1st Cuneo City Immunotherapy Conference (CCITC)

Immunotherapy in Hematological Malignancies 2018

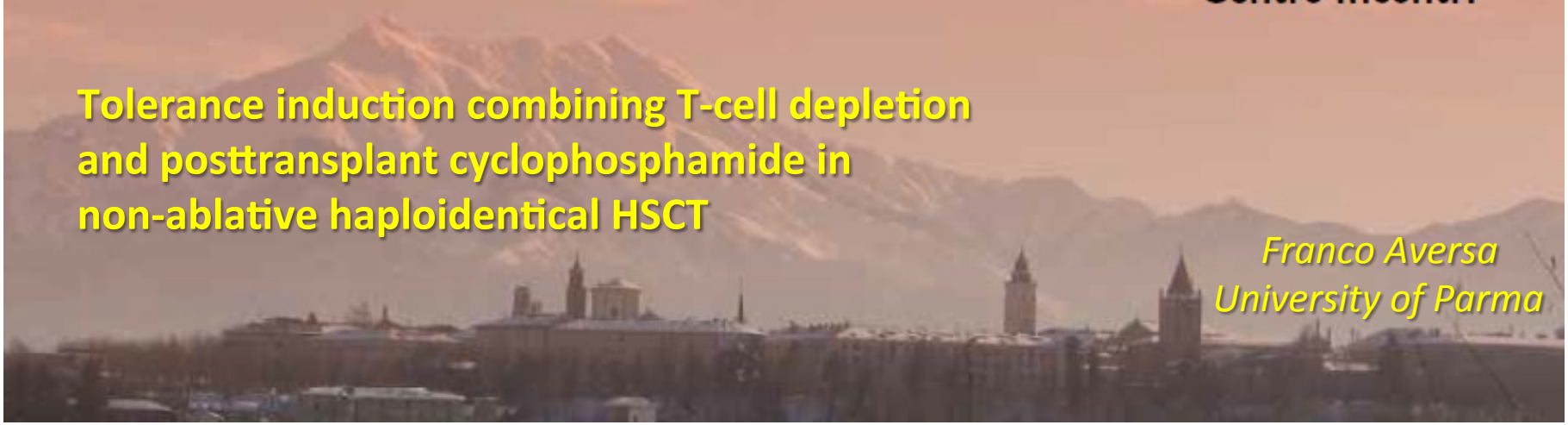
CUNEO

May 17-19, 2018

Centro Incontri

Tolerance induction combining T-cell depletion and posttransplant cyclophosphamide in non-ablative haploidentical HSCT

Franco Aversa
University of Parma



1st CUNEO CITY IMMUNOTHERAPY CONFERENCE (CCITC) - IMMUNOTHERAPY IN HEMATOLOGICAL MALIGNANCIES 2018

Cuneo, 17-19 maggio 2018

DICHIARAZIONE

Relatore: FRANCO AVERSA

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(GILEAD, MSD, ROCHE, ASTELLAS, PFIZER, BASILEA)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

TCD Haplo-HSCT in patients with Leukemia

Clinical problems:
Rejection & GvHD

→ **Mouse Models**

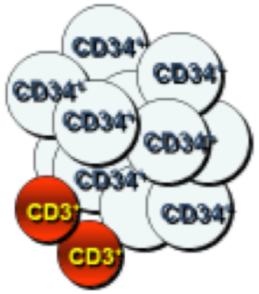
↓

Discovery of «veto» effect and Megadose

Haplo HSCT: MAC, immunoselected CD34⁺ cells, no post-Tx immune suppression.
(first pilot study launched in March 1993)

Myeloablative conditioning regimen

Megadose CD34⁺ (≥10 x 10⁶/kg)



Ex vivo T-cell depletion (CD3 ≤1 x 10⁴/kg)

No post-Tx immune suppression

Aversa et al
Blood 1994; NEJM 1998, JCO, 2005

gula activity of CD34+ cells: e nce for a ased mecha m mediated

GUR BLOOD, 15 MARCH 2005

li ugge at cells within the a endowed with ulatory *"veto like"* activity that ate their own engraftment.

The New England Journal of Medicine 1998;339:1186-93.

TREATMENT OF HIGH-RISK ACUTE LEUKEMIA WITH T-CELL–DEPLETED STEM CELLS FROM RELATED DONORS WITH ONE FULLY MISMATCHED HLA HAPLOTYPE

FRANCO AVERSA, M.D., ANTONIO TABILIO, M.D., ANDREA VELARDI, M.D., ISABEL CUNNINGHAM, M.D., ADELMO TERENZI, M.D., FRANCA FALZETTI, M.D., LOREDANA RUGGERI, M.D., GIULIANA BARBABIETOLA, M.D., CYNTHIA ARISTEI, M.D., PAOLO LATINI, M.D., YAIR REISNER, PH.D., AND MASSIMO F. MARTELLI, M.D.

VOLUME 23 · NUMBER 15 · MAY 20 2005

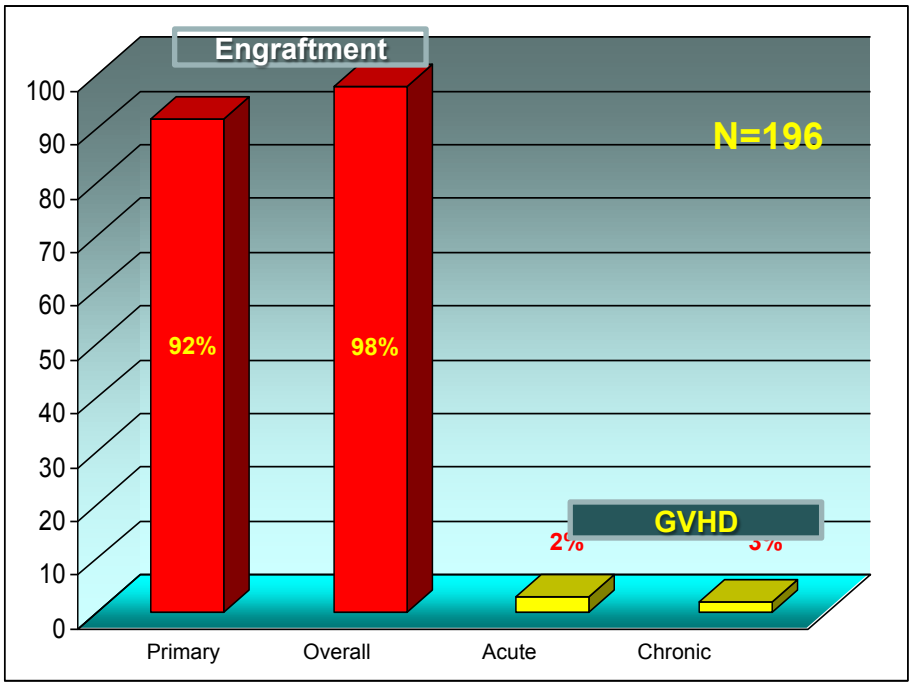
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Full Haplotype-Mismatched Hematopoietic Stem-Cell Transplantation: A Phase II Study in Patients With Acute Leukemia at High Risk of Relapse

Franco Aversa, Adelmo Terenzi, Antonio Tabilio, Franca Falzetti, Alessandra Carotti, Stelvio Ballanti, Rita Felicini, Flavio Falcinelli, Andrea Velardi, Loredana Ruggeri, Teresa Aloisi, Jean Pierre Saab, Antonella Santucci, Katia Perruccio, Maria Paola Martelli, Cristina Mecucci, Yair Reisner, and Massimo F. Martelli

Megadose TCD in haplo-HCT:

- can neutralize or tolerize host anti-donor T cells,
- can facilitate engraftment following a MAC
- prevents GVHD in the absence of any post- transplant immune suppressive therapy.



