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Role of ATG in sibling transplantation and myeloablative conditioning

Congress SFGM-TC Montpellier 22.11.2018

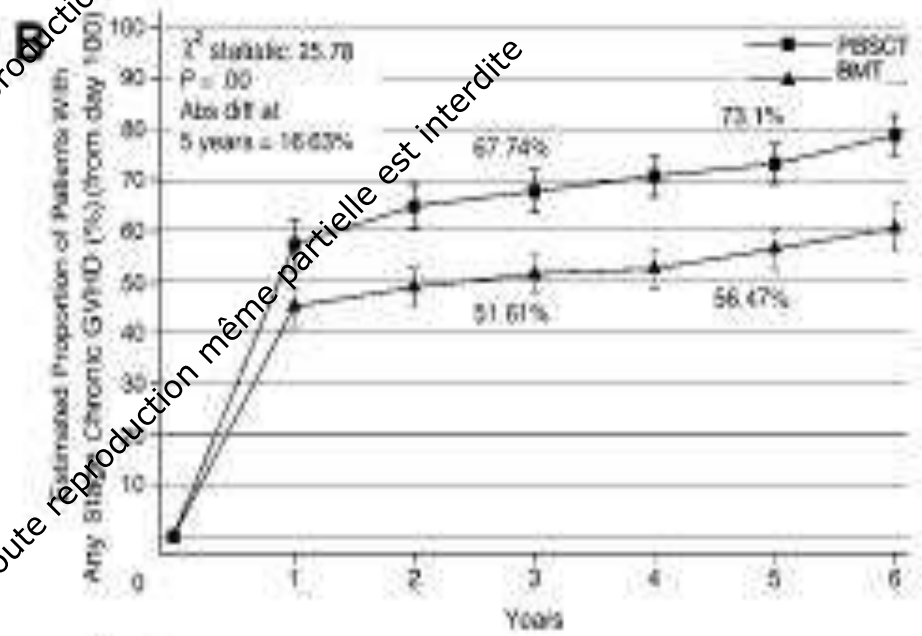
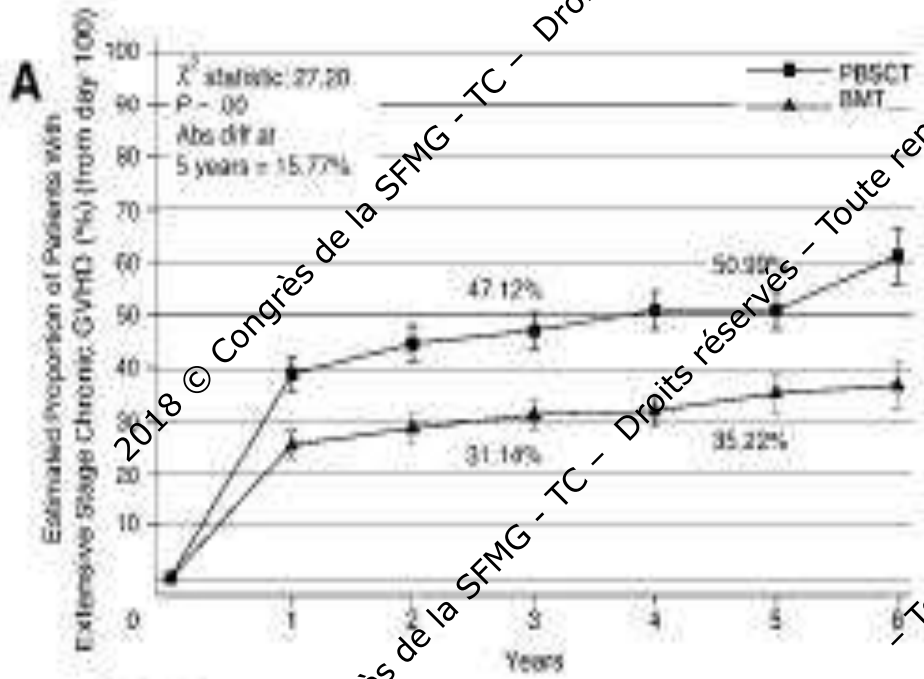
Prof. Nicolaus Kröger
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University Hospital Hamburg/Germany

Background

- **Acute and Chronic Graft-versus Host Disease (GvHD) are major complications after allogeneic stem cell transplantation and a major cause for morbidity and mortality.**
- **Chronic GVHD is the second leading cause of death among patients who survive for 2 years after transplantation** *(Wingard et al JCO 2011)*
- **Chronic GVHD is reducing QoL after stem cell transplantation**
- **Although some progress has been made in preventing acute GVHD, most attempts to reduce the risk of chronic GVHD have been unsuccessful**

(Kansu et al Blood 2001, Sullivan et al BBMT 1996)

Chronic GvHD



Events/person-years

PBSC:	150/325.09	13/26.20	5/99.81	5/83.55	0/40.83	5/23.19
BMT:	150/344.23	8/171.96	5/142.56	1/76.72	2/40.85	1/25.46

Events/person-years

PBSC:	267/325.09	25/126.20	9/99.81	6/83.55	3/40.83	5/23.19
BMT:	214/344.23	14/171.96	8/142.56	2/76.72	4/40.85	3/25.46

Extensive cGvHD after PBSC > 50% after 5 years
> 70% of allogeneic HSCT in Europe are done with PBSC

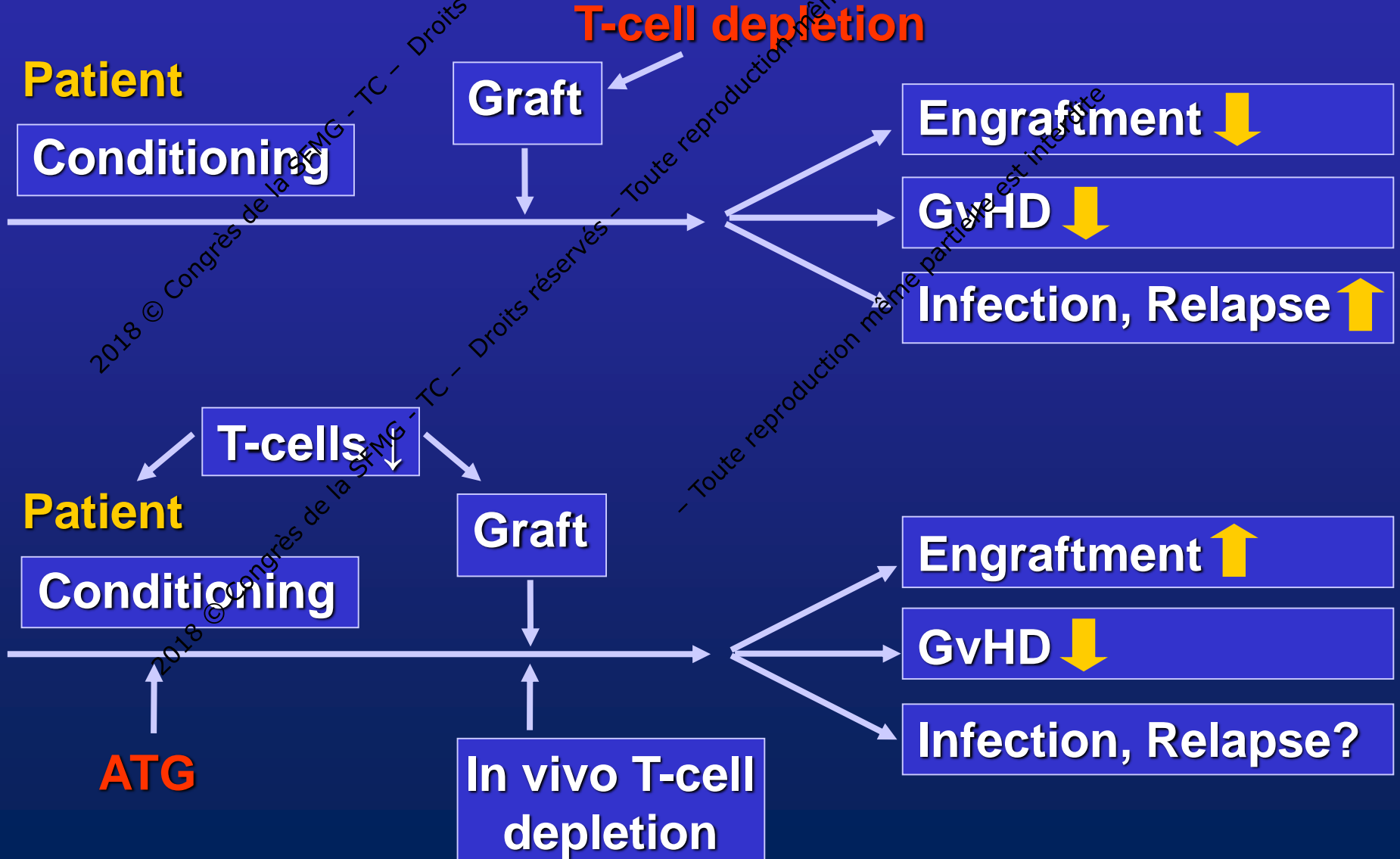
ATG/ATLG: Polyclonal Immunoglobulines

- Rabbit-anti-human thymocyte globulin (Thymoglobulin®)
 - Vaccination of rabbits with human thymocytes
- Rabbit-anti-human T-lymphocyte immune serum (former: ATG-Fresenius® now: ATLG Neovii®)
 - Vaccination against Jurkat cell line (T lymphoblastic cell line)
- Horse-anti-human globulin (ATGAM®)

ATG/ATLG: Mechanisms of Action

- **ATG induces dose-dependent T-cell depletion in blood and peripheral lymphoid tissues**
- **Depletion might involve complement-dependent lysis and activation-associated apoptosis**
- **Other functional properties (e.g. anergy) might contribute to immunosuppressive activity of ATG**

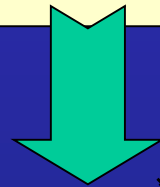
Difference between ATG and T-cell depletion



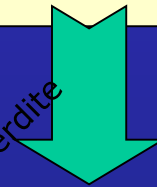
Target Antigens of ATG

<i>Immune Response Antigens</i>		<i>Adhesion & Cell Trafficking</i>	<i>Heterog. Pathway</i>
CD1a	CD28	CD11a/CD18 (FLA-1)	CD2
CD3/TCR	CD30	CD44	CD5
CD4	CD32	CD49/CD29 (VLA-4)	CD6
CD6	CD40	CD50 (ICAM-3)	CD11b
CD7	CD80	CD51/61	CD29
CD8	CD86	CD54 (ICAM-1)	CD38
CD16	CD152	CD56	CD40
CD19	(CTLA-4)	CD58 (LFA-3)	CD45
CD20	HLA class I	LPAM-1($\alpha 4\beta 7$)	CD95
CD25	HLA class II	CD102 (ICAM-2=	CD126
	$\beta 2$ -M		CD138
<i>Bonnefoy-Bérard et al. Transplantation. 1991;</i> <i>Bonnefoy-Bérard et al. Immunology. 1992,</i> <i>Bonnefoy-Bérard et al. Blood. 1992;</i> <i>Bonnefoy-Bérard et al. J Heart Lung Trans. 1996;</i> <i>Bourdage et al. Transplantation. 1995;</i>		CD195 (CCR5)	
		CD197 (CCR7)	
		CD184 (CXCR4)	

ATG Effect on B cells and Dendritic cells



**Antigen
presenting cell** ↓ ↓



**Treatment
B cell diseases?**



**Autoimmune
disease?**



**Reduce risk
of acute and
chronic
GvHD after
allo SCT**

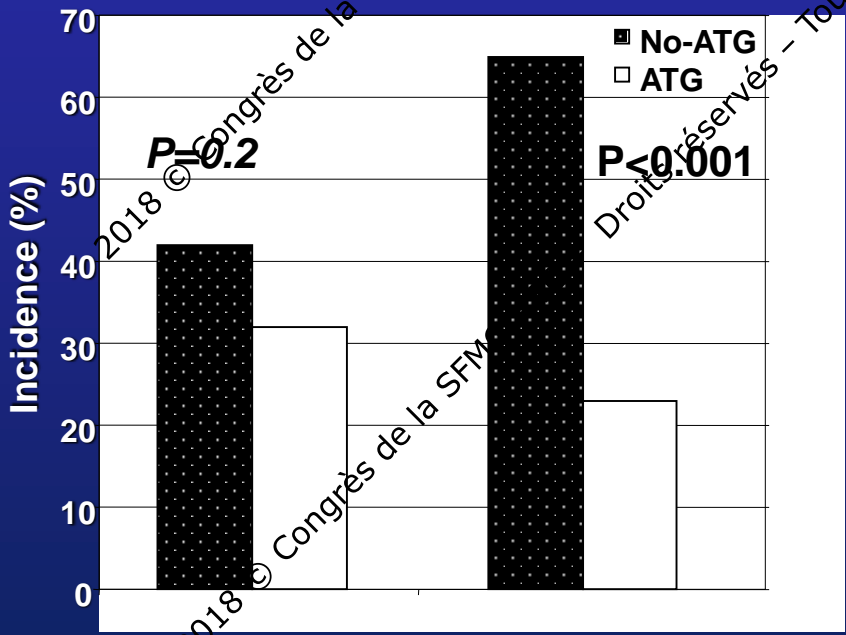
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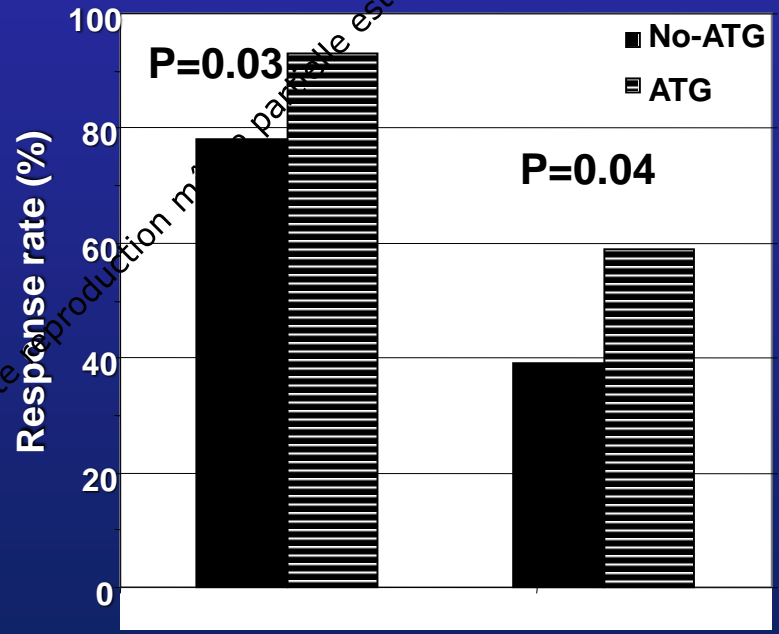
Allogeneic SCT w/o ATG in Multiple Myeloma (n=139)

