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Key Considerations for Biosimilars in Lymphoma

Andrew D. Zelenetz, MD, PhD
Memorial Sloan Kettering Cancer Center
New York, New York

Learning Objectives

- Differentiate between biosimilar and generic pharmacotherapies, based on manufacturing process and clinical and regulatory issues
- Outline the role of rituximab in lymphoid malignancies
- Discuss the challenges in the clinical deployment of a biosimilar rituximab

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Background

Biologics in Oncology

- Biologics represent approximately 50% of the pharmaceutical market in oncology

- Biologics play a critical role in clinical care:
  - Active therapy
    - Monoclonal antibodies
    - Antibody drug conjugates
    - Interferons
  - Supportive care
    - Myeloid growth factors
    - Erythropoietin stimulating agents

Nowicki M. *Kidney Blood Press Res.* 2007;30(5):267-272.

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Biologics vs Small Molecule Drugs

Definitions

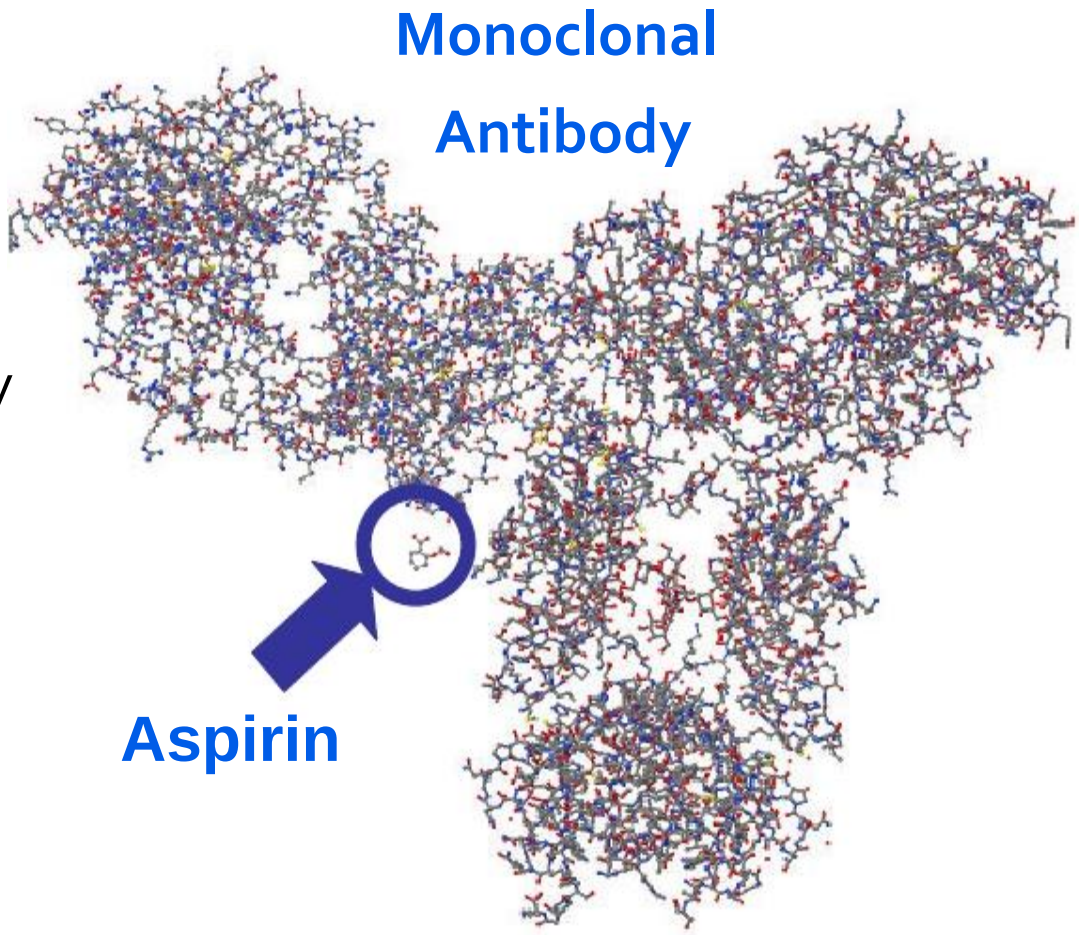
- Biologic
  - "Products of biotechnological origin that contain proteins derived from DNA technology and hybridoma techniques"
  - Use living organisms (eg, bacteria, yeasts, viruses, other animal cells) as part of production process

- Small Molecule Drugs
  - Synthesized through chemical reactions
  - Atomic structure can be verified

Nowicki M. *Kidney Blood Press Res.* 2007;30(5):267-272.

Small Molecule vs Biologic Drugs

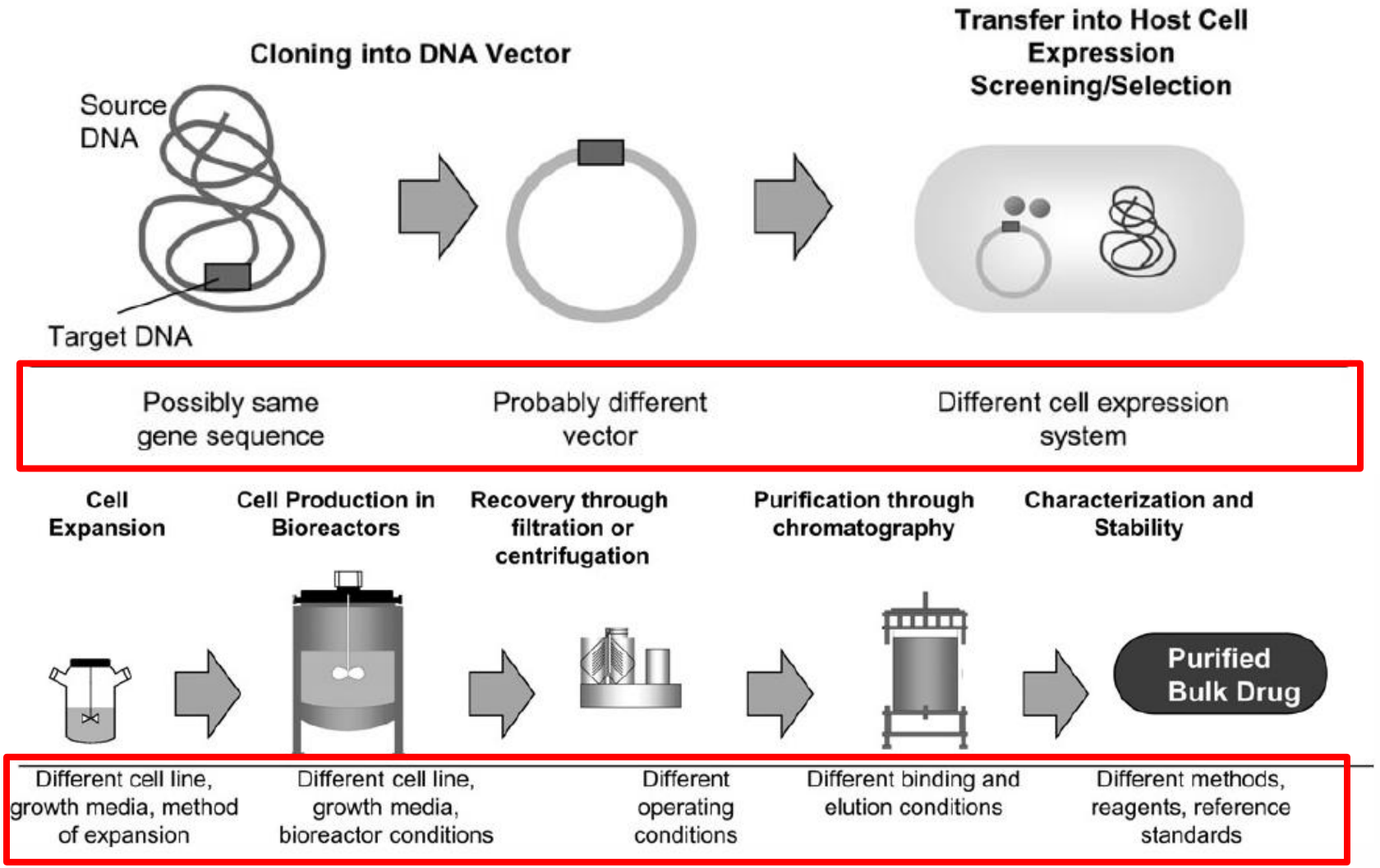
- Biological products are generally produced using a living system or organism
- Biological products may be manufactured through biotechnology, derived from natural sources, or produced synthetically



