Consensus

sui Farmaci Biosimilari in Oncologia

24 GIUGNO 2019

BARI

ISTITUTO TUMORI "GIOVANNI PAOLO II"
IRCCS OSPEDALE ONCOLOGICO DI BARI
viale Orazio Flacco, 65

11.45 **WORKSHOP 1**
Iter approvativo dei Farmaci biosimilari da parte di EMA e Studi di comparabilità

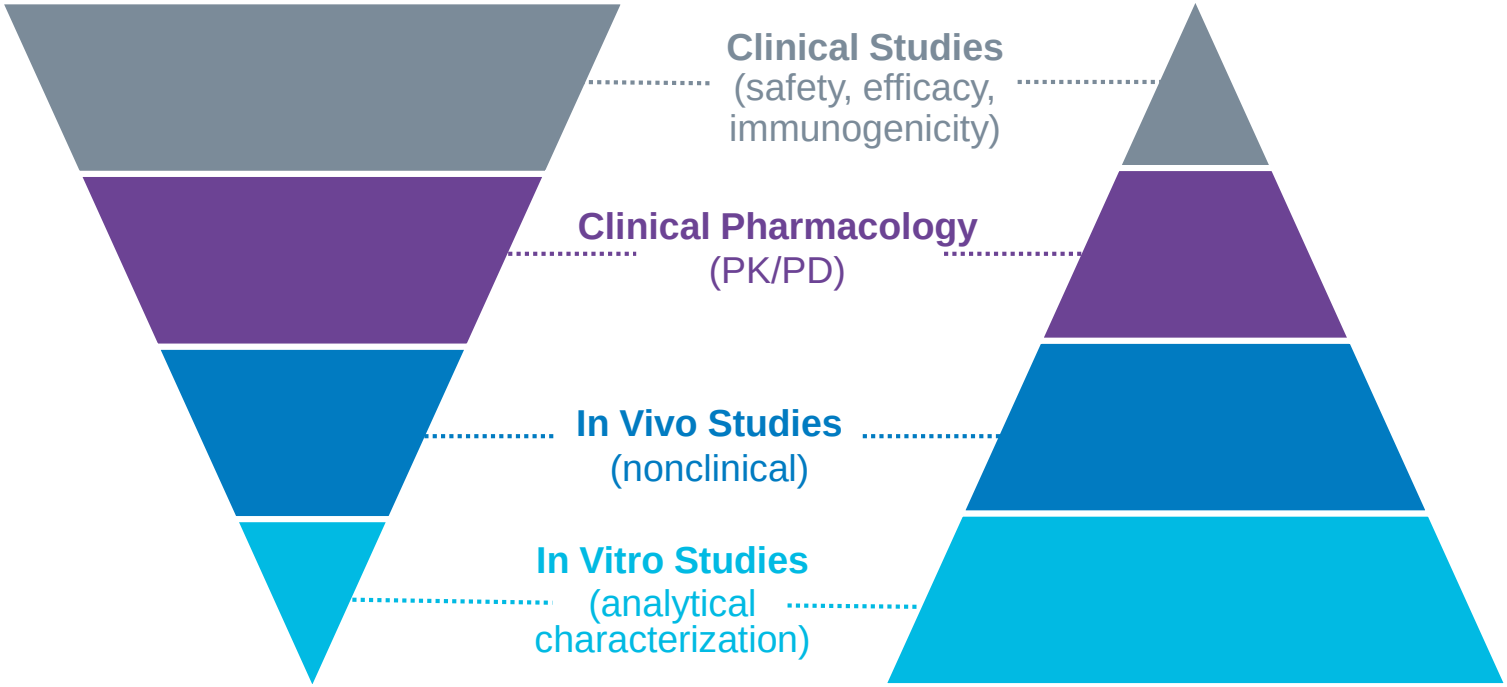
Chairmen: M. AIETA, F. GIOTTA, F. SCAGLIONE

- Studi clinici di comparabilità farmacocinetica e farmaco dinamica
- Studi clinici con disegno di non inferiorità e valutazione della sicurezza

Obiettivi, disegno ed endpoint di uno studio clinico che miri a dimostrare l'efficacia di un biosimilare NON sono gli stessi che sarebbero richiesti alla dimostrazione di efficacia di un nuovo farmaco.

Originator Development[1]

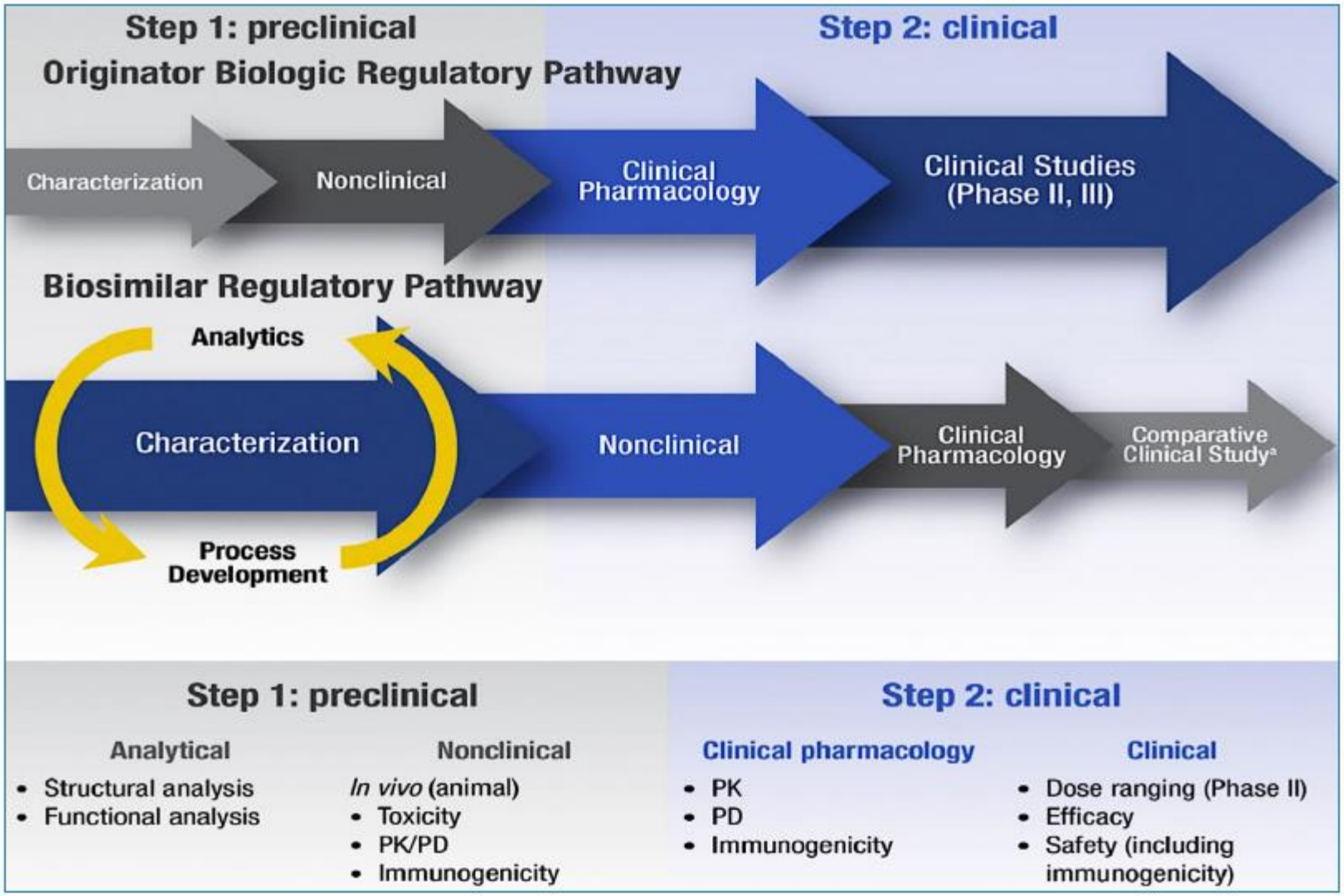
Demonstrate safety and effectiveness with adequate and well-controlled substantial evidence for a new product



Biosimilar Development[1-3]

Demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed

Development pathways for originator biologic and biosimilar



EMA ha definito le linee guida per la valutazione dei mAbs biosimilari (1)

30 May 2012
EMA/CHMP/BMWP/403543/2010
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues

Draft Agreed by Similar Biological Medicinal Products Working Party	October 2010
Adoption by CHMP for release for consultation	18 November 2010
End of consultation (deadline for comments)	31 May 2011
Final agreed by BMWP	March 2012
Adoption by CHMP	30 May 2012
Date for coming into effect	1 December 2012

Keywords	*Biosimilars, monoclonal antibodies, similar biological medicinal products, relevant animal model, non-clinical studies, in vitro studies, clinical use, clinical endpoints, extrapolation*

L'insieme dei **dati richiesti per l'approvazione di un biosimilare** è superiore a quello necessario per un generico, ma meno dettagliato del processo richiesto per la registrazione di un nuovo biologico o di un nuovo composto chimico (2)

1. *EMA. Guideline on similar biological medicinal products containing monoclonal antibodies-nonclinical and clinical issues. EMA/CHMP/BMWP/403543/2010. 2012 available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf Last access April 2014 ;*
2. ***2.*** *Niederwieser D, Schmitz S. Eur J Haematol. 2011;86(4):277-88*

FARMACI BIOSIMILARI IN ONCOLOGIA

Position Paper

LUGLIO 2018

- Comparability exercise
- Clinical studies non-inferiority/ equivalence
- Safety

