Update of Hematopoietic cell transplantation and gene therapy for thalassemia major

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- **HLA – identical HCT**
- **Unrelated donor HCT (marrow and UCB)**
- **HLA haploidentical BMT**

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Factors Influencing Survival after HLA-ID HCT

Risk Classification Pesaro

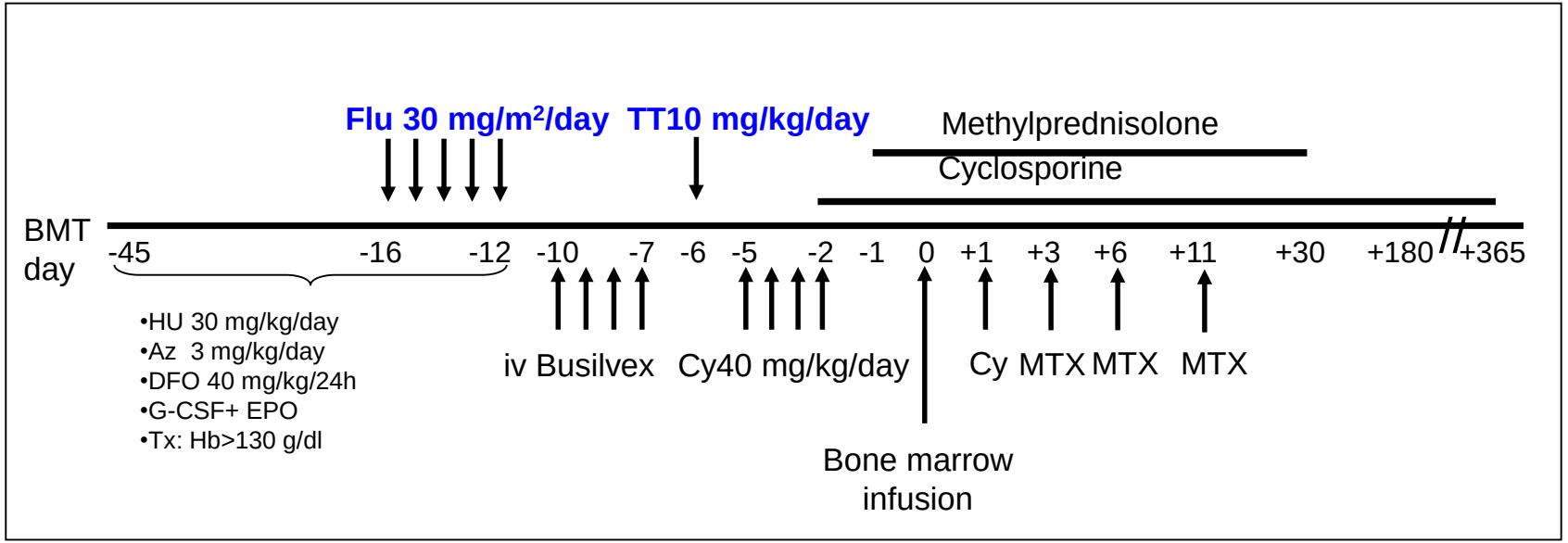
	Hepatomegaly >2 cm	Liver fibrosis	Chelation history
Class 1	No	No	Regular
Class 2	No/Yes	No/Yes	Regular/Irregular
Class 3	Yes	Yes	Irregular

Other (Mathews/Sabloff)

	Hepatomegaly >2 cm (Sabloff) or >5 cm (Mathews)	Age >7y
Good	No	No
Poor	Yes	Yes

[1]Lucarelli G et al NEJM, 1990, 322:417-21
[2]Lucarelli G et al Hemat Oncol Clin North Am 1991,5:549–56.
Mathews V et al BBMT 2007, 13:889
Sabloff M et al Blood 2011, 117:1745

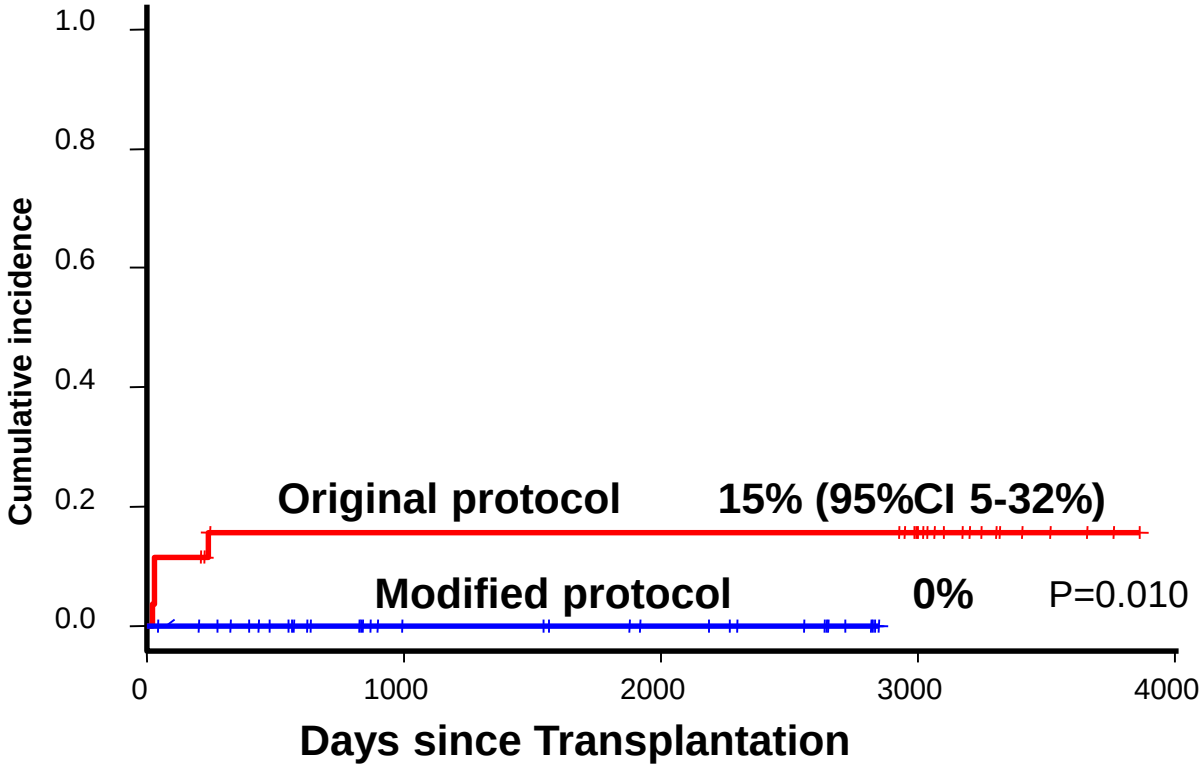
Class 3 Thalassemia
Modified Protocol 26. February 2007



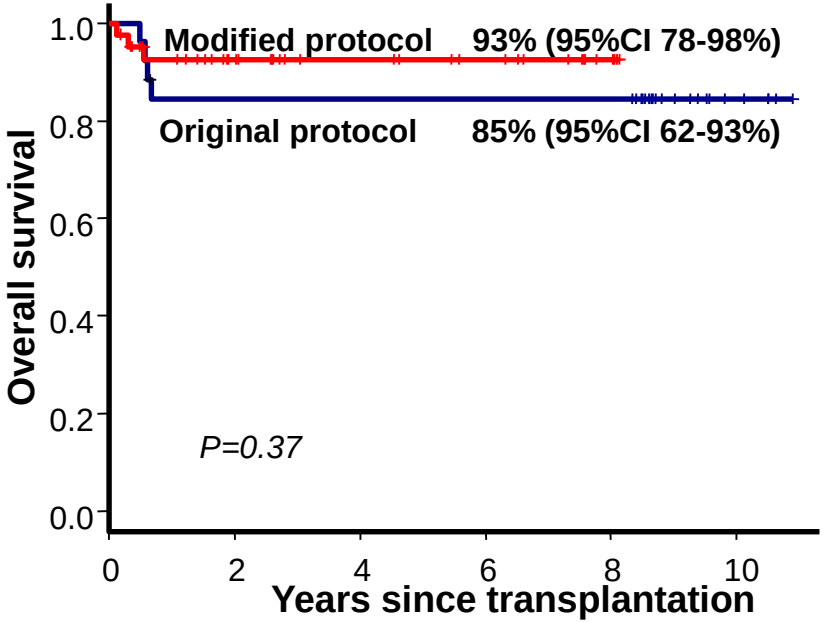
Hu indicates hydroxyurea; Az, azathioprine; DFO, deferoxamine; G-CSF, growth factor; EPO, erythropoietin; Tx, transfusions; Flu, fludarabine; TT, thiotepa; Cy, cyclophospamide; MTX, methotrexate; iv, intravenous.

