Biosimilars 101

A Comprehensive Guide for Breast Oncologists

Reference Slide Deck

What is a biosimilar?

What Are Biologics?

Biologics are active pharmaceutical ingredients prepared by the use of living systems, such as organisms, tissue cultures, or cells.

Most biologics cannot reasonably be produced by chemical synthesis

There are more than 250 biologic medicines on the market.

More than 350 million patients worldwide use biologic medicines.

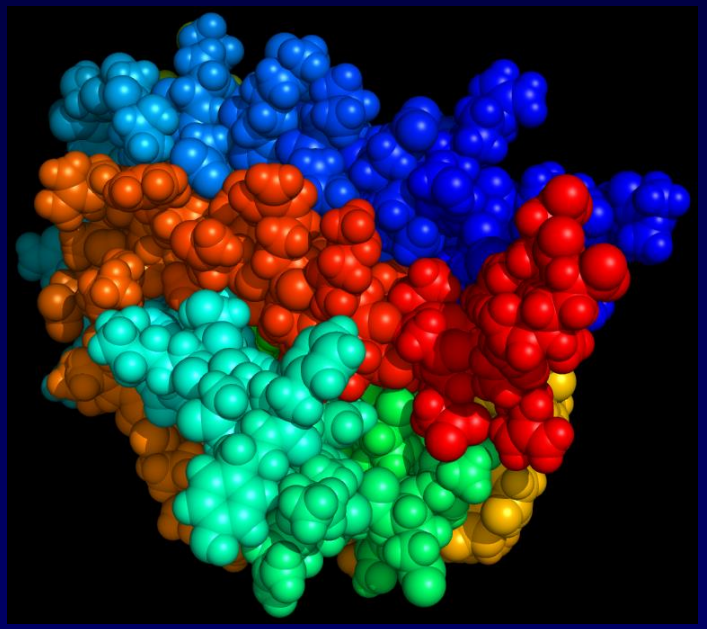
Greater than 50% of medicines in clinical development are biologic medicines.

International Federation of Pharmaceutical Manufacturers and Associations. *Biotherapeutic Medicines: Grasping the New Generation of Treatments*. Available at: http://www.ifpma.org/fileadmin/content/Publication/2012/IFPMA_BiotheraputicsWeb4.pdf. Accessed March 5, 2015.

Some Examples of Biologics and Chemical Drugs

- **Biologics**
  - Growth hormones (eg, filgrastim)
  - Erythropoietin-stimulating agents (eg, epoetin alfa)
  - Insulin
  - Monoclonal antibodies, eg,
    - Rituximab
    - Trastuzumab
    - Infliximab
    - Ipilimumab
  - Antibody-drug conjugates
  - Vaccines
  - Cytokines (eg, interferon)
- **Chemical Drugs**
  - Most common drugs are chemical drugs, including paracetamol, codeine, and many more
  - Tyrosine kinase inhibitors, eg,
    - Lapatinib
    - Imatinib
    - Erlotinib
  - Aromatase inhibitors (eg, anastrozole)
  - Proteasome inhibitors
    - Bortezomib
    - Carfilzomib
  - Chemotherapy

Biologics Are More Complex Than Chemical Drugs



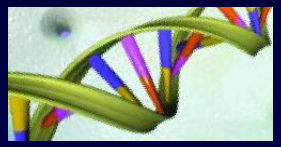
Human EPO
165 amino acids
MW ~ 34,000 Da

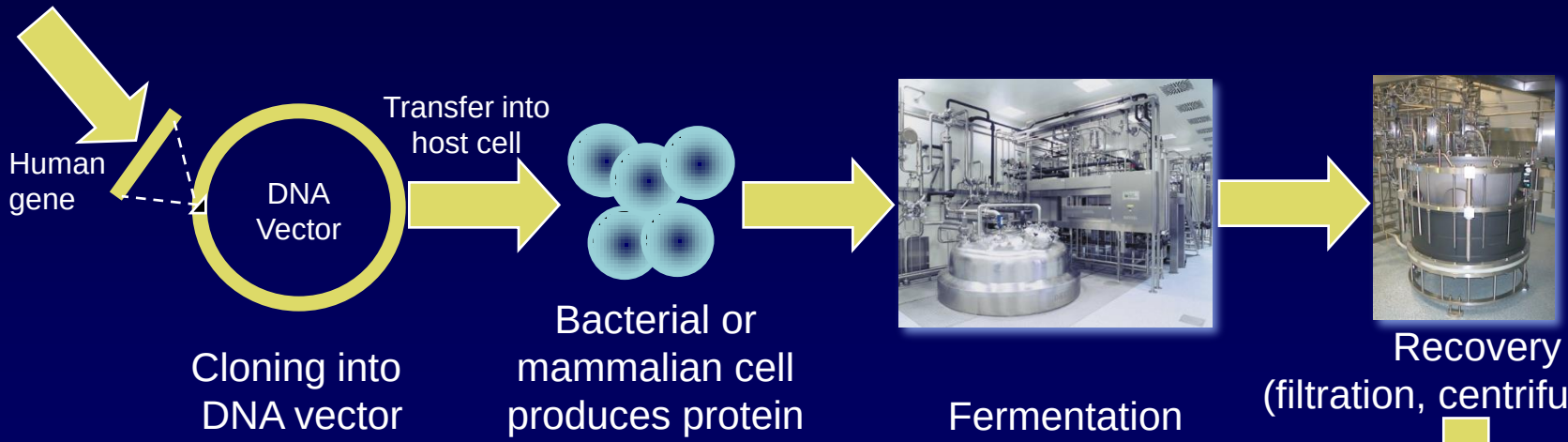
Cisplatin
$(NH_3)_2PtCl_2$
MW ~ 300 Da

Biologics are far more complex than traditional small molecule drugs in:

- **Molecular weight**
- **Structure (tertiary and quaternary structures, post-translational modifications)**
- **Manufacturing/ production process**
- **Immunogenicity**

Biologics Have a Complex Manufacturing Process





Formulation

The manufacturing process of a biological product is a sequence of critical steps, each having impact on the final product mixture

Heterogeneity of Biologics

- Biologics are heterogeneous, meaning a single biologic (eg, an antibody) can have a number of different variants
- A number of factors contribute to the heterogeneity of biologics
- Alterations to the manufacturing process can impact any one of these factors

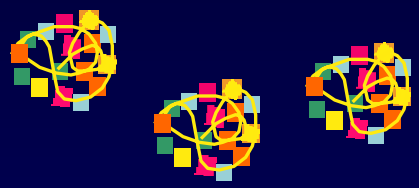
- Glycosylation
- Phosphorylation
- Sulfation
- Methylation
- N-acylation
- S-nitrosylation
- …
- Cell type and culture conditions

- Deamidation (eg, Asn to Asp)
- Racemization (L to D)
- Oxidation (Met, Tyr, His, Trp)
- Disulfide exchange
- …

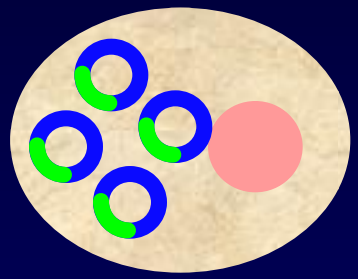
- External conditions (pH, additives, temperature...)

The Process Determines the Product

Biologics grown under different circumstances will have different variations

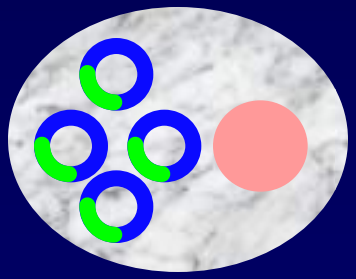


Inflximab, InFlixImab

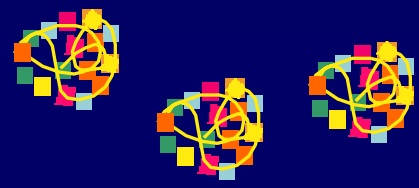


cDNA IFX

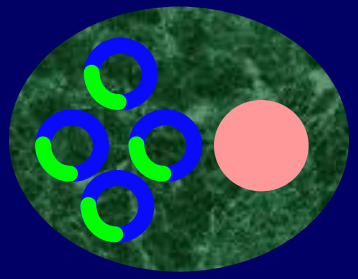
InFlIxImab, inflIXimaB



cDNA IFX



inflIXiMaB, Inflximab



cDNA IFX

Small Chemical Drugs vs Biologics

	Small Chemical Drugs	Biologics
Size	Small	Large
Structure	Simple	Complex
Stability	Stable	Unstable
Modification	Well defined	Many options
Manufacturing	• Predictable chemical process • Identical copy can be made	• Unique line of living cells • Impossible to ensure identical copy
Characterization	Easy to characterize fully	Difficult to characterize fully due to a mixture of related molecules
Immunogenicity	Nonimmunogenic	Immunogenic

What Are ‘Biosimilars’?

- A generic is a copy of a chemical drug that has gone off patent; generics are identical to their originator drug
- Biosimilars are copies of biologic drugs that have gone off patent; biosimilars are **similar** to their originator drug, as demonstrated through rigorous comparability studies
- Biosimilars are <u>not</u> generics

EMA BMWP: Terminology Matters

Term(s)	Definition	Implications
Biosimilar[a]	Copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy, and safety, based on a comprehensive comparability exercise.	Only very small differences between biosimilar and reference with reassurance that these are of no clinical relevance. Extrapolation of clinical indications acceptable if scientifically justified.
Me-too biological/biologic **Noninnovator biological/biologic**	Biological medicinal product developed on its own and not directly compared and analyzed against a licensed reference biological. May or may not have been compared clinically.	Unknown whether and which physico-chemical differences exist compared to other biologicals of the same product class. Clinical comparison alone usually not sensitive enough to pick up differences of potential relevance. Therefore, extrapolation of clinical indications problematic.
Second-generation (next-generation) biological/biologic **Biobetter**	Biological that has been structurally and/or functionally altered to achieve an improved or different clinical performance.	Usually stand-alone developments with a full development program. Clear (and intended) differences in the structure of the active substance, and most probably different clinical behavior due to, for example, different potency or immunogenicity. From a regulatory perspective, a claim for 'better' would have to be substantiated by data showing a clinically relevant advantage over a first- or previous-generation product.

BMWP-Biosimilar Medicinal Products Working Party at EMA

Weise M, et al. *Nat Biotechnol*. 2011;29(8):690-693.

[a]Comparable terms defined by the same/similar scientific principles include the WHO's 'similar biotherapeutic products' and Health Canada's (Toronto) 'subsequent-entry biologicals ‘

Things to Consider About Biosimilars

Molecular Properties

- More complex than chemical medicines

Manufacturing process is crucial to the product

- Extremely sensitive to changes in manufacturing and production
- Minor variations may produce vastly different products

Safety

- The long-term safety profile of biosimilars needs to be established
- Prescribers and patients should be aware of this to ensure appropriate introduction into clinical practice

Efficacy

- Can differ significantly with small changes in protein biophysical characteristics or in formulation of the drug product

How are biosimilars of monoclonal antibodies different from other biosimilars?

