Should we Mobilize with Mozobil™?

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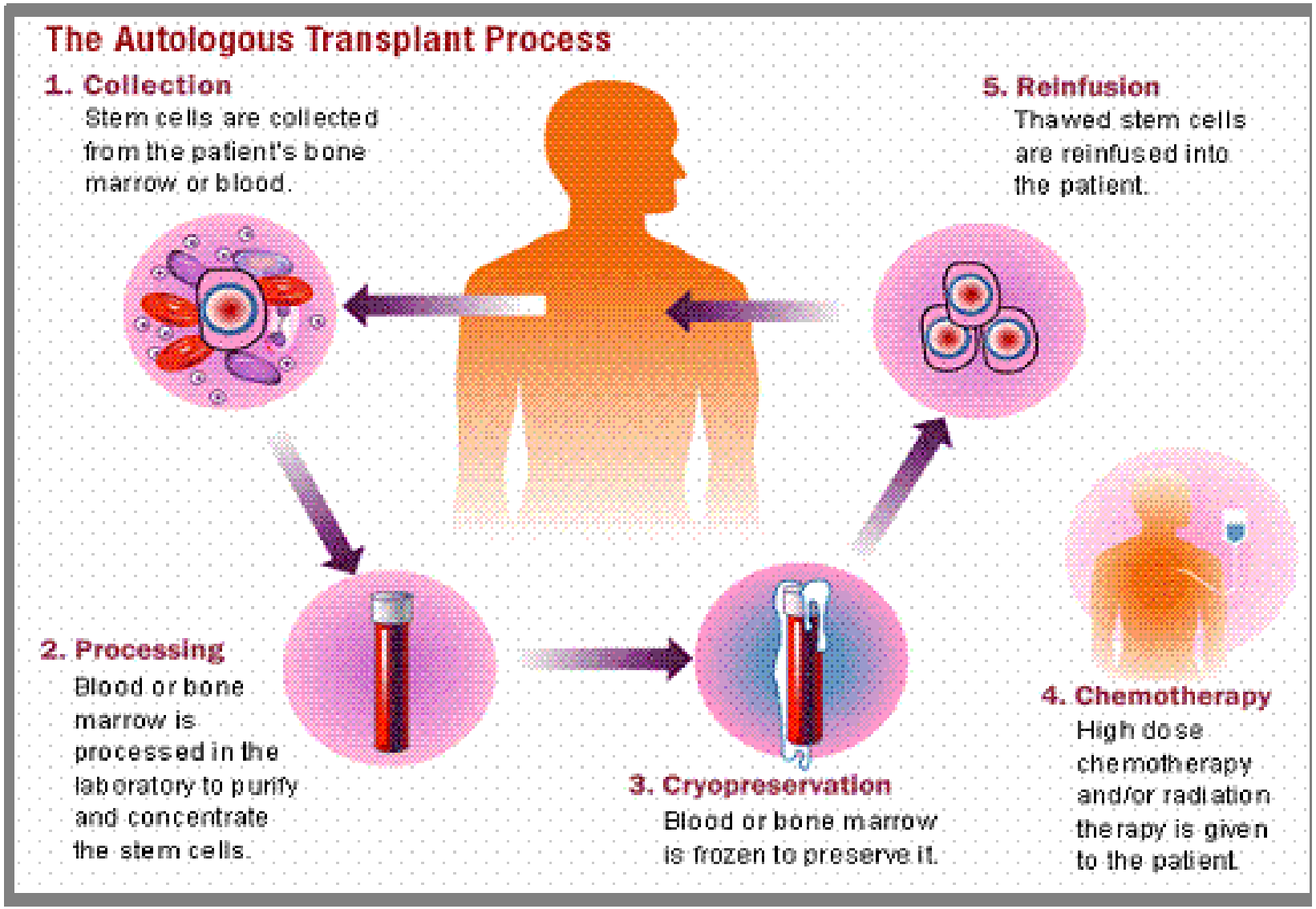
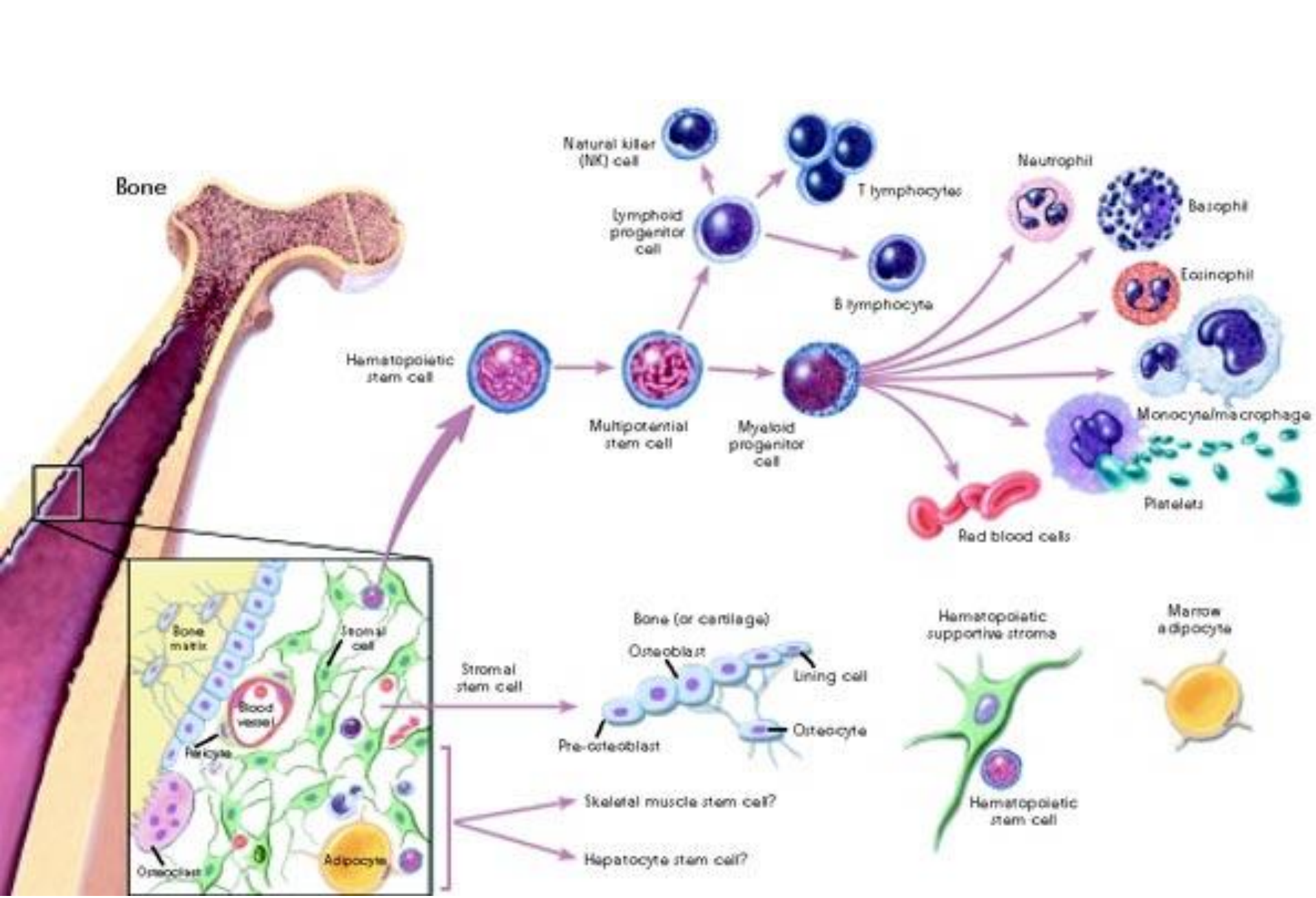
Doctor of Pharmacy Student
November 2012



