Can All Thalassemia Patients Be Cured with HSCT ?

Suradej Hongeng, MD

Ramathibodi Hospital, Mahidol University

Treatments for Severe Thalassemia

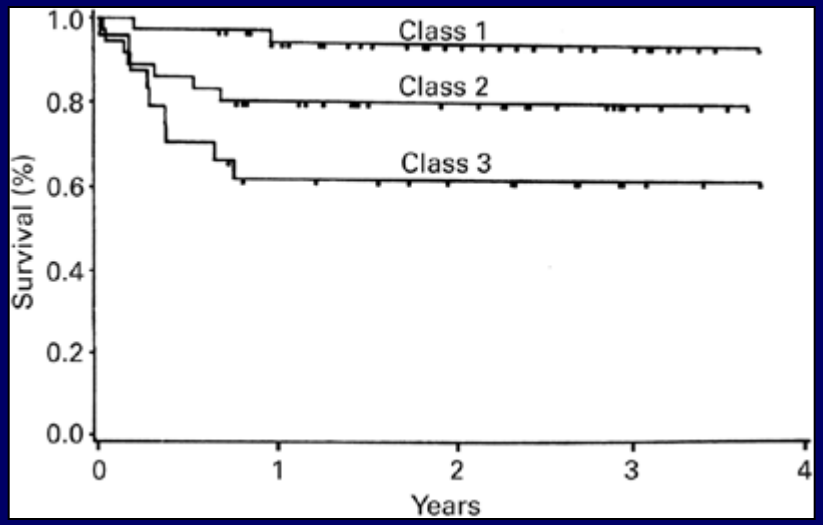
Palliative treatment

- Blood transfusion
- Iron chelation
- Splenectomy

Curative treatment

- Hematopoietic stem cell transplant (HSCT)
  - Allogeneic HSC
- Gene therapy
  - Autologous HSC

BMT in Thalassemia and Lucarelli Classification



Risk factors for BMT in thalassemia

Chelation	Regular vs Irregular
Hepatomegaly	Absent vs Present
Liver fibrosis	Absent vs Present

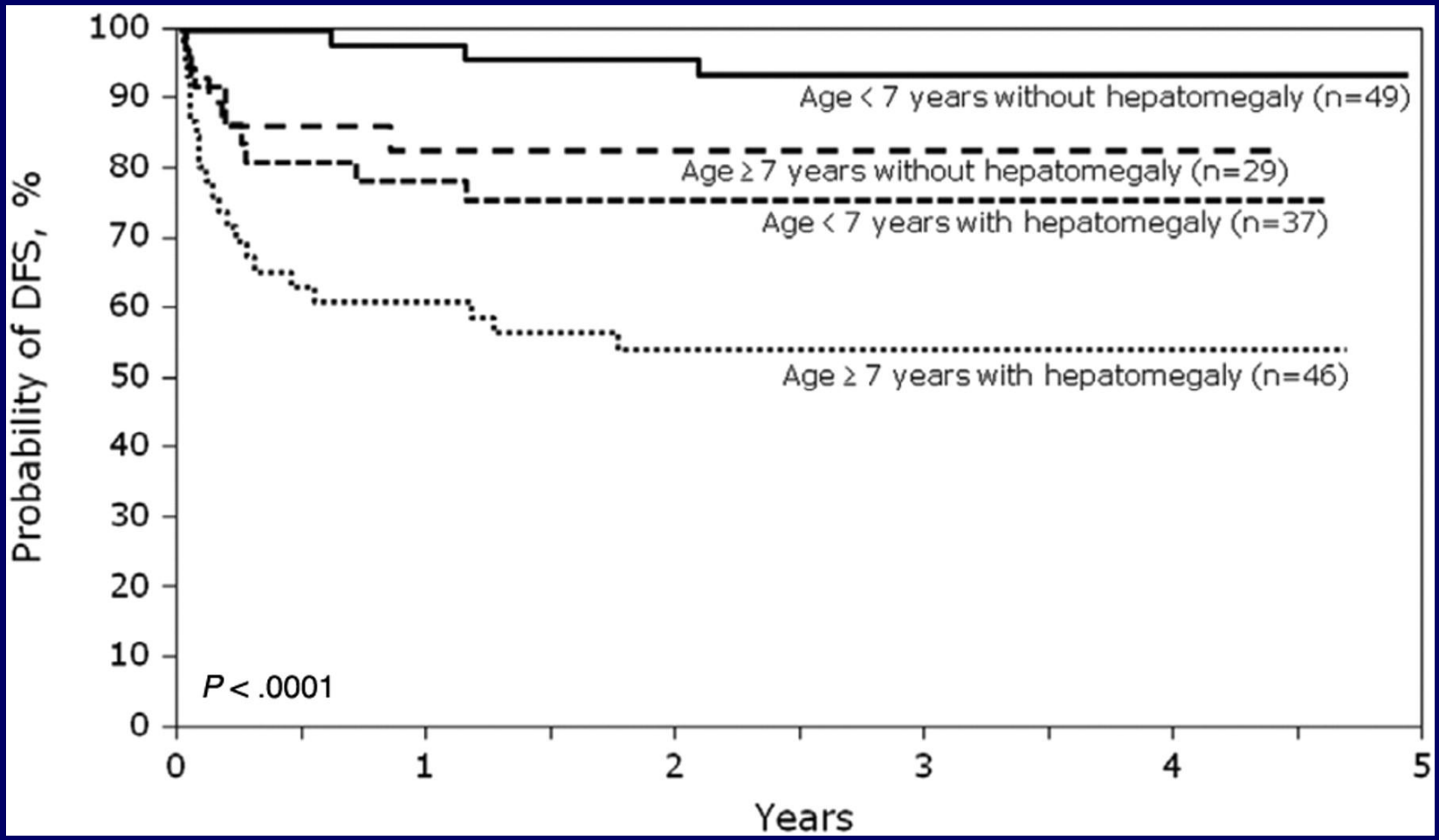
Risk classes for BMT in thalassemia

	Chelation	Hepatomegaly	Fibrosis
Class1	Regular	NO	NO
Class2	Reg/Irreg	NO/YES	NO/YES
Class3	Irregular	YES	YES

Lucarelli G et al. N Engl J Med 1990

HLA-matched sibling bone marrow transplantation for β-thalassemia major

Mitchell Sabloff,[1] Mammen Chandy,[2] Zhiwei Wang,[3] Brent R. Logan,[3] Ardeshir Ghavamzadeh,[4] Chi-Kong Li,[5] Syed Mohammad Irfan,[6] Christopher N. Bredeson,[7] Morton J. Cowan,[8] Robert Peter Gale,[9] Gregory A. Hale,[10] John Horan,[11] Suradej Hongeng,[12] Mary Eapen,[3] and Mark C. Walters[13]



Sabloff et al. ICBMTR, Blood 2011

Results of MRD in HSCT for Thal Patients

Reference	Patients	OS	TFS
Di Bartolomeo et al.	111	90	86
Argiolu et al.	37	88	88
Clift et al.	68	94	81
Lawson et al.	54	95	82
Ghavamzadehv et al.	60	83	73
Denninson et al.	50	76	68
Lin et al.	28	86	82
Lee et al.	44	86	82
Issaragrisil et al.	21	70	53

GUIDELINE ARTICLE

Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel

Emanuele Angelucci,[1] Susanne Matthes-Martin,[2] Donatella Baronciani,[3] Françoise Bernaudin,[4] Sonia Bonanomi,[5] Maria Domenica Cappellini,[6] Jean-Hugues Dalle,[7] Paolo Di Bartolomeo,[8] Cristina Díaz de Heredia,[9] Roswitha Dickerhoff,[10] Claudio Giardini,[11] Eliane Gluckman,[12] Ayad Achmed Hussein,[13] Naynesh Kamani,[14] Milen Minkov,[2] Franco Locatelli,[15] Vanderson Rocha,[16] Petr Sedlacek,[17] Frans Smiers,[18] Isabelle Thuret,[19] Isaac Yaniv,[20] Marina Cavazzana,[21,22,23,24] and Christina Peters;[2,25] on behalf of the EBMT Inborn Error and EBMT Paediatric Working Parties

Haematologica 2014

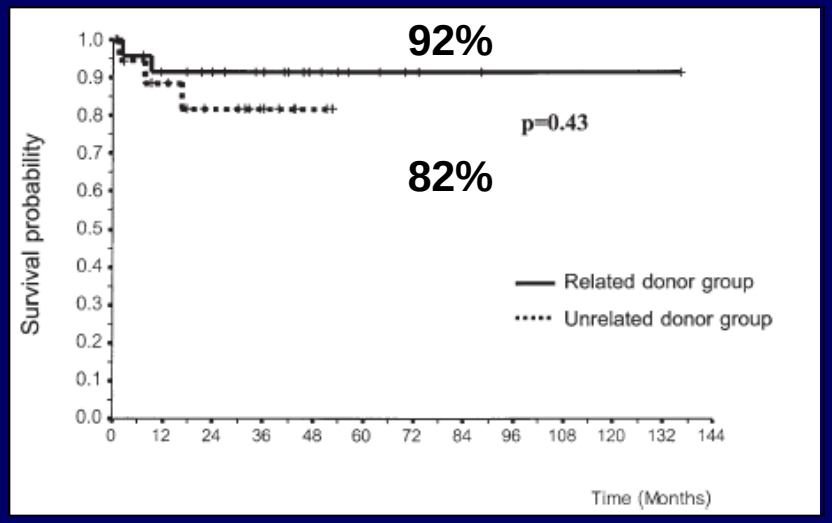
Table 2. Recent reports on matched sibling donor HSCT in children and adults with thalassaemia major.

