Biosimilars and Value-Based Oncology Treatment Pathways

This educational activity is supported by an educational grant from Teva Pharmaceuticals
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The Woodlands, Texas
Dr. Lyman: PI on Research Grant to Fred Hutchinson: Amgen

Dr. Rifkin: Advisory Board – Amgen, Coherus, EMD Serono (Fresenius), Pfizer
Learning Objectives

• Review the key clinical and regulatory concepts for the approval of biosimilar oncology treatments, including the totality of preclinical and clinical evidence; including safety, efficacy and immunogenicity, indication extrapolation, and interchangeability/substitution requirements

• Evaluate the latest advances, available clinical data, and emerging research surrounding biosimilar oncology treatments and their impact on the standard of oncology care

• Highlight the clinical, cost, and regulatory considerations that impact the integration of oncology biosimilar treatments into clinical pathways

• Discuss the anticipated benefits and challenges of integrating emerging biosimilars into oncology treatment pathways
Introduction

• The BPCI Act of 2009 authorized development, licensing, and regulatory approval of biosimilars in an effort to control rising costs

• The advent of biosimilars may yield a savings of $13 billion to $66 billion between 2014-2024

• The FDA has approved the first biosimilar while many biologic oncology biosimilars are under review or development that will radically change the oncology treatment landscape
Clinical pathways are also being developed by oncology organizations, health systems, and payers to rein in costs and increase efficiency while ensuring quality healthcare.

This session will explore the growing need for pathway professionals to incorporate biosimilar products within oncology clinical pathways.
Why the Need for Biosimilars?
### Why Interest in Biosimilars?

Rising Healthcare Costs

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**Cumulative Percent Increase**

- **Cancer drugs**
- **Cancer medical**
- **Healthcare**
- **US GDP**

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<table>
<thead>
<tr>
<th>Top 10 Medicare Drugs</th>
<th>Cost in Millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab</td>
<td>1220</td>
</tr>
<tr>
<td>Rituximab (oncology)</td>
<td>876</td>
</tr>
<tr>
<td>Infliximab</td>
<td>704</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>642</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>624</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>384</td>
</tr>
<tr>
<td>Denosumab</td>
<td>347</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>309</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>292</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>278</td>
</tr>
</tbody>
</table>

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More than 30% of spending on therapeutic drugs is concentrated in the top 5 therapy areas.

Rising Costs of Cancer Drugs

Cost of Cancer Drugs at Time of FDA Approval, 1965-2016

Global Spending on Biologics Continues to Increase

Global Biologics Sales, 2002-2017

- Biologics continue to outpace overall pharmaceutical drug spending growth
  - Expected to represent ~ 20% of global market value by 2017
- Patient access to biologic therapies is a concern

IMS Institute for Healthcare Informatics [website].
Unique Challenges for Oncology

- Pressure to use newest technologies/treatments
  - Sense of urgency as many cancer patients have a poor prognosis and are facing imminent death
- Providers often reluctant to switch to best supportive care, even at end of life
- Out-of-control cancer drug and test prices
  - Expensive treatments make appropriate cancer care a hardship or unaffordable
- In addition to high costs, most cancer treatments have potential serious complications


Evolution of the Oncologic and Supportive Care Market

- Assuming developed US market, oncology biosimilars market predicted to be $12 billion in 2020

Biosimilar Market Evolution, 2011-2020


## Potential Benefits of Biosimilars to the US Healthcare System

### Greater Competition
- Introduces competition and may drive down biologic costs
- Biosimilar manufacturers can take advantage of the latest technology

### Greater Patient Access
- Due to improved affordability, a greater proportion of eligible patients should be able to benefit from biologic treatment

### Foster Innovation
- Incentive for investment in the development of innovative new biologic products by originator companies
- Provides budgetary relief enabling the use of new treatments and therapies

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Prospects for Biosimilars in Oncology

- Biologic cancer treatments with > $20 billion in global spending are or will be targets for biosimilar development

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>2019</td>
<td>2019</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>2019</td>
<td>Expired</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2016</td>
<td>Expired</td>
</tr>
<tr>
<td>Denosumab</td>
<td>2017</td>
<td>2017</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Expired</td>
<td>Expired</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Expired</td>
<td>2017</td>
</tr>
</tbody>
</table>


Adapted from IMS Institute for Healthcare Informatics. *Innovation in Cancer Care and Implications for Health Systems: Global Oncology Trend Report.* 2014.
Introduction to Biosimilars: A Pathway to Decrease Cost and Increase Access

Robert M. Rifkin, MD, FACP
Biosimilars – Knowledge Gaps

• Defining:
  – Biologics, biosimilars, and biosimilarity
  – Interchangeability and the related rules regarding pharmacy level substitution
  – The role of biosimilars in clinical pathways

• Understanding:
  – The approval process and the use of “totality of evidence” to evaluate biosimilars
  – The safety and immunogenicity of a biosimilar are comparable to the originator biologic
  – The rationale for extrapolation of indications
  – The role of biosimilars in the Oncology Care Model (OCM)

What are Biosimilars?

