

Biosimilar Extrapolation in Breast Cancer

Romano Danesi, MD, PhD

Department of Clinical and Experimental Medicine
University of Pisa
Pisa, Italy

EJC SUPPLEMENTS II, NO. 3 (2013) I-II



ELSEVIER

Summary of Approval Process for Small-Molecule Generics, New Biologic Agents, and Biosimilars

New biologic agent (full dossier)

- Individual quality assessment
- Full preclinical program
- Phase I
- Phase II
- Phase III in all indications
- Risk-management plan

Biosimilar (reduced dossier)

- Individual quality assessment
- Comprehensive comparison with reference product
- Abbreviated preclinical program (tolerance, PK/PD)
- Phase I PK/PD study
- Phase III study in a sensitive, representative indication
- Risk-management plan

review

Annals of Oncology 19: 411–419, 2008
doi:10.1093/annonc/mdm345
Published online 14 September 2007

The challenge of biosimilars

H. Mellstedt^{1*}, D. Niederwieser² & H. Ludwig³

What is extrapolation?

Extrapolation involves the approval of a drug for indications for which it has not been evaluated in clinical trials



Comparative safety and efficacy studies (phase I and III) of a biosimilar in a single disease or specific patient population

(Indication A)



Approval in indication A



Extrapolation to other diseases or patient populations?



Indication B



Indication C



Indication D

Definitions

- Extrapolation plays a role in drug development and has a rational basis, but it is only applicable in limited circumstances, such as new indications in closely related diseases.
- The EMA has generally endorsed the concept of data extrapolation for biosimilars with the appropriate justification.
- The rationale is that if the biosimilar shows adequate comparability to the innovator product for one indication, it may be reasonable to extend the approval of the biosimilar to all the indications of the innovator product.
- The manufacturer must provide adequate scientific explanation, although 'adequate' is not always well defined. If the mechanism of action differs between indications, additional clinical data must be provided.

Extrapolation in Filgrastim Biosimilars

All of the biosimilar products' indications are extrapolated from CIN or from PK/PD data

Indication; Includes some pediatric use, refer to SPCs	Use*	Neupogen®	XM02	Zarzio®	Nivestim™	Neulasta®	Granocyte®
Reduction of CIN	85%	X	X	X	X	X	X
Neutropenia after myeloablative therapy followed by bone marrow transplantation	~7%	X	X	X	X		X
Mobilization of PBPCs for transplantation	~8%	X	X	X	X		X
Severe congenital, cyclic, or idiopathic neutropenia	<1%	X	X	X	X	X	
Neutropenia in advanced HIV	<1%	X	X	X	X	X	