Biologics vs Small Molecule Drugs

- Biologics have a complex manufacturing process
  - Multiple steps; proprietary processes
    - Alteration in processes by the originator requires validation of the product
  - Expected variation between manufacturers
  - Even small differences can result in a different end-product

Manufacturing Biosimilars



Mellstedt H, et al. *Ann Oncol.* 2008;19(3):411-419.

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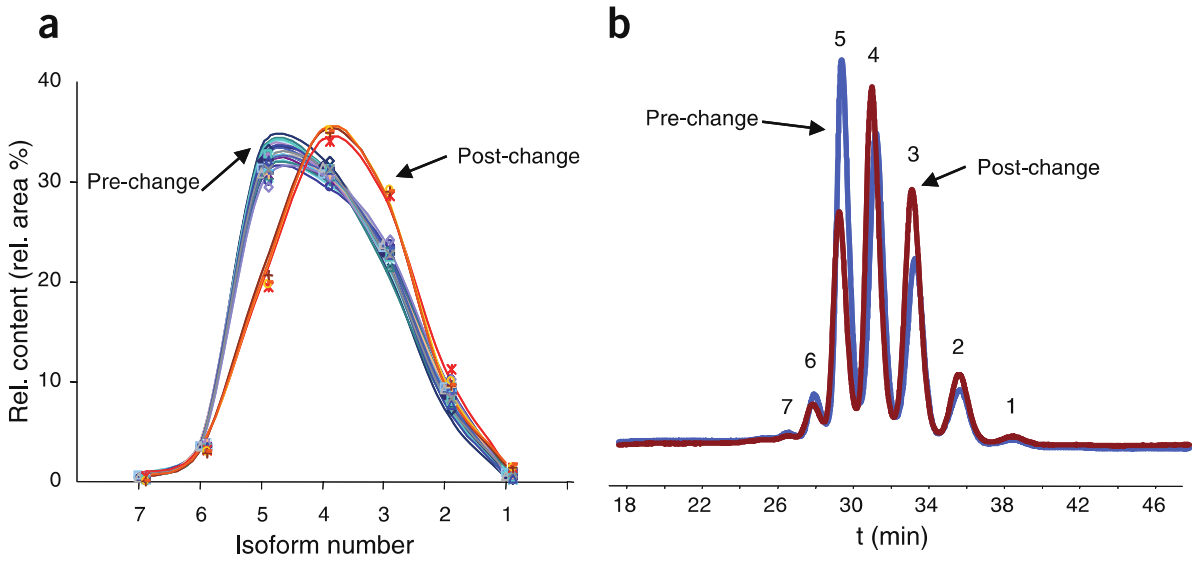
What Is Acceptable Variation? Lot to Lot Variation of Innovator Products: Darbepoietin



- Comparison of lots of darbepoietin by capillary zone electrophoresis pre- and post-EMA approved process change base on an extensive comparability exercise
  a. Relative isoform content
  b. Representative electropherograms

EMA, European Medicines Agency

Schiestl M, et al. *Nat Biotechnol*. 2011:29(4):310-312.

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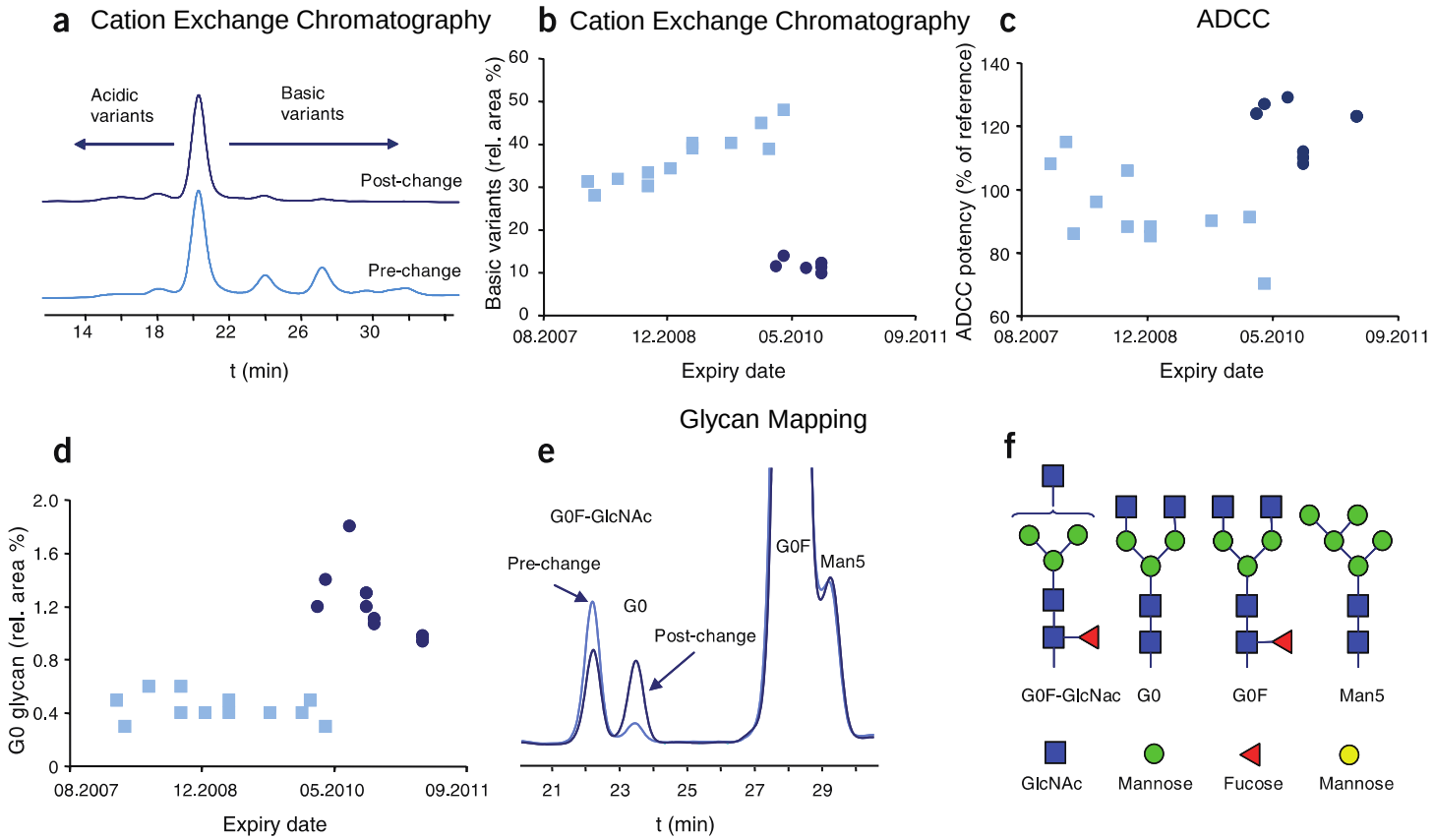
What Is Acceptable Variation? Lot to Lot Variation of Innovator Products: Rituximab



- Significant change in ADCC and glycan map for unfucosylated Go glycans (which impacts ADCC)

ADCC, Antibody-dependent cellular cytotoxicity

Schiestl M, et al. *Nat Biotechnol*. 2011:29(4):310-312.