ESMO Open
Cancer Horizons

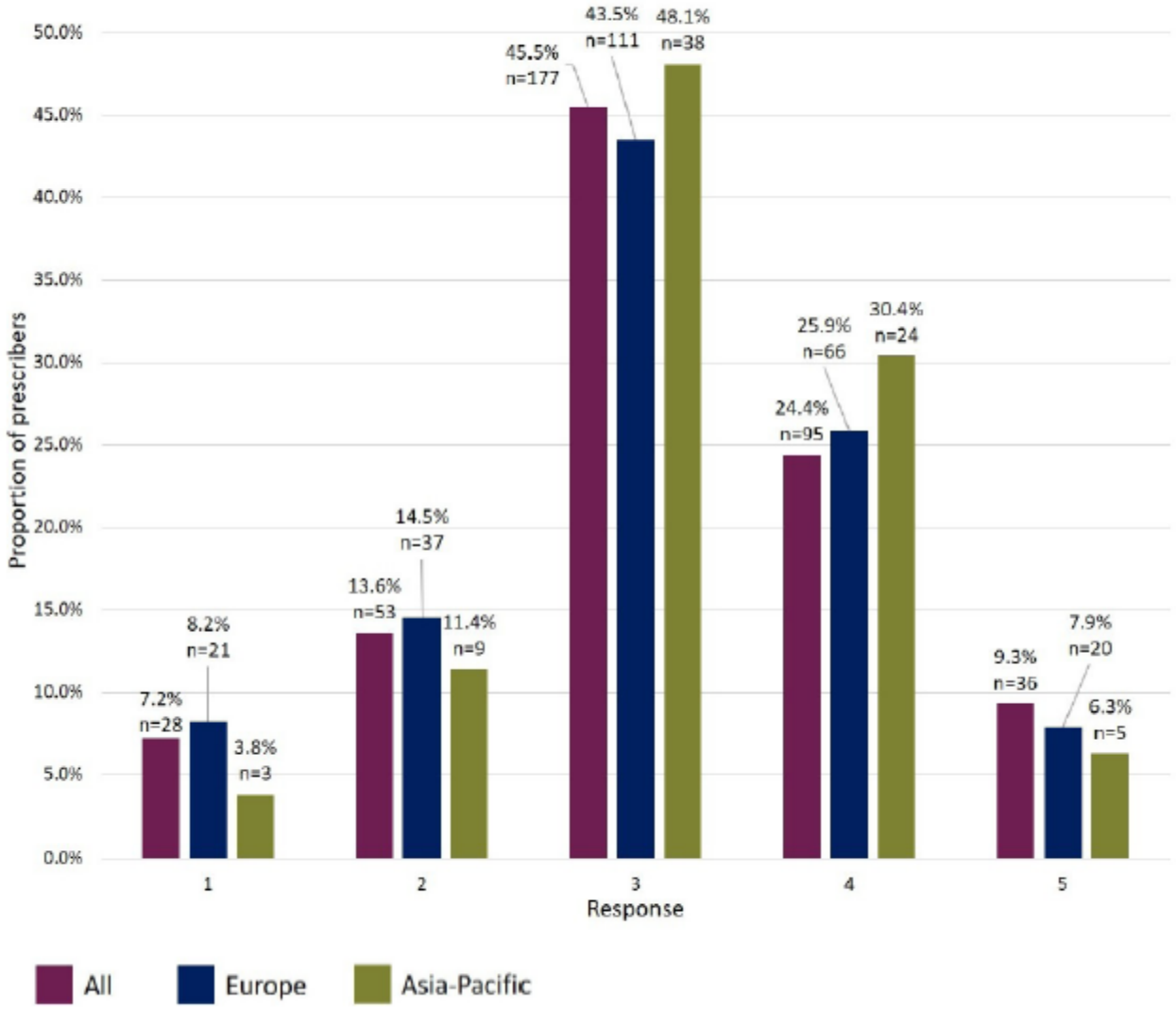
Knowledge and use of biosimilars in oncology: a survey by the European Society for Medical Oncology

Rosa Giuliani,[1] Josep Tabernero,[2] Fatima Cardoso,[3] Keith Hanson McGregor,[4] Malvika Vyas,[5] Elisabeth G E de Vries[6]

Data collection occurred between September and October 2017 and included both paper and online responses. During the ESMO 2017 Congress, attendees the 2017 ESMO Congress in Madrid, Spain.

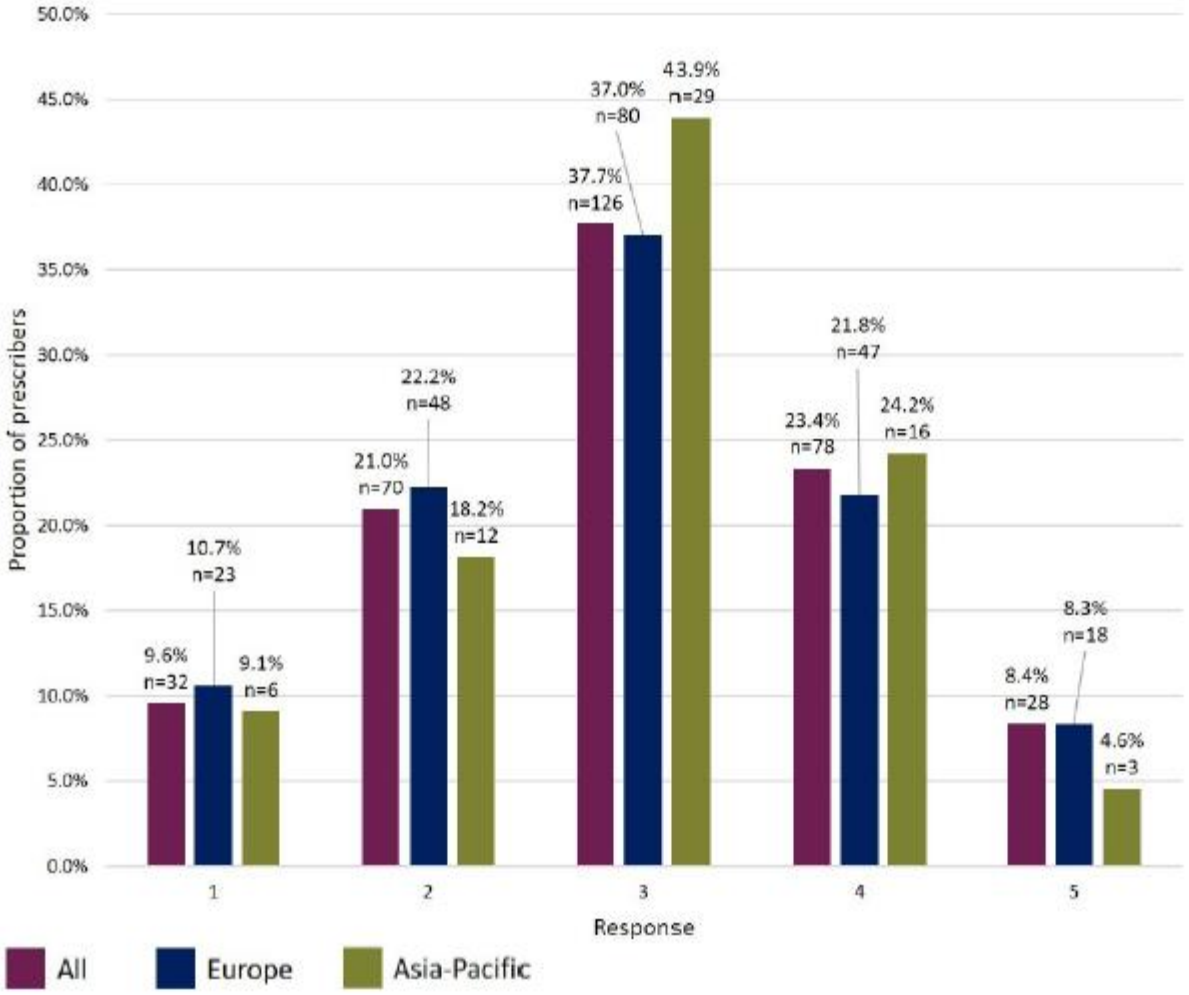
Giuliani R, *et al. ESMO Open* 2019;4:e000460. doi:10.1136/esmoopen-2018-000460

Rate of knowledge / understanding of biosimilars overall



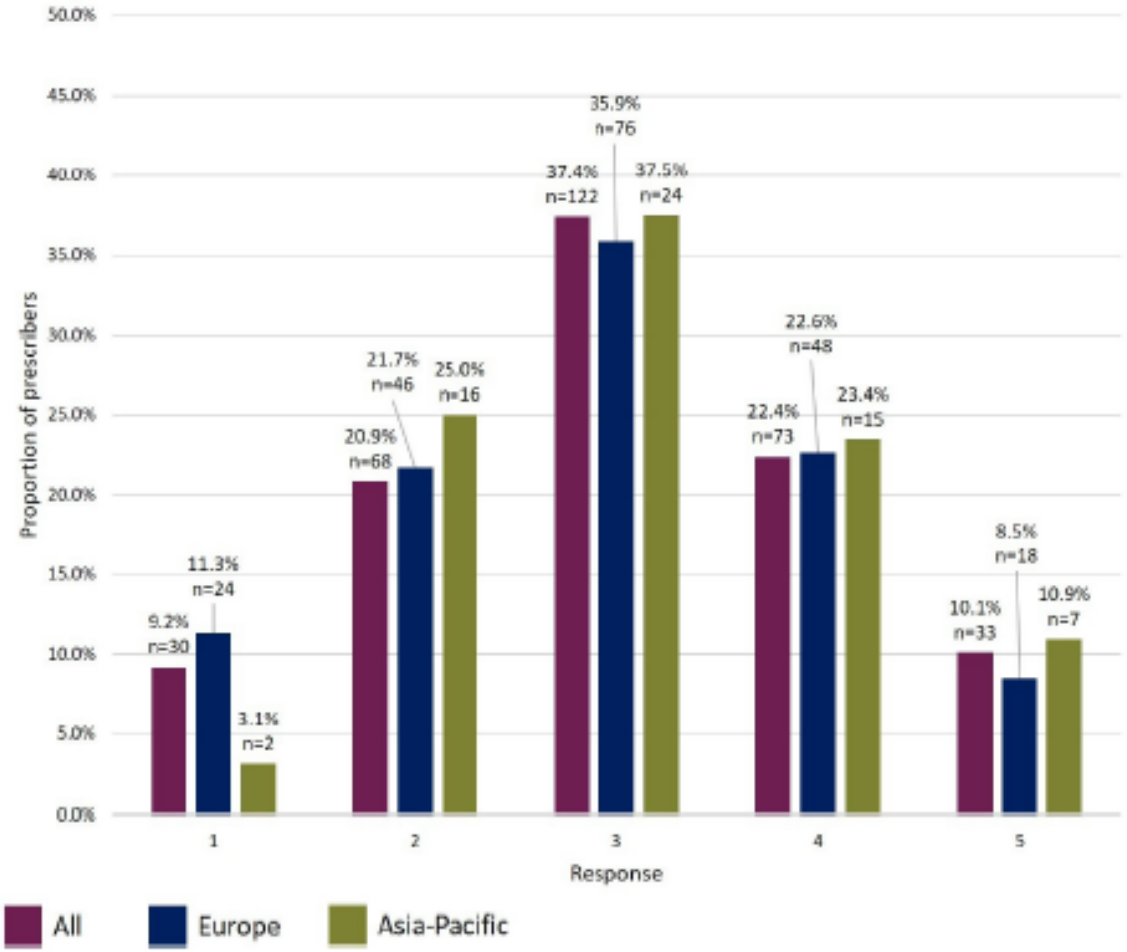
Giuliani R, et al. ESMO Open 2019; 4:e000460

