Progetto CANOA

CARCINOMA MAMMARIO:

QUALI NOVITÀ PER IL 2014?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

III Sessione "Biosimilari Da Anticorpi Monoclonali:
Le Evidenze Derivanti Da Studi Randomizzati"

Quali Problematiche?

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Pescantina (VR), 21 Marzo 2014

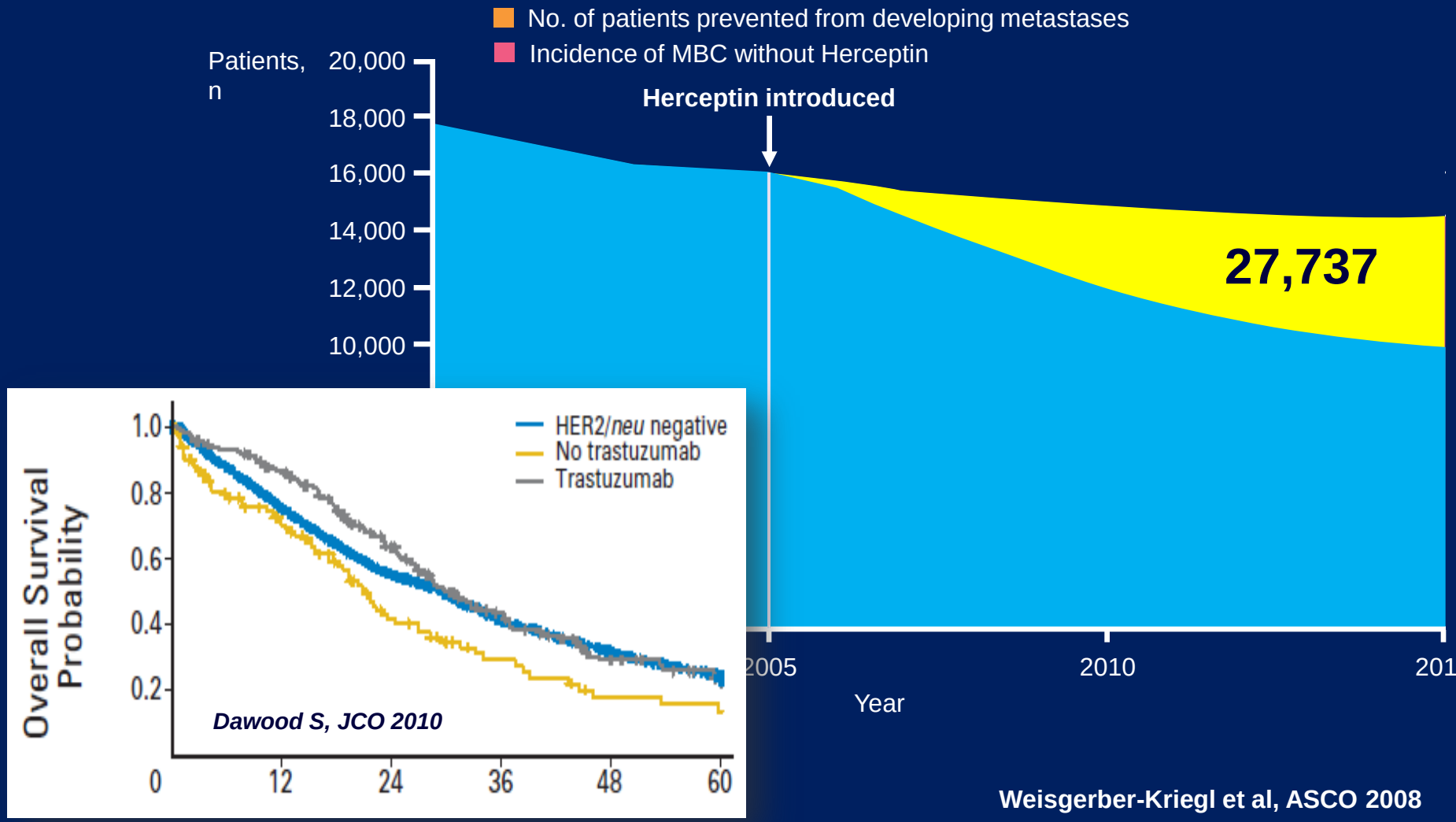
Quindi……Problematiche

- **Del Contesto clinico**
- **Del farmaco ‘antagonista’**
  - Trastuzumab
- **Intriseche allo sviluppo di mAb biosimilari**
- **Regolatorie**
  - (Altri) end-points da valutare
  - Post-marketing plan
  - Estrapolazione
  - Sostituzione automatica

Quindi……Problematiche

- **Del Contesto clinico**
  - ……..nell'interpretazione di una equiefficacia ***(end-point concordato con enti regolatori)*** di CT-P6 vs. Trastuzumab (in combinazione con Paclitaxel) nel **carcinoma della mammella avanzato HER2 positivo**
- **Del farmaco 'antagonista'**
  - In questo scenario, qual è la performance clinica di Trastuzumab?