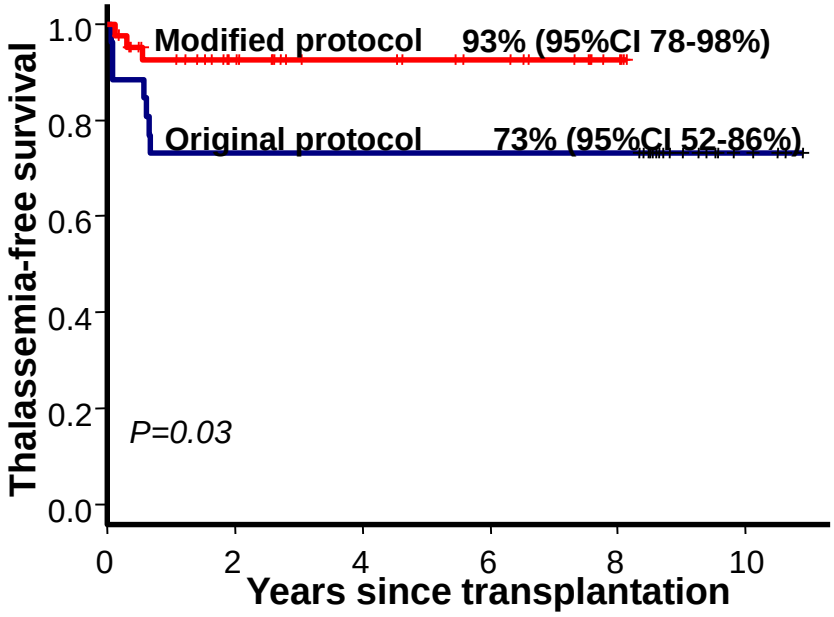
Gaziev J et al. Transplantation 2015 (Epub ahead of print)

Rejection


1.0
0.8
0.6
0.4
0.2
0.0
Cumulative incidence
Original protocol
15% (95%CI 5-32%)
Modified protocol
0%
P=0.010
0
1000
2000
3000
4000
Days since Transplantation

Survival and Thalassemia-free Survival





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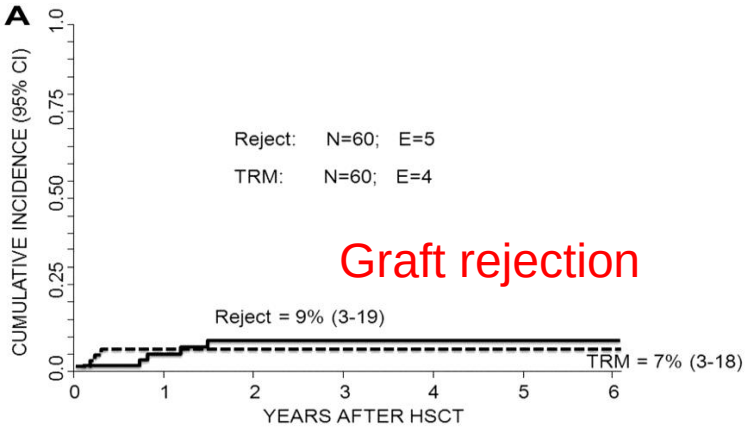
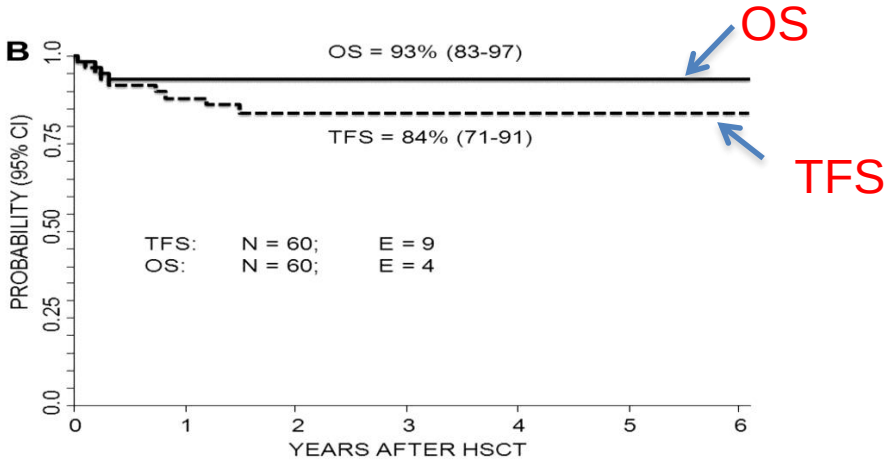
URTH trial – URD HCT for thal major (N=33)

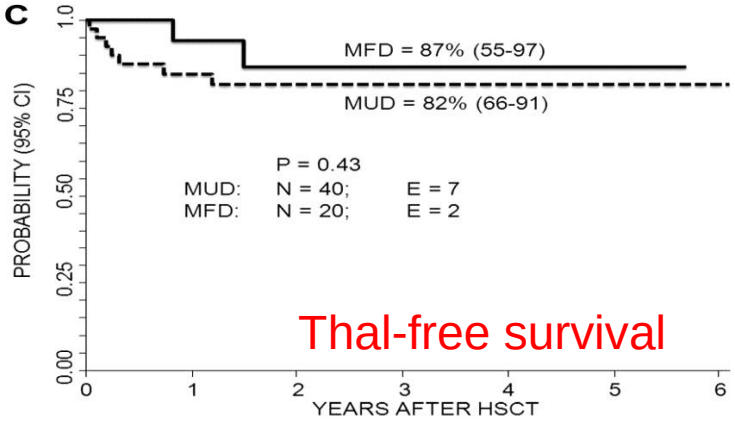
- **Median age 10y (BM) and 3.5y (UCB) with range, 1-17 years**
- **Received marrow (17) or UCB (16)**
- **HU, Campath, flu, thiotepa and melphalan**
- **Graft rejection in 1; cGVHD 29% (BM) and 23% (UCB)**
- **6 deaths related to infection, GVHD, or alveolar hemorrhage**
- **OS and EFS – 82% and 79%, respectively**

