Biosimilars in Oncology

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Conflict of Interest Disclosure
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• Institutional research funding from:
  – Pfizer, Novartis, Eli Lilly, Roche/Genentech, MacroGenics, Odonate, Merck, OBI, Eisai, Immunomedics, Daichi

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  – Lilly, Pfizer, Mylan, Puma, Amgen, Astra Zeneca
Biologics in Oncology

- Biologics represent approximately 50% of the pharmaceutical market in oncology
- Biologics play a critical role in clinical care:
  - Supportive care
    - Myeloid growth factors
    - Erythropoietin-stimulating agents
  - Active therapy
    - Monoclonal antibodies
    - Antibody-drug conjugates
    - Cytokines

Identical Copies of Biologics Cannot Be Made

Reference Biologics

Variations Over Time
Manufacturing/Process Changes
FDA: Demonstration of Comparability

Reference Biologics
Highly Similar
No Adverse Impact Upon Safety or Efficacy of the Drug Product

Biosimilars

NOT Identical

Reference Biologics

Generics

Identical

Small Molecule Drugs

Generics

Biosimilars ≠ Generics
Biosimilars Are Not Generics

The Objective of a Biosimilar Clinical Program Is to Demonstrate That There Are No Clinically Meaningful Differences Based on the Totality of the Evidence, Not to Reestablish Benefit

Standard Biologic Pathway [351(a)]

- Clinical studies
- Clinical pharmacology PK/PD
- Nonclinical
- Analytical

Biosimilar Pathway [351(k)]

- Clinical studies
- Clinical pharmacology PK/PD
- Nonclinical
- Analytical

McCamish M. Presented at: 2013 EMA Workshop on Biosimilars.
Drifts in ADCC-Related Quality Attributes of *Originator* Trastuzumab: Impact on Development of a Trastuzumab Biosimilar

Clinical Requirements

• 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
  – Immunogenicity and safety data

• Additional clinical trials as necessary
  – To rule out residual uncertainty
Currently Approved Oncology Biosimilars in the United States.... And More in Development!

<table>
<thead>
<tr>
<th>Product</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>trastuzumab-anns</td>
<td>June 2019</td>
</tr>
<tr>
<td>trastuzumab-qyyp</td>
<td>March 2019</td>
</tr>
<tr>
<td>trastuzumab-dttb</td>
<td>January 2019</td>
</tr>
<tr>
<td>trastuzumab-pkrb</td>
<td>December 2018</td>
</tr>
<tr>
<td>rituximab-abbs</td>
<td>November 2018</td>
</tr>
<tr>
<td>pegfilgrastim-cbqv</td>
<td>November 2018</td>
</tr>
<tr>
<td>filgrastim-aafi</td>
<td>July 2018</td>
</tr>
<tr>
<td>pegfilgrastim-jmdb</td>
<td>June 2018</td>
</tr>
<tr>
<td>trastuzumab-dkst</td>
<td>December 2017</td>
</tr>
<tr>
<td>bevacizumab-awwb</td>
<td>September 2017</td>
</tr>
<tr>
<td>filgrastim-sndz</td>
<td>March 2015</td>
</tr>
</tbody>
</table>

Integration Into Cancer Care

- Supportive care biosimilars (eg, filgrastim, peg-filgrastim) are acceptable to clinicians and patients
  - Biosimilar filgrastim in active clinical use
- Biosimilar cancer therapeutics (eg, rituximab, trastuzumab) have a higher bar for acceptance
  - Clinical trials with a short-term efficacy endpoint in a highly sensitive population
  - PK and PD endpoints
  - Immunogenicity
  - Safety
  - Post-approval surveillance
Comparative Clinical Studies

- **Purpose:** Exclude any clinically relevant differences between the biosimilar and the reference product and to address any residual uncertainty about biosimilarity
- **Conducted stepwise**
  - Immunogenicity studies followed by comparative clinical efficacy and safety
  - Extrapolation 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

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

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WHO-2. WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs), 2016.
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+ disease

**Neoadjuvant trials**
- All treatment naïve
- Short-term endpoint of pCR, one year drug exposure
- DFS and OS are long-term endpoints
- Post surgery treatment may impact long-term endpoints
Trastuzumab Biosimilars: The New Frontier