• Biosimilar
  – Products that have been shown to be highly similar to the reference product in appropriate comparative, head-to-head quality, non-clinical and clinical studies

• Intended Copies of Biological Products (“me-too biologics”)
  – Copies of already licensed biological products that have not met the regulatory criteria for biosimilars

• Biobetter
  – Biological that has been structurally and/or functionally altered to achieve an improved or different clinical performance
  – Must go through the full development and approval process

Traditional Pharmaceuticals vs Biologics

- Differences in size, structure, and complexity
- Generics are commonly small-molecule drugs
  - Small molecules <100 atoms
  - Manufactured by chemical synthesis
  - Well-defined stable structure held together by strong chemical bonds
- A biologic is complex and large
  - Large molecules: 5,000-20,000 atoms
  - Produced by living cells
  - Spatial structures (secondary and tertiary) based on relatively weak bonds and post-translational modifications to form the 3D conformation
Pathway for Biosimilar Approval in the US: Biologics Price Competition and Innovation Act (BPCI):

- Most biologics are approved under the Public Health Service Act (PHSA) (rather than the Food, Drug, and Cosmetics Act)
  - Drug Price Competition and Patent Term Restoration Act (informally known as Hatch-Waxman Act) which enabled generic drugs of 1984 does not apply
  - Prior to Biologics Price Competition and Innovation Act (BPCI), no abbreviated pathway in PHSA
- BPCI is a component of the Patient Protection and Affordable Care Act of 2010
  - Amends the Public Health Service Act to define an abbreviated application process for biosimilars
- FDA Safety and Innovation Act (FDASIA)
  - Biosimilar User Fee Act (BsUFA)
  - Collect fees from biopharmaceutical industry for timely review of applications
  - Performance metrics

Why the Difference in Regulatory Requirements?

- **Small molecules → Generics**
  - Proof of quality (identical chemical structure)
  - Pharmacokinetic bioequivalence
  - Relies on clinical data from reference product

- **Biologics → Biosimilars**
  - Proof of quality and similarity
  - Pharmacokinetic bioequivalence
  - Clinical data showing comparable safety and efficacy
## Biologics: A Regulatory Perspective

<table>
<thead>
<tr>
<th>Description</th>
<th>351(a) Originator</th>
<th>351(k) Biosimilar</th>
<th>351(k) Interchangeable Biosimilar</th>
<th>351(a) Non-originator Biologic</th>
<th>351(a) Next-generation “Bio-better”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-to market biologic molecule; will likely be the reference product</strong></td>
<td><strong>“Highly similar” to reference product; approved via biosimilars pathway</strong></td>
<td>A biosimilar deemed that can be substituted for the reference without permission from prescriber</td>
<td>It is “another brand name” of an already approved biologic</td>
<td>Biologic that has been altered to achieve improved clinical outcomes</td>
<td></td>
</tr>
<tr>
<td><strong>Depth of data submitted to the FDA</strong></td>
<td><strong>“Standard” data package: efficacy and safety</strong></td>
<td>Abbreviated data package for comparability</td>
<td>Abbreviated data package for comparability; more information on efficacy and safety</td>
<td>“Standard” data package: efficacy and safety</td>
<td>“Standard” data package: efficacy and safety</td>
</tr>
<tr>
<td><strong>Compared to originator?</strong></td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes or no</td>
<td>Likely (standard of care)</td>
</tr>
</tbody>
</table>

Key Underlying Principles of Biosimilar Development

- The clinical efficacy and safety of the biologic molecule has already been demonstrated by the innovator.

- The biosimilar sponsor only requires evidence that the candidate biosimilar is not significantly different from the reference product.
  - Goal is not to replicate unnecessary clinical trials.
  - Smaller-scale direct comparisons and extrapolation.

- When a biosimilar is approved, there should not be an expectation that there will be differences in safety and efficacy.