Adjuvant Trastuzumab predicted to prevent recurrence in almost 28,000 patients over a 10-year period in the 5 major EU countries



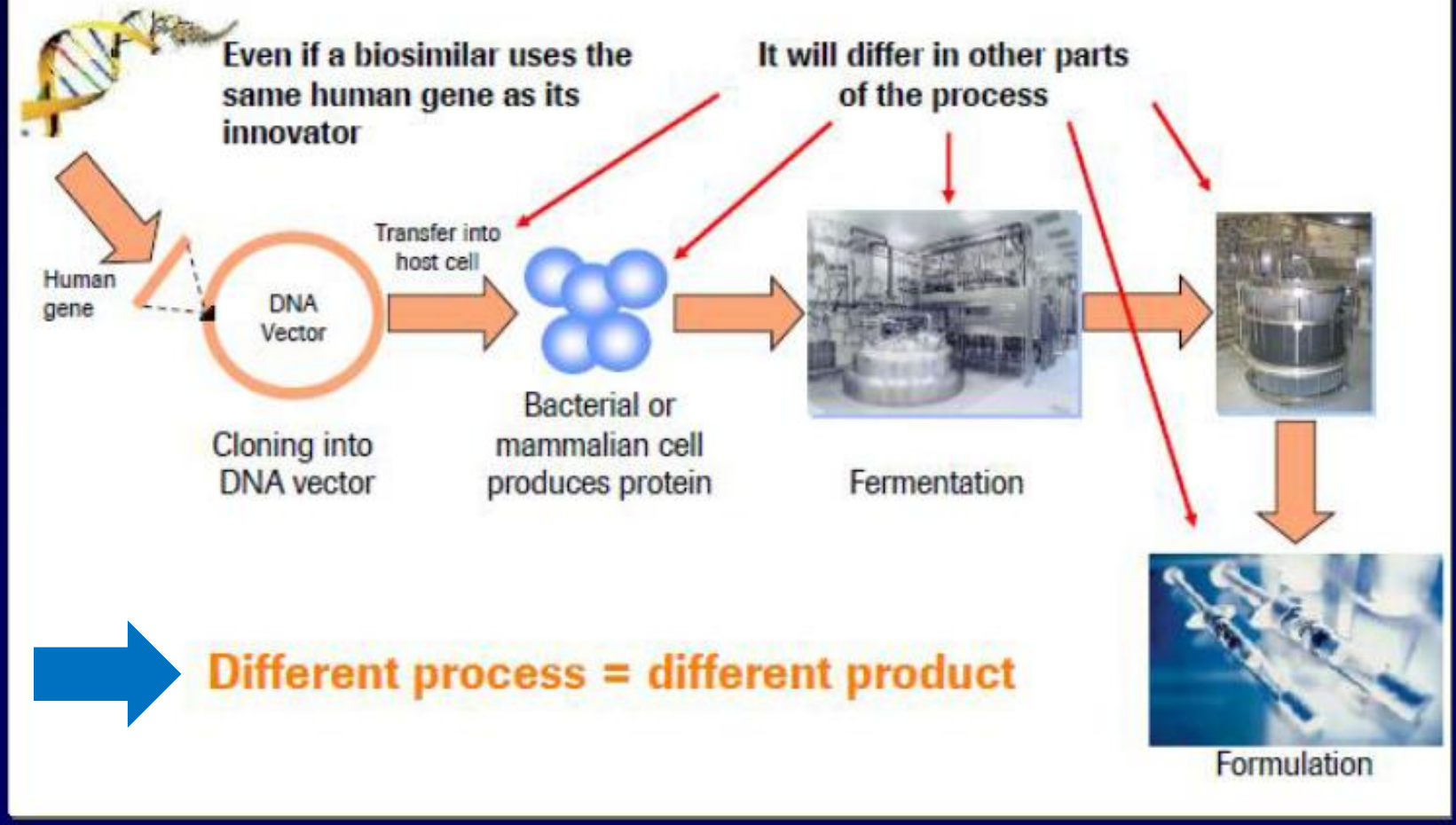
Weisgerber-Kriegl et al, ASCO 2008

Generici & Biosimilari

- **GENERICO**:
  - Copia di un farmaco di sintesi chimica il cui processo è ***standardizzato*** e ***costantemente riproducibile*** grazie alle metodiche analitiche attualmente disponibili;
- **BIOSIMILARE**:
  - Proviene da un ***processo produttivo biotecnologico*** che presenta nelle varie fasi ***un certo grado di variabilità*** tale per cui ***non è una copia esatta del prodotto originale, ma una sua riproduzione***, la cui qualità dipende da vari fattori.

