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# **Hematopoetic Stem Cell Mobilization**: Clinical & Competitive Assessment

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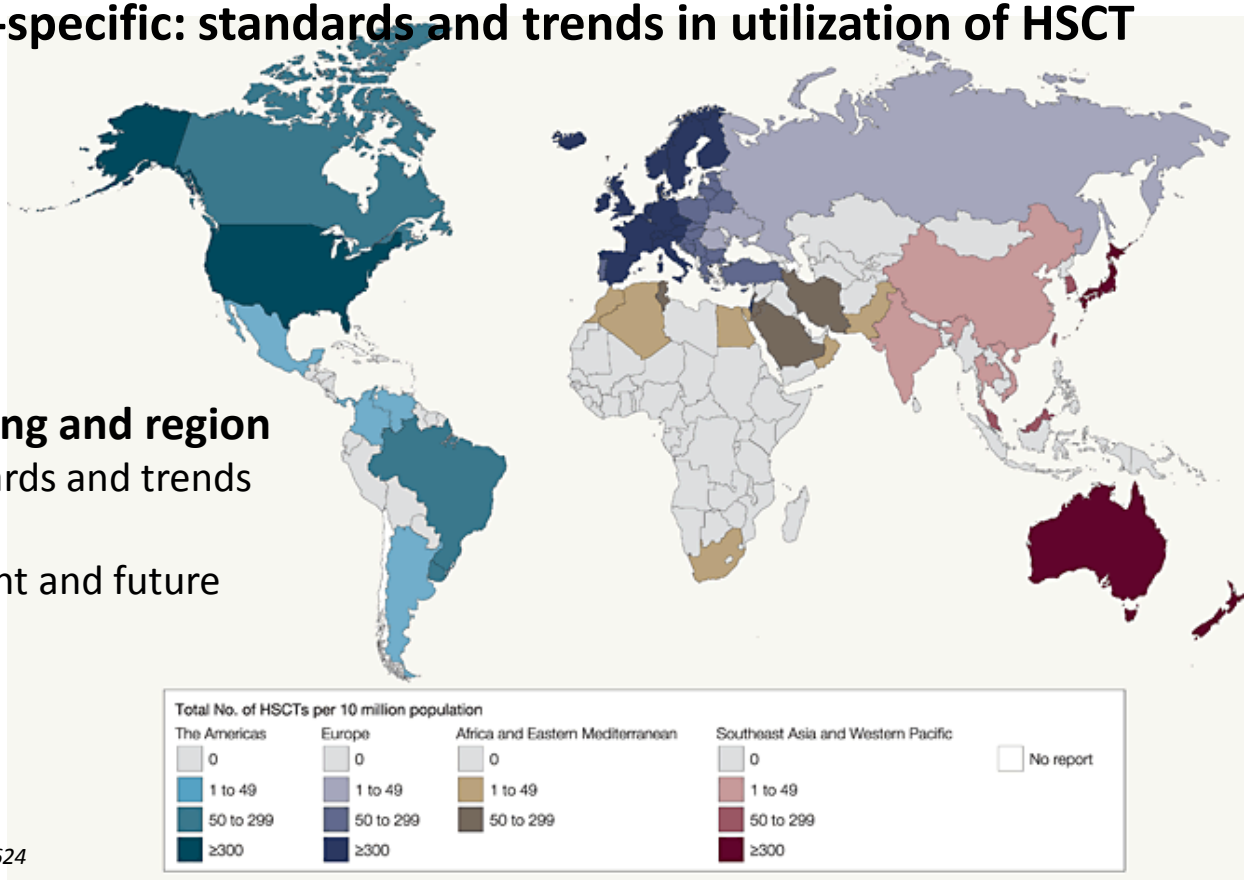
# CLINICAL ANALYSIS

