Autologous Stem Cell Transplantation: Current Perspectives in Myeloma and Lymphoma

April 7, 2016

Welcome and Introductions

Autologous Stem Cell Transplantation: Current Perspectives in Myeloma and Lymphoma

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Disclosures

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- Consulting/Grant Support
  - Celgene
- Speakers Bureau/Grant Support
  - Bristol-Myers Squibb

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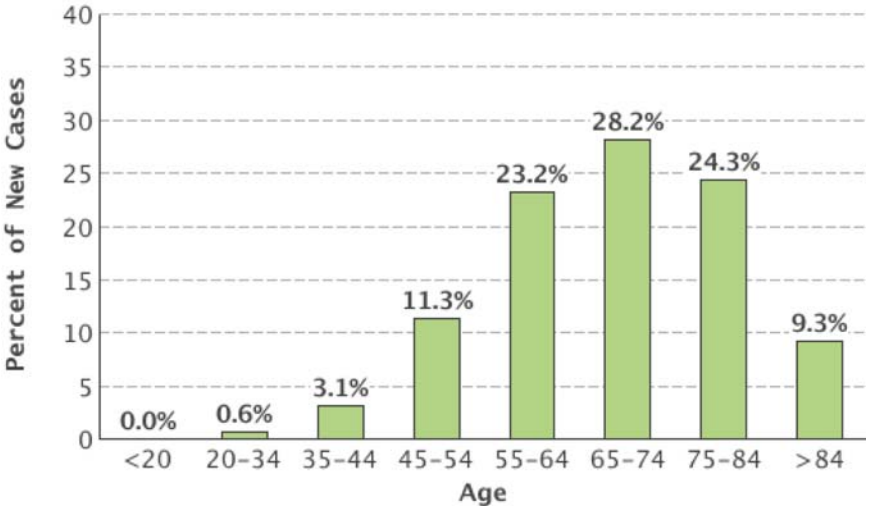
Incidence of Myeloma by Age



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Myeloma Symptoms: CRAB

C – elevated calcium

R – renal failure

A – anemia

B – bone disease

Active disease requires at least 30% plasma cells in the bone marrow

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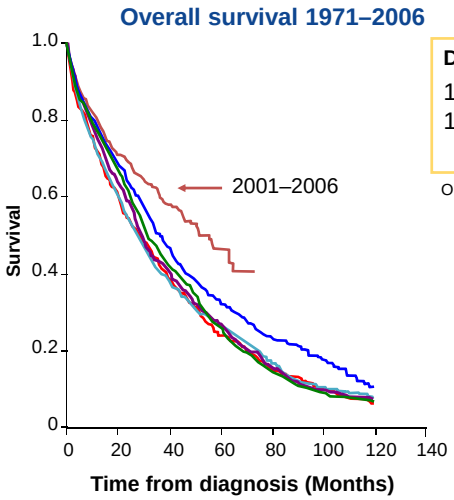
Trends in Overall Survival of MM



Diagnosis period	Median OS
1996–2006	45 months
1971–1996	30 months (*P*<0.001)

OS, overall survival.

1971–1976
1977–1982
1983–1988
1989–1994
1995–2000
2001–2006

Kumar SK, et al. *Blood*. 2008;111:2516-2520.

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Meta-Analysis of Autologous Transplant vs Conventional Chemotherapy – Overall Survival

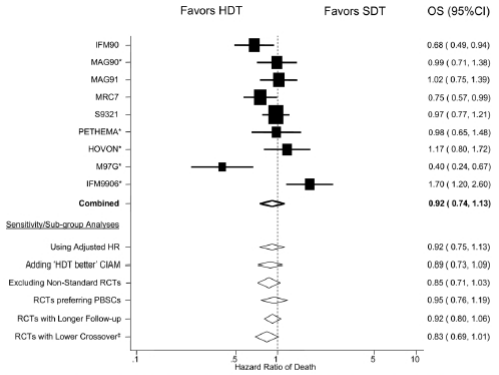

Figure 2. Forrest plot of overall survival (OS) benefit of upfront high-dose therapy and single autologous stem cell transplantation (HDT) in myeloma. The individual randomized controlled trials (RCTs) are indicated on the y axis. The summary effect estimate (hazard ratio [HR]) for individual RCTs are indicated by black rectangles (the size of the rectangle is proportional to the study weight), with the lines representing 95% confidence intervals (CIs). The overall summary effect estimate (HR) and 95% CI are indicated by the diamond below. Overall estimates after sensitivity and subgroup analyses are shown below. The corresponding values for HR (95% CI) are indicated alongside. *Nonstandard study. ‡ Two negative studies (HOVON, IFM9906) with missing crossover information were omitted from this analysis. PBSC indicates peripheral blood stem cell; SDT, nonmyeloablative standard-dose therapy.

High-dose Therapy with Single Autologous Transplantation versus Chemotherapy for Newly Diagnosed Multiple Myeloma: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Koreth, et.al. Biology of Blood and Marrow Transplantation 13:183-196 (2007)

Koreth, et.al. BBMT, 2007

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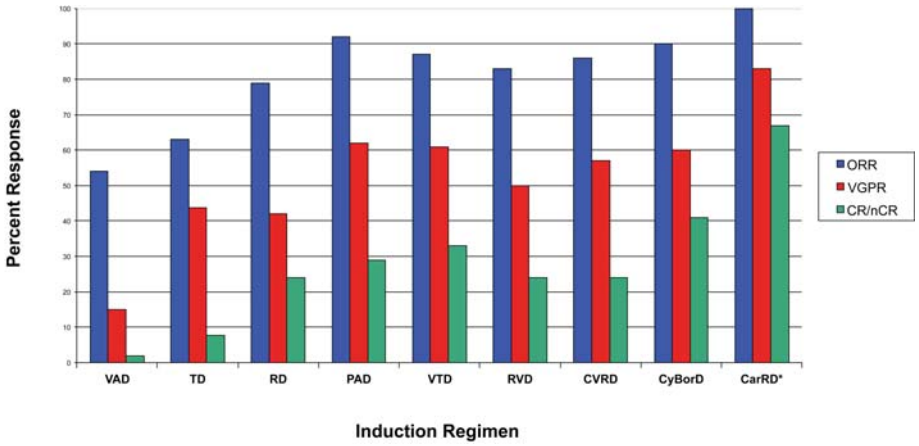
Improving Response Rates with Combination Therapies



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Is There a Role for Transplant in the Era of Novel Drugs?

RVD × 3
↓
Stem collection
↓
Transplant
↓
RVD×2
↓
Revlimid Maintenance

RVD × 3
↓
Stem collection
↓
RVD×5
↓
Revlimid Maintenance
⋮
Transplant at relapse

NCI Clinical Trial Identifier NCT01191060.