FARMACI BIOTECNOLOGICI E BIOSIMILARI Aiom

Manufacturing of Biologic Drugs: Unique & Complex Process



- It is impossible to make the exact copy

Source: PRIME Oncology Nov. 2013

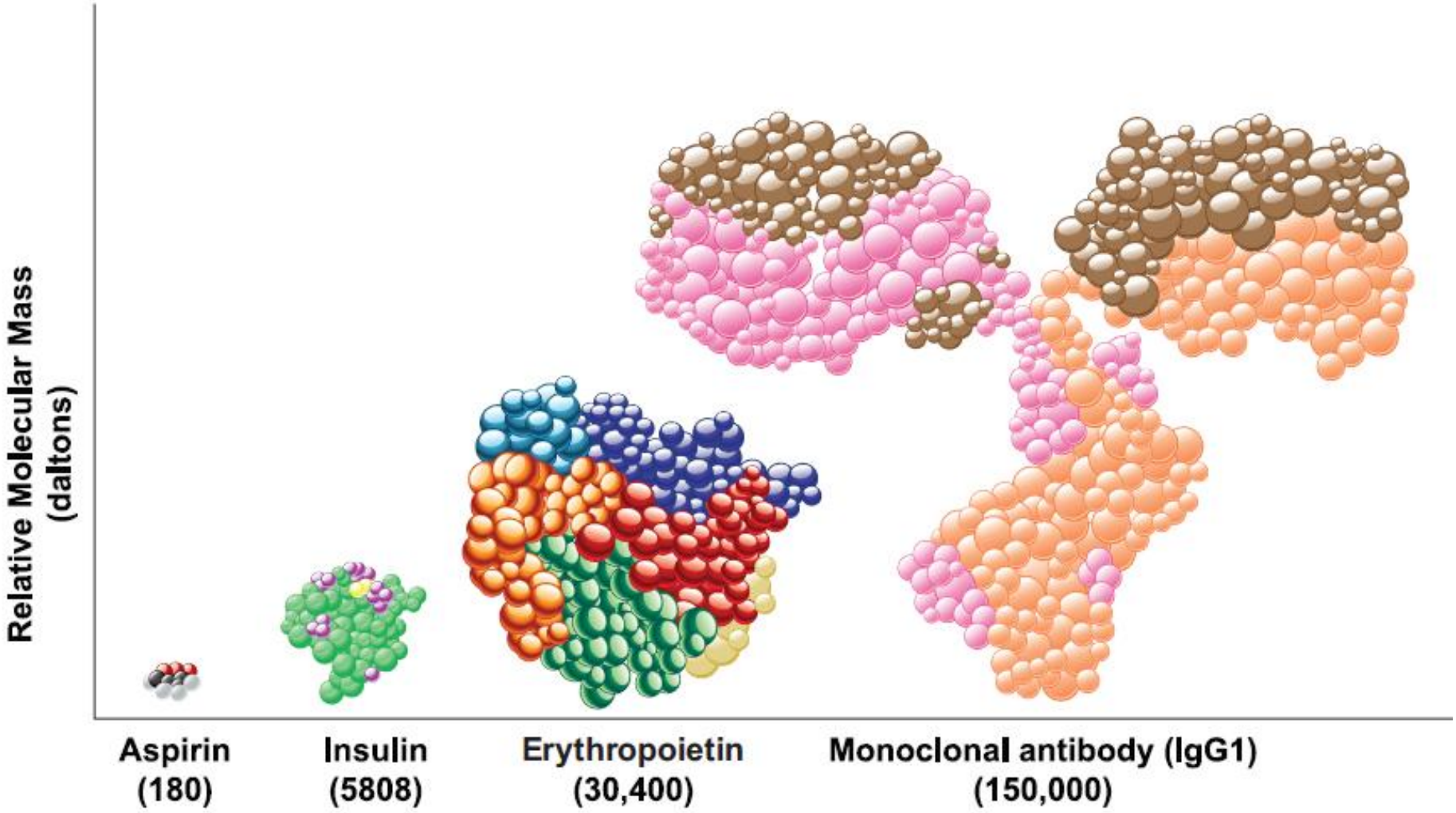
Diversi gradi di complessità

- ……La struttura molecolare dipende dal processo **(*'the product is the process'*: cioè il processo produttivo determina l'unicità del prodotto)**.
  - Ne consegue che la stessa molecola ottenuta da aziende diverse (o dalla stessa azienda in seguito a modifiche di processo) può presentare ***modificazioni strutturali significative*** e quindi ***differenti caratteristiche di sicurezza ed efficacia***.
- I farmaci biologici, per la ***variabilità intrinseca delle molecole*** e per la ***complessità delle tecniche di produzione***, sono particolarmente difficili da caratterizzare e da riprodurre……

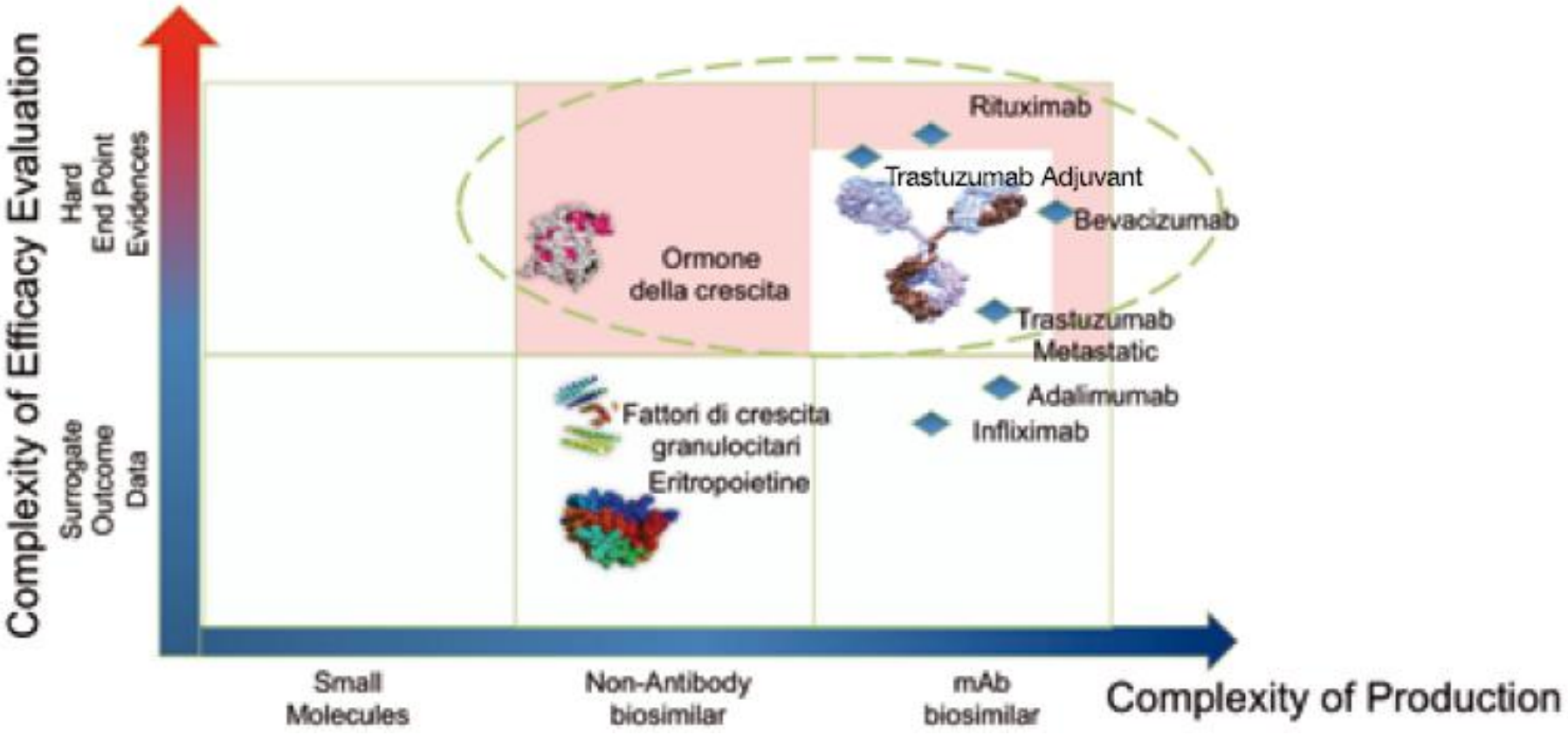
FARMACI BIOTECNOLOGICI E BIOSIMILARI Aiom

