# Transplantation for DLBCL & Follicular Lymphoma

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Associate Professor of Medicine
Scientific Director, CIBMTR
Medical College of Wisconsin
January 17, 2017

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A research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin

# Disclosures

## Research support:

- Takeda, Otsuka, Spectrum, Sanofi

## Speakers Bureau:

- Otsuka Pharmaceuticals; Celgene, Inc. (Inactive)
- Sanofi

## Consultancy:

- Cellerant Therapeutics
- MedImmune
- Celgene, Inc.
- Janssen R & D

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# Presentation Outline

- HCT utilization trends in hematological malignancies
- Current state of HCT in:
  - Diffuse Large B-cell Lymphoma
  - Follicular Lymphoma

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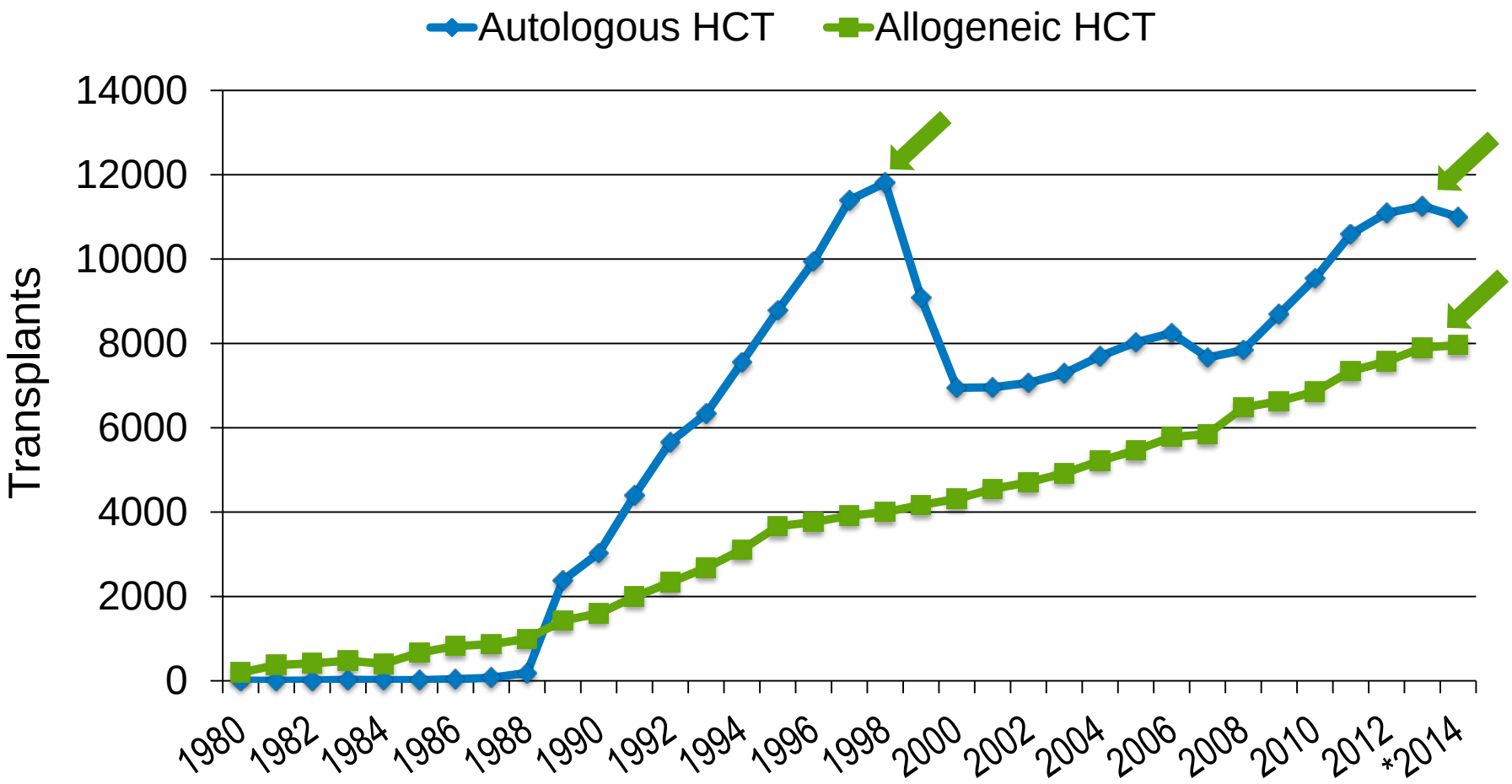
# Annual Number of Transplant Recipients in the US by Transplant Type (All Indications)

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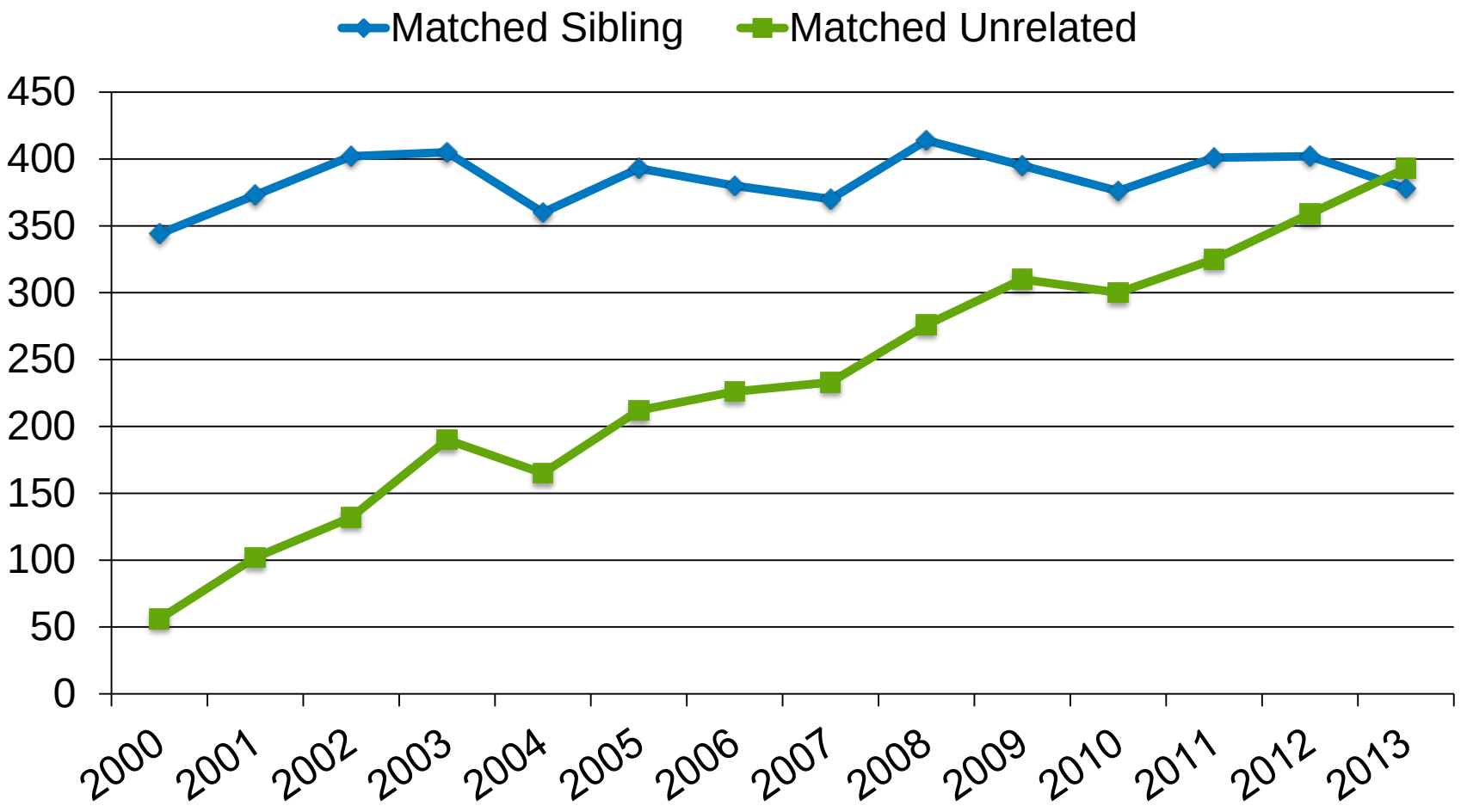
* 2014 Data incomplete

# Non-Hodgkin and Hodgkin Lymphoma Patients Undergoing Matched Donor AlloHCT from 2000-2013

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# Durable Control - An Unmet Need in Relapsed Lymphomas

- DLBCL: Relapsed or primary refractory disease
- Follicular: Early failure (≤2 years) or multiply relapsed disease
- Genomically high-risk disease

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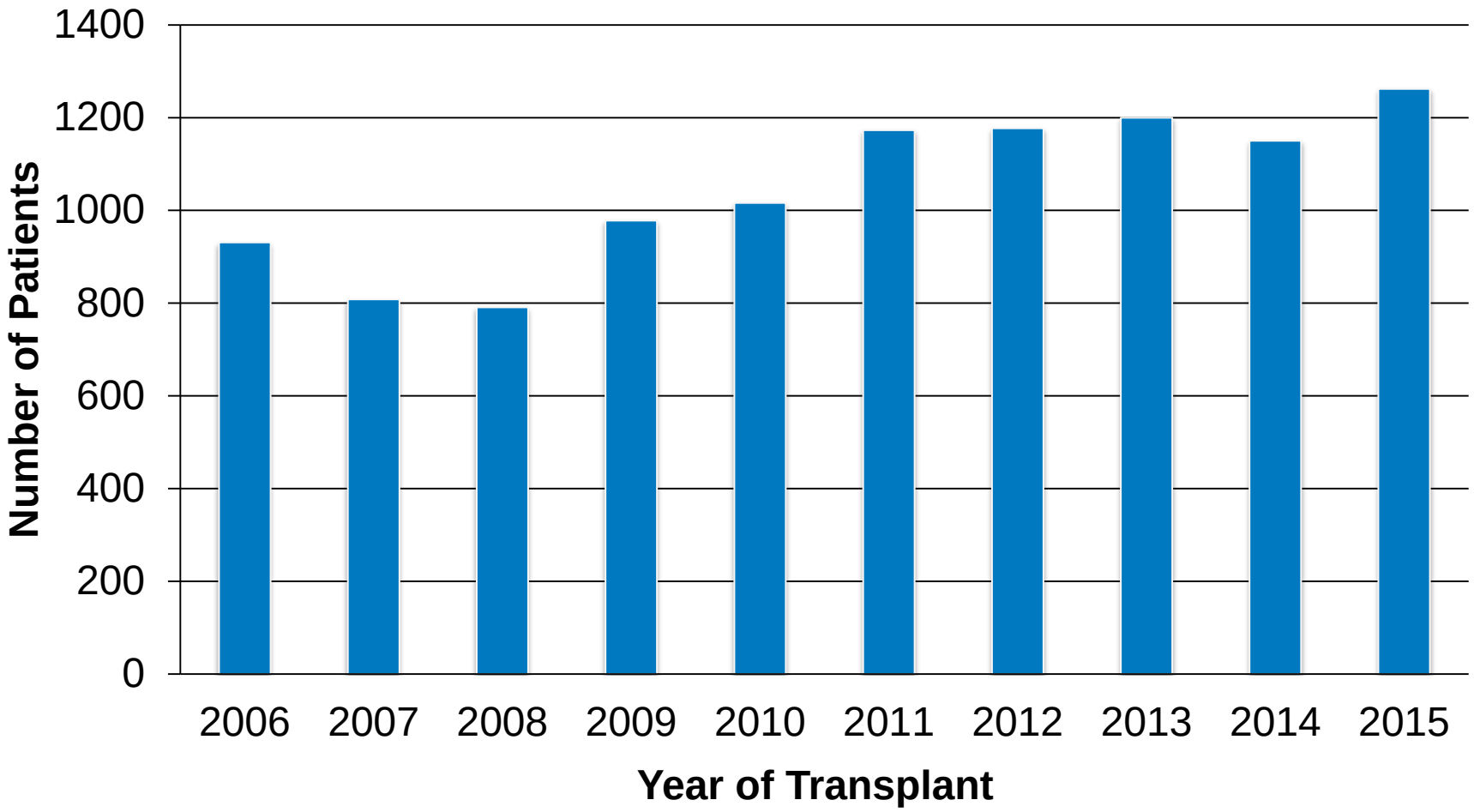
# Autologous Transplantation for DLBCL Between 2006-2015

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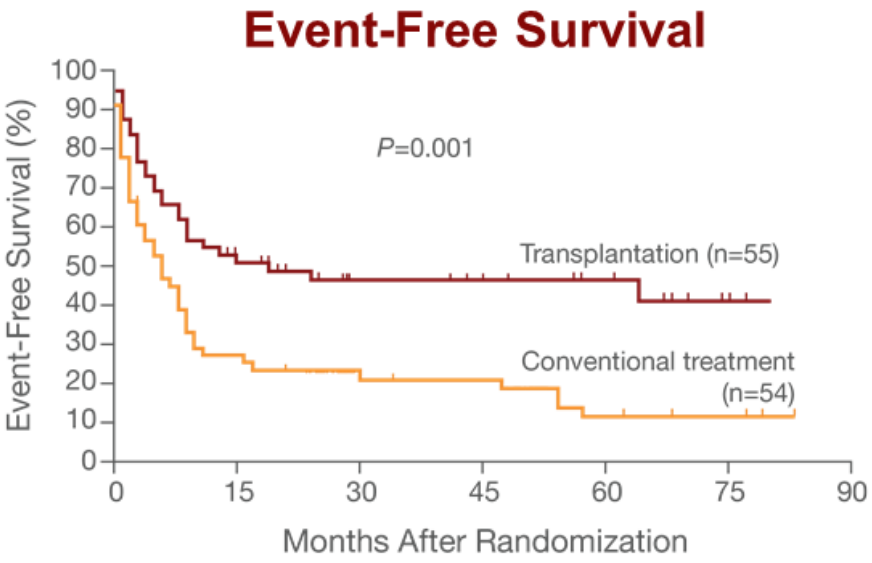
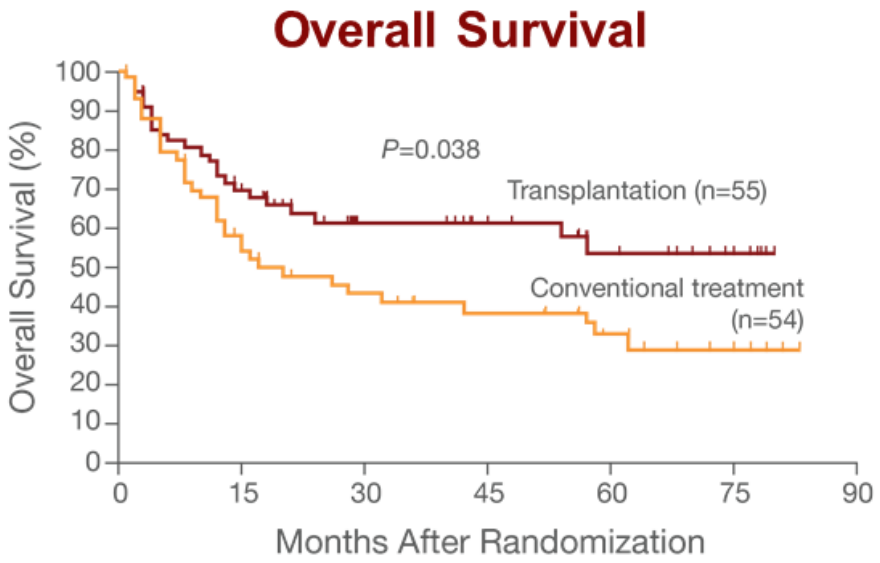
# Autologous HCT for relapsed DLBCL

## PARMA Study




In **relapsed** DLBCL, responding to salvage chemotherapy, autologous HCT remains standard-of-care

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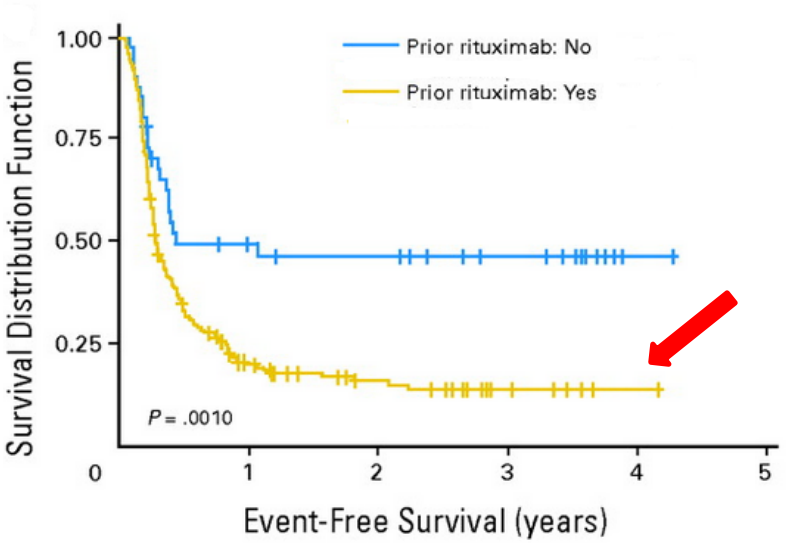
Philip T. NEJM 1995;333:1540-1545

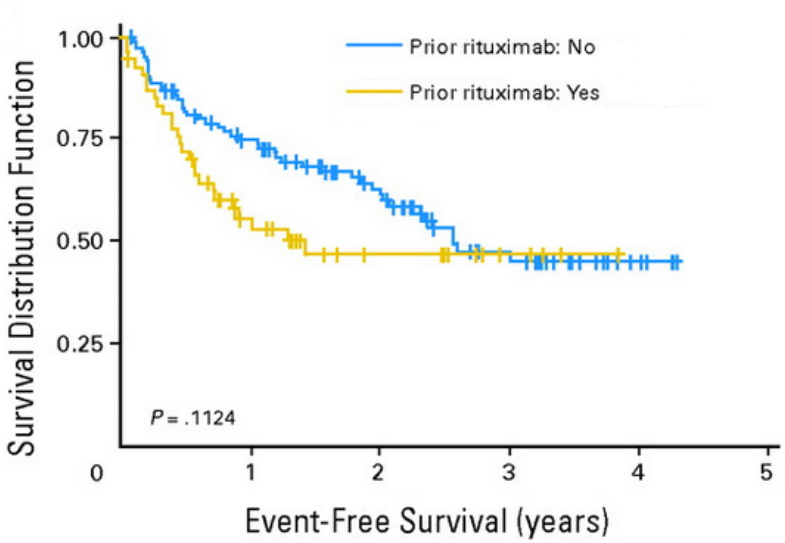
# AutoHCT after early R-CHOP failure?

