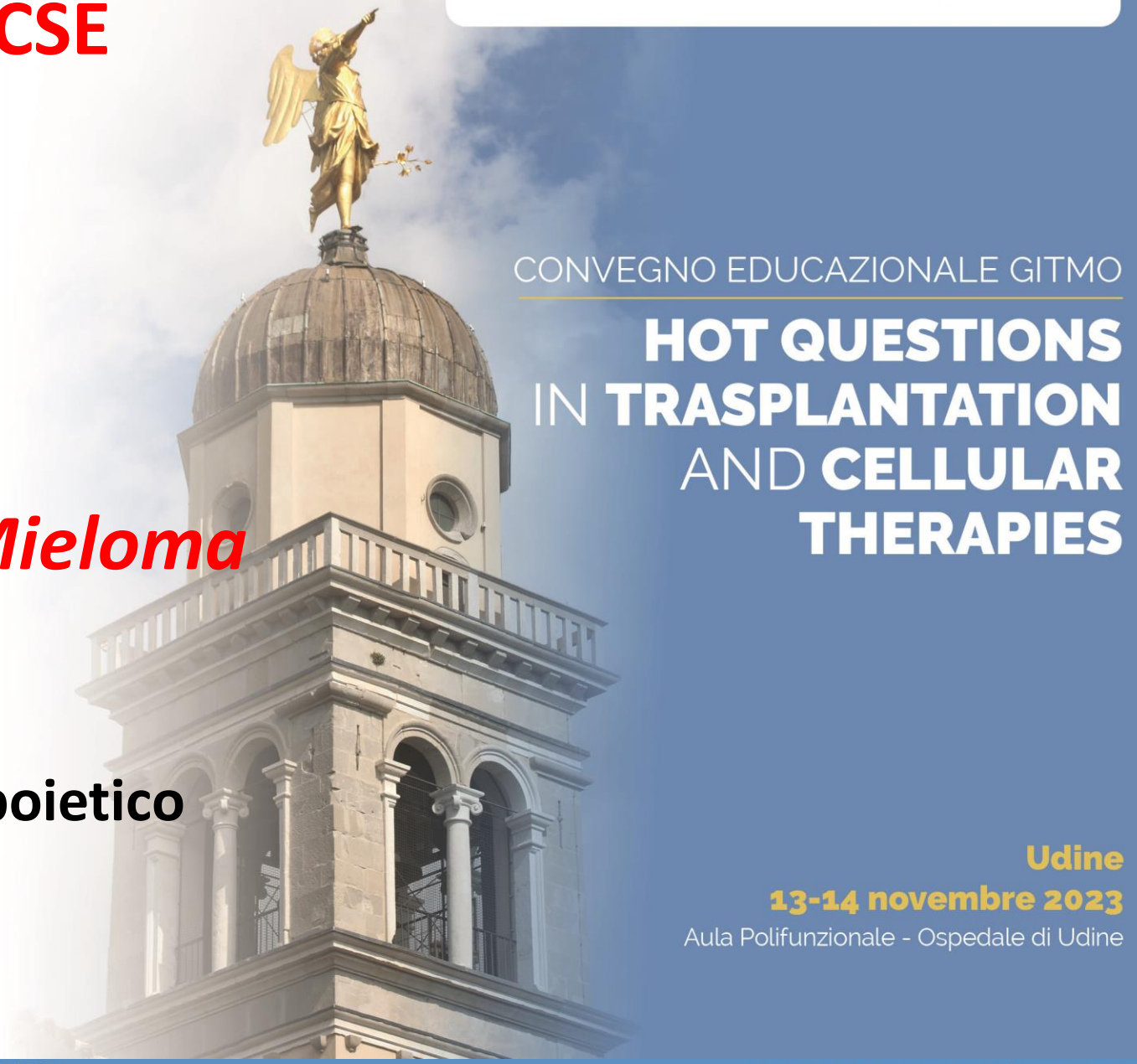
Mobilizzazione delle CSE

CHEMIO-FREE
Oppure
Chemio based
nel paziente affetto da Mieloma

Dr Giuseppe Milone
Programma di Trapianto Emopoietico
Policlinico di Catania



Dr Giuseppe Milone
Relevant COI
(from companies involved in HSC mobilizing agent):

-- 2020- trial on motixafortide (BiolineRX mobilizing agent)

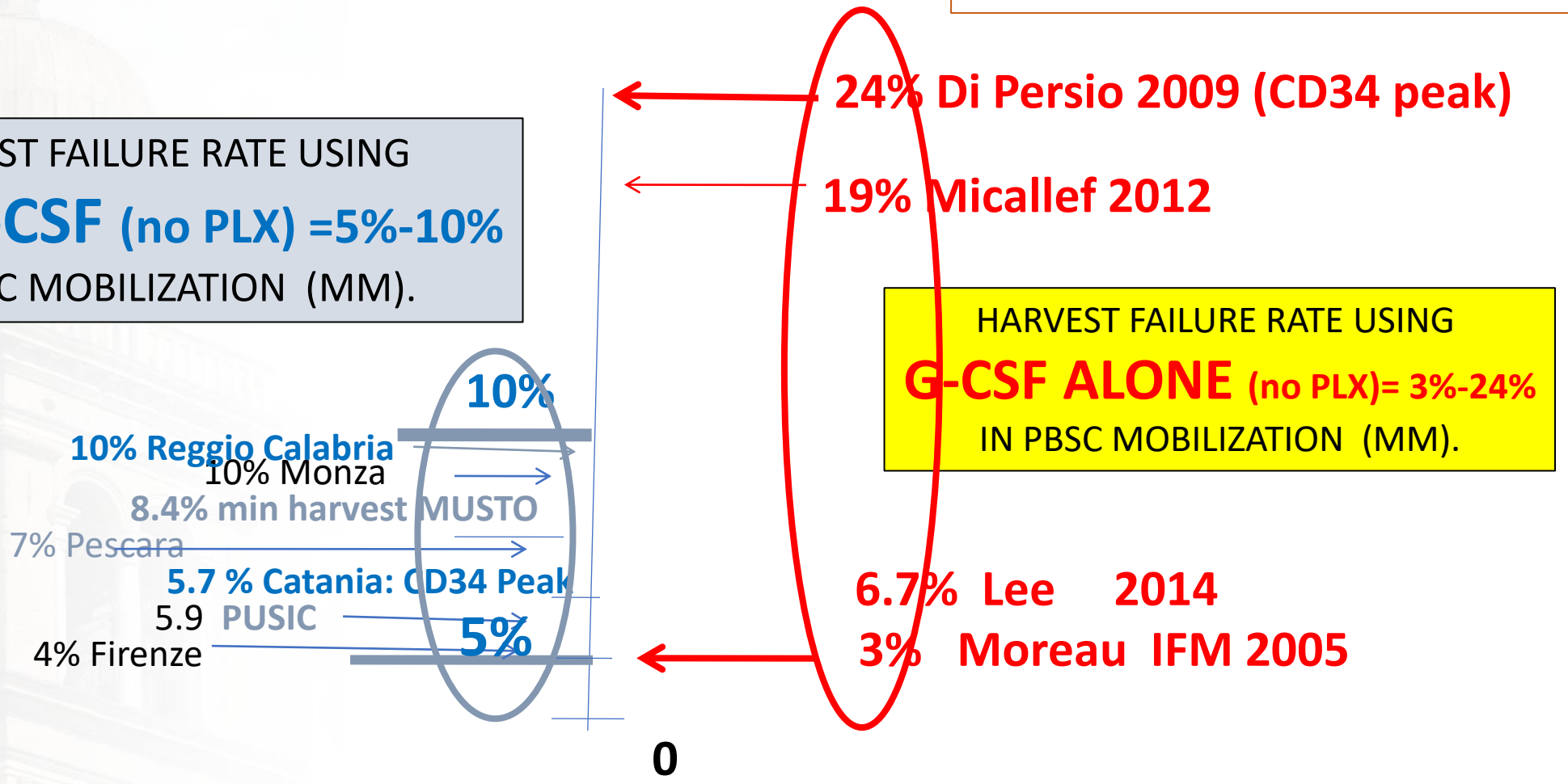
I RISULTATI DI DIFFERENTI MODALITA' DI MOBILIZZAZIONE SOFFRONO DI UNA DISCRETA VARIABILITA' e questo rende difficile raggiungere conclusioni certe

Cio' dipende dalla variabilità legata alle caratteristiche intrinseche del paziente ma anche dalla variabilita' con cui la mobilizzazione e la raccolta aferetica sono effettuate oltre che dal disegno dello studio.

HARVEST FAILURE RATE USING

CTX+G-CSF (no PLX) =5%-10%

IN PBSC MOBILIZATION (MM).



HARVEST FAILURE RATE USING

G-CSF ALONE (no PLX)= 3%-24%

IN PBSC MOBILIZATION (MM).

ALTRA DIFFICOLTA' NELLA COMPARAZIONE DI DIFFERENTI STRATEGIE MOBILIZZANTI

DERIVA DAL FATTO CHE GLI END POINTS SONO NUMEROSI E NON SEMPRE I DATI RELATIVI SONO DISPONIBILI

- CD34/Kg raccolte
- Numero di aferesi mediano da effettuare
- Quota di pazienti che fallisce la raccolta minima
- Quota di pazienti che fallisce la raccolta ottimale
- Quota di pazienti che abbisogna di piu' di 2 aferesi
- Quota di pazienti che necessita di PLX on demand
- Quota di pazienti che necessita di seconde mobilizzazioni
- Quota di pazienti che non puo' essere avviata a autotrapianto per insufficiente raccolta

Talvolta il denominatore è costituito dai pazienti che vanno ad aferesi e manca il numero dei pazienti che sono stati mobilizzati ma che non arrivano alla aferesi per varie cause

- Composizione linfocitaria dello inoculo
- Cellularita' totale e volume occupato dai prodotti aferetici nei tanks di azoto liquido
- Aferesi effettuate nei week-ends
- Volume di sangue processato

- Tossicita' dello schema mobilizzante
- Costi economici per farmaci e costi complessivi

COFATTORI RILEVANTI CHE POSSONO MODIFICARE I RISULTATI DELLA COMPARAZIONE

- Stadio di malattia
- Eta', genere (m;f)
- Tipologia e durata di pretrattamento **(LENA, DARA Radio, Alchilanti)**
- Soglie e algoritmi per l'impiego di Plerixafor

GLI END POINTS INDAGATI DOVREBBERO ESSERE, AL MINIMO:

- **EFFICACIA MOBILIZZANTE**
- **- fallimento CD34+ < 2x10e6/Kg**
- **- fallimento CD34+ < 4-5 x10e6/Kg**
- **TOSSICITA'**
- **COSTI**
- **RISORSE AFERETICHE IMPIEGATE**
- **PREDICIBILITA' RACCOLTA**
- **PRODOTTO (VOLUME/CNT/LINFOCITI)**
- **EFFETTI SULLA NEOPLASIA E SULLA OS**

GLI END POINTS INDAGATI DOVREBBERO ESSERE, AL MINIMO:

- **EFFICACIA MOBILIZZANTE**
- **- fallimento CD34+ < 2x10e6/Kg**
- **- fallimento CD34+ < 4-5 x10e6/Kg (vantaggio Y)**
- **TOSSICITA' (vantaggio X)**

- **COSTI**

- **RISORSE AFERETICHE IMPIEGATE (vantaggio X)**

- **PREDICIBILITA' RACCOLTA**

- **PRODOTTO (VOLUME/CNT/LINFOCITI) (vantaggio Y)**

- **EFFETTI SULLA NEOPLASIA E SULLA OS**

Biology of Blood and Marrow Transplantation 14:1045-1056 (2008)
© 2008 American Society for Blood and Marrow Transplantation
1083-8791/08/1409-0001$32.00/0
doi:10.1016/j.bbmt.2008.07.004

ASBMT
American Society for Blood and Marrow Transplantation

Impact of Mobilization and Remobilization Stra
on Achieving Sufficient Stem Cell Yields for Autologous
Transplantatio

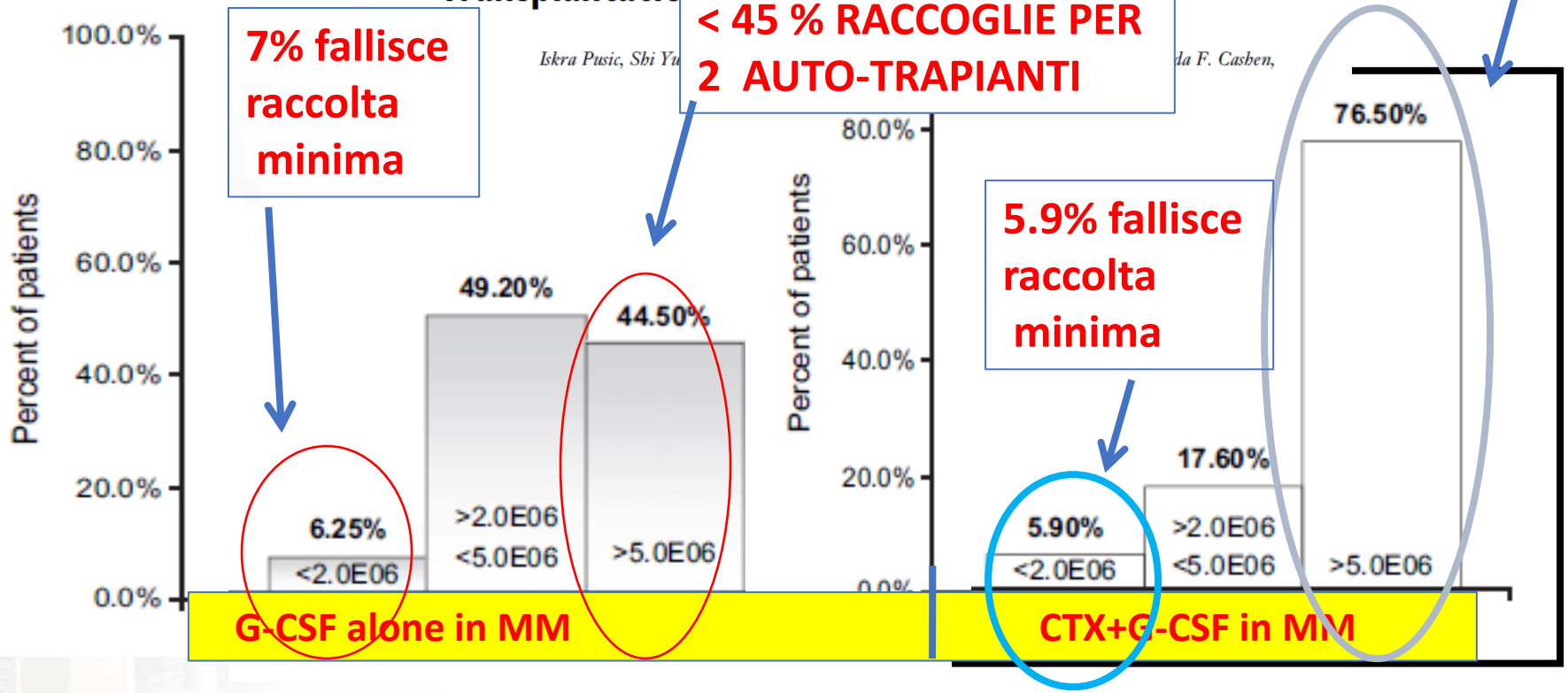
Iskra Pusic, Shi Yu *da F. Casben,*

75 % RACCOGLIE PER 2 AUTO-TRAPIANTI

7% fallisce raccolta minima

< 45 % RACCOGLIE PER 2 AUTO-TRAPIANTI

5.9% fallisce raccolta minima



ANCHE CONSIDERANDO UNA QUTA MINIMA DI 5x10e6/Kg CD34+ , SOLO IL 44.5% DEI PAZIENTI RACCOGLIE PER 2 TRAPIANTI UTILIZZANDO G-CSF da solo nel MM

