Mobilizzazione di cellule staminali emopoietiche “chemo free” nel Mieloma multiplo: è tempo di prime time ?
Bologna, 16 Marzo 2017

Chemioterapia per la raccolta di cellule staminali nel Mieloma Multiplo: pros/cons

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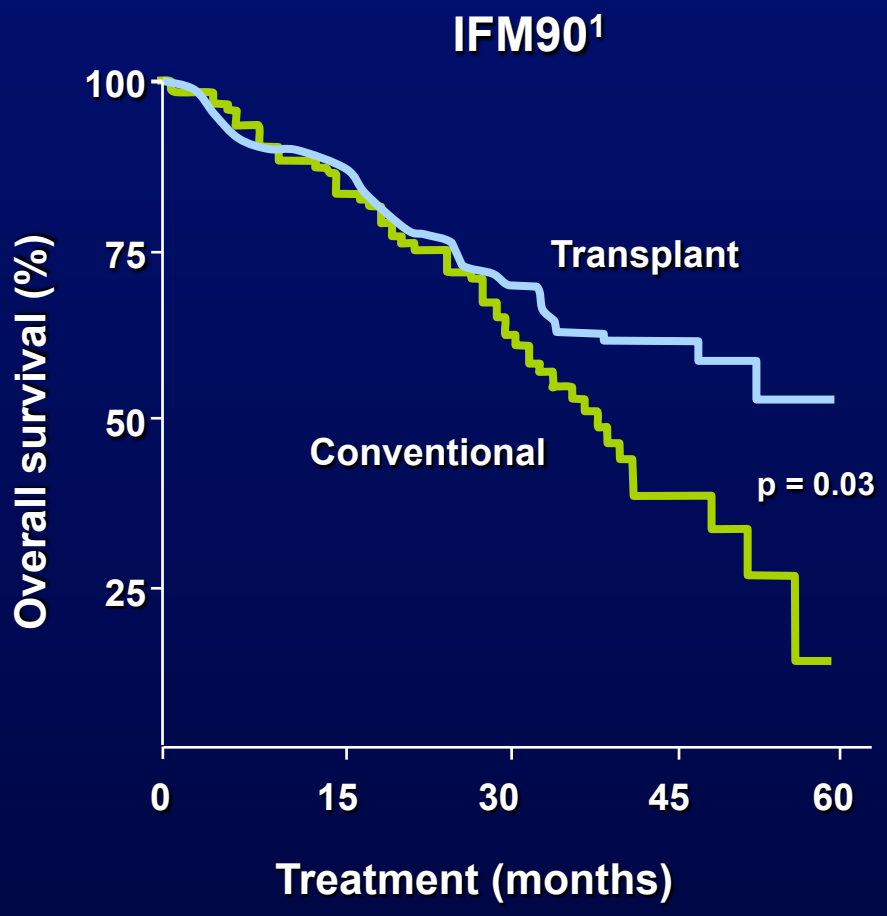
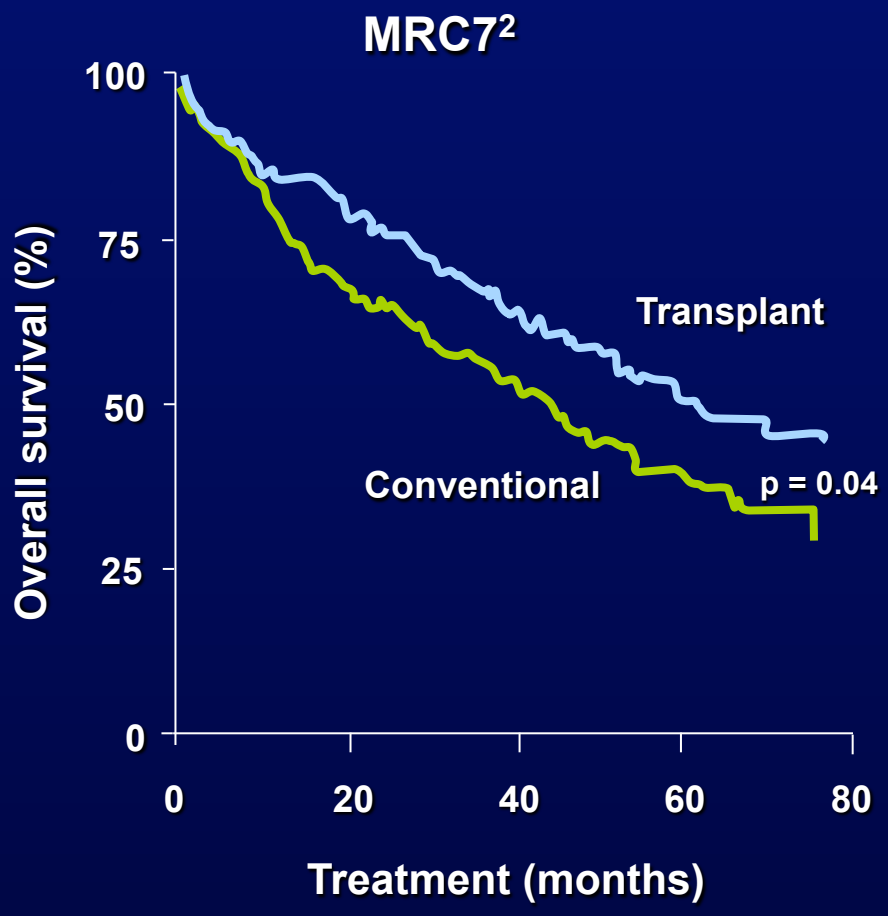
High-dose therapy in Multiple Myeloma



