Biosimilars: Oncology and Beyond

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Princess Margaret Cancer Centre
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Disclosure

• Honoraria
  – Apobiologix
• Expert testimony
  – Genentech/Roche
Outline

• Differences between biosimilars, innovator biologics and generic agents and potential clinical significance thereof.
• Regulatory pathways and choice of endpoints in registration trials.
• Automatic substitution and post-marketing surveillance of biosimilars.
• Economic implications
## Difference Between Biologics and Chemical Medicines

<table>
<thead>
<tr>
<th></th>
<th>Small Molecules</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Simple</td>
<td>Complex</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>Stable</td>
<td>Unstable</td>
</tr>
<tr>
<td><strong>Modification</strong></td>
<td>Well defined</td>
<td>Many options</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>• Predictable chemical process</td>
<td>• Unique line of living cells</td>
</tr>
<tr>
<td></td>
<td>• Identical copy can be made</td>
<td>• Impossible to ensure identical copy</td>
</tr>
<tr>
<td><strong>Characterization</strong></td>
<td>Easy to characterize fully</td>
<td>Difficult to characterize fully due to a mixture of related molecules</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Non-immunogenic</td>
<td>Immunogenic</td>
</tr>
</tbody>
</table>
Typical Protein Production Process

Different manufacturers will have different processes

START

Probably same gene sequence

Different vector

Different host cell

Different fermentation/culture conditions

Different downstream processing

Will result in different biophysical characteristics
Biosimilars Are Reverse Engineered

Reference product

Characterize reference product

Identify CQAs of reference product

Develop unique cell line and manufacturing process

Characterize biosimilar candidate and identify CQAs

Evaluate similarity to reference product

CQA = critical quality attribute
Extensive Analytical Characterization

Primary structure
Attributes related to the amino acid sequence and all post-translational modifications, including glycans

Integrity of the secondary, tertiary, and quaternary structure

Higher order structure

Product-related substances and impurities
Quantitative levels of product variants and their identities

General properties and excipients

Process-related impurities
Properties of the finished drug product, including strength and formulation

Stability
Degradation profiles denoting stability

Biological function
Biological and functional activities, including receptor binding and immunochemical properties

Impurities from host cells and downstream process

Receptor binding and immunochemical properties
Kinetics and thermodynamics of binding, related to functional activity

Degradation profiles denoting stability
Fingerprinting
Unwanted Immunogenicity

- Proteins
  - Patients
    - Induce antibodies
      - Neutralise biological effects and compromise further therapy *e.g.*, Factor VIII, GM-CSF
      - Alter pharmacokinetics
      - Cross-react with native protein and induce adverse reactions *e.g.*, EPO

No effect
Red Cell Aplasia (RCA): The Epoetin Alfa Story

• In the 1990s, RCA was reported in patients who were receiving treatment with SC epoetin alfa
  – Most cases occurred in patients who received Eprex, originator biologic

• After an intensive investigation, the most likely cause of the RCA was a formulation change leading to an interaction with the rubber stopper
  – Human serum albumin replaced with polysorbate 80 + glycine

• This caused antibody formation against all circulating erythropoietin

Approval based on totality of evidence

Direct comparison against authorized or licensed reference product

- Structure
- Function
- Non-clinical studies
- Human PK
- Human PD
- Clinical safety
- Clinical effectiveness
- Immunogenicity
- Risk management + pharmcovigilance
Efficacy of Biosimilars

• For erythropoietic agents or G-CSF, endpoints are easy to measure
  – Hemoglobin level
  – Neutrophil counts

• For antibody activity, the endpoint is efficacy, which is not reproducible and is difficult to assess
Efficacy of Biosimilar Antibodies

- Objective is to demonstrate similarity not equivalent efficacy. Therefore less definitive endpoint deemed acceptable.

- Most regulators identify “response rate” as a sufficiently sensitive endpoint for clinical trials of biosimilar antibodies both in oncology and in inflammatory diseases.

