ESPERIENZE ED UTILIZZO DEI BIOSIMILARI IN ONCOLOGIA

Vincenzo Formica, MD, PhD
Medical Oncology, Department of Systems Medicine
"Tor Vergata“ University

Formica, 22/11/2017

Biosimilari in Oncologia – come approcciare il problema

- Dimensione del problema – dimensione della sostenibilità economica
- Fattibilità tecnica
- Evidenze scientifiche

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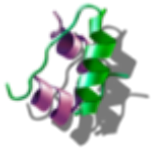
Monoclonal Antibodies Are Complex Proteins

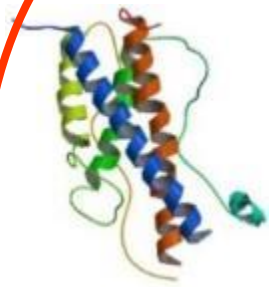
Dimensione del problema: Quanti sono i farmaci 'biosimilabili'?

Small Molecule

Acetylsalicylic acid[1]
~ 180 daltons



Insulin[2]
~ 5,700 daltons



Growth hormone[3]
191 amino acids
~ 22,000 daltons

Biologics

Monoclonal antibodies (mAb)
~ 1,300 amino acids[4]
~ 150,000 daltons[5]

Generic	Small Biologic	Large Biologic
Same Structure[6]	Highly Similar Structure[6–8]	

1. Aspirin (acetylsalicylic acid) prescribing information. Bayer, 2005; 2. Product Information: Insulin. Sigma Aldrich, 2014; 3. Growth Hormone. OMIM.org, 1986;
4. Voynov V, et al. mAbs 2009;1:580–2; 5. Lipman NS, et al. ILAR J 2005;46:258–68; 6. FDA. Information for consumers (biosimilars), 2015;
7. EMA. Guidelines on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, 2012;
8. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1), 2014.

Presenza dei MoAb 15 aa fa - 2001

	Adiuvante	I linea	II linea
K polmone	-	-	-
K mammella	-	-	**Trastuzumab**
K prostata	-	-	-
K colonretto	-	-	-
K gastrico	-	-	-
Melanoma	-	-	-
K cervice uterina	-	-	-
K ovaio	-	-	-
K testa-collo	-	-	-

Presenza dei MoAb nel 2017

	Adiuvante	I linea	II linea
K polmone	Durvalumab	Bevacizumamb Pebrolizumab	Nivolumab Pembrolizumab
K mammella	Trastuzumab	trastuzumab pertuzumab Bevacizumab	Trastuzumab TDM-1
K prostata	-	-	-
K colonretto	-	Bevacizumab Cetuximab Panitumumab	Bevacizumab Aflibercept Ramucirumab
K gastrico	-	Trastuzumab	Ramucirumab
Melanoma	Ipilimumab Nivolumab	Ipilimumab Nivolumab Pembrolizumab	Nivolumab Pembrolizumab
K cervice uterina		Bevacizumab	
K ovaio		Bevacizumab	Bevacizumab
K testa-collo	cetuximab	cetuximab	Cetuximab

Costi (approssimazione per pz di 70 kg)

Farmaco	Costo/fiala	n.Fiale per somministr.
Trastuzumab	1000€	3
Cetuximab	250 €	6
Bevacizumab	2000 €	2
Panitumumab	600 €	4
Aflibercept	1200 €	2
Ramucirumab	4700 €	1
Pertuzumab	4700 €	1
TDM-1	4800 €	2
Ipilimumab	6300 €	3
Nivolumab	2200 €	2
Pembrolizumab	5600 €	2

