Evaluating Oncology Biosimilars: Implementation Challenges and Opportunities

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Association of Community Cancer Centers

Faculty Disclosure

• Leigh M. Boehmer declares no existence of a financial interest in any amount related to the content of this activity.

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Learning Objectives

At the conclusion of this activity, participants should be better able to:

1. Define the challenges which have been encountered with the advent of oncology biosimilars in the U.S. market
2. Recognize the potential benefits of adopting supportive care and therapeutic oncology biosimilars
3. Determine strategies for optimal integration of oncology biosimilars into clinical practice

Biologics Price Competition and Innovation Act (BPCIA)

- Amends the Public Health Service Act
- Abbreviated Biologics License Application (BLA) pathway for biological products demonstrated to be biosimilar or interchangeable with an FDA-approved product
  - Biological product
  - Reference product (aka “innovator”)
  - **Biosimilar** or biosimilarity – highly similar to an innovator biologic (reference product) and the two have no clinically meaningful differences
  - **Extrapolation** – if two or more indications are closely related, an applicant can extrapolate the data to conclude a biosimilar will likely be effective
  - **Interchangeable** or interchangeability – must meet biosimilarity standards and produce the same clinical results as the reference product in any given patient

Variables to Successful Biosimilar Uptake

FDA Regulatory Pathway

Pharmacoeconomic Benefit

Payer and Institutional Acceptance

Manufacturing and Biosimilar Development

Pharmacovigilance

Safety and Efficacy

Successful Integration into Oncology Practice

Health Care Professional and Patient Acceptance

Scientific Community: Working Groups, Guidelines, Position Papers


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**Biologics and Biosimilars: Understanding the Difference**

- N = 1245 physicians (rheumatology, neurology, dermatology, nephrology, endocrinology, and oncology)
  - 376 American, 399 Latin American, and 470 Western European
- 91% US respondents indicated they prescribe biologic agents
- US physicians 41% more likely than Latin American and 43% more likely than European physicians to believe that biologic medicines with the same core name have identical chemical structures
- US physicians 34% more likely than Latin American and 43% more likely than European physicians to believe that biologics sharing the same core name have been tested and shown to produce the same therapeutic results in all approved indications


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**Which Drug Is a Biologic?**

<table>
<thead>
<tr>
<th>Professional Group</th>
<th>Correct</th>
<th>Incorrect</th>
<th>Don’t Know</th>
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<tr>
<td>Dermatologists</td>
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<td>82.8</td>
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<td>73.3</td>
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<td>6.2</td>
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<td>Hem-Oncologists</td>
<td>69.3</td>
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<td>7.8</td>
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<tr>
<td>Medical Oncologists</td>
<td>62.8</td>
<td>10.5</td>
<td>7.8</td>
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</table>

N = 1201

Which Drug Is a Biologic?

5 Major Provider Knowledge Gaps

- Defining biologics, biosimilars, and biosimilarity
- Understanding the biosimilar approval process and the use of “totality of evidence” to evaluate biosimilars
- Recognizing that the safety and immunogenicity of a biosimilar are comparable to the reference product
- Acknowledging the rationale for extrapolation of indications
- Explaining interchangeability and the related rules regarding pharmacy-level substitution
Academic Oncology Clinicians’ Understanding of Biosimilars

- N = 77 clinicians (52 physicians, 16 pharmacists, 9 advanced practice providers)
  - January–May 2018
  - Single, academic health care system in the United States
  - 98 clinicians originally contacted; response rate of 78.6%
- Survey covering 3 domains: clinician understanding, prescription preferences, and how/if patients should be involved
- Cognitively tested via 3 non-oncology clinicians familiar with biosimilar use
- Formal definition of biosimilar was provided during concluding “preferences” section to inform all opinion questions

Clinician Understanding Low, Educational Needs High

- 74% could not provide a satisfactory definition of biosimilar
  - “Clinician understanding” mean composite score (0-5) was 2.02; max achieved 3.5
- ≈40% considered biosimilars the same as generic products
- Most important factor in deciding to use a biosimilar was safety and efficacy (4.51 of 5)
- Only 46.8% of clinicians felt it was important or extremely important to disclose to patients they were being prescribed a biosimilar
  - 50.6% said it is important or extremely important to allow patients to participate in shared decision making when discussing possible biosimilar use
- 40% increase in prescribing likelihood was seen after a biosimilar was designated as an interchangeable product
Attitudes and Understanding About Biosimilars: An International Survey

