

# Treatment of diffuse large B cell lymphoma – a historical overview

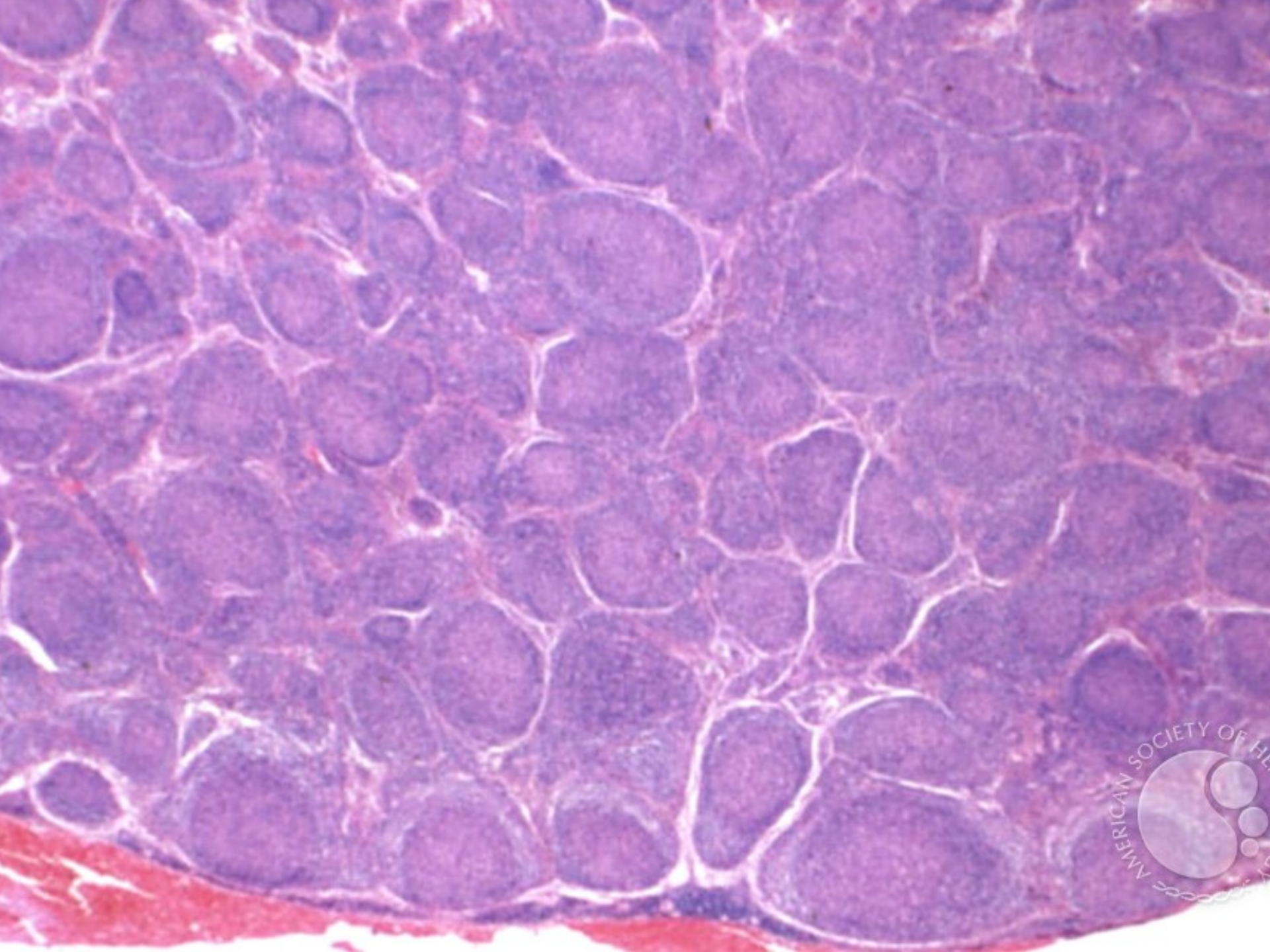
Edus H. Warren

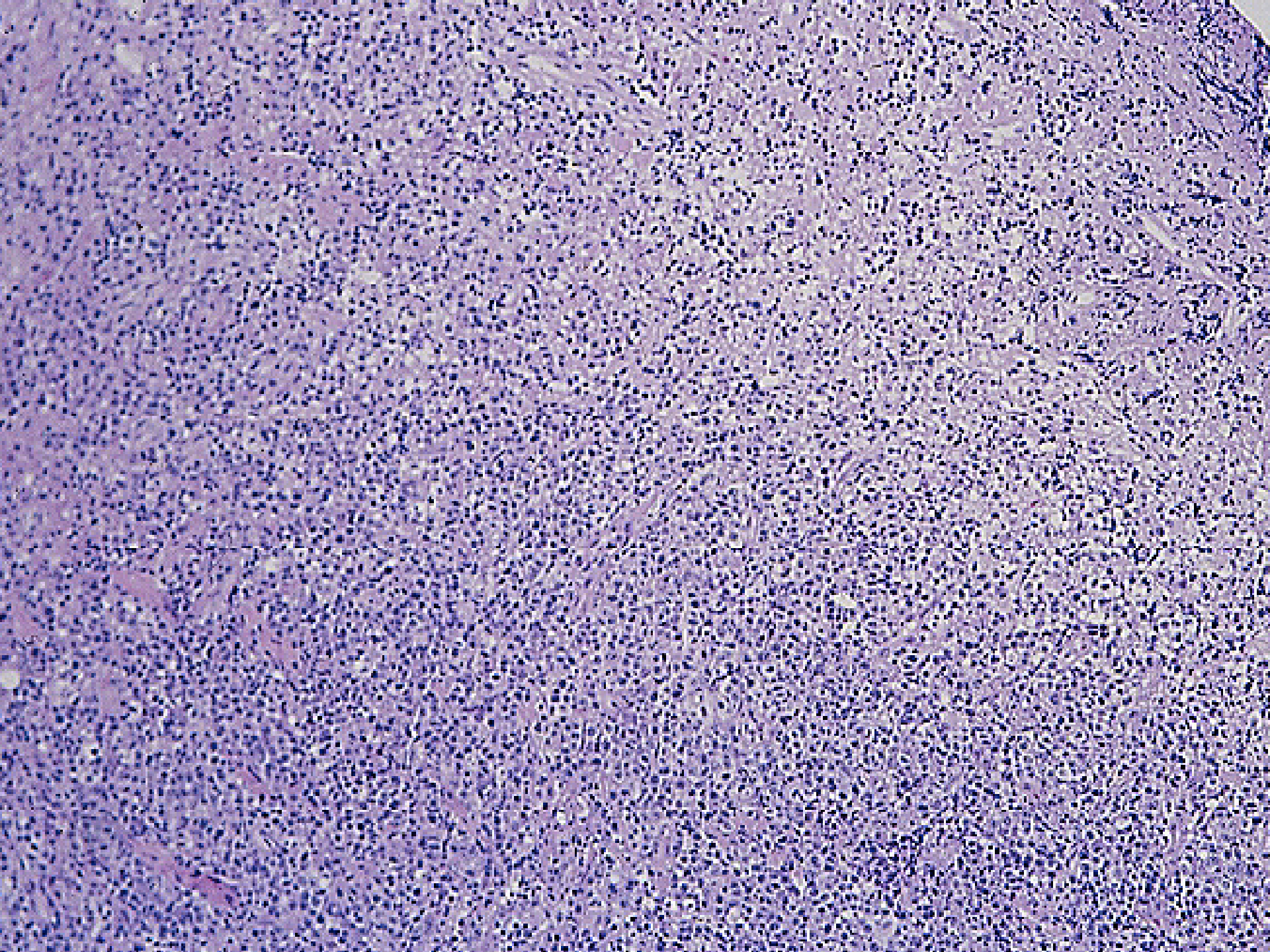
Lymphoma Tumor Board

Friday, March 11, 2016





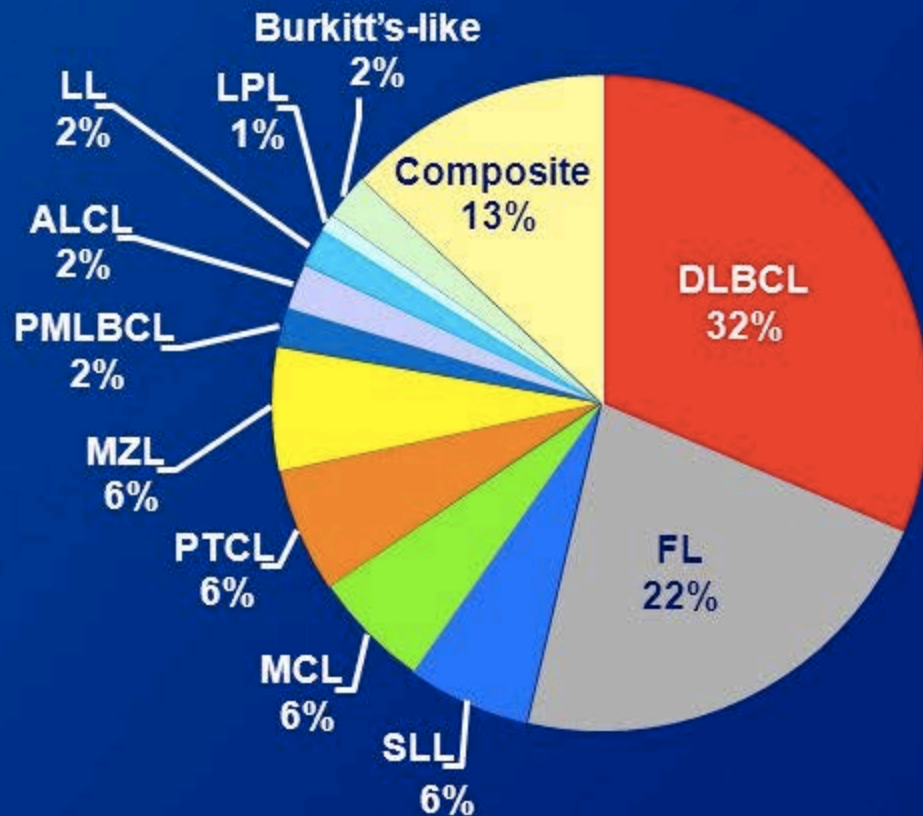






