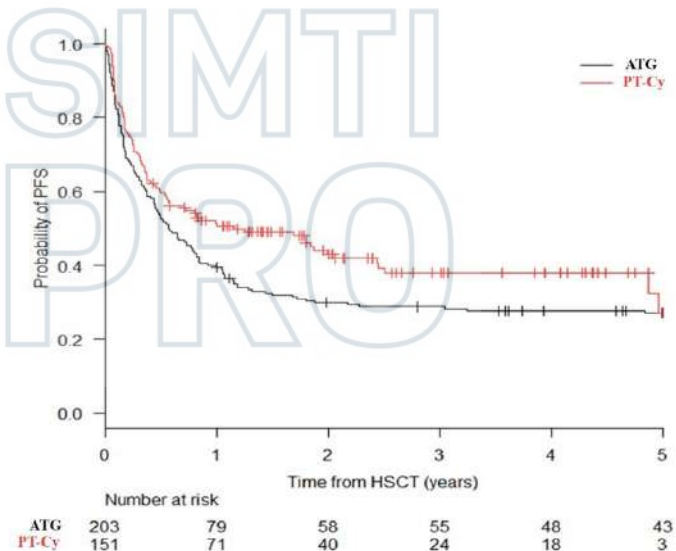
OS

- ◇ 36% at 3 years in ATG
- ◇ 44% at 3 years in PT-Cy



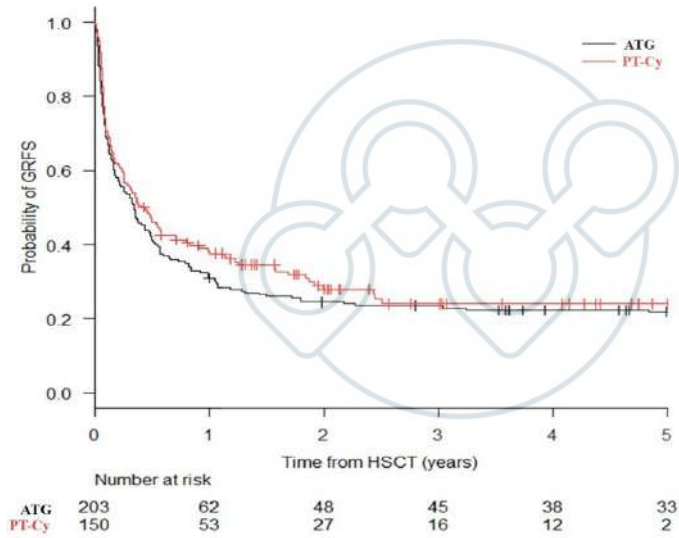
PFS

- ◇ 29% at 3 years in ATG
- ◇ 38% at 3 years in PT-Cy

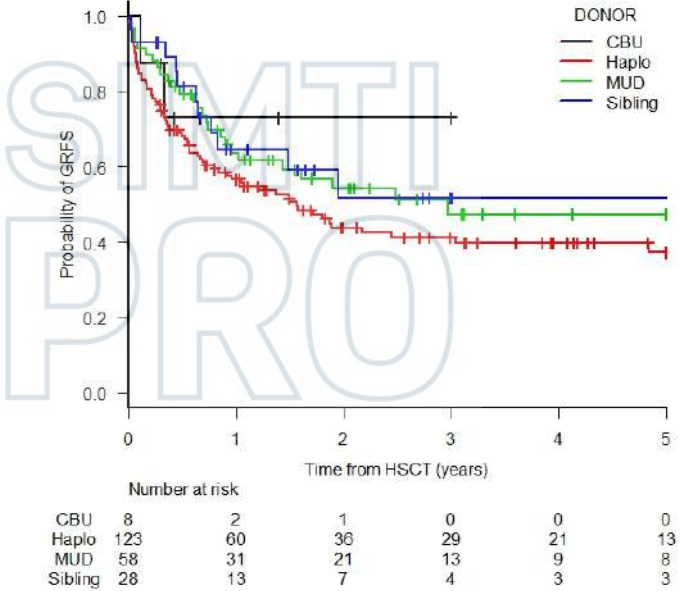


GVHD-free/relapse-free survival

GRFS was 24% in ATG and PT-Cy group at 3-year



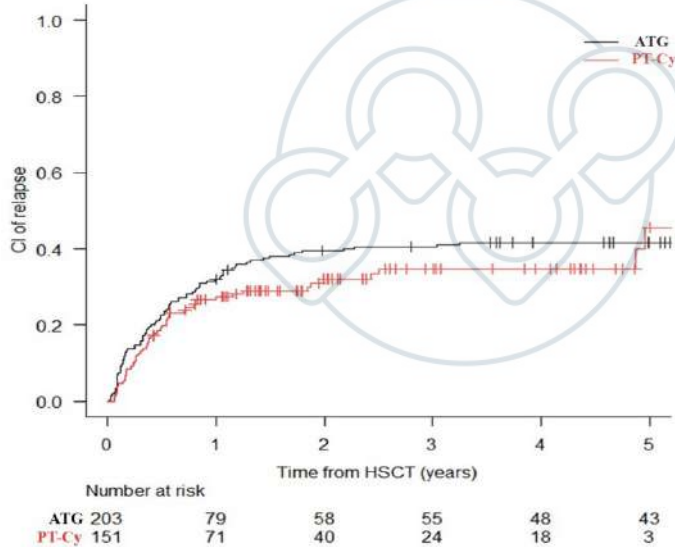
Similar GRFS for different donors in pts with CR at HSCT



Relapse and Transplant-related Mortality

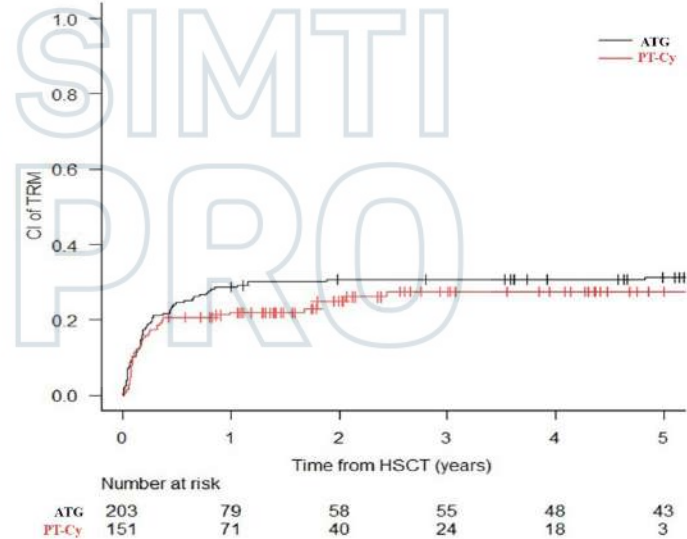
CI of Relapse

- ◇ 41% at 3 years in ATG
- ◇ 35% at 3 years in PT-Cy



CI of TRM

- ◇ 31% at 3 years in ATG
- ◇ 27% at 3 years in PT-Cy



Post-transplant cyclophosphamide versus anti-thymocyte globulin as graft-versus-host disease prophylaxis in haploidentical transplant



EUROPEAN
HEMATOLOGY
ASSOCIATION

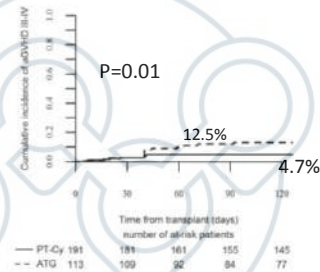
PTCY group
(n=193)

ATG group
(n=115)

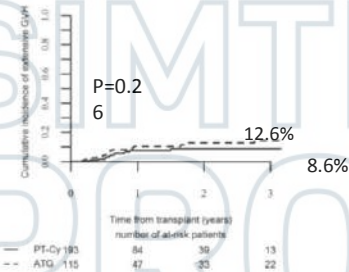
- Adults with AML in first or second CR (CR1 or CR2) at transplant
- Haplo-HSCT between 2007 and 2014
- RIC and MAC
- GVHD prophylaxis based on ATG or PT Cy