- N = 3198 patients, caregivers, and control general population members from the United States and European Union
- Eligibility criteria/groups included
  - Diagnosis of inflammatory bowel disease, rheumatoid arthritis, psoriasis, breast cancer, lung cancer, colorectal cancer, or non-Hodgkin lymphoma
  - “Diagnosed advocacy”: individuals with the above conditions who participated in patient support groups
  - Caregivers: had a loved one with the above conditions and was involved with their medical decisions
  - General population: aged 18-64 years, without any of the above conditions

Biosimilars Awareness and Current Use

<table>
<thead>
<tr>
<th></th>
<th>United States, %</th>
<th>European Union, %</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>General, N = 250</td>
<td>Diagnosed, N = 635</td>
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<tr>
<td><strong>Biologics – Awareness</strong></td>
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<tr>
<td>At least a general impression</td>
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<td>30</td>
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<td>Never heard of it</td>
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<td>33</td>
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<tr>
<td>Currently use</td>
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<td>6</td>
<td>9</td>
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<tr>
<td>Never heard of it</td>
<td>70</td>
<td>54</td>
</tr>
<tr>
<td>Currently use</td>
<td>N/A</td>
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## Biosimilars Awareness and Current Use

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<td>11 (30)</td>
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<td>6 (9)</td>
<td>20</td>
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<td>70 (54)</td>
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<tr>
<td>Currently use</td>
<td>N/A (2)</td>
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### Susan G. Komen Seeks to Educate Patients About Biosimilars

- Biosimilars are NOT generic drugs, but they are close
- Biosimilars are just as safe and effective as the original biologic drug
- Biosimilars will provide more treatment options
- Biosimilars should help reduce overall health care costs

Economic and Legal Issues Posing Significant Barriers to Biosimilar Uptake

- Enormous costs to bring biosimilars to market (relative to generics)
- Complex interchangeable regulatory requirements mean biosimilars function as therapeutic alternatives to reference products, not equivalents
  - In terms of quality, price, and manufacturer’s reputation
- Patent infringement and anti-competitive insurer contract lawsuits
- Competition with bio-betters, which offer incremental improvements on reference biologic (eg, new route of administration or extended duration of action)
- Formulary decisions of payers and pharmacy benefit managers
- Supply chain management, including reimbursement for and reliability of biosimilars


Payment Methodology for Biosimilars – Medicare Part B

<table>
<thead>
<tr>
<th></th>
<th>Reference Product</th>
<th>Biosimilar A</th>
<th>Biosimilar B</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAC (list price)</td>
<td>$1,000</td>
<td>$800</td>
<td>$700</td>
</tr>
<tr>
<td>ASP*</td>
<td>$800</td>
<td>$640</td>
<td>$560</td>
</tr>
<tr>
<td>6% of reference product’s ASP</td>
<td>$48</td>
<td></td>
<td></td>
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<tr>
<td>Payment rate (ASP + 6%) (prior to sequestration)</td>
<td>$848</td>
<td>$688</td>
<td>$608</td>
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<tr>
<td>Payment rate (ASP + 4.3%) (after sequestration)</td>
<td>$834</td>
<td>$674.40</td>
<td>$594.40</td>
</tr>
<tr>
<td>Patient cost-share (20%)†</td>
<td>$169.60</td>
<td>$137.60</td>
<td>$121.60</td>
</tr>
</tbody>
</table>

ASP, average sales price; WAC, wholesale acquisition cost.

*This example assumes the biologics’ (both reference and biosimilars) ASPs are 20% less than the WAC based on rebates over time.
†Sequestration lowers the 80% Medicare payment to physicians by 2%, but the patient cost-share remains at 20% of the original payment rate of ASP + 6%.

21

22
Hospital Outpatient Payment Methodology – 340B Biosimilars in Medicare Part B

<table>
<thead>
<tr>
<th></th>
<th>Reference Product</th>
<th>Biosimilar A, with pass-through status</th>
<th>Biosimilar A, without pass-through status</th>
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<tbody>
<tr>
<td>WAC (list price)</td>
<td>$1,000</td>
<td>$800</td>
<td>$800</td>
</tr>
<tr>
<td>ASP*</td>
<td>$800</td>
<td>$640</td>
<td>$640</td>
</tr>
<tr>
<td>6% of reference product’s ASP</td>
<td>$180</td>
<td>$48</td>
<td></td>
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<tr>
<td>22.5% of its own ASP</td>
<td>$620</td>
<td>n/a</td>
<td>$144</td>
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<tr>
<td>Payment rate (prior to sequestration)</td>
<td>$610.08</td>
<td>$676.99</td>
<td>$488.06</td>
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<tr>
<td>Payment rate (after sequestration)</td>
<td>$124</td>
<td>$137.60</td>
<td>$99.20</td>
</tr>
</tbody>
</table>

ASP, average sales price; WAC, wholesale acquisition cost.

