EMA ed esercizio di comparabilità: il metodologo

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EMA e definizione di BIOSIMILARE

"A biosimilar is a ***biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product*** *(reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established"*

EMA. http://www.ema.europa.eu/../WC500176768.pdf [Accessed May 2015].

- Il biosimilare presenta un certo grado di variabilità naturale
  - **un biosimilare e il suo prodotto di riferimento non sono identici, ma essenzialmente simili in termini di qualità, sicurezza ed efficacia**. Comunque "un biosimilare viene approvato quando è stato dimostrato che la variabilità naturale e le eventuali differenze rispetto al medicinale di riferimento non influiscono sulla sicurezza o sull'efficacia." (*Questions and Answers on biosimilar medicines* EMA/837805/2011 del 27 settembre 2012).

- Il biosimilare deve prevedere lo stesso dosaggio e la stessa via di somministrazione del farmaco di riferimento.

- Sono consentite differenze riguardanti soltanto gli eccipienti, la forma farmaceutica (es. soluzione pronta per l'uso alternativa a polvere solubile) o dispositivo di somministrazione (es. siringhe alternative a penne preriempite) sempre ammesso che tali differenze non peggiorino la sicurezza e l'efficacia del farmaco.

QUANDO e PERCHE'?

- La **protezione brevettuale** di diversi farmaci biologici di prima generazione è **scaduta**.
- I medicinali biosimilari hanno **costi inferiori** rispetto ai branded e sono importanti fattori per il mantenimento della **sostenibilità** economica dei servizi sanitari
- Se prezzo inferiore, uso in un più **alto numero di pazienti**.

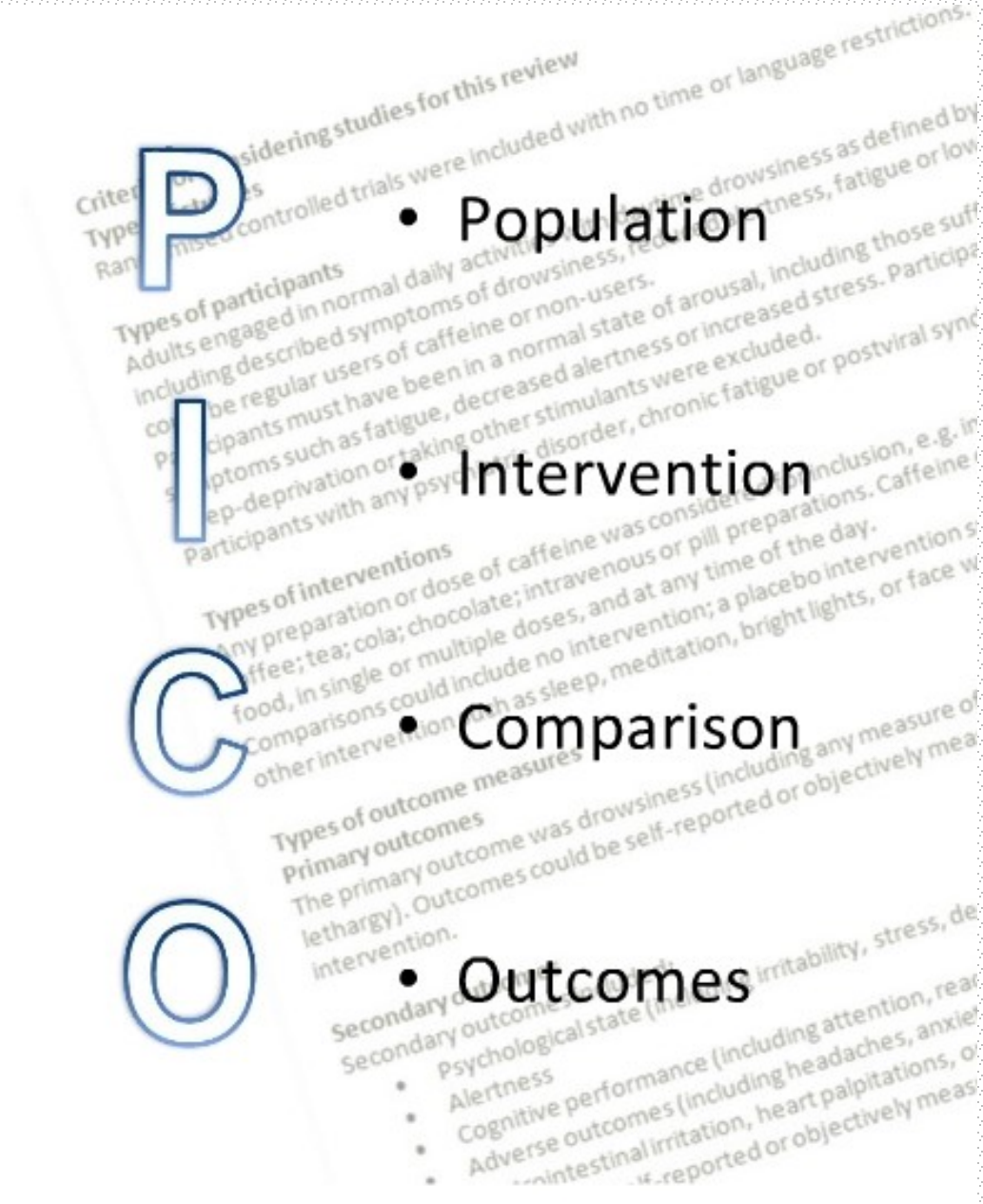
N.B. Non sono farmaci innovativi, ma possono stimolare l'innovazione

