Building Blocks for Biosimilar Integration in Cancer Care

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View faculty bios at www.ashpadvantage.com/biosimilarsinoncology

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Building Blocks for Biosimilar Integration in Cancer Care

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1.0 hr CE

Disclosure of Relevant Financial Relationships

Sandra Cuellar- speakers bureau for Genentech; advisory board for Coherus Biosciences, Inc.

Adam Brufsky- consultant for Amgen, Novartis, Pfizer, and Eisai

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Learning Objectives

- Describe the regulatory framework and approval pathway for biosimilar products.
- Define “extrapolation” and “interchangeability” and the respective data required in the biosimilar approval process.
- Interpret the endpoints commonly seen in clinical trials of biosimilars compared to those used for reference products.
- Explain the types of clinical trials used for regulatory approval of biosimilars using currently available oncology biosimilars as examples.

Abbreviations

- D-FEC- docetaxel-fluorouracil/epirubicin/cyclophosphamide
- EBC- early breast cancer
- EMA- European Medicines Agency
- EP/PR- estrogen receptor/progesterone receptor
- FDA- U.S. Food and Drug Administration
- INN- international nonproprietary name
- PK/PD- pharmacokinetic/pharmacodynamic
- Q3W- every 3 weeks
- WHO- World Health Organization
How many oncology patients on biologics do you personally provide care to each week?

a. Less than 25
b. 26-75
c. 76-125
d. More than 125
e. None - I am not directly involved in patient care
Building Blocks for Biosimilar Integration in Cancer Care

Rational Medicine Use

Patients receive medications appropriate to their clinical needs

Doses that meet their individual requirements

For adequate period of time

At the lowest cost to them and their community

WHO. The pursuit of responsible use of medicines: sharing and learning from country experiences. 2012.

Trends in Health Care Expenditures

Global spending on medicines reached $1.2 trillion in 2018 and is set to exceed $1.5 trillion by 2023

United States pharmaceutical expenditures increased 5.5% in 2018 for a total of $476.2 billion

Patient out-of-pocket costs increased to $61 billion

Biologics account for 38 – 40% of all pharmaceutical spending, but <2% of Americans use them

Top Antineoplastic Drugs by Expenditures in U.S. Clinics in 2018

<table>
<thead>
<tr>
<th>Drug</th>
<th>Expenditures ($ Thousands)</th>
<th>% Increase from 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>3,433,985</td>
<td>35.4</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>3,372,394</td>
<td>88.4</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2,882,704</td>
<td>2.6</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>2,471,007</td>
<td>8.8</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2,378,412</td>
<td>1.1</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>1,126,661</td>
<td>32.2</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>998,628</td>
<td>43</td>
</tr>
</tbody>
</table>

WHO. The pursuit of responsible use of medicines: sharing and learning from country experiences. 2012.

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Biosimilars are Needed to Disrupt Pharmaceutical Biologic Ecosystem

Biologics have revolutionized the treatment of cancer

Biologics are expensive, and costs have increased progressively

Introduction of biosimilars increases competition with reference (originator) biologic without compromising quality

Biologics Price Competition & Innovation (BCPI) Act of 2009

Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic</td>
<td>An approved product composed of proteins, nucleic acids, or combinations of these, or living entities such as cells and tissues, which is isolated from natural sources (humans, animals, microorganisms) and produced by biotechnology methods and other cutting edge technology</td>
</tr>
<tr>
<td>Biosimilar</td>
<td>A biologic product developed such that there are “no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency” and “demonstrates similarity to the reference product in terms of quality characteristics, biological activity, and efficacy based on a comprehensive comparability exercise”</td>
</tr>
<tr>
<td>Generic Drug</td>
<td>Small or low molecular weight chemically synthesized compounds consisting of a simple, well defined structure that is independent of the manufacturing process and easy to characterize completely</td>
</tr>
</tbody>
</table>

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# Building Blocks for Biosimilar Integration in Cancer Care

<table>
<thead>
<tr>
<th>Development cost</th>
<th>Generic</th>
<th>Biologic</th>
<th>Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>$2 – 3 million</td>
<td>$800 million</td>
<td>$100-300 million</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to market</th>
<th>2-3 years</th>
<th>8-10 years</th>
<th>7-8 years</th>
</tr>
</thead>
</table>