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RVD, Revlimid (lenalidomide), Velcade (bortezomib), dexamethasone

Transplant Delays Disease Recurrence

	RVd + ASCT (n = 350)	RVd, no ASCT (n = 350)
3-yr PFS, %	61	48
	Stratified log-rank *P* < .0002	
3-yr OS, %	88	88
	Stratified log-rank *P* = .25	
CR, %	58	46
	P < .01	
SPM, n (%)	23 (6.6)	18 (5.1)

CR, complete response; OS, overall survival; PFS, progression-free survival; SPM, second primary malignancy

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Depth of Response Correlates with Improved Outcomes

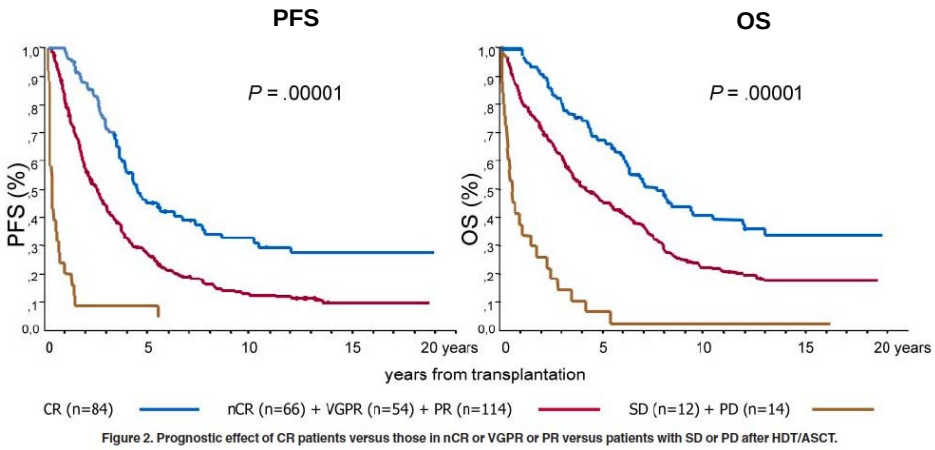

Figure 2. Prognostic effect of CR patients versus those in nCR or VGPR or PR versus patients with SD or PD after HDT/ASCT.

Martinez-Lopez et al *Blood*. 2011;118(3):529-534

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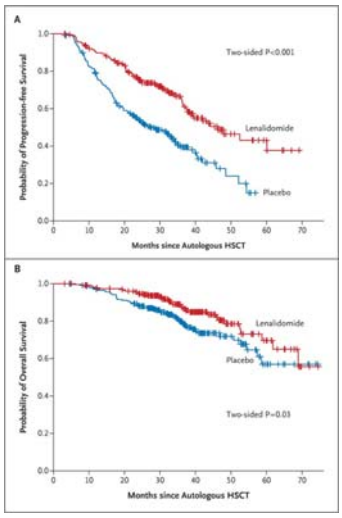
Role of Revlimid Maintenance Following Transplant



- Revlimid increased the benefit of transplant
- Revlimid improved the progression free survival

The NEW ENGLAND JOURNAL of MEDICINE

McCarthy PL et al. *N Engl J Med* 2012;366:1770-1781

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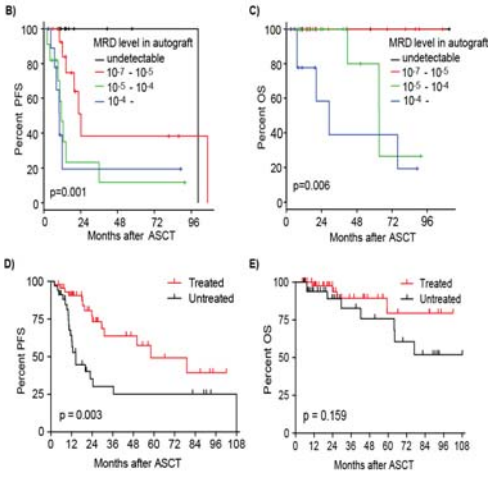
The Role of Minimal Residual Disease on Myeloma Outcomes

- Patients with evidence of minimal residual disease benefitted from maintenance therapy



Hiroyuki Takamatsu et al., ASH 1788. Prognostic Value of Sequencing-Based Minimal Residual Disease Detection in Patients with Multiple Myeloma Who Underwent Autologous Stem Cell Transplantation

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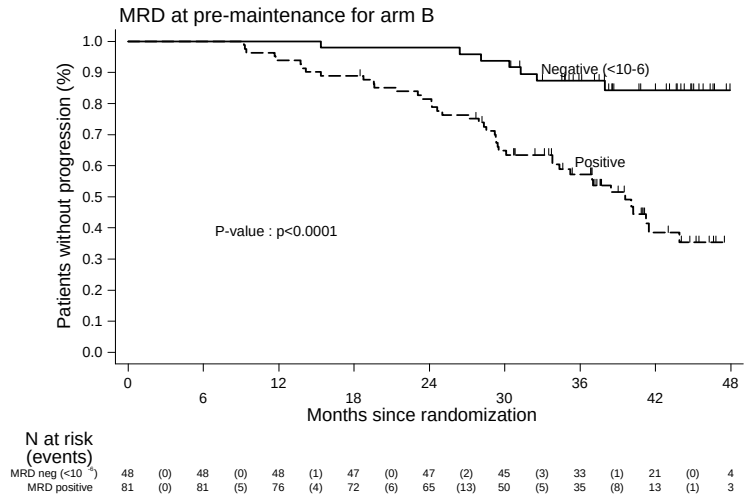
Maintenance Revlimid Improves Minimal Residual Disease



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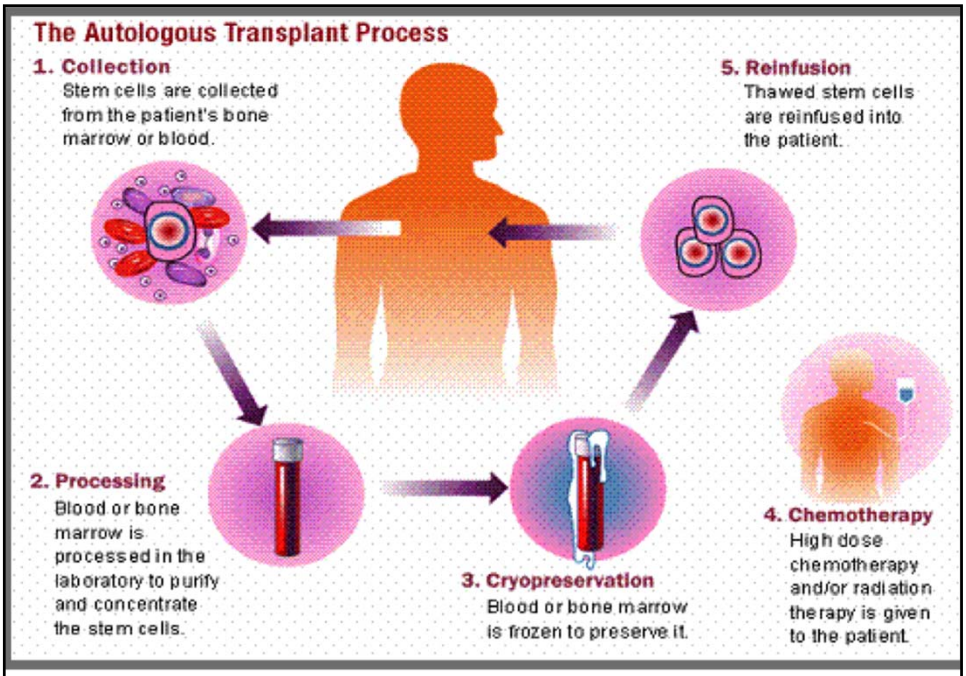

