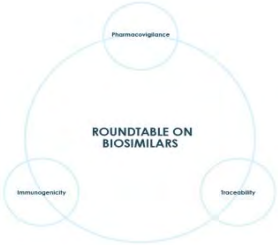
# Professor Joan Albanell, MD

- Professor of Oncology, Pompeu Fabra University, Spain
- Head of Medical Oncology Hospital del Mar, Spain
- Founding Member and Scientific Committee Coordinator, Spanish Breast Cancer Research Group
- Member and Coordinator of Biosimilars Working Group, Spanish Society of Medical Oncology

GaBI Scientific Meetings

ROUNDTABLE ON BIOSIMILARS
Pharmacovigilance, Traceability, Immunogenicity

15 November 2016, Real Academia Nacional de Farmacia, Madrid, Spain




# Oncologist perspective
# Antibody biosimilars in oncology: an analytical to clinical perspective

Professor Joan Albanell, MD, Spain

15 November 2016

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
*Building trust in cost-effective treatments*

Universidad de Alcalá

PPCI
Pro Pharma Communications International

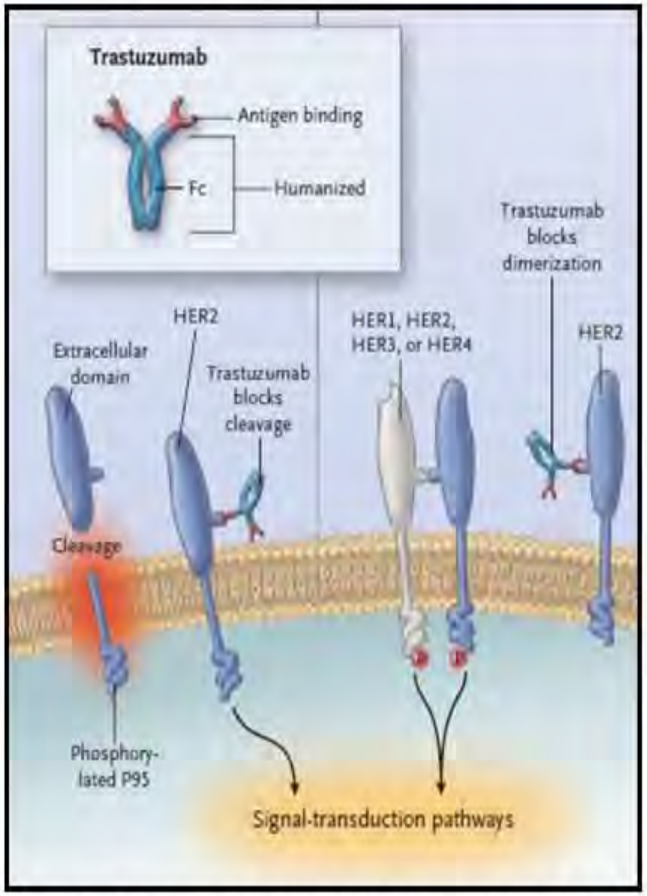
# Retos en el desarrollo de biosimilares en oncología: una perspectiva clínica

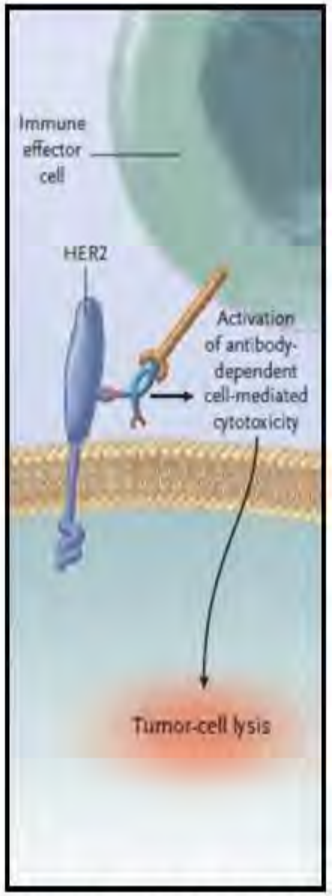
Joan Albanell
Servicio de Oncología Médica
Hospital del Mar, Barcelona

# SEOM Position on Biosimilar Antibodies

Unlike support therapy biosimilars such as erythropoietin and colony stimulating factors, which have easy to measure efficacy surrogate markers (haemoglobin concentrations, leukocyte levels), the development of antibody biosimilars poses significant challenges. This is due to the structural complexity of antibodies, their role in the treatment of a wide range of tumours, the limited correlation between efficacy surrogate markers and clinical benefits, and the heterogeneity of their mechanisms of action.