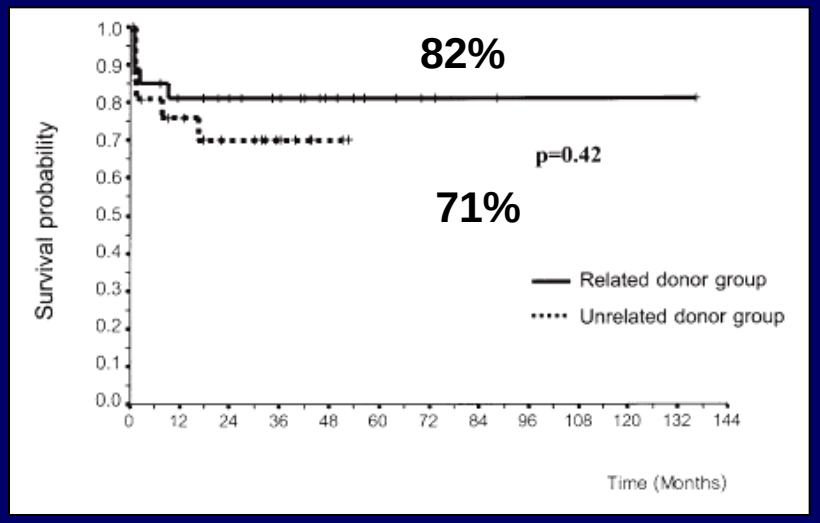
Author and Reference	N. of patients	Patient cohort / Pesaro risk category	Overall survival	Thalassemia free survival	Treatment related mortality	Comments
Galambrun *et al.*[12]	108	Children all categories of risk	15 years 86.8%	15 years 69.4%	15 years 12%	96 sibling donor Regimen: Bu-Cy ±ATG
Yesilipek *et al.*[13]	245	Children: Low: 41 Intermediate: 130 High: 63	1 year 85%	1 year 68%	1 year 7.75%	88 BM, 137 PB, 20 CB Regimen: Bu-Cy
Li *et al.*[14]	82	Children all risk categories	3 years 91%	3 years 87%	3 years 8%	52 MUD, 30 sibling Regimen Bu-Cy-Thiotepa, Fludarabine.
Choudhary *et al.*[15]	28	Children: Intermediate risk: 7 High risk: 21	78.5%	71.4%	21.4%	Regimen: Treosulfan-Thiotepa-Fludarabine.
Bernardo *et al.*[16]	60	Low: 27 Intermediate: 17, High: 4 Adults: 12	5 years 93%	5 years 84%	7%	20 sibling donor, 40 MUD. Regimen Treosulfan - Thiotepa - Fludarabine
Sabloff *et al.*[17]	179	Low: 2% Intermediate: 42% High: 36%	5 years: Intermediate risk: 91% High risk: 64%	5 years Intermediate risk: 88% High risk: 62%	Intermediate risk: 5/75 High risk 23/64	Bu-Cy + ATG in 77, Bu-Cy in 102
Ghavamzadeh *et al.*[18]	183	Children Low and intermediate	2 years PBSCs 83% BM 89%	2 years PBSCs 76% BM 76%	1 year PBSC 14% BM: 9%	87 PBSC , 96 BM Regimen: Bu-Cy
Iravani *et al.*[19]	52	Children high risk: 52	4.1 years 80%	4.1 years 65%	4.1 years 7/52	32 BM, 20 PBSC Regimen: Bu-Cy
Irfan *et al.*[20]	56	Children Low: 20 Intermediate : 20 High: 16	5 years BM: 73% PBSCs: 65%	5 years BM: 67% PBSCs: 55%	100 days: 10/56	29 BM, 27 PBSCs Lower risks: Bu-Cy High risk: Hydroxyurea-Azathioprine-Fludarabune-Bu-Cy
Locatelli *et al.*[21]	259	Median age 8 years (range 1-24) Low: 86 Intermediate: 122 High: 51	6 years 95%	6 years 86%	4%	Multicentric retrospective registry study. Regimens: Bu-Cy, Bu-Cy_Fludarabine, Bu-Cy-Thiotepa ±ATG.
Ullah *et al.*[22]	48	Low: 31 Intermediate: 11 High: 6	6 years 79%	6 years 75%	20.8%	Regimen: Bu-Cy
Di Bartolomeo *et al.*[23]	115	All categories	20 years 89.2%	20 years 85.7%	1 year 8.7%	20 years Pescara experience. Regimen: Bu-Cy
Gaziev *et al.*[24]	107	High risk	12 years 66%	12 years 62%	37%	Regimen: Bu-Cy or Hydroxyurea-Azathioprine-Fludarabine-Bu-Cy
Lawson *et al.*[25]	55	Low: 17 Intermediate: 27 High: 11	8 years 94.5%	8 years 81.8%	5,4%	Regimen: Bu-Cy±Campath or Fludarabine
Gaziev *et al.*[26]	68	6 low risk 23 intermediate risk 39 high risk	3 years 91%	3 years 87%	100 days 3%	Intravenous Busulfan based regimen
Chiesa *et al.*[27]	53	high risk children	2 years 96%	2 years 88%	2 years 4%	Intravenous Busulfan dose-adjustment policy.
Hussein *et al.*[28]	44	Low risk: 7 Intermediate risk: 24 High risk: 13	5 years 97.8%	5 years 86.4%	1 patient died	High risk patients received reduced intensity conditioning and had higher thalassemia recurrence rate (23%)
Mathews *et al.*[29]	50	High risk	3 years 86.6%	3 years 77.8%	13%	Treosulfan based conditioning

OS: overall survival; TFS: thalassemia free survival; TRM: transplant related survival; NR: not reported; Bu: busulfan; Cy: cyclophosphamide; ATG: antithymocyte globulin; BM: bone marrow; PBSC: peripheral blood stem cells; CB: cord blood.

HSCT in Thalassemia at Ramathibodi

Related n=28, Unrelated n=21 Total 49 patients





Overall survival (OS) and thalassemia free survival (TFS) in Thai children

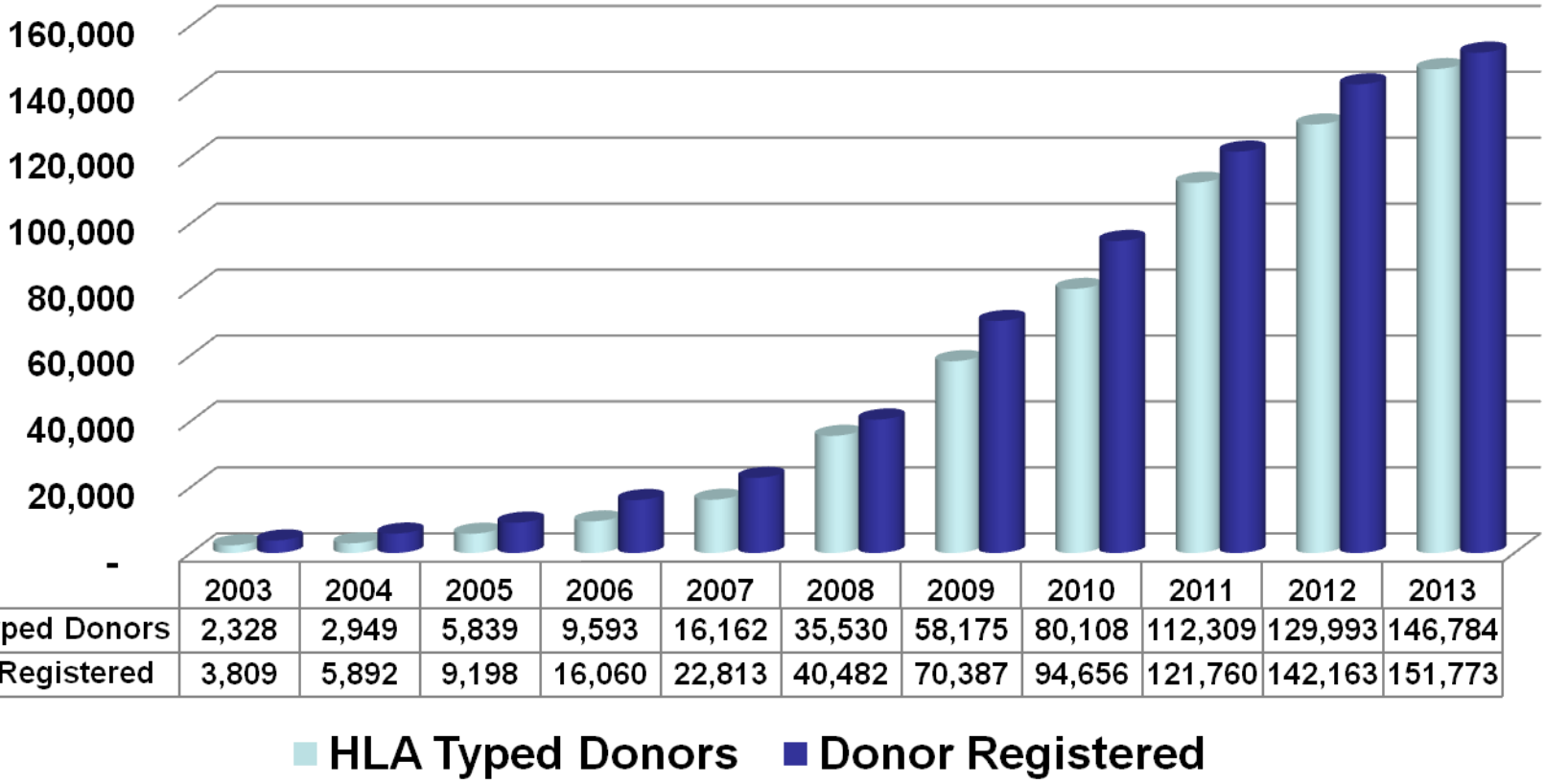
Hongeng S et al. Biol Blood Marrow Transplant 2006