Preclinical Assessment: Four Levels of Analytical Characterization

- High
  - Not similar → No further development through 351(k)
  - Similar
  - Highly similar → Additional information needed: analytical, comparative PK/PD, etc.
  - Highly similar with fingerprint-like similarity → High confidence; appropriate for targeted clinical studies
  - Very high confidence; appropriate for more targeted clinical studies

PK = pharmacokinetic; PD = pharmacodynamic.
Biosimilars – Clinical Trial Design

Biosimilars Phase I Study Design (Bridging)

Permits use of EU product in clinical trials

EU = European Union
Biosimilars – Typical Clinical Trial Design: Follicular Lymphoma (Low-Tumor Burden / Asymptomatic)

- Biosimilars Phase III Study Design
- Patients will be randomized in 1:1 ratio to rituximab-biosimilar or rituximab-EU
  - Randomization stratified into low-, medium-, and high-risk patients using the Follicular Lymphoma International Prognostic Index 2 (FLIPI2)

**Follicular Lymphoma Study Timeline**

**SCREENING**
- Rituximab Administration Days 1, 8, 15, 22
- R-EU
- R-Bio

**RANDOMIZATION**

**Follow-Up Visits – Safety & Response Evaluation**
- Week 26 Primary Endpoint
- Week 52 End of Study
- Week 39
- Week 13
- Day 29

**Follicular Lymphoma Study Timeline**
Challenges: Variability and Drift

- Significant differences in drug products (variability and drift) can arise due to:
  - production at different sites
  - changes to manufacturing processes after initial approval
    - FDA or EMA approval required for changes in manufacturing process
- Manufacturers need to be vigilant for any changes in production and must always assume that they can result in clinically significant issues

Both biologics and biosimilars are subject to product variability and drift!

EMA = European Medicines Agency.
Immunogenicity Concerns

• All biologics (not just biosimilars) confer a risk of immunogenicity
  – Related to patient, disease, and product factors
  – Consequences include neutralizing antibodies or cytokine release
  – Scientific tools for detecting immunogenicity exist, but they are not precise

• Changes to the structure of the protein increase variation in immunogenicity
  – Lot-to-lot and between manufacturers
  – Variations in manufacturing must be minimized

• Clinical consequences
  – Loss or diminished efficacy or safety
  – General immune responses (eg, allergy, anaphylaxis) - case reports of rare but serious adverse reactions have been reported

Specific clinical trial design will depend on what residual questions remain
- Clinical evaluation should evaluate relevant and sensitive endpoints
  - Trials do not need to establish primary efficacy and safety of the drug
- Clinical studies should be designed to demonstrate neither decreased nor increased activity
- The extent of trials will differ between ‘highly similar’ and ‘fingerprint similarity’

Clinical Immunogenicity
- Goal is to evaluate potential differences in incidence and severity of immune responses using endpoints such as antibody formation (binding, neutralizing), cytokine levels, etc
- FDA recommends a comparative parallel (ie, head-to-head) study

Framework for Extrapolation

Patient Factors
- Similarity of biologic disposition: PK/PD
- Organ function
- Age, ethnicity, etc

Disease Factors
- Defined MOA
- Similarity in target distribution
- Single vs combo therapy

Endpoint Factors
- Differential efficacy and toxicity
- Short-term vs long-term
- Sensitivity of surrogate outcomes

Quantitative Evidence
Disease progression: Disease models could be used to characterize differences in disease progression between groups.
PK and PD: using existing data and physiology-based PK (and PD) modelling and simulation to investigate the relationship between PK/PD, age and other important covariates.
Clinical response: quantitative synthesis or modelling of all existing data (in vitro, preclinical and clinical) to predict the degree of similarity in clinical response (efficacy, some safety aspects) between source and target population.

Determine Appropriateness of Indication Extrapolation
No extrapolation; extrapolation to some indications; extrapolation to all indications

MOA = mechanism of action.

What a Clinician Wants Before They Will Feel Comfortable With Extrapolation

- PK analysis is essential to show equivalent drug exposure
  - PK can differ by the clinical context
    (eg, rituximab for lymphoma vs rheumatoid arthritis)

- Monitoring for antidrug antibodies is a major safety measure

- Clinical efficacy should be demonstrated in appropriate patient populations
  - Independent trials in NHL and nonmalignant diseases (for rituximab)
  - Single agent activity in first-line follicular lymphoma as a sensitive indicator of activity (for rituximab)
  - Activity in the metastatic setting (for trastuzumab)

NHL = non-Hodgkin’s lymphoma
Challenges: Pharmacovigilance

- Post-approval pharmacovigilance for efficacy and safety of biologic agents is important and of particular importance when considering biosimilars
  - Product drift may occur over time and space
  - Rare or delayed toxicities may only emerge post-approval
  - Population-based assessments may identify rare safety concerns
  - Might be mandatory for some products
- Biosimilar manufacturers should work with FDA early to discuss approach

A biosimilar may also be designated as “interchangeable” if there is proof that:

- **Switching** or **alternating** between the biosimilar and the reference product does not affect safety or efficacy any more than using the reference product more than once without such alternating or switching.