http://b4tea.com/food-health/bone-marrow-transplant-procedure-wiki/

Autologous stem-cell transplantation

- Multiple myeloma
  - Following response to first-line induction therapy
- Non-Hodgkin's lymphoma
  - Relapsed or aggressive disease



http://stemcells.nih.gov/info/basics/basics4.asp

Standard of Care: G-CSF

- Granulocyte Colony Stimulating Factor
  - ↑ release of proteases
    - Proteases cleave proteins that anchor stem cells to the marrow stroma

- G-CSF 10 mcg/kg daily starting 4 days prior to apheresis continuing for ~7 days

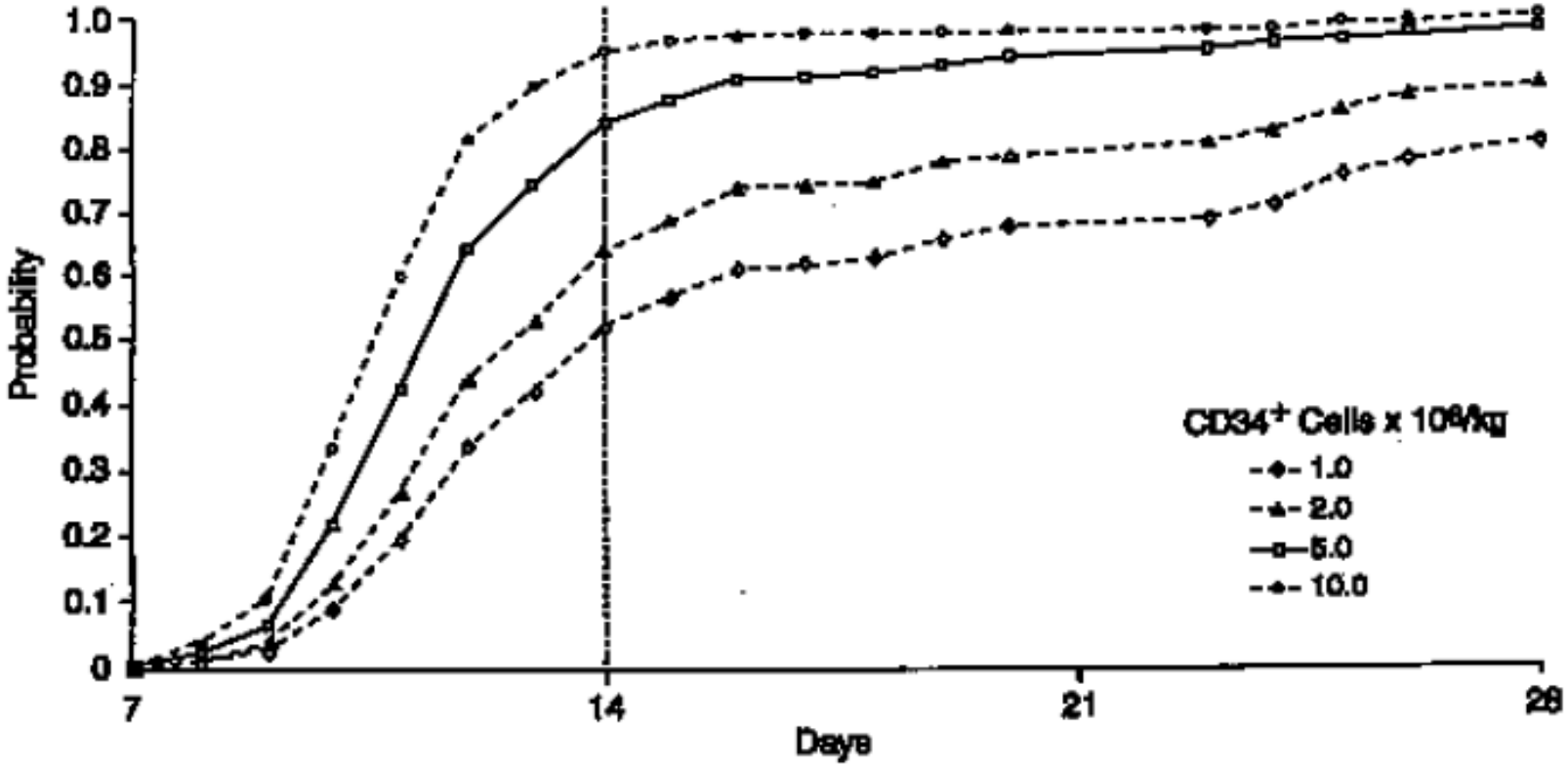
CD34

- CD34 cell surface molecule
  - Estimates number of stem cells
- Inadequate numbers associated with
  - delayed recovery of platelets and neutrophils
  - failure to engraft
- Minimum accepted CD34 is 2×10^6 CD34+ cells/kg
- Rapid recovery consistently attained with 5×10^6 CD34 cells/kg