# Relative Incidence of NHL Subtypes

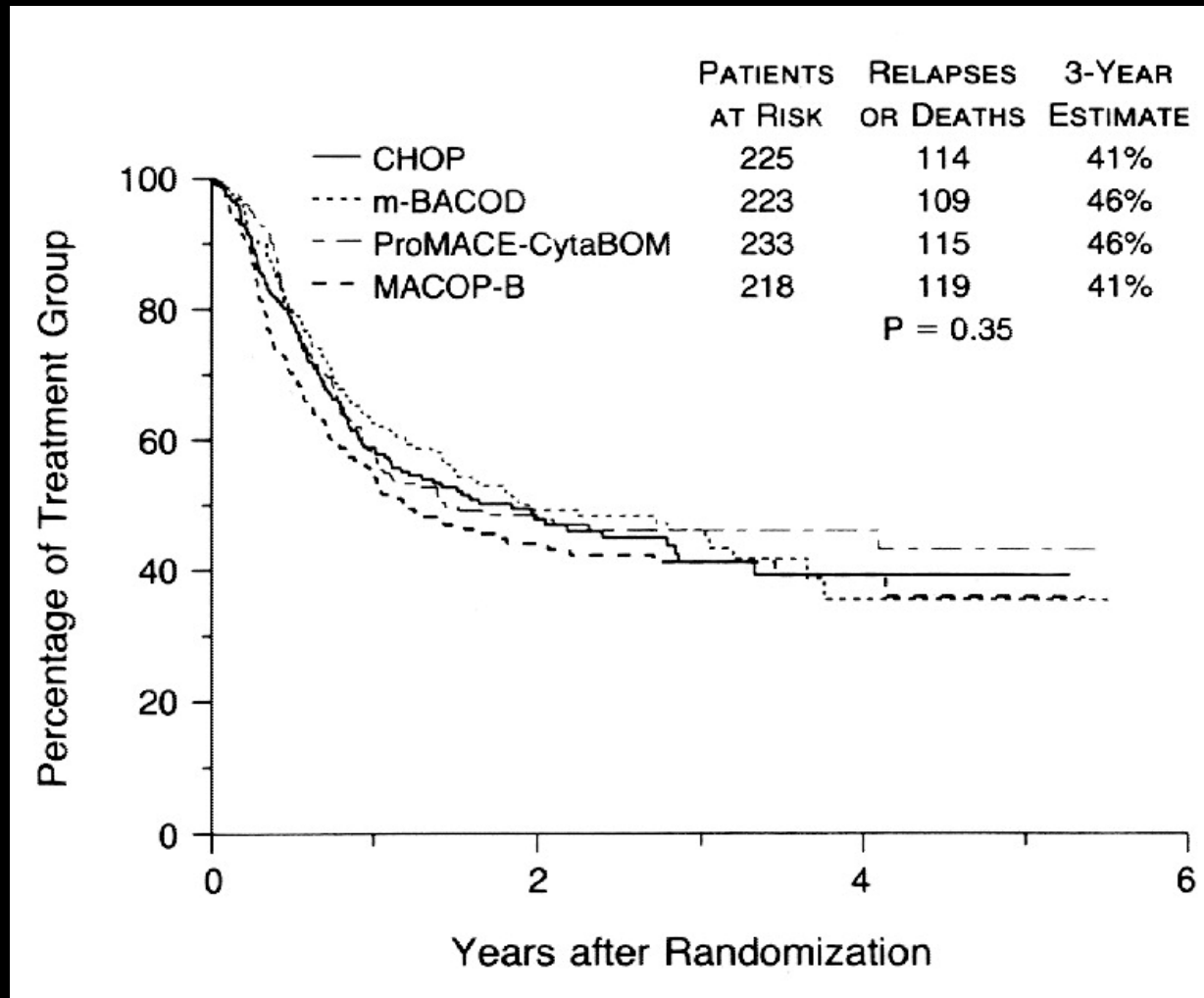
>71,000 new cases in US in 2015



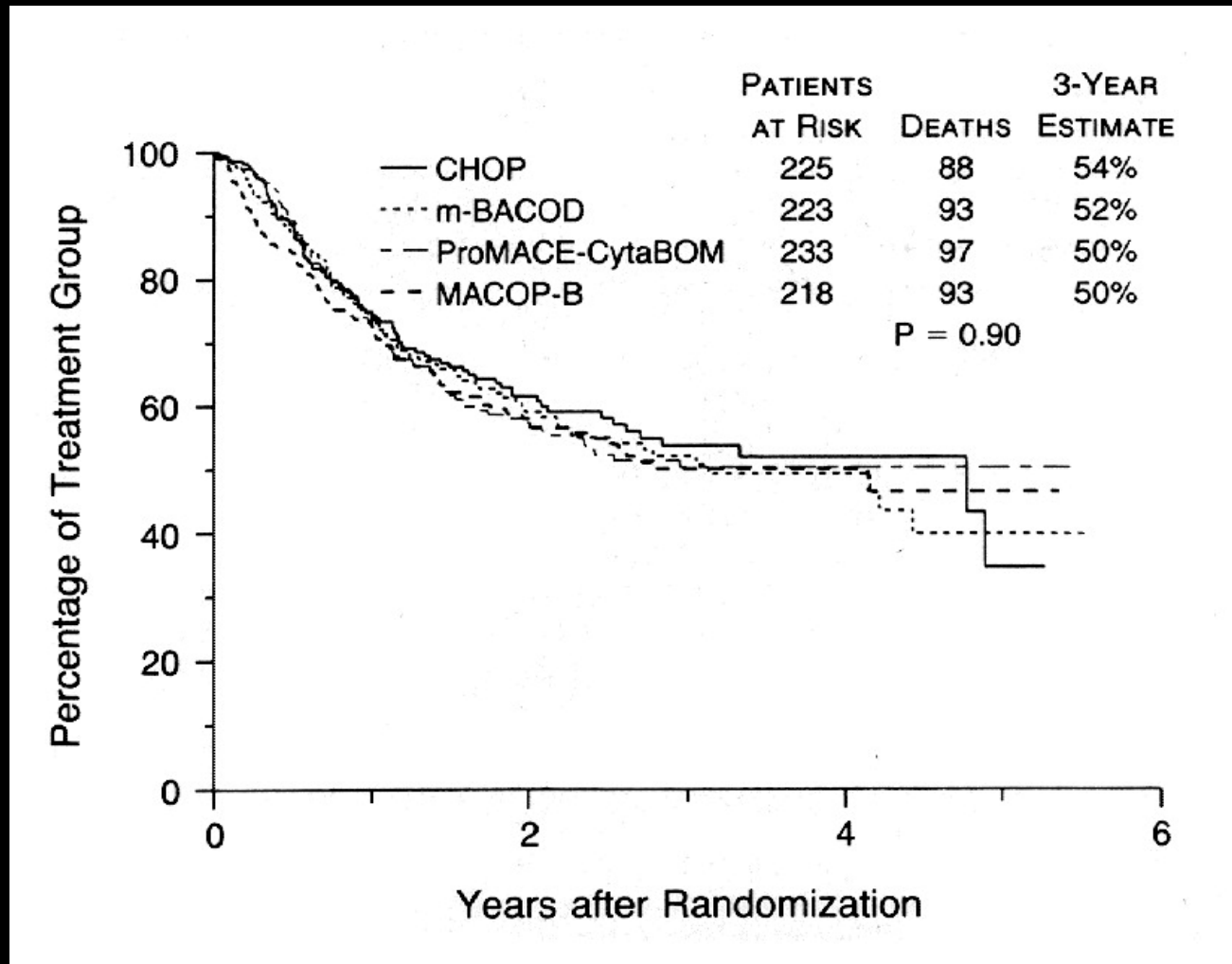
# Outline

- Fisher *et al.* – non-inferiority of CHOP to more complex regimens
- Coiffier *et al.* – superiority of R-CHOP to CHOP
  - Short term results