Dilemma of HSCT in Thal

Donor availability

Older patients

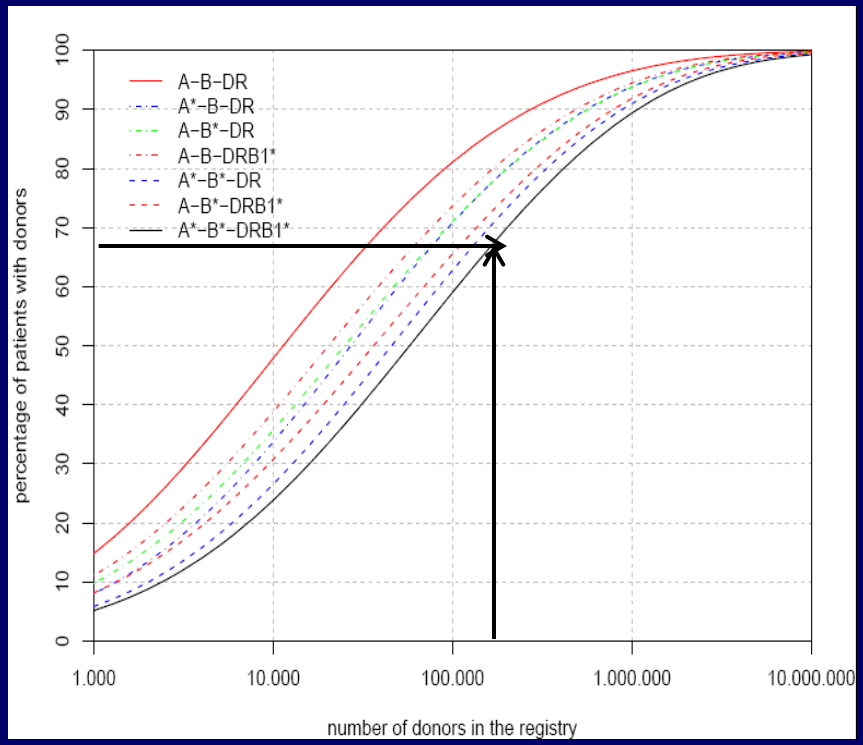
Stem Cell Donor in Registry
(November 2013)



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
HLA Typed Donors	2,328	2,949	5,839	9,593	16,162	35,530	58,175	80,108	112,309	129,993	146,784
Donor Registered	3,809	5,892	9,198	16,060	22,813	40,482	70,387	94,656	121,760	142,163	151,773

Propability in Finding HLA-A,-B,-DR Matched Donor

Percentage of patients with Donors



Number of Donors in Registry

New Stratification for High Risk Class 3 Patients

Definition

- **Older patients**
  - **Age ≥ 10 yrs**
  - **Hepatomegaly (liver > 3 cm below right costal margin)**

High Risk Class 3 Patients (Age ≥ 10 yrs) Pretransplant Management Program

- Hypertransfusion in order to decrease erythroid expansion especially to decrease spleen size
- Regular iron chelation for at least 6-12 months
- Hydroxyurea (Hb F enhancer) in order to decrease erythroid expansion: 20 mg/kg/day for at least 6-12 months

Sodani P et al. Blood 2004
Hongeng S et al. Am J Hematol 2007

Previous RTC Regimen (Early 8 Patients)

Busulfan oral (8-12 mg/kg)

Fludarabine (210 mg/m^2)

ATG (Fresinius 20 mg/kg)

±TLI 500 cGy

± Thiotepa 10 mg/kg

± Melphalan 100 mg/m^2

GVHD prophylaxis

CSA or FK506 and MMF

Reduced intensity stem cell transplantation for treatment of Class 3 Lucarelli severe thalassemia patients

Suradej Hongeng,[1]* Samart Pakakasama,[1] Ampaiwan Chuansumrit,[1] Nongnuch Sirachainan,[1] Thanyachai Sura,[2] Artit Ungkanont,[2] Suporn Chuncharunee,[2] Saengsuree Jootar,[2] and Surapol Issaragisil[3]

Am J Hematol, 2007

TABLE III. Characteristics of Previously Published Studies

References	Number of patients	Conditioning regimen	Stem cell source	Number of patients with stable engraftment	Number of deaths
2	7	Flu, TBI, ± ALG	BM	None	None
3	4	Flu, ALG, TBI	BM	1	None
4	4	Bu, Flu, ALG	PBSC	2	2
5	5	Bu, Flu, ALG, TLI	PBSC	5	None
Current Series	8	Bu, Flu, ALG, ± Thio, ± TLI	PBSC	6	None

Flu, fludarabine; TBI, total body irradiation; ALG, antilymphocyte globulin; TLI, total lymphoid irradiation; Thio, thiotepa; BM, bone marrow; PBSC, peripheral blood stem cell.

2 Iannone R, et al. BBMT 2003

3 Horan JT, et al. BMT 2005

4 Jacobsohn DA, et al. Lancet 2004

5 Krishnamurti L, et al. BMT 2006

Outcomes of Thalassemia Patients Undergoing Hematopoietic Stem Cell Transplant by Using a Standard Myeloablative (MAC) Versus a Novel Reduced Toxicity (RTC) Conditioning Regimen According to a New Risk Stratification

Suradej Hongeng, MD

Dept of Pediatrics, Faculty of Medicine
Ramathibodi Hospital, Mahidol University

Bangkok, Thailand

Novel Approach for High Risk Class 3 Patients

Pre transplant management

Hypertransfusion, chelation and hydroxyurea

Pretransplant immunosuppression (PTIS)

Flu + Dex (2 cycles)

Conditioning regimen

Bu + Flu + ATG

Pre-transplant Immunosuppression (PTIS)