Rate of knowledge / understanding biosimilars development process and threshold of clinical evidence required for approval



Giuliani R, et al. ESMO Open 2019; 4:e000460

Rate of knowledge / understanding clinical trials design and endpoint selection for biosimilars studies



Giuliani R, et al. ESMO Open 2019; 4:e000460

“comparability exercise” (esercizio di comparabilità): definizione

Procedura graduale e sperimentale, con cui il farmaco biosimilare viene confrontato da un punto di vista fisico-chimico, pre-clinico e clinico (in genere con studi clinici randomizzati) con il farmaco originatore.

Devono essere condotti per una specifica indicazione in un setting di pazienti simile a quello degli studi di riferimento del farmaco originatore ed utilizzando endpoint ritenuti sensibili per fare emergere eventuali differenze di attività o efficacia tra il biosimilare ed il corrispondente originatore.

“comparability exercise” (esercizio di comparabilità): obiettivo

Scopo del *comparability exercise* non è il dimostrare una miglior efficacia del farmaco biosimilare rispetto all’originatore, ma la sua similarità rispetto al farmaco di riferimento in termini di qualità, efficacia e sicurezza, inclusa l’immunogenicità, sia in fase preclinica che in fase clinica. Il *comparability exercise* ha anche lo scopo di garantire qualità ed omogeneità del prodotto e del processo produttivo

“comparability exercise” (esercizio di comparabilità): metodologia

L’esercizio di comparabilità è quindi basato su un robusto confronto “testa a testa” tra biosimilare e il medicinale di riferimento, secondo specifici standard di qualità, efficacia e sicurezza, avendo definito a priori le differenze ritenute accettabili, poiché non clinicamente rilevanti.

“comparability exercise” (esercizio di comparabilità): opportunità

L’ottenimento di un esito positivo dell’esercizio di comparabilità da parte di un farmaco biosimilare rispetto al proprio originatore deve tradursi nella **sostanziale equivalenza terapeutica** e profilo di sicurezza tra i due agenti; la successiva autorizzazione all’immissione in commercio del farmaco biosimilare, che deve avvenire fissandone un prezzo necessariamente inferiore a quello dell’originatore, deve essere accolta come opportunità di contribuire alla **sostenibilità** del sistema nell’ottica del perseguimento della riduzione dei costi con preservazione della efficacia.

BioDrugs
https://doi.org/10.1007/s40259-019-00362-5

ORIGINAL RESEARCH ARTICLE

Biological Characterization of SB3, a Trastuzumab Biosimilar, and the Influence of Changes in Reference Product Characteristics on the Similarity Assessment

Jae Hee Lee[1] · Kyungyeol Paek[1] · Jae Hyon Moon[1] · Sunyoung Ham[1] · Jinsu Song[1] · Seokkyun Kim[1]

Published online: 12 June 2019

Methods Analytical similarity was assessed with defined test procedures in terms of critical quality attributes (CQAs) that could affect efficacy, potency, and safety, as well as for the non-CQAs that are related to process consistency. The quality target was established using up to 154 lots of European Union (EU)- and US-sourced Herceptin® (reference product), analyzed during the developmental period of SB3.

Conclusion SB3 has been developed as a trastuzumab biosimilar approved in the EU and USA, and its manufacturing process is deemed to be robust and well-controlled within stringent quality target ranges.

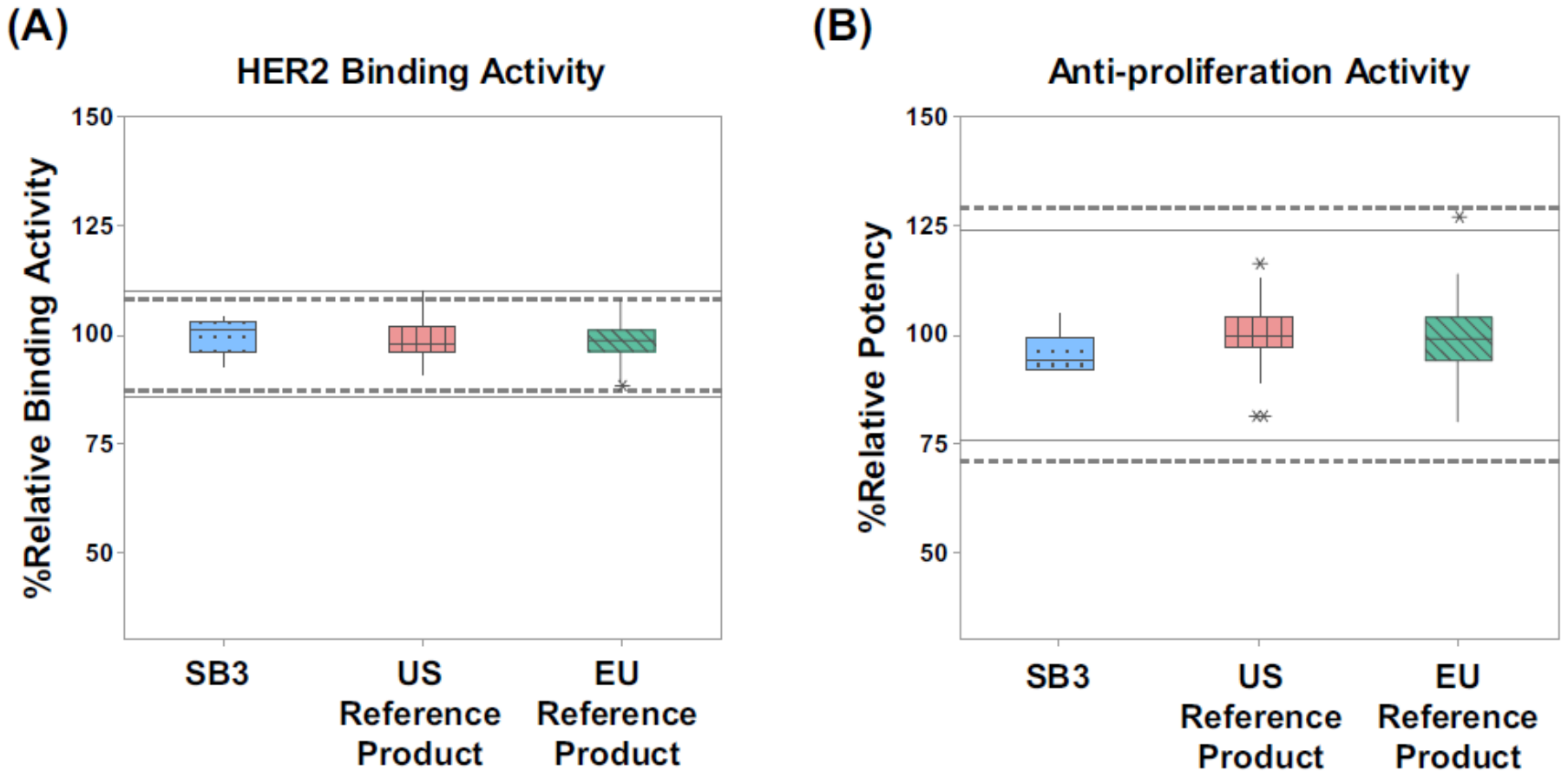
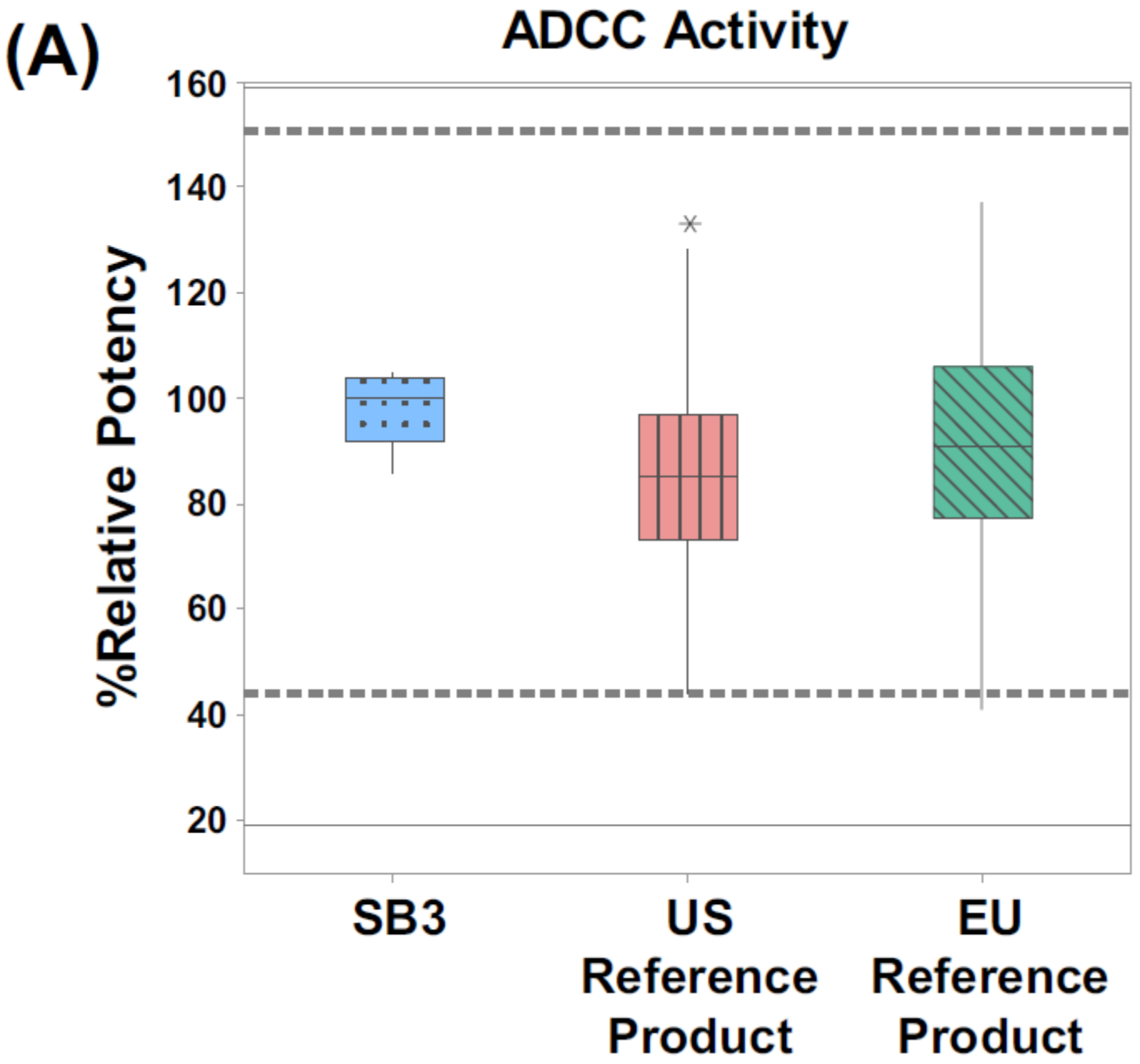