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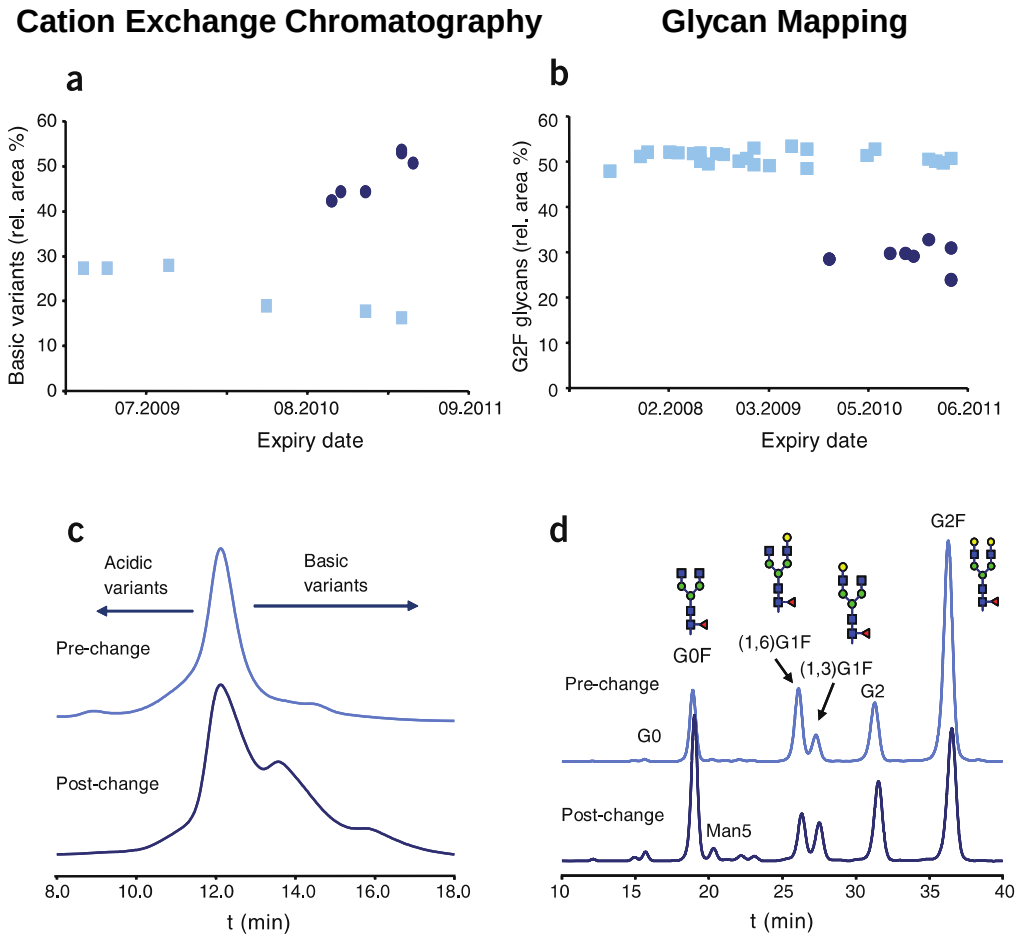
What Is Acceptable Variation? Lot to Lot Variation of Innovator Products: Etanercept



- Significant change in glycans and basic variants since in batches over time

Schiestl M, et al. *Nat Biotechnol*. 2011:29(4):310-312.

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Biologics vs Small Molecule Drugs

- Unlike generic small molecule drugs:
  - Biosimilars will not be identical to the reference product because of differences in manufacturing processes
  - We cannot determine if a biosimilar product is identical to the reference product

- Therefore, we must use preclinical and clinical (ie, safety/efficacy) studies to demonstrate comparability

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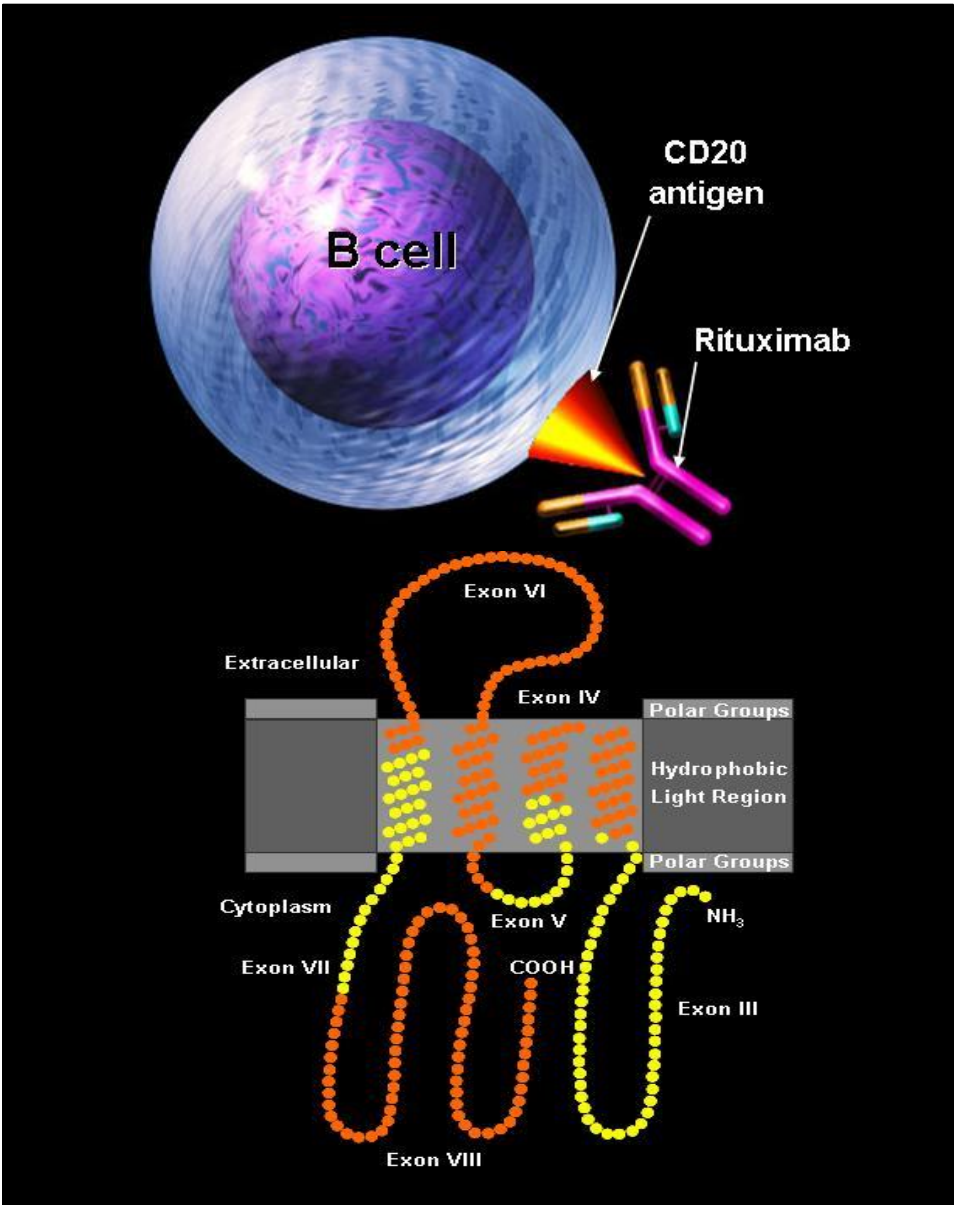
Biosimilars for Lymphoma: Rituximab as the Target Drug

