BIOSIMILARES:
EFICACIA Y SEGURIDAD

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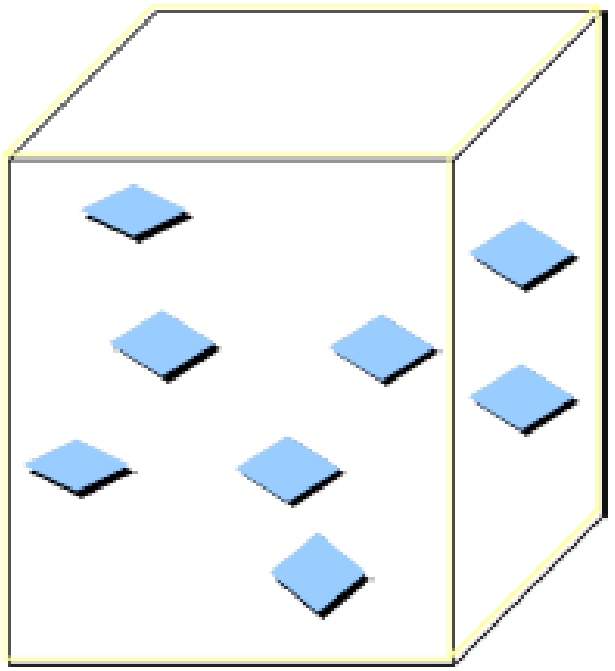
Some concepts about biosimilars

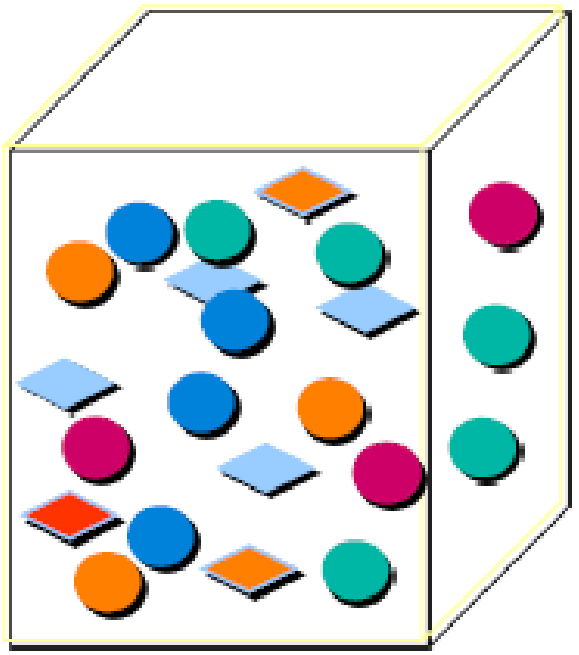
Size, Structure and Complexity

	Small Chemical Molecule	Chemical Molecule	Large Bilogical Molecule
SIZE	Aspirin 21 atoms	Human growth hormone (hGH) ~3000 atoms	IgG Antibody ~25000 atoms
COMPLEXITY	Bike ~ 20 lb	Car ~ 3000 lb	Commercial jet ~ 25000 lb (without oil)

