USO DI G-CSF BIOSIMILARI + PLERIXAFOR NELLA MOBILIZZAZIONE DI CSE AUTOLOGHE

Basilica S Apollinare in Classe: 534 dC: arte paleocristiana, architettura bizantina

Francesco Lanza

UOC di Ematologia &

Programma Trapianti della Romagna

Ravenna- AUSL Romagna

GIIMA- RAVENNA 2017

CD34+ YIELD

LOW NUMBER OF APHERESIS

GOALS OF STEM CELL COLLECTION ARE TO MAXIMIZE THE CD34+ CELLS COLLECTED PER KG RECIPIENT WEIGHT WITH THE LEAST NUMBER OF APHERESIS DAYS TO ACHIEVE THE CD34+ CELL DOSE NEEDED FOR HSCT

A "PURE" GRAFT

NO ADVERSE REACTION

Mobilisation Strategies used in Clinical Practice

Approved

- Haematopoietic growth factors
  - G-CSF, **filgrastim**
  - G-CSF, biosimilar Filgrastim
  - G-CSF, **lenograstim**
- **Plerixafor in combination with G-CSF for poorly mobilising patients**

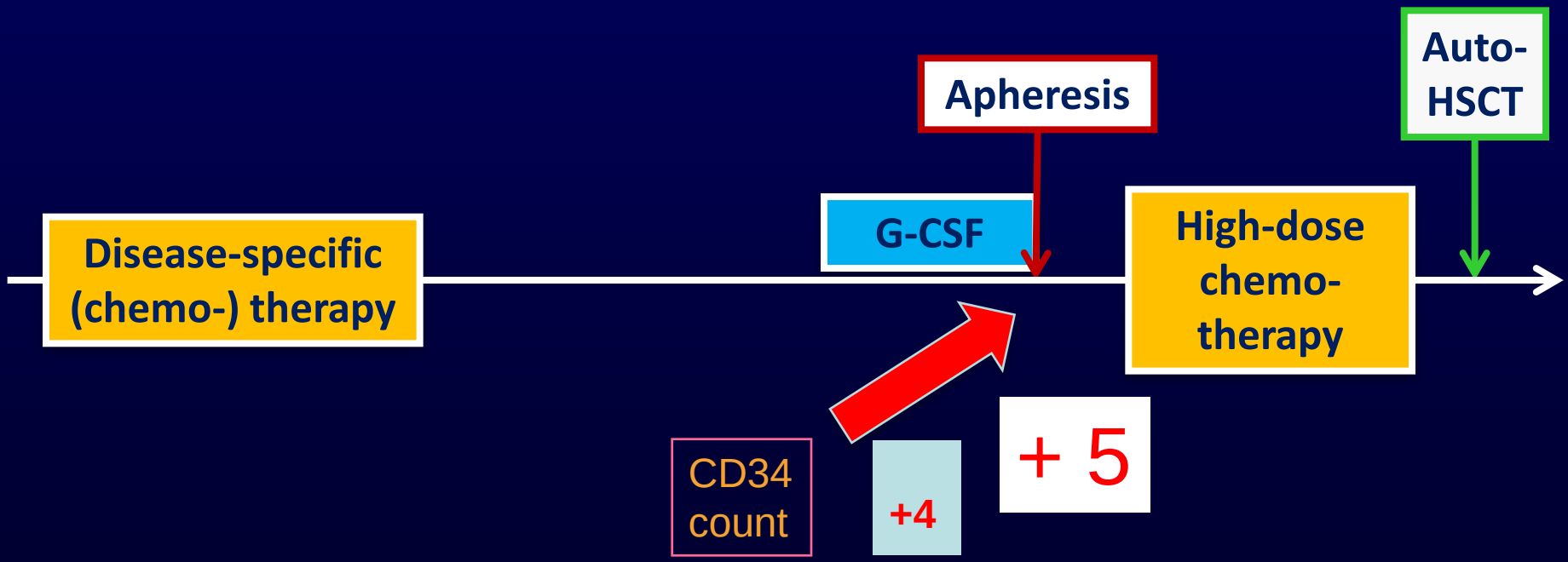
  (use on demand or just in time-pre-emptive)

Other Treatment Options

- Haematopoietic growth factors
  - **Peg-G-CSF (pegfilgrastim)**
  - **Lipeg G-CSF (Lonquex)**
  - **GM-CSF , SCF (US)**
- **Chemotherapeutic agents**
  - Chemotherapy apart from disease treatment
  - Disease-specific regimens
- Growth factor + chemotherapy