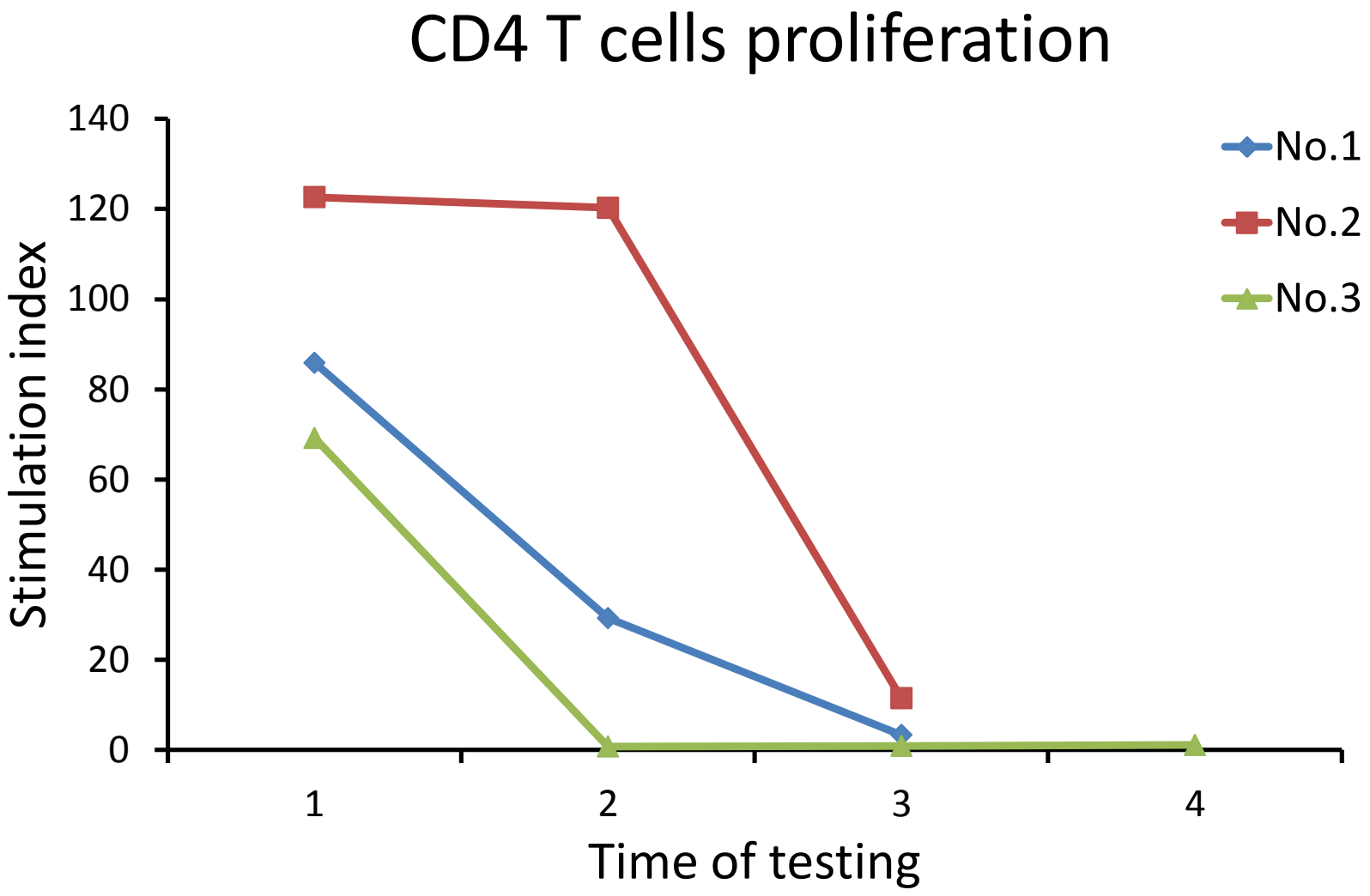
Fludarabine 40 mg/m^2 x 5 days

Dexamethasone 25 mg/m^2 x 5 days

1-2 cycles; 28-day cycle

PTIS is given prior to conditioning regimen

Decreased CD4 cell proliferation



Conditioning Regimen for High Risk Class 3 Patients

Past

Combination of cyclophosphamide & busulfan

- Too much alkylating agent regimen
- Too toxic

Novel RTC Regimen and GVHD Prophylaxis

Fludarabine 35 mg/m^2; d-9,-8,-7,-6,-5,-4

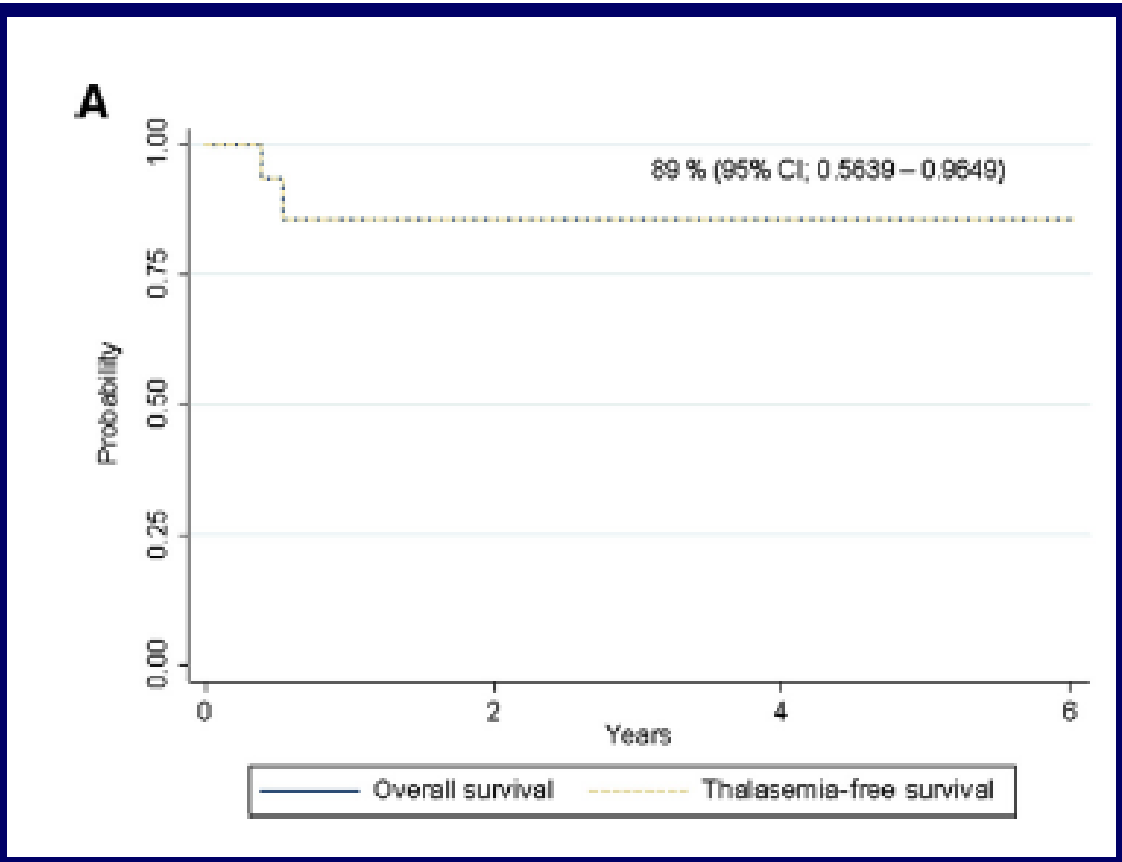
Busulfex 130 mg/m^2; d-9,-8,-7,-6

ATG (Thymoglobulin) 1.5 mg/kg; d-3,-2,-1

CSA or FK506 and MMF (60 days)

Pretransplant Immunosuppression followed by Reduced-Toxicity Conditioning and Stem Cell Transplantation in High-Risk Thalassemia: A Safe Approach to Disease Control

Usanarat Anurathapan [1], Samart Pakakasama [1], Piya Rujkijyanont [2], Nongnuch Sirachainan [1], Duantida Songdej [1], Ampaiwan Chuansumrit [1], Somtawin Sirireung [3], Pimlak Charoenkwan [4], Arunee Jetsrisuparb [5], Surapol Issaragrisil [6], Artit Ungkanont [7], Rosarin Sruamsiri [8], Supanart Srisala [9], Borje S. Andersson [10], Suradej Hongeng [1,*]



18 high risk class 3 patients

BBMT;2013

MAC vs Novel RTC

MAC Regimens and GVHD Prophylaxis

Related donor and age < 10 yrs

MAC regimen: Cyclo 200 mg/kg, Bu 14-16 mg/kg PO/IV

CSA + MTX

Unrelated group and < 10 yrs

MAC regimen: Cyclo 200 mg/kg, Bu 14-16 mg/kg PO/IV,

Flu 210 mg/m2 and ATG (Fresenius) 40 mg/kg

FK506 + MTX

HLA Matching

Related: 6 allele matching

Unrelated: (before 2006) 6 allele matching

(current) 8 allele matching

Study Population

120 thalassemia patients undergoing HSCT; 1989 – mid 2014

(Current number 135 pts)

Exclude cord blood transplant n = 7

Exclude previous RTC transplant n = 8

(Am J Hematol; 2007)

Exclude haploidentical transplant n = 7

Final number of patients n = 98 patients

Related n = 65; Unrelated n = 33

MAC n = 76; Novel RTC n = 22

Patient Characteristics

MAC

Related n= 50 , Unrelated n=26 (34%)

Mismatched HLA (1 Ag or 1 Allele) 12/76 (15%)

Novel RTC

Related n=15 , Unrelated n=7 (32%)

Mismatched HLA (1 Ag or 1 Allele) 5/22 (22%)

All received BM or PBSC.

Novel RTC Group

22 patients

2 out of 22 had second HSCT and 1 had third HSCT

Age; median = 16 (10-21) y/o

Male 8; Female 14

Splenectomy = 7 (Referral hospital)

All patients had liver > 5 cm below costal margin.

Ferritin level; median = 3100 (869-8350) ng/mL

Comorbidities

2 DM, 1 previous extramedullary hemopoiesis,

1 previous history of PHT

Novel RTC Group

21 patients received PBSC.

1 patient received BM.

Median CD34+ 9.4 (4.67-19.26) $x10^6$ cells/kg

MRD 13 MMRD 2 (DRB1)

MUD 4 MMUD 2 (C) MMUD 1 (A)

MAC vs RTC

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Outcomes of Thalassemia Patients Undergoing Hematopoietic Stem Cell Transplantation by Using a Standard Myeloablative versus a Novel Reduced-Toxicity Conditioning Regimen According to a New Risk Stratification

Usanarat Anurathapan [1], Samart Pakakasama [1], Pimsiri Mekjaruskul [1], Nongnuch Sirachainan [1], Duantida Songdej [1], Ampaiwan Chuansumrit [1], Pimlak Charoenkwan [2], Arunee Jetsrisuparb [3], Kleebsabai Sanpakit [4], Bunchoo Pongtanakul [4], Piya Rujkijyanont [5], Arunotai Meekaewkunchorn [6], Rosarin Sruamsiri [7], Artit Ungkanont [8], Surapol Issaragrisil [9], Borje S. Andersson [10], Suradej Hongeng [1,*]