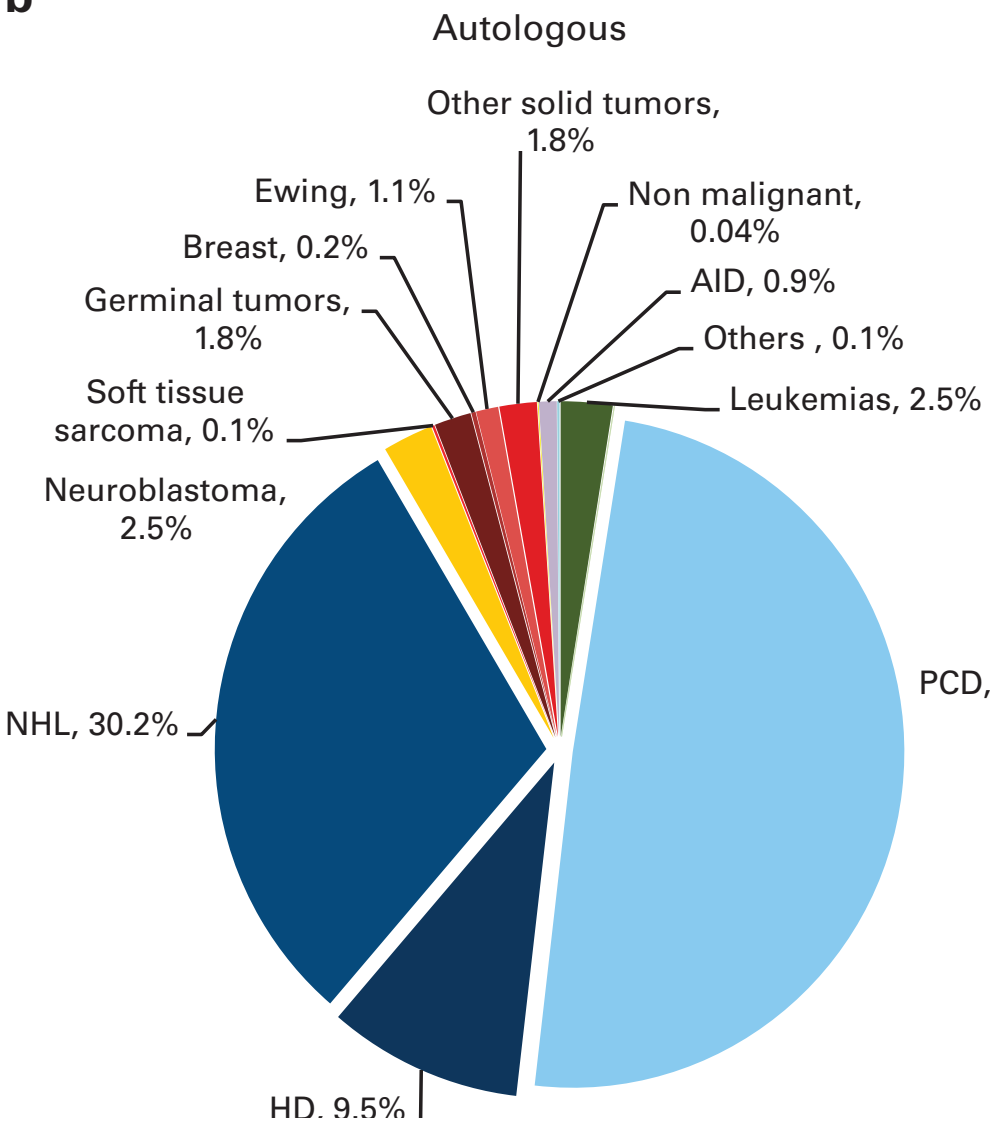


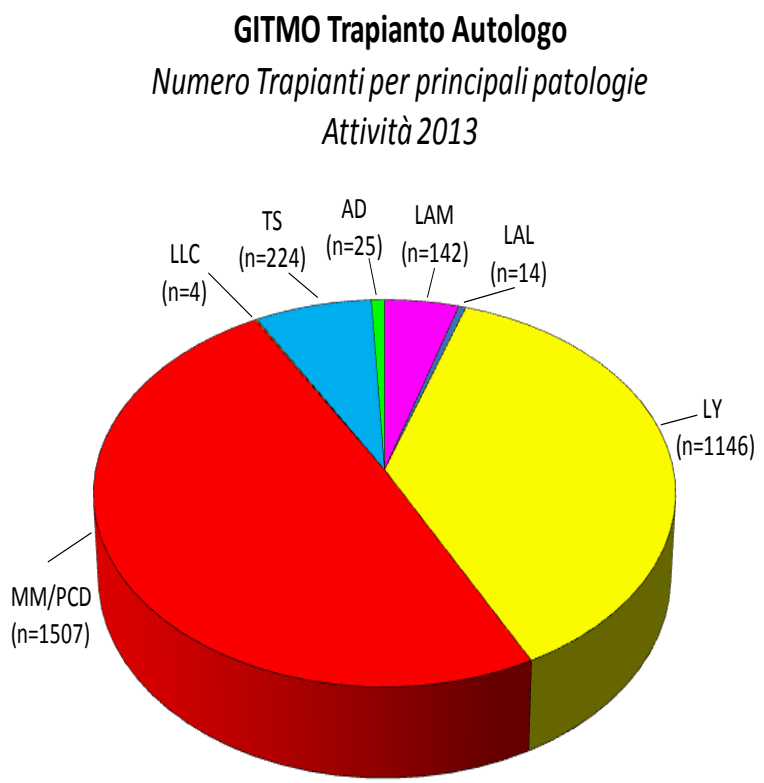
1. Attal M, et al. *N Engl J Med. 1996;335:91.*
2. Child JA, et al. *N Engl J Med. 2003;348:1875.*

Indications for ASCT in Europe in 2013

Bone Marrow Transplantation (2015), 1 – 7

b





Autologous SCT in Multiple Myeloma

- For Multiple Myeloma patients under the age of 65 treatment strategies include a maximum of 2 or 3 auto SCTs for upfront as well as for relapse treatment
- A major goal is therefore:

To mobilize sufficient stem cells to achieve prompt and durable hematopoietic reconstitution after high dose chemotherapy

Impact of $CD34^+$ cell yield in Multiple Myeloma

Clear correlation between $CD34^+$ cell dose and engraftment especially platelet engraftment [1-6]

- Most studies showed optimal dose ≥ 5 x 10^6 $CD34^+$cells/kg
- Most transplant centres recommended at least 2 x 10^6 $CD34^+$ cells/kg
- IMWG (International Myeloma Working Group) recommended: at least 4 x 10^6 $CD34^+$ cells/kg for transplantation and 8–10 x 10^6 $CD34^+$ cells/kg for tandem transplantation [7]

1. Tricot et al. Blood. 1995 Jan 15;85(2):588-96. 2. Weaver CH et al. Blood. 1995 Nov 15;86(10):3961-9.
3. Ketterer N et al. Blood. 1998 May 1;91(9):3148-55. 4. Siena E et al. J Clin Oncol. 2000 Mar;18(6):1360-77.
5. Allan DS et al. Bone Marrow Transplant. 2002 Jun;29(12):967-72. 6. Klaus J et al. Eur J Haematol. 2007 Jan;78(1):21-8.
7. Giralt C et al. Leukemia. 2009 Oct;23(10):1904-12.

Factors That Influence Collection and Engraftment of Autologous Peripheral-Blood Stem Cells

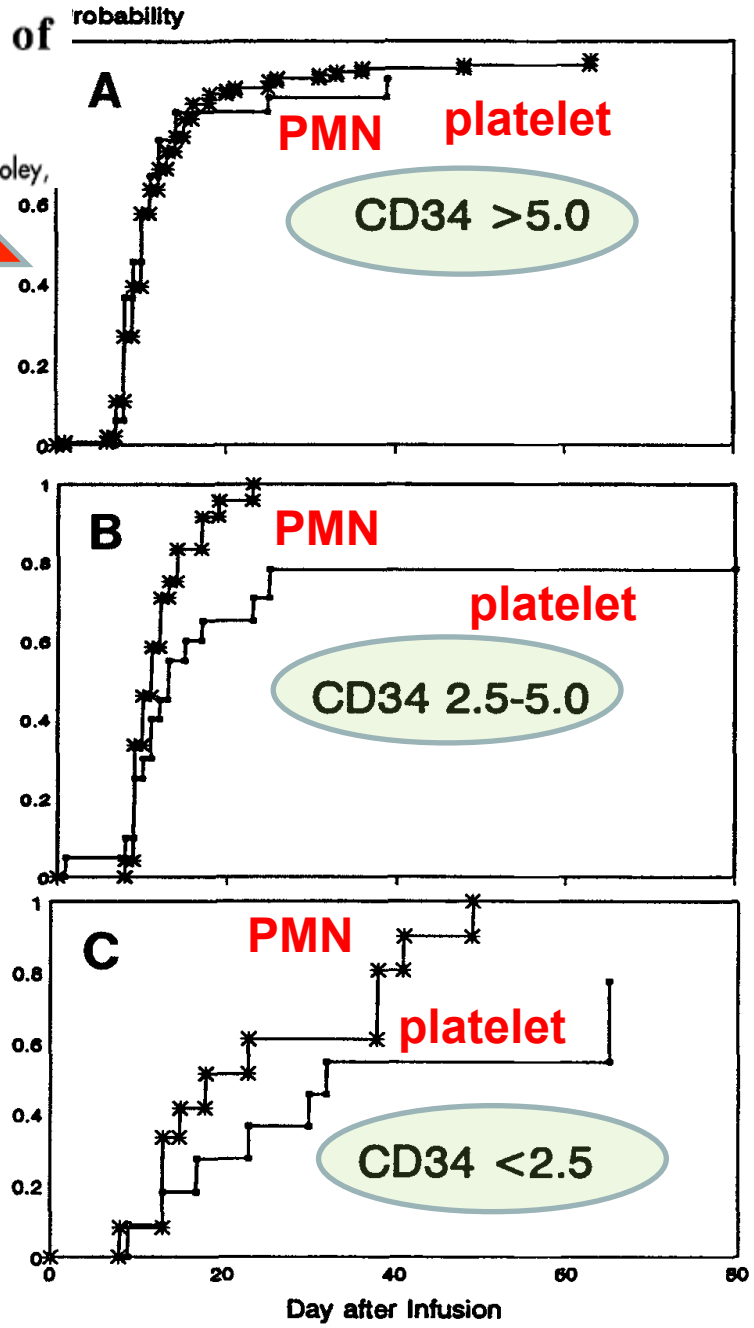
By William Bensinger, Fred Appelbaum, Scott Rowley, Rainer Storb, Jean Sanders, Kathy Lilleby, Ted Gooley,

