Therapeutic Advances in Treatment of Aplastic Anemia

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Today's Topics

1. First line treatment for aplastic anemia

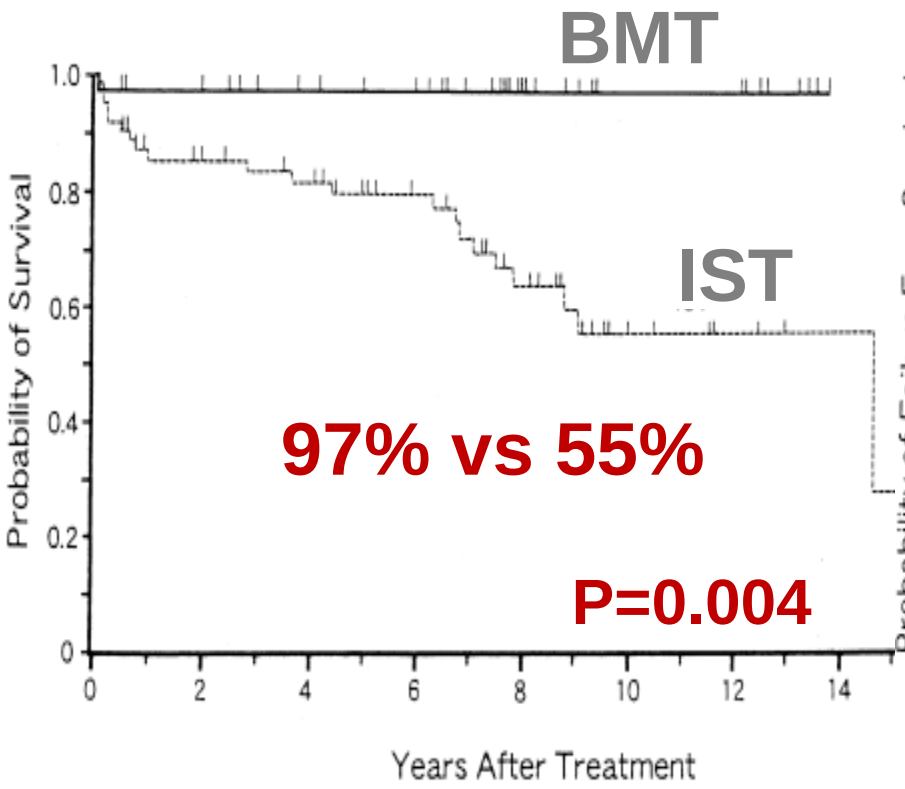
   transplantation vs. immunosuppressive therapy
2. Immunosuppressive therapy

   horse ATG vs. rabbit ATG
3. Mismatched family donor transplantation

- BMT from an HLA-matched family donor (MFD) is the treatment of choice for SAA in children.
- For children without an MFD, IST with a combination of ATG and CyA has been successful.
- However, this treatment approach is based on the results of comparative studies between these therapies conducted in the 1980s, and the outcomes of both BMT and IST have improved markedly over the past three decades.
- Therefore, updated evidence for treatment decisions in pediatric SAA is required.

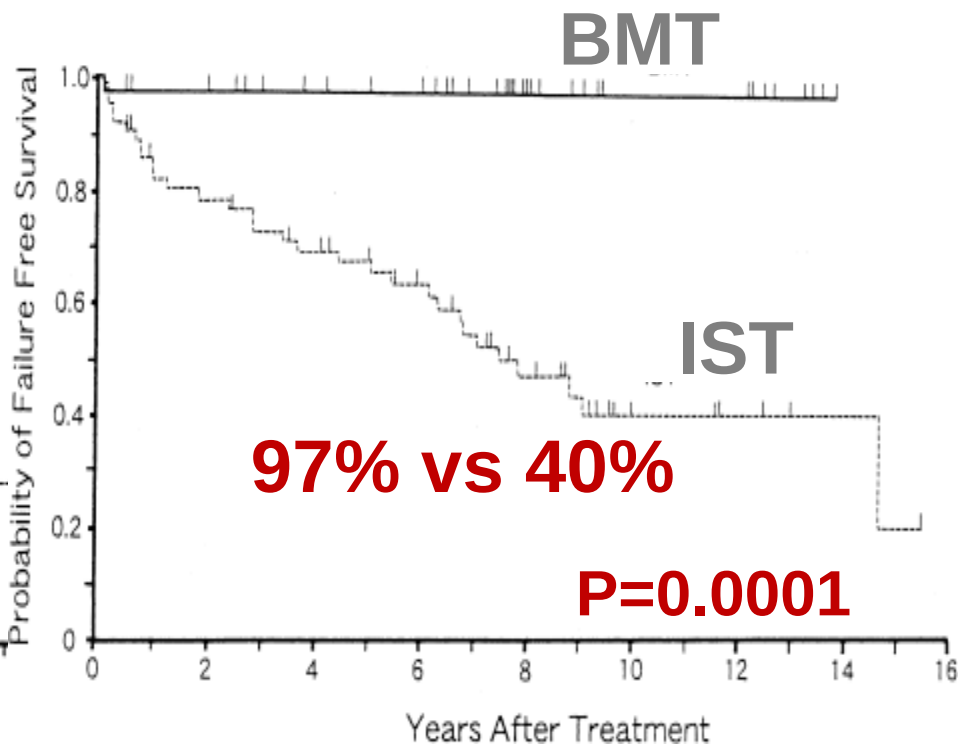
- **Nagoya group: 1984-1998**

- OS



- FFS

- ✓ Age: 0-16 y
- ✓ N=100



Kojima S et al. Br J Haematol. 2000 Oct;111(1):321-8

Objective

- To make an updated evidence for treatment decisions in pediatric SAA by comparing the outcomes of children with SAA who received IST or BMT from an MFD as first-line treatment.

Patients and Methods

- 599 children with SAA younger than 17 years received BMT from an MFD or IST as first-line treatment between 1992 and 2009.
  - registered in the TRUMP conducted by the JSHCT
  - enrolled in the multicenter trials of IST (AA-92/97) conducted by the Japan Childhood Aplastic Anemia Study Group

- The influence of potential risk factors on OS and FFS was assessed according to first-line treatment, time periods of treatment (1992-1999 and 2000-2009), age and other variables related to each treatment.

• Definition of treatment failure

- BMT

- ✓ Death
- ✓ Primary graft failure
- ✓ Relapse or secondary graft failure
- ✓ Second malignancy

- IST

- ✓ Death
- ✓ Relapse
- ✓ Disease progression requiring SCT or 2nd IST
- ✓ Clonal evolution
- ✓ PNH

• Patient and treatment characteristics

	BMT n=213	IST n=386
Age at diagnosis, y, med.(range)	10 (0-16)	9 (0-16)
Age at treatment, y, med.(range)	11 (0-16)	9 (0-16)
Gender male / female	119/94	217/169
Etiology, no. of patients (%)		
Idiopathic	204 (96)	312 (81)
Hepatitis	7 (3)	67 (17)
Others	2 (1)	7 (2)
Severity, no. of patients (%)		
VSAA	/	227 (59)
SAA	/	159 (41)
Interval diagnosis-treatment, d, med.(range)	84 (14-4605)	15 (1-180)
Time periods of treatment, no. of patients (%)		
1992-1999	121 (57)	155 (40)
2000-2009	92 (43)	231 (60)

• Patient and treatment characteristics

- BMT (n=213)

✓ **Conditioning regimen**

CY	213
+ ALG/ATG	87
+ Irradiation (TBI/TAI/TLI)	129

✓ **GVHD prophylaxis**

CyA+MTX	174
Others	39

- IST (n=386)

