XVII° Corso Nazionale di Aggiornamento per personale Medico, Tecnico ed Infermieristico

Società Italiana di Emaferesi e Manipolazione Cellulare
Palermo
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Il paziente cattvo mobilizzatore e l'uso del plerixaflor

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Disclosure

- Nessuna sponsorizzazione e/o rapporto economico con aziende farmaceutiche
- Ho ricevuto grant per partecipazione a congressi (iscrizione+viaggio e soggiorno) da Terumo-Caridian

SPECIAL REPORT

The EBMT activity survey: 1990–2010

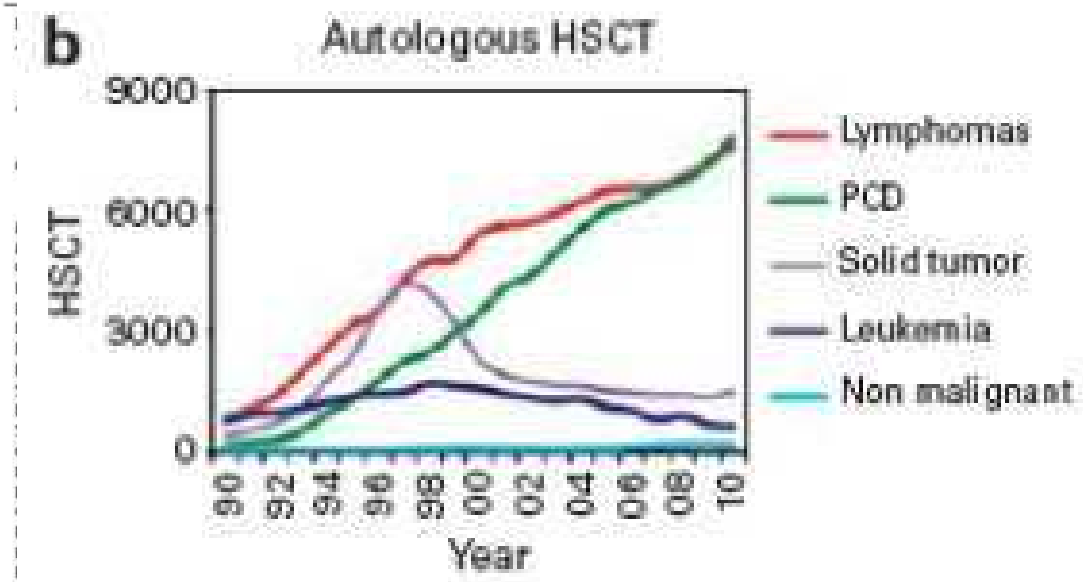
JR Passweg[1], H Baldomero[1], A Gratwohl[1], M Bregni[2], S Cesaro[3], P Dreger[4], T de Witte[5], D Farge-Bancel[6], B Gaspar[7], J Marsh[8], M Mohty[9], C Peters[10], A Tichelli[11], A Velardi[12], C Ruiz de Elvira[13], F Falkenburg[14], A Sureda[15], A Madrigal[16] and for the European Group for Blood and Marrow Transplantation (EBMT)

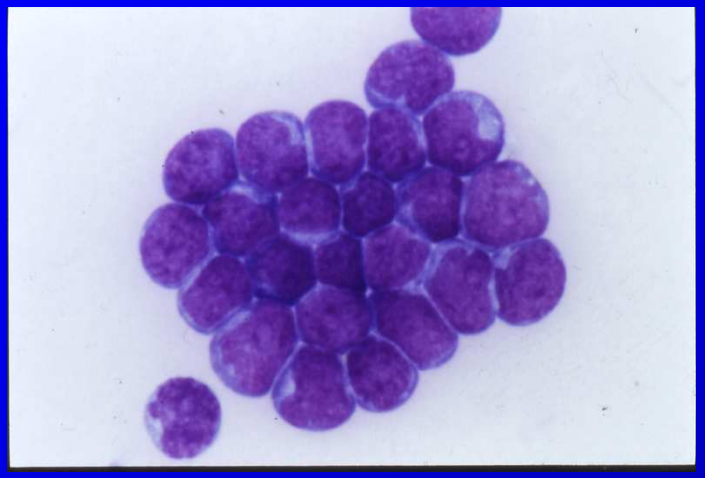
Bone Marrow Transplantation (2012) **47**, 906–923

Table 1. Numbers of hematopoietic stem cell transplants in Europe 2010 by indication, donor type and stem cell source

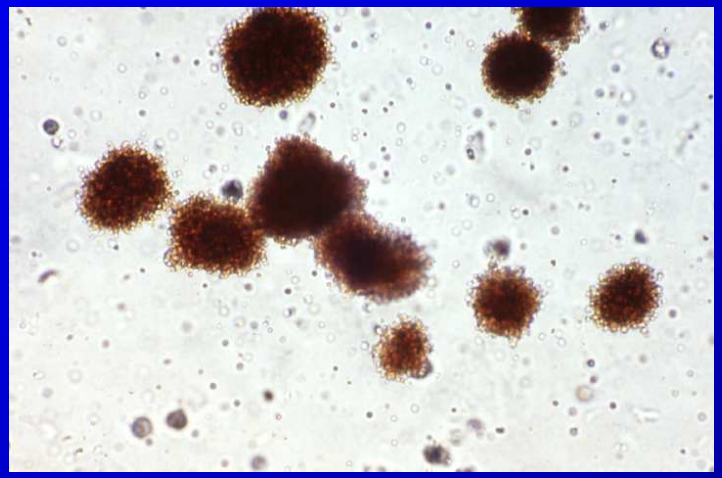
	Donor Source																	
	Nunber of patients																	
	Allogeneic												Autologous			Total		
	Family								Unrelated									
	HLA-identical			haplo-identical			twin						BM	BM +		Allo	Auto	Total
										BPC	Cord		only	PBPC	Cord			
										532	507		40	629	1	8685	670	9355
										508	213		33	483		3946	516	4462
										833	105		28	404		2298	432	2730
										775	108		5	79		1648	84	1732
										588	165		3	83		2007	86	2093
										368	82		1	55		1189	56	1245
										220	83		2	28		818	30	848
										167	23		1			416	1	417
										56	9					161		161
										111	14		1			255	1	256
										595	81		2	15	1	1434	18	1452
										244	9			2		475	2	477
										230	16		1	40		407	47	454
										865	83		60	15325		1977	15385	17362
										246	13		13	7597		546	7610	8156
										9				225		20	225	245
										138	24		21	2066		343	2087	2430
										472	46		26	5437		1068	5463	6531
										6	2		70	1433	1	81	1504	1585
										1			42	413	1	31	456	487
											1		3	42		6	45	51
													6	344		1	350	351
														65		1	65	66
													5	217		17	222	239
										5	1		14	352		25	366	391
										170	123		9	150	1	1449	160	1609
										77	10				1	499	1	500
										27	12					177		177
Hemoglobinopathies -thalassemia										7	2					216		216
Hemoglobinopathies - other	51	23	6	6	3				4	1	2					96		96
Primary immune deficiencies	84	9	6	34	24				69	43	62		7	2		331	9	340
Inherant disorders of metabolism	14	4		8	5				35	10	34		2			110	2	112
Auto immune disease	7	2			3				2	5	1			148		20	148	168
Others	18	13		1	2				11	21	18			17		84	17	101
Total patients	1386	3605	46	220	428	4	7	30	1223	4594	733	179		17554	3	12276	17736	30012
Total transplant	1434	3925	47	248	549	5	8	31	1295	5014	789	185		19829	3	13345	20017	33362

Abbreviations: MDS = myelodysplastic syndrome; MD/MPN = myelodysplastic/myeloproliferative neoplasm; MM = multiple myeloma.

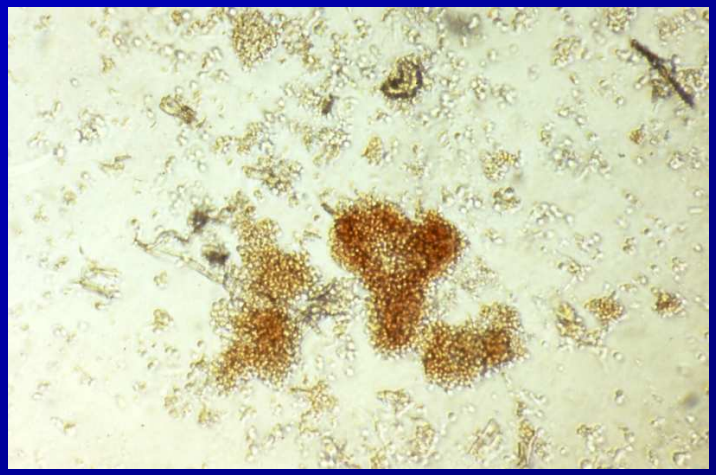




Cellule CD34+ (selezione positiva)



BFU-E



CFU-GM

Mobilizzazione delle cellule staminali

- **Le CSE sono presenti in misura maggiore nel midollo osseo rispetto al sangue periferico (in condizioni fisiologiche):**
  - **Nel midollo osseo il 3-5% delle cellule sono CD34+**
  - **nel sangue periferico solo 0.03-0.05% delle cellule sono CD34+**
  - **L'entità della mobilizzazione dipende dallo schema utilizzato:**
  - **Chemioterapia:**
    - **incremento delle CS nel sangue periferico nell'ordine di 20-25 volte**
  - **Fattori di crescita**
  - **. incremento delle CS nel sangue periferico nell'ordine di 16-25 volte**
  - **Terapia combinata (chemoterapia + fattori di crescita):**
    - **incremento delle CS nel sangue periferico fino a 100-160 volte.**

Presently available GF/mobilizing drugs

- G-CSF: filgrastim or lenograstim (10-16 µg/Kg/d sc) FDA approved
- GM-CSF: sargramostim (5-10 µg/Kg/d sc) FDA approved

- IL-6, 8, 12
- Stem Cell Factor (with G-CSF)
- Flt-3
- With/without CT

- pegfilgrastim
- AMD3100 (stromal derived factor-SDF-1$^{\alpha}$ inhibitor) Plerixafor
- ……

In steady-state conditions HSC are retained in the niche by the combined action of nestin + MSC and CD68+CD169+ Macrophages