TOTAL 308 pts

aGVHD III-IV

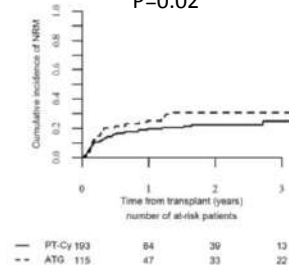


Extensive cGVHD



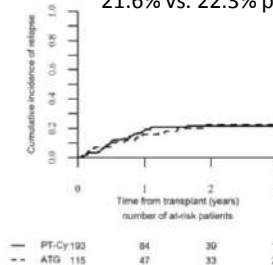
NRM

P=0.02



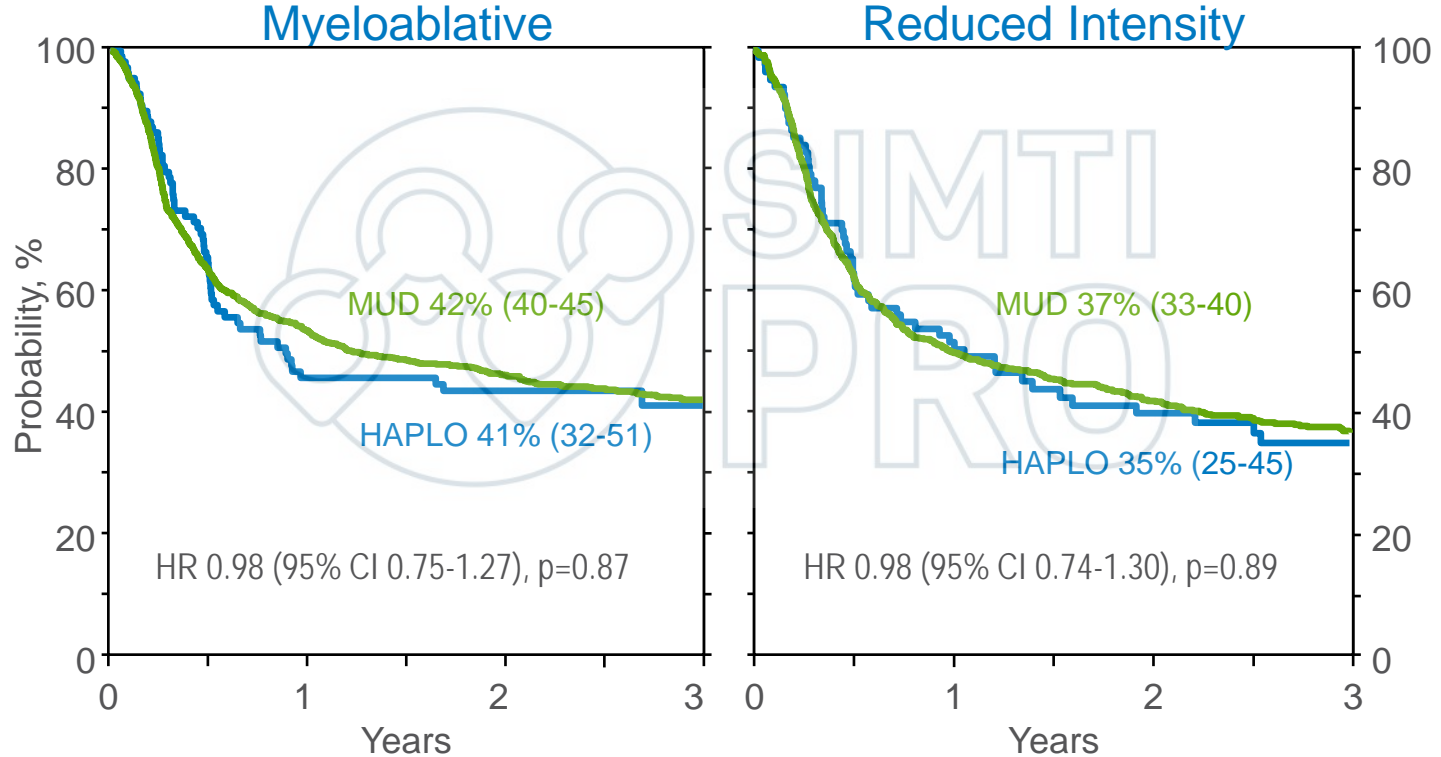
Relapse

21.6% vs. 22.3% p=0.97

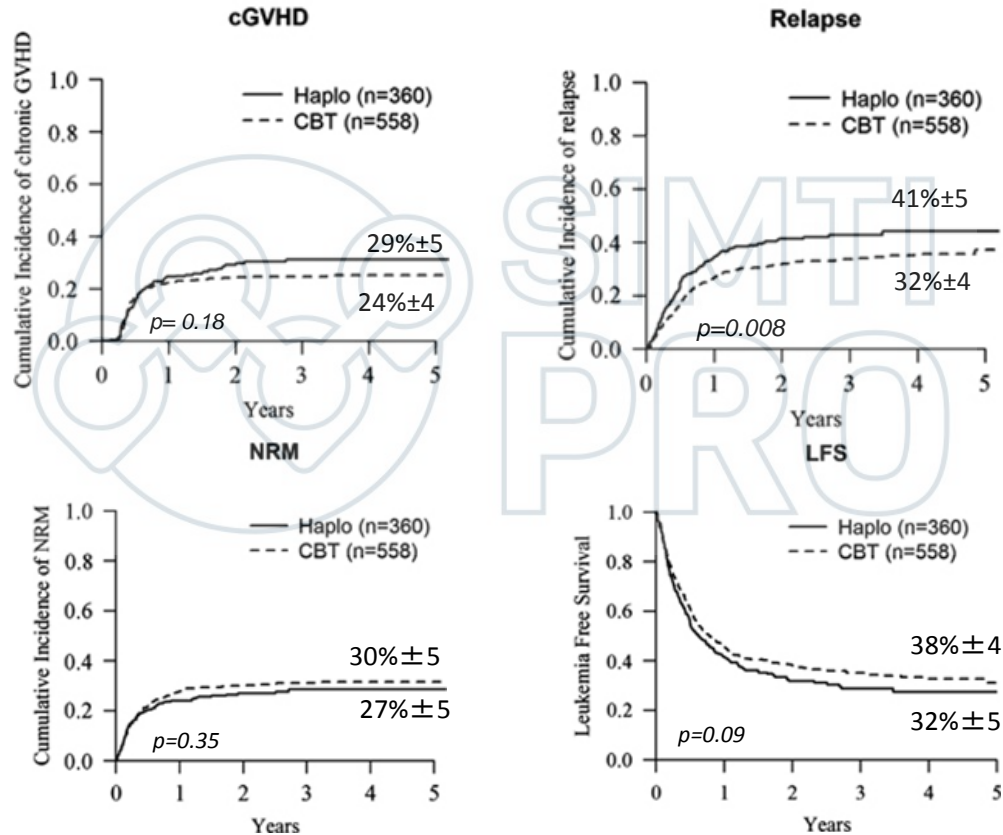