*This example assumes the biologics’ (both reference and biosimilars) ASPs are 20% less than the WAC based on rebates over time.


Bundled-Rebate Contracts

How Big Pharma Suppresses ‘Biosimilars’

Deals with insurers and pharmacy benefit managers at patient and taxpayer expense.
Bundled-Rebate Contracts

How Big Pharma Suppresses ‘Biosimilars’

Deals with insurers and pharmacy benefit managers at patient and taxpayer expense.

“... (rebate aspect of doing business) create(s) a perverse incentive to continuously raise prices.”
Alex Azar, Department of Health and Human Services Secretary

Educational Objectives

At the completion of this activity, participants will be able to:

1. Define the challenges which have been encountered with the advent of oncology biosimilars in the U.S. market
2. Recognize the potential benefits of adopting supportive care and therapeutic oncology biosimilars
3. Determine strategies for optimal integration of oncology biosimilars into clinical practice

# FDA-Approved Biosimilars: Oncology Indications

<table>
<thead>
<tr>
<th>Originator Product</th>
<th>Approval Date</th>
<th>Biosimilar Drug Name</th>
<th>Commercially Available</th>
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</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>March 2015</td>
<td>Zarxio (filgrastim-sndz)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>July 2018</td>
<td>Nivestym (filgrastim-aafi)</td>
<td>Yes</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>June 2018</td>
<td>Fulphila (pegfilgrastim-jmdb)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>November 2018</td>
<td>Udenyca (pegfilgrastim-cbqv)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>November 2019</td>
<td>Ziiextenzo (pegfilgrastim-bmez)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>June 2020</td>
<td>Nycephia (pegfilgrastim-apgf)</td>
<td>No</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>December 2017</td>
<td>Ogivri (trastuzumab-dkst)</td>
<td>Yes</td>
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<tr>
<td></td>
<td>December 2018</td>
<td>Herzyma (trastuzumab-pkrb)</td>
<td>Yes</td>
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<tr>
<td></td>
<td>January 2019</td>
<td>Ontruzant (trastuzumab-dttb)</td>
<td>Yes</td>
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<tr>
<td></td>
<td>March 2019</td>
<td>Trazimera (trastuzumab-qqyp)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>June 2019</td>
<td>Kanjinti (trastuzumab-anns)</td>
<td>Yes</td>
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<tr>
<td>Bevacizumab</td>
<td>September 2017</td>
<td>Mvasi (bevacizumab-awwb)</td>
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<tr>
<td></td>
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<td>Zirave (bevacizumab-bvzr)</td>
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<tr>
<td>rituximab</td>
<td>November 2018</td>
<td>Truxima (rituximab-abbs)</td>
<td>Yes</td>
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<tr>
<td></td>
<td>July 2019</td>
<td>Ruxience (rituximab-pvvr)</td>
<td>Yes</td>
</tr>
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In Development:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Approval Status</th>
<th>Number of Companies Developing</th>
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</thead>
<tbody>
<tr>
<td>Bevacizumab biosimilars and bio-betters</td>
<td>Approved; further approvals pending</td>
<td>&gt;20 companies</td>
</tr>
<tr>
<td>Cetuximab biosimilars and bio-betters</td>
<td>In development</td>
<td>6 companies</td>
</tr>
<tr>
<td>Denosumab</td>
<td>In development</td>
<td>3 companies</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Approved; further approvals pending</td>
<td>&gt;20 companies</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Approved; further approvals pending</td>
<td>&gt;20 companies</td>
</tr>
</tbody>
</table>
Biologic Market Relationships

Reference Biologic

Biosimilar

Price Competition

Purchase price

Patients

Prescribing decisions

Providers

Insurers

Cost sharing

Premiums

Payment rates and utilization management

Rebates

Potential for Health Care Cost Savings
Biosimilars will lead to an estimated reduction of how many $billion in direct spending on biologic drugs in the US between 2017-2026?

$54 billion
Potential for Health Care Cost Savings

- Insurers expected to benefit from lower biologic prices

Biosimilars will lead to an estimated reduction of how many $billion in direct spending on biologic drugs in the US between 2017-2026?