**Clinical studies**
- Bioequivalence studies in health volunteers
- Phase I, II, III (efficacy and safety)
- PK/PD studies in healthy volunteers
- Randomized comparison study in a sensitive population

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>20 - 50</th>
<th>800 - 1000</th>
<th>100 - 500</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Post-approval activities</th>
<th>Pharmacovigilance</th>
<th>Phase IV pharmacovigilance</th>
<th>Phase IV pharmacovigilance</th>
</tr>
</thead>
</table>

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**Pharmacovigilance**

- **Safety** – As more biosimilars are marketed and market uptake increases, real-world safety and efficacy data will emerge
  - Postmarketing pharmacovigilance efforts may likely be used to monitor safety and efficacy of biosimilars
  - European Medicines Agency mandated pharmacovigilance monitoring for all approved biosimilars
    - As a result, the European experience, with over 400 million patient days with biosimilars, suggests that lingering safety concerns about biosimilars have been addressed
  - There are NO provisions in the BCPI Act for pharmacovigilance plans of biosimilars
  - FDA interchangeability guidance document refers back to documents for all products
    - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005)

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Biologics/biosimilars have inherent heterogeneity, and slight differences in structure and clinically inactive components are expected


Unintended shifting of product attributes away from their intended value
- Changes in attributes over time are inherent to biologic drugs

Factors
- Inherent batch-to-batch variability in manufacturing process
- Process drifts that lead to gradual changes in attributes

Extensive characterization data are used to establish proven acceptable ranges for quality attributes

Building Blocks for Biosimilar Integration in Cancer Care

**FDA Guidance onNaming**

**Goal:** facilitate pharmacovigilance and prevent inadvertent substitution

- **INN + random 4 letter suffix for all biologics**
  - Unique
  - Devoid of meaning
  - 4 lower case letters, at least 3 are distinct
  - Nonproprietary
  - Example- Bevacizumab-awwb, Bevacizumab-bvzr

**Benefits**

- Common INN will group similar biologics in electronic information systems
- Having suffix for all products reduces perception that biosimilar is inferior to the reference product


**FDA Approved Biosimilars**

<table>
<thead>
<tr>
<th>Filgrastim</th>
<th>Pegfilgrastim</th>
<th>Trastuzumab</th>
<th>Bevacizumab</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim-sndz</td>
<td>Pegfilgrastim-jmdb</td>
<td>Trastuzumab-dkst</td>
<td>Bevacizumab-awwb</td>
<td>Rituximab-abbs</td>
</tr>
<tr>
<td>Filgrastim-aafi</td>
<td>Pegfilgrastim-cbqv</td>
<td>Trastuzumab-pkrb</td>
<td>Bevacizumab-bvzr</td>
<td>Rituximab-pvvr</td>
</tr>
<tr>
<td>Pegfilgrastim-bmez</td>
<td>Pegfilgrastim-bmez</td>
<td>Trastuzumab-dttb</td>
<td>Trastuzumab-qyyp</td>
<td></td>
</tr>
</tbody>
</table>

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Regulatory Framework for Biosimilars

FDA Definition of Biosimilar

- “The biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components, and there are **no clinically meaningful differences** between the biosimilar product and the reference product in terms of **safety, purity, and potency of the product.**”
- Must utilize same mechanism of action for the condition prescribed
- Must utilize same route of administration, dosage form, strength, and proposed condition as reference product
- Expected to produce same clinical result in any given patient

# FDA Approval Pathways

## How Do Clinical Development Pathways for New Biologics vs. Biosimilars Compare?

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>New Biologic – 351(a)</th>
<th>Biosimilar – 351(k)</th>
</tr>
</thead>
</table>
| Preclinical and animal toxicology studies | ▪ Defines pharmacologic, toxicologic effects prior to human studies  
▪ Dose and schedule determined; immunogenicity assessed  
▪ Clinical activity and safety evaluated in given patient population |
| Phase I and II       | ▪ Assessed in large population to confirm therapeutic benefit  
At each step, FDA determines if further studies are needed |
| Phase III            |                                          | ▪ Structural/functional analyses  
▪ Animal studies including assessment of toxicity  
▪ Human PK, PD, immunogenicity compared to reference biologic  
If requested by FDA because of residual uncertainty, typically designed to demonstrate equivalence or noninferiority to reference biologic |