Clinical considerations for biosimilar antibodies

*Håkan Mellstedt**



Are all '*Biosimilars*'…..*Similar*?



FARMACI BIOTECNOLOGICI E BIOSIMILARI Aiom

EMA [in dir. 2004/27/CE]

- ……Per i farmaci biosimilari, ***possono*** essere richiesti:
  - **Studi comparativi di PK e PD** con il prodotto di riferimento
  - **Trial comparativi sull'efficacia clinica**, insieme a valutazioni **sull'immunogenicità**:
    - studi di equivalenza con margini di equivalenza pre-specificati e clinicamente giustificati.
  - Un **Pharmacovigilance Plan** per i due anni successivi alla commercializzazione**.**

Se l'originator ha più di un'indicazione, l'efficacia e la sicurezza del biosimilare devono essere confermate o, se necessario, dimostrate separatamente per ciascuna delle indicazioni asserite.

FARMACI BIOTECNOLOGICI E BIOSIMILARI Aiom

‘Esercizio di Comparabilità’

Dossier	*Generici*	*Biosimilari*
Modulo 1 Informazioni amministrative	Completo	Completo
Modulo 2 Riassunti dei moduli successivi	Completo	Completo
Modulo 3 Qualità del prodotto	Completo	Completo + Esercizio di comparabilità*
Modulo 4 Relazioni non cliniche	Omesso / Referenze bibliografiche	Risultati delle prove precliniche + Esercizio di comparabilità*
Modulo 5 Relazione sugli studi clinici	Studio di bioequivalenza / biowaiver	Risultati delle sperimentazioni cliniche + Esercizio di comparabilità*

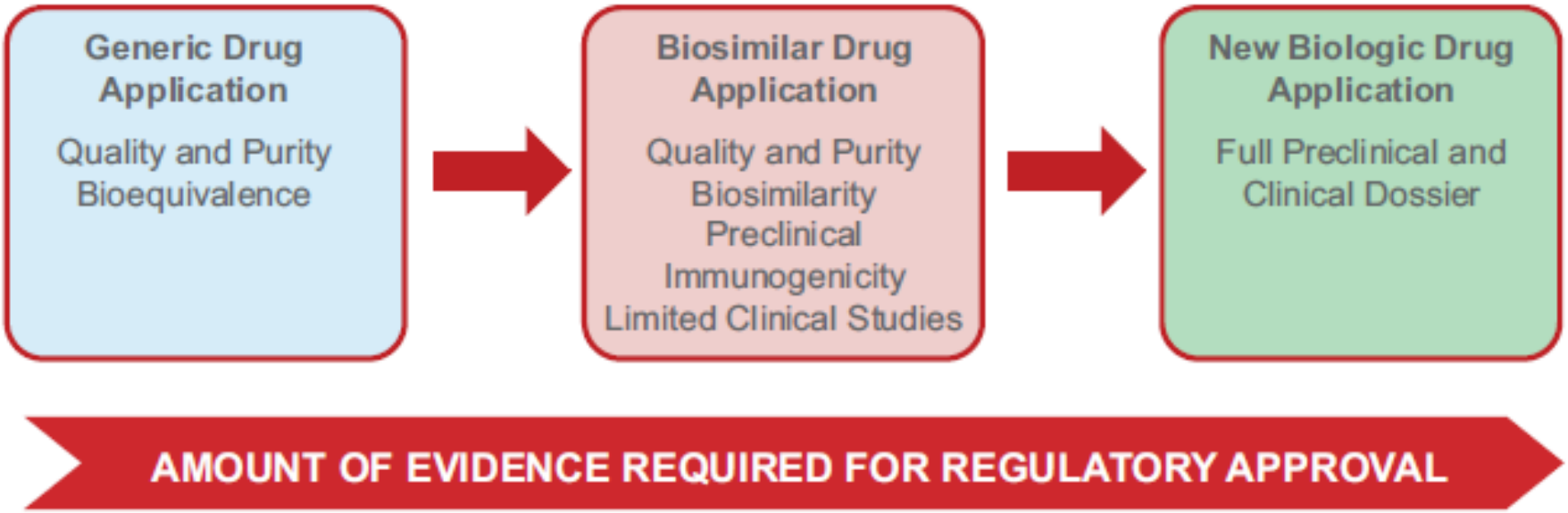
*L’esercizio di comparabilità deve essere fatto con un medicinale di riferimento autorizzato in Europa