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Efficacia - 2 esempi

- Trastuzumab adiuvante

The NEW ENGLAND JOURNAL of MEDICINE

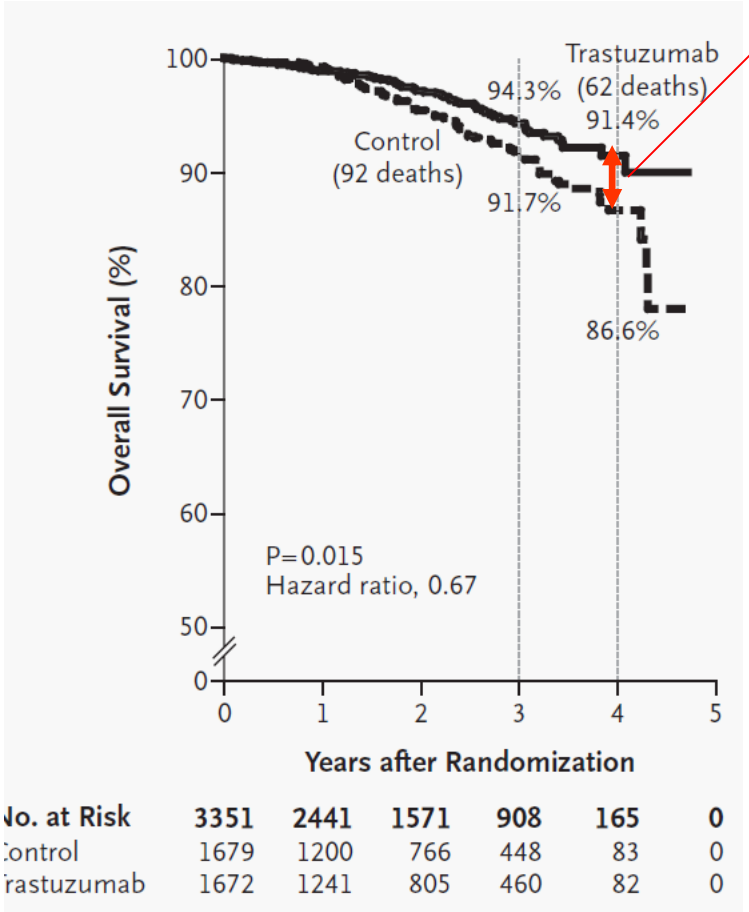
ORIGINAL ARTICLE

Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

Edward H. Romond, M.D., Edith A. Perez, M.D., John Bryant, Ph.D., Vera J. Suman, Ph.D., Charles E. Geyer, Jr., M.D., Nancy E. Davidson, M.D., Elizabeth Tan-Chiu, M.D., Silvana Martino, D.O., Soonmyung Paik, M.D., Peter A. Kaufman, M.D., Sandra M. Swain, M.D., Thomas M. Pisansky, M.D., Louis Fehrenbacher, M.D., Leila A. Kutteh, M.D., Victor G. Vogel, M.D., Daniel W. Visscher, M.D., Greg Yothers, Ph.D., Robert B. Jenkins, M.D., Ph.D., Ann M. Brown, Sc.D., Shaker R. Dakhil, M.D., Eleftherios P. Mamounas, M.D., M.P.H., Wilma L. Lingle, Ph.D., Pamela M. Klein, M.D., James N. Ingle, M.D., and Norman Wolmark, M.D.

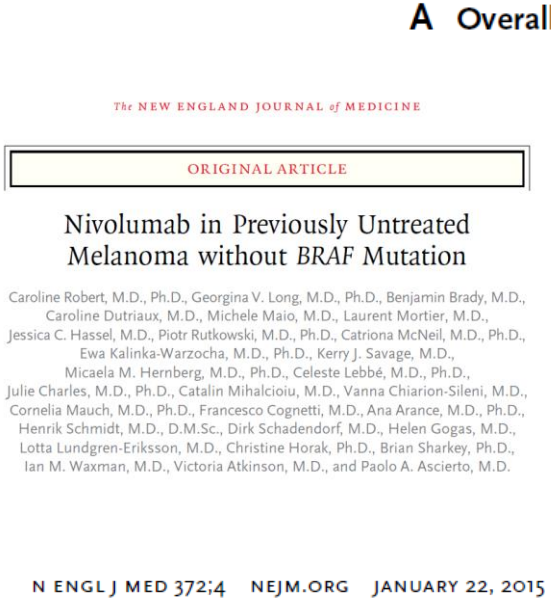
N ENGL J MED 353;16 WWW.NEJM.ORG OCTOBER 20, 2005