$54 billion

Potential for Health Care Cost Savings

- Insurers expected to benefit from lower biologic prices
- Patients may see lower insurance premiums in the long term
- Taxpayers may benefit in the future if lower spending on biologics is achieved in public systems
- Potential for actual savings, although dependent on competition, market penetration, sales, and timing of entry into the market

Biosimilars will lead to an estimated reduction of how many $billion in direct spending on biologic drugs in the US between 2017-2026?

$54 billion

European Cost-Savings Experience

• Infliximab biosimilar, CT-P13, approved by EMA for treating a variety of autoimmune disorders

• 5-year budget impact analysis model in United Kingdom, Italy, France, and Germany
  • Based on total population, annual population growth rate, and prevalence of rheumatoid arthritis

• Price of biosimilar unknown at time of calculation, so different discount scenarios (10%, 20%, and 30%) were applied
  • Market share assumed to be 25% in first year in all scenarios, then increased at variable rates (20%, 30%, and 40%, respectively)

• Total cost savings ranged from € 96 to € 433 million, at current exchange rates, over 5-year period

### U.S. Infliximab Biosimilars Utilization Patterns

- **Infliximab, infliximab-dyyb, infliximab-abda**
  - January 2015 – August 2018; HCPCS codes and NDCs
- Compared baseline patient characteristics and treatment indications
  - 125,412 claims for infliximab
  - 1,034 claims for infliximab-dyyb (available 11/2016)
  - 49 claims for infliximab-abda (available 7/2017)
- Median exposure episode gap 48-50 days


### Improvements in Patient Access

- Originator filgrastim decreased from 97% to 52% of monthly administrations
- Filgrastim-sndz increased to 32% of monthly administrations
  - Marketed at a 30% discount, pre-rebate price
  - 22% had previously received originator filgrastim, and 73% were “new users”
- Alternative biologic, tbo-filgrastim increased to 16% of monthly administrations
  - Marketed at a 45% discount, pre-rebate price

Improvements in Patient Access

- Originator filgrastim decreased from 97% to 52% of monthly administrations
- Filgrastim-sndz increased to 32% of monthly administrations
  - Marketed at a 30% discount, pre-rebate price
  - 22% had previously received originator filgrastim, and 73% were “new users”
- Alternative biologic, tbo-filgrastim increased to 16% of monthly administrations
  - Marketed at a 45% discount, pre-rebate price
- 2017 simulation, N = 20,000 patients with follicular lymphoma
  - Use of filgrastim-sndz versus filgrastim for chemotherapy-induced febrile neutropenia yielded savings between $6.54 million (5-day cycle) and $18.3 million (14-day cycle)
  - Savings would offset the costs of obinutuzumab treatment (6 cycles + 2 years) for 60 (5-day) and 169 (14-day) patients


Growth Factor Biosimilars

MW is a 64-year-old woman with newly diagnosed T2N2M0, HER2– breast cancer who is deemed to be a good candidate for neoadjuvant chemotherapy. Due to risk of febrile neutropenia, her provider has recommended use of daily filgrastim with each cycle. Precertification has identified, however, that her insurance company requires the use of filgrastim-sndz.
Growth Factor Biosimilars

Never having used this product before, her physician asks you if this agent is safe and efficacious. Which of the following responses is accurate?

A. There are no comparison data between filgrastim-sndz and filgrastim for the prevention of infection as manifested by febrile neutropenia.

B. Noninferiority data, compared to filgrastim, exist for this product and patients had no increase in adverse event frequency.

C. Noninferiority data exist for this product, but patients had a significant increase in hospitalizations due to febrile neutropenia.

D. Superiority data exist for this product, demonstrating patients spent fewer days with severe neutropenia during cycle 1 of chemotherapy.


Randomization (1:1:1:1)
- Filgrastim-sndz
- Filgrastim-sndz – filgrastim (alternating after each cycle)
- Filgrastim – filgrastim-sndz (alternating after each cycle)
- Filgrastim

**Randomization (1:1:1:1)**
- Filgrastim-sndz
- Filgrastim-sndz – filgrastim (alternating after each cycle)
- Filgrastim – filgrastim-sndz (alternating after each cycle)
- Filgrastim

**Growth Factor Treatment in Each of 6 Cycles:**

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
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<th>Cycle 6</th>
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<tr>
<td></td>
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<td>Reference → Reference</td>
<td>Reference → Reference</td>
</tr>
</tbody>
</table>