MUD vs Haplo

LFS adjusted for DRI, performance score, secondary AML

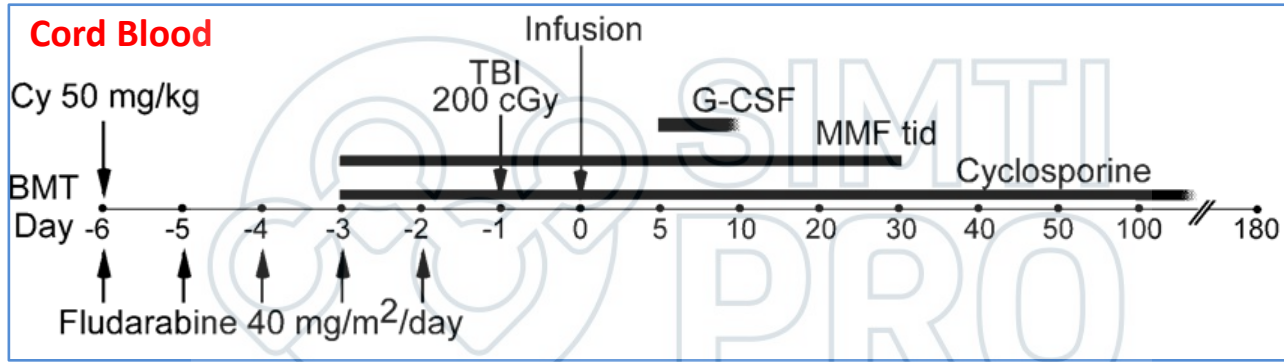


UCBT vs Haplo for adults with AML



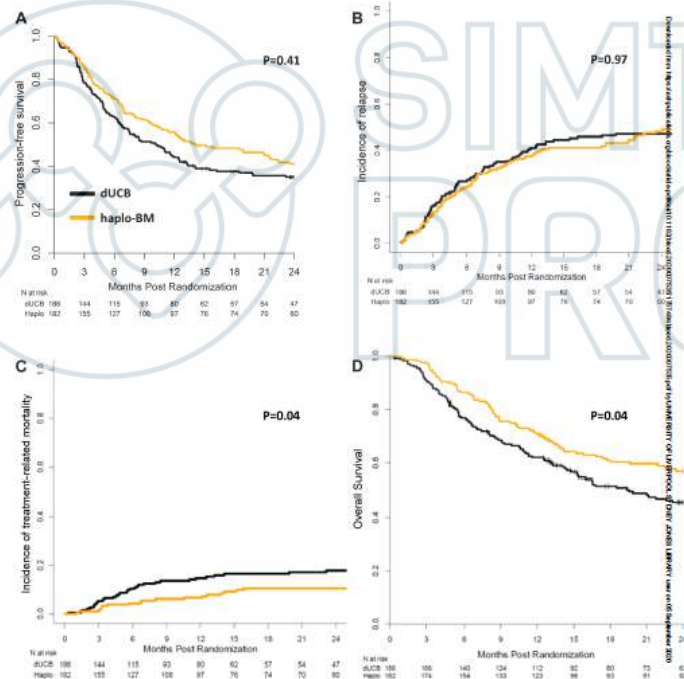
BMT CTN 1101 Trial