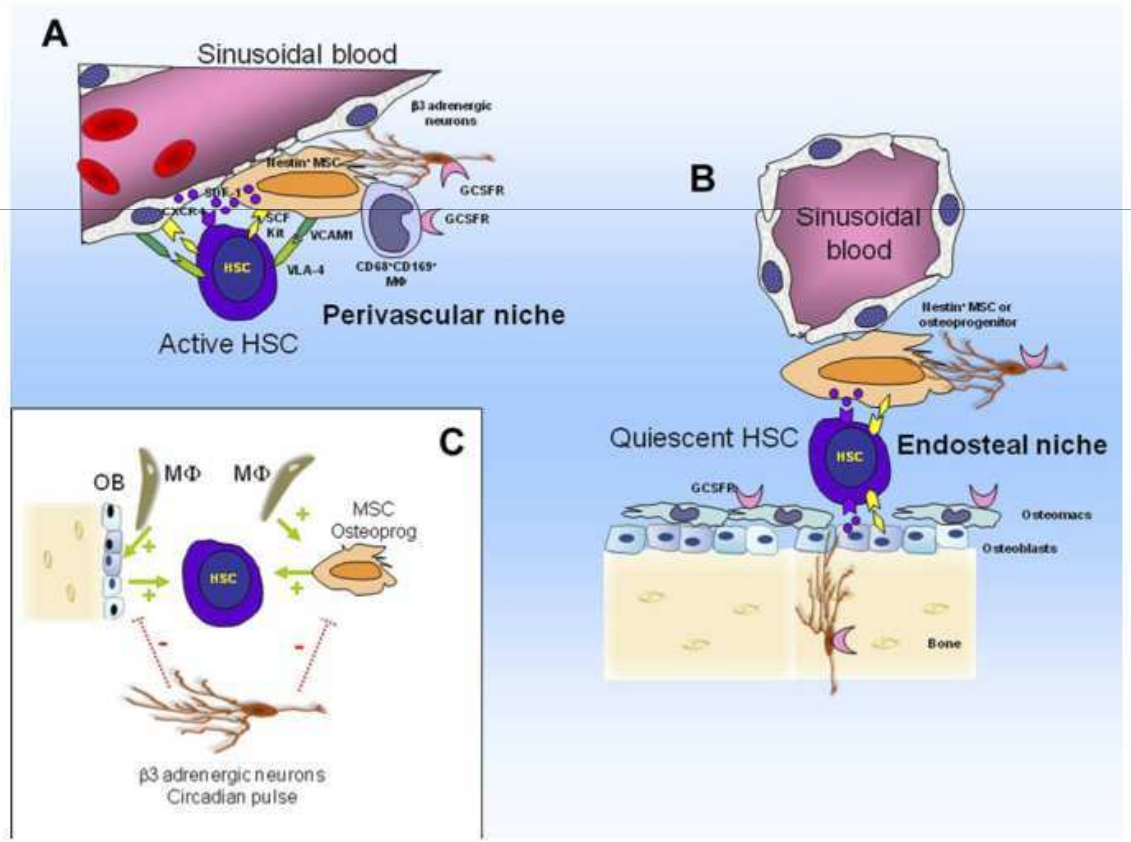
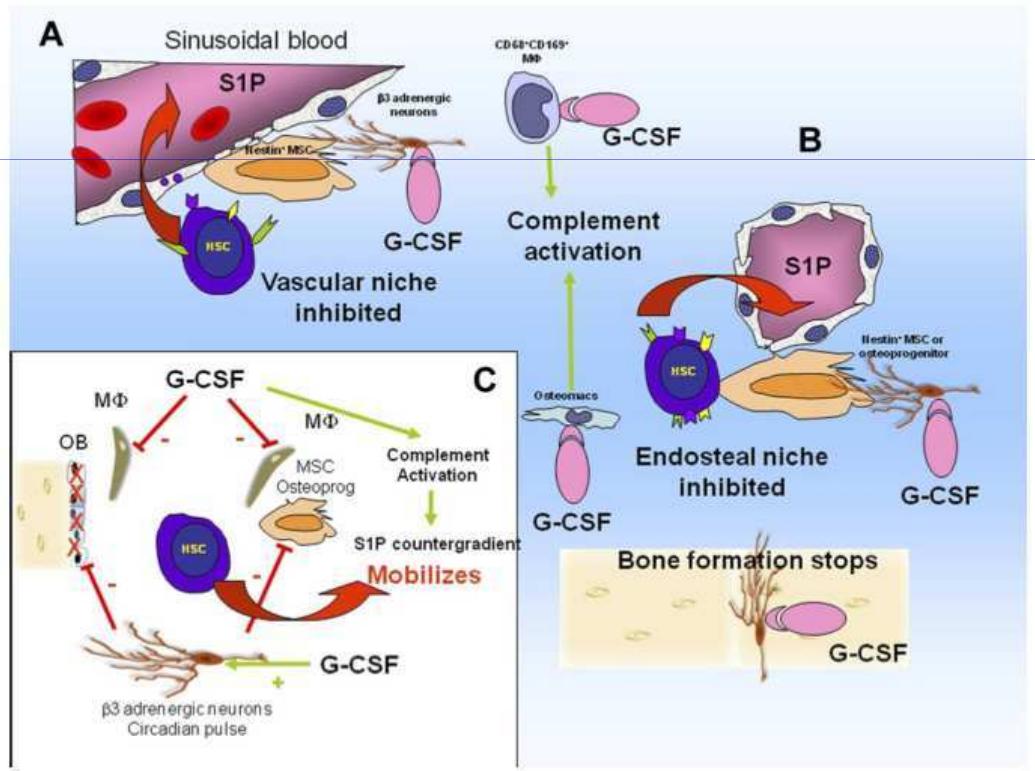
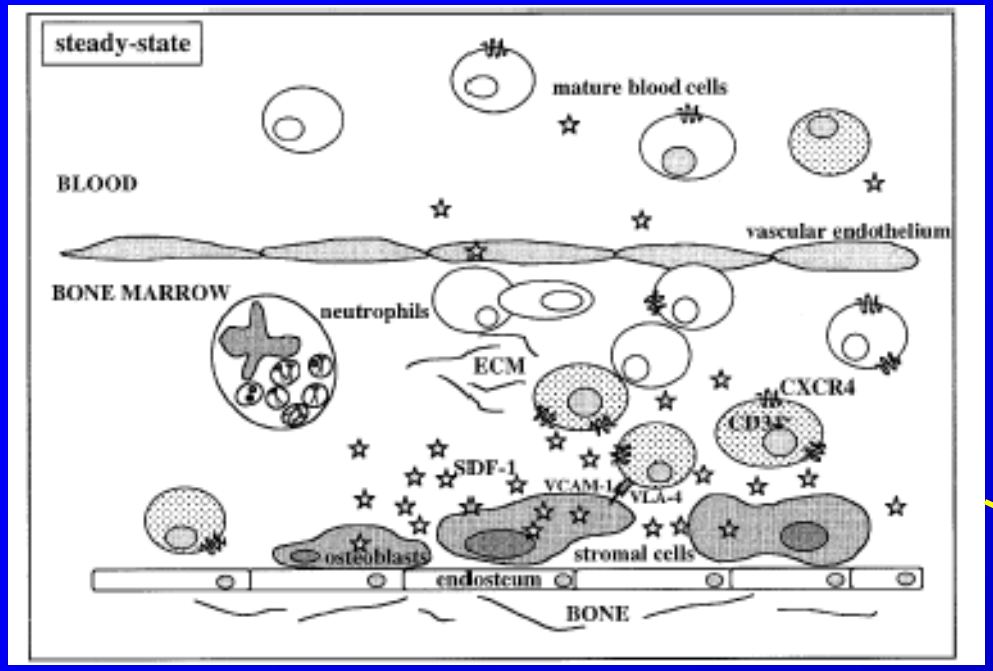


Figure 1. Model of HSC niche regulation in steady state. (A) Perivascular niches harboring active HSCs that regenerate the hematopoietic system. Active HSCs are in contact with perivascular nestin$^+$ MSCs and sinusoidal endothelial cells. Both MSCs and sinusoidal endothelial cells express SDF-1, transmembrane SCF, and VCAM-1 that retain HSCs within the niche via adhesive and chemotactic interactions. (B) Endosteal niches harboring quiescent HSCs. Quiescent HSCs are in contact with nestin$^+$ MSCs or osteoprogenitors or both. (C) Interactions between niches cells, HSCs, and adrenergic neurons. CD68$^+$ CD169$^+$ macrophages and osteomacs forming support function of nestin$^+$ MSCs, osteoprogenitors and osteoblasts which in turn maintain HSCs in steady state (stimulating feed-back illustrated by green arrow). Sympathetic β3 adrenergic nerves inhibit SDF-1 secretion by MSCs and osteoblasts after a circadian pulse (negative pulse illustrated by dotted red bars).

G-CSF activates CD68+CD169+ Macrophages with consequent loss of supportive functions for MSC (downreg of CXCL12, SCF and VCAM-1)
G-CSF reduces SDF-1 production by MSC through beta-adrenergic neuron activation

Figure 2. G-CSF deregulates niches and causes HSC mobilization. (A) G-CSF activates CD68$^+$ CD169$^+$ macrophages in perivascular niches. This suppresses macrophage supportive function for MSCs. Consequently, expression of CXCL12, SCF, and VCAM-1 is down-regulated. Complement cascade is activated, leading to erythrocyte lysis and release of S1P in the blood, creating a chemotactic counter gradient. Active HSCs are mobilized. (B) G-CSF suppresses osteomacs in endosteal niches. Osteoblasts are lost, bone formation stops, and expression of CXCL12, SCF, and VCAM-1 by MSCs and osteoprogenitors is down-regulated. Dormant HSCs are mobilized. (C) Schematic representation of interactions in response to G-CSF. β-adrenergic neuron activation by G-CSF inhibits SDF-1 production by MSCs, osteoprogenitors, and osteoblasts and inhibits bone formation by osteoblasts (solid red bars). Stimulation of osteomacs and CD169$^+$ macrophages by G-CSF (solid red bars) suppresses their supportive function for MSCs and osteoblasts. Consequently, expression of SDF-1, Kit ligand, and VCAM-1 by osteoprogenitors and MSCs is down-regulated. Complement cascade is activated by G-CSF, resulting in S1P release into the blood.





Filgrastim
MW core protein
18.6 kDa

G-CSF
MW glycoprotein
approx. 20 kDa

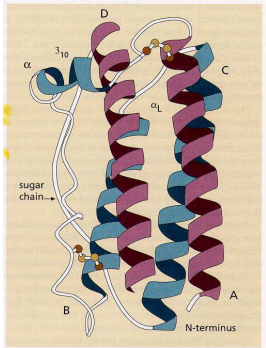
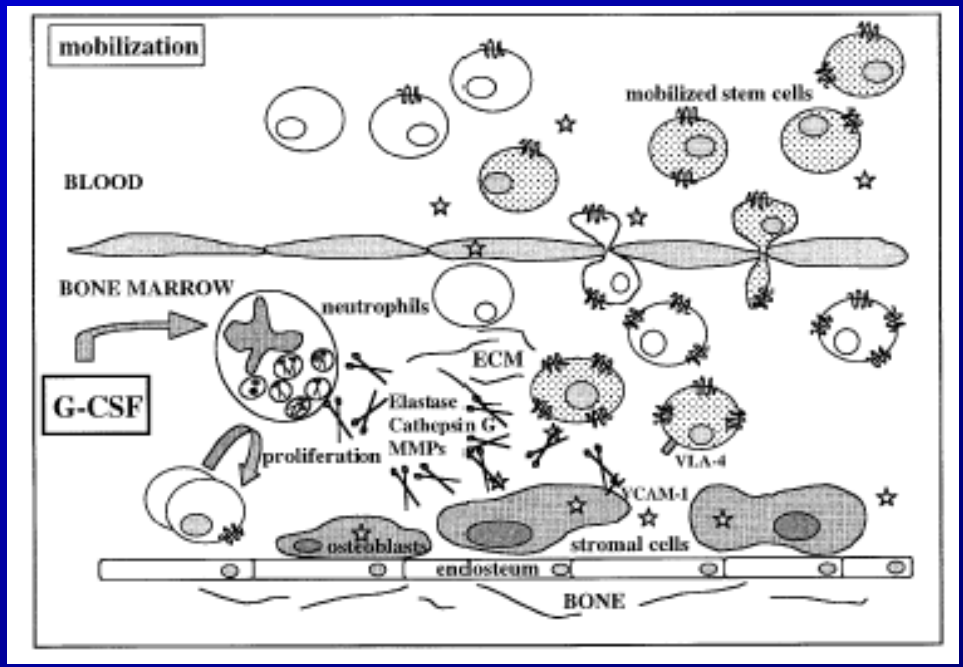


Figure 8.1b. Secondary structure of Filgrastim (recombinant G-CSF). Filgrastim is a 175-amino acid polypeptide. Its four anti-parallel α helices (A, B, C and D) and short 3-to-10 type helix (3_{10}) form a helical bundle. The two biologically active sites (α and α_L) are remote from modifications at the N terminus of the A helix and the sugar chain attached to loop C-D. *Note:* Filgrastim is not glycosylated; the sugar chain is included to illustrate its location in endogenous G-CSF.

G-CSF

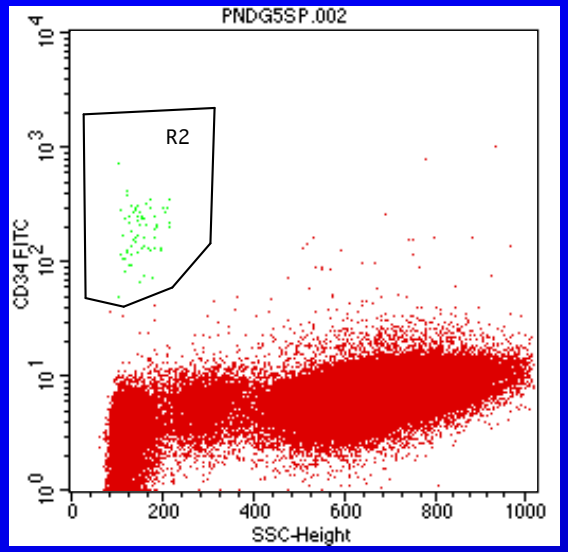
Azione in vivo

- Nel soggetto normale la somministrazione di G-CSF induce una rapida granulocitosi dovuta ad aumentata attività proliferativa dei progenitori e dei precursori dei neutrofili.
- Non modifica l'emivita dei neutrofili circolanti.
- Attiva alcune funzioni dei granulociti neutrofili (es. produzione superossidi)
- Aumenta la liberazione in circolo di progenitori immaturi.