Fig. 3 Comparison of the Fab-related biological activities of SB3 and reference product. Dotted line shows the similarity range (mean ± 3SD) of pre-altered EU-sourced reference product. Solid line shows the mean ± 3SD range including pre-altered and altered EU-sourced reference product. **a** HER2 binding activity and **b** anti-proliferation activity. *HER2* human epidermal growth factor receptor 2, *SD* standard deviation


(A)
ADCC Activity
%Relative Potency
160
140
120
100
80
60
40
20
SB3
US Reference Product
EU Reference Product

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],

3.4. Immunogenicity

Up to end of study, immunogenicity was low and comparable between groups. The overall incidence of ADAs and NAbs was 0.7% (n = 3) and 0.5% (n = 2), respectively, in each treatment group.

Tabella 1. Statistiche riassuntive dei parametri farmacocinetici*.

Statistica	SB3 (n=36)	UE-trastuzumab (n=36)	USA-trastuzumab (n=36)
AUC0-∞, µg • h/mL	34.783 (5614)	35.890 (5761)	37.370 (5620)
AUC0-last, µg • h/mL	34.321 (5349)	35.368 (5524)	36.690 (5342)
Cmax, µg/mL	154 (28)	153 (25)	156 (26)
Tmax, mediana (range), h	1,58 (1,52-95,95)	1,61 (1,53-48,07)	1,57 (1,53-24,03)
t1/2, h	196 (45)	198 (42)	215 (53)
CL, mL/h	13,83 (2,10)	13,52 (2,43)	12,82 (2,24)
Cday21, µg/mL†	23,4 (4,6)	25 (5,7)	25 (6,4)

*I dati sono espressi come media (SD) salvo diversa indicazione.
†Stimato utilizzando un modello a 2 compartimenti.
Legenda: C_{day21}= concentrazione al giorno 21; UE-trastuzumab= trastuzumab originato nell'Unione Europea; USA-trastuzumab= trastuzumab originato negli Stati Uniti.
Modificato da: Pivot et al.[6].

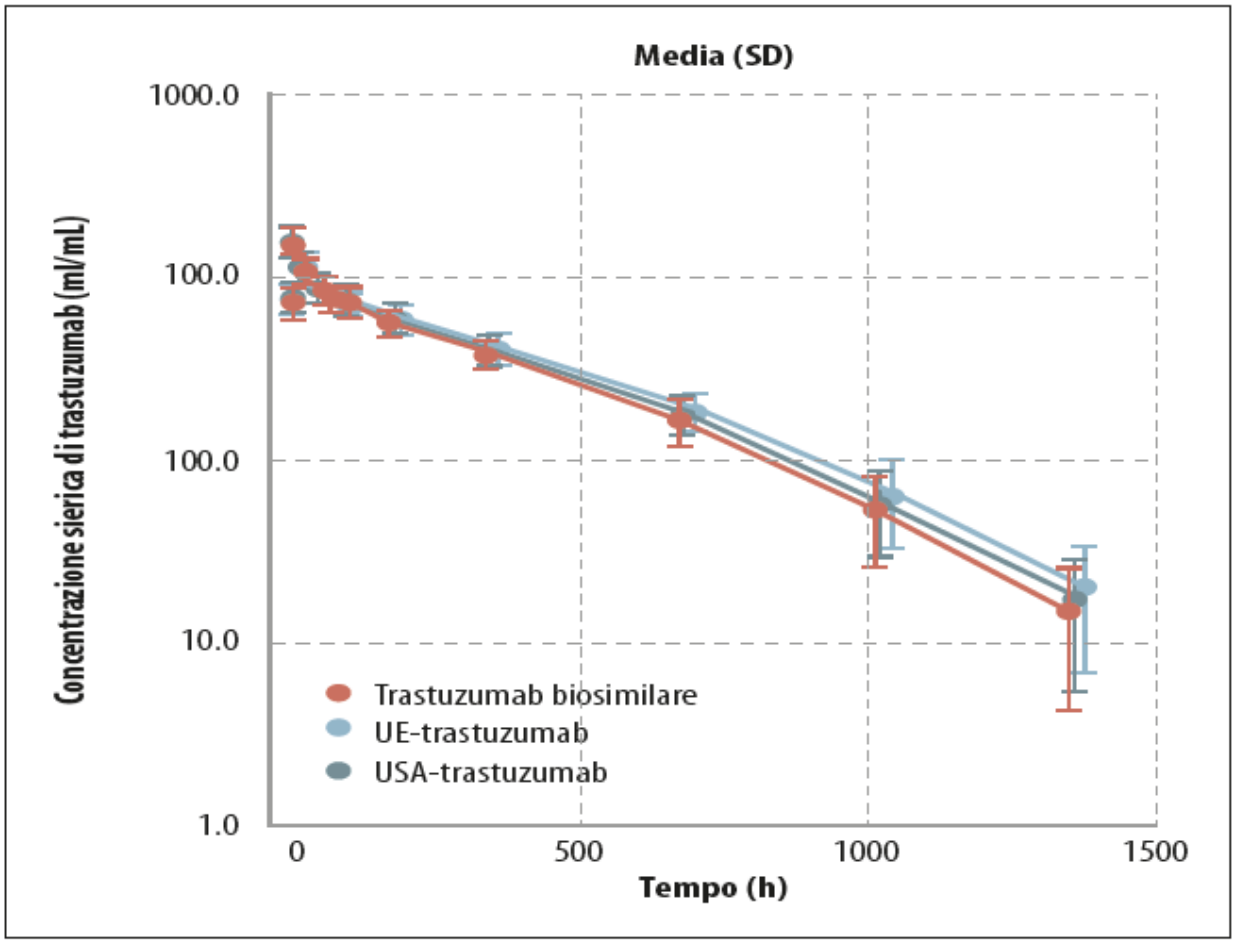


Figura 5. Profilo farmacocinetico di trastuzumab biosimilare SB3, UE-trastuzumab e USA-trastuzumab alla dose di 6 mg/kg in volontari sani di sesso maschile.
Modificata da Pivot et al.[6].