**Immunogenicity**

- Ability of a substance to provoke an immune response
- All biologics confer risk of immunogenicity
  - Related to patient, disease, and product factors
  - Consequences include neutralizing antibodies or cytokine release
- Changes to structure of protein increase variation in immunogenicity
  - Lot-to-lot and between manufacturer variability
- Clinical consequences
  - Loss or diminished efficacy or safety


**Biosimilar Pathway Represents a Paradigm Shift from Standard Originator Registration Pathway**

Establish biosimilarity based on totality of evidence, not reestablish benefit

Building Blocks for Biosimilar Integration in Cancer Care

Typical Structure and in vitro Assessment for Monoclonal Antibody Biosimilar

- Monoclonal antibody may have >40 attributes identified
- Attributes may be evaluated using >50 different assays
- Scientific understanding of how these attributes influence safety, efficacy, immunogenicity, and PK/PD is critical for biosimilar success

<table>
<thead>
<tr>
<th>Category</th>
<th>Attribute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fab-mediated biologic activity</td>
<td>Potency</td>
</tr>
<tr>
<td></td>
<td>Receptor binding</td>
</tr>
<tr>
<td></td>
<td>Receptor signaling</td>
</tr>
<tr>
<td></td>
<td>Receptor specificity</td>
</tr>
<tr>
<td>Fc-mediated biologic activity</td>
<td>Binding to FcRN</td>
</tr>
<tr>
<td></td>
<td>Complement-dependent cytotoxicity</td>
</tr>
<tr>
<td>Primary structure</td>
<td>Molecular weight</td>
</tr>
<tr>
<td></td>
<td>Protein sequence</td>
</tr>
<tr>
<td></td>
<td>Glycosylation</td>
</tr>
<tr>
<td>High order structure</td>
<td>Secondary &amp; tertiary structure</td>
</tr>
</tbody>
</table>

**Preclinical Assessment:**

4 Levels of Analytical Characterization

- Insufficient analytical similarity (not similar)
- Analytical similarity with residual uncertainty (similar)
- Tentative analytic similarity (highly similar)
- Fingerprint-like analytic similarity (highly similar with fingerprint-like similarity)
- High confidence; appropriate for targeted clinical studies
- Very high confidence; appropriate for more targeted preclinical and clinical studies


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Building Blocks for Biosimilar Integration in Cancer Care

**Equivalent Pharmacokinetics (PK)**
- Comparative PK human studies required
- Comparative PD human studies where clinically relevant markers available
- ‘go/no go’ step for biosimilars

**Biosimilars Clinical Trial Characteristics**
- Performed in populations that are sensitive to detect clinically meaningful differences between the biosimilar and reference product
- Demonstrate that the biosimilar candidate is neither decreased nor increased efficacy, and does not have an increased safety risk compared with reference product
- Endpoints need to be sensitive enough to detect a difference in activity if one exists

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**Biosimilarity: Summary**

- Biosimilar must demonstrate no significant difference from its reference product in terms of safety and efficacy
- Biosimilar analytical package = clinical package of reference product
- Biosimilar FDA approval based on TOTALITY of evidence: analytical data, non-clinical studies, PK/PD, safety, efficacy, and immunogenicity

[Link to FDA Guidance](https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics)

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Extrapolation and Interchangeability Paradigm

Biosimilar Development & Extrapolation

Demonstrating analytical & functional similarity between biosimilar candidate and its reference product can reduce the number and scope of subsequent clinical trials

If a biosimilar meets the requirements for biosimilarity, **extrapolation of data** may allow approval for **additional indications** for which the reference product is indicated without other dedicated clinical studies

Key principles for extrapolation include mechanism of action, totality of evidence showing comparability, safety profile without risk of immunogenicity

Building Blocks for Biosimilar Integration in Cancer Care

Framework for Extrapolation

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

Disease Factors
- Defined mechanism of action
- 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 to characterize differences in progression between groups.
PK/PD: modeling simulation with existing data to investigate the relationship between PK/PD, age, and other important variables.
Clinical response: quantitative synthesis or modeling of all existing data (in vitro, preclinical, and clinical) to predict degree of similarity between source and target population in clinical response (efficacy, some safety aspects).