Rituximab for NHL



Rituximab

- Chimeric molecule with a murine antigen binding domain
- Human κ constant region
- Human IgG1 constant region

CD20 antigen

- Hydrophobic, 35 kD phosphoprotein
- Expressed only on B lineage cells
- Present in more than 90% of B-cell lymphomas
- Important for cell cycle initiation and differentiation
- Does not shed or rapidly modulate off cell surface

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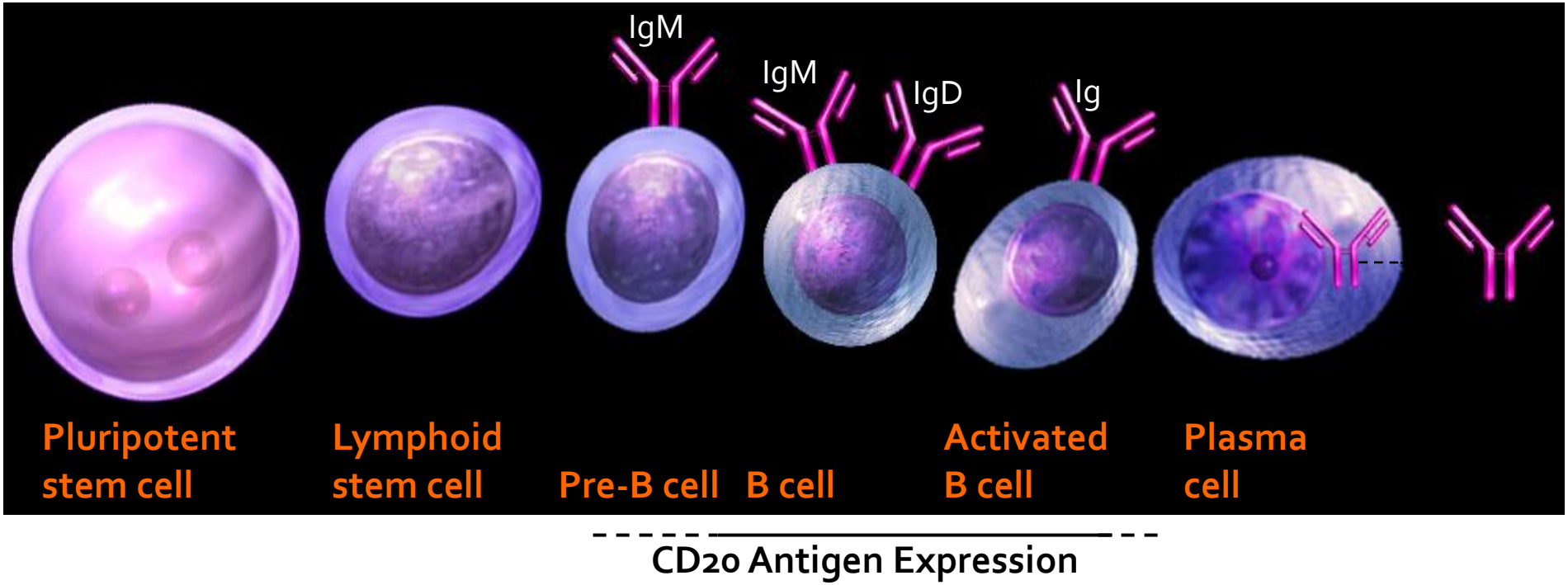
B-Cell Life Cycle and CD20 Tumor Specificity



CML	Precursor B-cell acute leukemias	B-cell lymphomas, CLL	Myeloma

CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia.

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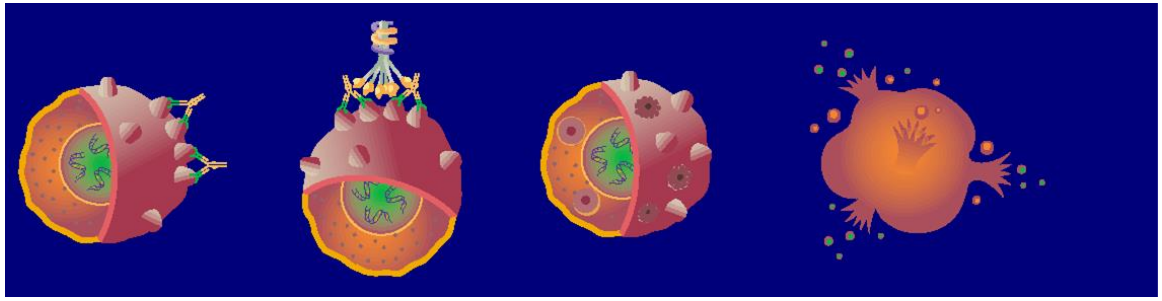
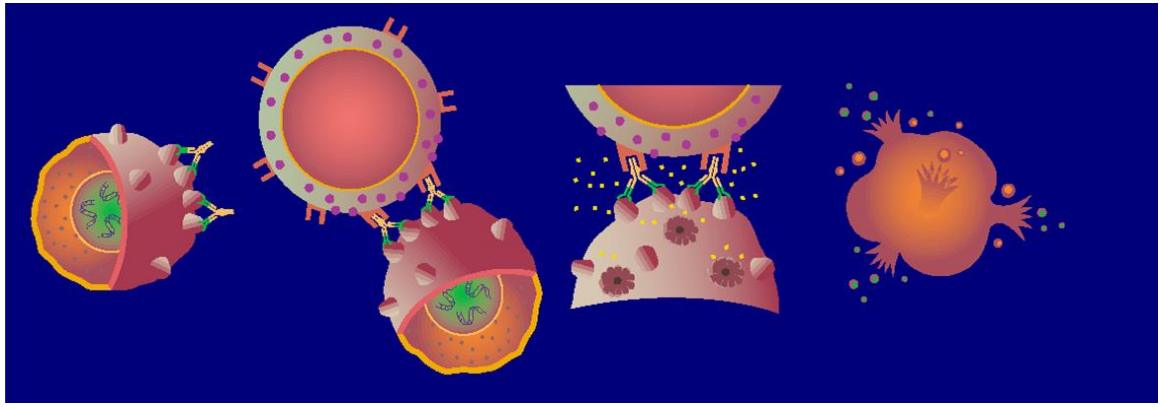
Rituximab: Proposed Mechanisms of Action (MOA)