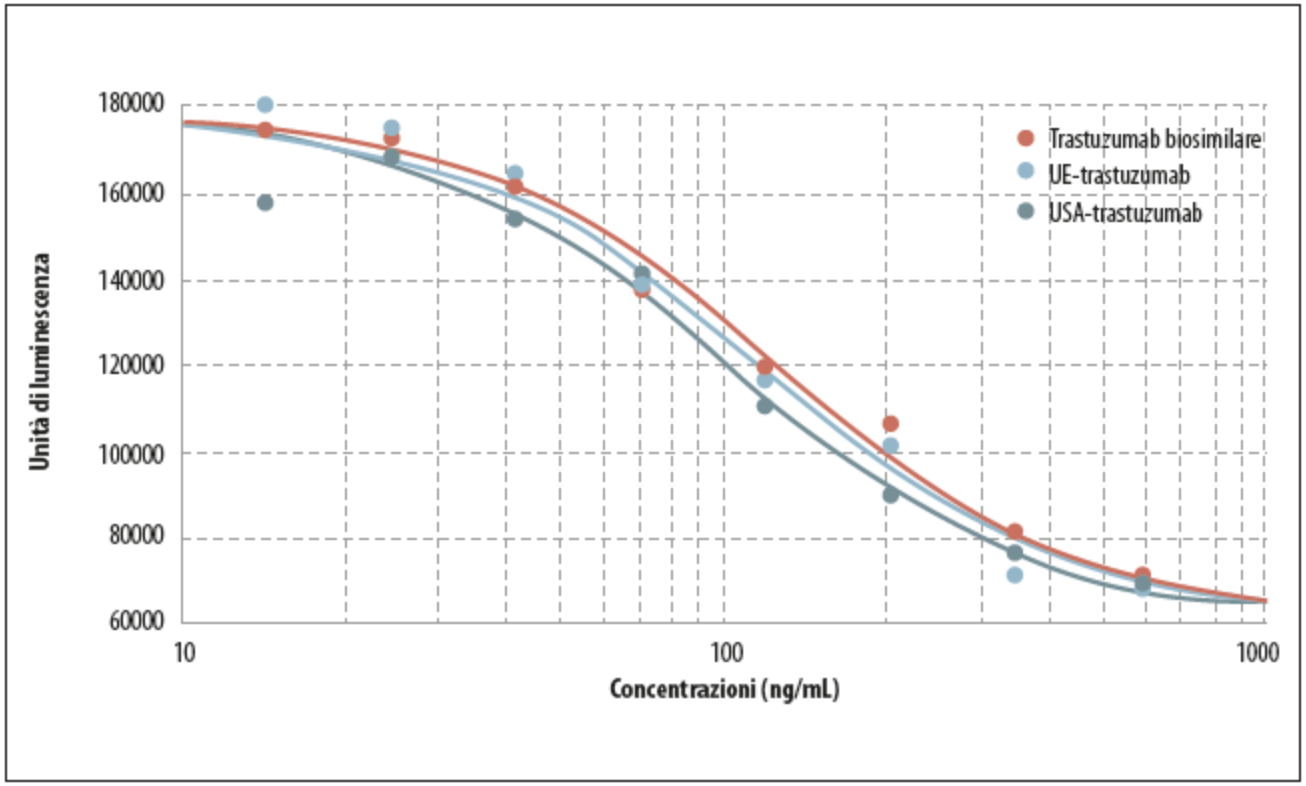


Figura 3. Effetto antiproliferativo in vitro di trastuzumab biosimilare SB3, UE-trastuzumab e USA-trastuzumab. *Modifica da* Pivot et al.[6].

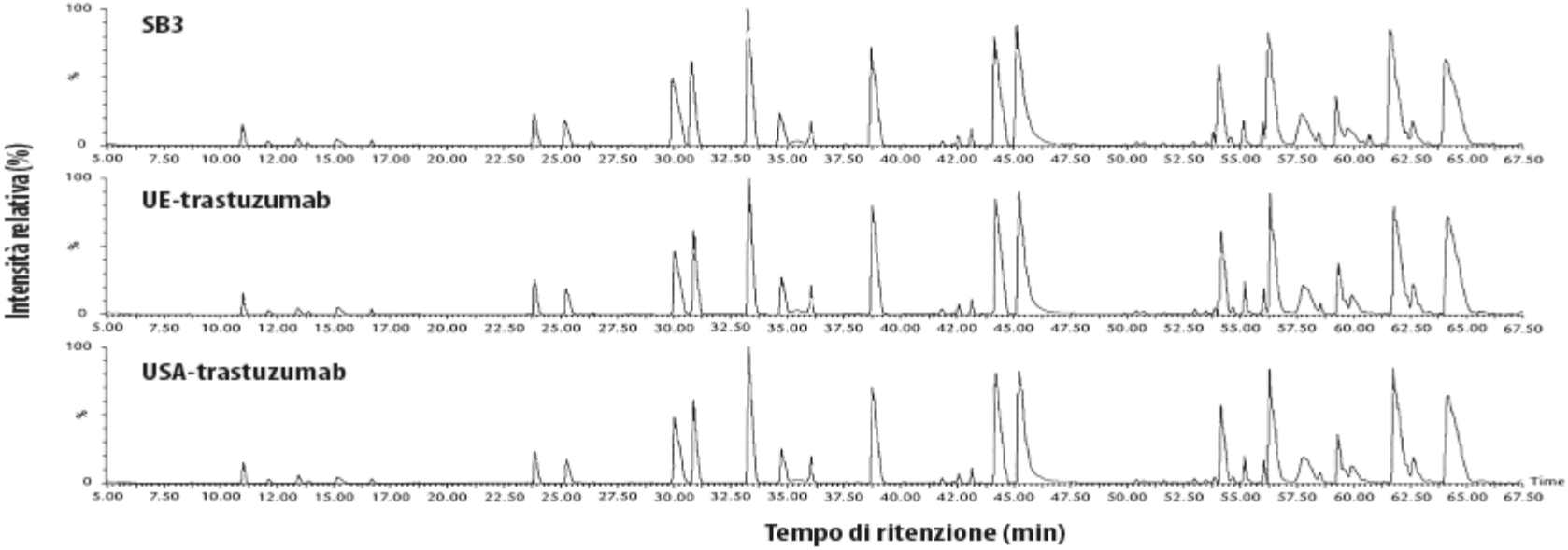


Figura 4. Mappatura di SB3, UE-trastuzumab e USA-trastuzumab utilizzando l'enzima di restrizione Lys-C.
Modificata da Pivot et al.[6].

Per la dimostrazione di biosimilarità, sono necessari studi di equivalenza

Studio di superiorità

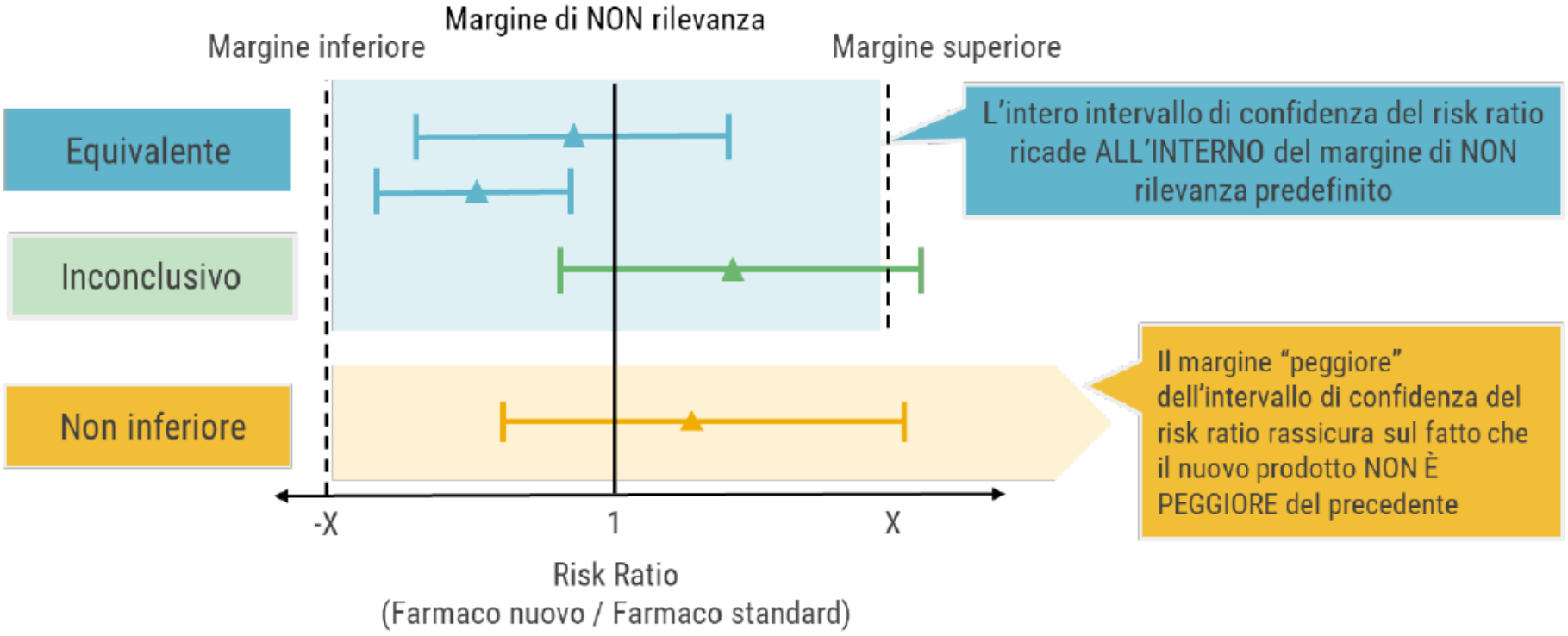
Dimostra che il farmaco è superiore al trattamento di controllo

Disegni usati per il confronto tra un nuovo farmaco e il trattamento standard

Per la dimostrazione di biosimilarità, sono necessari studi di equivalenza

Studio di equivalenza (basato su un margine pre-specificato)	Studio di non inferiorità	Studio di superiorità
Dimostra che il farmaco ha un effetto simile al comparator	Dimostra che il farmaco non è meno efficace del trattamento di controllo	Dimostra che il farmaco è superiore al trattamento di controllo
Usato per la registrazione dei farmaci biosimilari	Disegni usati per il confronto tra un nuovo farmaco e il trattamento standard	

…agli studi di equivalenza



X rappresenta il margine di NON rilevanza clinica, predefinito.

Risk ratio e intervallo di confidenza, per es. 90% o 95%.