G-CSF + PLX E' INDUBIAMENTE PIU' EFFICACE E ANCHE PIU' CONVENIENTE DAL PUNTO DI VISTA DELLA TOSSICITA'

G-CSF alone **(Di Persio 2009)**

51%
Raccolta sufficiente
per 2 autologhi
In max 4 aferesi

11.7% fallimento quota minima

34%
Raccolte sufficienti
Per 2 autologhi
In max 2 aferesi

Mediana aferesi
n. 2.5

G-CSF+PLX (Di Persio 2009)

75%
Raccolta sufficiente
per 2 autologhi
in max 4 aferesi.

4,7% Fallimento della quota minima

71.6% Raccolta sufficiente
per 2 autologhi
in max 2 aferesi.

Mediana aferesi
n. 1.0

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

Nigel Russell,[1] Kenny Douglas,[2] Anthony D. Ho,[3] Mohamad Mohty,[4] Kristina Carlson,[5] G.J. Ossenkoppele,[6] Giuseppe Milone,[7] Macarena Ortiz Pareja,[8] Daniel Shaheen,[9] Arnold Willemsen,[10] Nicky Whitaker,[11] and Christian Chabannon[12]

PREDICT (PROSPETTICO NON CONTROLLATO)

G-CSF + PLX universal

MM= n. 90 pts

98% patients within the MM group achieved minimum target cell collection (>2x10e6Kg)

2% Harvest Failure rate.

Median CD34 collected: 7.6 x10e6/Kg.

82% patients achieved the optimal cell collection

Cochrane Database Syst Rev. 2015 Oct 20;(10)

Additional plerixafor to granulocyte colony-stimulating factors for haematopoietic stem cell mobilisation for autologous transplantation in people with malignant lymphoma or multiple myeloma.

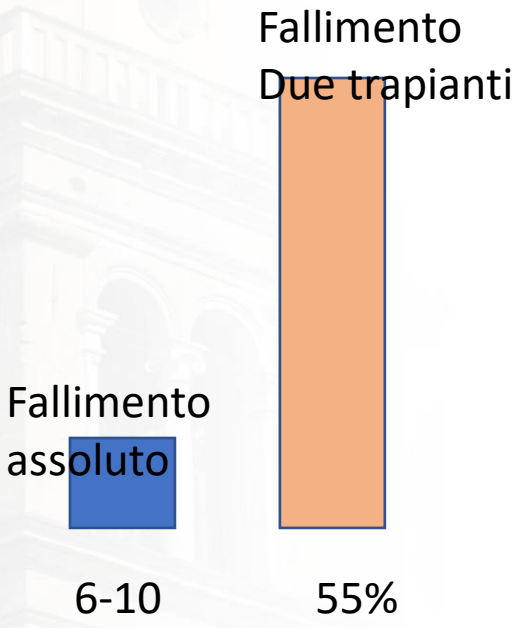
Hartmann T, Hübel K, Monsef I, Engert A, Skoetz N.

AUTHORS' CONCLUSIONS:

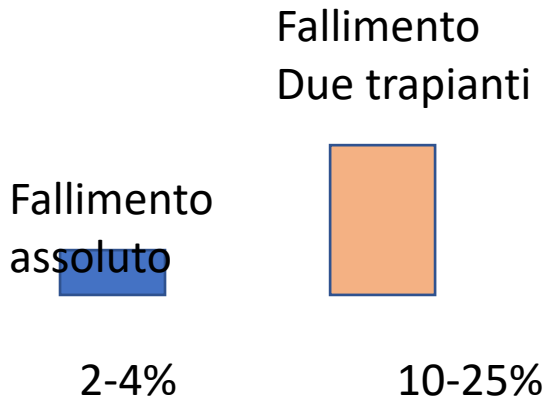
The results of the analysed data suggest that additional plerixafor leads to increased stem cell collection in a shorter time.

There was insufficient evidence to determine whether additional plerixafor affects survival or adverse events

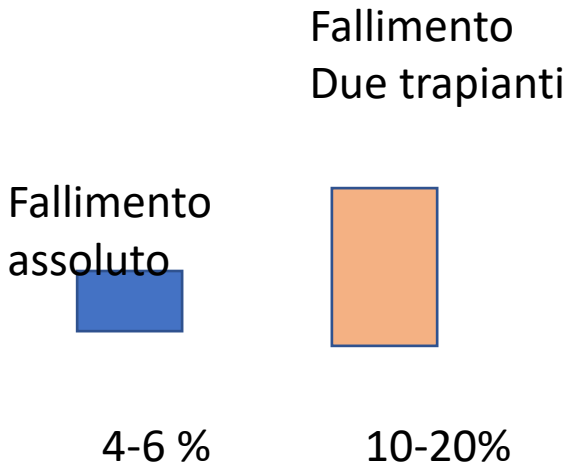
G-CSF alone



G-CSF+PLX



CTX+G-CSF



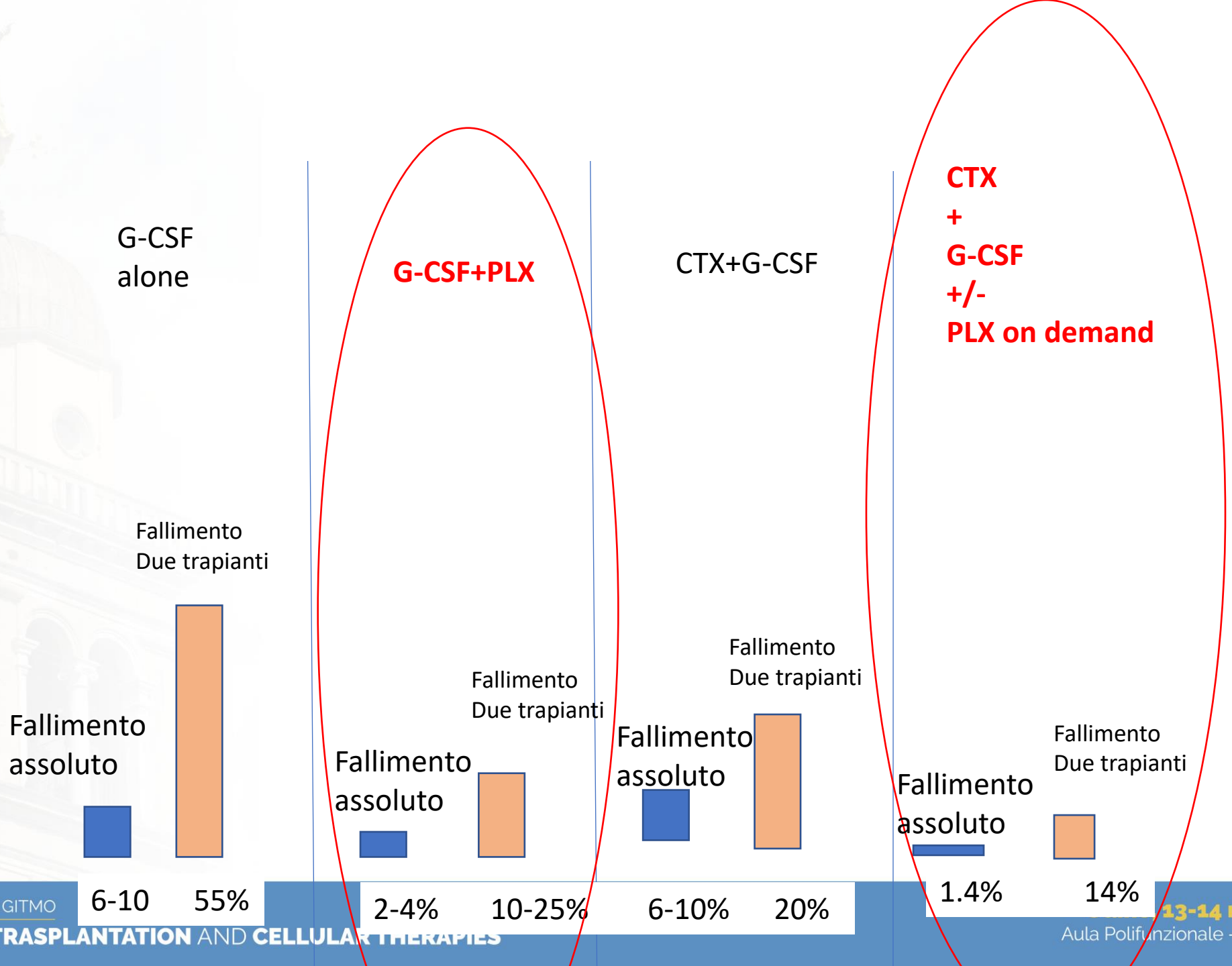
COMPARAZIONE COSTI PLX UNIVERSAL E CTX+G: COMPARABILE EFFICACIA MOBILIZZANTE

.		Fallimento	CD34+	> 5-6x10e6/Kg	COSTI
Antar	G+P on demand	0/27	7.5	88.%	7.886
	CTX 5 gr + G	0/56	15.5	96%	7.536
Awan	G+P univ.	0/33	11.6	96%	28.980
	CTX 3-4 gr + G	0/55	16.6	93%	22.504
Shaughnessy P	G+P univ.	0/33	10.7	100%	14.224
	CTX 3 gr + G	0/33	11.6	90%	$ 18.824

Vantaggio CTX

Vantaggio CTX

=


G-CSF
alone
Fallimento
Due trapianti
Fallimento
assoluto
6-10
55%
G-CSF+PLX
Fallimento
Due trapianti
Fallimento
assoluto
2-4%
10-25%
CTX+G-CSF
Fallimento
Due trapianti
Fallimento
assoluto
6-10%
20%
CTX
+
G-CSF
+/-
PLX on demand
Fallimento
Due trapianti
Fallimento
assoluto
1.4%
14%

	Failure of successful apheresis harvest ($CD34^+$ <2 × 10^6/kg)		
	Overall	Myeloma	Lymphoma
On-demand prospective study	4·0% (4/102)	2·8% (2/72)	6·7% (2/30)
Historical controls group (unadjusted)	20·9% (50/240)	16·4% (30/184)	35·8% (20/56)
P*	0·0001	0·003	0·003
Historical controls group (bias-adjusted)	17·4% (40/228)	15% (27/180)	26·5% (13/48)
P†	0·0008	0·006	0·02

	Total $CD34^+$ cells harvested (×10^6/kg)	Mean number of aphereses sessions per patient	Percentage of patients reaching target of 4 × 10^6/kg (Multiple Myeloma)
On-demand Prospective Study (*n* 102)	8·0	1·61	86·1%
Historical Controls (*n* 240)	6·65	1·43	68·8%
P	0·03	0·04	0·002

bjh research paper

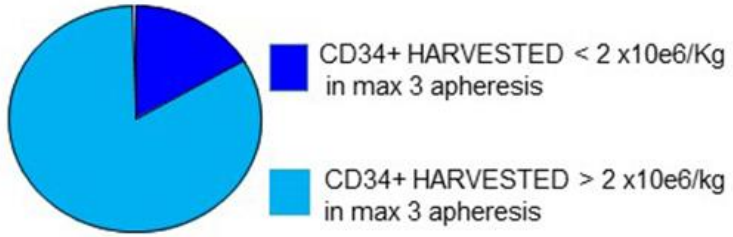
Plerixafor on-demand combined with chemotherapy and granulocyte colony-stimulating factor: significant improvement in peripheral blood stem cells mobilization and harvest with no increase in costs