Double UCBT vs HLA-haploidentical BMT in RIC setting



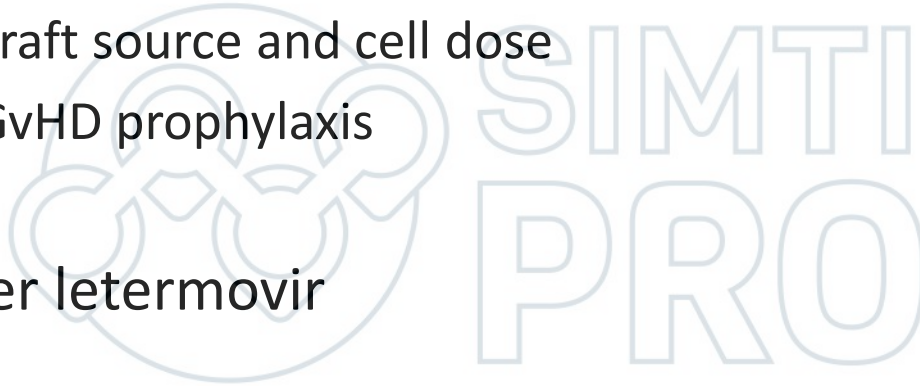
BMT CTN 1101 Trial

No significant difference in PFS between UCB and Haplo HCT for leukemia or lymphoma
 Low NRM after Haplo BMT, excess of relapse in both arm