Outcome of All 98 Patients

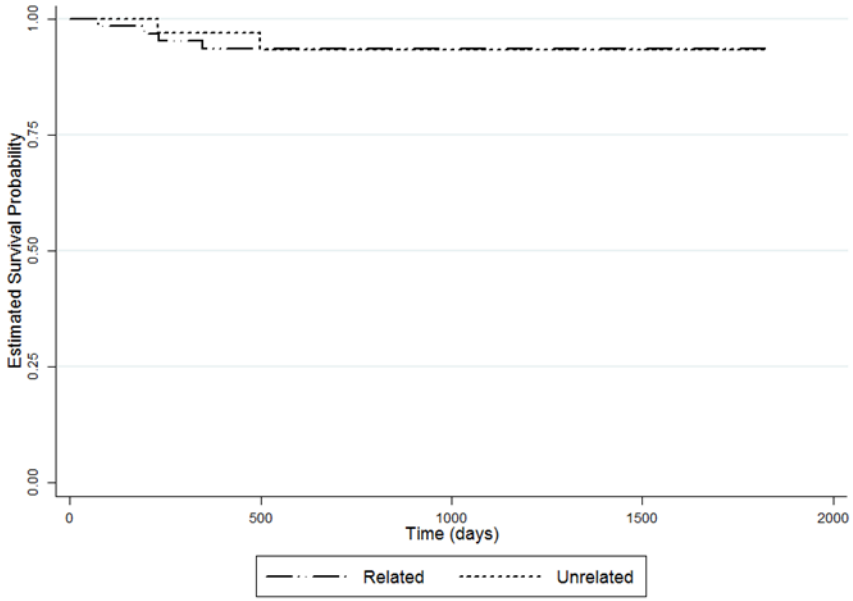
Overall survival = 94% (95%CI; 86.3%-97/1%)

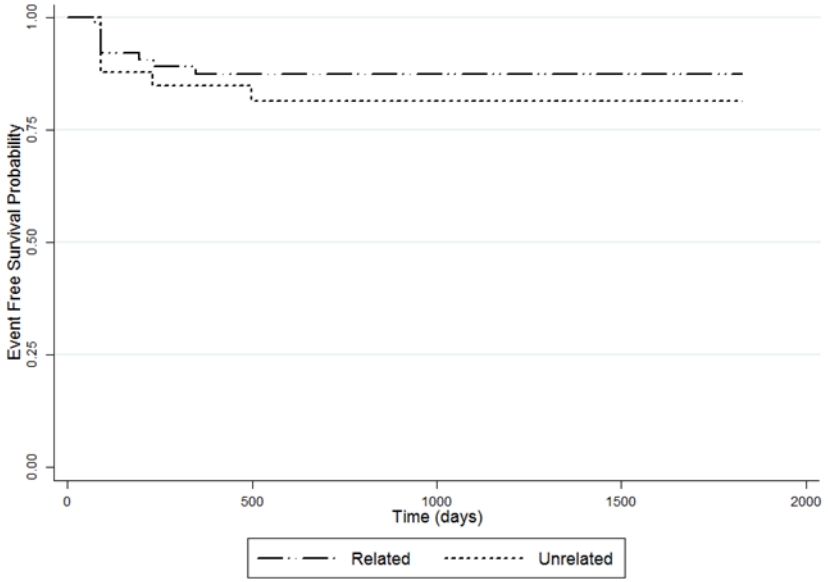
Event free survival = 87% (95%CI; 76.6%-91.1%)

Survival Rates Related (n=65) and Unrelated (n=33) HSCT in Thalassemias

OS Related vs Unrelated = 94%

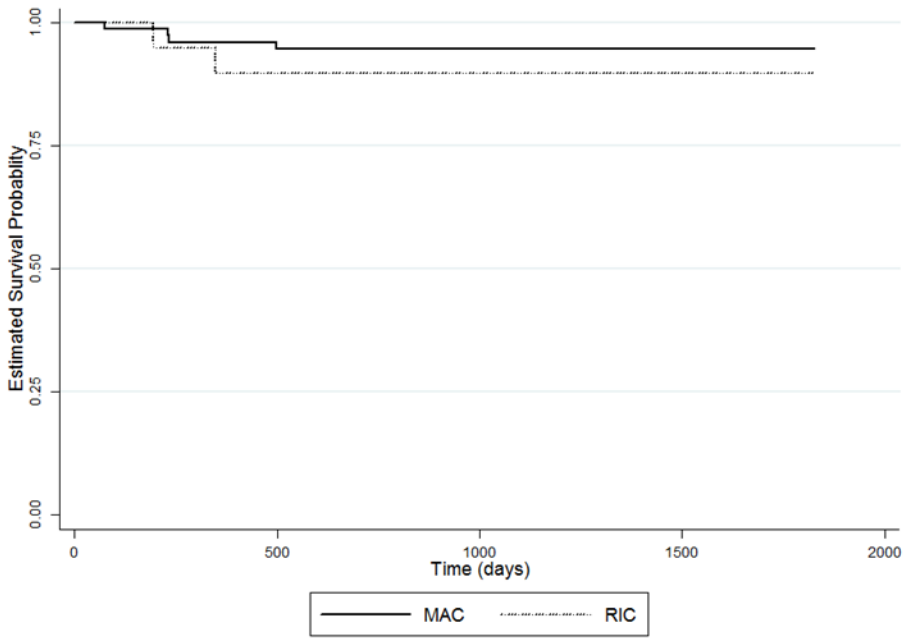
EFS Related = 88%
EFS Unrelated = 82%



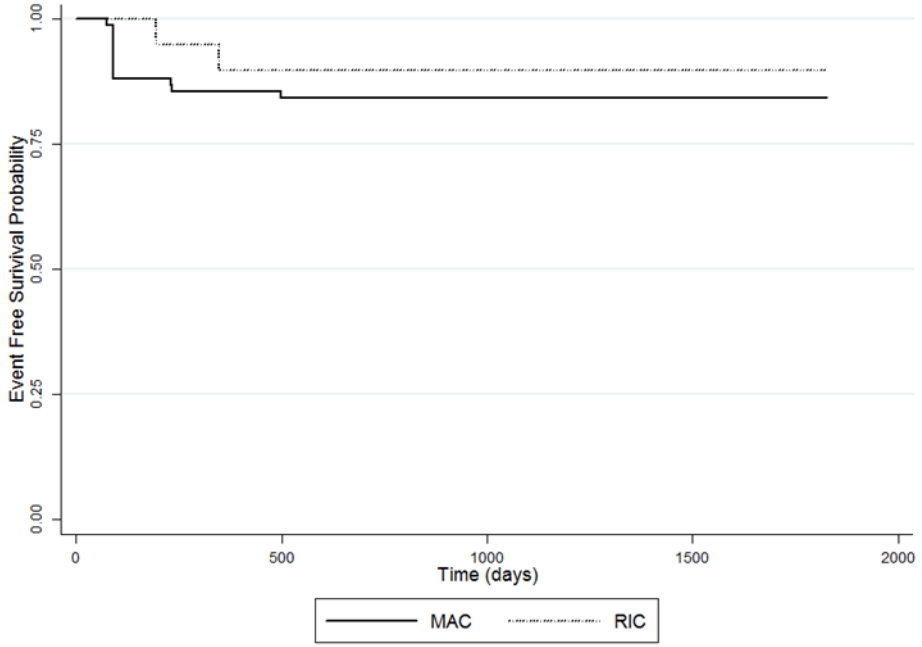


MAC (n = 76) vs Novel RTC (n= 22)

OS **MAC = 95%**
RTC = 90%



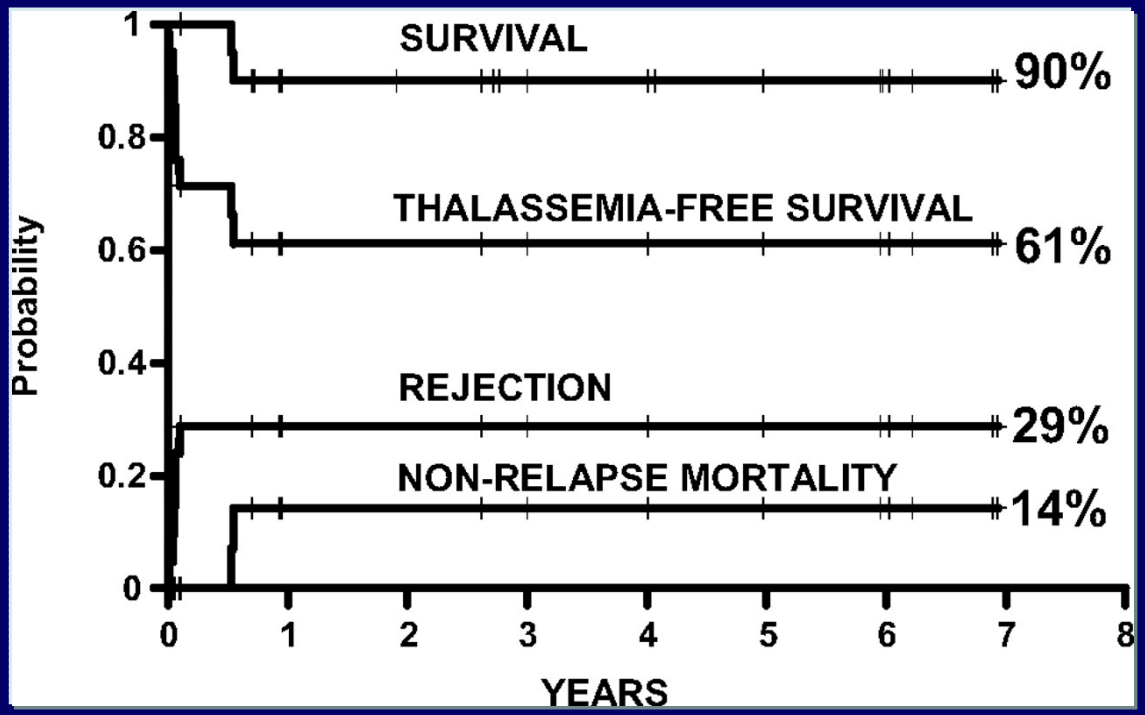
EFS **MAC = 88%**
RTC = 93%



MAC vs Novel RTC

	MAC	RTC
Acute GVHD gr III-IV	**3 (4%)**	**2 (10%)**
Chronic GVHD		
Limited	**6 (8%)**	**3 (13%)**
Extensive	**2 (3%)**	**0**
Dead	**3**	**2**
	1 Graft failure	**1 Fungal infection**
	1 Viral infection	**1 Accident**
	1 Secondary AML	