**Treatment Comparisons**
1. During cycle 1, between filgrastim-sndz and originator filgrastim treatment
2. Across all cycles, between alternating treatment and non-alternating treatment
3. Across all cycles, between non-alternating treatment (filgrastim-sndz versus filgrastim)
Filgrastim-sndz Compared With Filgrastim: Phase 3 Noninferiority Results

- N = 218 patients receiving neoadjuvant TAC chemotherapy
  - TAC = docetaxel 75 mg/m², doxorubicin 50 mg/m², and cyclophosphamide 500 mg/m² q3 weeks
  - Conducted at 25 centers in Russia, Ukraine, Hungary, Latvia, Slovakia, and Czech Republic
- Noninferiority of biosimilar was demonstrated
  - Primary efficacy end point was duration of severe neutropenia (DSN) during cycle 1: number of consecutive days from absolute neutrophil count (ANC) <0.5 x 10⁹/L to ≥0.5 x 10⁹/L
  - Filgrastim-sndz DSN was 1.17 ± 1.11 days (N = 101) and filgrastim DSN was 1.20 ± 1.02 days (N = 103); confidence interval lower boundary was −0.26 day (above predefined limit of −1 day)
- No clinically meaningful differences observed in incidence of febrile neutropenia (FN), hospitalization due to FN, infection incidence, or time to ANC recovery
- No significant differences in pattern or frequency of any adverse events

Additional Approved Growth Factor Biosimilars

- Filgrastim-aafi (Nivestym)
  - Second filgrastim biosimilar approved in the United States
  - Approved for the same indications as reference filgrastim
- Pegfilgrastim-jmdb (Fulphila)
  - First biosimilar to reference pegfilgrastim
  - Indicated to decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN
- Pegfilgrastim-cbqv (Udenyca)
  - Indicated to decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN
- Pegfilgrastim-bmez (Ziextenzo)
  - Indicated to decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN
- Pegfilgrastim-apgf (Nyvepria)
  - Indicated to decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN

- Nivestym [prescribing information]. New York, NY: Pfizer; 2018; Fulphila [prescribing information]. Zurich, Switzerland: Mylan GmbH; 2018;

Cancer Therapeutic Biosimilars: Trastuzumab

IL is a 60-year-old woman with recurrent ER/PR-negative, HER2+, metastatic breast cancer. Her oncologist has recommended docetaxel + trastuzumab, but your health system has recently discussed changing the formulary preferred agent to trastuzumab-dkst.
Cancer Therapeutic Biosimilars: Trastuzumab

Before agreeing to change any orders to this product, the oncologist asks you if this agent is safe and efficacious. She also has asked if it is any more cardiotoxic than trastuzumab. Which of the following is correct?

A. Overall response rates are lower, but the cardiotoxicity profile is better for the biosimilar.
B. Overall response rates are equivocal, but the cardiotoxicity profile is better for trastuzumab.
C. Overall response rates are equivocal, and cardiotoxicity profiles are essentially the same.
D. Overall response rates are better, and the cardiotoxicity profile is better for the biosimilar.

Multicenter, international, double-blind, randomized, parallel-group, phase 3 study comparing efficacy and safety of trastuzumab-dkst (MYL-14010) plus a taxane versus trastuzumab plus a taxane in patients with HER2+ metastatic breast cancer

Inclusion Criteria (N = 458)
1. HER2+, male or female patients with metastatic breast cancer, treatment naïve (for metastatic disease)
2. Eastern Cooperative Oncology Group Performance Status of 0-2
3. Normal left ventricular ejection fraction (LVEF)
4. ≥1 year since adjuvant therapy with trastuzumab

Trastuzumab-dkst: Overall Response Rate at Week 24

<table>
<thead>
<tr>
<th>Response type, No. (%)</th>
<th>Biosimilar + Taxane</th>
<th>Trastuzumab + Taxane</th>
<th>Difference, %</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>3 (1.3)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>157 (68.3)</td>
<td>146 (64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>48 (20.9)</td>
<td>49 (21.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>9 (3.9)</td>
<td>20 (8.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not evaluable</td>
<td>13 (5.7)</td>
<td>13 (5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response, No. (%)</td>
<td>160 (69.6)</td>
<td>146 (64)</td>
<td>5.53</td>
<td>1.09</td>
</tr>
<tr>
<td>90% CI, %</td>
<td>64.57-74.56</td>
<td>58.81-69.26</td>
<td>-1.7-12.69</td>
<td>0.974-1.211</td>
</tr>
</tbody>
</table>