Giuseppe Milone,[1,2] Massimo Martino,[3] Summary

Panel A

Control group: CTX 4 gr/sqm+G-CSF

Failure of apheretic harvest: 16.0%

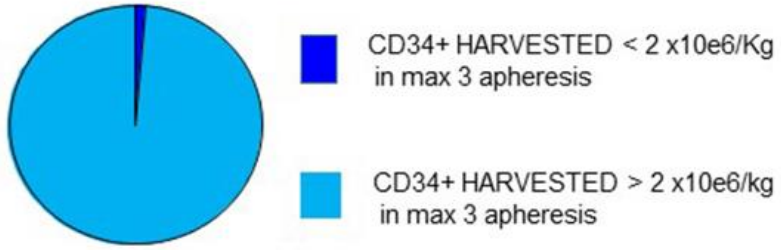


Success of apheretic harvest: 84.0%

p= 0.0001

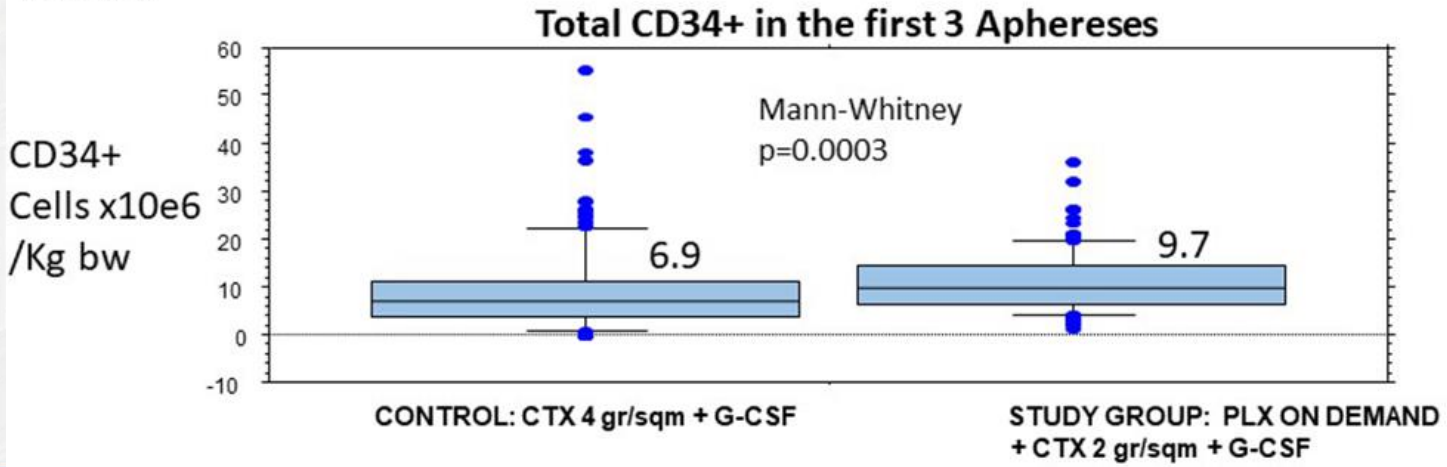
Study Group: On demand PLX+CTX 2 gr/sqm +G-CSF

Failure of apheretic harvest: 1.4%



Success of apheretic harvest: 98.6%

Panel B



	G-CSF alone		G-CSF+PLX		CTX 3-4gr+G+PLX		CTX 2gr+G+PLX	
	Failure rate <2x10e6/Kg	Not optimal harvest	Failure rate <2x10e6/Kg	Not optimal harvest	Failure rate <2x10e6/Kg	Not optimal harvest	Failure rate <2x10e6/Kg	Not optimal harvest
Di Persio Blood. 2009;113:5720-5726 randomized (n 302)	11.7%	49.0%	4.7%	25%				
PRAKASH Clin Lymphoma Myeloma Leuk. (2022)22(1):44-51 prospective. (n 105, G+PLX) MM and 156, contro G-CSF alonel)	12.8%	-----	3.8%	----				
RUSSEL N Haematologica 2014. (n 90) Prospective			2.0%	11%				
Johnsrud A 2021 Transpl and Cell therapy 27, (7), 2021, (n 397) Retrospective			6.3%	32%	6%	5%		
Johnsrud A 2021 (LENALIDOMIDE > 6 mo.) Retrospective			14.3%	49%	7.8%	9%		
Zannetti B 2021Transpl and Cell therapy 2021 Mar;27(3):244.e1-244.e8. (n 422) Retrospective			4.3%	21.4%	3.4%	8.9%	3.7%	9.6%
Milone G Leuk Res Rep. 2020 30;14:100227. (n 138) Prospective							1.4%	14.5%
Silvennoinen Bone Marrow Transplantation (2016) (n 69) (Randomized, Lenalidomide based)			23%	50%			6.0	38%

Cost and Clinical Analysis of Autologous Hematopoietic Stem Cell Mobilization with G-CSF and Plerixafor Compared to G-CSF and Cyclophosphamide

Paul Shaughnessy,[1] Miguel Islas-Ohlmayer,[1] Julie Murphy,[2] Maureen Hougham,[1]

IL CONFRONTO DEI COSTI PLX UNIVERSAL +G-CSF versus CTX +G-CSF VARIA A SECONDO DEL NUMERO DI AFERESI EFFETTUATO PER PAZIENTE

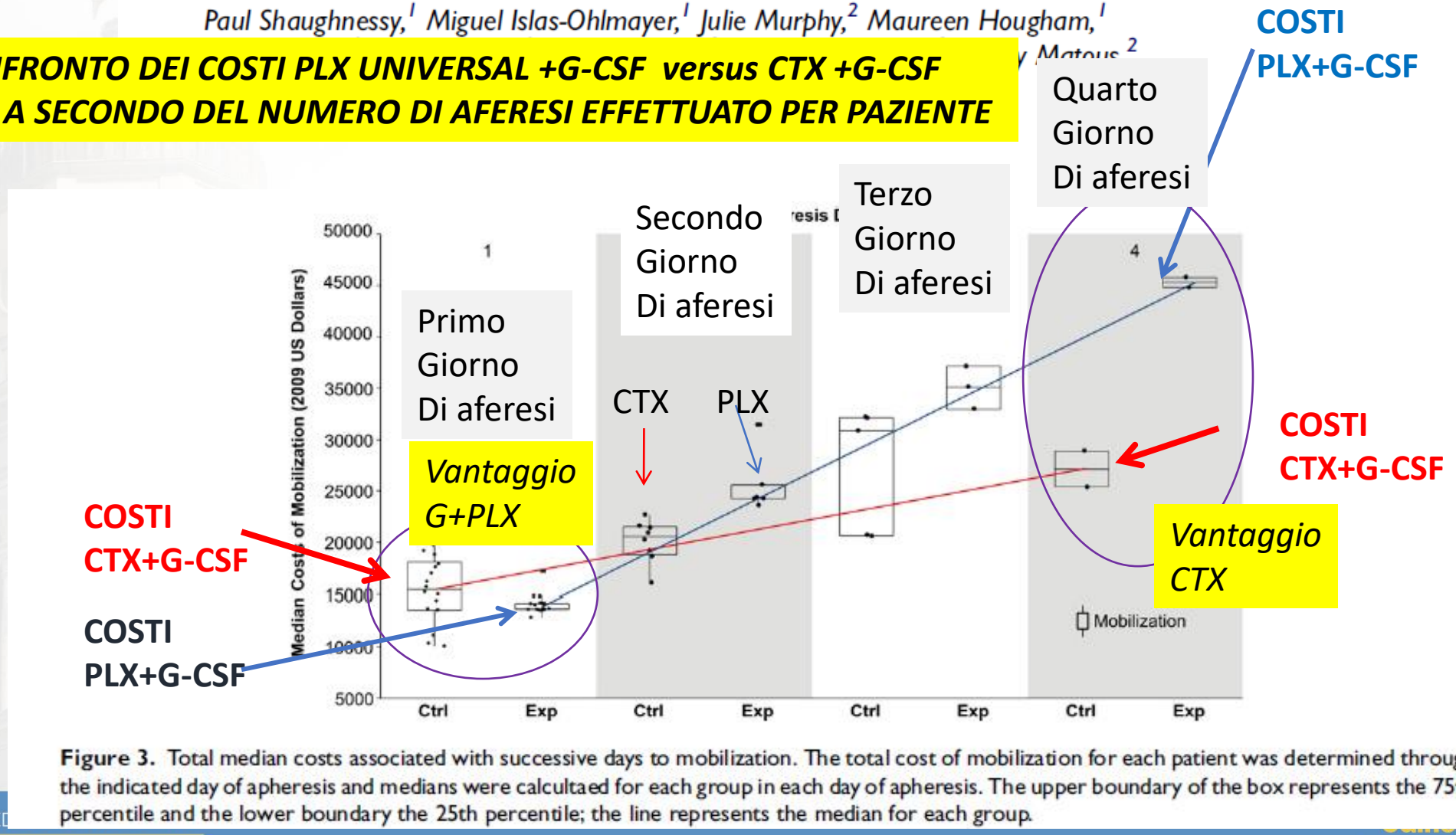


Figure 3. Total median costs associated with successive days to mobilization. The total cost of mobilization for each patient was determined through the indicated day of apheresis and medians were calcultaed for each group in each day of apheresis. The upper boundary of the box represents the 75th percentile and the lower boundary the 25th percentile; the line represents the median for each group.

VOLUMI DI SANGUE PROCESSATI IN VARI STUDI PLX+G-CSF

1 Awan F ,

All collections were performed with a COBE SPECTRA apheresis system

BY PROCESSING THREE TO FOUR BLOOD VOLUMES.

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2 *DiPersio, for the 3102 Investigators*

APHERESIS: THREE BLOOD VOLUME +/- 10%.

---

3 **COSTA LJ .**

At least THREE TOTAL BLOOD volumes were processed

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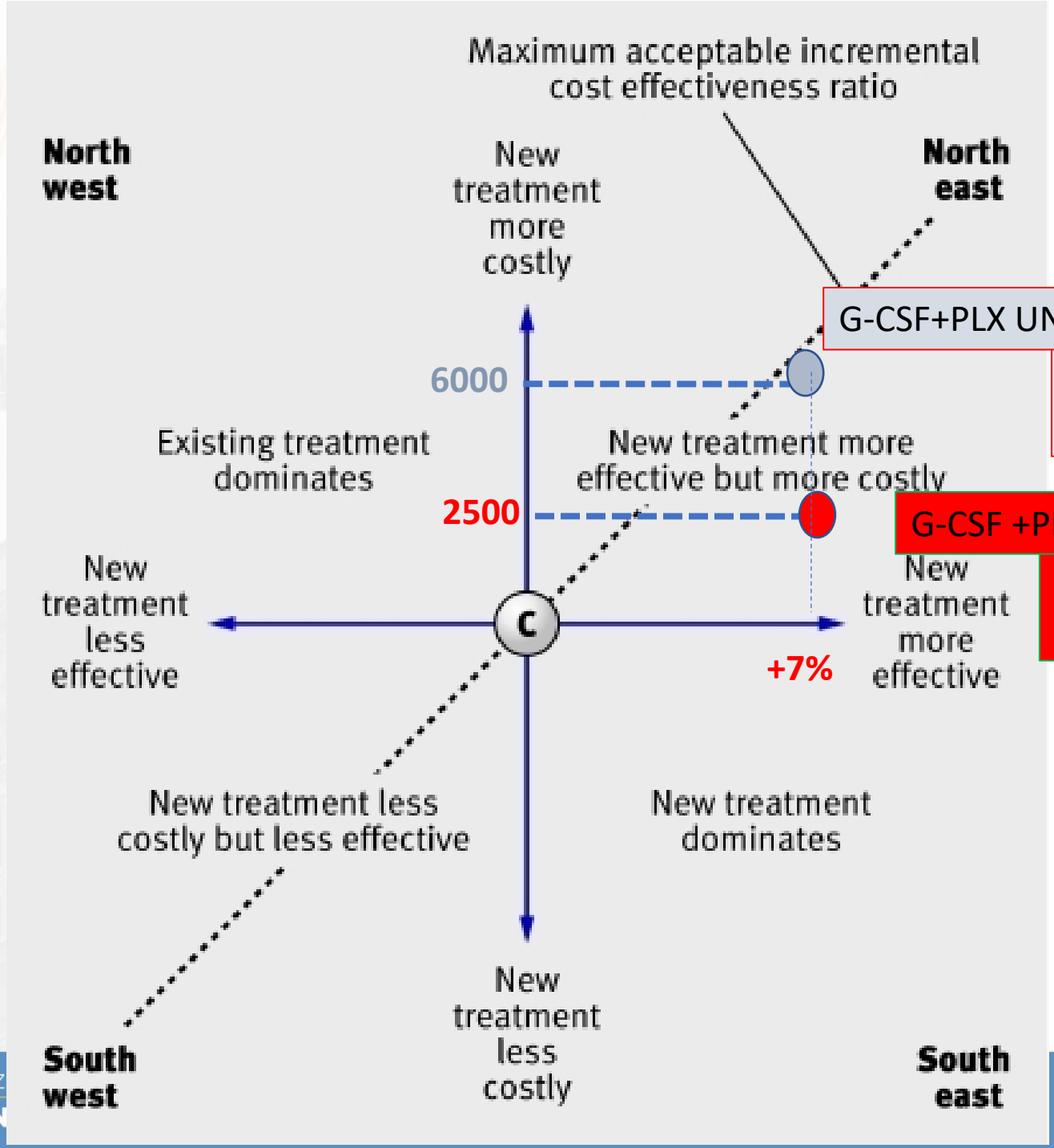
4 **ABHYANKAR S BMT 2012**

All patients underwent apheresis with 4–6 BLOOD VOLUMES processed.



IPOTESI DI DIFFERENTI ICER RELATIVI A:
-- G-CSF+PLX UNIVERSAL
-- G-CSF + PLX ON DEMAND

G-CSF+PLX UNIVERSAL

857 E. PER 1% MIGLIORAM . IN Failure R.

G-CSF +PLX ON DEMAND

357 E. PER 1% MIGLIORAM IN Failure R.

COMPARAZIONE COSTI PLX UNIVERSAL E CTX+G: COMPARABILE EFFICACIA MOBILIZZANTE

.		Fallimento	CD34+	> 5-6x10e6/Kg	COSTI	
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	CTX 3-4 gr + G	0/55	16.6	93%	22.504	
Shaughnessy P	G+P univ.	0/33	10.7	100%	14.224	- 25% Vantaggio G+PLX
	CTX 3 gr + G	0/33	11.6	90%	$ 18.824	

LA NEUTROPENIA FEBBRILE DOPO G-CSF ALONE È TIPICAMENTE ASSENTE, MENTRE DOPO CTX +G-CSF RAPPRESENTA UN PROBLEMA.