Current PBSC mobilisation strategies: *Steady state (cytokines only)*

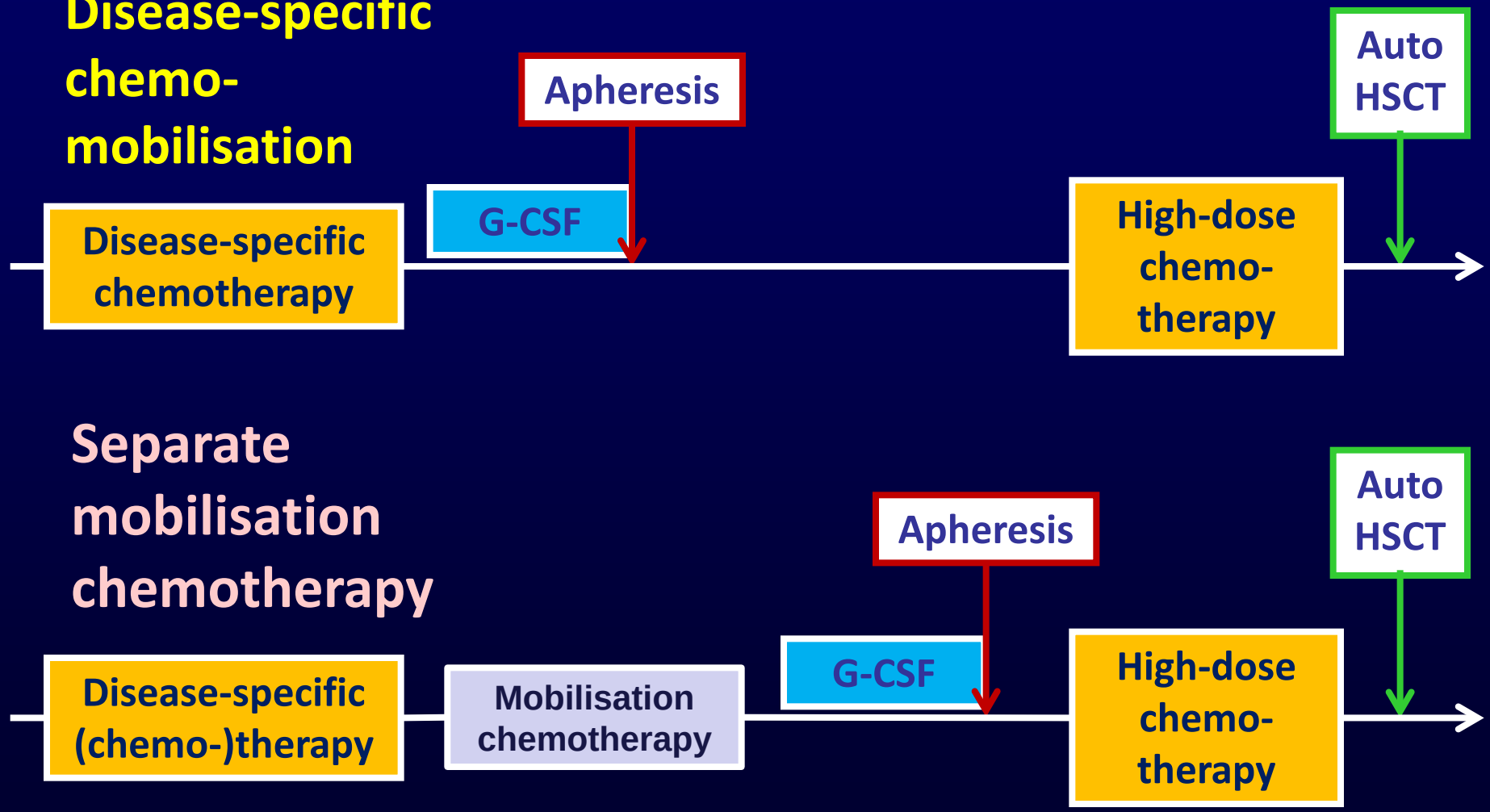
G-CSF monotherapy is the most commonly used steady state strategy



G-CSF, granulocyte colony-stimulating factor.

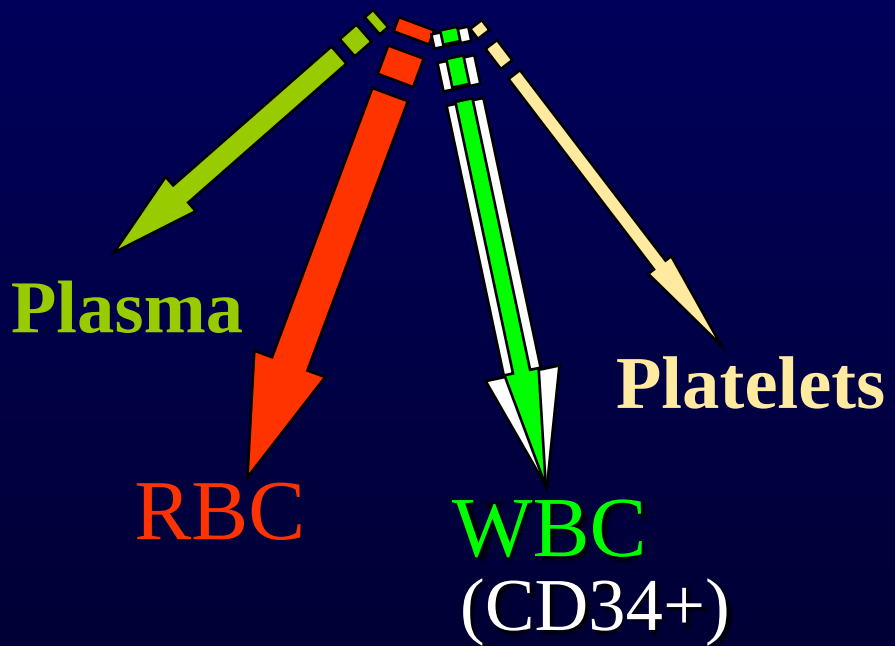
.