- Over-expression of HER2 implicated in the pathophysiology of ~ 25% of breast and 18% gastric and gastroesophageal tumors
- Trastuzumab has changed the treatment course for HER2+ tumors
  - In *metastatic breast cancer*, improves PFS, OS, and ORR
  - In *early stage breast cancer*, improves DFS and OS
  - As *neoadjuvant therapy*, improves pCR and DFS rates
  - Improves PFS, OS, and ORR in *metastatic gastric cancer*
  - Gold standard as treatment of early and late-stage HER2+ breast cancer
  - Is well tolerated with modest and manageable toxicity
HERITAGE: First-line Trastuzumab vs Biosimilar MYL-1401O in HER2+ Metastatic Breast Cancer

Part 1 Results for Multicenter, Randomized, Double-blind Phase III Equivalence Study

- Primary endpoint (week 24): ORR
- Secondary endpoints (week 48): tumor progression rate, PFS, OS

MYL-1401O 6 mg/kg IV Q3W* + taxane† for minimum of 8 cycles (n = 249)

Trastuzumab 6 mg/kg IV Q3W* + taxane† for minimum of 8 cycles (n = 251)

MYL-1401O 6 mg/kg IV Q3W* + taxane†

Trastuzumab 6 mg/kg IV Q3W* + taxane†

*After usual loading dose.
†Physician choice of docetaxel or paclitaxel
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>
</tbody>
</table>

| Ratio of ORR (90% CI)       | 1.09 (0.981, 1.218)     |
| Difference in ORR (90% CI) | 6.00 (-1.26, 13.11)     |

Stratified by taxane, tumor progression, tumor endocrine status.

\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.

ITT, intention-to-treat; ORR, overall response rate; RECIST, Response Evaluation Criteria In Solid Tumors.

Rugo et al. \textit{JAMA}. 2017;317:37-47 and ASCO 2018
### Similar Efficacy Between Trastuzumab-dkst and Trastuzumab Observed Through 48 Weeks

**Progression-free survival**

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab-dkst</th>
<th>Trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% CI)</td>
<td>11.1 (8.81-11.20)</td>
<td>11.1 (8.60-11.20)</td>
</tr>
</tbody>
</table>

**Log-rank P value**

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab-dkst</th>
<th>Trastuzumab</th>
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<tbody>
<tr>
<td>Log-rank P value</td>
<td>0.842 + censored</td>
<td></td>
</tr>
</tbody>
</table>

**Stratified hazard ratio (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab-dkst</th>
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<tbody>
<tr>
<td>Stratified hazard ratio (95% CI)</td>
<td>0.95 (0.714-1.251)</td>
<td>0.61 (0.360-1.039)</td>
</tr>
</tbody>
</table>

**P value**

<table>
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<tr>
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<th>Trastuzumab-dkst</th>
<th>Trastuzumab</th>
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<tbody>
<tr>
<td>P value</td>
<td>0.694</td>
<td></td>
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</table>

**Overall survival**

<table>
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<tr>
<th></th>
<th>Trastuzumab-dkst</th>
<th>Trastuzumab</th>
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<tbody>
<tr>
<td>Median (95% CI)</td>
<td>NE</td>
<td>NE</td>
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</table>

**Log-rank P value**

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<tbody>
<tr>
<td>Log-rank P value</td>
<td>0.131 + censored</td>
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**Stratified hazard ratio (95% CI)**

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**P value**

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</thead>
<tbody>
<tr>
<td>P value</td>
<td>0.694</td>
<td></td>
</tr>
</tbody>
</table>

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*a* Stratified by assigned taxane, tumor progression, and tumor endocrine status. *b* Assessments are ongoing and OS will be calculated after 240 deaths or 36 months.
Similar Efficacy Between Trastuzumab-dkst and Trastuzumab Observed Through 48 Weeks

Progression-Free Survival

Overall Survival (immature)

Log-rank $P=0.131$

Log-rank $P=0.842$
PFS at Week 48 Correlates with ORR at Week 24

- 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
  - An 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