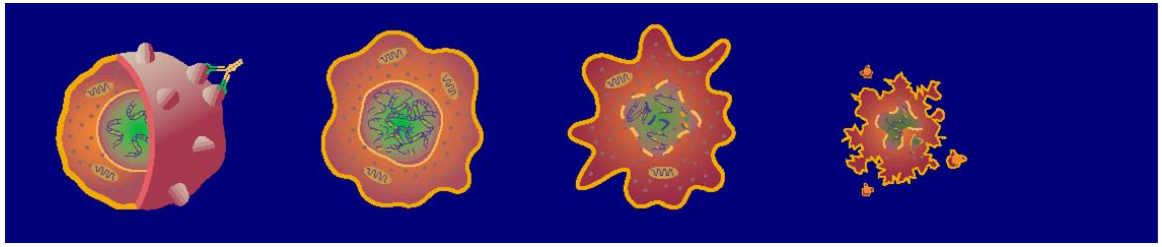
CDC



ADCC



Apoptosis



CDC, complement-dependent cytotoxicity

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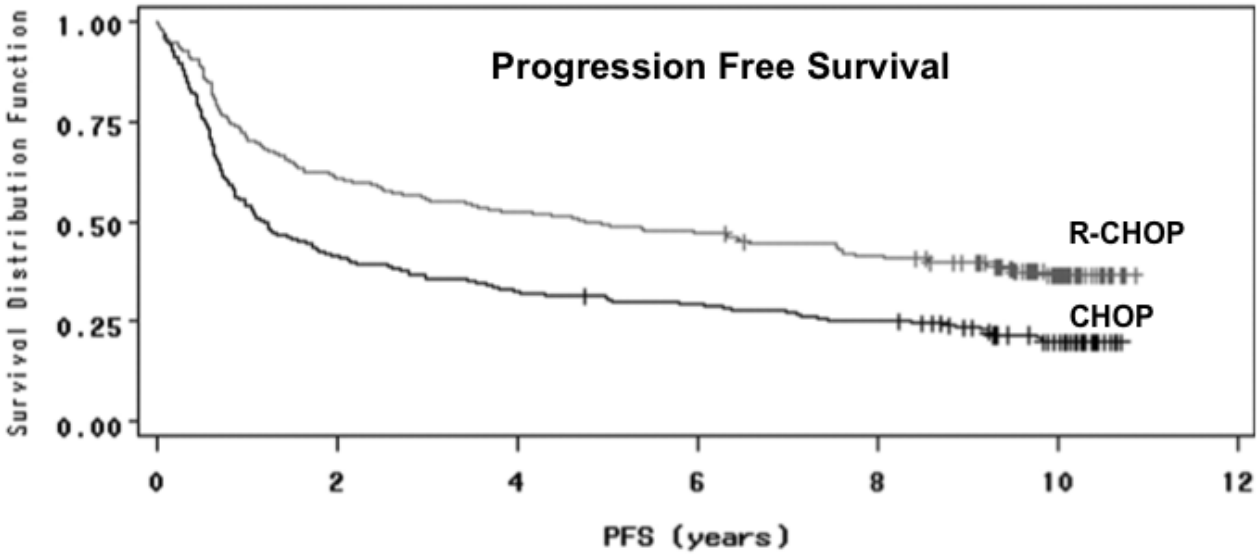
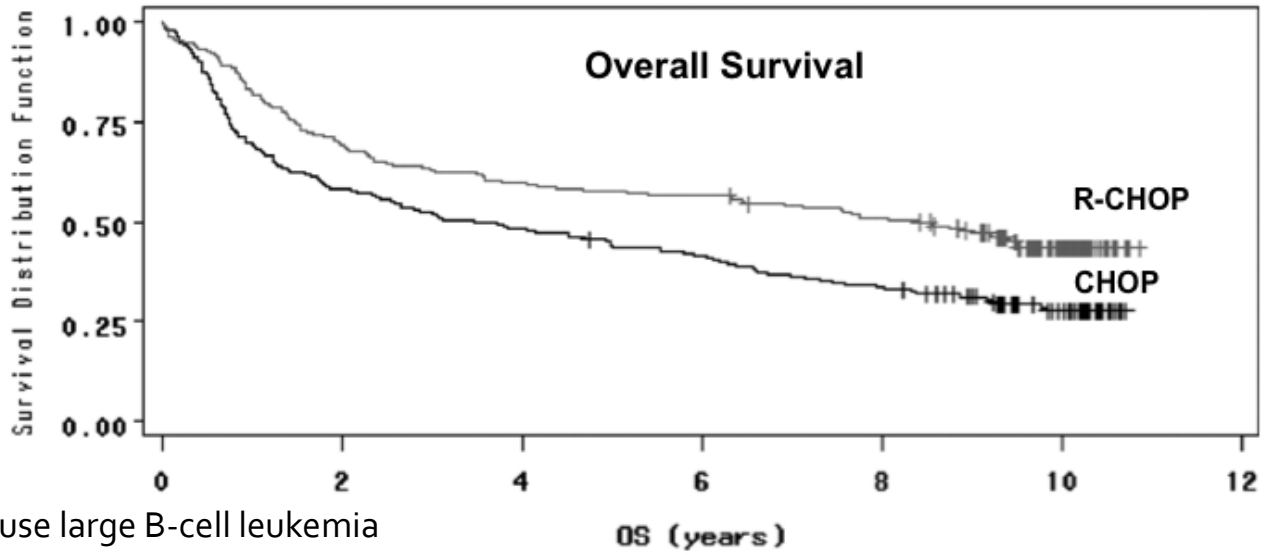
Rituximab in DLBCL: Addition of Rituximab to CHOP Improves Overall Survival (OS)





DLBCL, diffuse large B-cell leukemia

Coiffier B, et al. *Blood.* 2010;116(12):2040-2045.

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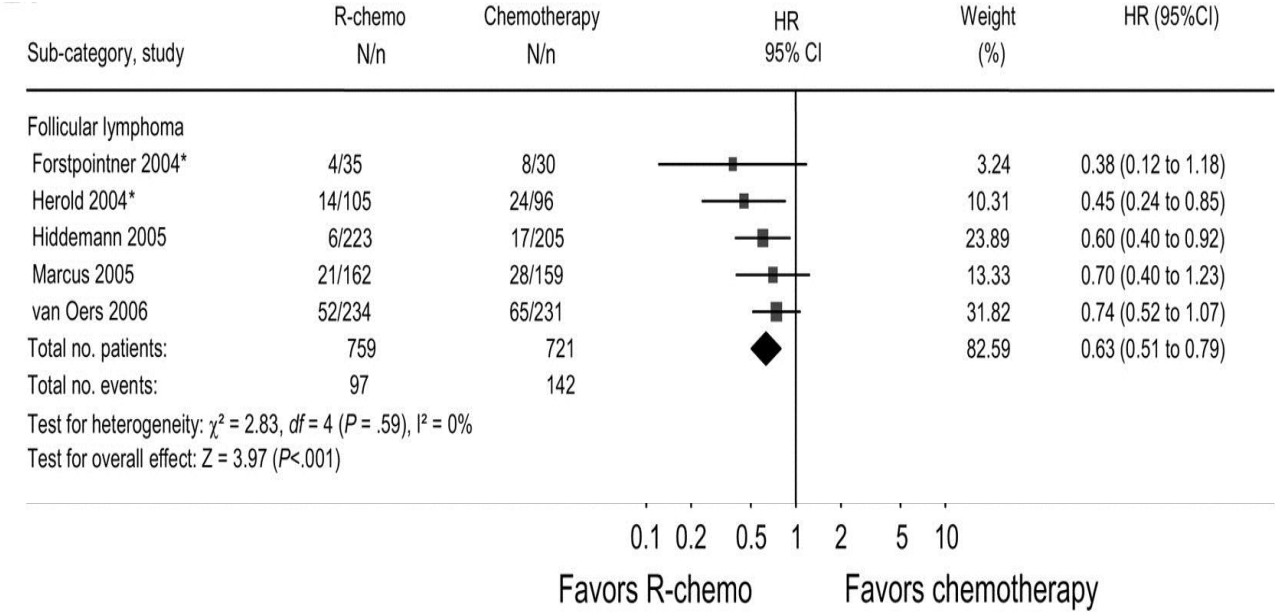
Rituximab in FL: Meta-Analysis Demonstrates an OS Advantage for R-Chemo vs Chemo Alone