## Region-specific: standards and trends in utilization of HSCT




**HSCT by disease setting and region**

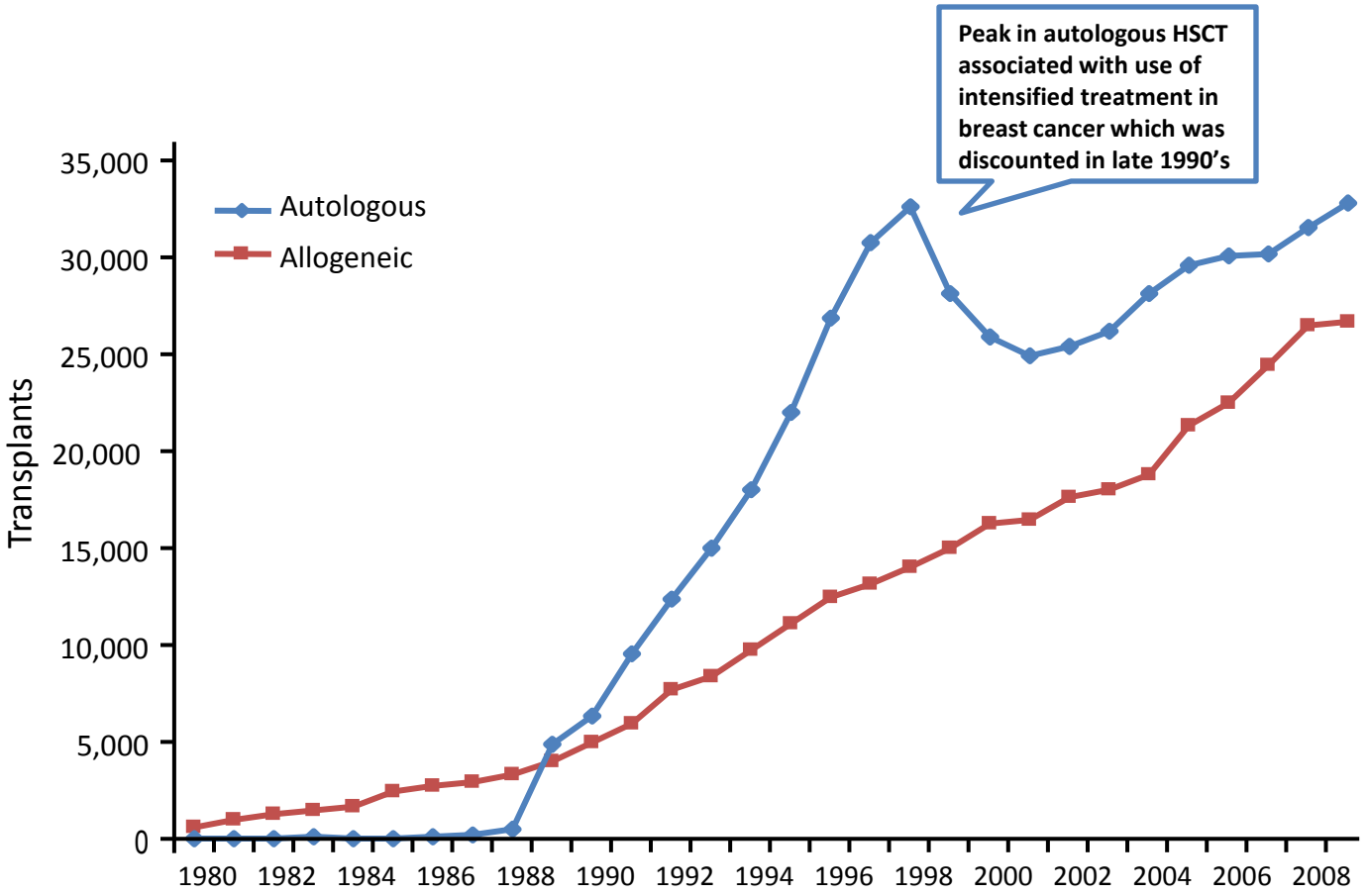
- Region-specific: standards and trends in utilization of HSCT
- Disease-specific: current and future role for HSCT

*Gratwohl, A. et al. JAMA 2010;303:1617-1624*

SUMMARY

# Region-specific: standards and trends in utilization of HSCT

- Increasing use of HSCT due to improved understanding of the science and biology:
  - expanded application to pt groups previously excluded because of age or disease indication
  - use of alternative sources of stem cells than bone marrow
  - use of alternative donors (unrelated, haploidentical)



