IRCCS Sacro Cuore Don Calabria
Cancer Care Center Negrar - Verona

ESMO Designated Centers of Integrated Oncology and Palliative Care

Con il Patrocinio di

AIOM Associazione Italiana di Oncologia Medica
RAO
SICO
Società Italiana di Psico-Oncologia

STUDI CLINICI: METODOLOGIA

Coordinatore
Dr.ssa Stefania Gori

Evento ECM MODULO 2

FORMAZIONE AVANZATA

NEGRAR
8/9 Marzo
2019

Centro Formazione
IRCCS Ospedale Sacro Cuore
Don Calabria

Biosimilari e P.I.C.O.

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

R. Danesi, PRIME Symposium, ESMO 2014

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

New biologic agent (full dossier)

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- 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

R. Danesi, PRIME Symposium, ESMO 2014

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 [redacted] and clinical endpoint is preferred
- Comparability should be demonstrated in scientifically appropriately sensitive clinical models and study conditions

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.

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

What Is a Sensitive and Homogenous Study Population?

- **Biosimilar antibodies should be studied in the population of patients in whom, *between the biosimilar and the reference product,***

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

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.
- This population will vary for each antibody and each disease in which the antibody is used
  - [redacted]
  - For biosimilar rituximab in lymphoma, the population is harder to identify because lymphomas are not homogenous

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

Immunogenicity Assessment

- Immunogenicity testing is key for biosimilar antibody clinical trials, as it is impossible to predict when an antibody might induce an immune response
- , ie, patients who are most likely to develop an immune reaction to treatment
- For example: in breast cancer, early disease would be a more sensitive population than metastatic disease, as

European Medicines Agency. Available at: http://ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128688.pdf.

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

Sensitive Endpoints for Biosimilar Antibody Clinical Trials

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

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

Sensitive Endpoints for Biosimilar Antibody Clinical Trials

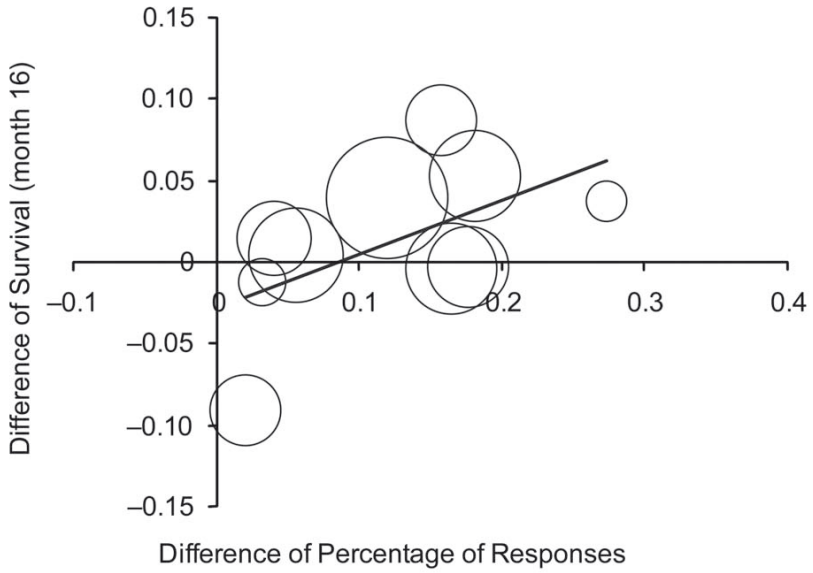
- EMA guidelines identify response as a sensitive endpoint for clinical trials of biosimilar antibodies
- The EMA does not accept overall survival as an appropriately sensitive endpoint for biosimilar antibody clinical trials
- As overall response rate this is a controversial endpoint for clinicians

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)

What is the most "Sensitive and Homogenous Population" in Breast Cancer?

- Biosimilar monoclonal 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.
- The most sensitive population to study trastuzumab biosimilars is early-stage breast cancer in the neoadjuvant setting

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

Christian Jackisch*[,1], Frank A Scappaticci[2], Dominik Heinzmann[3], Fabio Bisordi[3], Thomas Schreitmüller[3], Gunter von Minckwitz[4] & Javier Cortés[5]

Future Oncol. (Epub ahead of print)

Based on meta-analyses of randomized clinical trials with trastuzumab in HER2-positive breast cancer, we examined the relationship between ORR and PFS in MBC, and between tpCR and EFS in HER2-positive EBC.

Table 1. Selected publications of clinical trials in HER2-positive metastatic breast cancer.