Sviluppo di biosimilari e comparabilità

- La dimostrazione di biosimilarità avviene attraverso l'applicazione di procedure di **confronto "testa a testa" graduale** (*stepwise*), per fasi concepite su misura per ogni prodotto e che prevedono:

  - **studi di qualità** (comparabilità fisico-chimiche e biologiche tra biosimilare e riferimento):
    –completa caratterizzazione analitica,
    –studi di legame al recettore (se applicabili),
    – biotest;
  - **valutazione della comparabilità pre-clinica** (studi non clinici comparativi) valutano gli effetti fisiologici immediati sulle cellule. In assenza di alternative valide in vitro, quando il biosimilare è prodotto in un nuovo tipo di cellula od organismo e quando nel biosimilare sono introdotti eccipienti mai usati in precedenza, queste prove devono essere effettuate in vivo su modelli animali;
  - **studi clinici comparativi** Criteri necessari per stabilire l'equivalenza tra prodotti biologici:
    - Bioequivalenza: profilo PK e PD
    - Comparabilità clinica: RCTs con endpoint di R/B
    - Studi post marketing per farmacovigilanza

Comparabilità: RCTs con endpoint di R/B



Comparabilità: RCTs con endpoint di R/B

- The guiding principle is to **demonstrate similar efficacy and safety** compared to the reference medicinal product, not patient benefit
- Therefore, the [redacted] patient population and [redacted] is preferred

European Medicines Agency (EMA): Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues . Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf.

Comparabilità: RCTs con endpoint di R/B

Domanda:

- equivalenza
- non inferiorità

Δ: Quale background?

- alto
- basso

- Per il quesito di non inferiorità
  - La pianificazione del disegno e l'interpretazione dei risultati ottenuti devono utilizzare l'informazione ottenuta dall'innovator vs. lo standard precedente
  - biosimilare può essere considerato non inferiore se il limite superiore dell'IC95% della stima del confronto non supera un valore Δ tale da mantenere un vantaggio contro il precedente standard.
  - Come linea di riferimento si suggerisce che l'efficacia preservata dovrebbe essere almeno del 50%

- Per il quesito di equivalenza
  - I margini per dichiarare la non inferiorità e la superiorità dovranno essere simmetrici rispetto al valore di eguaglianza

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com
ELSEVIER

Original Research

A phase III study comparing SB3 (a proposed trastuzumab biosimilar) and trastuzumab reference product in HER2-positive early breast cancer treated neoadjuvant-adjuvant treatment: Final safety, immunogenicity and survival results

X. Pivot [a,*,1], I. Bondarenko [b], Z. Nowecki [c], M. Dvorkin [d], E. Trish
J.-H. Ahn [f], S.-A. Im [g], T. Sarosiek [h], S. Chatterjee [i], M.Z. Wojtukie

Original Article

A comparative phase III clinical study to evaluate efficacy and safety of TrastuRel™ (biosimilar trastuzumab) and innovator trastuzumab in patients with metastatic human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancer

Prasad Apsangikar, Sunil Chaudhry, Manoj Naik, Shashank Deoghare[1], Jamila Joseph[1]
Medical Affairs Group, [1]Clinical Research Group, Reliance Life Sciences, Navi Mumbai, Maharashtra, India
Correspondence to: Dr. Prasad Apsangikar, E-mail: prasad.apsangikar@relbio.com

CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial

Justin Stebbing, Yauheni Baranau, Valeriy Baryash, Alexey Manikhas, Vladimir Moiseyenko, Giorgi Dzagnidze, Edvard Zhavrid, Dmytro Boliukh, Daniil Stroyakovskii, Joanna Pikiel, Alexandru Eniu, Dmitry Komov, Gabriela Morar-Bolba, Rubi K Li, Andriy Rusyn, Sang Joon Lee, Sung Young Lee,

Efficacy and safety of ABP 980 compared with reference trastuzumab in women with HER2-positive early breast cancer (LILAC study): a randomised, double-blind, phase 3 trial

Gunter von Minckwitz, Marco Colleoni, Hans-Christian Kolberg, Serafin Morales, Patricia Santi, Zorica Tomasevic, Nan Zhang, Vladimir Hanes

Summary

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ORIGINAL REPORT

Phase III, Randomized, Double-Blind Study Comparing the Efficacy, Safety, and Immunogenicity of SB3 (Trastuzumab Biosimilar) and Reference Trastuzumab in Patients Treated With Neoadjuvant Therapy for Human Epidermal Growth Factor Receptor 2–Positive Early Breast Cancer

Xavier Pivot, Igor Bondarenko, Zbigniew Nowecki, Mikhail Dvorkin, Ekaterina Trishkina, Jin-Hee Ahn, Yuriy Vinnyk, Seock-Ah Im, Tomasz Sarosiek, Sanjoy Chatterjee, Marek Z. Wojtukiewicz, Vladimir Moiseyenko, Yaroslav Shparyk, Maximino Bello III, Vladimir Semiglazov, Sujeong Song, and Jaeyun Lim

Research

JAMA | Original Investigation

Effect of a Proposed Trastuzumab Biosimilar Compared With Trastuzumab on Overall Response Rate in Patients With ERBB2 (HER2)–Positive Metastatic Breast Cancer
A Randomized Clinical Trial

BJC British Journal of Cancer
www.nature.com/bjc

ARTICLE
Clinical Study

Neoadjuvant PF-05280014 (a potential trastuzumab biosimilar) versus trastuzumab for operable HER2+ breast cancer

BJC British Journal of Cancer
www.nature.com/bjc

ARTICLE
Clinical Study

PF-05280014 (a trastuzumab biosimilar) plus paclitaxel compared with reference trastuzumab plus paclitaxel for HER2-positive metastatic breast cancer: a randomised, double-blind study

Mark D. Pegram[1], Igor Bondarenko[2], Marina Moreira Costa Zorzetto[3], Sachin Hingmire[4], Hirotaka Iwase[5], Petr V. Krivorotko[6], Keun Seok Lee[7], Rubi K. Li[8], Joanna Pikiel[9], Rajesh Aggarwal[10], Reginald Ewesuedo[11], Amy Freyman[11], Ray Li[12], Alicia Vana[13], Donghua Yin[14], Charles Zacharchuk[11] and Elizabeth Tan-Chiu[13]