J Clin Oncol 13:2547-2555. © 1995

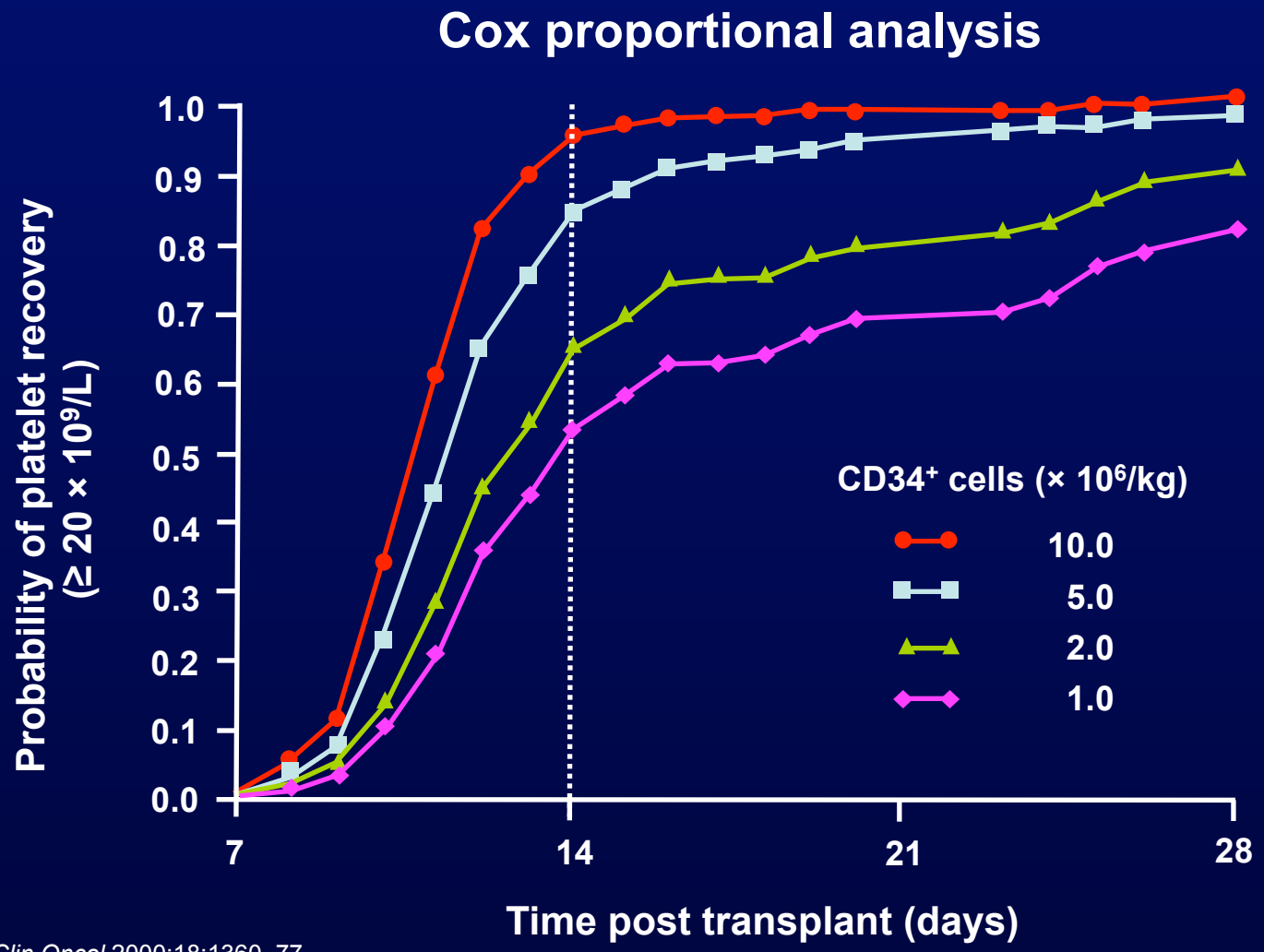
tempo of PMN engraftment was indistinguishable between patients who received 2.5 to 5.0 and >5.0 x 10^6 $CD34^+$ cells/kg.

In contrast, the probabilities for achieving platelet independence were different for each cell dose level

CD 34^+ dose

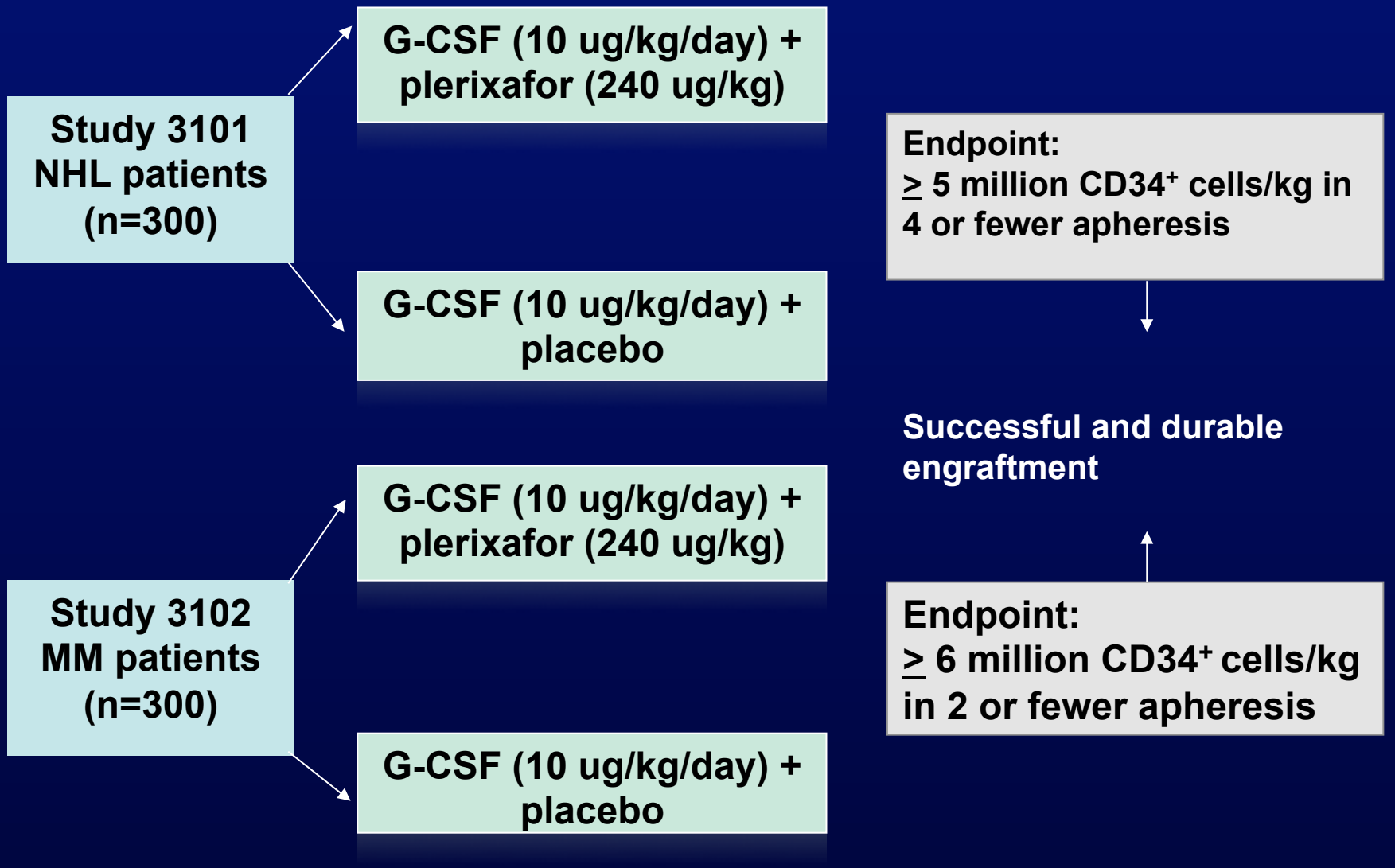


Relationship between transplanted dose and platelet recovery (to ≥ 20 × 10^9 cells/L)



Siena et al. *J Clin Oncol* 2000;18:1360–77.