✓ **IST protocol**

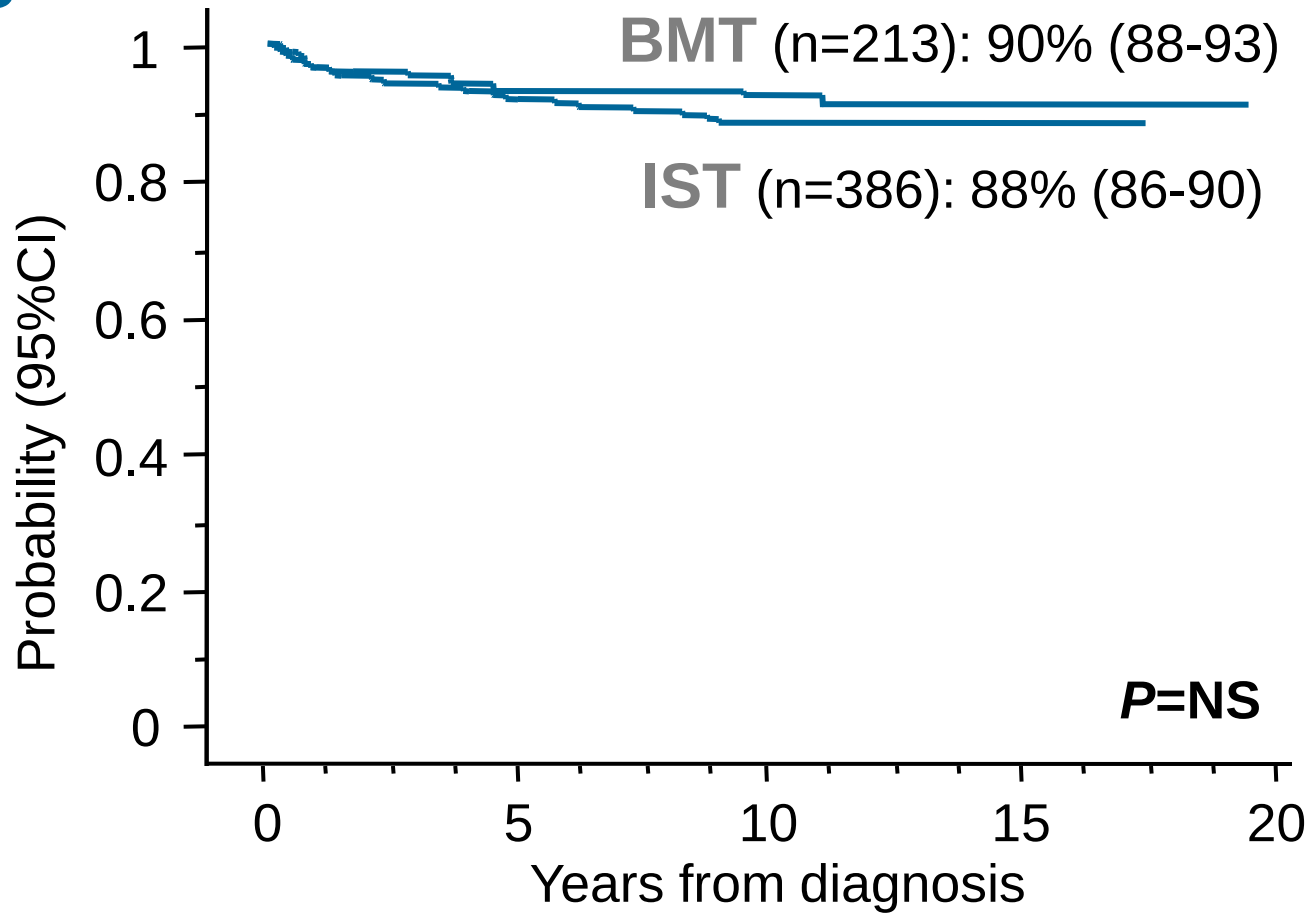
AA92	84
AA97	302

✓ **IST regimen**

CyA+ATG	140
CyA+ATG+G-CSF	246

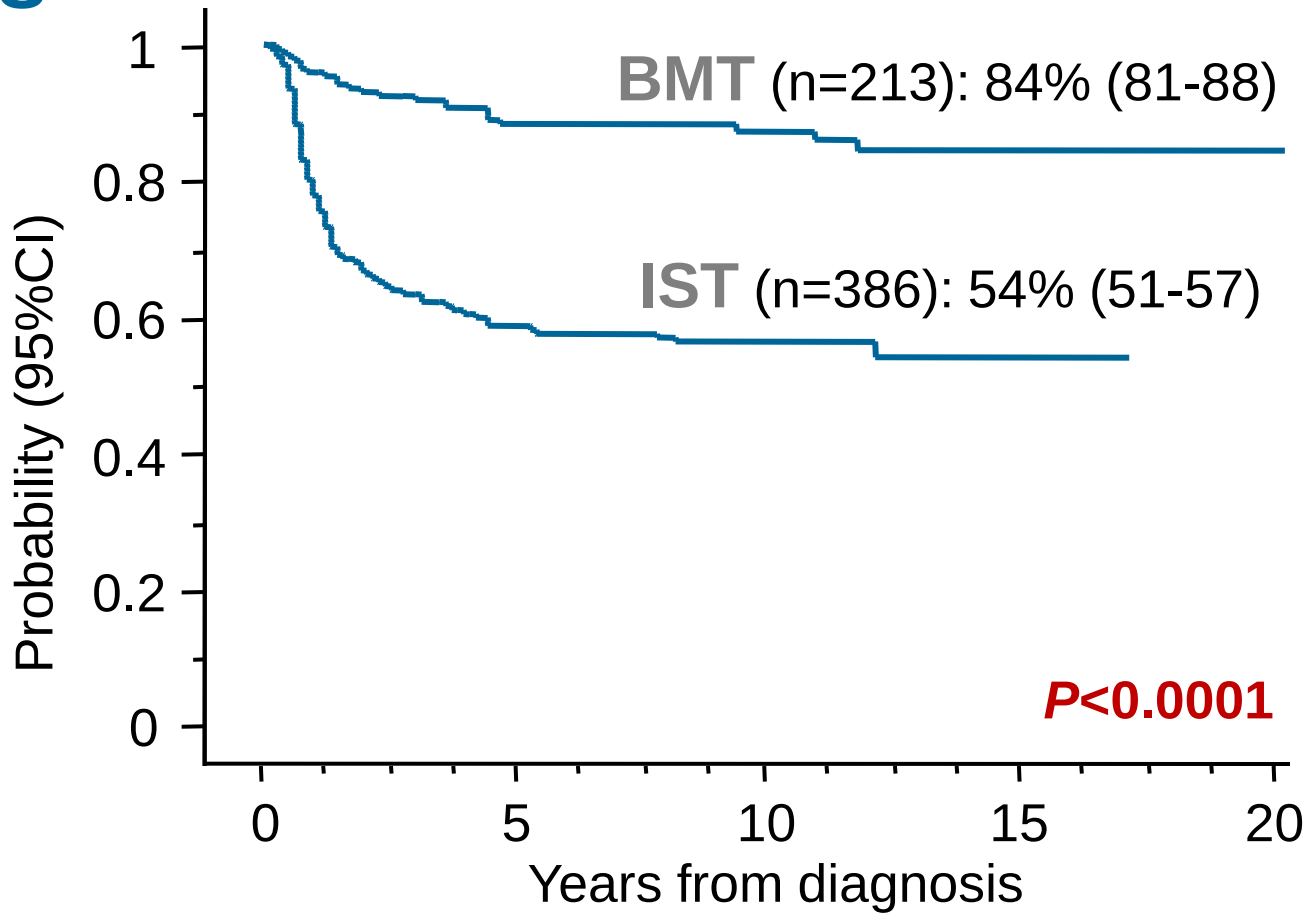
Results • First-line treatment: BMT vs. IST

- OS



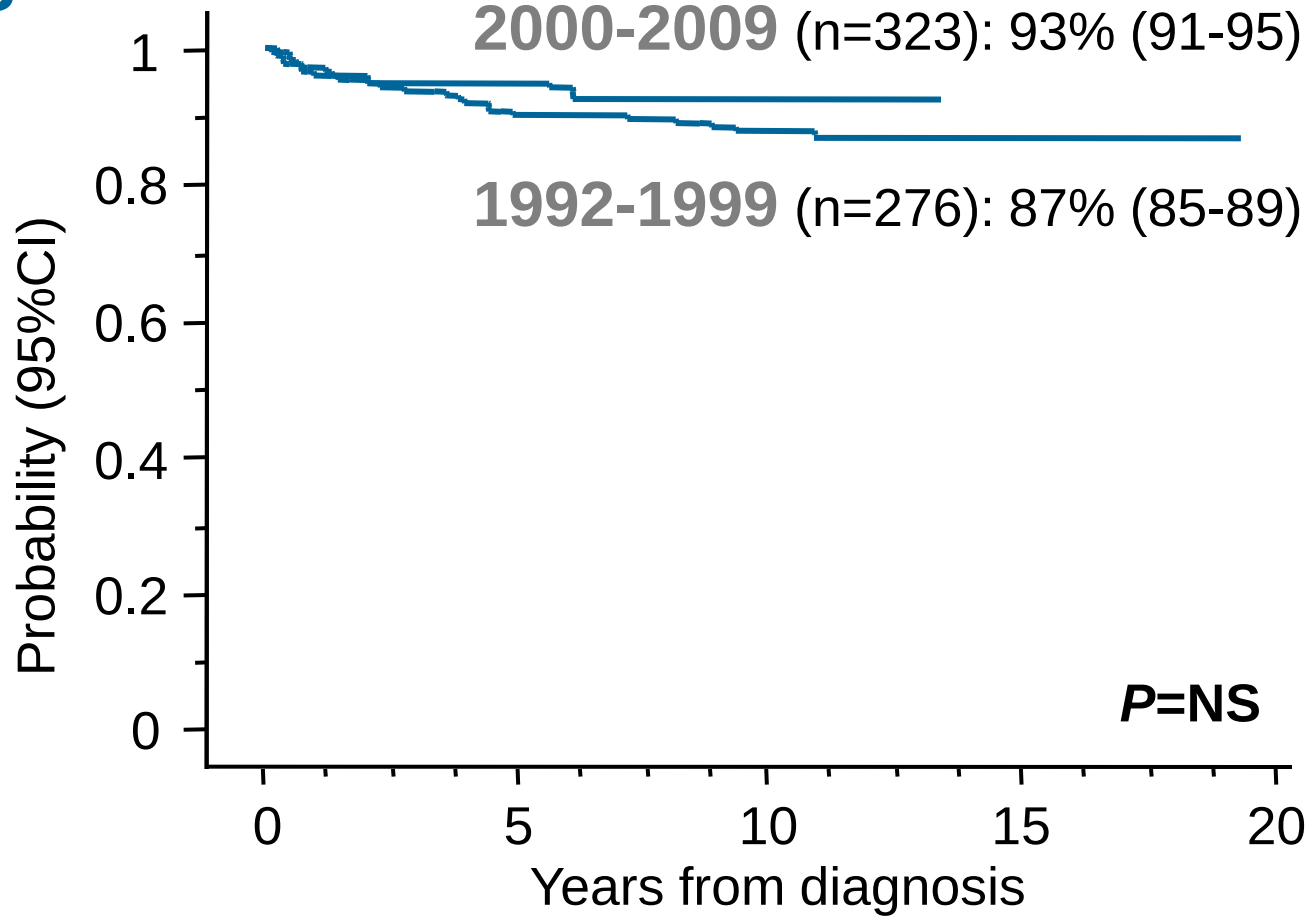
• First-line treatment : BMT vs. IST

- FFS



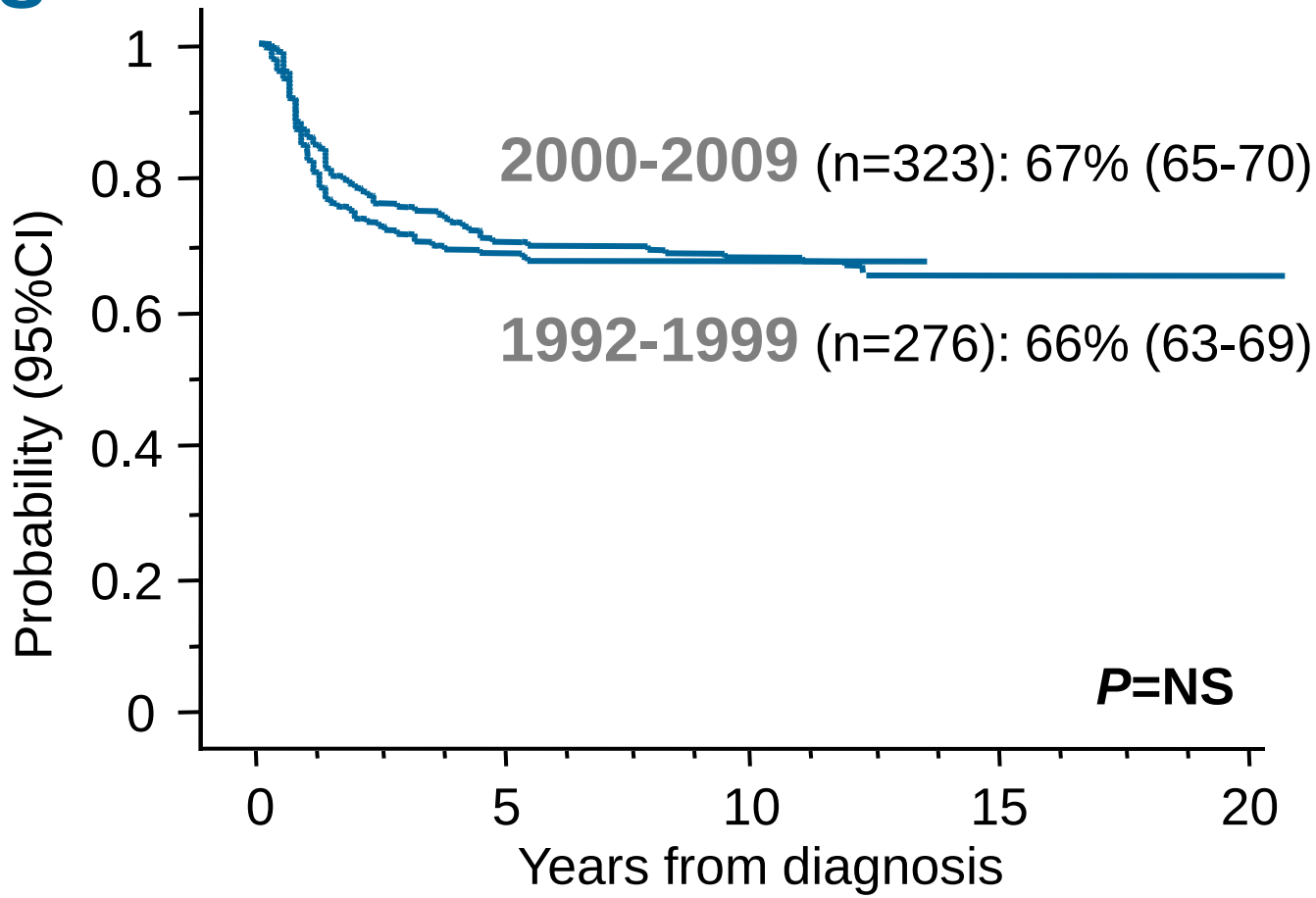
- **Time periods of treatment**

- OS



- **Time periods of treatment**

- FFS



• Multivariate analysis of favorable factors

- OS

Variable	Relative risk	95% CI	*P*
First-line treatment: BMT	1.619	0.881-2.977	NS
Treatment period: 2000-2009	1.536	0.556-2.753	NS
Age: <10 years	2.207	1.240-3.927	0.007

- FFS

Variable	Relative risk	95% CI	*P*
First-line treatment: BMT	4.497	2.935-6.891	<0.0001
Treatment period: 2000-2009	1.090	0.812-1.464	NS
Age: <10 years	1.113	0.833-1.488	NS

Summary

- The outcomes of both BMT and IST for pediatric SAA have reached plateau over the past two decades, and have improved than those in 1980s.
- While the OS did not differ between patients receiving IST and BMT, FFS was significantly inferior in patients receiving IST as compared to those receiving BMT.
- Our data clearly show a significant advantage for children receiving BMT from an MFD as first-line treatment.