Lapidot et al. Exp Hematol, 2002

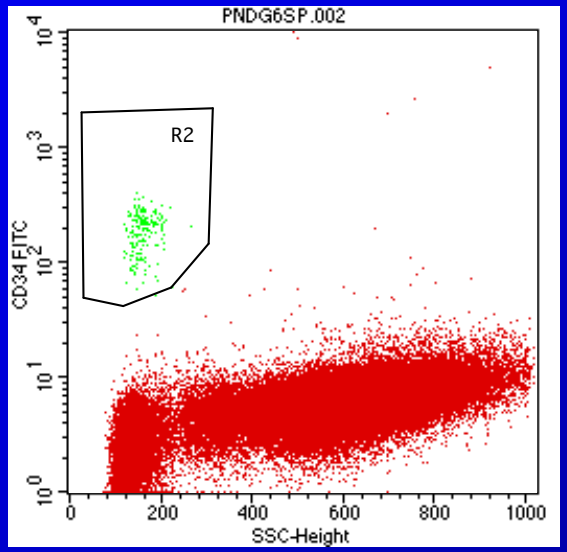
Mobilizzazione CD34+ mediante G-CSF 10µg/Kg/d



SP; gg +4, WBC 47.780/µL,

CD34+ 0,06%,

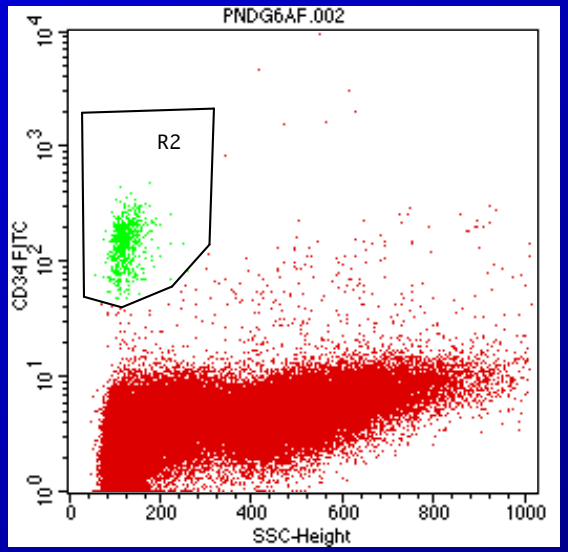
CD34+ = 30/ µL



SP, gg +5, WBC 47.890/µL,

CD34+ 0,17%,

CD34+= 81/ µL

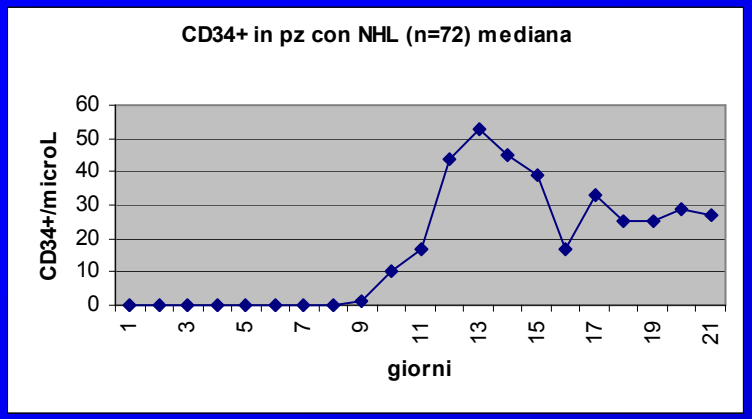


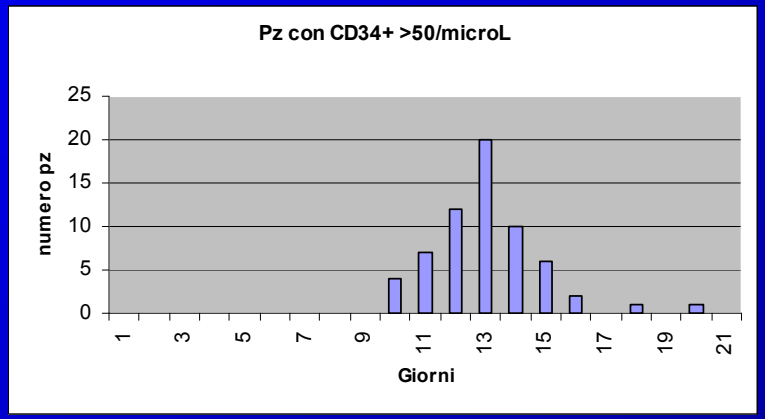
Aferesi, gg +5, WBC 353.250/µL,

CD34+ 0,80%,

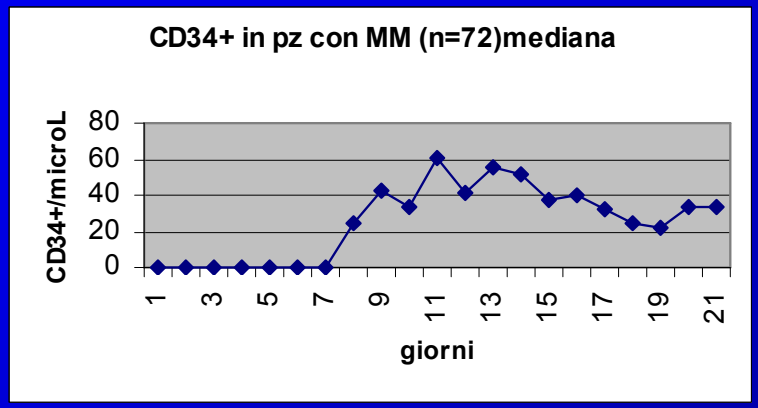
CD34+=2826/ µL

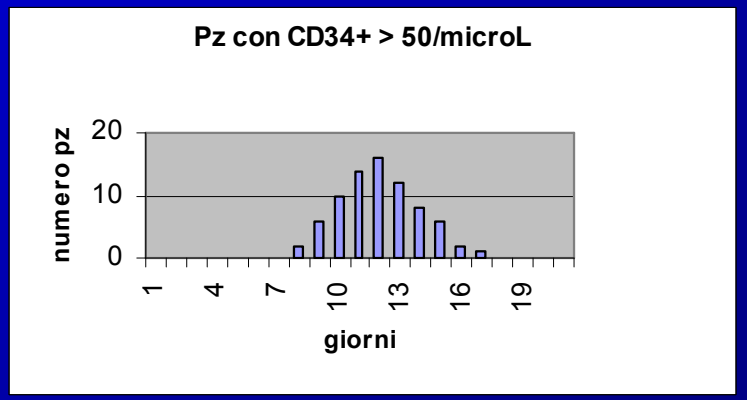
Cinetica di mobilizzazione delle CD34+ in alcune patologie-1





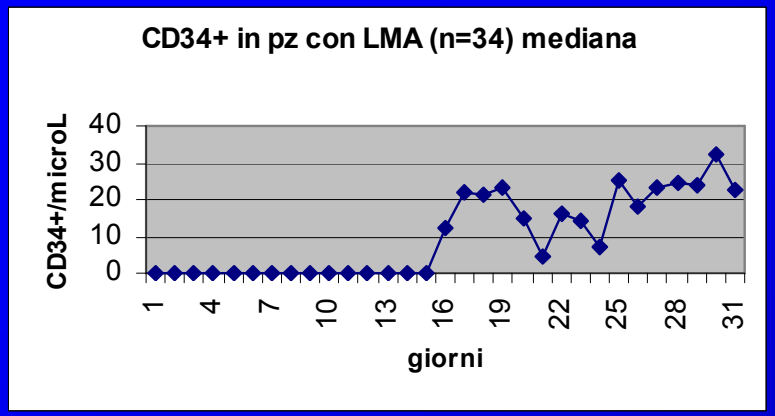
Pazienti affetti da NHL, età 47 (range 21-68)

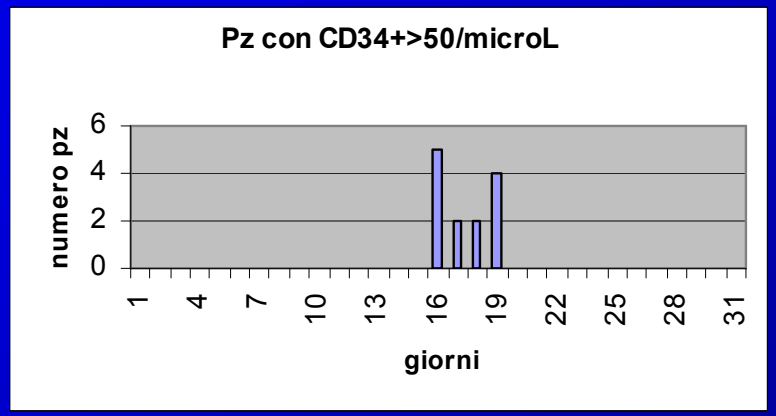




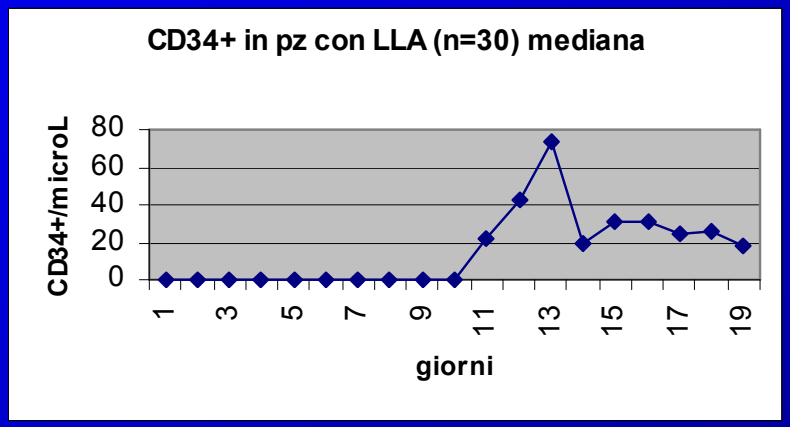
Pazienti affetti da MM, età 61 (range 31-71)

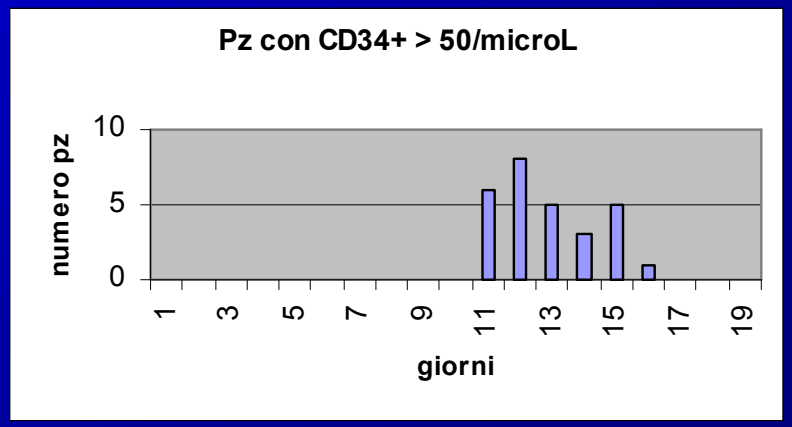
Cinetica di mobilizzazione delle CD34+ in alcune patologie-2





Pazienti affetti da LMA, età 50 (range 24-66)





Pazienti affetti da LLA, età 27 (range 5-69)

Management of poor peripheral blood stem cell mobilization: Incidence, predictive factors, alternative strategies and outcome. A retrospective analysis on 2177 patients from three major Italian institutions ☆

Paolo Perseghin [a,*], Elisabetta Terruzzi [b], Maria Dassi [a], Valentina Baldini [a], Matteo Parma [b], Paola Coluccia [c], Patrizia Accorsi [d], Giorgio Confalonieri [a], Luisa Tavecchia [a], Luisa Verga [b], Fernando Ravagnani [c], Antonio Iacone [d], E.M. Pogliani [b], Pietro Pioltelli [b]

Transfusion and Apheresis Science 41 (2009) 33–37

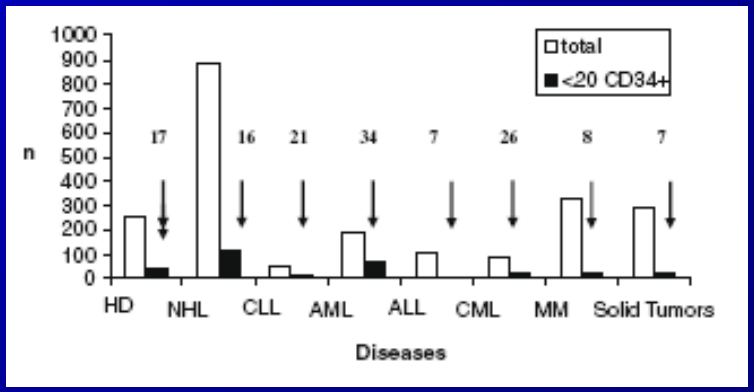
Table 2
Incidence of poor peripheral blood HSC mobilization (<20 CD34+/μL) in patients from three Italian academic institutions.