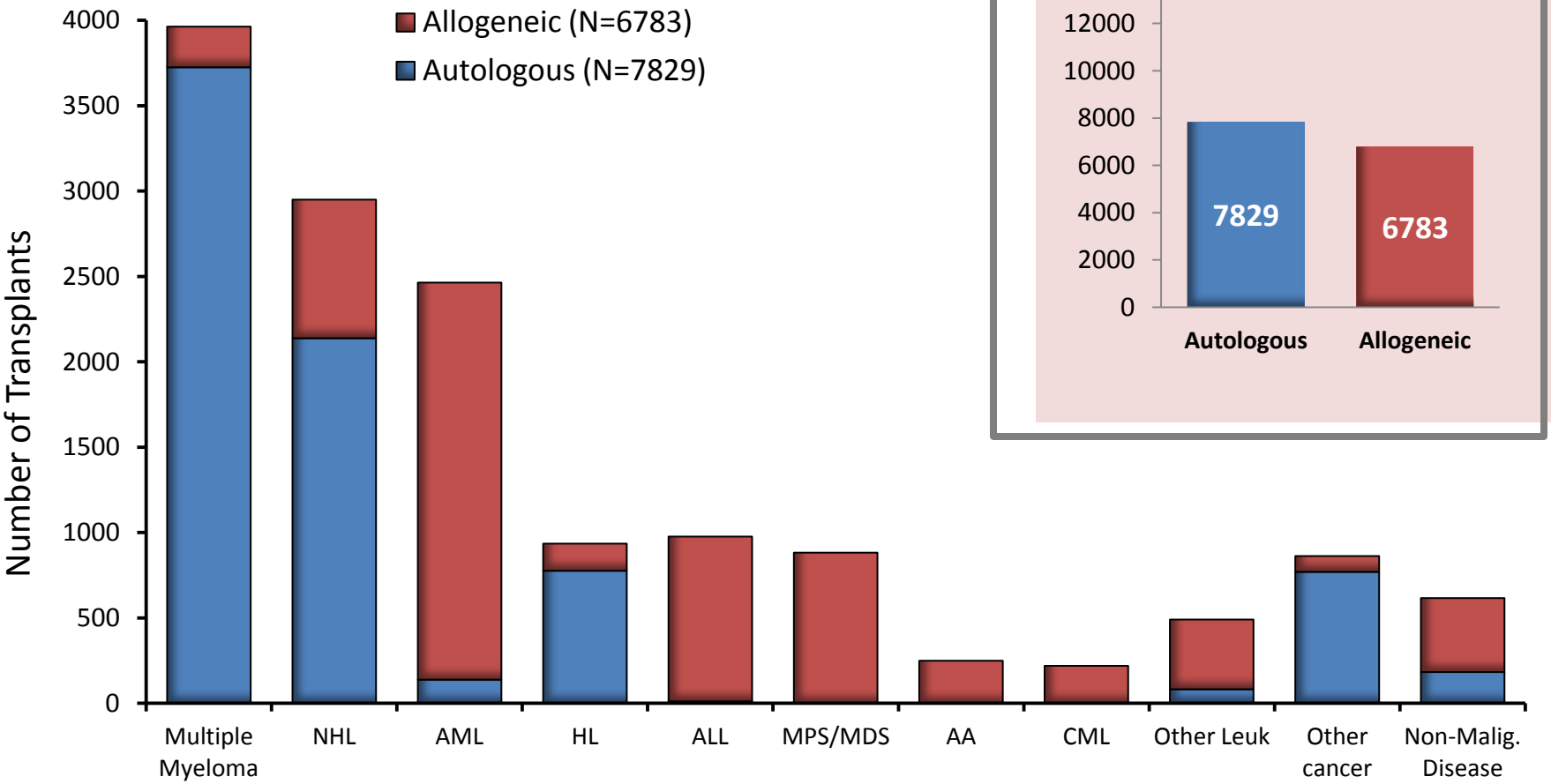
SUMMARY

# Region-specific: standards and trends in utilization of HSCT

- **Economic**: Increasing use of HSCT in previously underdeveloped markets parallels economic growth
- **Social**: Ethnic homogeneity in certain countries influences donor selection and long term morbidity outcomes post transplant
- **Medical**: Geographic differences in disease demographics impact HSCT indications; i.e., relatively higher rates of leukemia in Asia result in majorities of HSCT to be allogeneic