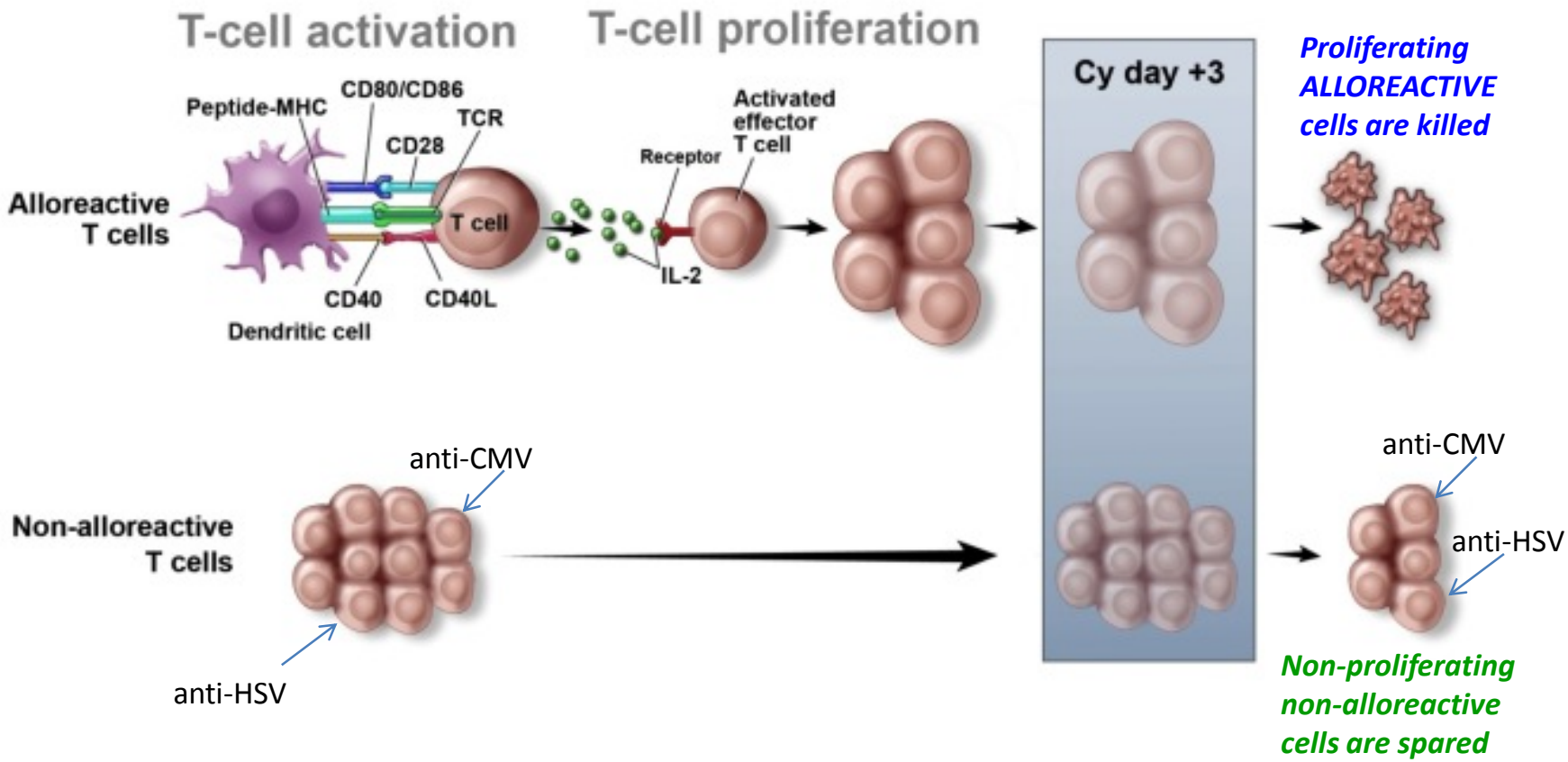
Challenge in HaploHSCT

- TCD haplo-HSCT, with its minimal risk of GVHD, if combined with a reduced intensity conditioning (RIC) could potentially offer safe treatment modality for:
  - Elderly,
  - Patients with hematological malignancies who cannot tolerate harsh conditioning,
  - Treatment of non-malignant hematological diseases.