Hot topics

- Immune reconstitutions and infections:
 - impact of graft source and cell dose
 - Impact of GvHD prophylaxis
- Changes after letermovir

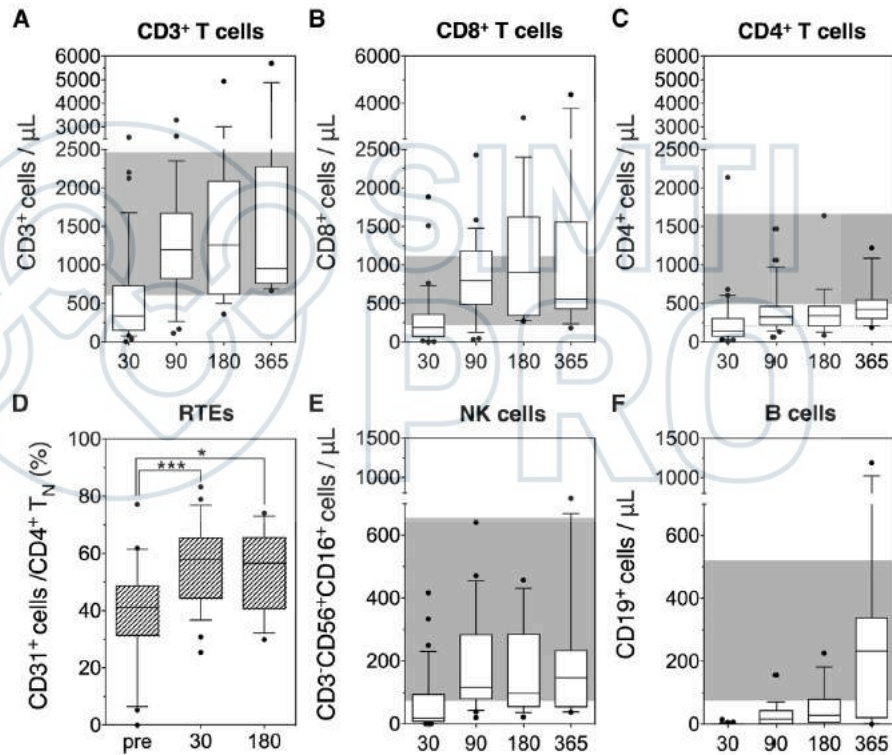




Post-transplantation Cyclophosphamide and Sirolimus after Haploidentical Hematopoietic Stem Cell Transplantation Using a Treosulfan-based Myeloablative Conditioning and Peripheral Blood Stem Cells

Nicoletta Ciceri^{1,2,3}, Raffaella Greco¹, Lara Crucitti^{1,3,4,5}, Mara Morelli¹, Fabio Giglio¹, Giorgia Levari^{1,2}, Andrea Assarelli¹, Matteo G. Carrabba¹, Laura Bellio¹, Raffaella Milani¹, Franca Lorenzini¹, Maria Teresa Lupo Scungilli¹, Ilago De Freitas¹, Sara Merkel¹, Massimo Bernardi¹, Consuelo Corti¹, Luca Vago^{1,3}, Chiara Bonini², Fabio Ciceri^{1,3,4}, Jacopo Peccatori¹

N. Ciceri et al. / Biol Blood Marrow Transplant 21 (2015) 1506–1514



Infections after Allogeneic Transplant with Post-Transplant Cyclophosphamide: Impact of Donor HLA Matching

Chiara Ottolini¹, Raffaella Greco¹, Laura Galli¹, Daniela Clerici¹, Françoisa Lorentino², Elisabetta Xue¹, Maria Teresa Lupo Stanghellini¹, Fabio Giglio¹, Lina Uhr¹, Marco Ripa^{1,3}, Paolo Scarpellini¹, Massimo Bernardi⁴, Consuelo Corri¹, Jacopo Peccatori¹, Antonella Castagna^{1,2}, Fabio Cierni^{1,3,4}