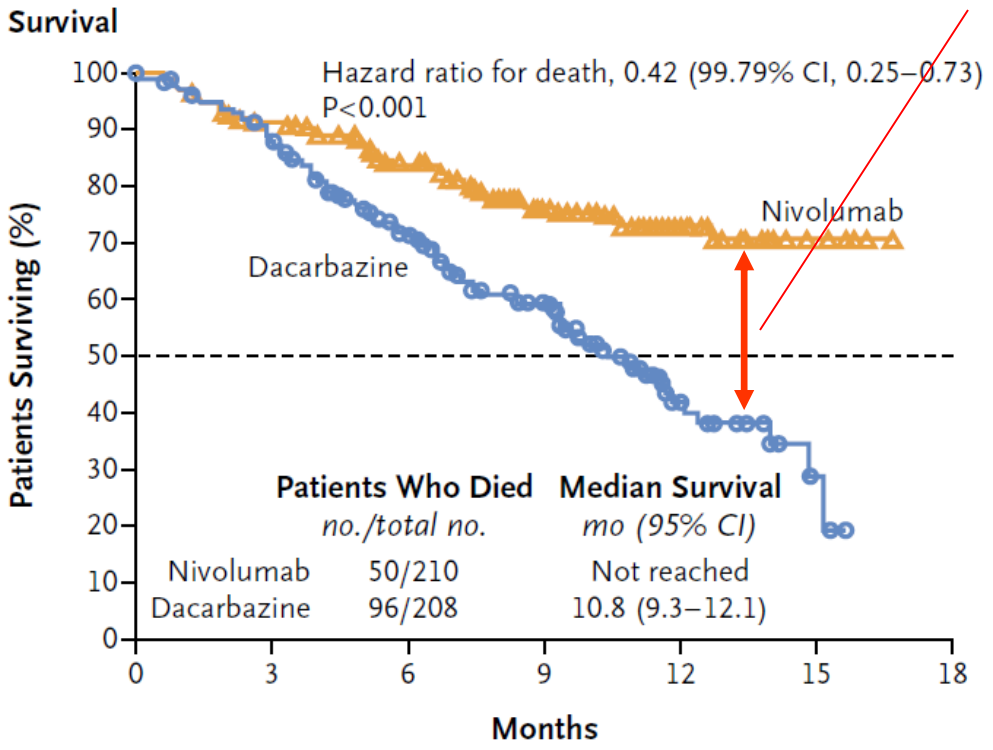
10% saved by trastuzumab



Efficacia - 2 esempi

- Immunoterapia nel melanoma





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