Trastuzumab-dkst: Cardiac Function (LVEF Values) Statistics

<table>
<thead>
<tr>
<th>Visit and Statistic</th>
<th>Biosimilar + Taxane Observed (N = 246)</th>
<th>Biosimilar + Taxane Change From Baseline</th>
<th>Trastuzumab + Taxane Observed (N = 244)</th>
<th>Trastuzumab + Taxane Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>64 (63.3-64.7)</td>
<td></td>
<td>64.1 (63.4-64.8)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>64 (51-82)</td>
<td></td>
<td>63 (51-84)</td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>63.6 (62.8-64.4)</td>
<td>-0.6 (-1.5-0.2)</td>
<td>63.2 (62.2-64.2)</td>
<td>-0.9 (-1.8--0.1)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>63.5 (50-81)</td>
<td>-1 (-13-21)</td>
<td>63 (41-82)</td>
<td>-1 (-19-13)</td>
</tr>
</tbody>
</table>

Phase 3 Trastuzumab Biosimilars: Trials Summary

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trastuzumab-ddtb (SB3)</th>
<th>Trastuzumab-anns (ABP 980)</th>
<th>Trastuzumab-pkrb (CT-P6)</th>
<th>Trastuzumab-dkst (MYL-14010)</th>
<th>Trastuzumab-qyyp (PF-05280014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>NCT02149524</td>
<td>NCT01901146</td>
<td>NCT02162667</td>
<td>NCT02472964</td>
<td>NCT01989676</td>
</tr>
<tr>
<td>Disease</td>
<td>EBC</td>
<td>EBC – both neoadjuvant and adjuvant</td>
<td>EBC – neo- and adjuvant/ Metastatic</td>
<td>Metastatic</td>
<td>Neoadjuvant/ Metastatic</td>
</tr>
<tr>
<td># Patients</td>
<td>800</td>
<td>696</td>
<td>549/475</td>
<td>500</td>
<td>226/707</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Equivalent rates of breast pathologic complete response</td>
<td>Similar rates of pathologic complete response</td>
<td>EBC: Similar rates of pathologic complete response, along with similar LVEF</td>
<td>Equivalent overall response rate at 24 weeks</td>
<td>Metastatic: Equivalent overall response rate at 25 and 33 weeks</td>
</tr>
</tbody>
</table>

EBC, early breast cancer.


Capecitabine + Cisplatin + Pembrolizumab + Trastuzumab-pkrb for HER2+ Advanced Gastric Cancer

- Multi-institutional, phase Ib/II trial

Pembrolizumab 200 mg IV D1 + trastuzumab-pkrb 6 mg/kg (after 8 mg/kg load) IV D1 + capecitabine 1000 mg/m² PO BID D1-14 + cisplatin 80 mg/m² IV D1 Q3 weeks (N = 43; no MSI-H/dMMR patients)
- PD-L1 status: 57.1% ≥CPS 1; 14.3% ≥CPS 10

Endpoints
Primary: Overall response rate (ORR) (per RECIST v1.1)
Secondary: PFS, OS, DoR, Safety

<table>
<thead>
<tr>
<th>Tumor shrinkage rate</th>
<th>ORR</th>
<th>DCR</th>
<th>PFS</th>
<th>OS</th>
<th>DoR</th>
<th>6-month PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>95.3%</td>
<td>76.7%</td>
<td>97.7%</td>
<td>8.6 mo (7.2-22, 95% CI)</td>
<td>18.4 mo (17.9-N/A, 95% CI)</td>
<td>10.8 mo (7.2-N/A, 95% CI)</td>
<td>76.7% (65.1-90.5, 95% CI)</td>
</tr>
</tbody>
</table>

CPS, combined positive score; DCR, disease control rate; PFS, progression free survival; OS=overall survival; DoR=duration of response.
- Treatment-related adverse events (≥G3) in 74.4% pts

Cancer Therapeutic Biosimilars:
Bevacizumab-awwb (Mvasi) Indications

- Metastatic colorectal cancer, in combination with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment
  - Not indicated for adjuvant treatment of surgically resected colorectal cancer
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan–based or fluoropyrimidine-oxaliplatin–based chemotherapy for the second-line treatment of patients who have progressed on a first-line bevacizumab product-containing regimen
- Nonsquamous non–small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent, or metastatic disease
- Glioblastoma with progressive disease following prior therapy, based on improvement in objective response rate
- Metastatic renal cell carcinoma, in combination with interferon alfa
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan


Cancer Therapeutic Biosimilars:
Bevacizumab-bvzr (Zirabev) Indications

- Metastatic colorectal cancer, in combination with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment
  - Not indicated for adjuvant treatment of surgically resected colorectal cancer
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan–based or fluoropyrimidine-oxaliplatin–based chemotherapy for the second-line treatment of patients who have progressed on a first-line bevacizumab product-containing regimen
- Nonsquamous non–small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent, or metastatic disease
- Recurrent glioblastoma in adults
- Metastatic renal cell carcinoma, in combination with interferon alfa
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan

Cancer Therapeutic Biosimilars: Rituximab-abbs (Truxima) Indications

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin lymphoma (NHL) as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy
- Nonprogressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with an anthracycline-based regimen
- Previously un-/treated CD20-positive chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide

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Cancer Therapeutic Biosimilars: Rituximab-pvvr (Ruxience) Indications

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin lymphoma (NHL) as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy
- Nonprogressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with an anthracycline-based regimen
- Previously untreated and previously treated CD20-positive chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide chemotherapy

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Educational Objectives

At the completion of this activity, participants will be able to:

1. Define the challenges which have been encountered with the advent of oncology biosimilars in the U.S. market
2. Recognize the potential benefits of adopting supportive care and therapeutic oncology biosimilars
3. Determine strategies for optimal integration of oncology biosimilars into clinical practice

Biosimilars: P&T Committee Considerations

- Clinical
  - Efficacy and safety data review, including immunogenicity
  - Indications, extrapolation(s)
- Product
  - Packaging, labeling, storage
  - Lookalike/sound-alike
- Institutional
  - Substitutions, interchangeability
  - Pharmacovigilance
  - Cost/Reimbursement
  - EHR limitations
  - Transitions of care

EHR, electronic health record.

Expedited Formulary Review Process

• Reference product is already on formulary
  • If not on formulary, the biosimilar must undergo “usual” review
• Biosimilarity has been demonstrated, including extrapolation of indications to reference product
• Institutional cost-savings can be achieved
  • Where multiple products are available, decision based on contracting, supply guarantee, payor coverage, assistance programs, etc.
• Mandatory on-market time prior to review?

Off-Label Use

• “Off-label utilization limited only if there is a scientific rationale.”
• Rituximab-pvvr
  • Using for rheumatoid arthritis?
• Rituximab-abbs
  • Using for pemphigus vulgaris?
• Rituximab/hyaluronidase human
  • Using for non-malignant conditions?
Consent Documentation

- Up-front acknowledgement of multiple “products” (i.e., peg-filgrastim products, trastuzumab products)
- Re-consent required with change to any new product
- If payor-based requirement to use a biosimilar, do you disclose that info to the patient?

Medication Order Processes

- Pharmacy department interchange “protocol”
  - Assumes a preferred product exists
  - “Register” care plan first with pre-certification team with upfront ordering of payor-preferred agent(s)
  - EHR-facilitated communication after provider order to change product(s) based on payor-preferred agent(s)
  - Allow product(s) to change during therapy (ex., new biosimilar on formulary on July 1st)
Clinical Scenario Samples

- NCCN Hematopoietic Growth Factors Guidelines
  - Filgrastim-sndz, -aafi and pegfilgrastim-jmdb, -cbqv, -bmez “appropriate substitutions for originator filgrastim and pegfilgrastim, respectively
  - Tbo-filgrastim has more restricted indication than filgrastim biosimilars
- NCCN Breast Cancer Guidelines
  - FDA-approved biosimilar is an appropriate substitute for trastuzumab
  - Trastuzumab/hyaluronidase-oysk injection for subcutaneous use may be substitute for trastuzumab

Alternative Payment Models – Biosimilars’ Budget Impact within the Oncology Care Model (OCM)

Scenario 1 (N = 500)
1. Receiving 6-cycles of FN*-risk stratified chemotherapy
2. Projected 1-yr total (drug and administration costs)
4. Assumes same growth factor usage rate

Scenario 2 (N = 500)
1. Same as scenario 1, except 10% more patients receive LA-EP2006 support for intermediate-FN* risk chemotherapy
2. Analysis of FN*-related healthcare utilization (e.g., emergency visits, hospitalizations)

FN, febrile neutropenia; M=million (U.S. dollars).