## CORAL Trial

**Relapse ≤1 year after diagnosis**




**Relapse >1year after diagnosis**

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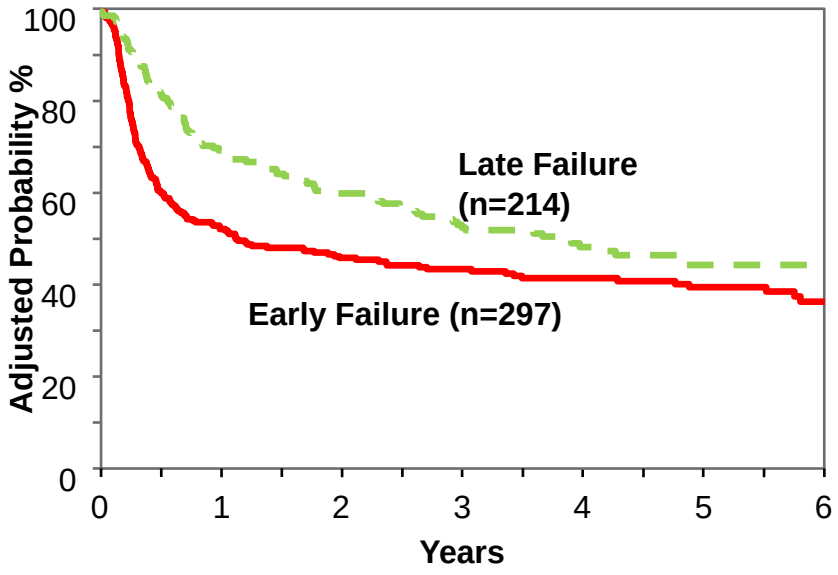
Gisselbrecht C. JCO. 2010;28:4184-90

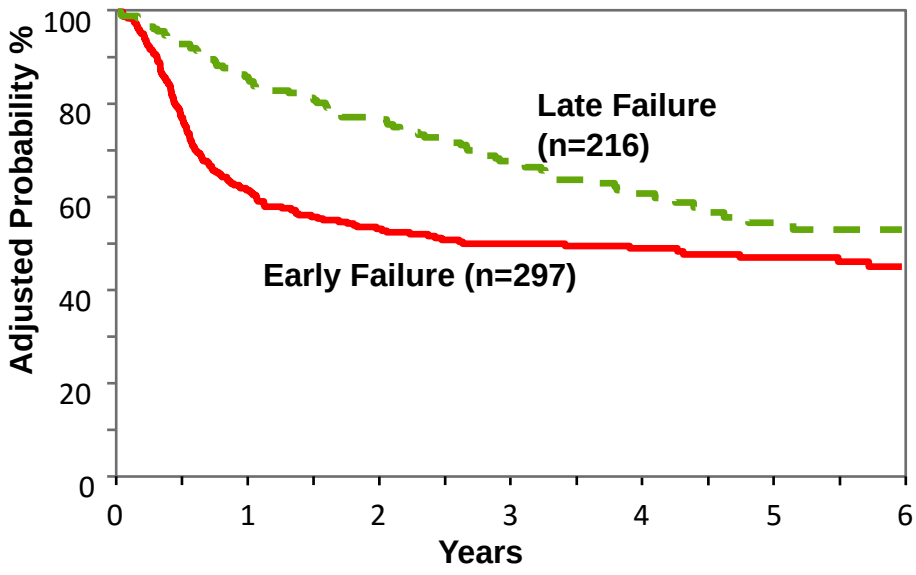
# AutoHCT after early R-CHOP failure?

## CIBMTR DATA

**Progression-free Survival**




**Overall Survival**

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Hamadani M. BBMT. 2014;20:1729-36.

# DLBCL & HCT: Areas of Controversy

- Prevention of post auto-HCT relapse
- Upfront HCT for clinically high-risk DLBCL
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# AutoHCT after early R-CHOP failure?

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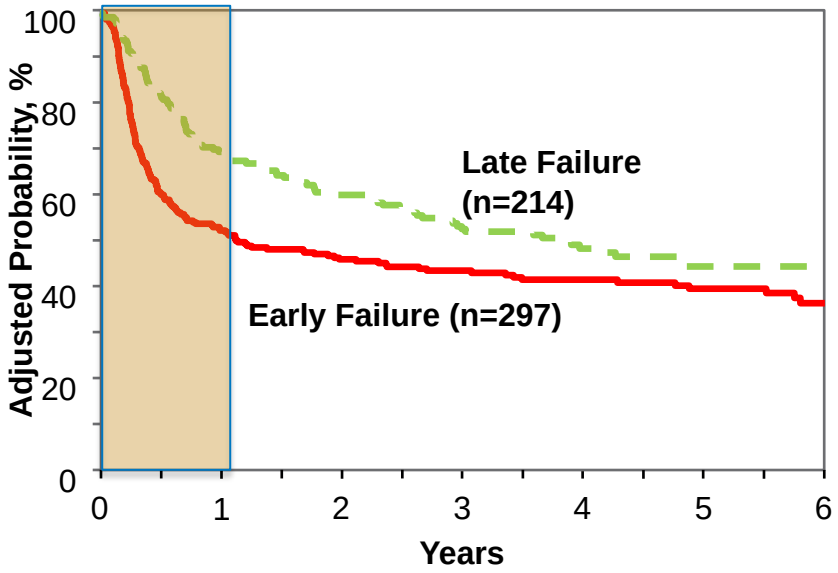
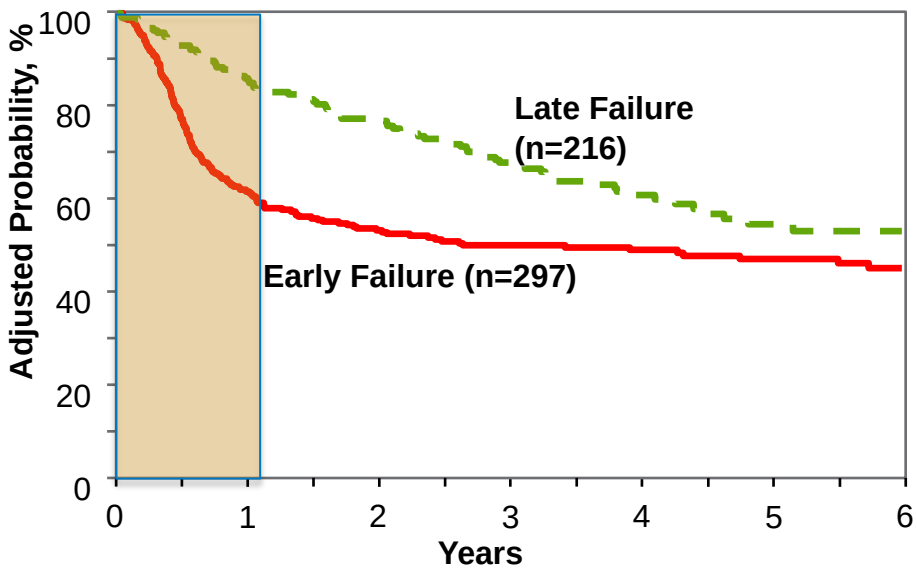



**Overall Survival**

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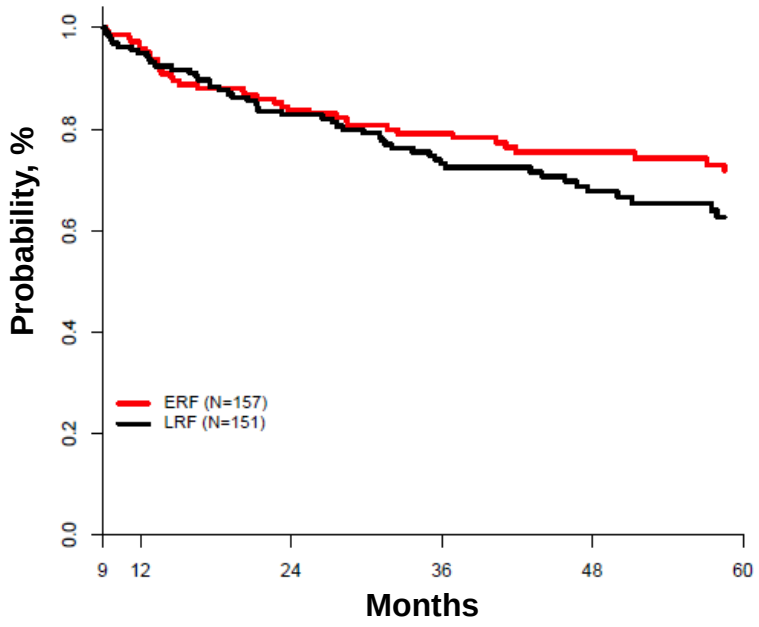
Hamadani M. BBMT. 2014;20:1729-36.

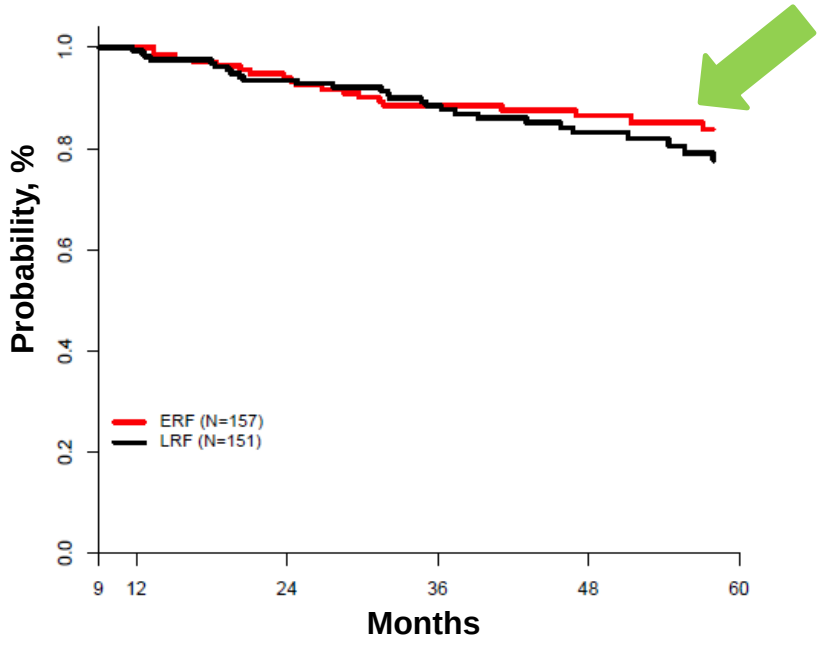
# AutoHCT after early R-CHOP failure?

## CIBMTR DATA

### PFS-Landmark Analysis




### OS-Landmark Analysis

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Hamadani M. BBMT. 2014;20:1729-36.

# BMT-CTN 1201: Post AutoHCT Ibrutinib Maintenance

**Relapsed/Refractory DLBCL-ABC**
**Salvage ≥PR, stem cells collected**

**Randomization**

**Arm A**

**ASCT:**
**+ Ibrutinib 560 mg until day -1**

**Ibrutinib x 12 months**

**Follow Up**

**Arm B**

**ASCT:**
**+ Placebo**

**Placebo x 12 months**

**Follow Up**

# DLBCL & HCT: Areas of Controversy

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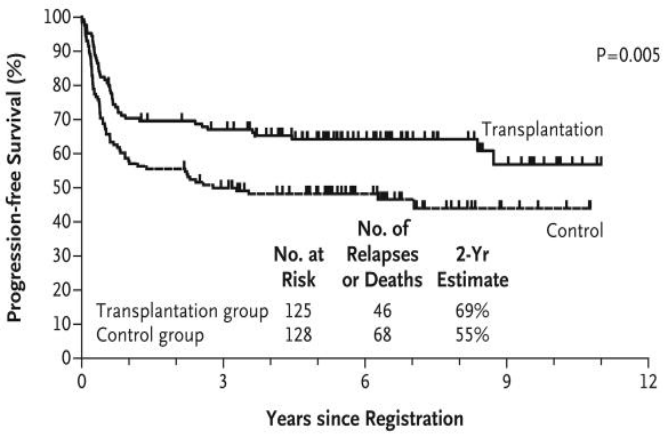
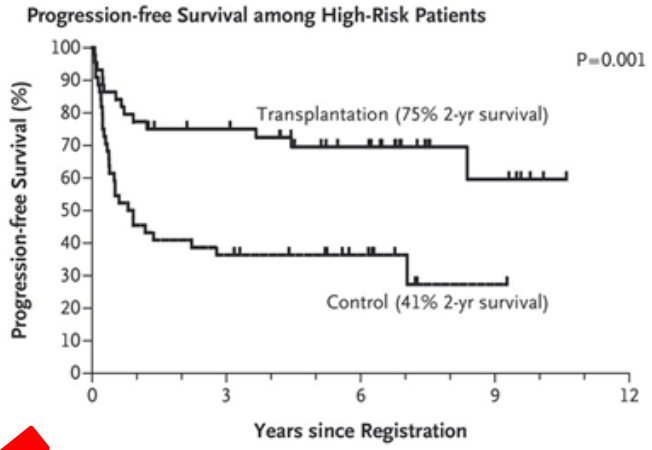
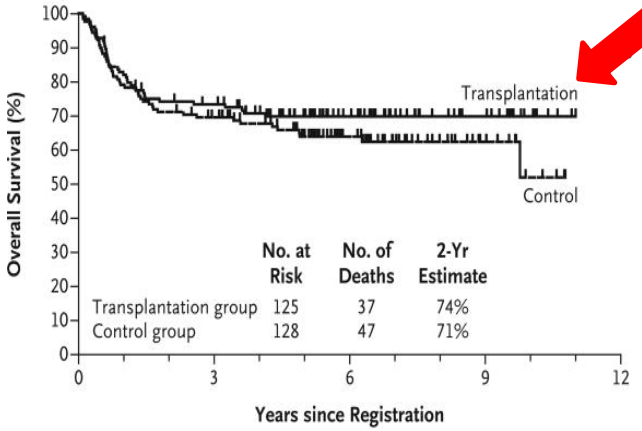
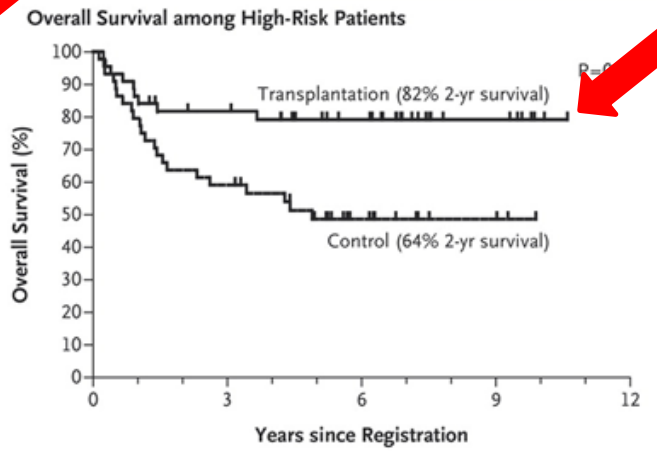
# Upfront Autologous HCT for DLBCL