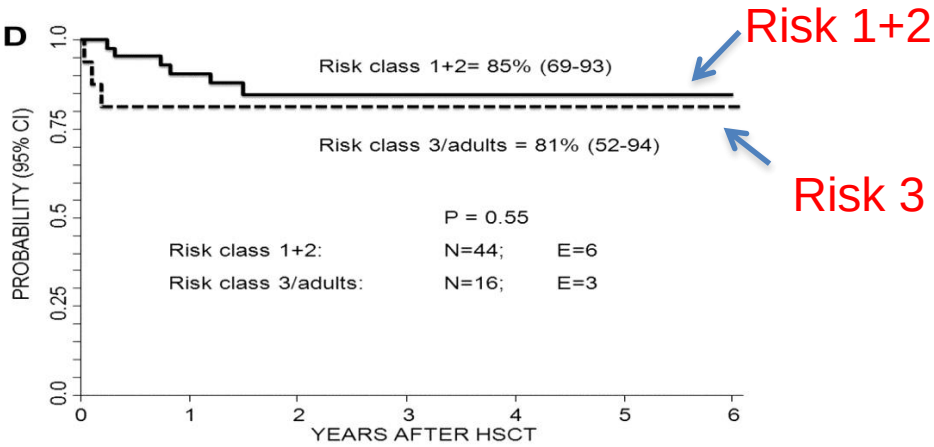
Shalani S et al. in preparation

Treosulfan-based conditioning for thalassemia major









Bernardo M E et al. Blood 2012;120:473-476

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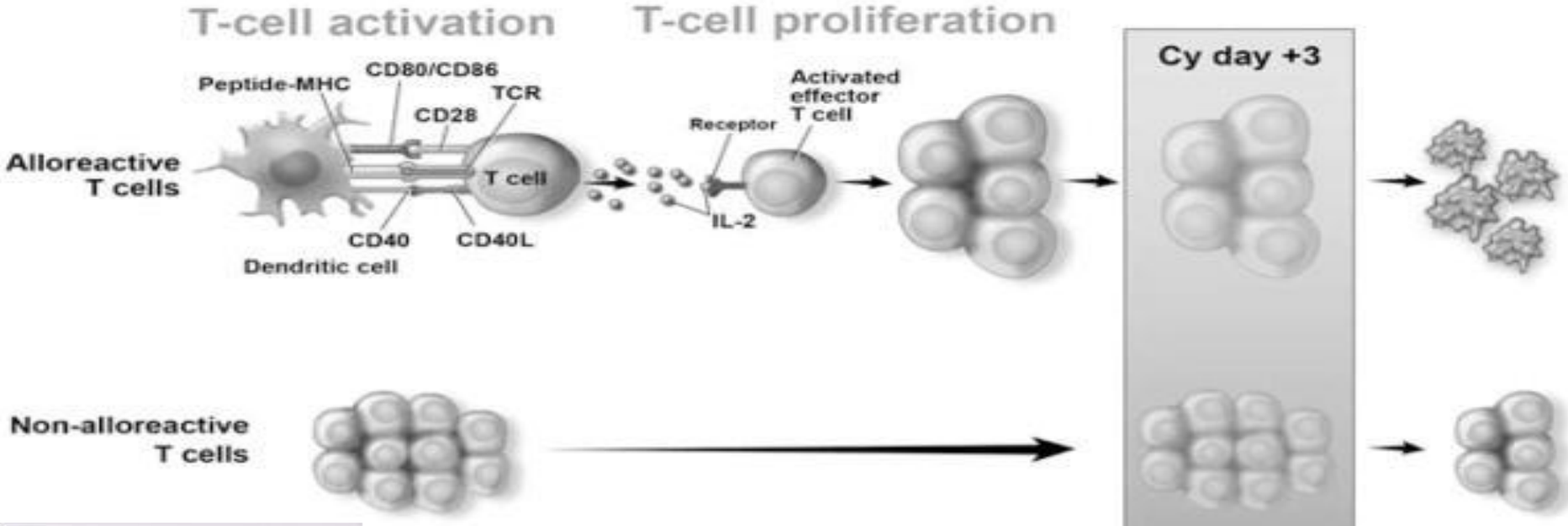
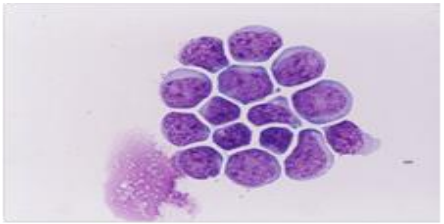
In Vivo T-cell depletion

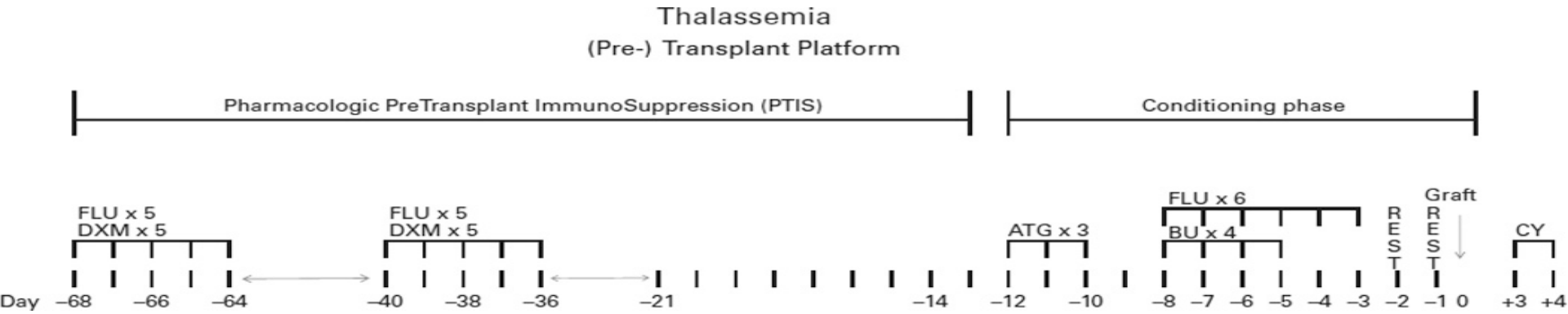




T-regulatory cells

BM CD34+ cells { **Express aldehyde dehydrogenase** }

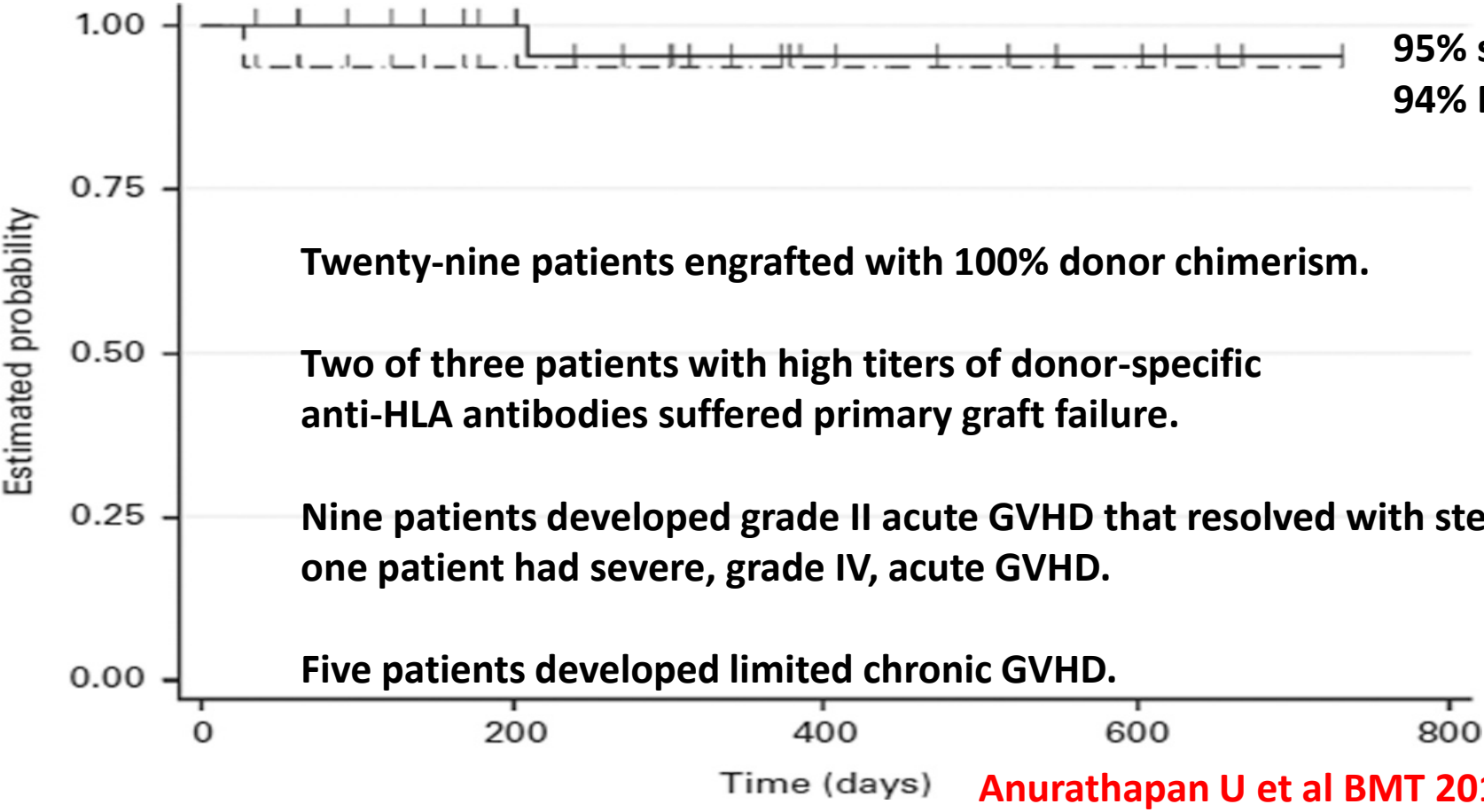
HCT for β Thalassemia and β Thalassemia/Hemoglobin E Patients from Haploidentical Donors