Working Hypothesis

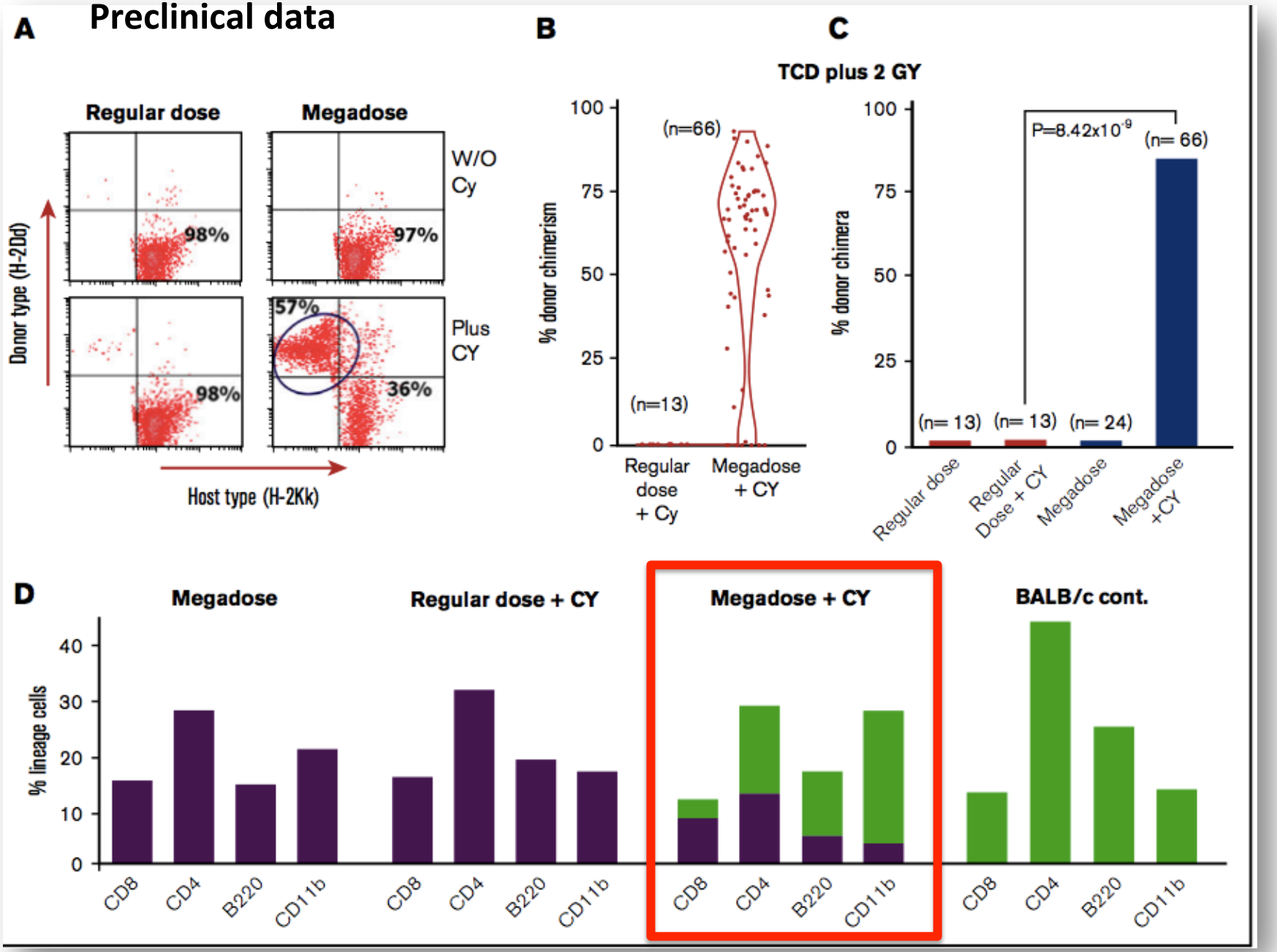
- **RIC** is associated with
  - High risk of graft rejection by the residual host T cells
- **Partial TCD (CD3/CD19**) is associated with
  - High risk of GvHD due to the infusion of CD3 > threshold for GVHD (>$1x10^5$/kg)
- **PTCY** is associated with
  - In vivo Depletion of bidirectional alloreactivity (HvG and GvH)

Selective allodepletion with high dose, post-transplantation cyclophosphamide (PT/Cy)



Luznik L et al, BBMT 2008.