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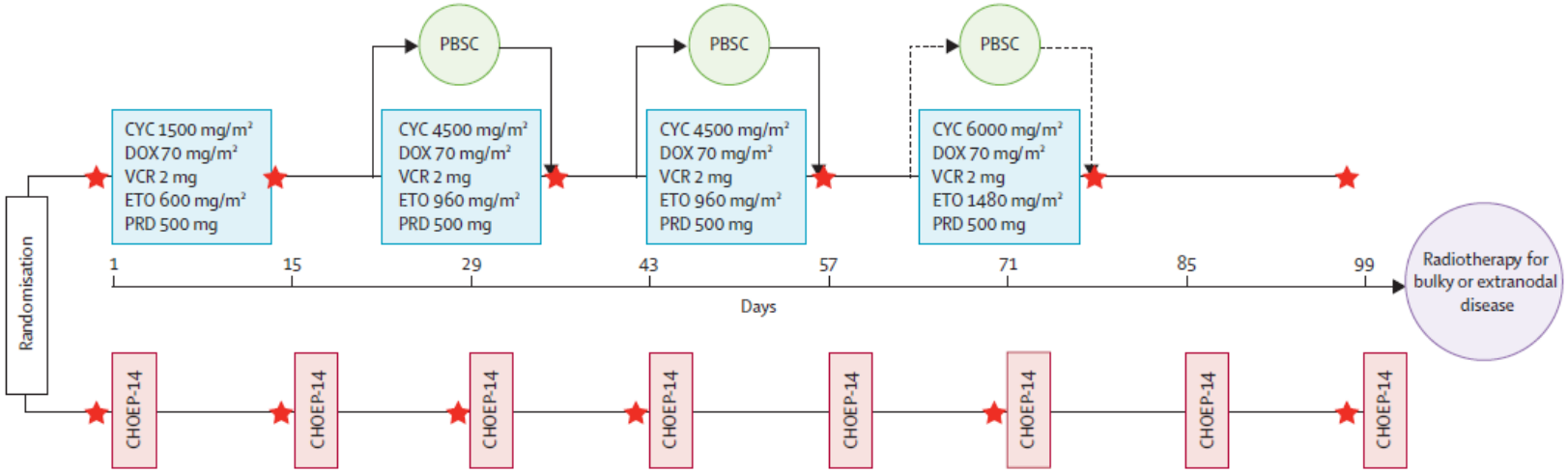
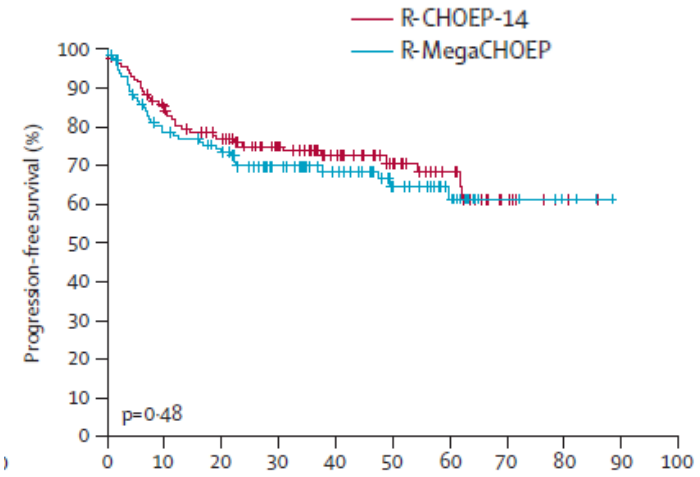
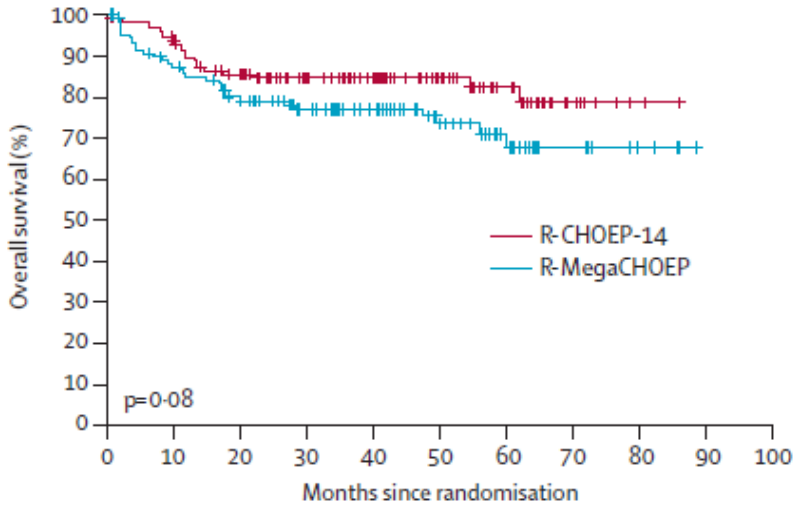
Stiff P. NEJM. 2013;369:1681-90.

# Upfront Autologous HCT for DLBCL

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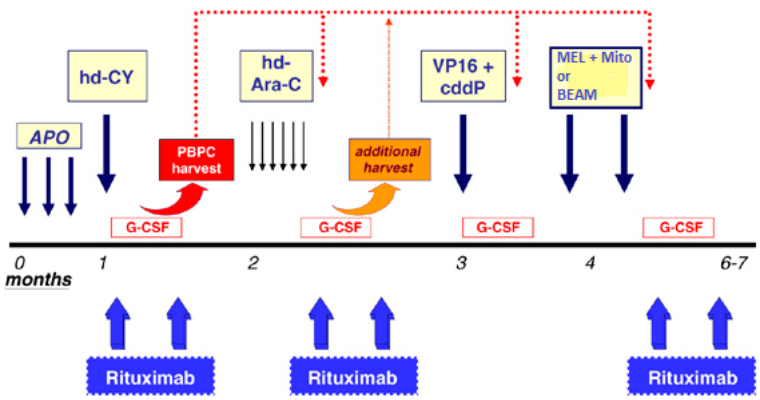
Schmitz N. Lancet Oncology. 2012;13:1250-59.

# Upfront Autologous HCT for DLBCL

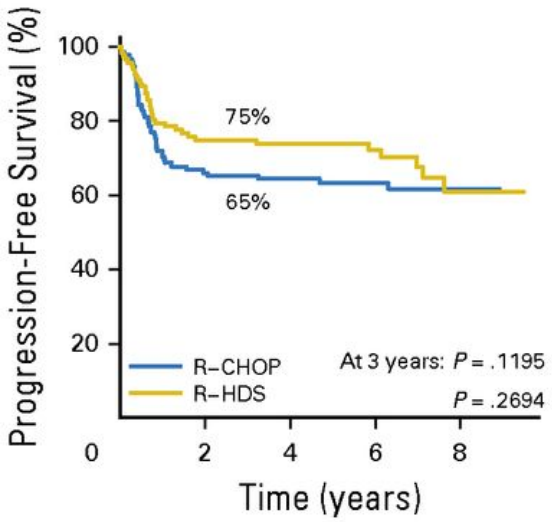
- New DLBCL
- Inter-high or
- High IPI

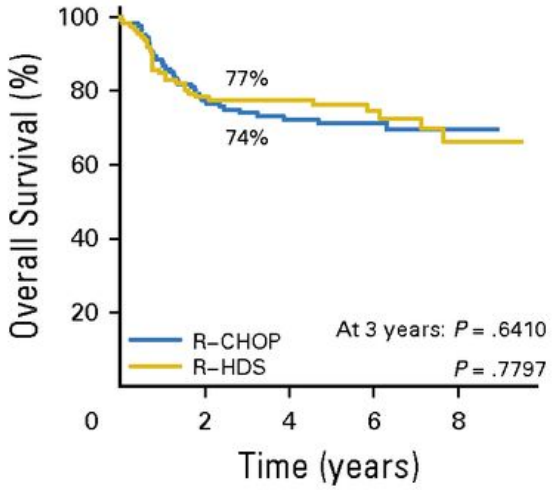
Randomize

R-CHOP14 x8




ITT Results

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Cortelazzo S. JCO. Epub Oct 3, 2016.

# DLBCL & HCT: Areas of Controversy

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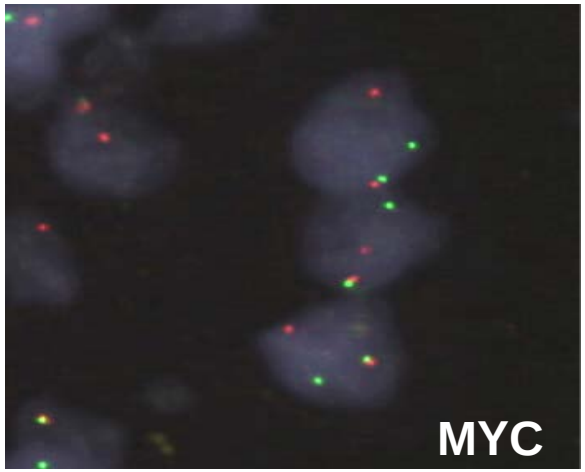
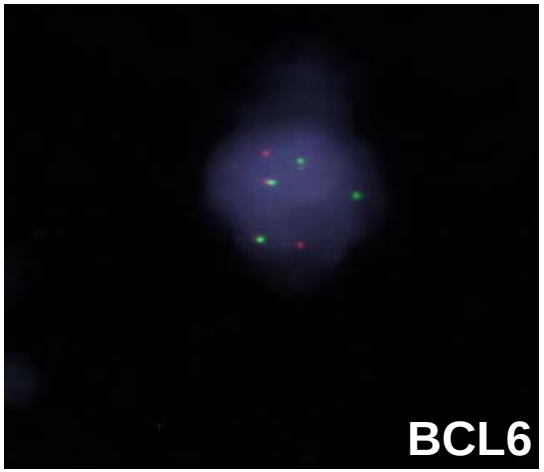
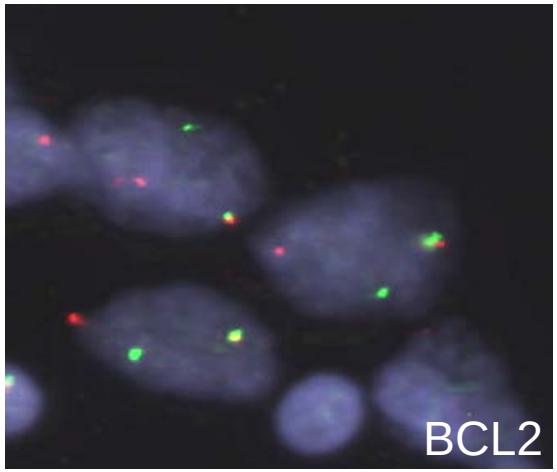
# Double-Hit DLBCL (DHL)

- **DLBCL with rearrangement of c-MYC plus BCL2 and/or BCL6**
  - 5-10% of newly diagnosed DLBCL
  - Dismal prognosis with standard R-CHOP

(Johnson et al. *Blood* 2009; Green et al. *JCO* 2012; Petrich et al. *Blood* 2014)

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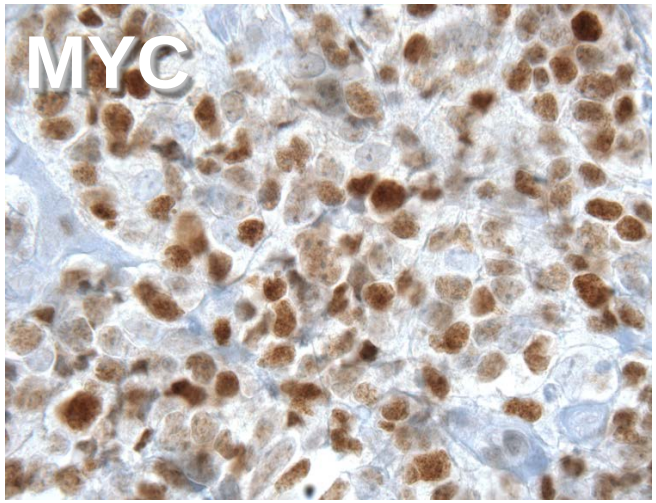
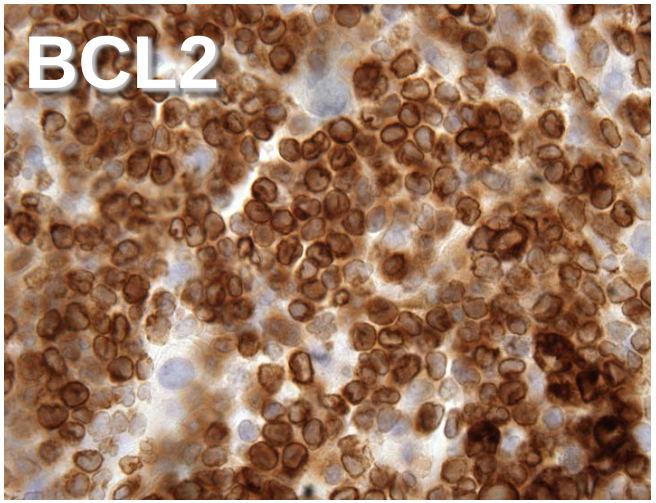
FISH with dual color break-apart probes for MYC, BCL2, BCL6.
Photos courtesy of V. Bedell, 63x Bioview imaging system.