Diseases	Monza (99–07)		INT Milan (02–07)		Pescara (00–07)		Total (%)	
	n	<20[a] (%)	*n*	<20[a] (%)	*n*	<20[a] (%)	*n*	<20[a] (%)
HD	45	7 (15)	141	29 (21)	66	8 (12)	252	44 (18)
NHL	176	38 (22)	529	67 (13)	176	35 (20)	881	140 (16)
CLL	7	5 (71)	27	5 (18)	17	1 (6)	51	11 (22)
AML	113	43 (38)	9	2 (22)	64	19 (30)	186	64 (34)
ALL	77	8 (10)	0	0	33	0 (0)	110	8 (7)
CML	78	18 (23)	0	0	3	3 (100)	81	21 (26)
MM	151	15 (10)	15	1 (5)	160	11 (7)	326	26 (8)
Solid tumors	0	0	240	19 (8)	50	2 (4)	290	21 (7)
Total (%)	647	134 (21)	961	123 (13)	569	79 (14)	2177	335 (15)

[a] <20 CD34+ cells/μL.

Prognostic factors which may negatively affect successful HSC collection.

- Age (<70 better)
- Gender (male better)
- Diagnosis (stage, BM involvement)
- Previous CT (number of cycles, HSC-toxic drugs such as BCNU or melphalan)
- Prior irradiation
- FUO/infections
- Time from last CT
- GF dose and administration (single or split dose)



CONFERENCE REPORT

Best practice for peripheral blood progenitor cell mobilization and collection in adults and children: results of a Società Italiana Di Emaferesi e Manipolazione Cellulare (SIDEM) and Gruppo Italiano Trapianto Midollo Osseo (GITMO) consensus process

Luca Pierelli, Paolo Perseghin, Monia Marchetti, Patrizia Accorsi, Renato Fanin, Chiara Messina, Attilio Olivieri, Marco Risso, Laura Salvaneschi, and Alberto Bosi for Società Italiana Di Emaferesi and Manipolazione Cellulare (SIDEM) and Gruppo Italiano Trapianto Midollo Osseo (GITMO)

Transfusion, 2012

- PBPC count
  9. Which is the optimal method for CD34+ cell count?
  10. Which is the optimal timing for CD34+ cell count?

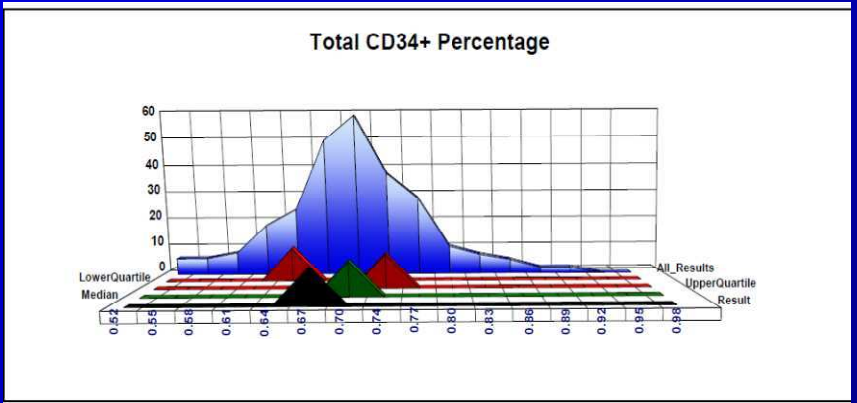
PBPC count

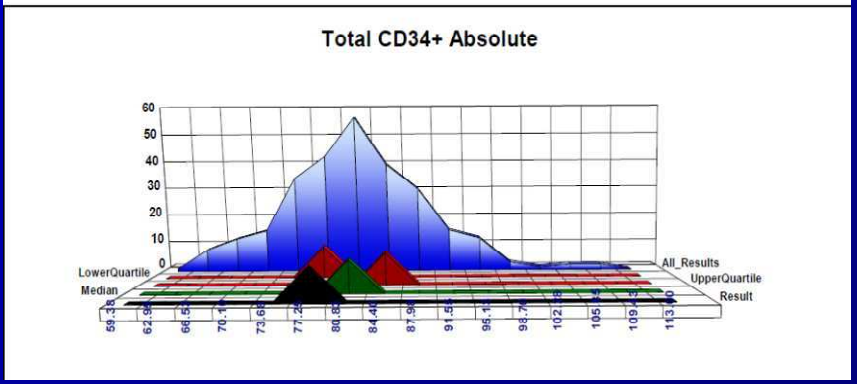
Question 9: Which is the optimal method for peripheral CD34+ cell count?

RECOMMENDATIONS. *An International Society of Hematotherapy and Graft Engineering (ISHAGE) double- or single-platform protocol should be used to count peripheral blood CD34+ cells. In the double-platform protocol, the hematology analyzer should be a last-generation counter with proper linearity, producing accurate WBC differentials and preferentially endowed with a dedicated analytical option: it should be maintained daily and calibrated.*

A viability test should be performed in samples from the harvested products.

All centers routinely performing CD34+ cell enumeration should undergo externally driven quality control (QC) programs.





Question 10: Which is the timing for peripheral CD34+ cell count?

RECOMMENDATIONS. *Daily monitoring of CD34+ cells in peripheral blood is recommended in healthy donors and patients mobilized with G-CSF alone, starting from the third to fourth days of G-CSF administration. CD34+ cell monitoring should start during hematologic recovery after chemotherapy, when the WBC count exceeds 0.5×10^9 to 1×10^9/L, according to the underlying disease.*

In patients receiving plerixafor, CD34+ cell count should be performed every morning after evening plerixafor administration, irrespective of WBC count.

Monitoring of CD34+ cells in peripheral blood should continue until the day of last leukapheresis.

Question 7: Which is the target PBPC dose?

RECOMMENDATIONS. *The minimum PBPC dose to be collected and infused to assure a low transplant-related morbidity is 2×10^6/kg/body weight CD34+ cells per planned transplant.*

The optimal PBPC dose to be collected and infused to assure a prompt hematopoietic recovery is 5×10^6/kg/body weight CD34+ cells per planned transplant.

The highest PBPC dose to be infused in patients with acute myeloid leukemia is 7×10^6/kg/body weight CD34+ cells, due to a reduced event-free survival at higher doses.

BACKGROUND. In the autologous setting a wide series of indications about the safe minimum dose of CD34+ cells to be infused following high-dose treatment have been reported. Full hematopoietic reconstitution was assured within 3 weeks from reinfusion only in patients receiving at least 2.5×10^6/kg/body weight.[60] A rapid and stable engraftment, that is, within 2 weeks, can be achieved with a higher probability when a CD34+ cell dose not lower than 5×10^6/kg/body weight is reinfused.[61]

Mobilization/collection failure % in lymphomas

Author	Country	n	Disease	Mobilisation regimen	Failure rate*
Stiff *et al.*	US	48	NHL, HD	SCF + G-CSF	30%
		54	NHL, HD	G-CSF	46%
Pusic *et al.*	US	467	NHL	G-CSF	27%
Flomenberg *et al.*	US	15	NHL	G-CSF	53%
Hosing *et al.*	US	149	NHL, HD	G-CSF alone G-CSF plus chemotherapy	20%
Russell *et al.*	EU + Australia	29	NHL	ICE + pegfilgrastim (6mg)	31%
		29	NHL	ICE + pegfilgrastim (12mg)	41%
		32	NHL	ICE + filgrastim (5 mcg/kg/day)	28%
Watts *et al.*	UK	78	NHL, HD	ESHAP	15%
		78	NHL, HD	1.5g Cy	29%
Pavone *et al.*	Italy	38	NHL	DHAP	15%
		34	NHL	5g Cy	11%
Bashey *et al.*	US	94	NHL	1.5g Cy	18%

*Proportion of patients collecting < 2 x 10^6 cells/kg

Mobilization/collection failure in myelomas

Author	Country	n	Disease	Mobilisation regimen	Failure rate*
Stiff *et al.*	US	48	NHL, HD	SCF + G-CSF	30%
		54	NHL, HD	G-CSF	46%
Pusic *et al.*	US	467	NHL	G-CSF	27%
Flomenberg *et al.*	US	15	NHL	G-CSF	53%
Hosing *et al.*	US	149	NHL, HD	G-CSF alone G-CSF plus chemotherapy	20%
Russell *et al.*	EU + Australia	29	NHL	ICE + pegfilgrastim (6mg)	31%
		29	NHL	ICE + pegfilgrastim (12mg)	41%
		32	NHL	ICE + filgrastim (5 mcg/kg/day)	28%
Watts *et al.*	UK	78	NHL, HD	ESHAP	15%
		78	NHL, HD	1.5g Cy	29%
Pavone *et al.*	Italy	38	NHL	DHAP	15%
		34	NHL	5g Cy	11%
Bashey *et al.*	US	94	NHL	1.5g Cy	18%

*Proportion of patients collecting < 2 x 10^6 cells/kg

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)

Bone Marrow Transplantation (2012) 47, 342–351

GITMO-WG deemed that the issue of 'poor mobilization' may pertain to three sequential phases:

(i) before the mobilizing treatment, when the mobilization procedure is planned;
(ii) during the mobilization procedure; and
(iii) at the completion of the whole PBSCs collection process.

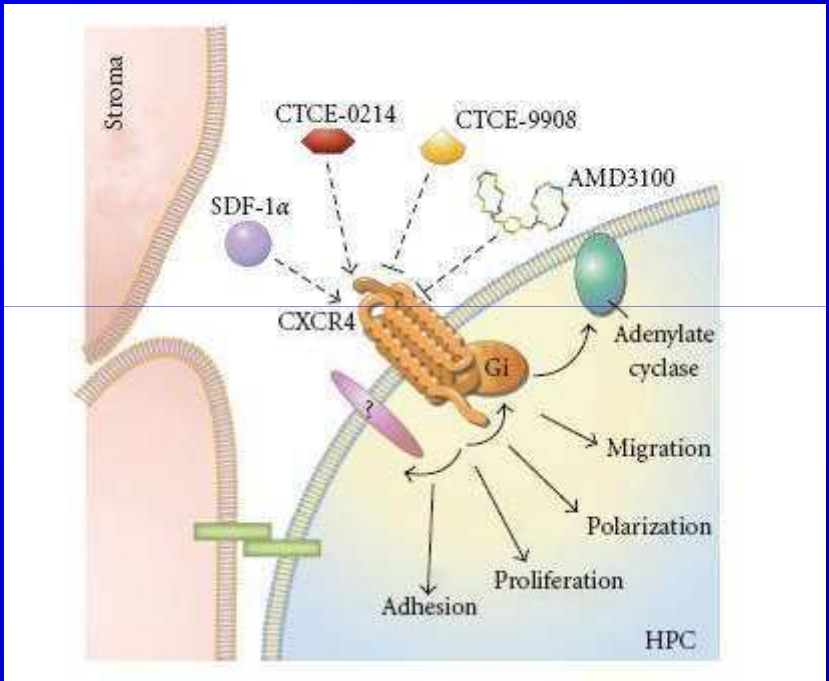
Table 2 Relative importance of the selected core set criteria, expressed both as conceptual and by operational definitions

Conceptual criteria	*Operational criteria*	*Rank (1–9)*	*Pairwise comparison*	*Variability (%)*
Harvested $CD34^+$ cells	Less than 2.0×10^6 harvested $CD34^+$ cells per kg per planned SCT by no more than three aphereses	8.7	0.26	47
Peak of $CD34^+$ cells	Peak $CD34^+$ cell count $<20/\mu L$ on days 4–6 after the start of mobilization with G-CSF alone or up to 18–20 days after chemotherapy and G-CSF	8.0	0.25	36
Refractory disease		6.0	0.08	74
Advanced disease	Advanced disease, that is, at least two previous cytotoxic lines	5.8	0.12	38
Extensive radiotherapy	Extensive radiotherapy to marrow bearing tissue	7.2	0.08	54
Previous exposure to fludarabine, melphalan, lenalidomide		6.6	0.06	47
Previous exposure to other therapies potentially affecting SC mobilization		4.8	0.03	67
Extensive BM involvement at mobilization		5.4	0.04	47
Poor BM cellularity at mobilization	BM cellularity <30% at mobilization	4.8	0.04	42
Old age	Age older than 65 years	5.1	0.02	50