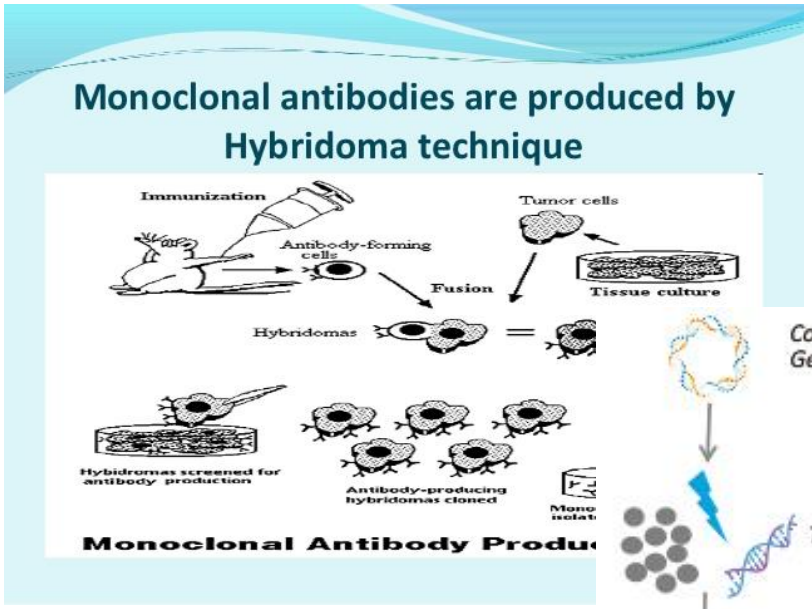
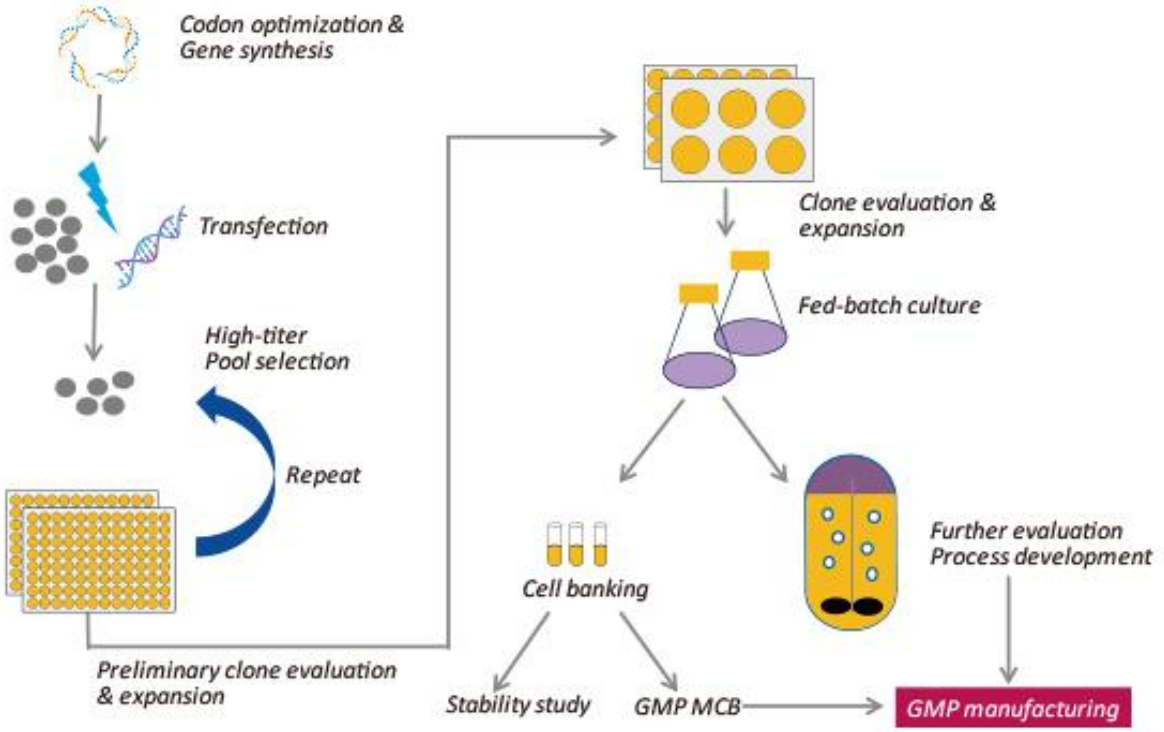
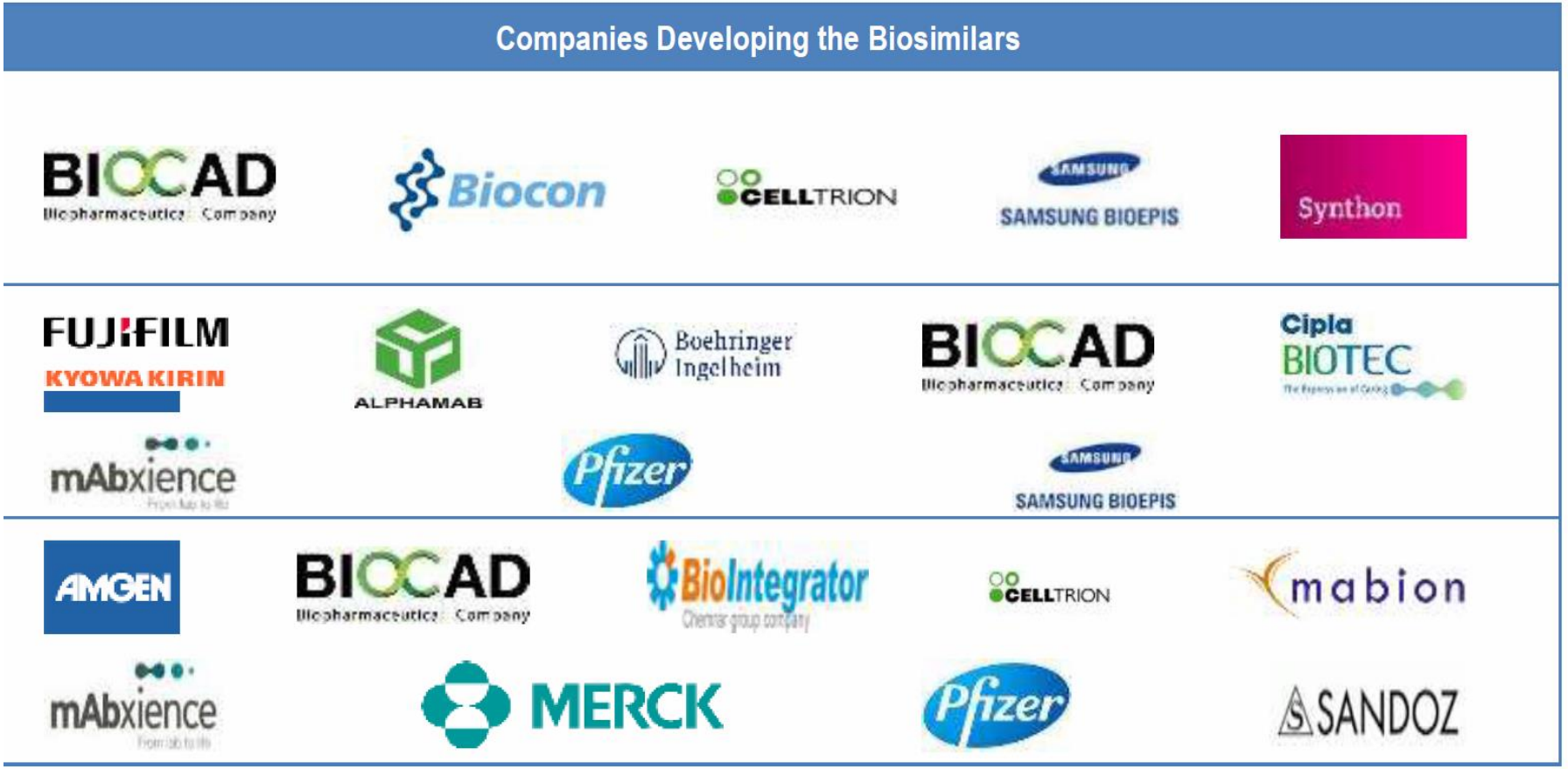
Fattibilità tecnica