Determine appropriateness of indication extrapolation
No extrapolation; extrapolation to some indications; extrapolation to all indications

Interchangeability
- Interchangeable is an FDA designation
- Requires different data standards than “biosimilarity” alone
- Dedicated switching study and postmarketing monitoring
- An interchangeable product may be substituted for the reference product without intervention of the health care provider who prescribed the reference product

Interchangeability

- 351(k) required conditions for interchangeability designation:
  - Biosimilarity established
  - Produces same clinical result in any given patient
  - Risk in terms of safety or efficacy of alternating or switching is not greater than risk of using innovator product without alternation or switch

- 351(i) interchangeability actionable definition:
  - “Product that may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.”
  - Substitution dependent on state law


Interchangeability Studies

Interchangeability Considerations: State level Regulatory Requirements

- Pharmacist substitution
  - State laws give pharmacists the authority to act independent of the prescriber to dispense the lowest cost, equivalent medicinal product
  - Prescribers may designate “brand medically necessary”
- State laws vary
  - Prescriber notification and patient notification and consent
- Providing legal immunity for pharmacists who make an interchangeable substitution in accordance with applicable laws
- Keep pharmacy records for a period of 2-3 years


Summary

- Biosimilars represent an opportunity to increase access and improve drug expenditures without compromising efficacy, safety, or quality
- Abbreviated pathway approval emphasis is the totality of evidence compared with reference product, not designed to replicate reference product approval pathway
- Healthcare providers need to understand extrapolation and interchangeability concepts to better integrate biosimilars into their health systems
Clinical Trials of Oncology Biosimilars

Adam Brufsky, M.D., Ph.D., FACP

Clinical Considerations in Demonstrating Biosimilarity

- **Patient Population**: Most sensitive population to show clinically meaningful differences
- **Dose**: Based on dose-response curve, Chosen to sensitively detect any differences
- **End Points**: Chosen to enable precise and meaningful comparison with the reference biologic
- **Design**: Non-inferiority or equivalence margins, Parallel or crossover (depending on half-life)

FDA. Guidance, Compliance & Regulatory Information (Biologics).
# Building Blocks for Biosimilar Integration in Cancer Care

## Selection of Endpoints for Oncology Biosimilar Clinical Trials

<table>
<thead>
<tr>
<th>Many potential endpoints:</th>
<th>Illustrative endpoints:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Event-free survival (EFS)</td>
<td>Originator studies</td>
</tr>
<tr>
<td>• Disease-free survival (DFS)</td>
<td>• Disease-free survival (DFS)</td>
</tr>
<tr>
<td>• Relapse-free survival (RFS)</td>
<td>Biosimilar studies</td>
</tr>
<tr>
<td>• Progression-free survival (PFS)</td>
<td>• Overall response rate (ORR)</td>
</tr>
<tr>
<td>• Overall survival (OS)</td>
<td>• Pathological complete response (pCR)</td>
</tr>
<tr>
<td>• Overall response rate (ORR)</td>
<td>&quot;A clinical endpoint that measures activity as a primary endpoint may be considered&quot;²</td>
</tr>
<tr>
<td>• Duration of response (DoR)</td>
<td>Less likely than survival endpoints to be influenced by factors such as previous lines of therapy and tumor burden</td>
</tr>
<tr>
<td>• Pathological complete response (pCR)</td>
<td></td>
</tr>
<tr>
<td>• Time to progression (TTP)</td>
<td></td>
</tr>
<tr>
<td>• Clinical benefit rate (CBR)</td>
<td></td>
</tr>
</tbody>
</table>


## Clinical Requirements: Establishing Biosimilarity

- At least one clinical pharmacokinetic study for establishing bioequivalence to the reference product
- At least one study of clinical safety, efficacy, and immunogenicity to establish clinical equivalence
  - Typically performed in the most sensitive population
  - Establishes similarity in efficacy using a short-term clinical endpoint
  - Immunogenicity and safety data
  - Is NOT meant to reproduce original efficacy trials, and long-term efficacy data is not required
- Additional clinical trials as necessary
  - To rule out residual uncertainty

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Comparative Clinical Studies