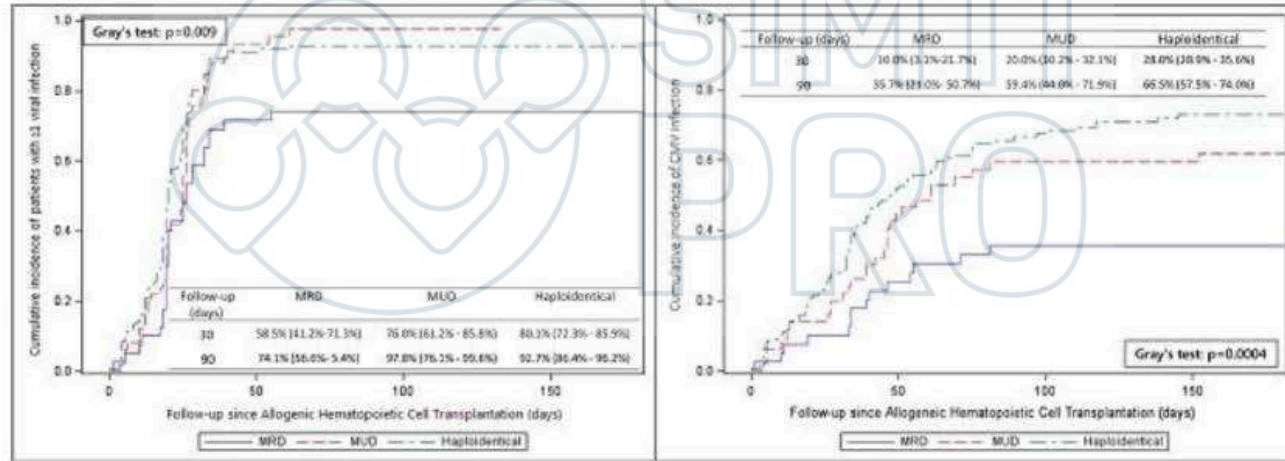


Figure 2. Cumulative incidence function of patients with ≥ 1 VIs (first occurrence among BKPyV-hemorrhagic cystitis and any positive viremia for CMV, HHV6, and ADV) or with CMV infection (end-organ disease or clinically significant infection leading to pre-emptive therapy or viremia not requiring pre-emptive therapy).



