*M-CERSI/FDA VIRTUAL WORKSHOP*

*Biosimilars: A Decade of Experience and Future Directions*

*April 13, 2022*

# Biosimilars in Oncology

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**and the University of Washington, Seattle WA**

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# Disclosures

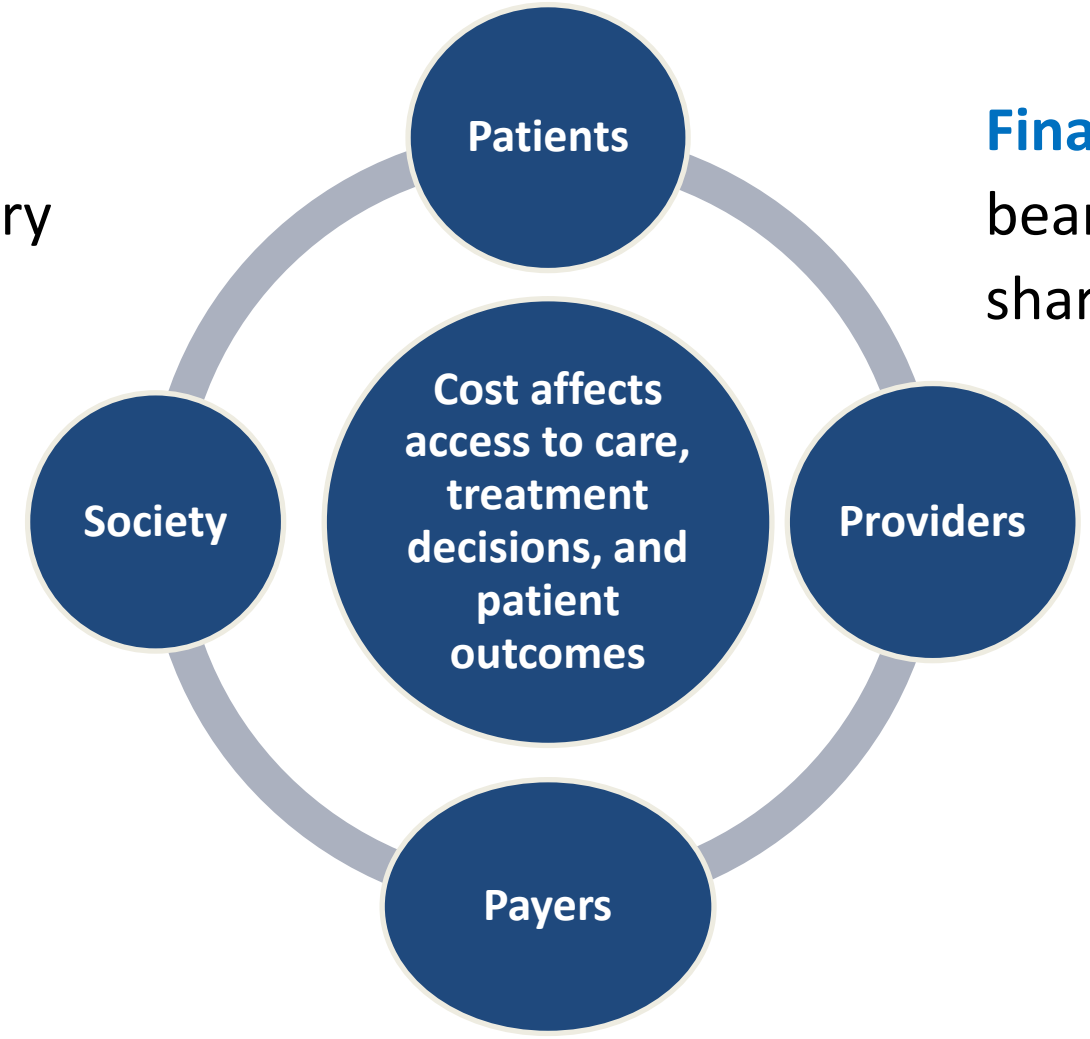
Member of the ASCO Working Group on Biosimilars in Oncology

PI on research grant to Fred Hutchinson Cancer Research Center from Amgen

Consultation: G1 Therapeutics; BeyondSpring; Sandoz; TEVA; SeaGen; ER Squibb; Merck; Samsung, Fresenius Kabi

# Impact of Rising Healthcare Costs

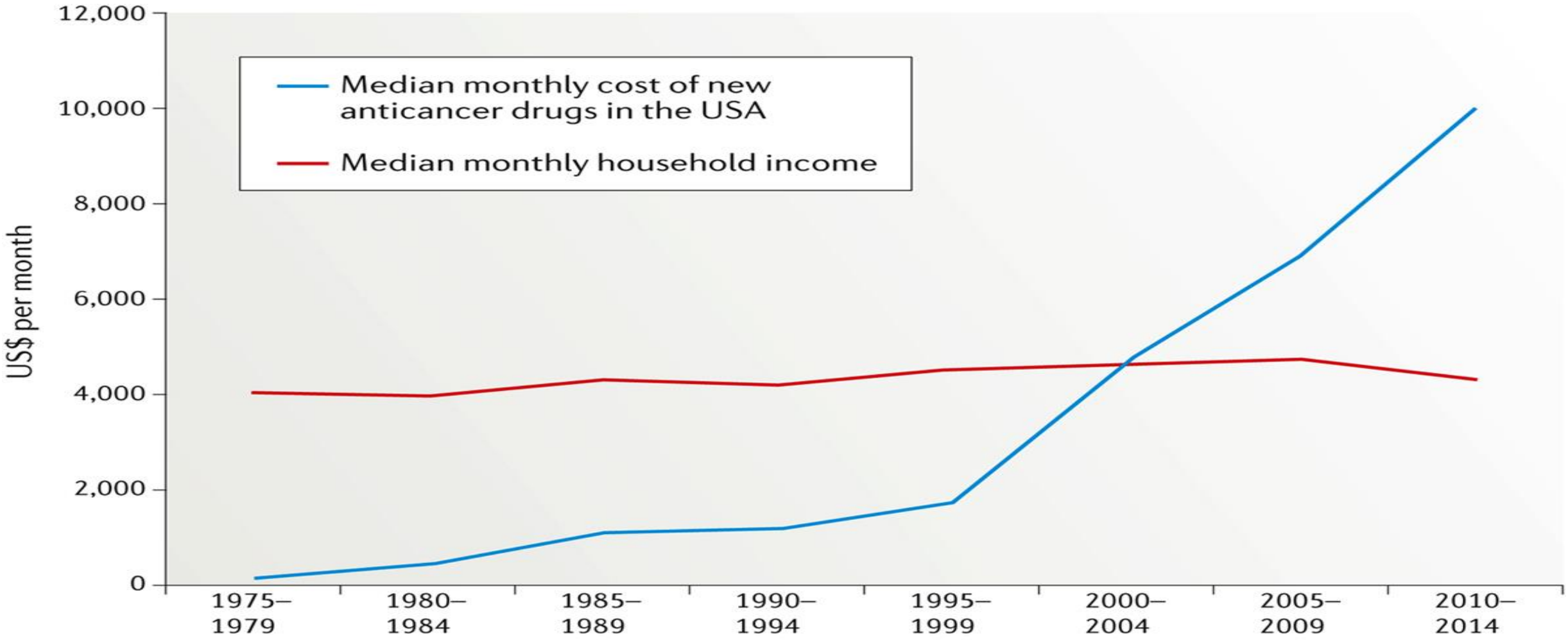
**Cost** and **quality** of cancer treatment vary widely across healthcare systems




**Financial toxicity:** patients bear an ever-increasing share of the expense

Lipscomb J. *Natl Cancer Inst Monogr*. 2013;2013:124-130; Tran G, Zafar SY. *Ann Transl Med*. 2018;6:166.

# Median monthly launch price of a new anticancer drug compared with median monthly household income: *USA 1975–2014*




Prasad V et al. *Nat Rev Clin Oncol.* 2017;14(6):381-390.

# Cancer Drugs Account for 6/10 Most Expensive Drugs

| Drug | Cost in $ Billions |
|---|---|
| Aflibercept | 2.57 |
| Pembrolizumab | 1.81 |
| Nivolumab | 1.72 |
| Rituximab | 1.70 |
| Denosumab | 1.42 |
| Pegfilgrastim | 1.37 |
| Ranibizumab | 1.22 |
| Infliximab | 1.15 |
| Bevacizumab | 1.01 |
| Trastuzumab | 0.82 |

Medicare Part B 2018

# What is a Biosimilar?

*"A biosimilar is a biological product that is highly similar to a US-licensed reference biological product for which there are no clinically meaningful differences in safety, purity, or potency of the product."*

FDA.https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm

VOLUME 36 · NUMBER 12 · APRIL 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

# American Society of Clinical Oncology Statement: Biosimilars in Oncology

*Gary H. Lyman, Edward Balaban, Michael Diaz, Andrea Ferris, Anne Tsao, Emile Voest, Robin Zon, Michael Francisco, Sybil Green, Shimere Sherwood, R. Donald Harvey, and Richard L. Schilsky*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*J Clin Oncol 36:1260-1265.* 

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**Biosimilars will play an important role in the future care of patients with cancer and will improve access to valuable medicines.**

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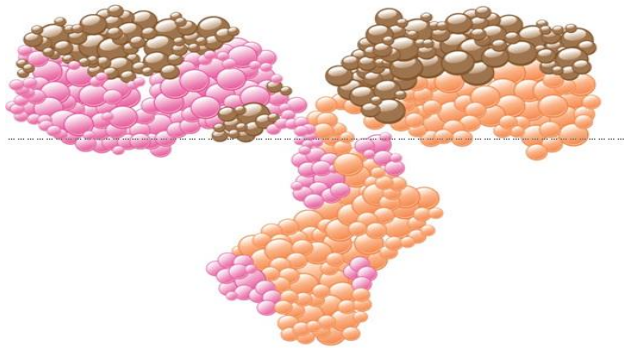
*J Clin Oncol 36:1260-1265.* 

# Biosimilars Are Biologics

*Large, Complex Molecules*



**Aspirin**
**MW 180**

**Monoclonal Antibody**
**MW 150,000**

| | CHEMICAL DRUGS | BIOLOGICS |
|---|---|---|
| Size | Small, low molecular weight | Large, high molecular weight |
| Structure | Simple, well-defined | Complex, heterogeneous |
| Manufacturing | • Reproducible chemical reactions<br>• Identical copies can be made | • Living cells or organisms<br>• Impossible to ensure identical copies |
| Characterization | Completely characterized | Impossible to fully characterize molecular composition |
| Stability | Relatively stable | Unstable, sensitive to external conditions |
| Immunogenicity | Mostly non-immunogenic | Immunogenic |

Declerck PJ. *GaBI Journal*. 2012;1(1)13-16.