| | US | JPN/Korea | Europe | Total |
|---|---|---|---|---|
| **Allogeneic** | **6,783** | **3,626** | **11,442** | **21,851** |
| Leukemia | 3,918 | 2,468 | 6,423 | 12,809 |
| Lymphoma | 973 | 381 | 1,332 | 2,686 |
| Myeloma | 238 | 59 | 569 | 866 |
| Other | 1,654 | 718 | 3,118 | 5,490 |
| **Autologous** | **7,829** | **2,126** | **1,6591** | **26,546** |
| Leukemia | 233 | 292 | 712 | 1,237 |
| Lymphoma | 973 | 913 | 7,146 | 9,032 |
| Myeloma | 3,725 | 722 | 7,149 | 11,596 |
| Other | 2,898 | 199 | 1,584 | 4,681 |
| **Total** | **14,612** | **5,752** | **28,033** | **48,397** |

# U.S. Transplants by Indication (2009)







*http://bloodcell.transplant.hrsa.gov, U.S. transplant data by disease report*

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# CLINICAL ANALYSIS

## Disease-specific: current and future role for HSCT

| | Multiple Myeloma | NHL: DLBCL | Hodgkin Disease | AML/ALL |
|---|---|---|---|---|
| **Type** | Auto | Auto | Auto | Allo |
| **Timing** | Newly diagnosed | Relapsed/ refractory | Relapsed/ refractory | 1st CR for high risk subset; relapsed pts |
| **CD34+ goal** | Minimal: 4M, optimal 8-10 M | Minimal: 2M, optimal 5M | | |
| **Unmet need** | Limited: <10% mobilization failure with addition of plerixafor | Mobilization in pts with prior exposure to chemotherapy results in 20-30% failure rate; plerixafor "rescues" majority of these failures Note: plerixafor not approved in HL | | Safety, convenience: |
| **Uncertainties** | Combination of active agents may eliminate need for intensification in 1L, potentially increasing ASCT in relapsed setting | Potential role for HDT/auto-SCT in 1L in high risk pts (~15% of pts) | Potential role for HDT/auto-SCT in 1L | Potential to increase HDT/SCT-eligibility with RIC or autologous SCT |

# MULTIPLE MYELOMA: overview

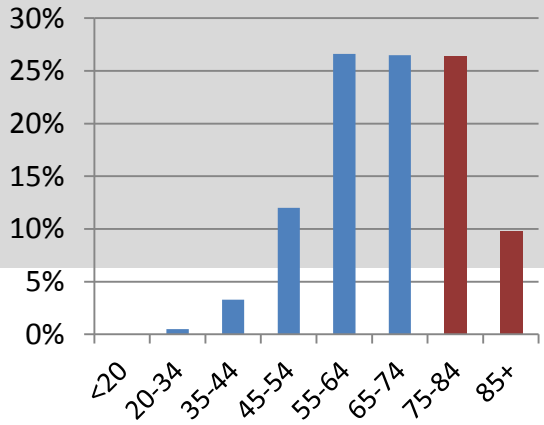
| Region | Incidence | Death | Allogeneic | Autologous | Recommended Timing |
|---|---|---|---|---|---|
| US | 20,580 | 10,580 | 222 | 3,723 | • Newly diagnosed, symptomatic<br>• At first progression |
| EU | 31,940 | 20,948 | 569 | 7,149 | |
| JPN/Korea | 5,804 | 4,234 | 59 | 722 | |

## EPIDEMIOLOGY

- Stage distribution and prognosis:

| ISS Stage | I | II | III |
|---|---|---|---|
| Distribution | 28% | 38% | 33% |
| Survival | 62 mo | 44 mo | 29 mo |

- Median age at diagnosis is 65 yrs old; 35% of pts >75 yrs old




## HSCT ELIGIBILITY

- Good performance status; no major co-morbidities
- Acceptable major organ function
- Age <70 yrs old
- Response to 1L therapy: CR1 or PR