Trial identification number	Study arms considered	Randomized patients (n)	Median follow-up (months)	ORR†	Hazard ratio† PFS (95% CI)	Ref.
H0648G#	P H + P	188	30	16.7% (16/96)§ 41.3% (38/92)†	2.63 (1.89–3.70)#	[3]
BO20231	H + D + A H + D	424	26	76.5% (140/183)§,¶ 65.9% (116/176)§,¶	0.72 (0.54–0.94)	[26]
WO20698	H + D + Per H + D	808	19.3	80.2% (275/343)§ 69.3% (233/336)§	0.62 (0.51–0.75)	[27]
TDM4450g	T-DM1 H + D	137	14	64.2% (43/67)¶ 58.0% (40/69)¶	0.59 (0.36–0.97)	[30]
US Oncology Research	H + P + C H + P	196	Mature‡	52.2% (48/92) 36.2% (34/94)	0.66 (0.59,–0.73)	[31]
BCIRG007	H + D + C H + D	263	Mature‡	72.7% (96/132) 72.5% (95/131)	0.91 (0.69–1.20)	[28]
MO16419	H + D + Cap H + D	225	24	70.5% (79/112) 72.7% (80/110)	0.72 (0.53–0.99)	[29]
STM01–102	H + P + M H + P	363	31	66.9% (121/181) 62.1% (113/182)	0.84 (0.65–1.08)	[32]

Table 2. Selected publications of clinical trials in HER2-positive early breast cancer.

Trial identification number	Study arms considered	Randomized patients (n)	Median follow-up (months)	tpCR§	Hazard ratio EFS (95% CI)†	Ref.
MO16432 (NOAH)	Neoadj CTX H + neoadj CTX	235	64.8	19.5% (23/118) 38.5% (45/117)	1.56 (1.08–2.27)	[9,10]
GBG–GeparQuattro‡	H + neoadj CTX including Cap H + neoadj CTX	445	64.8	45.3% (124/274) 43.3% (61/141)	0.89 (0.59–1.34)	[33,34]
BO22227	H SC + neoadj CTX H + neoadj CTX	596	21	39.2% (102/260) 34.2% (90/263)	0.88 (0.61–1.27)	[11] [BO22227, Submitted]

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Design					Predictions	
Equivalence margin (difference in ORR; %)	Trastuzumab reference ORR (%)†	Lower equivalence margin (%)	Resulting OR	Sample size‡	Predicted HR for PFS corresponding to the lower margin	
					Adjusted model	Standard model
5	63.5	58.5	1.234	3742	1.179	1.091
10	63.5	53.5	1.512	924	1.369	1.242
	63.5	48.5	1.847			1.411

Design					Predictions	
Equivalence margin (difference in tpCR; %)	Trastuzumab reference tpCR (%)	Lower equivalence margin (%)	Resulting OR	Sample size‡	Predicted HR for EFS corresponding to the lower margin	
					Adjusted model	Standard model
5	37.3	32.3	1.247	3764	1.070	1.074
10	37.3	27.3	1.584	932	1.205	1.213
	37.3	22.3	2.074			1.392

The use of tpCR in the HER2-positive neoadjuvant EBC setting as a sensitive end point was associated with a lower potential loss in long-term efficacy of a biosimilar candidate than the use of ORR in the HER2-positive MBC setting.

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, Francisco J Esteva

Lancet Oncol 2017; 18: 917–28

Added value of this study

We did a randomised, double-blind, active-controlled, phase 3 trial to establish the equivalence of CT-P6 to reference trastuzumab in terms of efficacy in patients with HER2-positive, operable, early-stage breast cancer treated in the neoadjuvant setting. Whereas previous studies of trastuzumab biosimilars have used the proportion of patients with an overall response as a primary endpoint, we used pathological complete response (pCR)

European Journal of Cancer 93 (2018) 19–27

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

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

X. Pivot [a,*,1], I. Bondarenko [b], Z. Nowecki [c], M. Dvorkin [d], E. Trishkina [e], J.-H. Ahn [f], S.-A. Im [g], T. Sarosiek [h], S. Chatterjee [i], M.Z. Wojtukiewicz [j], Y. Shparyk [k], V. Moiseyenko [l], M. Bello III [m], V. Semiglazov [n], Y. Lee [o], J. Lim [o]

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

Philip E. Lammers[1], Magdolna Dank[2], Riccardo Masetti[3], Richat Abbas[4], Fiona Hilton[5], Jennifer Coppola[6] and Ira Jacobs[6]