Fattibilità tecnica





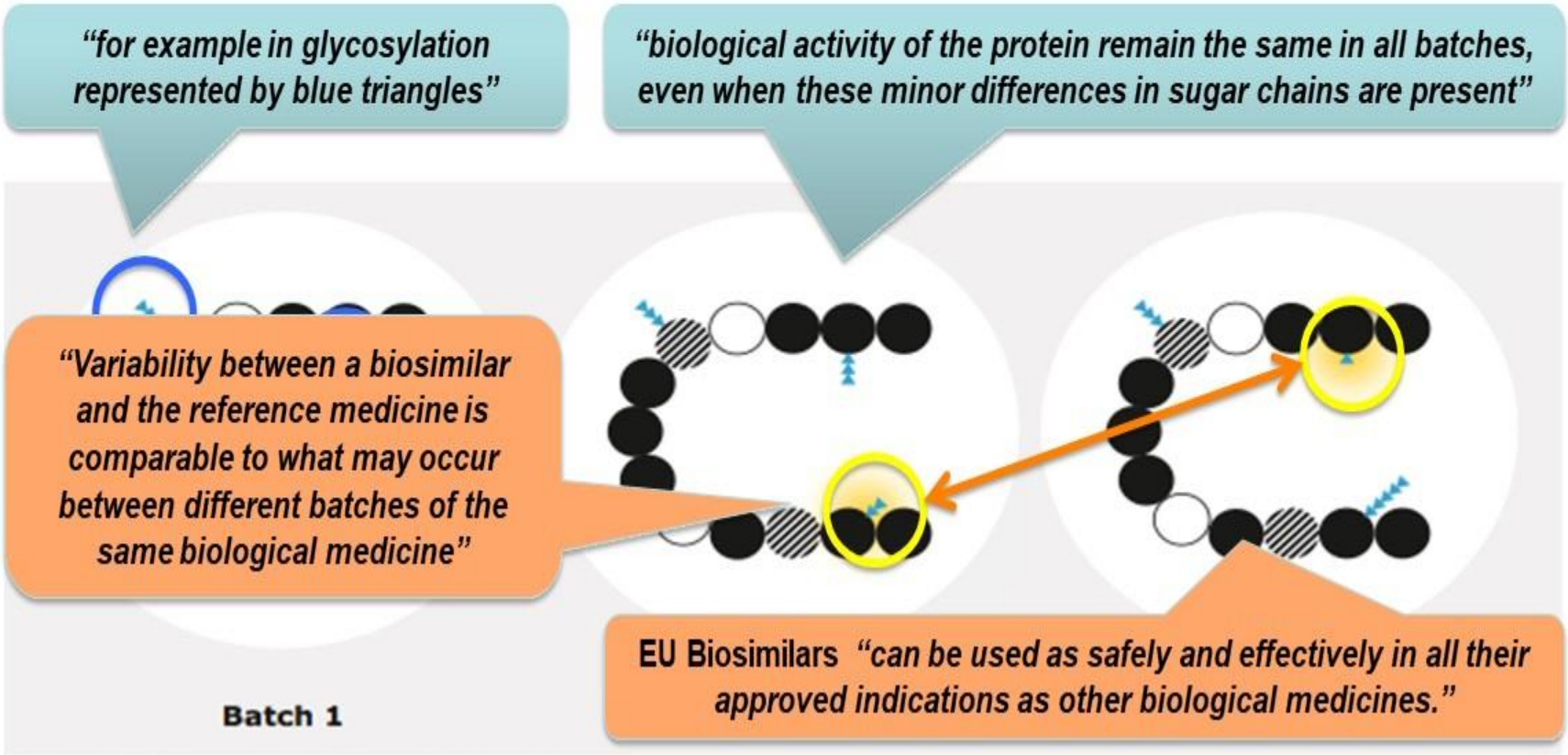
A number of companies have biosimilars in active clinical development or already approved