The designation of “interchangeability” requires higher standards than “biosimilarity” alone.
Interchangeability

- Interchangeability - use of a biosimilar without impacting on safety or efficacy if it is alternated or switching between the biosimilar and the innovator compared to the use of the innovator without alternation or switching
- Draft guidance on interchangeability evaluation issued by FDA
  - There are no approved interchangeable drugs
- A drug must be designated to be interchangeable to permit drug substitution by a pharmacist
  - Drug substitution rule and regulations are determined at the State level
  - Designation of a biosimilar as interchangeable does not automatically allow drug substitution

Clinician Perspective: Finding the Right Balance

Approval Process Requires Too Large Amount of Data

Biosimilar Development and Regulatory Approval Process

Benefits
- Greater healthcare provider confidence in biosimilar product
- Greater acceptance and uptake of biosimilar?
- Fewer safety concerns

Risks
- Higher development costs
- Lower pharmacoeconomic benefit over innovator product

Approval Process Requires Too Little Amount of Data

Benefits
- Lower development costs
- Greater pharmacoeconomic benefit over innovator product

Risks
- Lower healthcare provider confidence in biosimilar product
- Less acceptance and uptake of biosimilar?
- Greater safety concerns
Clinician Perspective: Addressing Concerns

- Physicians skeptical of efficacy, safety, and impact on reimbursement; concerned that use will be forced upon them
- Physician perception will be that cost is the main issue
- Strong clinical data will be important for acceptance
- Education essential to accelerate uptake after approval
  - Unbiased experts, focused on clinical data
  - National meetings and online education

Current Status on Oncology Biosimilars in the US

Gary H. Lyman MD, MPH, FASCO, FRCP
Oncology Biosimilars Available or Under Review in the United States

• Supportive care agents
  – Erythropoietin
  – Filgrastim
  – Pegfilgrastim

• Therapeutic agents
  – Bevacizumab
  – Rituximab
  – Trastuzumab
• Pegfilgrastim, filgrastim, tbo-filgrastim, as well as filgrastim-sndz and other biosimilars, as they become available, can be used for the prevention of treatment-related febrile neutropenia

• The choice of agent depends on convenience, cost, and the clinical situation
# Bevacizumab Biosimilars with Registered Phase III Clinical Trials (Patent Expiration: 2019)

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Disease</th>
<th>Primary Endpoint</th>
<th>Available Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP 215 * NCT01966003, completed</td>
<td>NSCLC</td>
<td>ORR</td>
<td>Phase III: Clinical equivalence with bevacizumab (N=642)</td>
</tr>
<tr>
<td>BCD-021** NCT01763645, active</td>
<td>NSCLC</td>
<td>ORR</td>
<td>Phase III: Noninferiority; similar efficacy (ORR), safety, and immunogenicity to bevacizumab (N=138)</td>
</tr>
<tr>
<td>BI-69552 NCT02272413, active</td>
<td>NSCLC</td>
<td>ORR</td>
<td>Phase I: Bioequivalence to bevacizumab in healthy individuals</td>
</tr>
<tr>
<td>PF-06439535 NCT02364999, enrolling</td>
<td>NSCLC</td>
<td>ORR</td>
<td>Preclinical: Similar structure and in vitro biological activity; similar in vivo toxicologic and toxicokinetic to bevacizumab</td>
</tr>
<tr>
<td>SB8 NCT02754882, enrolling</td>
<td>NSCLC</td>
<td>ORR</td>
<td>No findings yet</td>
</tr>
</tbody>
</table>

*Recommended for approval by ODAC to the FDA. **Submitted to the FDA.

NSCLC = non-small cell lung cancer.


Bevacizumab Biosimilar ABP-215 PH III Trial: NSCLC

Stage IV or recurrent metastatic, nonsquamous NSCLC
Initiating 1st-line carboplatin/paclitaxel

Screening

Primary endpoint:
RR of ORR\textsuperscript{a}

ABP215 15 mg/kg IV + carboplatin/paclitaxel Q3W (n = 328)

Bevacizumab 15 mg/kg IV + carboplatin/paclitaxel Q3W (n = 314)

D = day; EOS = end of study; q3w = every 3 weeks; RR = risk ratio.

\textsuperscript{a} PR or CR by RECIST v1.1.