Current PBSC mobilisation strategies:
Chemo-mobilisation

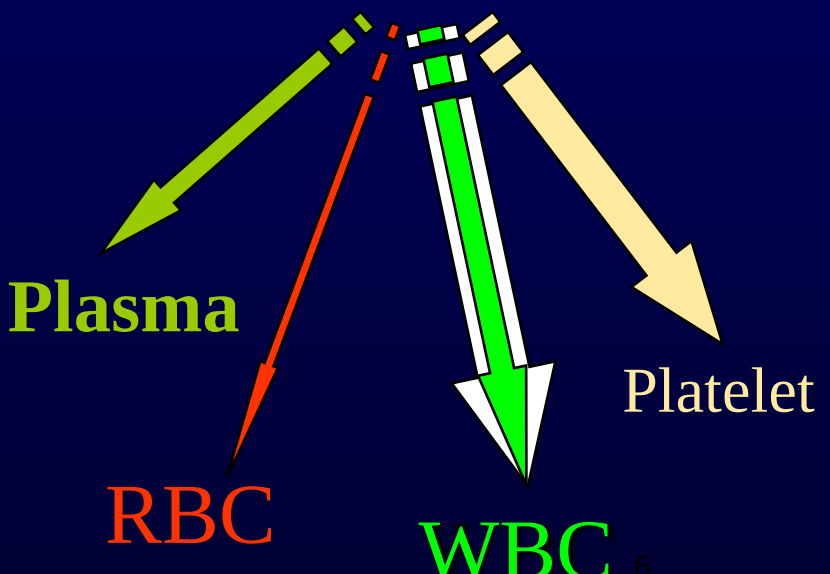


GRAFT COMPOSITION

BONE MARROW



PBSC



(CD34+)

TOTAL NUCLEATED CELLS (TNC) and MNC

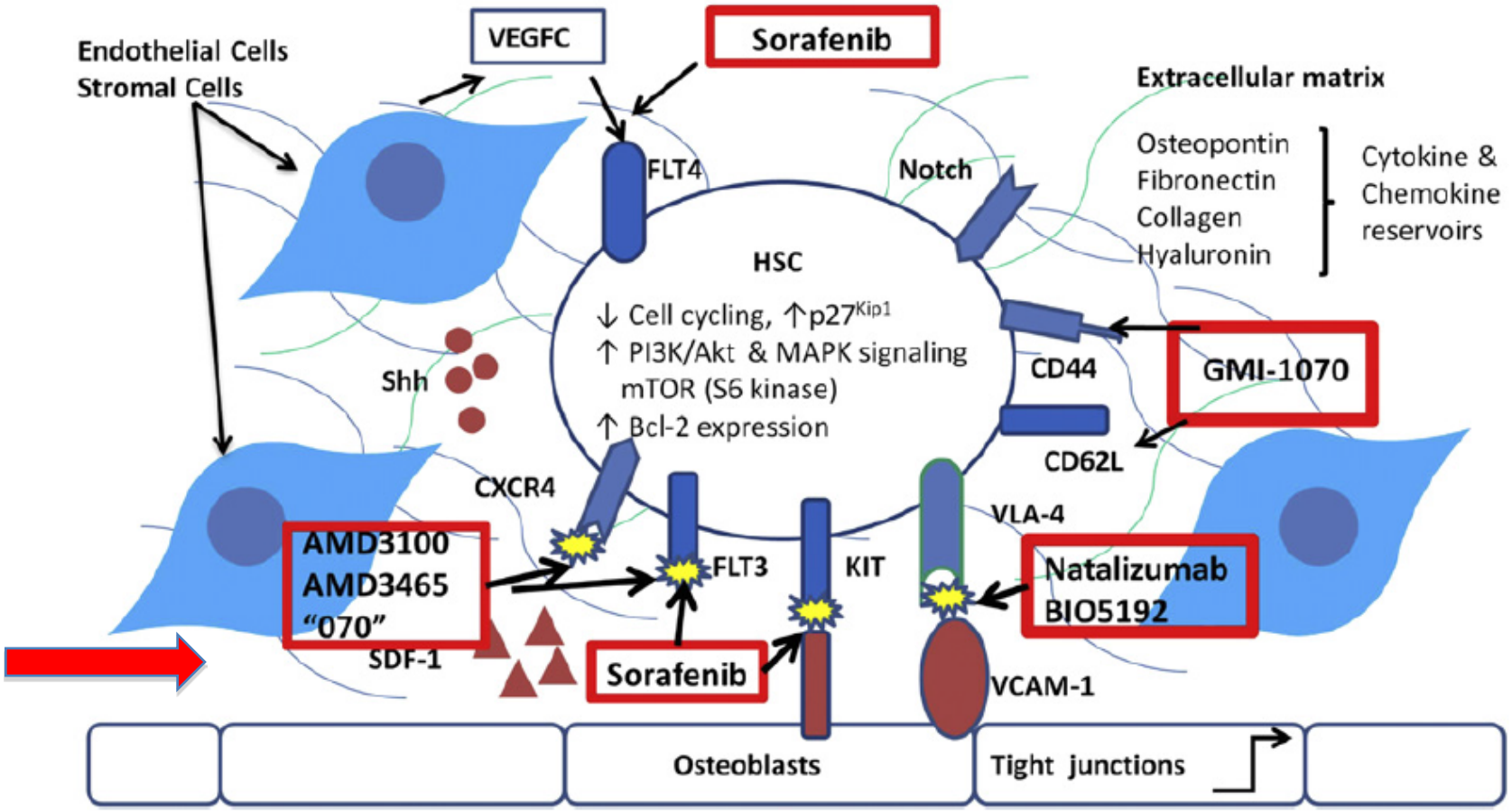
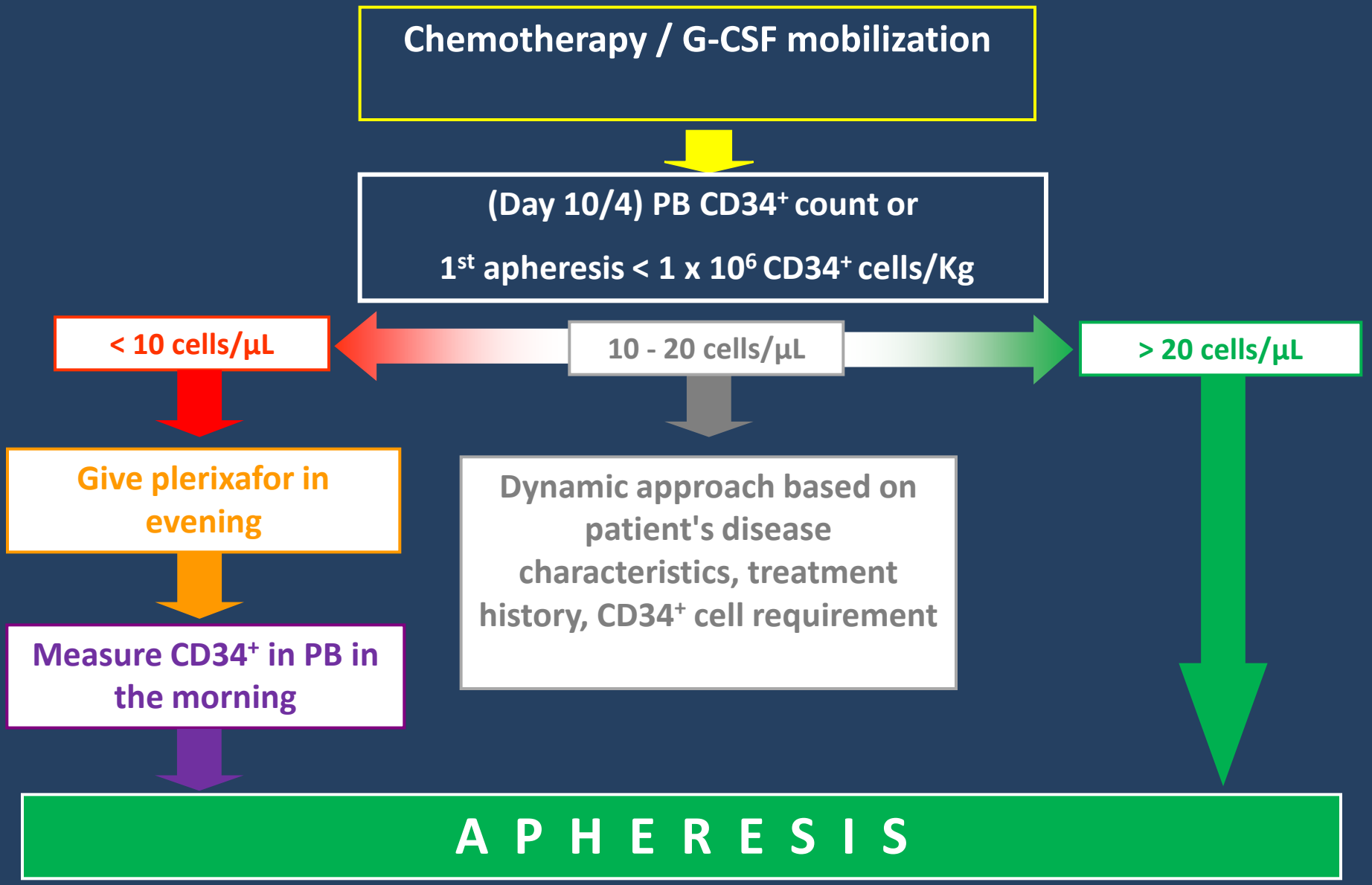