- Purpose: exclude any clinically relevant differences between the biosimilar and the reference product and address any residual uncertainty about biosimilarity
- Conducted stepwise
  - Immunogenicity studies followed by comparative clinical efficacy and safety studies
  - Extrapolation of data is a critical concept

Selecting a Valid Clinical Endpoint

- Critical and challenging for biosimilars
- Sensitive endpoints are recommended

**Patient Criteria**
- Overall survival

**Disease Criteria**
- Objective response rate
- Disease-free survival
- Disease-free progression
- Pathological complete response

Endpoints for biosimilar clinical trials
- Clinically relevant, short-term objective measure capable of detecting differences
- Continuous endpoints may be preferred over binary endpoints
- Length of the study should be sufficient to allow for adequate safety and immunogenicity assessments

Optimal Clinical Trial Setting?

**First-line metastatic trials**
- Most treatment-naïve
- Long drug exposure for a majority to assess safety and immunogenicity
- Highly sensitive endpoint (ORR) that allows evaluation of secondary endpoints (PFS/OS) in realistic time frame
- ORR correlates with PFS and OS in HER2+ breast cancer

**Neoadjuvant trials**
- All treatment-naïve
- Short-term endpoint of pCR, 1-year drug exposure
- DFS and OS are long-term endpoints
- Post-surgery treatment may impact long-term endpoints

Case Study: Trastuzumab
Trastuzumab Biosimilars

- Trastuzumab-dkst (MYL-14010; Mylan/Biocon; Ogivri)*
- Trastuzumab-pkrb (CT-P6; Celltrion; Herzuma)*
- Trastuzumab-dttb (SB3; Samsung; Ontruzant)*
- Trastuzumab-qyyp (PF-05280014; Pfizer; Trazimera)*
- Trastuzumab-anns (ABP 980; Amgen/Allergan; Kanjinti)*

- BCD-022 (Biocad)
- DMB-3111 (Meiji Seika)

*FDA/EC approval  


Summary of Phase III Trials for Trastuzumab Biosimilars

<table>
<thead>
<tr>
<th>Trial</th>
<th>MYL-14010 (Trastuzumab-dkst)</th>
<th>CT-P6 (Trastuzumab-pkrb)</th>
<th>SB3 (Trastuzumab-dttb)</th>
<th>PF-05280014 (Trastuzumab-qyyp)</th>
<th>ABP-980 (trastuzumab-anns)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>Metastatic</td>
<td>EBC and Metastatic</td>
<td>EBC</td>
<td>Neoadjuvant Metastatic</td>
<td>EBC</td>
</tr>
<tr>
<td>No. of patients</td>
<td>500</td>
<td>549</td>
<td>800</td>
<td>225/707</td>
<td>725</td>
</tr>
<tr>
<td>Stage of development</td>
<td>FDA approved (December 2017)</td>
<td>FDA approved (December 2018)</td>
<td>FDA approved (January 2019)</td>
<td>FDA approved (March 2019)</td>
<td>FDA approved (June 2019)</td>
</tr>
</tbody>
</table>
Trastuzumab-dkst (MYL-14010; Ogivri)

- FDA approval for HER2+ breast cancer and HER2+ gastric/esophagogastric junction (GEJ) adenocarcinoma (Dec 2017)
- Dosing similar to reference trastuzumab

HERITAGE: First-line Trastuzumab vs. Biosimilar MYL-1401O in HER2+ Metastatic Breast Cancer

*After usual loading dose.  
†Physician choice of docetaxel or paclitaxel  
SD = stable disease  
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Primary Endpoint:
Ratio of ORR (90% CI) at Week 24 Within the Prespecified Equivalence Margin Supports Similar Efficacy

Best ORR at week 24 in the ITT population\textsuperscript{a}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trastuzumab-dkst N=230</th>
<th>Trastuzumab N=228</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>161 (70.0)</td>
<td>146 (64.0)</td>
</tr>
<tr>
<td>Ratio of ORR (90% CI)</td>
<td>1.09 (0.981, 1.218)</td>
<td></td>
</tr>
<tr>
<td>Difference in ORR (90% CI)</td>
<td>6.00 (-1.26,13.11)</td>
<td></td>
</tr>
</tbody>
</table>

Stratified by assigned taxane, tumor progression, and tumor endocrine status.
ITT, intention-to-treat; ORR, overall response rate; RECIST, Response Evaluation Criteria In Solid Tumors.
\textsuperscript{a}Ratio of best ORR (defined as a complete or partial response per RECIST 1.1) by week 24 based on cumulative assessment done by a single, central, blinded oncologist.