• 2-sided CIs fell within the predefined equivalence margin for RR (0.67, 1.5)
• Efficacy (ORR)*: 128 (39%) ABP 215; 131 (42%) ref bevacizumab
• Clinical equivalence**
  – 0.93 RR of ORR between APB 215 and bevacizumab (2-sided 90% CI, 0.80-1.09) in ITT populations***
  – Prespecified equivalence margin (90% CI, 0.67-1.5)
• Safety: Comparable frequency, type, and severity of AEs
• Immunogenicity: Similar, few patients developed ADA for ABP 215 (n = 4) and bevacizumab (n = 7); no patients developed neutralizing antibodies*

*ITT set, ORR based on RECIST v1.1; **2-sided CIs fell within the predefined equivalence margin for RR (0.67, 1.5); ***Based on generalized linear model adjusted for randomization stratification factors geographic region, ECOG Performance Status, and sex.
ADA = antidrug antibodies; ITT = intent-to-treat.
Rituximab Biosimilars With Registered Phase III Trials (Patent Expiration: 2016)

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Primary Endpoint</th>
<th>Disease</th>
<th>Available Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP2013 NCT01419665, active</td>
<td>ORR</td>
<td>FL</td>
<td>Phase III: Equivalent ORR and similar efficacy, PK, PD, and safety to rituximab-EU in patients with FL (N=629)</td>
</tr>
<tr>
<td>BCD-020 NCT01701232, enrolling</td>
<td>CD20+ count, ORR</td>
<td>Indolent NHL</td>
<td>Phase III: Equivalent PK and similar PD and safety to rituximab in indolent NHL; similar ORR and safety in BCNHL (n=92) Phase III: Equivalent efficacy of BCD-020 compared with rituximab in patients with RA (N=160)</td>
</tr>
<tr>
<td>PF-05280586 NCT02213263, enrolled</td>
<td>ORR</td>
<td>LTBFL</td>
<td>Preclinical: Similar structural and in vitro characteristics and in vivo PK and immunogenicity to rituximab Phase I: Similar PK to rituximab-EU and –US; comparable effectiveness, immunogenicity, and safety to rituximab in patients with active RA</td>
</tr>
<tr>
<td>HLX01 NCT02787239, enrolling</td>
<td>ORR</td>
<td>DLBCL</td>
<td>Phase I/II studies completed, data not published</td>
</tr>
</tbody>
</table>

BCNHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; LTBFL = low-tumor-burden follicular lymphoma; ORR = overall response rate; NHL = non-Hodgkin lymphoma; RA = rheumatoid arthritis.

## Rituximab Biosimilars With Registered Phase III Trials

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Endpoint</th>
<th>Disease</th>
<th>Available Data</th>
</tr>
</thead>
</table>
| CT-P10         | ORR      | FL      | Phase III: Equivalent PK; similar efficacy, PD, immunogenicity, and safety profile to rituximab in patients with RA (N=189)  
Phase III: Noninferiority of efficacy compared with rituximab in previously untreated AFL; similar PK and comparable B-cell kinetics and immunogenicity to rituximab in AFL (N=121) |
| NCT02260804, enrolling NCT02162771, active |          |         |                                                                                                                                               |
| RTXM82         | ORR      | DLBCL   | Phase III: Comparable PK and safety profile (immunogenicity) to rituximab in combination with CHOP as first-line treatment of DLBCL at interim analysis of 24 patients |
| NCT02268045, active |          |         |                                                                                                                                               |
| ABP798         | RD, ORR  | NHL     | No published data                                                                                                                             |
| NCT02747043, enrolling |          |         |                                                                                                                                               |
| MabionCD20     | PK       | DLBCL   | No published data                                                                                                                             |
| NCT02617485    |          |         |                                                                                                                                               |

*BLA accepted for review by the FDA June 29, 2017.

AFL = advanced-stage follicular lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; RD = risk difference.

Rituximab Biosimilar CT-P10

- Trials conducted in 600+ patients; up to 104 weeks of data
- Phase III Trial: 140 newly diagnosed AFL patients randomly assigned to either CT-P10 (n=66) or rituximab (n=68) in combination with CVP
  - ORR= 64/66 (97.0%) CT-P10 group; 63/68 (92.6%) rituximab group (4.3%; one-sided 97.5% CI −4.25)
  - CT-P10 demonstrated similar PK (AUCtau and CmaxSS) and safety when administered in combination with CVP
  - Ratio of geometric least squares means (CT-P10/rituximab)*
    • 102.25% (90% CI 94.05-111.17) for AUCtau
    • 100.67% (93.84-108.00) for CmaxSS
  - Treatment-emergent AEs: 58/70 (83%) CT-P10 group; 56/70 (80%) rituximab group
  - B-cell kinetics and immunogenicity were comparable

*All CIs within the bioequivalence margin of 80-125%.
AFL = advanced follicular lymphoma; BLA = biologic licensing application; CVP = cyclophosphamide, vincristine, prednisone; AE = adverse event.
### Trastuzumab Biosimilars with Registered Phase III Clinical Trials (Patent Expiration: 2019)