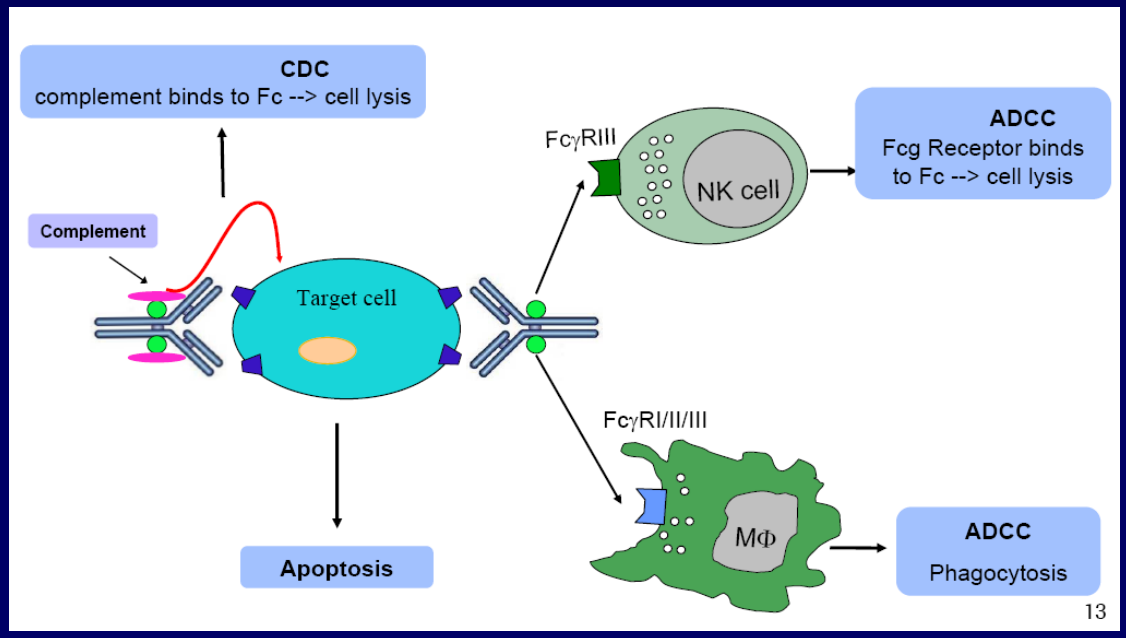
Biosimilar Antibodies Are More Complex Than Other Biosimilars

Biosimilar antibodies have similar clinical issues, but technically are far more advanced than more simple biosimilars

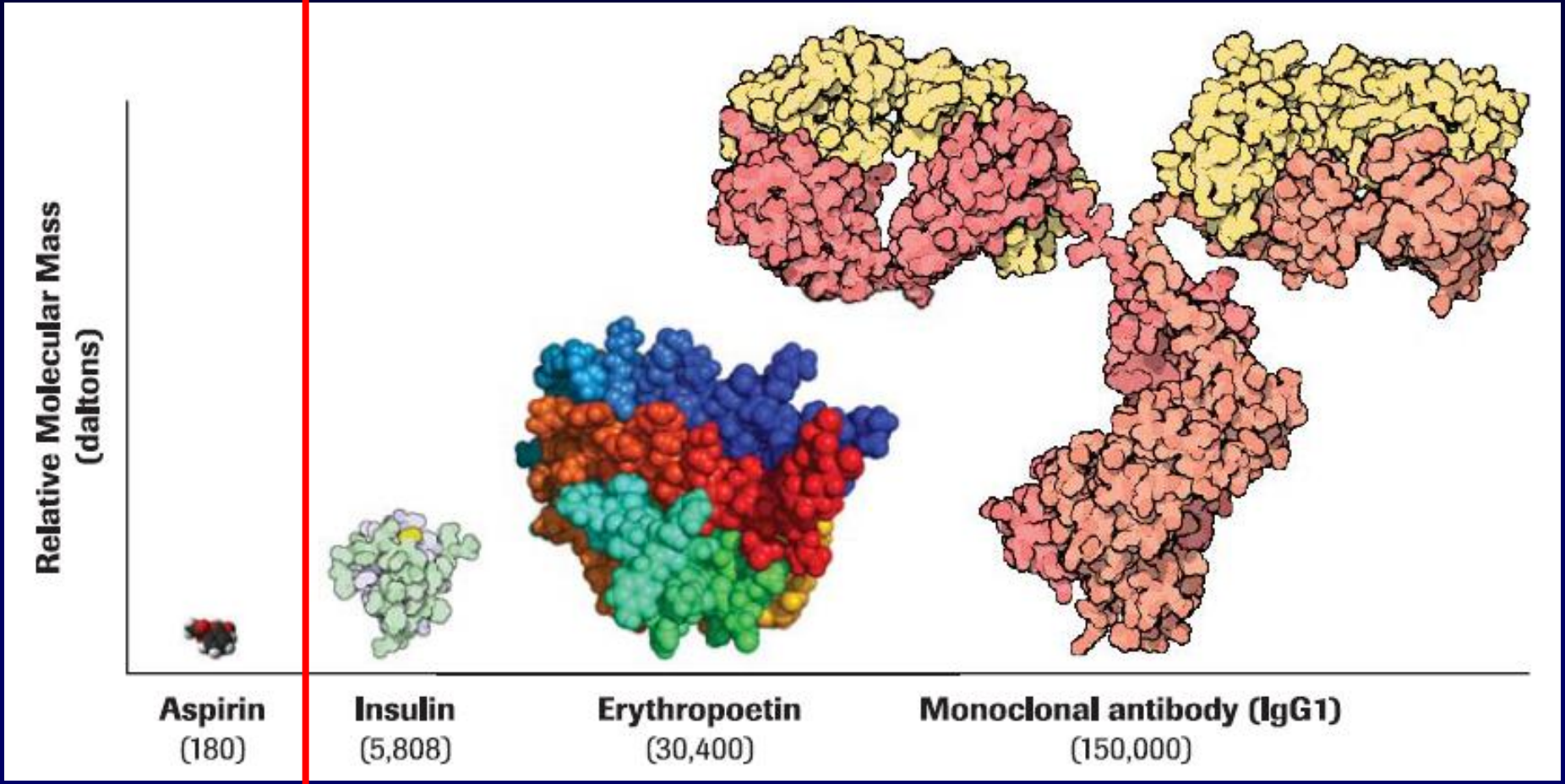
Very complex production

Very complex mechanism of action

Complex (oncology) indications



Monoclonal Antibodies Are More Complex Than ‘Simple’ Biologics



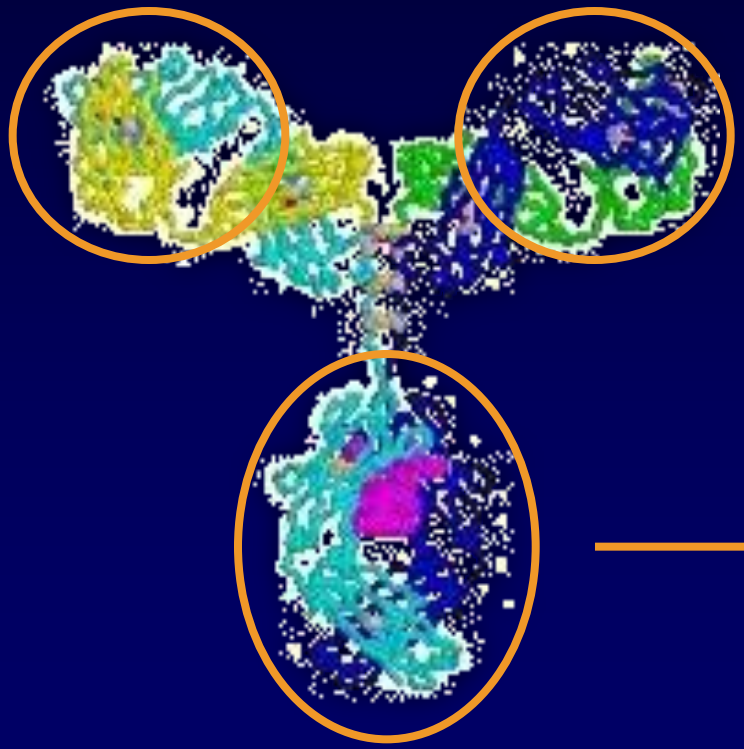
Small-molecule drug

‘Simple’ biologics

‘Complex’ biologics

Revers L, et al. *Can Pharmacists J*. 2010;143:134-139.

Monoclonal Antibodies Have Multiple Functions



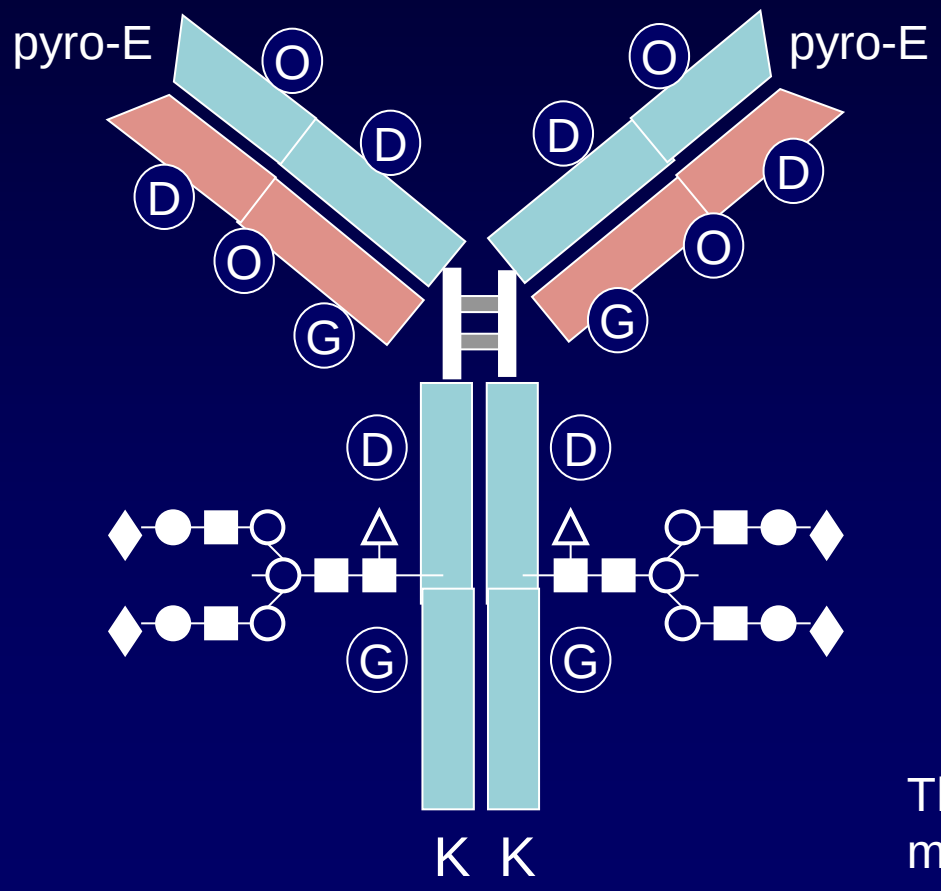
CDRs

- Selected for optimum target-mediated effects (light-chain and heavy-chain variable binding domains)

Fc region

- Different isotypes with different effector functions
- Contains 2 glycosylation sites (1 in each of the 2 chains)