Protein microheterogeneity



Small molecule



Protein-based drug

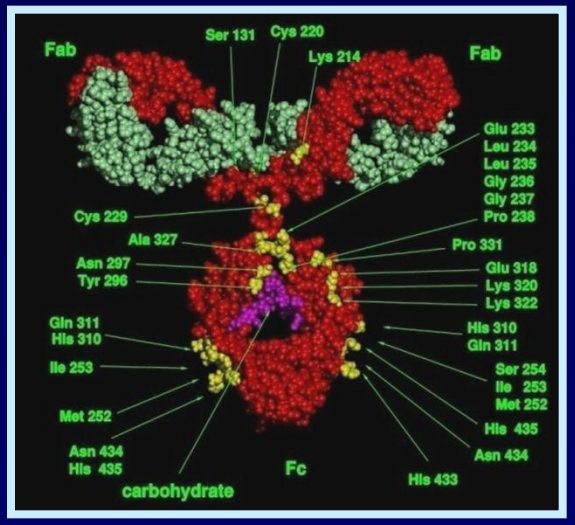
Complexity of Biological Products

Inherent complexity

- Size
- Structure
- Physiochemistry
- Heterogeneity

Added complexity

- Manufacturing process
- Formulation
- Handling
- Route of administration

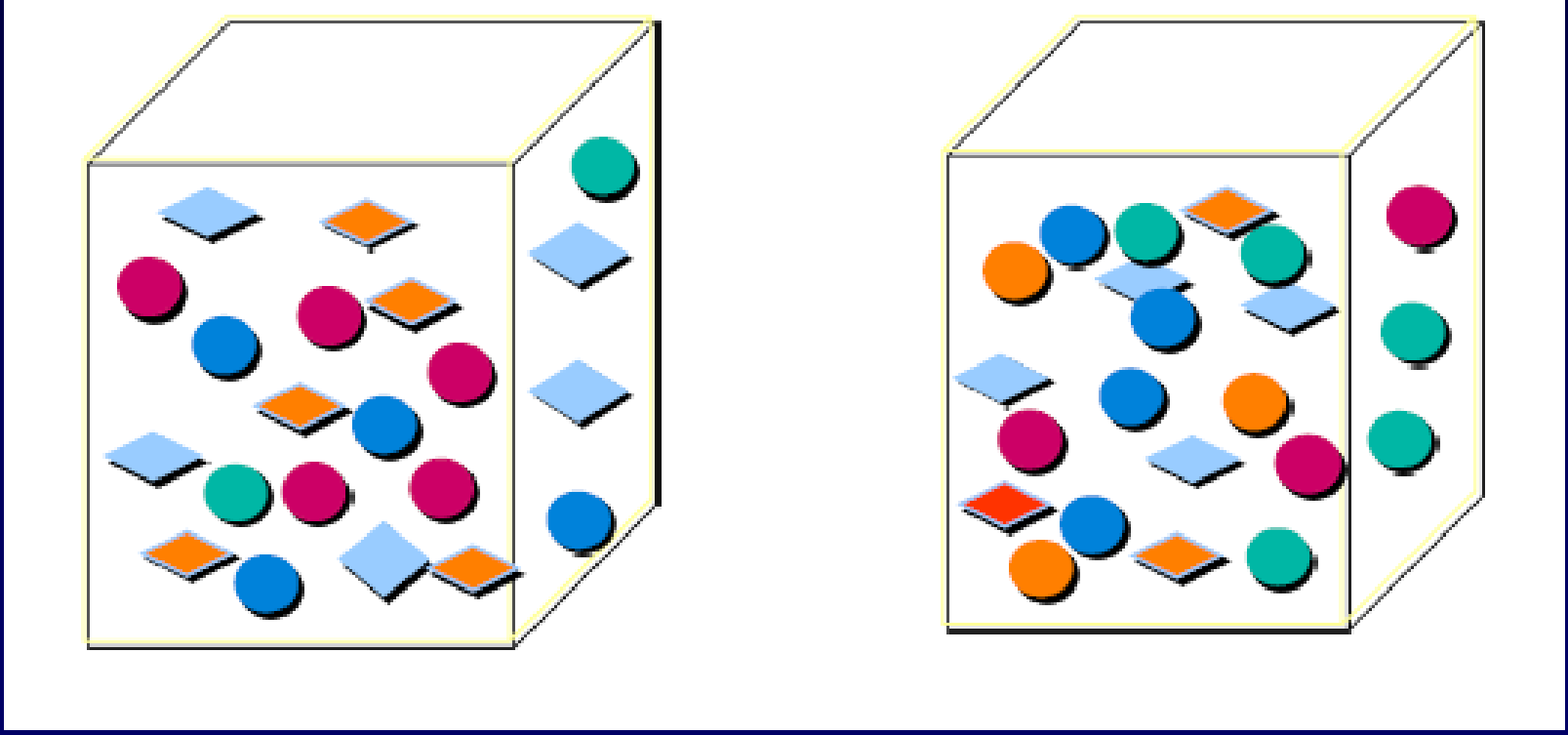


Impossible to make an exact copy

The Product is the process

Process 1

Process 2



Product X

Product Y

Immunogenicity

The key issues for protein drugs

Factors contributing to immunity

- **Host related:**
  - Genetic predisposition (MHC alleles)
  - Concomittant therapy (interferon)
  - Immunosuppression (Cancer)
  - Activated immune system due to infection
- **Product related**
  - Structural properties
  - Glycosylation
  - Impurities
  - Formulation
  - Storage
  - Aggregates
- **Treatment related**
  - Route of administration
  - Dose
  - Length of treatment

MHC, major histocompatability complex

Biosimilar Monoclonal Antibodies in Breast Cancer

What EMA Guideline on Biosimilar Antibodies Says

- The guiding principle is **to demonstrate similar efficacy and safety** compared to the reference medicinal product
- Therefore, in general 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://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

What is a Sensitive and Homogenous Study Population in Breast Cancer?