  - Long term results
- Récher *et al.* – superiority of R-ACVBP to R-CHOP in low-risk DLBCL
- Wilson *et al.* – DA-R-EPOCH for DLBCL
- Dunleavey *et al.* – DA-R-EPOCH for PMLBCL

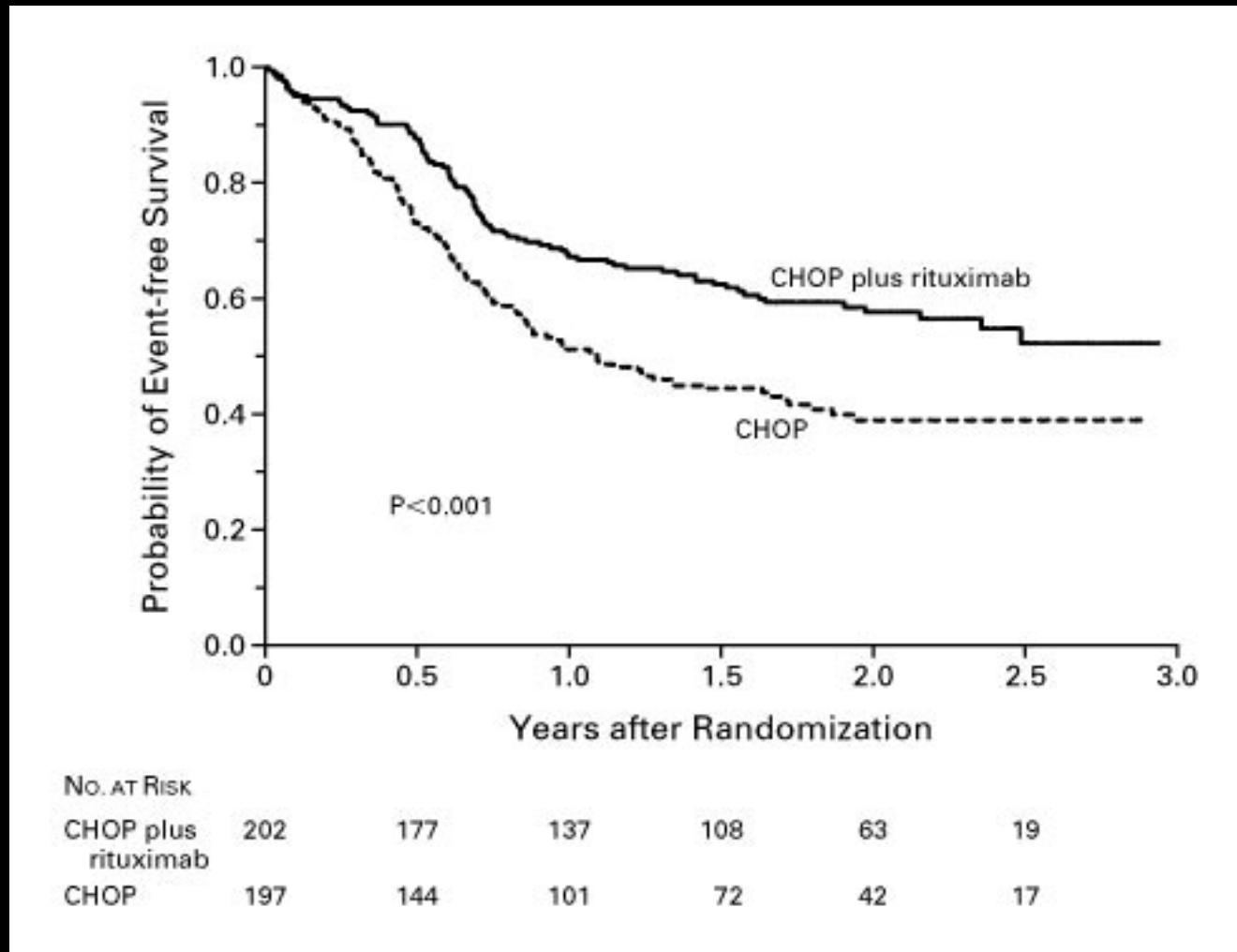
# Time to Treatment Failure in the Treatment Groups