- Good performance status
- Age < 65 yrs
- CR1

## Mobilization Guidelines

**IMWG recommendations**:

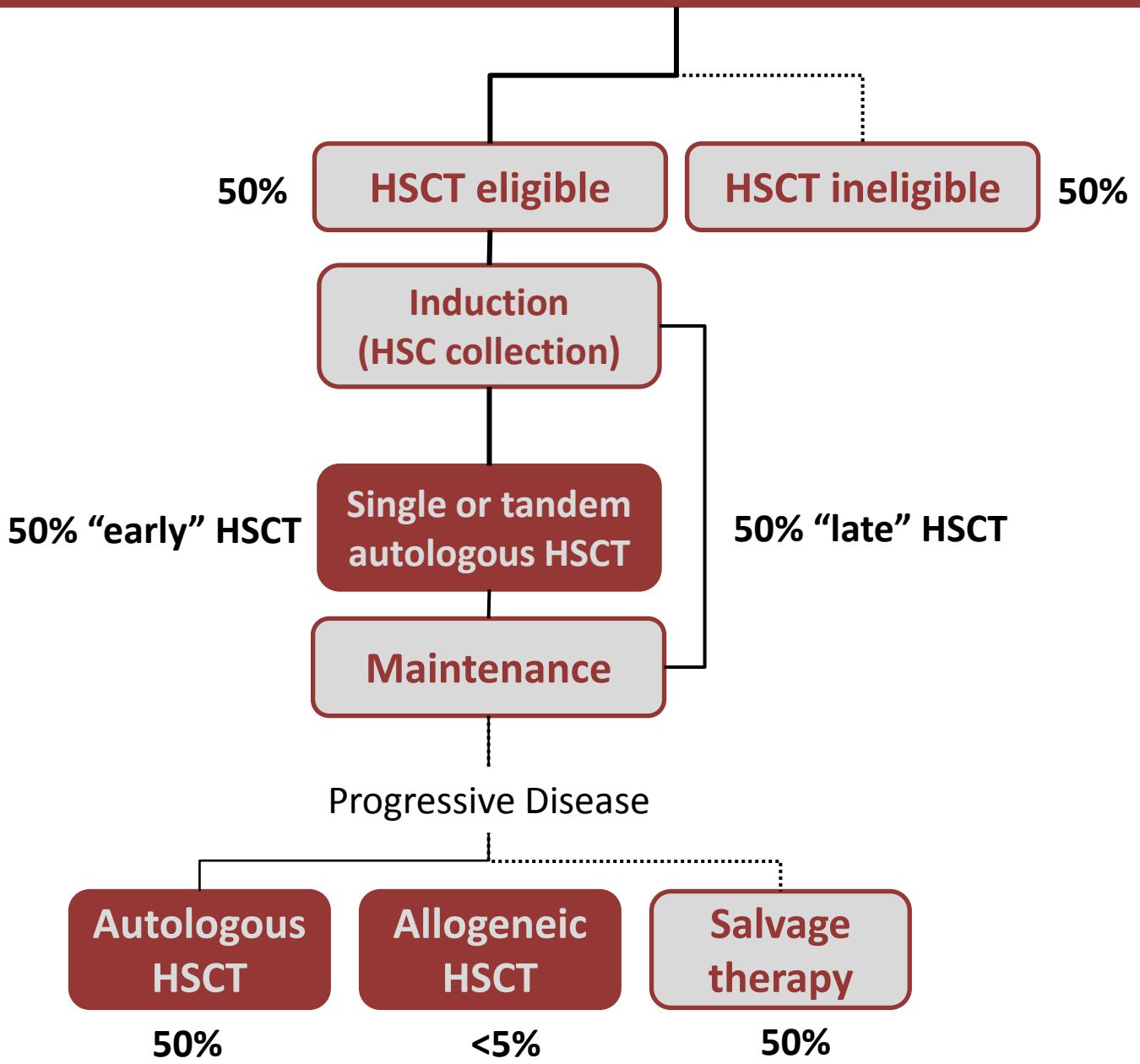
- Minimum target of 4M CD34+ cells/kg, ideally 8–10M
- ***G-CSF*** for pts <65 yrs old and <4 cycles of induction therapy
- ***G-CSF/chemotherapy*** for pts 4+ cycles of induction therapy with lenalidomide
- ***G-CSF/plerixafor*** for pts >65 yrs old with insufficient mobilization at first apheresis (<2M CD34+ cells)