The Structure of Monoclonal Antibodies Is Highly Complex and Variable

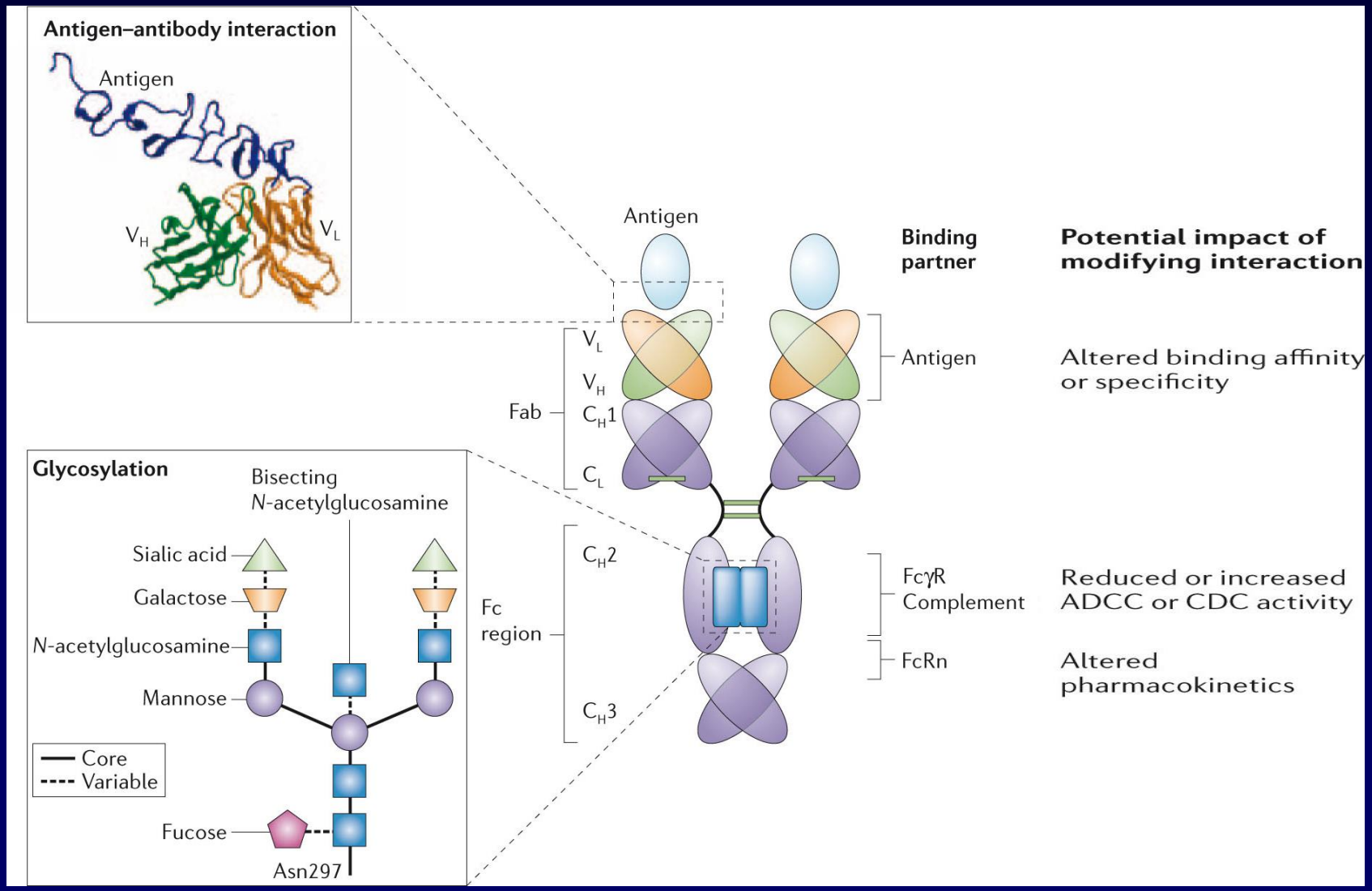


- Pyro-Glu (2)
- Deamidation (3 x 2)
- Methionine oxidation (2 x 2)
- Glycation (2 x 2)
- High mannose, G0, G1, G1, G2 (5)
- Sialylation (5)
- C-term Lys (2)

The large number of sites for modification means exponential potential for diversity: 2 x 6 x 4 x 4 x 5 x 5 x 2 = 9600 potential variants of each HALF of the antibody!

Kozlowski S, et al. *Adv Drug Deliv Rev*. 2006;58(5-6):707-722.

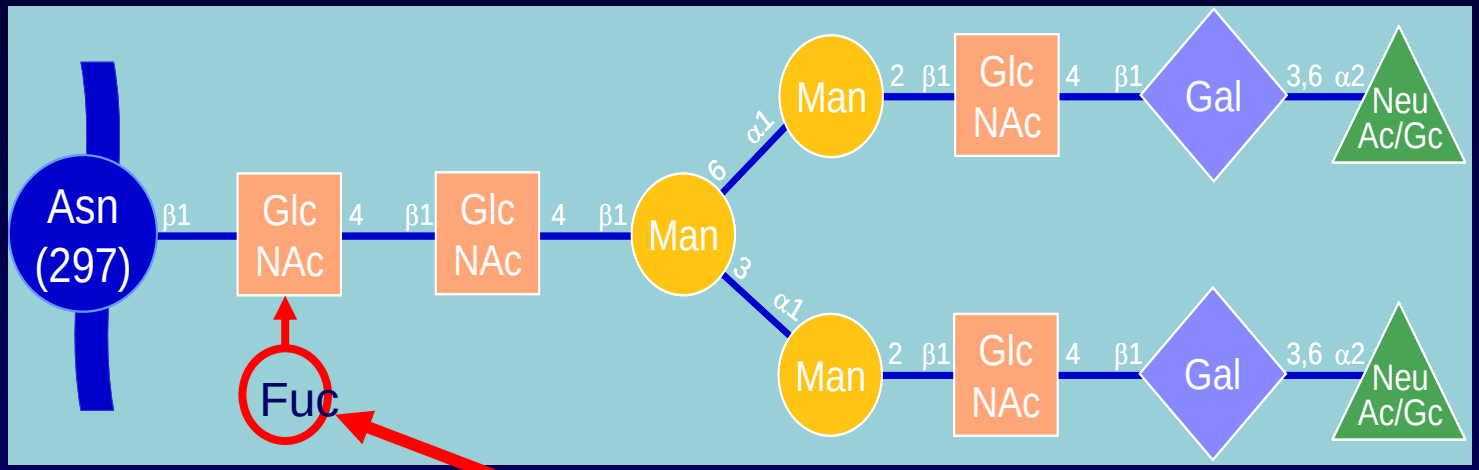
Posttranslational Modifications May Impact Antibody Activity

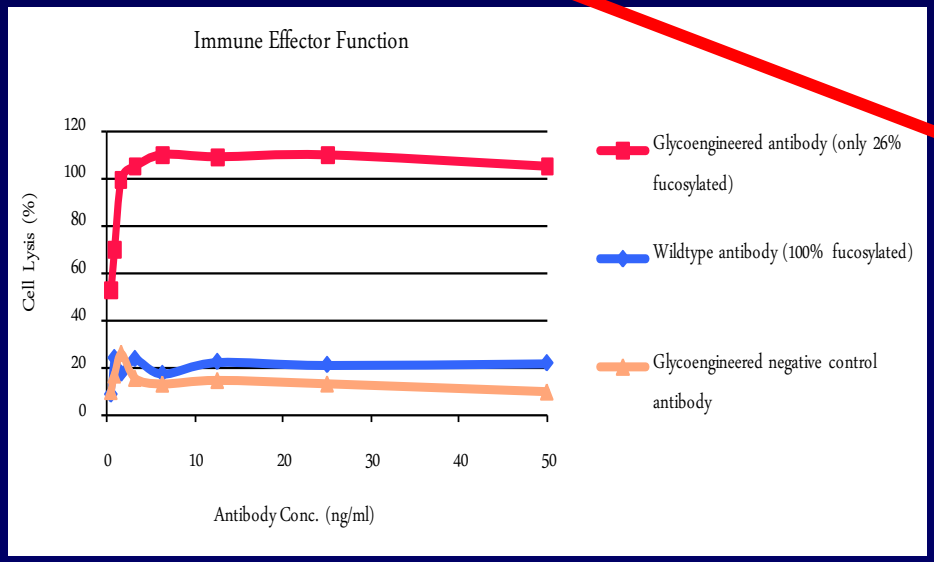


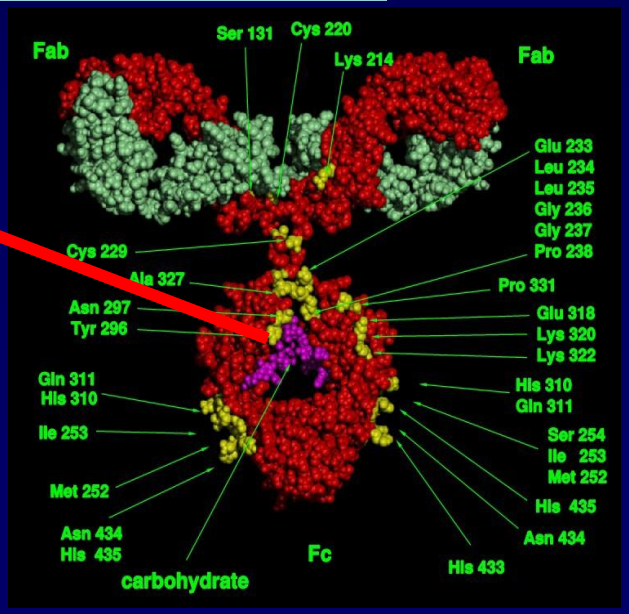
Carter PJ. *Nat Rev Immunol.* 2006;6(5):343-357.

A Small Change Can Make a Big Difference

Example: Immune Effector Function of an Antibody Molecule

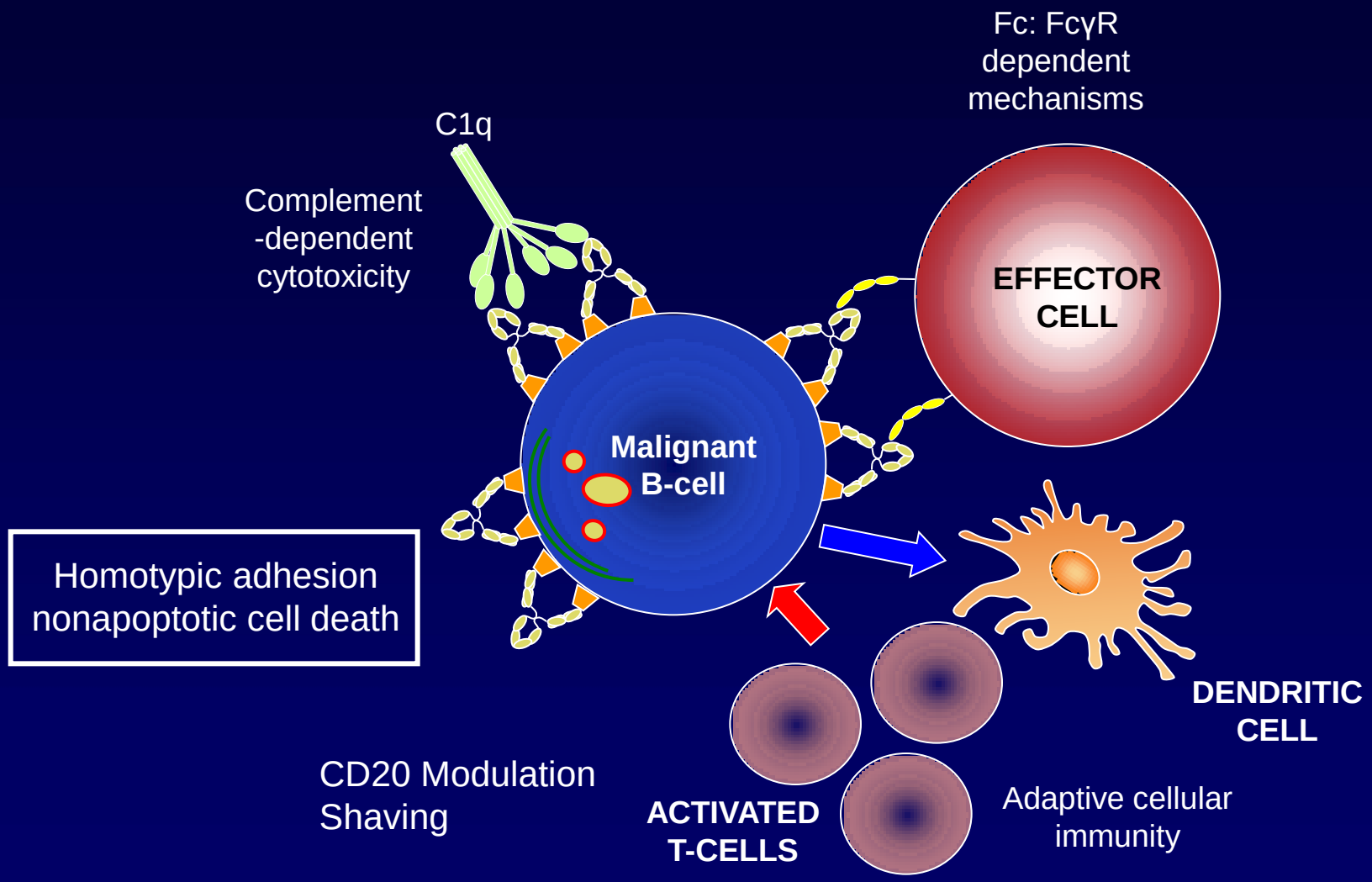






Adapted from*: M. Clark*.