Proposed definitions (GITMO ad-hoc expert panel)

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

Plerixafor
Modalità d'azione



- Si lega in modo reversibile al recettore CXCR4 e blocca l'interazione con l'SDF-1

Dosaggio del Plerixafor

- Somministrare plerixafor dopo 4 giorni di G-CSF
- Dose raccomandata negli adulti
  - Somministrare 240 μg/kg (peso corporeo effettivo) con iniezione SC
  - La dose non deve superare 40 mg/die indipendentemente dal peso corporeo
    - Il plerixafor non è stato valutato in pazienti che pesano più del 175% del loro peso corporeo ideale
    - Si ha un'esperienza limitata su pazienti >160 kg
  - Ogni fiala contiene 1,2 ml di una soluzione da 20 mg/ml
  - Volume da somministrare (in ml) = 0,012 x peso corporeo (in kg)
- Dosaggio in adulti con insufficienza renale
  - Ridurre la dose di un 33% a 160 μg/kg nei pazienti con insufficienza renale da moderata a severa (CL_{CR} 20-50 ml/min)
  - La dose massima è di 27 mg/die

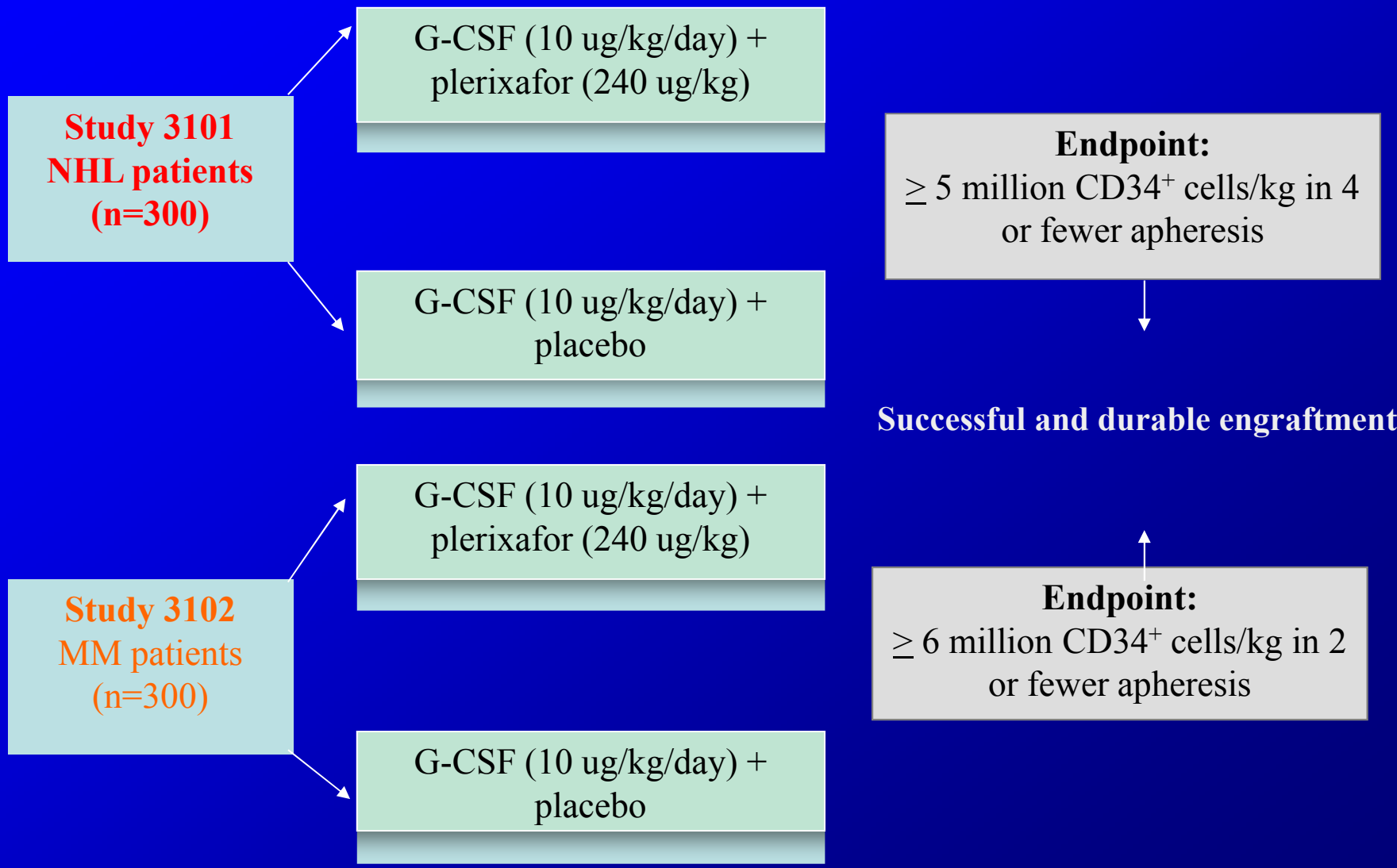
Raccomandazioni del produttore

Informazioni importanti sulla sicurezza

Aspetto sicurezza	Raccomandazione
Potenziale mobilizzazione di cellule tumorali in pazienti affetti da linfoma e MM	La rilevanza clinica del rischio teorico di mobilizzazione delle cellule tumorali non è stata pienamente chiarita. In studi clinici condotti su pazienti affetti da LNH e MM, non è stata osservata alcuna mobilizzazione delle cellule tumorali con plerixafor
Mobilizzazione delle cellule tumorali nei pazienti leucemici	Plerixafor non è raccomandato per la mobilizzazione delle cellule staminali ematopoietiche e la relativa raccolta nei pazienti con leucemia
Aumento dei leucociti in circolo	Durante la terapia con plerixafor i conteggi dei globuli bianchi devono essere monitorati; affidarsi al giudizio clinico quando si somministra plerixafor a pazienti con leucociti nel sangue periferico >50.000 cellule/µl
Uso in gravidanza	Plerixafor non deve essere usato durante la gravidanza, a meno che la condizione clinica della donna richieda un trattamento con plerixafor
Effetto sulle dimensioni della milza	I soggetti ai quali viene somministrato plerixafor in combinazione con G-CSF che riferiscono dolore addominale in alto a sinistra e/o dolore scapolare o alla spalla devono essere valutati per verificare l'integrità della milza
Trombocitopenia	I conteggi delle piastrine devono essere monitorati in tutti i pazienti trattati con plerixafor e sottoposti ad aferesi

Informazioni Sanofi

Plerixafor Phase III Trials – Study Design



blood

2009 113: 5720-5726
Prepublished online Apr 10, 2009;
doi:10.1182/blood-2008-08-174946

Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma

John F. DiPersio, Edward A. Stadtmauer, Auayporn Nademanee, Ivana N. M. Micallef, Patrick J. Stiff, Jonathan L. Kaufman, Richard T. Maziarz, Chitra Hosing, Stefan Früehauf, Mitchell Horwitz, Dennis Cooper, Gary Bridger, Gary Calandra and for the 3102 Investigators

Study 3102
MM patients
(n=300)

Kinetics of collections

% of patients reaching ≥6 x 10e6 CD34+/kg

median CD34+ cells collected on each apheresis day

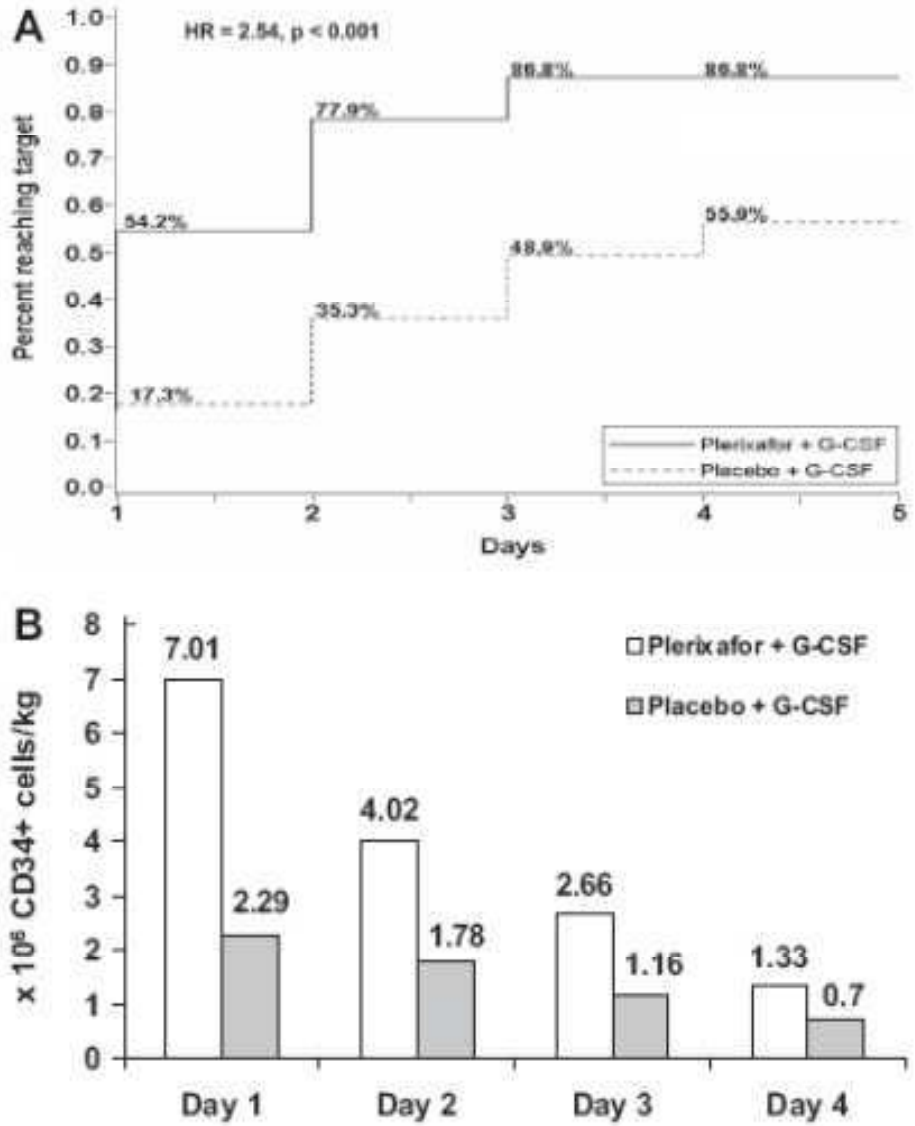
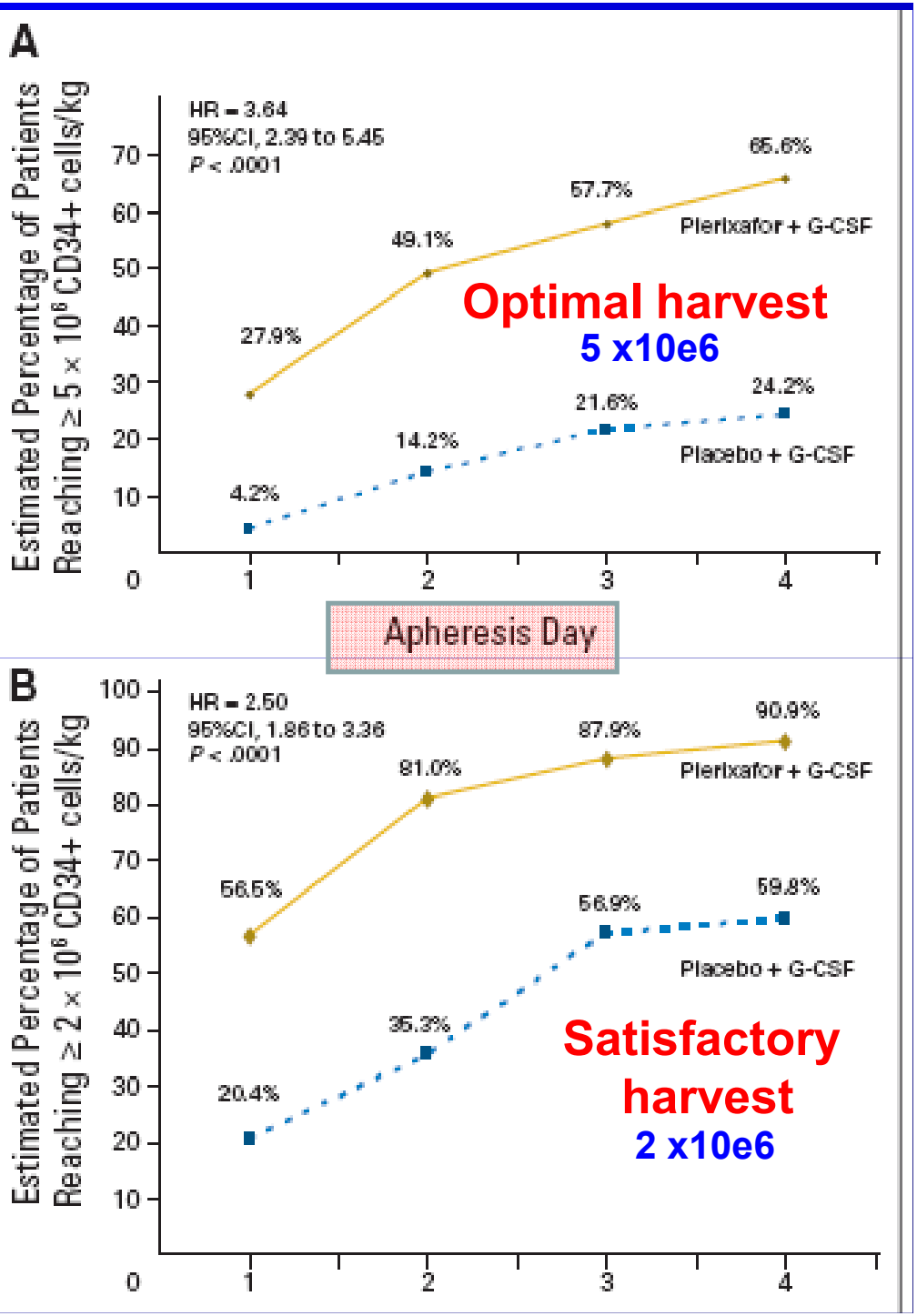