Haploidentical HSCT (34+ selection)



22 pts

Myeloablative regimen; Cyclo, Bu, Flu,Thiotepa and ATG

GVHD prophylaxis

CSA

Sodani et al, Blood 2010

Cyclophosphamide post HSC Infusion

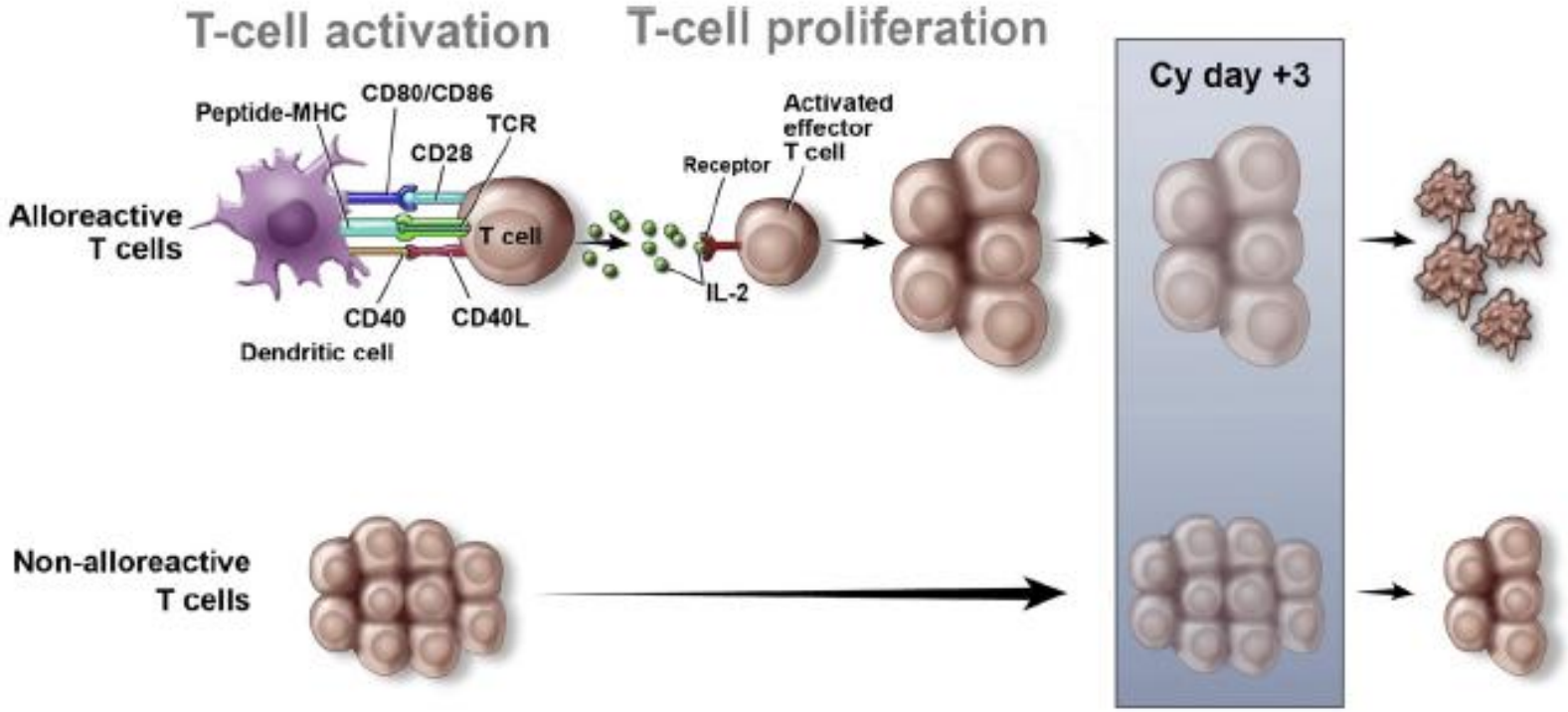


Figure 1. Activated T cells are relatively more sensitive to the effects of cyclophosphamide compared to resting T cells. Following nonmyeloablative conditioning, both donor and host T cells are exposed to alloantigens, resulting in activation and proliferation of T cells capable of host-versus-graft and graft-versus-host reactions. Expansion of the alloreactive clones occurs in the first 3 days after transplant, at which point cyclophosphamide is given to deplete activated T cells. Hematopoietic stem cells and resting T cells are relatively resistant to cyclophosphamide, which preserves T cells that recognize viral antigens and enhances immune reconstitution.

All Thalassemia Patients May Be Cured with HSCT?

TFS in related or unrelated for all age group
(including pts age older than 10 yrs) in our center is 90%.

Haploindentical HSCT in 17 severe thalassemia patients
(11/17 pts age > 10 yr)
Reduced toxicity conditioning plus cyclophosphamide post transplant
Sixteen of 17 pts survived without thalassemia.
1 pt had GvHD gr IV. 2 had graft failure.
Event free survival rate 95%
Follow up time; 4-20 months

MRD vs MUD vs Haplo-HSCT

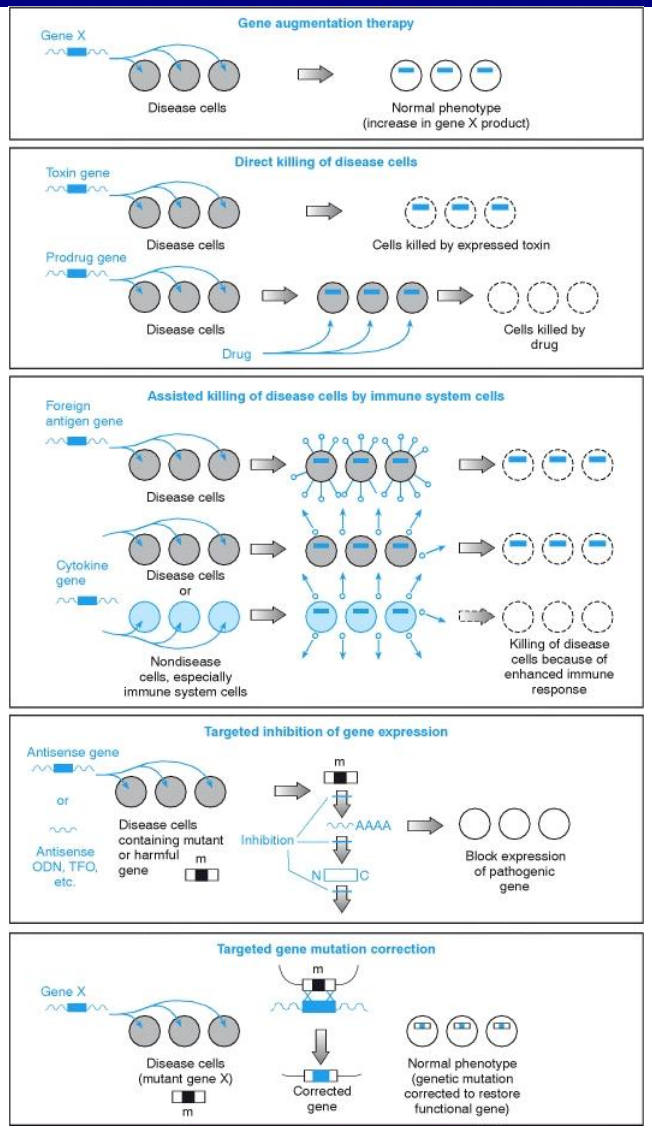
Event free survival rates

MRD (n = 65) = 88%
MUD (n = 33) = 82%
Haplo (n = 17) = 95%

p = 0.49

Gene Therapy

Methods of Gene Therapy



Transfusion independence and *HMGA2* activation after gene therapy of human β-thalassaemia

Marina Cavazzana-Calvo[1,2]*, Emmanuel Payen[3,4,5]*, Olivier Negre[3,4,5,6], Gary Wang[7], Kathleen Hehir[8], Floriane Fusil[3,4,5], Julian Down[8], Maria Denaro[8], Troy Brady[7], Karen Westerman[8,9], Resy Cavallesco[9], Beatrix Gillet-Legrand[6], Laure Caccavelli[1,2], Riccardo Sgarra[10], Leila Maouche-Chrétien[3,4], Françoise Bernaudin[11], Robert Girot[12], Ronald Dorazio[8], Geert-Jan Mulder[8], Axel Polack[8], Arthur Bank[13], Jean Soulier[5], Jérôme Larghero[5], Nabil Kabbara[5], Bruno Dalle[5], Bernard Gourmel[5], Gérard Socie[5], Stany Chrétien[3,4,9], Nathalie Cartier[14], Patrick Aubourg[14], Alain Fischer[1,2], Kenneth Cornetta[15], Frédéric Galacteros[16], Yves Beuzard[3,4,5], Eliane Gluckman[5], Frederick Bushman[7], Salima Hacein-Bey-Abina[1,2]* & Philippe Leboulch[3,4,9]*