- Regulators have a preference for equivalence studies
  - Compared to superiority or non-inferiority studies.
Regulatory Approval Status

• Canada
  • Somatropin - 2009
  • Infliximab – 2014
  • Filgrastim – 2015
  • Etanercept – 2017
  • Pegfilgrastim (Lapelga) – 2018
  • Bevacizumab – 2018
  • Pegfilgrastim (Fulphila) – 2018
  • Adalimumab – 2018

• Notable approvals in other developed economies
  • Rituximab EMA approval February 2017
  • Multiple trastuzumab FDA approvals 2017-2018
Importance of naming

• Goals:
  – Identify relationship between the “biosimilar” and “reference” or “originator”
    • Therapeutic category
    • Dosing
  – Differentiate products
    • Support pharmacovigilance
    • Intended product administered to patient
    • Outcomes and ADR attributed to correct product
    • Avoid “sound alike” or “look alike” errors
  – Facilitate effective product “track and trace”
Economic Implications

• With generics, the price reduction from the originator is up to 80%
• Similar numbers are not expected for biosimilars, as there are higher development costs
  – Development time 6-9 years with biosimilars, as compared to 3 years with generics
  – Biosimilars require phase I and large phase III trials, whereas generics only require bioequivalence studies
  – Manufacturing costs of $250-$450 million for complex biosimilars
  – Post-approval pharmacovigilance programs
• A price reduction of 15%-30% is expected with biosimilars
• However, presence of biosimilars will likely result in competitive decrease in the price of the originator
  – Emergence of generics resulted in a 20-70% decrease in the originator drug’s price

Simple Biosimilars

Examples: Filgrastim / Pegfilgrastim
DEMONSTRATION OF PD/EFFICACY SIMILARITY OF 
GRASTOFIL® AND NEUPOGEN®: AUEC ANC

3-Arm Bridging Study
300 mcg S.C. Single Dose

Mean ANC time course

- Apo-Filgrastim (Grastofil), 300 mcg
- Neupogen, 300 mcg (EU)
- Neupogen, 300 mcg (USA)

ANC (cells x 10^9/L)

Time (Hours)
**SUPPORTIVE EVIDENCE OF EFFICACY**

**PHASE III STUDY-KWI-300-104**

<table>
<thead>
<tr>
<th>Non-Comparative Study</th>
<th>in Early Stage Female Breast Cancer Patients undergoing TAC chemotherapy in adjuvant setting (120 Patients)</th>
</tr>
</thead>
</table>
| **Study Overview**    | **Treatment Phase:**  
|                       | • 6 cycles of TAC chemotherapy treatment.  
|                       | • Chemotherapy was repeated every 3 weeks for up to 6 cycles.  
|                       | • Treatment with Neukine (Grastofil®) began on day 2 of every chemotherapy cycle (at least 24 hours after chemotherapy) with dosage of 5μg/kg/day body weight per day Neukine (Grastofil®) for up to 6 cycles of chemotherapy.  
| **Safety Follow Up:** | • Up to 30 weeks following completion of TAC chemotherapy  
|                       | • Safety follow up assessments on weeks 20, 24, 36, and 48 with focus on immunogenicity  
| **Primary objective:** | Assessment of safety (including immunogenicity) of Neukine (Grastofil®)  
| **Secondary objective:** | Assessment of efficacy of Neukine (Grastofil®)  
|                       | Primary Efficacy Endpoint: Duration of Severe Neutropenia in Cycle 1  
|                       | CD34+ count in Cycle 1 was assessed as a secondary efficacy endpoint |
### COMPARATIVE INCIDENCE OF FEBRILE NEUTROPENIA IN CYCLE 1 IN BREAST CANCER PATIENTS