The NEW ENGLAND JOURNAL of MEDICINE

HEALTH LAW, ETHICS, AND HUMAN RIGHTS

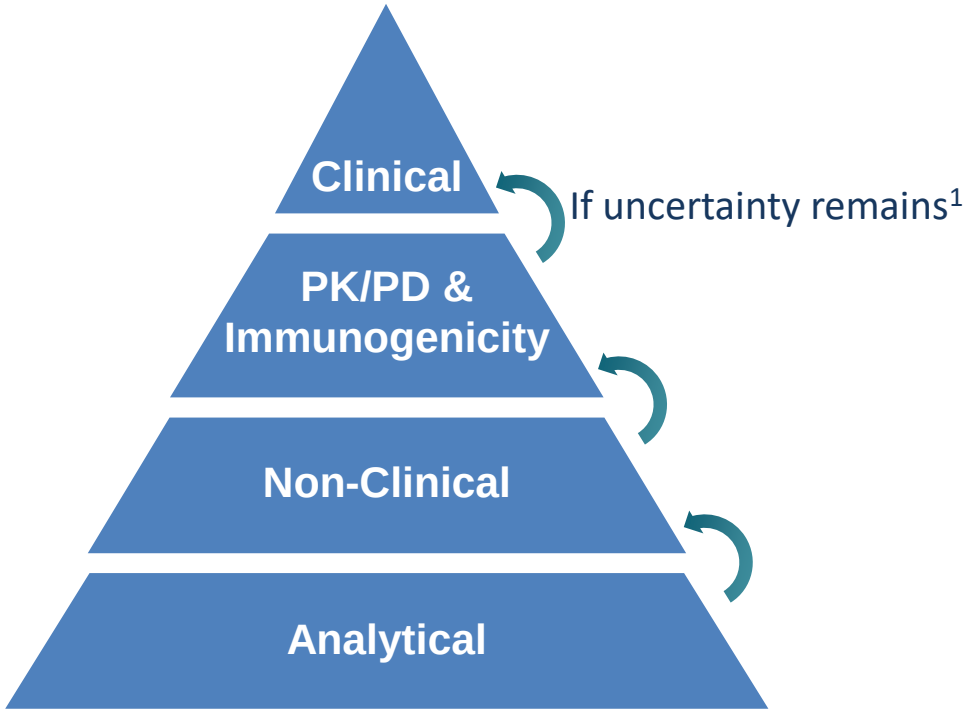
# Rationale, Opportunities, and Reality of Biosimilar Medications

Gary H. Lyman, M.D., M.P.H., Robin Zon, M.D., R. Donald Harvey, Pharm.D., and Richard L. Schilsky, M.D.

## Requirements for Biosimilarity

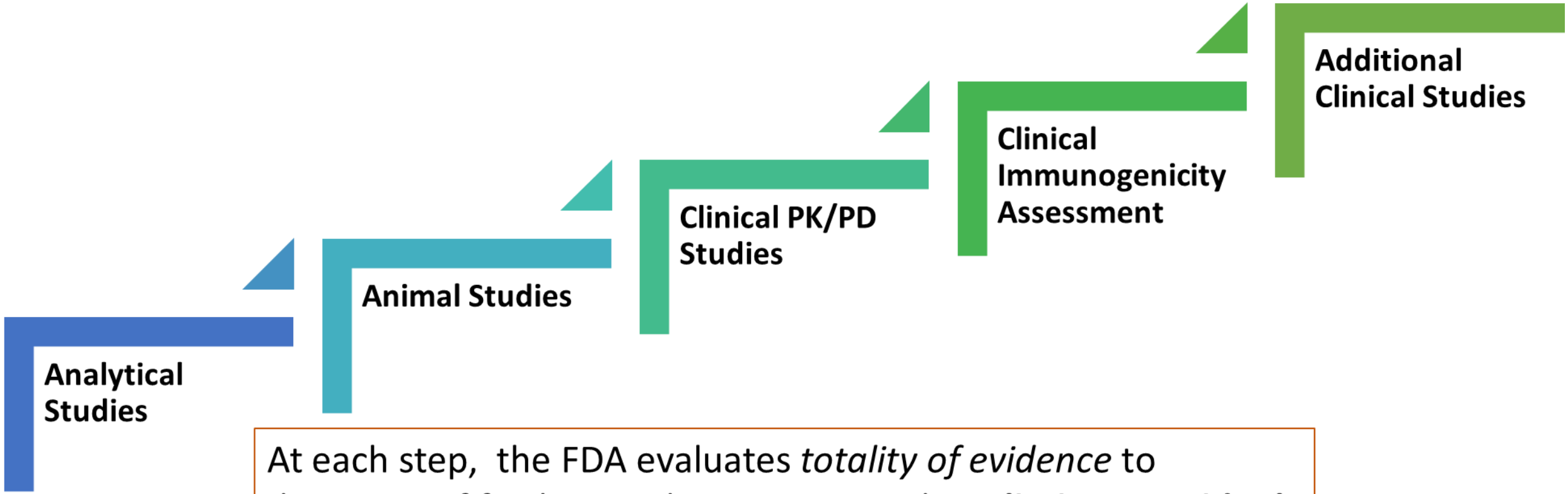
- Biological product is highly similar to reference product notwithstanding minor differences in clinically inactive components
- No clinically meaningful differences between biological product and reference product in terms of safety, purity, and potency

## Stepwise Evidence Development




Lyman GH et al. *N Engl J Med* 2018;378(21):2036-2044.

# Approval Pathway for Biosimilars in the United States: Totality of Evidence

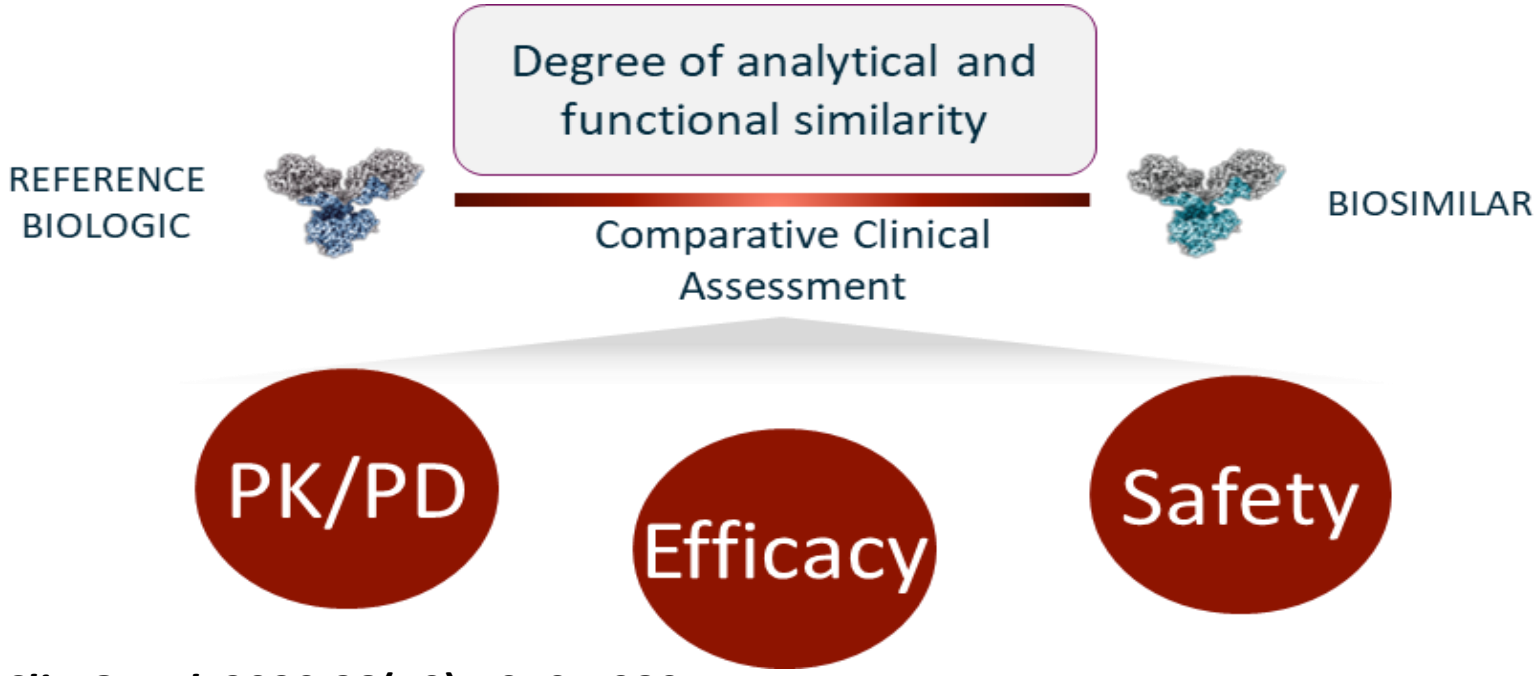



At each step, the FDA evaluates *totality of evidence* to determine if further studies are required to **eliminate residual uncertainty** between biosimilar and reference biologic

FDA. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. 2015.