Monoclonal Antibodies Have Different Mechanisms of Action



Alduaij W, et al. *Blood*. 2011;117(11):2993-3001.

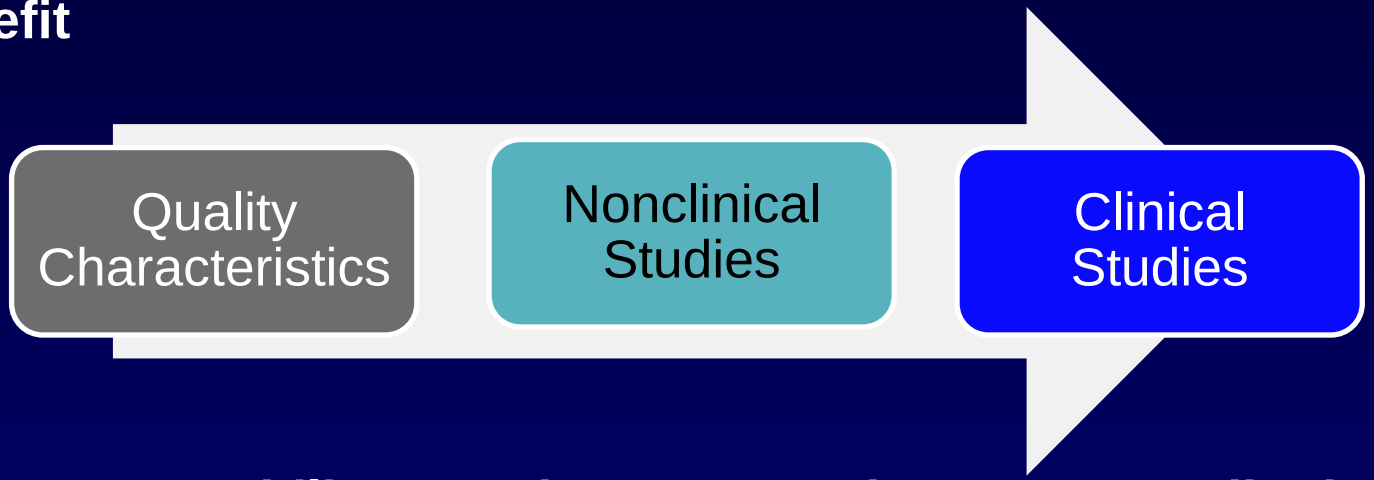
How are biosimilars regulated in Europe?

The Principle of Biosimilarity

- **Biosimilars are approved on the basis of abbreviated nonclinical and clinical development programs depending on similarity to a reference biologic product**
- **Demonstration of biosimilarity is not a therapeutic equivalence trial, but a comparability exercise**
- **The goal of the biosimilarity exercise is to establish that there is not likely to be any clinically significant difference between the biosimilar and the originator**

Biosimilar Approval: Key Points

- **The development of biosimilars involves stepwise comparability exercises designed to demonstrate biosimilarity, not clinical benefit**



- **If the comparability exercises are not done as prescribed, the product will not be eligible to be called a biosimilar**
- **Biosimilars are not “generic medicines,” and many characteristics associated with the authorization process do not apply**
- **Like other biologics, biosimilars require regulatory oversight to appropriately manage their risks and benefits**

Global Regulatory Environment

- **All regulators require:**
  - **Comparative analytical program**
  - **Clinical program**
  - **Postapproval commitment to pharmacovigilance**
  - **High degree of analytical similarities**
  - **High degree of preclinical and clinical similarities**

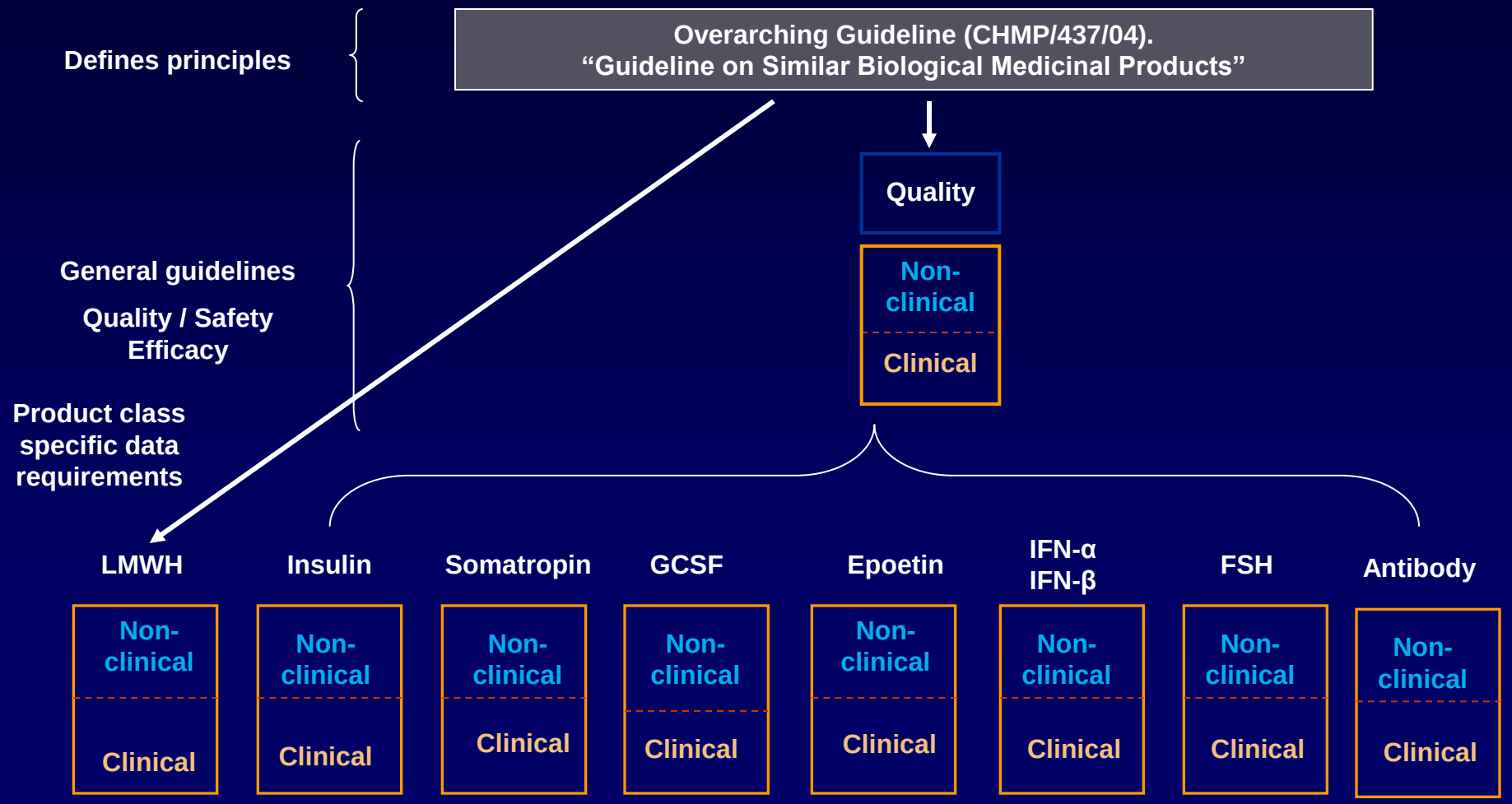
  - **All regulators permit extrapolation when scientifically justified**

Biosimilars Are Approved Via a Stepwise Pathway with a Reduced Dossier

Steps	Requirements
Quality	Individual quality assessment Very comprehensive comparison with reference product
Nonclinical	Abbreviated program; tolerance, PK/PD Comparison to reference product
Clinical	Ph I PK/PD study No Ph II Ph III equivalence study vs reference product in one representative indication Immunogenicity assessment Risk-management plan

European Medicines Agency (EMA) Guidelines. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Accessed 5 March 2015.

EMA Guidelines on Biosimilars



European Medicines Agency (EMA) Guidelines. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Accessed 5 March 2015.

EMA Guidelines on Biosimilar Antibodies

- **Preclinical:** ***In vitro*** **pharmacodynamic (PD) and pharmacokinetic (PK) studies;** ***in vivo*** **animal studies if necessary and when an appropriate model system exists**
  - **PD studies should include antigen binding, FcR, and complement binding, and Fab and Fc activity**
- **Clinical: Comparative clinical studies between the biosimilar and reference antibody should always be conducted**
  - **Human PK and PD:**
    - **PK comparability in a sufficiently sensitive and homogenous population, ideally a single-dose study in healthy volunteers**
    - **PD comparability studies if possible, especially a dose-concentration-response relationship or a time-response relationship; if adequate comparability is shown in PD studies (clear dose-response relationship and a PD marker that can be related to patient outcome), there is no need for further clinical studies. This is difficult, as there is often a lack of appropriately defined PD endpoints.**

European Medicines Agency (EMA) Guidelines. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Accessed 5 March 2015.

EMA Guidelines on Biosimilar Antibodies

- **Clinical (con't):**
  - **Efficacy:** **If PD studies cannot convincingly show comparability, clinical efficacy should be demonstrated in adequately powered randomized parallel group comparative trials, preferably double-blind, normal equivalence trials. The most sensitive patient population and clinical endpoint should be used in these studies.**
    - **Considerations for anticancer indications: demonstrate similar efficacy and safety, not patient benefit; primary endpoint that measures clinical activity (eg, ORR); survival data should be recorded, and novel endpoints may be tested.**
  - **Safety:** **At all steps of clinical evaluation, comparable safety (type, frequency, and severity of AEs) and immunogenicity should be demonstrated.**

European Medicines Agency (EMA) Guidelines. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Accessed 5 March 2015.

EMA Guidelines on Biosimilar Antibodies

- **Extrapolation:** Is possible if biosimilarity is confirmed in the comparability studies and the mechanism of action is known to be the same
- **Pharmacovigilance:** A risk management plan should be presented as part of the marketing authorization procedure
  - Safety in extrapolated indications
  - Rare and serious adverse events described for the reference product
  - Detection of novel safety signals
  - Activities to obtain additional immunogenicity data if needed

European Medicines Agency (EMA) Guidelines. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Accessed 5 March 2015.

What biosimilars are currently approved in the EU?

Biosimilars in Europe Pre-2013

Biosimilar	INN	Manufacturer	Approval
Omnitrope	Somatropin	Sandoz (Novartis)	2006
Binocrit	Epoetin alfa	Sandoz (Novartis)	2007
Epoetin Alfa Hexal	Epoetin alfa	Hexal (Novartis)	2007
Abseamed	Epoetin alfa	Medice	2007
Silapo	Epoetin zeta	Stada	2007
Retacrit	Epoetin zeta	Hospira	2007
Rationgrastim	Filgrastim	Ratiopharm	2008
Biograstim	Filgrastim	CT Arzneimittel	2008
Tevagrastim	Filgrastim	Teva	2008
Zarzio	Filgrastim	Sandoz (Novartis)	2009
Filgrastim Hexal	Filgrastim	Hexal (Novartis)	2009
Nivestim	Filgrastim	Hospira	2010

EMA Website. Availiable at: http://http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jspAccessed 5 March 2015.