<table>
<thead>
<tr>
<th>G-CSF Product</th>
<th>Chemotherapy schedule</th>
<th>% of chemotherapy-naive patients</th>
<th>No. of study subjects</th>
<th>Incidence FN n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neukine (Grastofil®) (KWI-300-104)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neupogen® (Sandoz FDA Advisory Committee Briefing Document, Jan 7 2015) Study EP06-302</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neupogen®</td>
<td>Docetaxel: 75 mg/m²</td>
<td>72</td>
<td>75</td>
<td>15%*</td>
</tr>
<tr>
<td>(De Bono et al., 2009)</td>
<td>Doxorubicin: 60 mg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q3W Up to 4 cycles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neupogen®</td>
<td>Docetaxel: 75 mg/m²</td>
<td>88</td>
<td>147</td>
<td>12%*</td>
</tr>
<tr>
<td>(De Bono et al., 2009)</td>
<td>Doxorubicin: 60 mg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q3W Up to 4 cycles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neupogen®</td>
<td>Docetaxel: 75 mg/m²</td>
<td>100</td>
<td>136</td>
<td>12.5%***</td>
</tr>
<tr>
<td>(Del Riggio et al., 2009)</td>
<td>Doxorubicin: 60 mg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q3W Up to 4 cycles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neupogen®</td>
<td>Docetaxel: 75 mg/m²</td>
<td>NA</td>
<td>85</td>
<td>2.4%**</td>
</tr>
<tr>
<td>(Mokhtar et al., 2010; EPAR)</td>
<td>Doxorubicin: 60 mg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q3W Up to 6 cycles</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Duration of severe neutropenia: **1.40 days (SD 1.07 days)**
- Zarxio: **1.17 days**
- Neupogen: **1.20 days**

*The definition of febrile Neutropenia (FN) used for the study was an ANC <0.5 X 10⁹/L and concurrent oral-equivalent temperature ≥38.2 °C; **The definition of febrile Neutropenia (FN) used for the study was an ANC <0.5 X 10⁹/L and concurrent oral-equivalent temperature ≥38.3 °C.*
Phase I - PD Results - Absolute Neutrophil Cell Count

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relative Mean Ratio, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{\text{max}}$</td>
<td>96.3</td>
<td>92.6 - 100.1</td>
</tr>
<tr>
<td>AUEC</td>
<td>98.8</td>
<td>96.0 - 101.6</td>
</tr>
</tbody>
</table>

Mean Cell Count - Time Profile of Absolute Neutrophil Count (Linear Plot)

The Relative Mean Ratio and the 95% CI of the primary pharmacodynamic endpoint parameters for ANC were contained within the pre-defined acceptance margins of 80-125%.

Phase III - Efficacy Results: DSN in Cycle 1

Duration of Severe Neutropenia in Cycle 1 following treatment with APO-Peg, US-licensed and EU-approved Neulasta

### FAS-As Randomized

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean</td>
<td>1.63</td>
<td>1.39</td>
<td>1.61</td>
<td>0.24</td>
<td>0.02</td>
<td>0.21</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.47 to 1.79</td>
<td>1.17 to 1.61</td>
<td>1.38 to 1.83</td>
<td>-0.03 to 0.51</td>
<td>-0.25 to 0.30</td>
<td>-0.10 to 0.53</td>
</tr>
</tbody>
</table>

*LS = Least Square, CI = Confidence Interval*

### FAS-As Treated

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean</td>
<td>1.62</td>
<td>1.39</td>
<td>1.63</td>
<td>0.23</td>
<td>-0.01</td>
<td>0.24</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.46 to 1.77</td>
<td>1.17 to 1.61</td>
<td>1.41 to 1.86</td>
<td>-0.04 to 0.50</td>
<td>-0.29 to 0.26</td>
<td>-0.07 to 0.56</td>
</tr>
</tbody>
</table>

*LS = Least Square, CI = Confidence Interval*

Note: Comparisons falling within or on the equivalence ranges are shown in bold.
Complex Biosimilars

Monoclonal Antibodies
Examples: Infliximab / Trastuzumab
Comparative PK Study in Ankylosing Spondylitis

Note: Values below the lower limit of quantification (LLOQ) have been set equal to LLOQ

CT-P13 N = 125
INX N = 125

Phase 3 Equivalence Trial in Rheumatoid Arthritis

ACR20 Improvement at Week 30

(A) 100
80
60
40
20
0
100
90
80
70
60
50
40
30
20
10
0

Response rate (%)