Today's Topics

1. First line treatment for aplastic anemia

   transplantation vs. immunosuppressive therapy

2. Immunosuppressive therapy

   horse ATG vs. rabbit ATG

3. Mismatched family donor transplantation

Comparisons of major ATG products

	Lymphoglobulin® (Genzyme)	ATGAM®	Thymoglobulin® (Genzyme)	Fresenius®*
Species				
Immunogen	Thymocytes	Thymocytes	Thymocytes	Jurkat cell line
Concentration mg/ml	10-20	50	10-20	20
Dosage for SAA	10 (China)- 15 mg/kg/d x 5(8) days (Europe, Japan)	40 mg/kg/d x4 days NIH	2.5 (Korea, Brasil)- 3.5/ 3.75 (Europe, NIH, Japan) mg/kg/d x5 days	5 mg/kg/d for 5 days Japan, China

Horse v.s Rabit (ATGAM vs. Thymo)

Prospective Randomized Study, NIH (n=120)

Group I	Horse ATG ATGAM (40 mg/kg/d x 4 days)	+CSA
Group II	Rabitt ATG Thymoglobulin (3.5 mg/kg/d x 5 days)	+CSA

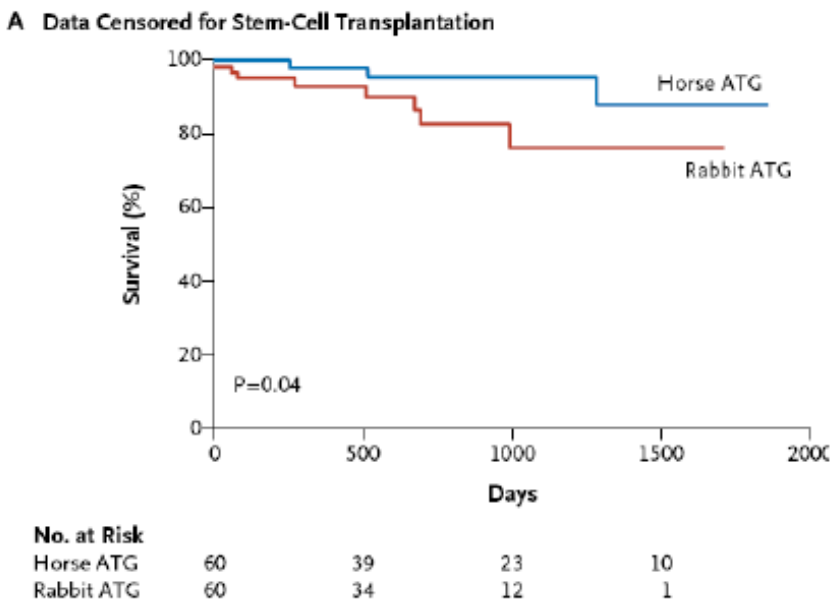
Table 2. Hematologic Response at 3 and 6 Months to Horse ATG and Rabbit ATG.

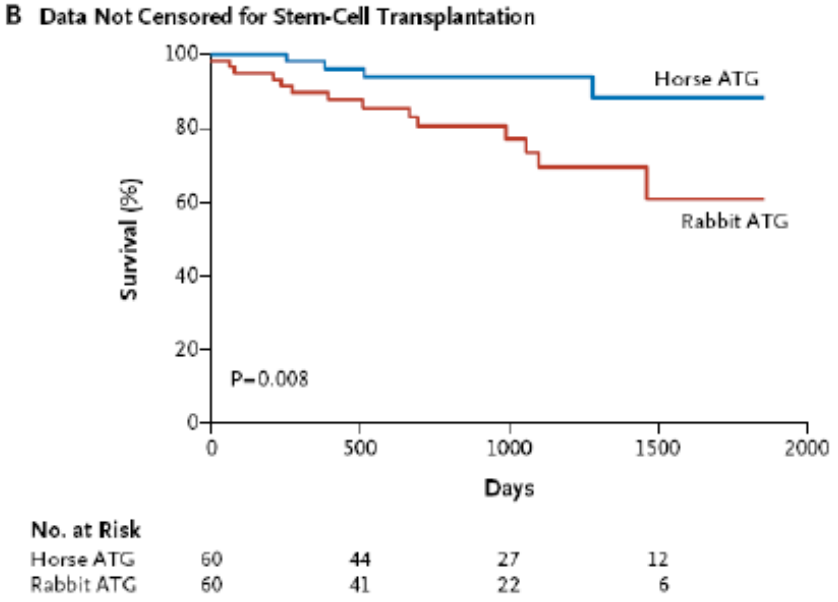
Response	Horse ATG (N=60)	95% CI	Rabbit ATG (N=60)	95% CI	P Value
	no. (%)		*no. (%)*		
At 3 mo	37 (62)	49–74	20 (33)	21–46	0.002
At 6 mo	41 (68)	56–80	22 (37)	24–49	<0.001

Scheinberg P, NEJM 2011

Horse v.s Rabitt (ATGAM vs. Thymo)

Prospective Randomized Study, NIH (n=120)

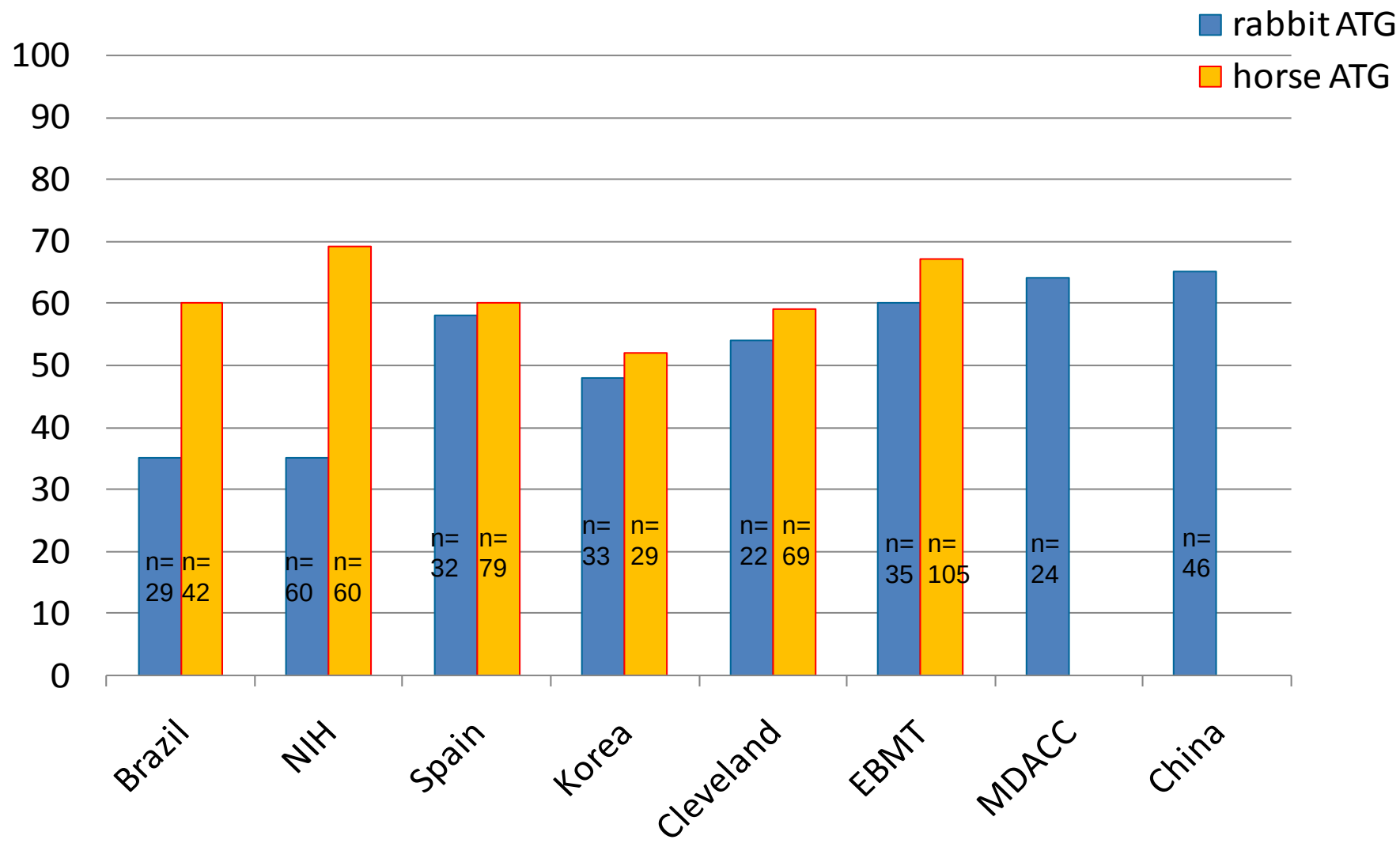


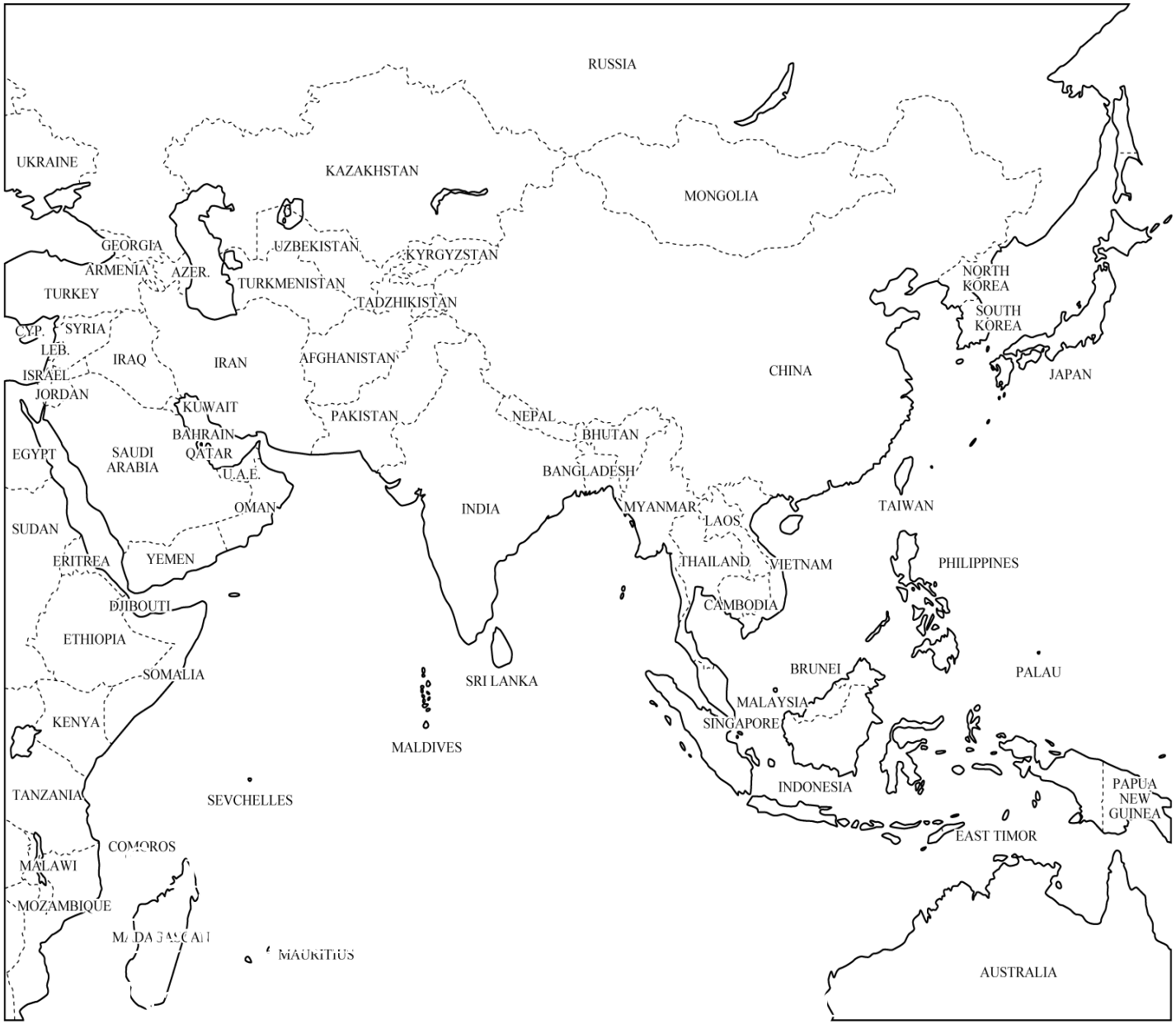


Cause of death	Horse-ATG	Rabbit-ATG
Intracranial bleeding	1	2
Infektion	1	3
TRM	1	6
Other	1	3