Based on the results of this meta-analysis and the supporting phase III trials, rituximab in combination with chemotherapy is the STANDARD OF CARE patients requiring therapy (CATEGORY 1)

In these trials, PFS benefit is disproportionately large compare to the OS benefit

The optimal R-CHEMO regimen remains undefined.

FL, follicular lymphoma; PFS, progression-free survival

Schulz H, et al. *J Natl Cancer Inst.* 2007;99(9):706-714.

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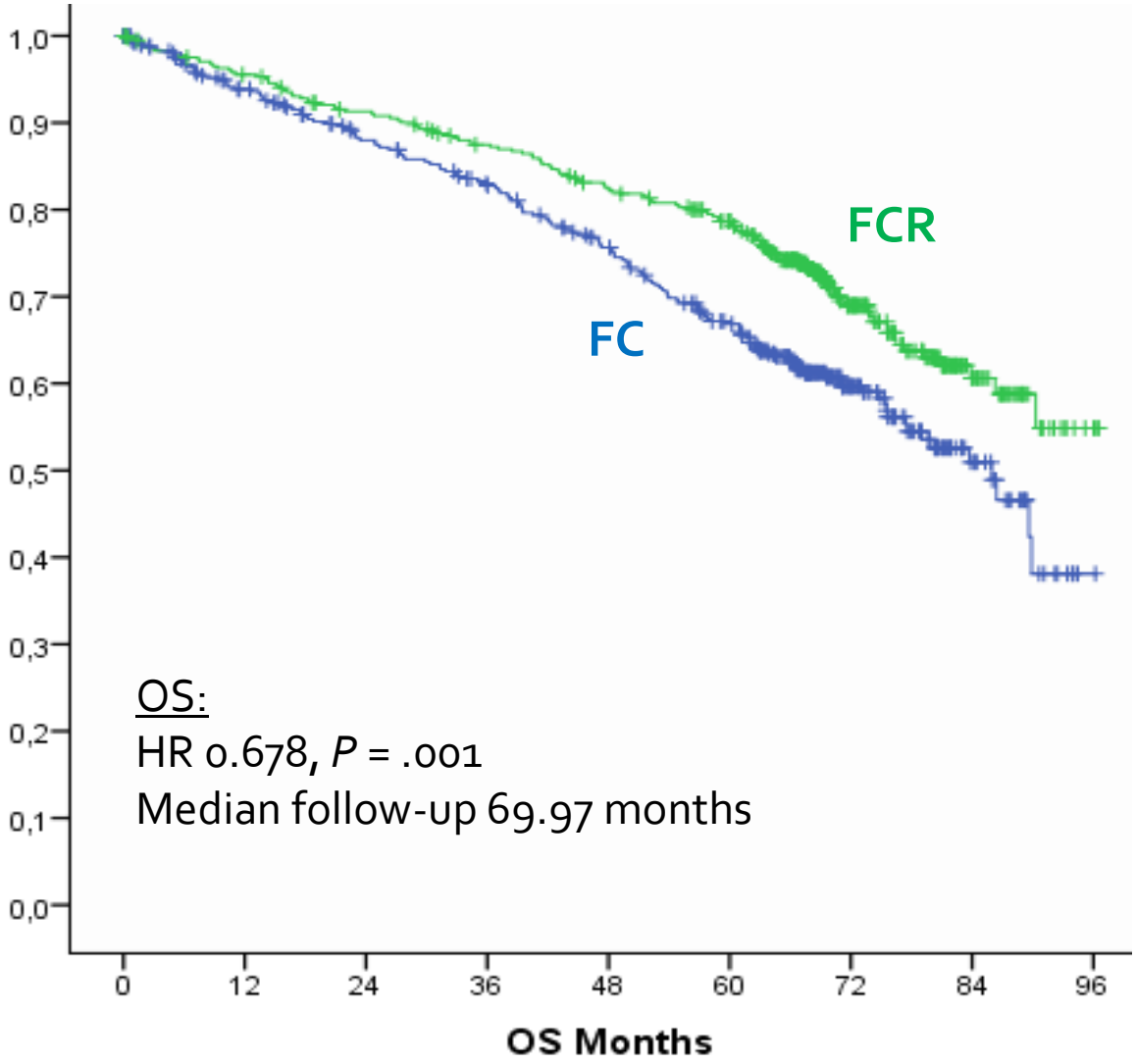
Rituximab in CLL: Addition of rituximab to FC Improves OS (CLL8)



Fischer K, et al. *Blood.* 2012;120: Abstract 435.

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Do We Need a Biosimilar for Rituximab?

- The typical dose of rituximab if 375 mg/m^2
  - Estimated average wholesale price is $4000 per dose
  - Cost for
    - 4-week induction: $16,000
    - 2 years maintenance: $32,000
    - 6 doses with R-CHOP: $24,000

- These are average wholesale costs, not charges, which can be double this

- Ex-US prices are not very much lower
  - Cost in countries like India and China are prohibitive

- Cost limits availability and therefore compromises outcome

Development of rituximab biosimilars

- Worldwide annual sale of rituximab are $7 billion US
  - Malignant conditions: B cell lymphoma
  - Benign conditions: Rheumatoid arthritis
  - EU Patent expiration: 2013
  - US Patent expiration: 2018
- This has led many companies (both traditional innovators and generic companies) to launched efforts in rituximab biosimilars

Ongoing Development

AMGEN® (ABP 798)

Boehringer Ingelheim (BI 695500)

Hospira

BIOCAD Biopharmaceutical Company (BCD-20)

SANDOZ Biopharmaceuticals (GP2013)

CELLTRION (CT-10)

Halted Development

Lonza

TEVA (TL011)

SAMSUNG BIOLOGICS (SAIT101)