ITT Population

PP Population

CT-P13 N = 302
INX N = 304

<table>
<thead>
<tr>
<th></th>
<th>CT-P6 (Compare) (Celltrion)</th>
<th>MYL-1401O (Heritage) (Mylan)</th>
<th>BCD-022 (Biocad)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial identifier</td>
<td>NCT01084876</td>
<td>NCT02472964</td>
<td>NCT01764022</td>
</tr>
<tr>
<td>Trial design</td>
<td>Randomized Double-blind</td>
<td>Randomized Double-blind</td>
<td>Randomized</td>
</tr>
<tr>
<td>Comparator</td>
<td>Herceptin®</td>
<td>Herceptin®</td>
<td>Herceptin®</td>
</tr>
<tr>
<td>Disease</td>
<td>MBC</td>
<td>MBC</td>
<td>MBC</td>
</tr>
<tr>
<td>Chemo</td>
<td>Paclitaxel</td>
<td>Taxane</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Efficacy, Safety</td>
<td>Efficacy, Safety</td>
<td>RR, PK Safety, Immunogenicity,</td>
</tr>
<tr>
<td>No of pts</td>
<td>475</td>
<td>500</td>
<td>110</td>
</tr>
<tr>
<td>Locations</td>
<td>South Korea, Russia, Ukraine, Romania, India, ...</td>
<td>Eastern Europe, South Asia and South Africa</td>
<td>Russia, Belarus, India</td>
</tr>
</tbody>
</table>

http://clinicaltrials.gov/
# Heritage Trial
## Overall Response Rate

<table>
<thead>
<tr>
<th>Week 24 response</th>
<th>MYL-1401O + Taxane (n = 249)</th>
<th>Trastuzumab + Taxane (n = 251)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>3 (1.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>157 (68.3%)</td>
<td>146 (64.0%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>48 (20.9%)</td>
<td>49 (21.5%)</td>
</tr>
<tr>
<td><strong>Overall response rate</strong></td>
<td><strong>160 (69.6%)</strong></td>
<td><strong>146 (64.0%)</strong></td>
</tr>
<tr>
<td><strong>Difference, % [95% CI]</strong></td>
<td><strong>+5.53% (-3.08% to +14.04%)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Rugo H et al. JAMA. 2017 Jan 3;317(1):37-47
Double-blind RCTs comparing biosimilars to trastuzumab as neoadjuvant (and adjuvant) therapy for HER2+ breast cancer

<table>
<thead>
<tr>
<th>Presenter</th>
<th>N</th>
<th>Neoadjuvant cycles (chemo)</th>
<th>Biosimilar</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Minckwitz</td>
<td>725</td>
<td>4 (paclitaxel) after 4 x AC</td>
<td>ABP 980</td>
<td>pCR</td>
</tr>
<tr>
<td>Stebbing *</td>
<td>549</td>
<td>8 (4Doc→4FEC)</td>
<td>CT-P6</td>
<td>pCR</td>
</tr>
<tr>
<td>Pivot §</td>
<td>875</td>
<td>8 (4Doc→4FEC)</td>
<td>SB3</td>
<td>pCR &amp; EFS (12mos)</td>
</tr>
<tr>
<td>Lammers</td>
<td>226</td>
<td>6 (Doc/carbo)</td>
<td>PF-05280014</td>
<td>pK (cycle 5 trough) &amp; pCR</td>
</tr>
</tbody>
</table>

ESMO 2017, Madrid
* Lancet Oncol 2017 18: 917-28
§ J Clin Oncol 2018 (Epub ahead of print)
Each RCTs found similar (i) rate of pCR & (ii) safety of the biosimilar and trastuzumab

<table>
<thead>
<tr>
<th>Presenter</th>
<th>N</th>
<th>Biosimilar</th>
<th>pCR (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biosimilar</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Von Minckwitz</td>
<td>725</td>
<td>ABP 980</td>
<td>48%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>Stebbing *</td>
<td>549</td>
<td>CT-P6</td>
<td>47%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Pivot §</td>
<td>875</td>
<td>SB3</td>
<td>52%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Lammers</td>
<td>226</td>
<td>PF-05280014</td>
<td>51%</td>
<td>47%</td>
<td></td>
</tr>
</tbody>
</table>

No significant difference between arms in any endpoint

ESMO 2017, Madrid
* Lancet Oncol 2017 18: 917-28
§ J Clin Oncol 2018 (Epub ahead of print)
Summary

- A biological product can be biosimilar only if it has successfully gone through the stepwise (Q/S/E) “comparability exercise”.
- Regulatory approval is based on the totality of evidence including extensive, comparative pre-clinical data.
- Experience with currently approved simple biosimilars cannot simply be transferred to biosimilar antibodies.
  - Substantial role for post-marketing surveillance and pharmacovigilance.