•Estimated, may vary by country
CIN, chemotherapy induced neutropenia

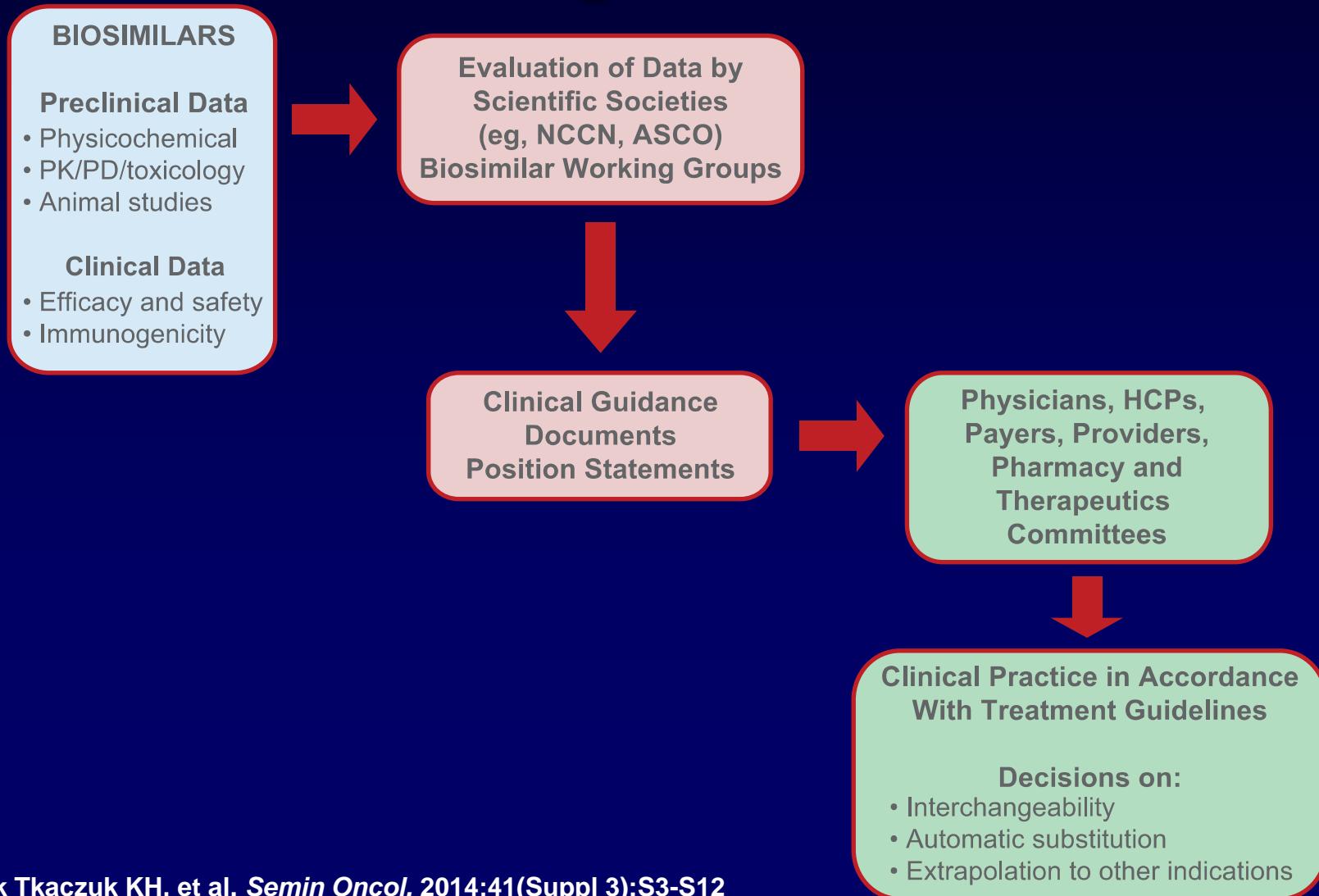
Extrapolated

Biosimilars in Oncology: From Development to Clinical Practice

Katherine H. Rak Tkaczuk^a and Ira Allen Jacobs^b

Seminars in Oncology, Vol 41, No 2, Suppl 3, April 2014, pp S3-S12

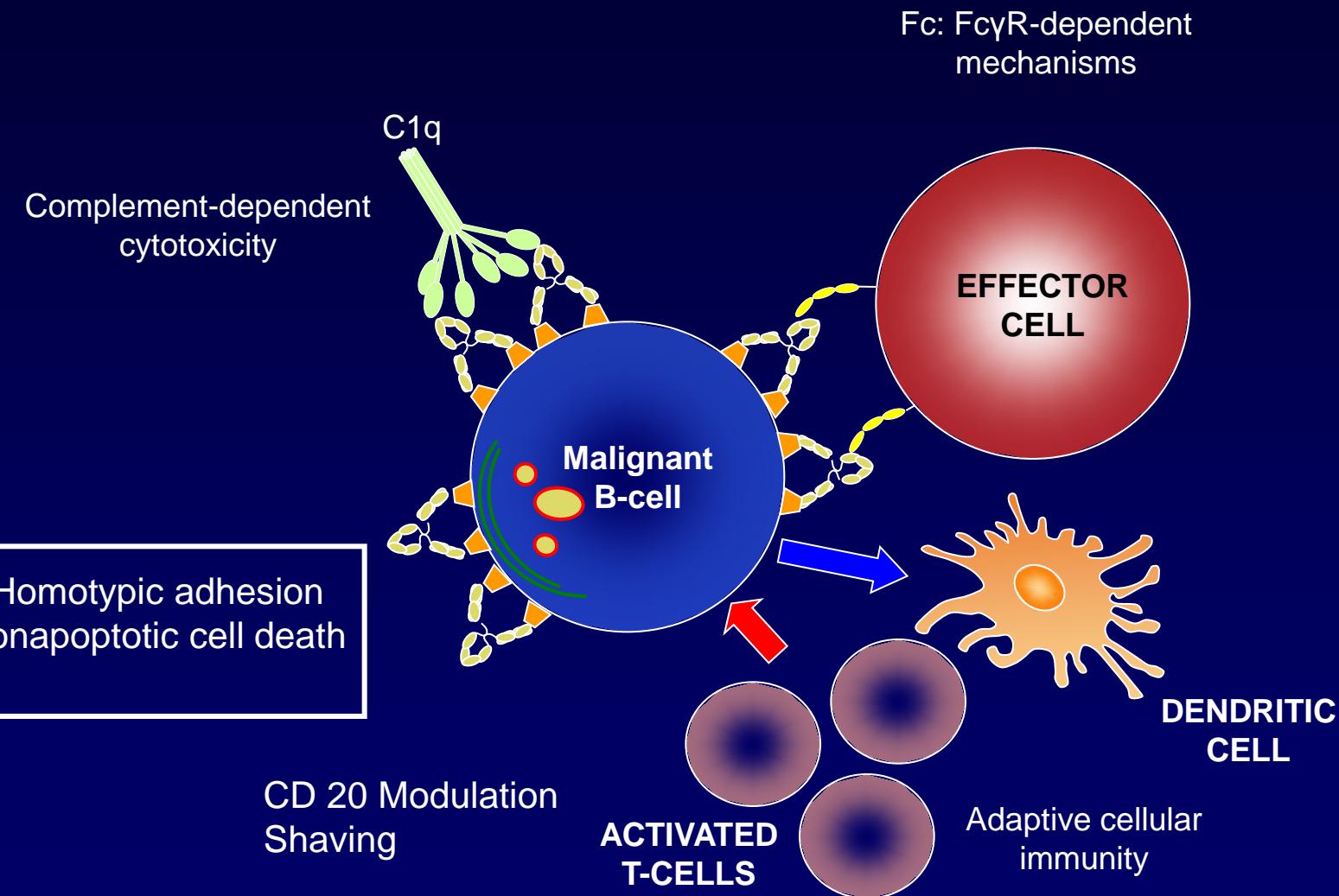
Potential Role of Scientific Societies in Evaluating Biosimilar Data