Plerixafor Phase III Trial – **Study Design**



Study 3102
MM patients
(n=300)

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

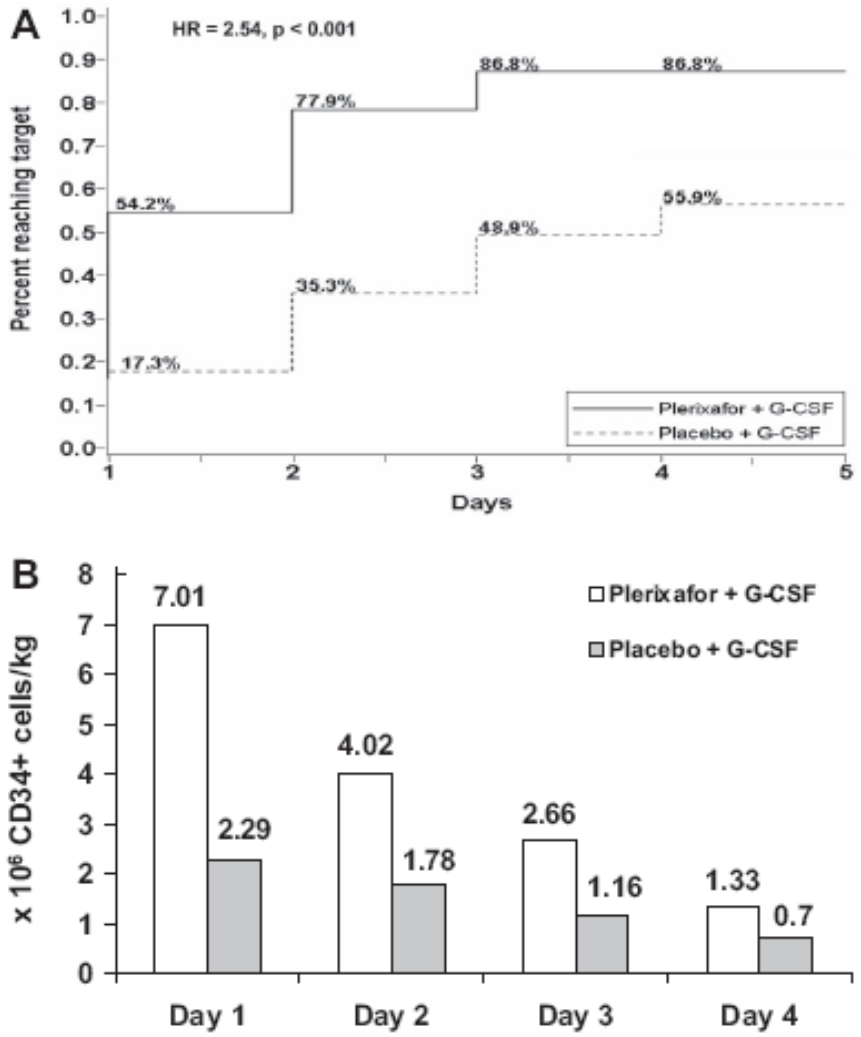


Figure 3. Kinetics of CD34/kg collection. (A) Kaplan-Meier estimate of proportion of patients reaching 6×10^6 or more $CD34^+$ cells/kg. (B) Median $CD34^+$ cells collected on each apheresis day.

Efficacy (MM)

	Plerixafor + G-CSF (n = 148)	Placebo + G-CSF (n = 154)	*p*[a]
Primary endpoint[1] Patients achieving ≥ 6 × 10^6 $CD34^+$ cells/kg in ≤ 2 days of apheresis, n (%)[1]	106 (71.6%)	53 (34.4%)	< 0.001
Secondary endpoint[1] Patients achieving ≥ 6 × 10^6 $CD34^+$ cells/kg in ≤ 4 days of apheresis, n (%)[1]	112 (75.7%)	79 (51.3%)	< 0.001
Patients proceeding to transplant, n (%)[2]	142 (96.0%)	136 (88.3%)	0.014

a Estimate of treatment effect: *p* value assessed by Cochran-Mantel-Haenszel test, blocked by study centre, and Pearson chi-squared with similar results.

DiPersio et al. *Blood* 2009;113:5720–5726.

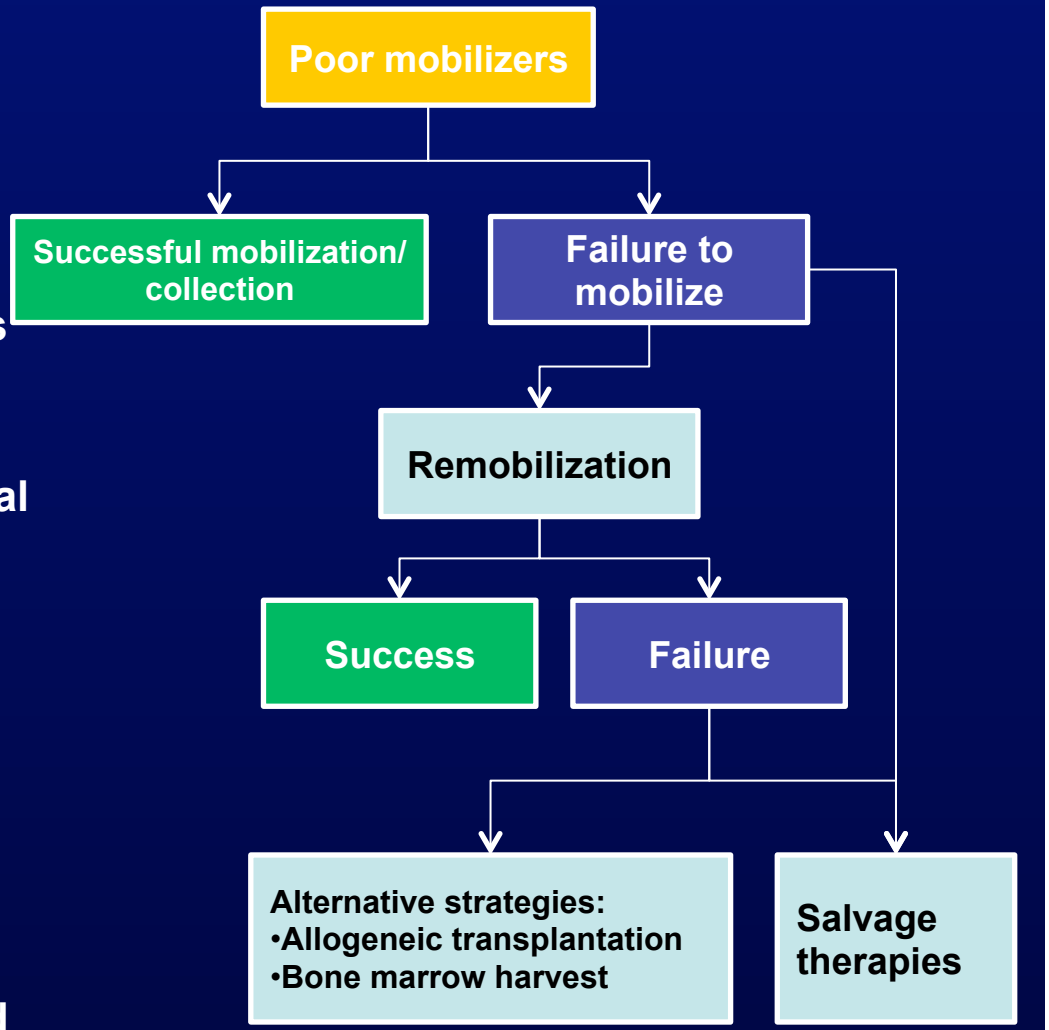
Failure to mobilize is detrimental to the patient and requires additional costs to manage

Patients failing to mobilize require additional treatment which may include:

- **Remobilization procedures. While some may be successful, some patients may still fail to collect targets after remobilization [1,2]**
- **Alternative procedures (allogeneic/ BMT) which are considered suboptimal relative to ASCT [2,3]**
- **Patients who are not suitable for further procedures may only receive salvage/ palliative care**