# Overall Survival in the Treatment Groups



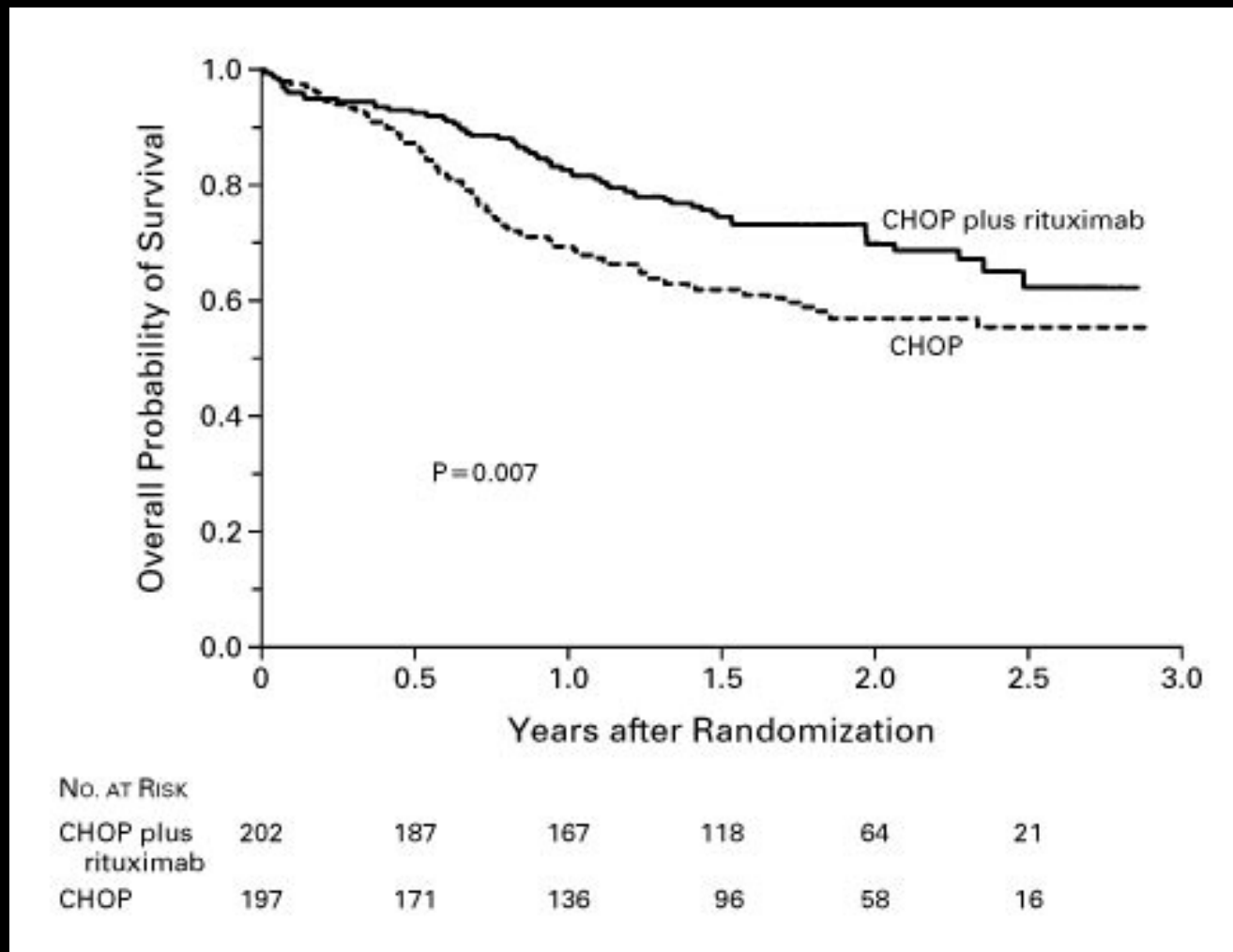
# Event-free Survival among 399 Patients Assigned to Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) or with CHOP plus Rituximab