Scheinberg P, NEJM 2011

horse vs rabbit ATG

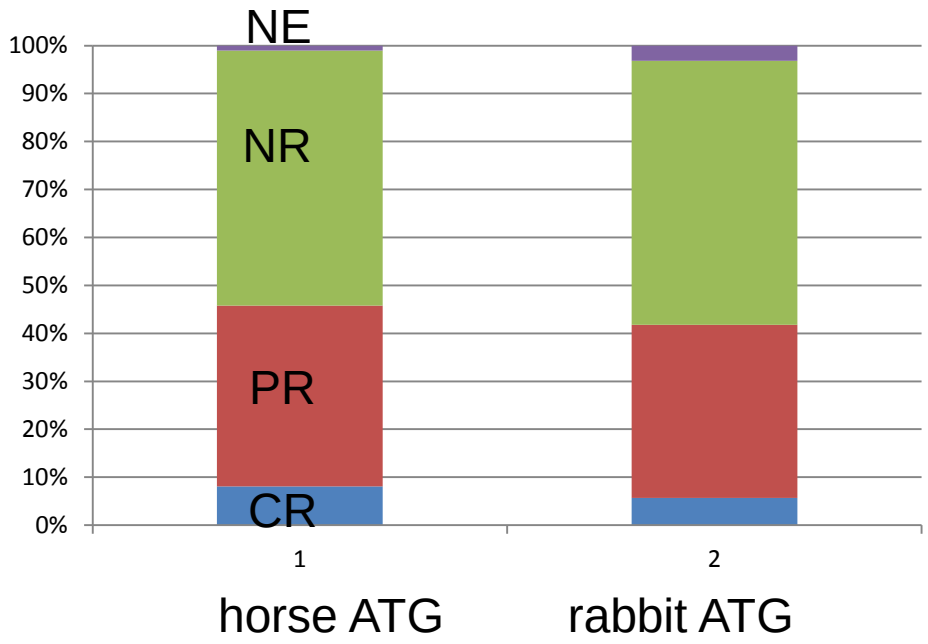



RUSSIA
UKRAINE
KAZAKHSTAN
MONGOLIA
GEORGIA
ARMENIA
AZER.
UZBEKISTAN
KYRGYZSTAN
TURKMENISTAN
TADZHIKISTAN
TURKEY
NORTH KOREA
SOUTH KOREA
CYP.
SYRIA
LEB.
IRAQ
IRAN
AFGHANISTAN
CHINA
JAPAN
ISRAEL
JORDAN
KUWAIT
PAKISTAN
NEPAL
BHUTAN
BAHRAIN
QATAR
EGYPT
SAUDI ARABIA
U.A.E.
BANGLADESH
OMAN
INDIA
MYANMAR
TAIWAN
SUDAN
LAOS
ERITREA
YEMEN
THAILAND
VIETNAM
PHILIPPINES
DJIBOUTI
CAMBODIA
ETHIOPIA
BRUNEI
PALAU
SOMALIA
SRI LANKA
MALAYSIA
KENYA
SINGAPORE
MALDIVES
INDONESIA
PAPUA NEW GUINEA
TANZANIA
SEVCHELLES
EAST TIMOR
COMOROS
MALAWI
MOZAMBIQUE
MADAGASCAR
MAURITIUS
AUSTRALIA

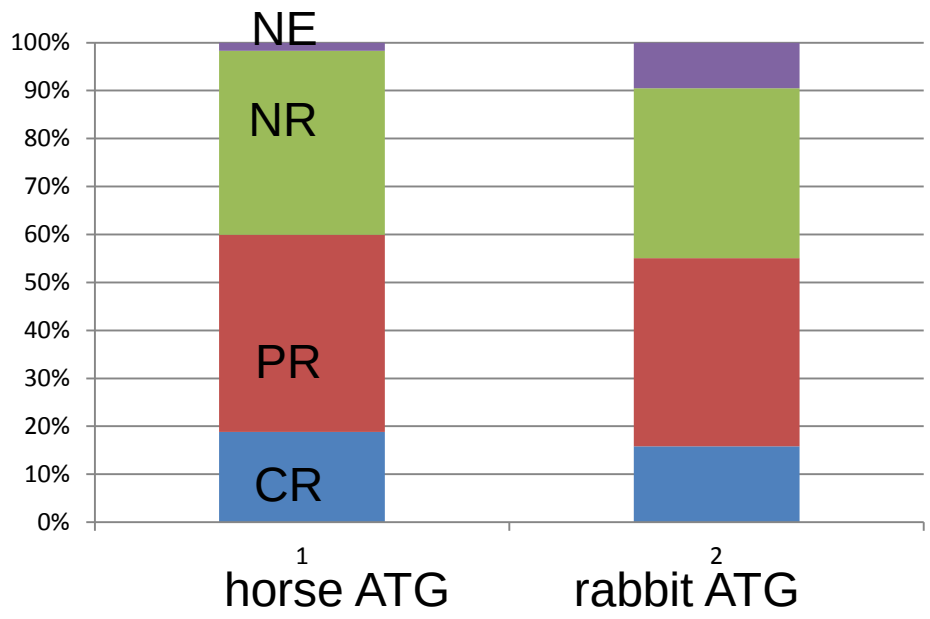
Patient Characteristics

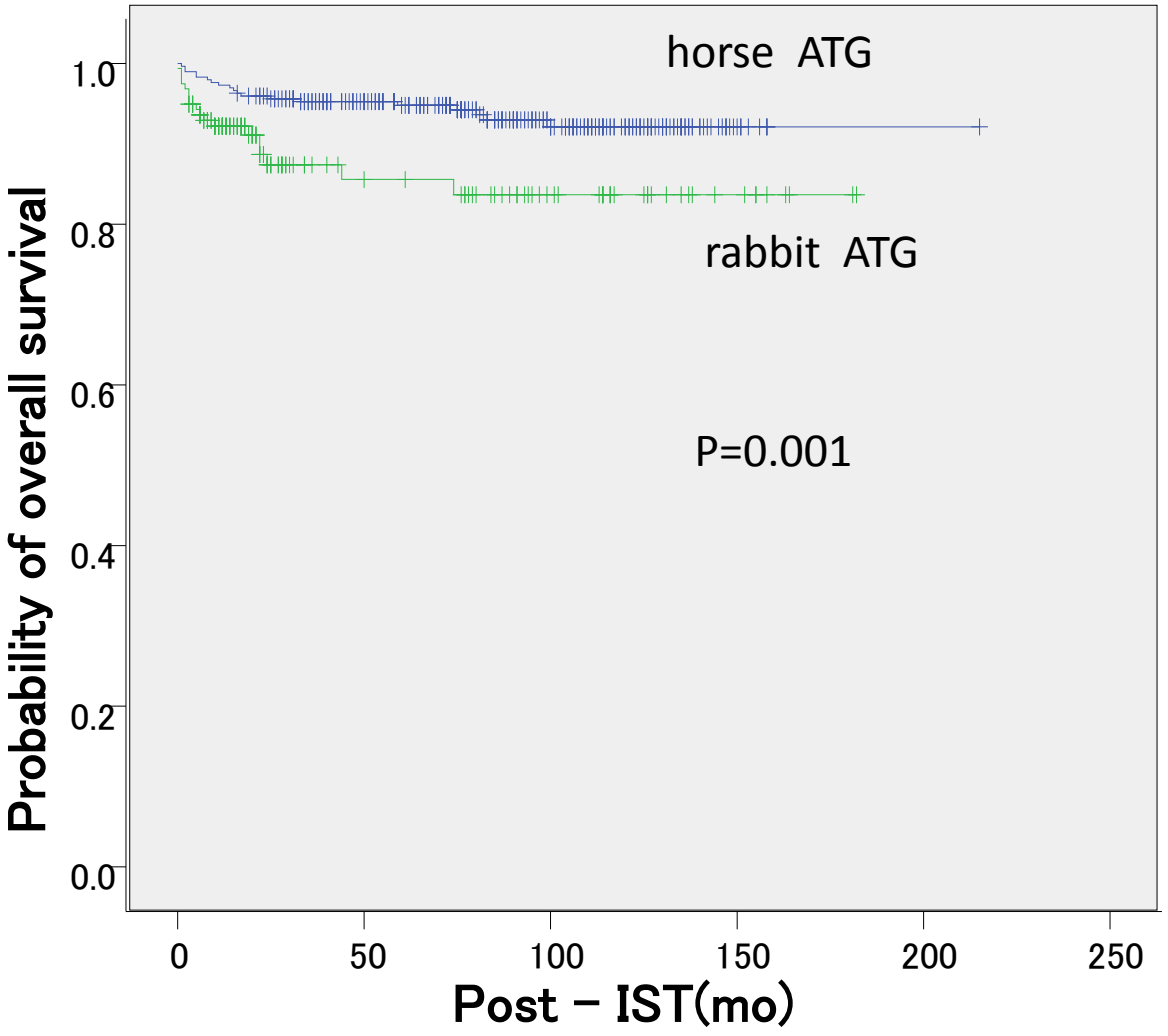
	Total cohort (N=455)	horse ATG (n=297)	rabbit ATG (n=158)	P-value
Median age at diagnosis (range), years	8 (0 - 17)	8 (0 - 17)	6.5 (1 - 16)	0.005
Gender, male/female	246 / 209	172 / 125	74 / 84	0.024
Etiology, n of patients (%)				<0.001
Idiopathic	386 (85)	242 (81)	144 (91)	
Hepatitis	53 (12)	47 (16)	6 (4)	
Others	16 (3)	8 (3)	8 (5)	
Severity of AA, n of patients (%)				0.02
VSAA	272 (60)	166 (56)	106 (67)	
SAA	183 (40)	131 (44)	52 (33)	
Interval between diagnosis and IST				0.02
<18days ≧ 18days	224 / 231	160 / 137	64 / 94	0.01
Median WBC count (range), $x10^9$/L	2,100 (4 - 21,020)	1,900 (20 - 8,500)	3,100 (4 -21,020)	<0.001
≥ 2.0 x 10^9/L, n of patients (%)	246	136	110	
< 2.0 x 10^9/L, n of patients (%)	200	160	40	