- ‘***similarità throughout***’ (‘***in tutto***’):
  - il prodotto biosimilare non deve presentare ***alcuna differenza clinica significativa*** rispetto all’originatore.

Table 1 – Summary of approval process for small-molecule generics, new biologic agents, and biosimilars [2]

	Small-molecule generic	New biologic agent (full dossier)	Biosimilar (reduced dossier)
Quality	• Individual quality assessment • Comparison with reference product	• Individual quality assessment	• Individual quality assessment • Comprehensive comparison with reference product
Pre-clinical	• No data required	• Full pre-clinical program	• Abbreviated pre-clinical program (tolerance, PK/PD)
Clinical	• Bioequivalence study	• Phase I • Phase II • Phase III in all indications • Risk-management plan	• Phase I PK/PD study • Phase III study in a sensitive, representative indication • Risk-management plan

EJC SUPPLEMENTS 11, NO. 3 (2013) 1–11



Seminars in Oncology, Vol 41, No S1, February 2014, pp S15-S25

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. Available at: http://ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Accessed 18 November 2013.

Source: PRIME Oncology Nov. 2013

Clinical Trials of Biosimilars Are Different From Those of Originators

	Biosimilar	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**

Source: PRIME Oncology Nov. 2013

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 18 November 2013.

Source: PRIME Oncology Nov. 2013

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***.
  - **….but we are (generally) dealing with equivalence/non-inferiority trials**
- 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
  - **True in particular if we choose ORR!!!!!**

***MODIFIED*: Source: PRIME Oncology Nov. 2013**

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**

***MODIFIED*: Source: PRIME Oncology Nov. 2013**

Ongoing Phase III Trials of Trastuzumab Biosimilars

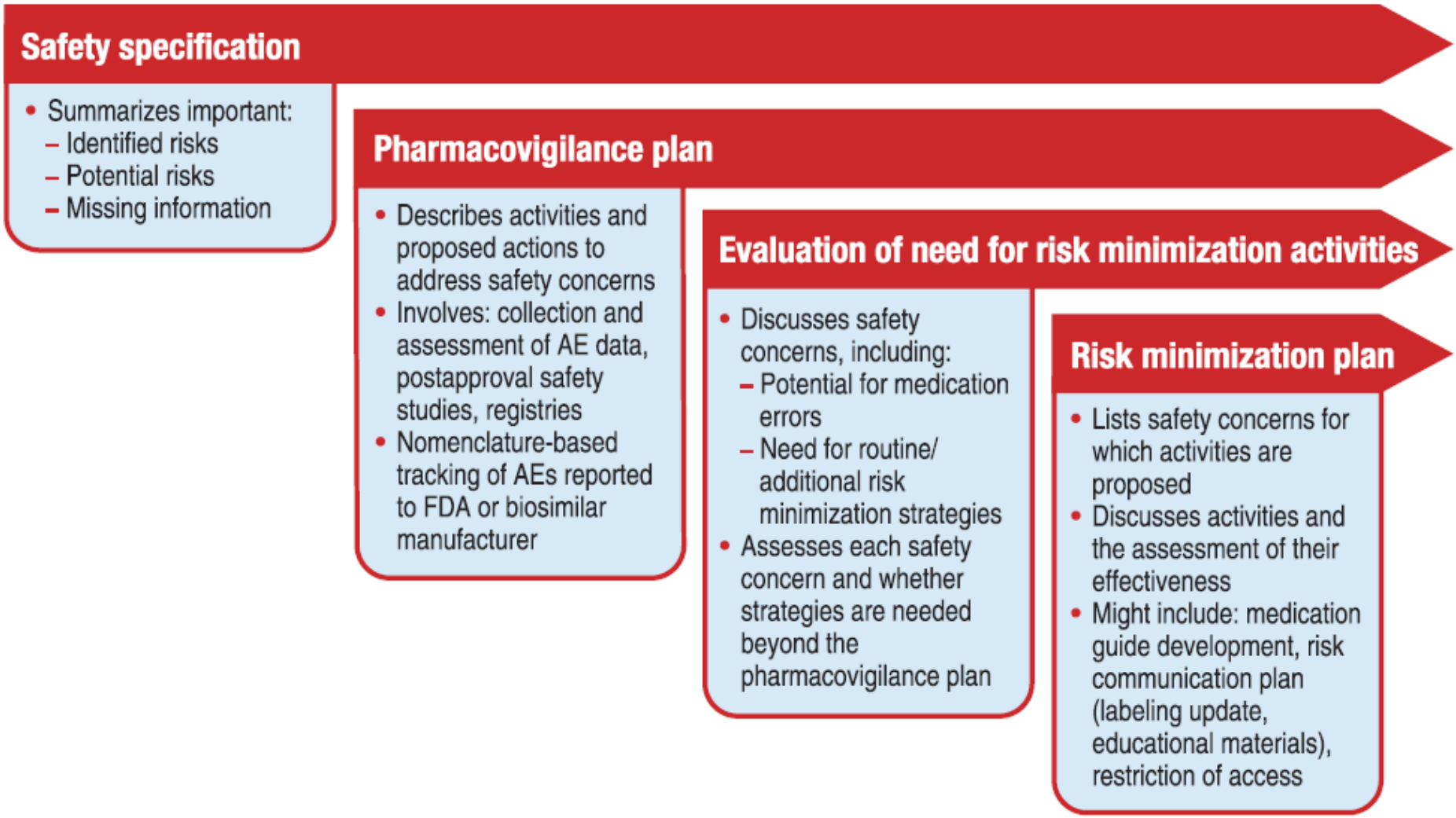
	ABP-980 (Amgen)	BCD-022 (Biocad)	PF-05280014 (Pfizer)*
Trial identifier	NCT01901146	NCT01764022	N/A
Trial design	Randomized double-blind	Randomized	Randomized double-blind
Comparator	Herceptin®	Herceptin®	Herceptin®
Disease	EBC	MBC	MBC
Chemo	Epirubicin, Cyclophosphamide, Paclitaxel	Paclitaxel	Paclitaxel
Endpoints	pCR	RR, PK Safety, Immunogenicity	
No of pts	588	110	?
Status	On hold (quality issues)	Ongoing	Enrollment expected Winter 2013/14