New Biosimilars 2013-2015

Biosimilar	INN	Manufacturer	Approval
Remsima	Infliximab	Celltrion	2013
Inflectra	Infliximab	Hospira	2013
Ovaleap	Follitropin alfa	Teva	2013
Grastrofil	Filgrastim	Apotex	2013
Bemfola	Follitropin alpha	Finox Biotech AG	2014
Abasaglar	Insulin glargine	Lilly-Boehringer	2014
Accofil	Filgrastim	Accord	2014

Biosimilars under evaluation

None at EMA

Celltrion's biosimilar trastuzumab approved in S. Korea (January 2014)

March 6, 2015: Sandoz's Zarzio (filgrastim)

Approved by US FDA—first biosimilar in the US

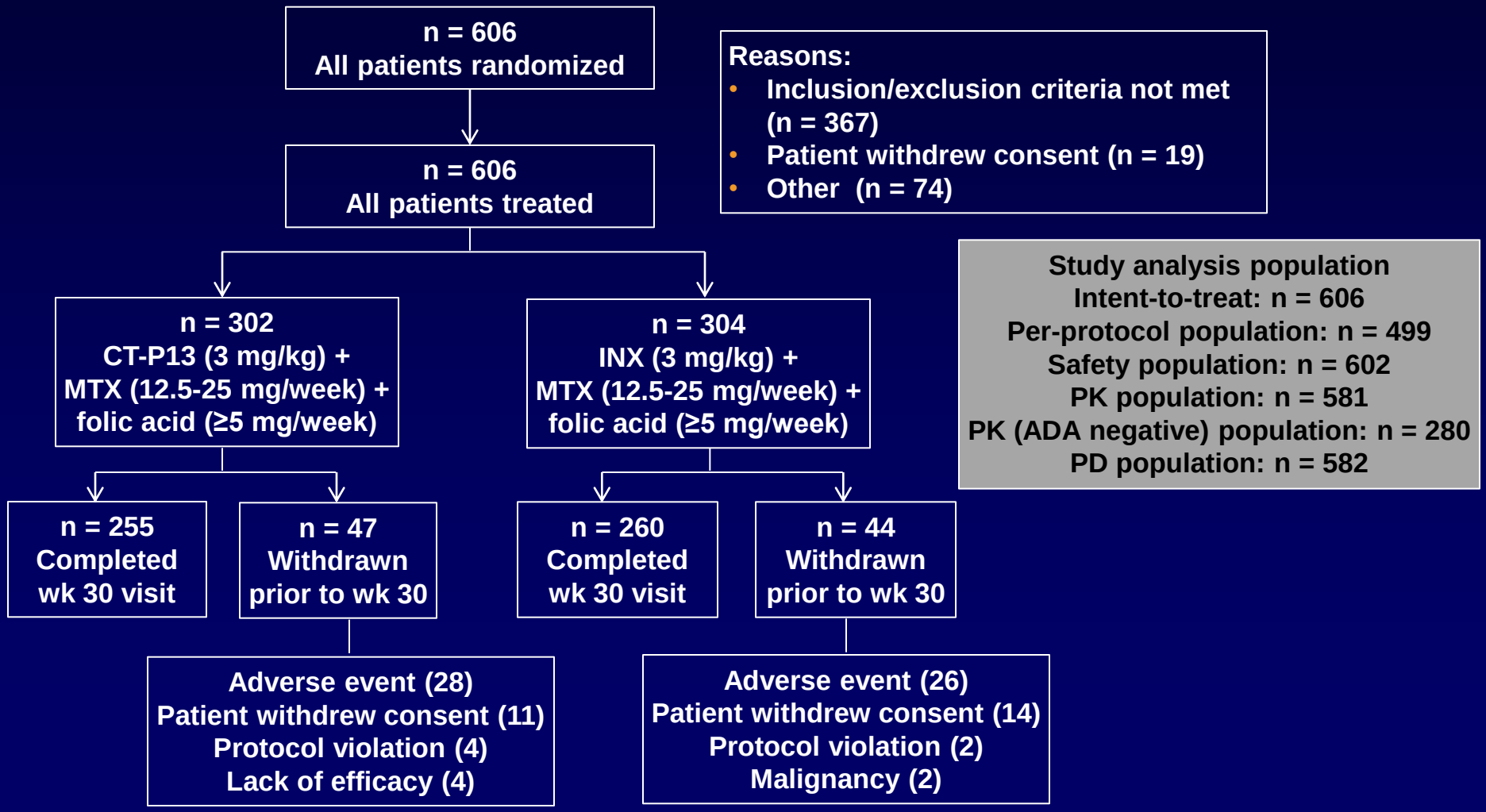
EMA Website. Availiable at: http://http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jspAccessed 5 March 2015.

The First Biosimilar Monoclonal Antibody

- On 10 September 2013, the European Commission granted full approval to a biosimilar of infliximab, an anti-TNF-α antibody
  - This is the first approval of a biosimilar antibody in Europe
  - Developed by the Korean company Celltrion
  - Co-marketed in Europe by Celltrion Health Care Hungary as Remsima and by Hospira UK as Inflectra
- Approval was based on a phase I PK study in ankylosing spondylitis and a phase III equivalence trial in rheumatoid arthritis (RA)

Remsima European Public Assessment Report. Available at: http://www.ema.europa.eu. Accessed 5 March 2015..

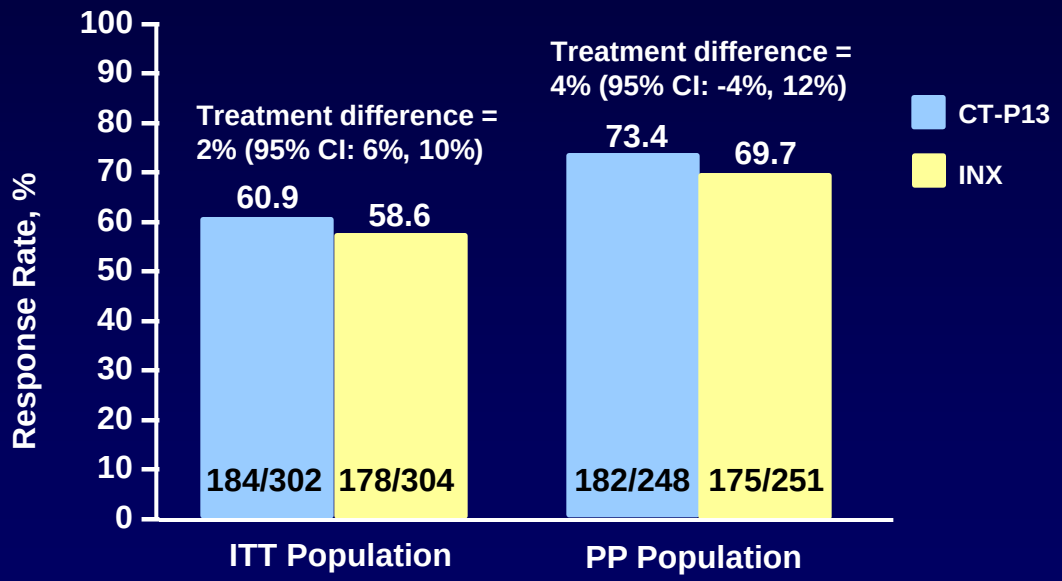
CT-P13 Pivotal Phase III Randomized, Double-Blind Equivalence Study in RA



Yoo DH, et al. *Ann Rheum Dis.* 2013;72(10):1613-1620.

Results From CT-P13 Phase III Equivalence Trial

- **Primary efficacy endpoint: ACR20 response at week 30**



- **Safety: Treatment-emergent adverse events were seen in 35.2% of patients treated with CT-P13 and 35.9% of patients treated with INX**
- **Immunogenicity: Equivalent levels of anti-infliximab antibodies were detected in both treatment arms at week 14 and week 30**

Yoo DH, et al. *Ann Rheum Dis.* 2013;72(10):1613-1620.

Extrapolation of Indications for Remsima and Inflectra

- The originator infliximab, Remicade®, is approved for rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and psoriasis
- In the biosimilar approval, Remsima and Inflectra were granted full extrapolation to all indications of Remicade
- The decision to extrapolate was based on careful examination of quality, nonclinical, and clinical data as well as mechanism of action
- There is a post-approval requirement for a phase IV trial in Crohn's disease, which is currently underway

Remsima European Public Assessment Report. Available at http://www.ema.europa.eu. Accessed 2 November 2013.

How do clinical trials for biosimilar monoclonal antibodies different from other clinical trials?

Biosimilar Antibody Clinical Trials

- The guiding principle is to **demonstrate similar efficacy and safety** compared to the reference medicinal product, not patient benefit
- Therefore, the most sensitive patient population and clinical endpoint is preferred
- Comparability should be demonstrated in scientifically appropriately sensitive clinical models and study conditions

European Medicines Agency. Available at: http://ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. Accessed 5 March 2015.

Clinical Trials of Biosimilar mAbs Are Different From Those of Originators

	Biosimilar mAbs	Originator
Patient Population	**Sensitive and homogeneous patient population**	**Any**
Clinical Design	**Comparative versus innovator (equivalence studies)**	**Superiority versus 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**

What Is a Sensitive and Homogenous Study Population?

- **Biosimilar antibodies should be studied in the population of patients in whom, *if there is a difference between the biosimilar and the reference product*, that difference will most easily be detected.**
- **This population will vary for each antibody and each disease in which the antibody is used**
  - **With biosimilar trastuzumab in breast cancer, the most sensitive population is adjuvant/neoadjuvant disease**
  - **For biosimilar rituximab in lymphoma, the population is harder to identify because lymphomas are not homogenous**

Sensitive Endpoints for Biosimilar Antibody Clinical Trials

- EMA guidelines identify response as a sensitive endpoint for clinical trials of biosimilar antibodies
- The EMA does not accept overall survival as an appropriately sensitive endpoint for biosimilar antibody clinical trials
- As overall response rate (ORR) does not always correlate with survival, this is a controversial endpoint for clinicians
  - Current clinical trials of biosimilar trastuzumab and biosimilar rituximab use ORR as primary endpoints
  - For trastuzumab, pathologic complete response (pCR) in the neoadjuvant setting may be the most sensitive endpoint
  - Long-term survival may be used as a secondary endpoint

Why is Neoadjuvant/Adjuvant a Sensitive Population to Study Similarity of Herceptin® and Biosimilar Trastuzumab?

Topic	Metastatic Population	Neoadjuvant/Adjuvant population
PK	✘ Affected by patient's health status & tumor 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 (eg, 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

Are any biosimilars in development for breast cancer?

Ongoing Trials of Trastuzumab Biosimilars

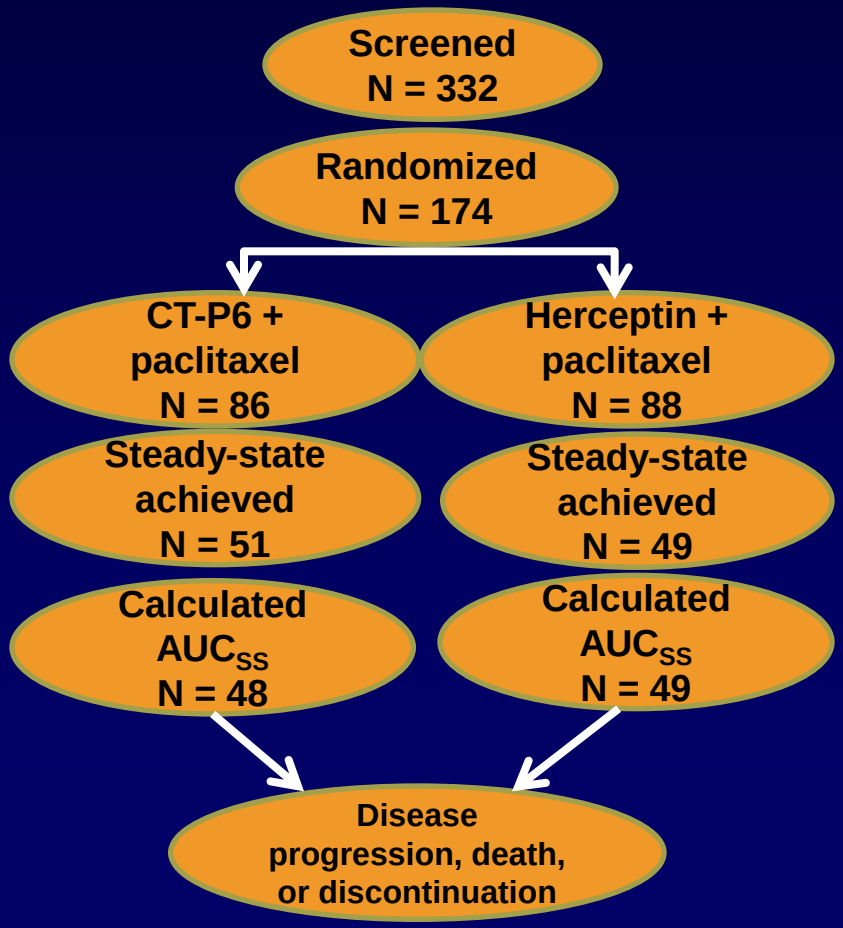
Companies Developing Trastuzumab Biosimilars

Company	Biosimilar Name	Status
Celltrion	CT-P6	Global phase III trial completed (IM ASCO 2013 #629), approved in Korea; application pending in other countries
Biocon	CANM ab	Phase III trial completed in India, but results pending, approval in India blocked by court injunction
BIOCAD	BCD-022	Phase III trial ongoing in Russia, India, Ukraine, and Belarus
Amgen, Synthon, Actavis	ABP 980	Phase I trial complete in Europe and phase III trial recruiting
BioCND and Genor	GB221	Phase I trial completed in Australia
Pfizer	PF-05280014	Phase I REFLECTIONS B327-02 trial recruiting
Hospira	NR	Clinical studies ongoing
Dr Reddy's Laboratories	NR	Clinical studies pending
Intas	NR	Clinical studies pending
PlantForm	NR	Clinical studies expected to begin in 2014
Mylan Inc.	Hertraz	Phase III trial completed in India but approval blocked by court injunction
Samsung Bioepis Co	SB3	Phase III trial recruiting in Czech Republic
Shanghai CP Guojan Pharm Co	CMAB302	Phase II trial completed

Thill M. *Expert Rev Anticancer Ther.* 2015;15(3):331-338.