RIDURRE LA DOSE DI CTX DA 3-4 GR a 2 gr CONSENTE UNA SPICCATA RIDUZIONE DELLA TOSSICITÀ

Autore	Dose CTX (gr)	Neutropenia febbrile (%)	
Hamadani	1.5	5.8	Basse dosi CTX
Milone	2	5	
Hamadani	3	16.3	Dosi intermedie CTX
Awan	3	16	
Gertz	3	10	
Milone	4	14	
Orciuolo	3-4	5	
Fitoussi	4	70	Alte dosi CTX
Antar	5	60	

1. Hamadani M, et al. Biol Blood Marrow Transplant 2012;18:1128-1135
2. Fitoussi O et al. Bone Marrow Transplantation 2001; 27:837–842
3. Gertz MA et al. Bone Marrow Transplantation 2009;43:619–625
4. Milone G, et al. Leuk Lymphoma 2018;59:42-48
5. Antar A, et al. Bone Marrow Transplant. 2015;50(6):813-7
6. Awan F, et al. Bone Marrow Transplant 2013;48(10):1279-84
7. Orciuolo Leukemia Research 2011; 35:899

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Plerixafor on-demand in association with low-dose cyclophosphamide and G-CSF in the mobilization of patients with multiple myeloma: High effectiveness, low toxicity, and affordable cost

Giuseppe Milone [a,*], Concetta Conticello [a], Salvatore Leotta [a], Maria Grazia Michieli [b],

Table. 4

Estimates of costs of the first mobilization, of salvage mobilization, and overall mobilization costs in the two groups.

	Unit cost	Control Group CTX 4 g/m^2 + G-CSF	Plx on-demand Study Group
(D) Infectious episode cost	w/o hospital admission= 517 euro	11.1% 11.1 × 517 = 5,738 euro 5,738 euro	4.3% 4.3×517 = 2,223 euro 2,223 euro

La mobilizzazione CHEMIO-FREE, presenta alcuni indubbi vantaggi:

A -- Prodotto aferetico ricco di linfociti, adatto alla Immunoterapia Post trapianto.

B -- Predicibilità del giorno di raccolta

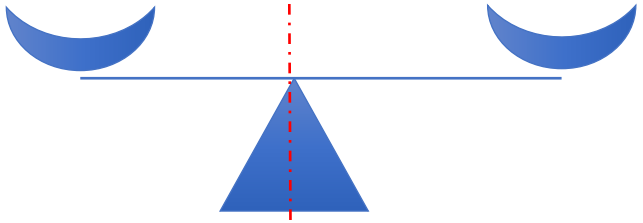
C--Non tossicita' da chemioterapia

CHEMIO BASED

CHEMIO-FREE

Minore contaminazione neoplastica

Maggiore contenuto di linfociti



4) ESISTE UN MIGLIORAMENTO DELLA PROGNOSI LEGATO AD UN PRODOTTO CON RIDOTTA CONTAMINAZIONE NEOPLASTICA ??

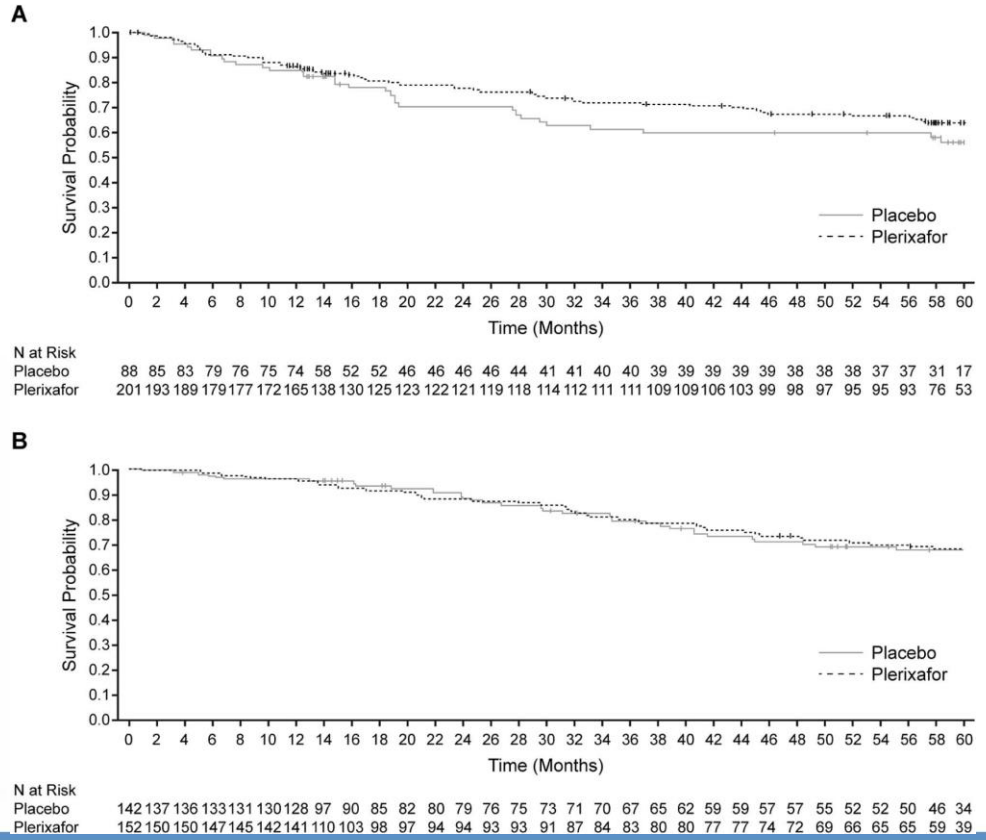
5) ESISTE UN MIGLIORAMENTO DELLA PROGNOSI ASSOCIATO ALL' UTILIZZO DI PRODOTTI CON PIU' ELEVATO CONTENUTO DI LINFOCITI ??

NONOSTANTE LA DOSE LINFOCITARIA INFUSA PUO' AVERE UNA INFLUENZA SULLA DFS, I PAZIENTI MOBILIZZATI CON PLX + G-CSF O CON PLACEBO + G-CSF HANNO EGUALE OUTCOME

Plerixafor Plus Granulocyte Colony-Stimulating Factor for Patients with Non-Hodgkin Lymphoma and Multiple Myeloma: Long-Term Follow-Up Report

Ivana N. Micallef, Patrick J. Stiff, Auayporn P. Nademanee, Richard T. Maziarz, Mitchell E. Horwitz, Edward A. Stadtmauer, Jonathan L. Kaufman, John M. McCarty, Rita Vargo, Peter D. Cheverton, Martin Struijs, Brian Bolwell, John F. DiPersio

Biology of Blood and Marrow Transplantation 24(6):1187-1195 (June 2018)



Biology of Blood and Marrow Transplantation 2018 24, 1187-1195

Bone Marrow Transplantation (2015) **50,** 1513–1518

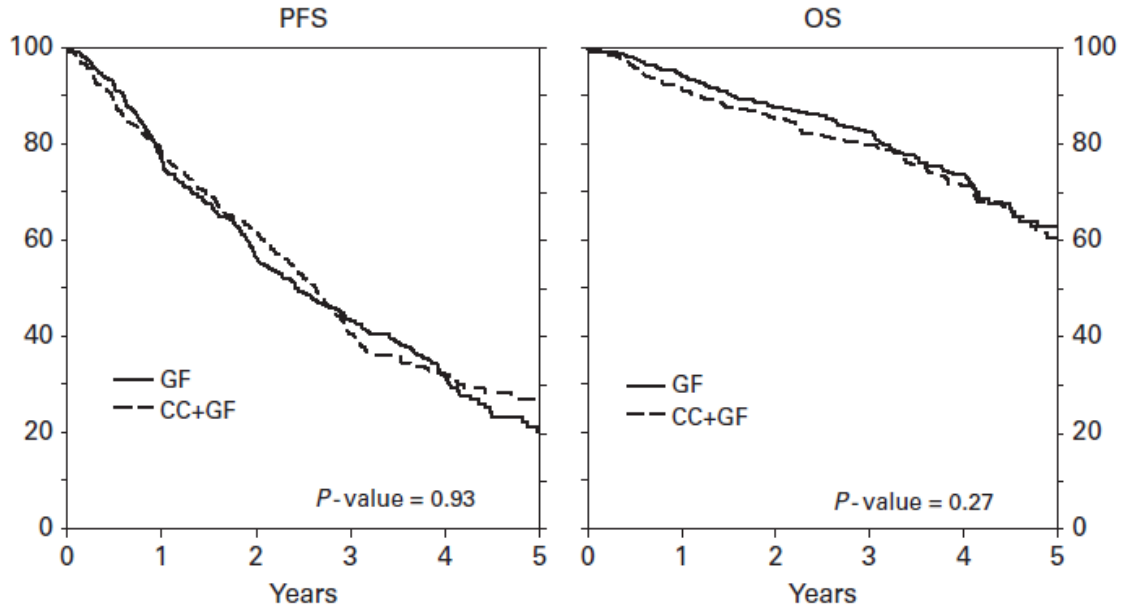
www.nature.com/bmt

ORIGINAL ARTICLE

Contribution of chemotherapy mobilization to disease control in multiple myeloma treated with autologous hematopoietic cell transplantation

GL Uy[1,43], LJ Costa[2,43], PN Hari[3], M-J Zhang[3,4], J-X Huang[3], KC Anderson[5], CN Bredeson[6], NS Callander[7], RF Cornell[8], MAD Perez[9],

We compared these mobilization strategies in a retrospective analysis of 968 patients with MM from the CIBMTR database who received an auto-HCT in the US and Canada between 2007 and 2012.



djusted probability of PFS and OS according to the method of mobilization.

We cannot exclude the possibility that a subset of patients with high disease burden or who are refractory to initial immunomodulatory agent and proteasome inhibitor therapy may benefit from Chemio +GF mobilization

SVANTAGGI DELLA MOBILIZZAZZIONE CHEMIO FREE

L' effetto antineoplastico è assente

quota di CD34+ raccolte ridotta rispetto a schemi Chemio-based
Soprattutto in assenza di PLX

Elevata percentuale di pazienti che richiede PLX on demand (50-70%)

I migliori risultati sono ottenuti con «Large Volume Leukoapheresis»

Maggior numero di sacche di prodotto congelato nei tanks ad azoto

LE RISORSE DI CONGELAMENTO E STOCCAGGIO SONO SUPERIORI NEL CASO DI MOBILIZZAZIONE CHEMIO-FREE

Journal of Clinical Apheresis 25:202–208 (2010)

Plerixafor Mobilization Leads to a Lower Ratio of CD34+ Cells to Total Nucleated Cells which Results in Greater Storage Costs

Yvette C. Tanhehco,[1] Jill Adamski,[1] Mary Sell,[1] Kathleen Cunningham,[2] Christa Eisenmann,[1] Deborah Magee,[1] Edward A. Stadtmauer,[2] and Una O'Doherty[1]*

Numero di Sacche Criopreservate Per paziente

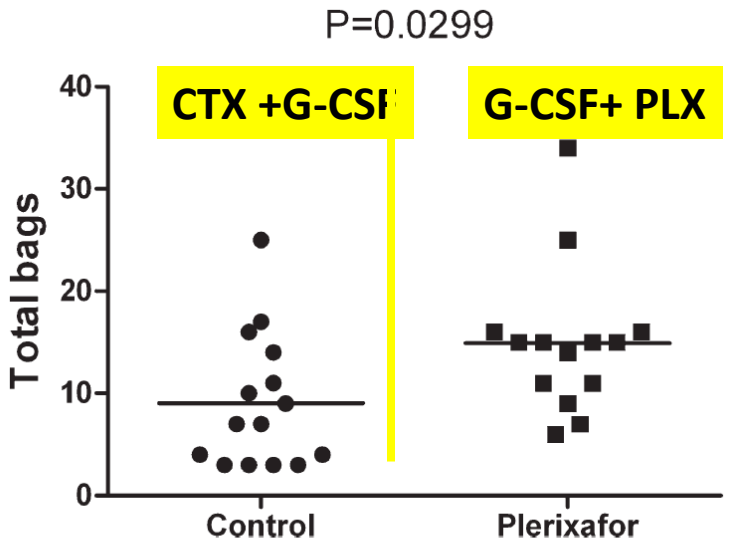


Fig. 2. Plerixafor mobilization leads to increased storage bag requirements. Mean total storage bags required in the control group (9 bags) was less compared to the plerixafor group (15 bags), ($P = 0.0299$).