BACKGROUND: This randomised, double-blind study compared pharmacokinetics, efficacy, safety and immunogenicity of PF-05280014 (potential trastuzumab biosimilar) and trastuzumab reference product (Herceptin) sourced from the European Union (trastuzumab-EU) as neoadjuvant treatment for operable human epidermal growth factor receptor 2 (HER2)-positive breast cancer.
METHODS: Patients ($N = 226$), stratified by primary tumour size and hormone receptor status, were randomised 1:1 to PF-05280014 or trastuzumab-EU (8 mg/kg loading dose; 6 mg/kg thereafter), each with docetaxel and carboplatin, every 3 weeks for six treatment cycles. Primary endpoint was percentage of patients with trough plasma concentration (C_{trough}) >20 µg/ml at Cycle 5 (Cycle 6 predose). Efficacy endpoints included pathological complete response and objective response rate. Non-inferiority of PF-05280014 to trastuzumab-EU was declared if the lower limit of the 95% confidence interval for the stratified difference between groups in the percentage of patients with Cycle 5 C_{trough} >20 µg/ml was above the prespecified non-inferiority margin of – 12.5%.
RESULTS: For PF-05280014 vs trastuzumab-EU patients, respectively, 92.1% vs 93.3% had Cycle 5 C_{trough} >20 µg/ml; the lower limit of the 95% confidence interval (− 8.02%, 6.49%) for the stratified difference between groups was above the non-inferiority margin (– 12.5%). Pathological complete response (47.0% vs 50.0%) and central radiology review-assessed objective response (88.1% vs 82.0%) rates were comparable. Incidence of all-causality, grade 3–4 treatment-emergent adverse events was 38.1% vs 45.5%; antidrug antibody rates were 0% vs 0.89%.
CONCLUSIONS: PF-05280014 demonstrated non-inferior pharmacokinetics and comparable efficacy, safety and immunogenicity to trastuzumab-EU in patients with operable HER2-positive breast cancer receiving neoadjuvant chemotherapy.

British Journal of Cancer (2018) 119:266–273; https://doi.org/10.1038/s41416-018-0147-1

Conclusions

- Several biosimilars of trastuzumab are currently in development, including phase III trials
- Biosimilars are tested in a reduced clinical trial program, so [redacted] of these trials
  - A trial examining response rate in metastatic breast cancer may not be appropriately sensitive
  - Pathologic complete response as an endpoint for a clinical trial in neoadjuvant breast cancer represents a more sensitive approach

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

Conclusions

- Several biosimilars of trastuzumab are currently in development, including phase III trials
- Biosimilars are tested in a reduced clinical trial program, so special attention must be paid to the patient population and endpoints of these trials
  - A trial examining response rate in metastatic breast cancer may not be appropriately sensitive
  - Pathologic complete response as an endpoint for a clinical trial in neoadjuvant breast cancer represents a more sensitive approach
- How trastuzumab biosimilars are tested in clinical trial may determine how they are used in the clinic

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

What is extrapolation?

R. Danesi, PRIME Symposium, ESMO 2014 (modif. glp)

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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

R. Danesi, PRIME Symposium, ESMO 2014 (modif. glp)

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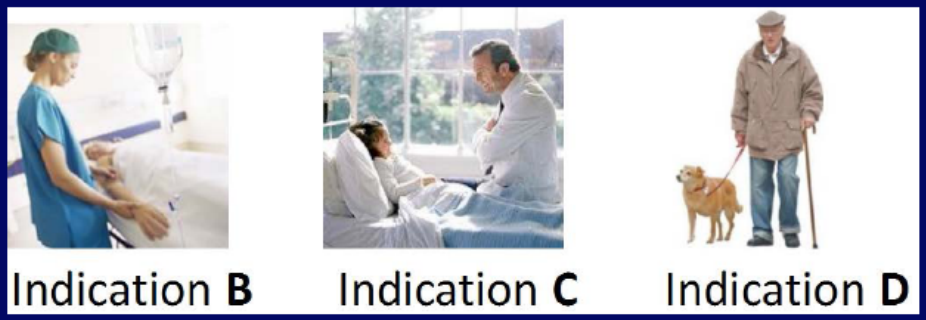
↓

Approval in indication A

↓

Extrapolation to other diseases or patient populations?



R. Danesi, PRIME Symposium, ESMO 2014 (modif. glp)

Expert perspectives on biosimilar monoclonal antibodies in breast cancer

J. Cortés · G. Curigliano · V. Diéras

Breast Cancer Res Treat Published online: 23 February 2014

Current opinion regarding extrapolation of indications for biosimilar mAbs holds that [redacted] of the reference antibody.