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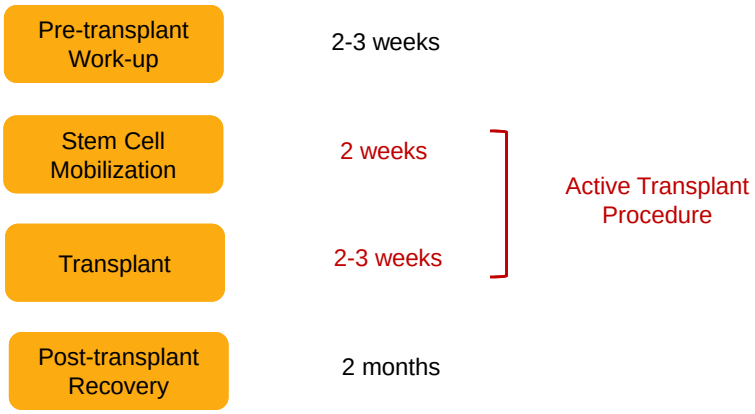
Transplant Logistics



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An Approach to High-Risk Disease Marrow Infiltrating Lymphocytes (MILs)

- Cells obtained from the bone marrow of patients
- Shown to have a high degree of myeloma activity
- Are grown in the lab and then given back to the patients

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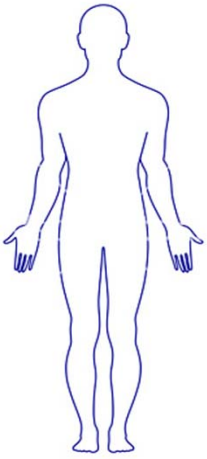
MILs Logistics

3. Stem Cell Transplant

2. MILs Expansion



4. Reinfusion of MILs

1. MILs harvested

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MILs Trial for High-Risk Myeloma J1343 (n=90)

MILs BM Harvest

↓

Mel 200 Auto SCT
(Randomization 2:1)

↙ ↘

Tadalafil days 2-11

↓

MILs d+3, +4

Tadalafil days 2-11

↘ ↙

Lenalidomide 5mg
~day 60 until disease progression

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Autologous Stem Cell Transplantation: Current Perspectives in Myeloma and Lymphoma

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- Consulting
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- Other
  - National Comprehensive Cancer Networks
    (Panel Co-Chair & Speaker)
  - The American Journal of Managed Care
    (Journal Editor/Meeting Speaker)
- Speakers Bureau
  - Ultimate Medical Learning Company

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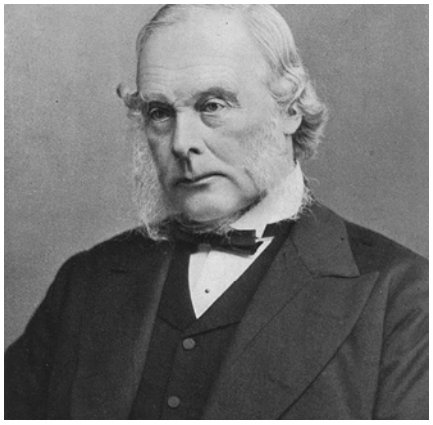
A Rapidly Evolving Understanding of Lymphoma

Thomas Hodgkin
Hodgkin Lymphoma



From Morphology to a Genomic Understanding of Lymphomas

- Hodgkin lymphoma first described in 1832
- First system for classifying non-Hodgkin lymphoma proposed 1956
- The World Health Organization (WHO) classification system now differentiates nearly 80 different forms of lymphoma
- Lymphomas initially described based upon the appear of cells on pathology slides
- Modern description and classification of lymphomas include genetic, molecular, genomic, proteomic and viral information

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Incidence of Non-Hodgkin (NHL) and Hodgkin Lymphoma (HL)

- NHL estimated new cases 2015 – 71,850
  - 4.3% of all new cancer cases
  - Estimated deaths in 2015 - 19,790
  - Patients surviving 5 years – 70%
- HL estimated new cases 2015 – 9,050
  - 0.5% of all new cancer cases
  - Estimated deaths in 2015 – 1,150
  - Patients survival 5 years – 85.9%

http://seer.cancer.gov/statfacts/html/nhl.html
http://seer.cancer.gov/statfacts/html/hodg.html

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Factors That Increase Risk of, or Contribute to, Development of Lymphomas

- Advancing age
- Inherited genetic disorders
  - Wiskott-Aldrich syndrome, X-linked hypogammaglobulinemia, Chédiak-Higashi, ataxia-telangiectasia syndrome
- Viral infections
  - Epstein barre virus
  - Cytomegalovirus
  - HHV-8
  - HIV infection
  - Human T-cell leukemia virus
  - Hepatitis C
- Bacterial infections
  - *Helicobacter pylori*

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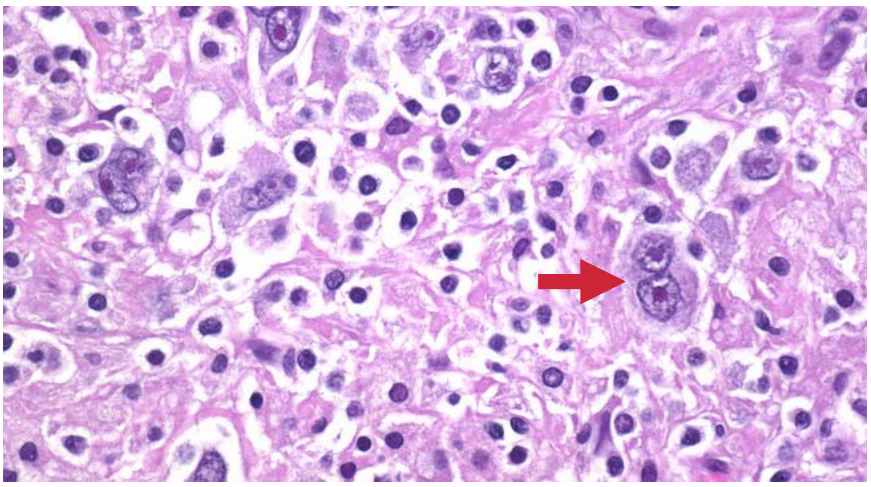
Hodgkin Lymphoma (Reed-Sternberg Cells)



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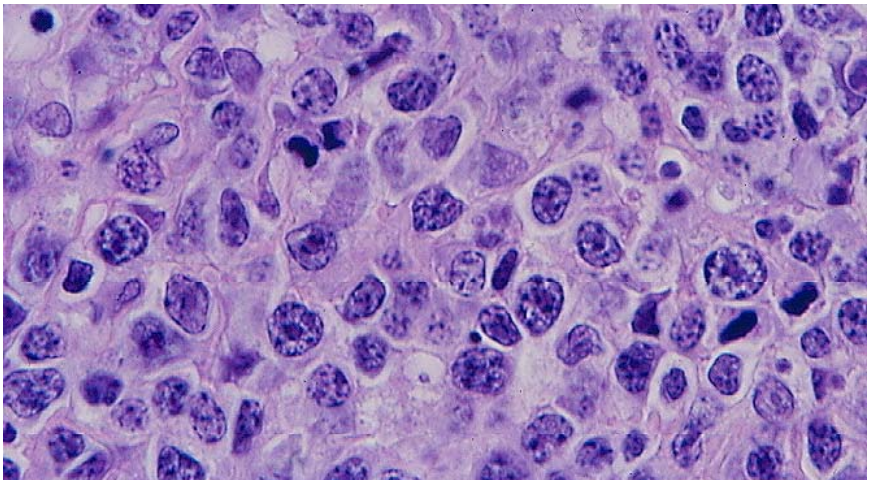
Diffuse Large B-cell Lymphoma