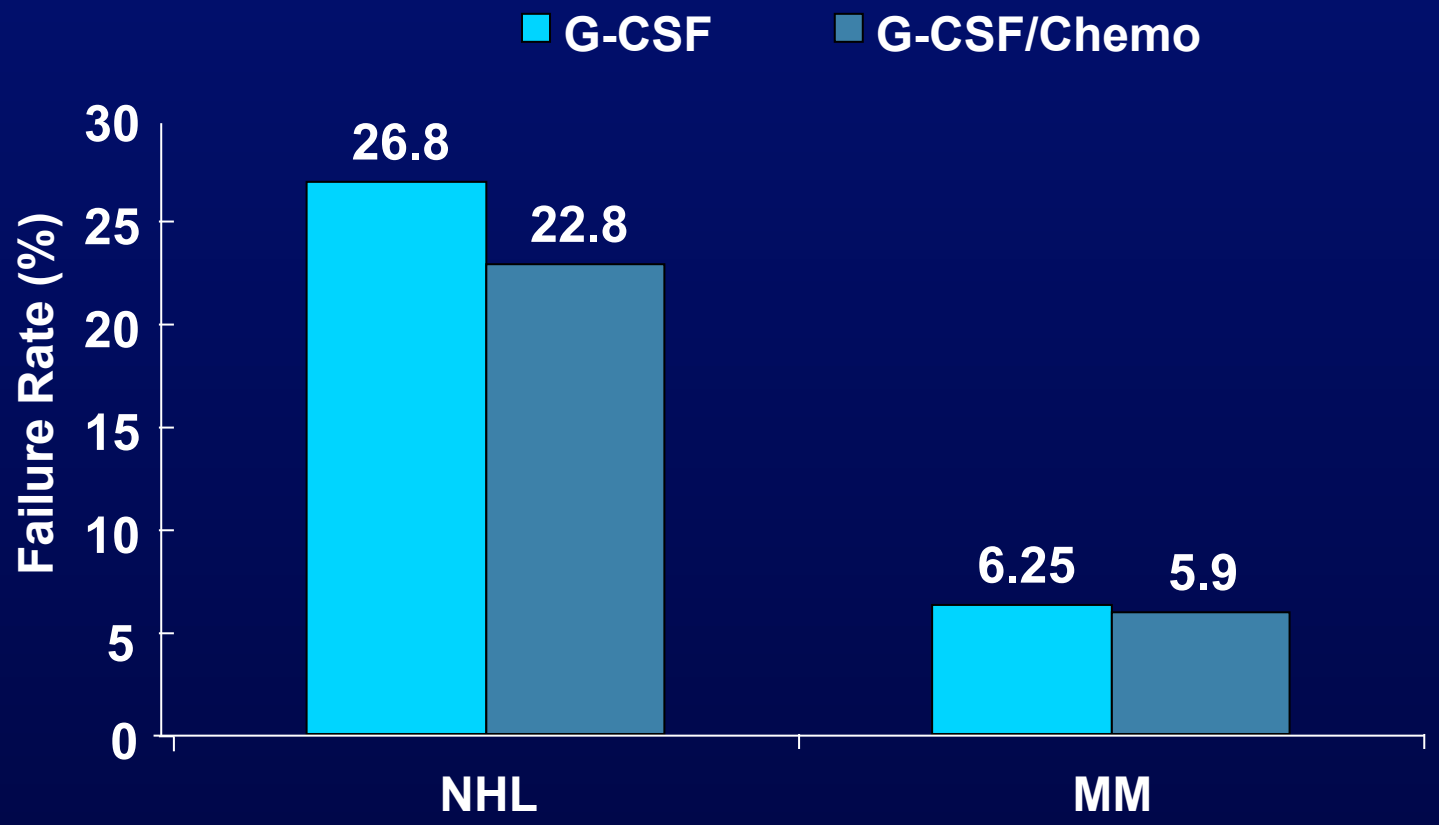
Failure to mobilize is costly due to the requirement for remobilizations or further treatment

- **For example Van Agthoven[4] estimated the cost of bone marrow harvest as ~ €19,000, versus ~ €15,000 for ASCT**



1 Pusic et al (2008) Biol Blood Marrow Transplant 14 (9):1045-1056.
2 Jantunen E, Kvalheim G (2010) Eur J Haematol 85 (6):463-471.
3 Jantunen E, Kuittinen T (2008) European journal of haematology 80 (4):287-295.
4 Van Agthoven et al (2001) Eur J Cancer 37: 1781 - 1789

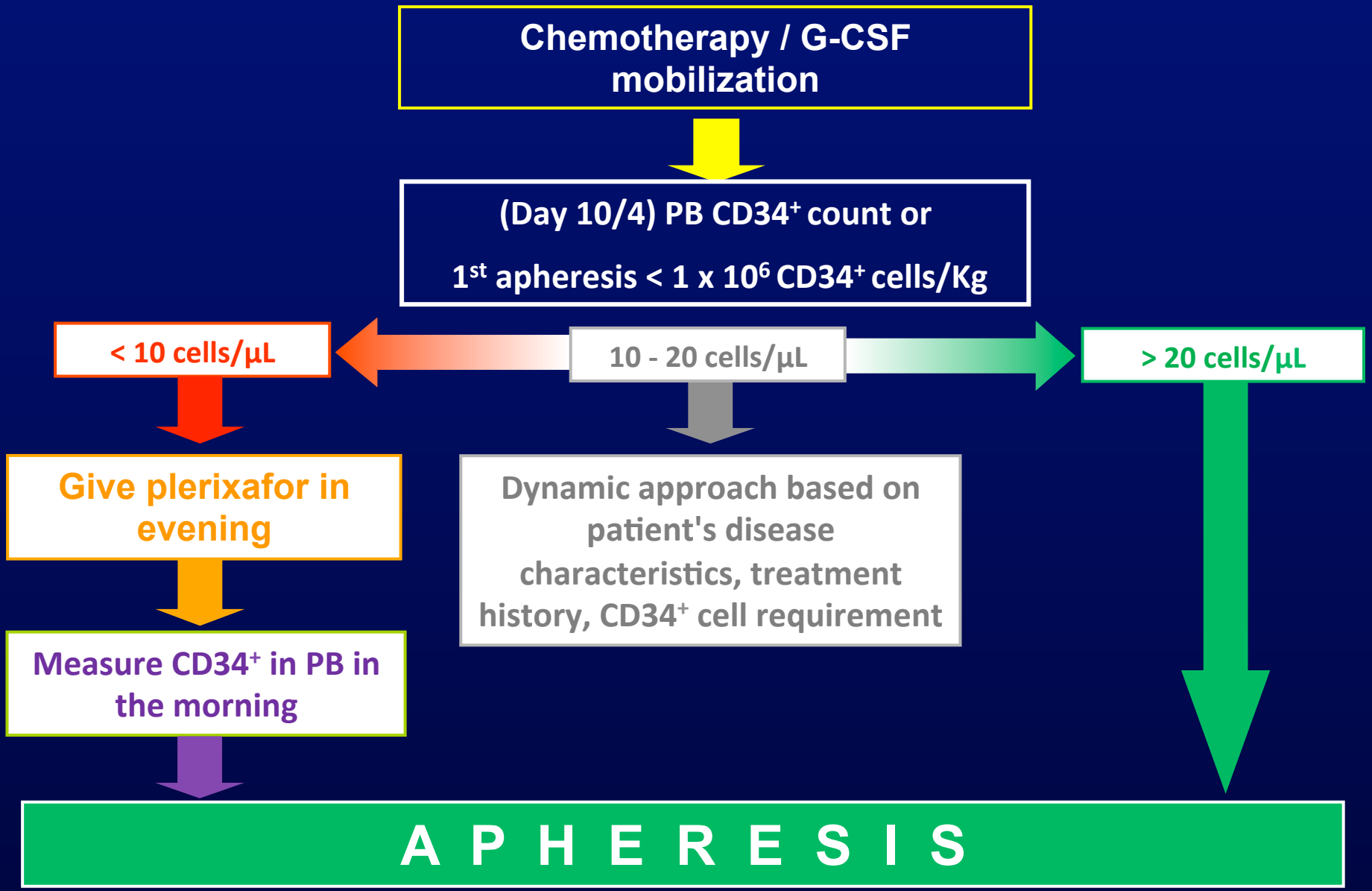
Failure Rates of G-CSF ± Chemotherapy Mobilization Regimens



Chemo, chemotherapy; G-CSF, granulocyte colony stimulating factor; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma.