CONCLUSIONI

EFFICACIA MOBILIZZANTE (vantaggio CTX)

TOSSICITA' (vantaggio PLX)

COSTI (vantaggio CTX se low dose)

RISORSE AFERETICHE E DI STOCCAGGIO (vantaggio CTX)

PREDICIBILITA' RACCOLTA (vantaggio PLX)

PRODOTTO (dubbio)

RISULTATI SULLA OS (dubbio)

DE GRUYTER OPEN | Radiology and Oncology | Ljubljana | Slovenia | www.radioloncol.com | RADIOLOGY ONCOLOGY

research

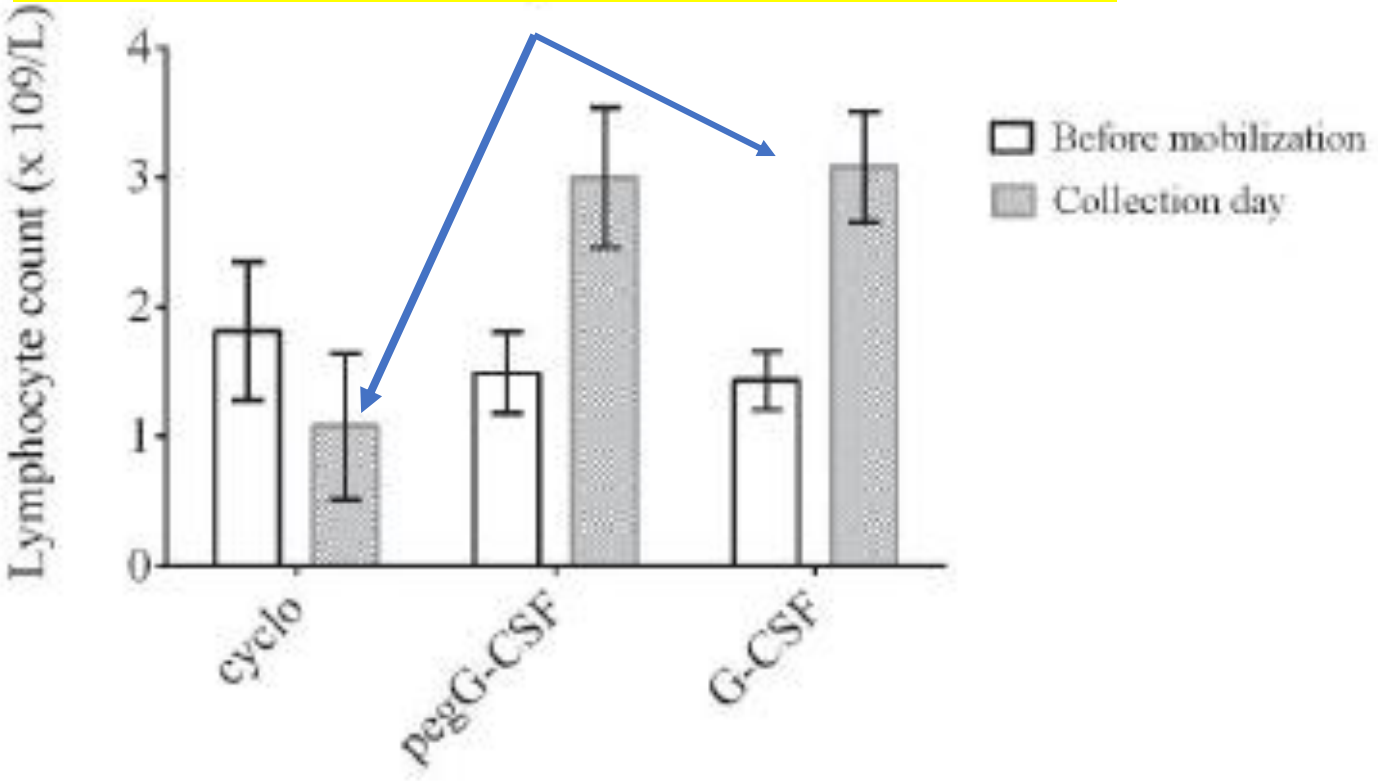
Mobilization with cyclophosphamide reduces the number of lymphocyte subpopulations in the leukapheresis product and delays their reconstitution after autologous hematopoietic stem cell transplantation in patients with multiple myeloma

Matevz Skerget[1], Barbara Sl

[1] Department of hematology, Universi

Radiol Oncol 2016; 50(4): 402-408.

Dopo PLX + G-CSF SI RACCOLGONO PIU' LINFOCITI IN CONFRONTO A QUANTI SE NE RACCOLGONO DOPO CTX



Bone Marrow Transplantation (2004) 33, 291–298

www.nature.com/bmt

Immune reconstitution

Infused peripheral blood autograft absolute lymphocyte count correlates with day 15 absolute lymphocyte count and clinical outcome after autologous peripheral hematopoietic stem cell transplantation in non-Hodgkin's lymphoma

LF Porrata[1], MR Litzow[1], DJ Inwards[1], DA Gastineau[1,2], SB Moore[2], AA Pineda[2], KL Bundy[2], DJ Padley[2], D Persky[3], SM Ansell[1], INM Micallef[1] and SN Markovic[1]

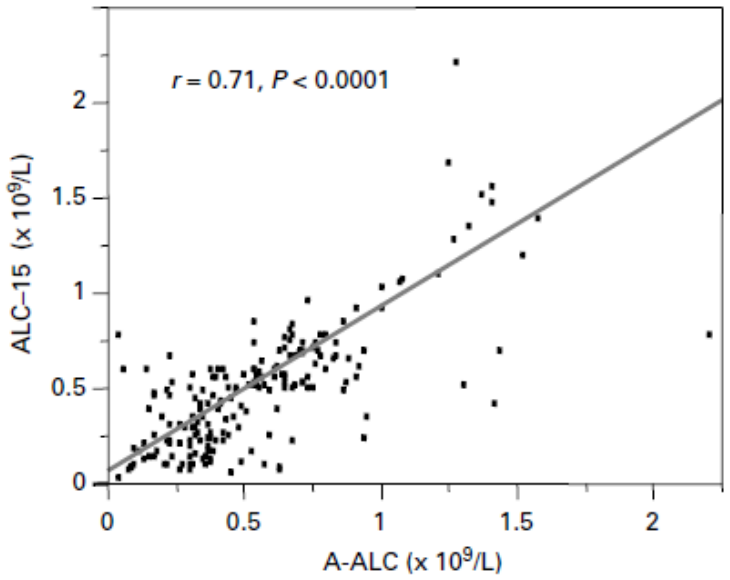
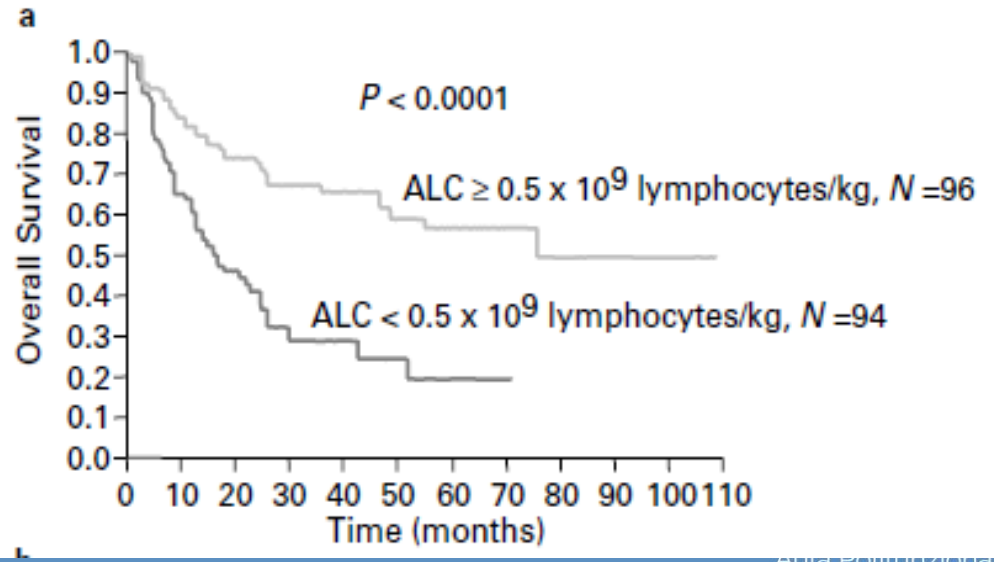


Figure 1 Scattered plot comparing the infused A-ALC and the absolute lymphocyte count (ALC) recovery at day 15 after APHSCT. Strong correlation was identified between the infused A-ALC and the ALC recovery at day 15 after APHSCT (Spearman correlation rho factor, $r = 0.71$, $P < 0.0001$).

L'UTILITA' CLINICA DI INFONDERE UN ELEVATO NUMERO DI LINFOCITI NELL'INOCULO RIMANE PERO' NON CONFERMATA



Leukemia Research Reports 14 (2020) 100227

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Plerixafor on-demand in association with low-dose cyclophosphamide and G-CSF in the mobilization of patients with multiple myeloma: High effectiveness, low toxicity, and affordable cost

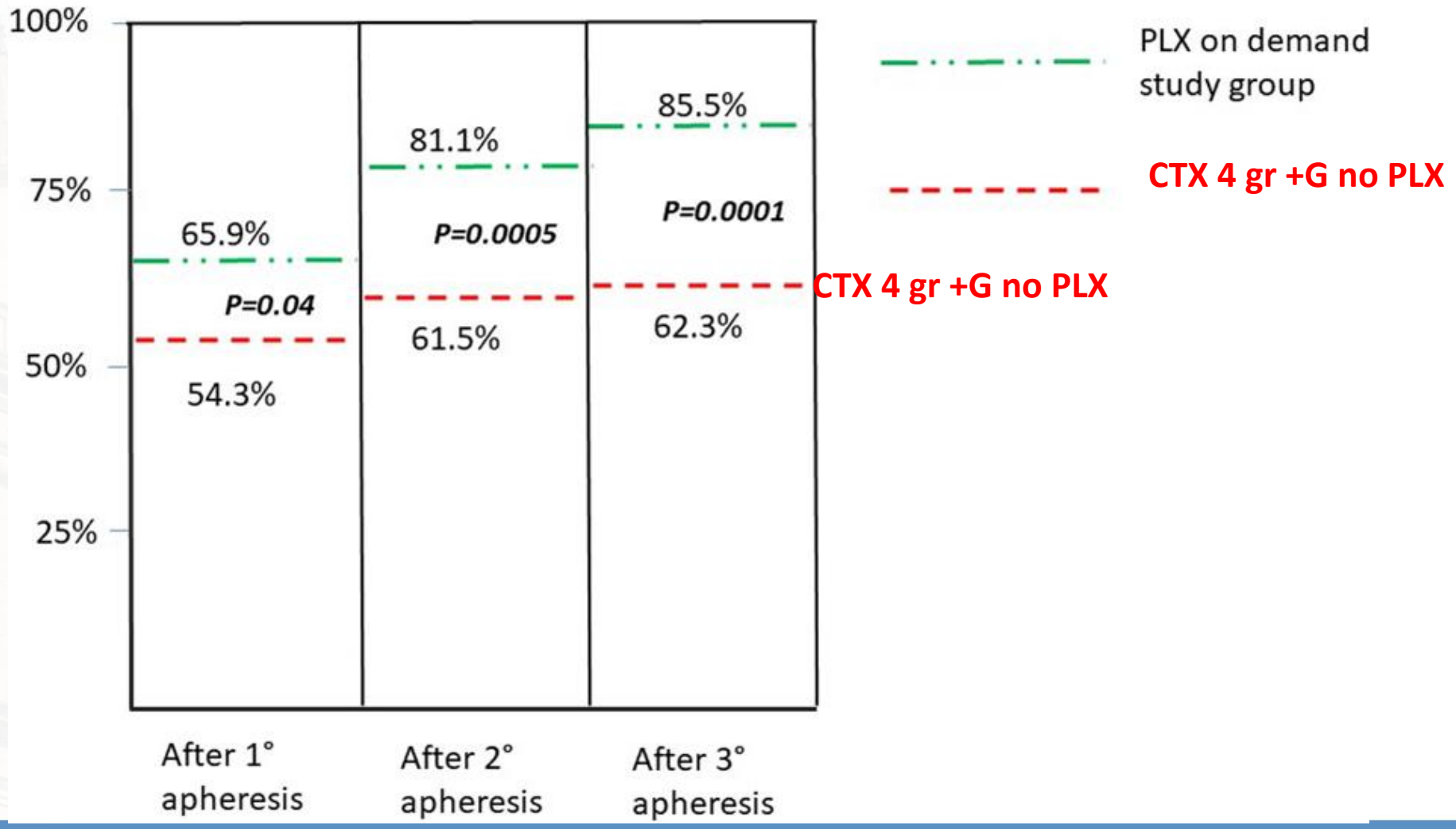
Giuseppe Milone [a,*], Concetta Conticello [a], Salvatore Leotta [a], Maria Grazia Michieli [b], Massimo Martino [c], Anna Lia Di Marco [a], Andrea Spadaro [a], Alessandra Cupri [a], Annalisa Condorelli [a], Giulio Antonio Milone [a], Uros Markovic [a], Roberta Sciortino [a], Giovanni Schininà [a], Gaetano Moschetti [d], Loredana Villari [a,f], Riccardo Saccardi [e,g], for GITMO

This prospective study was aimed to determine the effectiveness and the toxicity of a mobilization strategy based on low-dose CTX (2 g/m2) and G-CSF in conjunction with PLX on-demand in patients with MM.

One hundred thirty-eight patients with MM were enrolled from three Italian centres, from October 30, 2014, to June 18, 2018.

We compared results with a historical control group (n = 138) in which CTX was administered at the dose of 4 g/m2 along with G-CSF at the dose of 5 to 10 µg/kg from day 3 to the end of collections.