GVHD



acute GvHD II°-IV° chronic GvHD

Remission



Overall response complete response

Role of ATG in HLA-identical sibling SCT

- 1. ATG and ATLG has been shown to reduce the risk of acute and chronic graft –versus host disease after unrelated hematopoietic stem cell transplantation** (*Bacigalupo et al 2003, Finke et al., 2009, Walker et al 2016*)
- 2. Despite reducing GvHD there was no obvious risk of relapse in a randomized trial**
- 3. The role of ATG in HLA identical sibling SCT remains to be determined**

Background

- **Allogeneic stem cell transplantation from HLA-identical siblings with an unmanipulated graft resulted in an incidence of acute GvHD of approximately 30 - 60%.**
- **The treatment-related mortality for patients with acute GvHD grade III or IV is high.**
- **For chronic GvHD the three-year risk of treatment-related mortality is 28 % in case of limited disease and 48 % in case of extensive disease.**

HLA-identical sibling SCT w/o ATG: Early Hamburg experience *(BMT 2002)*

	<i>ATG-group</i>	<i>Non-ATG group</i>	<i>p-value</i>
Number of patients	45	57	n. s.
Diagnosis:			
– AML, 1 st CR	21	26	n. s.
– CML, 1 st CP	24	31	n. s.
Median age (range)	39 (11-58)	33 (16-57)	n.s.
Median months of follow-up (range)	26 (7-75)	65 (1-126)	< 0.001
HLA-identical	38	51	n. s.
one HLA mismatch	7	6	n. s.
Male / female	21/24	31/26	n.s.
Stem cell source BM/PBSC	42/3	46/11	0.02

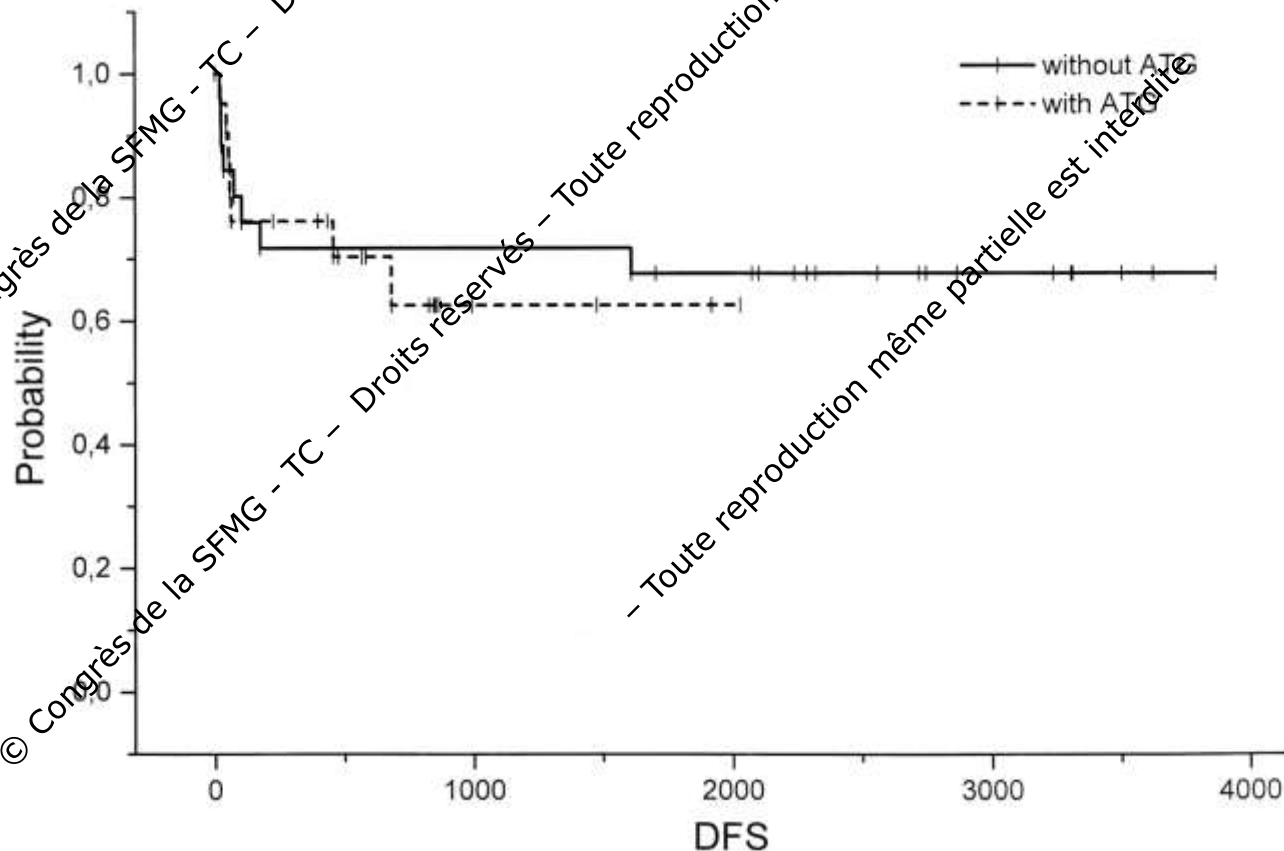
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Male / female	21/24	31/26	n.s.
Stem cell source BM/PBSC	42/3	46/11	0.02

Results

	ATG (Fresenius)	non-ATG	p-value
Median leukocyte engraftment > 1 /nl	16 days (range 12-33)	17 days (range 11-29)	ns
Median platelet engraftment > 20 /nl	24 days (range 14-277)	19 days (range 11-34)	0.002
Graft-failure	0	1	ns
Acute GvHD (II-IV)	20%	47%	0.004
Acute GvHD (III/IV)	7%	22%	0.002
Chronic GvHD (overall)	36%	67%	0.005
Chronic GvHD extensive	17%	33%	0.08
Probability of relapse (3 years)	4%	15%	ns

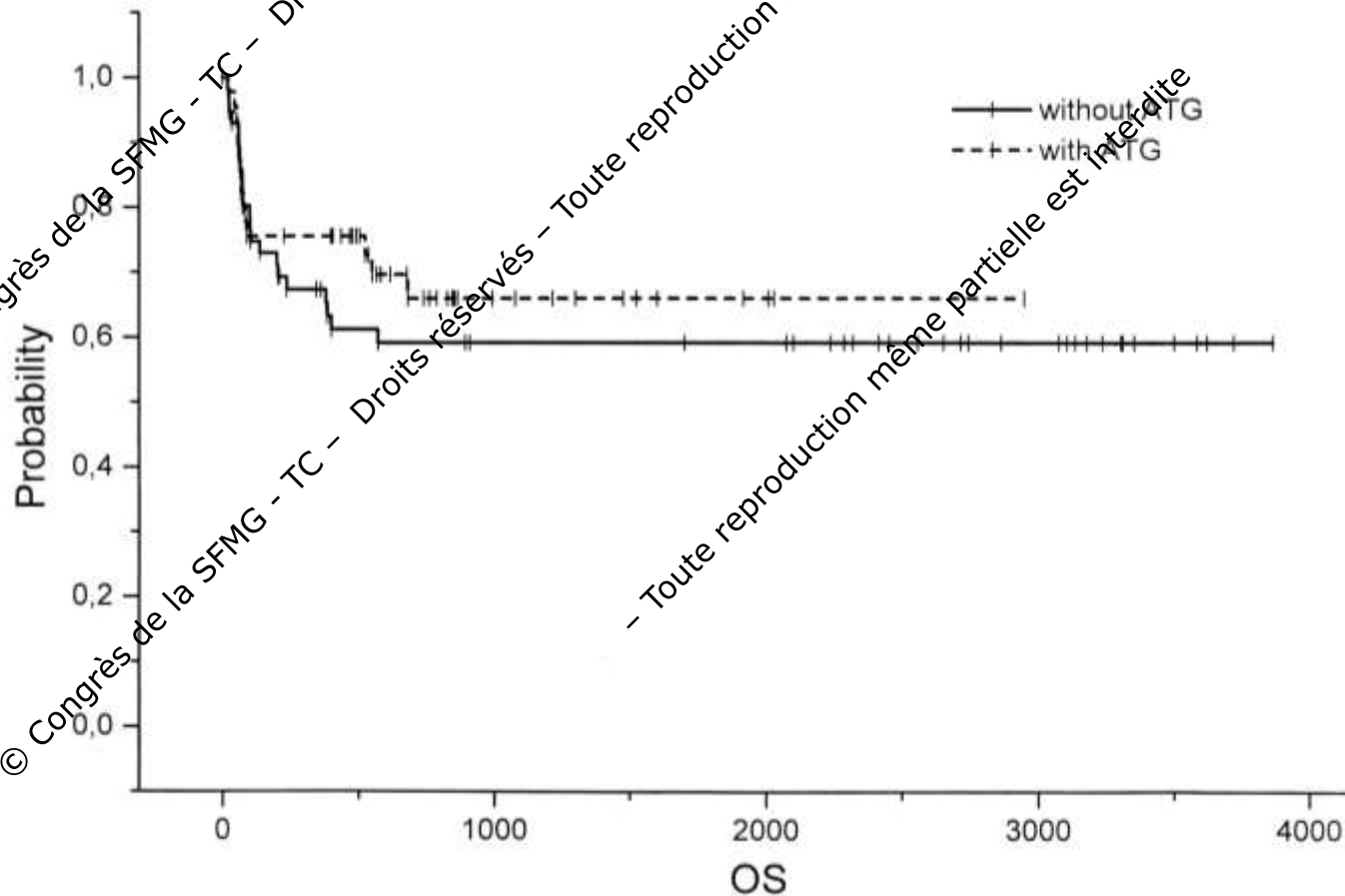
Estimated *disease-free* survival (5 years)



ATG: 64% (50 - 78%)
Non-ATG: 55% (43 - 67%)

Kröger et al., BMT 2002

Estimated overall survival (5 years)



ATG: 66% (51 - 81%)
Non-ATG: 59% (43 - 67%)

ATG in related stem cell transplantation Hamburg experience (1990-2011): n=462

n = 462

(exclusion: < 18 y, Aplastic anemia, myelofibrosis)

female:

190

male:

272

median age:

43 y (18 – 73)

Diagnosis:

AML:

181

ALL:

55

CML:

87

MDS:

36

Lymphoprolif. Disorders: 103

good risk:

238

bad risk:

218

ATG in related stem cell transplantation Hamburg experience (1990-2011)

	ATG (med. dose: 30 mg/kg) n = 178	Non ATG n = 284	p-value
< 2000	43%	37%	
2000-2005	37%	31%	
2006-2011	19%	34%	n. s.
female:	39%	42%	
male:	61%	58%	n. s.
HLA-matched:	89%	94%	
mismatched:	11%	6%	0.08
Source			
KM	43%	41%	
FBSC	57%	59%	n. s.
CMV pos. (recipient)	64%	57%	n. s.
Conditioning			
RIC :	35%	21%	
MAC :	65%	79%	0.001

ATG in related stem cell transplantation Hamburg experience (1990-2011)