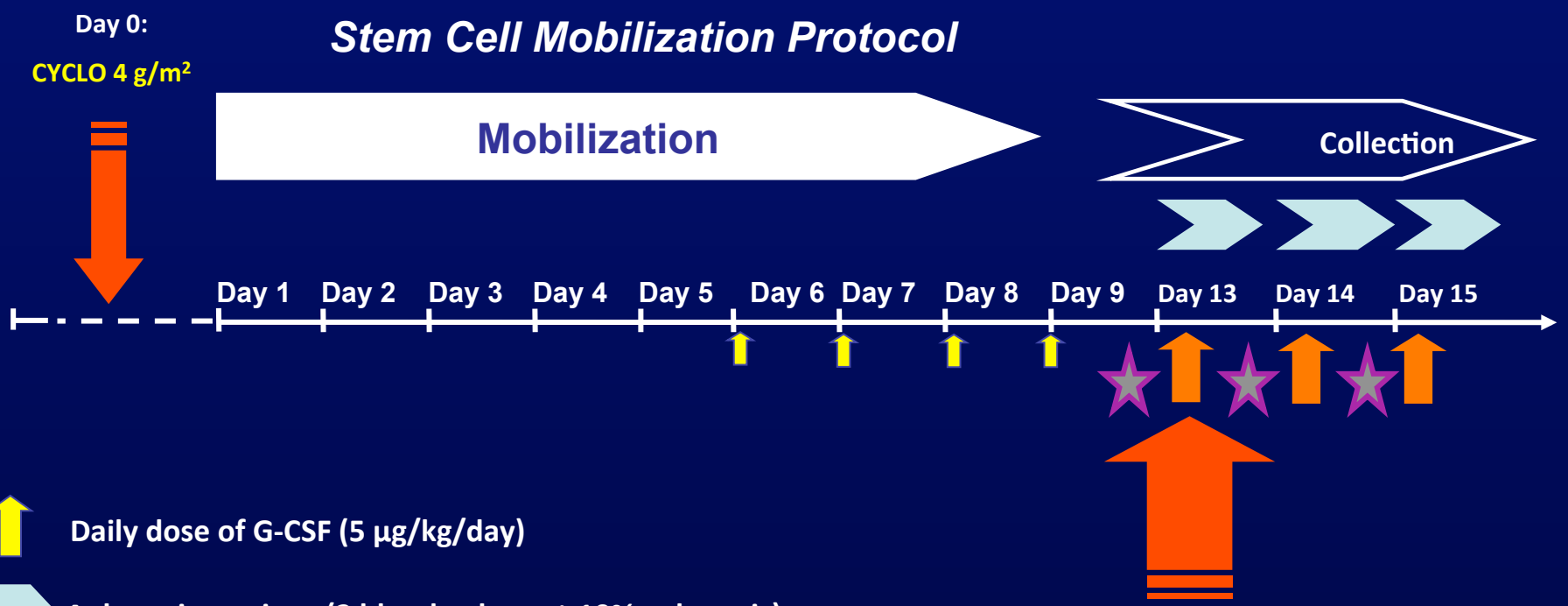
Pusic et al. *Biol Blood Marrow Transplant* 2008;14:1045–1056.

Pre-emptive use of plerixafor in auto-SCT



Jantunen E, Lemoli RM., Transfusion. 2012
Mohty M et al., BMT 2014

"Pre-emptive" use of plerixafor after cyclophosphamide 4g/m^2



Daily dose of G-CSF (5 µg/kg/day)

Apheresis sessions (2 blood volume ± 10% apheresis)

Plerixafor (240 µg/kg/day SC)
- given in the evening at 10:00 PM prior to each apheresis

G-CSF dose of 5 µg/kg/day at 07:00 after each plerixafor dose, about 2 hours prior to starting apheresis

Day +13 is the predicted mobilization day. If CD34 count is not high enough to go on the machine, patient needs "pre-emptive" plerixafor

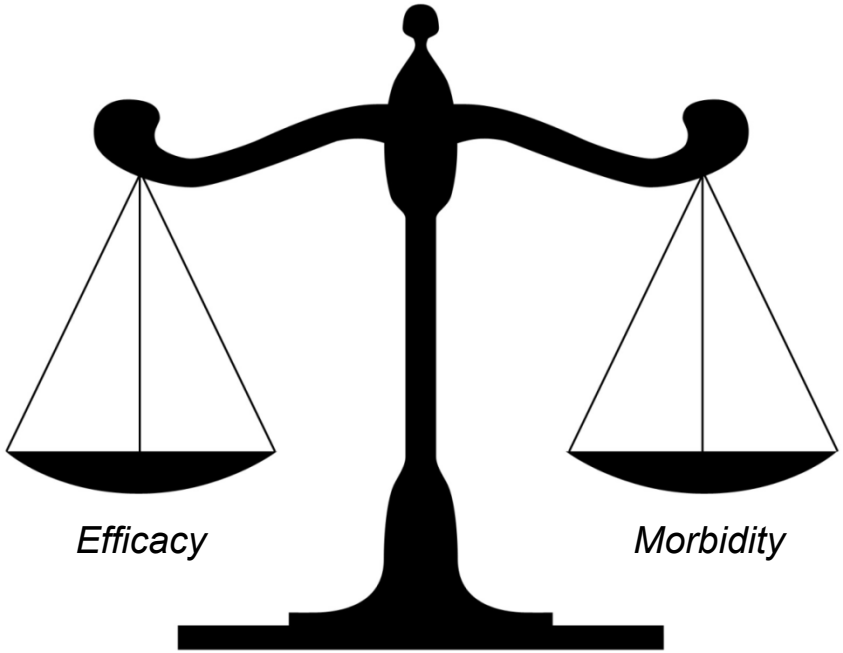
Lemoli RM, unpublished

Important issues associated with stem cell mobilization beside $CD34^+$ cell yield in Multiple Myeloma

- Mobilization of clonal myeloma cells[1-4]
- Collection technique[5]
- Higher number of lymphocytes and dendritic cells in apheresis product [6-11]
- Morbidity and use of financial resources
- Predictivity of mobilizing strategies
- Anti-tumor effect of chemotherapy (Cy[12], Eto, Bort)

1. Zhou P et al. Blood. 2003 Jul 15;102(2):477-9.
2. Stewart AK et al. J Clin Oncol. 2001 Sep 1;19(17):3771-9.
3. Bourhis JH et al. Haematologica. 2007 Aug;92(8):1083-90.
4. Fruehauf S et al. Bone Marrow Transplant. 2010 Feb;45(2):269-75.
5. Moog R. Transfus Apher Sci. 2008 Jun;38(3):229-36.
6. Porrata LF et al. Leukemia. 2004 Jun;18(6):1085-92.
7. Hiwase DK et al. Biol Blood Marrow Transplant. 2008 Jan;14(1):116-24.
8. Atta EH et al. Am J Hematol. 2009 Jan;84(1):21-8.
9. Holtan SG et al. Clin Lymphoma Myeloma. 2007 Jan;7(4):315-8.
10. Gazitt Y et al. Stem Cells Dev. 2006 Apr;15(2):269-77.
11. Retting et al., 2009
12. Desikan KR et al. JCO 1998; 16: 1547-53

Chemotherapy vs. steady state mobilization for the collection of HSC in Multiple Myeloma



Is the efficacy of both approaches similar? What are the differences in side effect profiles?

1) Damon L. et al. BBMT 2006. Cy (6 gr/m^2) or Eto (2 gr/m^2): 71% response (17% CR-no stringent criteria). Patients proceeding to ASCT= 81% (5% did not due to toxicity). Three weeks cytopenia. TRM= 2.5%
2) Desikan RK. Et al. JCO 1998. Cy (6 gr/m^2) vs G-CSF: Increased % hospitalization (100% ,Cy), plt and rbc transfusion (86% ,Cy), higher % FUO and documented infections. Similar efficacy (77% vs 82% pts achieved SC target). No difference for engraftment despite higher numbers of $CD34^+$ cells in Cy group (approx 11x 10^6/Kg vs 3 x 10^6/Kg). Antitumor effect of Cy= 10% pts partial response.

International myeloma working group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100)