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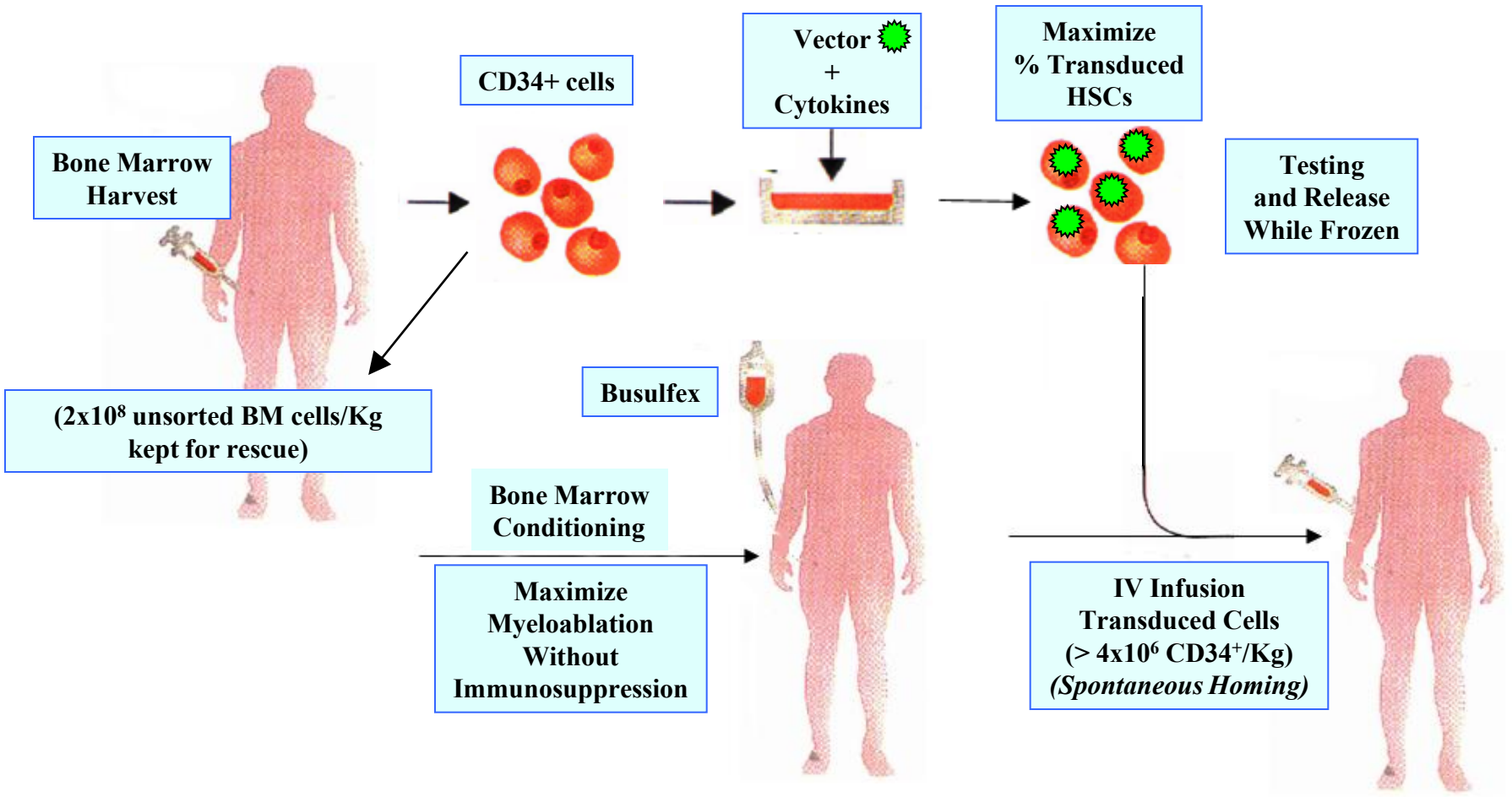
Overview of the clinical protocol



bluebirdbio™

Abstract # 549

Initial results from the Northstar Study (HGB-204): A Phase 1/2 Study of Gene Therapy for β-Thalassemia Major via Transplantation of Autologous Hematopoietic Stem Cells Transduced *Ex-Vivo* with a Lentiviral $\beta^{A\text{-}T87Q}$-Globin Vector

Alexis A. Thompson, John E. J. Rasko, Suradej Hongeng, Janet L. Kwiatkowski, Gary Schiller, Christof von Kalle, Marina Cavazzana, Philippe Leboulch, Alexandria Petrusich, Sandeep Soni, Mark C. Walters

Subject and Cellular Product Characteristics

Subject Number	Age	Sex	Genotype	Birth Country	Splenectomy	Transfusion Requirement[a]	VCN in Cellular Product [b]	$CD34^+$ Cell Dose (x 10^6/kg)
1102	18	F	β^0/β^E	USA	Yes	137	1.0/1.1	6.5
1104	21	F	β^0/β^E	Thailand	No	153	0.7/0.7	5.4
1106	20	F	β^0/β^0	Pakistan	No	197	1.5	13.5
1107	26	F	β^0/β^0	Australia	No	223	1.0	15.0
1108	18	F	β^0/β^+	USA	Yes	144	0.9	7.9
1109	29	M	β^0/A^c	USA	Yes	158	0.6/0.6	10.1
1110	33	F	β^0/β^0	USA	Yes	172	0.7	6.3

[a] mean pRBC requirement in cc/kg/year, over the 2 years prior to consent

[b] VCN= mean number of vector copies per CD34+ cell

[c] Subject 1109 has alpha gene triplication, resulting in an autosomal dominant beta thalassemia phenotype.

Clinical Safety for Infused Subjects

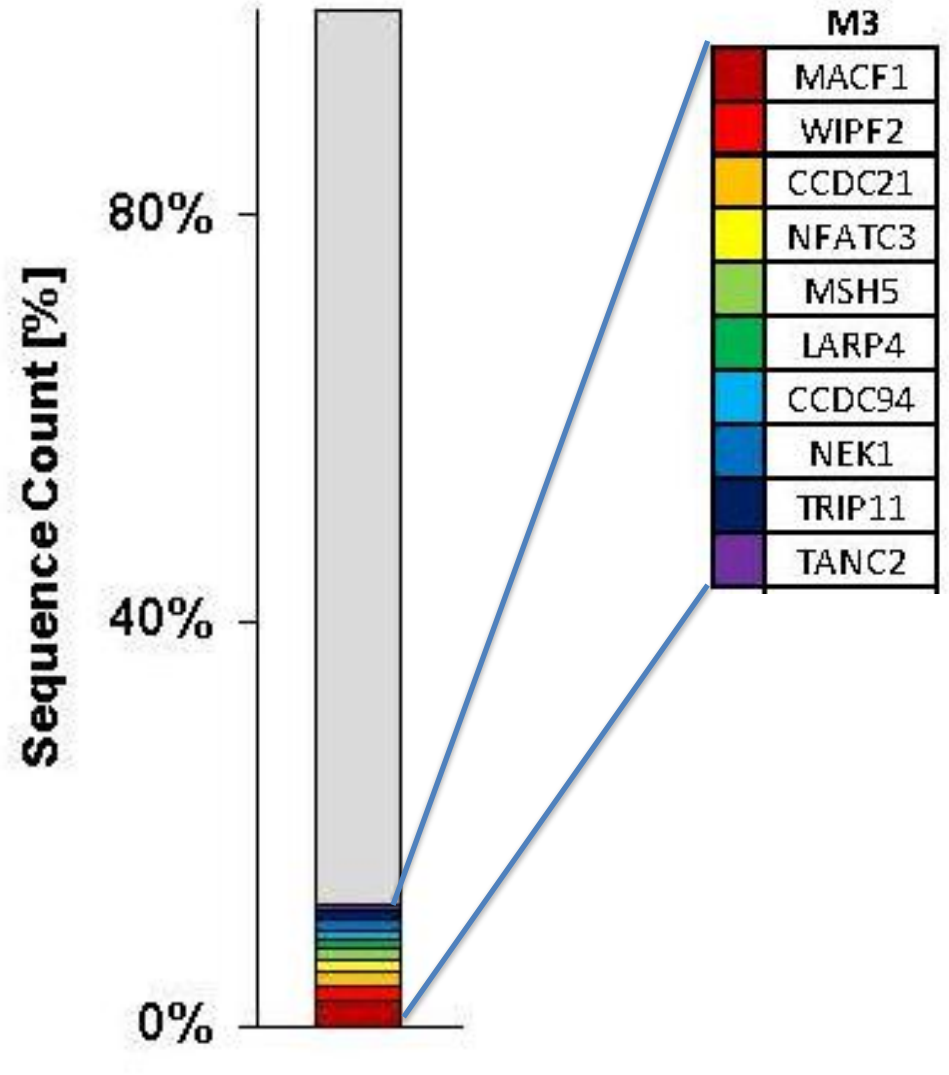
	Subject 1102	Subject 1106	Subject 1104	Subject 1107
Follow up period	6 months	3 months	2 months	1 month
Neutrophil engraftment ANC > 500/µL	Day +17	Day +29	Day +18	Day +14
Platelet engraftment Unsupported platelet count > 20,000/µL	Day +28	Day +30	Day +31	Day +27
Non-laboratory ≥Grade 3 AEs	• Mucositis • Bacteremia • Febrile neutropenia	• Mucositis • Epistaxis • Febrile neutropenia	• Mucositis	• Mucositis • Infection • Headache
SAEs post-infusion	None	None	Catheter Thrombosis	None