Phase I/IIb Randomized Clinical Trial Comparing PK and Safety of Herceptin and its Biosimilar CT-P6 in Metastatic Breast Cancer

- **Multicenter trial: Korea, Russia, Ukraine, Latvia, Serbia**
- **MBC, HER2 FISH+ with measurable disease, no prior trastuzumab and CT for MBC, > than 12 months from adjuvant/ neoadjuvant trastuzumab and CT**



Primary Endpoint:
- Area under the curve at steady state (AUC_{ss})

Secondary Endpoint:
- Trough concentration at steady state ($C_{trough\ ss}$)

Tertiary Endpoints:
- Average concentration ($C_{av,ss}$)
- Minimum concentration (C_{min})
- Maximum concentration (C_{max})
- Peak to trough fluctuation ratio (PTF)
- Clearance at steady state (CL_{ss})
- Terminal elimination rate constant (λ_z)
- Mean residence time at steady state (MRT_{ss})
- Terminal half life ($t_{½}$)
- Apparent volume of distribution at steady state (Vz_{ss})

Safety Objectives: Cardiotoxicity, infusion reaction/ hypersensitivity

Im Y, et al. Presented at 13th St Gallen International Breast Cancer Conference; 13-16 March 2013; St Gallen, Switzerland. Poster 268.

Phase I/IIb Trial Comparing Herceptin and its Biosimilar CT-P6 in MBC: Results

- Multicenter trial: Korea, Russia, Ukraine, Latvia, Serbia

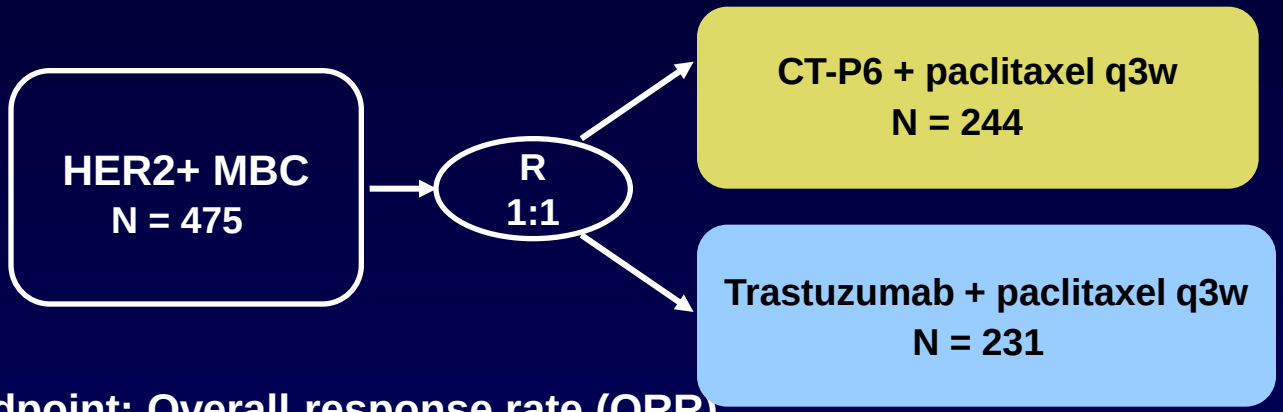
Parameter	Treatment	N	Geometric mean	% CV	Ratio (%)	90% CI	*P* value
AUC_{SS} (µgh/mL)	CT-P6	48	32,000	43.5	104.57	93.64, 116.78	.5029
	Herceptin	49	30,600	30.9			
$C_{trough\ SS}$ (µg/mL)	CT-P6	51	19.5	37.0	101.35	87.94, 116.82	.8754
	Herceptin	49	19.2	39.6			

Conclusions of the study:

- CT-P6 demonstrated equivalent PK profile to Herceptin
- CT-P6 well tolerated with a comparable safety profile to Herceptin
- (infusion-related reaction, cardiotoxicity, and infection)

Im Y, et al. Presented at 13th St Gallen International Breast Cancer Conference; 13-16 March 2013; St Gallen, Switzerland. Poster 268.

Compare Trial: Double-Blind, Randomized, Parallel Group, Phase III Study to Demonstrate Equivalence in Efficacy and Safety of CT-P6/Paclitaxel vs Trastuzumab/Paclitaxel in MBC



Primary endpoint: Overall response rate (ORR)

Inclusion Criteria:

- MBC with measurable lesions
- HER2 + IHC or FISH centrally confirmed
- No prior trastuzumab and/or chemo Tx in metastatic setting
- >12 months since prior adjuvant or neoadjuvant trastuzumab and/or chemo
- ECOG 0 or 1

Exclusion Criteria:

- Prior chemo for MBC
- CNS metastases
- Baseline LVEF ≤50% or history of CHF

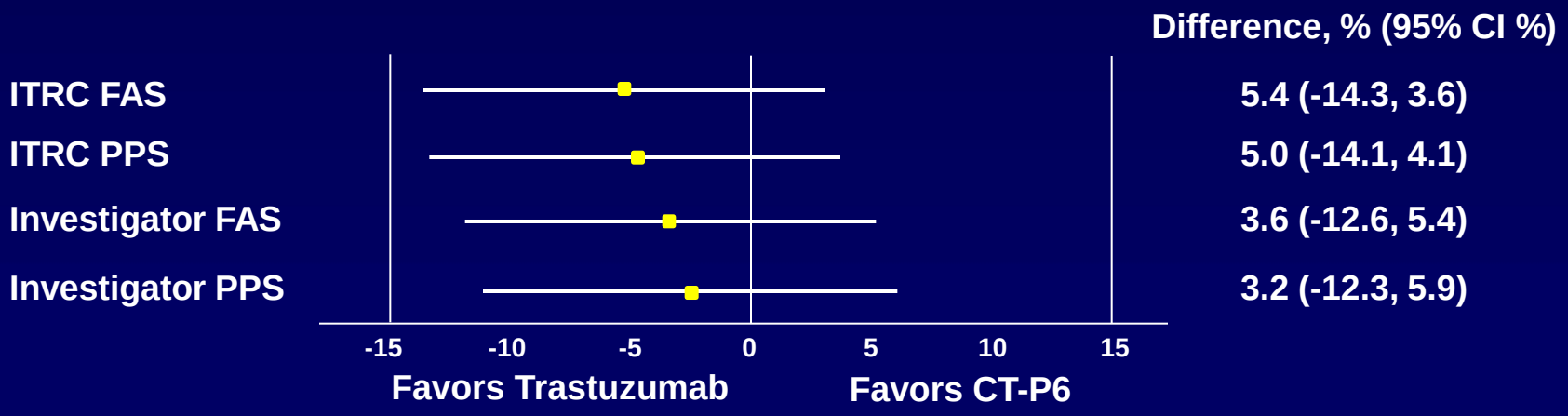
Im YH, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 629.

Patient Characteristics	CT-P6 + Paclitaxel (n = 244)	Trastuzumab + Paclitaxel (n = 231)
Age (years)		
Median (range)	54 (31-75)	53 (25-78)
≥65 years	34 (13.9)	22 (9.5)
<65 years	210 (86.1)	209 (90.5)
Ethnicity, no (%)		
Caucasian	158 (64.8)	141 (61.0)
Asian	86 (35.2)	90 (39.0)
Prior neoadjuvant or adjuvant therapy, n (%)	130 (53.3)	121 (52.4)
Trastuzumab	8 (3.3)	8 (3.5)
Taxane	33 (13.5	31 (13.4)
Anthracycline	111 (45.5)	106 (45.9)
Baseline ECOG PS score, n (%)		
Score 0	128 (52.5)	116 (50.2)
Score 1	115 (47.1)	115 (49.8)
Disease status		
Initial metastatic	90 (36.9)	84 (36.4)
Recurrence	154 (63.1)	147 (63.6)
Disease-free interval, months (range)	23.8 (0.9-148.2)	20 (0.5-384.9)

Im YH, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 629.

Compare: Overall Response Rate

	ITRC		Investigator	
	CT-P6 + Paclitaxel (n = 244)	Trastuzumab + Paclitaxel (n = 231)	CT-P6 + Paclitaxel (n = 244)	Trastuzumab + Paclitaxel (n = 231)
Complete response	9 (3.7%)	4 (1.7%)	12 (4.9%)	6 (2.6%)
Partial response	129 (52.9%)	139 (60.2%)	146 (59.8%)	152 (65.8%)
Stable disease	49 (20.1%)	38 (16.5%)	61 (25.0%)	56 (24.2%)
Overall response rate	138 (56.6%)	143 (61.9%)	158 (64.8%)	158 (68.4%)
Difference, % [95% CI]	5.4 [-14.3, 3.6]		3.6 [-12.6, 5.4]	

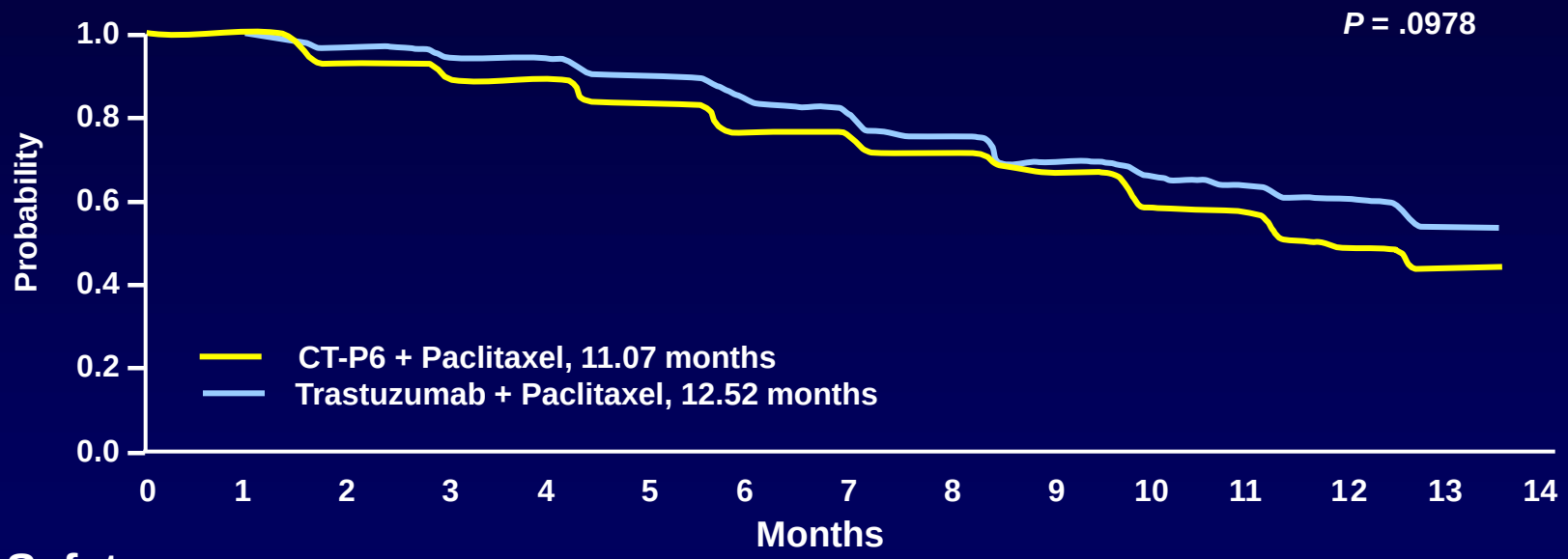


FAS, Full analysis set; PPS, per protocol patients set
Difference in proportion of complete response or partial response. Confidence interval estimated using the exact method.