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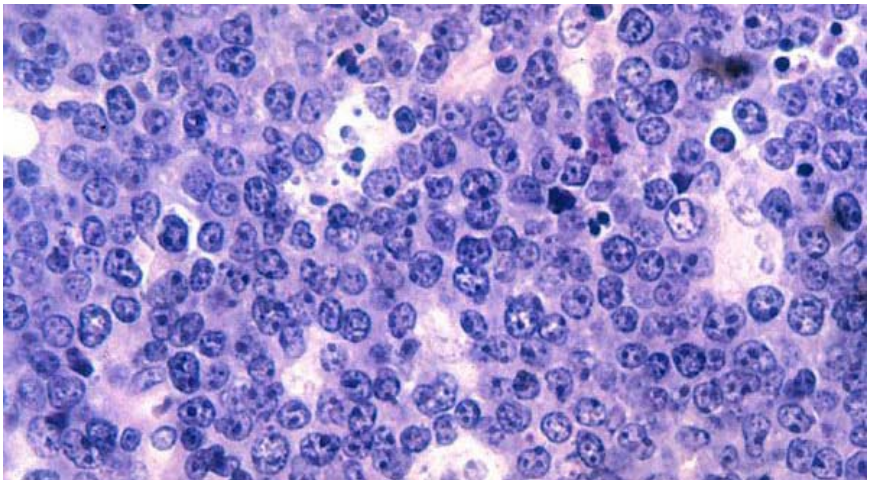
Burkitt Lymphoma



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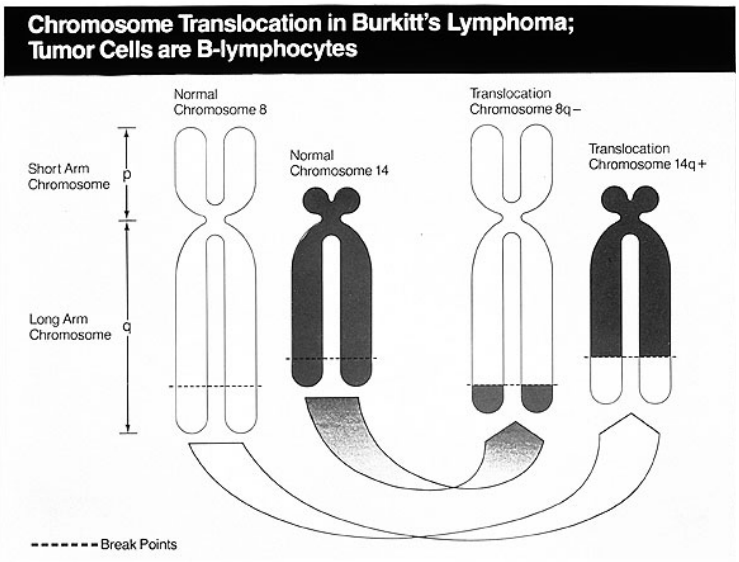
Characteristic Genetic Changes Associated with Burkitt Lymphoma



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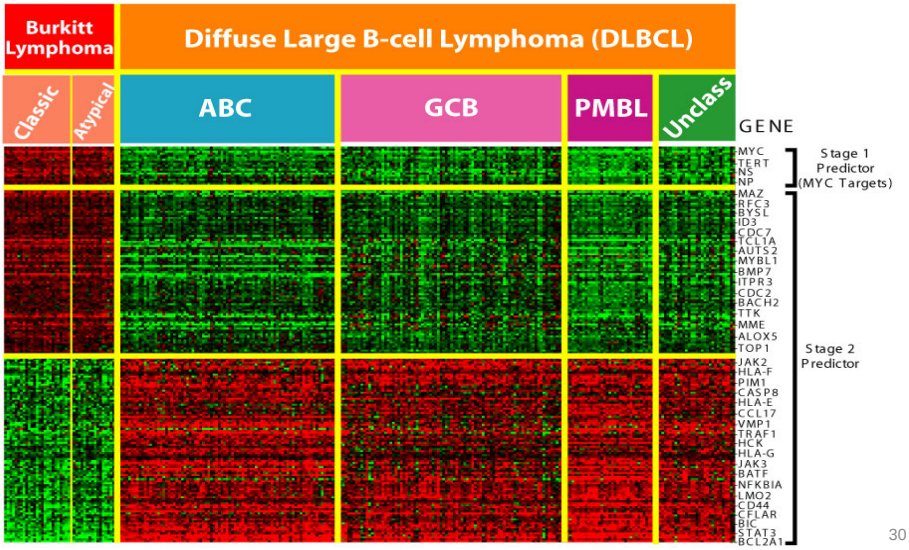
Characterizing Aggressive Non-Hodgkin Lymphoma on a Genomic Level



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Immense Diversity of Lymphoma Subtypes

- WHO classification scheme differentiates many subtypes of NHL and HL (>65)
- Lymphoma treatment and prognosis differs markedly based upon subtype
- B-cell lymphomas are more common than T-cell derived lymphomas
- Lymphomas of follicular subtypes are typically less aggressive at presentation and associated with a more protracted course
- Diffuse large B-cell Lymphoma (DLBCL) is most common subtype (up to 40% of lymphomas diagnosed in US)
- Unlike some solid tumors, patients with relapsed or persistent lymphomas may have an important second chance for cure through the use of an autologous bone marrow/blood stem cell transplant

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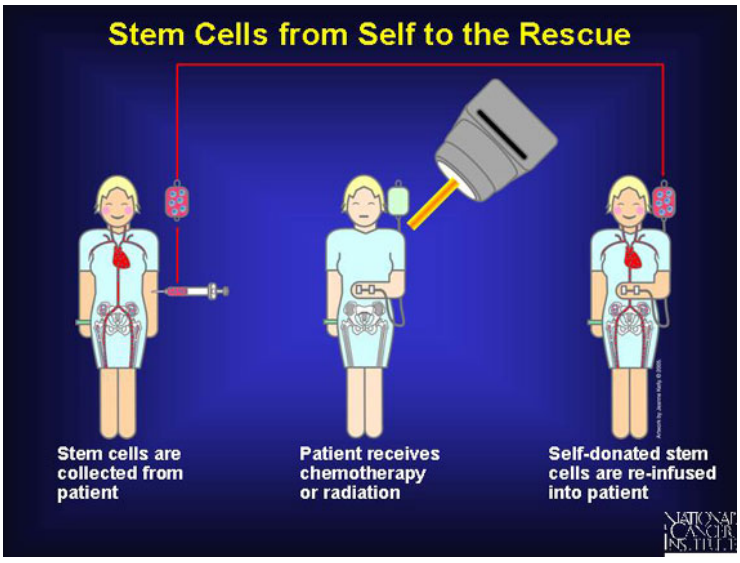
Autologous Blood Stem Cell Transplantation