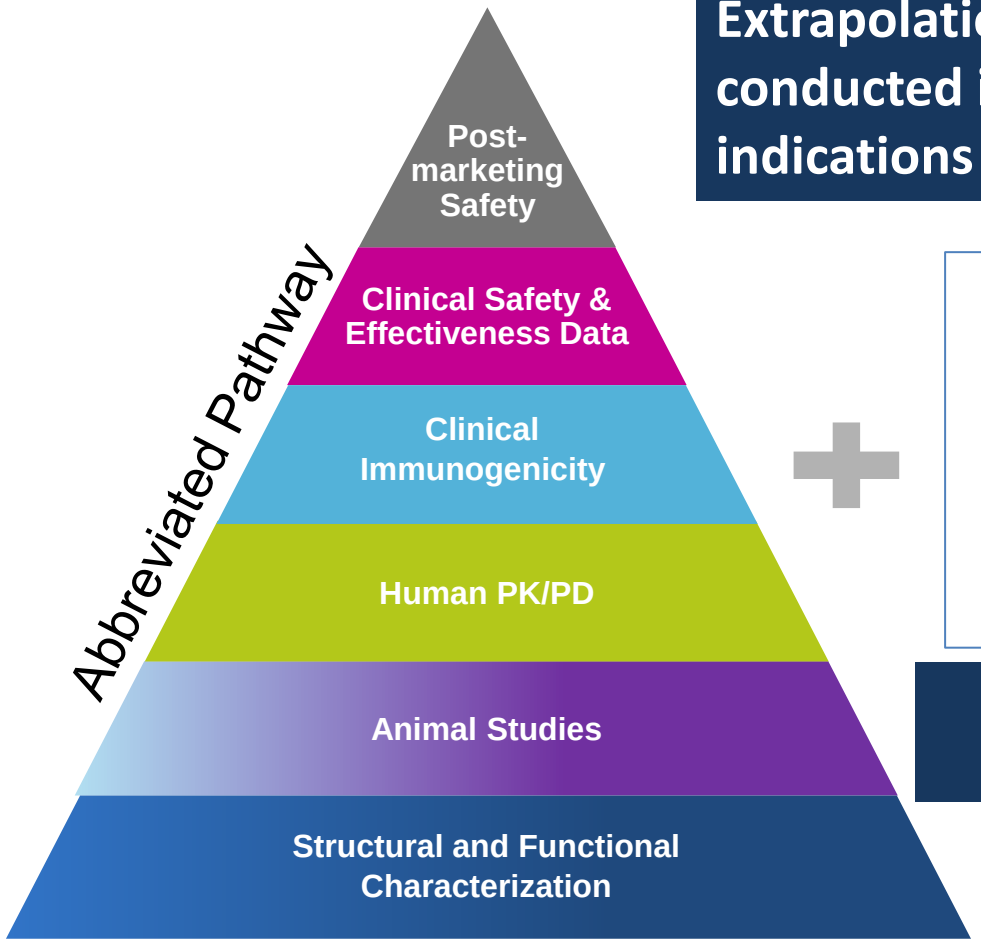
# Fundamental Principles for Establishing Clinical Biosimilarity

- Goal of biosimilar clinical trial is to demonstrate similar efficacy and safety (not benefit) compared with reference products
- The clinical trial program for a potential biosimilar includes assessments of PK, PD (if feasible), efficacy, and safety
  - Short-term surrogate endpoints (ORR, pCR) often utilized




Stebbing J et al. *J Clin Oncol*. 2020;38(10):1070-1080.

# Biosimilars: Extrapolation to Indications Not Clinically Studied




**Extrapolation of data from a clinical trial of a biosimilar conducted in one disease to support approval for additional indications for which the reference product is already licensed**

**Convincing evidence to support extrapolation to a reference biologic's approved indications**

**Extrapolated Indications**

**Extrapolation will not be automatic: scientific justification required for each additional indication**

- **MOA in each condition**
- **PK and biodistribution**
- **Expected toxicities**
- **Any other factor**

US Food and Drug Administration. https://www.fda.gov/drugs/biosimilars/industry-information-and-guidance

# Variability and Drift

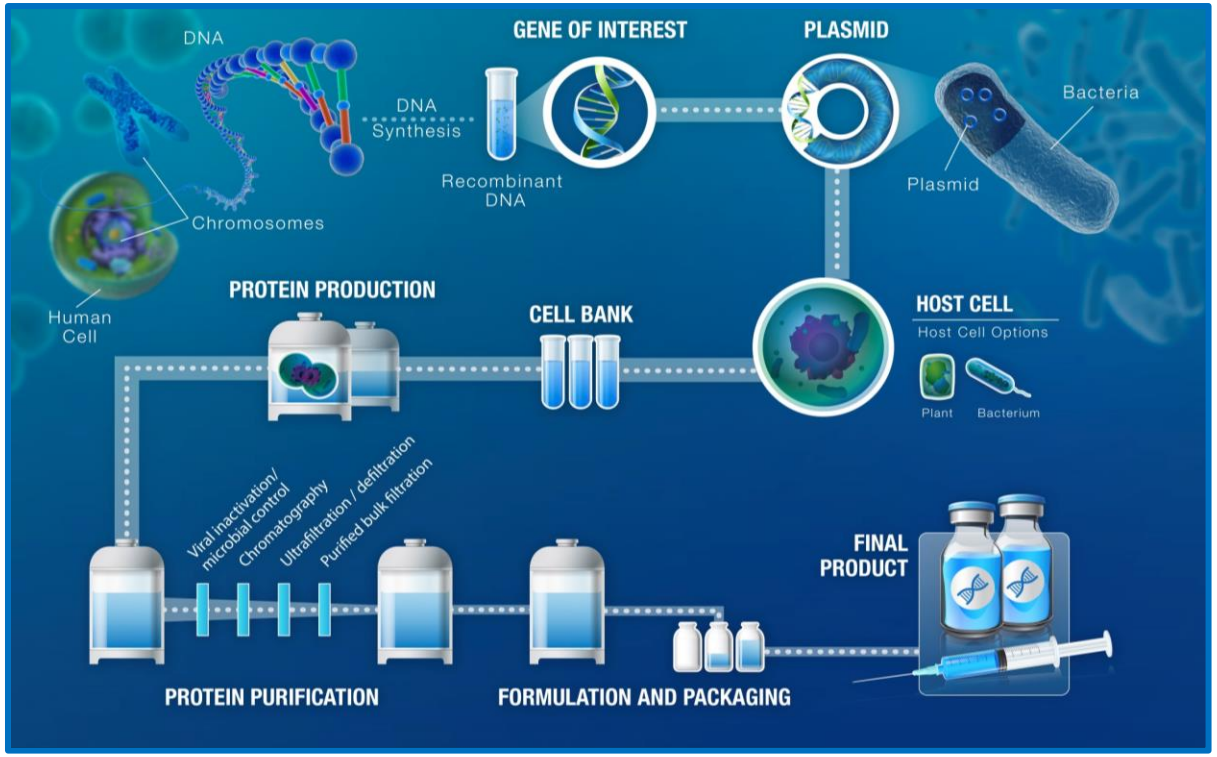
- **Significant differences in drug products (variability and drift) can arise due to:**
  - **Production at different sites**
  - **Changes to manufacturing processes after initial approval**
  - **FDA or EMA approval required for changes in manufacturing process**
- **Manufacturers need to be vigilant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

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

Ramanan S et al. *BioDrugs*. 2014;28(4):363-372.