The Multinational Association of Supportive Care in Cancer • Annual Meeting 2019 • www.mascc.org/meeting
CR, complete response; ORR, overall response rate; PFS, progression-free survival; PR, partial response. Rugo et al, ASCO 2018
**HERITAGE: Safety Profile at Week 24**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>MYL-1401O + Taxane  (n = 247)</th>
<th>Trastuzumab + Taxane (n = 246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AE, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 serious AE</td>
<td>38.1</td>
<td>36.2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27.5</td>
<td>25.2</td>
</tr>
<tr>
<td>Neutropenia with fever</td>
<td>4.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Deaths due to serious AEs, n</td>
<td>4*</td>
<td>4†</td>
</tr>
<tr>
<td>Median LFEV values, % (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>64.0 (51 to 82)</td>
<td>63.0 (51 to 84)</td>
</tr>
<tr>
<td>Wk 24</td>
<td>63.5 (50 to 81)</td>
<td>63.0 (41 to 82)</td>
</tr>
<tr>
<td>Change from BL to Wk 24</td>
<td>-1.0 (-13 to 21)</td>
<td>-1.0 (-19 to 13)</td>
</tr>
</tbody>
</table>

## Incidence of AEs Is Low During Monotherapy

<table>
<thead>
<tr>
<th>AEs, patients, %</th>
<th>Combination therapy: weeks 1-24</th>
<th>Monotherapy: weeks 24-48</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trastuzumab-dkst + taxane</td>
<td>Trastuzumab + taxane</td>
</tr>
<tr>
<td></td>
<td>N=247</td>
<td>N=246</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>57.5</td>
<td>53.3</td>
</tr>
<tr>
<td>Asthenia</td>
<td>21.9</td>
<td>16.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>19.8</td>
<td>13.8</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>14.2</td>
<td>11.4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12.1</td>
<td>4.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.5</td>
<td>7.7</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>6.9</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Only 513 of 5015 total TEAEs (10%) started during monotherapy treatment.

AE, adverse event; TEAE, treatment-emergent AE.
Immunogenicity was similarly low for both MYL-1401O and trastuzumab arms
- Overall antidrug antibody rates: 2.4% vs 2.8%, respectively
- Median titer in antibody-positive pts: 2.5 vs 2.3, respectively

Trough $C_{\text{min}}$ comparable between arms at Wk 15 (cycle 6)
- Ratio of geometric LSMS: 103.88% (90% CI: 93.7% to 115.11%)

Population pharmacokinetics similar between MYL-1401O and trastuzumab arms
- Dose-normalized mean $C_{\text{max}}$: 0.4321 vs 0.4196 µg/mL/mg, respectively
- Dose-normalized mean AUC: 98.350 vs 94.391 µg·d/mL/mg, respectively

HERITAGE: Overall Survival at 36 Months

# HERITAGE Study Data in Clinical Perspective

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HERITAGE STUDY</th>
<th>HISTORICAL DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR 24 Weeks (Primary)</td>
<td>MYL-1401O 70%</td>
<td>1st line HER2+ MBC 55-69%</td>
</tr>
<tr>
<td></td>
<td>Herceptin 64%</td>
<td></td>
</tr>
<tr>
<td>ORR ratio (90% CI): FDA Requirement</td>
<td>1.09 (0.981, 1.218)</td>
<td>N/A</td>
</tr>
<tr>
<td>ORR difference (95% CI): EMA Requirement</td>
<td>6.0% (-2.64%, 14.45%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Time to Progression (TTP) 48 Weeks</td>
<td>11.1 Months</td>
<td>11.3 -12.4 Months</td>
</tr>
<tr>
<td>Overall Survival 48 Weeks</td>
<td>89.1%</td>
<td>75%-89%</td>
</tr>
<tr>
<td>Safety &amp; Toxicity</td>
<td>Comparable</td>
<td>Consistent</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>3.9% 3.4%-6.1%</td>
<td>3.4%-7.1%</td>
</tr>
<tr>
<td>Exposure</td>
<td>Comparable</td>
<td>Consistent</td>
</tr>
</tbody>
</table>

**References:**
CT-P6 Compared With Trastuzumab

Study Design – Dose Scheme


Primary endpoint: pCR

CT-P6 8 mg/kg loading dose; 6mg/kg IV every 3 weeks
Herceptin 8 mg/kg loading dose; 6mg/kg IV every 3 weeks
Docetaxel 75 mg/m² IV every 3 weeks
(Fluorouracil (500mg/m²), Epirubicin (75mg/m²), Cyclophosphamide (500mg/m²) IV q3wk