Fig. 1. Interacting tethers involved in stem cell-stromal interactions [22]. Small molecule and antibody inhibitors of these pathways are shown in the red boxes. This research was originally published in *Blood* [22]. ©The American Society of Hematology. Reproduced with permission of American Society of Hematology (ASH) via Copyright Clearance Center.

Pre-emptive use of plerixafor in auto-SCT



adapted from: Mohty, Lanza et al. EBMT consensus- BMT 2014

BMT, ***2014*** Mar 31;0. doi: 10.1038/bmt.2014.39

Autologous haematopoietic stem cell mobilisation in patients with multiple myeloma and lymphoma:

First part of a consensus on behalf of the EBMT investigators

M Mohty, France; K Hübel, Germany; N Kröger, Germany; M Aljurf, Saudi Arabia; J Apperley, UK; G Basak, Poland; A Bazarbachi, Lebanon; K Douglas, UK; I Gabriel, UK; L Garderet, France; C Geraldes, Portugal; O Jaksic, Croatia; M Kattan, USA; Z Koristek, Czech Republic; **F Lanza,** Italy; RM Lemoli, Italy; L Mendeleeva, Russia; G Mikala, Hungary; N Mikhailova, Russia; A Nagler, Israel; HC Schouten, The Netherlands; D Selleslag, Belgium; S Suciu, Belgium; A Sureda, UK; N Worel, Austria; P Wuchter, Germany; C Chabannon, France; and RF Duarte, Spain

All authors contributed equally to this work

Bone Marrow Transplantation (2011), 1 – 5
© 2011 Macmillan Publishers Limited All rights reserved 0268-3369/11
www.nature.com/bmt

ORIGINAL ARTICLE

European data on stem cell mobilization with plerixafor in non-Hodgkin's lymphoma, Hodgkin's lymphoma and multiple myeloma patients. A subgroup analysis of the European Consortium of stem cell mobilization