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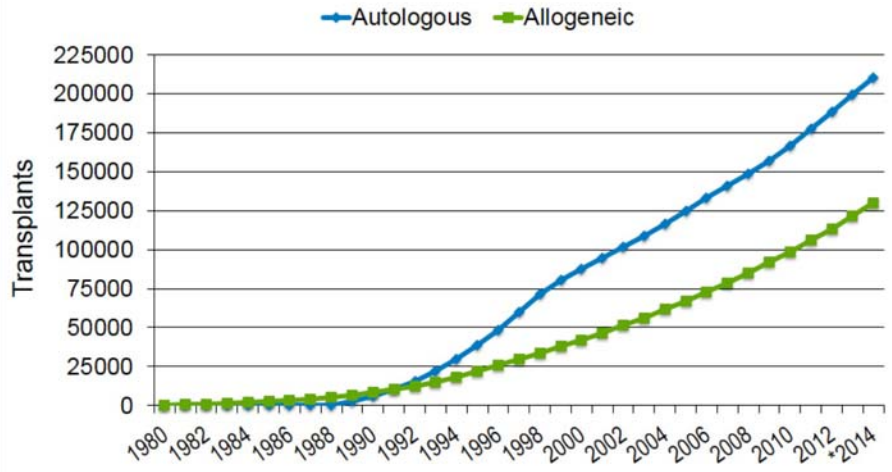
Cumulative Plot of Transplant Recipients in the US by Transplant Type



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*2014 Data incomplete

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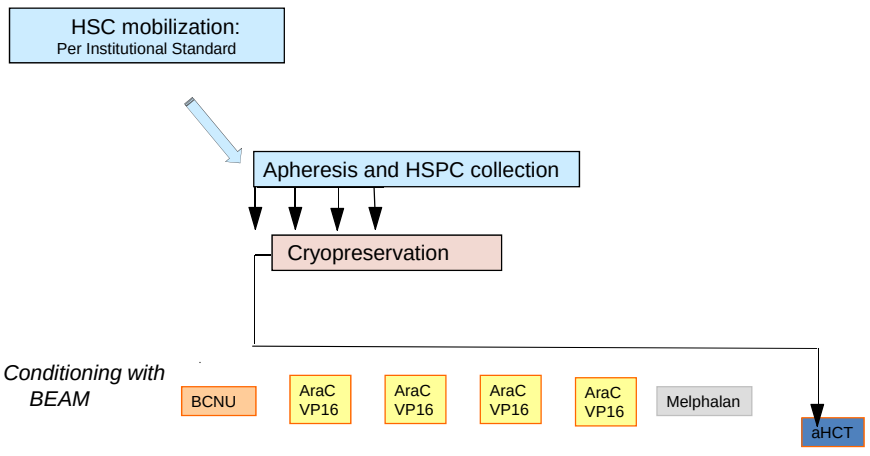
Autologous Hematopoietic Cell Transplantation BMT CTN/AMC 0803/071



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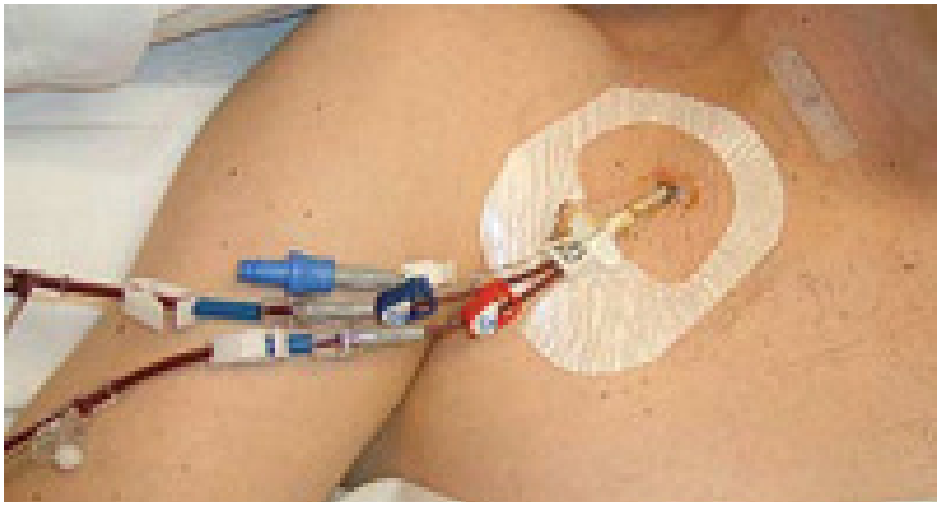
Collection of Autologous Blood Stem Cells



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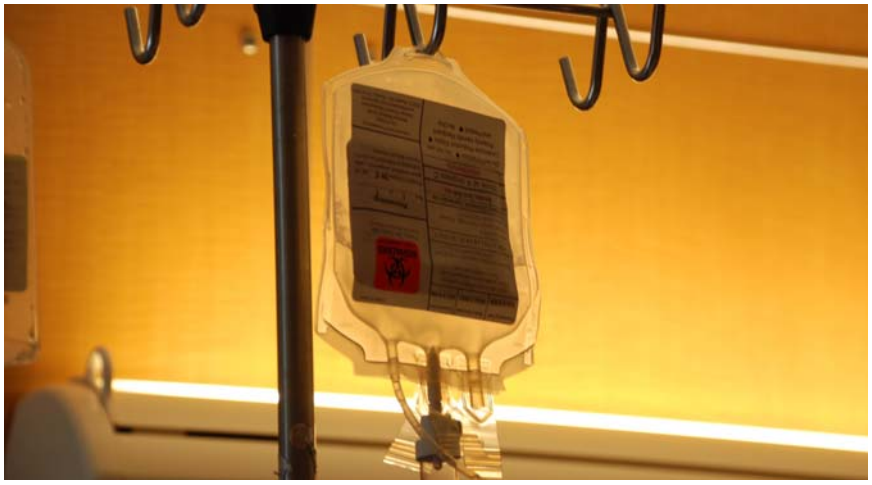
Autologous Stem Cell Transplantation



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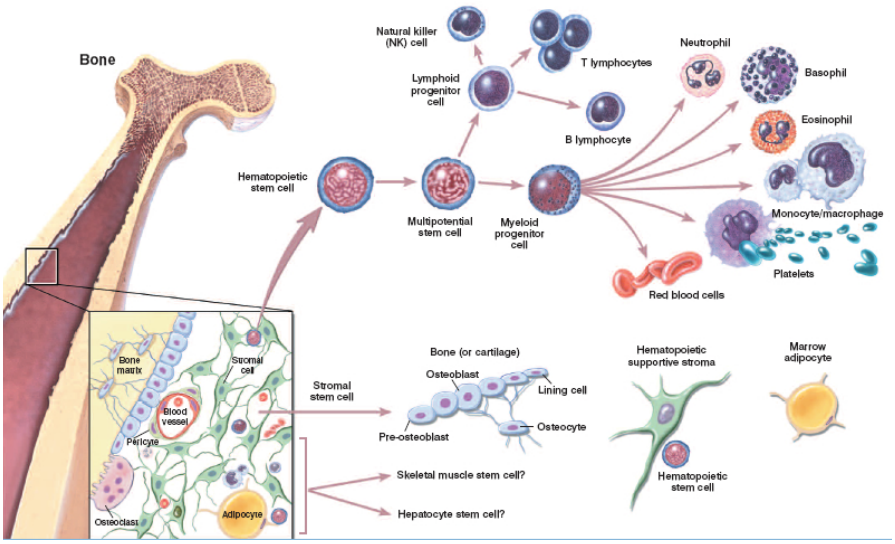
Reconstitution of Hematopoiesis After Transplantation



