Biosimilars in Oncology: Healthcare and clinical considerations

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BIO ONCOLOGY CARE

Disclosures

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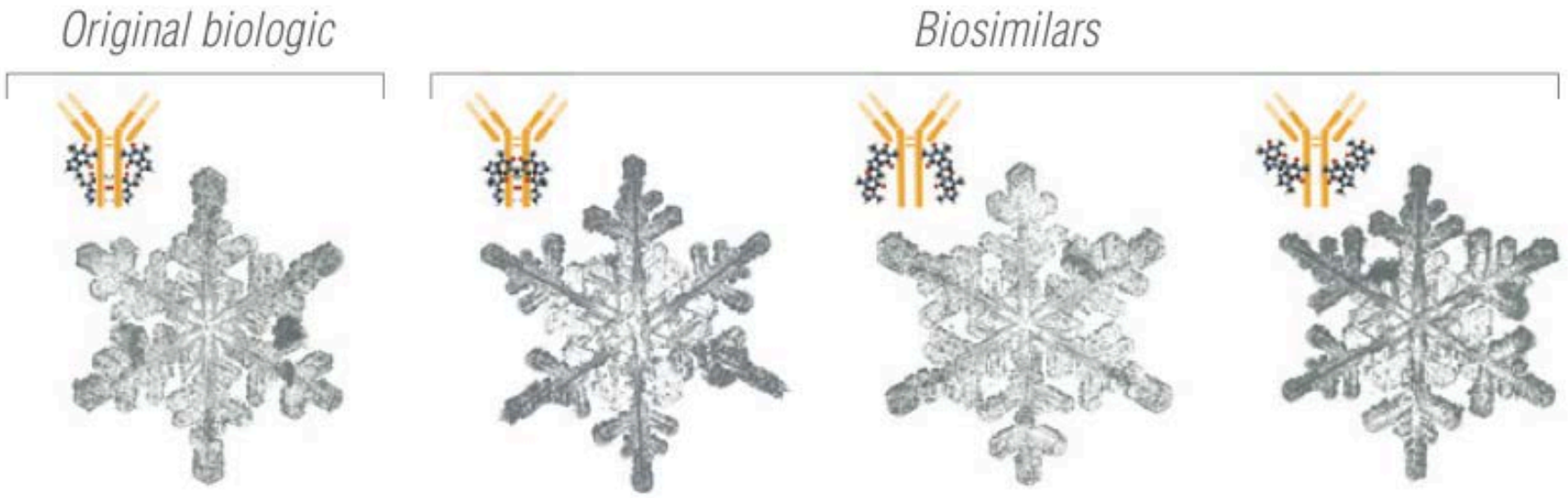
Background

- The reality of biosimilars
- Questions addressed by a physician
- The example of trastuzumab in breast cancer
- Barriers and opportunities for extension of biosimilars

Introduction

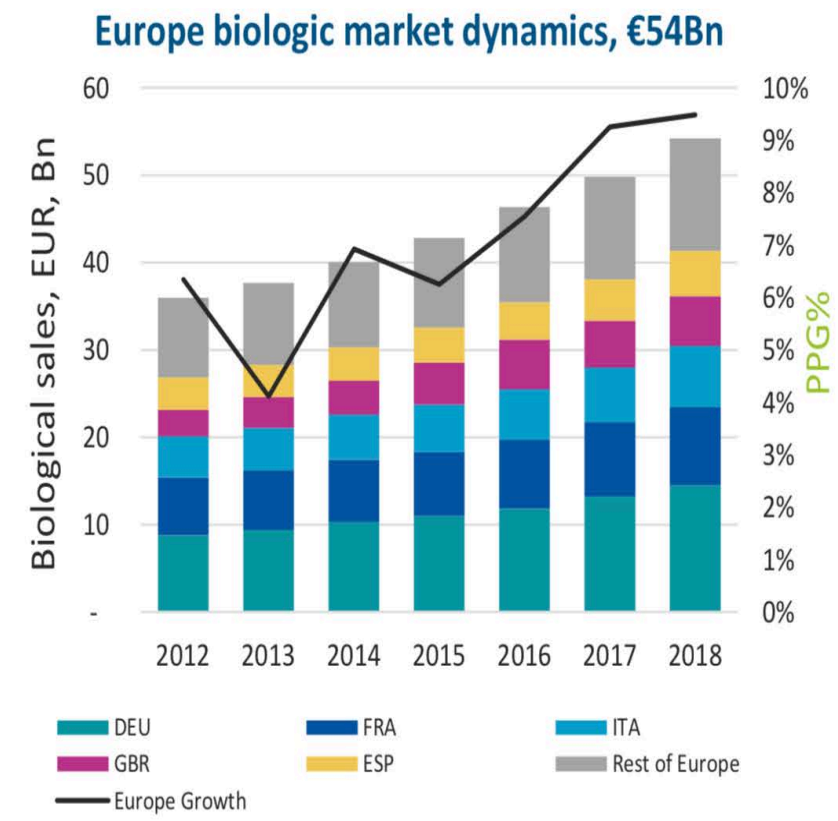
- Biologics are a 20th Century development.
- Biologics are much larger and more complex compared chemical drugs.
- Biosimilars are not generics, they are similar but not identical.
- Monoclonal antibodies introduce another layer of complexity for biosimilars manufacturers.
- Slight alteration in manufacturing of biologics can lead to clinically relevant changes, particularly concerning potency.
- Key biologics patent expired.



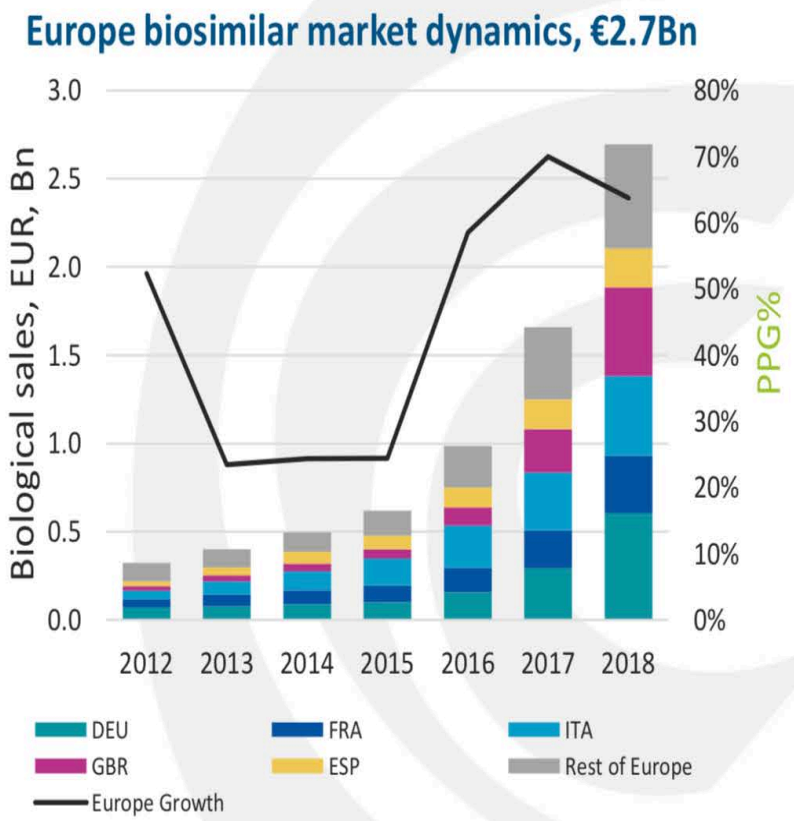
- **The promise of bio-similar is to provide cost savings, increase patient access, and promote innovation**