K Hübel[1], MM Fresen[1], JF Apperley[2], GW Basak[3], KW Douglas[4], IH Gabriel[2], C Geraldes[5], O Jaksic[6], Z Koristek[7], N Kröger[8], F Lanza[9], RM Lemoli[10], G Mikala[11], D Selleslag[12], N Worel[13], M Mohty[14] and RF Duarte[15]

The effectiveness of the novel hematopoietic stem cell mobilizing agent plerixafor was evaluated in nationwide compassionate use programs in 13 European countries. A total of 580 poor mobilizers with non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL) and multiple myeloma (MM) were enrolled. All patients received plerixafor plus granulocyte CSF with or without chemotherapy. Overall, the collection yield was significantly higher in MM patients ($>2.0\times10^6$ CD34+ cells/kg: 81.6%; $>5.0\times10^6$ CD34+ cells/kg: 32.0%) than in NHL patients ($>2.0\times10^6$ CD34+ cells/kg: 64.8%; $>5.0\times10^6$ CD34+ cells/kg: 12.6%; $P<0.0001$) and also significantly higher in HL patients ($>2.0\times10^6$ CD34+ cells/kg: 81.5%; $>5.0\times10^6$ CD34+ cells/kg: 22.2%) than in NHL patients ($P=0.013$). In a subgroup analysis, there were no significant differences in mobilization success comparing patients with diffuse large B-cell lymphoma, follicular lymphoma and mantle cell lymphoma. Our data emphasize the role of plerixafor in poor mobilizers, but further strategies to improve the apheresis yield especially in patients with NHL are required.

Bone Marrow Transplantation advance online publication, 14 November 2011; doi:10.1038/bmt.2011.216

Keywords: plerixafor; mobilization; lymphoma subtypes; European centers

EXPERT OPINION

Plerixafor: what we still have to learn

Francesco Lanza, Angelo Gardellini, Daniele Laszlo & Massimo Martino[†]

[†]*Azienda Ospedaliera BMM, Department of Oncology and Hematology, Hematology and Bone Marrow Transplant Unit, Reggio Calabria, Italy*

Plerixafor, a hematopoietic stem cell mobilizer, is indicated in combination with G-CSF to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma. Current evidence suggests that the addition of plerixafor with chemotherapy plus G-CSF is safe and effective in the large majority of the patients with low blood $CD34^+$ cell count after mobilization and/or poor yield after the first collection. Nevertheless, there are several questions strongly debated, and in this paper, we would like to identify areas of possible future use and development of the drug.

Keywords: autologous transplantation, mobilization, peripheral blood stem cells, plerixafor

Expert Opin. Biol. Ther. [Early Online]

1. Introduction

Plerixafor (PLX) is a new mobilization agent that is approved for use in combination with G-CSF to mobilize hematopoietic stem cells (HSCs) in patients with multiple myeloma (MM) and non-Hodgkin lymphoma (NHL) and scheduled for high-dose chemotherapy and autologous transplant [1]. PLX significantly improves the mobilization capacity of G-CSF, and published data have shown that the association of PLX plus chemotherapy is feasible, safe and able to improve HSCs mobilization by several fold [2]. Nevertheless, there are several questions strongly debated, and in this paper, we would like to identify areas of possible future use and development of the drug.

Open

Bone Marrow Transplantation (2011), 1–10
© 2011 Macmillan Publishers Limited All rights reserved 0268-3369/11
www.nature.com/bmt

ORIGINAL ARTICLE

Proposed definition of 'poor mobilizer' in lymphoma and multiple myeloma: an analytic hierarchy process by *ad hoc* working group Gruppo italianoTrapianto di Midollo Osseo

A Olivieri[1], M Marchetti[2], R Lemoli[3], C Tarella[4], A Iacone[5], F Lanza[6], A Rambaldi[7] and A Bosi[8] on behalf of the Italian Group for Stem Cell Transplantation (GITMO)

A patient with MM or lymphoma and candidate for ASCT is a:

'Proven' poor mobiliser	If he/she received adequate mobilisation (G-CSF dose ≥ 10 µg/kg if used alone or ≥ 5 µg/kg after chemotherapy) and he/she shows: peak $CD34^+$ circulating cell count < 20/µL on days 4–6 after start of mobilisation with G-CSF alone or up to 18–20 days after chemotherapy and G-CSF **OR** < 2. × 10^6 harvested $CD34^+$ cells/kg per planned SCT by ≤ 3 aphereses
'Predicted' poor mobiliser	If he/she fulfils ≥ 1 major criterion or ≥ 2 minor criteria **Major criteria** •Failed previous mobilisation attempt •Prior extensive radiotherapy to marrow-bearing tissue •Full courses of previous therapy including melphalan, fludarabine or other therapies potentially affecting stem cell mobilisation **Minor criteria** •Advanced phase disease, i.e. ≥ 2 prior cytotoxic lines •Refractory disease •Extensive BM involvement at mobilisation •BM cellularity < 30% at mobilisation •Age > 65 years

Key concepts and critical issues on epoetin and filgrastim biosimilars. A position paper from the Italian Society of Hematology, Italian Society of Experimental Hematology, and Italian Group for Bone Marrow Transplantation

Giovanni Barosi,[1] Alberto Bosi,[2] Maria P. Abbracchio,[3] Romano Danesi,[4] Armando Genazzani,[5] Paolo Corradini,[6] Fabrizio Pane,[7] and Sante Tura[8]