L'esempio del trastuzumab: le diverse indicazioni

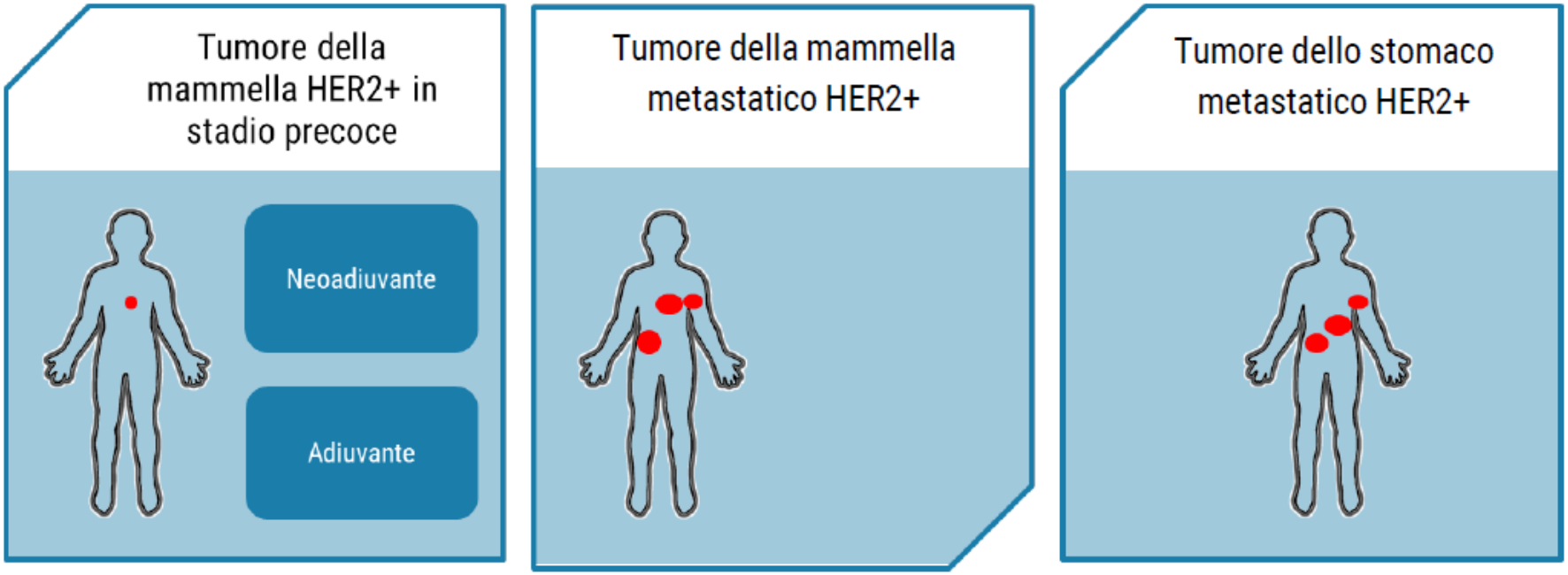
Tumore della mammella HER2+

- Tumore della mammella metastatico
- Trattamento adiuvante del tumore della mammella in stadio iniziale
- Trattamento neoadiuvante

Tumore dello stomaco HER2+

- Tumore dello stomaco o della giunzione gastroesofagea, metastatico

Studi clinici per biosimilare di trastuzumab: potenziali popolazioni di studio



Studi clinici per biosimilare di trastuzumab: potenziali popolazioni di studio

Tumore della mammella HER2+ in stadio precoce

- Popolazione più omogenea
  - Nessuno o limitati trattamenti precedenti
- Maggiore possibilità che le differenze eventualmente osservate tra i gruppi siano attribuibili al farmaco

Tumore della mammella HER2+ metastatico

Tumore dello stomaco HER2+ metastatico

- Popolazione più eterogenea
  - Possibile diversità di trattamenti precedenti sia farmacologici, sia chirurgici, sia radioterapici.
  - Possibile diversità di patologie concomitanti, sedi di malattia, sintomi, etc.
- Minore possibilità che le differenze eventualmente osservate tra i gruppi siano attribuibili al farmaco

ID 509

A Randomized, Double-Blind, Phase III Study Comparing SB3 (Trastuzumab Biosimilar) With Originator Trastuzumab In Patients Treated by Neoadjuvant Therapy for HER2-Positive Early Breast Cancer

Discussant: Aleix Prat, MD, PhD

Authors: X. Pivot, I. Bondarenko, M. Dvorkin, E. Trishkina, JH. Ahn, SA. Im, T. Sarosiek, S. Chattopadhyay, M. Wojtukiewicz, V. Moiseyenko Y. Shparyk, M. Bello III, V. Semiglazov, SJ. Song, JY. Lim

Study sponsored by Samsung Bioepis Co., Ltd.

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

VOLUME 36 · NUMBER 10 · APRIL 1, 2018

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

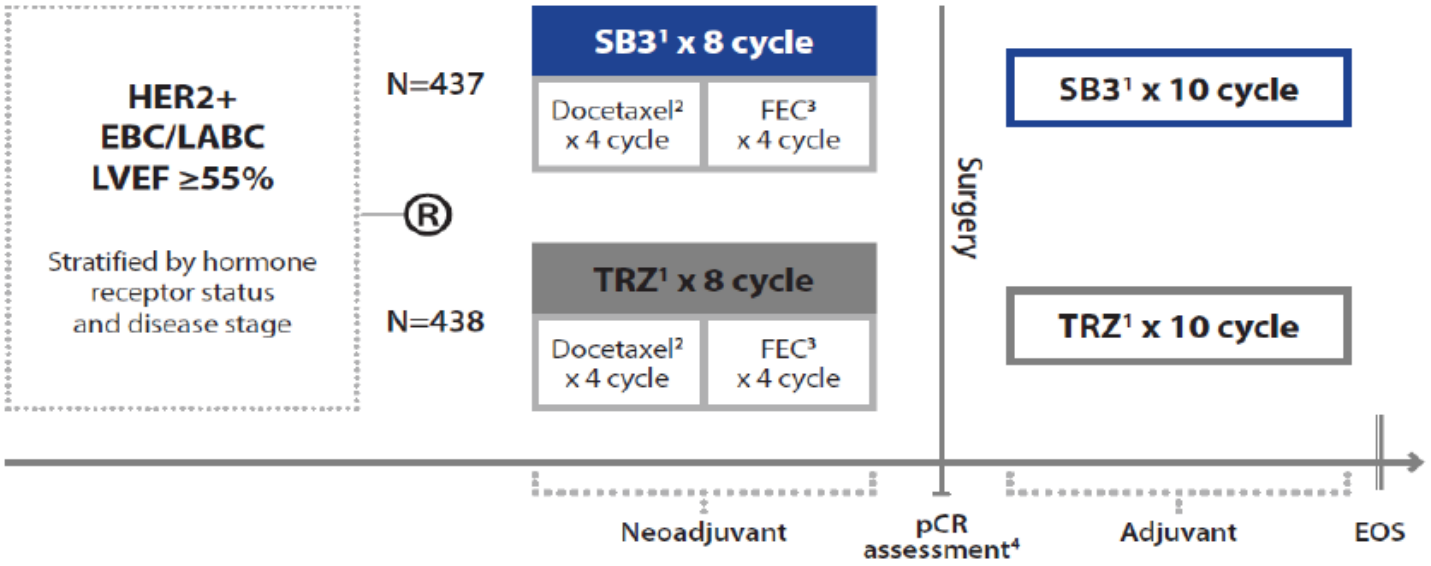
Phase III, Randomized, Double-Blind Study Comparing the Efficacy, Safety, and Immunogenicity of SB3 (Trastuzumab Biosimilar) and Reference Trastuzumab in Patients Treated With Neoadjuvant Therapy for Human Epidermal Growth Factor Receptor 2–Positive Early Breast Cancer

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

Conclusion

Equivalence for efficacy was demonstrated between SB3 and TRZ on the basis of the ratio of bpCR rates. Safety and immunogenicity were comparable.

Phase III SB3 Study Design



EOS, end of study; LVEF, left ventricular ejection fraction; ®, randomization
[1]Loading dose of 8 mg/kg and then maintenance dose of 6 mg/kg every 3 weeks
[2]Docetaxel 75 mg/m every 3 weeks
[3]5-fluorouracil 500 mg/m², epirubicin 75 mg/m², and cyclophosphamide 500 mg/m² every 3 weeks
[4]Primary endpoint: breast pathological complete response (bpCR)

Primary endpoint: breast pathologic complete response (bpCR) rate at surgery.
Secondary endpoints: total pathologic complete response (tpCR), overall response rate (ORR), event free survival (EFS), overall survival (OS), safety, pharmacokinetic, and immunogenicity

Pivot X, et al. J Clin Oncol 2018; 36:968-974

Key Eligibility Criteria

Inclusion criteria	Exclusion criteria
▪ Female age 18-65 years ▪ Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 ▪ Non-metastatic, unilateral newly diagnosed primary breast cancer, including inflammatory breast cancer ▪ Known hormone receptor (estrogen and progesterone receptor) status ▪ Baseline left ventricular ejection fraction (LVEF) ≥55% ▪ Informed consent	▪ Metastatic (stage IV) or bilateral breast cancer ▪ Pregnant or lactating women ▪ Concurrent hormone therapy ▪ History of radiation therapy, immunotherapy, chemotherapy, or biotherapy (including prior HER2 directed therapy) ▪ Serious cardiac, pulmonary, or other illness

Equivalence Margin

Equivalence is declared if:

95% CI of the difference in the bpCR rate between treatments is entirely contained within the equivalence margin of [-13%, 13%]