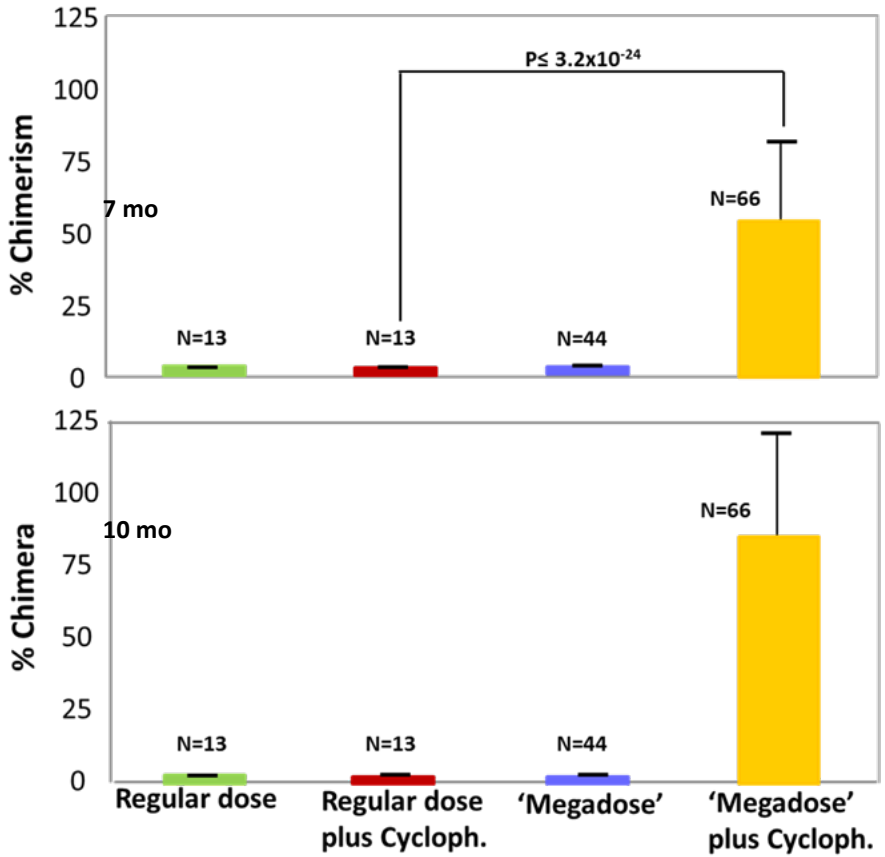
Preclinical data

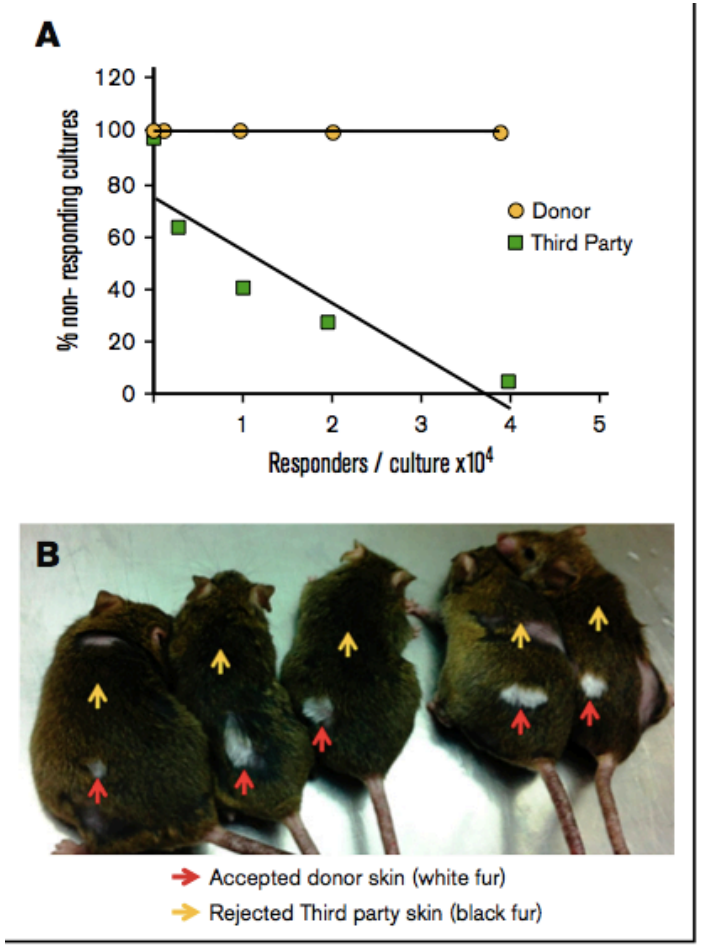


Aversa F, Reisner Y et al, Blood Adv 2017

Preclinical data

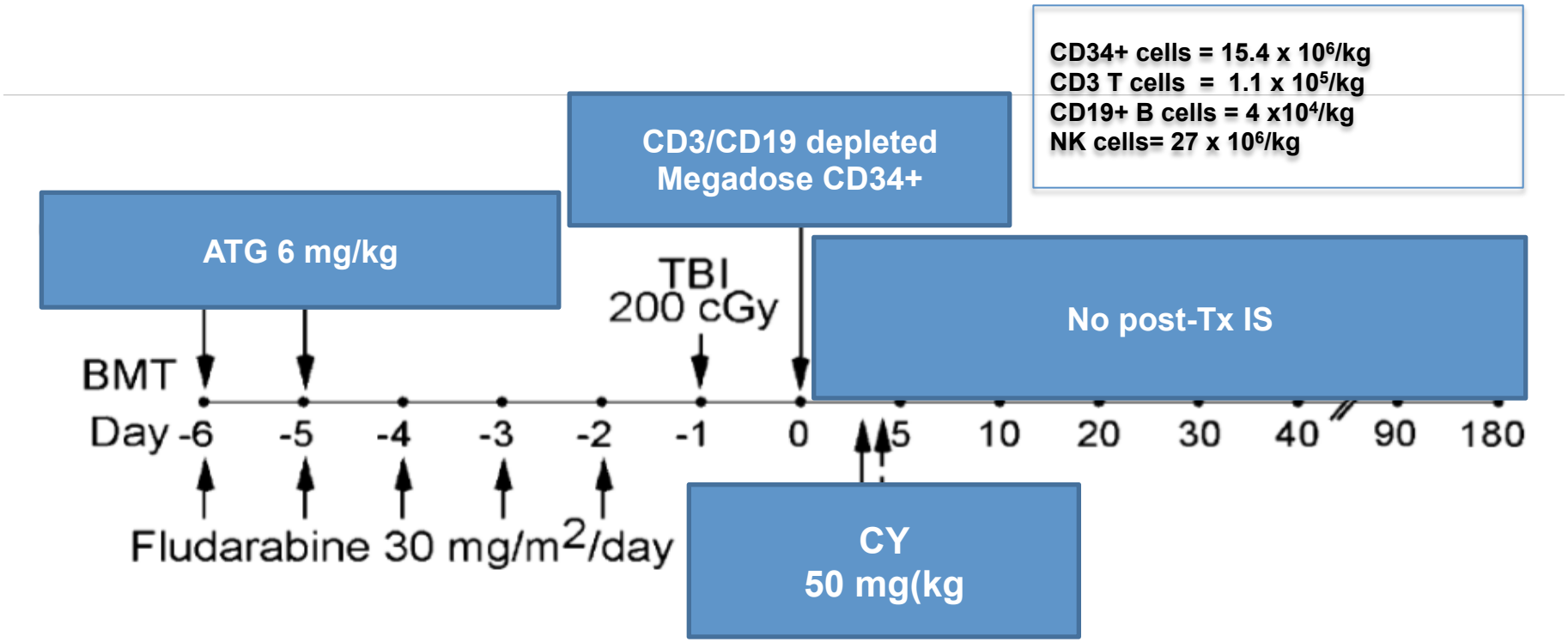
Chimerism Level:
7-10 Months after SCT





Aversa F, Reisner Y et al, Blood Adv 2017

Pilot clinical study



Luznik L et al, BBMT 2008.

EudraCT number studio clinico: 2013-003628-35

REGULAR ARTICLE

blood advances

Immune tolerance induction by nonmyeloablative haploidentical HSCT combining T-cell depletion and posttransplant cyclophosphamide