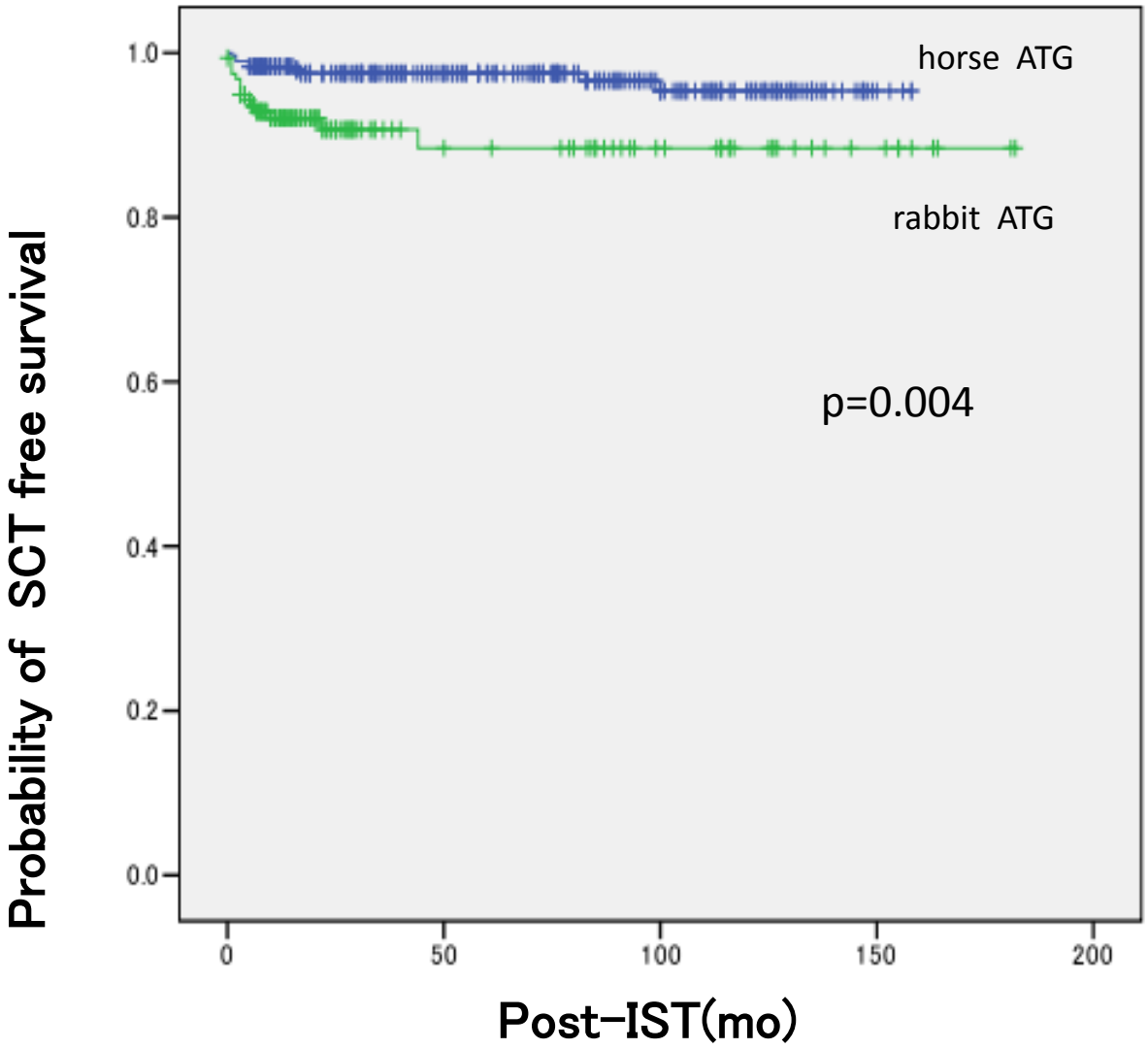
Response at 3M



Response at 6M

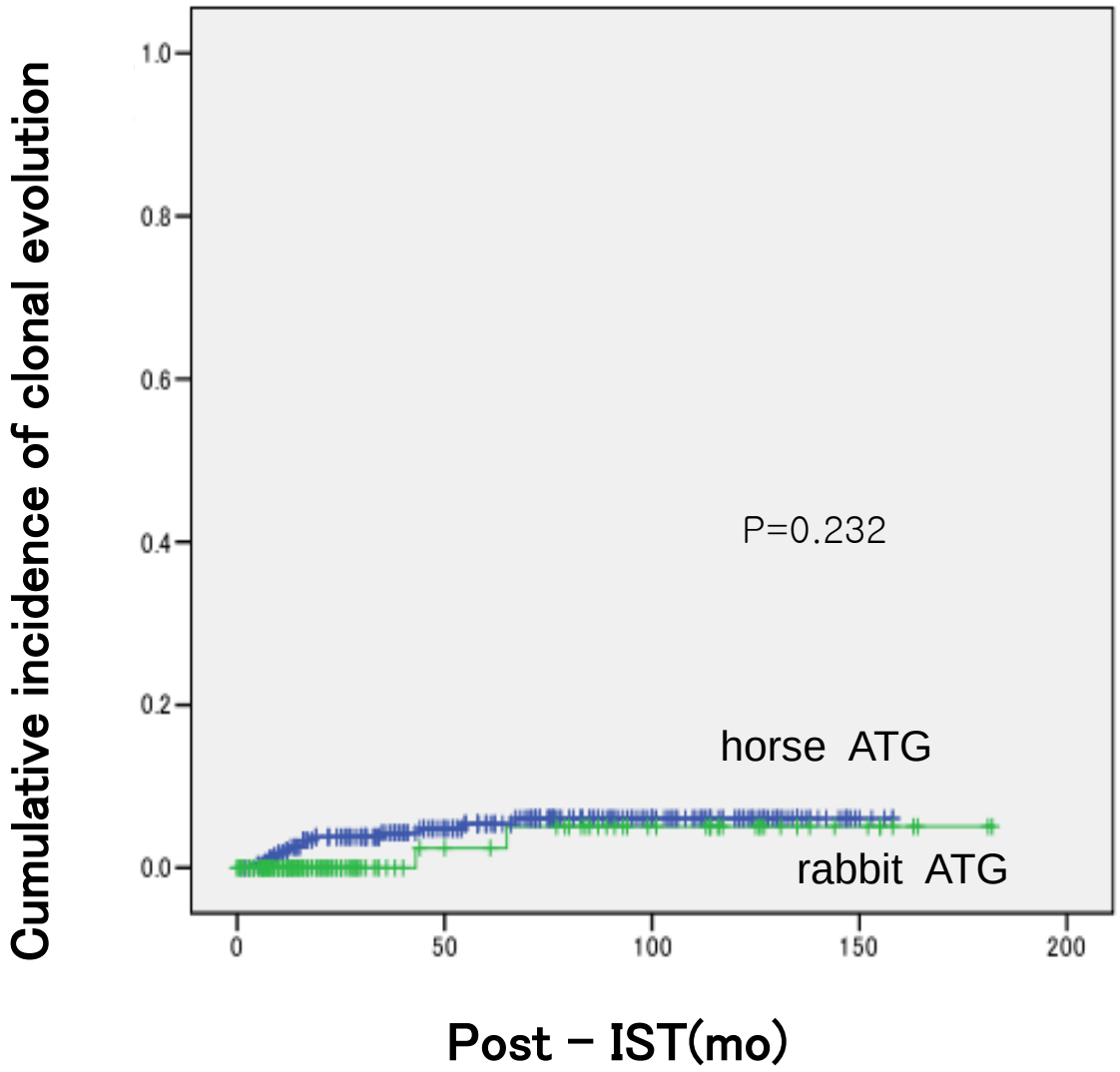


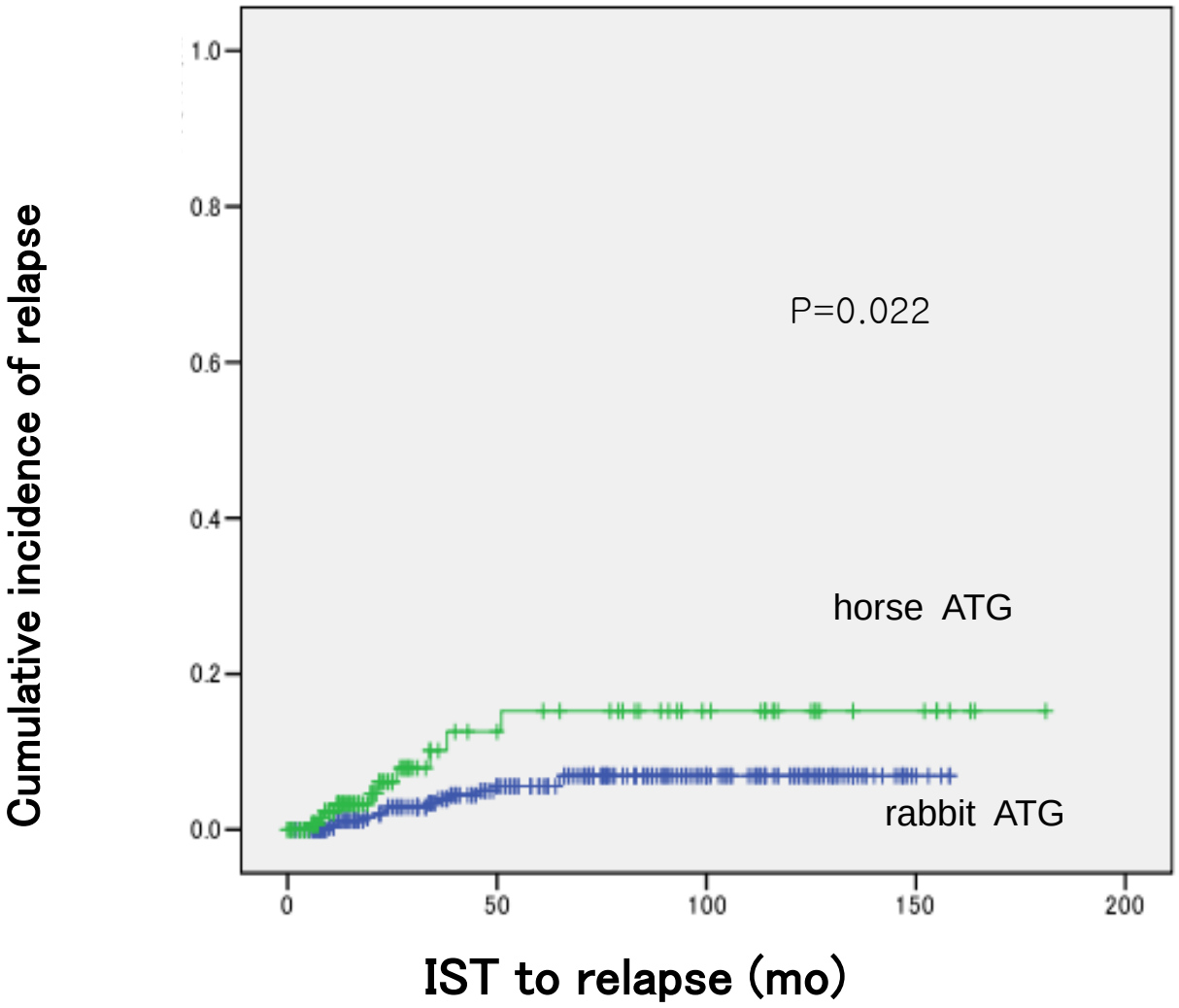

horse ATG
rabbit ATG
P=0.001
Probability of overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
Post − IST(mo)


horse ATG
rabbit ATG
p=0.004
Probability of SCT free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
Post-IST(mo)

Causes of death

	horse ATG	rabbit ATG
TRM of SCT	7	4
MDS/AML	3	0
Infection	3	8
Hemochromatosis	1	0
Hemolysis	1	0
Accident	1	1
Bleeding	0	6


Cumulative incidence of clonal evolution
1.0
0.8
0.6
0.4
0.2
0.0
P=0.232
horse ATG
rabbit ATG
0
50
100
150
200
Post – IST(mo)


Cumulative incidence of relapse
1.0
0.8
0.6
0.4
0.2
0.0
P=0.022
horse ATG
rabbit ATG
0
50
100
150
200
IST to relapse (mo)

Conclusion

Our results suggest that use of rabbit anti-thymocyte globuline may be reasonable for children with SAA when horse ATG is not available.