# MYC/BCL2 Double Expressing DLBCL (DEL)

- **DLBCL with coexpression of c-MYC and BCL2 proteins by immunohistochemistry**
  - 21-34% of newly diagnosed DLBCL
  - Poor outcomes after R-CHOP, independent of other factors

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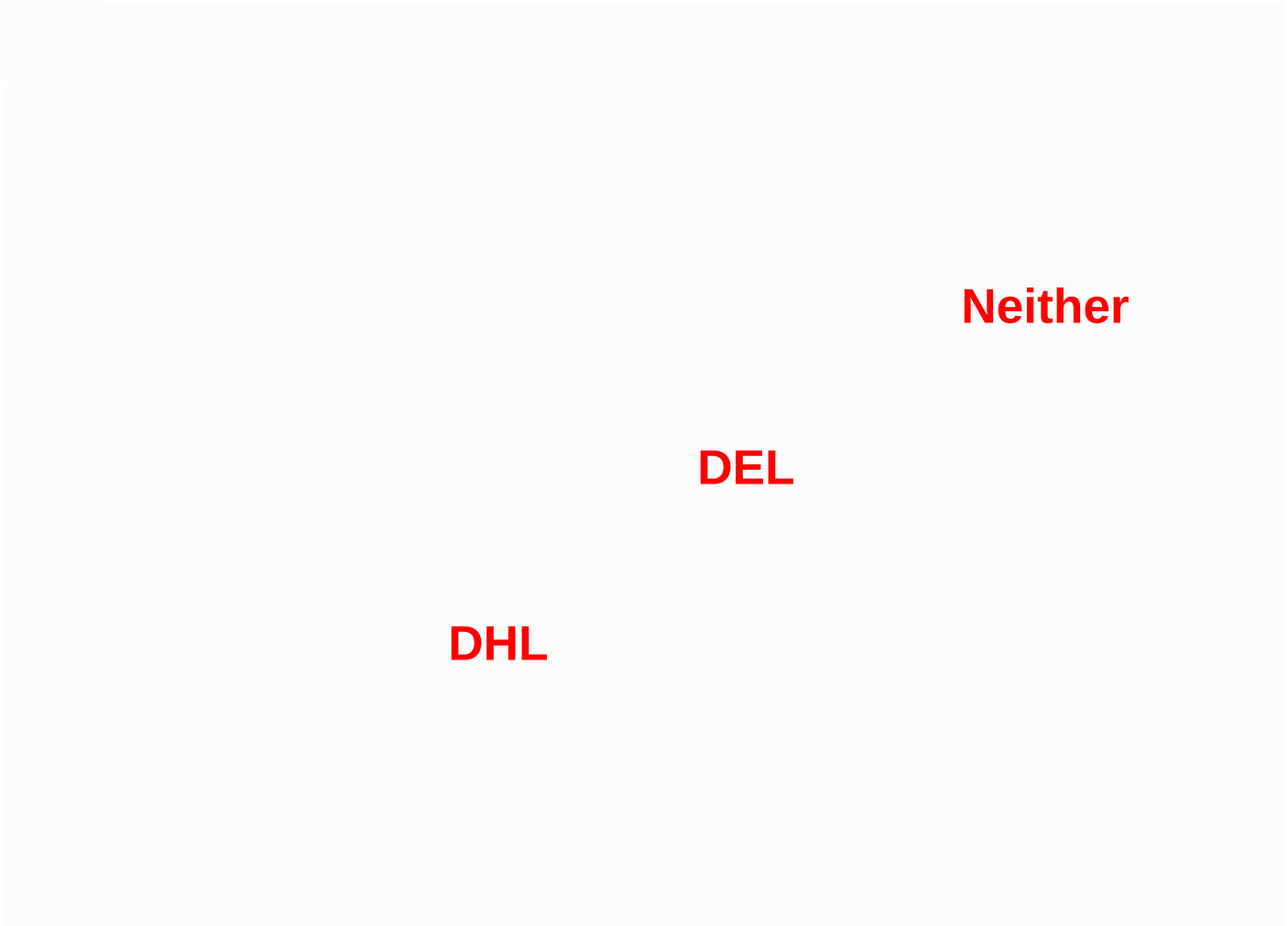
Photos courtesy of S. Rodig, 1000x

# Outcomes in DEL and DHL after R-CHOP

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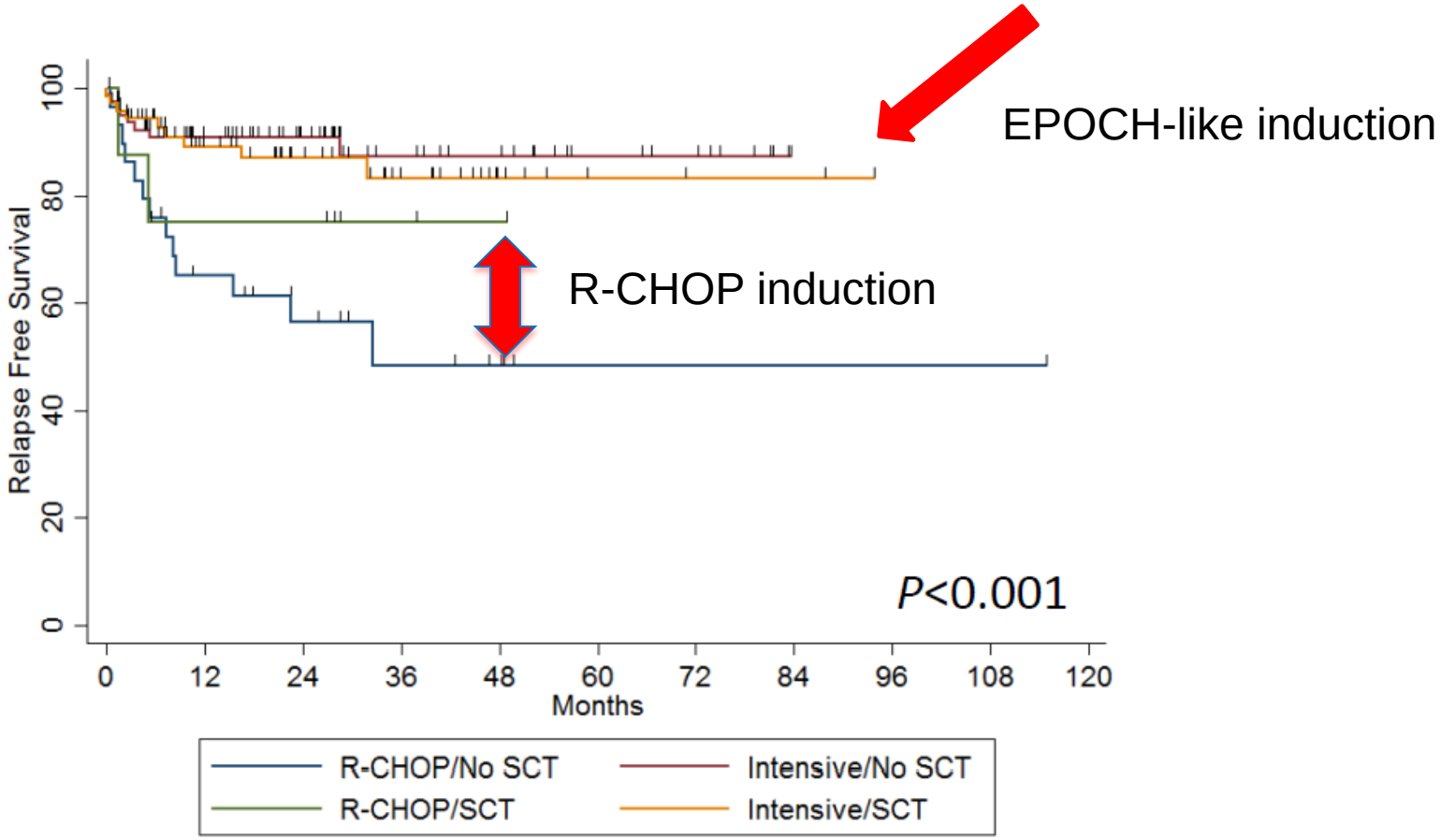
Johnson N. JCO. 2012;30:3452-9

# DHL & Upfront Autologous HCT

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Landsburg D. ASH abs. 2016

# DLBCL & HCT: Areas of Controversy

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# REFINE Study – Ultra High-risk DLBCL

| | HR (95% C.I.) | P-value |
|---|---|---|
| **Early Failure** | | |
| Early relapse | 1 | |
| Residual disease | 1.33 (0.58-3.04) | 0.49 |
| Primary progressive | 2.46 (1.23-4.88) | 0.01 |
| **NCCN-IPI** | | |
| Low | 1 | |
| Intermediate-low | 1.41 (0.46-4.28) | 0.54 |
| Inter-high/ High | 3.16 (1.02-9.82) | 0.047 |
| **MYC Rearrangement** | | |
| Absent | 1 | |
| Present | 3.52 (1.60-7.72) | 0.002 |

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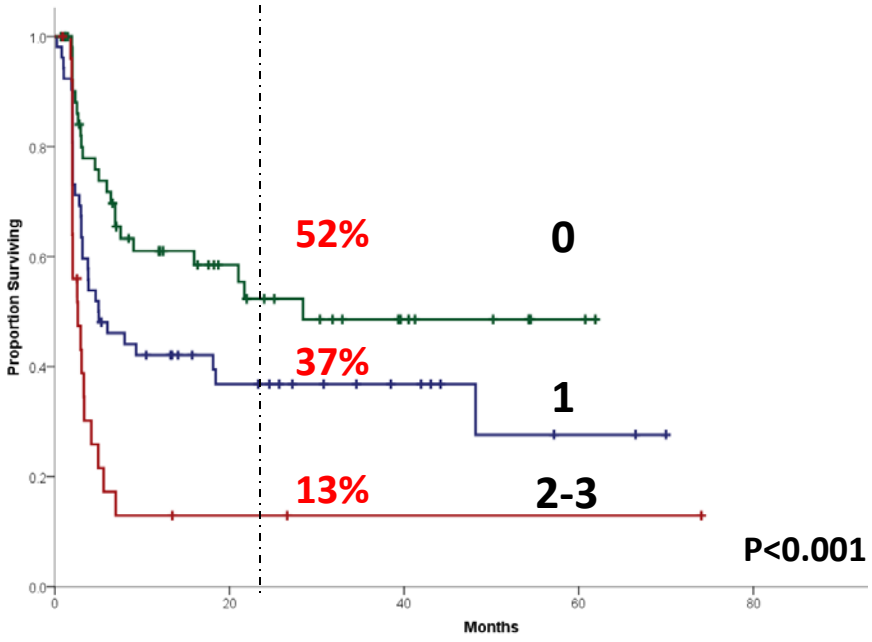
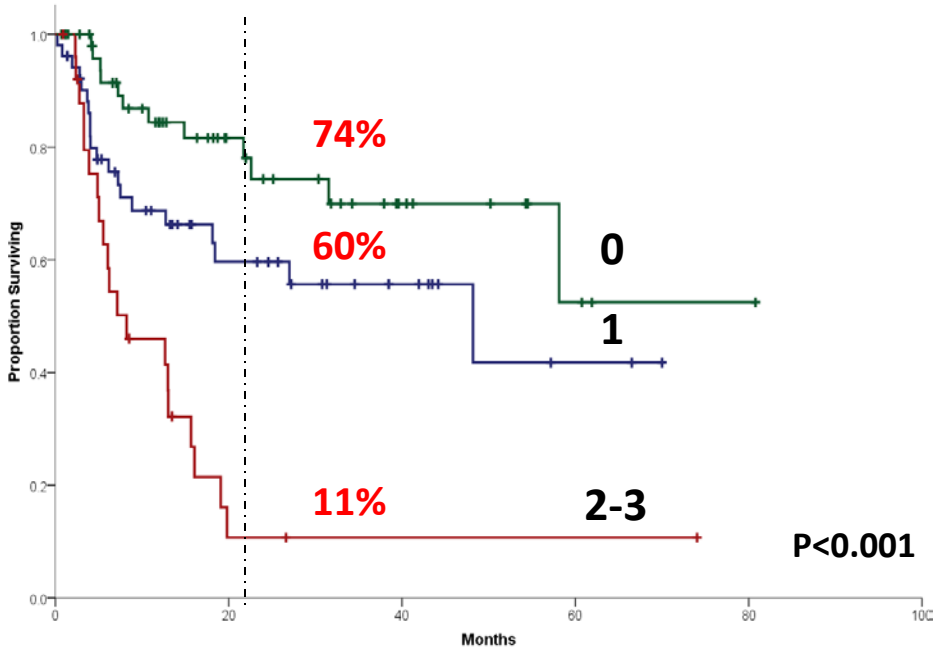
Costa L & Hamadani M. Am J Hematol. 2016 Epub.

# REFINE Study – UHR Survival

## Progression-free Survival




## Overall Survival

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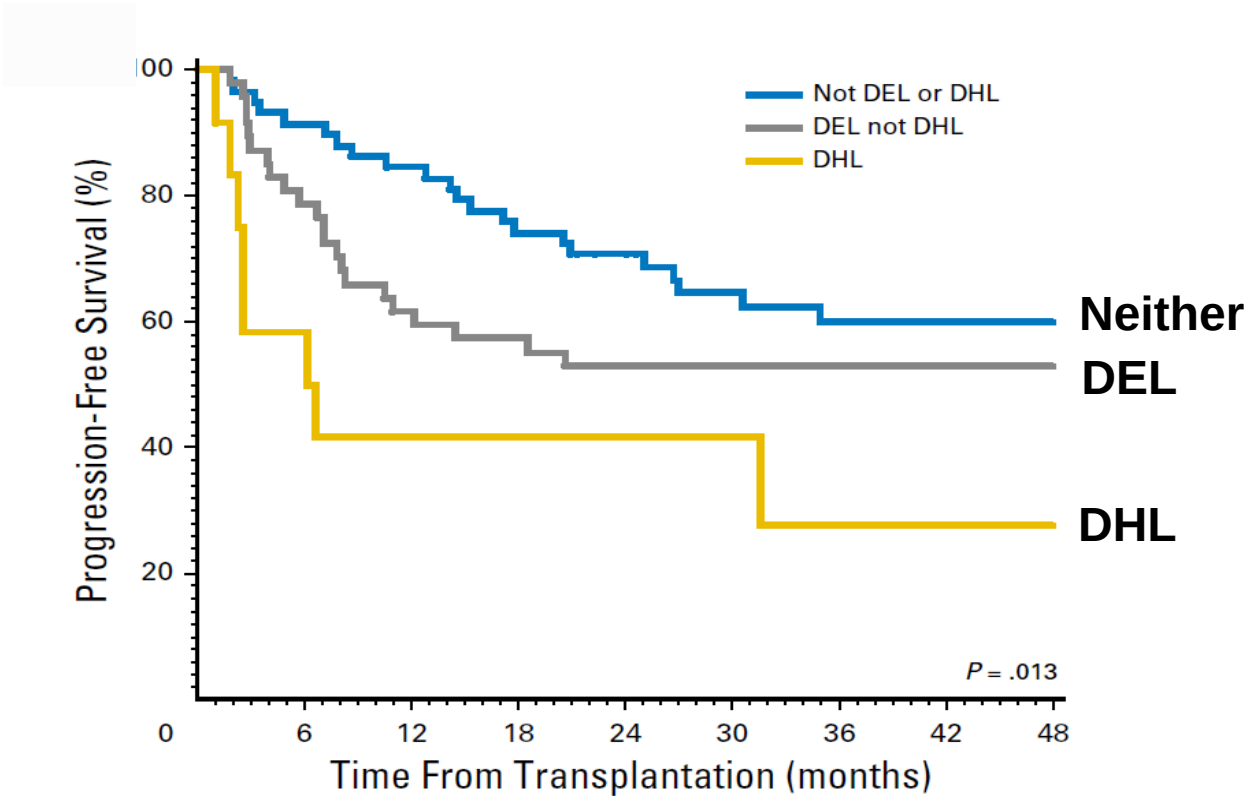
# Auto-HCT in Relapsed DEL and DHL DLBCL

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Herrera A. JCO. 2017;35:24-31.

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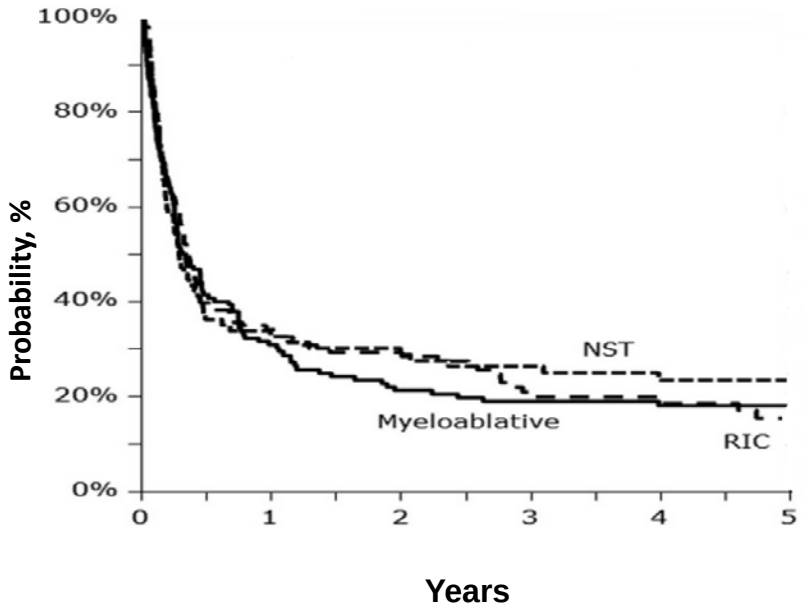
# Allogeneic HCT for DLBCL

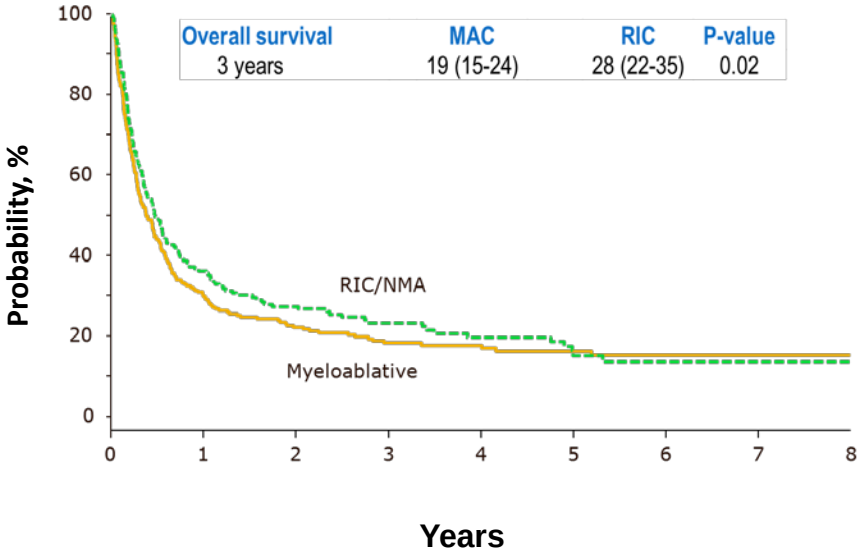
## CIBMTR DATA

### Chemosensitive DLBCL




Bacher U. Blood. 2012;120:4256-62.