Biologics growth continues to outstrip total pharma and impact expenditure

Biologics account for over ¼ of European sales



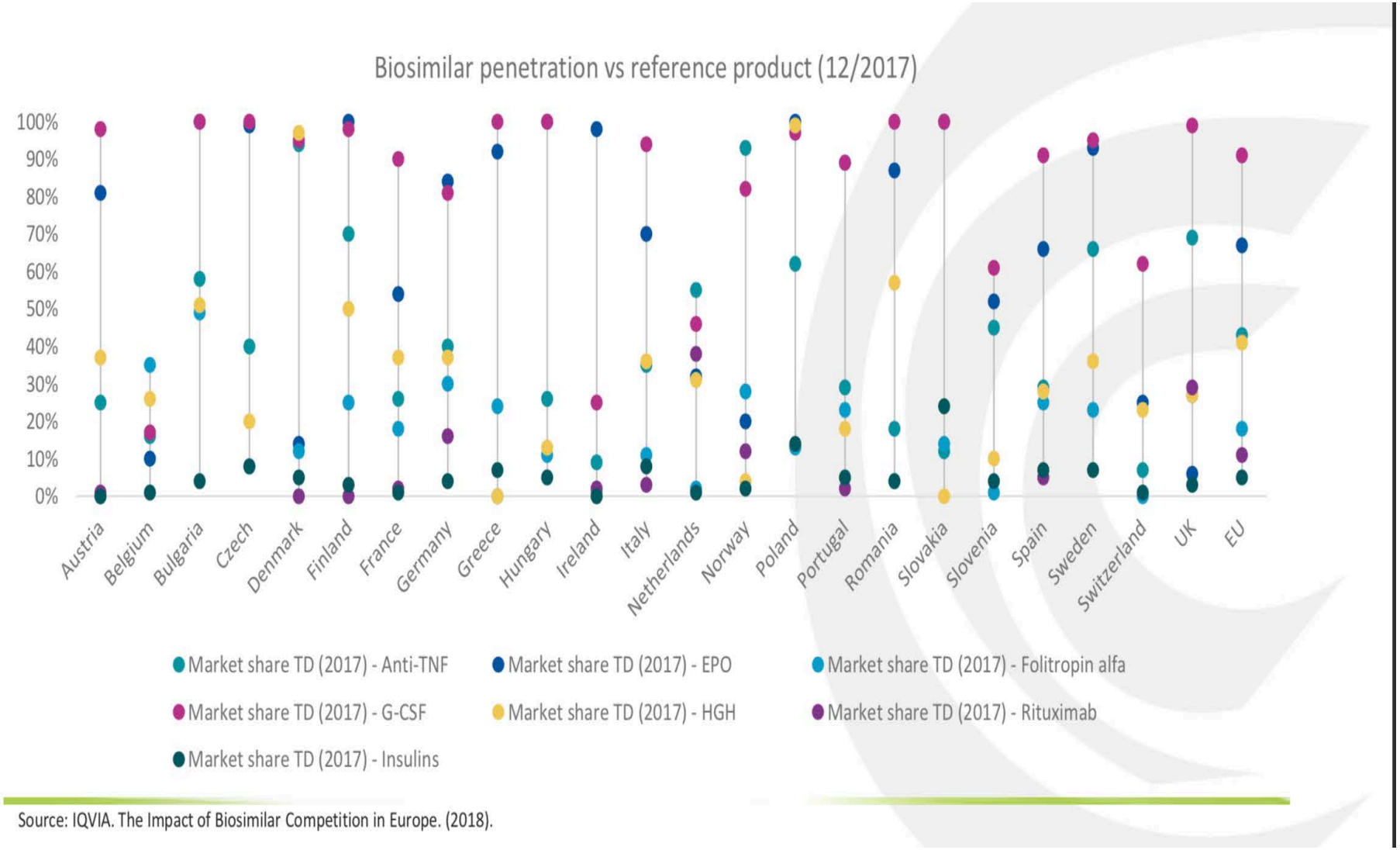
Biosimilars only account for 5.0%



Such a trend is putting additional financial pressure on healthcare budgets

Source: IQVIA

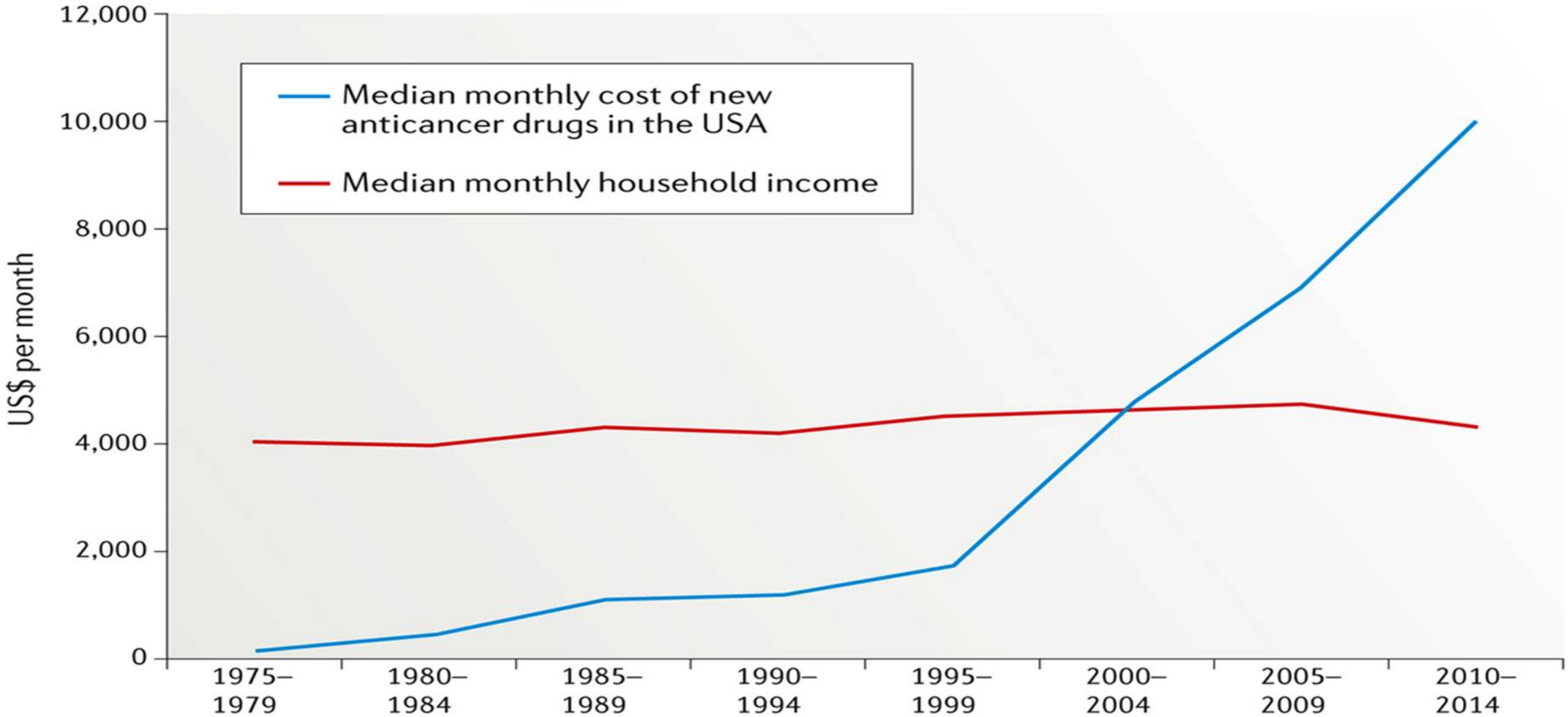
Use of biosimilar medicines varies greatly by country and therapeutic area



Source: IQVIA. The Impact of Biosimilar Competition in Europe. (2018).