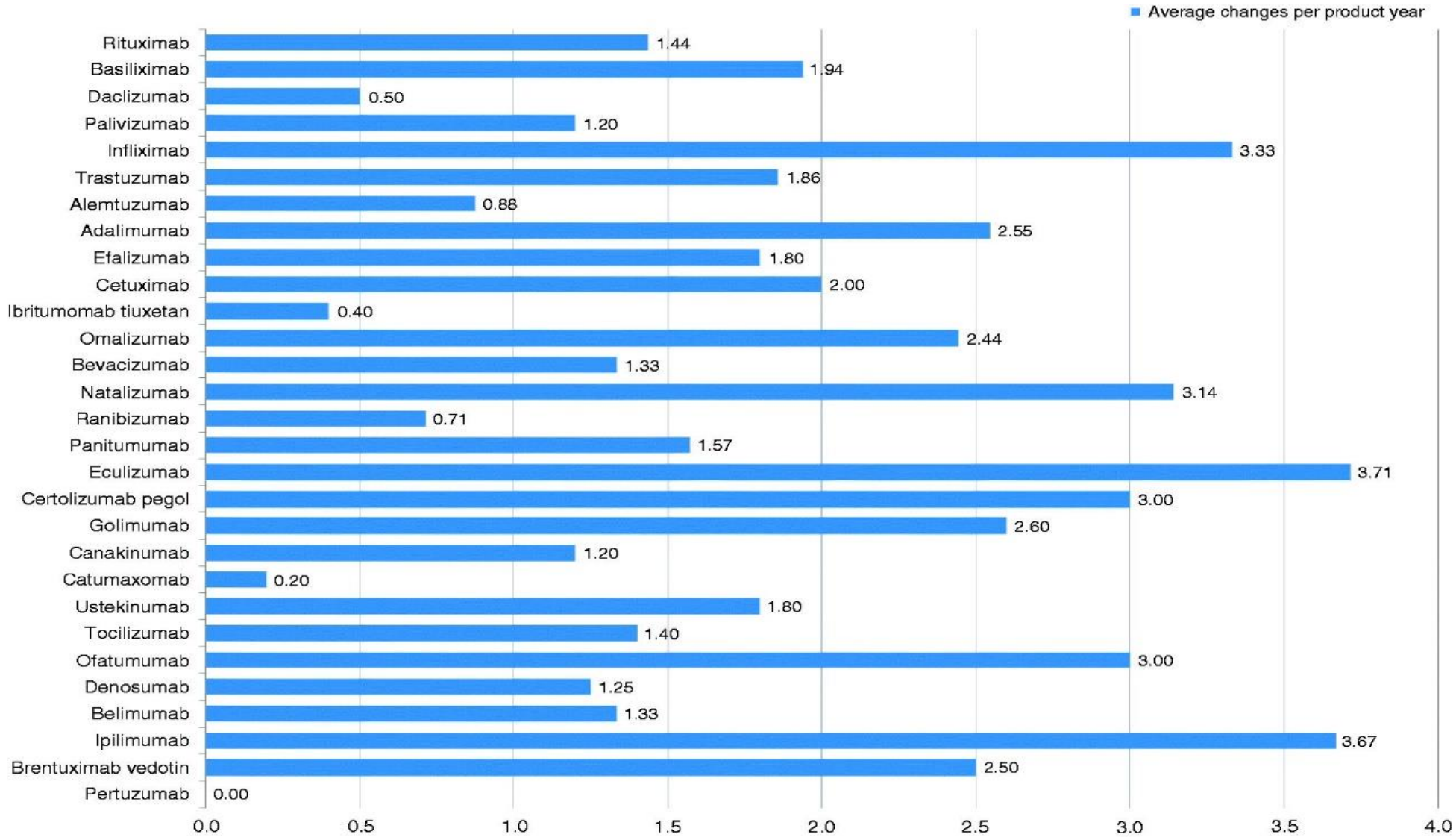
# Sources of Biologic Variability

- Expression system (plasmid, cells)
- Fermentation conditions, raw materials
- Protein purification (method, scale, reagents)
- Final purity
- Potency/activity
- Concentration
- Packaging (container, excipients)
- Sterility




Markovic I. http://ncifrederick.cancer.gov/research/brb/workshops/presentation/12_markovic_4-4-07_reviewed.ppt.

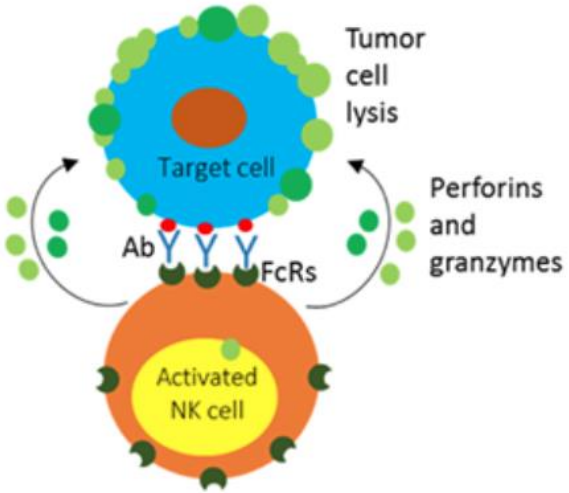
# Average Number of Manufacturing Changes/Year




**Vezér B et al. *Curr Med Res Opin.* 2016;32(5):829-834.**

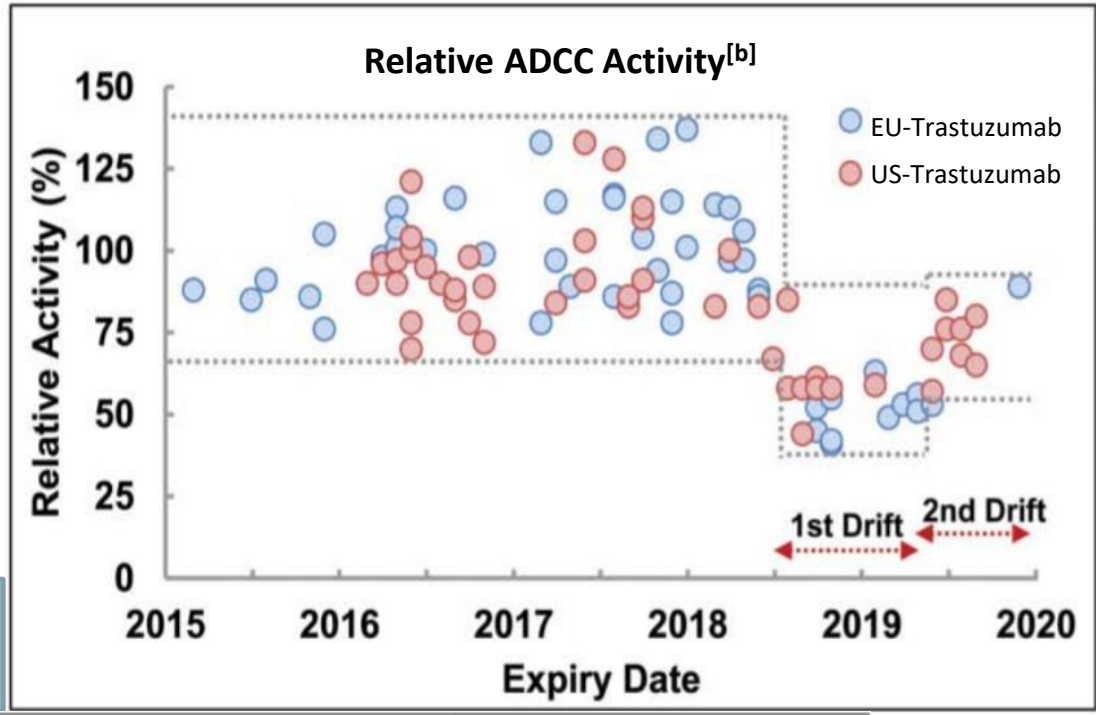
# Variability and Drift in Practice

**Overview of ADCC[a]**

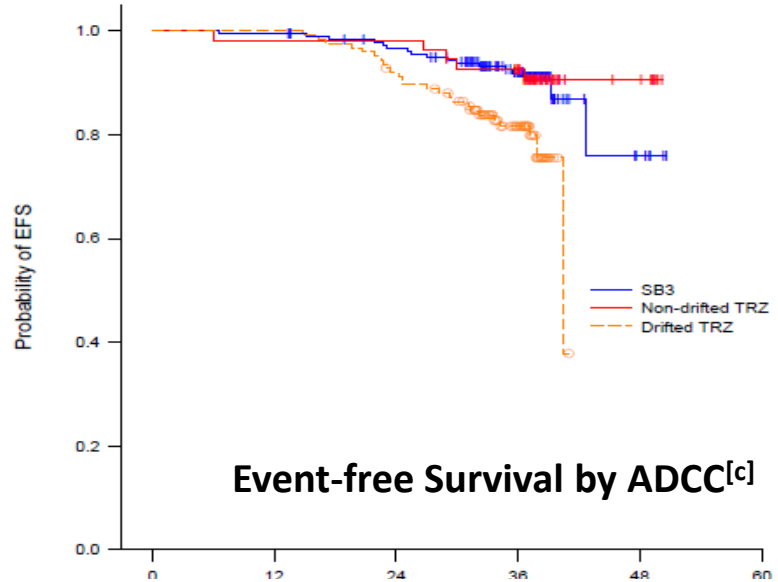



**ADCC = antibody-dependent cellular cytotoxicity**

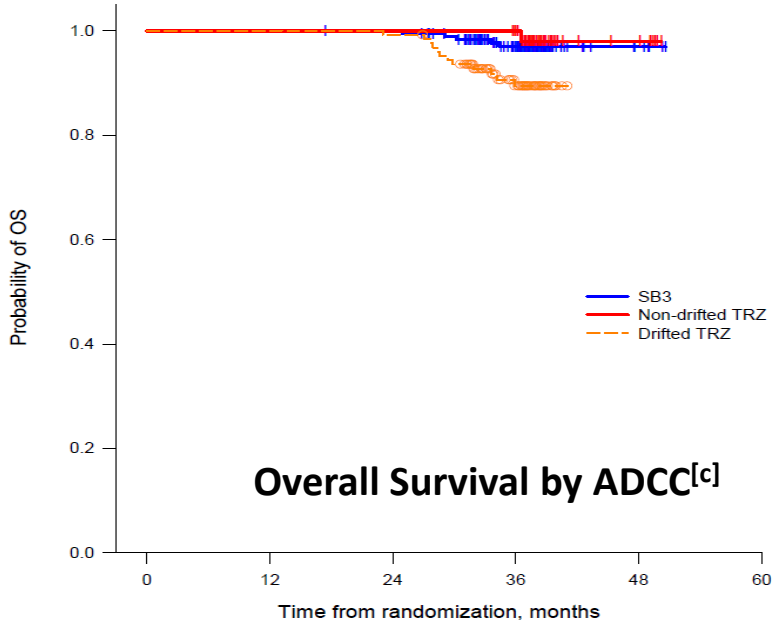
**Relative ADCC Activity[b]**




| Covariates | HR (95% CI) | P-value |
|---|---|---|
| **Full model** | | |
| Treatment (TRZ vs. SB3) | 1.34 (0.48, 3.71) | 0.5723 |
| bpCR (Yes vs. No) | 1.70 (0.92, 3.16) | 0.0937 |
| ADCC status (Non-drifted vs. Drifted) | 3.28 (1.22, 8.82) | 0.0189 |
| Hormone receptor (Positive vs. Negative) | 1.25 (0.69, 2.26) | 0.4644 |
| Breast cancer type (Operable vs. Locally advanced) | 1.32 (0.73, 2.38) | 0.3559 |
| Age (≥45 years vs. <45 years) | 1.14 (0.54, 2.41) | 0.7355 |
| Menopausal status (Yes vs. No) | 1.16 (0.58, 2.29) | 0.6747 |
| **Model with backward variable selection** | | |
| bpCR (Yes vs. No) | 1.66 (0.91, 3.03) | 0.0995 |
| ADCC status (Non-drifted vs. Drifted) | 2.65 (1.48, 4.75) | 0.0010 |