Alternative Payment Models – Biosimilars’ Budget Impact within the Oncology Care Model (OCM)

Scenario 1 (N = 500)
1. Receiving 6-cycles of FN*-risk stratified chemotherapy
2. Projected 1-yr total (drug and administration costs)
4. Assumes same growth factor usage rate

Scenario 2 (N = 500)
1. Same as scenario 1, except 10% more patients receive LA-EP2006 support for intermediate-FN* risk chemotherapy
2. Analysis of FN*-related healthcare utilization (e.g., emergency visits, hospitalizations)

107 pts receive growth factor
$3.02M for pegfilgrastim vs. $2.42M for pegfilgrastim-bmez
$1.05M healthcare utilization costs

129 pts receive growth factor
$3.02M for pegfilgrastim vs. $2.91M for pegfilgrastim-bmez
$1.02M healthcare utilization costs

FN, febrile neutropenia; M=million (U.S. dollars).

Pegfilgrastim Biosimilars – Bending the Cost Curve

- Medicare Part B pegfilgrastim reimbursement (80% of ASP + 6%) increased at steady $292/yr for the first 30 months of the OCM
- Since Q3 2018, average pegfilgrastim reimbursement has held steady at $3543 through 6/30/2019
- Projected Medicare savings of $79.1M in 2019 and $157.9M in 2020
- Most of savings not due to biosimilar use (90.6% of patients in Q2 2019 still receiving pegfilgrastim)

Biologics and Biosimilar Substitution:
Select State-Level Regulatory Requirements

- Prescriber may designate “brand medically necessary”
- Specifying notification or communication with prescriber if substitution is made
- Patient notification and/or consent when/before a substitution is made
- Pharmacist required to explain cost/pricing difference to patients
- Keeping pharmacy records for a period of 2-3 years
- Providing legal immunity for pharmacists who make an interchangeable substitution in accordance with applicable laws
- Mandating state (typically the Board of Pharmacy) maintenance of FDA-approved interchangeable products list


<table>
<thead>
<tr>
<th>State</th>
<th>Bill Number</th>
<th>Signed Date</th>
<th>FDA Must Certify Interchangeability</th>
<th>Prescriber Notification</th>
<th>Patient Notification</th>
<th>Prescriber May Block With “Brand Medically Necessary”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massachusetts</td>
<td>H 3734</td>
<td>6/2014</td>
<td>Yes</td>
<td>Yes, including EHR</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Connecticut</td>
<td>S 197</td>
<td>2018</td>
<td>Yes</td>
<td>Yes, 3 days</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>New Hampshire</td>
<td>H 1791</td>
<td>2018</td>
<td>Yes</td>
<td>Yes, 3 days (Communication)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>New York</td>
<td>S 4788</td>
<td>10/2017</td>
<td>Yes</td>
<td>Yes, 5 days (Communication)</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td>Rhode Island</td>
<td>S 2755/H 7816</td>
<td>6/2016</td>
<td>Yes</td>
<td>Yes, 5 days (Communication)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Pharmacists’ Role

• Provider education: biosimilar and interchangeable definitions, approval pathway (including efficacy and safety data), and potential for cost savings
• Patient education: comparison of differences between biosimilars and generic drugs, information on how biosimilars are approved, and potential for improved access and lower drug costs
• Advocate with and for medical societies, government sources, and patient-facing organizations to provide public awareness and education programs, along with making reputable materials available to patients
• Involvement in formulary management (eg, Pharmacy and Therapeutics Committee), the medication use process, and creation of policies and procedures that allow for utilization of biosimilars (eg, automatic substitution, where possible)
• Involvement in pharmacovigilance, supporting patient adherence, and reporting of postmarketing adverse events


Key Takeaways

• A clear need for education of providers and patients regarding biosimilars has been documented
• Biosimilars have the potential to realize enormous cost savings for health care payers, providers, and patients, but uptake has been slow due to a variety of factors
• Improvement in patient access has already been established as a result of supportive care biosimilar utilization in the United States
• Approval of interchangeables may increase prescribing/utilization of biosimilars
• Decisions about biosimilar use should be a result of shared-decision making with patients and/or their healthcare proxy
• Biosimilars have been proposed as a necessary element of successful implementation of various alternative payment models
• Pharmacists play a vital role in the education, advocacy, and safety monitoring of biosimilars
Sources Cited


Sources Cited

- Fulphila [prescribing information]. Zurich, Switzerland: Mylan GmbH; 2018.
Sources Cited


Sources Cited

• Truxima [prescribing information]. North Wales, PA: Teva Pharmaceuticals; 2019.
Sources Cited


Thank You