Thirty-one patients underwent haplo-SCT.
Their median age was ten years (range, 2 to 20 years).
Four patients had homozygous β-thalassemia and 27 had β-thalassemia/hemoglobin E.
Eleven patients received PBPC from the father and twenty patients from the mother.

Anurathapan U et al BMT 2016, 51:813

HCT for β Thalassemia and β Thalassemia/Hemoglobin E Patients from Haploidentical Donors



95% survival
94% EFS

Twenty-nine patients engrafted with 100% donor chimerism.

Two of three patients with high titers of donor-specific anti-HLA antibodies suffered primary graft failure.

Nine patients developed grade II acute GVHD that resolved with steroids, one patient had severe, grade IV, acute GVHD.

Five patients developed limited chronic GVHD.

Anurathapan U et al BMT 2016, 51:813

- **Gene therapy for transfusion-dep thalassemia**

- **Genomic editing**

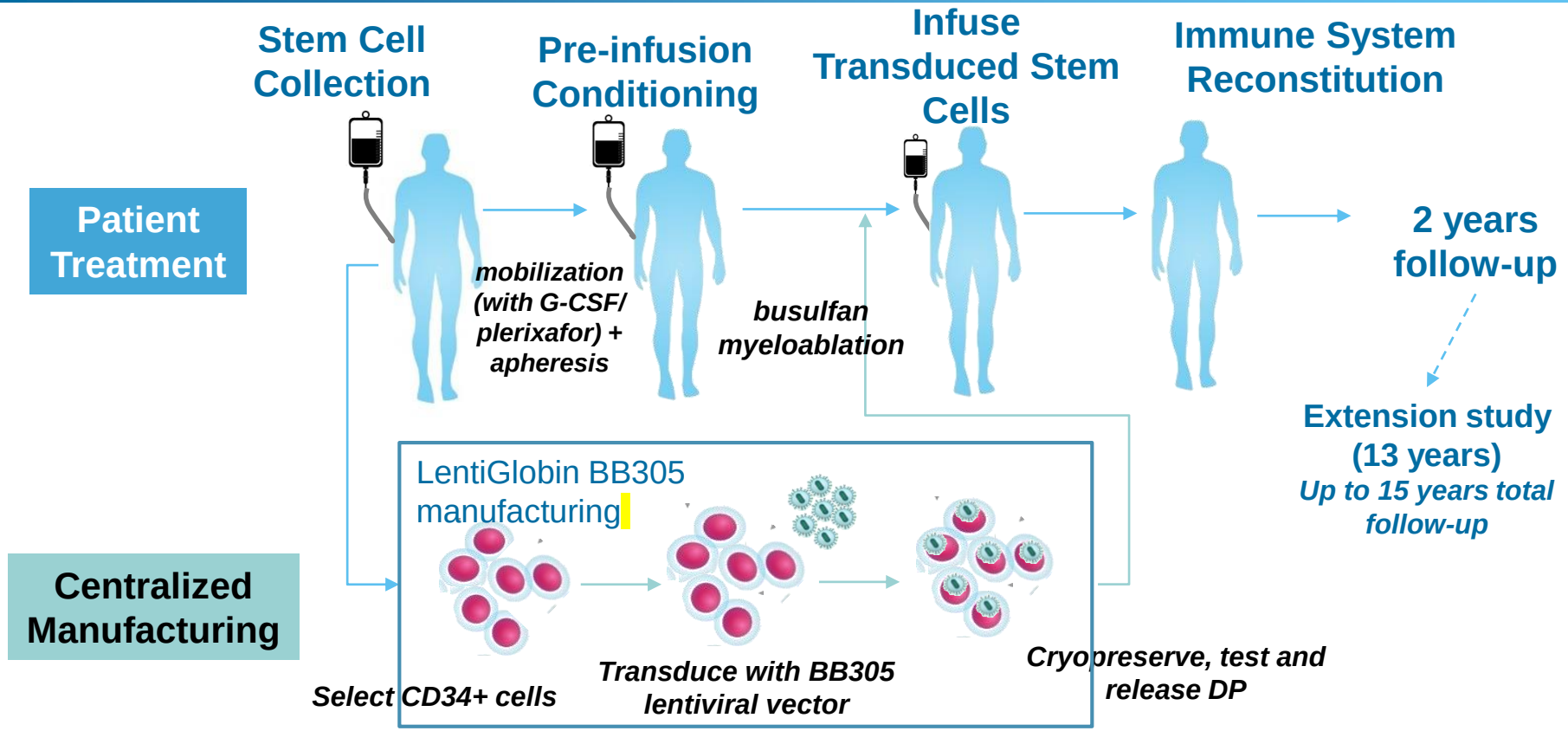
Northstar (HGB-204) study of LentiGlobin BB305 gene therapy in TDT

- International, multi-center, Phase 1/2, open-label, single-arm study in adolescents/adults with TDT
- Primary objectives: Safety and efficacy of LentiGlobin BB305 Drug Product in transfusion-dependent β-thalassemia (TDT)
- 18 treated patients (fully enrolled)
  - Ages 18-35y (N=15), 12-17y (N=3)
  - Transfusion dependence: ≥8 red blood cell (pRBC) transfusions/year or ≥100mL/kg/year in the 2 years before enrollment

Status

All 18 patients have ≥ 6 months follow-up
2 patients have completed 2-year analysis