Schneider CK, Vleminckx C, Gravanis I et al (2012) Setting the stage for biosimilar monoclonal antibodies. Nat Biotechnol 30:1179–1185

For HER2-positive breast cancer, this would mean clinical testing of a biosimilar trastuzumab in the adjuvant or neoadjuvant setting, with extrapolation to metastatic breast cancer. The converse, a biosimilar tested in the metastatic setting extrapolated to early breast cancer, would not be acceptable.

GRADE

P

I

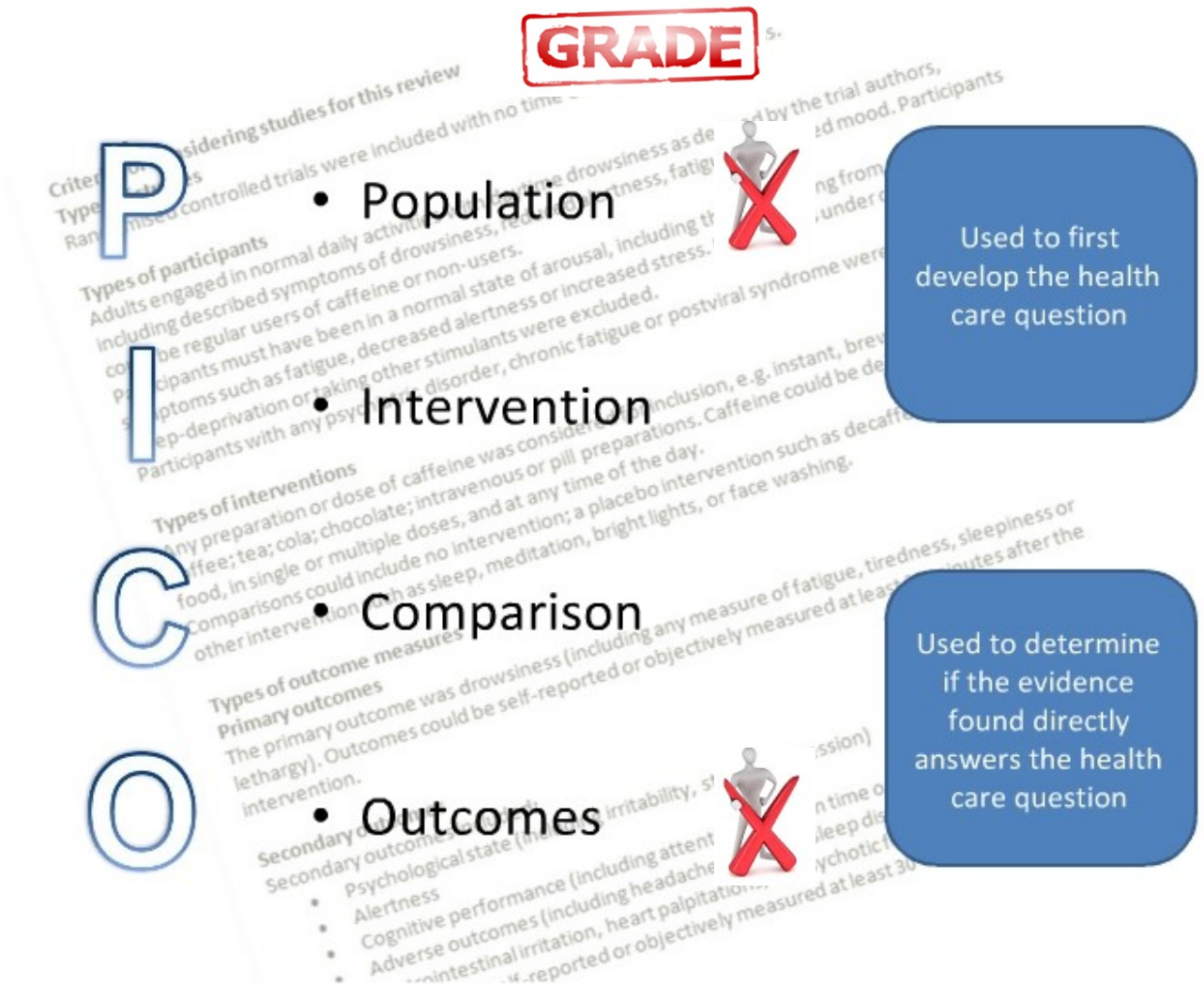
C

O

Used to first develop the health care question

Used to determine if the evidence found directly answers the health care question

Per un quesito terapeutico riguardante il trasferimento d'uso di un biosimilare di trastuzumab* in fase adiuvante o in fase metastatica:



* sviluppato in fase neo-adiuvante con pCR come endpoint