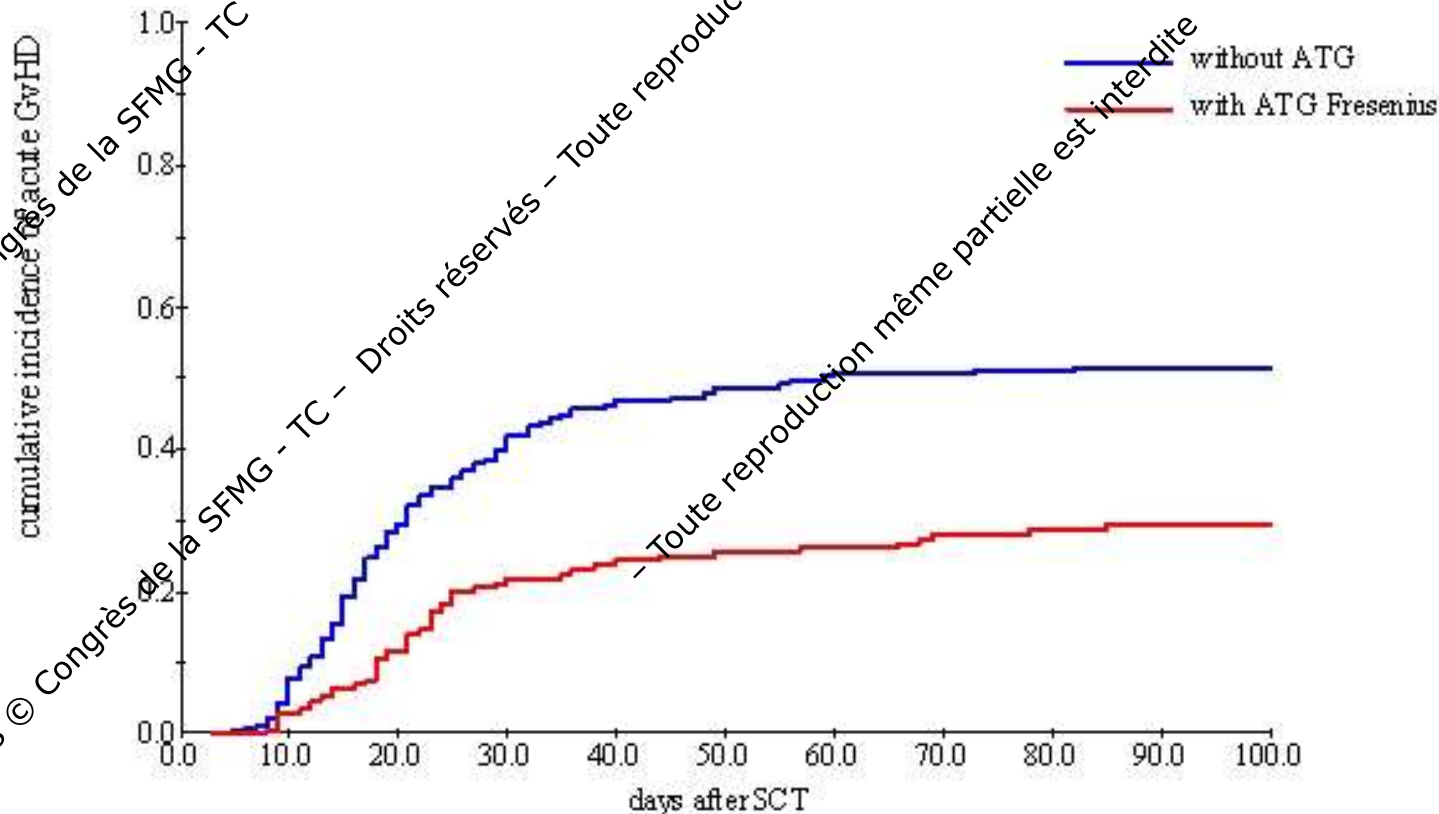
	ATG	non ATG	p-value
Recipient age			
< 43	38%	58%	0.001
> 43	62%	38%	
good risk	46 %	56%	0.03
bad risk	54%	44%	
Follow up	90 months (41 - 152)	107 months (56 – 144)	n. s.

ATG in related stem cell transplantation Hamburg experience (1990-2011)

	<i>ATG</i>	<i>non ATG</i>	
Graft failure:	0.6%	1.1%	n. s.
acute GvHD			
0/I	71%	50%	
II	16%	22%	p < 0.001
III/IV	12%	28%	
chronic GvHD	42%	63%	p < 0.001

ATG in related stem cell transplantation Hamburg experience (1990-2011)

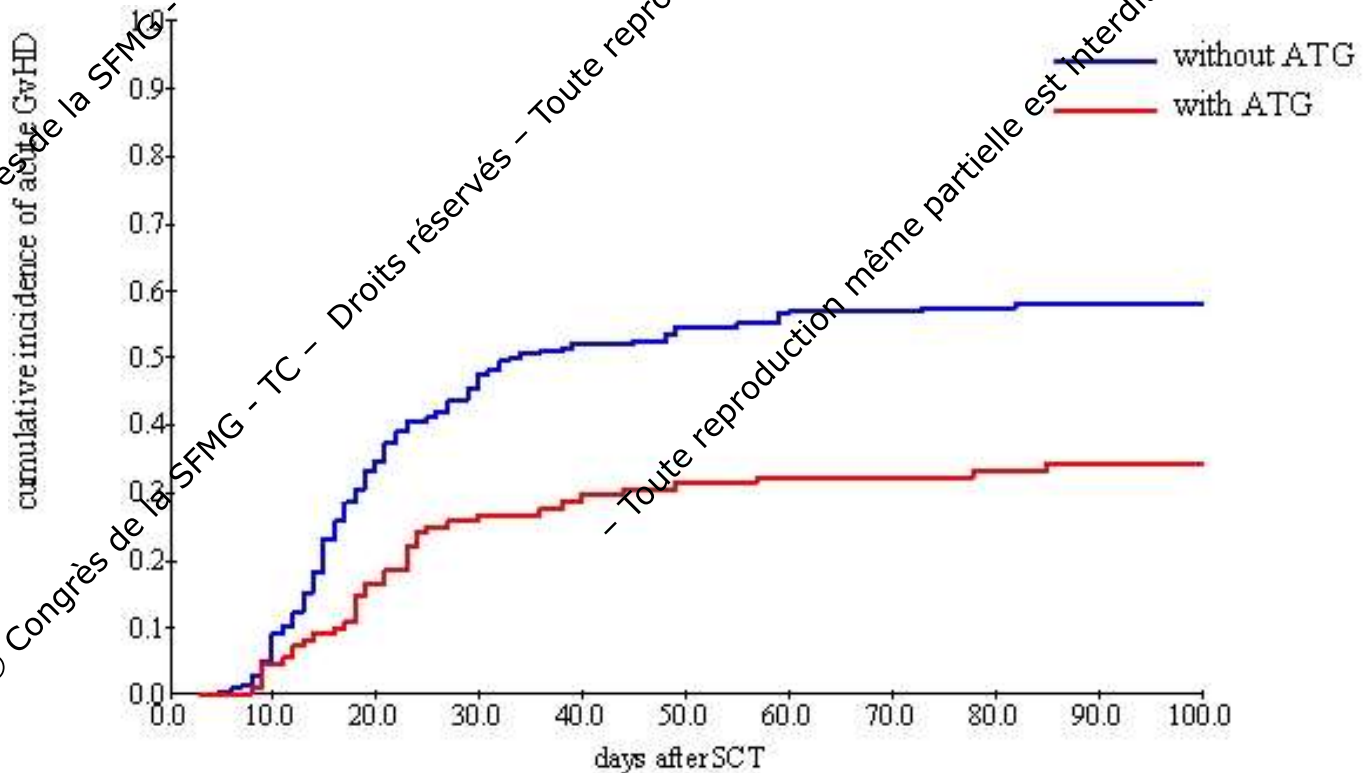
aGvHD



Number at Risk	0.0	10.0	20.0	30.0	40.0	50.0	60.0	70.0	80.0	90.0	100.0
without ATG	284	265	177	136	115	107	96	96	89	86	80
with ATG Fresenius	178	170	140	107	99	93	90	86	83	79	75
Total	462	435	317	243	214	200	186	182	172	165	155

ATG in related stem cell transplantation Hamburg experience (1990-2011)

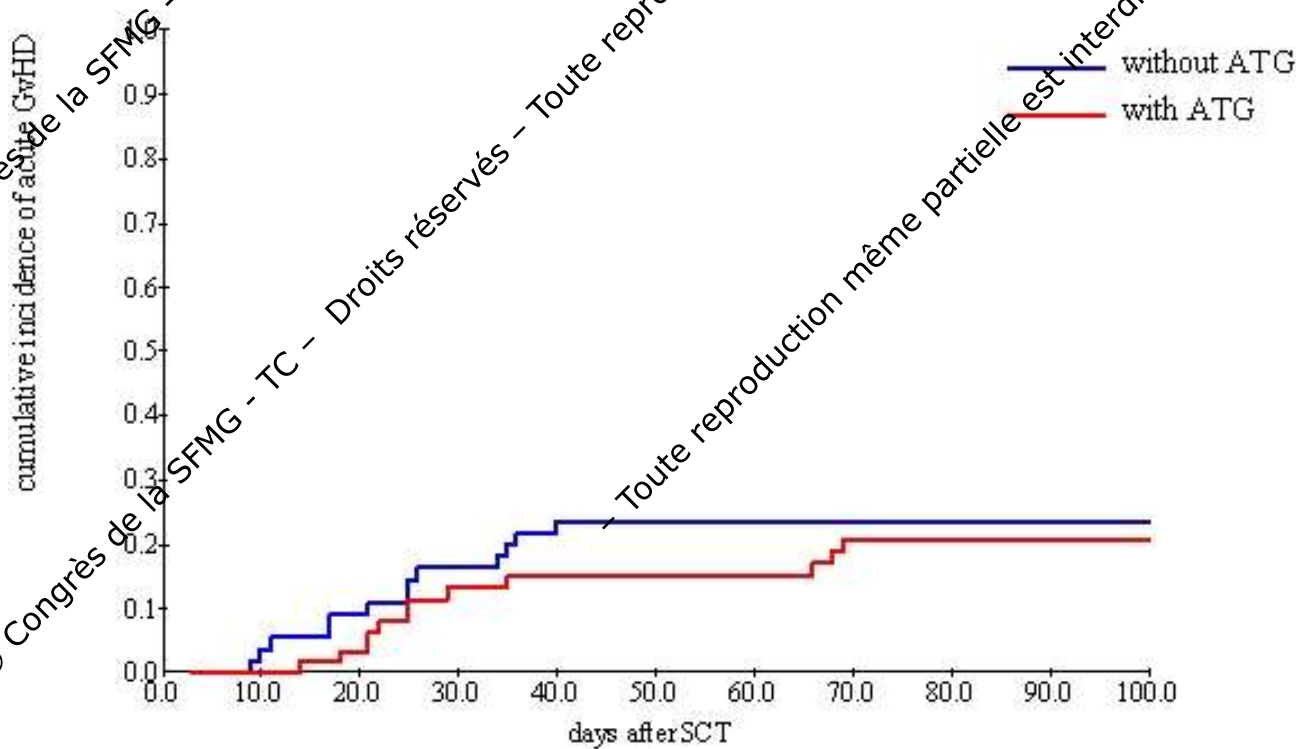
aGvHD: After standard conditioning



Number at Risk											
—	225	212	140	110	93	86	77	77	74	72	68
—	116	110	85	69	64	61	59	59	58	55	51
Total	341	322	225	179	157	147	136	136	132	127	119

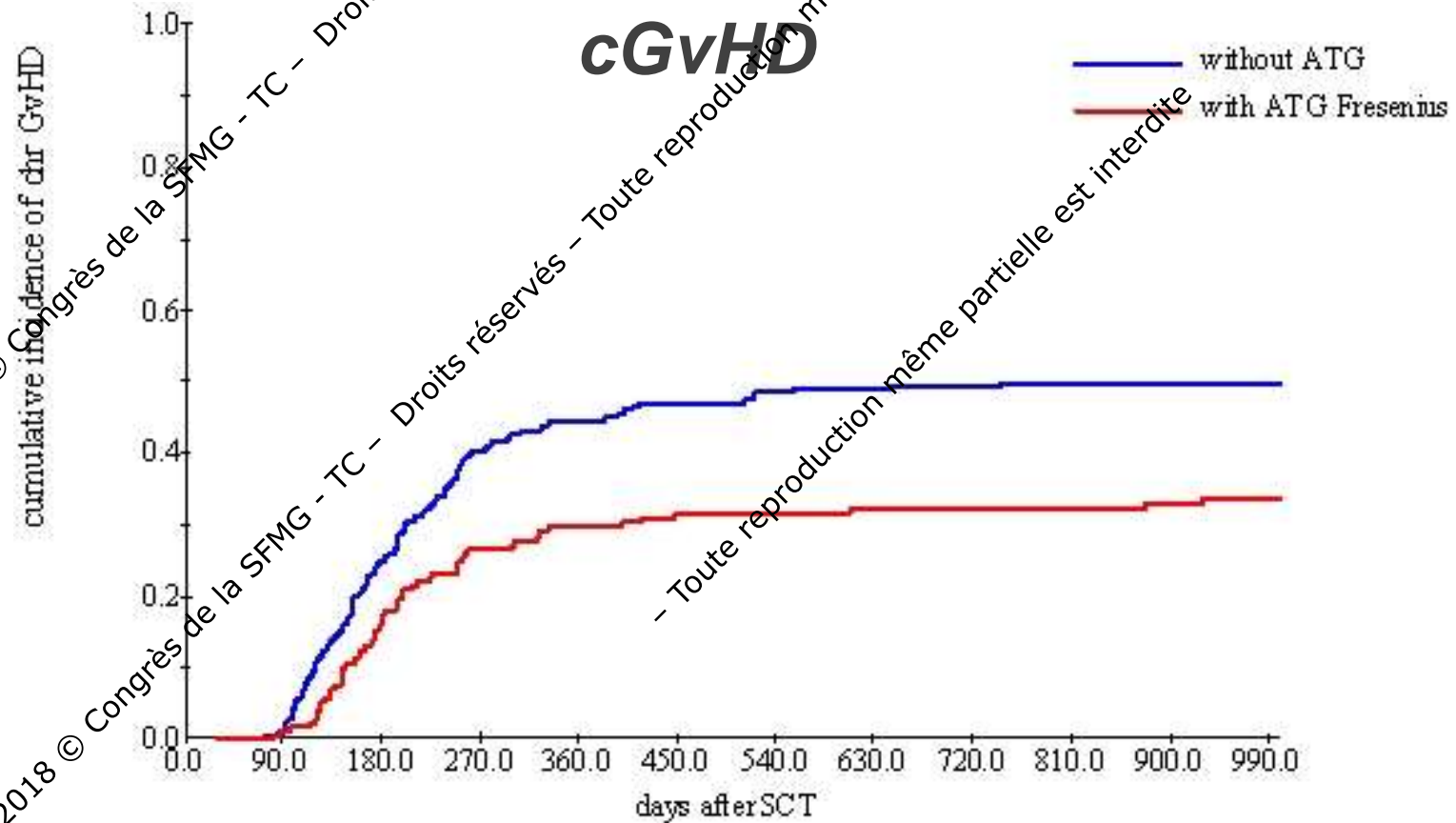
ATG in related stem cell transplantation Hamburg experience (1990-2011)

aGvHD: After reduced intensity conditioning



Number at Risk		0.0	10.0	20.0	30.0	40.0	50.0	60.0	70.0	80.0	90.0	100.0
—	59	59	53	50	43	39	39	39	39	39	39	29
—	62	62	62	59	47	44	44	44	38	38	38	35
Total		121	115	109	90	83	83	83	77	77	77	64