NEOADIUVANTE

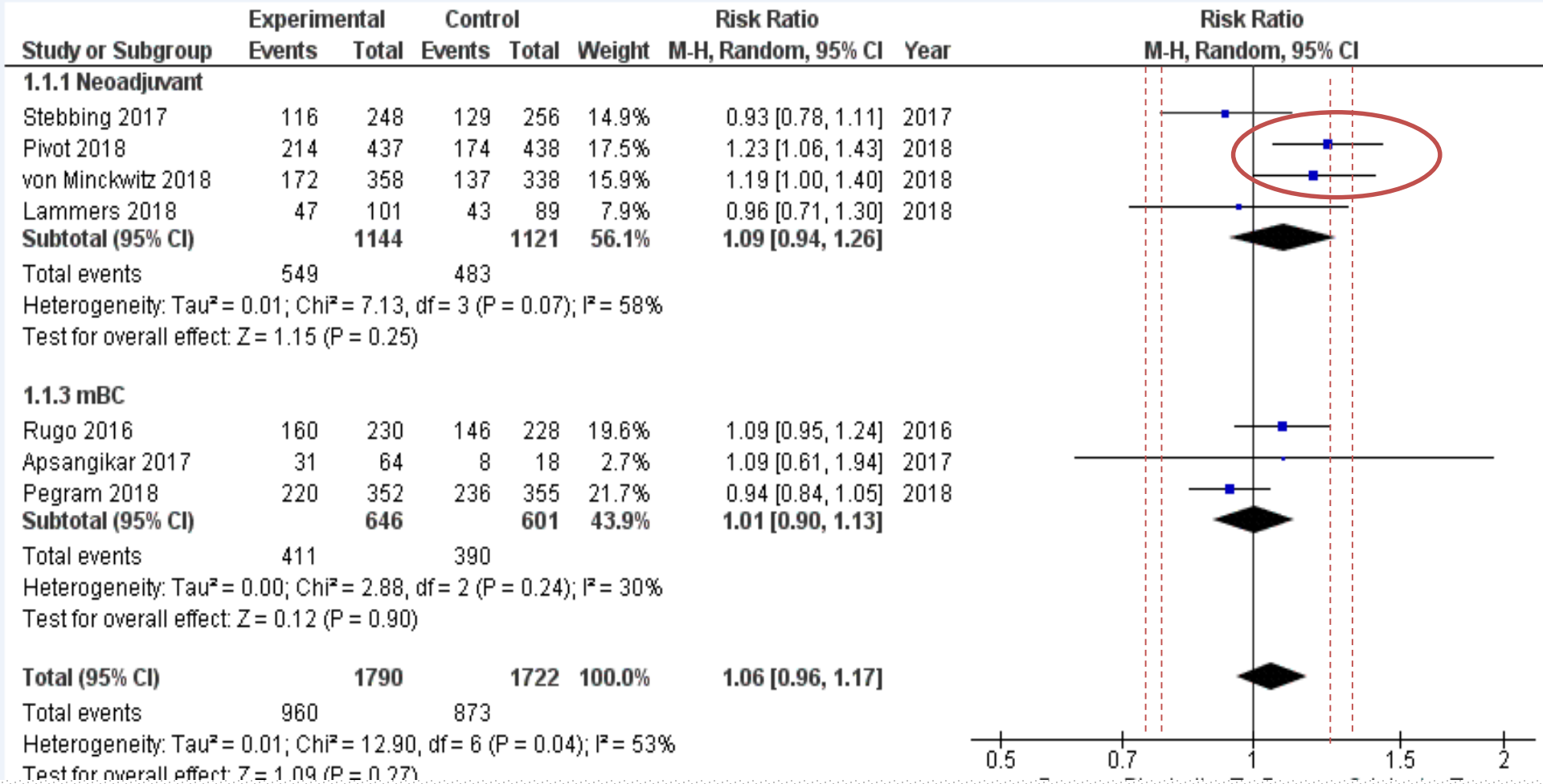
ref	P	I	C	O	disegno	Delta/Margin	sample	results
Stebbing 2017 International	HER2+ operable BC	CT-P6 (6mg/kg every 3 week)	TRZ		equivalence	95%CI 0.74 – 1.35*	549 pts	0.93 (0.78 – 1.11)
Lammers 2018 International	HER2+ operable BC	PF-05280014 + docetaxel and carboplatin (every 3 week 6mg/kg)	TRZ+ docetaxel and carbop	pCR (not e)	Non-inferiority	95%CI No non-inferiority margin provided	226 pts	0,96 (0.71 – 1,30)
Pivot 2018	HER2+ operable BC	SB3 (every 3 week 6mg/kg)	TRZ		equivalence	95%CI 0,785 – 1,546*	875 pts	1,23 (1,06 – 1,43)
Von Minckwitz 2018	HER2+ operable BC	ABO 980 (every 3 week 6mg/kg)	TRZ		equivalence	90%CI 0,759 – 1,318*	725 pts	1,188 (1,033 – 1,366)

* Prior derivata da meta-analisi

BC Metastatico

ref	P	I	C	O	disegno	Delta/Margin	sample	results
Rugo 2016 International	HER2+ mBC	T biosimilar (every 3 weeks 6 mg/kg over 30 min)+ taxane	TRZ+taxane	Overall	equivalenza	90%CI 0.81 – 1.24*	500 pts	1.09 (0.974 – 1.211)
Pegram 2018 International	HER2+ mBC	PF-05280014 (every 3 weeks 6 mg/kg over 30 min)+ taxane	TR	te	equivalence	95%CI 0.80 – 1.25*	707 pts	0.94 (0.842 – 1.049)
Apsangikar 2019 India	HER2+ mBC	T biosimilar (every 3 weeks 6 mg/kg over 30 min)+	TRZ	Objective response rate	non-inferiority	95%CI No non-inferiority margin provided	106 pts (PP=82)	1,08 (0,61 – 1,94)