### Chemorefractory DLBCL




Hamadani M. BBMT. 2013:746-53.

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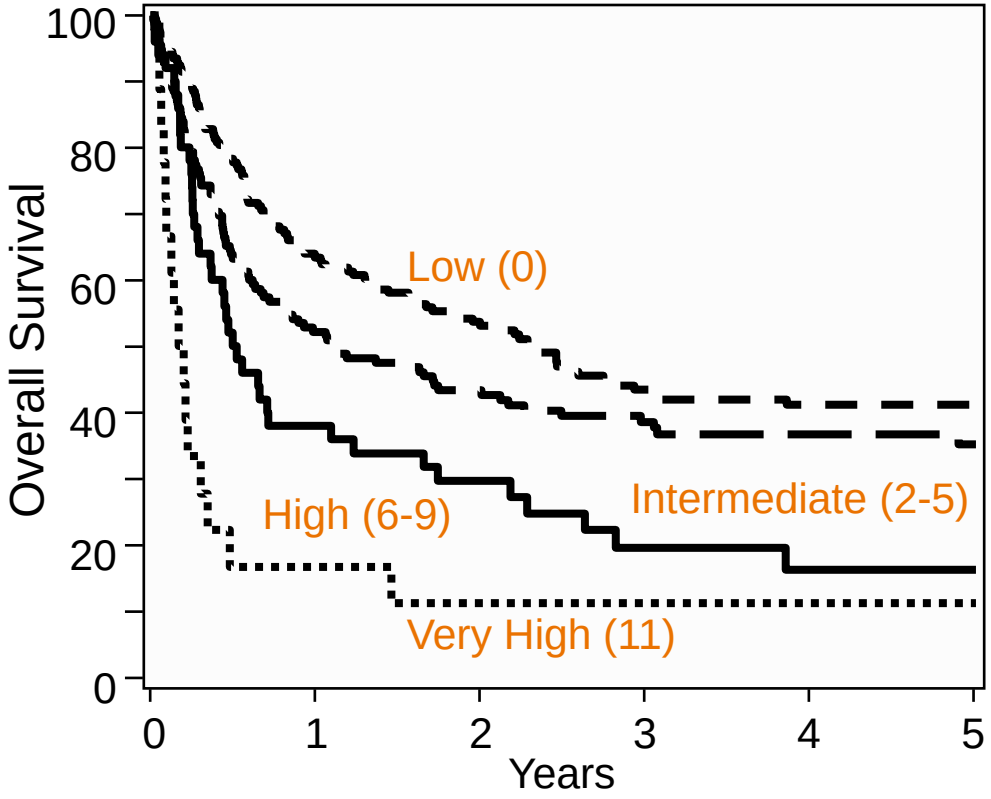
# Allogeneic HCT for DLBCL

## CIBMTR DATA




**Prognostic Factors:**

| | |
|---|---|
| KPS <80 | = 4points |
| Chemoresistant | = 5points |
| auto to alloHCT <1yr | = 2points |

**3-year OS:**

| | |
|---|---|
| Low | = 43% |
| Intermediate | = 39% |
| High | = 19% |
| Very High | = 11% |

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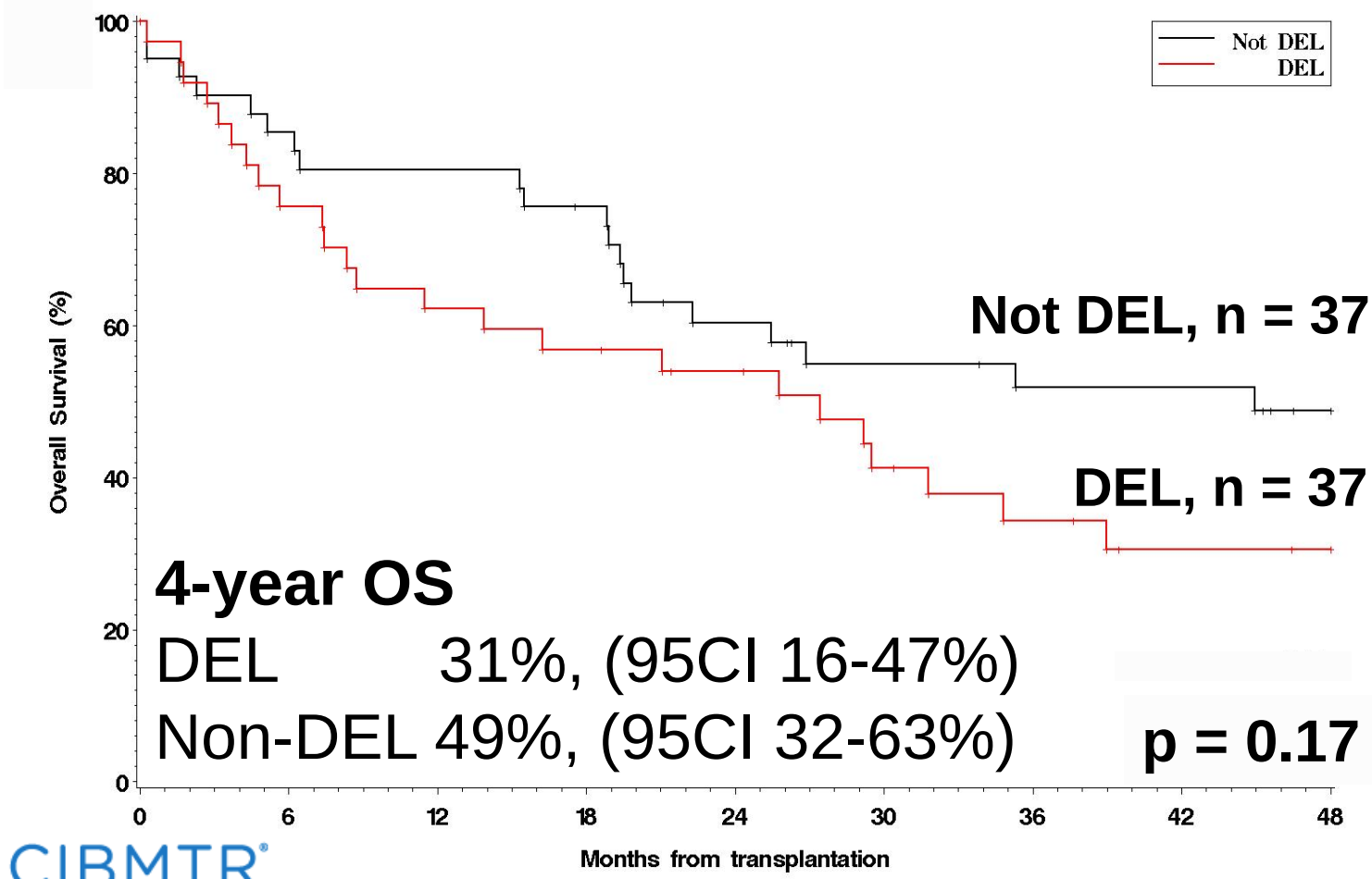
Fenske T & Hamadani M. BJH. 2016;174:235-48.

# Allogeneic HCT in Relapsed DEL DLBCL

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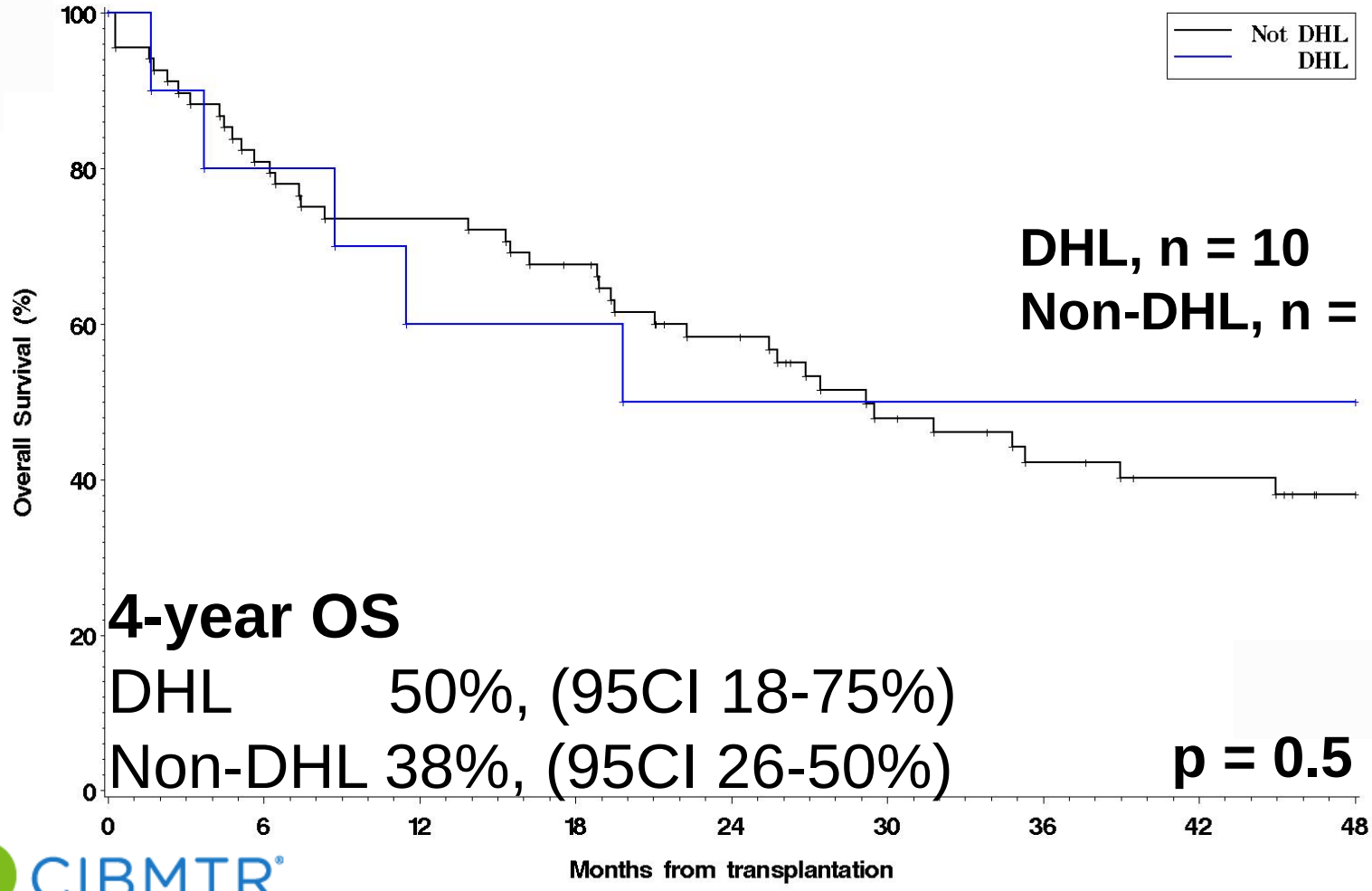
Herrera A. ASH abs: 2016.

# Allogeneic HCT in Relapsed DHL DLBCL




**DHL, n = 10**
**Non-DHL, n = 68**

**4-year OS**

DHL 50%, (95CI 18-75%)

Non-DHL 38%, (95CI 26-50%)

**p = 0.5**

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Herrera A. ASH abs: 2016.

# DLBCL & HCT: Areas of Controversy

- Prevention of post auto-HCT relapse
- Upfront HCT for clinically high-risk DLBCL
- Upfront auto for genomic high-risk DLBCL
- Identifying ultra high-risk DLBCL
- Is there still a role for allogeneic HCT?

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# Presentation Outline

- HCT utilization trends in hematological malignancies
- Current state of HCT in:
  - Diffuse Large B-cell Lymphoma
  - Follicular Lymphoma

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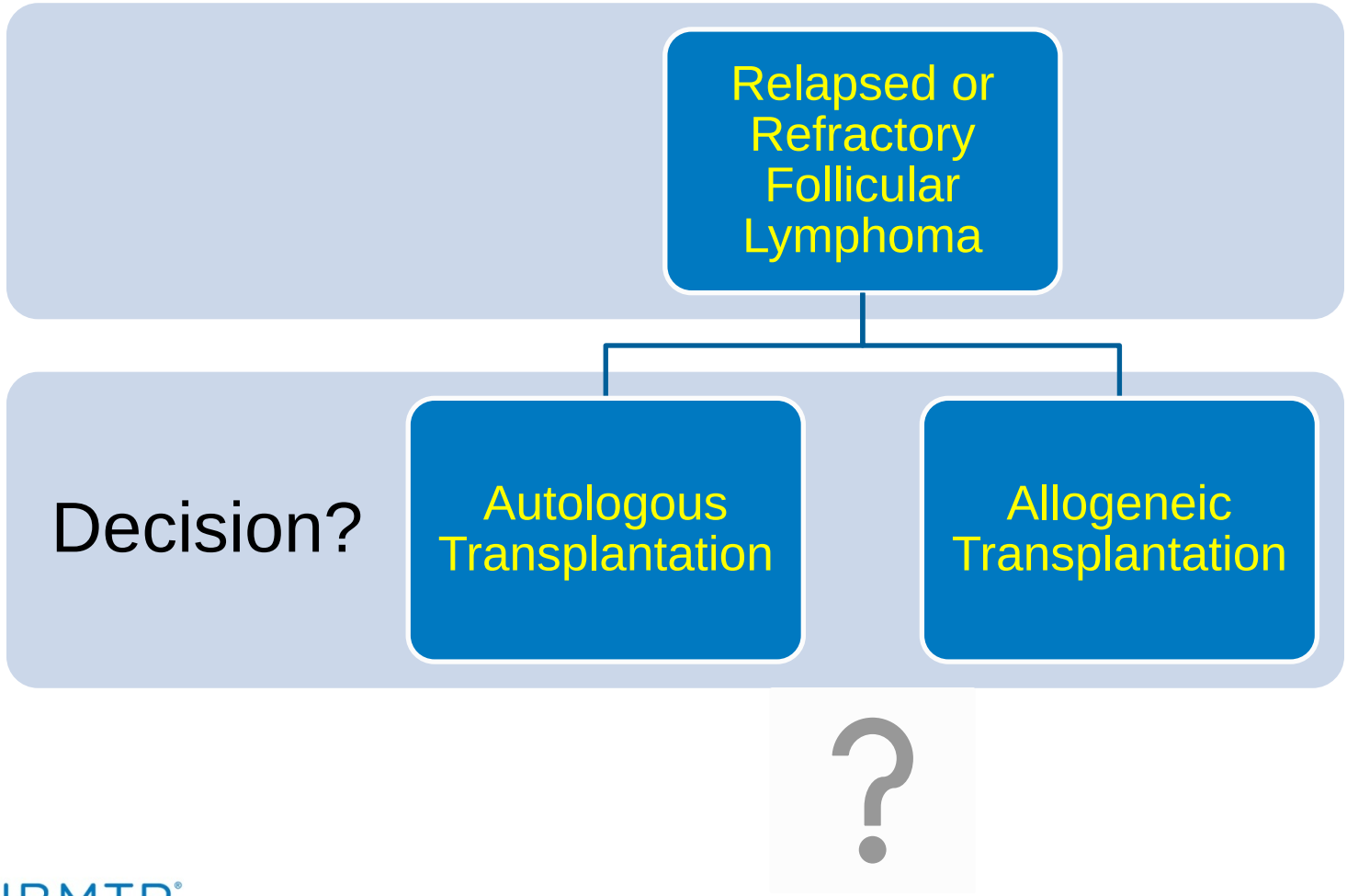
# HCT for Relapsed Follicular Lymphoma?