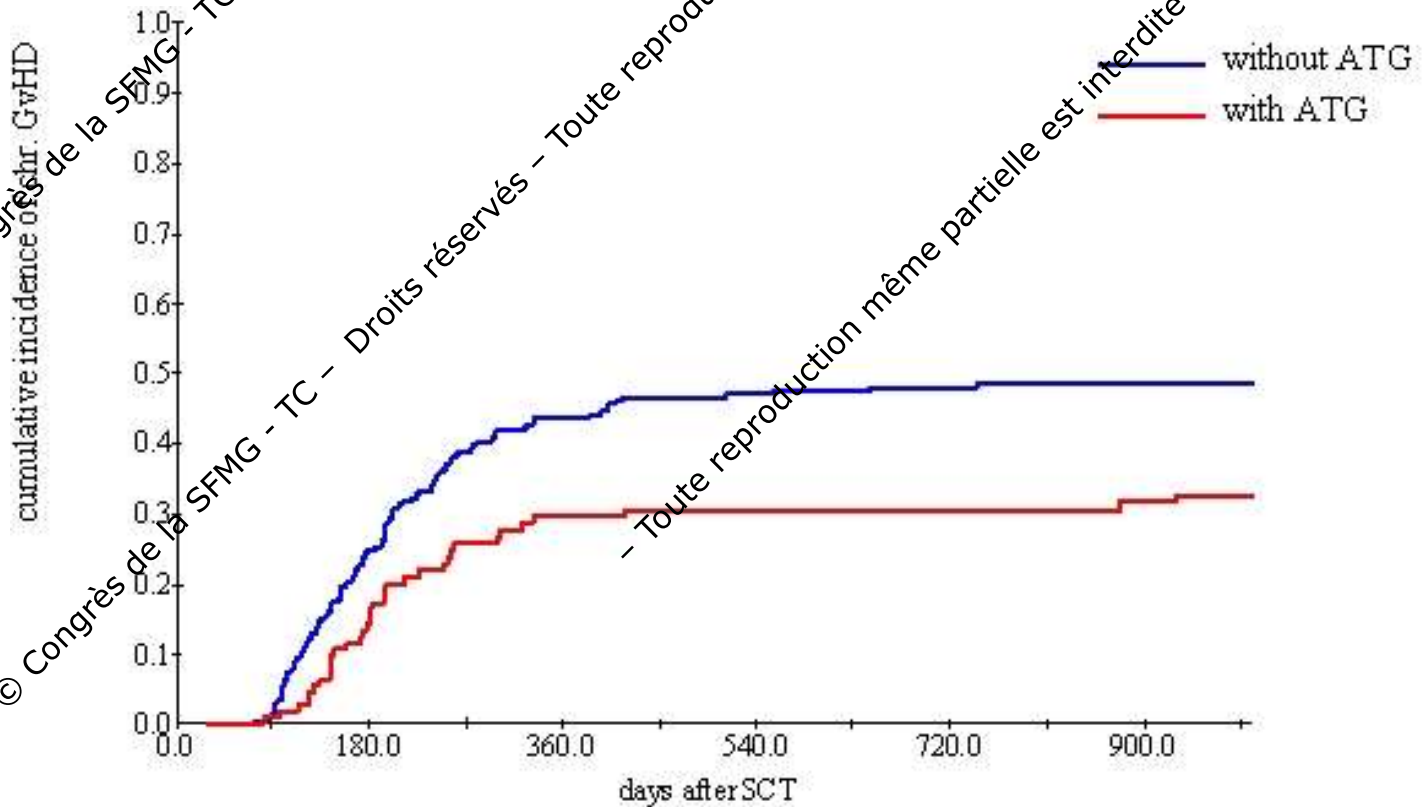
ATG in related stem cell transplantation Hamburg experience (1990-2011)



Number at Risk		90.0	180.0	270.0	360.0	450.0	540.0	630.0	720.0	810.0	900.0	990.0
—	284	215	120	72	59	50	44	43	40	37	37	37
—	178	138	95	74	64	59	59	57	57	57	49	48
Total		462	353	215	146	109	103	100	97	94	86	85

ATG in related stem cell transplantation Hamburg experience (1990-2011)

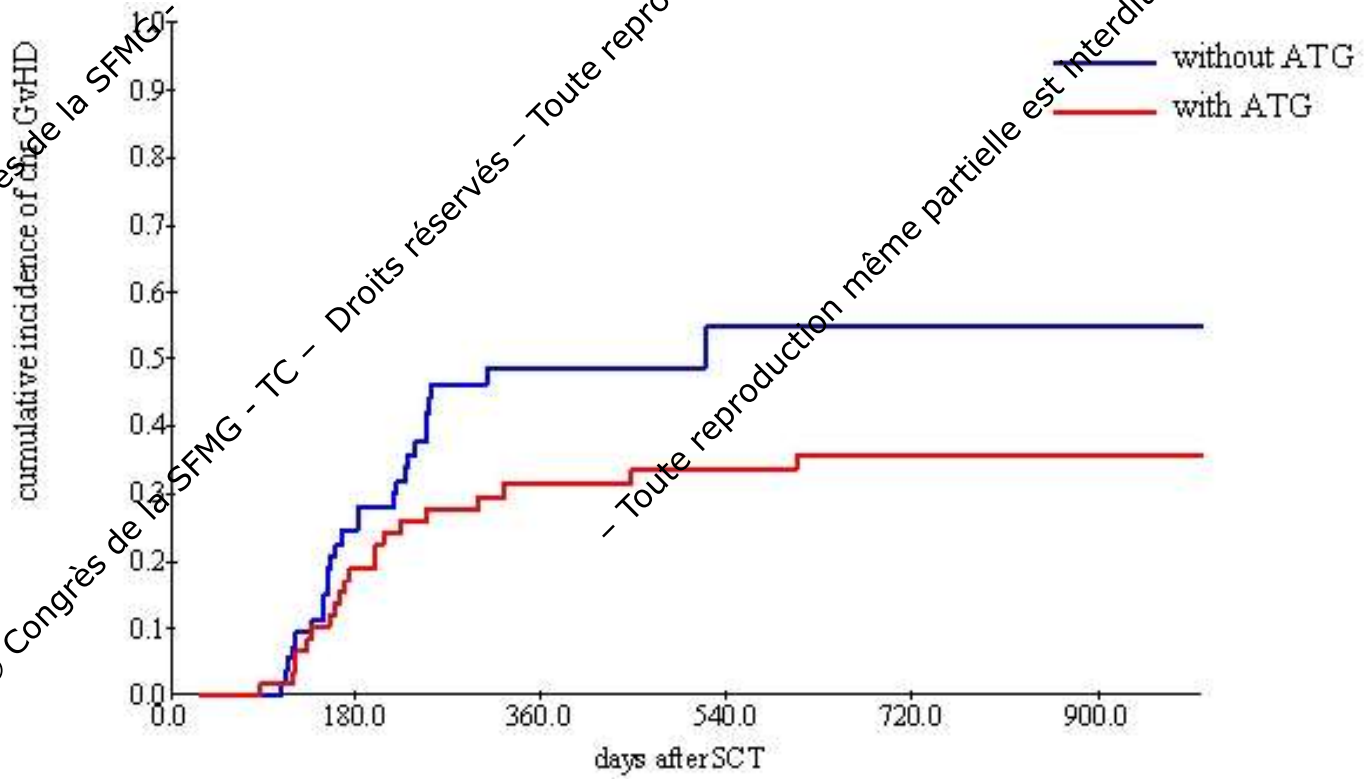
cGvHD: After standard conditioning



Number at Risk						
—	225	98	52	40	36	33
—	116	62	42	41	41	35
Total	341	160	94	81	77	68

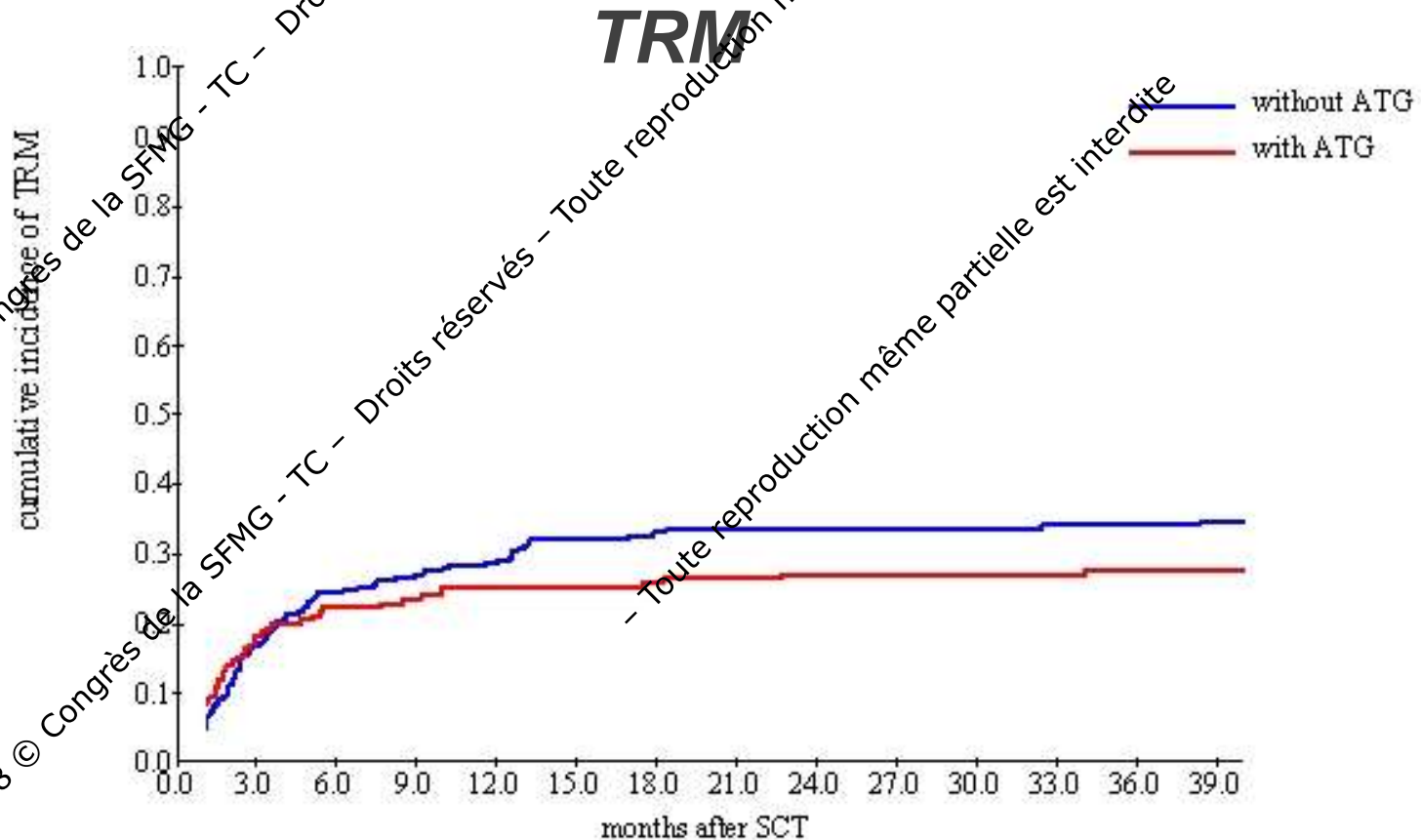
ATG in related stem cell transplantation Hamburg experience (1990-2011)

cGvHD: After reduced intensity conditioning



Number at Risk						
— without ATG	59	23	8	5	5	5
— with ATG	62	34	22	19	18	18
Total	121	57	30	24	23	23

ATG in related stem cell transplantation Hamburg experience (1990-2011)