Biology of Blood and Marrow Transplantation 1998; 4:84–92

Ann Pharmacother 2010;44:107-16

Probability of platelet recovery



Failure to mobilize adequate CD34+ cells

- **5–30% of patients fail to mobilize minimum amount**
  - Extent of previous treatment
    - Number of cycles
    - Chemotherapy agent received
    - Lenalidomide, fludarabine, melphan
  - Radiation treatment
  - Bone marrow involvement
  - Age >70 yrs

Plerixafor (Mozobil™)

- CXCR4 chemokine receptor antagonist
- CXCR4 receptor
  - Transmembrane G-protein-coupled receptor expressed on CD34+ cells
- CXCR4 receptor + stromal cell-derived factor-1a
  - retains CD34+ cells in the bone marrow
- Blocking this interaction leads to the mobilization of stem cells into the peripheral blood

Keating. Drugs 2011

Plerixafor

- Indication:
  - Combination with G-CSF
  - Mobilization of stem cells and subsequent autologous stem-cell transplantation
  - Patients with non-Hodgkin's Lymphoma or multiple myeloma
- NOC December 2011
- Cost per vial $7555

Keating Drugs 2011

Clinical Question

P	Multiple Myeloma Non Hodgkin's Lymphoma G-CSF
I	Plerixafor
C	Placebo
O	% of patients that undergo transplant Engraftment Mortality Safety

Search Strategy

Databases	PubMed, Cochrane, Clinical trials.gov, Google Scholar, IPA, Web of Science, EMBASE
Search Terms	Plerixafor, AMD3100, Multiple Myeloma, Non Hodgkin's Lymphoma
Limits	Human, English, RCT
Results	1 Randomized crossover trial n=25 2 Phase III RCTs

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

BLOOD, 4 JUNE 2009 • VOLUME 113, NUMBER 23

Dipersio JF et al, 2009

MC, R, DB, PCT, n=302	
P	Multiple Myeloma G-CSF 10 mcg/kg ≤ 8 days 1st mobilization >90% first remission 68% male Mean age 58 Mostly Caucasian
I	Plerixafor
C	Placebo
O	Primary: % ≥ 6 x 10^6 CD34 cells/kg in ≤ to **2 apheresis days** Secondary: % ≥ 6 x 10^6 CD34 cells/kg in ≤ 4 apheresis days **% ≥ 2 x 10^6 CD34 cells/kg in ≤ 4 apheresis days** # of apheresis days required to reach ≥ 6 x 10^6 CD34 cells/kg **Days to neutrophil and platelet engraftment** % maintaining durable graft at 100 days, 6 months, and 12 months

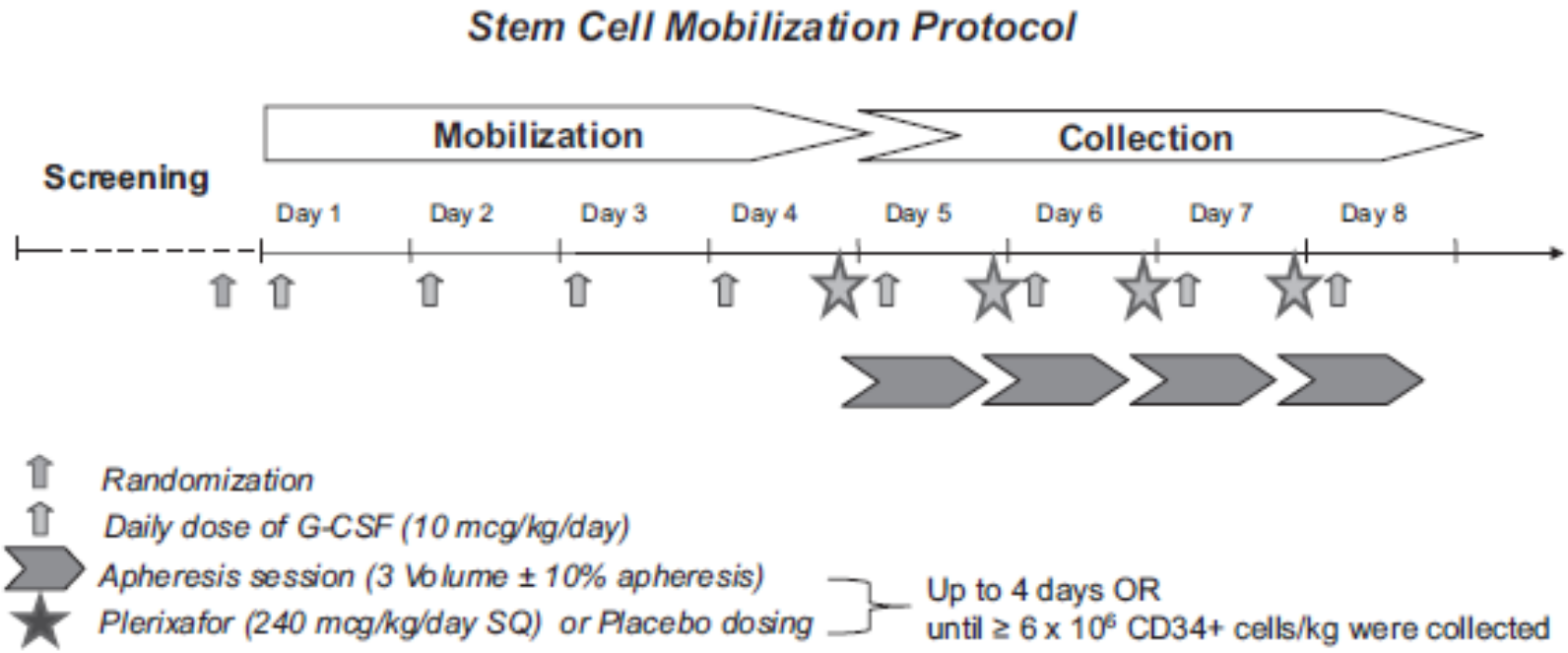
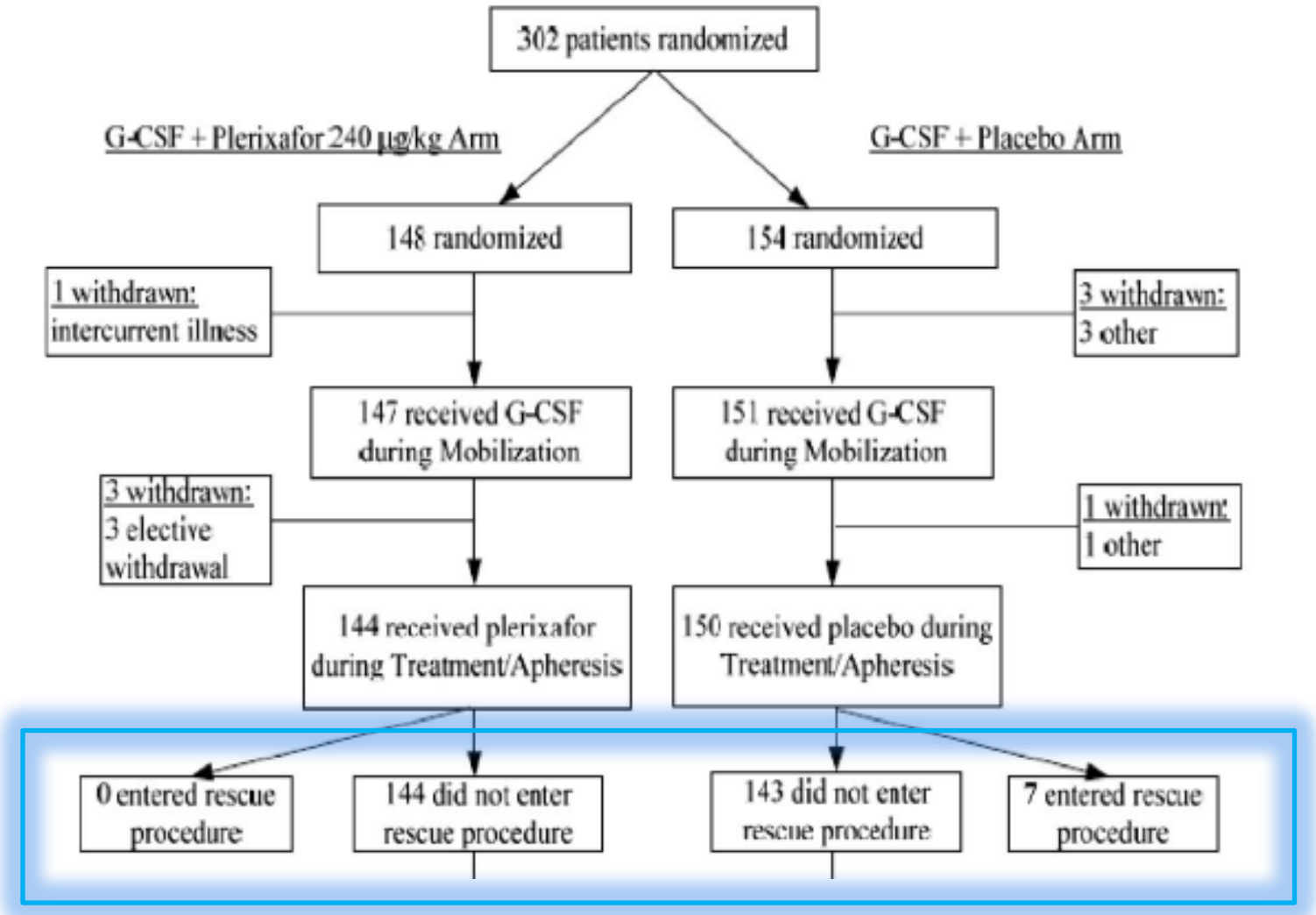