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Criteria for Autologous Stem Cell Transplantation

- Chemotherapy-sensitive relapsed and persistent aggressive NHL
- Relapsed and persistent HL
- Adequate organ function to tolerate intensity of transplant process
- Ability to mobilize and collect adequate numbers of autologous blood stem cells

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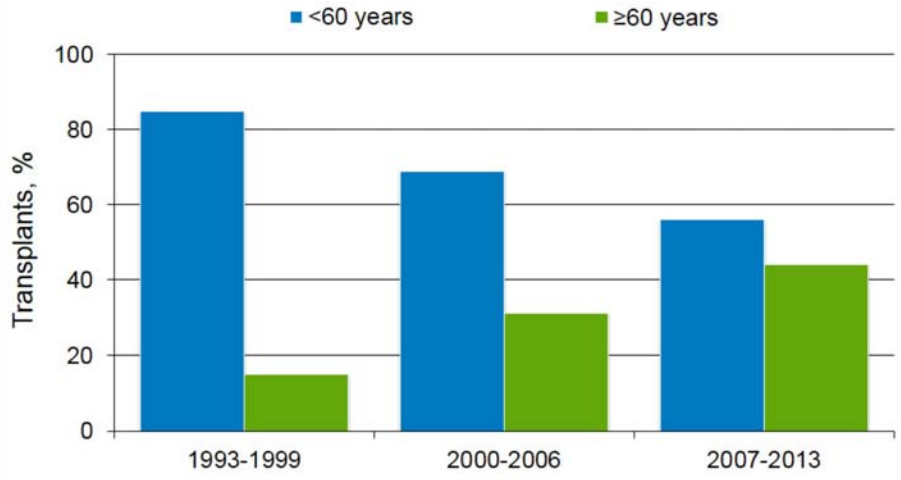
Trends in Autologous Transplants by Recipient Age*



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*Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

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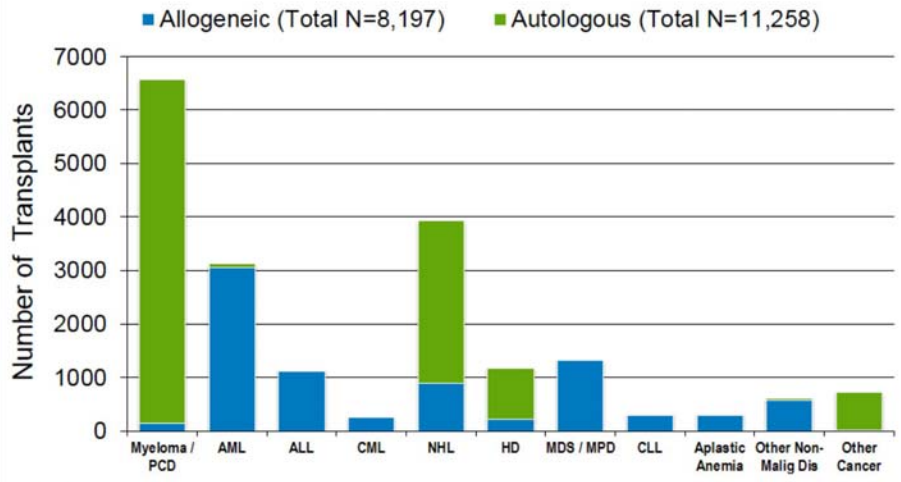
Indications for Hematopoietic Stem Cell Transplants in the US, 2013



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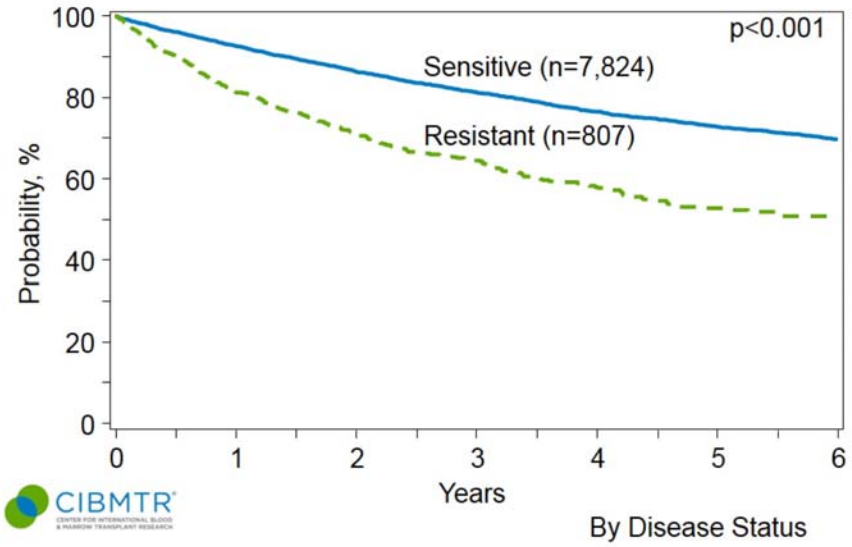
Survival After Autologous Transplants for Hodgkin Lymphoma, 2003-2013



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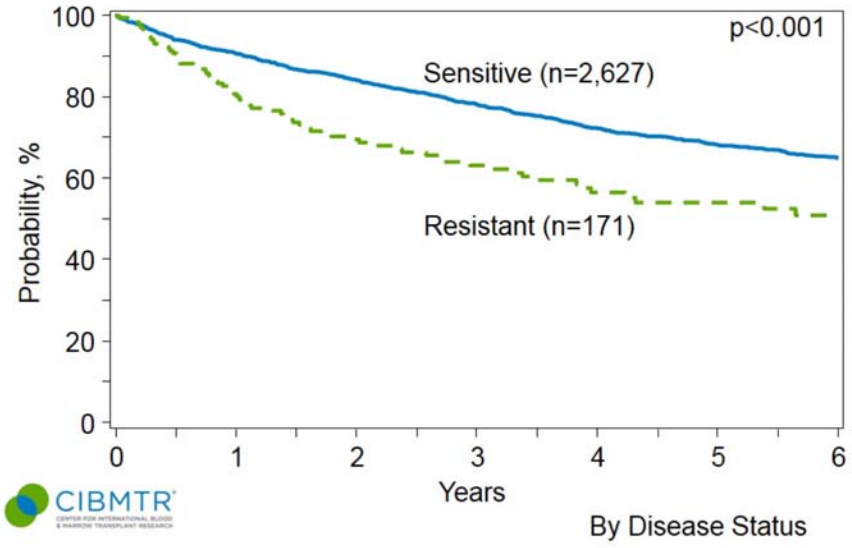
Survival After Autologous Transplants for Follicular Lymphoma, 2003-2013