[1]Laboratory of Clinical Epidemiology and Center for the Study of Myelofibrosis, IRCCS Policlinico S. Matteo Foundation, Pavia; [2]Bone Marrow Transplantation Unit, Department of Hematology, University of Florence; [3]Department of Pharmacological Sciences Laboratory of Molecular and Cellular Pharmacology of Purinergic Transmission, University of Milan, Milan; [4]Division of Pharmacology, Department of Internal Medicine, University of Pisa, Pisa; [5]DiSCAFF, Università del Piemonte Orientale, Novara; [6]Division of Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori University of Milan, Milan; [7]EINGE Biotecnologie Avanzate and Hematology Division, Department of Biochemistry and Medical Biotechnology, University Federico II, Naples; [8]University of Bologna, Bologna, Italy.;
E-mail: barosig@smatteo.pv.it *doi:10.3324/haematol.2011.041210*

SIE

Open Access **Editorial**

ESMO Open
Cancer Horizons

CrossMark

The ESMO position paper on biosimilars in oncology: enhancing the provision of accurate education and information

Martin Schiestl,[1] Andriy Krendyukov[2]

BIOSIMILARS

European Journal of Haematology

European Journal of Haematology 88 (154–158

ORIGINAL ARTICLE

Plerixafor and Filgrastim XM02 (Tevagastrim®) as a first line peripheral blood stem cell mobilisation strategy in patients with multiple myeloma and lymphoma candidated to autologous bone marrow transplantation

Giovanna Andreola[1], Aleksandra Babic[1], Cristina Rabascio[2], Mara Negri[1], Giovanni Martinelli[1] and Daniele Laszlo[1]

[1]Stem Cell Collection Unit, [2]Laboratory of Haematology-Oncology, Haematoncology Division, European Institute of Oncology, Milan, Italy

Comparison of biosimilar filgrastim**, originator** filgrastim**, and lenograstim for autologous stem cell mobilization in patients with multiple myeloma.**

Lisenko K, Baertsch MA, Meiser R, Pavel P, Bruckner T, Kriegsmann M, Schmitt A, Witzens-Harig M, Ho AD, Hillengass J, Wuchter P.
Heidelberg University, Heidelberg, Germany.

Transfusion 2017

STUDY DESIGN AND METHODS: mobilization data of 250 patients with MM in first-line therapy were included. chemomobilization with CAD until completion of PBSC collection. **RESULTS:** All but one patient reached the collection goal of a minimum of at least 2 × 106 CD34+ cells/kg body weight during a median of one (range, one to three) leukapheresis session.

No significant differences in CD34+ mobilization and collection yields between the filgrastim-mobilized (median, 10.5; range, 2.7-40.4), Filgrastim Hexal-mobilized (median, 9.9; range, 0.2-26.0), and lenograstim-mobilized (median, 10.7; range, 3.1-27.9 CD34+ cells × 106 /kg body weight) patients were observed.

CONCLUSION: this retrospective study did not detect any significant differences between the three G-CSF variants.

STUDIO MULTICENTRICO SUL RUOLO DEL G-CSF BIOSIMILARE IN COMBINAZIONE AL PLERIXAFOR NELLA MOBILIZZAZIONE DI CELLULE STAMINALI AI FINI DI TRAPIANTO: STUDIO GITMO

Ravenna- Milano (IEO)- S Giovanni Rotondo- IRCSS-Rio Nero in Vulture- Firenze- Reggio Calabria- Cremona- Studio Gitmo

ORIGINAL ARTICLE

Factors affecting successful mobilization with plerixafor: an Italian prospective survey in 215 patients with multiple myeloma and lymphoma

Francesco Lanza, Roberto M. Lemoli, Attilio Olivieri, Daniele Laszlo, Massimo Martino, Giorgina Specchia, Vincenzo Pavone, Manuela Imola, Annalisa Pasini, Giuseppe Milone, Ilaria Scortechini, Elisabetta Todisco, Elena Guggiari, Nicola Cascavilla, Giovanni Martinelli, Alessandro Rambaldi, and Alberto Bosi

Received for publication January 16, 2013; revision received February 26, 2013, and accepted March 4, 2013.
doi: 10.1111/trf.12265
TRANSFUSION **,**,**,**.

F. Lanza[1], F. Saraceni[1], A. Pezzi[1], M. Martino[2], A. Bosi[3], N. Cascavilla[4], P. Musto[5], E. Zuffa[1], M. Tani[1], C. Cellini[1], D. Laszlo[6], F. Bonifazi[7], on behalf of GITMO (Italian Society for Transplantation)

Received: 1 June 2017 | Accepted: 2 June 2017

DOI: 10.1002/ajh.24817

WILEY AJH

CORRESPONDENCE

A comparative analysis of biosimilar vs. originator filgrastim in combination with plerixafor for stem cell mobilization in lymphoma and multiple myeloma: a propensity-score weighted multicenter approach

imbalances between the two study groups in terms of patient and mobilization characteristics.[5]