*References*

http://seer.cancer.gov/statfacts/

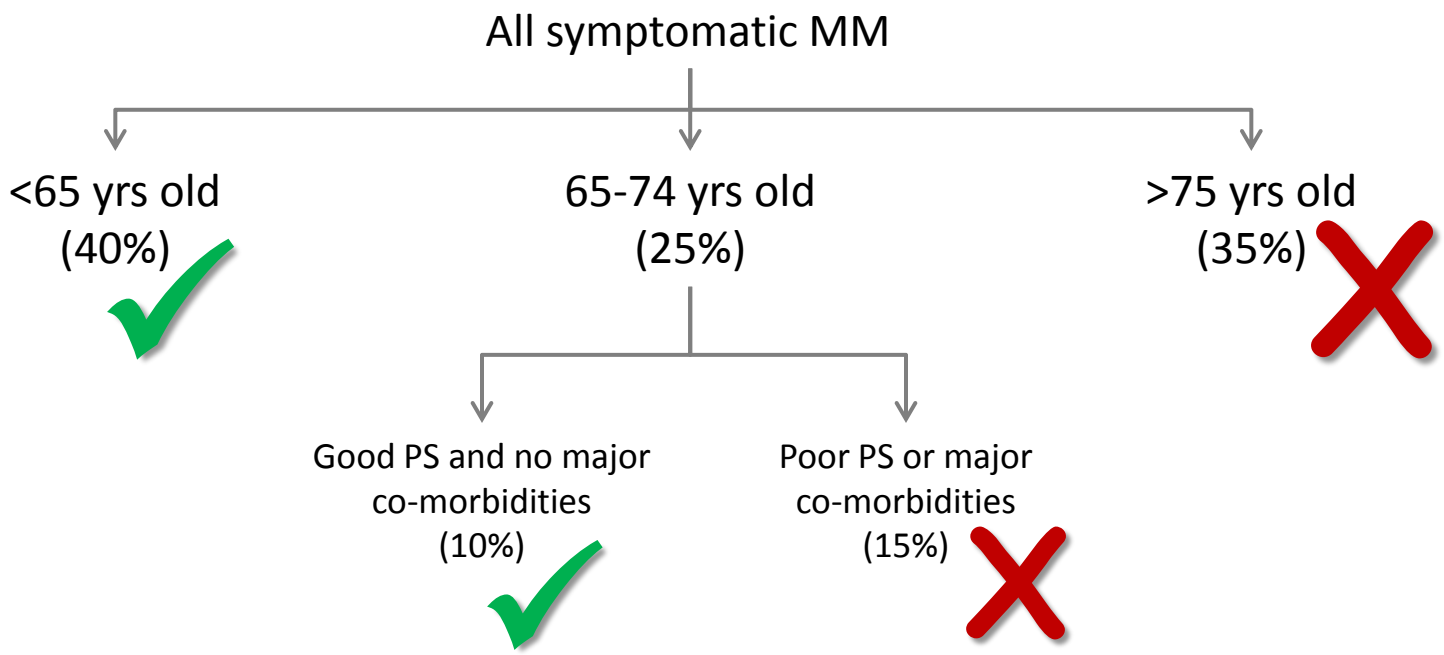
Kumar et al., Blood. 2009;114:1729

# MULTIPLE MYELOMA: patient flow



# MULTIPLE MYELOMA: HSCT

## Defining the eligible population for HSCT

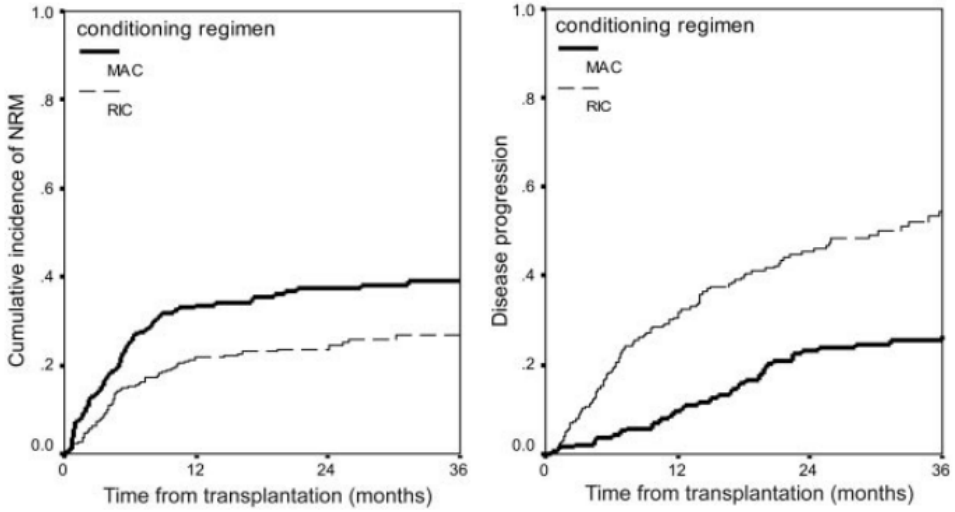


# MULTIPLE MYELOMA: HSCT

## Auto vs. allo HSCT:

- Autologous HSCT improves survival, but disease progression remains an issue
- Myeloablative Allo-SCT is potentially curative, but is associated with high treatment-related mortality; reduced intensity conditioning reduces TRM but increases relapse rate *(Crawley et al., Blood. 2007;109:3588)*
- Auto-SCT followed by maintenance is recommended over myeloablative alloHSCT ; Allo-RIC in myeloma only recommended in the context of clinical trials *(Lokhorst et al., JCO. 2010; 28:4521)*

| Allo-SCT | MAC | RIC | P-value |
|---|---|---|---|
| 2-yr TRM | 37% | 24% | 0.002 |
| 3-PFS | 34.5% | 18.9% | 0.001 |
| Median OS | 50.8 mo | 38.1 mo | NS |



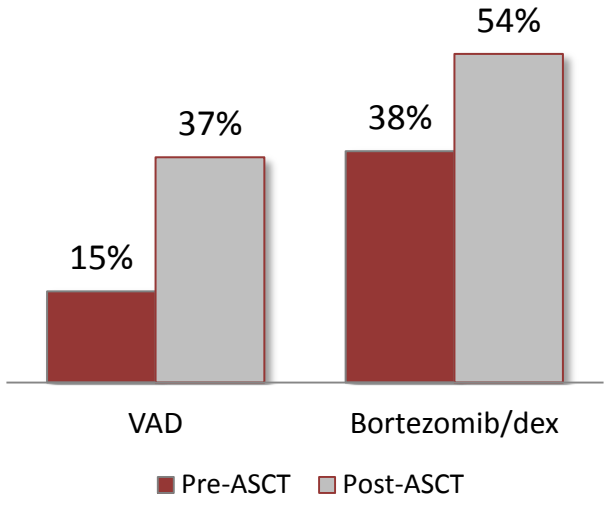

## Ongoing Trials

| Sponsor | Design | Patients | N | Endpoint | Status |
|---|---|---|---|---|---|
| Germany | Phase II randomized Auto/AlloHSCT vs Auto/AutoHSCT + maintenance Thalidomide | up to 55 yrs | 220 | 4 yr EFS | Aug 2008-2014 |