A prospective randmized multicenter study of comparing different dosages of rabbit ATG in patients with SAA

Primary objective:
Hematologic response in patients with IST after 180 days

Secondary objectives:
Evaluation of the presence and frequency of EBV-activation and EBV-associated lymphoproliferative disorders

Planned Study Duration:
The total study duration is 3 years. The study ends 6 months after enrolment of the last patient (total study end). Study duration for each patients is 6 months (from beginning of therapy).

Study Population:
A total of 320 SAA patients will be enrolled. 160 patients will be randomaized to arm A, 160 patients to arm B.

Today's Topics

1. First line treatment for aplastic anemia

   transplantation vs. immunosuppressive therapy

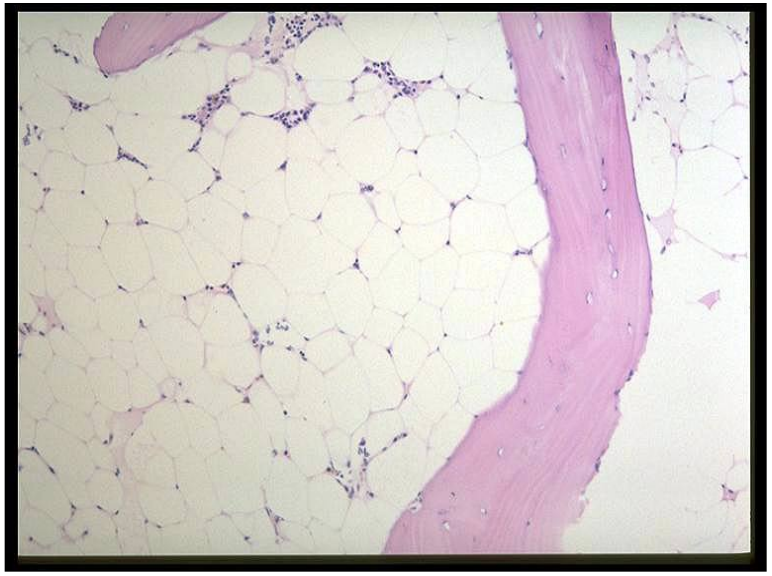
2. Immunosuppressive therapy

   horse ATG vs. rabbit ATG

3. Mismatched family donor transplantation

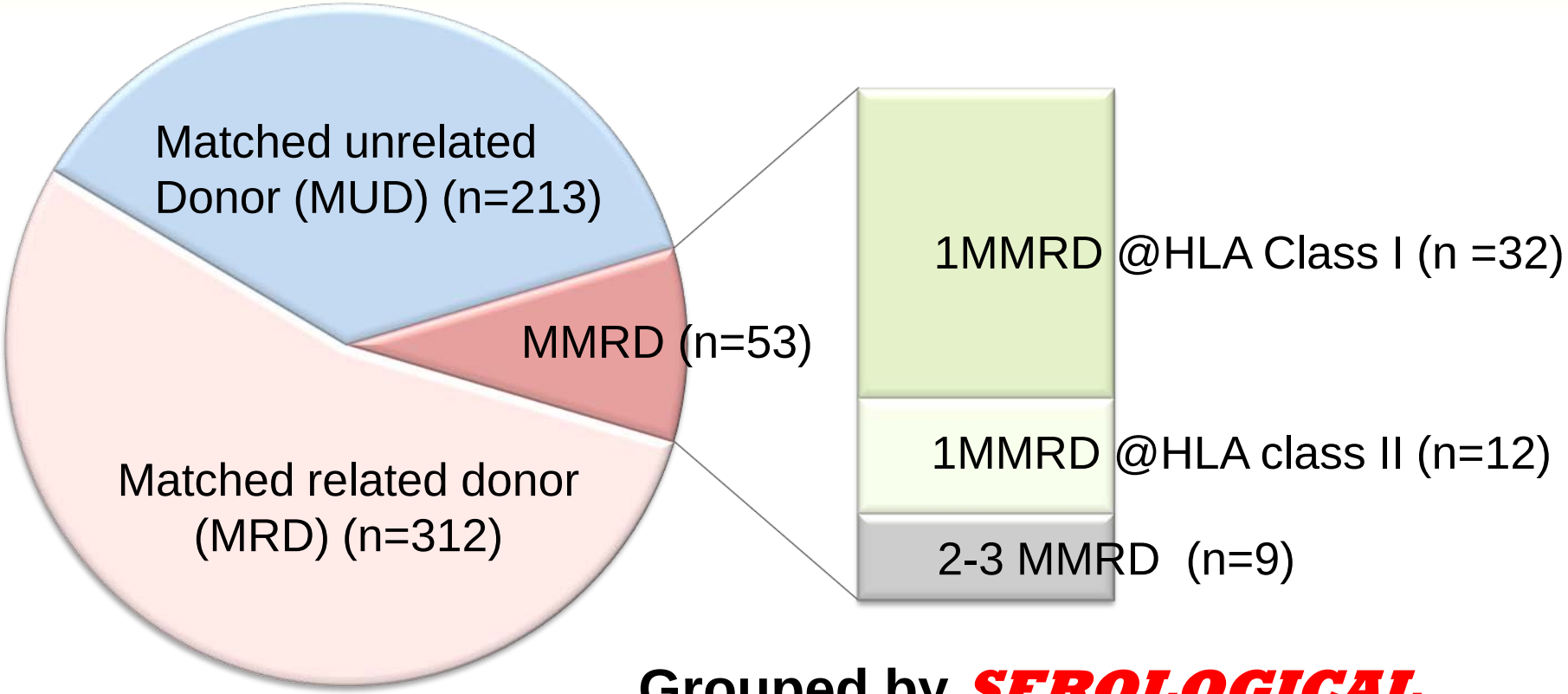
- The ***FIRST LINE THERAPY*** for children with severe AA is allo HSCT from HLA matched family donor,
- and IST is indicated for patients without HLA matched suitable donor.

- While the ***SECOND LINE THERAPY*** for children who failed to IST is allogeneic HSCT from HLA matched unrelated donor,



- HSCT from ***HLA MISMATCHED FAMILY DONOR*** has also been indicated without enough evidence in pediatric AA cohort more than decades.

PATIENTS (N = 578)



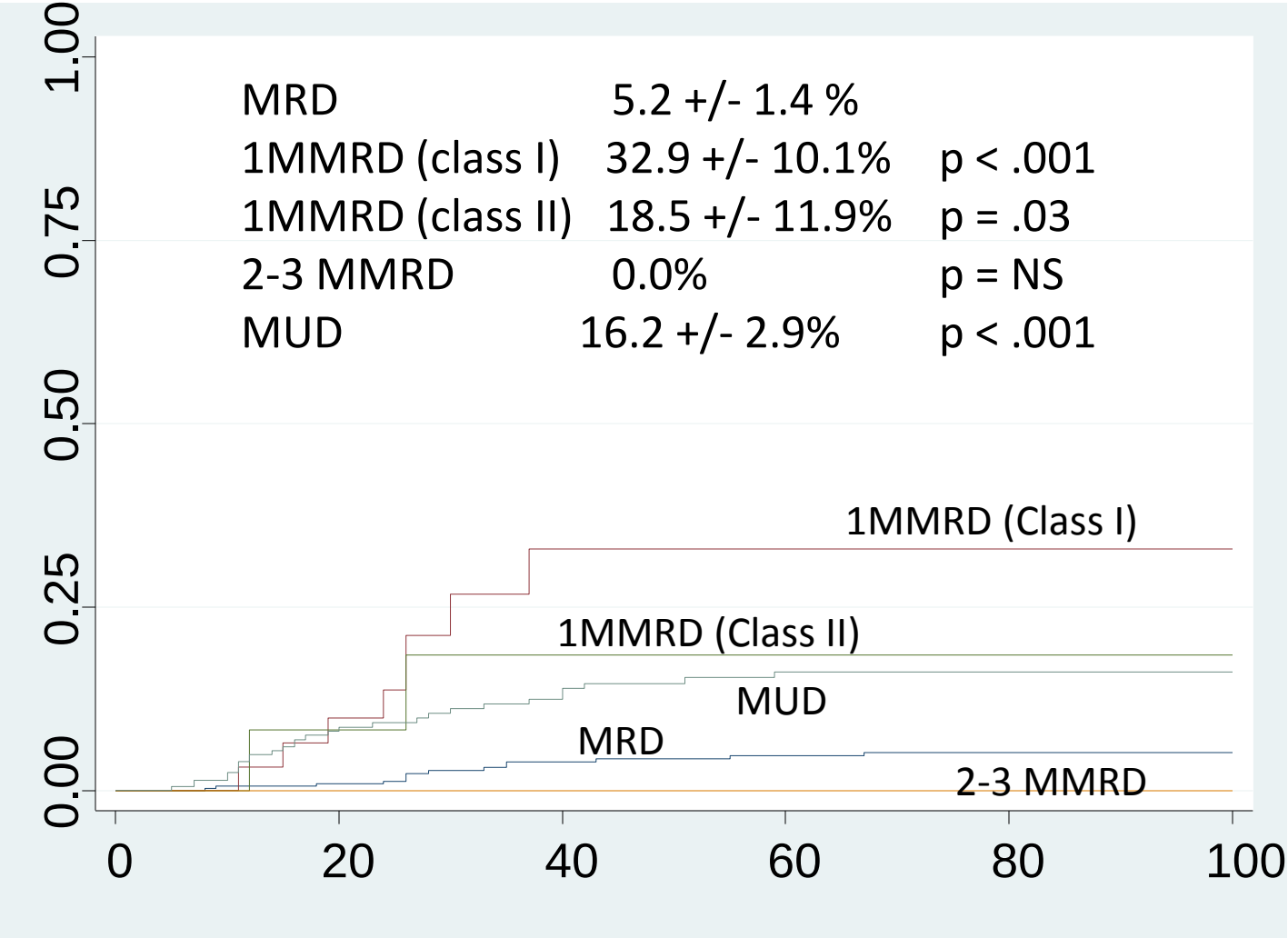
Grouped by *SEROLOGICAL* HLA typing data (A, B, and DR)

- **578 children (0-19 y) with AA**
- **Received BMT between 1990-2009**
- **Available for serological HLA data (A, B, and DR)**
- **Registered to *The Japan Society for Hematopoietic Cell Transplantation***