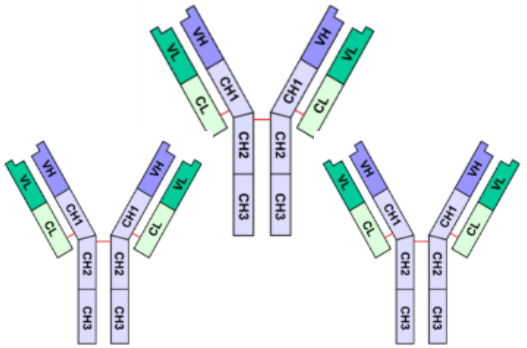

**Event-free Survival by ADCC[c]**




**Overall Survival by ADCC[c]**


a. Weiner LM et al. *Nat Rev Immunol* 2010;10:317-327
b. Kim S et al. *MAbs.* 2017;9(4):704-714;
c. Pivot X et al. *Eur J Cancer*. 2019;120:1-9.
d. Luftner D et al Target Oncol 2020;15:467-475

# Immunogenicity




- Concern for all biologics (not just biosimilars)
- Consequences
  - Loss of efficacy
  - Neutralization of endogenous protein and administered biologic agent
  - General immune responses (eg, allergy, anaphylaxis)
- FDA guidance regarding immunogenicity assessment
  - Comparative parallel design (ie, head-to-head study)

Ebbers HC et al. *Exp Opin Biol Ther*. 2012;12(11):1473-1485; Chamberlain PD. *Biosimilars*. 2014;4:23-43.

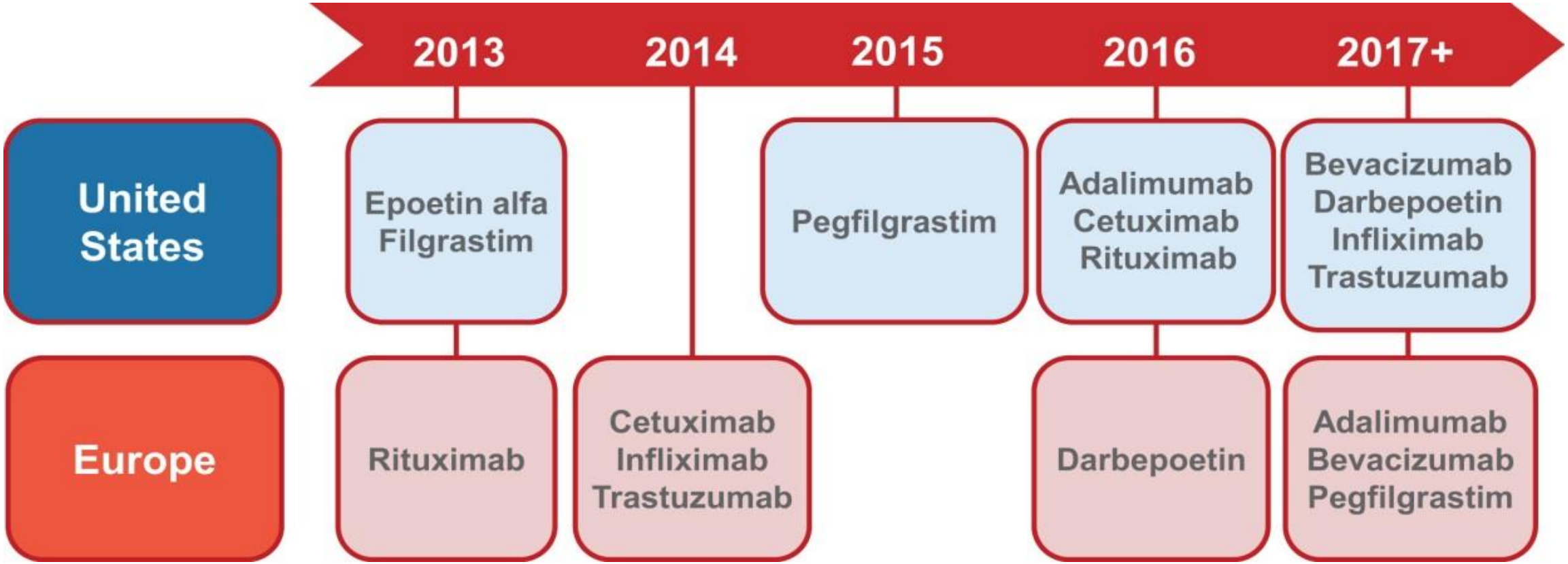
# Interchangeability and Substitution


- The designation of interchangeability" requires higher standards than "biosimilarity" alone: same result when switched/alternated with reference product
- Interchangeable biosimilar may be substituted *without intervention* of provider
- However,
  - Must be approved by FDA as "interchangeable"
  - State substitution laws will impact practice


FDA. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm.
NCSL. http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-%20and-substitution-of-biosimilars.aspx .

# Biologic Product Patents Expiring By 2020

**Biologic cancer treatments with >$20 billion in global spending targets for biosimilar development**




http://www.gabionline.net/Biosimilars/General/US-67-billion-worth-of-biosimilar-patents-expiring-before-2020

# FDA-Approved Biosimilars

## *Oncology Biosimilars [N=18/34]*

| 2015/2016 | 2017 | 2018 | 2019 | 2020/2022* |
|---|---|---|---|---|
| **Filgrastim-sndz [Zarxio®]** Neupogen® | Infliximab-abda [Renflexis®] Remicade® | **Epoetin alfa-epbx [Retacrit®]** Epogen® | **Trastuzumab-dttb [Ontruzant™ ]** Herceptin® | **Pegfilgrastim-apgf [Nyvepria™]** Neulasta® |
| Infliximab-dyyb [Inflectra®] Remicade® | Adalimumab-adbm [Cyltezo®] Humira® | **Pegfilgrastim-jmdb [Fulphila™]** Neulasta® | **Trastuzumab-qyyp [Trazimera™]** Herceptin® | Adalimumab-fkjp [Hulio™] Humira® |
| Etanercept-szzs [Erelzi®] Enbrel® | **Bevacizumab-awwb [Mvasi™] Avastin®** | **Filgrastim-aafi [Nivestym™]** Neupogen® | Etanercept-ykro [Eticovo®] Enbrel® | **Rituximab-arrx [Riabni™] Rituxan@** |
| Adalimumab-atto [Amjevita™] Humira® | **Trastuzumab-dkst [Ogivri™]** Herceptin® | Adalimumab-adaz [Hyrimoz™] Humira® | **Trastuzumab-anns [Kaninti™] Herceptin®** | Insulin glargine-yfgn [Semglee™]] Lantus |
| | Infliximab-qbtx [Ixifi™]* Remicade® | **Pegfilgrastim-cbqv [Udenyca™]** Neulasta® | **Bevacizumab-bvzr [Zirabev™] Avastin®** | Ranibizumab-nuna [Byooviz™] Lucentis® |
| | | **trastuzumab-pkrb [Herzuma™]** Herceptin® | **Rituximab-pvvr [Ruxience™] Rituxan®** | Insulin glargine-aglr [Rezvoglar™] Lantus |
| | | **Rituximab-abbs [Truxima™]** Rituxan® Herceptin® | Adalimumab-bwwd [Hadlima™] Humira® ] | Adalimumab-aqvh [Yusimry™] Humira® |
| | | | **Pegfilgrastim-bmez [Ziextenxo™** Neulasta® | **Filgrastim-ayow [Releuko]** Neupogen® |
| | | | Adalimumab-afzb [Abilada™] Humira® | |
| | | | Infliximab -axxq [Avzola™] Remicade® | |

*** Through April 2022**

FOCUS ON QUALITY

# Use of Biosimilar Medications in Oncology

Zeina Nahleh, MD[1]; Gary H. Lyman, MD, MPH[2]; Richard L. Schilsky, MD[3]; Douglas E. Peterson, DMD, PhD[4]; Scott T. Tagawa, MD, MS[5]; Mariana Chavez-MacGregor, MD, MSc[6]; R. Bryan Rumble, MSc[7]; and Shilpi Gupta, MD[8]