# Trastuzumab mechanisms of action are complex and their relative role in clinical activity largely uncharacterised

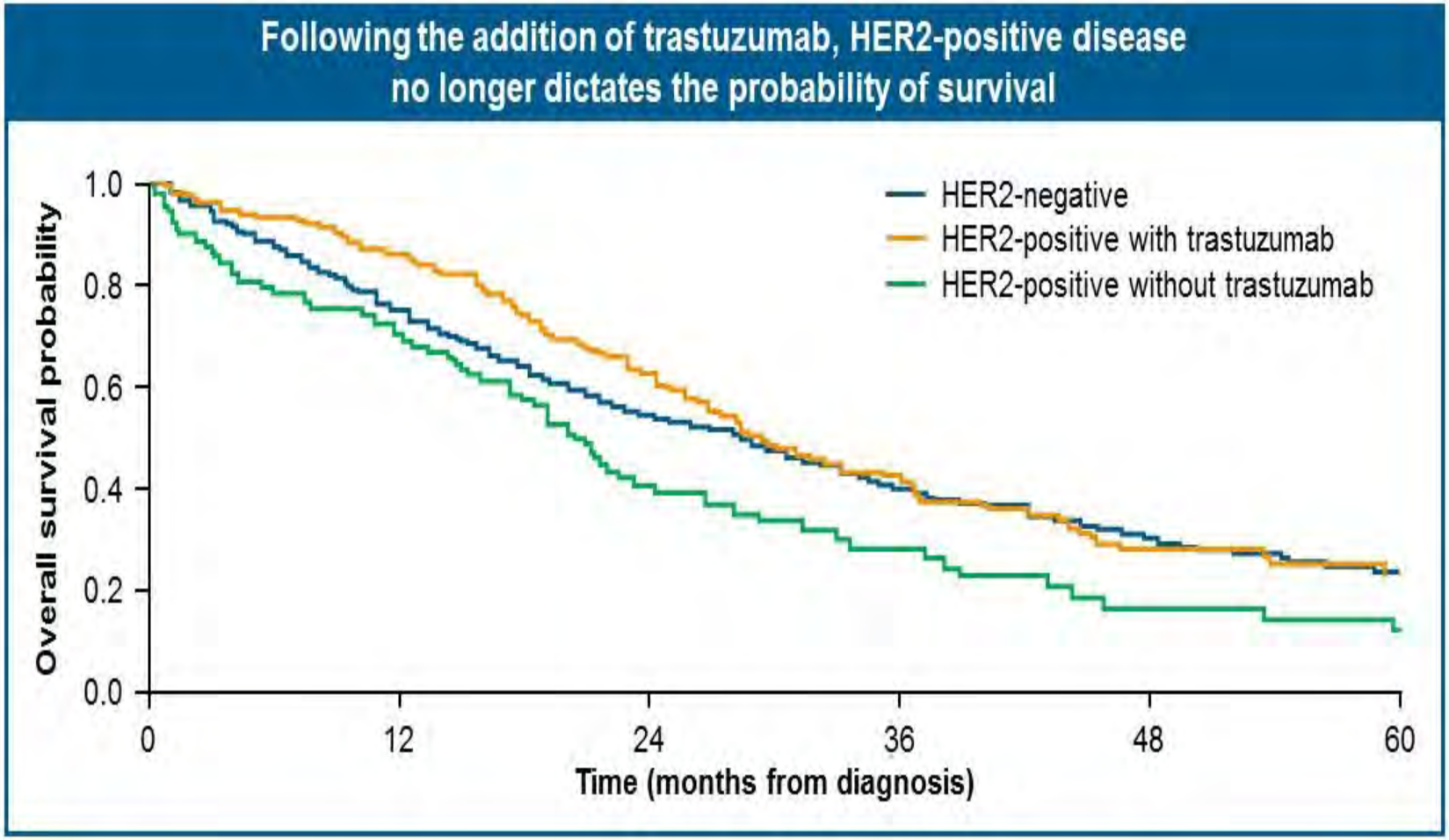



Junttila TT, et al. Cancer Cell 2009;15:429–40; Lane HA, et al. Mol Cell Biol 2000;20:3210–23; Lee H, et al. Cancer Res 2001;61:4467–73; Yakes FM, et al. Cancer Res 2002;62:4132–41; Molina MA, et al. Cancer Res 2001;61:4744–9; Pegram M, et al. Oncogene 1999;18:2241–51; Lewis GD, et al. Cancer Immunol Immunother 1993;37:255–63; Aguilar Z, et al. Oncogene 1999;18:6050–62; Clynes RA, et al. Nat Med 2000;6:443–6