- **Biosimilars should be studied in the population of patients in whom – *if there is a difference between biosimilar and reference product* – that difference will most easily be detected.**
- **The neoadjuvant/adjuvant patient population is, for example, a homogeneous and sensitive population to establish similarity of Herceptin and biosimilar trastuzumab**

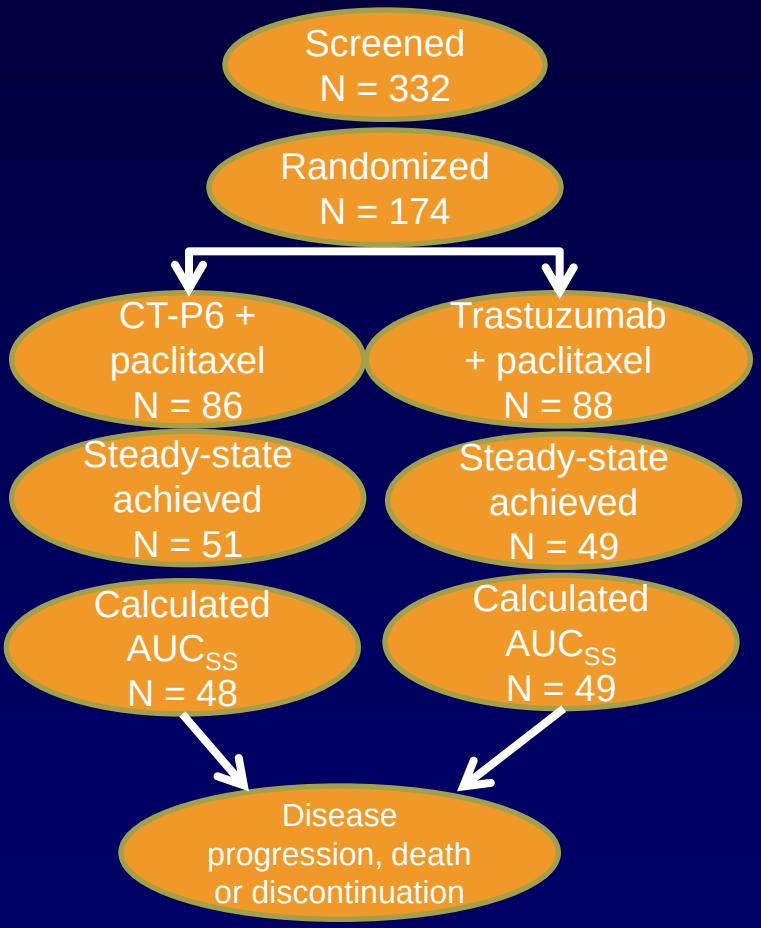
Sensitive Endpoints for Biosimilar Monoclonal Antibody Clinical Trials

- EMA guidelines identify ORR as a sufficiently sensitive endpoint for clinical trials of biosimilar antibodies
- Very often ORR does not correlate to survival
- Survival endpoints such as overall survival or progression-free survival may provide superior data, but are not convenient for a biosimilar antibody trial
- Which endpoint should be used in a biosimilar antibody trial remains a controversial issue
  - Current clinical trials of biosimilar trastuzumab use response and safety as primary endpoints
  - The goal of biosimilar trials is to demonstrate comparability, which ORR allows, not necessarily efficacy

Development of a Biosimilar Trastuzumab

Phase I/IIb Randomized Clinical Trial Comparing PK and Safety of Trastuzumab and its Biosimilar CT-P6

- **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

Presented at 13th St Gallen International Breast Cancer Conference 2013: Poster 268.