Criteria for Extrapolation of Clinical Data for Biosimilars to Other Indications of the Ref Product

- Does the product meets criteria for biosimilarity with the reference product (eg, purity, safety, and potency in one condition of use for the reference product)?
- Is a similar mechanism of action expected for the proposed indication (eg, type and location of cell target, relationship between product structure and target/receptor interactions, signaling pathway)?
- Can similar PK be expected in the patient population?
- Is there any anticipated difference in TOX in the desired patient population?
- Are there other factors that may influence safety and efficacy in the target population for the new indication (eg, comorbidities, concomitant medications)?

Monoclonal Antibodies Have Different Mechanisms of Action



acology

journal homepage: www.elsevier.com/locate/yrtpch



Biosimilars approval process

Leyre Zuñiga, Begoña Calvo *

FDA Guideline on Extrapolation

- The draft FDA guidance allow the use of clinical efficacy and safety data for one indication to be extrapolated to other indications for the reference biologic.
- In general, extrapolation of data may be allowed for biosimilars as long as sufficient justification can be provided for the new indication (eg, similar anticipated mechanism of action for the biosimilar) and a rationale for similar PK, efficacy, safety, and immunogenicity can be provided for the new target population.

EMA Guideline on Extrapolation

- Under certain circumstances, the EMA allows extrapolation of indication, ie, a biosimilar that has demonstrated comparable safety and efficacy in the “most sensitive” indication can be assumed to be able to extrapolate that safety and efficacy to other indications of the reference product.
- However, this extrapolation is only allowed if the indications share the same mode of action and if it is “appropriately justified by current scientific knowledge,” without conducting specific clinical studies for each of those indications (EMEA/CHMP/BMWP/42832/05).

EMA Guideline on Extrapolation

- In case the originally authorized medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.
- Justification will depend on, eg, clinical experience, literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications.
- Possible safety issues in different subpopulations should also be addressed. In any case, the company should justify the approach taken during the development of the product (EMEA/CHMP/BMWP/42832/05).

Extrapolation of Indication

- The possible extrapolation of therapeutic equivalence to other indications can only be performed under a recognized scientific approach under very strict principles.
- Extrapolation from one indication to another must remain a case-by-case approach (the product-specific guidelines should address the conditions for the product concerned).
- The development of the first indication of the biosimilar must be related to a complete and well-designed clinical program, and extrapolation to another indication has to be included in the corresponding product-specific guidelines with the pre-definition of the statistical approach.

Extrapolation of Indication

- Safety cannot be extrapolated at any indication.
- Until such time as the necessary data are available, ie development data correlated to post-authorization clinical and pharmacovigilance data, clinical studies to evaluate safety should be undertaken in order to ensure that a proper benefit-risk evaluaion is performed on an on-going basis until the appropriate dataset is available.

icals 39 (2011) 270–277

Biosimilars clinical development program: Confirmatory clinical trials: A virtual/simulated case study comparing equivalence and non-inferiority approaches

Mark P. Fletcher^{*,1}

The Issue of Extrapolation of Indication

- Demonstration of equivalence or non-inferiority of the biosimilar in one indication should not routinely allow extrapolation to other indications for which the RBP has been approved without additional clinical data. Extrapolation may be reasonable if all of the following conditions are fulfilled:
- The relevant mechanism of action and targets are the same
- Safety and immunogenicity of the biosimilar have been well characterized and there are no additional safety issues expected for the extrapolated indication(s), for which clinical data on the SBP is not being provided; eg, immunogenicity data in immunosuppressed patients would not allow extrapolation to an indication in healthy subjects;
- If the efficacy trial used a non-inferiority study design and demonstrated safety and efficacy of the biosimilar compared to the reference product, the applicant should provide convincing arguments that this finding can be applied to the extrapolated indications.