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# Auto-HCT for Relapsed FL – CUP Trial

Relapsed FL
Age < 66yrs
(N=140)

↓

Chemotherapy

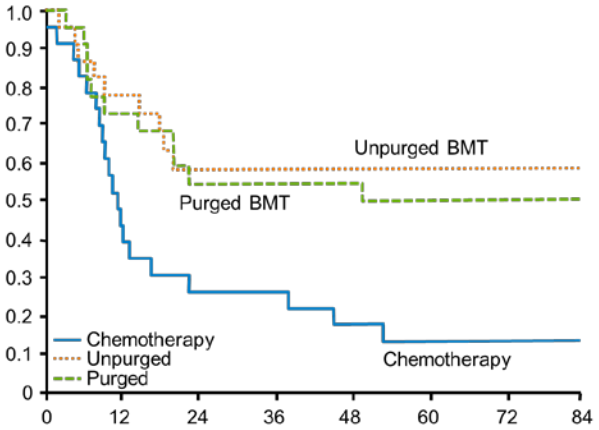
↓

CR or PR?

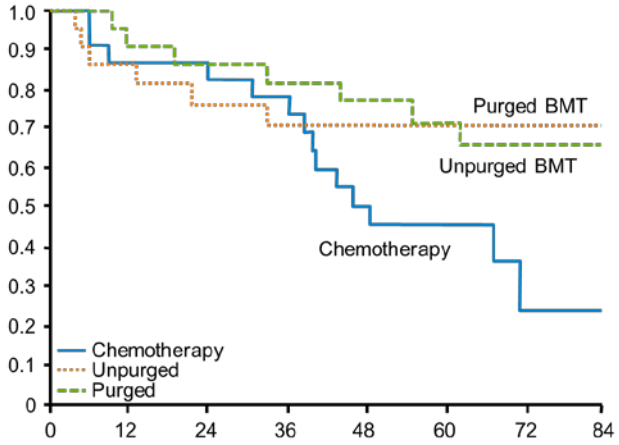
→ RANDOMIZATION

- Chemotherapy (n=24)
- Purged-Auto (n=32)
- Unpurged-Auto (n=33)

## Progression-free Survival




## Overall Survival

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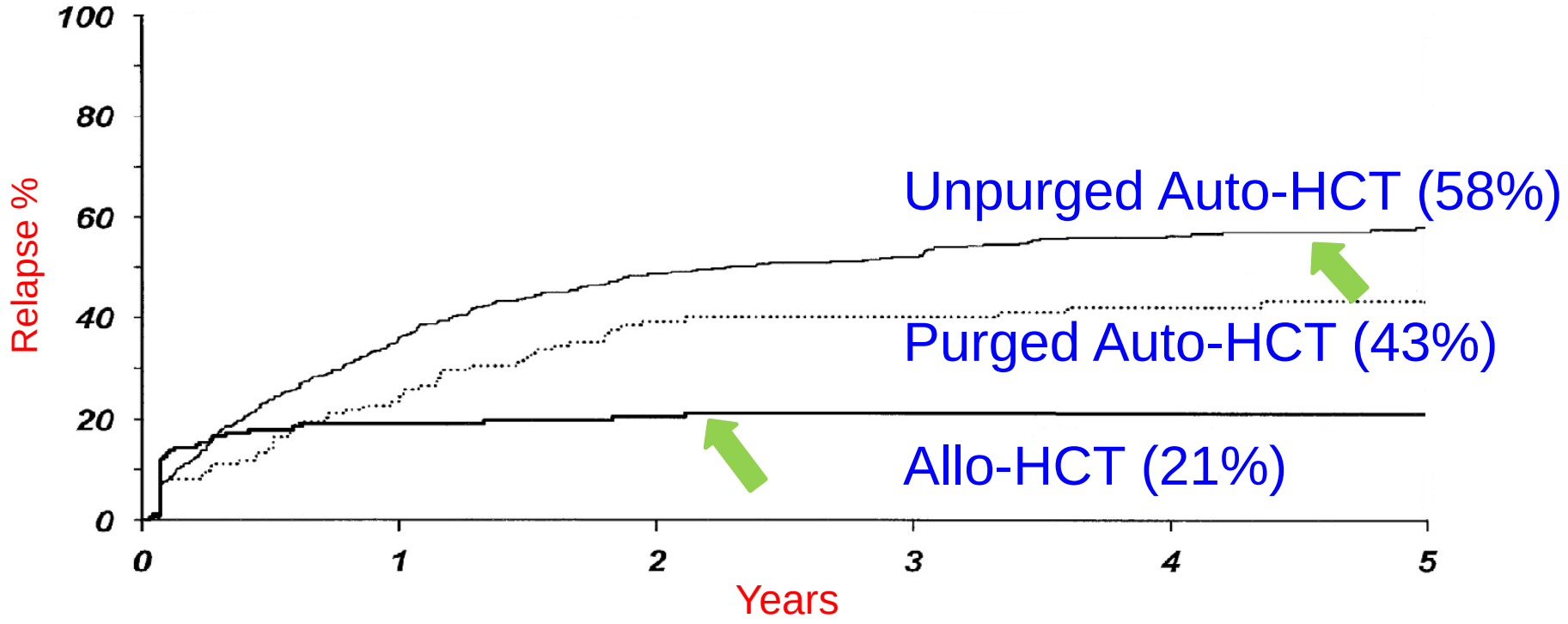
Schouten. JCO. 2003;21:3918-27.

# Is Autologous HCT Curative for Relapsed FL?

## CIBMTR DATA

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van Besien K. Blood. 2003;102:3521-9.

# Is Autologous HCT Curative for Relapsed FL?

| Author | N | OS | Second Cancers |
|---|---|---|---|
| Rohatiner (2007) | 121 | 54% (10 years) | - 12.4% sMDS/AML |
| Montoto (2007) | 693 | 52% (10 years) | - 9% sCA |
| Sebban (2008) | GELF-86 GELF-94 254 | +R/-T = 70% +R/+T = 93% (5 years) | - Not reported |

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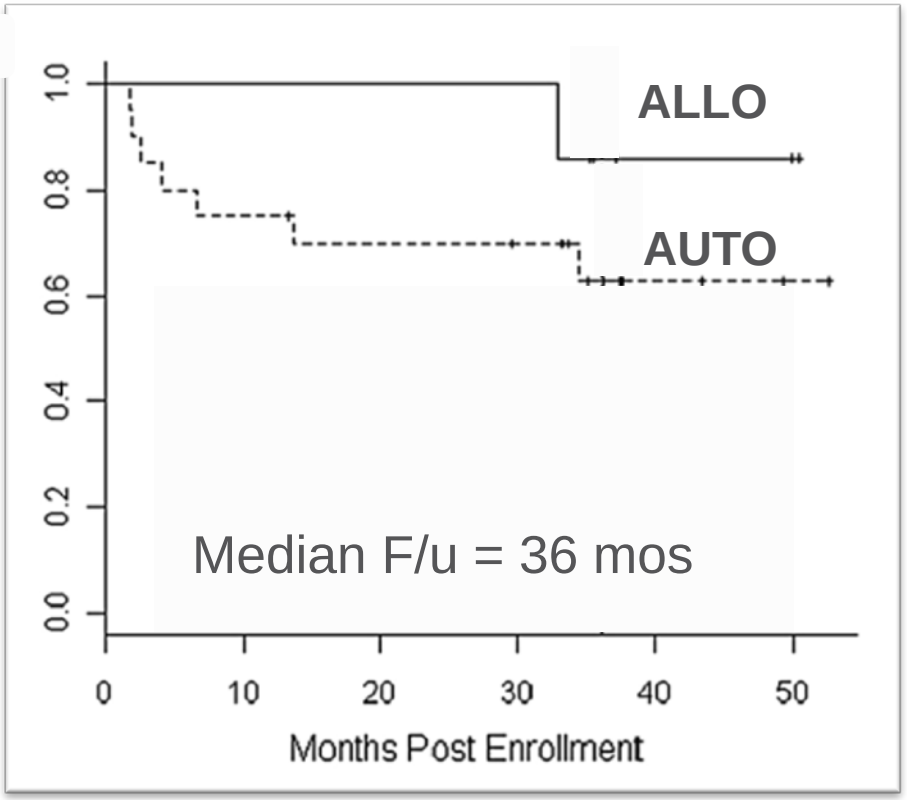
# CTN #0202: AutoHCT vs RIC AlloHCT for Relapsed Follicular NHL

- **Biologic assignment with matched sib donor**
- **Randomized: autoHCT vs RIC alloHCT**
- **N = 250 (projected)**

- **N = 30 (2004-2006)**
- **Closed early due to poor accrual**
  - 22 autoHCT
  - 8 alloHCT

**PFS**

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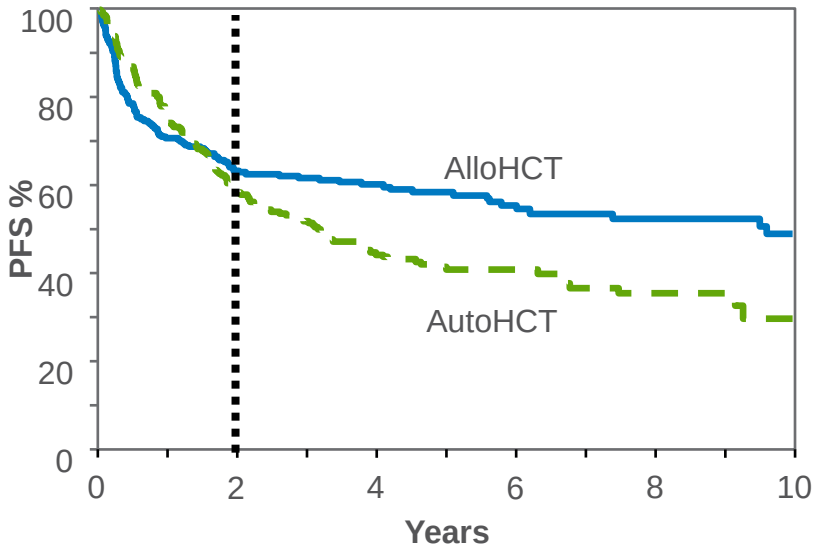
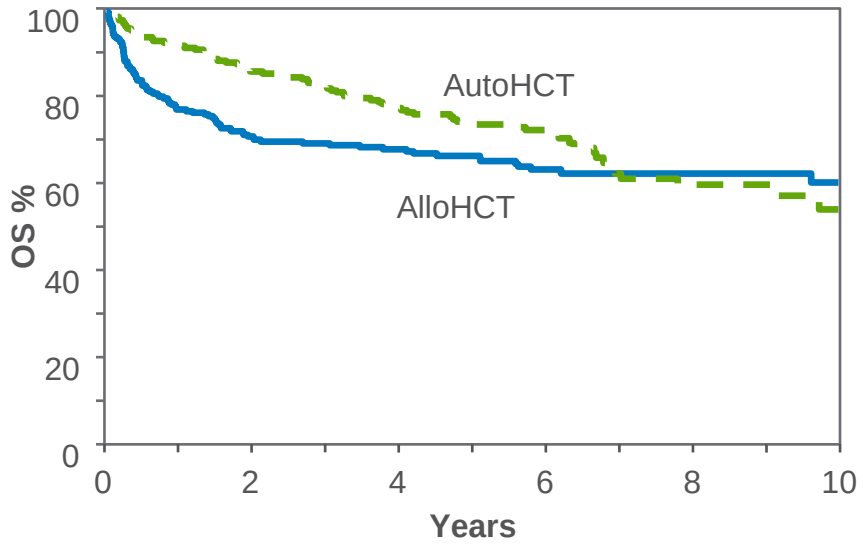
Slide Courtesy: Ginna Laport, MD

# Auto vs. Allo for FL: CIBMTR Data




| | N | 5-yr PFS | 5-yr OS |
|---|---|---|---|
| AutoHCT | 249 | 41% | 74% |
| AlloHCT | 267 | 58% | 66% |

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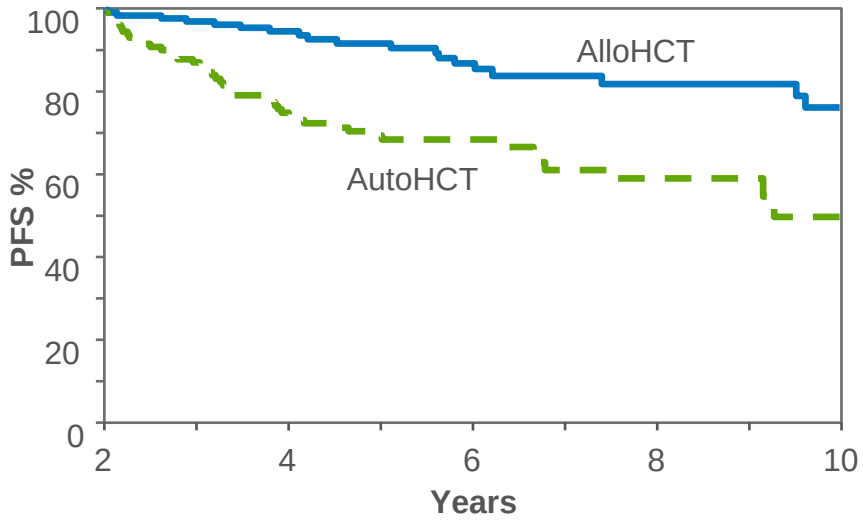
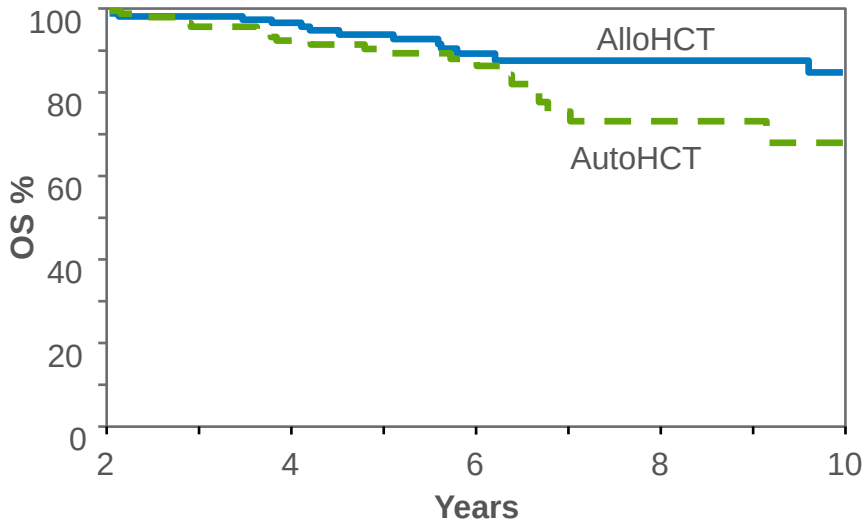
Klyuchnikov & Hamadani. BBMT. 2015;21:2091-9.