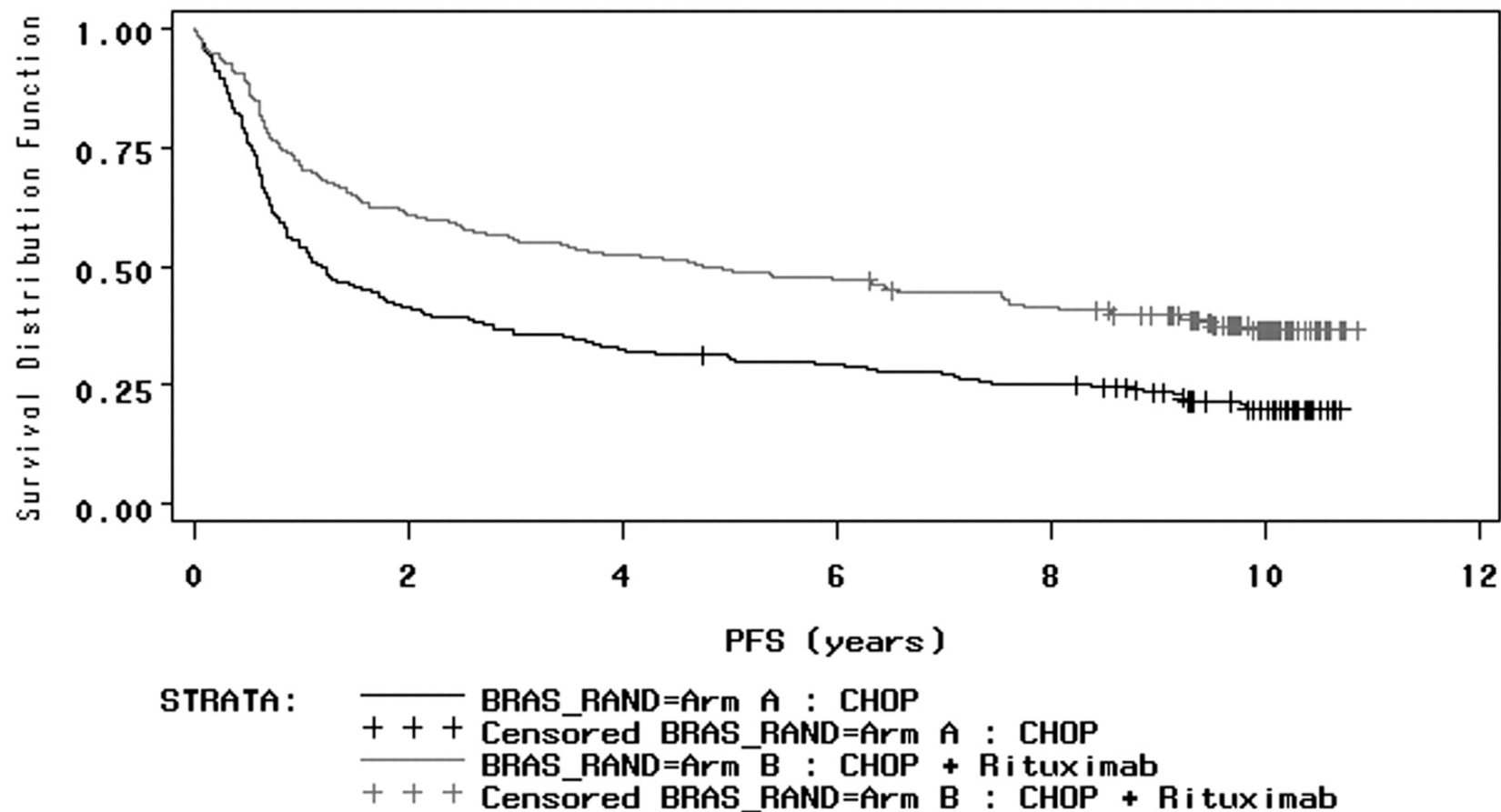




# Overall Survival among 399 Patients Assigned to Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) or with CHOP plus Rituximab

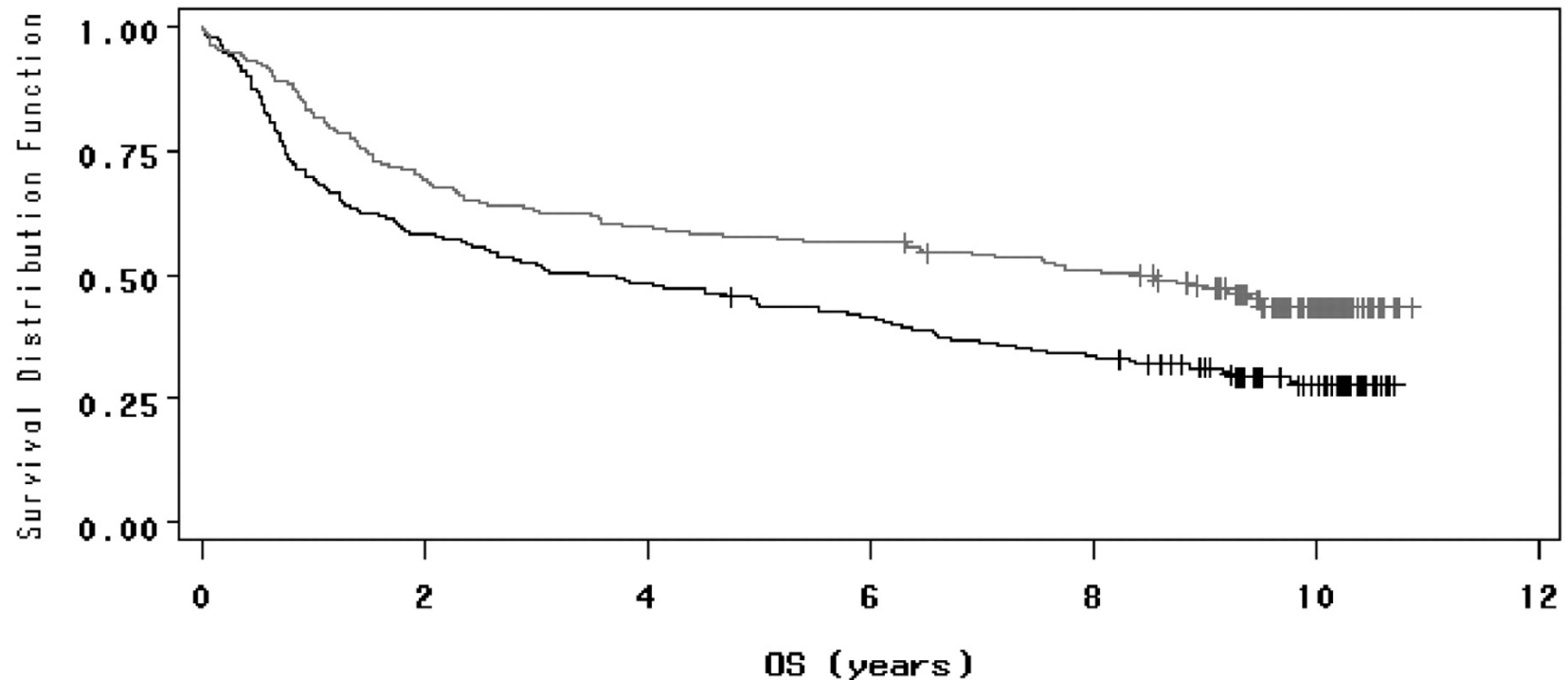


# Progression-free survival in patients treated with CHOP and R-CHOP



Bertrand Coiffier *et al.* Blood 2010; 116:2040-2045

# Overall survival in patients treated with CHOP and R-CHOP



STRATA: ——— BRAS\_RANDOM=Arm A : CHOP  
+ + + Censored BRAS\_RANDOM=Arm A : CHOP  
- - - BRAS\_RANDOM=Arm B : CHOP + Rituximab  
+ + + Censored BRAS\_RANDOM=Arm B : CHOP + Rituximab