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?

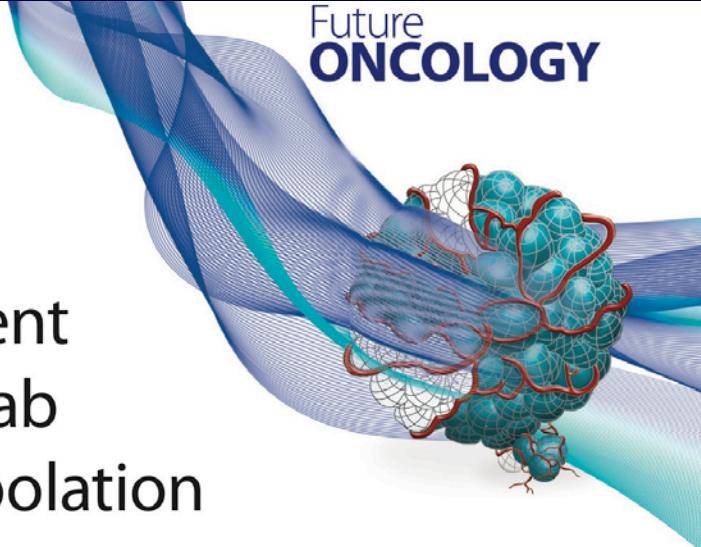
RESEARCH ARTICLE

For reprint orders, please contact: reprints@futuremedicine.com

Neoadjuvant breast cancer treatment as a sensitive setting for trastuzumab biosimilar development and extrapolation

Christian Jackisch^{*1}, Frank A Scappaticci², Dominik Heinzmann³, Fabio Bisordi³, Thomas Schreitmüller³, Gunter von Minckwitz⁴ & Javier Cortés⁵

Future
ONCOLOGY



**Slides Removed at
Presenter's Request**

Detection of Anti-Drug Antibodies in the BO22227 Study

Patients Tested Positive For Anti-Drug Antibodies Post-baseline (%; n/N)	Intravenous arm n = 296*	Subcutaneous arm n = 295*	Arms pooled N = 591
All	71 (21/296)	14.6 (43/295)	10.8 (64/591)
	<i>In patients testing positive for anti-drug antibodies</i>		
Positive on-treatment only	57.1 (12/21)	51.2 (22/43)	53.1 (34/64)
Positive during treatment-free follow-up only	38.1 (8/21)	37.2 (16/43)	37.5 (24/64)
Positive during both treatment and treatment-free follow-up	4.8 (1/21)	11.6 (5/43)	9.4 (6/64)

*Patients with at least one post-baseline immunogenicity testing

Conclusions of the Study

- tpCR as an endpoint allows the design of trials with feasible sample sizes.
- Characterization of immunogenicity may be feasible during a treatment-free follow-up, which occurs in the early breast cancer setting.
- Low rates of anti-drug antibodies, as well as limited sample size and follow-up time will likely limit the full characterization of the impact of immunogenicity on (long-term) clinical outcomes.
- Similarity in efficacy, safety, and immunogenicity between the trastuzumab reference product and a biosimilar candidate in the neoadjuvant-adjuvant setting would provide a better basis for extrapolation to the HER2+ metastatic breast cancer setting than the reverse process.
- Continued follow-up of immunogenicity and long-term clinical outcomes is critical to ensure comparable efficacy and safety.

Conclusions

- Because biosimilars are approved through an abbreviated clinical trial program and may not be tested in all indications of the originator, extrapolation of indications is an issue of great concern.
- Supporters of extrapolation suggest that extrapolation of scientific evidence should be seen as a logical consequence of the comparability exercise principle, which is founded in physiochemical and biological characterization.
- Any uncertainties should be addressed via comparative clinical data.
- Furthermore, extrapolation must be viewed not as a “bonus” for the developer of the biosimilar, but rather as the applicant’s burden to collect and demonstrate stringent scientific evidence.
- Finally, if extrapolation of data is allowed, the package labeling should explicitly state this along with the clinical data used to support extrapolation.