Education of Providers, Patients and Policy Makers

Launch price of new anticancer drugs compared with household income



Prasad, V. *et al.* (2017) *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2017.31

Education of Providers, Patients and Policy Makers
Finding the Right Balance for Oncology

Approval Process Requires Too Large Amount of Data

Benefits
- Greater healthcare provider confidence in biosimilar product
- Greater acceptance and uptake of biosimilar?
- Fewer safety concerns

Risks
- Higher development costs
- Lower pharmacoeconomic benefit over innovator product

Biosimilar Development and Regulatory Approval Process

Approval Process Requires Too Little Amount of Data

Benefits
- Lower development costs
- Greater pharmacoeconomic benefit over innovator product

Risks
- Lower healthcare provider confidence in biosimilar product
- Less acceptance and uptake of biosimilar?
- Greater safety concerns

The NEW ENGLAND JOURNAL of MEDICINE

HEALTH LAW, ETHICS, AND HUMAN RIGHTS

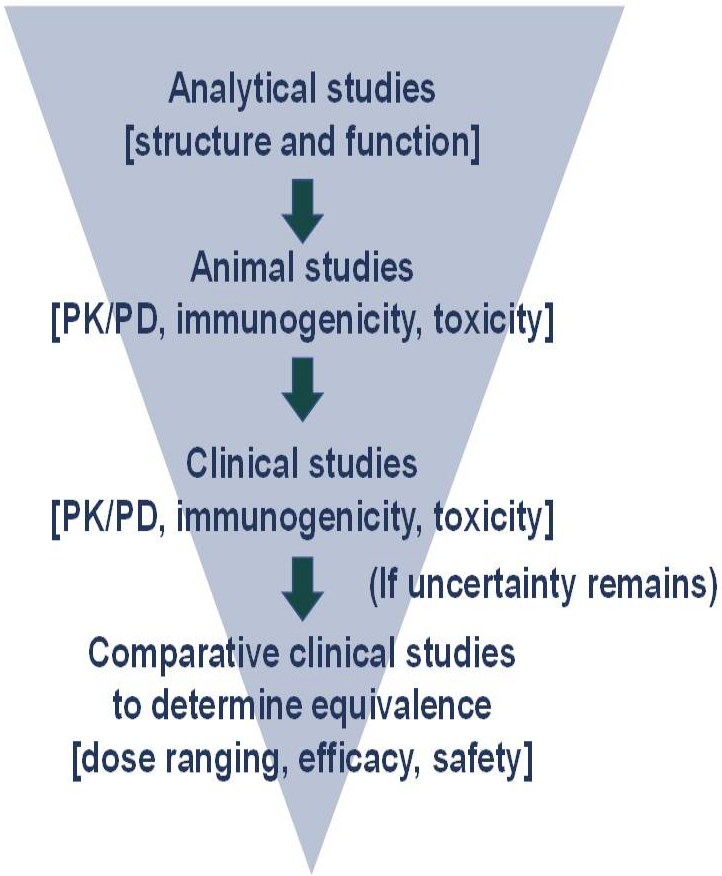
Rationale, Opportunities, and Reality of Biosimilar Medications

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

Table 4. Biosimilar Agents Approved for Use in the United States.*

Reference Product by Generic Name (Trade Name, Manufacturer)	Biosimilar Agent by Nonproprietary Name (Trade Name, Manufacturer)	Year Approved	Year Marketed
Nononcology			
Infliximab (Remicade, Janssen Biotech)	Infliximab-dyyb (Inflectra, Celltrion/Pfizer)	2016	2016
	Infliximab-abda (Renflexis, Samsung Bioepis)	2017	2017
	Infliximab-qbtx (Ixifi, Pfizer)	2017	Not available
Etanercept (Enbrel, Amgen)	Etanercept-szzs (Erelzi, Sandoz)	2016	Not available
Adalimumab (Humira, AbbVie)	Adalimumab-atto (Amjevita, Amgen)	2016	Not available
	Adalimumab-adbm (Cyltezo, Boehringer Ingelheim)	2017	Not available
Oncology			
Filgrastim (Neupogen, Amgen)	Filgrastim-sndz (Zarxio, Sandoz)	2015	2015
Bevacizumab (Avastin, Genentech)	Bevacizumab-awwb (Mvasi, Amgen)	2017	Not available
Trastuzumab (Herceptin, Genentech)	Trastuzumab-dkst (Ogivri, Mylan/Biocon)	2017	Not available

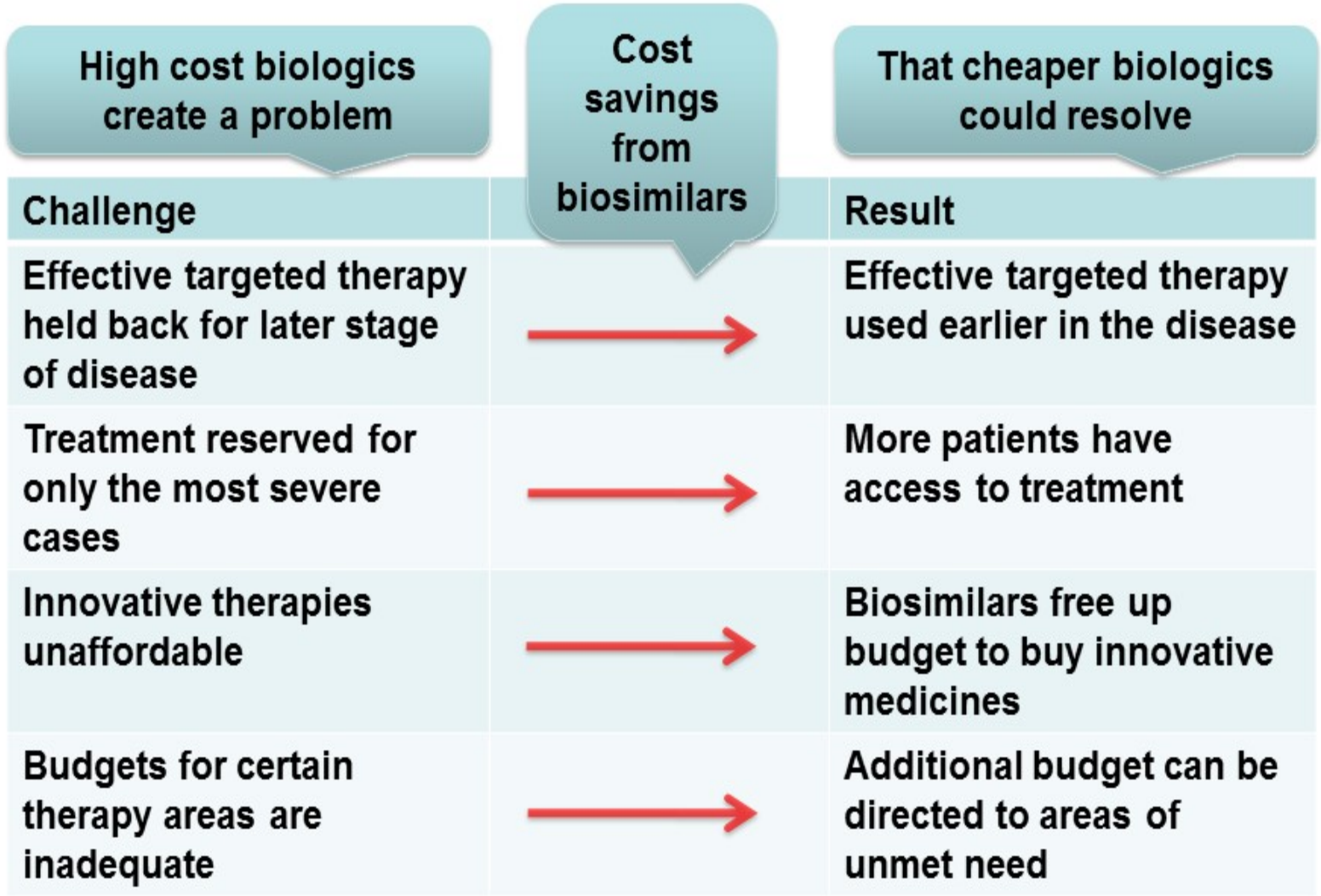
* No biosimilar agent approved in the United States has been designated as an interchangeable product.