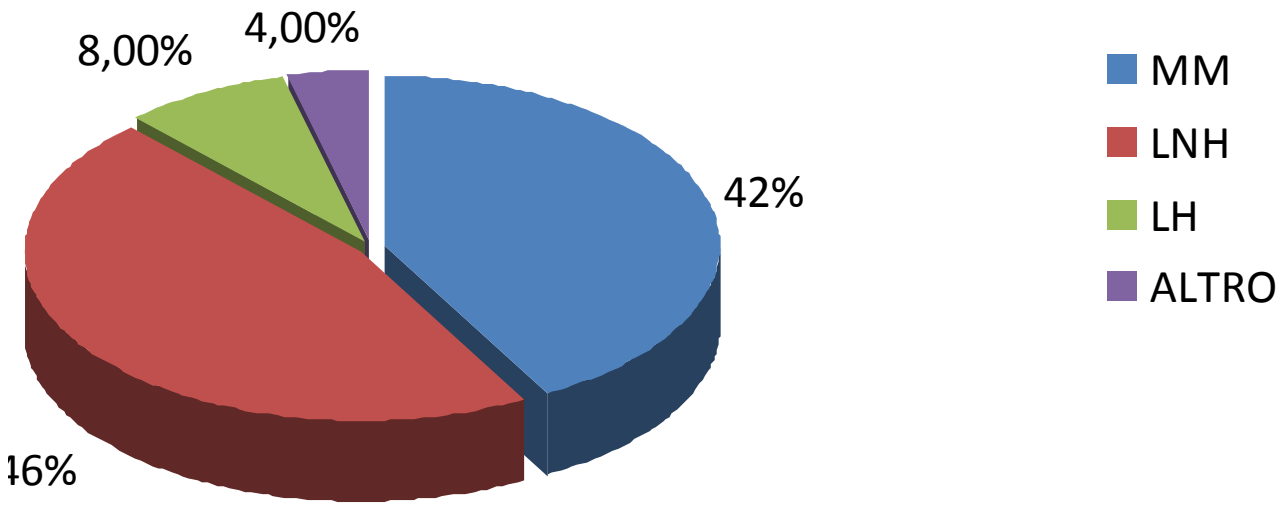
A total of 296 patients were included in the analysis. Forty-two percent of patients ($n = 123$) were affected by MM, 49% ($n = 143$) by NHL and 9% ($n = 29$) by HL. Forty percent of patients ($n = 118$) underwent chemo-mobilization, while 60% ($n = 178$) steady-state mobilization. One hundred and ninety-seven patients (67%) received originator filgrastim combined with plerixafor (OR + PLX), while 99 patients (33%) were given biosimilar filgrastim and plerixafor (BIO + PLX). The median PB-CD34+ count before and after plerixafor administration were 8/mcl (IQR 3–12), and 33/mcl (IQR 15–58), respectively, with an average 6-fold increase.

Patients included in the BIO + PLX cohort were more likely to exceed the PB-CD34+ threshold of 5/mcl before plerixafor administration, as compared to the OR + PLX group, as evidenced by propensity score weighted analysis (weighted OR = 3.6; robust 95% CI 1.5–8.4). Further, patients receiving BIO + PLX showed higher probability of reaching the PB-CD34+ threshold of 20/mcl after plerixafor

DISEASE	PATIENTS (n.)	%
MM	43	42%
LNH	47	46%
LH	8	8%
OTHER	4	4%
total patients	102	100%

BIOSIMILAR G-CSF AND PLERIXAFOR

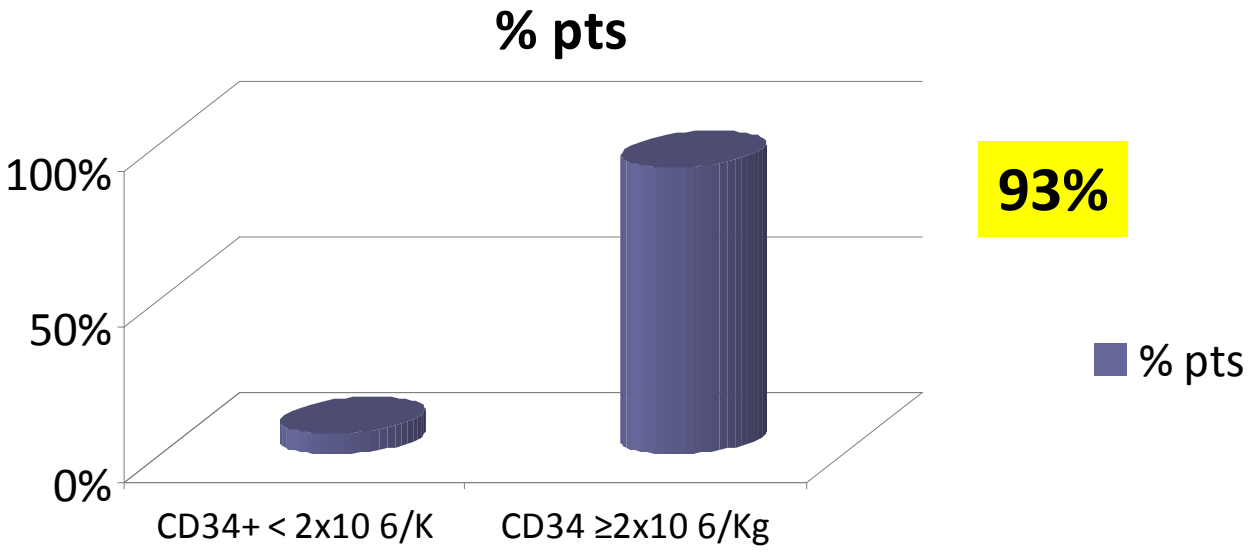
DISEASE TREATED



CD34+ CELLS/ μL POST-MOBILIZATION WITH PLERIXAFOR AND G-CSF BIOSIMILAR

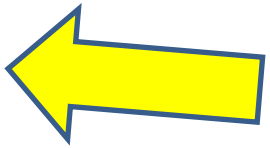
	CD34< 20/μL (Mobilized Blood)	CD34 ≥20/μL
% of patients (N=43)	12% (11 pts)	88% (83 pts)

Median CD34+ cells/μL = 50 x10^6/μL
(3-208 range) (30-72 IQR)