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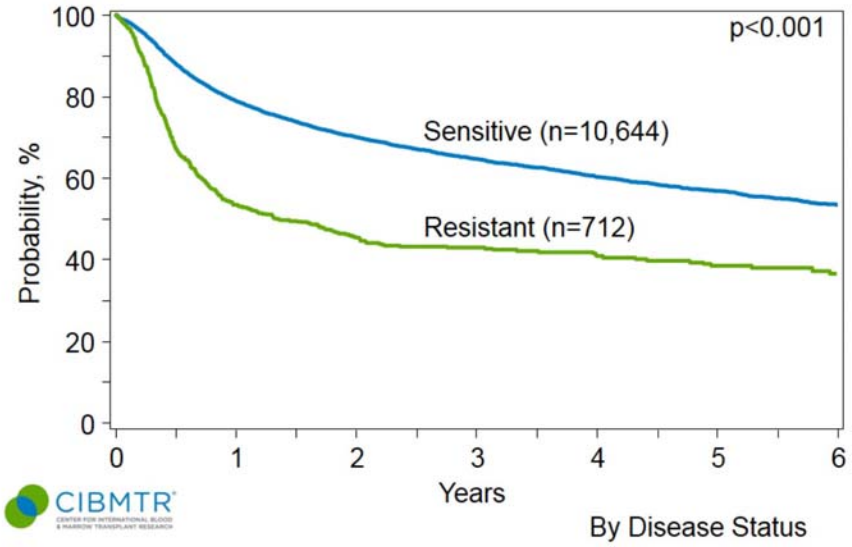
Survival After Autologous Transplants for Diffuse Large B-cell Lymphoma (DLBCL), 2003-2013



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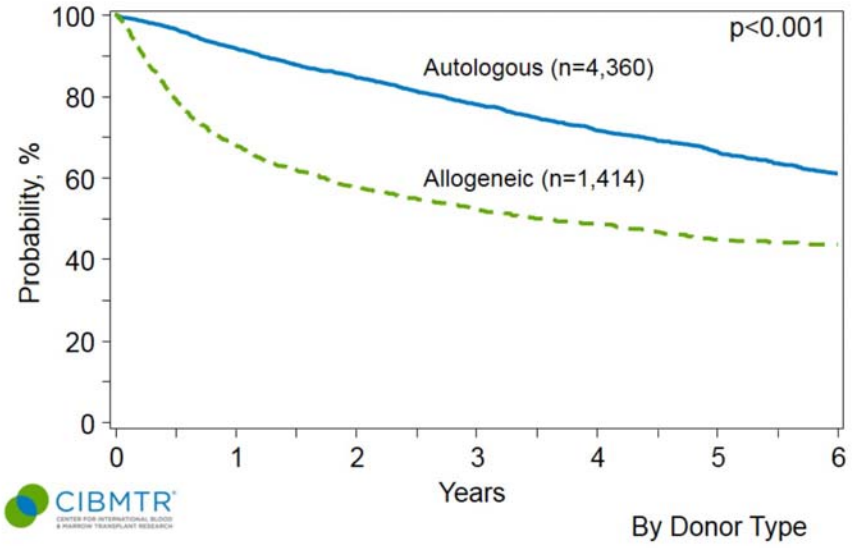
Survival After Transplants for Mantle Cell Lymphoma, 2003-2013



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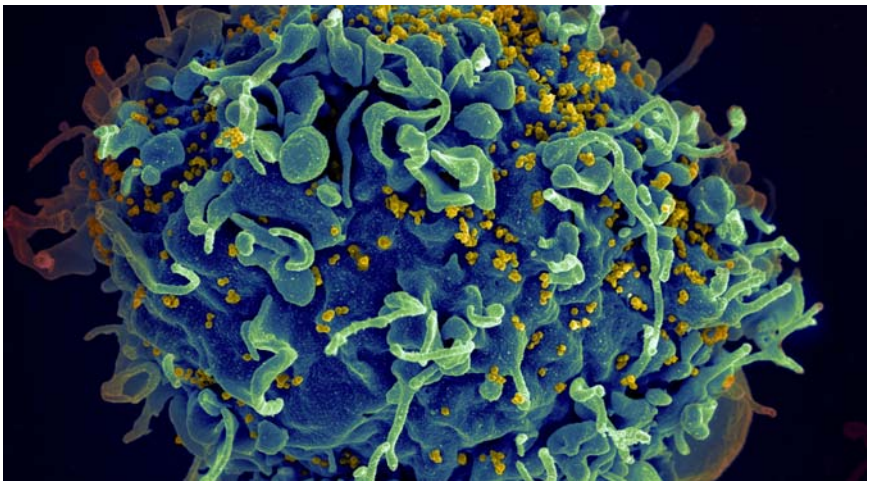
HIV Infecting CD4+ T-cells



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Autologous HCT for ARL

Publication	Failure to mobilize	Patients (n)	Tx related mortality	Median f/u (months)	Overall survival
Krishnan et al. 2005	0	20	5%	32	85%
Spitzer et al. 2008	2	20	5%	5.8	>50%
Re et al. 2003	4	10	0	18	39%
Re et al. 2009	6	27	0	44	75%
Gabare et al. 2004	NA	14	NA	1	71%
Serrano et al. 2005	0	11	0	32	73%
Balsalobre 2009	NA	68	7.5%	32	61%

First case report: Gabare et al, BMT 1996; 18: 1195-7

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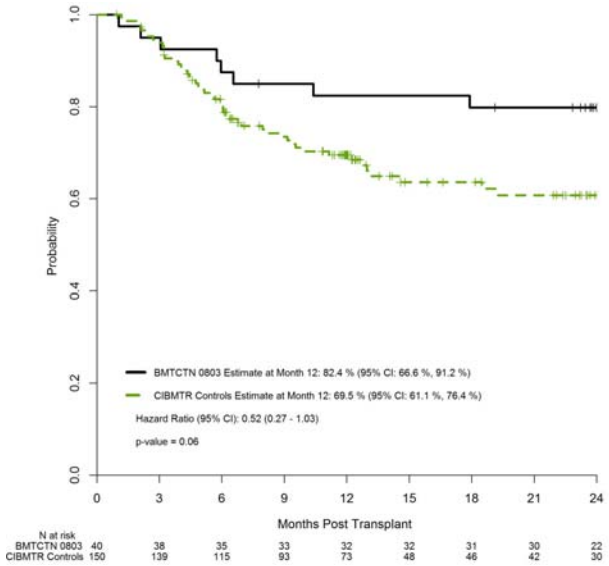
Progression-free Survival



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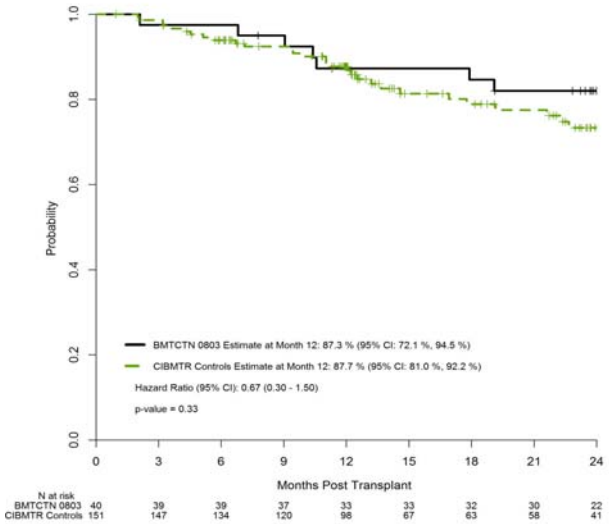
Overall Survival: HIV-Infected Patients vs. 151 CIBMTR non-HIV-infected Patients