**TABLE 2.** FDA-Approved Oncology Supportive Biosimilars

| Reference Products | Biosimilar Name | Biosimilar Manufacturer | FDA Approval | FDA Indications and Usage |
|---|---|---|---|---|
| Epoetin alfa | Epoetin alfa-epbx<br>Epoetin alfa-epbx information | Hospira Inc | May 15, 2018 | Treatment of anemia because of the following:<br>CKD in patients on dialysis and not on dialysis<br>Zidovudine in patients with HIV infection<br>Effects of concomitant myelosuppressive chemotherapy, and upon initiation, when there is a minimum of two additional months of planned chemotherapy<br>Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, and nonvascular surgery |
| Filgrastim | Filgrastim-sndz<br>Filgrastim-sndz information[43] | Sandoz Inc | March 6, 2015 | To decrease the incidence of infection' as manifested by febrile neutropenia' in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever<br>To reduce the time to neutrophil recovery and the duration of fever, after induction or consolidation chemotherapy treatment of patients with AML<br>To reduce the duration of neutropenia and neutropenia-related clinical sequelae' eg' febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT<br>To mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis<br>To reduce the incidence and duration of sequelae of severe neutropenia in symptomatic patients with congenital neutropenia' cyclic neutropenia' or idiopathic neutropenia |
| | Filgrastim-aafi<br>Filgrastim-aafi information[44] | Pfizer Inc | July 20, 2018 | To decrease the incidence of infection' as manifested by febrile neutropenia' in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with significant incidence of severe neutropenia with fever<br>To reduce time to neutrophil recovery and duration of fever, after induction or consolidation chemotherapy treatment of patients with AML<br>To reduce the duration of neutropenia and neutropenia-related clinical sequelae' e.g.' febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT<br>To mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis<br>To reduce the incidence and duration of sequelae of severe neutropenia in symptomatic patients with congenital neutropenia' cyclic neutropenia' or idiopathic neutropenia |
| Pegfilgrastim | Pegfilgrastim-jmdb<br>Pegfilgrastim-jmdb information[45] | Mylan N.V. | June 4, 2018 | To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia |
| | Pegfilgrastim-cbqv<br>Pegfilgrastim-cbqv information[46] | | November 2, 2018 | To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with clinically significant incidence of febrile neutropenia |
| | Pegfilgrastim-bmez<br>Pegfilgrastim-bmez information | Sandoz Inc | November 4, 2019 | To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia |
| | Pegfilgrastim-apgf<br>Pegfilgrastim-apgf information[47] | Pfizer Inc | June 10, 2020 | To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia |

Abbreviations: AML, acute myeloid leukemia; BMT, bone marrow transplantation; CKD, chronic kidney disease; FDA, US Food and Drug Administration.

**TABLE 1.** FDA-Approved Cancer Therapeutic Biosimilars

| Reference Product | Biosimilar Name | Biosimilar Manufacturer | FDA Approval | FDA Indications and Usage |
|---|---|---|---|---|
| Bevacizumab | Bevacizumab-awwb<br>Bevacizumab-awwb information[17] | Amgen Inc | September 14, 2017 | Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment<br>Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan–based or fluoropyrimidine-oxaliplatin–based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product–containing regimen<br>Unresectable, locally advanced, recurrent, or metastatic nonsquamous non–small-cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment<br>Recurrent glioblastoma in adults<br>Metastatic renal cell carcinoma in combination with interferon-α<br>Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan |
| | Bevacizumab-bvzr<br>Bevacizumab-bvzr information[18] | Pfizer Inc | June 27, 2019 | Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment<br>Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan–based or fluoropyrimidine-oxaliplatin–based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product–containing regimen<br>Unresectable, locally advanced, recurrent, or metastatic nonsquamous non–small-cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment<br>Recurrent glioblastoma in adults<br>Metastatic renal cell carcinoma in combination with interferon-α<br>Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan |
| Rituximab | Rituximab-abbs<br>Rituximab-abbs information[19] | Celltrion Inc | December 14, 2018 | NHL<br>CLL<br>RA<br>GPA (Wegener's granulomatosis) and MPA |
| | Rituximab-pvvr<br>Rituximab-pvvr information[20] | Pfizer Inc | July 23, 2019 | NHL<br>CLL<br>GPA (Wegener's granulomatosis) and MPA in combination with glucocorticoids |
| | Rituximab-arrx<br>Rituximab-arrx information[21] | Amgen Inc | December 17, 2020 | NHL<br>CLL<br>GPA (Wegener's granulomatosis) and MPA in combination with glucocorticoids |
| Trastuzumab | Trastuzumab-dkst<br>Trastuzumab-dkst information[22] | Mylan GmbH | December 1, 2017 | Breast cancer, HER2-overexpressing, early or metastatic<br>Metastatic gastric/GE junction cancer, HER2-overexpressing |
| | Trastuzumab-dttb<br>Trastuzumab-dttb information[23] | Samsung Bioepis Co Ltd | January 18, 2019 | Breast cancer, HER2-overexpressing, early or metastatic<br>Metastatic gastric/GE junction cancer, HER2-overexpressing |
| | Trastuzumab-pkrb<br>Trastuzumab-pkrb information[24] | Celltrion Inc | December 14, 2018 | HER2-overexpressing breast cancer (early or metastatic) |
| | Trastuzumab-qyyp<br>Trastuzumab-qyyp information[25] | Pfizer Inc | March 11, 2019 | Breast cancer, HER2-overexpressing, early or metastatic<br>Metastatic gastric/GE junction cancer, HER2-overexpressing |
| | Trastuzumab-anns<br>Trastuzumab-anns information[26] | Amgen Inc | June 13, 2019 | Breast cancer, HER2-overexpressing, early or metastatic<br>Metastatic gastric/GE junction cancer, HER2-overexpressing |

Abbreviations: CLL, chronic lymphocytic leukemia; FDA, US Food and Drug Administration; GE, gastroesophageal; GPA, granulomatosis with polyangiitis; HER2, human epidermal growth factor receptor 2; MPA, microscopic polyangiitis; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis.

**Nahieh Z, Lyman GH, Schilsky R et *al JCO JCO Oncol Pract* 2022; 18: 177-186**

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| | Pegfilgrastim-apgf<br>Pegfilgrastim-apgf information[47] | Pfizer Inc | June 10, 2020 | To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia |

Abbreviations: AML, acute myeloid leukemia; BMT, bone marrow transplantation; CKD, chronic kidney disease; FDA, US Food and Drug Administration.

**TABLE 1.** FDA-Approved Cancer Therapeutic Biosimilars

| Reference Product | Biosimilar Name | Biosimilar Manufacturer | FDA Approval | FDA Indications and Usage |
|---|---|---|---|---|
| Bevacizumab | Bevacizumab-awwb<br>Bevacizumab-awwb information[17] | Amgen Inc | September 14, 2017 | Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment<br>Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan–based or fluoropyrimidine-oxaliplatin–based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product–containing regimen<br>Unresectable, locally advanced, recurrent, or metastatic nonsquamous non–small-cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment<br>Recurrent glioblastoma in adults<br>Metastatic renal cell carcinoma in combination with interferon-α<br>Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan |
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| Rituximab | Rituximab-abbs<br>Rituximab-abbs information[19] | Celltrion Inc | December 14, 2018 | NHL<br>CLL<br>RA<br>GPA (Wegener's granulomatosis) and MPA |
| | Rituximab-pvvr<br>Rituximab-pvvr information[20] | Pfizer Inc | July 23, 2019 | NHL<br>CLL<br>GPA (Wegener's granulomatosis) and MPA in combination with glucocorticoids |
| | Rituximab-arrx<br>Rituximab-arrx information[21] | Amgen Inc | December 17, 2020 | NHL<br>CLL<br>GPA (Wegener's granulomatosis) and MPA in combination with glucocorticoids |
| Trastuzumab | Trastuzumab-dkst<br>Trastuzumab-dkst information[22] | Mylan GmbH | December 1, 2017 | Breast cancer, HER2-overexpressing, early or metastatic<br>Metastatic gastric/GE junction cancer, HER2-overexpressing |
| | Trastuzumab-dttb<br>Trastuzumab-dttb information[23] | Samsung Bioepis Co Ltd | January 18, 2019 | Breast cancer, HER2-overexpressing, early or metastatic<br>Metastatic gastric/GE junction cancer, HER2-overexpressing |
| | Trastuzumab-pkrb<br>Trastuzumab-pkrb information[24] | Celltrion Inc | December 14, 2018 | HER2-overexpressing breast cancer (early or metastatic) |
| | Trastuzumab-qyyp<br>Trastuzumab-qyyp information[25] | Pfizer Inc | March 11, 2019 | Breast cancer, HER2-overexpressing, early or metastatic<br>Metastatic gastric/GE junction cancer, HER2-overexpressing |
| | Trastuzumab-anns<br>Trastuzumab-anns information[26] | Amgen Inc | June 13, 2019 | Breast cancer, HER2-overexpressing, early or metastatic<br>Metastatic gastric/GE junction cancer, HER2-overexpressing |

Abbreviations: CLL, chronic lymphocytic leukemia; FDA, US Food and Drug Administration; GE, gastroesophageal; GPA, granulomatosis with polyangiitis; HER2, human epidermal growth factor receptor 2; MPA, microscopic polyangiitis; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis.