* Prior derivata da meta-analisi


Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
Year
M-H, Random, 95% CI
1.1.1 Neoadjuvant
Stebbing 2017 116 248 129 256 14.9% 0.93 [0.78, 1.11] 2017
Pivot 2018 214 437 174 438 17.5% 1.23 [1.06, 1.43] 2018
von Minckwitz 2018 172 358 137 338 15.9% 1.19 [1.00, 1.40] 2018
Lammers 2018 47 101 43 89 7.9% 0.96 [0.71, 1.30] 2018
Subtotal (95% CI) 1144 1121 56.1% 1.09 [0.94, 1.26]
Total events 549 483
Heterogeneity: Tau² = 0.01; Chi² = 7.13, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 1.15 (P = 0.25)
1.1.3 mBC
Rugo 2016 160 230 146 228 19.6% 1.09 [0.95, 1.24] 2016
Apsangikar 2017 31 64 8 18 2.7% 1.09 [0.61, 1.94] 2017
Pegram 2018 220 352 236 355 21.7% 0.94 [0.84, 1.05] 2018
Subtotal (95% CI) 646 601 43.9% 1.01 [0.90, 1.13]
Total events 411 390
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 0.12 (P = 0.90)
Total (95% CI) 1790 1722 100.0% 1.06 [0.96, 1.17]
Total events 960 873
Heterogeneity: Tau² = 0.01; Chi² = 12.90, df = 6 (P = 0.04); I² = 53%
Test for overall effect: Z = 1.09 (P = 0.27)
0.5
0.7
1
1.5
2

Comparabilità: RCTs con endpoint di R/B

- [redacted] as a sensitive endpoint for clinical trials of biosimilar antibodies
- [redacted] as an appropriately sensitive endpoint for biosimilar antibody clinical trials

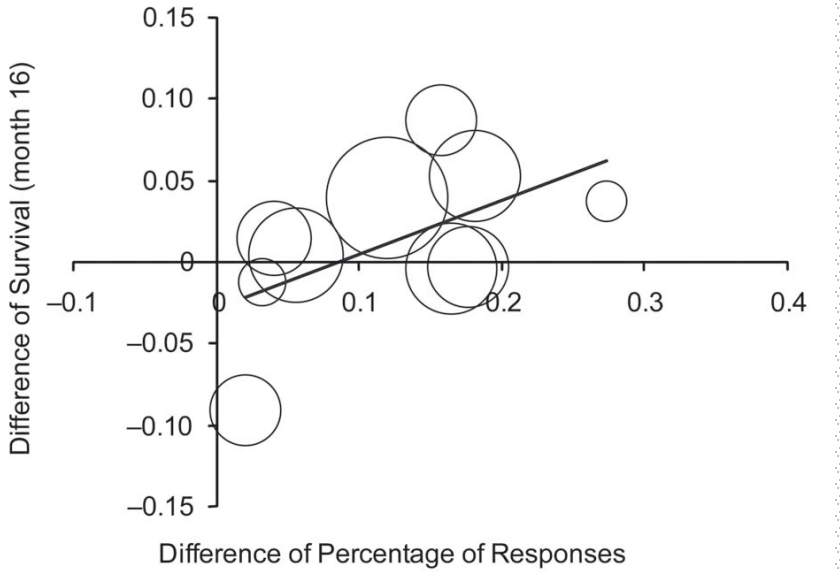
- As overall response rate [redacted] this is a controversial endpoint for clinicians

M. Thill, PRIME Symposium, ESMO 2014 (modif. glp)

Objective Response to Chemotherapy As a Potential Surrogate End Point of Survival in Metastatic Breast Cancer Patients

Paolo Bruzzi, Lucia Del Mastro, Maria P. Sormani, Lars Bastholt, Marco Danova, Christian Focan, George Fountzilas, James Paul, Riccardo Rosso, and Marco Venturini

J Clin Oncol 23:5117-5125. © 2005 by American Society of Clinical Oncology



On the basis of these results, it is not possible to conclude that objective response to any first-line chemotherapy (not to mention second-line chemotherapy) is associated with a survival benefit.

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
  - [redacted]
  - Long-term survival may be used as a secondary endpoint

M. Thill, PRIME Symposium, ESMO 2014 (modif. glp)