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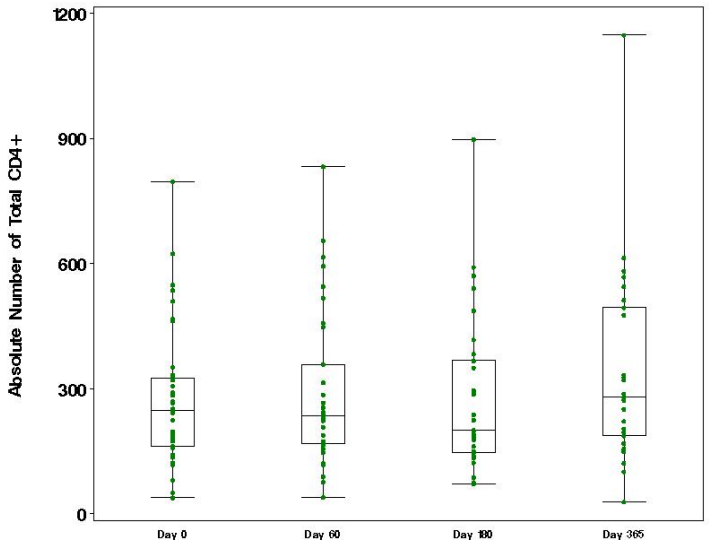
CD4+ T-cell Reconstitution Post-AHCT



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Growing Armamentarium of Immunotherapeutic Agents for B-cell Malignancies

- Monoclonal antibodies
  - Rituximab in NHL
  - CAMPATH in CLL
- Monoclonal antibody-drug conjugates
  - Brentuximab
  - Inotuzumab
- Bi-specific antibodies
  - Blinatumomab
- T-cell based therapeutics*
  - Chimeric antigen receptor T-cells

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Problem: Current Outcomes in Diffuse Large B-cell Lymphoma and Mantle Cell Lymphoma Are Not Acceptable!

- DLBCL is the most common subtype of NHL (30%). Survival without treatment is measured in months.
- Up to 70% of patients have advanced stage disease at diagnosis
- With standard treatment, 60% of patients are still alive and disease free at 5 years.
- Patients who relapse or who cannot achieve first remission are not curable without transplant

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CAR T-cell Therapeutics

- Form of adoptive immunotherapy
- Autologous T-cells engineered to express T-cell receptor (TCR) with CD19 specificity
- Target cells killed by T-cell specific tumor killing
- Important toxicities
  - Tumor lysis syndrome
  - Cytokine release syndrome
  - Macrophage activation syndrome
  - Neurological toxicities
  - B-cell aplasia
- In vivo persistence of CAR T-cells

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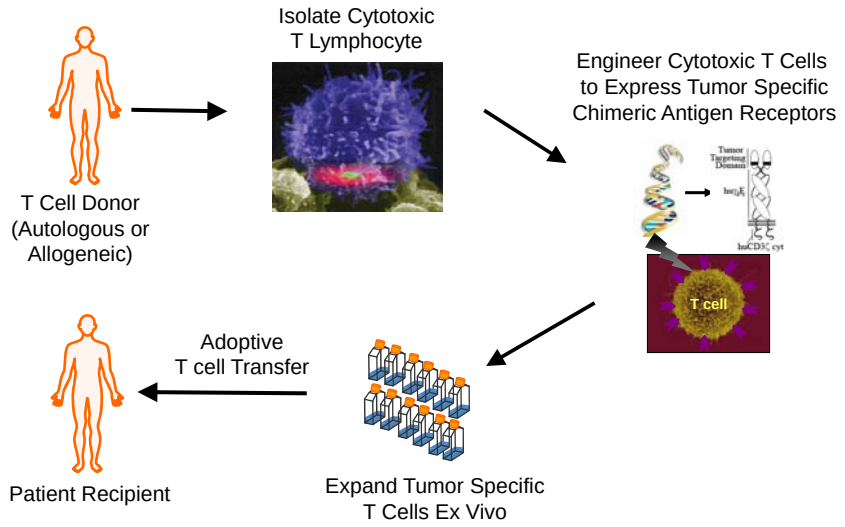
Adoptive T Cell Therapy for Cancer



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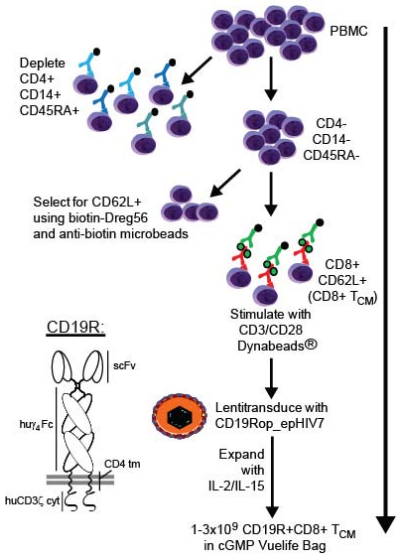
Platform for Manufacturing T_{CM} Derived CD19CAR+ T Cells



Day : Bioprocess

Day 1: Leukapheresis

Day 2: CliniMACS Selection of Tcm; Dynabead stimulation

Day 5: Lentiviral Transduction; Initiate Expansion

Day 14-30: Dynabead Removal

Day 26-40: Cryopresservation

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Promise and Risks of CAR T-cell Therapeutics

- CAR T-cells and other T-cell therapeutics are under study in clinical trials
- Potential risks of CAR T-cells based treatments include
  - Cytokine release syndrome
  - Tumor lysis syndrome
  - Neurological toxicities
  - Persisting low B-cell counts

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Summary and Future Directions

- Treatment for patients with relapsed and refractory NHL and HL is increasingly effective
- Autologous transplant is an important component in the cure of many patients with relapsed or persistent aggressive NHL and HL
- Patient with HIV infection have transplant outcomes equivalent to those of patients without HIV-infection
- T-cell-based therapeutics may allow us to improve upon the success of autologous transplant

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Why This Work is Never Complete

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Question & Answer Session

The speaker's slides are available for download at www.LLS.org/programs

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Autologous Stem Cell Transplantation: Current Perspectives in Myeloma and Lymphoma

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

someday is today®

The Leukemia & Lymphoma Society (LLS) offers:

• Live, weekly Online Chats are moderated by an oncology social worker and provide a friendly forum to share experiences.

- **WEBSITE: www.LLS.org/chat**

• What to ask: For a list of suggested questions to ask about certain topics, download and print any of the following guides.

- **WEBSITE: www.LLS.org/whattoask**

• Free publications are available ranging from disease specific information to health insurance options and resources to help patients and their families cope with the financial aspects of cancer.

- **WEBSITE: www.LLS.org/booklets**

• For more information about blood cancers and other LLS programs, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE: (800) 955-4572**
- **EMAIL: infocenter@LLS.org**

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