*Ewesuedo R, et al. To be presented at SABCS 2013: Abstract OT1-1-03.

Source: PRIME Oncology Nov. 2013

Biosimilar Safety Considerations in Clinical Practice

Edwin Choy[a] *and Ira Allen Jacobs*[b]



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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

Source: PRIME Oncology Nov. 2013

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 EBC population to the metastatic population is possible ***while extrapolation from the MBC to the EBC population may represents a risk for the patients***

***MODIFIED*: Source: PRIME Oncology Nov. 2013**

What May Be the Most Sensitive Patient Population for Biosimilar Trastuzumab Trials?

Topic	Metastatic Population
PK	✘ Affected by patient's health status & tumor burden
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, prior use of anti-Her 2 drug, performance status) • Population with heterogeneous characteristics affecting final clinical outcome.
Immunogenicity	✘ Immune system affected by performance status and concomitant chemotherapies received

***MODIFIED*: Source: PRIME Oncology Nov. 2013**

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

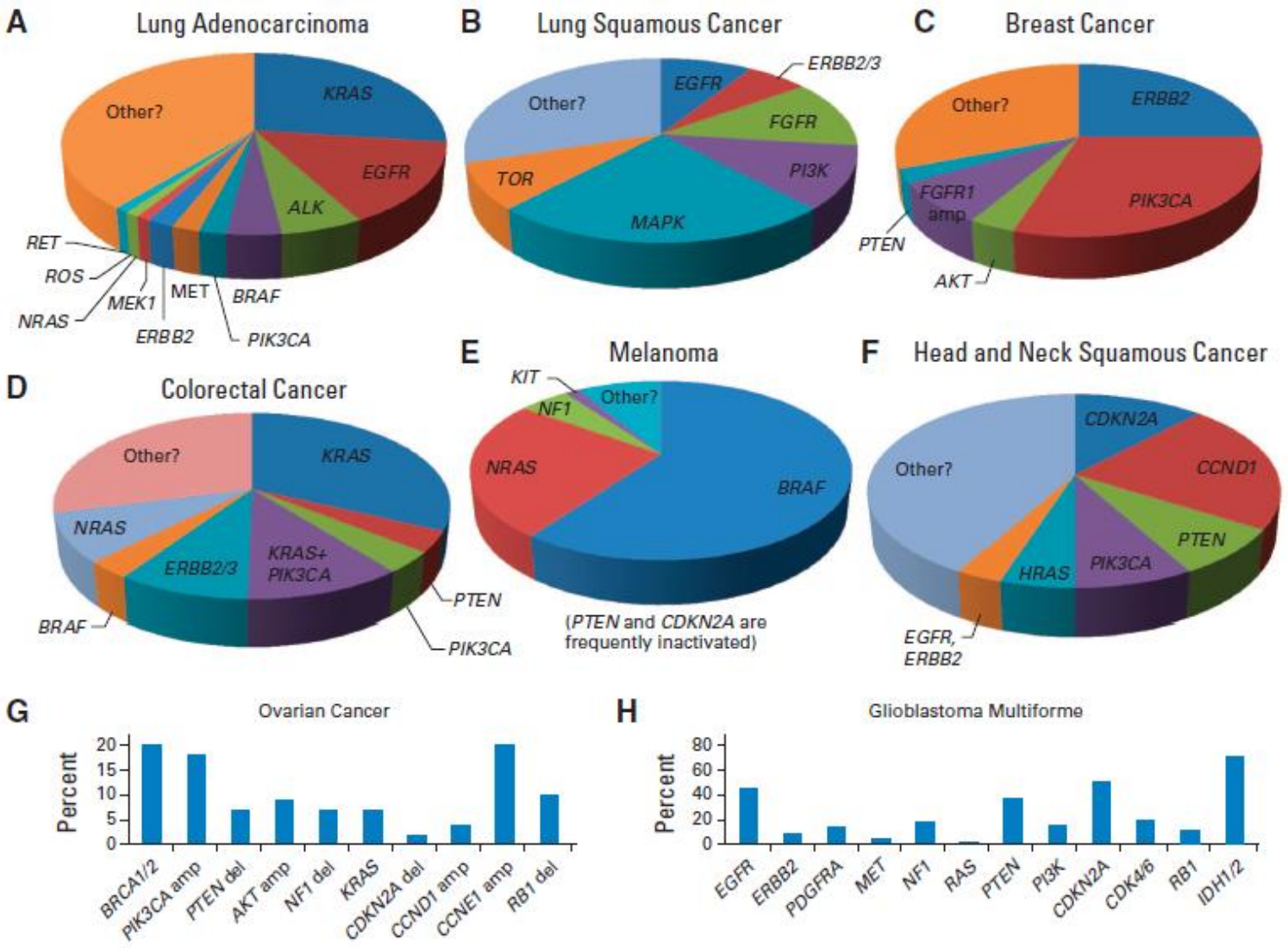
Source: PRIME Oncology Nov. 2013

Substitution in the EU: A National Prerogative