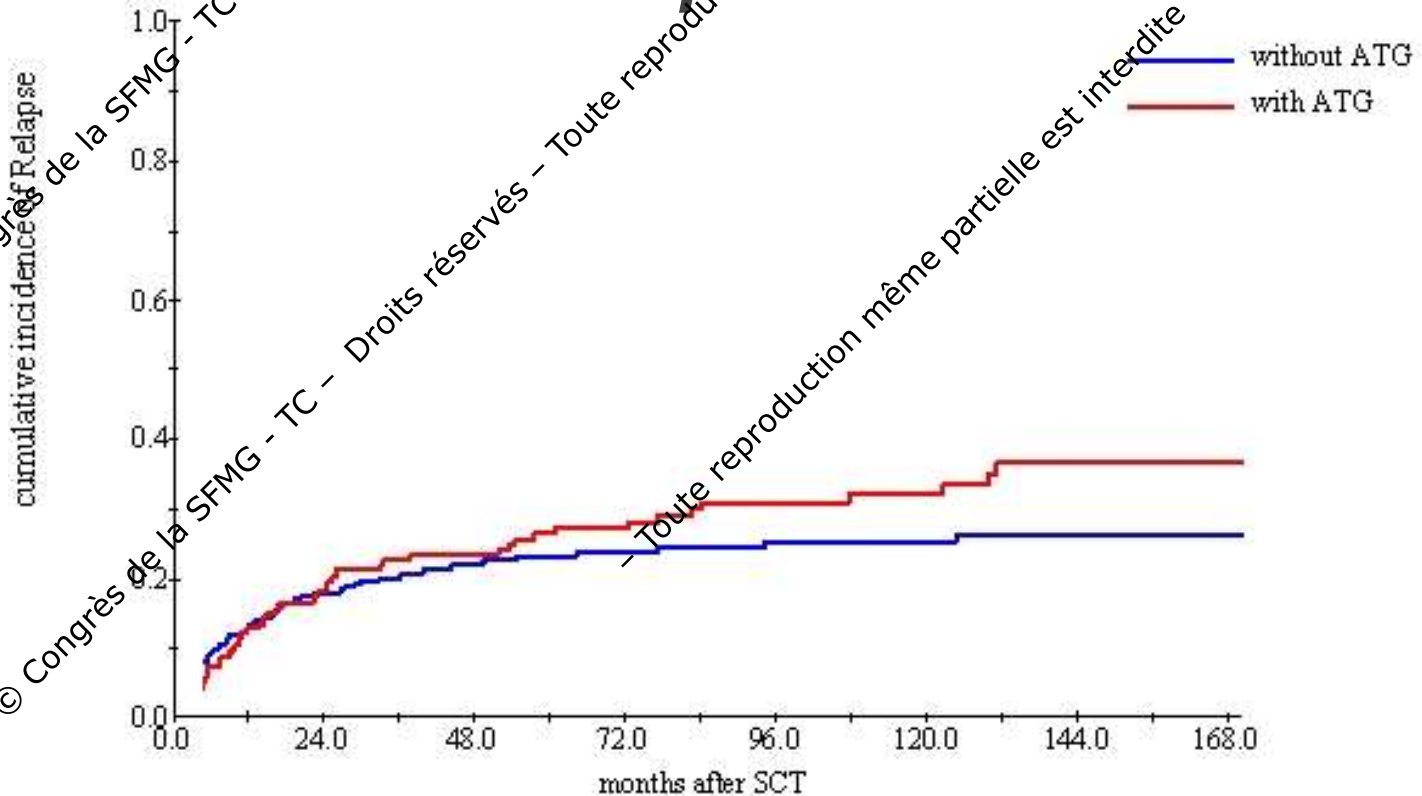


Number at Risk

—	284	225	190	167	158	142	131	130	130	130	130	109	105	102
—	177	141	124	115	110	110	95	94	91	91	91	91	77	77
Total	461	366	314	282	268	252	226	224	221	221	221	200	182	179

ATG in related stem cell transplantation Hamburg experience (1990-2011)

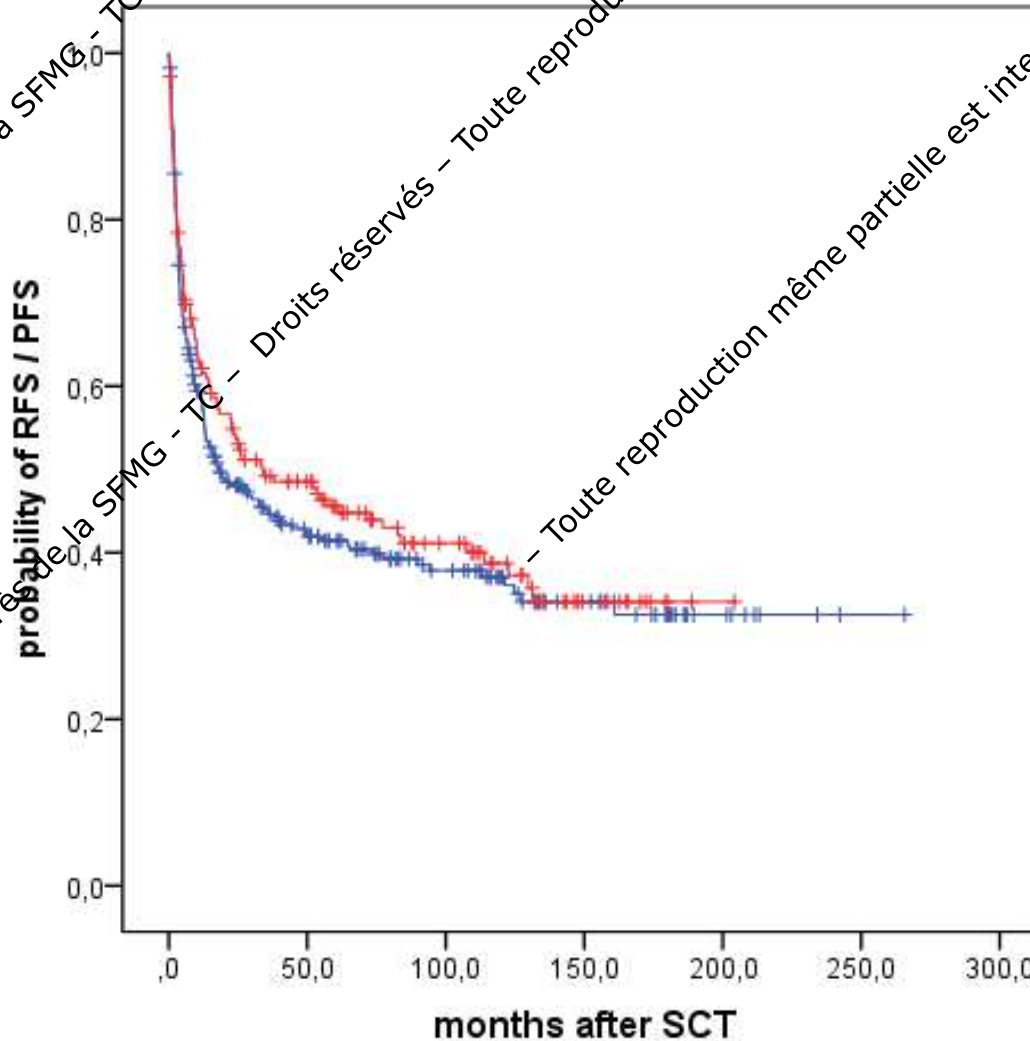
Relapse



Number at Risk									
—	284	122	94	79	55	55	37	37	
—	177	90	74	57	45	37	22	22	
Total	461	212	168	136	100	92	59	59	

ATG in related stem cell transplantation Hamburg experience (1990-2011)

Relapse-free survival



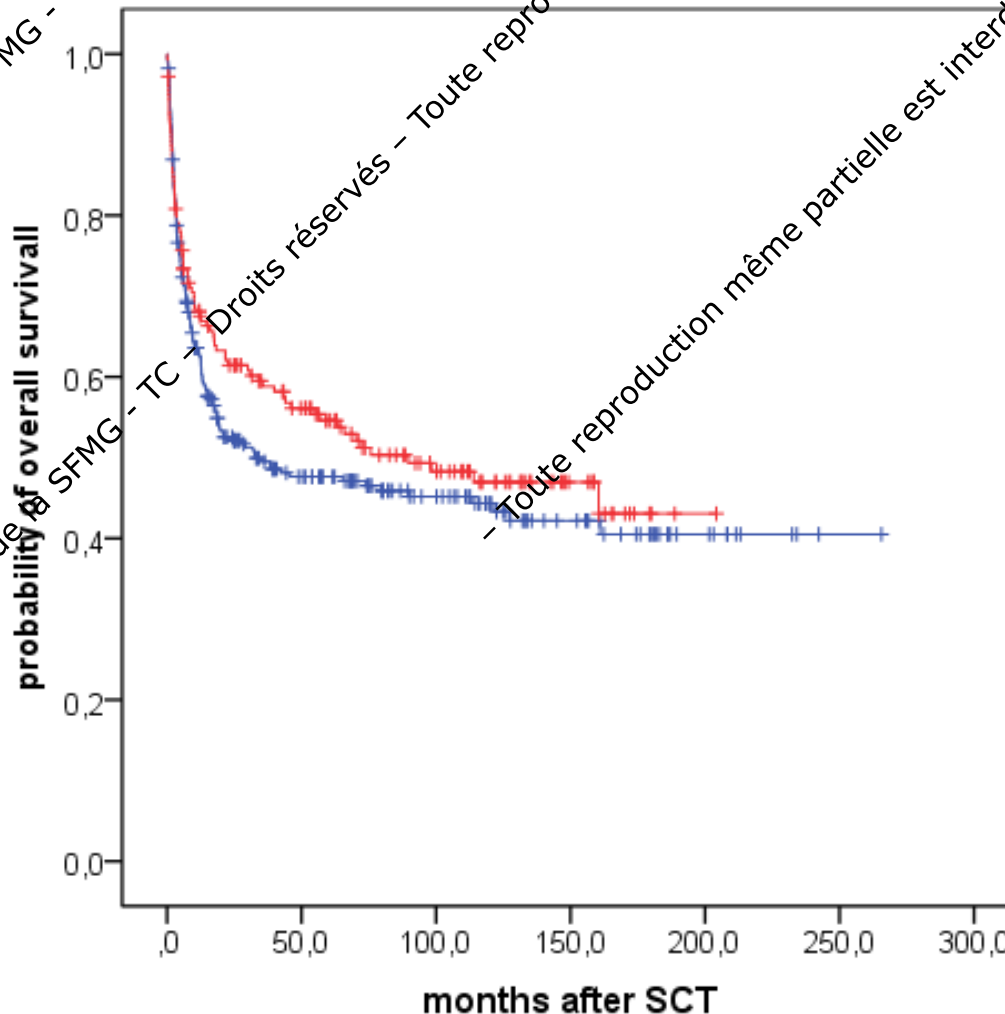
— with ATG
— without ATG

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ATG in related stem cell transplantation Hamburg experience (1990-2011)

Overall survival



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months after SCT

HLA ident. sibling transplants (n=245)

ATG 15-30 mg/kg: Bologna Experience

	BM wo ATG Group 1	PBSC wo ATG Group 2	PBSC w ATG Group 3	p
N° of patients	52	146	47	
Age (median)	39	41	43	ns
Gender: M/F	27/25	95/51	33/14	ns
Interv. dg BMT (mos)	11.5	13	15	ns
Conditioning regimen				
MA/RIC	43/9	123/23	35/12	
%MA	83%	84%	70%	0.53
Median follow up (mos)	95	93	54	0.0001
% of living patients	52%	49%	57%	0.712

HLA ident. sibling transplants (n=245) ATG 15-30 mg/kg (Bologna)

	<i>BM wo ATG Group 1</i>	<i>PBSC wo ATG Group 2</i>	<i>PBSC w ATG Group 3</i>	
Diagnosis				
AML	19	38	8	0.029
ALL	5	19	2	
CML	9	24	15	0.06
Lymphomas	8	20	11	0.421
MM	8	40	7	
MDS	1	3	2	ns
other	2	2	2	ns
Early phase at transplant (AL in 1.CR, LPD in CR, CML in 1.CP)	22/52 42%	55/146 37.6%	18/47 38%	0.712

ATG vs no ATG in HLA identical sibling SCT

aGVHD grade	Group 1 (BM)	Group 2 (PBSC)	Group 3 (PBSC+ATG)	p
0	24 (46%)	73 (50%)	31 (66%)	0.692
I	13 (25%)	30 (20%)	6 (13%)	
II	8 (15%)	20 (14%)	5 (10.5%)	
III	5 (10%)	15 (10%)	4 (8.5%)	
IV	2 (4%)	8 (6%)	1 (2%)	
III-IV	7 (14%)	23 (16%)	5 (10.5%)	0.672
II-IV	15 (29%)	43 (30%)	10 (21%)	0.542