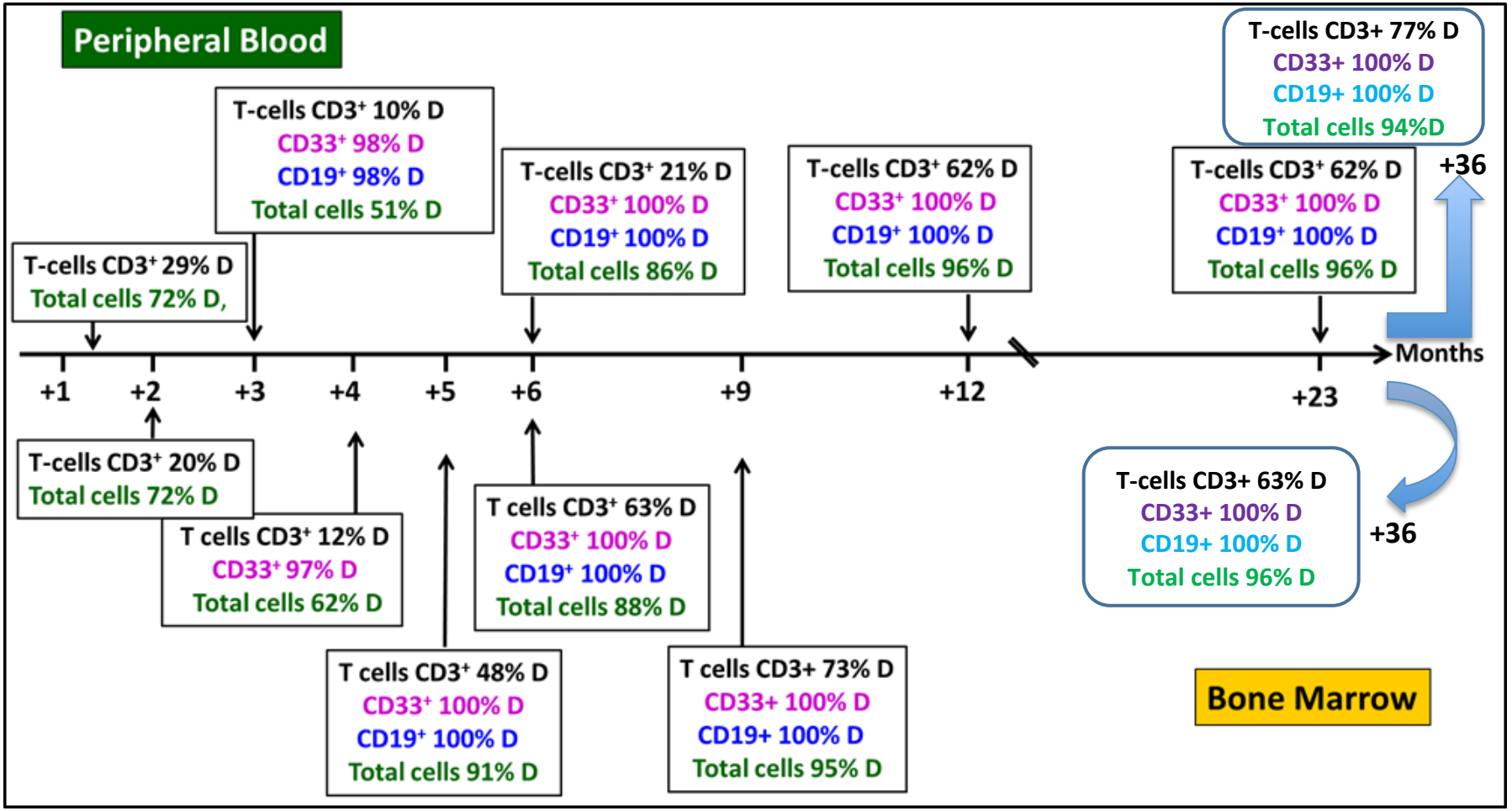
Franco Aversa,[1,*] Esther Bachar-Lustig,[2,*] Noga Or-Geva,[2] Lucia Prezioso,[1] Sabrina Bonomini,[1] Ilenia Manfra,[1] Alessandro Monti,[1] Chiara Schifano,[1] Yael Zlotnikov-Klionsky,[2] Massimo F. Martelli,[3] Gabriella Sammarelli,[1] Maria Sassi,[4] Maurizio Soli,[4] Silvia Giuliodori,[5] Magda Benecchi,[5] Nicola Giuliani,[1] Frank Lohr,[6] Silvia Pratissoli,[6] and Yair Reisner[2]