# Auto vs. Allo for FL: CIBMTR Data
# Long-term survivors




| Landmark | N | 5-yr PFS | 5-yr OS |
|---|---|---|---|
| AutoHCT | 138 | 68% | 91% |
| AlloHCT | 138 | 92% | 94% |

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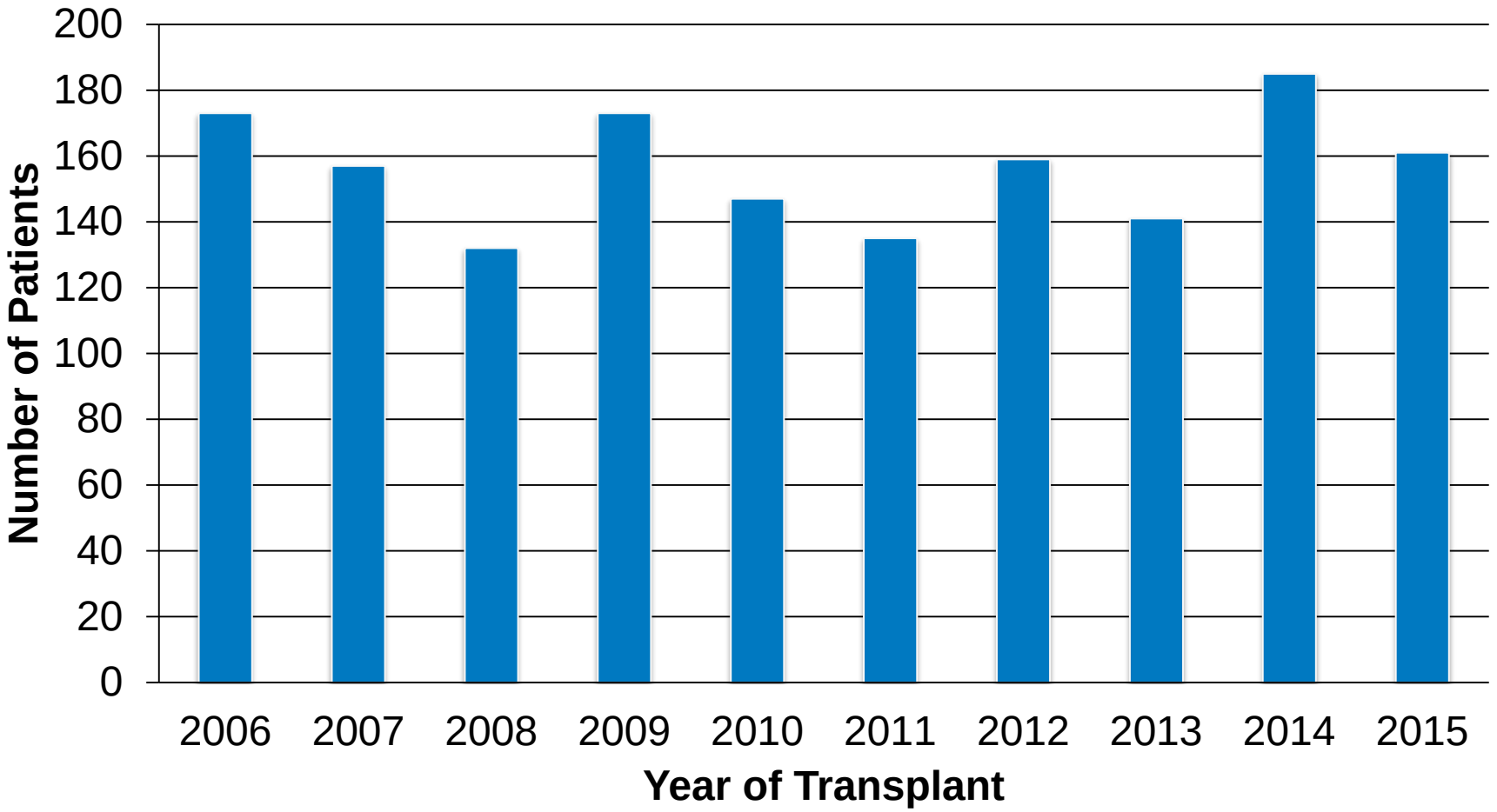
Klyuchnikov & Hamadani. BBMT. 2015;21:2091-9.

# Autologous HCT for Follicular Lymphoma Between 2006-2015

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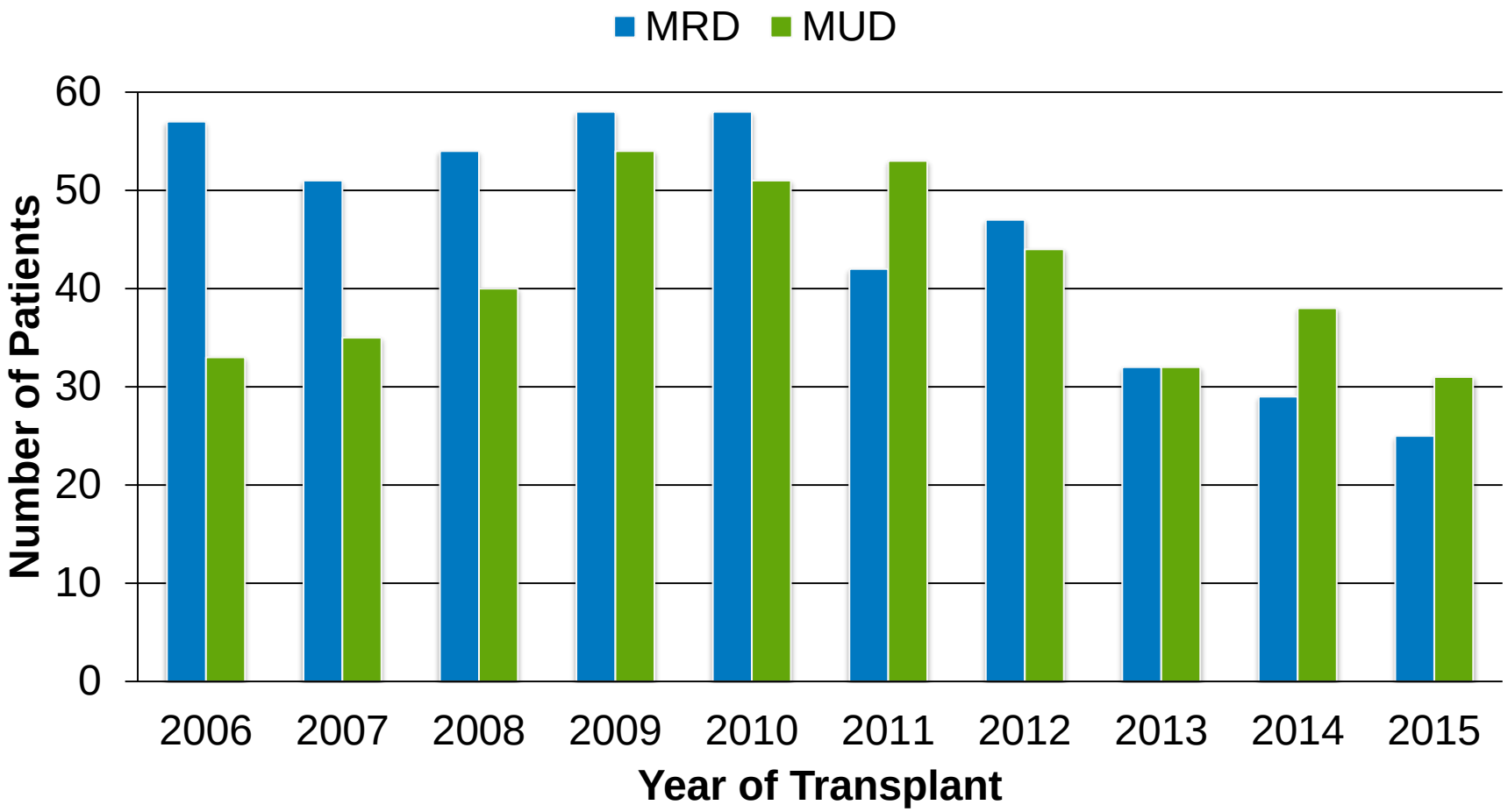
# Allogeneic HCT for Follicular Lymphoma Between 2006-2015

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# Autologous HCT Underutilized in U.S.A

- No more than 1-1.5% of follicular lymphoma patients in USA undergo autologous HCT
- An auto vs. allo (or non HCT therapy) trial is unlikely to be performed now
- Re-defining FL patients likely to benefit from HCT is an unmet need

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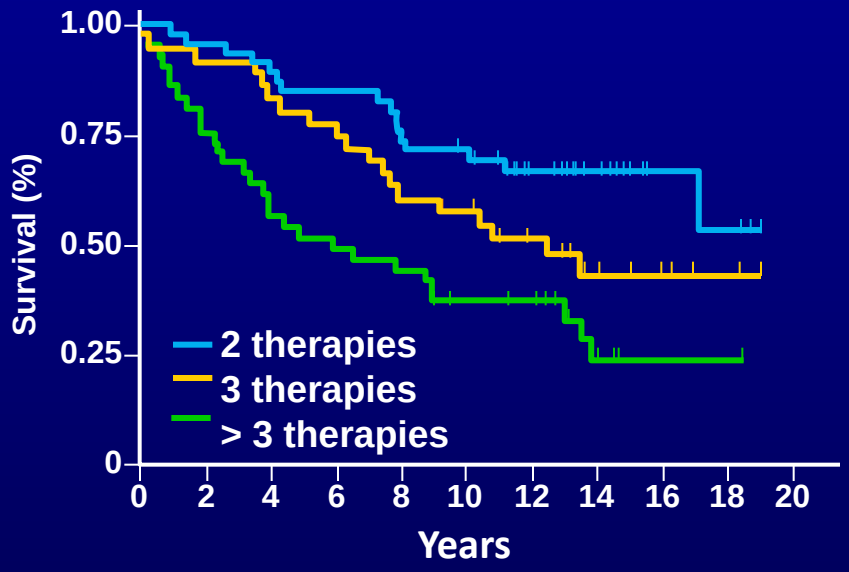
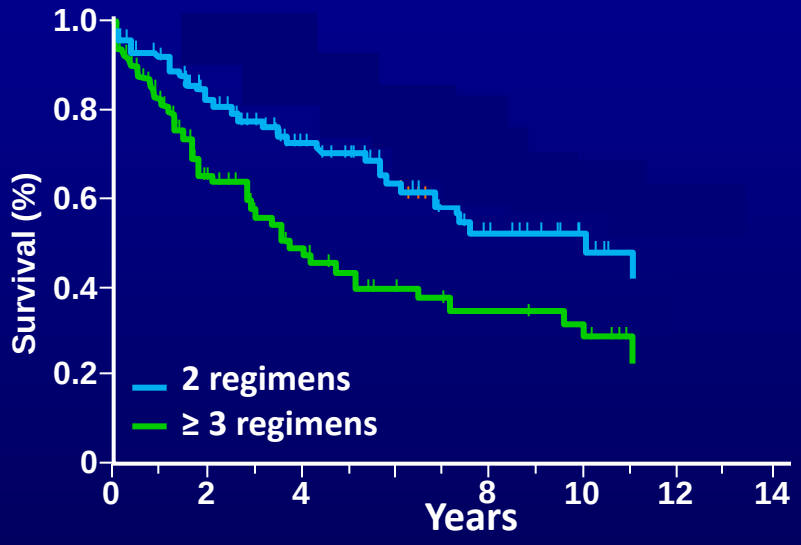
# Number of Prior Regimens often used to judge suitability ofr AutoHCT in FL




N = 121; Median F/U = 13yrs

Rohatiner et al, JCO 2007;25:2554.

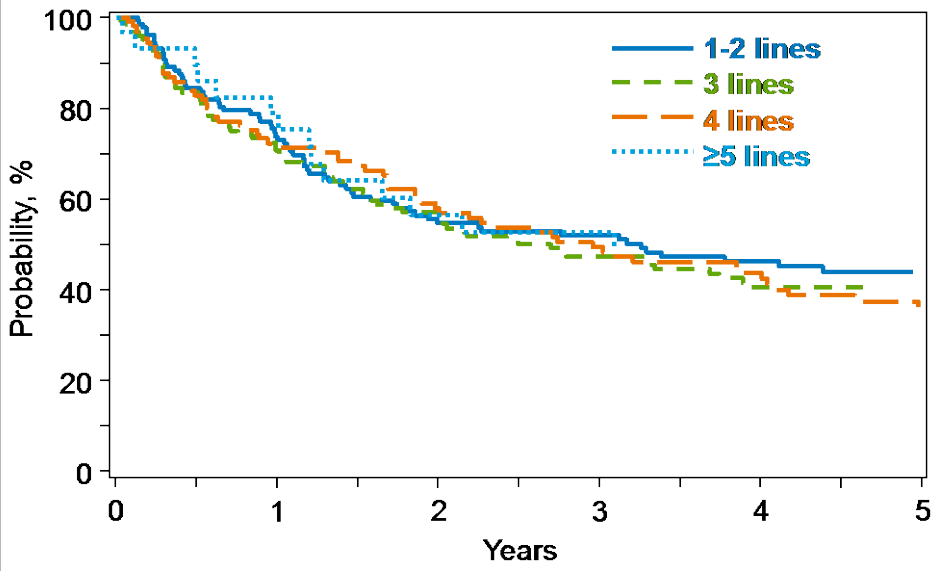



N = 248; Median F/U = 6yrs

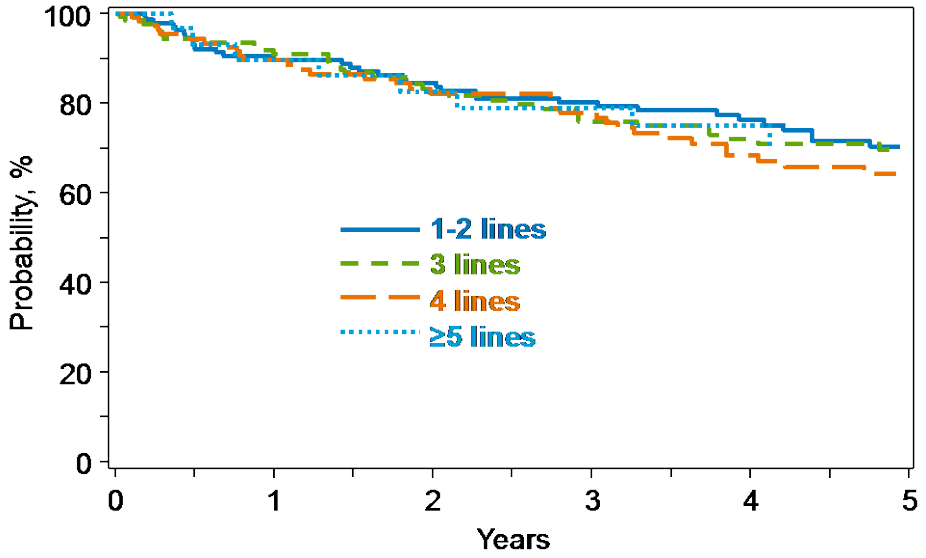
Vose et al, BBMT 2008;14:36.

# Does Number of Prior Therapy Paradigm Hold true in Rituximab Era?

**Progression-free Survival**




**Overall Survival**

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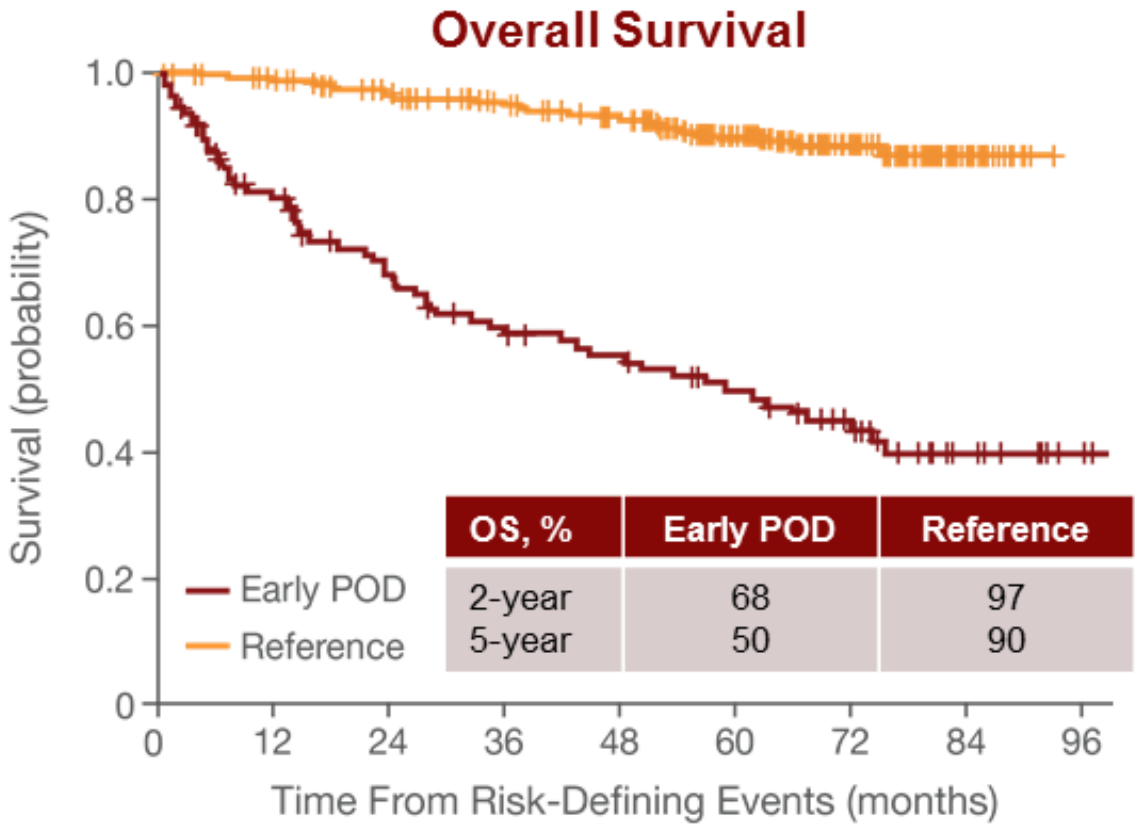
CIBMTR LY13-03 unpublished data