Overview of the clinical protocol



Safety summary

N=18 treated patients

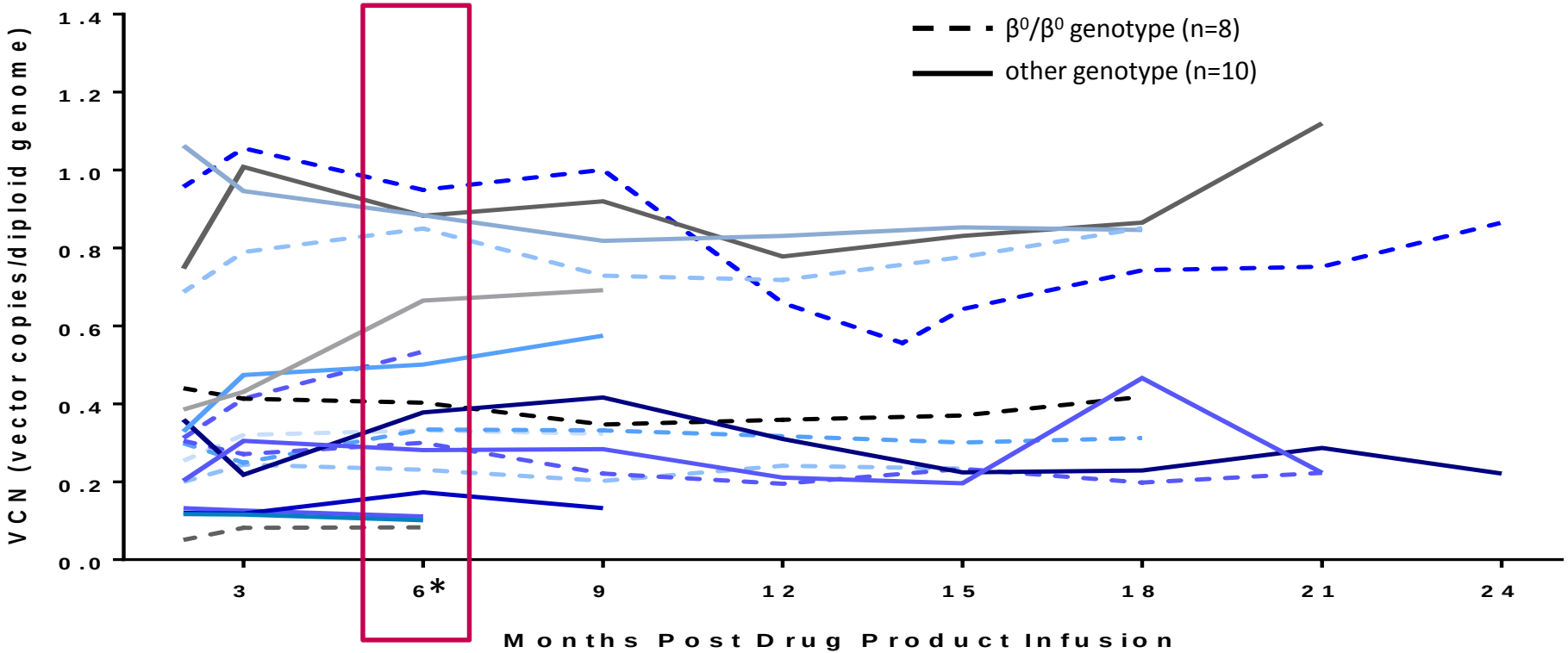
Non-laboratory[1] Grade ≥3 non-serious AEs reported in ≥2 patients	Incidence[2]
Stomatitis	12
Febrile neutropenia	10
Pharyngeal inflammation	5
Epistaxis	2
Fever	2

All Serious AEs	Incidence[2]
Veno-occlusive liver disease (Grade 3)	2
Appendicitis (Grade 3)	1
Cellulitis (Grade 3)	1
Thrombosis in central catheter (Grade 2)	1
Intracardiac thrombus (Grade 3)	1

- Six Grade 1 adverse events (AEs) related or possibly related to LentiGlobin

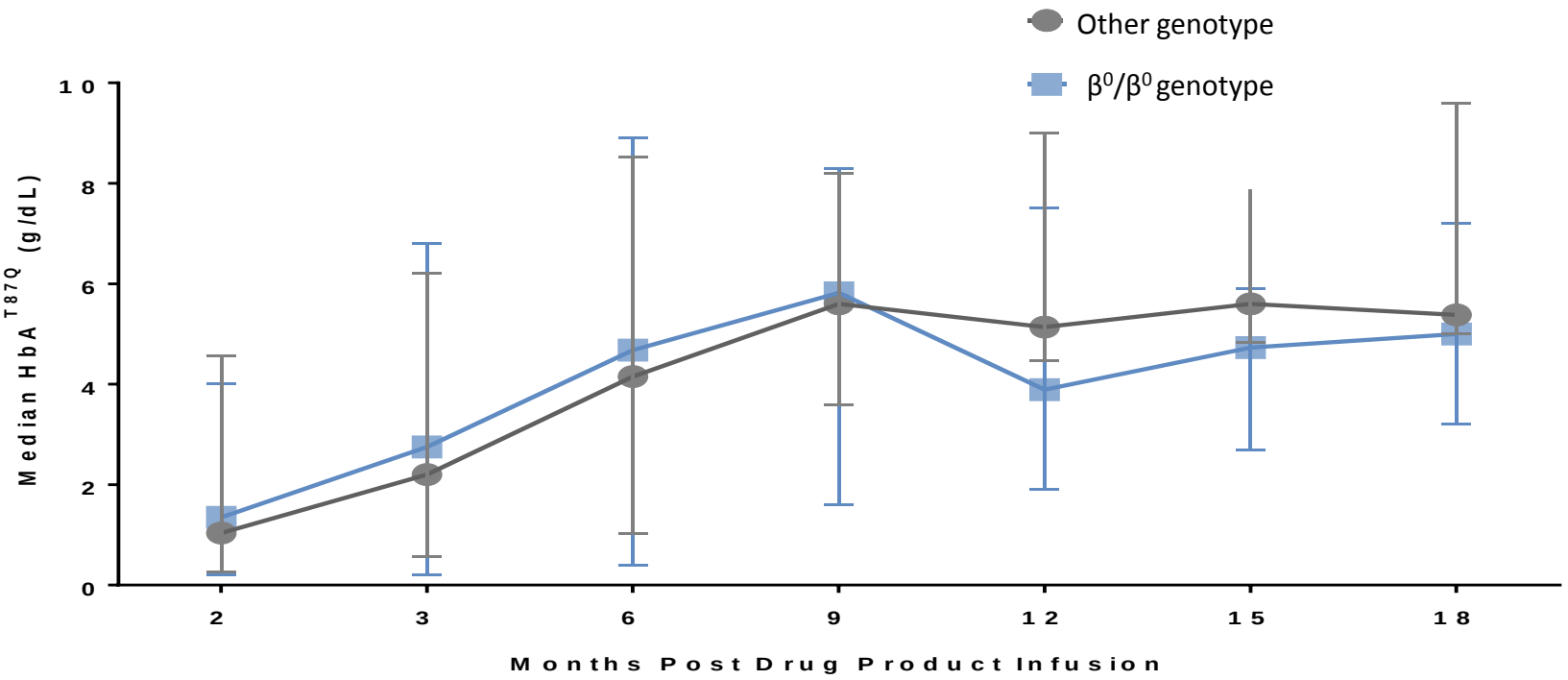
1. Hematologic laboratory parameters commonly abnormal post-transplant have been excluded from this table
2. Incidence from start of conditioning (Day -8) to data cut-off

VCN in peripheral blood over time



*Median peripheral VCN at month 6: β0/β0 genotype 0.3 [range 0.1-1.0]; other genotype 0.4 [range 0.1-0.9]