<table>
<thead>
<tr>
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<th>Primary Endpoint</th>
<th>Disease</th>
<th>Available Data</th>
</tr>
</thead>
</table>
| BCD-022 NCT01764022, complete | ORR | HER2+ MBC | Phase I: BCD-022 showed similar PK and safety to trastuzumab in patients with HER2+ MBC  
Phase III: Noninferiority to trastuzumab; similar safety, tolerability, and immunogenicity (N=126) |
| PF-05280014 NCT01989676, active | PK, pCR (2nd), ORR | HER2+ EBC | Preclinical: PF-05280014 showed similar structural and functional properties, PK, and immunogenicity profiles to trastuzumab  
Phase I: PF-05280014 showed similar PK, safety, and immunogenicity to trastuzumab in 105 healthy volunteers  
Phase III: Positive top-line results announced via press release (N=226) |
| ABP 980* NCT01901146, complete | pCR | HER2+ EBC | Phase I: ABP 980 showed comparable PK, PD, safety, tolerability, and immunogenicity to trastuzumab in healthy volunteers |

*BLA submitted to FDA July 31, 2017. **BLA accepted by the FDA. ***Approved by FDA ODAC.
OS = overall survival; PFS = progression-free survival; TTP = time to progression; TTR = time to response.
### Biosimilar Trastuzumab Biosimilars with Registered Phase III Clinical Trials (Patent Expiration: 2019)

*BLA submitted to FDA July 31, 2017. **BLA accepted for review by the FDA. ***Recommended for approval by ODAC to the FDA.

<table>
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</thead>
<tbody>
<tr>
<td>CT-P6**</td>
<td>pCR</td>
<td>HER2+ EBC</td>
<td>Phase I/IIB: CT-P6 showed equivalent PK and similar safety to trastuzumab in patients with HER2+ MBC</td>
</tr>
<tr>
<td>NCT01084876, active</td>
<td>ORR</td>
<td>HER2+ EBC</td>
<td>Phase III: Similar efficacy (pCR) to neoadjuvant trastuzumab; also similar secondary endpoints (ORR, PK, PD, and safety; N=549)</td>
</tr>
<tr>
<td></td>
<td>ORR</td>
<td>HER2+ MBC</td>
<td>Phase III: CT-P6 showed similar efficacy (ORR) and safety to trastuzumab in combination with paclitaxel (N=475)</td>
</tr>
<tr>
<td></td>
<td>ORR</td>
<td>HER2+ MBC</td>
<td>Phase III: Similar efficacy (ORR, TTP, TTR) and safety to trastuzumab (N=475)</td>
</tr>
<tr>
<td>SB3-G31-BC</td>
<td>pCR</td>
<td>HER2+ EBC</td>
<td>Phase III: Equivalent breast pCR rate to trastuzumab; similar safety, PK, and immunogenicity (N=875)</td>
</tr>
<tr>
<td>NCT02149524, complete</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hercules/Myl14010***</td>
<td>ORR</td>
<td>HER2+ MBC</td>
<td>Phase III: Equivalent Week 24 ORR in combination with taxanes; equivalent Week 46 TTP, PFS, or OS (N=500)</td>
</tr>
<tr>
<td>NCT02472064, active</td>
<td></td>
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* OS = overall survival; PFS = progression-free survival; TTP = time to progression; TTR = time to response.

Trastuzumab Biosimilar CT-P6 PH III Trial: HER2+ Early BRCA Neoadjuvant/Adjuvant Setting

<table>
<thead>
<tr>
<th>Efficacy Endpoints</th>
<th>CT-P6</th>
<th>Reference Trastuzumab</th>
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<tr>
<td>PP</td>
<td>n=248</td>
<td>n=256</td>
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<td>pCR (ypT0/is, ypN0)</td>
<td>46.8% (40.5-53.2)</td>
<td>50.4% (44.1-56.7)</td>
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<td>Stage I and II</td>
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<td>55.0%</td>
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<tr>
<td>Stage IIIa</td>
<td>36.2%</td>
<td>33.3%</td>
</tr>
<tr>
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<td>55.1% (48.8-61.3)</td>
</tr>
<tr>
<td>pCR without DCIS (ypT0, ypN0)</td>
<td>39.9% (33.8-46.3)</td>
<td>41.4% (35.3-47.7)</td>
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<tr>
<td>Overall response rate**</td>
<td>88.3% (83.6-92.0)</td>
<td>89.5% (85.0-92.9)</td>
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<tr>
<td>ITT</td>
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<td>N=278</td>
</tr>
<tr>
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Trastuzumab Biosimilar CT-P6 PH III Trial: HER2+ Early BRCA Neoadjuvant/Adjuvant Setting: Efficacy Endpoints

### Efficacy Endpoints

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The 95% CIs for the risk ratio estimate were within the equivalence margin (0.74, 1.35) in PPS and ITT analysis.