PATIENT CHARACTERISTICS

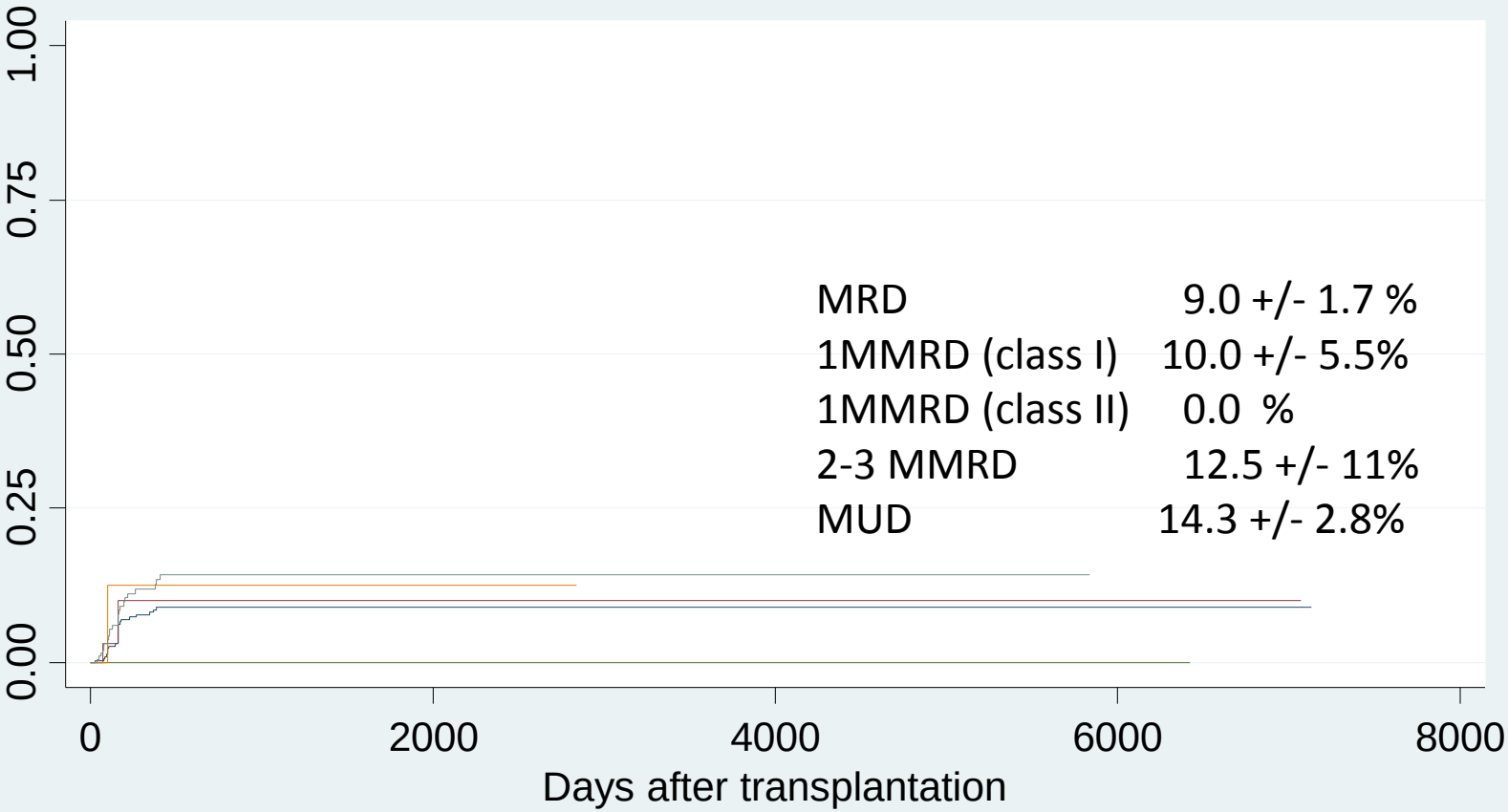
	MRD	1MMRD		2-3 MMRD	MUD
		Class I	Class II		
n	312	32	12	9	213
Donor, n (%)					
Sibling	294 (94%)	22 (69%)	4 (33%)	1 (11%)	-
Others Related	18 (6%)	10 (31%)	8 (67%)	8 (89%)	-
Unrelated donor	-	-	-	-	213 (100%)
Gender, n (%)					
Male	176 (56%)	19 (59%)	7 (58%)	3 (33%)	120 (56%)
Female	136 (44%)	13 (41%)	5 (42%)	6 (67%)	93 (44%)
Age, median (range)	11.5 (0 - 19)	9 (1 - 16)	9 (1 - 19)	10 (1 - 17)	11 (1 - 19)
Age, n (%)					
< 10 y	106 (34%)	17 (53%)	7 (58%)	4 (44%)	87 (41%)
10y - 19 y	206 (66%)	15 (47%)	5 (42%)	5 (56%)	126 (59%)

ACUTE GVHD (grade III – IV)



Days after transplantation

CHRONIC GVHD (Extensive)

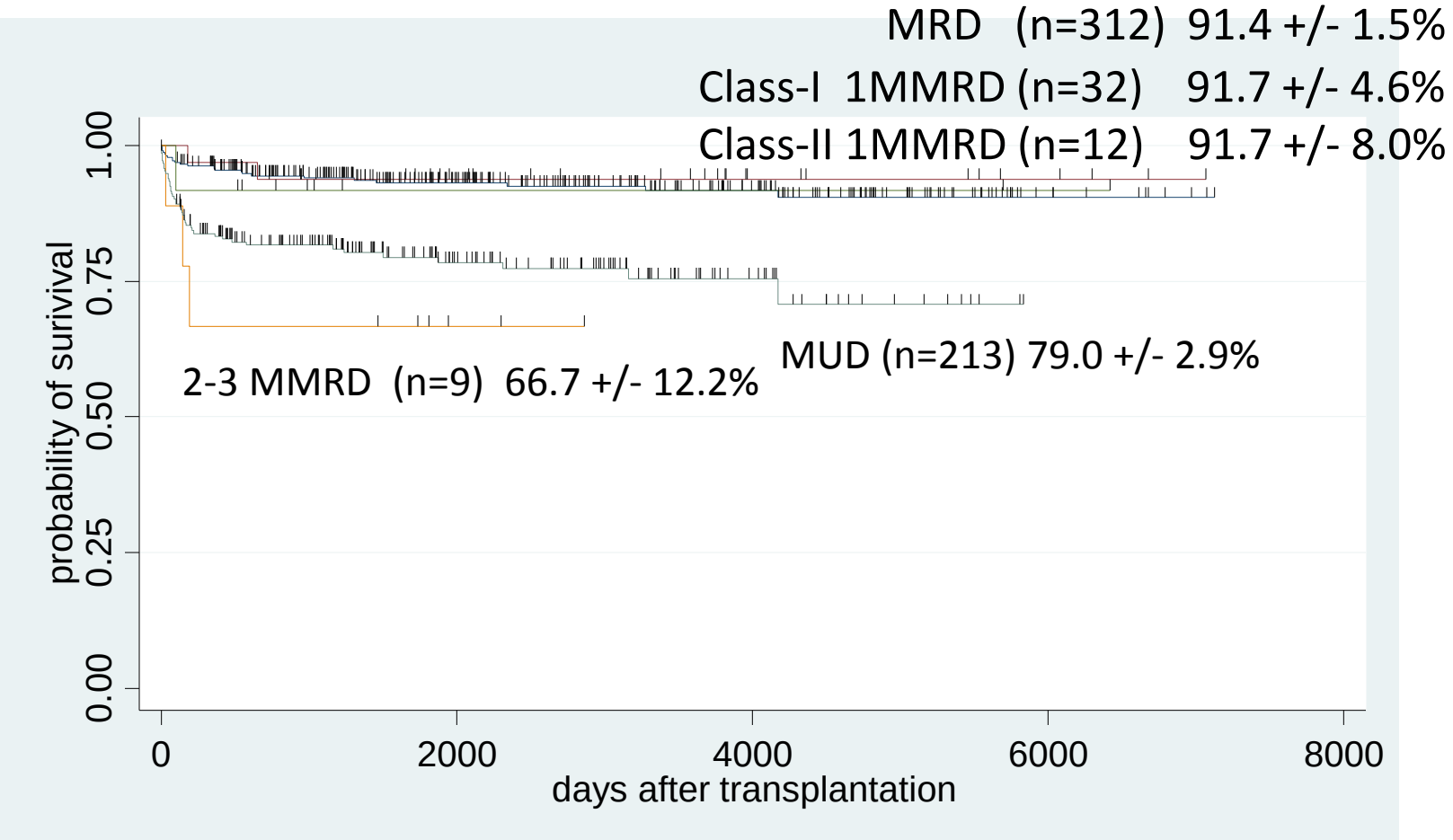


P= Not significant

CAUSES OF DEATH

	TOTAL COHORT (75 death/578 patients)
Engraftment failure	5
Acute GVHD	4
Chronic GVHD	4
Bleeding	7
ARDS	2
Infection	18
IP	8
Organ failure	19
Secondary malignancy	4
Others	4

5-year OVERALL SURVIVAL



UNIVARIATE ANALYSIS OF OS

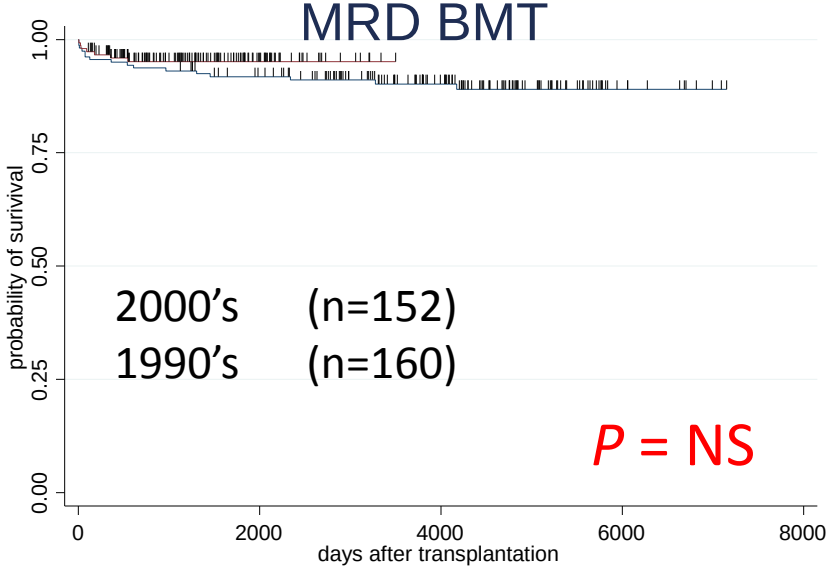
		HR (95% CI)	*P*-value
Age			
	<10	1	
	>=10	2.496 (1.436-4.338)	0.001
Period of SCT			
	1990-1999	1.751 (1.080-2.838)	0.023
	2000-2009	1	
Conditioning			
	non TBI	1	<0.001
	TBI	2.364 (1.465-3.817)	
RBC transfusion			
	<20	1	
	>=20	4.839 (2.942-7.959)	<0.001
PLT transfusion			
	<20	1	
	>=20	3.892 (2.353-6.437)	<0.001
Donor			
	MRD	1	
	1MMRD (Class I)	0.781 (0.184-3.315)	NS
	Class II 1MMRD (Class II)	1.195 (0.161-8.850)	NS
	HAPLO	5.701 (1.706-19.059)	0.005
	MUD	3.470 (2.098-5.739)	<0.001

MULTIVARIATE ANALYSIS OF OS

		HR (95% CI)	*P*-value
Age			
	<10	1	0.002
	>=10	2.647 (1.515-4.622)	
Period of SCT			
	1990-1999	2.210 (1.515-4.622)	0.001
	2000-2009	1	
Donor			
	MRD	1	
	1MMRD (Class I)	0.847 (0.199-3.605)	NS
	1MMRD (Class II)	1.930 (0.257-14.504)	NS
	2-3 MMRD	6.238 (1.866-20.856)	0.003
	MUD	4.308 (2.588-7.170)	<0.001

(2000-2009 vs. 1990-1999)

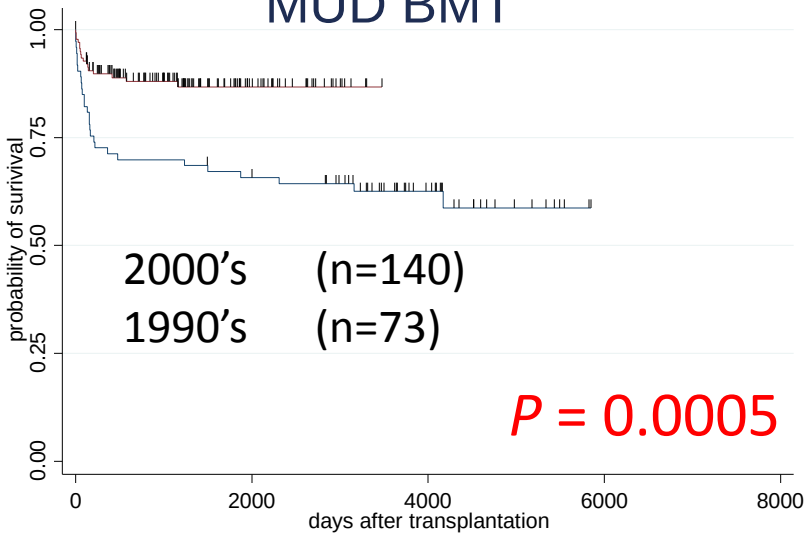
MRD BMT



2000's (n=152)
1990's (n=160)