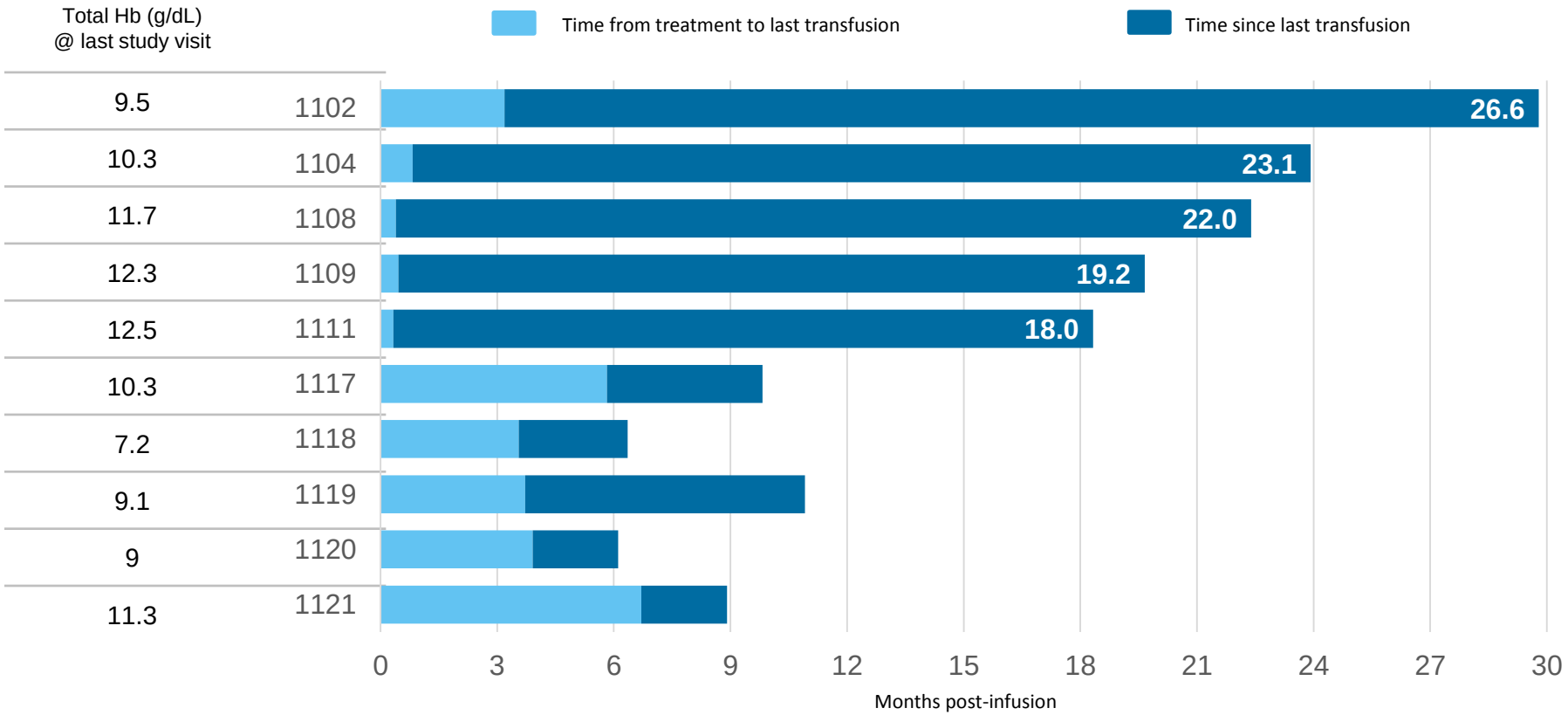
HbA^{T87Q} production increases to month 9, then stabilizes



N:	**18**	**18**	**18**	**14**	**10**	**10**	**8**
Median (g/dL)	**1.1**	**2.6**	**4.6**	**5.6**	**4.9**	**5.1**	**5.4**

data as of September 16, 2016

Patients with non-β^0/β^0 genotypes and ≥1 year follow-up have 18 to 27 months since last RBC transfusion



Median follow-up for patients with non-β^0/β^0 genotypes (N=10) 14.7 months (range 6.3-29.8)

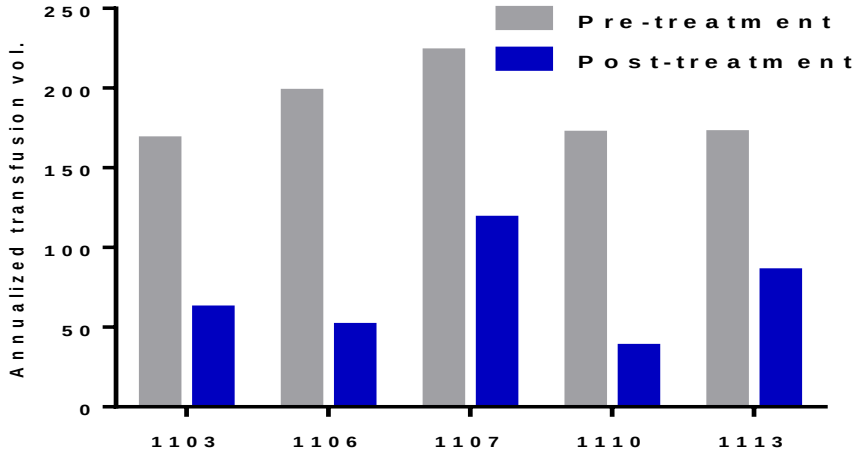
data as of September 16, 2016

Reduction in RBC transfusion requirements in patients with β^0/β^0 genotypes with ≥12 months follow-up

63%

Median Reduction in Transfusion Volume

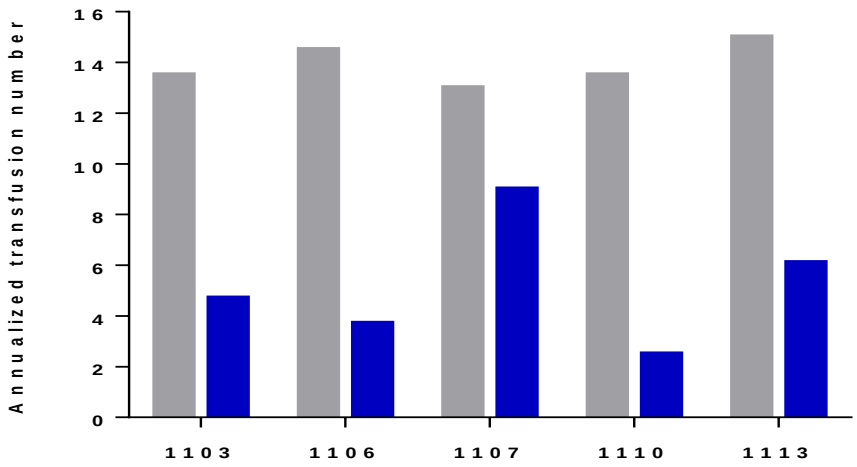
(range 47%-78%)



65%

Median Reduction in Number of Transfusions

(range 31%-81%)