- Pt # 1
  - 54 y, male, MM, Tx June 2015
- Pt # 2
  - 50 y, male, MM, Tx Nov 2015
- Pt # 3
  - 49 y, female, HD, Tx Dec 2016

Aversa et al. Blood Adv 2017

Chimerism analysis at different time points (% donor cells out of the total PBMC and BM)

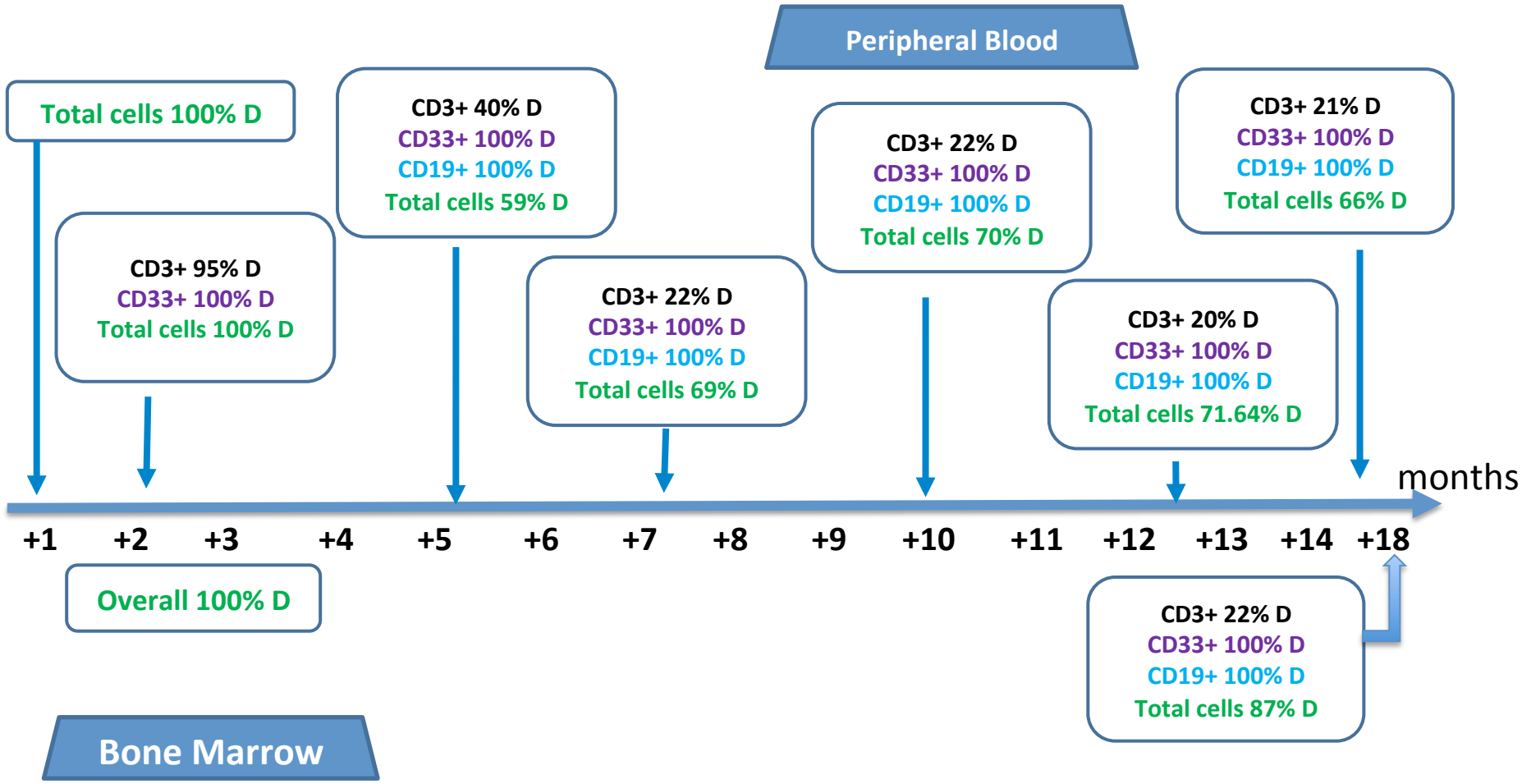
pt 1



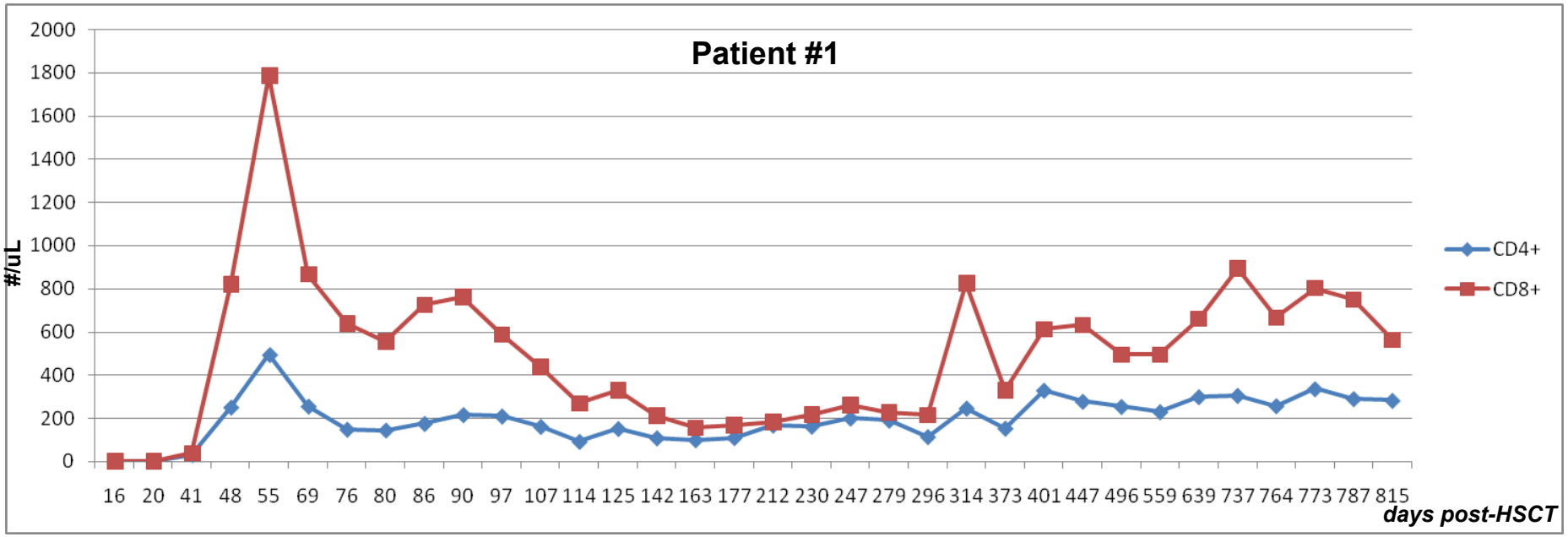
Aversa et al. Blood Adv 2017

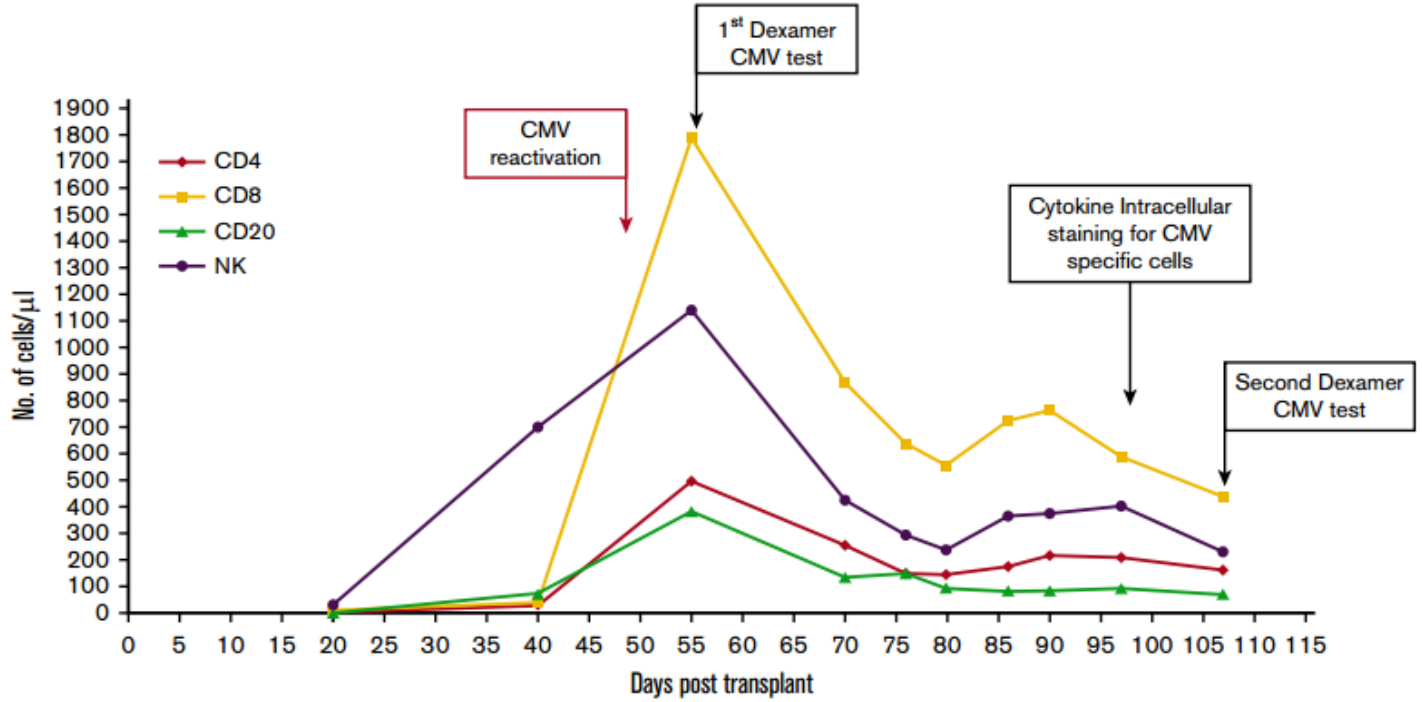
Chimerism analysis at different time points (% donor cells out of the total PBMC and BM)

 # pt 3



Aversa et al. Blood Adv 2017

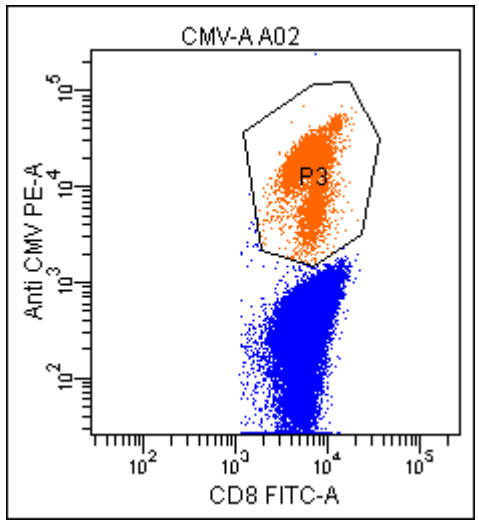

Patient #1
#/uL
2000
1800
1600
1400
1200
1000
800
600
400
200
0
16 20 41 48 55 69 76 80 86 90 97 107 114 125 142 163 177 212 230 247 279 296 314 373 401 447 496 559 639 737 764 773 787 815
days post-HSCT
CD4+
CD8+


1st Dexamer CMV test
CMV reactivation
Cytokine Intracellular staining for CMV specific cells
Second Dexamer CMV test
CD4
CD8
CD20
NK
No. of cells/µl
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115
Days post transplant