	CD34< 2x10 6/Kg (Mobilized Blood)	CD34 ≥2x10 6/Kg
% of patients	7% (7 pts)	93% (90 pts)

	CD34< 2x10 6/Kg (Mobilized Blood)	CD34 = 2-5 x10 6/Kg	CD34 ≥ 5 x10 6/Kg
% of patients	7% (7 pts)	58% (56 pts)	35% (34 pts)



	Pazienti totali	MM	NHL	HL
FOLD INCREASE $CD34^+$ CELLS/µL	4.9	4.5	5.3	5.2

Comparative evaluation of mobilization capacity of originator G-CSF vs biosimilar G-CSF(both of them used in combination with plerixafor)

	ORIGINATOR n=197	BIOSIMILARE n=99
CD34>20 uL	57%	88%
	OR= 6.7 (95% CI 2.5-18.3)	
CD34>2x10e6/Kg	82%	93%
	OR= 4.0 (95% CI 1.2-13.1)	

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Results of a Prospective Randomized, Open-Label, Noninferiority Study of Tbo-Filgrastim (Granix) versus Filgrastim (Neupogen) in Combination with Plerixafor for Autologous Stem Cell Mobilization in Patients with Multiple Myelo

Pavan K
Keith St
Amanda

[1] Division of
[2] Division of
[3] Division of

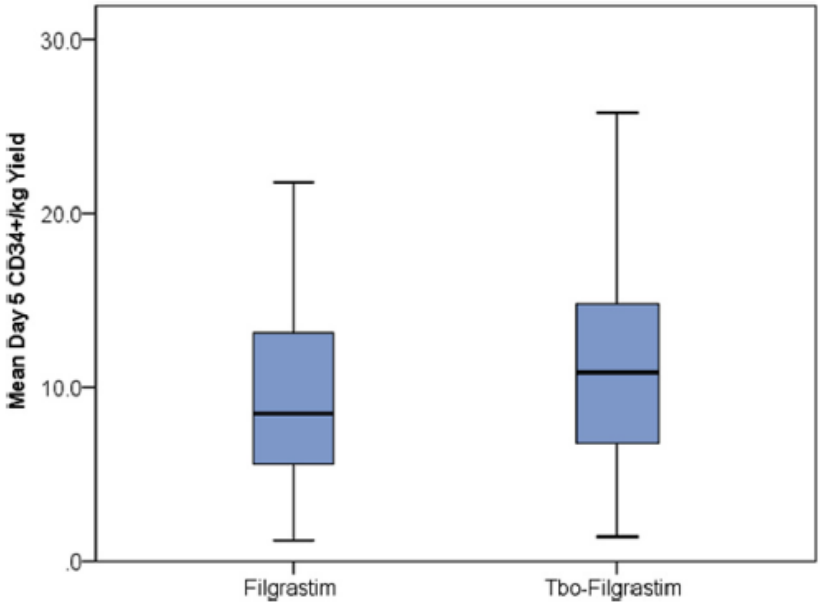


Figure 2. Day 5 mean CD34⁺ peripheral blood stem cell collection yield in the tbo-filgrastim and filgrastim arms.

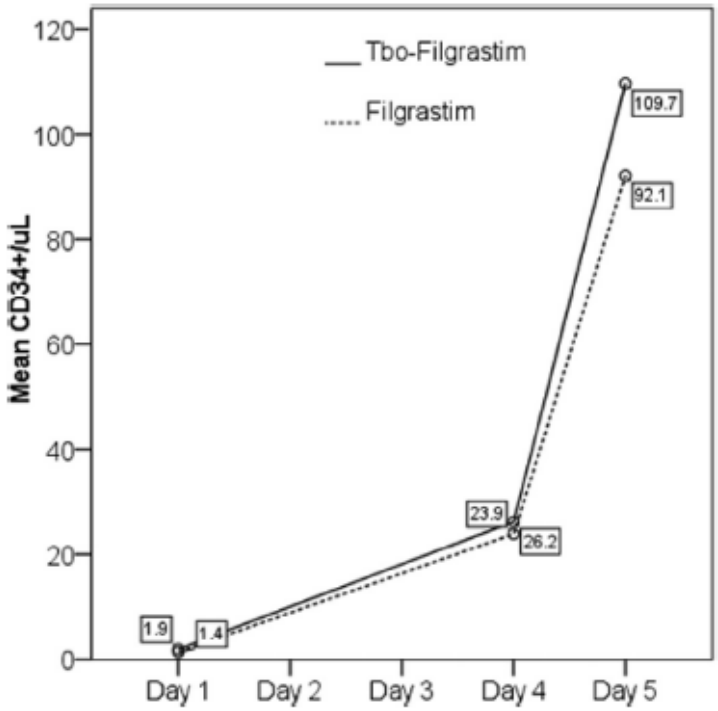


Figure 3. Mean peripheral blood CD34⁺ cell mobilization by treatment arm.

CONCLUSIONI

- Le CSE mobilizzate con G-CSF BIOSIMILARE + plerixafor sono numericamente e funzionalmente sovrapponibili a quelle raccolte dopo G-CSF originator.
- Le CSE raccolte con plerixafor hanno caratteristiche funzionali differenti rispetto alle CSE mobilizzate con G-CSF +/- Chemio (Aumento di linfociti e calo PMN)
- I dati attuali derivano da studi retrospettivi e risentono dalle modalità di impiego del PLX (on demand o poor (very poor) mobilizers con precedente fallimento di Mob
- **Necessità di studi prospettici nel settore**