Rugo HS et al. JAMA. 2017; 317:37-47. ASCO 2018

Similar Efficacy Between Trastuzumab-dkst and Trastuzumab Observed Through 48 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Progression-free survival</th>
<th>Overall survival\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trastuzumab-dkst</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>11.1 (8.81-11.20)</td>
<td>11.1 (8.60-11.20)</td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>0.842 + censored</td>
<td>0.131 + censored</td>
</tr>
<tr>
<td>Stratified hazard ratio (95% CI)\textsuperscript{a}</td>
<td>0.95 (0.714-1.251)</td>
<td>0.61 (0.360-1.039)</td>
</tr>
<tr>
<td>P value</td>
<td>0.694</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Stratified by assigned taxane, tumor progression, and tumor endocrine status. \textsuperscript{b}Assessments are ongoing and OS will be calculated after 240 deaths or 36 months.

NE = not evaluable

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**Building Blocks for Biosimilar Integration in Cancer Care**

### PFS at Week 48 Correlates with ORR at Week 24

**ORR at week 24 with PFS at week 48**

- At week 24, 1.3% and 0% of patients demonstrated CR, and 68.3% and 64.0% demonstrated PR, with trastuzumab-dkst and trastuzumab, respectively.
- At week 48:
  - Additional 2 patients (1 per group) demonstrated CR and an additional 5 patients demonstrated PR in the trastuzumab group.
  - The confirmed ORR is 70.0% and 66.7% with trastuzumab-dkst and trastuzumab, respectively.

**ORR at week 24 with PFS probability**

- Biserial correlation coefficient in the total sample is \( r_b = 0.752 \).

CR, complete response; ORR, overall response rate; PFS, progression-free survival; PR, partial response.

### Trastuzumab-pkrb

**Trastuzumab-pkrb (CT-P6; Herzuma)**

- Randomized double-blind neoadjuvant trial for HER2+ breast cancer.
- D-FEC concurrently Q3W.
- 549 patients.
- pCR 50.4% for trastuzumab; 46.8% for trastuzumab-pkrb; equivalence.
- No toxicity differences.

D-FEC- docetaxel-fluorouracil/epirubicin/cyclophosphamide, Q3W- every 3 weeks

CT-P6 Compared With Trastuzumab

**Neoadjuvant phase**
- Enrollment
- Randomization

**Adjuvant phase**
- Surgery

Primary endpoint: pCR

Follow up:
- Up to 3 years from the last enrolled date

<table>
<thead>
<tr>
<th>Schedule</th>
<th>CT-P6</th>
<th>Trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose</td>
<td>8 mg/kg IV</td>
<td>8 mg/kg IV</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>6 mg/kg IV every 3 weeks</td>
<td>6 mg/kg IV every 3 weeks</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>75 mg/m² IV every 3 weeks</td>
<td></td>
</tr>
<tr>
<td>5-Flourouracil, Epirubicin, Cyclophosphamide</td>
<td>500 mg/m², 75 mg/m², 500 mg/m² IV every 3 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Surgery

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>N=248 (CT-P6)</th>
<th>N=256 (Trastuzumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pCR rate (95% CI)</td>
<td>46.77% (40.43, 53.19)</td>
<td>50.39% (44.10, 56.68)</td>
</tr>
<tr>
<td>Difference in pCR rate (95% CI)</td>
<td>-3.62% (-12.38, 5.16)</td>
<td></td>
</tr>
<tr>
<td>Risk Ratio Estimate (95% CI)</td>
<td>0.9282 (0.7753 – 1.1113)</td>
<td></td>
</tr>
<tr>
<td>Total pCR rate excluding DCIS (95% CI)</td>
<td>39.92% (33.78, 46.31)</td>
<td>41.41% (35.31, 47.71)</td>
</tr>
<tr>
<td>Difference in pCR rate (95% CI)</td>
<td>-1.49% (-10.22, 7.31)</td>
<td></td>
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<tr>
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</tr>
<tr>
<td>Breast pCR rate (95% CI)</td>
<td>51.61% (45.20, 57.98)</td>
<td>55.08% (48.76, 61.28)</td>
</tr>
<tr>
<td>Difference in pCR rate (95% CI)</td>
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<td></td>
</tr>
<tr>
<td>Risk Ratio Estimate (95% CI)</td>
<td>0.9371 (0.7957 – 1.1036)</td>
<td></td>
</tr>
</tbody>
</table>