Bertrand Coiffier *et al.* Blood 2010; 116:2040-2045

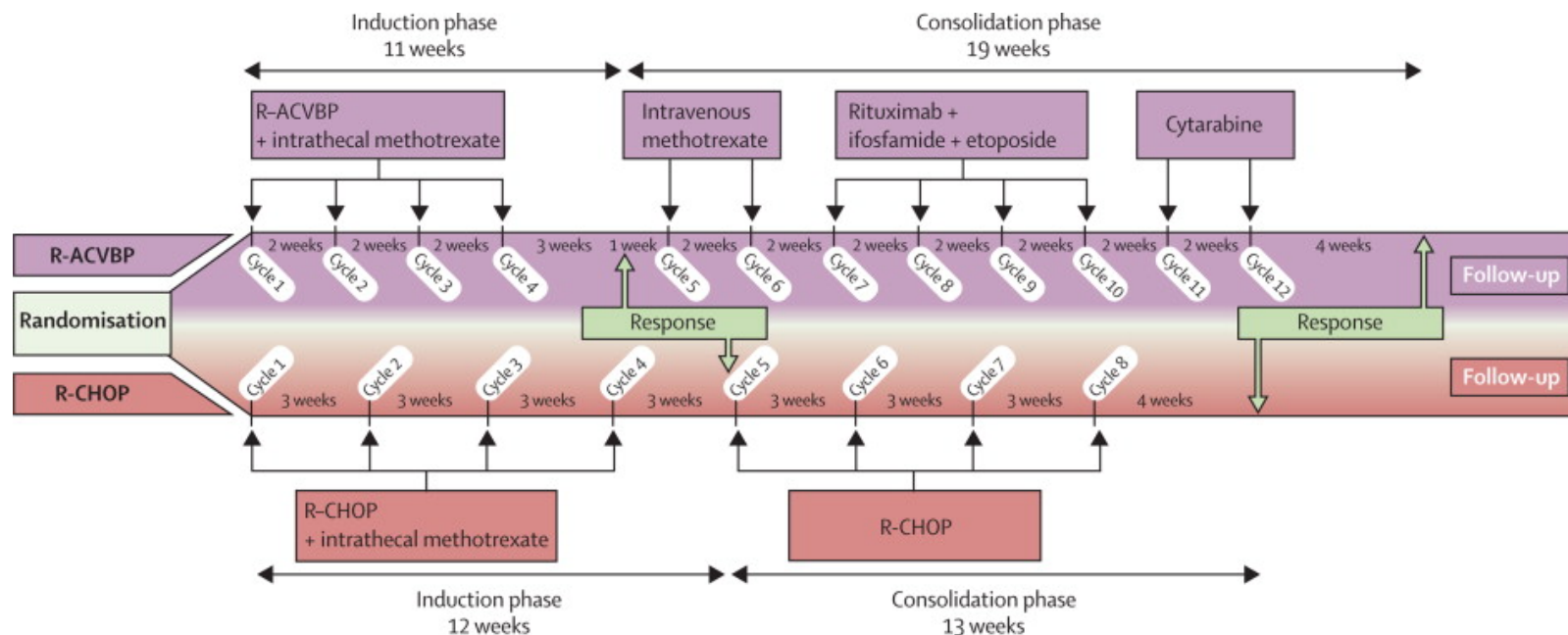


Figure 1. Protocol outline

R-ACVBP=rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone.

R-CHOP=rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone.

Christian Récher, Bertrand Coiffier, Corinne Haioun, Thierry Jo Molina, Christophe Fermé, Olivier Casasnovas, Catherine Thiéblemont, André Bosly, Guy Laurent, Franck Morschhauser, Hervé Ghesquières, Fabrice Jardin, Serge Bologna, Christophe Fruchart, Bernadette Corront, Jean Gabarre, Christophe Bonnet, Maud Janvier, Danielle Canoni, Jean-Philippe Jais, Gilles Salles, Hervé Tilly

**Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial**

**Lancet**, Volume 378, Issue 9806, 2011, 1858–1867

[http://dx.doi.org/10.1016/S0140-6736\(11\)61040-4](http://dx.doi.org/10.1016/S0140-6736(11)61040-4)



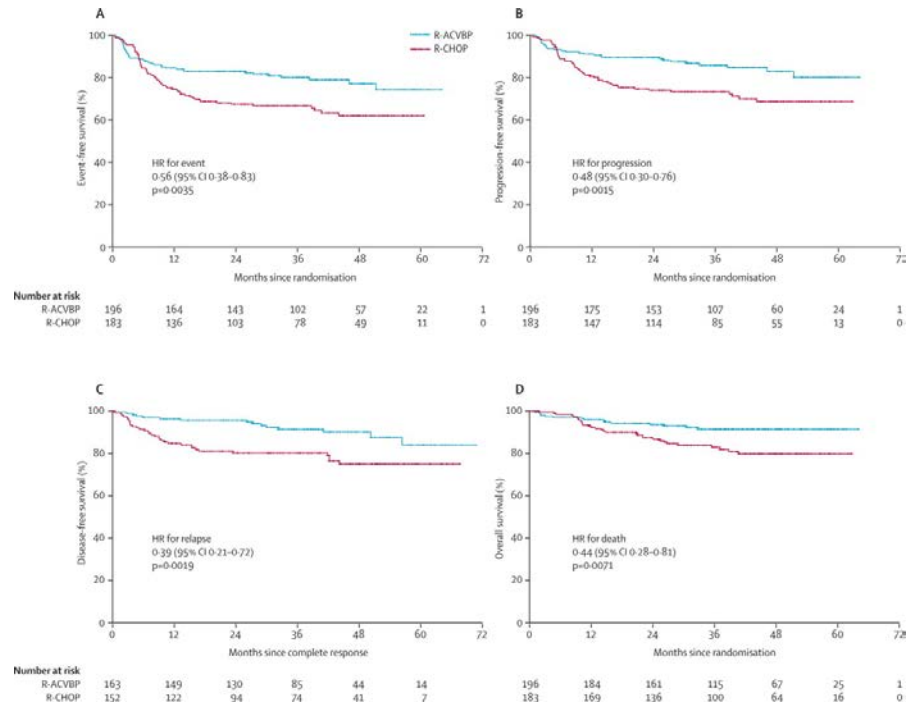


Figure 3. Kaplan-Meier estimates of outcomes by treatment group. Event-free survival for the 379 patients in the intention-to-treat population (A). Progression-free survival for the 379 patients in the intention-to-treat population (B). Disease-free survival for...

Christian Récher, Bertrand Coiffier, Corinne Haioun, Thierry Jo Molina, Christophe Fermé, Olivier Casasnovas, Catherine Thiéblemont, André Bosly, Guy Laurent, Franck Morschhauser, Hervé Ghesquières, Fabrice Jardin, Serge Bologna, Christophe Fruchart, Bernadette Corront, Jean Gabarre, Christophe Bonnet, Maud Janvier, Danielle Canoni, Jean-Philippe Jais, Gilles Salles, Hervé Tilly