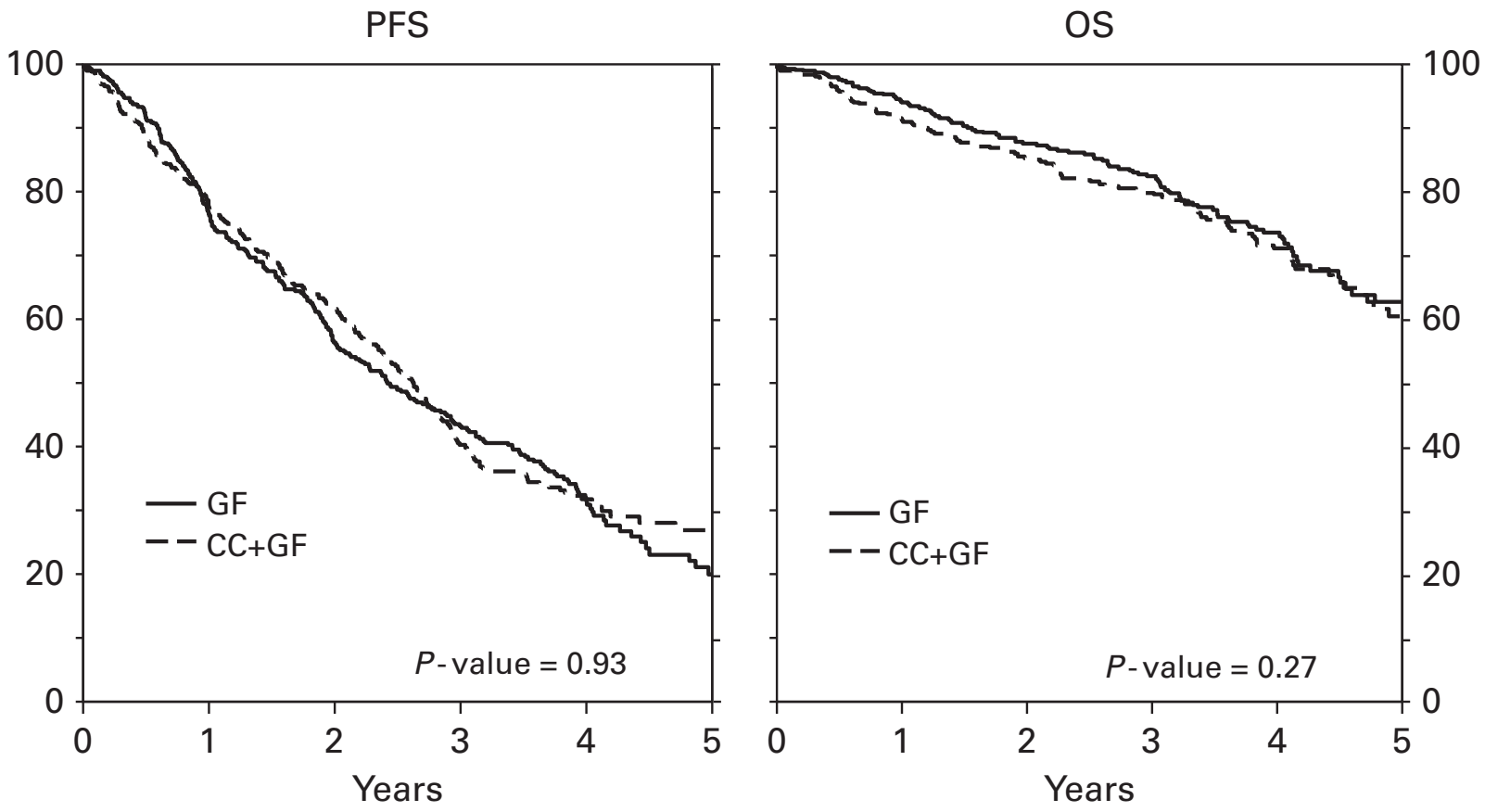
Leukemia (2009), 1–9

S Giralt[1], EA Stadtmauer[2], JL Harousseau[3], A Palumbo[4], W Bensinger[5], RL Comenzo[6], S Kumar[7], NC Munshi[8], A Dispenzieri[7], R Kyle[7], G Merlini[9], J San Miguel[10], H Ludwig[11], R Hajek[12], S Jagannath[13], J Blade[14], S Lonial[15], MA Dimopoulos[16], H Einsele[17], B Barlogie[18], KC Anderson[8], M Gertz[7], M Attal[19], P Tosi[20], P Sonneveld[21], M Boccadoro[4], G Morgan[22], O Sezer[23], MV Mateos[10], M Cavo[24], D Joshua[25], I Turesson[26], W Chen[27], K Shimizu[28], R Powles[29], PG Richardson[8], R Niesvizky[30], SV Rajkumar[7] and BGM Durie[31] on behalf of the IMWG[32]

Table 2 Pros and Cons of commonly used mobilization strategies in patients with myeloma

Strategy	*Frequency used*	*Pros*	*Cons*	*Comments*
Single agent filgrastim	Most common	Ease of use Cost Effective >80% of time Minimal toxicity Predictable	Only moderate CD34 yield No anti-myeloma effect	Current gold standard
Cyclophosphamide plus filgrastim	Most common chemomobilization used	Predictability Overcomes lenalidomide stem cell effect Well tolerated Predictable	Cytopenias and infectious complications Adds costs Minimal anti-myeloma effect Resource utilization	Doses over 4 g/m^2 associated with more toxicity without clear clinical benefit
Combination chemotherapy plus filgrastim	In some selected centers or for patients with high tumor burden	Disease control *In vivo* purging	Toxicity Cytopenias and infectious complications Cost and delays in eventual transplantation	DTPACE and modified CVAD commonly used. No comparative trials
Combination growth factors	Filgrastim and GMCSF explored now rarely used	Theoretical improvement in graft composition	Costs GMCSF not available in Europe	No proven benefit

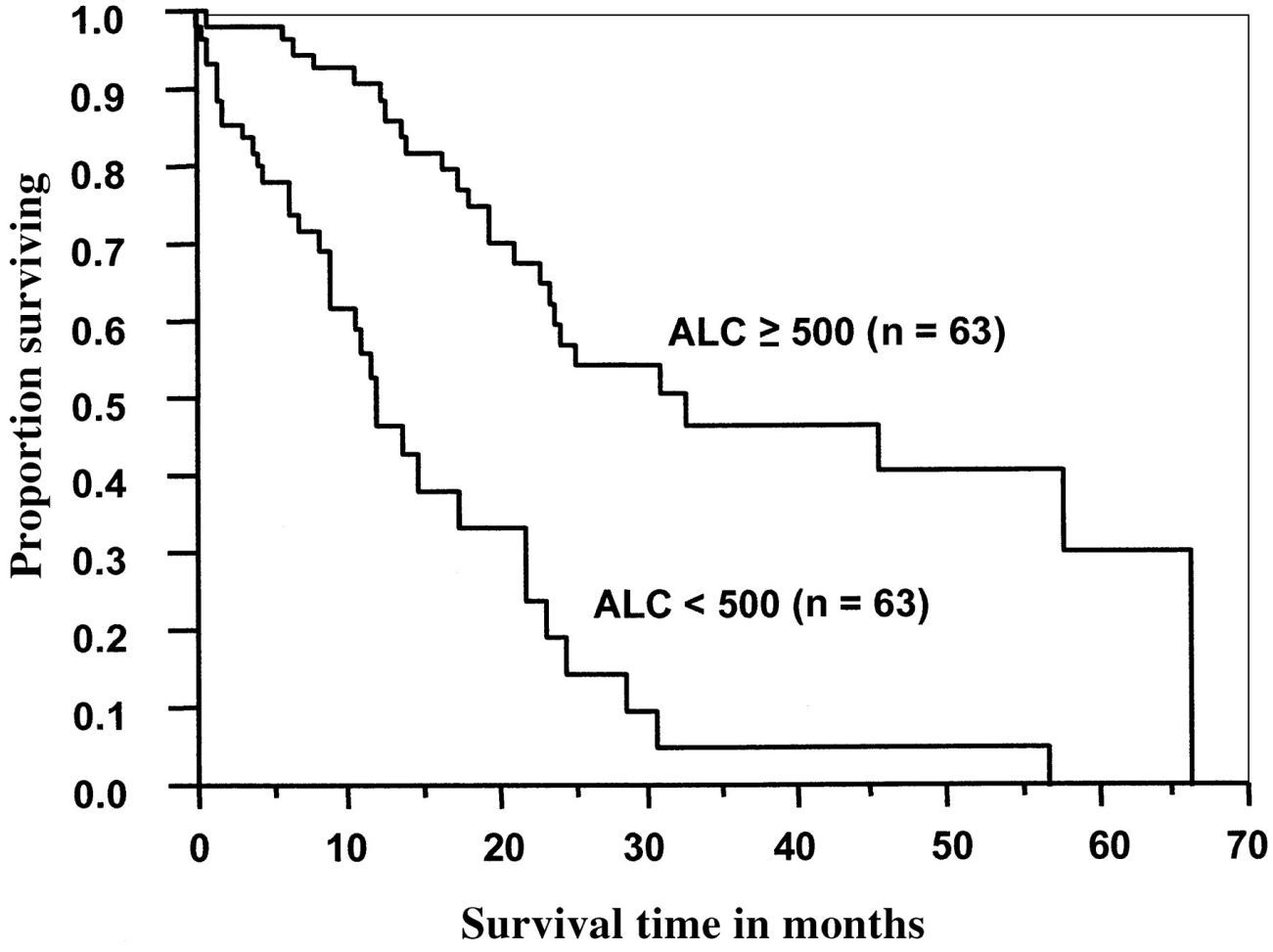
Adjusted probability of PFS and OS according to the method of mobilization.



CC-GF versus GF-only mobilization in myeloma
GL Uy *et al*

Overall survival of 126 patients with multiple myeloma as a function of ALC recovery at day 15 after ASCT. Median overall survival time for patients with an ALC greater than or equal to 500 cells/μL was 33 months versus 12 months for patients with an ALC less than 500 cells/μL (P < .0001).