Im YH, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 629.

Compare: Time to Progression

Time to progression in the responder group by independent review committee (full analysis set, 1 year data)



- **Safety**
  - **CT-P6 was well tolerated with a safety profile comparable to trastuzumab (Herceptin)**
  - **No immunogenicity data available**

Im YH, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 629.

Safety

	CT-P6 + Paclitaxel		Trastuzumab + Paclitaxel		*P* value	
	All	≥G3	All	≥G3	All	≥G3
Total serious adverse events	33	28	28	24	.6477	.7048
All adverse events	224	110	214	107	.7336	.7865
Hematologic events						
Anemia	187	10	180	4	.7388	.1274
Neutropenia	142	81	140	82	.5931	.5975

Im YH, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 629.

Nonhematologic Adverse Events

	CT-P6 + Paclitaxel		Trastuzumab + Paclitaxel		*P* Value	
	All	≥G3	All	≥G3	All	≥G3
Cardiotoxicity	15	6	14	3	.9684	.3539
Hypersensitivity	118	11	127	11	.1492	.8954
Peripheral neuropathy						
Sensorimotor	4	3	5	1	.6748	.3423
Sensory	48	7	50	4	.5954	.4101
Unspecified	63	14	56	13	.6917	.9587
Nausea / Vomiting	48	2	44	2	.8633	.9561
Fatigue and/or asthenia	73	5	63	3	.5238	.5252
Diarrhea	34	1	41	1	.2545	.9690
Stomatitis	14	0	16	0	.5945	NE
Alopecia	122	0	127	3	.2775	.0741
Myalgia	47	1	52	2	.3836	.5307
Pain in extremity	22	2	29	6	.2132	.1323
Arthralgia	21	0	30	0	.1232	NE
Infections	57	10	46	8	0.3622	.7171

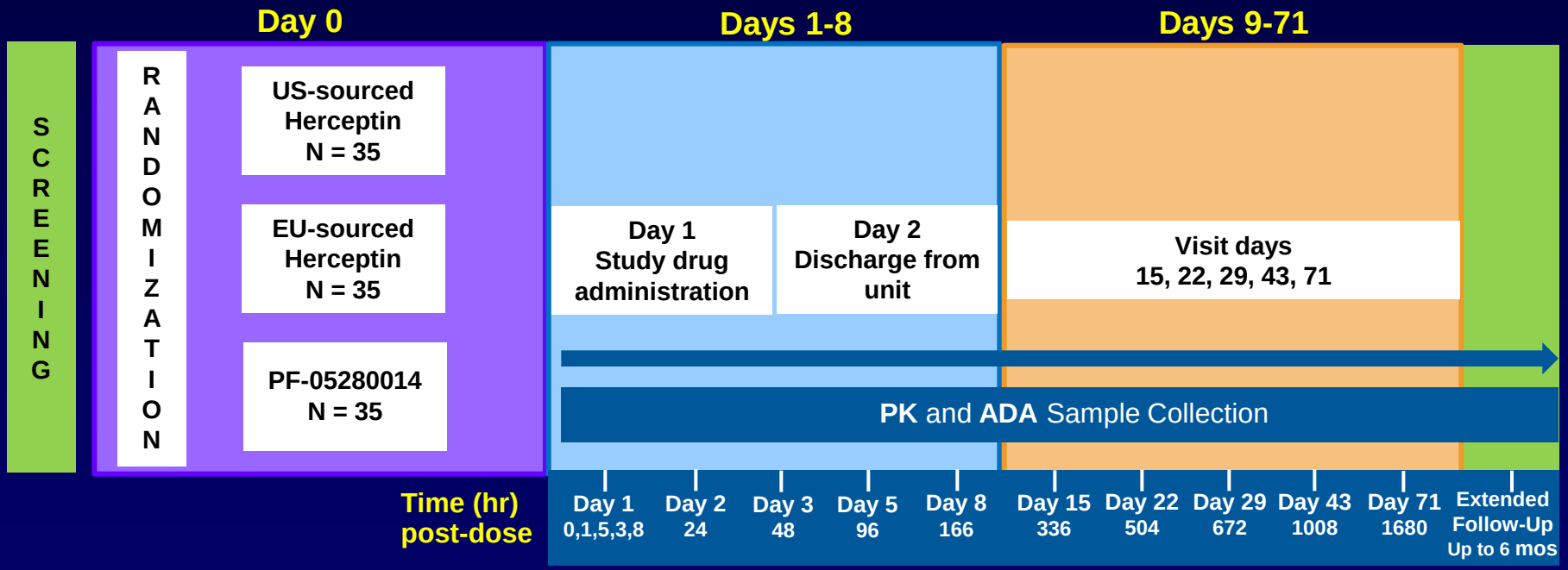
Im YH, et al. *J Clin Oncol*. 2013;31(suppl): Abstract 629.

Current Status: CT-P6

- CT-P6 (braneded Herzuma) has been approved by the Korean Ministry of Food and Drug Safety for all indications of Herceptin, including gastric cancer
- No application has been submitted to the EMA or other regulatory bodies
- Phase III trial of CT-P6 vs Herceptin in 532 women with HER2+ early breast cancer is planned (NCT-02162667)
  - Primary endpoint: pathologic complete response after surgery and 8 cycles neoadjuvant therapy
  - Current status: Planned, not yet enrolling

A Phase I Pharmacokinetics Trial Comparing PF-05280014 and Trastuzumab in Healthy Volunteers

- In this double-blind, randomized, 3-arm trial, 105 healthy male volunteers aged 18-55 were randomized to receive a single 6 mg/kg dose of PF-05280014, trastuzumab-US, or trastuzumab-EU

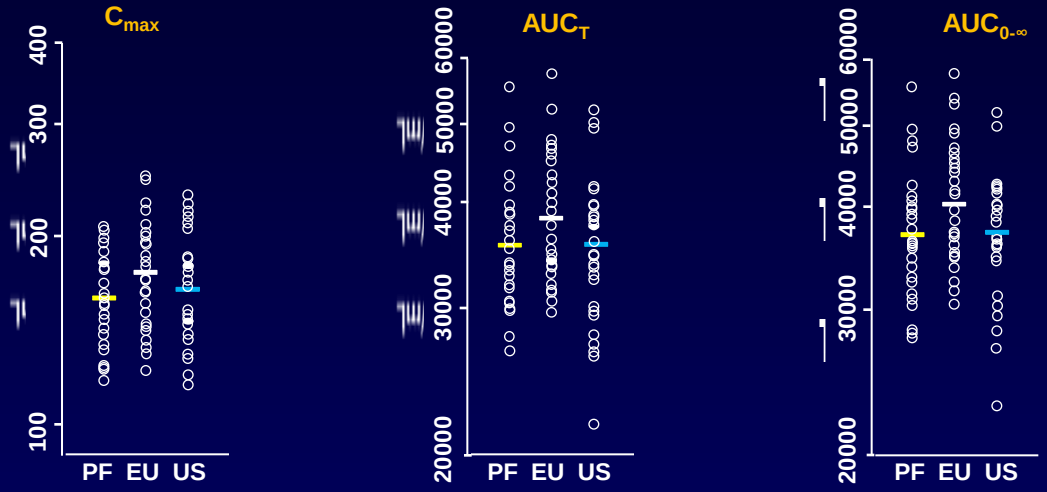


- Primary endpoints
  - Maximum serum concentration (C_{max}) of the administered mAb
  - Area under the serum concentration-time curve (AUC) from time 0 to the last timepoint with measurable concentration of the administered mAb (AUC_T)

Yin D, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 612.

PF-05280014 Phase I Results

Individual and Mean Estimates of C_{max}, AUC_T, and $AUC_{0-\infty}$ of PF-05280014, Trastuzumab-EU, and Trastuzumab-US



$AUC_{0-\infty}$, area under the concentration-time curve from time 0 extrapolated to infinte time; AUC_T, area under the concentration-time curve from time 0 to last measurable administered monoclonal antibody; C_{max}, maximum serum concentration; EU, trastuzumab EU; PF, PF-05280014; US, trastuzumab-US

Statistical Comparison of PK Exposure Parameters Between Test and Reference Products

			Geometric Mean			
Test	Reference	Parameter*	Test	Reference	Ratio, %†	90% CI, %
PF-05280014	Trastuzumab-US	C_{max}	157	161	97.41	90.71-104.62
		AUC_T	35210	35230	99.94	93.08-107.31
		$AUC_{0-\infty}$	36650	36710	99.83	93.06-107.09
PF-05280014	Trastuzumab-EU	C_{max}	157	171	91.49	85.32-98.09
		AUC_T	35210	38000	92.66	86.44-99.34
		$AUC_{0-\infty}$	36650	39770	92.15	86.03-98.69
Trastuzumab-EU	Trastuzumab-US	C_{max}	171	161	106.48	99.20-114.30
		AUC_T	38000	35230	107.85	100.50-115.75
		$AUC_{0-\infty}$	39770	36710	108.34	101.05-116.16

*C_{max}, AUC_T and $AUC_{0-\infty}$ were in units of μg/mL, μg·hr/mL, respectively. †Test/reference ratio of adjusted geometric means.

Yin D, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 612.

PF-05280014 Safety

Treatment-Emergent Adverse Events Regardless of Causality Occurring in ≥5% of Total Subjects (Modified ITT Population)

	PF-05280014 n = 35	Trastuzumab-EU n = 35	Trastuzumab n = 35
Subjects with any AE n (%)	28 (80.0)	29 (82.9)	29 (82.9)
Eye disorders, n (%)			
Conjunctival hyperemia	4 (11.4)	1 (2.9)	2 (5.7)
Gastrointestinal disorders, n (%)			
Diarrhea	3 (8.6)	2 (5.7)	1 (2.9)
Nausea	5 (14.3)	5 (14.3)	3 (8.6)
General disorders and administration site conditions, n (%)			
Pyrexia	10 (28.6)	3 (8.6)	2 (5.7)
Chills	9 (25.7)	7 (20.0)	5 (14.3)
Fatigue	3 (8.6)	3 (8.6)	3 (8.6)
Infections and infestations, n (%)			
Nasopharyngitis	3 (8.6)	3 (8.6)	2 (5.7)
Pharyngitis	1 (2.9)	4 (11.4)	2 (5.7)
Injury, poisoning and procedural complications, n (%)			
Infusion-related	13 (37.1)	10 (28.6)	7 (20.0)
Musculoskeletal and connective tissue disorders, n (%)			
Myalgia	2 (5.7)	2 (5.7)	2 (5.7)
Nervous system disorders, n (%)			
Headache	10 (28.6)	12 (34.3)	8 (22.9)
Dizziness	1 (2.9)	4 (11.4)	2 (5.7)
Respiratory, thoracic and mediastinal disorders, n (%)			
Cough	1 (2.9)	4 (11.4)	1 (2.9)

Yin D, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 612.