Figure 3. Kinetics of CD34/kg collection. (A) Kaplan-Meier estimate of proportion of patients reaching 6×10^6 or more CD34+ cells/kg. (B) Median CD34+ cells collected on each apheresis day.

Study 3101
NHL patients
(n=300)

Proportion of patients reaching 5 or 2 x10e6 CD34 cells/kg

Median number of apheresis days required to achieve 5x10e6 CD34 cells/kg was 3 days in the plerixafor group,
and not estimable in the placebo group, as less than 50% of patients reached the
target within 4 apheresis days.

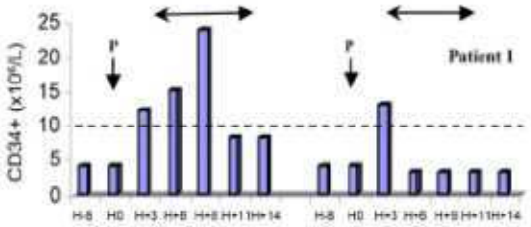


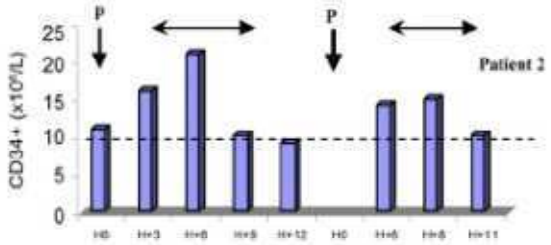
A specific time course for mobilization of peripheral blood CD34+ cells after plerixafor injection in very poor mobilizer patients: impact on the timing of the apheresis procedure

François Lefrère, Laeticia Mauge, Delphine Réa, Jean-Antoine Ribeil, Liliane Dal Cortivo, Anne C. Brignier, Charbel Aoun, Jérôme Larghéro, Marina Cavazzana-Calvo, and Jean-Michel Micléa

Transfusion, 2012

CONCLUSION: Had such patients been tested for PB CD34+ cell mobilization according to conventional criteria (i.e., 11 hr after plerixafor administration), apheresis would not have been performed at the optimal timing. For very poor stem cell mobilizer patients, early monitoring of PB CD34+ cell count may be required for the optimal initiation of apheresis.

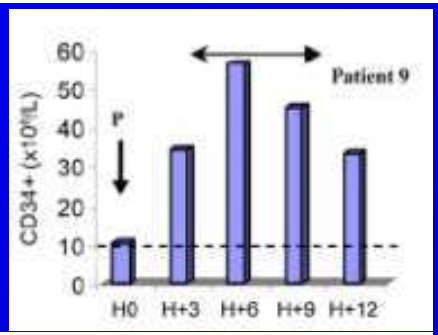




G-CSF 10µg/Kg x 5gg,

Ple at 5 a.m. gg +5

Controlli ogni 3 h



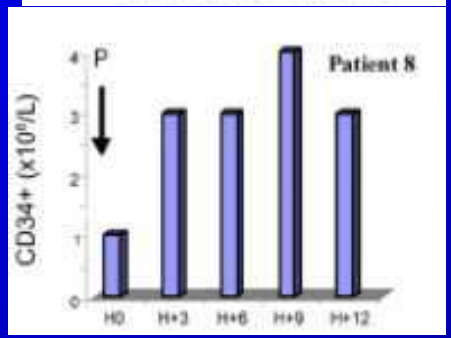


TABLE 2. Results of stem cell mobilization and collection after plerixafor and G-CSF administration

Patient	Time interval between plerixafor administration and the first PB CD34+ >10 × 10⁶/L (hr)	Time interval from plerixafor administration to the beginning of apheresis (hr)	Time interval from plerixafor administration to the PB CD34+ ×10⁶/L peak (hr)	PB CD34+ peak (×10⁶/L)	Time interval between plerixafor administration and first decrease in PB CD34+ ×10⁶/L (hr)	CD34+/kg collected	Number of apheresis procedures performed after plerixafor administration
1	H+3	H+4	H+8	23	H+11	2.5	2
2	H+3	H+4	H+6	21	H+9	3.5	2
3	H+3	H+4	H+8	41	H+9	4.5	1
4	Not reached	H+7	H+6	9	H+9	1.4	2
5	H+3	H+4	H+6	17	H+9	2.75	1
6	H+3	H+4	H+8	12	H+10	2.85	2
7	H+3	H+4	H+9	55	H+11	3.6	2
8	Not reached	Not performed	H+9	4	H+12	-	Not collected
9	H+3	H+4	H+6	56	H+9	8.2	1
10	H+5	H+6	H+5	10	H+7	1.5	2
11	H+3	H+4	H+6	25	H+8	2.95	1
12	H+3	H+4	H+9	50	H+12	5.18	2
13	H+3	H+4	H+8	13	H+11	1.5	1

Plerixafor and G-CSF for first-line steady-state autologous peripheral blood stem cell mobilization in lymphoma and multiple myeloma: results of the prospective PREDICT trial

by Nigel Russell, Kenny Douglas, Anthony Ho, Mohamad Mohty, Kristina Carlson, Gert J. Ossenkoppele, Giuseppe Milone, Macarena Ortiz Pareja, Daniel J. Shaheen, Arnold Willemsen, Nicky Whitaker, and Christian Chabannon

Haematologica 2012 [Epub ahead of print]

Table 3. Mobilization features.**

	MM n=90	NHL n=25
No. of patients undergoing apheresis (%)^	89 (99)	22 (88)
Fold change# in PB CD34+ cells/µl, Median (range)	2.6 (0.2-94.0)	2.6 (0.4-5.5)
CD34+ cells/kg x 10^6 collected, Median (range)	7.6 (1.5-24.0)	5.2 (0.2-16.7)
No. of patients collecting minimal cell dose [≥2x10^6 CD34+ cells/kg] (%)	88 (98)	20 (80)
Days to collect minimal cell dose, Median (range)	1 (1-3)	1 (1-3)
No. of patients collecting optimal cell dose [≥5x10^6 NHL and ≥6x10^6 MM CD34+ cells/kg] (%)	80 (89)	12 (48)*
Days to collect optimal cell dose, Median (range)	1 (1-4)	3 (1-3)

Based on outcomes from the current trial and from previous trials, as well as on data obtained from the compassionate use program in both the US and EU, introduction of plerixafor appears to be an effective, safe and efficient approach to improve already existing mobilization regimens. Further, the combination of plerixafor with G-CSF may represent an alternative to the administration of myelosuppressive agents such as cyclophosphamide when this is not strictly required by treatment of the underlying malignancy, such as is increasingly the case for patients with multiple myeloma.

Figure 3a. Percentage of patients achieving minimal (≥ 2 x 10^6) cell dose by apheresis day.

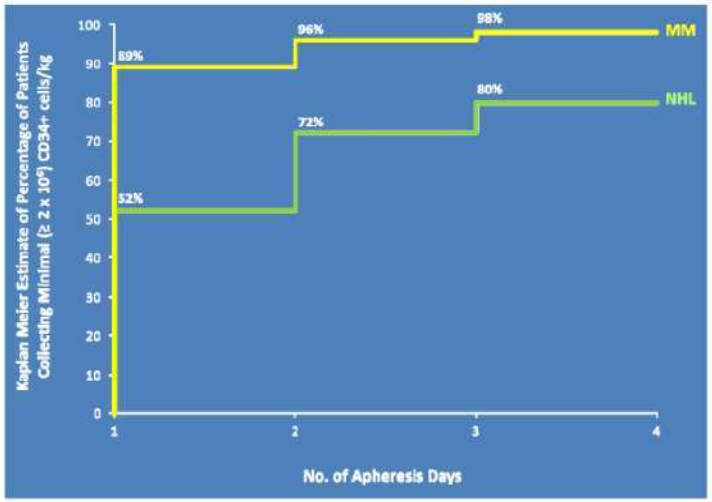
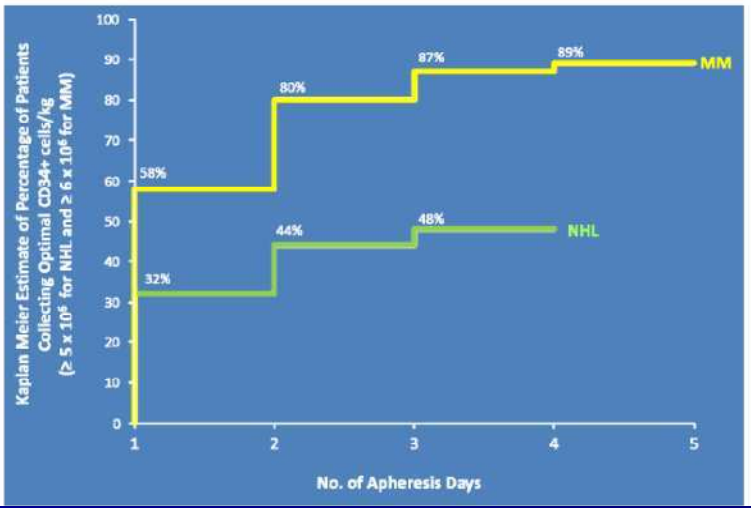


Figure 3b. Percentage of patients achieving optimal cell dose by apheresis day.



REVIEW

Bone Marrow Transplantation (2012) **47**, 1154 – 1163

Novel agents and approaches for stem cell mobilization in normal donors and patients

ŞM Bakanay and T Demirer

PCM= plasma-cell myeloma

Table 3. Phase-II studies of PBPC mobilization with chemotherapy plus pegfilgrastim

	Number of patients, indication	*Pegfilgrastim dose, schedule*	*Onset of apheresis, median (range)*	*Total CD34+ yield × 10^6/kg, median (range)*	*Number of apheresis, median (range)*	*Patients (%) achieving the target*
Steidl[54]	12, PCM	12 mg, 3 days after CY	13 (11–15)	7.4 (4.9–38)	1 (1–2)	100%, $\geqslant 4 \times 10^6$/kg
Fruehauf[55]	26, PCM	12 mg, 1 day after CAD	13 (10–20)	9.7 (4.9–40.5)	2 (1–4)	88%, $\geqslant 7.5 \times 10^6$/kg
Isidori[56]	25, lymphoma	6 mg, 3 day after IEV	14 (13–16) peak PB34+ reached	8.7 (1.78–17.3)	1	96%, $\geqslant 2 \times 10^6$/kg
Putkonen[58]	38, PCM, lymphoma, CLL	6–18 mg, 1 day after chemotherapy	10 (10–18)	4.9 (1.6–27)	1 (1–3)	79%, $\geqslant 4 \times 10^6$/kg (single), $\geqslant 6 \times 10^6$/kg (tandem)
Simona[59]	38, lymphoma	6 mg, 1 day after ESHAP	10 (8–12)	9.42 (2.4–47.6)	1	83%, $\geqslant 5 \times 10^6$/kg

Abbreviations: CAD = CY, adriamycin, dexamethasone; ESHAP = etoposide, cytarabin, cisplatin, methyl prednisolone; IEV = ifosfamide, epirubicine, etoposide.