Hudis CA. N Engl J Med 2007;357:39–51

# Trastuzumab improves the prognostic outcomes associated with HER2: clinical practice data




Dawood et al. J Clin Oncol 2010;28:92–98

# Adjuvant trastuzumab reduces the risk of relapse by 50%

*The New England Journal of Medicine*

October 2005;33:16

**Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer**

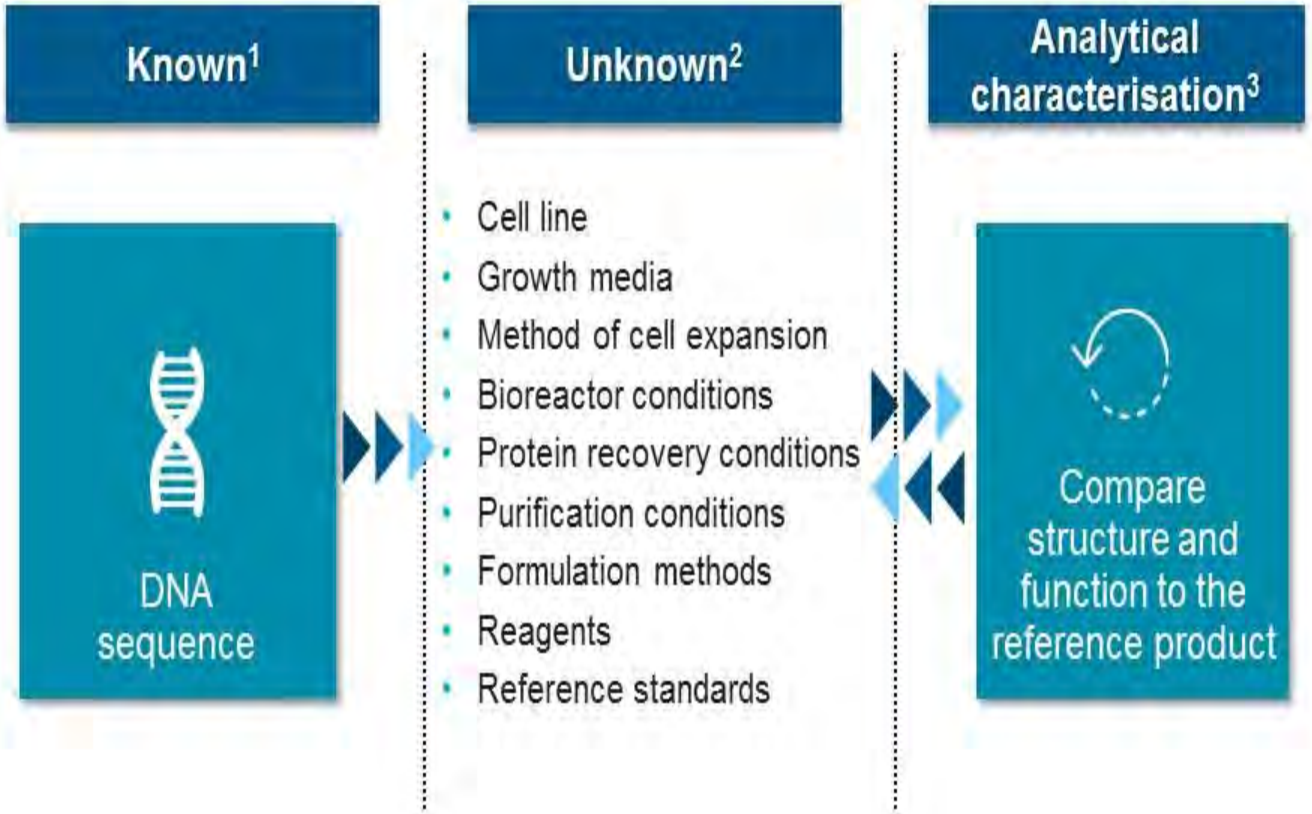
Martine J Piccart-Gebhart, Marion Procter, Brian Leyland-Jones, et al.

**Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer**

Edward H Romond, Edith A Perez, John Bryant, et al.