Figure 1. A detailed description of the study treatment.

Blood 2009;113:5720-5726

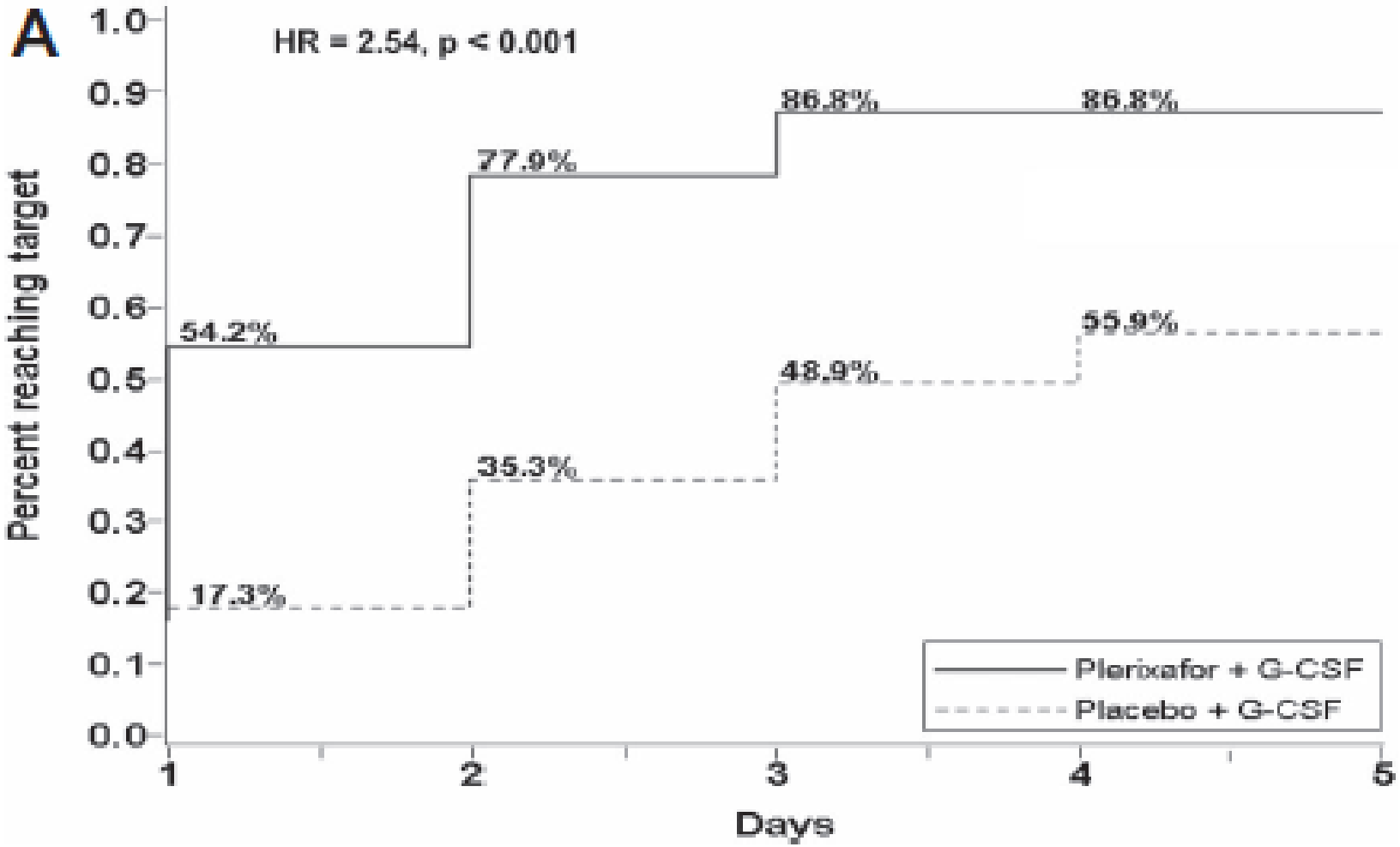


Blood 2009;113:5720-5726

Results

	% ≥ 6 x 10^6 CD34 ≤ 2 days	**% proceed to transplant**
Plerixafor n=148	71.6	95.3
Placebo n=154	34.4	88.3
	P < .001	*P = .031*