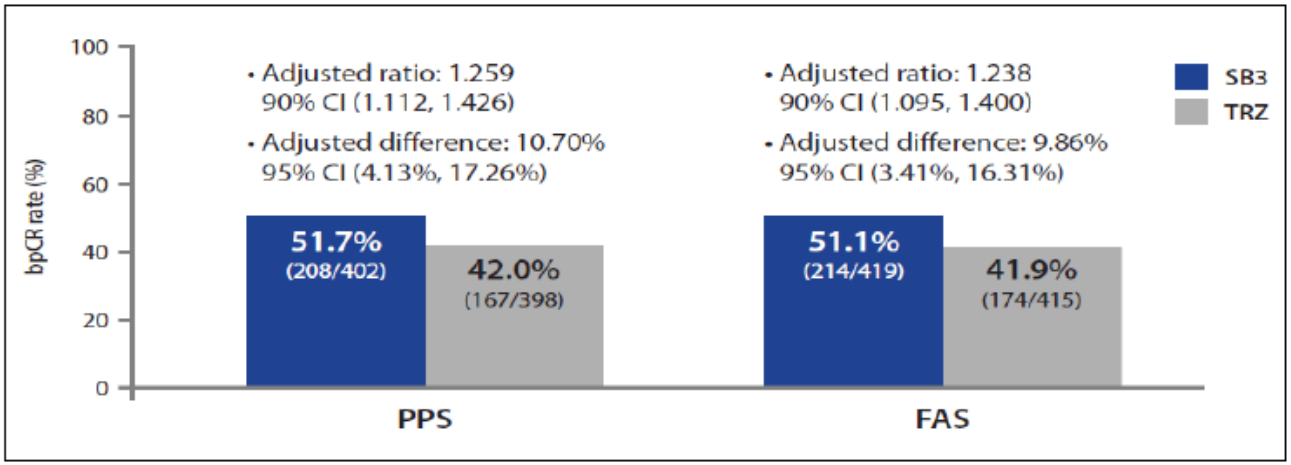
OR

90% CI of the ratio in the bpCR rate between treatments is entirely contained within the equivalence margin of [0.785, 1.546]

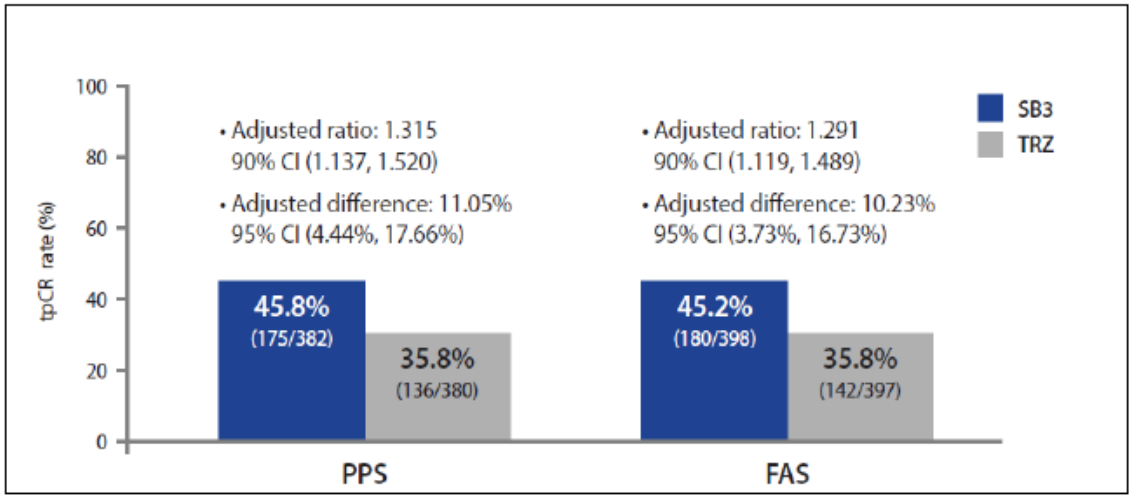
Pivot X, et al. J Clin Oncol 2018; 36:968-974

Efficacy Result

bpCR



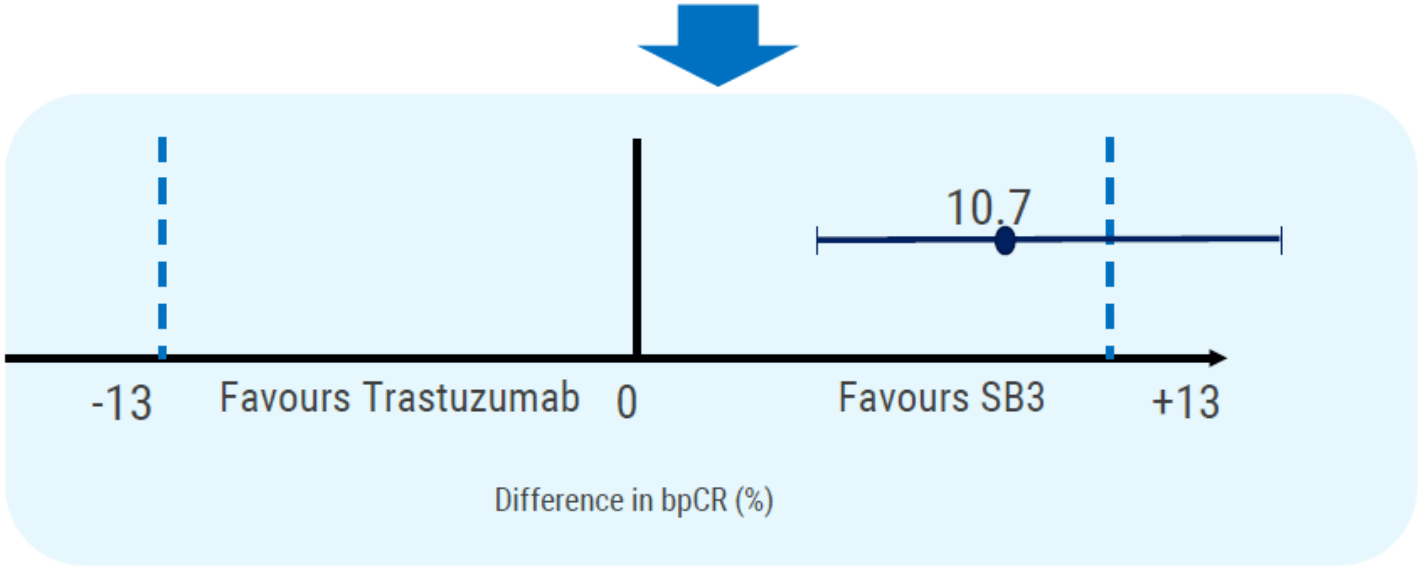
tpCR



Pivot X, et al. J Clin Oncol 2018; 36:968-974

Efficacy Result

Primary endpoint	SB3 (n=402)	Trastuzumab (n=398)
bpCR	51.7%	42%
Risk difference, (95% CI) Ratio (95% CI)	10.7% (4.13, 17.26) 1.259 (1.112 – 1.426)	



Pivot X, et al. J Clin Oncol 2018; 36:968-974

Summary of safety during overall study period

	SB3 (N=437)	TRZ (N=438)
Patients with ≥ 1 TEAE, n (%)	426 (97.5)	421 (96.1)
Frequently reported TEAEs ≥ 20% , n (%)		
Alopecia	299 (68.4)	283 (64.6)
Neutropenia	294 (67.3)	282 (64.4)
Nausea	144 (33.0)	135 (30.8)
Leukopenia	125 (28.6)	114 (26.0)
Anaemia	96 (22.0)	95 (21.7)
Diarrhoea	92 (21.1)	67 (15.3)
Fatigue	88 (20.1)	80 (18.3)
TEAEs of special interest, n (%)	48 (11.0)	53 (12.1)
Infusion-related reaction	37 (8.5)	44 (10.0)
Left ventricular systolic dysfunction (asymptomatic)	11 (2.5)	8 (1.8)
Congestive heart failure (symptomatic)	3 (0.7)	1 (0.2)
Serious TEAEs, n (%)	56 (12.8)	58 (13.2)
Deaths*, n (%)	1 (0.2)	5 (1.1)

Pivot X, et al. J Clin Oncol 2018; 36:968-974

4. Sicurezza

Le associazioni dei pazienti ritengono importante una attenta valutazione degli eventuali effetti collaterali dei biosimilari nella fase post-marketing, enfatizzando l'aspetto della farmacovigilanza, peraltro ben sottolineata dal Position Paper di AIFA 2018.

Conclusions

- Equivalence was demonstrated between SB3 and TRZ based on the ratio of bpCR rates in patients treated by neoadjuvant therapy for HER2-positive early breast cancer.
- Safety, PK, and immunogenicity were comparable.
- Complete safety and survival data will follow.