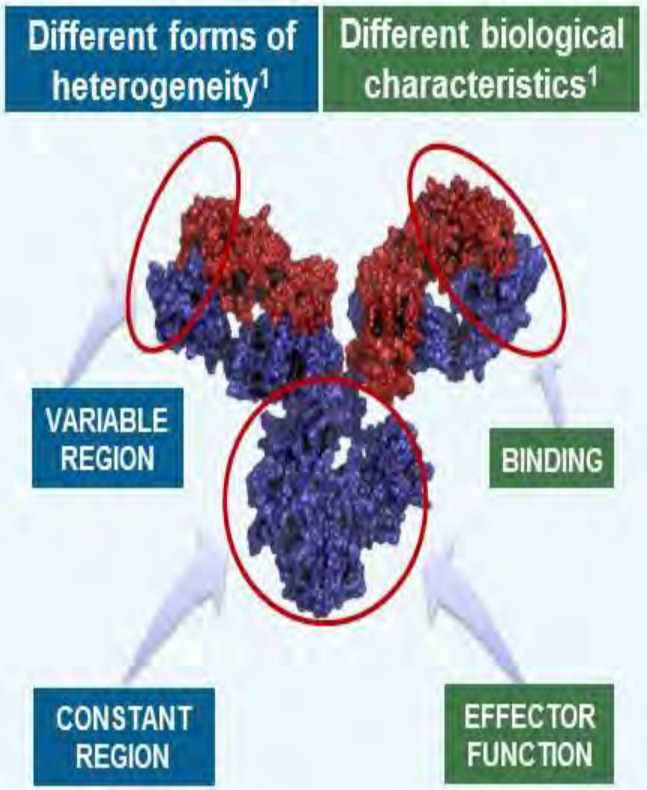
Piccart-Gebhart MJ, et al. N Engl J Med 2005;353:1659–1672;
Romond EH, et al. N Engl J Med 2005;353:1673–1684

# Biosimilar manufacturers have limited knowledge of the reference product




1. Roger SD. Nephrology (Carlton) 2006;11:341–346;
2. Mellstedt H, et al. Ann Oncol 2008;19:411–419;
3. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for Industry, 2015

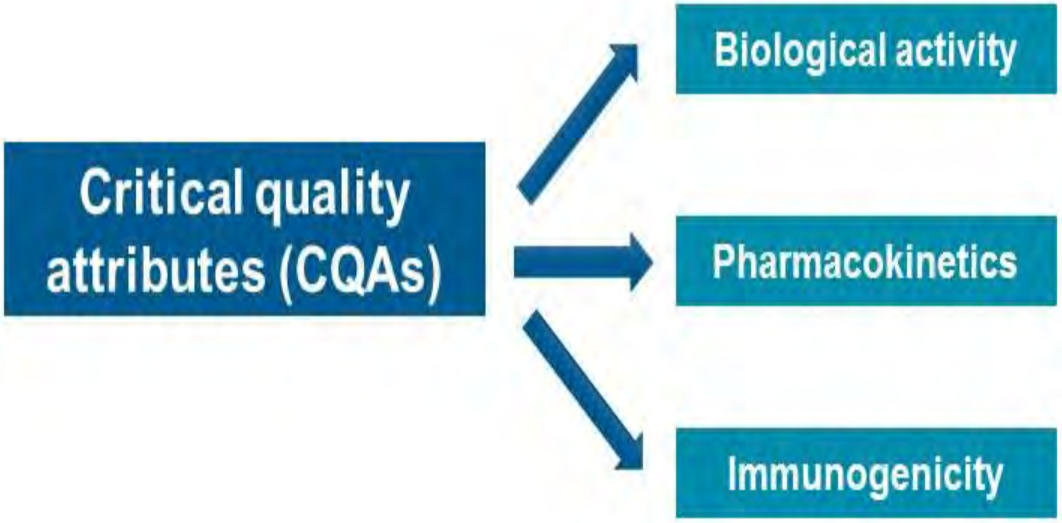
# Monoclonal antibodies (mAbs) are heterogeneous, complex proteins and sensitive to manufacturing conditions




- Manufacturing processes affect post-translational modifications[2–4]
  - Cell type and culture conditions
  - Purification
  - Raw materials
- Post-translational modifications can affect[5]
  - Mechanism of action
  - Bioavailability, clearance
  - Immunogenicity
  - Effector functions
  - Binding