**Supportive Care Biosimilars**

**Nahieh Z, Lyman GH, Schilsky R et *al JCO JCO Oncol Pract* 2022; 18: 177-186**

FOCUS ON QUALITY

# Use of Biosimilar Medications in Oncology

Zeina Nahleh, MD[1]; Gary H. Lyman, MD, MPH[2]; Richard L. Schilsky, MD[3]; Douglas E. Peterson, DMD, PhD[4]; Scott T. Tagawa, MD, MS[5]; Mariana Chavez-MacGregor, MD, MSc[6]; R. Bryan Rumble, MSc[7]; and Shilpi Gupta, MD[8]

**TABLE 2.** FDA-Approved Oncology Supportive Biosimilars

| Reference Products | Biosimilar Name | Biosimilar Manufacturer | FDA Approval | FDA Indications and Usage |
|---|---|---|---|---|
| Epoetin alfa | Epoetin alfa-epbx<br>Epoetin alfa-epbx information | Hospira Inc | May 15, 2018 | Treatment of anemia because of the following:<br>CKD in patients on dialysis and not on dialysis<br>Zidovudine in patients with HIV infection<br>Effects of concomitant myelosuppressive chemotherapy, and upon initiation, when there is a minimum of two additional months planned chemotherapy<br>Reduction of allogeneic RBC transfusions in pa going elective, noncardiac, and nonvascular surgery |
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Supportive Care Biosimilars

Cancer Therapeutic Biosimilars

Nahieh Z, Lyman GH, Schilsky R et *al JCO JCO Oncol Pract* 2022; 18: 177-186

# Oncology Biosimilars Approval in EU and US:
## *Monoclonal Antibodies & Granulocyte-Colony Stimulating Factor*

| Reference Product | EMA Approval[1] | FDA Approval[2] |
|---|---|---|
| **Filgrastim** (Neupogen, Amgen) | Ratiograstim (Ratiopharm) | Granix (TEVA)<br>Zarxio (Sandoz)<br>Nivestym (Pfizer)<br>Releuko (Kashiv) |
| | Tevagrastim (Teva) | |
| | Filgrastim Hexal (Hexal) | |
| | Zarzio (Sandoz) | |
| | Nivestim (Hospira) | |
| | Grastofil (Apotex) | |
| | Accofil (Accord) | |
| **Pegfilgrastim** (Neulasta, Amgen) | Pelgraz (Accord) | Fulphila (Mylan)<br>Udenyca (Coherus)<br>Ziextenxo (Sandoz)<br>Nyvepria (Pfizer) |
| | Udenyca (Coherus) | |
| | Fulphila (Mylan) | |
| | Pelmeg (Cinfa) | |
| | Ziextenzo (Sandoz) | |

| Reference Product | EMA Approval[1] | FDA Approval[2] |
|---|---|---|
| **Rituximab** (Rituxan, Biogen/Genentech) | Truxima (Celltrion) | Truxima (Celltrion)<br>Ruxience (Pfizer)<br>Riabni (Amgen) |
| | Riximyo (Sandoz) | |
| | Rixathon (Sandoz) | |
| | Blitzima (Celltrion) | |
| | Ritemvia (Celltrion) | |
| | Rituzena (Celltrion) | |
| **Trastuzumab** (Herceptin, Genentech) | Ontruzant (Samsung Bioepis) | Ogivri (Mylan/Biocon)<br>Herzuma (Celltrion)<br>Ontruzant (Samsung Bioepis)<br>Trazimera (Pfizer)<br>Kanjinti (Amgen) |
| | Herzuma (Celltrion Healthcare) | |
| | Kanjinti (Amgen) | |
| | Trazimera (Pfizer) | |
| | Ogivri (Mylan/Biocon) | |
| **Bevacizumab** (Avastin, Genentech) | Mvasi (Amgen) | Mvasi (Amgen/Allergan)<br>Zirabev (Pfizer) |
| | Zirabev (Pfizer) | |

**Nahieh Z, Lyman GH, Schilsky R et *al JCO JCO Oncol Pract* 2022; 18: 177-186**

ASCO special articles

# Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Guideline Update

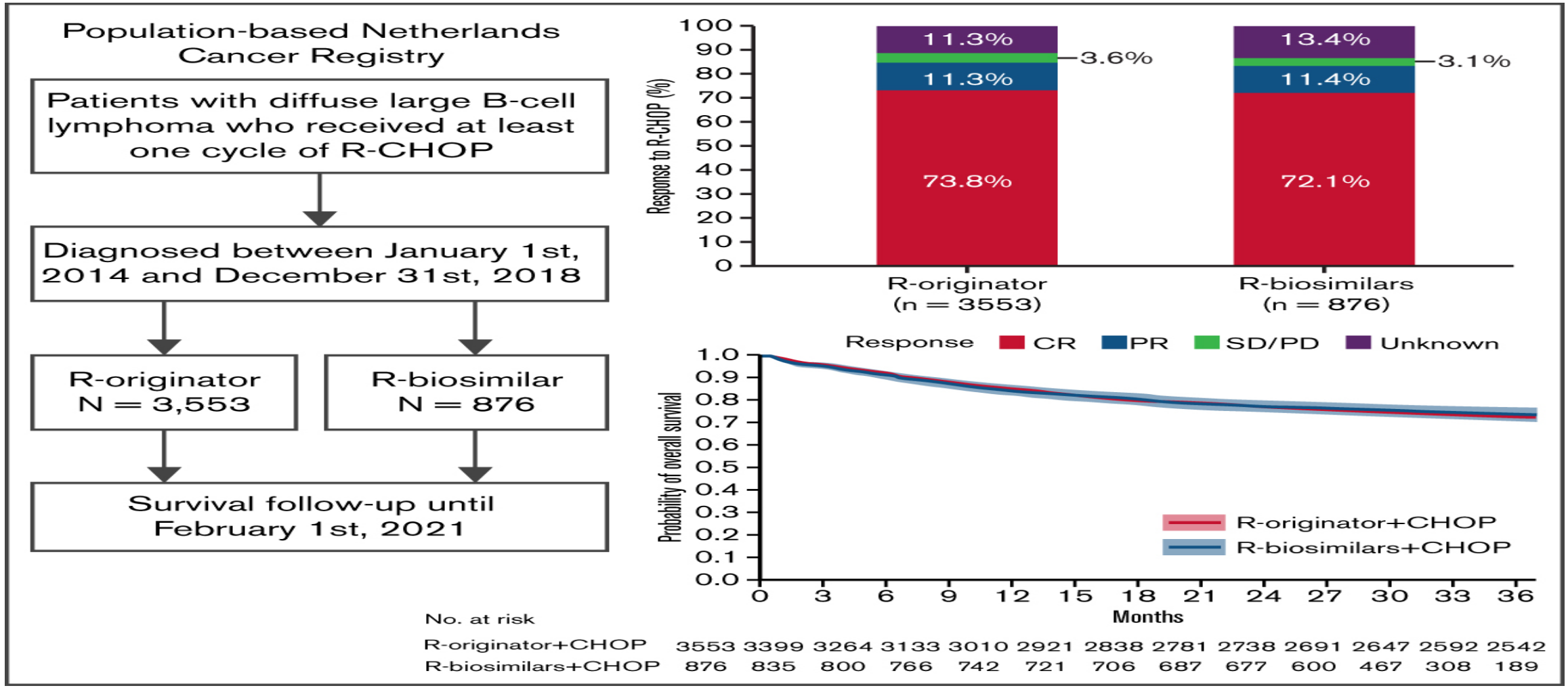
Neelima Denduluri, MD[1]; Mark R. Somerfield, PhD[2]; Mariana Chavez-MacGregor, MD, MSc[3]; Amy H. Comander, MD[4]; Zoneddy Dayao, MD[5]; Andrea Eisen, MD[6,7]; Rachel A. Freedman, MD, MPH[8]; Ragisha Gopalakrishnan, MD[9]; Stephanie L. Graff, MD[10]; Michael J. Hassett, MD, MPH[8]; Tari A. King, MD[8,11]; Gary H. Lyman, MD, MPH[12]; Gillian Rice Maupin, JD[13]; Raquel Nunes, MD[14]; Cheryl L. Perkins, MD, RPh[15]; Melinda L. Telli, MD[16]; Maureen E. Trudeau, MD[6,7]; Antonio C. Wolff, MD[14]; and Sharon H. Giordano, MD, MPH[3]

***Clinicians may offer any of the available and approved formulations of trastuzumab including trastuzumab…and available biosimilars.***

**Denduluri N et al: J Clin Oncol 2021; 39: 685-693**

# Impact of rituximab biosimilars on overall survival in DLBCL

## *A Dutch population-based study*



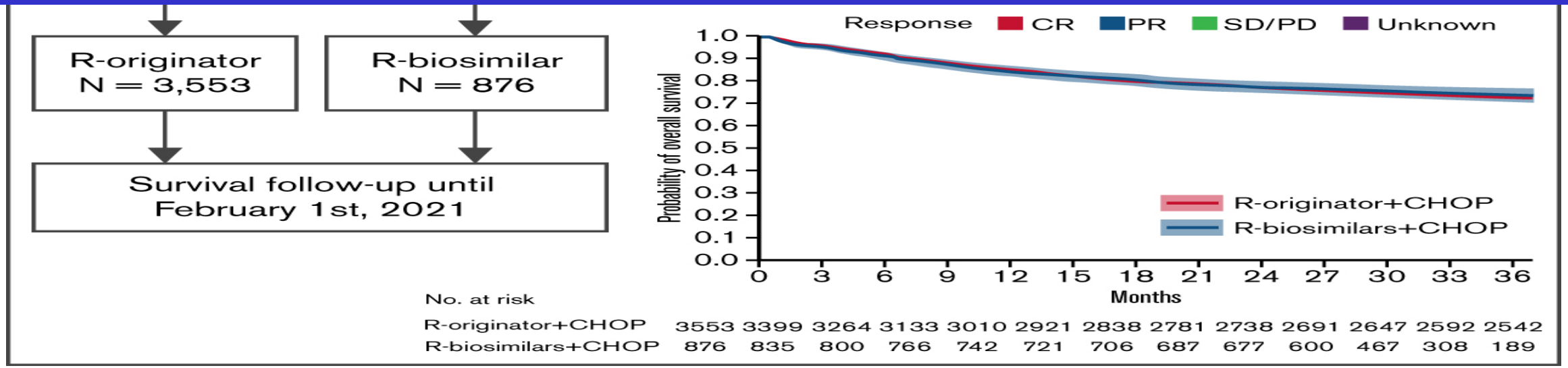

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

**Brink M et al, Blood Adv; 2021; 5: 2958-2964**

# Impact of rituximab biosimilars on overall survival in DLBCL

*A Dutch population-based study*

✓ **Three-year OS did not differ between DLBCL patients treated with rituximab biosimilars or the rituximab originator**