Current Status: PF-05280014

- **Two phase III trials of PF-05280014 in breast cancer are planned**
  - **Trial B327002 of PF-05280014 vs Herceptin in 690 women with metastatic breast cancer (NCT01989676)**
    - **Concomitant therapy: Paclitaxel**
    - **Primary endpoint: ORR**
    - **Current status: Enrolling**
  - **Trial B327-04 of PF-05280014 vs Herceptin for the neoadjuvant treatment of women with operable HER2+ breast cancer (NCT02187744)**
    - **Concomitant therapy: Docetaxel and paclitaxel**
    - **Primary endpoint: Percentage of patients with steady-state drug concentrations >20 µg/mL**
    - **Current status: Planned, not yet initiated**

Phase III Trials of Neoadjuvant Trastuzumab Biosimilars in Early-Stage Breast Cancer

	SB-3 (Samsung Bioepis)	ABP-980 (Amgen)	CT-P6 (Celltrion)
Trial identifier	NCT02149524	NCT01901146	NCT02162667
Trial design	Randomized double-blind	Randomized double-blind	Randomized double-blind
Comparator	Herceptin	Herceptin	Herceptin
Disease	EBC	EBC	EBC
Chemo	?	Epirubicin, cyclophosphamide, paclitaxel	Docetaxel followed by FEC (5-fluorouracil, epirubicin, and cyclophosphamide)
Primary endpoint	pCR (breast)	pCR (breast)	pCR (breast/LN)
No of pts	498	556	532
Status	Ongoing	Ongoing	Planning to start in 2014

National Institutes of Health. Clinical Trials.gov Website. Available at: www.clinicaltrials.gov. Accessed 5 March 2015.

What is extrapolation?

Extrapolation

- Extrapolation is the use of data from a study in one indication to justify the use of a drug in another indication
- Current examples of extrapolation
  - Biosimilar G-CSF tested in chemotherapy-induced neutropenia, approved for many indications, including mobilization of peripheral blood cells for transplantation
  - Biosimilar infliximab tested in rheumatoid arthritis, approved for many additional indications including Crohn's disease and colitis
- Potential future extrapolation
  - Biosimilar trastuzumab tested in metastatic breast cancer and approved for gastric cancer or neoadjuvant breast cancer
  - Biosimilar rituximab tested in rheumatoid arthritis and then approved for lymphoma

EMA Position on Extrapolation for Biosimilars

- EMA Guidelines: "Extrapolation of clinical efficacy and safety data to other indications of the reference antibody not specifically studied during the clinical development of the biosimilar antibody is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification."
- Extrapolation is complex and must be decided on a case by case basis
  - Biosimilar infliximab granted extrapolation to all indications because of mechanism of action, studies in two therapy areas, and noncritical nature of treatment
  - In the case of critical illnesses such as cancer, extrapolation may be a concern and must be handled cautiously

European Medicines Agency. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. Accessed 5 March 2015.

Justification for Extrapolation

- Justification depends on several factors, including clinical experience, available literature, whether or not the same mechanisms of action or same receptors are used in all indications, and possible safety issues in different subpopulations
- If different mechanisms of action are relevant (or the MoA is unknown), additional data to support extrapolation may be needed
  - Eg, an antibody is used both as an immunomodulator and as a cancer treatment
- Safety and immunogenicity data must also be taken into consideration

Challenges for Extrapolation of Biosimilar Antibodies

- Net contribution of each mechanism of action (ADCC, CDC, apoptosis) *in vivo* is unknown
- Preclinical and nonclinical testing suggests different contribution of mechanism of action (MOA), depending on host and disease factors, ie,
  - Concomitant medication (steroids, chemotherapy)
  - Intact effector mechanisms (complement, NK cells)
  - Receptor number and density
- MOA for some indications is sometimes not fully understood, even for the originator antibody
- Clinical endpoints for biosimilar antibodies difficult to establish

Challenges for Extrapolation of Efficacy Across Indications for Biosimilar Antibodies

Trastuzumab is used in different ways across tumor types and disease settings

- In combination with different chemotherapies, hormonal therapies, and as single agent (maintenance)
- Neoadjuvant and adjuvant Herceptin in breast cancer
- Herceptin in metastatic breast cancer
- Herceptin in metastatic gastric cancer

Additional Considerations for Extrapolation

- **Is the trial design suitable to determine biosimilarity?**
  - **Patient population and endpoints**
  - **Dosage and route of administration**
  - **Concomitant therapies**
- **Are the study results robust, and are any differences appropriately accounted for?**
- **Was the duration of the study adequate?**
- **If patient populations are different in each indication (eg, cancer patient vs patient with autoimmunity), what rationale is given for extrapolation between these populations?**

Is Extrapolation of Indications Possible With Biosimilar Trastuzumab?

- Early and metastatic patient populations are different regarding disease burden, chemo regimens, concomitant medications, immune response
- The early breast cancer setting is the most sensitive clinical setting to investigate immunogenicity of trastuzumab biosimilars
- Extrapolation of immunogenicity/efficacy/safety data obtained in the early breast cancer population to the metastatic population is possible while extrapolation from the metastatic population to the early breast cancer population may represent a risk for the patients
- Trastuzumab plus pertuzumab is now the standard of care for first-line metastatic breast cancer. How will biosimilars fit into this? A phase I of biosimilar trastuzumab plus pertuzumab?

What safety measures are in place after biosimilars are approved?

Pharmacovigilance

- Pharmacovigilance (PV) relates to the detection, assessment, understanding, and prevention of adverse effects after a product is available on the market.
- The EMA guidelines state that a comprehensive PV plan should be sent to the authorities together with the data package, and such a plan should be established at the time of approval of the product.
- New EU pharmacovigilance legislation recommends enhanced postauthorization data collection and additional monitoring for medical products such as those with new active substances and new biological products, including biosimilars.
  - Beginning in 2013 the SmPC and package leaflet for these products must include a black triangle and an explanatory statement on additional monitoring

European Commission Public Health. Available at: http://ec.europa.eu/health/human-use/pharmacovigilance/ Accessed 5 March 2015. EMA Guideline on Good Pharmacovigilance Practices. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/04/WC500142282.pdf. Accessed 5 March 2015.

Postmarket Monitoring: EU Risk Management Plans

- **"Comprehensive and proactive application of scientifically based methodologies to identify, assess, communicate, and mitigate risk throughout a drug's life cycle so as to establish and maintain a favorable benefit-risk profile."**
- **Mandatory for biologics (immune reactions)**
- **Four steps for a particular risk:**

Step	Description	Risk Management Plan
1. Detection	Identify risk	Pharmacovigilance
2. Assessment	Understand/monitor risk	
3. Communication	HCP education	Risk minimization
4. Minimization	Act to reduce risk	

Zuñiga L, et al. *Pharmacoepidemiol Drug Saf*. 2010 Jul;19(7):661-669.

Aspects of the Risk Management Plan for mAbs (EMA Guideline)

- Safety in indications licensed for the reference mAb that are claimed based on extrapolation of efficacy and safety data, including long-term safety data unless otherwise justified
- Occurrence of rare and particularly serious adverse events described and predicted, based on the pharmacology, for the reference mAb
- The pharmacovigilance plan should be proportionate to identified and potential risks, and should be informed by the safety specification for the reference mAb in addition to relevant knowledge regarding similar biological products as appropriate
- Detection of novel safety signals, as for any other biological medicinal product
- Activities to obtain additional immunogenicity data, if considered needed

Immunogenicity of Biological Medicinal Products

- Not predictable with analytical methods
- No standardized antibody tests available
- Immune system is more sensitive than *in vitro* technology
- Respiratory sensitizing cannot be excluded
- Different consequences of antibody formation

Immune Reactions to Biologic Therapeutics May Lead to Altered Efficacy or SAEs

- Anaphylaxis
- Infusion reaction
- Cross-reactivity to endogenous protein
- Adverse events
- Altered pharmacokinetics
- Loss of efficacy
- No clinical effect detected

Jahn EM, et al. *N Biotechnol.* 2009;25(5):280-286.

Patient Population for Immunogenicity Testing

- The same therapeutic protein will induce different levels of immune response in different patient populations
- **Immunogenicity testing should be done in the most sensitive patient population**, ie, patients who are most likely to develop an immune reaction to treatment

European Medicines Agency (EMA) Guidelines. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128688.pdf. Accessed 5 March 2015.

Immunogenicity Testing: A Tiered Approach

Screening assays: for 'identification' of all antitherapeutic binding antibodies

- Enzyme-linked immunosorbent assays (ELISAs): direct, bridging, other formats
- Radioimmunoprecipitation assays (RIPA)
- Surface plasmon resonance (SPR)
- Other technologies

Confirmatory assays: for confirming antibodies

Neutralization assays: for distinguishing neutralizing & nonneutralizing antibodies

- Cell-based assay
- Non-cell-based ligand-binding assay

International Nonproprietary Names (INNs)

- A global system of unique names for drug substances, regulated by the World Health Organization (WHO).
- Small-molecule generic drugs have the same active ingredients as their originator drugs and are assigned the same INNs, even if they are produced in different ways.
- Currently, even though biosimilars are not identical to their originator drug, they are given the same INN. This might potentially affect traceability, lead to automatic substitution, and negatively impact safety surveillance programs.
- This is under discussion at WHO and may change in the near future.

Traceability of Biologic Products

- **The key component to monitor product safety is knowing what product is associated with a given adverse event (AE)**
- **Because biosimilars are given the same INN as the originator drug, use of proprietary (brand) name in prescriptions and patient files is recommended in addition to INN**
  - Section 4.4 of MabThera SmPC: “In order to improve the traceability of biological medicinal products, the trade name of the administered product should be clearly recorded (or stated) in the patient file”[1]

1. MabThera [Summary of Product Characteristics.] Grenzach-Wyhlen, Germany; Roche Pharma AG; 2013.

Substitution (EMA Guideline)

- Refers to a national policy which permits the switch from one to another medicine that has been demonstrated to have the same quality, efficacy, and safety
- Typically occurs at retail and hospital pharmacies
- "Depending on the handling of biosimilars and reference medicinal products in clinical practice at national level, 'switching' and 'interchanging' of medicines that contain a given mAb might occur. Thus applicants are recommended to follow further development in the field and consider these aspects as part of the risk management plan."

European Medicines Agency (EMA) Guidelines. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128688.pdf. Accessed 5 March 2015.

Automatic Substitution

- Automatic substitution = substitution by a pharmacist without the physican's consent
- Generic drugs may be automatically substituted for reference drugs because they are therapeutically equivalent
- Biosimilars are **similar** to the originator drugs, **not identical**, and there is currently no scientific basis to substitute different products
- Regulatory decisions on substitution are left to individual countries

Interchangeability/Substitution of Biosimilars

- Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be made following the opinion of a *qualified healthcare professional*.[1]
- There is currently no scientific basis for automatic substitution of biosimilars
- Automatic substitution of a biosimilar for its originator (or vice versa) impairs traceability and pharmacovigilance activities

EMA Session on Identification and Traceability of Biological Products. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/05/WC500127933.pdf. Accessed 5 March 2015.

Summary (1)

- **Biosimilars are approved copies of biologic drugs that have demonstrated similarity in physicochemical aspects, efficacy, and safety in a step-wise comparability program**
- **Biosimilars of small-molecule biologics have been approved in Europe since 2006; the first biosimilar monoclonal antibody was approved in 2013**
- **Several biosimilars of trastuzumab are currently in development, including phase III trials**

Summary (2)

- Biosimilars are tested in a reduced clinical trial program, so special attention must be paid to the patient population and endpoints of these trials
  - A trial examining response rate in metastatic breast cancer may not be appropriately sensitive
  - Pathologic complete response as an endpoint for a clinical trial in neoadjuvant breast cancer represents a more sensitive approach
- Extrapolation of a biosimilar trastuzumab will depend on how it was tested in clinical trial—a biosimilar only tested in the metastatic population would not be appropriate for the adjuvant setting
- Post-marketing pharmacovigilance efforts, including good traceability, are essential to ensure patient safety