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

The NEW ENGLAND JOURNAL of MEDICINE

The promise of biosimilar medicines



Ref: [1] Adapted from Henry D, Taylor C. Semin Oncol 2014;41(Suppl 3):S13–20

Reality

The ~~promise~~ of biosimilar medicines

Cost savings from biosimilars

Challenge		Result
Effective targeted therapy held back for later stage of disease	→	Effective targeted therapy used earlier in the disease
Treatment reserved for only the most severe cases	→	More patients have access to treatment
Innovative therapies unaffordable	→	Biosimilars free up budget to buy innovative medicines
Budgets for certain therapy areas are inadequate	→	Additional budget can be directed to areas of unmet need

Ref: [1] Adapted from Henry D, Taylor C. Semin Oncol 2014;41(Suppl 3):S13–20

ASCO Statement: Biosimilars in Oncology

ASCO offers guidance on these issues:

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

Safety and efficacy of Biosimilars

Interchange-ability, switching and substitution

Naming, labeling and regulatory considerations

Value of biosimilars

Prescriber and patient education

Lyman GH et al. J Clin Oncol. 2018;36(12):1260-1265.

ESMO Open
Cancer Horizons

Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers

Josep Tabernero,[1] Malvika Vyas,[2] Rosa Giuliani,[3] Dirk Arnold,[4] Fatima Cardoso,[5] Paolo G Casali,[6] Andres Cervantes,[7] Alexander MM Eggermont,[8] Alexandru Eniu,[9] Jacek Jassem,[10] George Pentheroudakis,[11] Solange Peters,[12] Stefan Rauh,[13] Christoph C Zielinski,[14] Rolf A Stahel,[15] Emile Voest,[16] Jean-Yves Douillard,[2] Keith McGregor,[2] Fortunato Ciardiello[17]

BIOSIMILARS

Education

- E-learning modules for oncologists and patients
- Infographic for patients

Engagement

- Representing clinician's perspective in various meetings
- Submitted proposal for biosimilars to be included in EML WHO 2019

Papers

- *e.g.* ESMO survey results paper ESMO Open 2018; ESMO Position Paper on Biosimilars (2016), etc.

Awareness

- Special sessions at ESMO meetings
- Biosimilars page & portal on ESMO website

Questions addressed by a physician

- What kind of clinical trials can we ask for?
- Therapeutic equivalence?
- Non-inferiority?

- Can we ask for all indications?
- Can we extrapolate efficacy?
- Can we extrapolate safety??

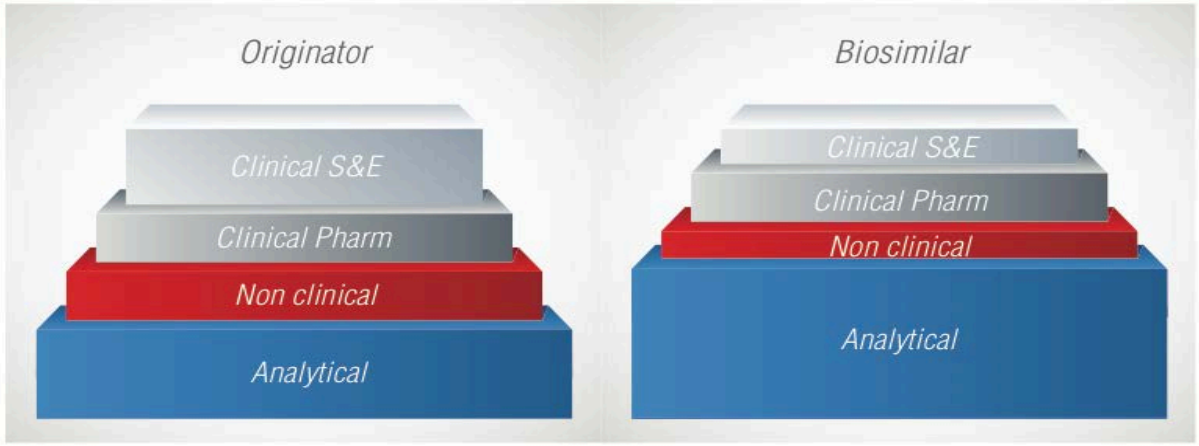
- What endpoints can we ask for?
- (Activity or Benefit?)
- (Phase II or Phase III endpoints?)

Key Differences in Requirement and Study Design for Bio-similar and Innovator Clinical Trials

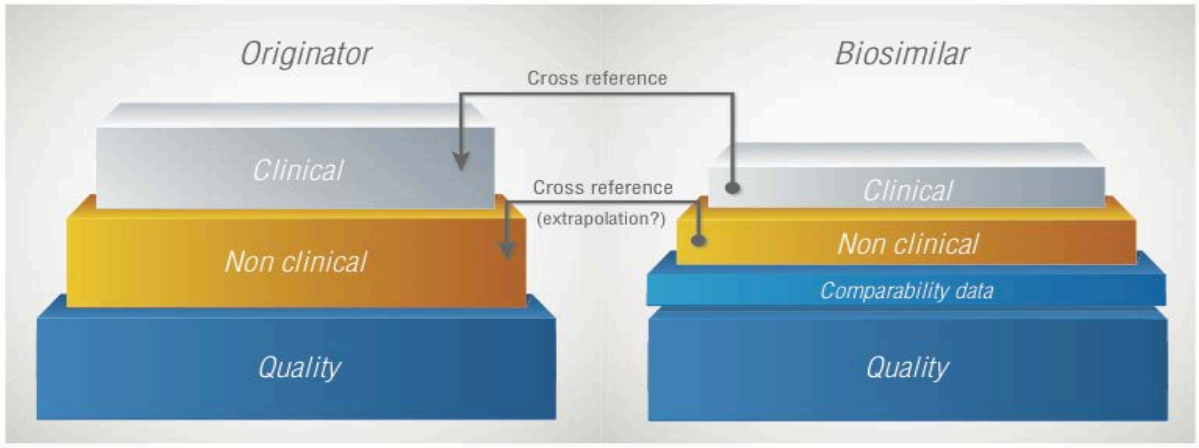
	Bio-similar	Innovator
Patient Population	Sensitive and homogeneous patient population	Any
Clinical Design	Comparative versus innovator (non-inferiority studies)	Superiority vs standard of care
Study Endpoints	Sensitive Clinically validated PD markers; ORR, pCR	Clinical outcomes data (OS, PFS) or accepted/established surrogates
Safety	Similar safety profile to innovator	Acceptable risk/benefit profile vs standard of care
Immunogenicity (tested in most sensitive population)	Similar immunogenicity profile to innovator	Acceptable risk/benefit profile vs standard of care
Extrapolation	Possible if justified	Not allowed