# MULTIPLE MYELOMA: HSCT

## HSCT vs. no HSCT

- Historical rationale for ASCT in treatment-naïve pts: increase depth of response to induction therapy as CR/VGPR post-ASCT associated with improved outcome
- Current induction therapy with bortezomib and/or lenalidomide result in significantly higher CR/VGPR rates:
  - → **do pts in CR or VGPR after induction further benefit from immediate ASCT?**
- Palumbo et al randomized pts to either additional CT or ASCT following induction therapy: ASCT resulted in improved PFS, impact on OS not yet available (*Palumbo et al, EHA 2011*)




| | CR | 18-mo PFS |
|---|---|---|
| **MPR** | 20% | 68% |
| **ASCT** | 25% | 78% |
| | P=0.49 | HR 0.58; p=0.006 |

## Ongoing Trials

| Sponsor | Design | Pts | N | Endpoint | Status |
|---|---|---|---|---|---|
| DFCI (multicenter) | Lenalidomide, bortezomib, dexamethasone (RVD) ± ASCT + maintenance lenalidomide | | 300 | PFS | Sept 2010 |
| France (multicenter) | Lenalidomide, bortezomib, dexamethasone (RVD) ± ASCT + maintenance lenalidomide | | 700 | PFS | Oct 2010 |

# COMPETITIVE ANALYSIS

TOC:

**Approved agents by MOA and disease setting**

- G-CSF approval history by region, clinical data
- Mozobil approval history by region, clinical data, ongoing trials