Proportion of patients reaching CD34+ cells > 5x10e6/Kg after first, second and third apheresis in the two groups



RISULTATI PRELIMINARI MOBILIZZAZIONE MM
LOW DOSE CTX 2 gr/m^2 + G-CSF + PLX ON DEMAND

STUDIO PROSPETTICO SULLA MOB NEL MM

Pazienti trattati: 121

MM tutti in prima mobilizzazione

Dopo la terapia induzione

CTX 2 gr/m^2 (ricovero 2 gg) +

G-CSF 10 mcg/Kg + PLX ON DEMAND

RISULTATI:

Fallimenti raccolta minima 2x10^6/Kg= 1,4 %

Fallimenti raccolta ottimale >5x10^6/Kg=14,5%

Numero medio aferesi:

Raccolta media CD34+/Kg: 10.3 x10^6

Raccolta mediana CD34+/Kg: 9.8 x10^6

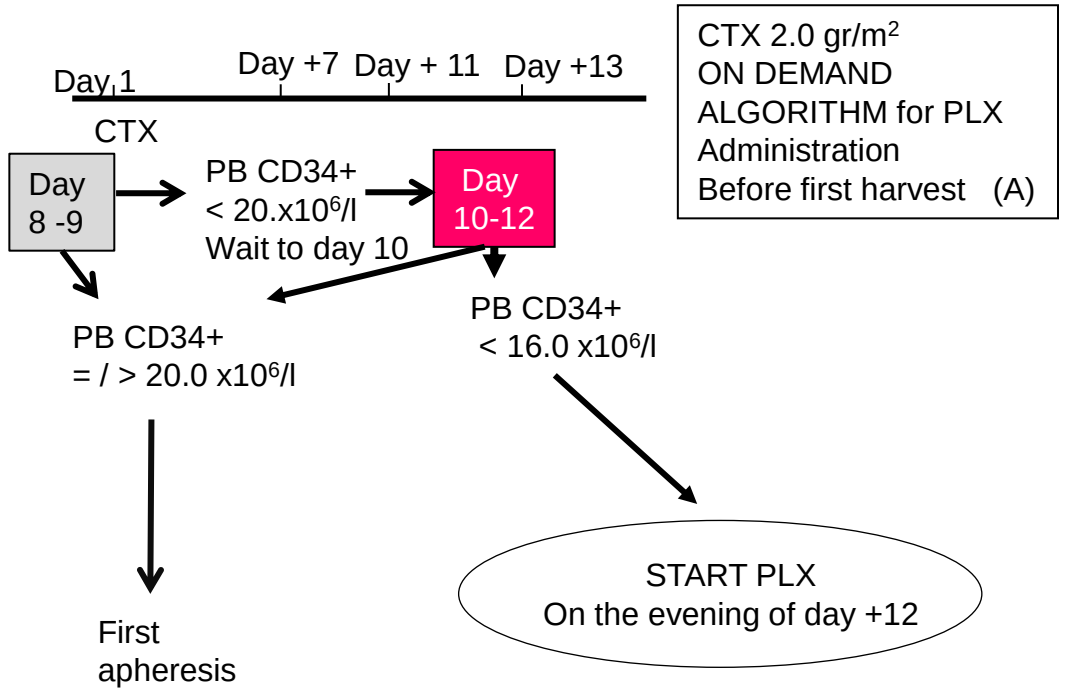
Necessita' di impiego PLX=17%

Numero medio di fiale somministrate=1,3

TOSSICITA'

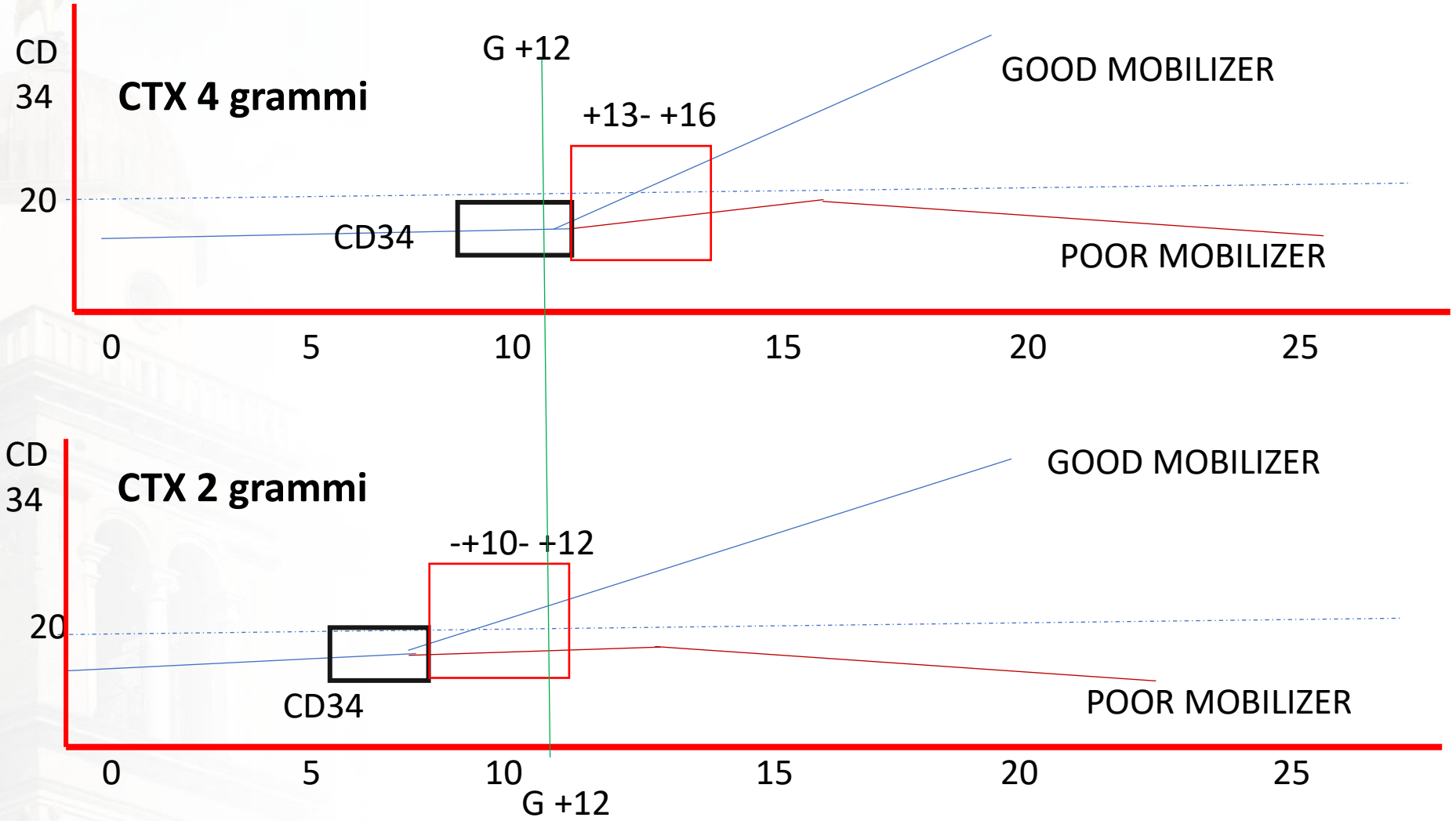
Infezioni neutropenia febbrile=5%

Algoritmo disegnato anche per effettuare Le Raccolte Lu-Ve (non nel week end):

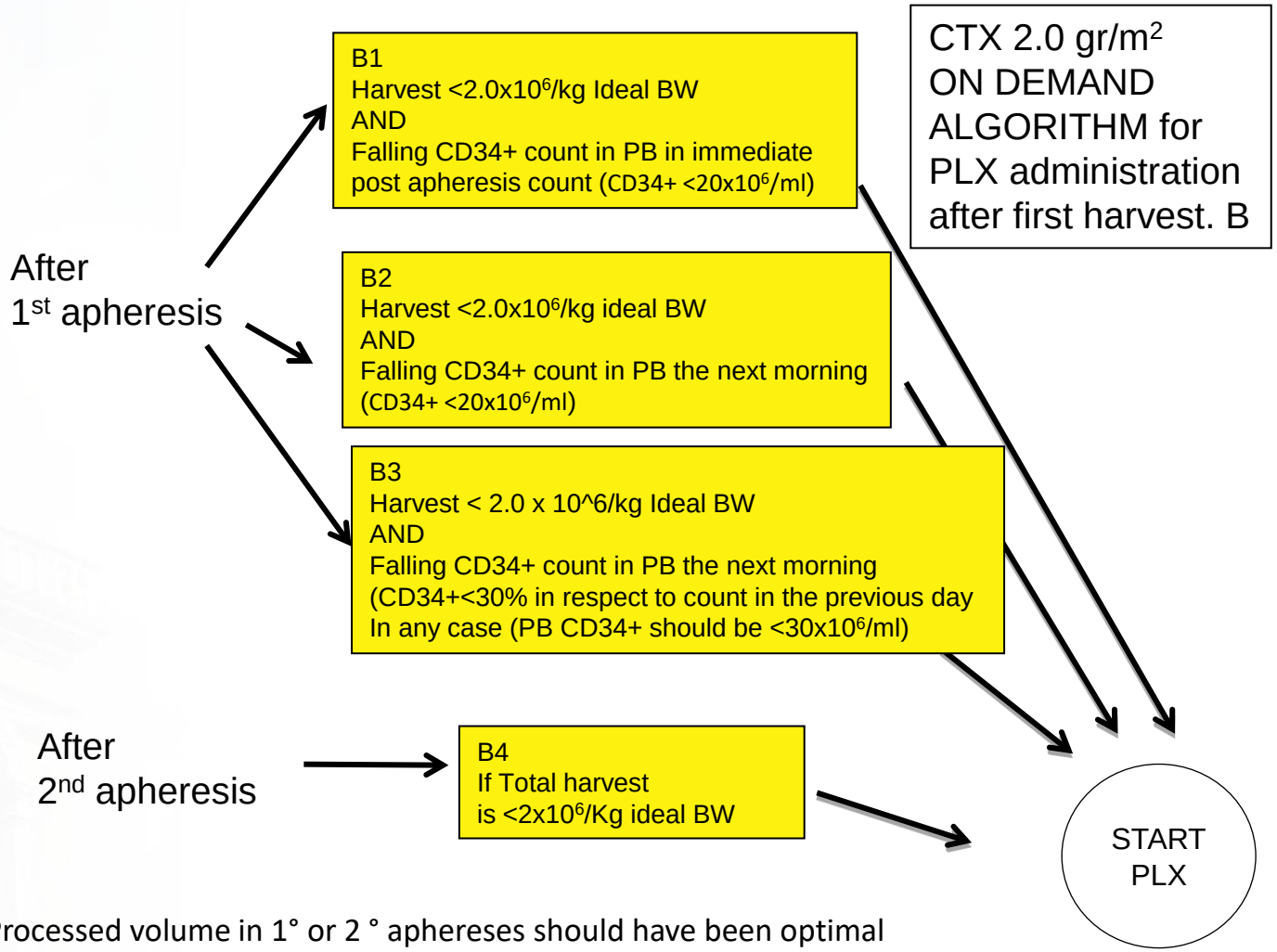


Milone G et al, in preparation

LA FINESTRA TEMPORALE CHE DÀ INFORMAZIONI SULLA ENTITÀ DELLA MOBILIZZAZIONE E' POSIZIONATA A TEMPI DIFFERENTI CHE DIPENDONO DALLA DOSE DELLA CHEMIOTERAPIA E DAL TIPO DI CHEMIOTERAPIA SOMMINISTRATA



Milone G, et al. British Journal of Haematology 2014;164:113-123

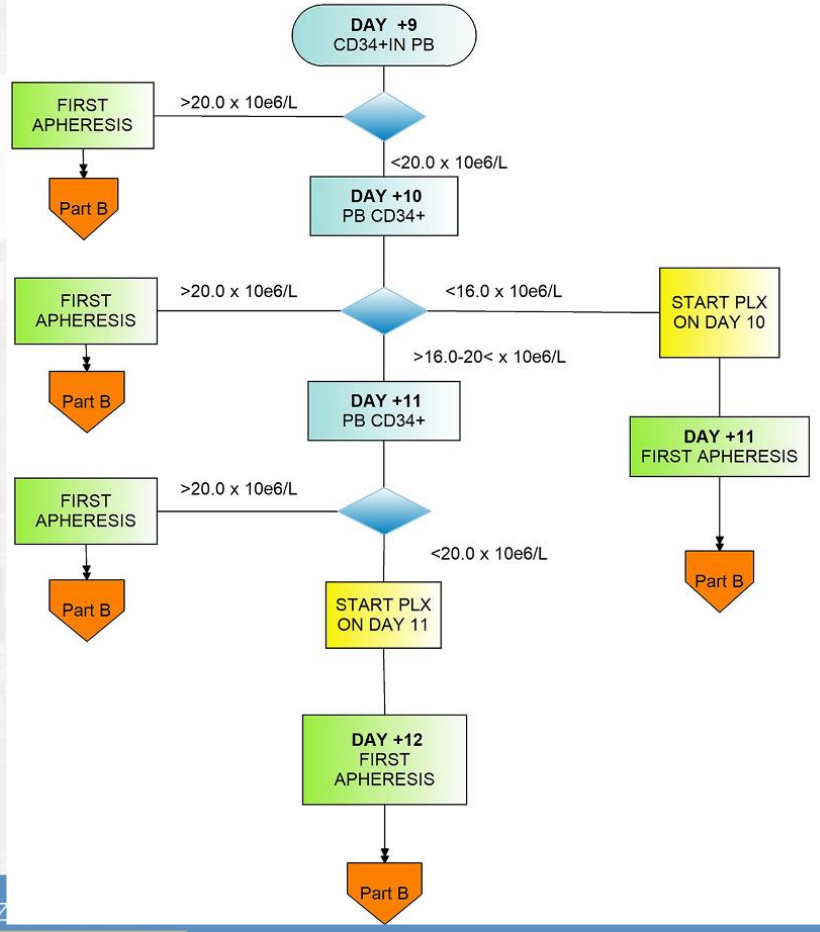


Processed volume in 1° or 2 ° aphereses should have been optimal (at least 1.5 blood volume).