Randomization

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

Surgery

Enrollment

Neoadjuvant phase

Adjuvant phase

## Pathological Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Per-Protocol</th>
<th></th>
<th></th>
<th>Risk Ratio Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT-P6 (N=248)</strong></td>
<td></td>
<td><strong>Reference Trastuzumab (N=256)</strong></td>
<td><strong>Difference of pCR rate (95% CI)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total pCR rate</strong></td>
<td>46.77%</td>
<td>50.39%</td>
<td>-3.62%</td>
<td>0.9282</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(40.43, 53.19)</td>
<td>(44.10, 56.68)</td>
<td>(-12.38, 5.16)</td>
<td>(0.7753 – 1.1113)</td>
</tr>
<tr>
<td><em>Primary endpoint</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total pCR rate</strong></td>
<td>39.92%</td>
<td>41.41%</td>
<td>-1.49%</td>
<td>0.9641</td>
</tr>
<tr>
<td>excluding DCIS (95% CI)</td>
<td>(33.78, 46.31)</td>
<td>(35.31, 47.71)</td>
<td>(-10.22, 7.31)</td>
<td>(0.7806 – 1.1906)</td>
</tr>
<tr>
<td><strong>Breast pCR rate</strong></td>
<td>51.61%</td>
<td>55.08%</td>
<td>-3.47%</td>
<td>0.9371</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(45.20, 57.98)</td>
<td>(48.76, 61.28)</td>
<td>(-12.18, 5.34)</td>
<td>(0.7957 – 1.1036)</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.


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SB-3: 1 Year Follow-Up Data

- 367 patients with HER2-positive early breast cancer or locally advanced breast cancer
  - Randomized to receive SB-3 trastuzumab biosimilar (186 pts) or originator trastuzumab (181 pts) concurrently with chemotherapy
- After 30.1 months of treatment with SB-3 and 30.2 months of reference product
  - No statistically significant difference in EFS between outcomes in the biosimilar arm (96.7%) and the reference product (98.2%) (hazard ratio [HR], 1.19; 95% CI, 0.23-6.18; \( P = .8376 \))
## Summary of Phase III Trials for Trastuzumab Biosimilars

<table>
<thead>
<tr>
<th>SB-3 (<em>Trastuzumab-dttb</em>)</th>
<th>ABP-980 (<em>Trastuzumab-pkrb</em>)</th>
<th>CT-P6 (<em>Trastuzumab-dkst</em>)</th>
<th>MYL-14010 (<em>Trastuzumab-qyyp</em>)</th>
<th>PF-05280014 (<em>Trastuzumab-qyyp</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>NCT02149524</td>
<td>NCT01901146</td>
<td>NCT02162667</td>
<td>NCT02472964</td>
</tr>
<tr>
<td>Disease</td>
<td>EBC</td>
<td>EBC</td>
<td>EBC and Metastatic</td>
<td>Metastatic</td>
</tr>
<tr>
<td>No. of patients</td>
<td>800</td>
<td>725</td>
<td>549</td>
<td>500</td>
</tr>
<tr>
<td>Stage of development</td>
<td>FDA approved (January 2019)</td>
<td>FDA approved (June 2019)</td>
<td>FDA approved (December 2018)</td>
<td>FDA approved (December 2017)</td>
</tr>
</tbody>
</table>

EBC: Early breast cancer
Pharmacovigilance

- Safety – As more biosimilars are marketed and market uptake increases, real-world safety and efficacy data will emerge.
  - Post-marketing pharmacovigilance efforts may likely be utilized to monitor safety and efficacy of biosimilars.
  - European Medicines Agency mandated pharmacovigilance monitoring for all approved biosimilars approved.
    - As a result, the European experience, with over 400 million patient days with biosimilars, suggests that biosimilars would satisfy lingering safety concerns
  - There are NO provisions in the Biologics Price Competition and Innovation Act (BPCIA) for pharmacovigilance plans of biosimilars.
  - FDA interchangeability guidance document refers back to documents for all products
    - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005)
Unique Issues Relevant to Biosimilars

- Extrapolation
- Interchangeability
- Naming


*The suffix –sndz was named prior to the FDA-designation for biosimilar suffixes

Core name FDA-designated suffix must have:
No recognizable meaning, 4 letters and lowercase
Summary

• The goals of the biosimilar clinical trial program are to demonstrate similar efficacy and safety compared to the reference product and to address residual uncertainty—not to re-establish 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 efficiencies to the health care system
  – A variety of therapeutic options
Biosimilars: Improving Access to Biologic Therapy Worldwide