How to Develop a Rituximab Biosimilar

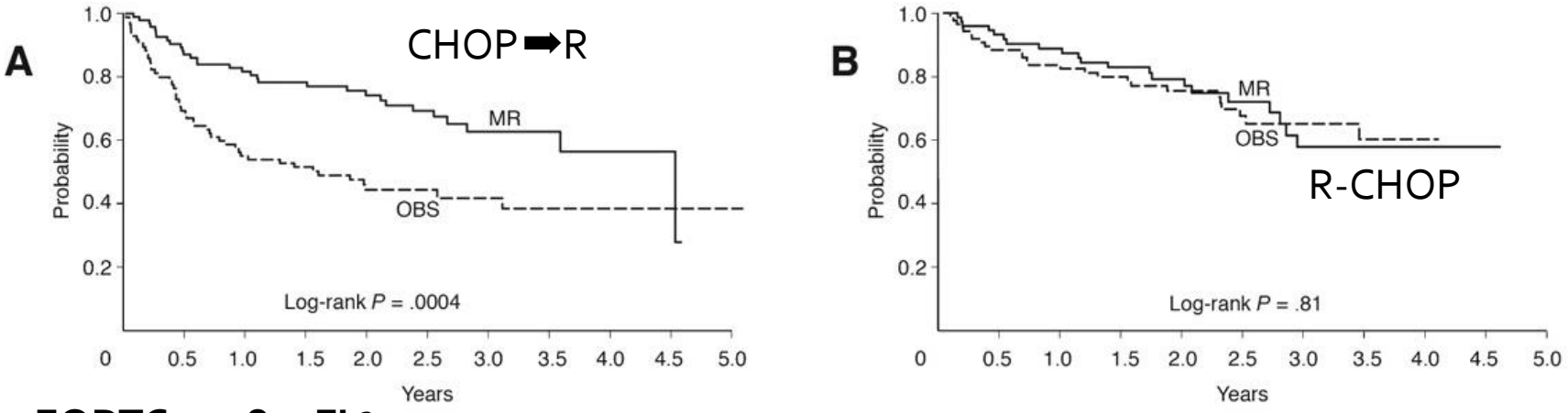
- Assume the preclinical evaluation is acceptable, what trials would convince me to use a biosimilar?

- What is the MOA
  - Single agent: Antibody-dependent cell-mediated toxicity is probably the key, but contribution from complement-mediated cytotoxicity and some direct apoptosis

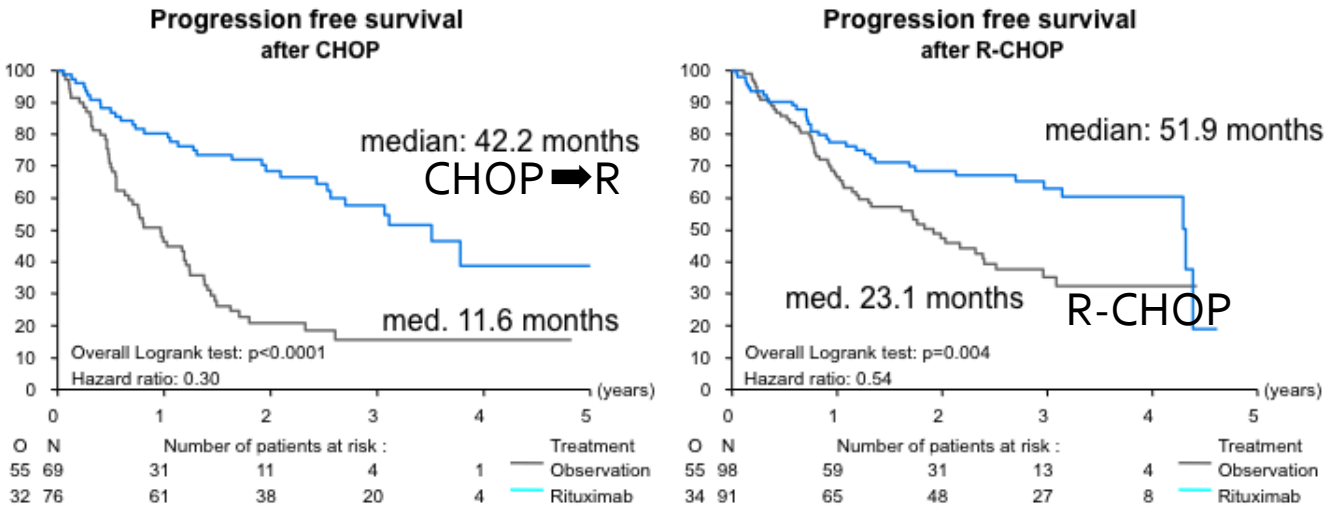
  - Chemoimmunotherapy: Chemotherapy sensitization of tumor cells is likely important in addition to the immune effects

Rituximab/Chemotherapy: Is There Synergy?

ECOG 4494/CALG 9793: DLBCL[1]



EORTC 20981: FL[2]



1. Habermann TM, et al. *J Clin Oncol.* 2006;24(19):3121-3127.
2. Van Oers MH, et al. *J Clin Oncol.* 2010;28(17):2853-2858.

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How to Develop a Rituximab Biosimilar

- Single agent
  - Most sensitive population: Single-agent rituximab in untreated FL
  - Problem: Rituximab not approved in this population!
  - Alternative: Rituximab vs biosimilar in patients with relapsed FL
  - Problem: Little use in the population today
  - How can we get the study done?
- Chemoimmunotherapy
  - Most sensitive population: Diffuse large B-cell lymphoma
  - Two-sided equivalence study would be ~600 patients
  - What would be the motivation for a patient to participate?

Rituximab Biosimilar Trials (Partial List)

- Title: Study of RTXM83 Plus CHOP Chemotherapy Versus a Rituximab Plus CHOP Therapy in Patients With Non Hodgkin's Lymphoma
  - Conditions: Diffuse Large B-cell Lymphoma
  - Interventions: Biological: RTXM83
  - URL: http://ClinicalTrials.gov/show/NCT02268045
- Title: GP2013 in the Treatment of Patients With Previously Untreated, Advanced Stage Follicular Lymphoma
  - Conditions: Follicular Lymphoma
  - Interventions: Biological: GP2013|Biological: rituximab
  - URL: http://ClinicalTrials.gov/show/NCT01419665
- Title: Demonstrate the Equivalence of CT-P10 to MabThera With Respect to the Pharmacokinetic Profile in Patients With Rheumatoid Arthritis
  - Conditions: Rheumatoid Arthritis
  - Interventions: Biological: rituximab
  - URL: http://ClinicalTrials.gov/show/NCT01534884
- Title: Provide Initial Evidence of Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy to Support the Pivotal CT-P10 Therapeutic Equivalence Trial
  - Conditions: Diffuse Large B-Cell Lymphoma
  - Interventions: Biological: rituximab
  - URL: http://ClinicalTrials.gov/show/NCT01534949
- Title: Study of Safety and Efficacy of BCD-020 Comparing to MabThera in Patients With Rheumatoid Arthritis
  - Conditions: Rheumatoid Arthritis
  - Interventions: Drug: Rituximab
  - URL: http://ClinicalTrials.gov/show/NCT01759030

Rituximab Biosimilar Trials (Partial List)

- Title: Pharmacokinetics and Pharmacodynamics of BI 695500 vs. Rituximab as First Line-treatment in Patients With Low Tumor Burden Lymphoma
  - Conditions: Lymphoma, Follicular
  - Interventions: Drug: BI 695500|Drug: MabThera
  - URL: http://ClinicalTrials.gov/show/NCT01950273
- Title: Efficacy, Pharmacokinetics, and Safety of BI 695500 in Patients With Rheumatoid Arthritis
  - Conditions: Arthritis, Rheumatoid
  - Interventions: Drug: BI 695500|Drug: BI 695500|Drug: rituximab|Drug: rituximab|Drug: rituximab
  - URL: http://ClinicalTrials.gov/show/NCT01682512
- Title: Safety and Efficacy of BI 695500 in Patients With Moderately to Severely Active Rheumatoid Arthritis
  - Conditions: Arthritis, Rheumatoid
  - Interventions: Drug: BI 695500
  - URL: http://ClinicalTrials.gov/show/NCT01955733
- Title: Safety and Efficacy Study of BCD-020 in Therapy of Non-Hodgkin's Lymphoma
  - Conditions: Follicular Non-Hodgkin's Lymphoma|Nodal Marginal Zone Lymphoma|Splenic Marginal Zone Lymphoma
  - Interventions: Biological: rituximab
  - URL: http://ClinicalTrials.gov/show/NCT01701232
- Title: Study of Safety and Efficacy of BCD-020 Comparing to MabThera in Patients With Rheumatoid Arthritis
  - Conditions: Rheumatoid Arthritis
  - Interventions: Drug: Rituximab
  - URL: http://ClinicalTrials.gov/show/NCT01759030