P = NS

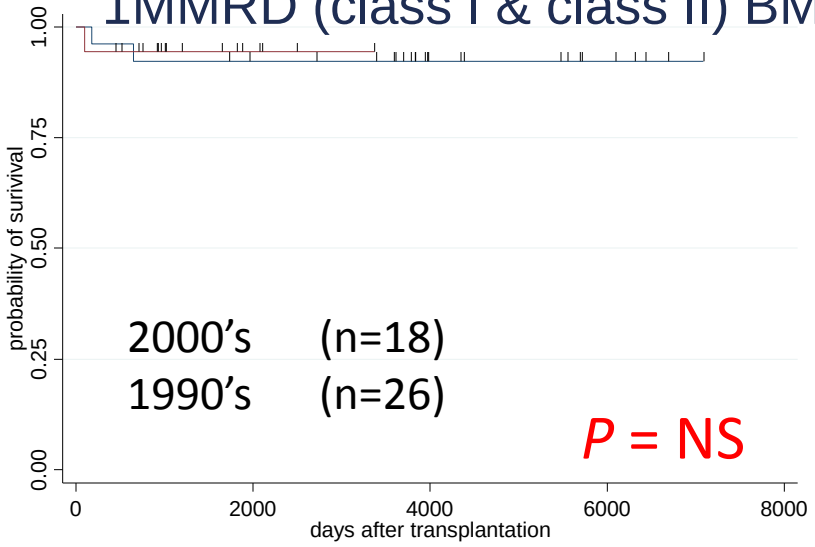
MUD BMT



2000's (n=140)
1990's (n=73)

P = 0.0005

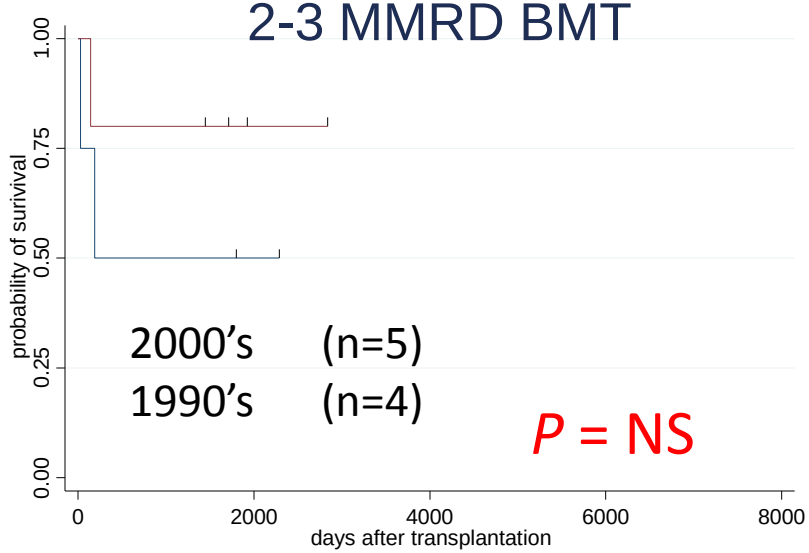
1MMRD (class I & class II) BMT



2000's (n=18)
1990's (n=26)

P = NS

2-3 MMRD BMT



2000's (n=5)
1990's (n=4)

P = NS

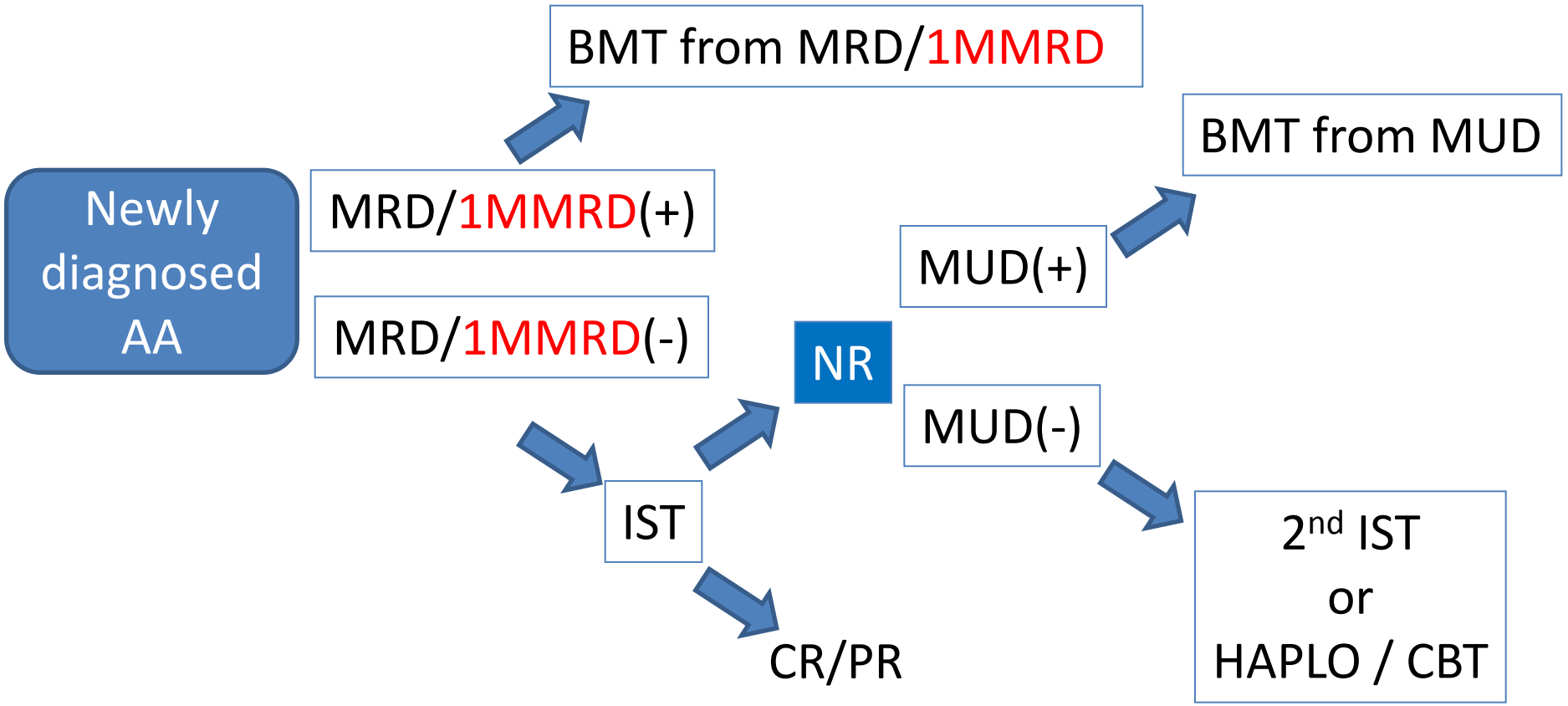
CONCLUSION

- ✓ Our analysis revealed that patient survival outcome of 1MMRD transplantation was compatible to MRD.

- ✓ 2-3 mismatched related donor (haploidentical donor) could be selected as a donor candidate for patients who need urgent transplantation.

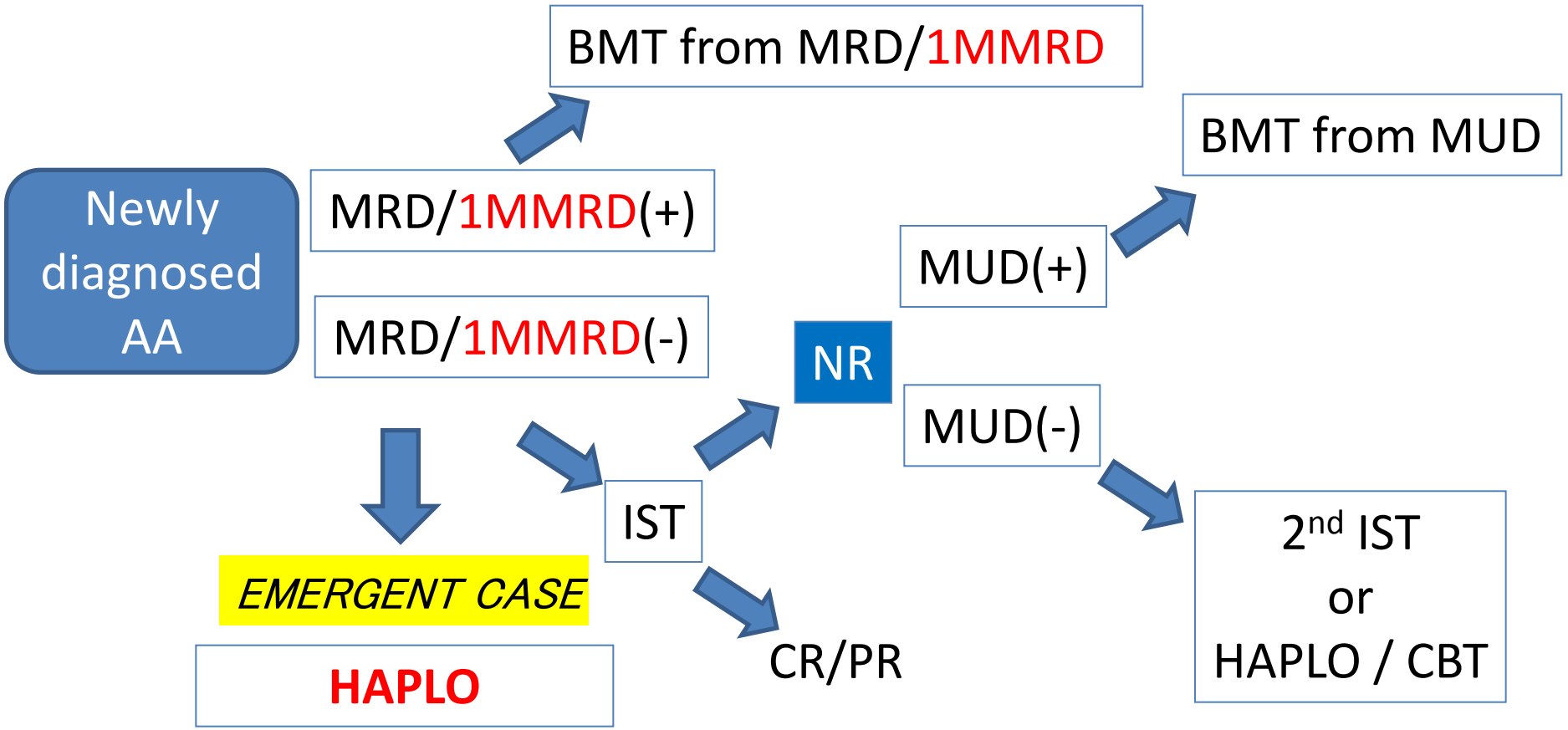
UPDATED

TREATMENT ALGORISM FOR CHILDREN WITH AA



UPDATED

TREATMENT ALGORISM FOR CHILDREN WITH AA



Acknowledgement

- Asian Pacific Blood and Marrow Transplantation Group : Childhood Aplastic Anemia Study Group
  Dao Chul Jeong, Xiao Fan Zhu

- The Japan Society for Hematopoietic Cell Transplantation Childhood Aplastic Anemia Working Group
  Hideki Muramatsu, Hiromasa Yabe, Akira Kikuchi, Ryoji Kobayashi

- Japan Childhood Aplastic Anemia Study Group
  Nao Yoshida, Yoshiyuki Takahashi, Akira Ohara