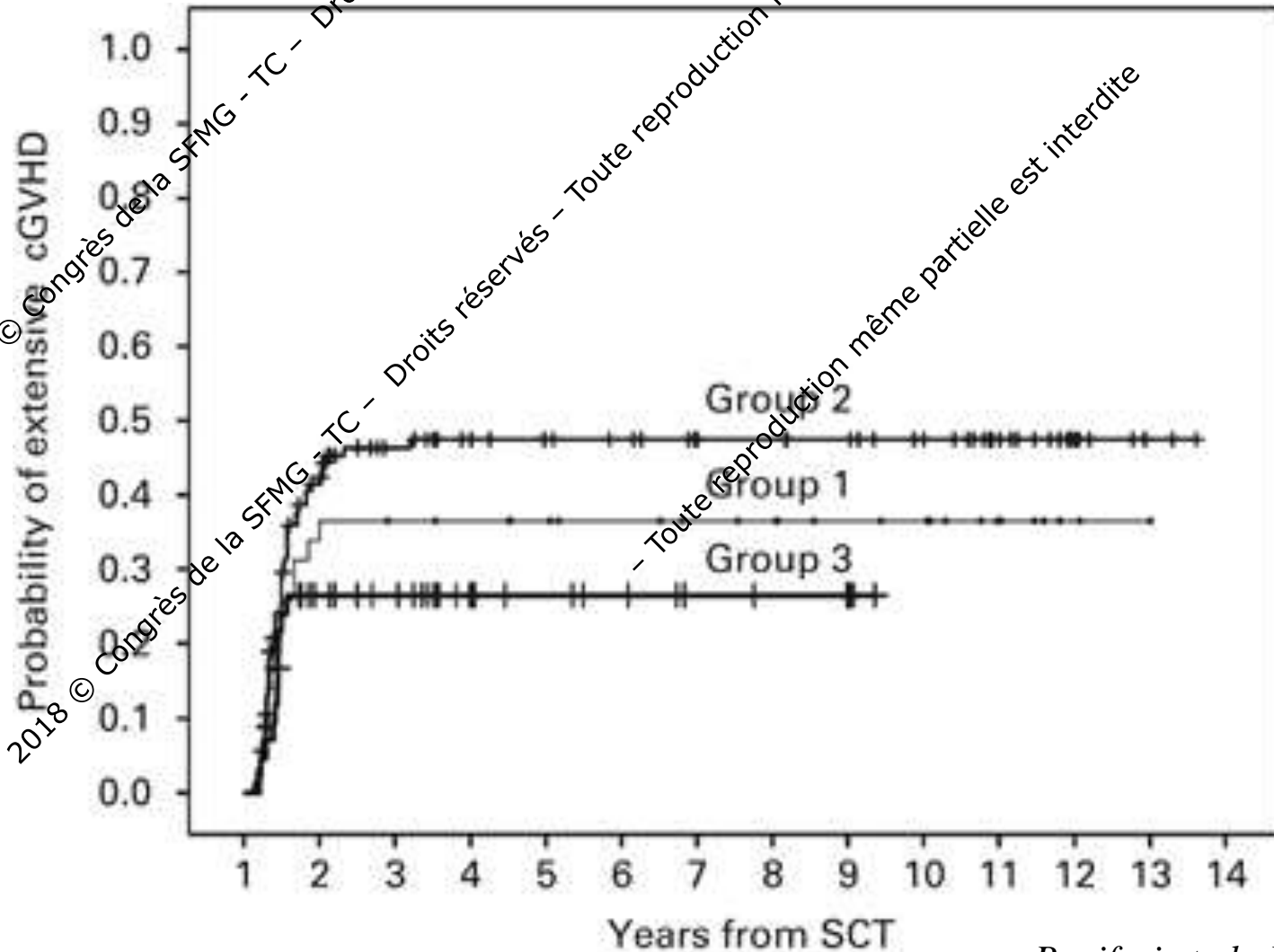
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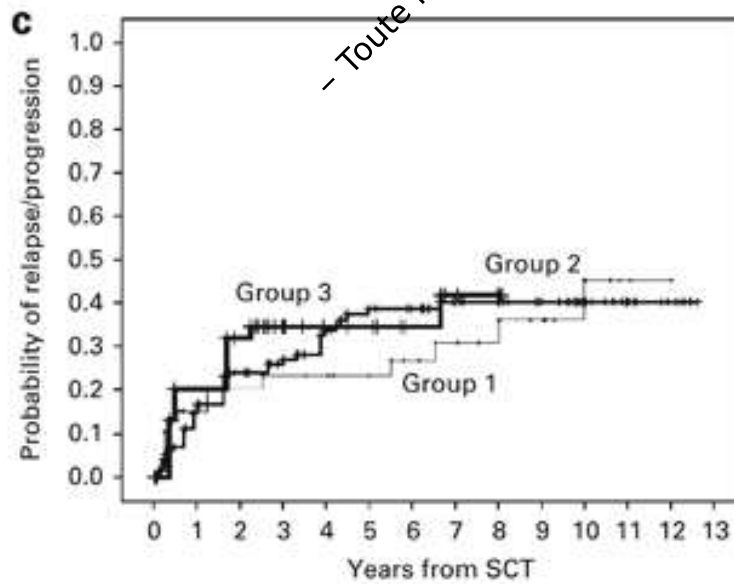
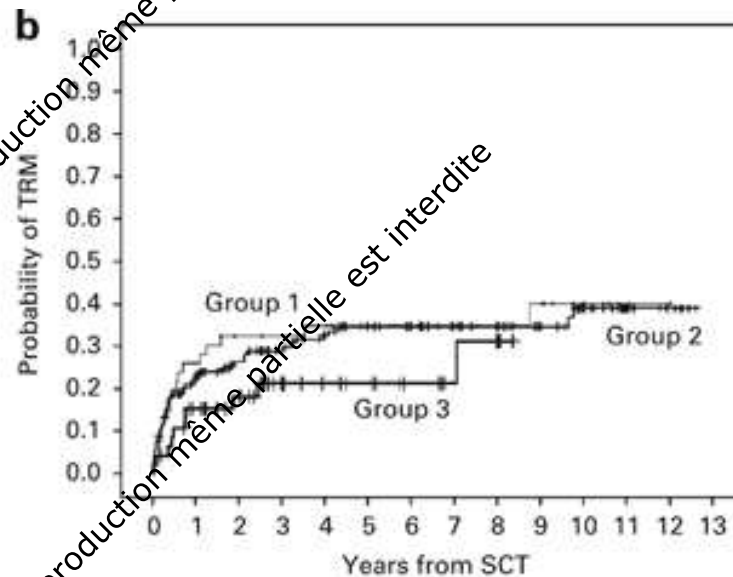
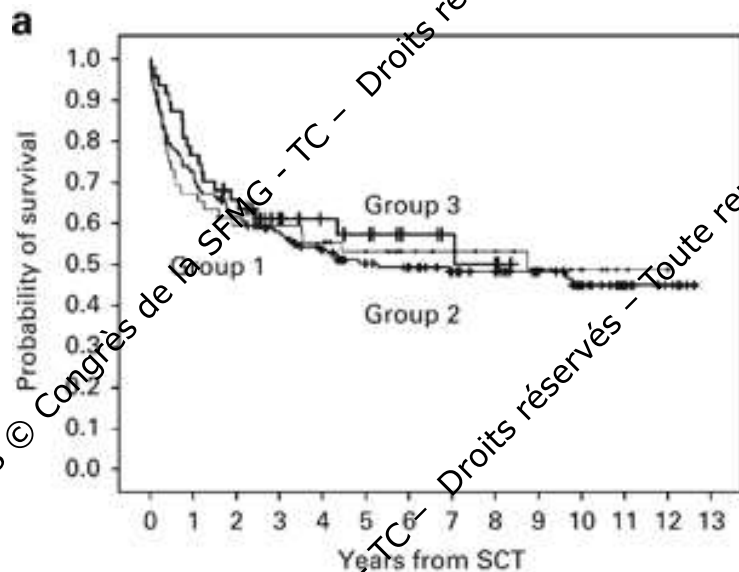
ATG vs no ATG in HLA identical sibling SCT

	Group 1 (BM)	Group 2 (PBSC)	Group 3 (PBSC+ATG)	p
Total n° of patients	52	146	47	
Not evaluable	7 (13.4%)	22 (15.1%)	4 (8.5%)	
NO cGVHD	18 (34.6%)	41 (28.1%)	21 (46.8%)	
Yes, limited	12 (23.1%)	24 (16.4%)	12 (27.6%)	
Yes, extensive	15 (29.9%)	59 (40.4%)	10 (21.3%)	p=0.03

ATG vs no ATG in HLA identical sibling SCT



ATG vs no ATG in HLA identical sibling SCT



ORIGINAL ARTICLE

Antilymphocyte Globulin for Prevention of Chronic Graft-versus-Host Disease

Nicolaus Kröger, M.D., Carlos Solano, M.D., Christine Wolschke, M.D., Giuseppe Bandini, M.D., Francesca Patrino, M.D., Massimo Pini, M.D., Arnon Nagler, M.D., Carmine Selleri, M.D., Antonio Risitano, M.D., Ph.D., Giuseppe Messina, M.D., Wolfgang Bereng, M.D., Jaime Pérez de Oteiza, M.D., Rafael Duarte, M.D., Angelo Michele Carella, M.D., Michele Cimminiello, M.D., Stefano Guidi, M.D., Jürgen Finke, M.D., Nicola Mordini, M.D., Christelle Ferra, M.D., Jorge Sierra, M.D., Ph.D., Domenico Russo, M.D., Mario Petrini, M.D., Giuseppe Milone, M.D., Fabio Benedetti, M.D., Marion Heinzelmann, Domenico Pastore, M.D., Manuel Jurado, M.D., Elisabetta Terruzzi, M.D., Franco Narni, M.D., Andreas Völp, Ph.D., Francis Ayuk, M.D., Tapani Ruutu, M.D., and Francesca Bonifazi, M.D.

Randomisation: ATG FamilyStudy

AML / ALL
(1. + 2.CR) HLA-identical sibling/ PBSC

ARM A

ARM B

One conditioning regimen

1	TBI (12 Gy) + Cyclophosphamide (120 mg/kg)	TBI (12 Gy) + Cyclophosphamide (120 mg/kg)
2	TBI (12 Gy) + VP-16 (30 – 45 mg/kg) + Cyclophosphamide (120 mg/kg)	TBI (12 Gy) + VP-16 (30 – 45 mg/kg) + Cyclophosphamide (120 mg/kg)
3	Busulfan (16 mg/kg p. o. <u>oder</u> 12,8 mg/kg i. v.) + Cyclophosphamide (120 mg/kg)	Busulfan (16 mg/kg p. o. <u>oder</u> 12,8 mg/kg i. v.) + Cyclophosphamide (120 mg/kg KG)

+ ATG (Fresenius) (3x10 mg/kg KG an Tag -3,-2 and -1)

Primary endpoint

Comparison of cumulative incidence of chronic GvHD (limited or extensive) after allogeneic peripheral blood stem cell transplantation from HLA-identical siblings with or without anti-T-lymphocyte-globulin according to the revised Seattle criteria of Lee et al.

Patients and transplant characteristics

	ATG ARM	NON ATG ARM	P
N of patients (*)	83	72	
Age, yrs, median (range)	39 (18-64)	43.5 (21-61)	0.04
Gender, male, n (%)	53 (63.9)	40 (55.6)	0.29
Diagnosis-SCT, mos, median (1st-3rd Qs)	5.2 (3.9-7.1)	5.3 (4.3-6.7)	0.87
Diagnosis			0.17
• AML, n (%)	55 (66.3)	55 (76.4)	
• ALL, n (%)	28 (33.7)	17 (23.6)	
High cytogenetic risk pts, n/n evaluable (%)	31/67 (46.3)	22/63 (34.9)	0.19
Courses of chemotherapy, med. (range)	2 (1-10)	2 (1-8)	0.89
Disease status at transplant			
• 1st CR, n (%)	73 (88)	66 (91.7)	0.45
• 2nd CR, n (%)	10 (12)	6 (8.3)	

*Safety data set and efficacy data set corresponds. 168 pts were enrolled, 7 were excluded before randomization and 6 were withdrawn from the analysis before SCT because leukemia progression or cancellation of the donor.

Results (1)

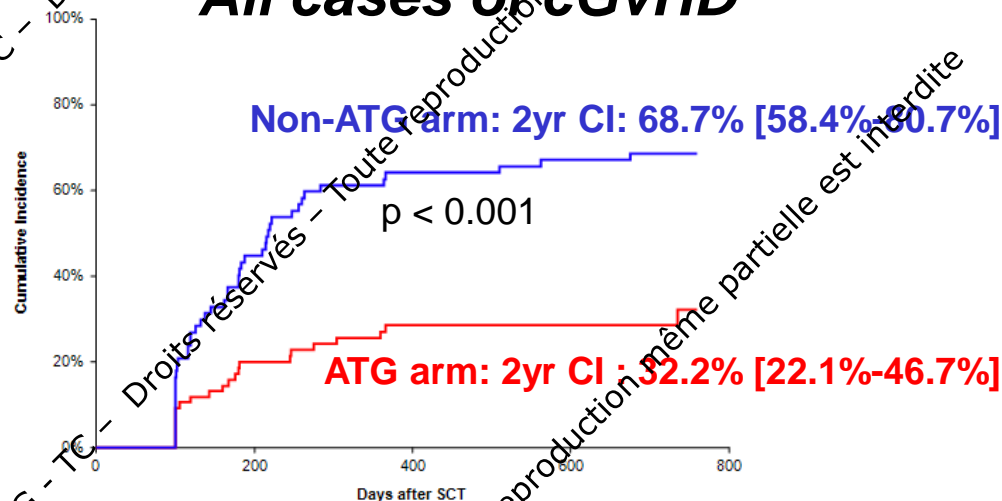
	ATG ARM	NON ATG ARM	P
Graft failure, n (%)	0	1 (1.4)	
Engraftment			
•Days to ANC $\geq 0.5 \times 10^9/L$, median (range)	18 (10-31)	15 (11-34)	<0.0001
•Days to platelets $\geq 20 \times 10^9/L$, median (range)	20 (10-110)	13 (6-29)	<0.0001
Acute GvHD (before day +100)			0.20
Yes, n (%)	21 (25.3)	25 (34.7)	
Overall grade aGvHD			0.15
Grade I, n (%)	12 (14.5)	12 (16.7)	
Grade II, n (%)	7 (8.4)	7 (9.7)	
Grade III, n (%)	2 (2.4)	4 (5.6)	
Grade IV, n (%)	0	2 (2.8)	
Grade II-IV, n (%)	9 (10.8)	13 (18.1)	0.13
Grade III-IV, n (%)	2 (2.4)	6 (8.3)	0.10

Results (2)

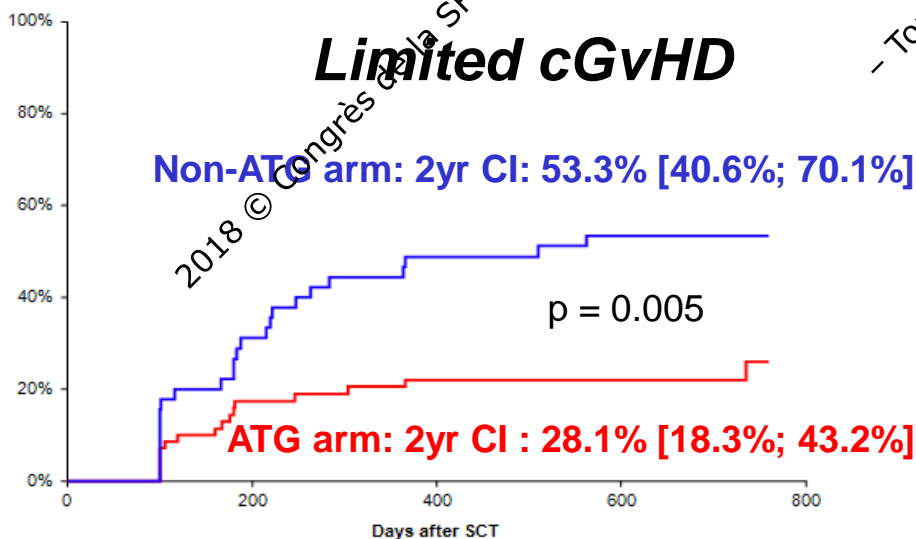
Chronic GvHD	ATG ARM	NON ATG ARM	P
Yes, n (%)	22 (27)	46 (64)	<0.001
Grade according revised Seattle criteria			<0.001
None	58 (70)	25 (35)	
Limited, n (%)	17 (21)	22 (31)	
Extensive, n (%)	5 (6)	24 (33)	
Grade according NIH criteria			<0.001
None	54 (68)	21 (31)	
Mild, n (%)	13 (16)	12 (18)	
Moderate, n (%)	7 (9)	18 (27)	
Severe, n (%)	2 (3)	16 (24)	
Day of onset, median (1st-3rd Qs)	164 (91-246)	164 (101-220)	0.80
Type of onset			0.93
De novo, n (% of cGvHD)	10 (46)	23 (50)	
Quiescent, n (% of cGvHD)	8 (36)	16 (35)	
Progressive, n (% of cGvHD)	4 (18)	7 (15)	