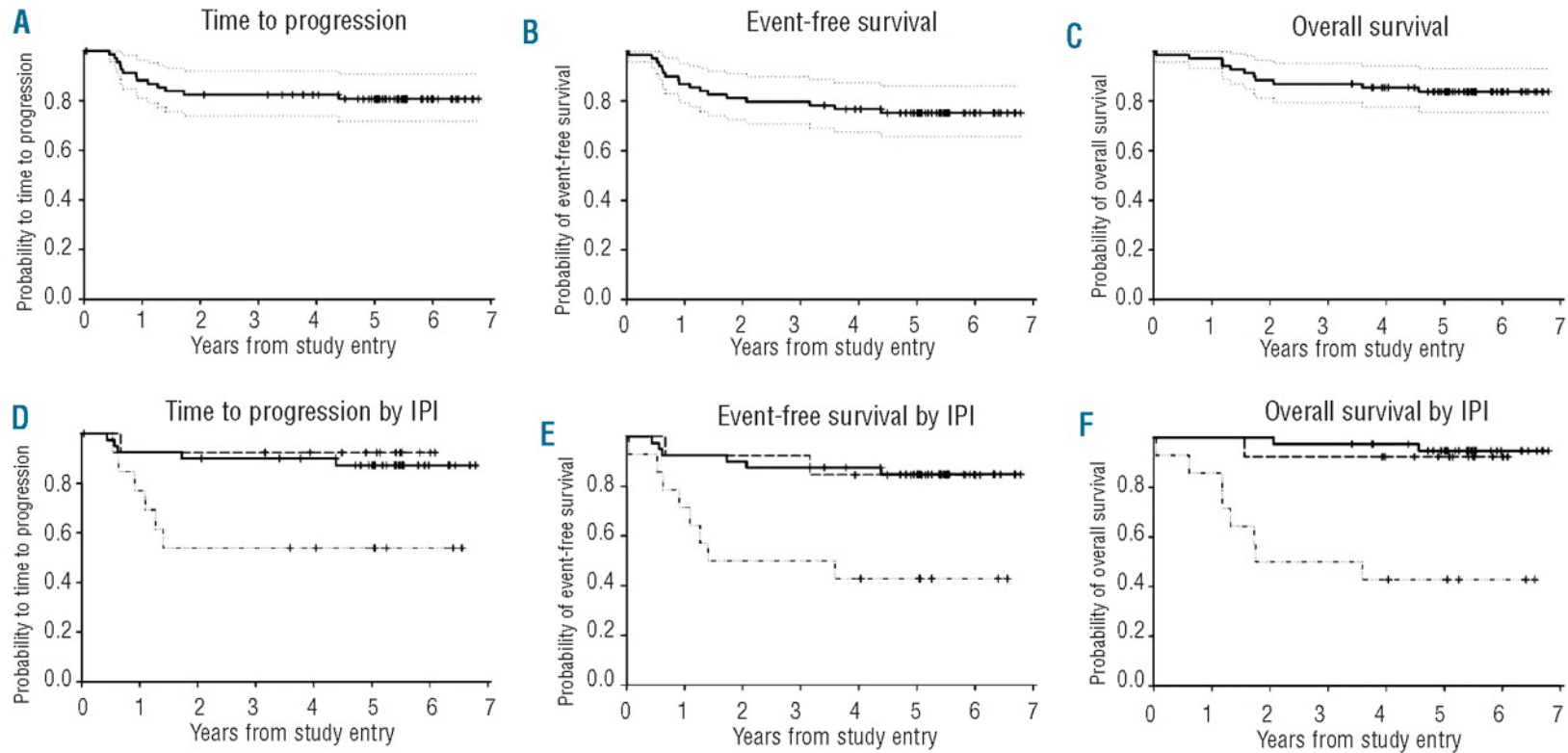
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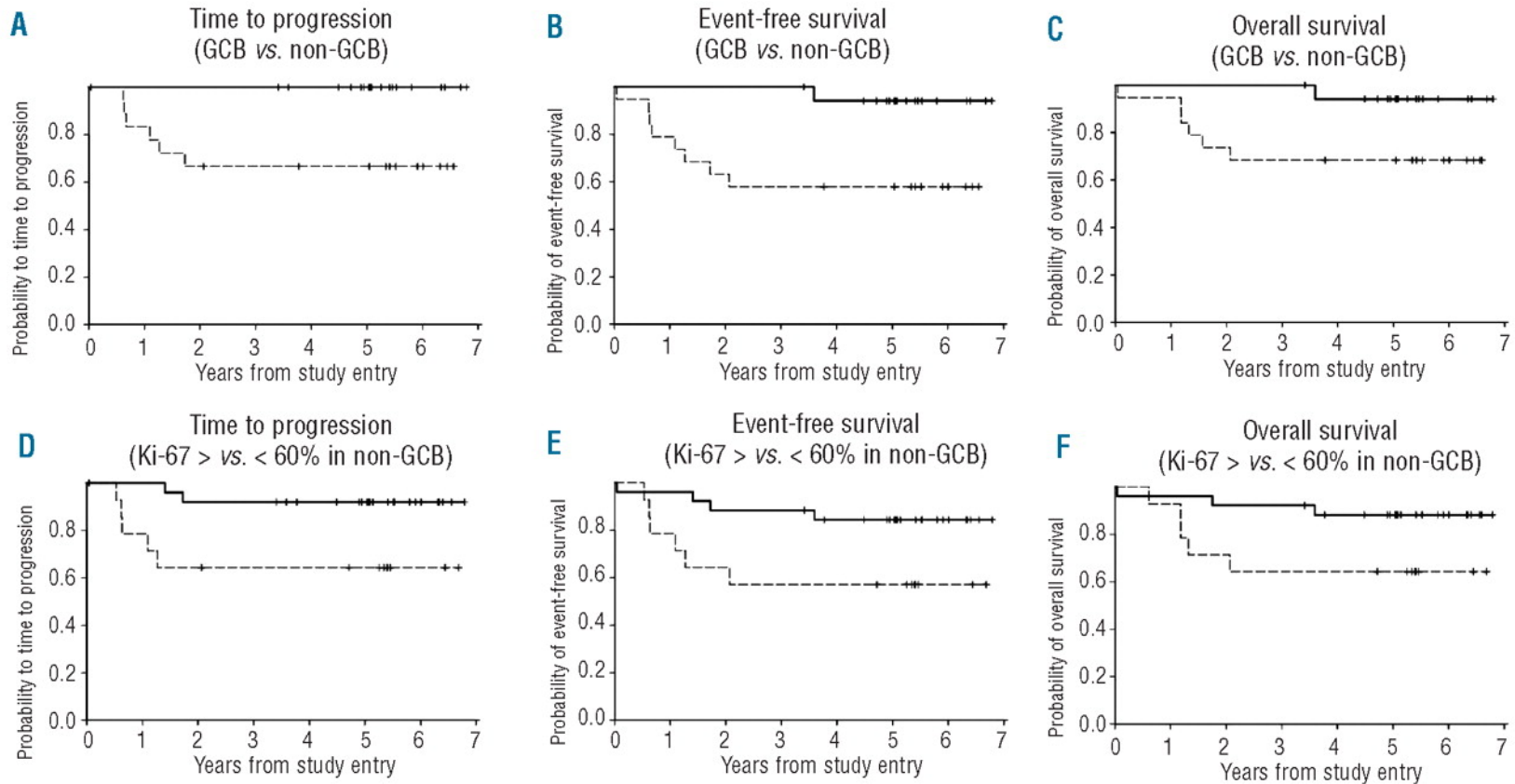