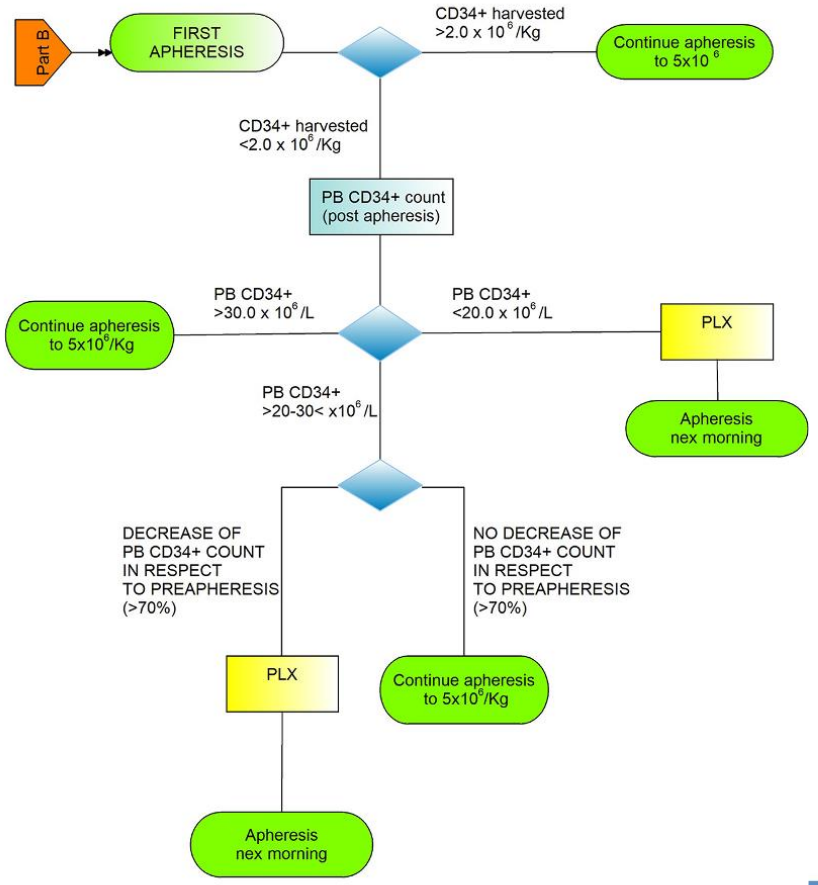
Adattato da: Milone G, et al. British Journal of Haematology 2014;164:113-123

CTX 2 gr/sqm + G-CSF + PLX ON DEMAND

Part A Timing of start the first apheresis and use of PLX before first haverst



Part B Using of PLX in case of poor apheretic harvest after 1° or 2° apheresis



nature medicine

Article

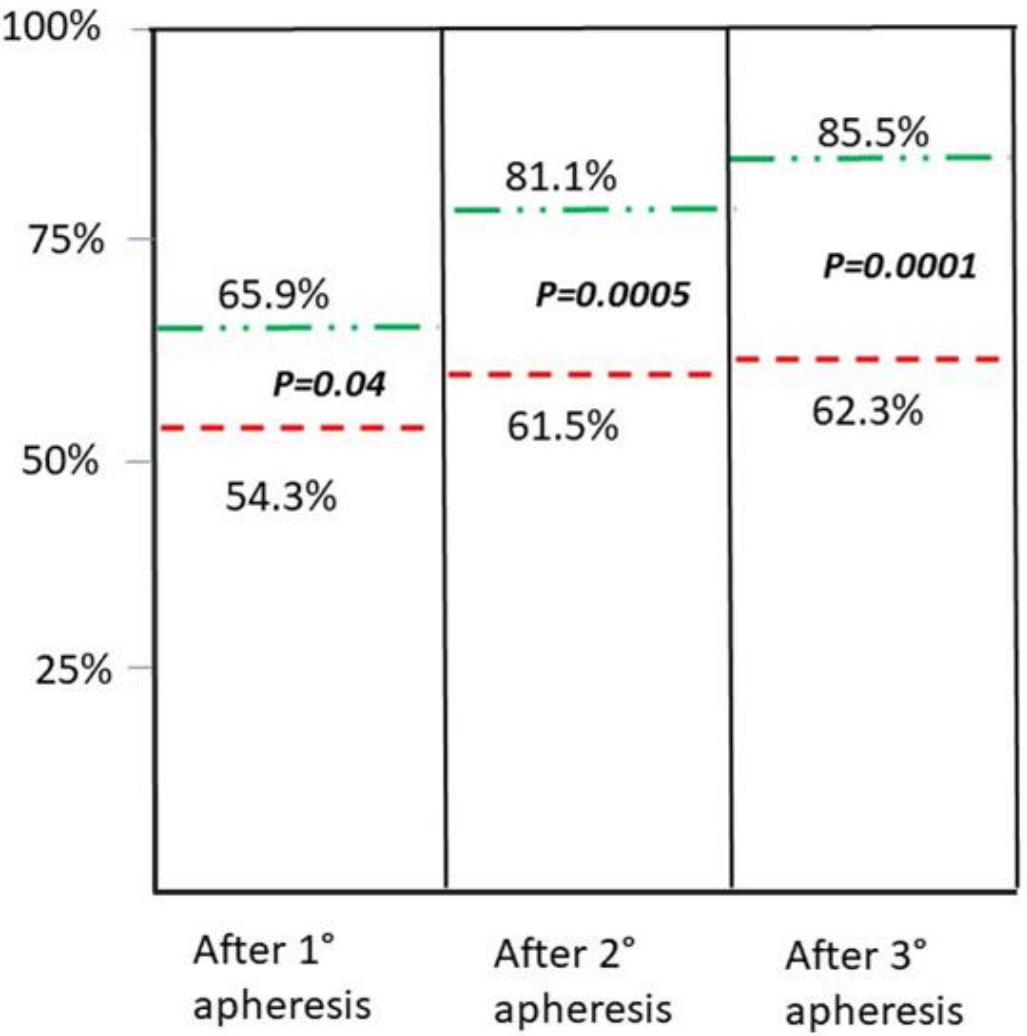
https://doi.org/10.1038/s41591-023-02273-z

Motixafortide and G-CSF to mobilize hematopoietic stem cells for autologous transplantation in multiple randomized phase 3 trial

Extended Data Table 2 | GENESIS Trial Primary and Secondary Endpoints

	Motixafortide + G-CSF	Placebo + G-CSF	OR (95% CI)	P-value	Plerixafor + G-CSF
% collecting ≥6 x 10^6 CD34+ cells/kg in ≤ 2 apheresis	92.5%	26.2%	53.3 (14.1, 201.3)	<0.0001	78.6%
% collecting ≥6 x 10^6 CD34+ cells/kg in 1 apheresis	88.8%	9.5%	118 (25.4, 549.4)	<0.0001	50.0%
% collecting ≥2 x 10^6 CD34+ cells/kg in 1 apheresis	96.3%	64.3%	18.90 (4.5, 80.0)	<0.0001	100.0%
Median # of CD34+ cells/kg collected in 1 apheresis	10.8 x 10^6 (range 0.5-39.4)	2.25 x 10^6 (range 0.2-10.6)	-	-	5.47 x 10^6
Median # of CD34+ cells/kg infused for ASCT	5.2 x 10^6 (range 2.2-26.7)	3.3 x 10^6 (range 2.0-14.8)	-	-	3.14 x 10^6
Median time to neutrophil engraftment (days)	12 (95% CI 11-12)	12 (95% CI 11-12)	Not Estimable	0.9554	13
Median time to platelet engraftment (days)	18 (95% CI 17-19)	17 (95% CI 17-18)	0.95 (0.2, 5.7)	0.9554	18.5
Graft durability (D+100)	92.2%	91.9%	1.04 (0.2, 4.5)	0.96	-

Proportion of patients reaching CD34+ cells > 5x10
after first, second and third apheresis in the two gr



nature medicine

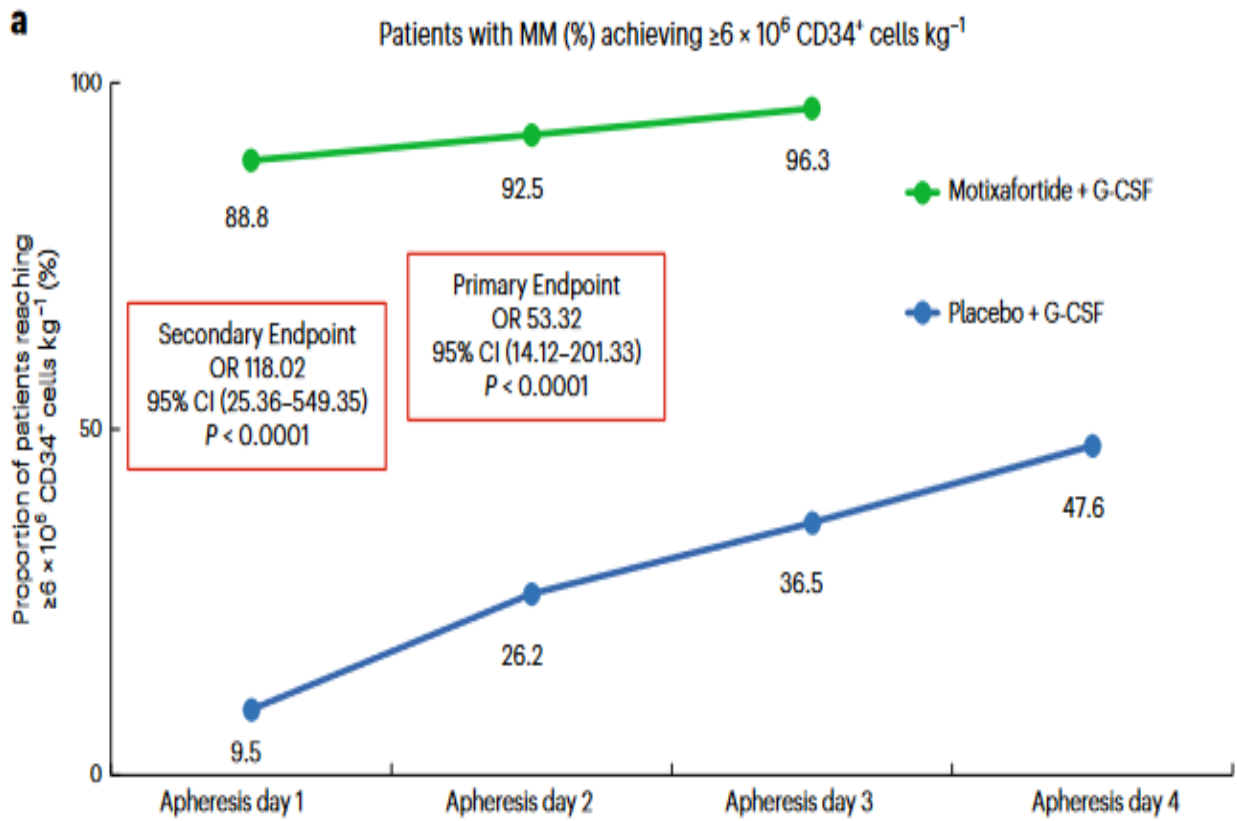
Article

https://doi.org/10.1038/s41591-023-02273-z

Motixafortide and G-CSF to mobilize hematopoietic stem cells for autologous transplantation in multiple myeloma: a randomized phase 3 trial

Article

https://doi.org/10.1038/s41



E’ G-CSF +PLX LA MIGLIORE STRATEGIA DI MOBILIZZAZIONE NEL MM ANCHE VERSUS *CTX low dose + G-CSF + PLX on demand* ?

G-CSF +/- PLX

A) CTX 4 gr dose + G-CSF +/- PLX

B) CTX LOW DOSE dose + G-CSF +/- PLX

How Motixafortide Works

Motixafortide leverages the expression of the CXCR4 receptor on different immune cells and potentiates the immune system against the tumor. Among CXCR4-expressing immune cells, some exhibit anti-tumoral activity, such as effector T cells and some exhibit pro-tumoral activity and support tumor growth. By blocking the CXCR4 receptor, motixafortide was shown, in a Phase 2 study in pancreatic cancer patients, to enhance anti-tumoral activity and to ameliorate the following pro-tumoral activities:

- Releasing immune cells (NK, B, and T cells) to periphery by blocking their CXCR4-mediated retention in bone marrow stroma.
- Enabling infiltration of effector T cells into the tumor, by blocking their CXCR4-mediated retention on CXCL12-secreting fibroblasts at the edge of the tumor.
- Relieving immunosuppression by blocking CXCR4-mediated infiltration of immunosuppressor cells into the tumor.

Transplantation and Cellular Therapy 29 (2023) 174.e1–174.e10

ELSEVIER

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cel

Full Length Article
Autologous

Stem Cell Mobilization Yields with Daratumumab- and Lenalidomide-Containing Quadruplet Induction Therapy in Newly Diagnosed Multiple Myeloma: Findings from the MASTER and GRIFFIN Trials

Saurabh Chhabra[1,*], Natalie Callander[2], Nicole L. Watts[3], Luciano J. Costa[3], Bicky Thapa[4],

PLERIXAFOR use: **D-KRd (97%;** 112 of 116) **D-RVd (72%;** 68 of 95) receiving **RVd (55%;** 44 of 80).

$CD34^+$ collection: **6.0 × 10^6/kg** after **D-KRd**, **8.3 × 10^6/kg** after **D-RVd** induction, **9.4 × 10^6/ after RVd**

Received: 6 August 2023 | Accepted: 25 September 2023
DOI: 10.1111/bjh.19141

ORIGINAL PAPER

Insight into the mechanism of CD34$^+$ cell mobilisation impairment in multiple myeloma patients treated with anti-CD38 therapy

Ondrej Venglar[1,2,3] | Veronika Kapustova[2,3] | Anjana Anilkumar Sithara[1,2,3] |