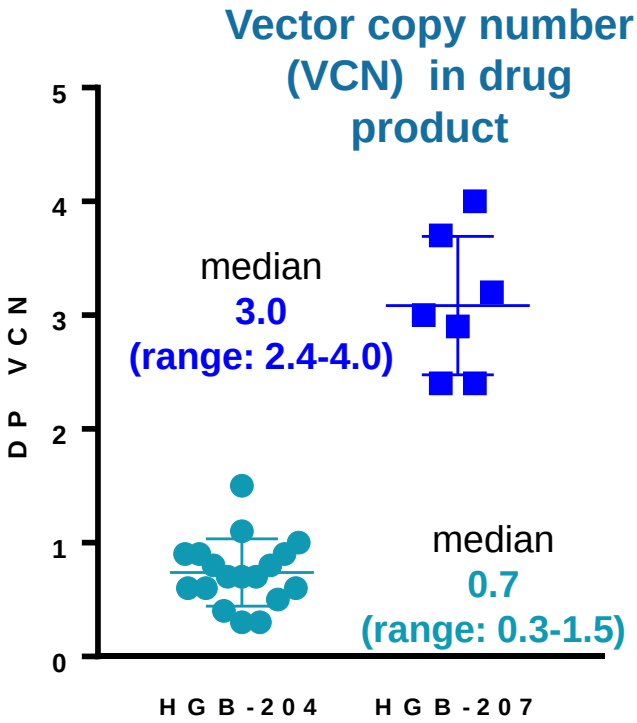


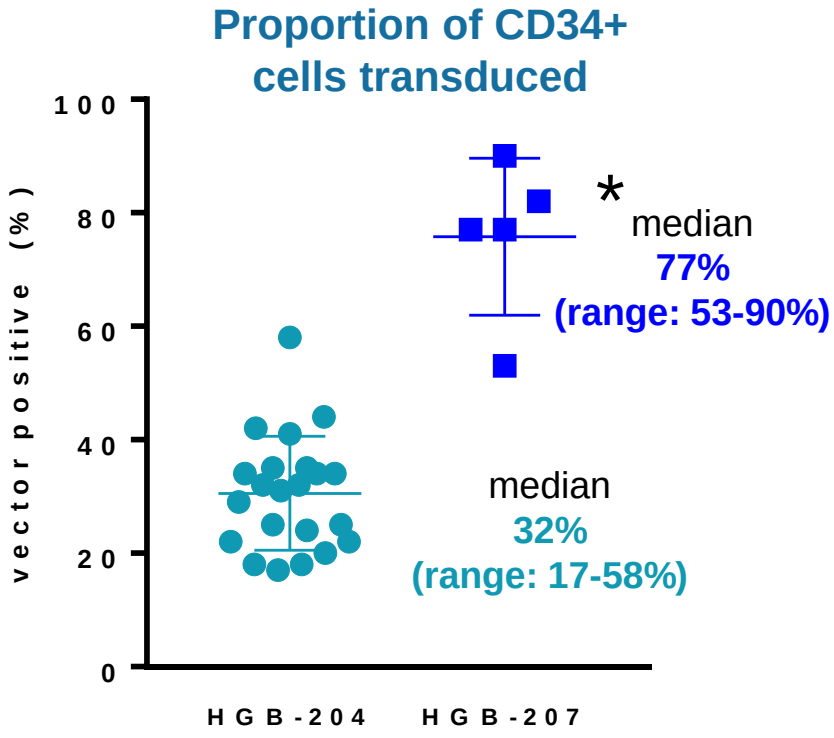
Post-treatment: annualized on-study volume and number of transfusions based on observed values starting at month 6 through data cut-off

Median follow-up for patients with β^0/β^0 genotypes (N=8) 17.3 months (range 6.7-25.4)

data as of September 16, 2016

Refined manufacturing process yields higher drug product vector copy number and proportion of transduced cells

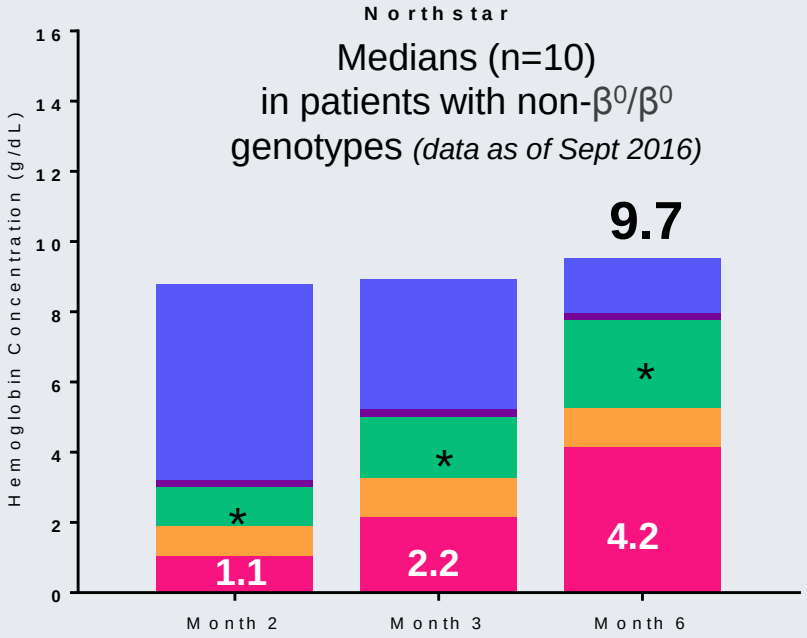




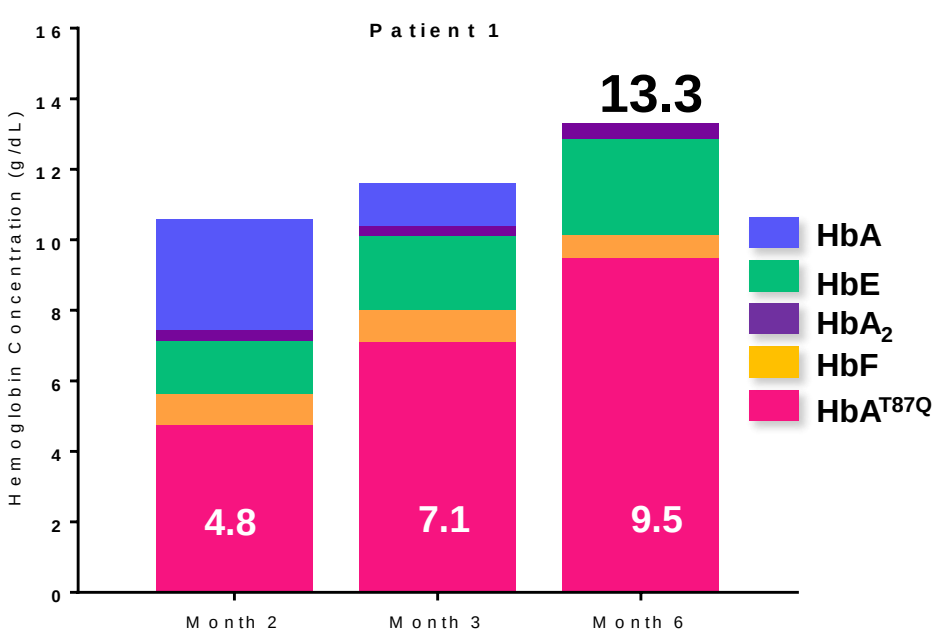
* Samples from EU manufacturing pending vector positive analysis

First patient treated in Northstar-2 achieved normal total Hb without transfusions

HGB-204



HGB-207



Last RBC transfusion: Day 33

* n=6 patients in Northstar study with HbE genotype

Northstar 3 (HGB-212)

HGB-212

β^0/β^0 genotypes

Phase 3, multi-center, global study

- N=15 adults, adolescents and pediatric patients
- **Initiation planned for 2017**