Time to reach 6 x 10^6 CD34



Kinetics of CD34/kg collection. (A) Kaplan-Meier estimate of proportion of patients reaching 6 x 106 or more CD34 cells/kg.

Results

	Plerixafor	Placebo
Engraftment (%)	99.3	100
Days to neutrophil (median)	11	11
Days to platelet (median)	18	18
12 month survival (%)	95.3	96.1

Considerations

- Intention to treat analysis
- Blinding measures were not reported
- Excluded patients thought to be at high risk of failure
- Excluded patients who failed prior mobilization

VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

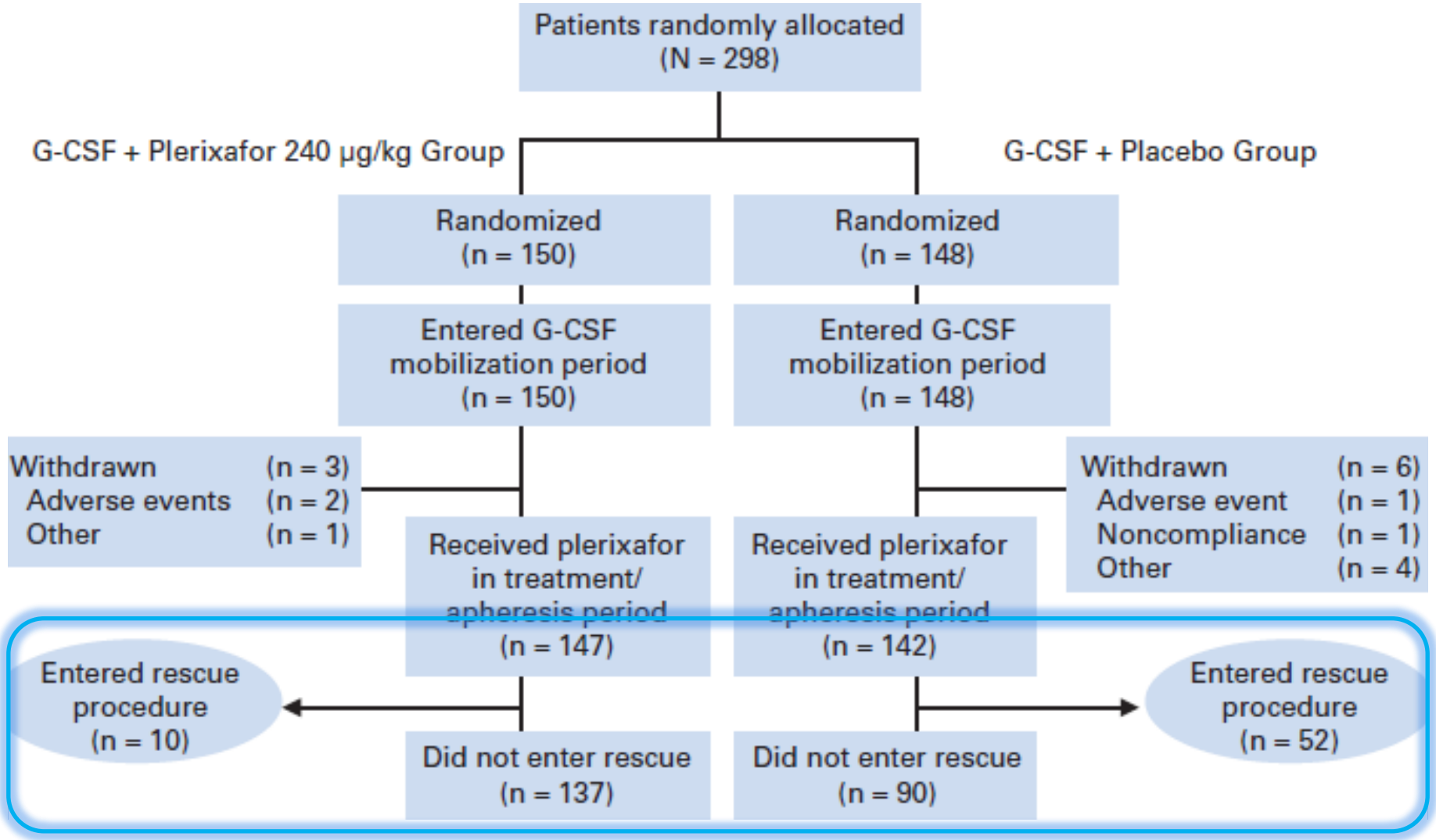
ORIGINAL REPORT

Phase III Prospective Randomized Double-Blind Placebo-Controlled Trial of Plerixafor Plus Granulocyte Colony-Stimulating Factor Compared With Placebo Plus Granulocyte Colony-Stimulating Factor for Autologous Stem-Cell Mobilization and Transplantation for Patients With Non-Hodgkin's Lymphoma

John F. DiPersio, Ivana N. Micallef, Patrick J. Stiff, Brian J. Bolwell, Richard T. Maziarz, Eric Jacobsen, Auayporn Nademanee, John McCarty, Gary Bridger, and Gary Calandra