Comparison of originator and bio-similar marketing approvals process in the US and EU

United States



European Union



Biosimilar Regulatory Framework Comparison

	Similarity concept	Substitution	Extrapolation across indications	Immuno-genicity	Unique INN; pharmaco-vigilance required
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	Concept created by EU	Decided at member state level in EU	Ok if justified both in the EU and in the WHO guidance	Needs to be studied in human pre and post approval in EU and according to WHO guideline	INN is independent from the regulatory pathway used for approval PV is needed for all products in EU and according to WHO guideline
World Health Organization	Principle of EU followed by WHO (main difference is WHO have not issued product specific non-clinical or clinical guidelines)	Not addressed in WHO guidance			

WHO specific **EMA specific** **Guidance common to both agencies**

Key Insight

Countries adopting EMA and/or WHO guidance will have a robust biosimilar approval pathway

Phase III: which population, which endpoints ?

In principle, the most sensitive disease model to detect differences in both efficacy and safety should be used in a homogeneous patient population to reduce variability.

In oncology, that would mean response rate rather than (overall) survival, possibly in early stage patients; it would also mean immunocompetent subjects

But HTA bodies (and clinicians) may require the most relevant population…

Extrapolation of indications

1. Without extrapolation, the biosimilar concept is dead

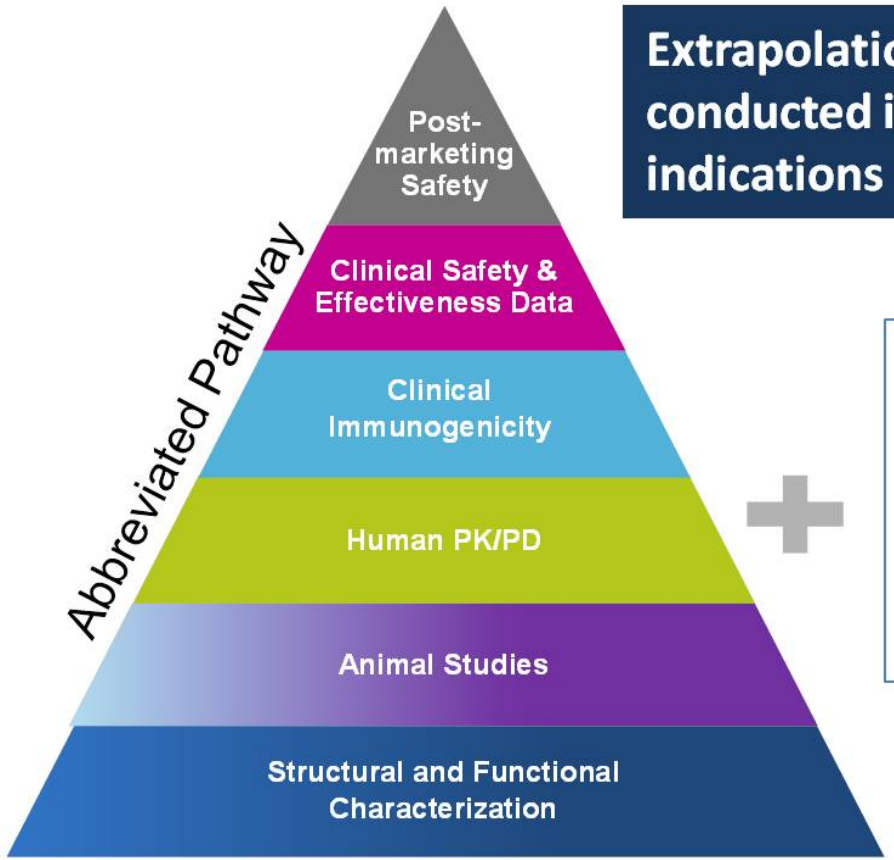
2. Justification of the extrapolated indication (rather than separate demonstration of equivalence) is on a case-by-case basis

   → criteria for the decision? (e.g. mechanism of action, receptor number and affinity…)

   → could guidelines help?

Rationale for Post-Approval Evidence Development and Surveillance

Extrapolation



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

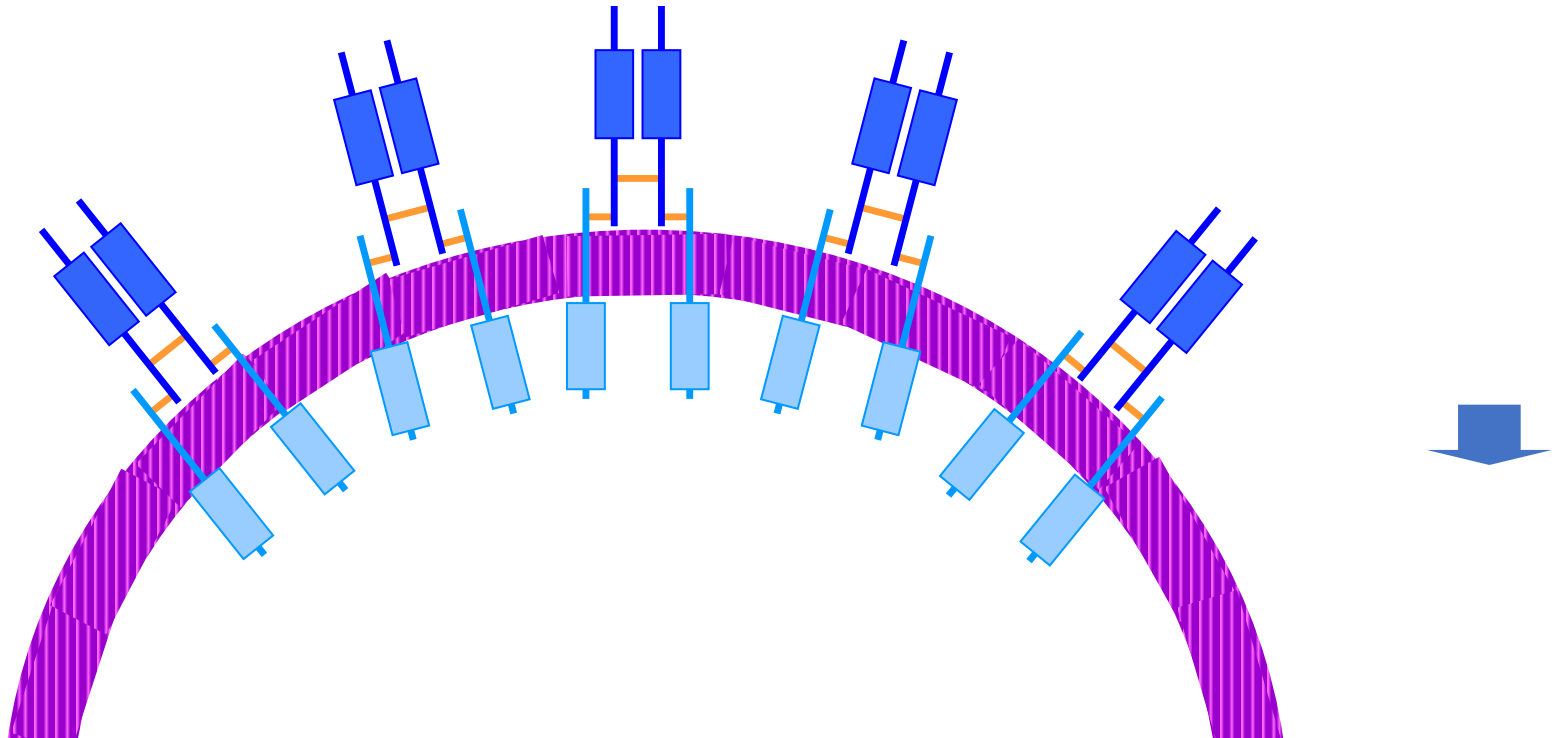
If a biosimilar trastuzumab were to show adequate comparability to reference Trastuzumab in MBC patients, do you believe it would be appropriate to extrapolate these data to the adjuvant setting?