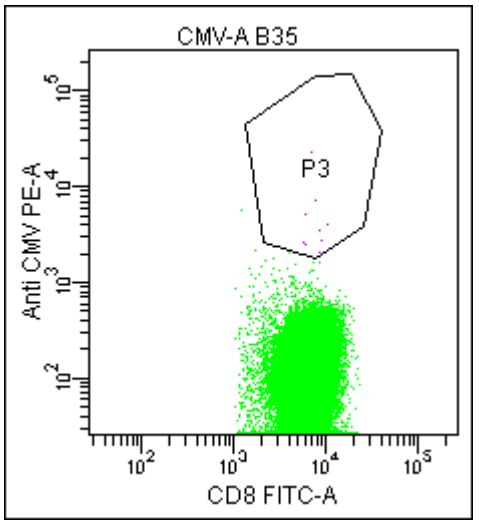
CMV-specific CD8⁺ T cell: +55d

HLA status:
Donor **A 02**, 03 – **B 35,** 08
Recipient **A 02**, B 08

A 02



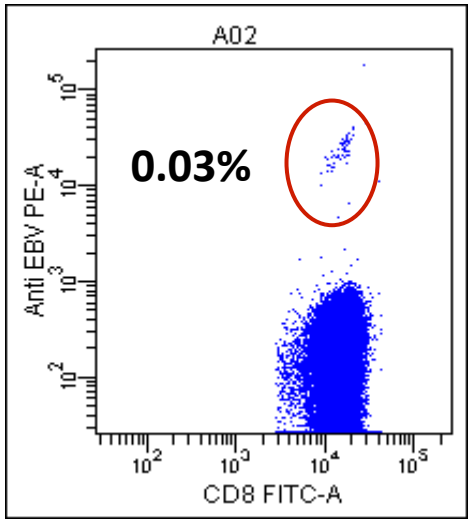
B 35



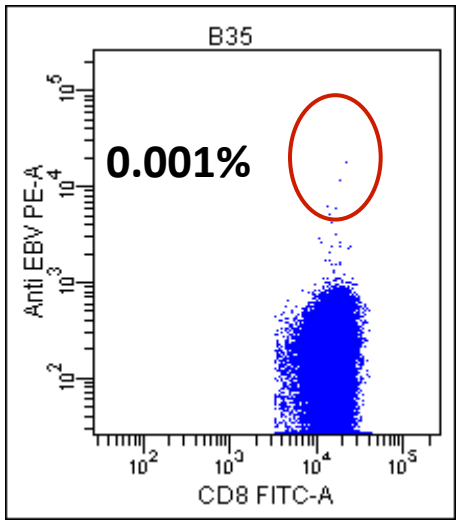
EBV-specific CD8⁺ T cell: +114d

HLA status:
Donor **A 02**, 03 – **B 35,** 08
Recipient **A 02**, - B 08

A 02



B 35



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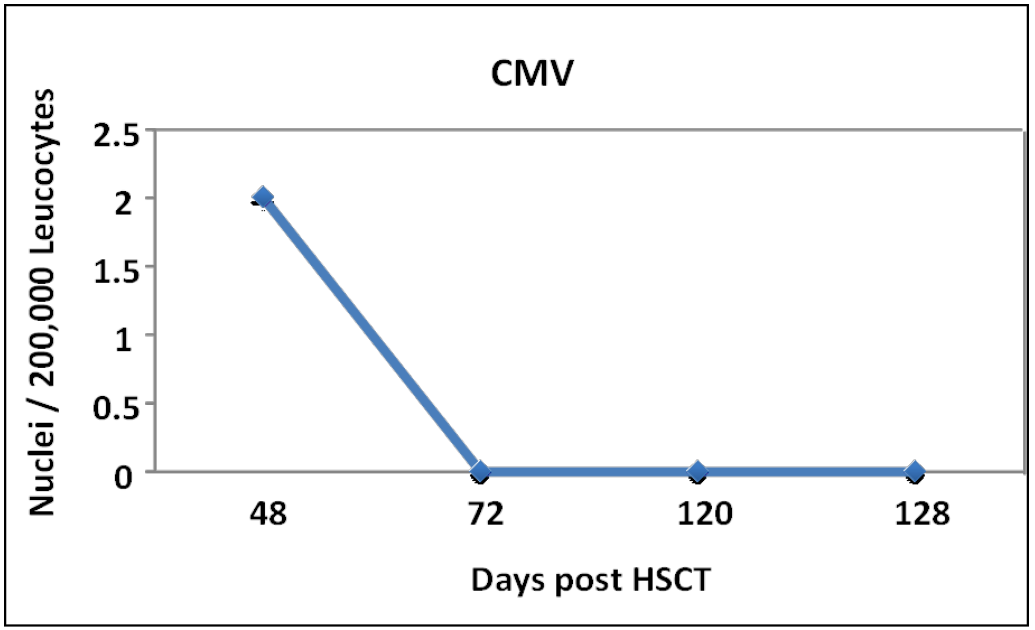
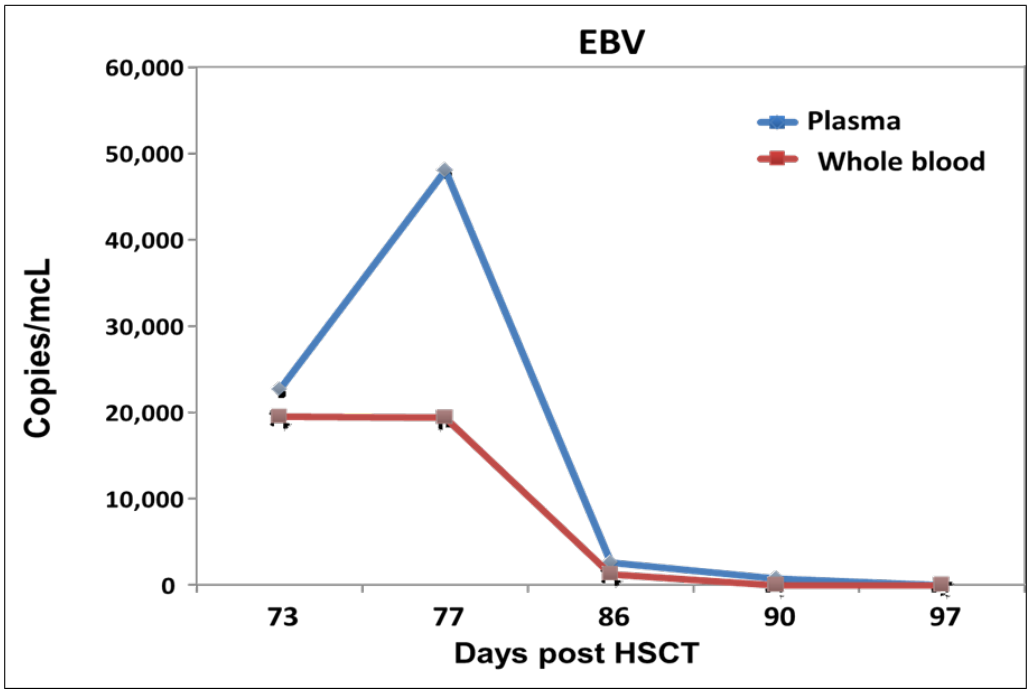
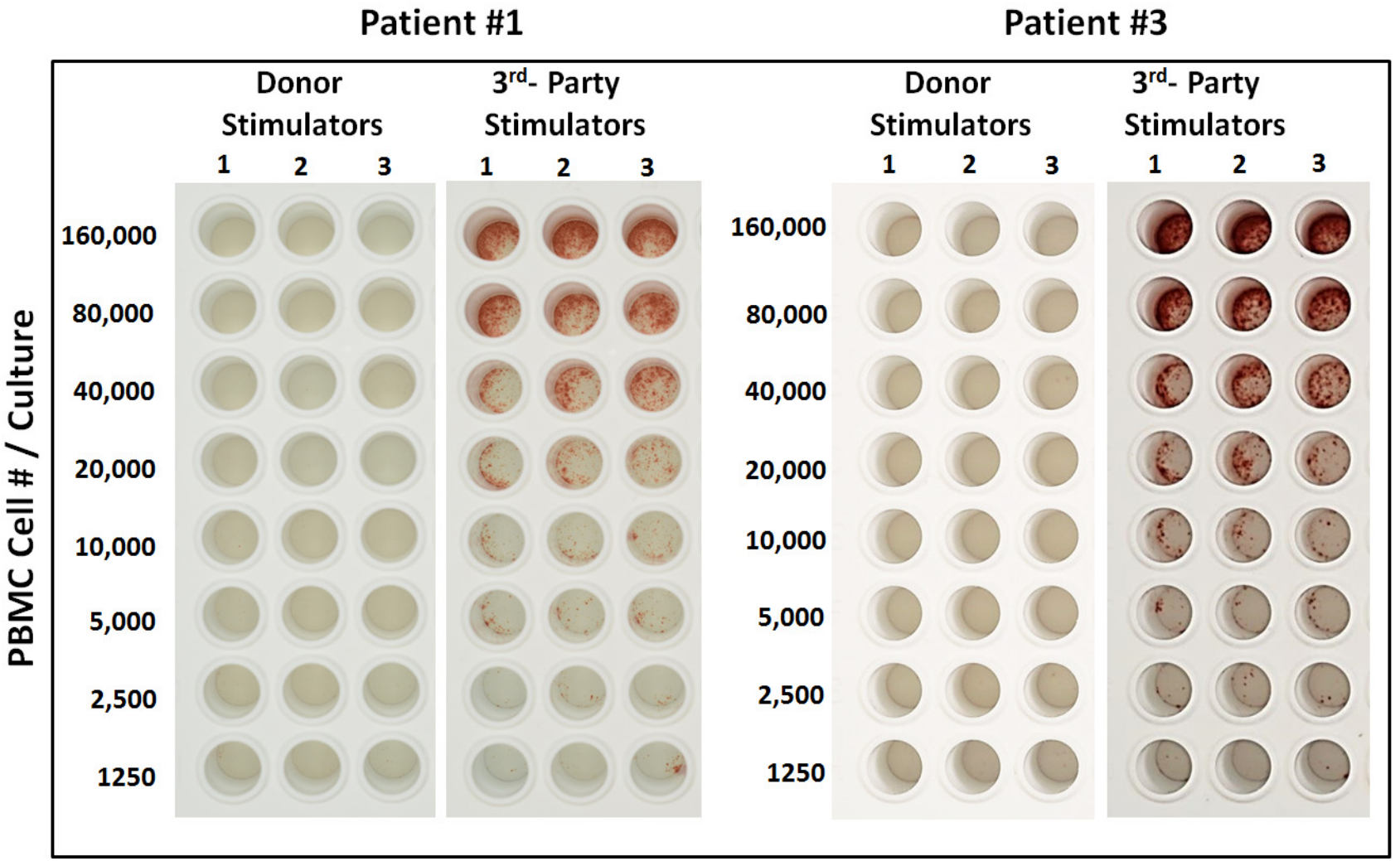
Immune Control of CMV and EBV Reactivation