Dipersio JF et al, 2009

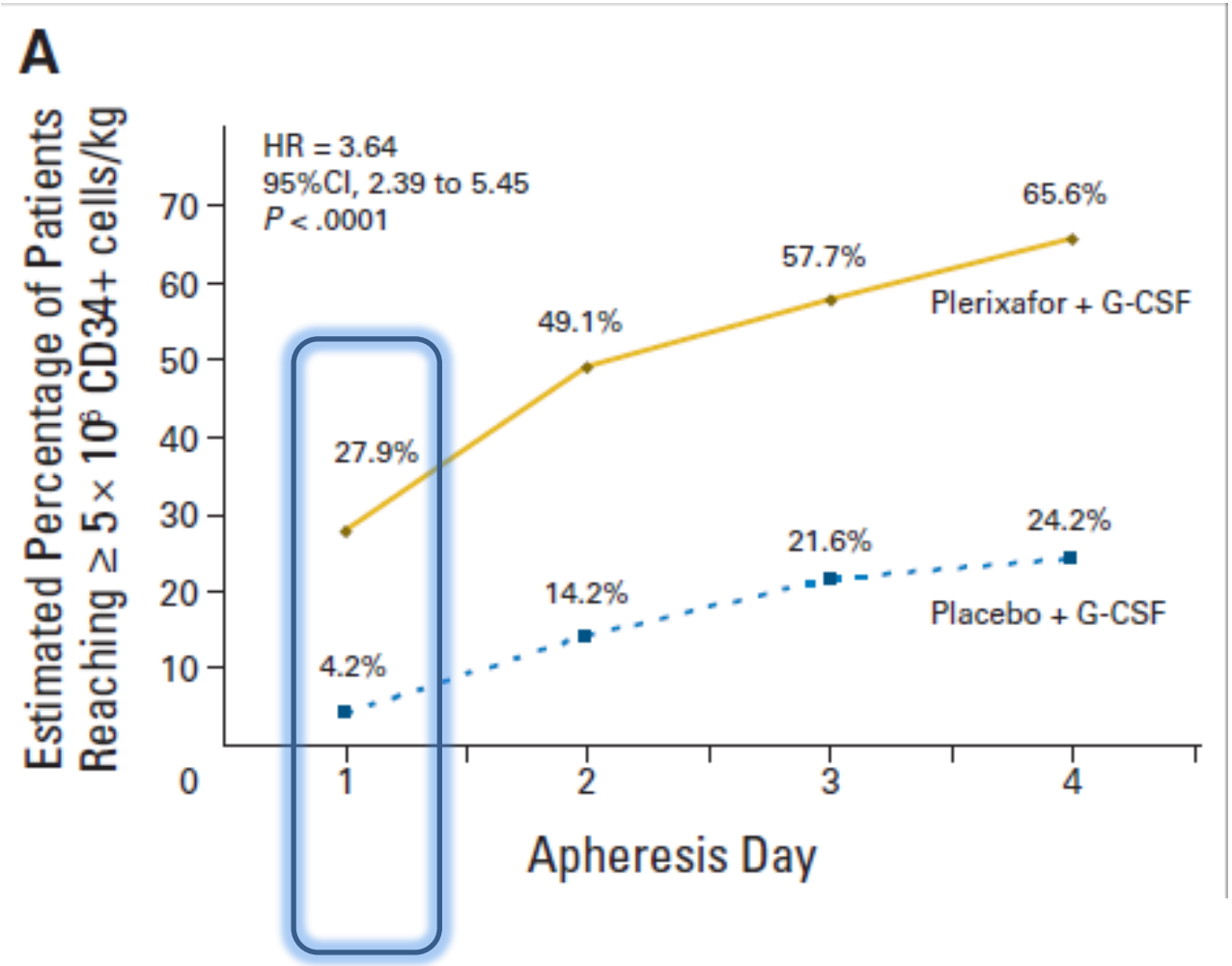
MC, R, DB, PCT, n=298	
P	Non-Hodgkin's Lymphoma G-CSF 10 mcg/kg ≤ 8 days 1st mobilization 50% second remission 68% male Mean age 58 Mostly Caucasian
I	Plerixafor 240 mcg/kg (starting on day 4 up to 8 days)
C	Placebo
O	Primary: % who collected ≥ **5 x 10^6 CD34 cells/kg in ≤ 4 apheresis days** Secondary: **% ≥ 2 x 10^6 CD34 cells/kg in ≤ 4 apheresis days** # of apheresis days required to reach ≥ 5 x 10^6 CD34cells/kg # of days to neutrophil and platelet engraftment % maintaining durable graft at 100 days, 6 months, and 12 months


Patients randomly allocated
(N = 298)
G-CSF + Plerixafor 240 µg/kg Group
G-CSF + Placebo Group
Randomized
(n = 150)
Randomized
(n = 148)
Entered G-CSF
mobilization period
(n = 150)
Entered G-CSF
mobilization period
(n = 148)
Withdrawn (n = 3)
Adverse events (n = 2)
Other (n = 1)
Withdrawn (n = 6)
Adverse event (n = 1)
Noncompliance (n = 1)
Other (n = 4)
Received plerixafor
in treatment/
apheresis period
(n = 147)
Received plerixafor
in treatment/
apheresis period
(n = 142)
Entered rescue
procedure
(n = 10)
Entered rescue
procedure
(n = 52)
Did not enter rescue
(n = 137)
Did not enter rescue
(n = 90)