# Kaplan-Meier plots of survival outcomes of all patients



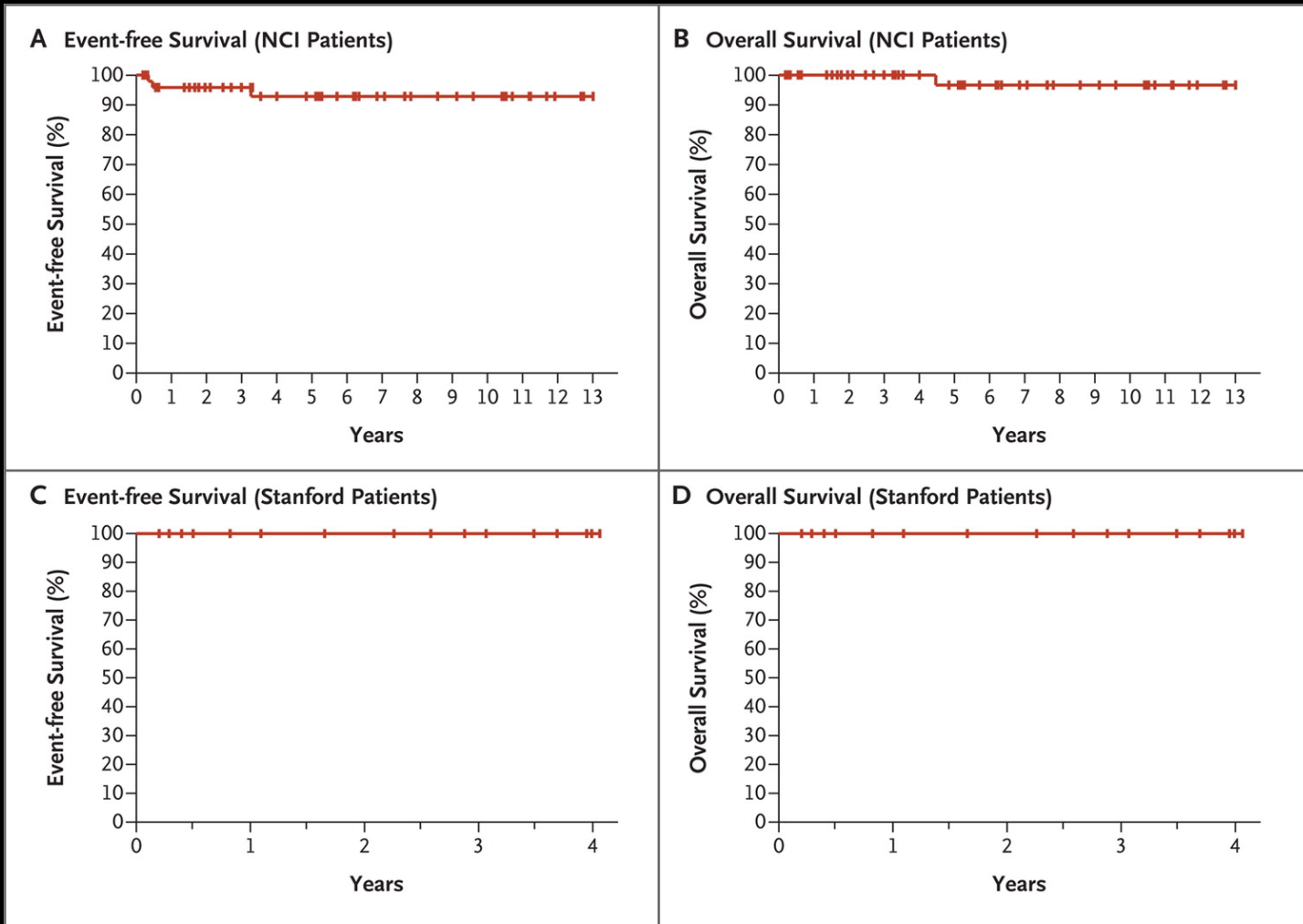
Wyndham H. Wilson *et al.* Haematologica 2012;97:758-765

# Kaplan-Meier plots of survival outcomes patients with biomarkers



Wyndham H. Wilson *et al.* Haematologica 2012;97:758-765

# Kaplan–Meier Estimates of Event-free and Overall Survival of Patients with Primary Mediastinal B-Cell Lymphoma Receiving DA-EPOCH-R, According to Study Group





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https://clinicaltrials.gov/ct2/show/NCT00118209

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## Rituximab and Combination Chemotherapy in Treating Patients With Diffuse Large B-Cell Lymphoma

**This study is ongoing, but not recruiting participants.**

**Sponsor:**  
Alliance for Clinical Trials in Oncology

**Collaborator:**  
National Cancer Institute (NCI)

**Information provided by (Responsible Party):**  
Alliance for Clinical Trials in Oncology

**ClinicalTrials.gov Identifier:**  
NCT00118209  
  
First received: July 8, 2005  
Last updated: September 18, 2015  
Last verified: September 2015  
[History of Changes](#)

**Purpose**

**RATIONALE:** Monoclonal antibodies, such as rituximab, can block cancer growth in different ways. Some block the ability of cancer cells to grow and spread. Others find cancer cells and help kill them or carry cancer-killing substances to them. Drugs used in chemotherapy work in different ways to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Giving rituximab together with combination chemotherapy may kill more cancer cells. It is not yet known which combination chemotherapy regimen is more effective when given with rituximab in treating diffuse large B-cell lymphoma.

**PURPOSE:** This randomized phase III trial is studying rituximab when given together with two different combination chemotherapy regimens to compare how well they work in treating patients with diffuse large B-cell lymphoma.

Condition	Intervention	Phase
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Arms	Assigned Interventions
<p>Active Comparator: Arm A - R-CHOP</p> <p>Patients receive the following treatment:</p> <ul style="list-style-type: none"> <li>Rituximab 375 mg/m<sup>2</sup> IV infusion on Day 1 prior to CHOP chemotherapy</li> <li>Cyclophosphamide 750 mg/m<sup>2</sup> IV on Day 1</li> <li>Doxorubicin 50 mg/m<sup>2</sup> IV on Day 1</li> <li>Vincristine 1.4 mg/m<sup>2</sup> IV (2 mg cap) on Day 1</li> <li>Prednisone 40 mg/m<sup>2</sup>/day PO on Days 1-5</li> <li>filgrastim or pegfilgrastim as defined in the protocol</li> </ul> <p>Required ancillary medications is administered during all cycles as defined in the protocol.</p> <p>Cycles will be repeated every 21 days for 6 treatment cycles. Restaging will occur after Cycles 4 and 6.</p>	<p>Biological: rituximab IV Drug: cyclophosphamide IV Drug: doxorubicin IV or CIVI Drug: vincristine IV or CIVI Drug: prednisone oral Drug: filgrastim IV Drug: pegfilgrastim IV</p>
<p>Experimental: Arm B - DA-EPOCH-R</p> <p>Patients receive the following treatment:</p> <p>Cycle 1 Doses:</p> <ul style="list-style-type: none"> <li>Rituximab 375 mg/m<sup>2</sup> IV infusion on Day 1 prior to EPOCH chemotherapy</li> <li>Doxorubicin 10 mg/m<sup>2</sup>/day CIVI on Days 1-4</li> <li>Etoposide 50 mg/m<sup>2</sup>/day CIVI on Days 1-4</li> <li>Vincristine 0.4 mg/m<sup>2</sup>/day (no cap) CIVI on Days 1-4 (total 1.6 mg/m<sup>2</sup> over 96 hours)</li> <li>Cyclophosphamide 750 mg/m<sup>2</sup> IV on Day 5 (following completion of 96 hour infusions)</li> <li>Prednisone 60 mg/m<sup>2</sup> PO BID on Days 1-5</li> <li>Administer filgrastim 480 mcg subcutaneous daily from Day 6 until ANC &gt; 5000 after the nadir (nadir usually between Days 10-12) or for 10 days (Days 6-15) if the ANC is not being monitored, during every cycle.</li> </ul> <p>Doses for subsequent cycles will be determined by the absolute neutrophil (ANC) or platelet nadir from the previous cycle.</p> <p>Required ancillary medications are administered during all cycles as defined in the protocol.</p> <p>Cycles will be repeated every 21 days for a maximum of 6 cycles. Restaging will occur after Cycles 4 and 6.</p>	<p>Biological: rituximab IV Drug: cyclophosphamide IV Drug: doxorubicin IV or CIVI Drug: vincristine IV or CIVI Drug: prednisone oral Drug: etoposide CIVI Drug: filgrastim IV</p>