**Investigation agents by MOA**

- CXCR4/12 antagonist
- VLA4

SUMMARY

# Approved agents by MOA and disease setting

| Agent | | Filgrastim (Neupogen; Amgen) | Lenograstim (Granocyte; Chugai) | Ancestim (StemGen; Amgen) | Plerixafor (Mozobil; Sanofi) |
|---|---|---|---|---|---|
| Class | | granulocyte-colony stimulating factor (G-CSF) | granulocyte-colony stimulating factor (G-CSF) | Stem cell factor (SCF) | CXCR4 inhibitor |
| Regulatory status | FDA | Approved ✓ | Not Approved ✗ | Not approved by FDA/EMEA; available in Canada and Australia | Approved ✓ |
| | EMEA | Approved ✓ | Approved ✓ | | Approved **(poor mobilizers)** ✓ |
| Indication | Allo | Not approved (but widely used) | In Peripheral Blood Progenitor Cells (PBPCs) Mobilisation<br>• In pts after chemotherapy or with Granocyte alone<br>• **In healthy donors** | Not approved ✗ | Not approved ✗ |
| | Auto | PBPCs mobilisation in pts undergoing peripheral blood progenitor cell collection and therapy | | Indicated for use in combination **with NEUPOGEN®**(filgrastim) in the setting of autologous HSC transplantation for pts **at risk of poor mobilization** | In combination **with G-CSF** to mobilize HSCs to the peripheral blood for collection and subsequent autologous transplantation in pts with **NHL and MM** |

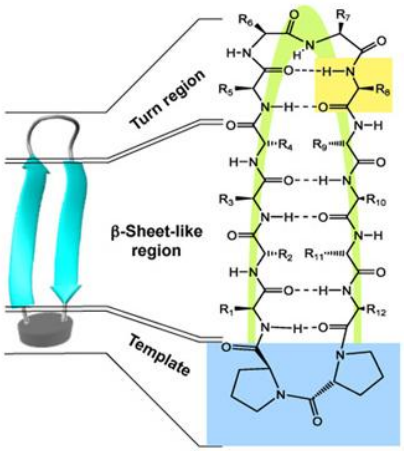
- G-CSF are standard in HSC mobilization, with or without chemotherapy
  - Filgrastim is not approved for use in healthy volunteers, but is widely used in the US
- Ancestim is only available in Canada and Australia; usage limited to poor mobilizers
- Plerixafor received a broad label from the FDA and a far more restricted label from the EMEA; treatment guidelines also suggest role in poor mobilizing pts only
  - Plerixafor is not approved for use in healthy volunteers or as part of chemo-mobilization

# CXCR4 inhibitors: POL6326

| | |
|---|---|
| **Product** | POL6326 |
| **Company** | Polyphor, Switzerland |
| **Drug Class/MOA** | CXCLR4 antagonist; β-hairpin Protein Epitope Mimetic (PEM) |
| **Lead Indication** | HSC mobilization |
| **Development status** | Phase II, Multiple Myeloma<br>Phase I/II, Sibling donors |

PEM Design

- Loop size and sequence
- Amino acid building blocks
- Template




## Clinical Summary

- Phase I study completed July 2008
  - Demonstrated drug safety and efficacy in healthy volunteers
- Phase II, single center in MM (NCT01105403)
  - N = 16; 75% mobilized >2M CD34+ with ≤2 aphereses
  - All pts transplanted with POL6326-mobilized HSCs demonstrated successful engraftment
  - Adverse Events: grade 1 pruritus at infusion site (n=1)
- A Phase I/II in HLA-Matched Sibling Donor (NCT01413568)
  - Endpoint: reduce the number of allogeneic donors who require 2nd leukopheresis to obtain ≥ 2MCD34+ cells from 33% (8 in 24) of the donors in our historic group who received 240mcg/kg SC AMD3100 (plerixafor) to 11% (3 in 27) of donors receiving IV POL6326
  - Estimated completion: February 2013

## PK/PD Summary

| | |
|---|---|
| **Administration** | IV, 120 min |
| **$T_{1/2}$** | N/A |
| **Dose** | Up to 1200 µg/kg |
| **Time to CD34+ peak** | 30 min |
| **Mean CD34+ cell counts at peak** | NA |


*References*

- ASH Annual Meeting, 2010, Abstract 824
- http://www.polyphor.com/