Effect of ATLG on cGvHD after HLA-identical allogeneic SCT for acute leukemia

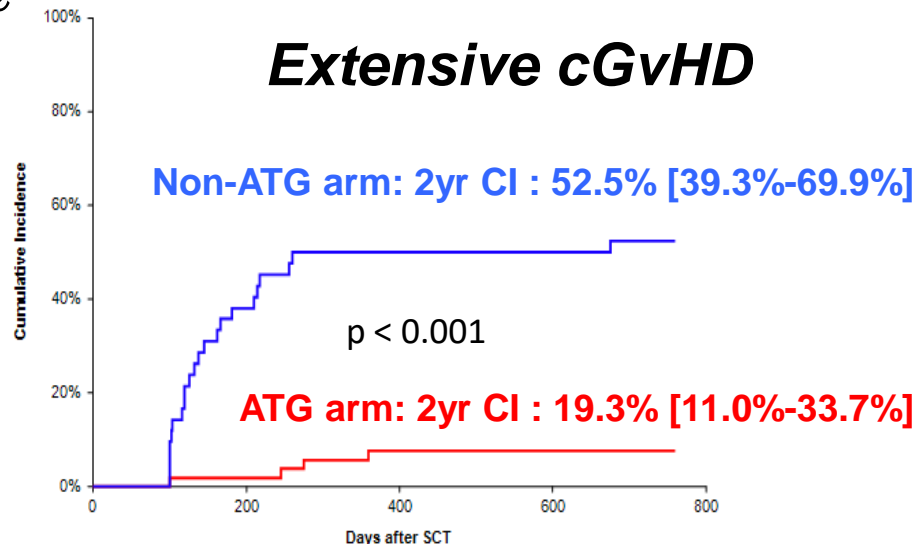
All cases of cGvHD



Limited cGvHD



Extensive cGvHD



cGvHD maximum organ involvement (NIH criteria $G \geq 2$)

Organ	ATG-arm n=83	Non ATG arm n=72	Risk difference and 95% CI
Skin	0%	14 (19.4%)	-19.4% [-30.0%; -10.7%]
Oral mucosa	1 (1.2%)	7 (9.7%)	-8.5% [-17.6%; -1.3%]
Eyes	0 (0.0%)	12 (16.7%)	-16.7% [-26.9%; -8.5%]
Liver	5 (6.0%)	11 (15.3%)	-9.3% [-19.9%; +0.5%]
GI tract	1 (1.2%)	2 (2.8%)	-1.8% [-8.4%; +4.1%]
Lung	1 (1.2%)	4 (5.6%)	-4.4% [-12.3%; +1.9%]
Genital	1 (1.2%)	0 (0.0%)	+1.2% [-4.0%; +6.5%]
Joint and fascia	0 (0.0%)	3 (4.2%)	-4.2% [-11.5%; +1.0%]

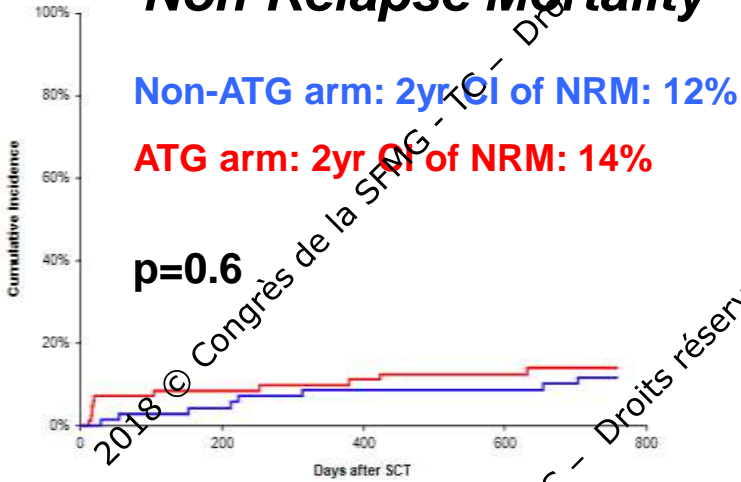
Infections incidence

	ATG-arm n=83	Non ATG arm n=72	Risk difference and 95% CI
All infections	48 (57.8%)	39 (54.2%)	+3.7% [-11.7%; +18.9%]
• CMV reactivation	18 (21.7%)	18 (25.0%)	-3.3% [-16.7%; +9.9%]
• EBV reactivation	3 (3.6%)	1 (1.4%)	+2.2% [-4.3%; +8.8%]
• PTLD	0	0	0% [-5.1%; 4.4%]
• Lung infection	6 (7.2%)	10 (13.9%)	-6.7% [-17.2%; 3.2%]
• Fungal infection	4 (3.6%)	4 (4.2%)	-0.6% [-8.3%; +6.5%]

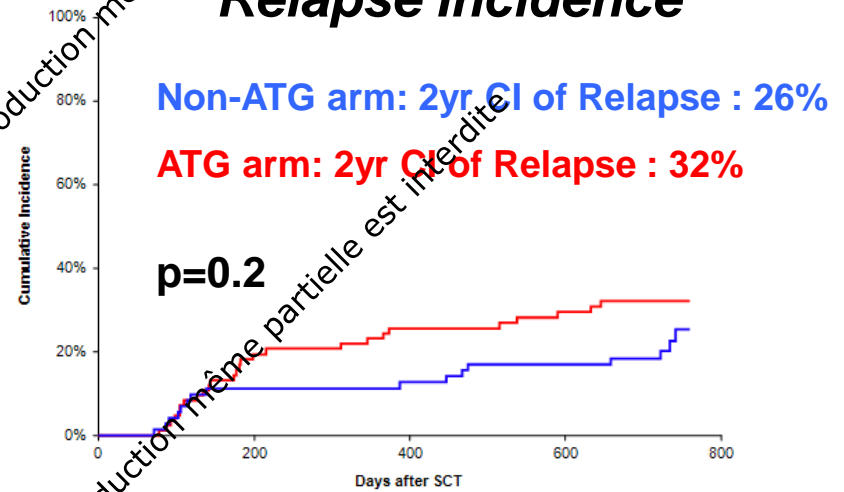
PTLD: Post-transplant lymphoproliferative disease