- Total pCR: Pathologic complete response of breast and axillary nodes regardless of DCIS
- Breast pCR: Pathologic complete response of the absence of invasive neoplastic cells in the breast
- Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ; pCR, pathological complete response.


Pathological Response Rates

### Per-Protocol

<table>
<thead>
<tr>
<th>Schedule</th>
<th>CT-P6 (N=248)</th>
<th>Reference Trastuzumab (N=256)</th>
<th>Difference in pCR rate (95% CI)</th>
<th>Risk Ratio Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pCR rate (95% CI) Primary endpoint</td>
<td>46.77% (40.43, 53.19)</td>
<td>50.39% (44.10, 56.68)</td>
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**Trastuzumab-dttb (SB3; Ontruzant)**

- FDA approval for HER2+ breast cancer in adjuvant and metastatic setting, and HER2+ metastatic gastric cancer (Jan 2019)
- Dosing same as trastuzumab
- Phase III neoadjuvant trial of D-FEC with concurrent trastuzumab or trastuzumab-dttb (SB3)
- N = 800
- Primary: Breast pCR 51.7% with trastuzumab-dttb; 42.0% with trastuzumab (hazard ratio 1.26 [1.085-1.46])
- pCR: 45.8% vs. 35.8%
- EFS at 12 months: 93.7% vs. 93.4%
- No differences in PK or toxicity


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**SB3: 1 Year Follow-Up Data**

- 800 patients with HER2-positive early breast cancer or locally advanced breast cancer were randomized to receive either the SB3 trastuzumab biosimilar or its reference concurrently with chemotherapy
- Breast pCR rates were 51.7% and 42% with SB3 and trastuzumab, respectively
  - Ratio of 1.259 fell within the prespecified range for similarity
- At 437 days of follow-up
  - 12-month EFS similar in the two arms; 93.7% and 93%, respectively
- No differences in safety or immunogenicity

Trastuzumab-qyyp (PF-05280014; Trazimera)

- Randomized, double-blind trial for HER2+ metastatic breast cancer (MBC)
- Paclitaxel weekly 3 of 4 weeks with trastuzumab or trastuzumab-qyyp
- After week 33, could give Q3W
- ORR 66.5% trastuzumab; 62.5% trastuzumab-qyyp
- Median PFS 12 months in both study arms
- OS at 12 months 87% vs. 89%
- No toxicity differences


Study Design: LILAC (trastuzumab-anns, ABP 980)

*827 subjects enrolled and 725 subjects randomized.

Building Blocks for Biosimilar Integration in Cancer Care

Summary

- Biosimilar development emphasizes analytical tests, the most sensitive tests to detect any differences, and the scientific justification to support extrapolation of indications.
- The goals of the biosimilar clinical trial program are to demonstrate similar efficacy and safety compared with the reference product and to address residual uncertainty—not to reestablish benefit.
- Experience with biosimilars has resulted in their introduction into multiple treatment guidelines and position statements about their use and clinical value.
- Biosimilars may offer a variety of potential benefits to patients, payers, and health care providers, including:
  - Additional treatment choices at potentially lower cost to the health care system.
  - Increased access to biologics, which may lead to improved overall health outcomes.
  - Possible savings and improved efficiencies for the health care system.
  - A variety of therapeutic options.

Consider these practice changes. Which will you make?

- Educate other healthcare providers about biosimilars and their effective use.
- Educate patients with cancer about the appropriate, effective, and safe use of available biosimilars.
- Discuss with colleagues the logistical considerations for incorporating biosimilars at my organization.
- Recommend biologics/biosimilars to other healthcare providers for patients with applicable cancers.
- Discuss with colleagues the transition from originator products to biosimilars to guide the treatment of patients with applicable cancers.