# Early failure of R-chemo identifies an Ultra high-risk subset of FL:

**National LymphoCare Study**

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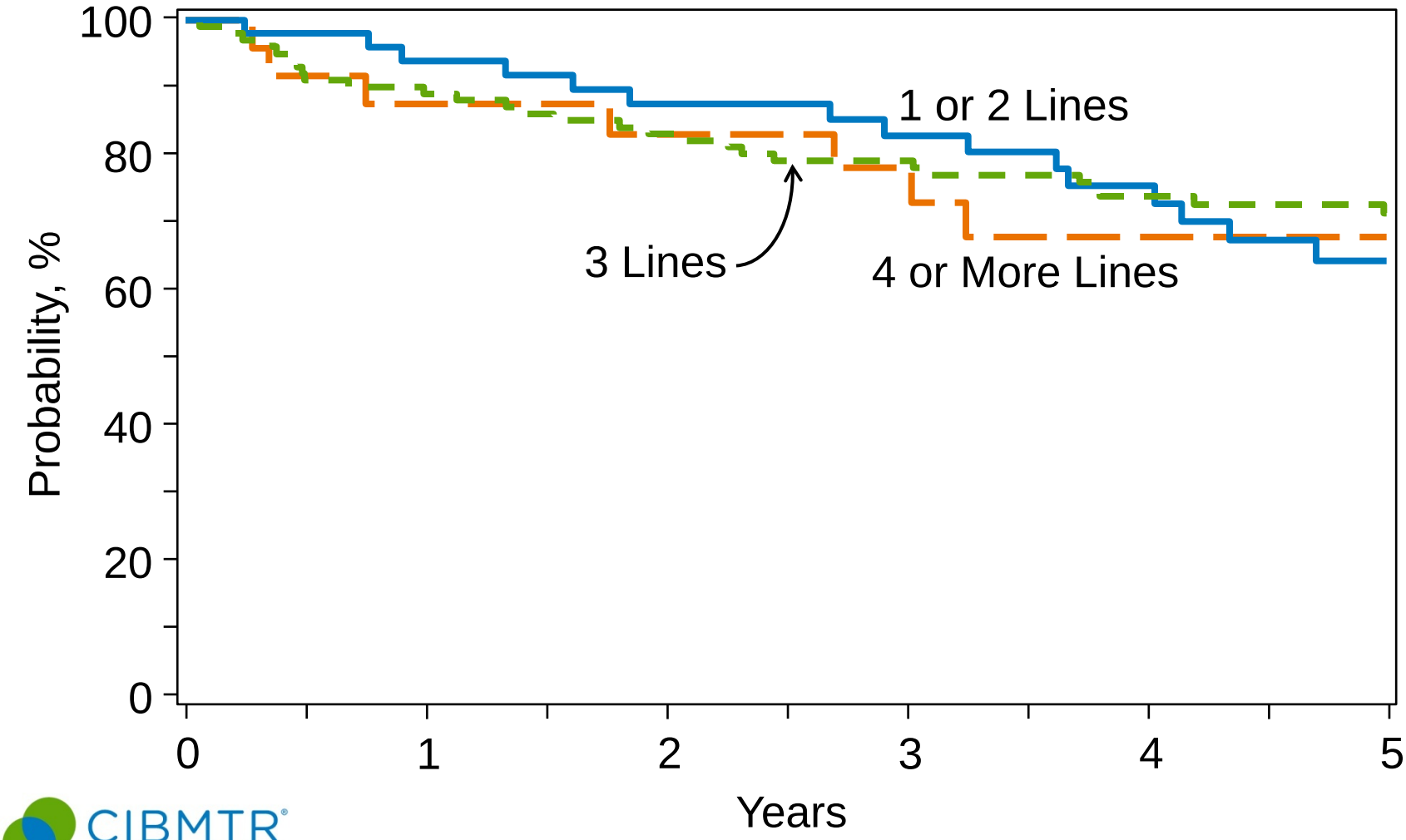
Casulo C. JCO. 2015;33:2516-22.

# Should autologous HCT be considered in UHR FL?

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CIBMTR. Unpublished data

# HCT in UHR FL: Key Registry Studies

- NLCS & CIBMTR Collaboration: Auto-HCT vs. no-HCT study. Results will be available 2017 BMT Tandem meetings
- CIBMTR analysis of auto-HCT vs. allo-HCT underway. Results will be available 2017 ASCO meetings

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# Questions for 2017 & Beyond

- Define role of upfront autoHCT in DHL/DEL
- Is autoHCT an option for relapse UHR DLBCL?
- In relapsed DEL/DHL should allogeneic HCT be investigated?
- Auto vs. Allo for NLCS defined UHR FL
- Urgent need for transplant registries to capture molecular risk-data (e.g. DHL/DEL status) and develop tissue bank

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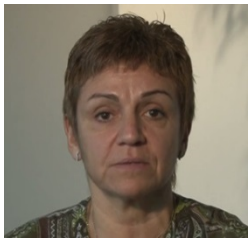
# Acknowledgements

## CIBMTR & LYWC







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Philippe Armand

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# Thank you!

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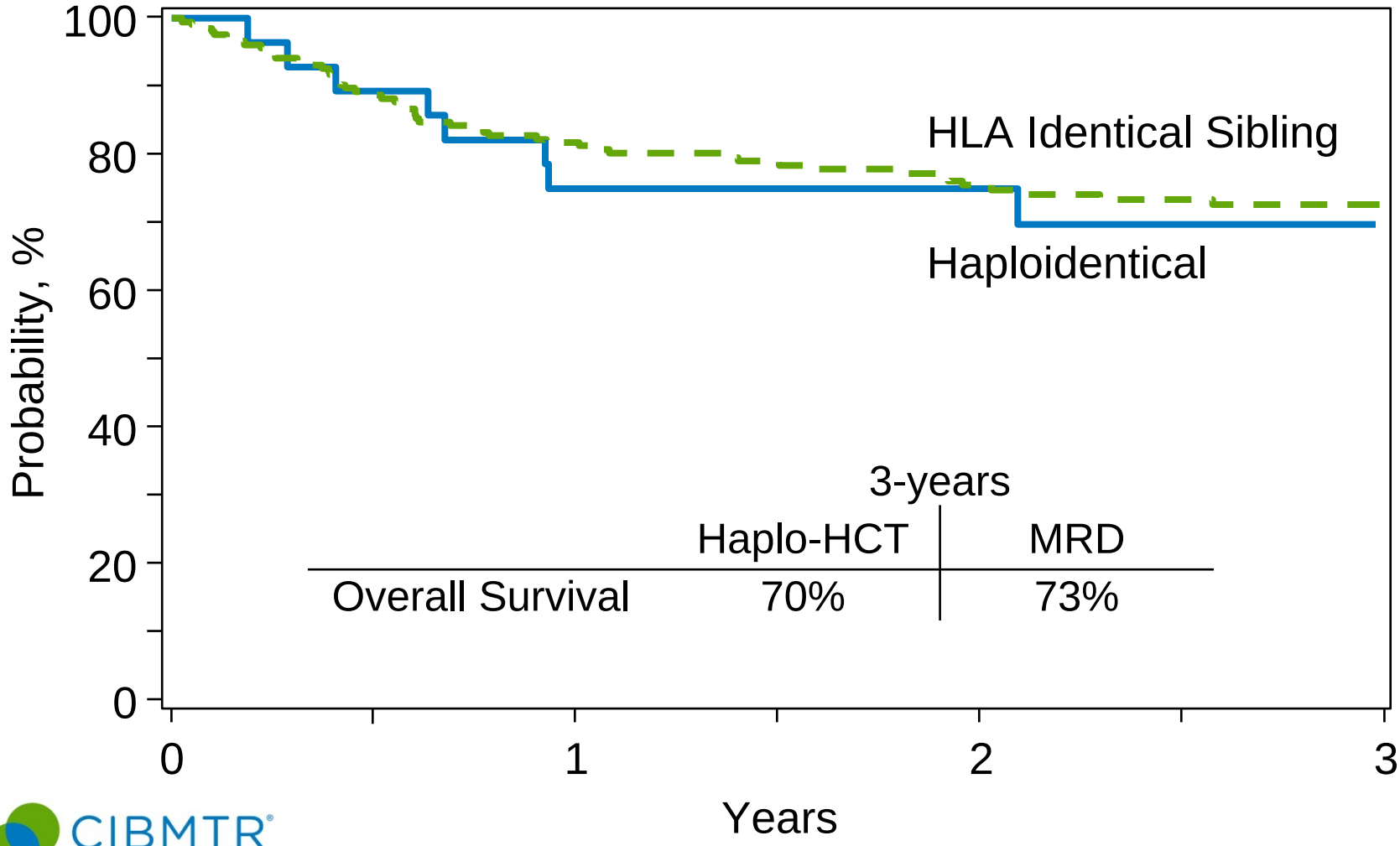
# Overall Survival in Follicular Lymphoma Patients

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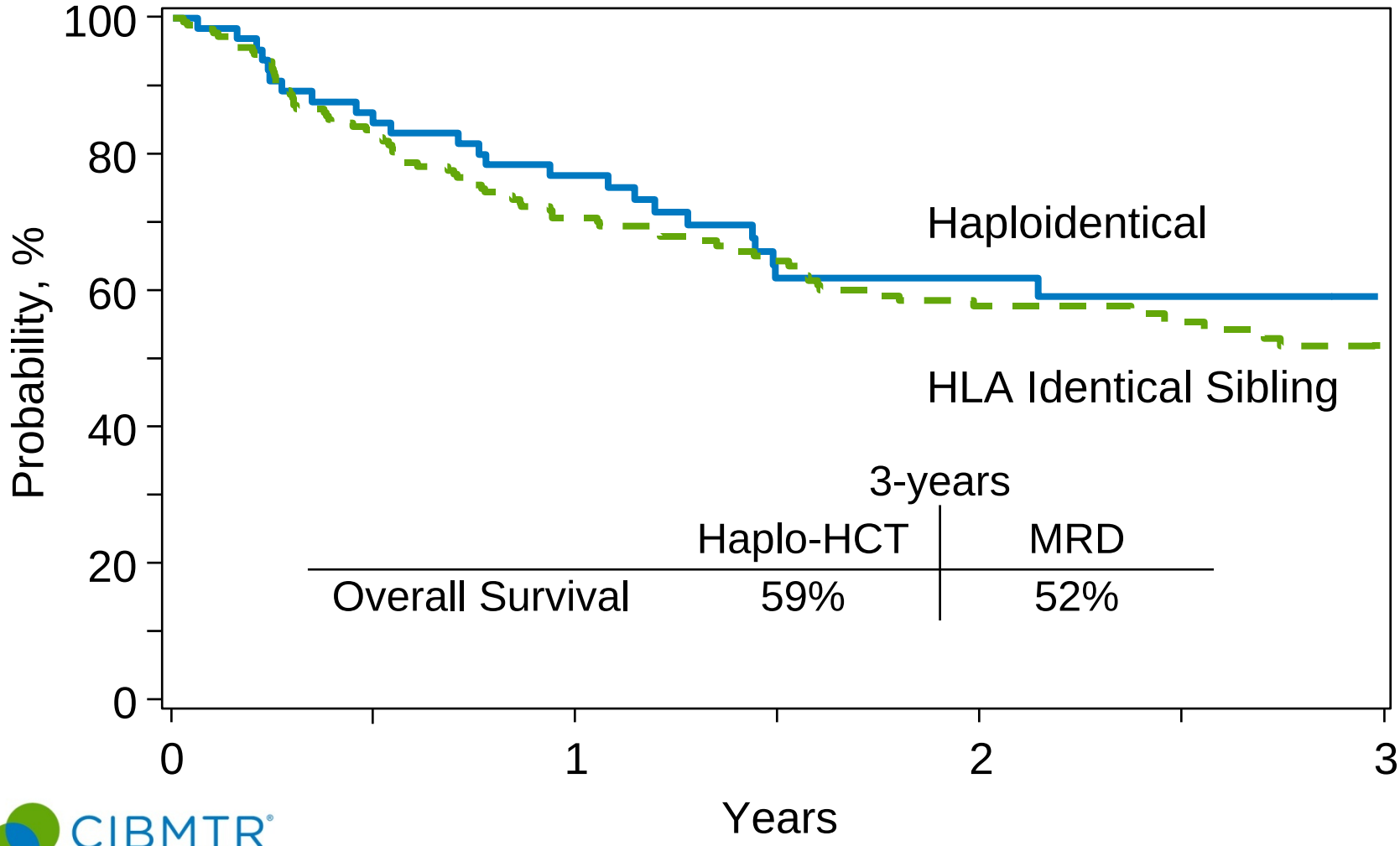
CIBMTR Data

# Overall Survival in DLBCL Patients

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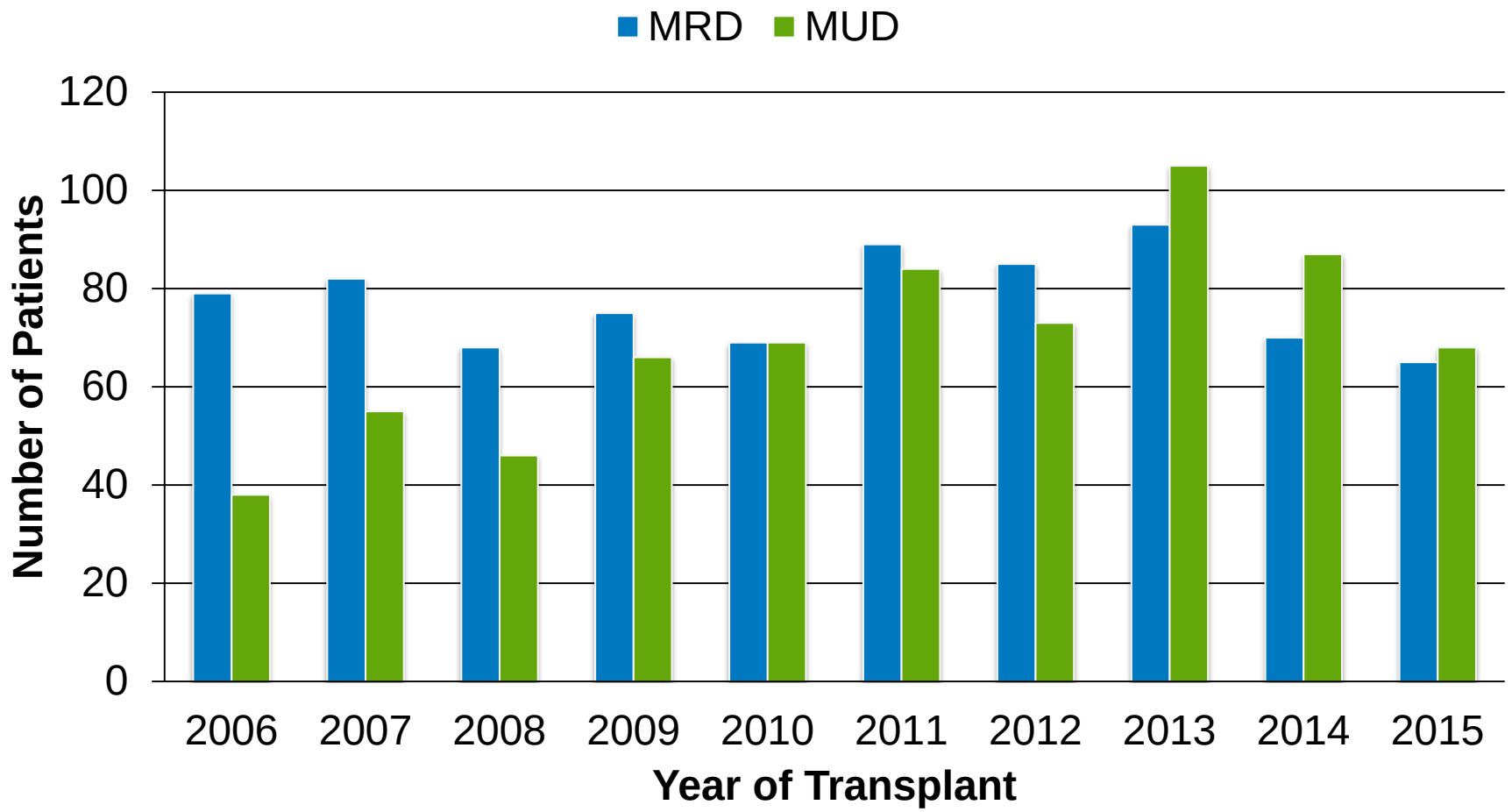
CIBMTR Data

# Allogeneic Transplant for DLBCL Between 2006-2015

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