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



Porrata LF et al. Blood 2001;98:579-585

Multiple Myeloma cell mobilization and positive selection of CD34^{+} HSC for tumor cell purging

CD34 OR S313 POSITIVE CELLS SELECTION BY AVIDIN-BIOTIN IMMUNOADSORPTION

C.TASSI, A.FORTUNA, A.BONTADINI, R.M.LEMOLI, M.GOBBI*, P.L.TAZZARI**

HAEMATOLOGICA
Vol. 76 - Supplement No. 1 - March 1991

blood 1996 87: 1625-1634

Concomitant mobilization of plasma cells and hematopoietic progenitors into peripheral blood of multiple myeloma patients: positive selection and transplantation of enriched CD34+ cells to remove circulating tumor cells

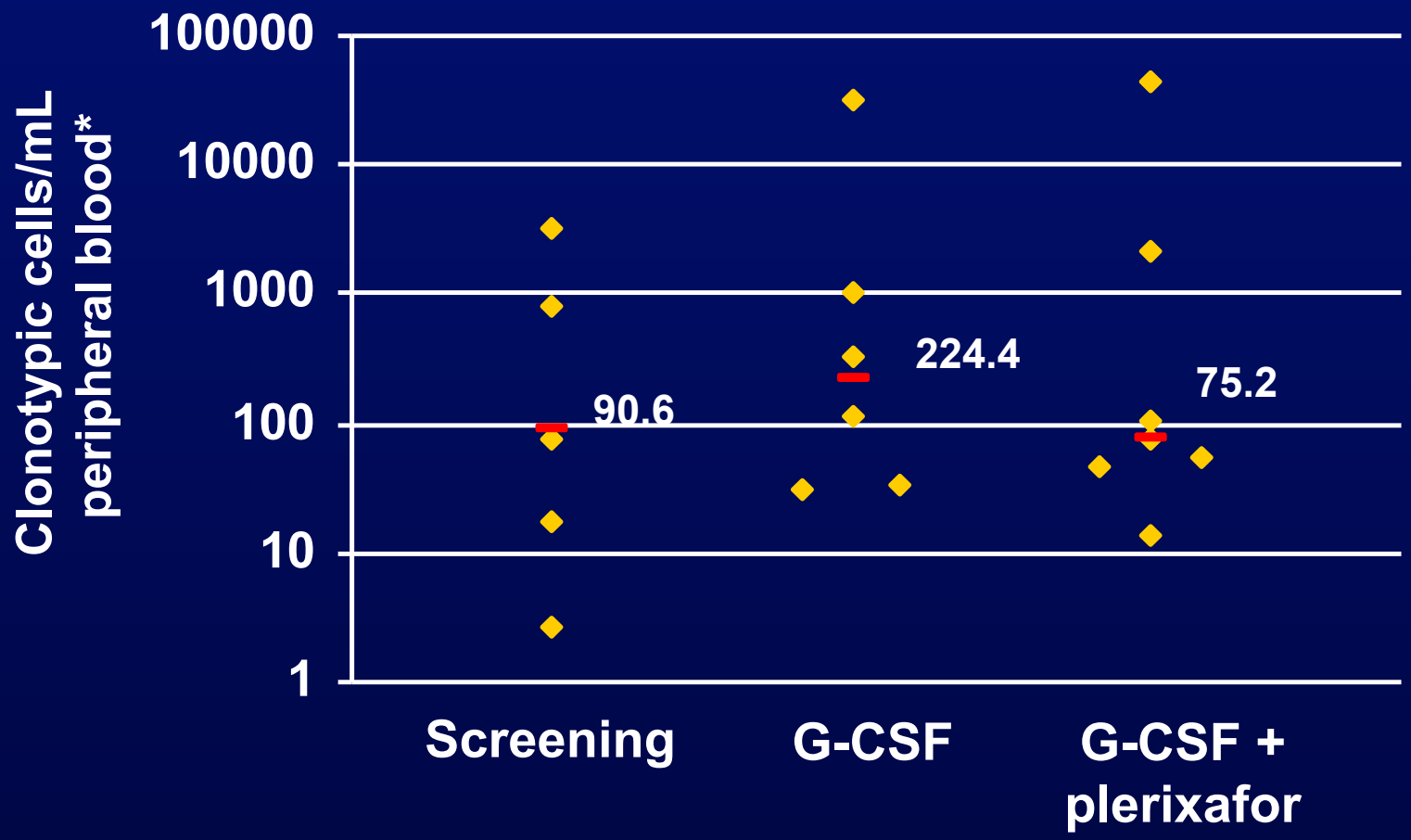
RM Lemoli, A Fortuna, MR Motta, S Rizzi, V Giudice, A Nannetti, G Martinelli, M Cavo, M Amabile, S Mangianti, M Fogli, R Conte and S Tura

blood 2000 95: 2234-2239

Engraftment, clinical, and molecular follow-up of patients with multiple myeloma who were reinfused with highly purified CD34+ cells to support single or tandem high-dose chemotherapy

Roberto M. Lemoli, Giovanni Martinelli, Elena Zamagni, Maria Rosa Motta, Simonetta Rizzi, Carolina Terragna, Roberto Rondelli, Sonia Ronconi, Antonio Curti, Francesca Bonifazi, Sante Tura and Michele Cavo

Are tumor cells mobilized after plerixafor administration?

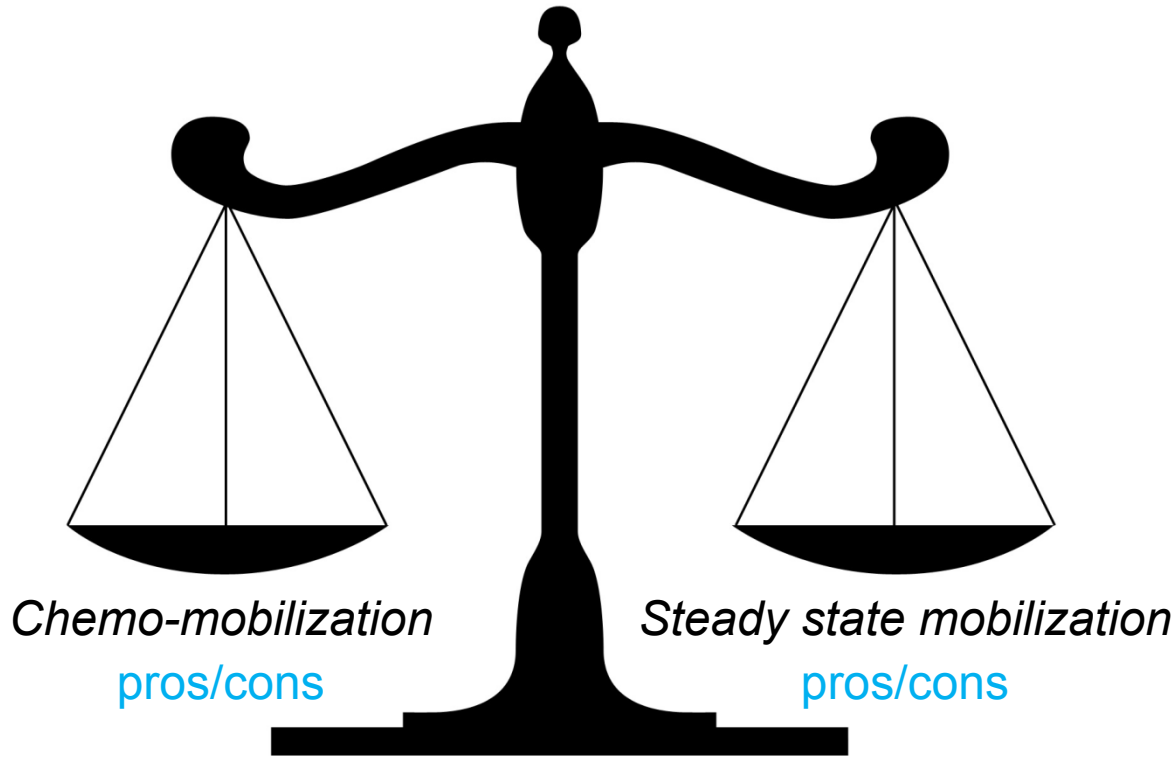


*** Detection by quantitative allele-specific oligonucleotide (ASO)-PCR**

Fruehauf et al. *Bone Marrow Transplant* 2010;45:269–75.

Chemotherapy vs. steady state mobilization for the collection of HSC in Multiple Myeloma

Weighing up the evidence



Chemo-mobilization

pros/cons

Steady state mobilization

pros/cons