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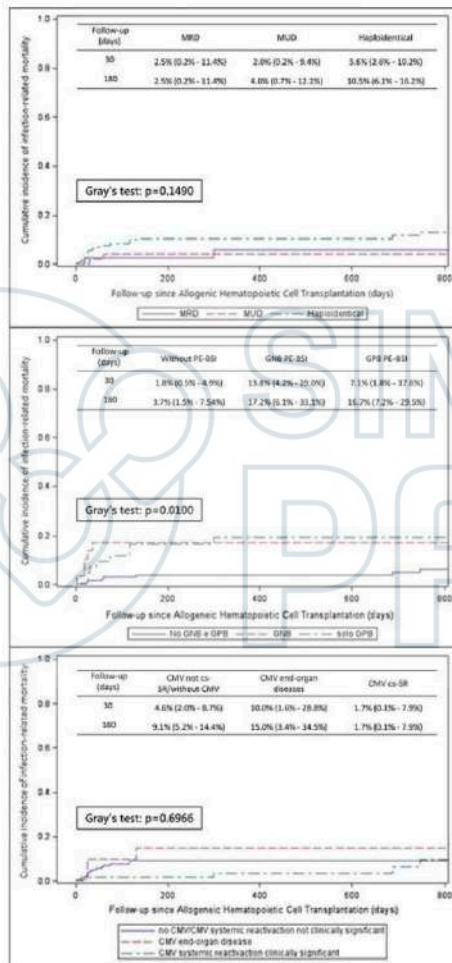
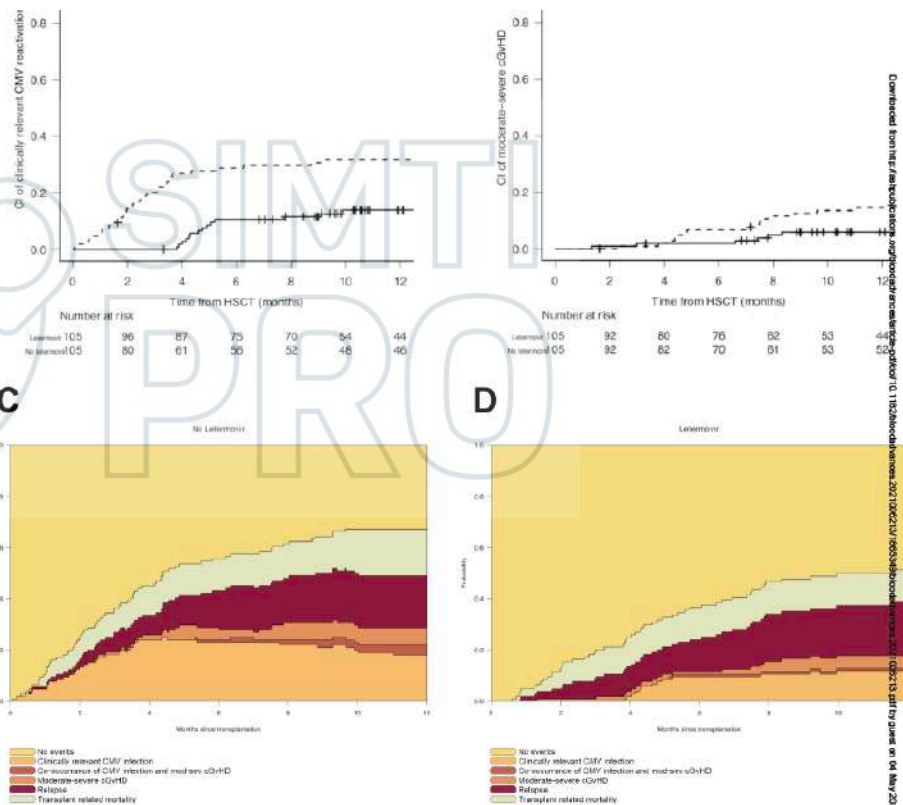


Figure 3. Cumulative incidence of IRM

Letermovir reduces chronic GVHD risk in calcineurin inhibitor-free GVHD prophylaxis after hematopoietic cell transplantation

1 Table 1. Patients' characteristics

	Letermovir (N=105)	No Letermovir (N=105)	p
Patient age, median (IQR)	60 (47-66)	55 (45-64)	0.14
Patient gender, male	68 (65%)	69 (66%)	0.885
Disease			0.717
AML	80 (57%)	58 (55%)	
ALL	8 (7.5%)	13 (12.5%)	
MDS or MPN	26 (25%)	24 (23%)	
Myeloma or Lymphoma	11 (10.5%)	10 (9.5%)	
Disease status			0.381
CR1	46 (44%)	38 (36%)	
CR>1	13 (12%)	19 (18%)	
Active disease	46 (44%)	48 (46%)	
DRi			0.363
Low	7 (7%)	5 (5%)	
Intermediate	59 (56%)	70 (66.5%)	
High	32 (30%)	22 (21%)	
Very high	7 (7%)	8 (7.5%)	
Donor			0.525
CBU	10 (9.5%)	14 (13%)	
MMRD	19 (18%)	24 (23%)	
MMUD	18 (17%)	19 (18%)	
MUD	47 (45%)	35 (33.5%)	
MRD	11 (10.5%)	13 (12.5%)	
H/D CMV serostatus			0.209
Pos/neg	54 (51%)	46 (44%)	
Pos/pos	51 (49%)	59 (56%)	
Stem cell source			0.39
PB	95 (90.5%)	91 (87%)	
CBU	10 (9.5%)	14 (13%)	
GvHD prophylaxis			0.06
PTCy-sirolimus-MMF	80 (76%)	79 (75%)	
PTCy-sirolimus	11 (10%)	14 (13%)	
Sirolimus-MMF	8 (8%)	12 (12%)	
Other sirolimus-based	6 (6%)	0	





GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