Table 4. Different dosing schedules of pegfilgrastim and comparison with filgrastim

	Patients and method	*Median onset of apheresis*	*Median CD34+ yield × 10^6/kg*	*Target achieved by patients (%)*	*Comment*
Bruns[60]	PCM ($n = 45$) Non-randomized study Pegfil 6 mg versus Pegfil 12 mg versus Fil 8 μg/kg/day; started on day 4 of CY	12 versus 13 versus 15	10.2 versus 7.4 versus 8.6	$\geqslant 4 \times 10^6$/kg All patients	Earlier onset of apheresis in pegfilgrastim, no difference in CD34+ cell yield
Russel[61]	NHL ($n = 90$), most heavily pretreated patients Randomized study Pegfil 6 mg versus Pegfil 12 mg versus Fil 5 μg/kg/day; started 1d after ICE	14 versus 12.5 versus 14	4.9 versus 4.4 versus 5.1	$\geqslant 2 \times 10^6$/kg 69 versus 59 versus 72 $\geqslant 5 \times 10^6$/kg 41 versus 45 versus 56	No difference between groups
Tricot[62]	PCM ($n = 237$) Pegfil 6 mg on day 6 and day 13 versus Fil 2 × 5 μg/kg started after DT-PACE	ND	14.5 versus 10.0	$\geqslant 15 \times 10^6$/kg 71.7 versus 17.7 $\geqslant 5 \times 10^6$/kg 89.1 versus 71.9	Significant difference on first day and first three apheresis yields

Abbreviations: DT-PACE = dexamethasone, thalidomide, cisplatin, adriamycine, CY, etoposide; ICE = ifosfamide, carboplatin, etoposide; ND = not determined.

Table 2. Agents investigated as adjunct to G-CSF for PBPC mobilization

Growth factors
GM-CSF
Recombinant human EPO
Recombinant human SCF
Recombinant human TPO
Parathyroid hormone
Recombinant human growth hormone
Chemokine axis mobilizers
AMD3100
GRO-β analogs (SB-251353)
Other small molecules and peptides
Very late antigen-1 antibodies
Retinoic acid receptor-α agonists
TPO-receptor agonists

Table 5. Potential agents targeting the chemokine axis in the stem cell niche

	Receptor	*Mechanism of action*
Macrophage inflammatory protein-1α (MIP-1α, CCL3)	CCR1, CCR2	Unknown
SDF-1α peptide analogs CTCE-0021, CTCE-0214 Met-SDF-1β AMD3100	CXCR4	Alteration of SDF-1/CXCR4 signaling
IL-8 (CXCL8) GRO proteins GRO-β (CXCL2) SB-251353	CXCR2	Neutrophil-dependent upregulation of matrix metalloproteinase-9 activity, may ultimately impact the SDF-1/CXCR4 axis

Table 6. Phase-II Clinical trials with plerixafor plus G-CSF

	Stewart[85]	Cashen[86]	Stiff[87]	Gazitt[88]
Patient diagnosis (*n*)	NHL (8) PCM (14)	HL (22)	NHL (23)[a] PCM (26)[a]	NHL (10)[a]
Median fold increase in PB CD34 cells/μL after plerixafor	2.9 (2.0–7.6)	3.2 (1.7–5.7)	2.5 (1.3–6.0)	2–6
Median (range) apheresis days	1 (1–5)	2 (1–5)	2 (1–5)	1–2
Median (range) collected total CD34 cells $\times 10^6$/kg	9.2	6.6 (0.9–10.4)	5.9 (1.5–22.5)	3.0 (1.99–6.99)
$\geqslant 2 \times 10^6$ CD34 cells/kg, *n* (%)	22 (100)	21 (95)	47 (95.9)	10 (100)
$\geqslant 5 \times 10^6$ CD34 cells/kg, *n* (%)	20 (90.9)	15 (68)	11 (22.4)	1 (10)

[a]Included heavily pretreated patients.

Table 7. Phase-III clinical trials of PBPC mobilization with plerixafor plus G-CSF

	PCM study[89]		NHL study[90]	
	Plerixafor+G-CSF (*n* = 148)	Placebo+G-CSF (*n* = 154)	Plerixafor+G-CSF (*n* = 150)	Placebo+G-CSF (*n* = 148)
Achieved primary endpoint (%)	71.6	34.4	59.3	19.6
Achieved min. collection (%)	95.9	92.9	86.7	47.3
Fold increase in PB CD34/μL	4.8	1.7	5.0	1.4
Median number of apheresis days to collect the target	1	4	3	NE[a]
Median (range) collected CD34 cells $\times 10^6$/kg	10.96 (0.66–104.57)	6.18 (0.11–42.66)	5.69 (0.03–29.22)	1.98 (0.06–15)
Failed mobilization (%)	0	4.6	7.3	38.5

Abbreviation: PCM = plasma cell myeloma.
[a]Median time was not estimable (NE) as <50% of patients reached the target within four apheresis days.

CONCLUSION

As stem cell interactions with the BM microenvironment are better understood, new mobilizing agents targeting pathways in regulating stem cell trafficking are emerging. A patient-adapted approach in initial stem cell mobilization to prevent further mobilization attempts and to decrease the time to transplantation and costs, as well as morbidity of remobilization, is encouraging. Combining various cytokines, which target different molecular targets in the stem cell niche, not only for increasing stem cell yield but also to improve the quality of graft content and the associated transplantation outcomes are promising areas of research.

Table 8. Pharmacokinetic characteristics of plerixafor

Dosage, route	240 μg/kg actual body weight, s.c.
Peak plasma concentration	30–60 min
Plasma half-life	4 h (3–5)
Distribution	Up to 58% bound to plasma proteins Mainly extravascular fluid space
Metabolism	Not related to cytochrome-P450
Elimination	Renal
Median maximum increase in PB CD34+cells/kg from baseline	4.2 fold (3–5.5)
Time to maximum increase in PB CD34+cells/kg	10 h
Special consideration in renal failure	Cr Cl >50 mL/min, 240 μg/kg (max. 40 mg/day) Cr Cl ⩽50 mL/min, 160 μg/kg (max. 27 mg/day)

Bone Marrow Transplantation (2012) **47**, 1154 – 1163

Sviluppi

- Utilizzo in caso di predicted poor mobilizer in corso di mobilizzazione

Plerixafor Added to Chemotherapy Plus G-CSF Is Safe and Allows Adequate PBSC Collection in Predicted Poor Mobilizer Patients with Multiple Myeloma or Lymphoma

Attolico et al, BBMT 2012

Table 2. Details of Mobilization Schedules, White Blood Cells Count, and CD34⁺ Cells Kinetics and Collections in MM and Lymphoma Patients

Characteristics	MM	Lymphoma
CHT mobilizing regimen	HD-CTX: 12 VP16: 3 Others: 2	DHAP: 13 HyperCVAD: 2 VP16: 2 Others: 3
Plerixafor injections:, median (range)	2 (1-3)	1 (1-2)
WBC before plerixafor ($\times 10^3/\mu L$):, median (range)	17 (2.1-68)	8.15 (1.4-61)
WBC 11 hours after plerixafor ($\times 10^3/\mu L$), median (range)	26.5 (3.5-79)	16.1 (7.2-65)
$CD34^+$ before plerixafor ($\times 10^3/\mu L$):, median (range)	6 (2-32)	5 (0-26)
$CD34^+$ 11 hours after plerixafor ($\times 10^3/\mu L$): median (range)	33 (6-201)	29 (0-116)
Fold increase $CD34^+$ count:, median (range)	4 (2-25)	3 (0-32)
Total number of $CD34^+$ cells collected ($\times 10^6$/kg):, median (range)	4.9 (0-15.2)	2.65 (0-8.2)
Total number of apheresis: median (range)	2 (0-3)	1 (0-2)

MM indicates multiple myeloma; CHT, chemotherapy; HD-CTX, high-dose cytoxan; DHAP, dihydroxyacetone phosphate; CVAD, cyclophosphamide, vincristine, doxorubicin; WBC, white blood cell.

37 pz con MM o NHL

27/37 (73%) CD34 +> $2x10^6$/KG

Table 5. Disease Status after Mobilization and before ASCT and Outcome in the 24 MM and Lymphoma Patients

Transplanted Patients	Disease	Response after Chemomobilization	Conditioning Regimens	ANC >500/mL	PLT >20 x 10^3/mL	PLT >50 x 10^3/mL	Response at Day +90	Status at Day +90
1	HL	CR	FEAM [24]	12	17	19	CR	A
2	HL	SD	FEAM [24]	13	18	30	NE	NE
3	HL	PR	BEAM [25]	14	21	38	PR	A
4	NHL	PR	FEAM [24]	17	22	36	CR	A
5	NHL	CR	FEAM [24]	14	17	22	CR	A
6	NHL	PR	FEAM [24]	20	88	NR	PR	A
7	NHL	SD	FEAM [24]	14	34	NR	NE	NE
8	NHL	CR	BEAM [25]	10	9	26	CR	A
9	NHL	CR	TEAM [26]	23	10	24	CR	A
10	NHL	CR	Thio-Mel	16	30	180	CR	A
11	NHL	PR	BEAM [25]	12	15	33	PR	A
12	MM	nCR	Mel 200	11	15	18	nCR	A
13	MM	PR	Mel 200	11	11	16	PR	A
14	MM	VGPR	Mel 200	16	16	22	VGPR	A
15	MM	PR	Mel 200	13	13	16	PR	A
16								
17								
18								
19								
20								
21								
22								
23								
24								

In conclusion, our data encourage the use of plerixafor after chemotherapy followed by G-CSF in lymphoma or MM patients identified as predicted PMs. The patients underwent this mobilization regimen without major toxicities, and most of them achieved minimum safe doses of $CD34^+$ cells for ASCT within a few days of apheresis and rapid engraftment. This strategy needs to be evaluated in a larger group of lymphoma and MM patients, who are identified as PMs according to well-standardized criteria and receiving homogeneous mobilizing protocols.

Summary median (rar

ASCT indicat
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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

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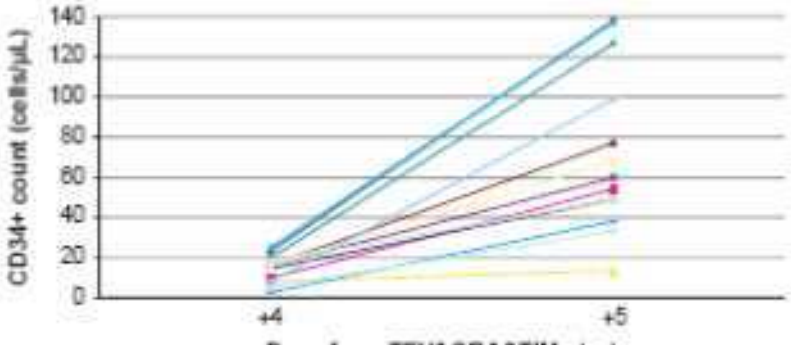
Table 1 Patients' characteristics

Patients (*N*)	14
Gender	M 6, F 8
Median age	55 yr (19–67)
Diagnosis	4 Non-Hodgkin lymphoma 2 Hodgkin lymphoma 8 MM
Median number of previous chemotherapy lines	1 (1–4)
Induction therapies	
NHL	
R-CHOP	4
HL	
BEACOPP	2
MM	
THALDODEX	6
VELDEX	2

R-CHOP, rituximab, cyclophosphamide, adriamycin, vincristine, prednisone; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, THALDODEX, thalidomide, liposomal doxorubicin, dexamethasone; VELDEX, velcade, dexamethasone; MM, multiple myeloma; NHL, non-Hodgkin's lymphomas.



To date, 7 of 14 patients have undergone high-dose chemotherapy followed by stem cell infusion. The remaining seven patients are scheduled for treatment in the near future. Engraftment occurred in all evaluable patients with a time to ANC >500 of 12 d (range 9–13) and to PLT >20 000 of 13 (range 9–19) d after the transplant.