If a biosimilar trastuzumab were to show adequate comparability to reference Trastuzumab in Neoadjuvant/EBC setting , do you believe it would be appropriate to extrapolate these data to the MBC setting?

What may be the most sensitive patient population for biosimilar trastuzumab trials?

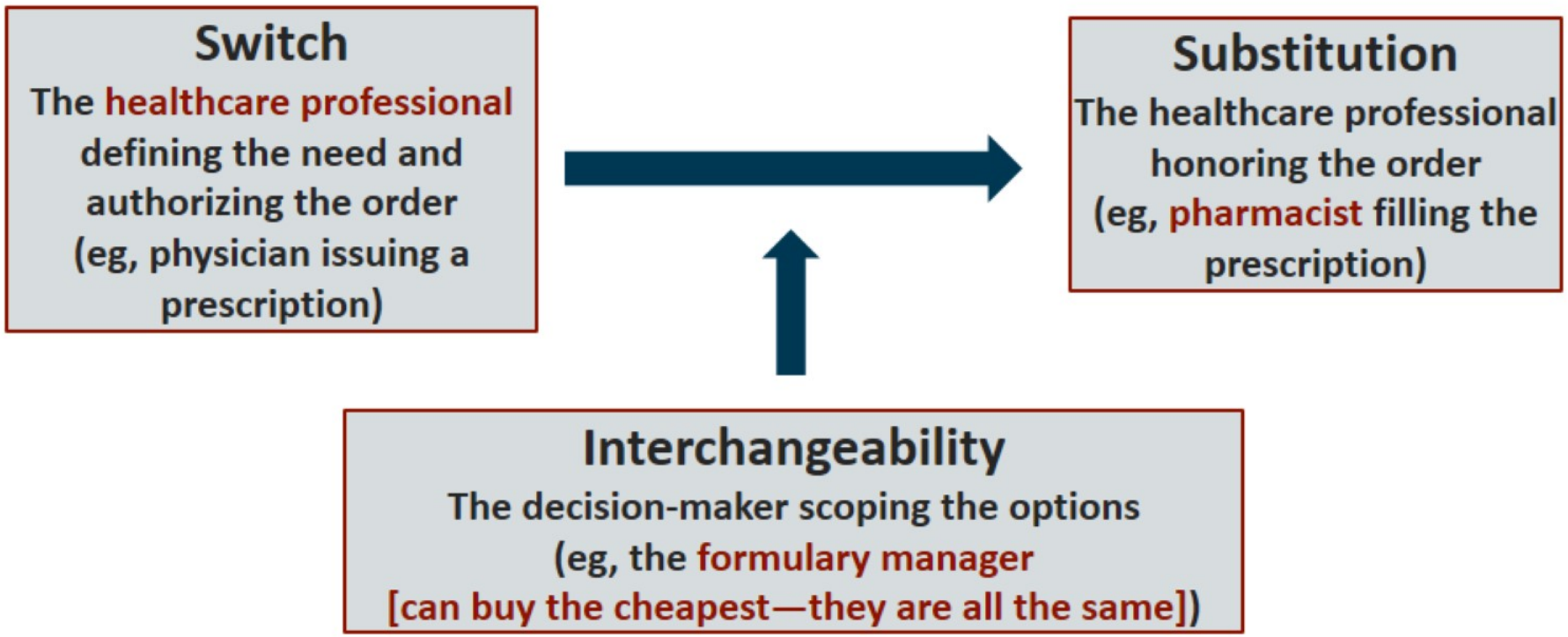
Topic	Metastatic Population	Neoadjuvant/Adjuvant population
PK	✗ Affected by patient's health status & tumour burden	✓ Homogeneous population can be selected ✗ Variability is also observed
	✓ Healthy Volunteers	
PD	✗ Clinically validated PD marker not available	
Clinical efficacy/safety	✗ • Difficult to select homogeneous group • Need to control and stratify for multiple factors (eg, prior use of chemotherapy, performance status). • Population with heterogeneous characteristics affecting final clinical outcome.	✓ • Populations less likely to be confounded by baseline characteristics and external factors • Sub-group of patients with higher responses could be identified (e.g. hormone receptor negative patients)
Immunogenicity	✗ Immune system affected by performance status and concomitant chemotherapies received	✓ Immune system impaired during chemotherapy cycles, but likely to recover to *normal* status thereafter

Antibody-Dependent Cellular Cytotoxicity (ADCC)

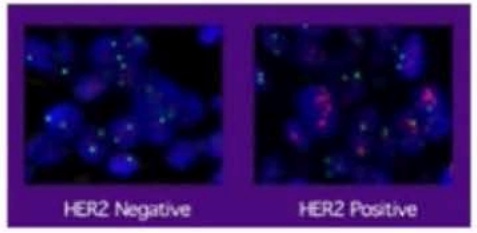


In Europe: The Vocabulary Distinguishes Replacement by Different Agents in the Process

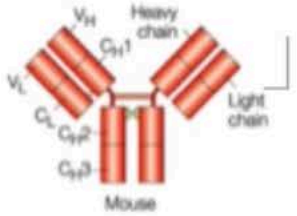
There are 3 families of decision-makers who replace one version of a drug with another



The HER-2 journey



HER2 gene is cloned[2]
HER2 protein found to be overexpressed in breast tumours[3]

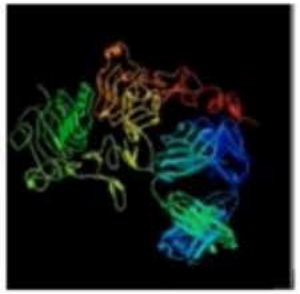


Anti-HER2 monoclonal mouse antibody developed[5]

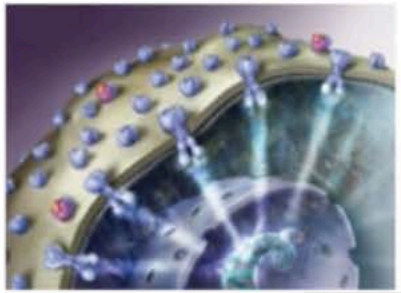
Trastuzumab clinical trials begin

1984 | 1985 | 1987 | 1989 | 1992 | 1993–1995

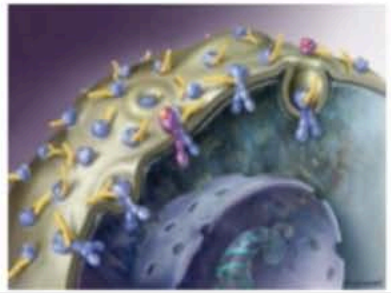
HER2/neu gene identified[1]