- **Gene therapy for transfusion-dep thalassemia**

- **Genomic editing**

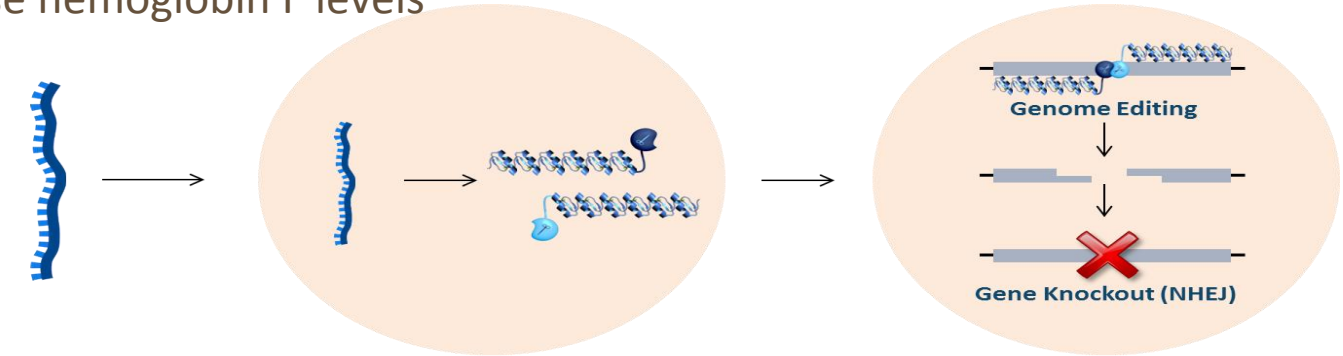
Sangamo-Bioverativ Partnership is Developing a New Therapy for β-thalassemia using ZFNs

Technology

Zinc finger nuclease (ZFN)-mediated non-viral gene therapy for beta-thalassemia is based on the use of genome-editing technology to modify a patient's own blood stem cells to increase hemoglobin F levels

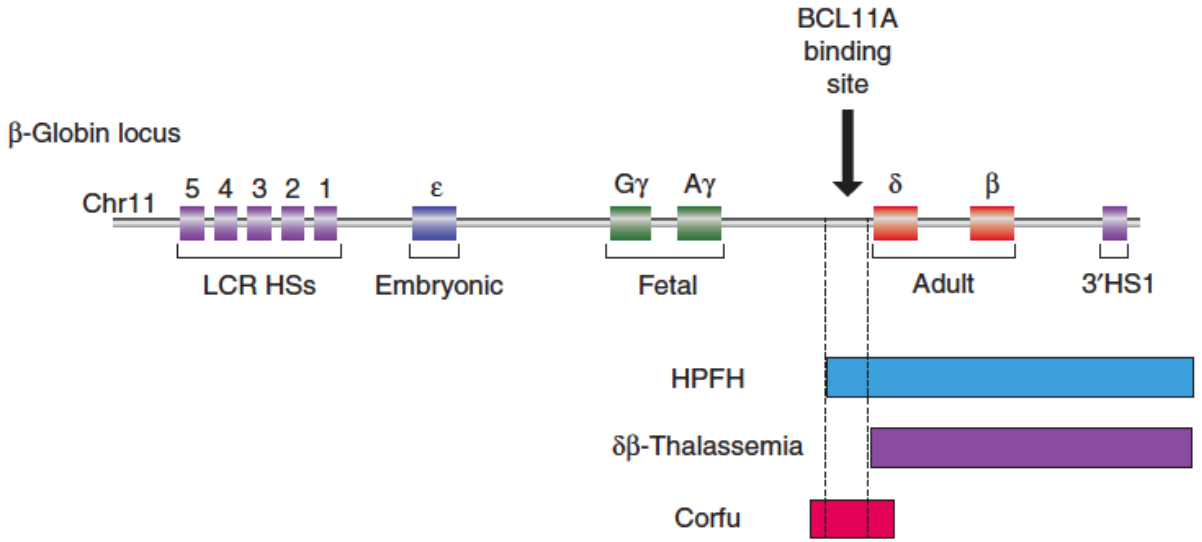
Potential Clinical Profile

Trials will explore potential to reduce symptoms in transfusion-dependent β-thalassemia



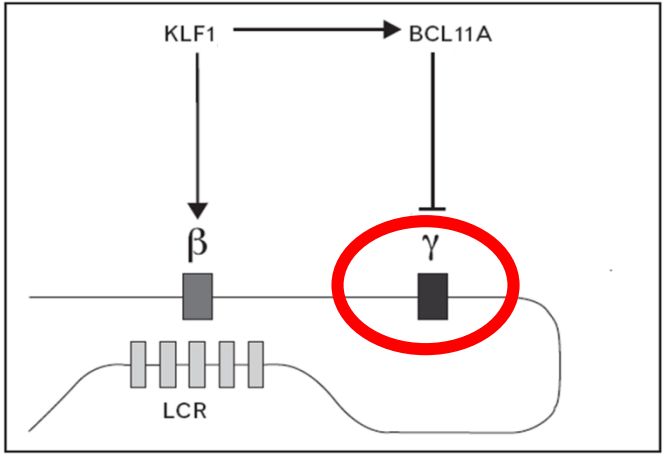
Modulators of Fetal hemoglobin
New Therapy for β-thalassemia using ZFNs

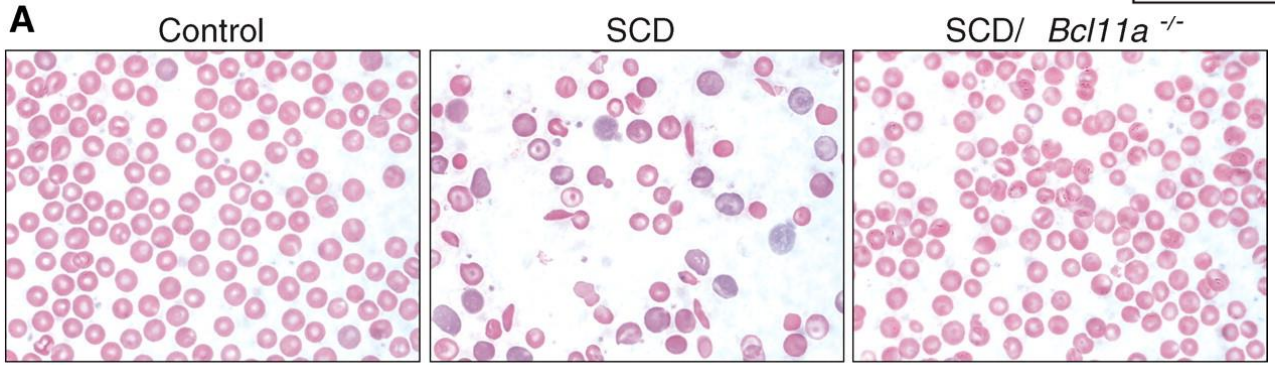
1. β-globin locus (chromo 11)
2. HBS1L-MYB intergenic region (chromo 6)
3. BCL11a (chromo 2)



Modulators of Fetal hemoglobin
New Therapy for β-thalassemia using ZFNs

Data from: Xu J, et al. Correction of sickle cell disease in adult mice by interference with fetal hemoglobin silencing. *Science*. 2011 334:993-6.





Summary and conclusions

- **LentiGlobin BB305 gene therapy shows promising results in TDT**
- **Toxicity profile remains consistent with single-agent busulfan conditioning, with no evidence of clonal dominance**
- **LentiGlobin VCN strongly correlated with HbA^{T87Q} level at Month 6**
- **Enhanced manufacturing procedure appears to be promising for increasing the VCN**
- **The future of curative therapies that will have broad availability might follow advances in gene therapy and genomic modification in HSCs**

HGB-204 study sites and investigators

Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University
- Alexis Thompson
- Morris Kletzel
- Katherine Hammond

Children's Hospital of Philadelphia, UPenn
- Janet Kwiatkowski
- Tamara Movsesova
- David Teachey

UCSF Benioff Children's Hospital, Oakland
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- Cyrus Bascon
- Marci Moriarty
- Elliott Vichinsky
- Ash Lal

German Cancer Research Center (DKFZ)
- Christof von Kalle

Groupe Hosp. Universitaire Ouest, Paris
- Marina Cavazzana-Calvo

University of California, Los Angeles
- Gary Schiller

Royal Prince Alfred Hospital, Sydney Medical School, University of Sydney
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- Joy Ho
- Linda Pallot
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- Mohammed Asmal
- Amy Findling
- Christina White

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