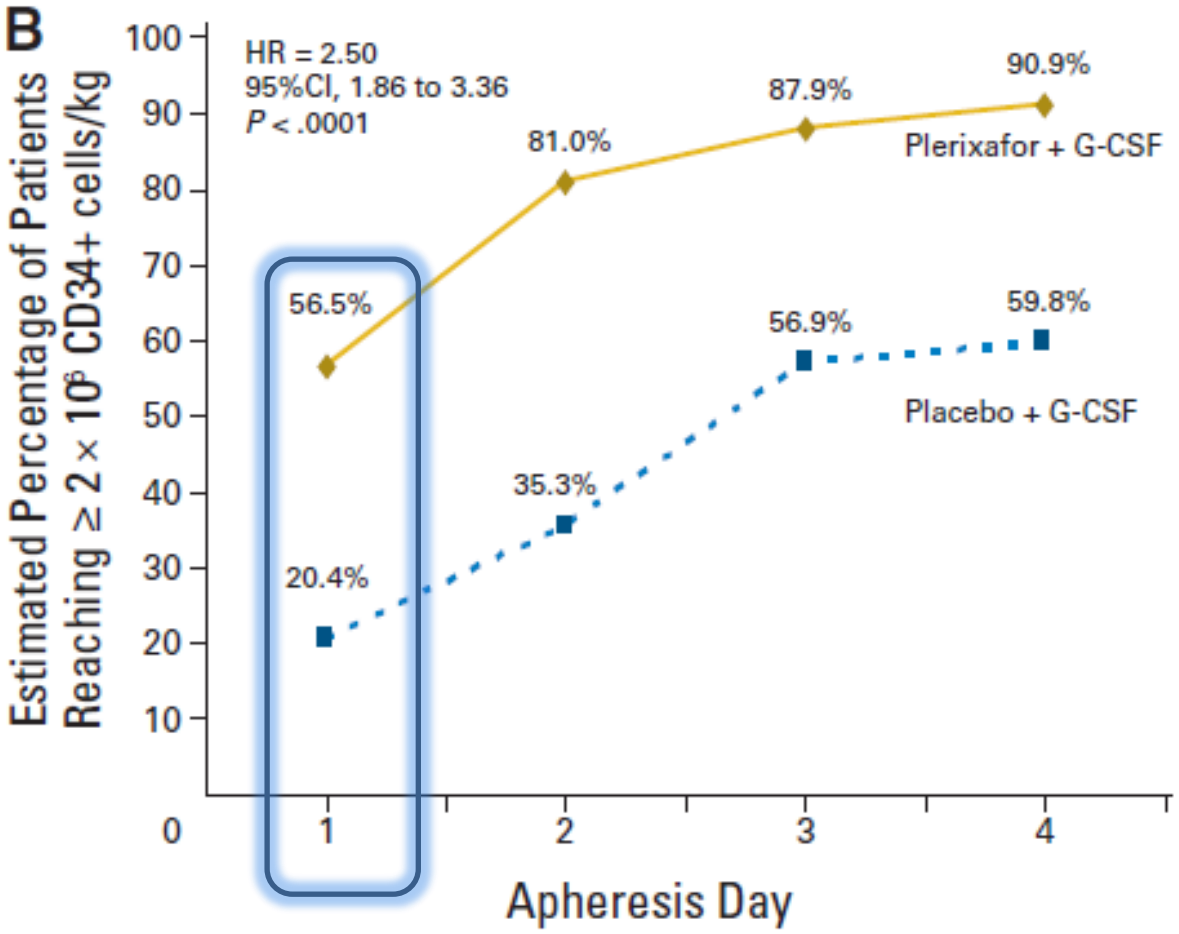
Results

	% ≥ 5 x 10^6 CD34 ≤ 4 days	% transplant	% Survival (12 month)
Plerixafor n=150	59.3	90.0	88.0
Placebo n=148	19.6	55.4	87.2
	P < .001	*P < .001*	

Time to reach 5 x 10^6 CD34



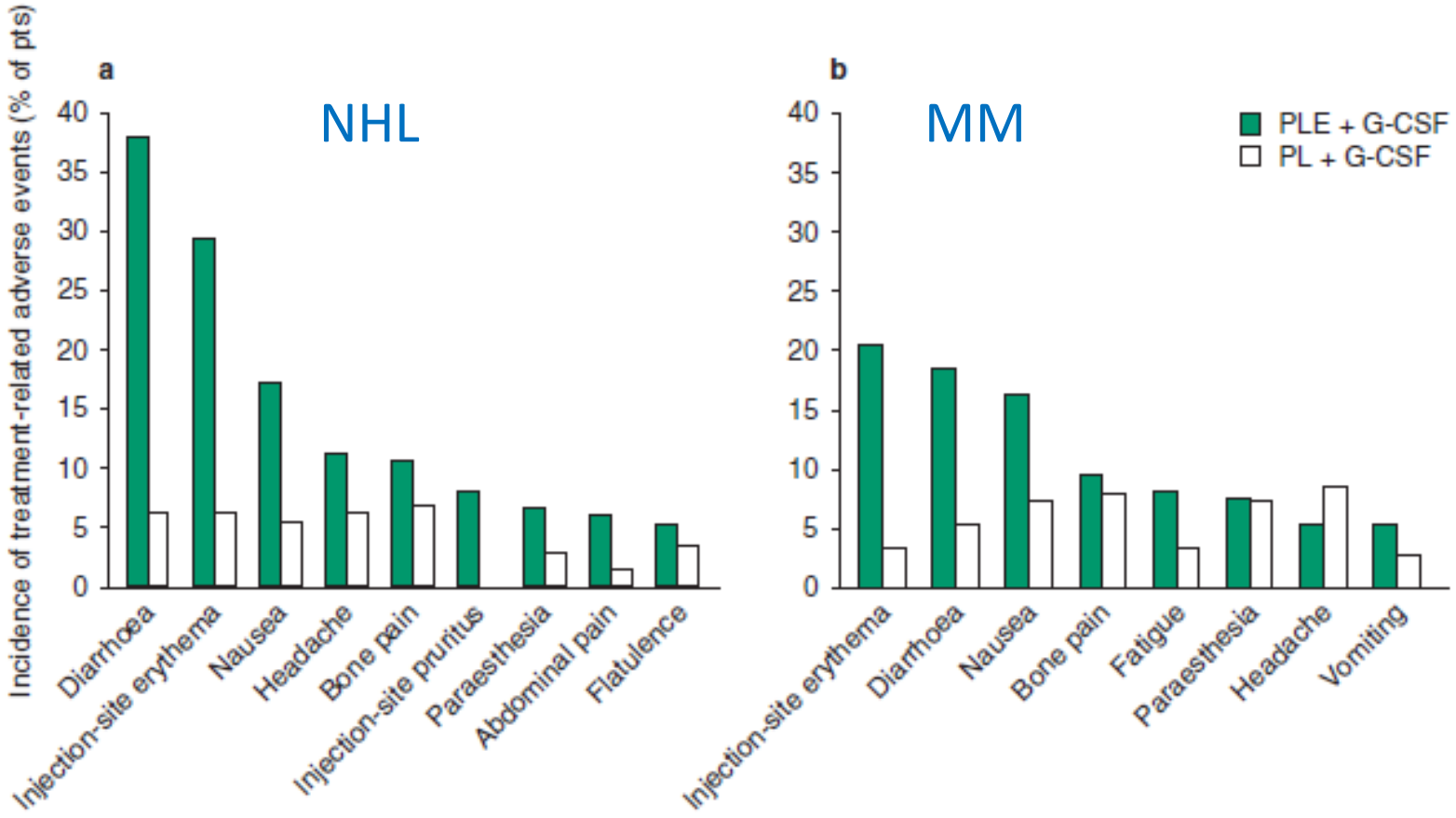
Time to reach 2 x 10^6 CD34



Results

- All patients had successful neutrophil engraftment
  - Median time = 10 days
- 98% had successful platelet engraftment
  - Median time = 20 days
- 2 graft failures in plerixafor group at 12 months