HER2 overexpression associated with more aggressive phenotype[4]



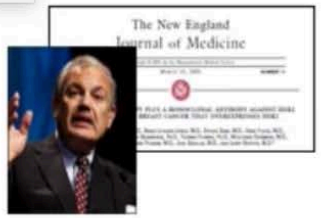
Anti-HER2 monoclonal mouse antibody humanised: trastuzumab[6]



1. Ullrich A, *et al. Nature* 1984; 309:418–4253;
2. Ishii S, *et al. Proc Natl Acad Sci USA* 1985; 82:4920–4924
3. Sainsbury JR, *et al. Lancet* 1985; 1:364–366;
4. Di Fiore PP, *et al. Science* 1987; 237:178–182

HER-2 EBC
Key trials timeline

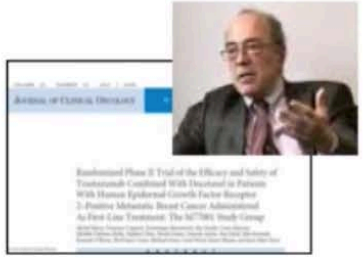
video-title



US approval:
HER2-positive MBC[1]

1998

2000



EU approval:
HER2-positive MBC[2]

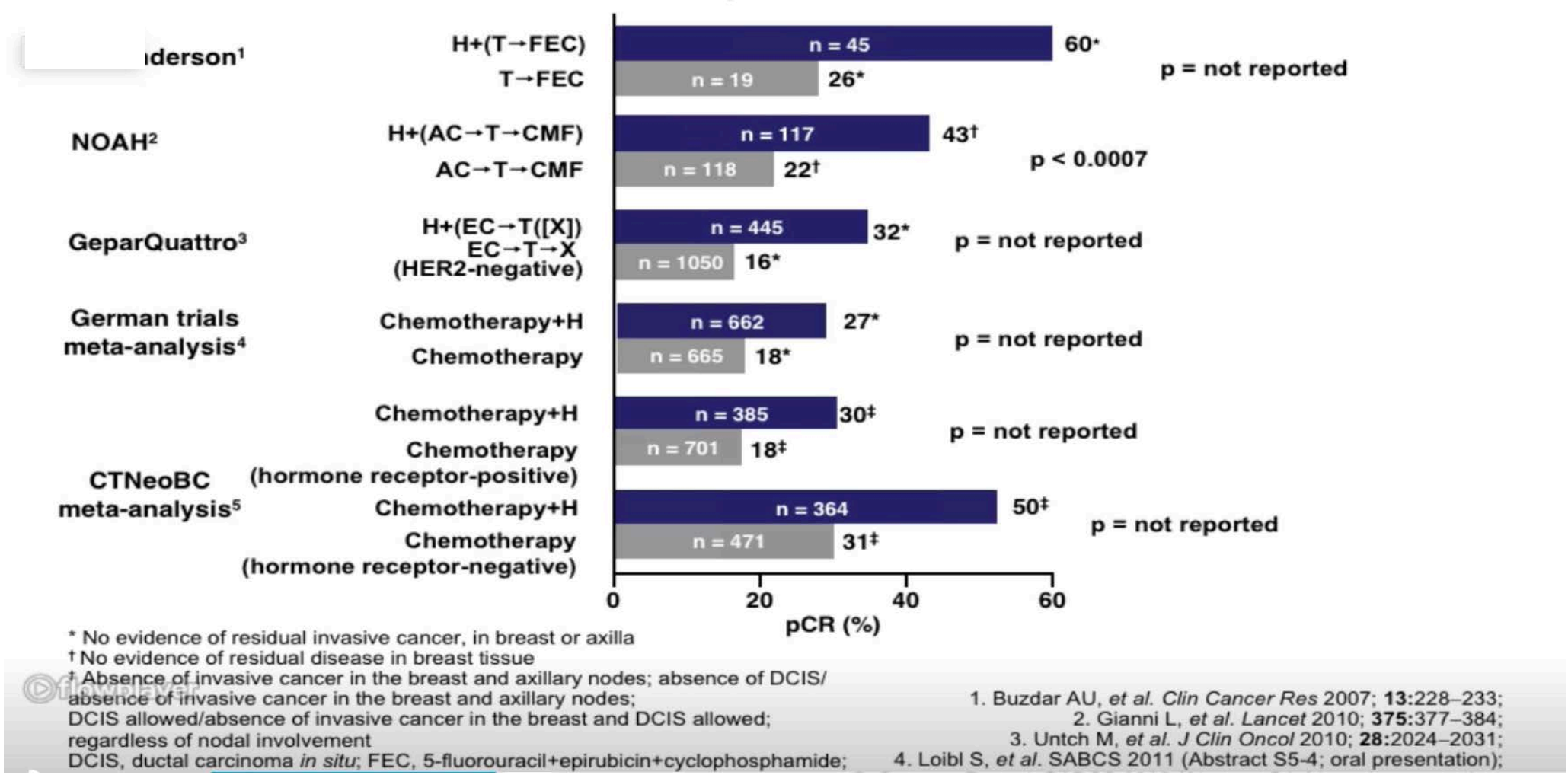
EU/US approval:
HER2-positive EBC[3]

2006

2017

1. Slamon DJ, *et al. N Engl J Med* 2001; **344**:783–792;
2. Marty M, *et al. J Clin Oncol* 2005; **23**:4265–4274;
3. Piccart-Gebhart MJ, *et al. N Engl J Med* 2005; **353**:1659–1672;
4. Perez EA, *et al. J Clin Oncol* 2011; **29**:4491–4497;
5. Goldhirsch A, *et al. Lancet* 2013 [Epub ahead of print].

Impact on pCR rates from the addition of trastuzumab to neoadjuvant chemotherapy in patients with HER-positive EBC



* No evidence of residual invasive cancer, in breast or axilla
† No evidence of residual disease in breast tissue
‡ Absence of invasive cancer in the breast and axillary nodes; absence of DCIS/ absence of invasive cancer in the breast and axillary nodes; DCIS allowed/absence of invasive cancer in the breast and DCIS allowed; regardless of nodal involvement
DCIS, ductal carcinoma *in situ*; FEC, 5-fluorouracil+epirubicin+cyclophosphamide;

1. Buzdar AU, *et al. Clin Cancer Res* 2007; **13:**228–233;
2. Gianni L, *et al. Lancet* 2010; **375:**377–384;
3. Untch M, *et al. J Clin Oncol* 2010; **28:**2024–2031;
4. Loibl S, *et al.* SABCS 2011 (Abstract S5-4; oral presentation);

Strategies to develop biosimilars in breast cancer

Setting	Primary Endpoint	Clinical Consideration
Neo-adjuvant	pCR	Validated endpoint Homogeneous Popn.
Metastatic	Response Rate PFS	Early assessment

Biosimilar trastuzumab in Phase 3 clinical trials: populations and endpoints selected