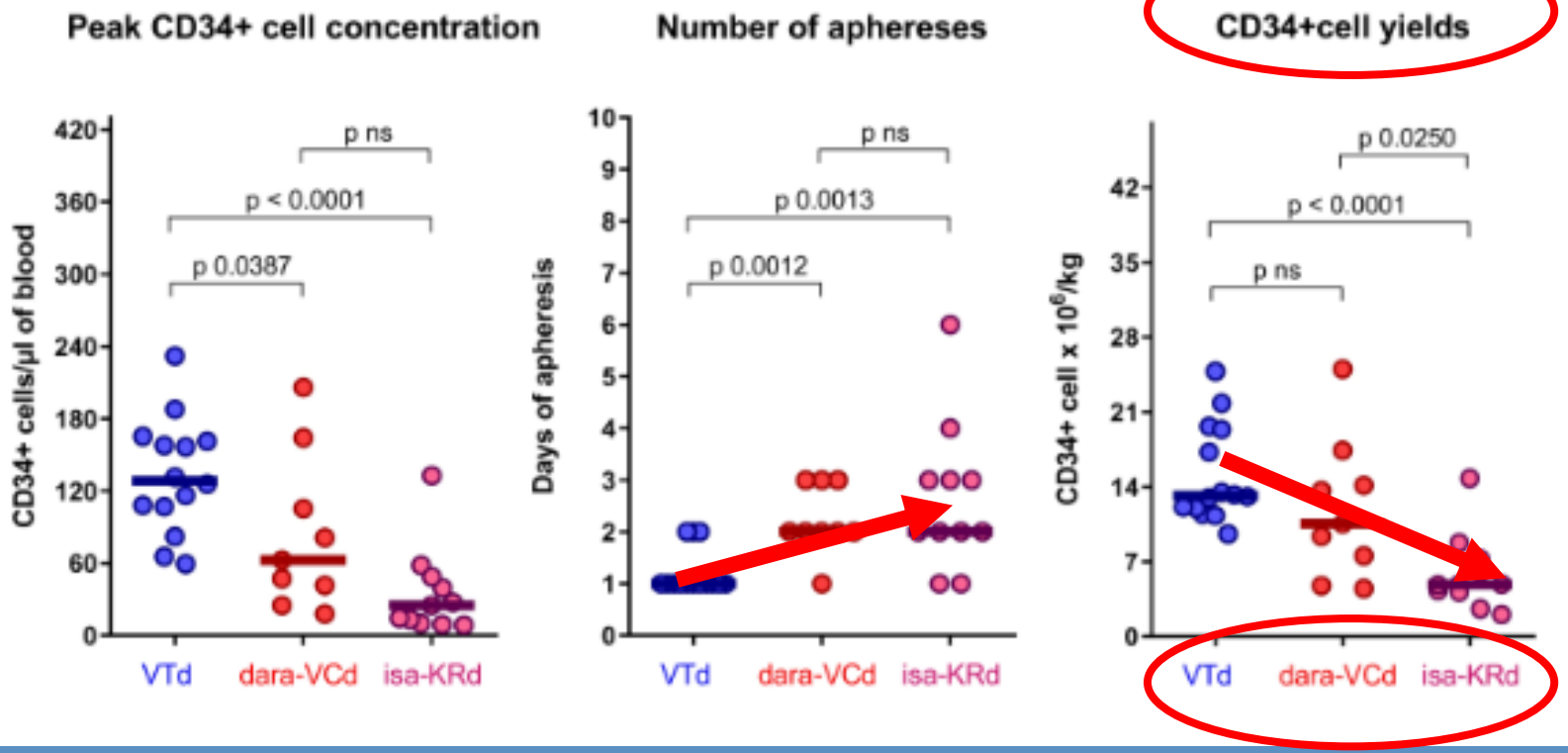
[1]Faculty of Science, University of Ostrava, Ostrava, Czech Republic
[2]Department of Hematooncology, Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic
[3]Department of Hematooncology, University

DARA AND ISA DETERMINE IMPAIRAMENT OF CD34 HARVEST

Summary
Induction therapy followed by CD34$^+$ cell mobilisation and autologous transplantation represents standard of care for multiple myeloma (MM). However, the anti-CD38 monoclonal antibodies daratumumab and isatuximab have been associated

Mobilization was induced with cyclophosphamide 2.5 g/m^2 on day 1 followed by 10 µg/kg/day of G-CSF

Plerixafor at a standard dose of 0.24 mg/kg/day was given to patients for whom >1.5 x 10^6 CD34+ cells/kg in total could not be collected after 2 days of apheresis.



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BJHaem

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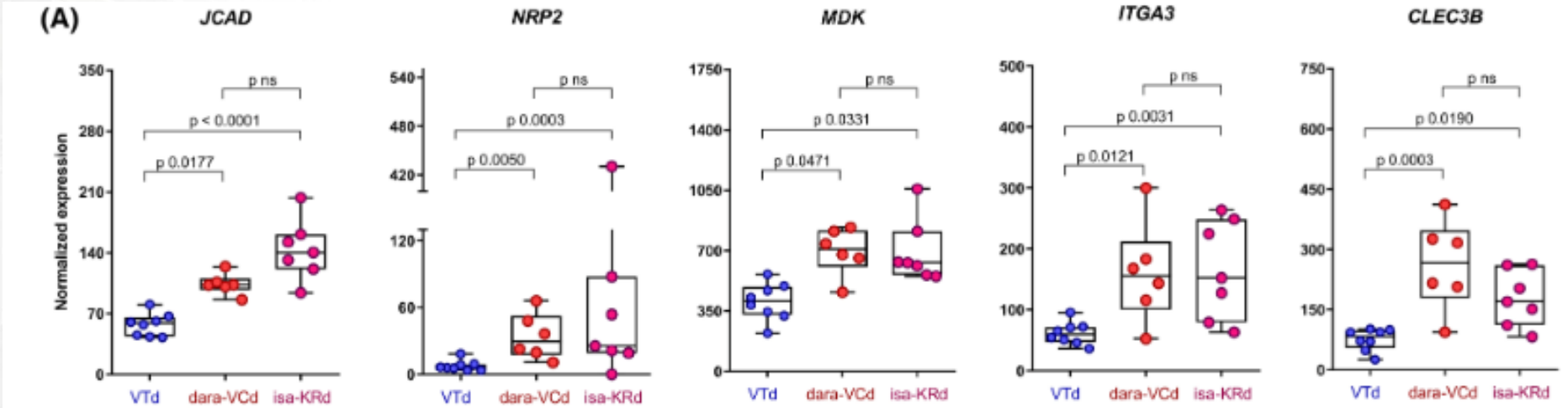
Ondrej Venglar[1,2,3] | Veronika Kapustova[2,3] | Anjana Anilkumar Sithara[1,2,3] | David Zihala[1,2,3] | Ludmila Muronova[2,3] | Tereza Sevcikova[1,2,3] | Jan Vrana[3] | Alexander Vdovin[1,2,3] | Jakub Radocha[4] | Petra Krhovska[5] | Matous Hrdinka[1,2,3] | Michal Turjap[6] | Tereza Popkova[2,3] | Zuzana Chyra[1,2,3] | Lucie Broskevicova[2,3] | Michal Simicek[1,2,3] | Zdenek Koristek[2,3] | Roman Hajek[2,3] | Tomas Jelinek[2,3]

adhesion genes are overexpressed in CD34$^+$ cells after dara-VCd/isa-KRd
and *JCAD*, *NRP2*, *MDK*, *ITGA3* and *CLEC3B* were identified as potential target genes.



OGUNNIYI
Leukemia and Lymphoma 2017
UPFRONT G-CSF+PLX IN MM
RETROSPECTIVE STUDY
MSKCC

92% RACCOLGONO PER 2 TRAPIANTI

1.4% failure rate

Retrospettivo

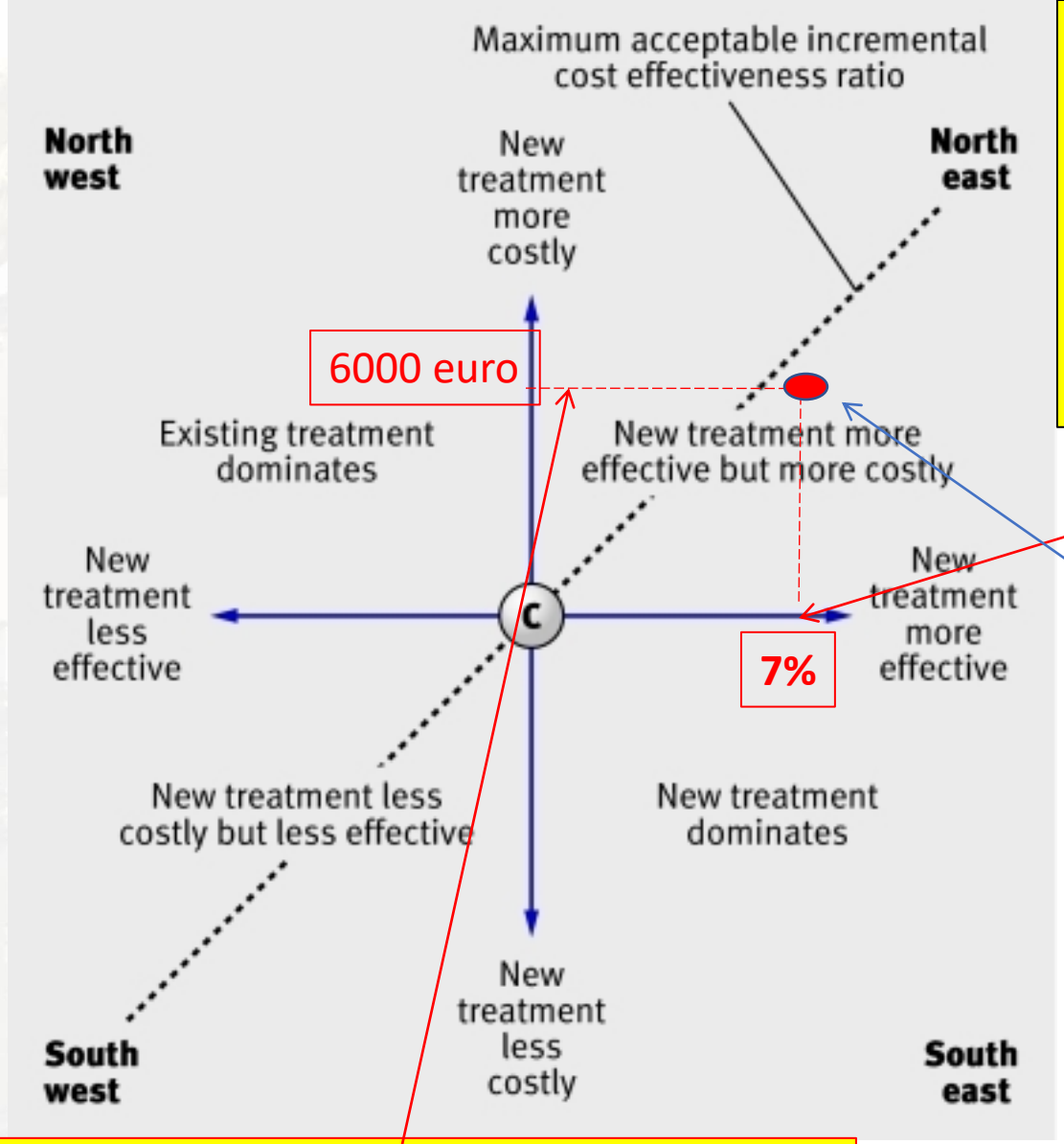
G-CSF+PLX
Nel MM
(138 pts mobilizzati Upfront)

< 5.0 X10E6/Kg = 7.2%
< 4.0 X10E6/Kg = 4.3%
<2.0 X10E6/Kg= 1.4%

Multivariata per mancata risposta
(DEFINED AS A HARVEST < 5x10e6/Kg)

MULTIVARIATE IMPORTANT FOR FAILURE RATE:

- **-- WBC <4.000**
- **-- Razza bianca**
- **-- Precedente prima linea con lenalidomide**



INCREMENTAL EFFECTIVENESS OF PXL universal ADDED TO G-CSF=

From 11.7% to 4.7%= 7%

Incremental Cost-Effectiveness Ratio (ICER)

Del PLX Aggiunto al G-CSF:

6000 euro/ 7% =
857 EURO PER 1%
INCREASE IN success rate

Incremental Cost 6000 euro

c	CTX 4 gr	CTX 4gr + PLX	CTX 2 gr + PLX	Totals
below 4x10^6/Kg	29.834	16.535	9.756	22.636
over 4 x10^67Kg	70.166	83.465	90.244	77.364
Totals	100.000	100.000	100.000	100.000

Fisher test: 0.009

	TOTAL	CTX 4 gr	CTX 4gr + PLX (soglia PLX: 20 CD34)	CTX 2 gr + PLX (soglia per PLX:16 CD34)
0	5.158	8.287	2.362	0.000
1	63.037	65.193	51.181	90.244
2	22.923	19.337	33.858	4.878
3	6.590	5.525	9.449	2.439
4	1.433	1.105	2.362	0.000
5	.860	.552	.787	2.439
Total	100.000	100.000	100.000	100.000

IMPEGNO ECONOMICO MOBILIZZAZIONE BASATA SU CTX E' NEI PRIMI 8-9 GG

Impegno Economico Della degenza per Somministrazione CTX

1 5 7 11 13
R R

Impegno Economico trattamento complicanze

IMPEGNO ECONOMICO G-CSF+PLX NEI GIORNI DI HARVEST

Impegno Economico Prima somministrazione PLX

Impegno Economico Seconda somministrazione PLX

1 2 3 4 5 6
R R

LINFOMI		G-CSF alone	G-CSF + PLX		CHEMIO +G	CHEMIO +G+PLX
		Failure rate <2x10e6/	Failure rate <2x10e6/		Failure rate <2x10e6/	Failure rate <2x10e6/Kg
Di Persio (J Clin Oncol 27:4767-4773)	Randomized	52%	13%			
Liu W, (Front Med 2021 Feb 2;8:609116), (n 101)	Randomised	38%				
Milone G (Bone Marrow Transplant. 2003 31. (n 52)	Randomized	50%			39%	
RUSSEL N (Haematologica 2013; 98(2)	Prospective single arm		20%			
Partannen (2017 Ann Hematol 96:1897-1906) (n 72)	Prospective single arm					8%
Milone G (Br J Haematol. 2014, 164(1):113-23) (n 69)	Prospective with an historical arm				29.9%	6.4%
Hubel Kai (Bone Marrow Transplantation. 2019, 54:123–129), (n 90)	Retrospective				17%	10%
SWINN T (Intern Med J. 2022,)(n 81)	Retrospective				23%	5%

STUDI
PLX UP FRONT

UNIVERSAL PLX

BLOOD, 4 JUNE 2009 - VOLUME 113, NUMBER 23

CLINICAL TRIALS AND OBSERVATIONS

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,[1] Edward A. Stadtmauer,[2] Auayporn Nademanee,[3] Ivana N. M. Micallef,[4] Patrick J. Stiff,[5] Jonathan L. Kaufman,[6] Richard T. Maziarz,[7] Chitra Hosing,[8] Stefan Früehauf,[9] Mitchell Horwitz,[10] Dennis Cooper,[11] Gary Bridger,[12] and Gary Calandra,[12] for the 3102 Investigators

DI PERSIO 2009 **MM= 148 pts**

95.3% of 148 participants in the plerixafor had more than or equal to 2 x 106 CD34+ cells/kg in two or fewer apheresis days

HARVEST FAILURE 4.7% Versus 11.7%.
Mobilization failure 1.6% .

71.6% reached CD34 cells/kg > 6 x 10e6 in 2 or fewer days of apheresis (106 pts /148). Median CD34 collected: 10.96 x10e6/Kg.