Safety



Drugs 2011; 71 (12)

Considerations

- Intention to treat analysis
- Patients who failed GCSF higher than typical
  - We would expect less because of the patients included
- Excluded patients who failed previous mobilization and those thought to be at high risk of failure
- Drug company sponsored and investigators funded by Genzyme
  - Both trials, main aim was to seek drug approval

Summary

- Reach targets faster in multiple myeloma
  - 88% of patients with multiple myeloma do not require additional medication
- Clinically appreciable effect in non-Hodgkin's
  - More patients to transplantation 90% vs 55%
- Seems to mobilize patients effectively
  - Graft maintained for 12 months
- Same authors
  - Difficult to make conclusions without repetitive findings

Summary

NHL

- % of patient of patients able to undergo transplant 
- Engraftment 
- Mortality 
- Quality of Life 
- Safety 

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Supplemental slides....

Is there a place Plerixafor could be utilized?

- 13 observational trials
  - 8 failed previous mobilization
  - 3 risk based approach/predicted to be poor responders
  - 1 second ASCT
  - 1 heavily pre treated

Summary of observational data

	n	# transplants	% transplant
Calandra C et al.	98	71	72%
Worel N et al.	25	12	48%
Selleslag D et al.	19	10	52%
Tekgündüz E et al.	20	16	80%
Hubel K et al.	7	6	85%
Fowler CJ et al.	16	13	81%
Micallef IN et al.	52	33	63%
total	237	161	68%

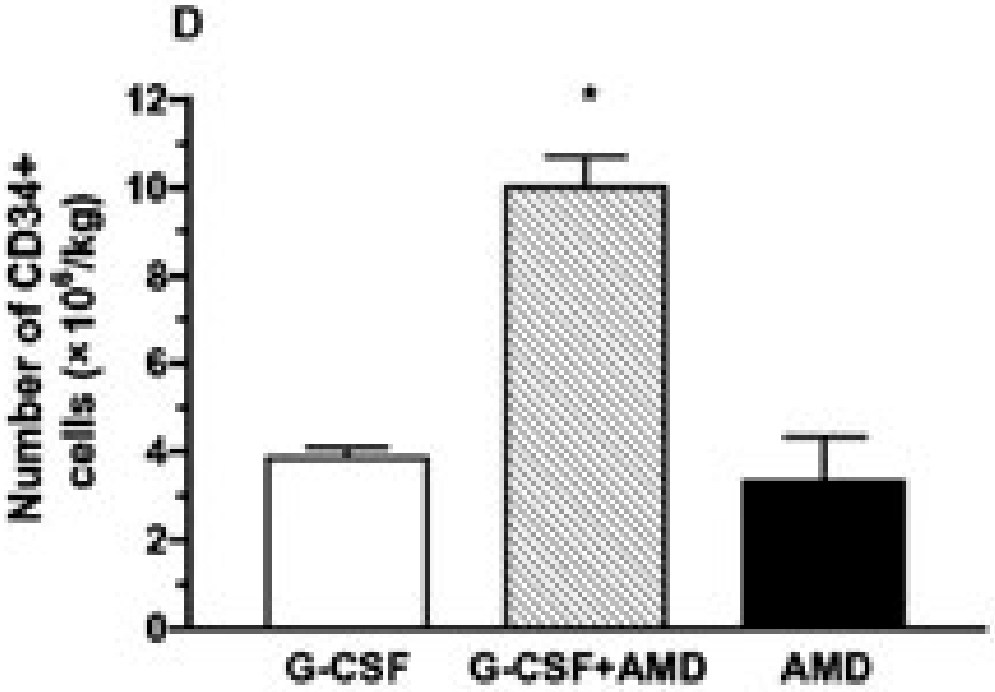
Was Plerixafor Studied on it's own?

TRANSPLANTATION AND CELLULAR ENGINEERING

Augmented mobilization and collection of CD34+ hematopoietic cells from normal human volunteers stimulated with granulocyte–colony-stimulating factor by single-dose administration of AMD3100, a CXCR4 antagonist

W. Conrad Liles, Elin Rodger, Hal E. Broxmeyer, Christine Dehner, Karin Badel, Gary Calandra, Jeff Christensen, Brent Wood, Thomas H. Price, and David C. Dale

Phase I, Open label, Healthy Volunteers



TRANSFUSION 2005;45:295-300

American Society for Blood and Marrow Transplantation

Plerixafor (Mozobil®) Alone to Mobilize Hematopoietic Stem Cells from Multiple Myeloma Patients for Autologous Transplantation

Neal Flomenberg,[1] Raymond L. Comenzo,[2] Karin Badel,[3] Gary Calandra[3]

Biol Blood Marrow Transplant 16: 695-700 (2010)

"All patients mobilized enough cells for at least 1 transplant, and demonstrated prompt recovery of hematopoietic function"

"Despite these successes, mobilization with plerixafor alone was modest."

Miscellaneous

- Autologous transplantation
  - Cost generally exceeds $80,000
- Plerixafor dose
  - 0.24 mg/kg body weight
- Cost of apheresis procedure $1917.13 per day
- One less day of apheresis saves $US 6600 per patient

Ann Pharmacother 2010;44:107-16

Table 2. Outcomes of Hematopoietic Stem-Cell Transplantation in Selected Diseases.*

Disease	Most Common Preparative Regimen	100-Day Mortality Rate	5-Yr Event-free Survival
		percent	
Autologous transplantation			
Diffuse large-cell non-Hodgkin's lymphoma	Carmustine, cyclophosphamide, and etoposide		
First chemotherapy-sensitive relapse		3–5	45–50
Second chemotherapy-sensitive relapse		5–8	30–35
Refractory		10–20	5–10

- **Multiple myeloma:**
  - Used at initial diagnosis
  - Does not cure, it does improve survival
  - Two autologous transplantations in succession may further improve survival among patients with myeloma
- **Non-Hodgkin's lymphoma:**
  - Autologous transplantation is substantially better than chemotherapy for treating the **first relapse** of large-cell that is sensitive to chemotherapy

N Engl J Med 2006;354:1813-26

Baseline demographics of RCTs

	NHL	MM
1st complete remission	30%	10%
1st partial remission	<20%	>80%
2nd complete	20%	0
2nd partial	30%	6%