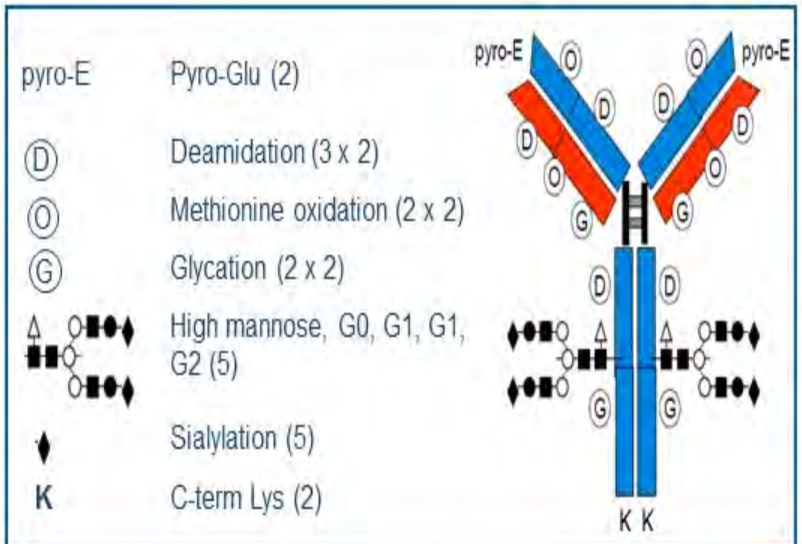
1. Jimenez AG, et al. Oral presentation at ICH GCG ASEAN Training Workshop on ICH Q5C, 2011;
2. Declerck P, et al. Pharm Res 2016;33:261–8; 3. Grampp G, et al. BioDrugs. 2013;27:305–16;
4. Blauvelt A, et al. Br J Dermatol 2016;174:282–6; 5. Dörner T, et al. Nat Rev Rheumatol 2015;11:713–24

# Analytical foundation of mAb biosimilars



# Glycosylation differences may lead to differences in biological function

## Antibodies are subject to post-translational modification, including glycosylation




Modifications may result in approximately $10^8$ potential variants[1,2]

| Examples of changes in Fc glycans | Biological effect |
|---|---|
| 20% loss of total sialic acid content[3] | 50% loss of circulating protein |
| Differential glycosylation[4] | Affects CDC and ADCC |
| Fucose deficiency[5] | Enhanced ADCC |
| Increase in terminal galactosylation[6] | Enhanced CDC |
| Increase in mannose[7] | Increase in clearance |
| Increase in terminal GlcNAc[6] | Increase in clearance; decrease in CDC |

1. Jefferis R. Biotechnol Prog. 2005;21:11-16; 2. Kozlowski S & Swann, P. Adv Drug Del Rev 2006;58:707-722;
3. Van Den Hamer CJ, et al. J Biol Chem.1970;245:4397-4402; 4. Wright A, et al. Trends Biotechnol.1997;15:26-32;
5. Shields RL, et al. J Biol Chem 2002;277:26733-26740; 6. Raju TS. Curr Opin Immunol. 2008;20:471-478;
7. Alessandri L, et al. MAbs. 2012;4:509-520.

CDC, complement dependent cytotoxicity; GlcNAc, N-acetylglucosamine

# Biosimilar mAbs: key clinical aspects

## Facts

Similar, but not identical, particularly glycosylation (immune response)

Complex mechanisms of action and insufficiently characterised

## Challenges

Clinical trial: sensitive population and endpoint?

Extrapolation?

Interchangeability?

# SEOM Position on Biosimilar Antibodies

SEOM's position on the possibility of **extrapolating** from a specific trial with a homogeneous population with a clinical endpoint capable of detecting differences in activity (defined as a sensitive endpoint), to other indications in which the drug's mechanisms of action, the disease biology, and the treatment objectives (for example, prolonging survival in metastatic disease in one indication and avoiding relapses or increasing the cure rate in early stage disease, in another one) can be different, is that it should be done **only on a case-by-case basis** and when the mechanism of action is clear.

# SEOM Position on Biosimilar Antibodies

SEOM's position is that since the biosimilar and the reference biologic are different drugs, **interchangeability should not be automatic at the time of dispensation and it can only be acceptable in certain cases, with clinical justification, if conducted by the prescribing physician**, who is also accountable for the treatment before the patient. The situation would be different if there were specific clinical studies proving the safety of interchangeability at an individual level, as regulated by the FDA. However, viability of these clinical trials is difficult.

# SEOM Position on Biosimilar Antibodies

SEOM agrees with the need to **prescribe by brand name** and, furthermore, requires that before introducing a biosimilar in a hospital, **adequate circuits** are established for prescription, dispensation, administration and registration using the brand name. **Pharmacovigilance** of biosimilars is regulated as obligatory at a European level to rule out differences with the original biologic in relation to efficacy or toxicity among the real population.