Phase I/IIb Trial Comparing Herceptin and Its Biosimilar CT-P6: Results

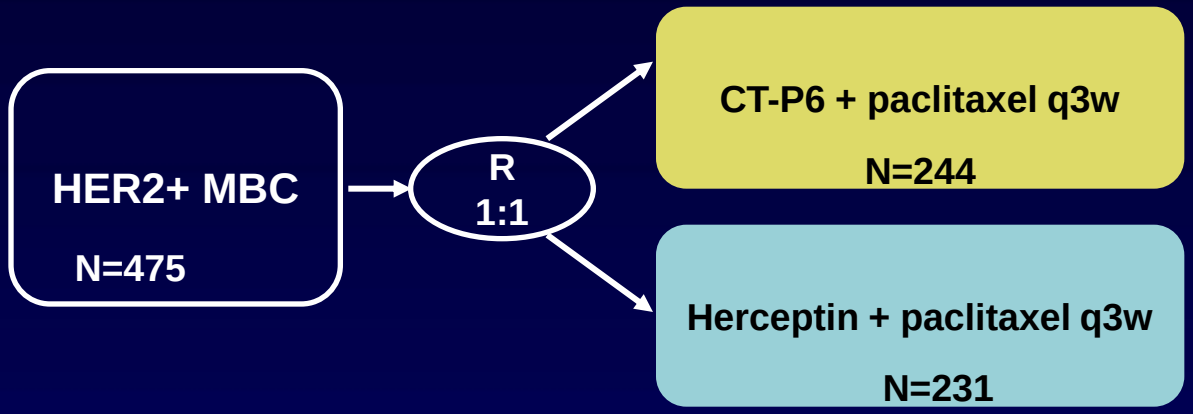
Parameter	Treatment	N	Geometric mean	% CV	Ratio (%)	90% CI	*P*-value
AUC_{SS} (µgh/mL)	CT-P6	48	32,000	43.5	104.57	93.64, 116.78	.5029
	Trastuzumab	49	30,600	30.9			
$C_{trough\ SS}$ (µg/mL)	CT-P6	51	19.5	37.0	101.35	87.94, 116.82	.8754
	Trastuzumab	49	19.2	39.6			

Conclusions of the study:

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

Presented at 13th St Gallen International Breast Cancer Conference 2013: Poster 268.

Compare Trial: Double-blind, Randomised, Parallel Group, Phase III Study to Demonstrate Equivalence in Efficacy and Safety of CT-P6/paclitaxel vs Herceptin/paclitaxel in MBC



Inclusion Criteria:

- MBC with measurable lesions
- Her 2 + 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

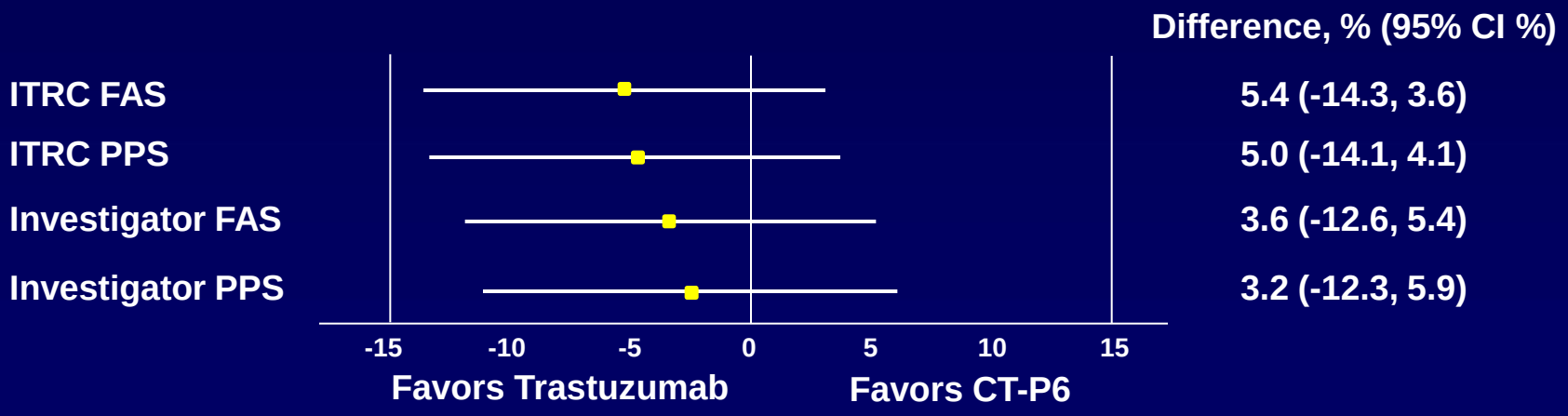
Exclusion Criteria:

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

Im YH, J Clin Oncol 31, 2013 (suppl; abstr 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]	

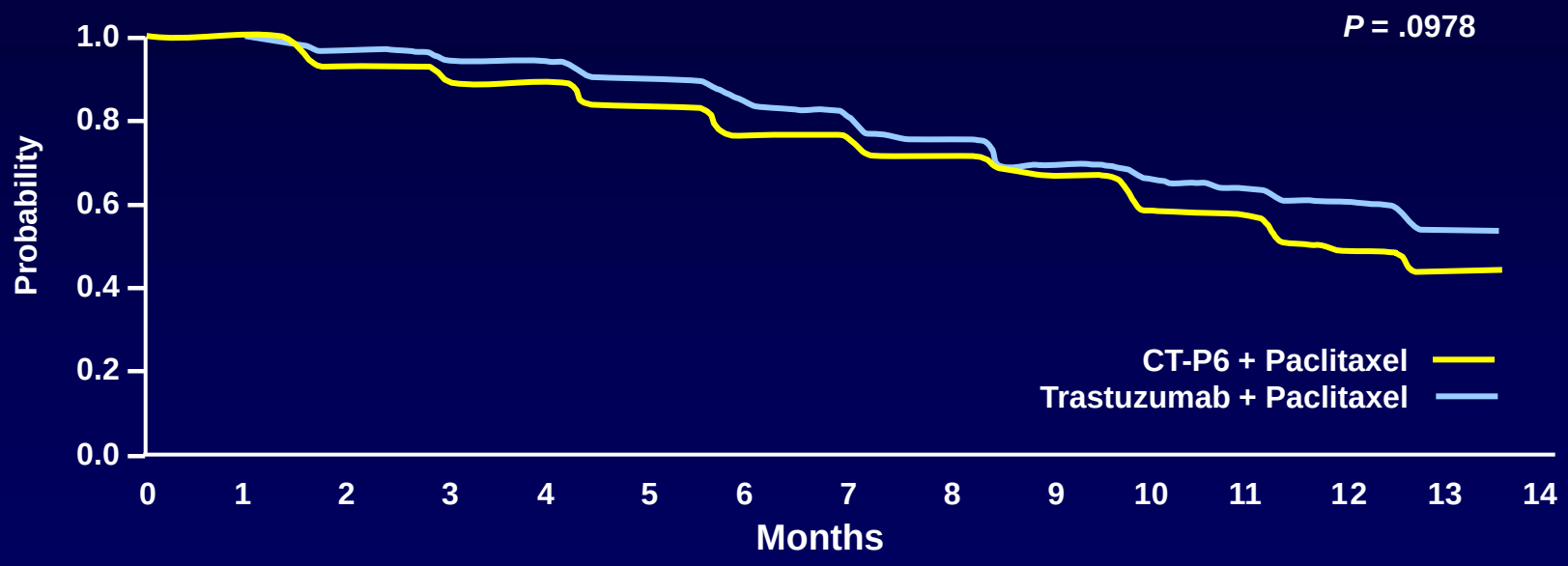


FAS, Full analysis set; PPS, per protocol patients set
Difference in proportion of complete response or partial response. Confidence interval estimated using the exact method.

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)

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

Extrapolation of Indications Only Possible if Immunogenicity is Investigated in the Most Sensitive Population

- Risk assessment of immunogenicity requires
  - Multidisciplinary approach
  - Related pivotal aspects that must be considered are
    - Rate of occurrence and clinical consequences of unwanted immunogenicity
    - If they can be prevented
    - If they can be measured
    - If they can be treated; is there a therapeutic alternative?
- In oncology setting it can be challenging
  - How to distinguish loss of clinical response due to natural progression (unavoidable) from neutralization by anti-mAb antibody response (potentially treatable)

* Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. London 24 May 2012. EMA/CHMP/BMWP/86289/2010

Conclusions

- Biosimilars of trastuzumab are under development
- The aim of clinical trials with biosimilar trastuzumab is to show equivalence and not patient benefit, as this was shown with Herceptin
- The neoadjuvant/adjuvant patient population may represent a homogeneous and sensitive population to establish similarity of biosimilar trastuzumab to Herceptin
- If biosimilars of trastuzumab are approved, several challenging issues will need to be addressed such as maintaining appropriate pharmacovigilance, extrapolating across indications, and automatic substitution and switching