Aversa et al. Blood Adv 2017

Analysis of CTLp against donor and 3rd party target cells by INF-γ ELISPOT assay



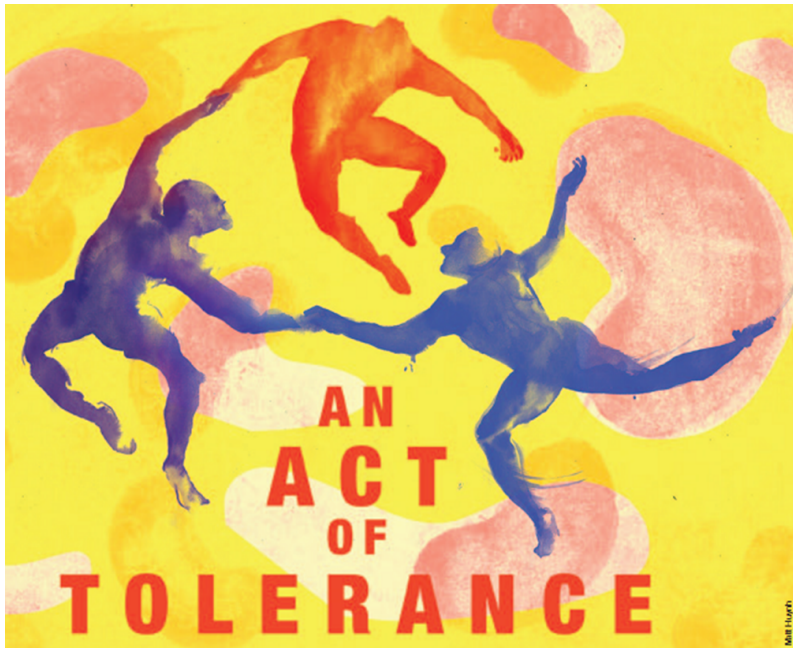
Aversa et al. Blood Avs 2017

Pt # 2

- 50 yr, male, advanced MM with unfavorable cytogenetics (complex karyotype: 50 XY, +5, +7, +9, -13, +19, +21 and a 13q14 monosomy on FISH).
- Previous therapy: Len-Dex , tandem autoHSCT, Lena x 36 months. Relapse, VD x 8 →vgPR
- Nov 2015, haploHSCT, from a cousin. Transient engraftment (50% donor cells on day +17), graft failure (0.04% donor-type chimerism) on day +30. Spontaneous rescue.
- After 5 months, second haploHSCT (different donor), our standard MAC+alfa/beta TCD
- At 2 yrs: full donor, no sign of GvHD, very good immunological reconstitution, excellent quality of life, and CR.

Future applications:

- Non-malignant hematological disorders
- solid organ transplantation



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Giannalisa Todaro
Tania Maldacena

Lab Exp Hematol
Giovanni Roti
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Andrea Gherli
Anna Montanaro
Giorgio Rastelli
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Chiara Schifano
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