Trastuzumab Biosimilar MYL-1401O PH-III Trial: HER2+ MBC

- HER2+ BC; No prior therapy for m-disease (N=500)
- Randomized to MYL1401O or reference trastuzumab (q 3 weeks, ≥ 8 cycles + taxane)
- Primary endpoints: Objective ORR at Week 24
- Secondary endpoints: TTP, PFS, OS at Week 48, safety

MBC = metastatic breast cancer.
Trastuzumab Biosimilar MYL-14010 PH-III Trial: HER2+ MBC

• Efficacy - No significant differences in
  – TTP (41.3% vs 43.0%; −1.7%; 95% CI, −11.1%-6.9%; \(P = .68\))
  – PFS (44.3% vs 44.7%; −0.4%; 95% CI, −9.4%-8.7%; \(P = .84\))
  – OS (89.1% vs 85.1%; 4.0%; 95% CI, −2.1%-10.3%; \(P = .13\))

• Safety
  – At least 1 AE: 98.6% (239) MYL-14010; 94.7% (233) trastuzumab
  – Most common AEs (biosimilar vs trastuzumab): neutropenia (57.5% vs 53.3%), peripheral neuropathy (23.1% vs 24.8%), and diarrhea (20.6% vs 20.7%)

### Extrapolation of Indication

<table>
<thead>
<tr>
<th>Trastuzumab*</th>
<th>Bevacizumab</th>
<th>Cetuximab</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Met CRC</td>
<td>LA or RA HNSCC</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Met gastric adenocarcinoma</td>
<td>NSCLC</td>
<td>LR or met HNSCC</td>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>GEJ adenocarcinoma</td>
<td>Glioblastoma</td>
<td>KRAS wild-type, EGFR+ met CRC</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Met RCC</td>
<td></td>
<td></td>
<td>Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Cervical</td>
<td></td>
<td></td>
<td>Microscopic polyangiitis</td>
</tr>
<tr>
<td>Ovarian, fallopian tube, peritoneal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* All indications for HER2+ disease.

GEJ = gastroesophageal junction; HNSCC = head and neck squamous cell carcinoma; LR = locoregional; met = metastatic; RA = regionally advanced; RCC = renal cell carcinoma.
Integrating Biosimilars Into Oncology Practice

Opportunities and Challenges

- Reduce unsustainable increase in healthcare costs and increase pt access to biologic agents
- Approval based on limited clinical data vs reference
- Biologic variability, drift, and immunogenicity
- Extrapolation of biosimilar indications to indications for which the reference product was approved
- Interchangeability and automatic substitution
- Need for pharmacovigilance and physician and pt education
- High quality, clinically driven pathways provide an opportunity for improving efficiency and effectiveness while containing costs and enhancing patient access to high quality cancer care
Biosimilars and Value-Based Oncology Treatment Pathways

Robert M. Rifkin, MD, FACP
ASCO Criteria for High-Quality Clinical Pathways in Oncology

<table>
<thead>
<tr>
<th>Criteria for High Quality Pathways</th>
<th>Development</th>
<th>Implementation &amp; Use</th>
<th>Analytics</th>
</tr>
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<tbody>
<tr>
<td>Expert Driven &amp; Reflects Stakeholder Input</td>
<td>Clear &amp; Achievable Expected Outcomes</td>
<td>Efficient &amp; Public Reporting of Performance Metrics</td>
<td></td>
</tr>
<tr>
<td>Transparent, Evidence-Based, Patient-Focused, Clinically Driven, &amp; Up to Date</td>
<td>Integrated, Cost-Effective Technology &amp; Decision Support</td>
<td>Outcomes-Driven Incentives</td>
<td></td>
</tr>
<tr>
<td>Comprehensive &amp; Promotes Participation in Clinical Trials</td>
<td>Efficient Processes for Communication &amp; Adjudication</td>
<td>Promote Research in Value and Impact of Pathways and Care Transformation</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Pathways in The US Oncology Network
US Oncology Pathways Evolution

- **2005** Pathways concept identified
- **2006** First PWs released: Breast, Colon, NSCLC, SCLC, Prostate, MM, Ovarian
- **2009** 1st Pathways Publication
- **2010** 1st Innovent contract signed
- **2010** Practice Pathway Improvement (PPI) Program launched
- **2010** Value Pathways powered by NCCN™ launched
- **2011** 300,000 regimens assessed for Pathways
- **2013** NCCN co-development: Value Pathways powered by NCCN™
- **2014** Clear Value Plus™ technology platform launched
- **2014** Practice Pathway Improvement (PPI) Program launched
- **2014** Innovent results published
- **2015** Clear Value Plus™ technology platform launched
- **2016** October 100,000 regimens assessed for PWs via CVP
- **2017** April 117 Practices, 1,648 Providers, 4 EHR integrations, 170,000 regimens