Grazie per l'attenzione

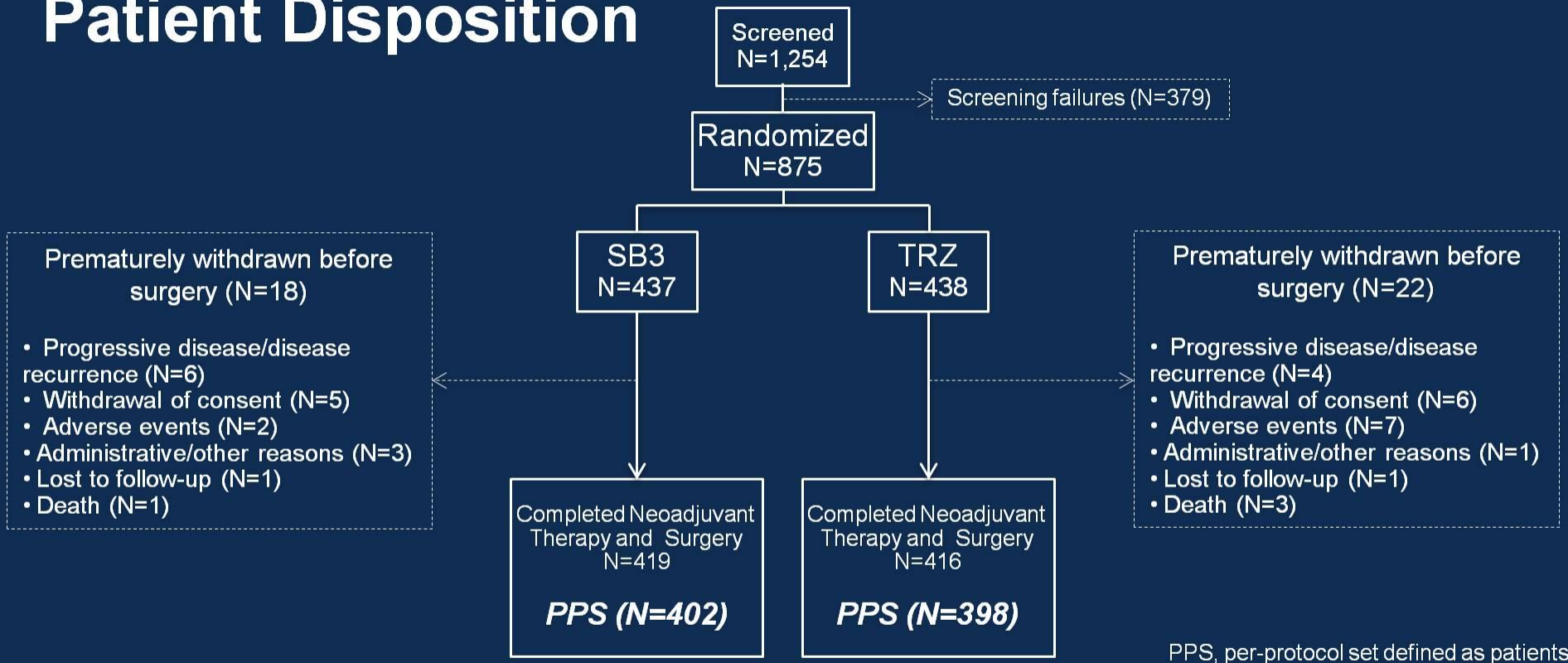
Grazie per l'attenzione

Background

- SB3, a proposed trastuzumab biosimilar, has been extensively characterized and compared with reference trastuzumab (TRZ).
- SB3 and TRZ have identical primary amino acid sequence and demonstrated highly similar structural, physiochemical, and biological activities.
- Pharmacokinetic (PK) equivalence was demonstrated between SB3 and TRZ in healthy subjects.[1]

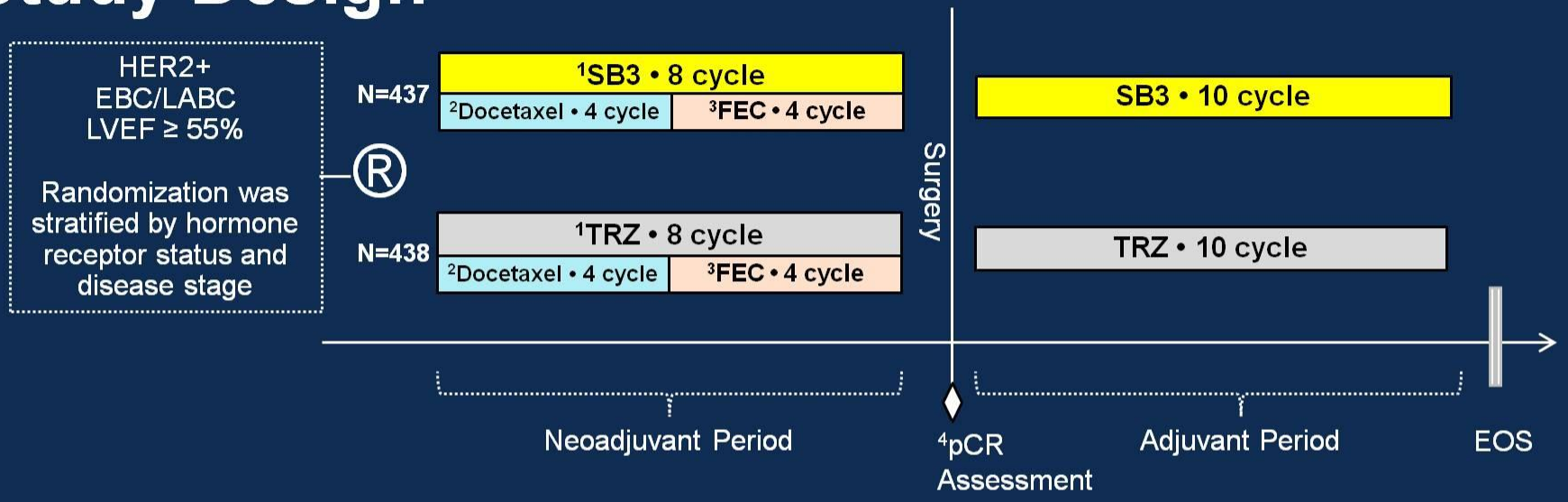
1. Pivot X, Curtit E, Lee Y, Golor G, et al. Clin Ther. 2016;38:1665-73

Patient Disposition



PPS, per-protocol set defined as patients who completed 8 cycles of neoadjuvant therapy and surgery without pre-specified major protocol deviations.

Study Design



[1]Loading dose of 8 mg/kg and then a maintenance dose of 6 mg/kg every 3 weeks

[2]Docetaxel 75 mg/m^2

[3]5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2

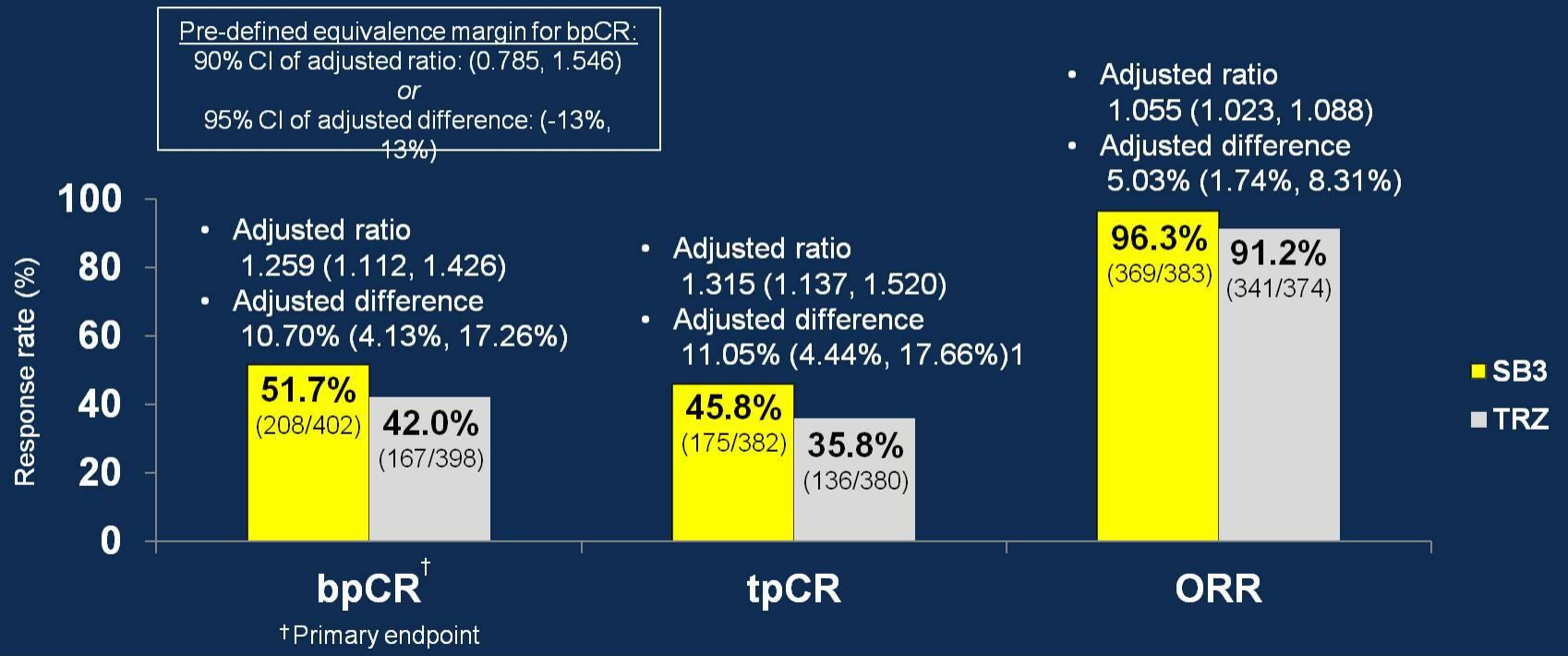
[4]Primary endpoint: pCR in breast tumor

TRZ, reference trastuzumab; pCR, pathological complete response; R, randomization; EOS, end of study

HER2+, human epidermal growth factor receptor 2 positive; EBC, early breast cancer; LABC, locally advanced breast cancer; LVEF, left ventricular ejection fraction

Efficacy in Per-Protocol Set (PPS)

- Equivalence was demonstrated between SB3 and TRZ.



Safety Profile (Neoadjuvant Period)

- Overall safety was comparable between SB3 and TRZ.

	SB3 (N=437)	TRZ (N=438)
TEAEs, n (%)	422 (96.6)	417 (95.2)
Grade 1	22 (5.0)	27 (6.2)
Grade 2	84 (19.2)	83 (18.9)
Grade 3	113 (25.9)	122 (27.9)
Grade 4	202 (46.2)	182 (41.6)
Grade 5	1 (0.2)	3 (0.7)
TEAEs of special interest, n (%)	42 (9.6)	47 (10.7)
Infusion-related reaction	36 (8.2)	44 (10.0)
Left ventricular systolic dysfunction	4 (0.9)	3 (0.7)
Congestive heart failure	2 (0.5)	0 (0.0)
Serious TEAEs, n (%)	46 (10.5)	47 (10.7)

TEAE, Treatment Emergent Adverse Events; SAE, serious adverse event; n, number of patients with TEAEs; If a patient has multiple events of the same severity or relationship, they were counted only once in that severity or relationship.