Niederwieser D, et al. *Eur J Haematol.* 2011;86(4):277-288; Czech Society of Oncology. Available at: http://www.linkos.cz/press-releases/opinion-of-the-czech-society-for-oncology-on-the-possibility-of-biosimilar-substitution/. Accessed October 2013; Generics and Biosimilars Initiative. Available at: http://gabionline.net/Biosimilars/News/Greece-says-no-to-automatic-substitution-of-biologicals. Accessed October 2013; Baumgartel C. *GaBI Journal* 2013;2:8.

Source: PRIME Oncology Nov. 2013

…..we are referring to *Sensitive* and *Homogenous* patients' Population



The Future of Drug Development? Seeking Evidence of Activity of Novel Drugs in Small Groups of Patients

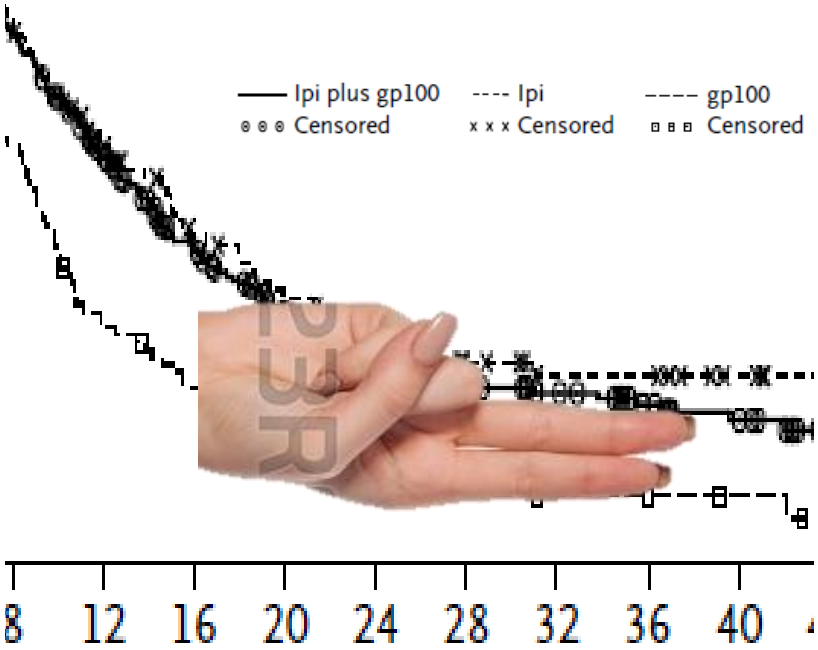
- Given the ***growing fragmentation*** of all classic tumor types into small subgroups, it is essential to:
  - obtain consensus regarding **the best ways to establish the activity of new treatments in rare molecular subsets**.
- Randomized trials still provide us ***with the highest level of certainty***.
- What circumstances could make randomized studies more feasible?
  - Designing studies aiming for **large differences between treatment arms** (which is what would be expected for therapies targeting the subtype aberration)
  - **Global collaboration** (Investigators' networking)
  - **Harmonization of rules and legislation** with respect to clinical trials.

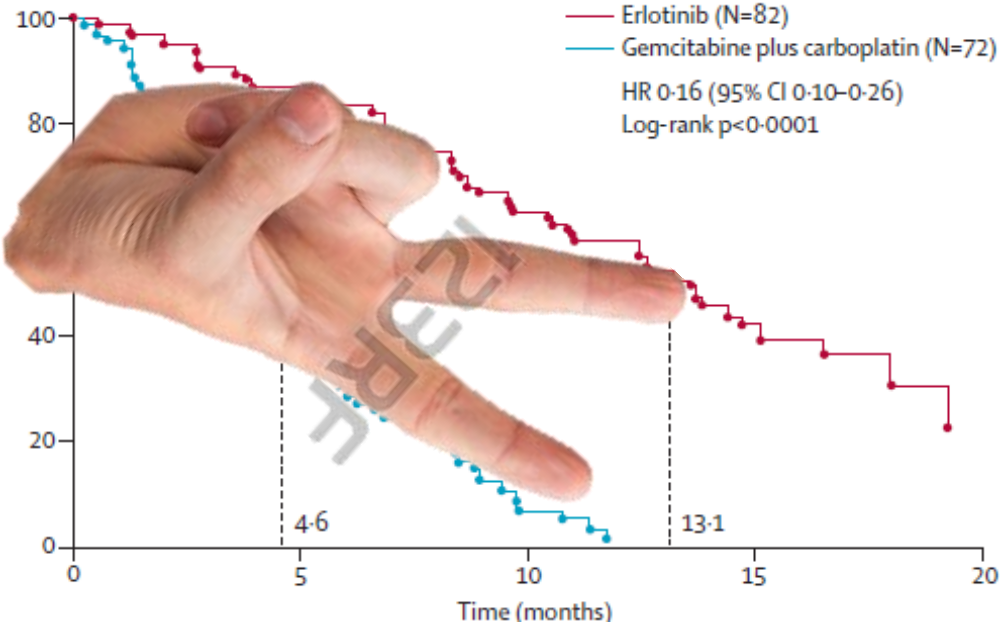
Published Ahead of Print on April 29, 2013 as 10.1200/JCO.2013.48.7645