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# Impact of rituximab biosimilars on overall survival in DLBCL

*A Dutch population-based study*

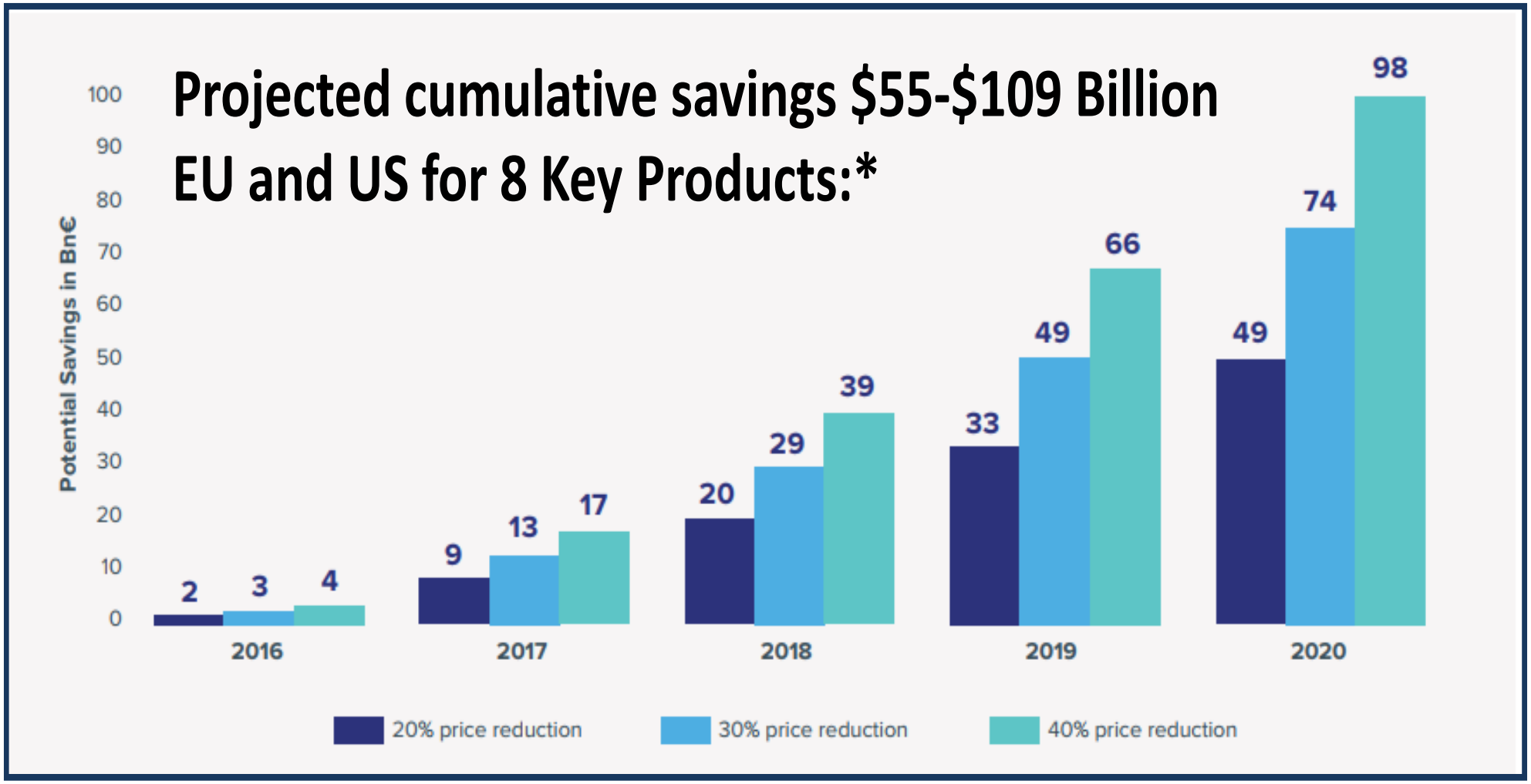
✓ Three-year OS did not differ between DLBCL patients treated with rituximab biosimilars or the rituximab originator

✓ By the end of 2018, 91% of purchased rituximab in the Netherlands were biosimilars, accounting for a 43% reduction in annual costs



Brink M et al, Blood Adv; 2021; 5: 2958-2964

# Remaining Challenges and Opportunities Ahead

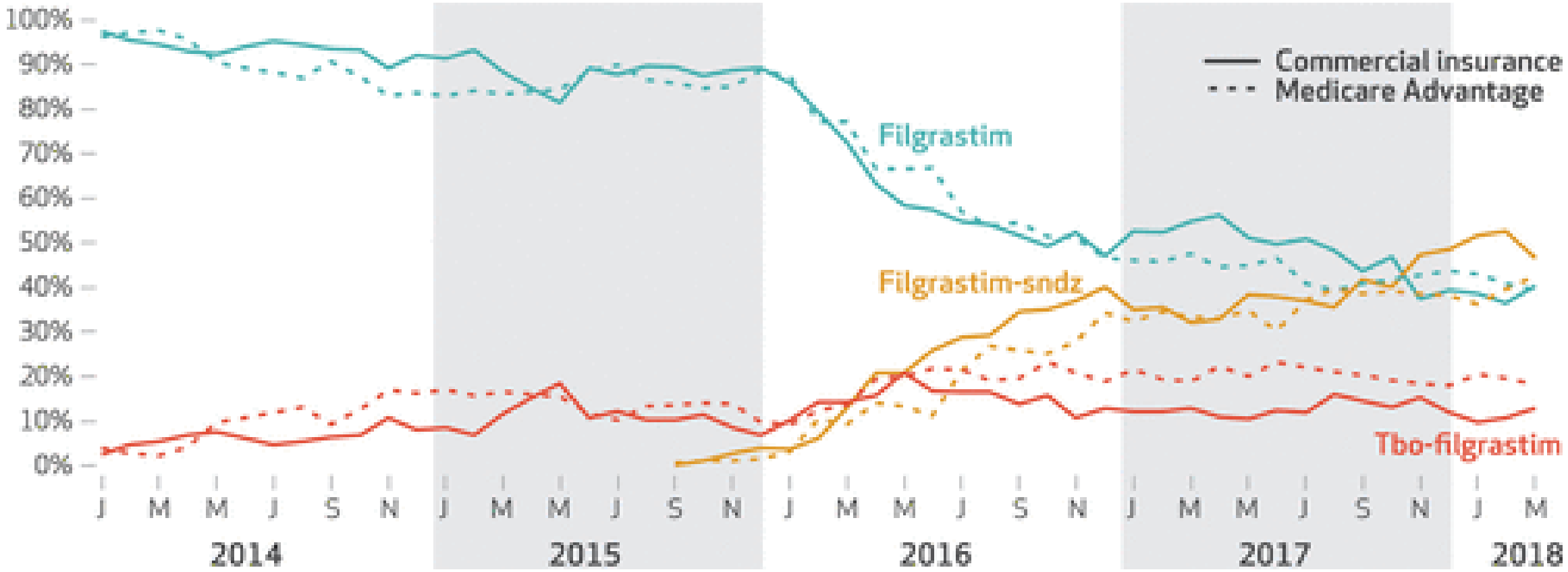



*adalimumab, insulin glargine, etanercept, infliximab, rituximab, peg-filgrastim, trastuzumab and follitropin alpha

IMS Institute for Healthcare Informatics. https://www.medicinesforeurope.com/wp-content/uploads/2016/03/IMS-Institute-Biosimilar-Report-March-2016-FINAL.pdf.

# Early Adoption of Biosimilar Hematopoietic Growth Factors

**Percent administrations among patients with commercial insurance or Medicare Advantage**




Karaca-Mandic P et al *Health Aff.* 2019;38(11):1887-1892.

# Integrating Biosimilars into Oncology Practice

## *Opportunities and Challenges*

### Challenges

- Approval based on limited clinical data vs reference
- Patent challenges to availability (patent dance)
- Biologic variability, drift, and immunogenicity
- Extrapolation of biosimilar indications to indications for which the reference product was approved
- Interchangeability and automatic substitution
- Need for pharmacovigilance and physician and patient education
- Administrative burden due to multiple agents

### Opportunities

- Reduce unsustainable increases in healthcare costs and increase pt access to biologic agents
- Integration into clinical practice, guidelines and pathways provides opportunity for improving efficiency and effectiveness while containing costs and enhancing patient access to high-quality cancer care

# Conclusions

- Biosimilar supportive care agents have been available in the US for 4-5 years and have been integrated into clinical practice guidelines and pathways.
- Several biosimilar cancer therapeutics have only recently been approved in the US and are becoming integrated into guidelines and practice.
- For competition to have an impact on drug prices, it will be necessary for multiple competitors in a class to be clinically available for a significant period of time.
- Uptake of biosimilars will depend upon continued monitoring of safety and efficacy and their appropriate integration into clinically-driven practice guidelines and pathways.
- Continued professional education concerning development, regulatory approval, and post-approval surveillance for durable efficacy and safety in real-world practice is essential.

# THANK YOU