Rituximab Biosimilar Trials (Partial List)

- Title: GP2013 in Japanese Patients With CD20 Positive Low Tumor Burden Indolent B-cell Non-Hodgkin's Lymphoma
  - Conditions: Indolent B-cell Non-Hodgkin's Lymphoma
  - Interventions: Drug: GP2013
  - URL: http://ClinicalTrials.gov/show/NCT01933516

- Title: GP2013 in the Treatment of RA Patients Refractory to or Intolerant of Standard Therapy
  - Conditions: Rheumatoid Arthritis
  - Interventions: Biological: GP2013|Biological: rituximab
  - URL: http://ClinicalTrials.gov/show/NCT01274182

Extrapolation in Rituximab

- From "Biosimilars: what clinicians should know"[1]
  - "Extrapolation of efficacy and safety data to other indications of the reference product that have not been investigated during the clinical development of the biosimilar always requires convincing scientific justification, which should address the mechanism of action, toxicities, and immunogenicity in each indication of use."

- With a rituximab biosimilar can we extrapolate:
  - From non-malignant use (eg, RA) to lymphoma?
  - From use in lymphoma to autoimmune disease?
  - From single agent to combination?
  - From combination to single agent?

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[1]Weise M, et al. *Blood*. 2012;120(26):5111-5117.

Challenges to the deployment of biosimilar rituximab

- Uses of rituximab
  - Addition of rituximab to curative intent regimens, examples include: R-CHOP; DA-EPCOH-R for DLBCL; R-CODOX-M/R-IVAC for BL
  - Addition of rituximab to improve outcome but with high risk of recurrence, examples include R-CVP, R-CHOP, R-bendamustine for indolent lymphoma, R-Flu, FCR for CLL
  - Extended administration of rituximab as maintenance in indolent lymphoma
  - Rituximab single agent as palliation in B cell lymphoma

- In non-curative settings (or relapse in curative settings) RETREATMENT with rituximab is nearly universal

- How do these considerations impact a biosimilar?

What we need to know

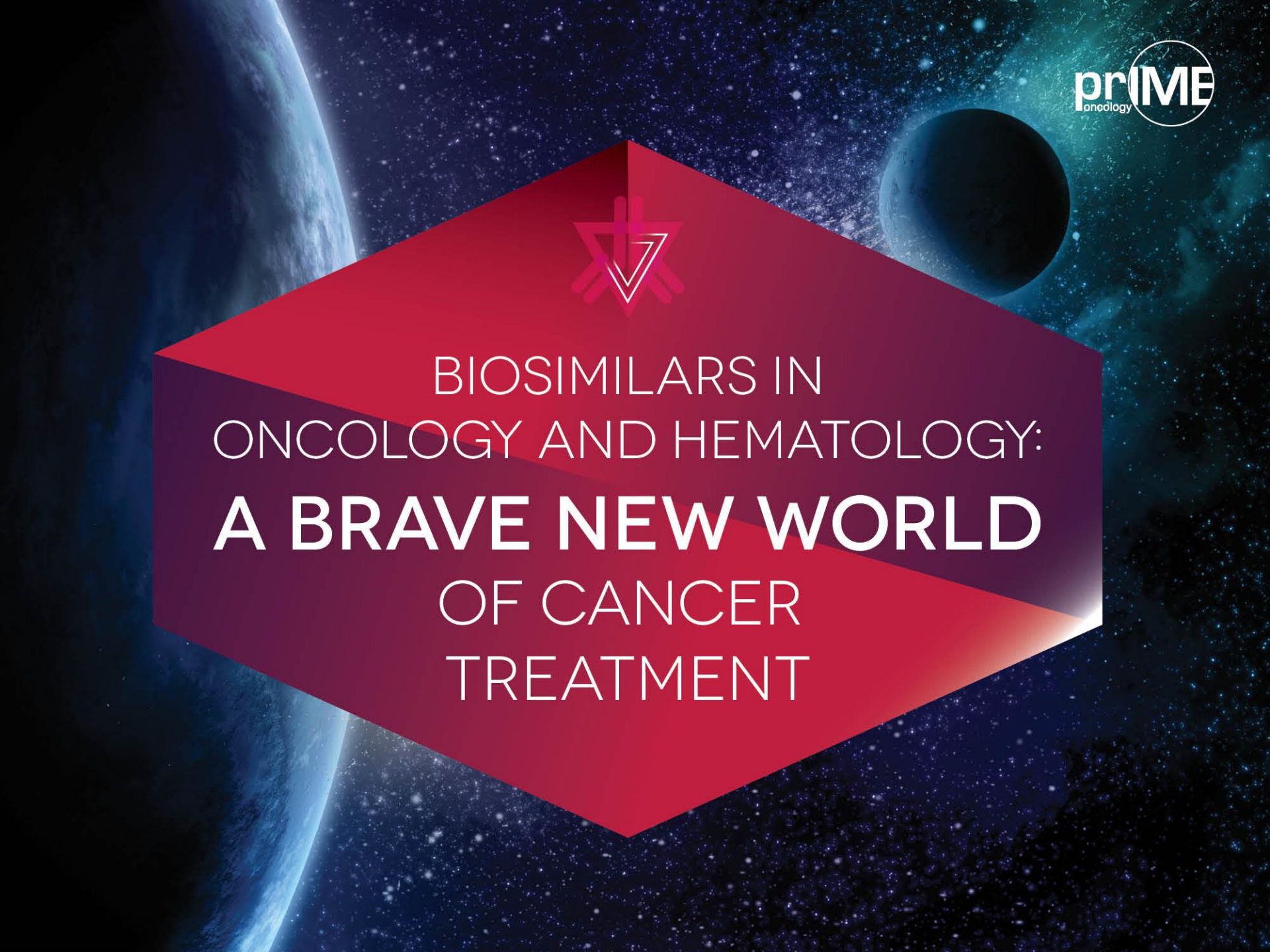
- Immunogenicity
  - Does order of exposure impact the risk of an immune reaction?

- In the absence of documented interchangeability is it safe
  - To use a biosimilar for relapse if rituximab was used initially (and vice versa)?
  - To use different agents during maintenance therapy?

- What happens when patients receive care from more than one provider ("snow birds" for instance)?

Conclusions

- Biologic drugs have become the centerpiece of clinical care in oncology
- Biologics are complex drug than cannot be made "generic"
- Biosimilars are inherently different drugs but may not be clinically meaningfully different
- FDA and EMA have provided guidance for the development and approval of biosimilars
- Rituximab as a case study is a clear target for biosimilar development
  - Hurdle is identifying appropriate patients and trials to provide the clinical basis for safety and efficacy
  - Practical issues in deployment when interchangeability is not established
  - What is the pharmacovigilance required?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