As of 21 November 2014
Subject 1108 was infused 06Nov2014 and no data is available

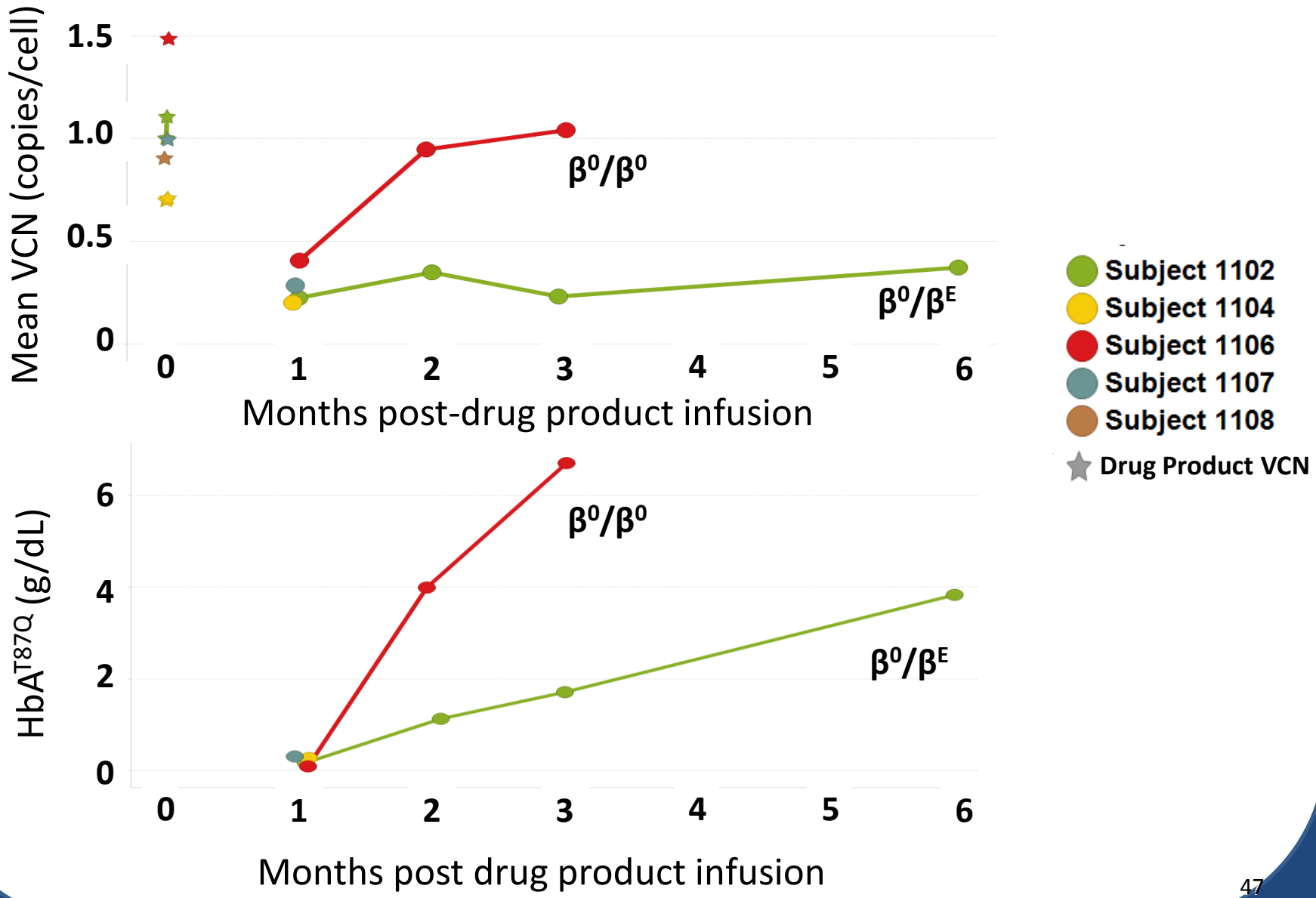
- **All AEs consistent with myeloablative conditioning**
- **No ≥Grade 3 AEs related to drug product, no RCL at 3 and 6 months**

Integration Site Analysis: Subject 1102 at Month 3

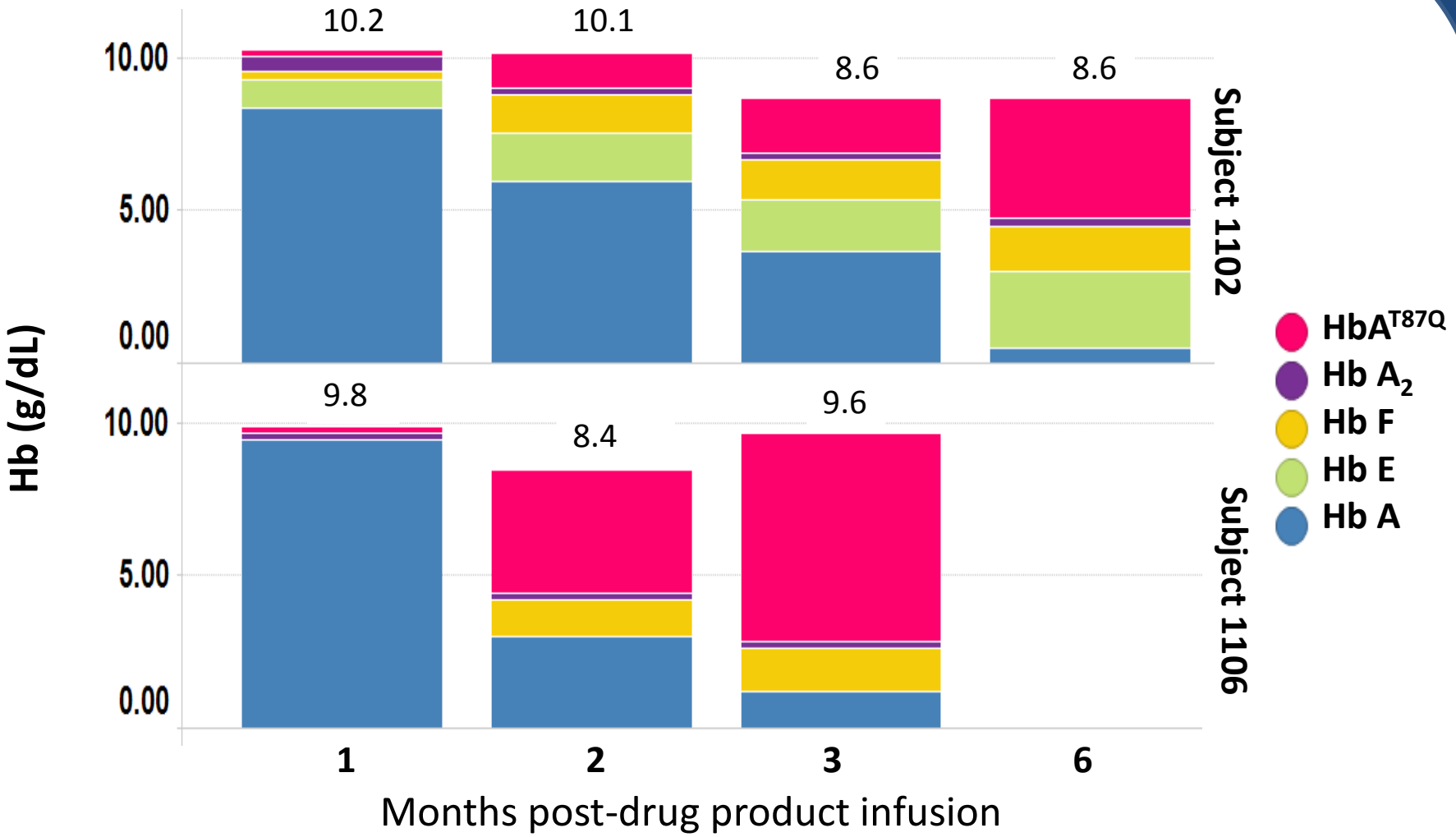
- 2393 unique gene-marked clones identified
- No clonal dominance observed
- Top 10 clones combined represent 12.4% of all clones detected
- Early polyclonal repopulation



VCN and HbA^{T87Q} in Peripheral Blood



Hemoglobin Fractions in Whole Blood



- Subject 1102 (β^0/β^E) producing **3.8** g/dL HbA^{T87Q} at 6 Months
- Subject 1106 (β^0/β^0) producing **6.8** g/dL HbA^{T87Q} at 3 Months

Conclusion

Outcomes of HSCT for thal in both MRD and MUD are favorable.

Outcomes of HSCT for all age group among thal pts are also favorable.

Whether the novel RTC regimen should be studied in younger thalassemia patients is needed to be investigated.

Autologous HSC with gene addition may give a new hope for cure for thal patients.

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