Results: ATG Family Study

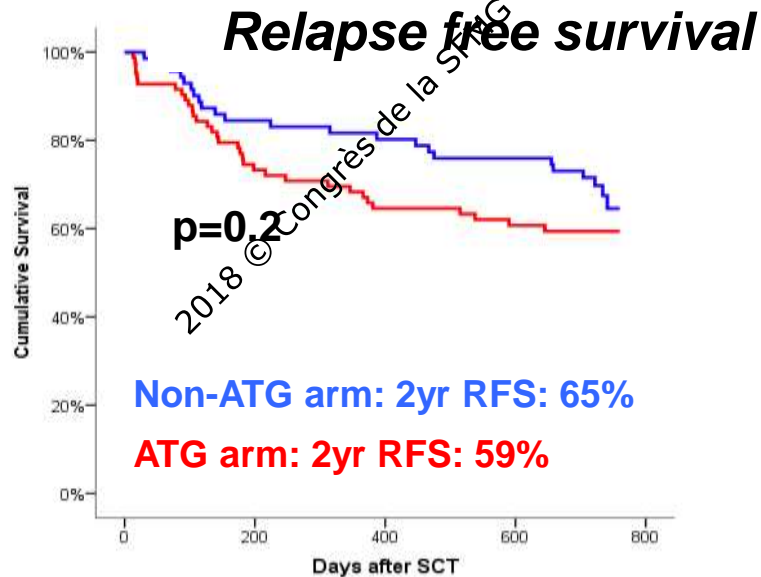
Non-Relapse Mortality



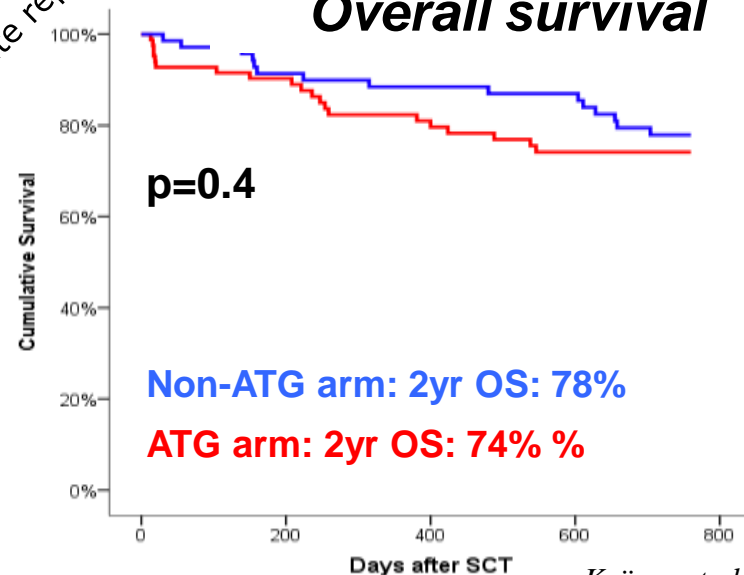
Relapse Incidence



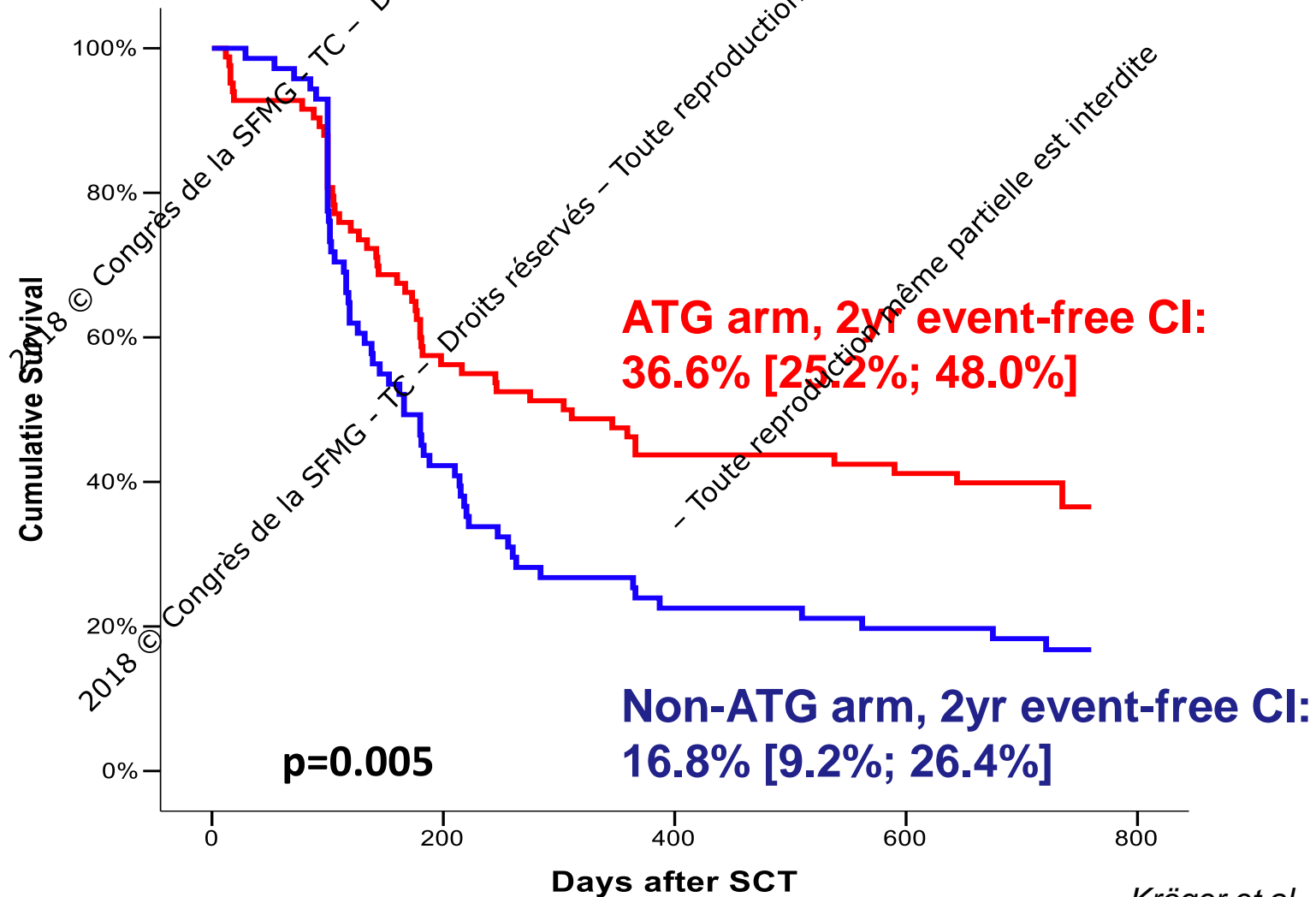
Relapse free survival



Overall survival



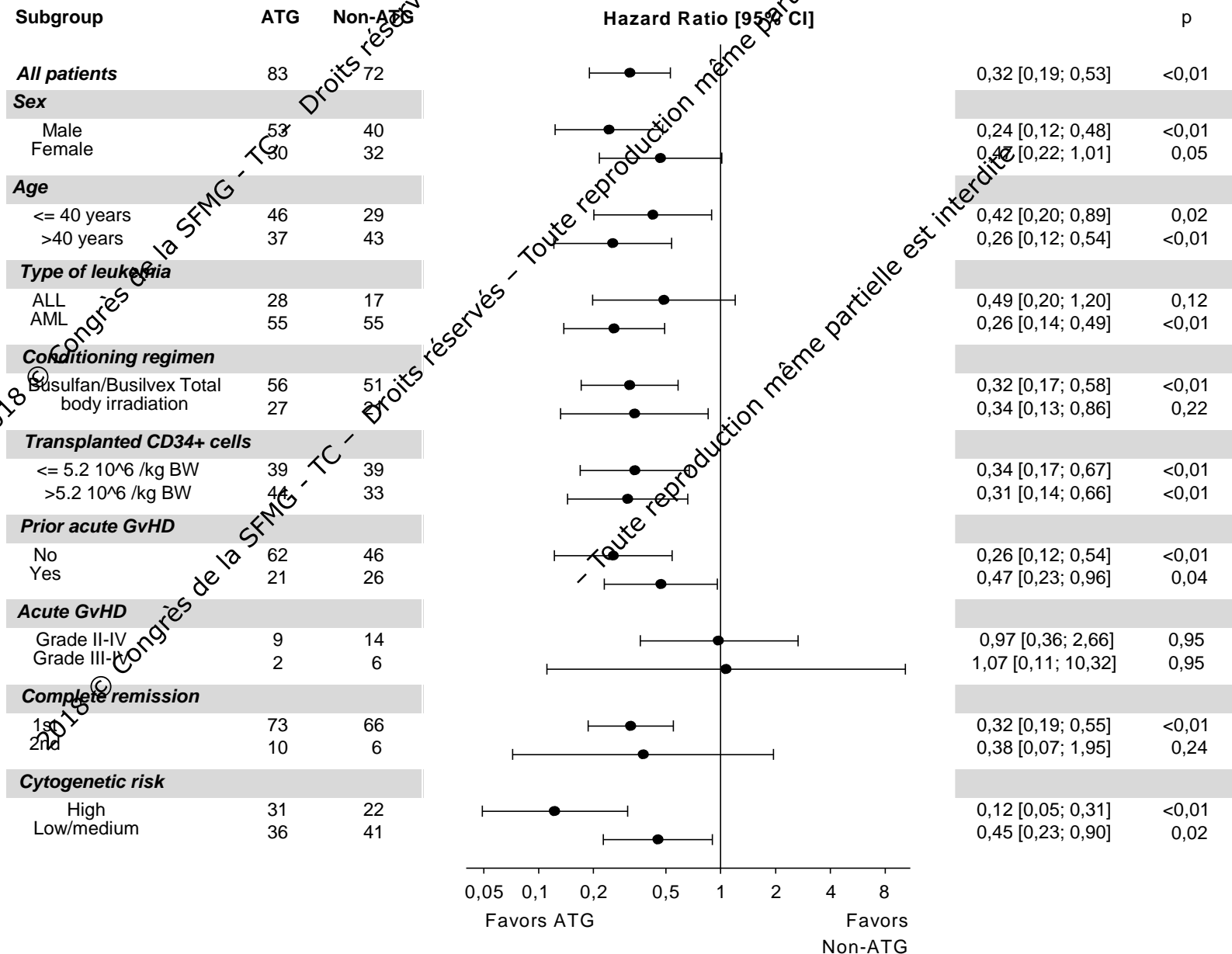
Composite endpoint cGvHD/relapse-free survival



Multiple Cox regression models

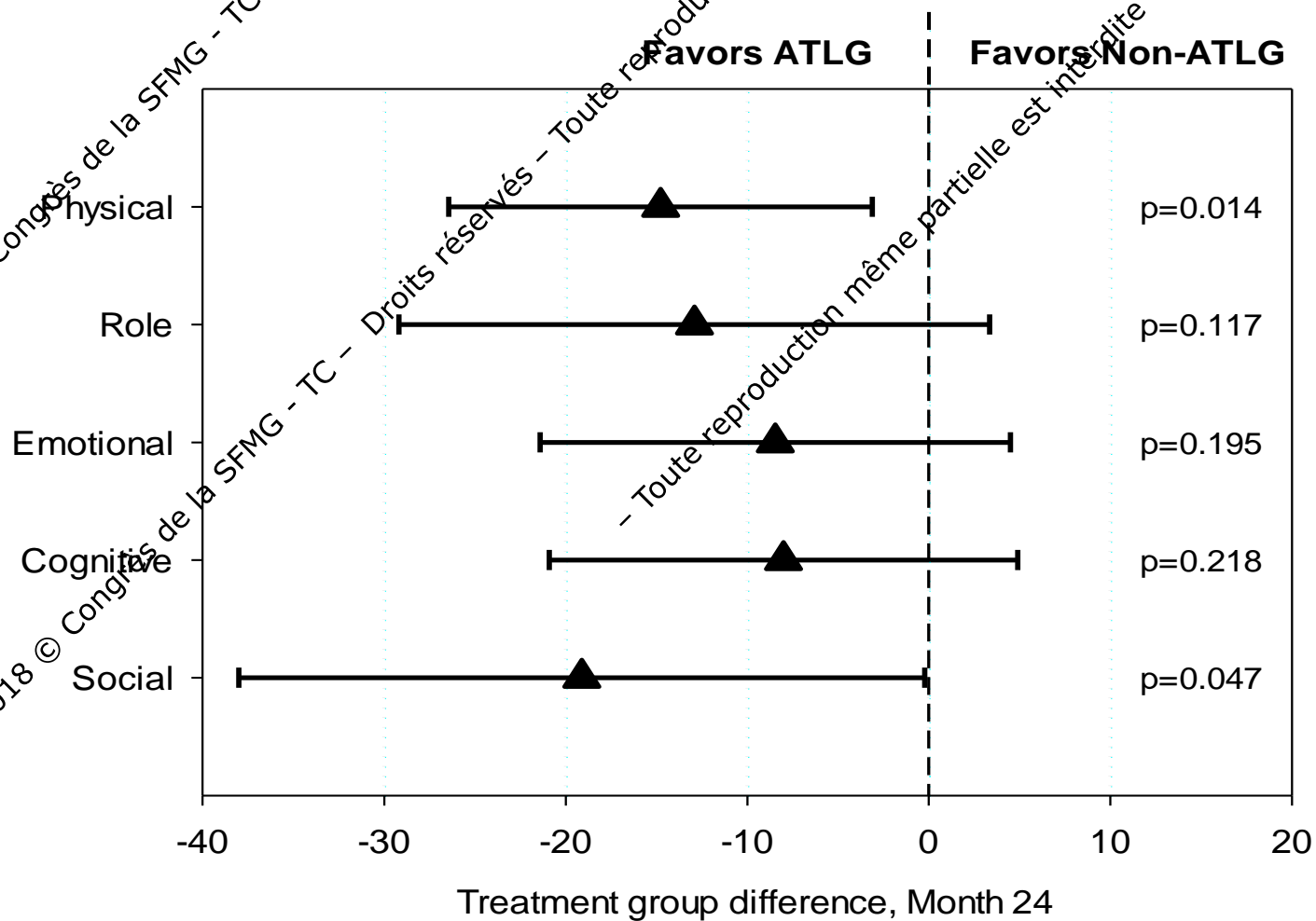
Outcome	Predictors in the model	p	Exp(b)	95% CI
cGvHD	ATG vs. Non-ATG	0.001	0.37	0.21 – 0.65
	Female donor, male recipient	0.02	2.01	1.11 – 3.65
	aGvHD grade	<0.001	1.62	1.29 – 2.05
Relapse-free survival	ATG vs. Non-ATG	0.91	1.03	0.57 – 1.88
Overall survival	ATG vs. Non-ATG	0.47	0.74	0.34 – 1.65
	ALL vs. AML	0.02	2.64	1.18 – 5.89

Impact of ATG on cGvHD in subgroups of patients

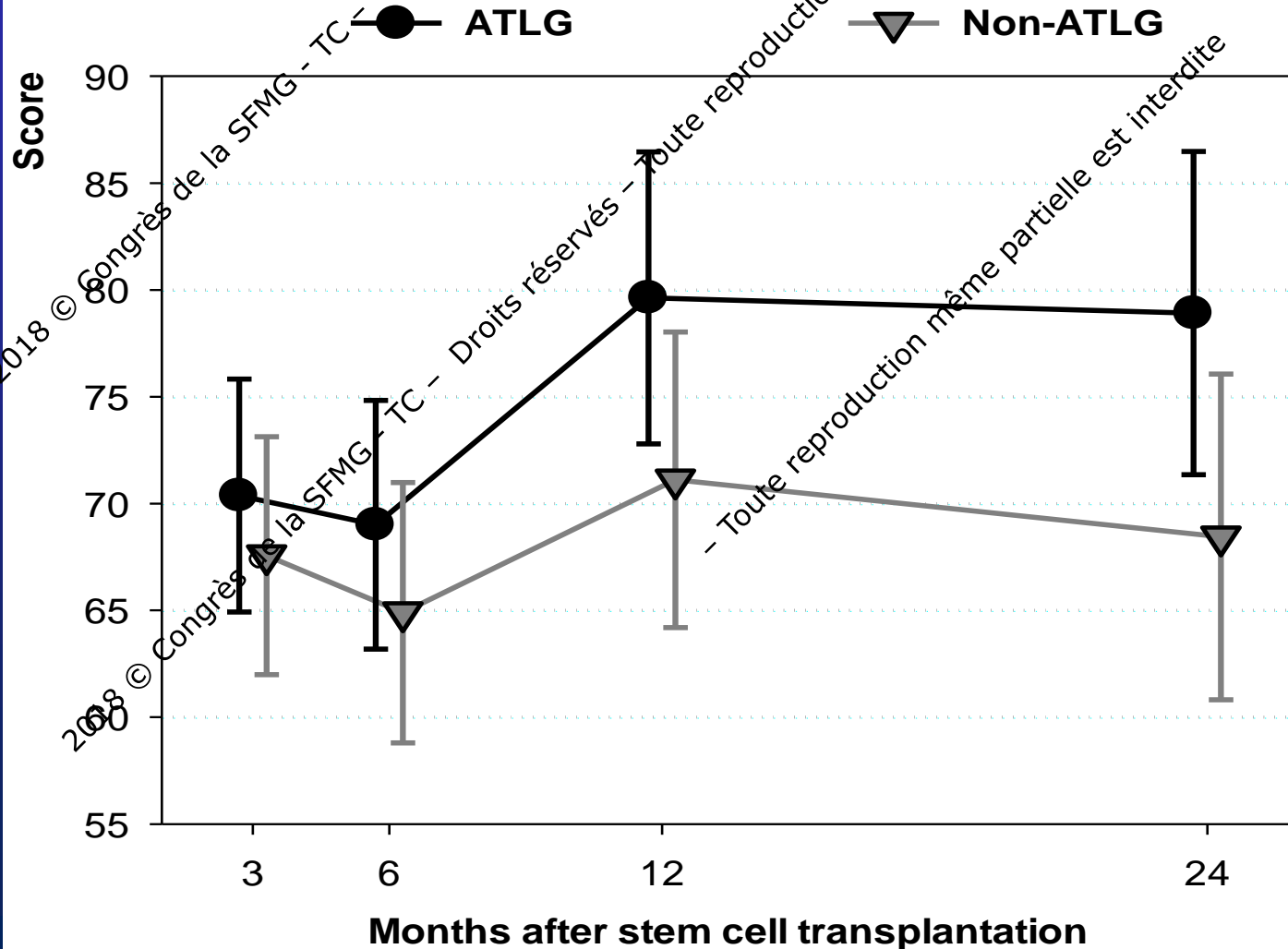


Quality of Life: QLQ-30 functional scores

Function



Global health status scoring (QLQ-30)



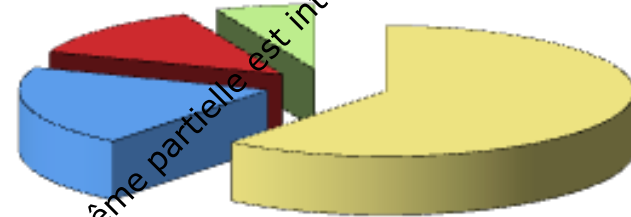
Summary

- 1. ATG/ATLG prevent acute and to a more extend chronic GvHD after HLA-identical sibling transplantation without obvious increase of relapse, leading to a better:**
 - a) Quality of Life**
 - b) GvHD/Relapse-free survival**
- 2. ATG and ATLG are different brands with different properties and doses are not interchangeable**
- 3. Optimal dosing and schedule needs to be determined according disease status and presumably also for different diseases**

ACKNOWLEDGEMENTS

All the patients All participants centers (each BMT team, coordinators & nurses)

1. Bologna, Italy
2. Hamburg, Germany
3. Valencia, Spain
4. Udine, Italy
5. Alessandria, Italy
6. Tel Hashomer, Israel
7. Napoli, Italy
8. Reggio Calabria, Italy
9. Tübingen, Germany
10. Madrid, Spain
11. Barcelona, Spain
12. San Giovanni Rotondo, Italy
13. Potenza, Italy
14. Firenze, Italy
15. Freiburg, Germany
16. Cuneo, Italy
17. Badalona, Spain
18. Barcelona, Spain
19. Brescia, Italy
20. Pisa, Italy
21. Catania, Italy
22. Verona, Italy
23. Bari, Italy
24. Granada, Spain
25. Monza, Italy
26. Modena, Italy
27. Frankfurt, Germany



■ Italy ■ Germany ■ Spain ■ Israel

Andrea Völp for statistics and data analysis

Markus Goebel for data management

NEOVII for research grant



Universitätsklinikum
Hamburg-Eppendorf



UNIVERSITAT ID VALÈNCIA