“Cattivi mobilizzatori”

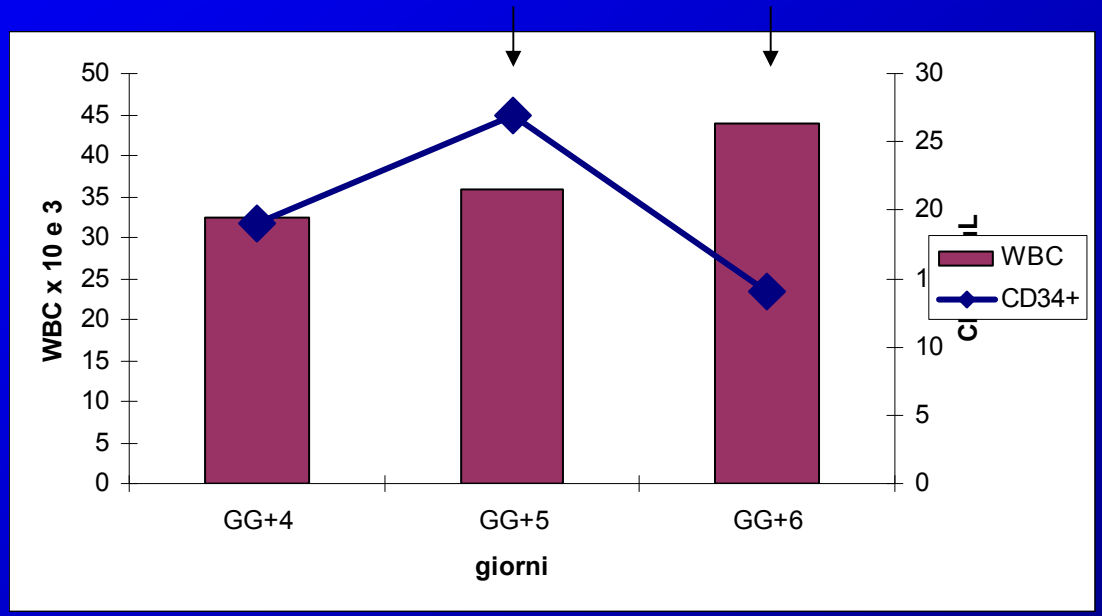
Nel 2% dei donatori stimolati con G-CSF (10 µG/Kg/d) la resa di CD34+ (dopo LVL- 20 litri) è stata < $2x10^6$/Kg

Nel 25 % la resa è stata < $5x10^6$/Kg

E’ possibile prevedere il “cattivo mobilizzatore?”

NO!

Donatore: M, 37 aa, 76 Kg
Ricevente: 90 KG
CD34+ richieste: 720 x 10e6
CD34+ raccolte:
aferesi 1: 214 aferesi 2: 79 totale : 293 x10e6



- Donatori allogenici

Plerixafor and Filgrastim For Mobilization of Donor Peripheral Blood Stem Cells Before A Donor Peripheral Blood Stem Cell Transplant in Treating Patients With Hematologic Malignancies

Fred Hutchinson Cancer Research Center

Collaborator: National Cancer Institute (NCI)

ClinicalTrials.gov Identifier:NCT01076270

Plerixafor and Sargramostim (GM-CSF) for Mobilization of Allogeneic Sibling Donors

VERIFIED BY: WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, JULY 2012

FIRST RECEIVED: JULY 6, 2010 | LAST UPDATED: JULY 19, 2012

PHASE: PHASE 2 | START DATE: NOVEMBER 2010

OVERALL STATUS: RECRUITING | ESTIMATED ENROLLMENT: 34

Unfrozen autologous hematopoietic stem cells (HSC) transplantation in myeloma patients.

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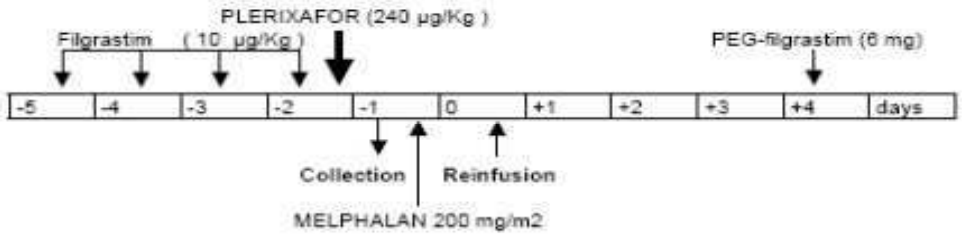
Pz	Età	peso	CD34 +/µL	CD34 +/Kg	N° Af	O.S. (mesi)
CP	51	70	55	4.7	1	+23
PA	66	70	17*	2.7	1	+33
MA	66	72	20	2.4	1	+34
CE	65	50	81	6.1	1	+11
CF	69	63	26	3.2	1	+19
PP	66	68	31	2.41	1	+16
BA	68	75	4	-	-	Recidiva Ora pr
Mediana	66	69	26	2.95	1	21

Filgrastim 10 µg/Kg x 4gg + Plerixaflor 240 µg/Kg 1-2 somm.

* Dopo la II° somministrazione di Plerixaflor



Vantaggio: Questa metodica consente di utilizzare in toto il prodotto raccolto, evitando il 10-15 % di perdita legato alle procedure di congelamento/ scongelamento, con di concerto anche una riduzione dei costi operativi.

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Attività cpp-MI09 (dal maggio 2005)

- 17 donatori (9 M, 8 F) sottoposti a raccolta CSE
  - 3 donazioni per centri esteri
  - 7 donatori dal ns cd MI09 (10 riferiti da altri centri)
- 1 selezionato (donazione sospesa)
- 2 sottoposti a linfocitoaferesi (DLI)

Età : 37 (25-48)

Peso: 73 (50-107)

WBC gg+4: 39.530 x 10^3/µL (21.960-67.420)

WBC gg+5: 45.010 x 10^3/µL (27.090-71.500)

In 14 casi è stata necessaria una sola raccolta, in 3 due raccolte

(mediana CD34+/Kg del ricevente: 6,3 (3.25-11.24)

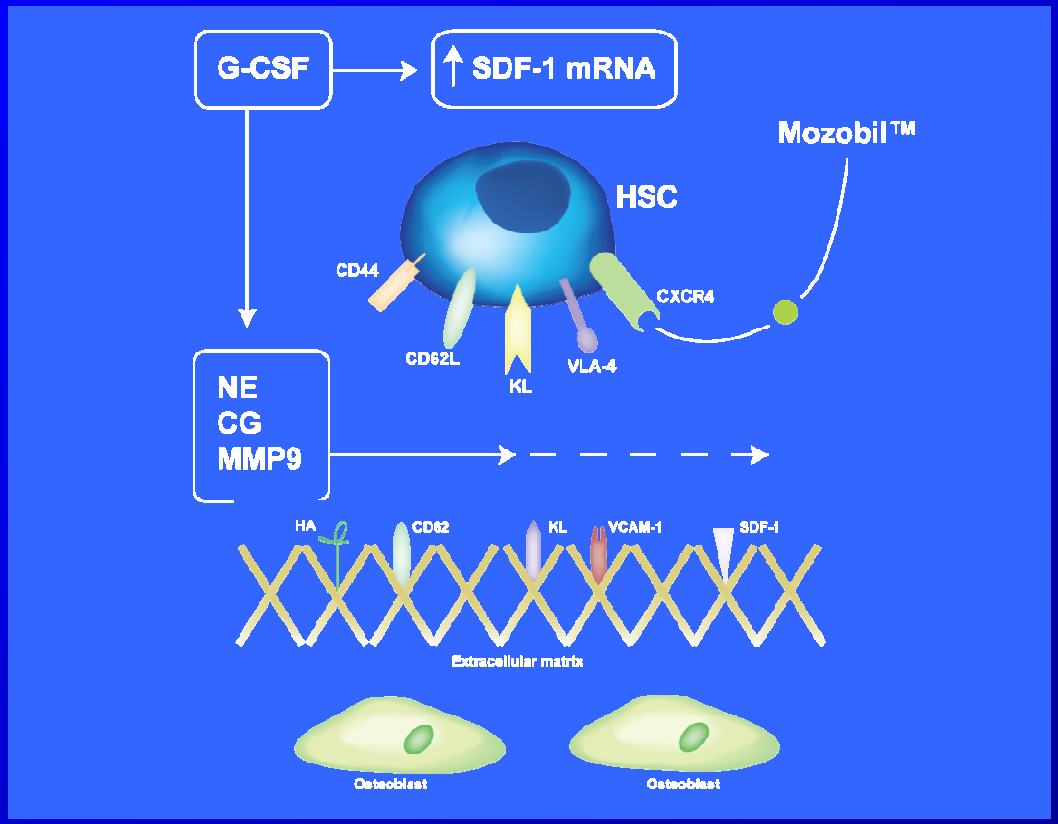
In un caso reinfuse PLT autologhe

Mediana CD34+ richieste: 350 (150-720) x 10^6

Mediana CD34+ raccolte: 415 (225-787) x 10^6

(mediana CD34+/Kg del ricevente: 6,3 (3.25-11.24)

In 8/17 presenza di osteomialgie trattate con analgesici
In 3 casi cefalea
F/u a lungo termine in corso, non EC riferiti a medio termini



Slide set Sanofi

REVIEW ARTICLE

Biosimilar agents in oncology/haematology: from approval to practice

Dietger Niederwieser[1], Stephan Schmitz[2]

European Journal of Haematology 86 (277–288)

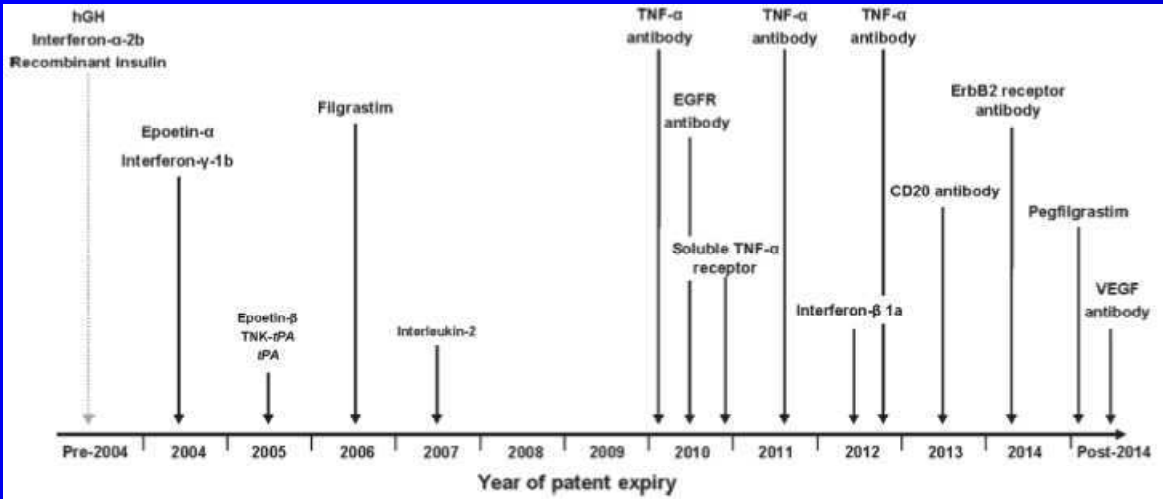


Table 1 Overview of oncology/haematology biosimilars licensed in Europe

Molecule	INN	Brand name
Biosimilar erythropoietins		
HX575	Epoetin alfa[1]	Abseamed® (39) Binocrit® (40) Epoetin alfa Hexal®(41)
SB309	Epoetin zeta[2]	Retacrit® (37) Silapo® (38)
Biosimilar G-CSFs		
XM02	Filgrastim[3]	Tevagrastim® (43) Ratiograstim® (44) Filgrastim ratiopharm® (46) Biograstim® (45)
EP2006	Filgrastim[4]	Zarzio® (47) Filgrastim Hexal® (48)
PLD108	Filgrastim	Nivestim® (49)

Hematopoietic stem cells (HSC)

HSC distribution

- **In BM 3-5% of cells show positivity to CD34 antigen**
- **In PB 0.03-0.05% of circulating leukocytes are CD34+**

HSC mobilizations depends on:

- **Chemotherapy (CT) regimen**:
  - May induce a 20-25 fold increase of PB CD34+ cells
- **Growth factors (GF)**
- **.** May induce a 16-25 fold increase of PB CD34+ cells

- **Combined therapy** (CT+GF)):
  - Up to a 100-160 fold increase of circulating CD34+ cells.