*May 2008 100,000 regimens assessed for Pathways

*2006 Pathways decision support logic released in iKM

*March 2011 300,000 regimens assessed for Pathways

*April 2015 500,000 regimens assessed for Pathways

*October 2016 100,000 regimens assessed for PWs via CVP

*April 2017 117 Practices, 1,648 Providers, 4 EHR integrations, 170,000 regimens

*1st PWs released: Breast, Colon, NSCLC, SCLC, Prostate, MM, Ovarian

- New PW development
- Clear Value Plus EHR Integration
Biosimilar Adoption: Barriers in US (post-approval)*

| Physician behavior | • The basic 2: “Why would you ever switch a patient away from gold standard”; “Buying the brand supports new R&D for your specialty”
|                    | • Exit from the therapy altogether |
| Lack of patient incentive | • No direct benefit, other than potentially the copay
|                    | • Isolated from copay or coinsurance through patient assistance plans |
| Boots on the ground | • Pharma will reargue the logic of biosimilar approvability with each doctor – “inferior clinical package”
|                    | • Biosimilars can’t match the innovator reach |
| Professional societies | • Often close relations or funded by innovators
|                    | • Recommending bodies can support or resist biosimilars (eg, use of filgrastim in healthy volunteers in EU; use of Remsima (infliximab biosimilar) in GI patients) |
| Service wrapper | • Innovators have direct-to-patient services
|                    | • Costs (including copay assistance) can reach 20% of drug revenue
|                    | • A conflict of interest for channel company that owns specialty pharmacies |

Biosimilars belong on Clinical Pathways!!

*Courtesy R. Rifkin
Biosimilars: Everyone’s Dilemma

How do you differentiate something that is “essentially the same”?
Integrating Biosimilars Into The Oncology Care Model and Value-Based Pathways
Overview: Oncology Care Model (OCM)

Goal
To advance “better care; smarter spending; healthier people”.

Who’s eligible to participate:
Medicare FFS beneficiaries starting chemo for all cancer types

Practice Transformation
- Patient Navigation
- Access to Care 24/7
- IOM Care Plan
- Advance Care Planning
- Team Care
- Reporting Practice & Claims Based Measures
- Eligibility & Enrollment

Two forms of payment:
- $160 per beneficiary/ month fee
- Performance-based payment to incentivize practices to lower total cost of care

OCM Focuses on Total Cost of Care

Total health care expenditures will be calculated beginning AFTER the first chemotherapy administration or fill date (for orals)

- Inpatient
- Surgery
- Medications & Biosimilars
- Radiation Oncology
- Lab and Imaging
- Emergency Department
The OCM: Cost of Care Based on CMS Summary Data *

*National data registry based on 2,355,000 episodes
OCM Concepts of Change

- Eligibility & Enrollment
- Clinical (work flows)
- Navigation
- Access to Care 24/7
- Documentation
- Billing
1. Provide 24/7 patient access to an appropriate clinician who has real-time access to patient’s medical records

2. Use an ONC-certified EHR and attest to Stage 2 of Meaningful Use by the end of the third model performance year

3. Utilize data for continuous quality improvement

4. Provide core functions of patient navigation

5. Document a care plan that contains the 13 components in the Institute of Medicine Care Management Plan.

6. Treatments consistent with nationally recognized clinical guidelines or pathways
Value Pathways powered by NCCN

A Way to Increase Access and Decrease Cost
Integrates Well with the Oncology Care Model

Physician-led clinical pathways
Co-developed with NCCN

NCCN Guidelines®
Value Pathways powered by NCCN
Value Pathways powered by NCCN™: Meet ASCO Criteria for High-Quality Clinical Pathways in Oncology

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<td>✓</td>
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<td>15) Promotes Research and Continuous Quality Improvement</td>
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Results: Impact of Integrated Decision Support

- 9 practices, 633 providers and 30,666 regimens assessed

After utilization of Clear Value Plus Decision Making Tool:
- Increase in pathways adherence (+7.2%)
- Increase in data elements captured per decision

Biosimilars and Clinical Pathways: Benefits to Stakeholders and Society

- Biosimilars: Additional options at lower cost
- Savings and efficiencies to health system
- Foster innovation
- Increase access to biologics
- Better health outcomes

Conclusions

• New reimbursement models are driving new care delivery models:
  – Quality, performance, and resource consumption will be measured for all Medicare providers [MIPS, Advanced Alternative Payment Models (APMs)]
  – The value of drugs and technology will be scrutinized much more carefully by providers

• Decision support tools can improve documentation of critical data elements and reduce missing data.

• Decision support tools can be used in a practice to facilitate assessable data, improve compliance with guidelines, and allow attestation of quality metrics

• Adherence to clinical pathways remains a cornerstone for value-based care
• Biosimilars will not only decrease the cost of healthcare, but will add value

Do pathways add value? I think they do…
Biosimilars – The perfect fit.
Questions?