The NEW ENGLAND JOURNAL of MEDICINE

The '*Two-Fingers*' Rule

- **Clinically Meaningful Data if '*at least*' two fingers separates curves!**





Hodi et al, NEJM 2010

Zhou et al [OPTIMAL], Lancet Oncol 2011

‘Registrative Dicotomy’

…to have your drug approved…

Sensitive & Homogeneous Population

Brand new drug

Great Superiority

Demonstrate ‘Large’ advantages

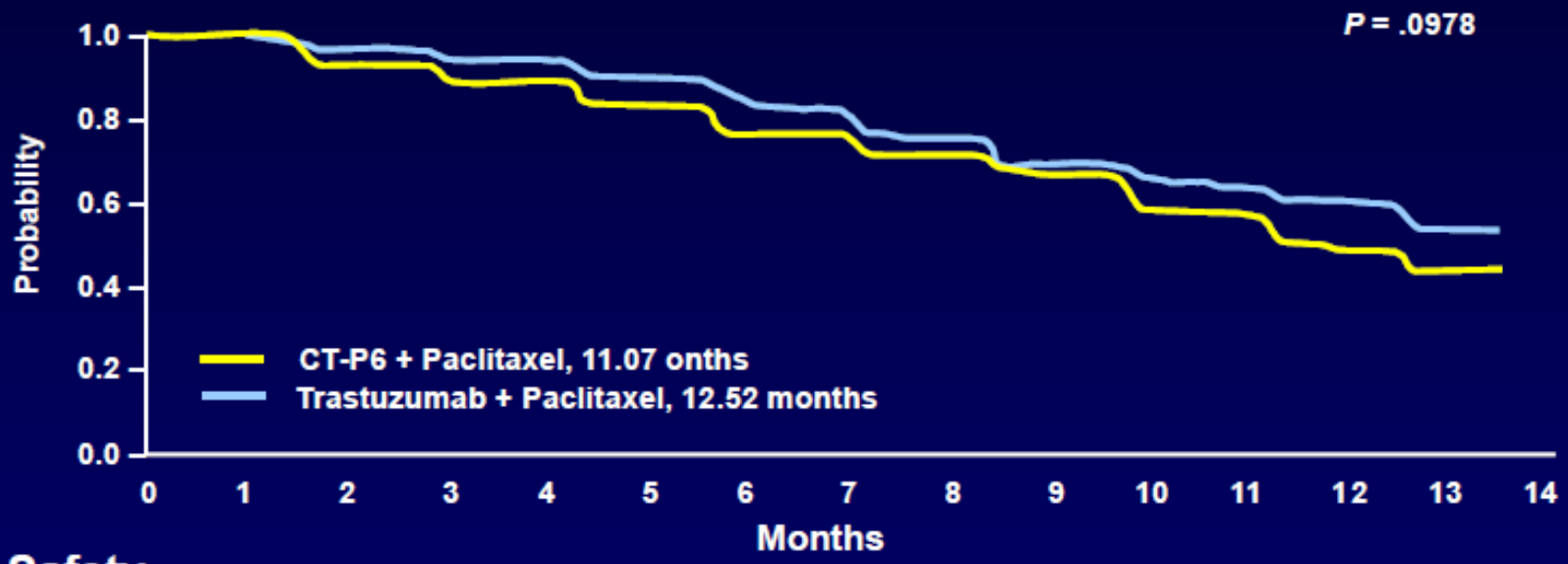
Biosimilar

Equivalence/non-inferiority

…..Tolerate small dis-advantages

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.

***MODIFIED*: Source: PRIME Oncology Nov. 2013**

Conclusions

- The development of biosimilar mAbs is complicated by:
  - **their complex molecular structure**
  - **potential for post-translational modifications**
  - **multidimensional manufacturing process.**
- ***In an effort to ensure patient safety and to address issues of microheterogeneities between biosimilars (including the potential for immunogenicity), robust clinical development programs must be required for each new agent.***

Mellstedt H, EJC [Suppl.] 2013

Conclusions

- Each marketing application should include:
  - **studies supporting the use of the agent in target disease states and patient populations,**
  - **a robust post-marketing pharmacovigilance plan.**
- Biosimilars **have the potential to benefit patients** and change the overall treatment landscape; however, **they also require great responsibility from the wider healthcare community to ensure their appropriate development and use**.

Mellstedt H, EJC [Suppl.] 2013