Biosimilar	Company	HER2+ EBC		HER2+ MBC	
ABP 980	Amgen	✓ Neoadjuvant + adjuvant pCR (breast and lymph)	n=827	–	–
BCD-022	Biocad	–	–	✓ 1st line ORR	n=206
CT-P6	Celltrion	✓ Neoadjuvant + adjuvant pCR (breast and lymph)	n=562	✓ 1st line ORR	n=383
MYL-1401O	Mylan/ Biocon	–	–	✓ 1st line ORR	n=600
PF-05280014	Pfizer	✓ Neoadjuvant Powered for PK endpoints	n=220	✓ 1st line ORR	n=690
SB3	Merck/ Samsung Bioepis	✓ Neoadjuvant pCR (breast only)	n=806	–	–

Rugo HS, et al. Cancer Treat Rev 2016;46:73–79;
Additional data sourced from clinicaltrials.gov, August 2016

Trastuzumab biosimilar implications:Depends on which lens:Physician/ Clinical trials lens

- Study Design and Endpoints
- Definition of Equivalence/Non-Inferiority
- Indication Extrapolation
  - Curative vs. Metastatic Setting
  - Disease Site (e.g Breast vs. Gastric)
  - Combination with other Chemotherapy Agents and
  - Combination with other Biologics (e.g. Pertuzumab/Lapatinib)
- Interchangeability
- Automatic Substitution
- Increased Access
- Long term Toxicity

Biosimilar implications: Depends on which lens Regulatory Agencies

- Indication Extrapolation
- Manufacturing Quality Assurance
- Pharmacovigilance (post-marketing)
- Naming

Biosimilar implications: Depends on which lens Funding bodies

Significant Cost Reduction (up to 30-40% c/w Originator)

- US: cost savings by 2025: $44.2 Billion (11 biosimilars)
- EU: Cost savings between 11.8 Billion to 33.4 Billion Euros between 2007-2020

Increased Access

Automatic Substitution

Interchangeability

Mulcahy et al RAND Corporation 2015

How the patients received the message of biosimilars?

Information and education: biosimilar medicines as therapeutic alternative

National Position on Physician-led switching

Link: Overview of positions on EU physician-led switching for biosimilar medicines

National/Targeted Information campaign

National Plan/Ambition

UK: https://www.england.nhs.uk/wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf
FR: http://solidarites-sante.gouv.fr/IMG/pdf/dossier_sns_2017_vdef.pdf
DK: http://ec.europa.eu/docsroom/documents/26630

We are given clear leadership on rational medicine use

World Health Organization

If we stand for anything as physicians – it must be for the rational, appropriate, proper, correct use of medicines

- "Medicine use is rational (appropriate, proper, correct) when
  - patients receive the appropriate medicines,
  - in doses that meet their own individual requirements,
  - for an adequate period of time, and
  - at the lowest cost both to them and the community
- Irrational (inappropriate, improper, incorrect) use of medicines
  - is when one or more of these conditions are not met."
    - (WHO World Medicines Situation Report, 2011)

Ref: [1] WHO, The World Medicines Situation 2011. Available at: http://apps.who.int/medicinedocs/documents/s20054en/s20054en.pdf?ua=1, accessed Sept 2016

blood

Prepublished online April 25, 2013;
doi:10.1182/blood-2013-03-490003

Price of drugs for chronic myeloid leukemia (CML), reflection of the unsustainable cancer drug prices: perspective of CML Experts

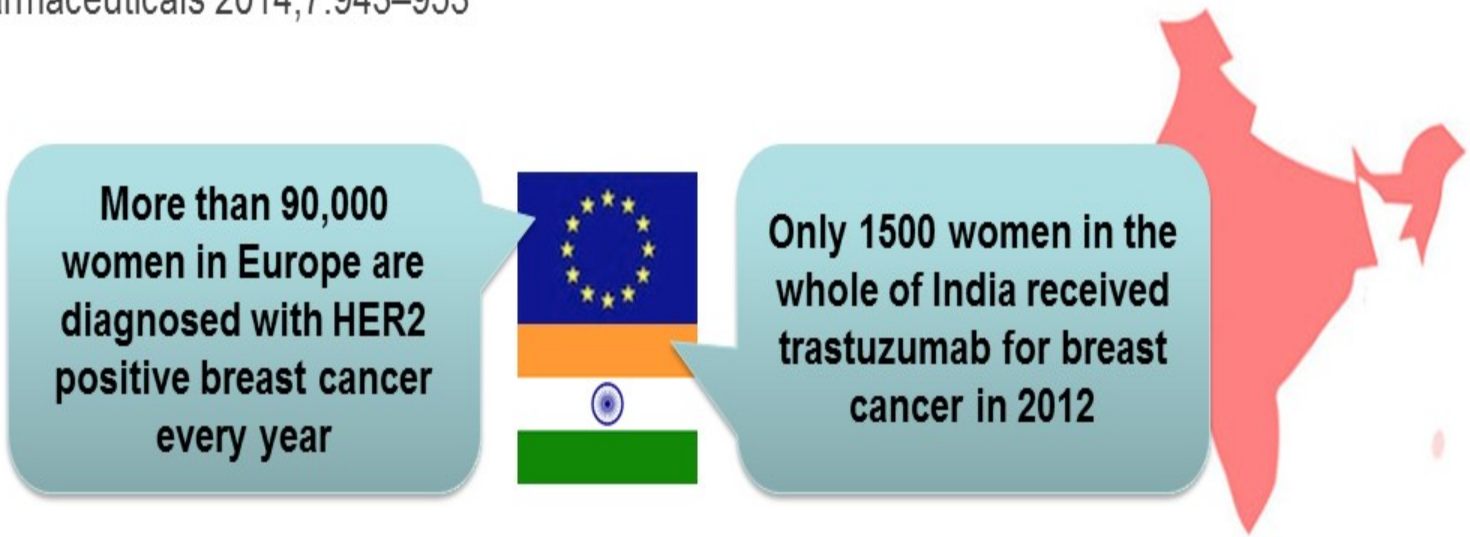
Experts in chronic myeloid leukemia

We believe the unsustainable drug prices in CML and cancer may be causing harm to patients. Lowering the prices of TKIs will improve treatment penetration, increase compliance and adherence to treatment, expand the population of patients with CML who live longer and continue on TKI therapy, and (paradoxically) increase revenues to pharmaceutical companies from sales of TKIs.

Cost and access:
A survey of oncologists – USA

- **Even in the wealthiest countries there are barriers to accessing the best treatment**

- **A third of US oncologists would offer more trastuzumab to breast cancer patients if a lower cost biosimilar was available!**
  - Lammers P, et al. Barriers to the use of trastuzumab for HER2+ breast cancer and the potential impact of biosimilars: A physician survey in the United States and emerging markets. Pharmaceuticals 2014;7:943–953



Refs: [1] Lammers P, et al. Pharmaceuticals 2014;7:943–953; [2] Pharmafile 19/08/13. Available at: http://www.pharmafile.com/news/180576/roche-abandons-herceptin-patents-india; accessed Sept 2016 [2] India map outline by Simon Berry. CCO License for modification and commercial use. https://www.flickr.com/photos/colalife/11646328634. Accessed Sept 27, 2016

Need a coordinated and collaborative approach

Conclusions

- What clinicians and patients need to know about the effective and safe use of biosimilars
  - Extensive comparative data (molecular characterization, PD,PK)
  - Confirmatory clinical data (sensitive efficcy endpoints)
  - Human immunogenicity data (safety)
  - Interchangeability and acive postmarketing surveillance
- Education od providers, physicians and patients is of outmost importance