The European Commission and Europe's Regulators write

1

- *"Consecutive batches of the same biological medicine may show a small degree of variability within accepted ranges"*

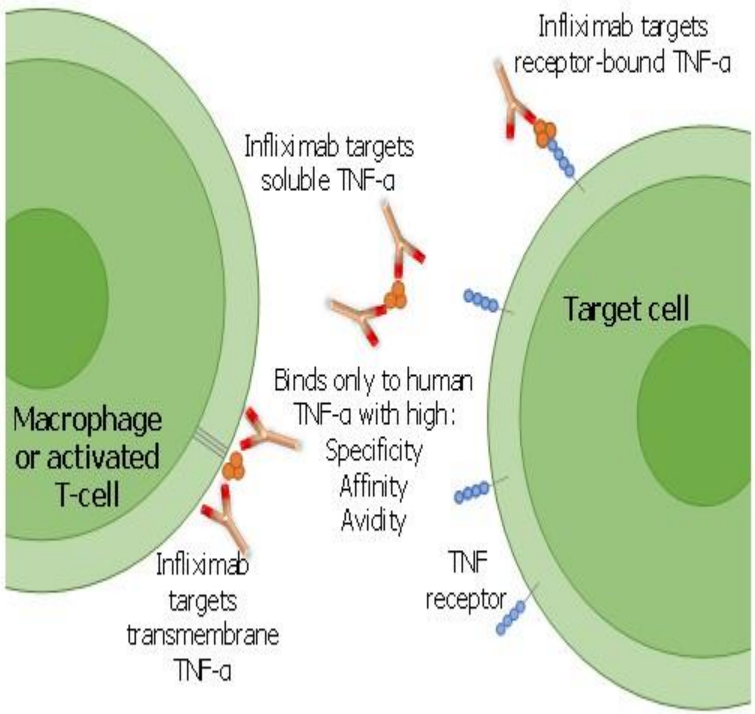


Ref: [1] Biosimilars in the EU - Information guide for healthcare professionals.
Prepared jointly by the European Medicines Agency and the European Commission. Updated on 27 April 2017

Biosimilars mAbs are more complex but indications may also be extrapolated: infliximab biosimilars

2

Infliximab mode of action



Key clinical data and extrapolation

CT-P13, SB2
Infliximab biosimilars

RA
Confirmatory equivalence trial

CT-P13: Phase 1 PK in ankylosing spondylitis

or

SB2: Phase 1 PK in healthy subjects

Extrapolated to **Crohn's disease**

Extrapolated to **Ulcerative colitis**

Extrapolated to **Ankylosing spondylitis**

Extrapolated to **Psoriatic arthritis**

Extrapolated to **Psoriasis**

EMA. European Product Assessment Reports for Remsima®, Inflectra® and Flixabi®. Accessed April 2017

RA, rheumatoid arthritis

Presenza dei MoAb nel 2017

2

	Adiuvante	I linea	II linea
K polmone	Durvalumab	Bevacizumamb Pebrolizumab	Nivolumab Pembrolizumab
K mammella	Trastuzumab	trastuzumab pertuzumab Bevacizumab	TDM-1 Trastuzumab
K prostata	-	-	-
K colonretto	-	Bevacizumab Cetuximab Panitumumab	Bevacizumab Aflibercept Ramucirumab
K gastrico	-	Trastuzumab	Ramucirumab
Melanoma	Ipilimumab Nivolumab	Ipilimumab Nivolumab Pembrolizumab	Nivolumab Pembrolizumab
K cervice uterina		Bevacizumab	
K ovaio		Bevacizumab	Bevacizumab
K testa-collo	cetuximab	cetuximab	Cetuximab

The promise of biosimilar medicines

High cost biologics create a problem

Cost savings from biosimilars

That cheaper biologics could resolve

Challenge		Result
Effective targeted therapy held back for later stage of disease	→	Effective targeted therapy used earlier in the disease
Treatment reserved for only the most severe cases	→	More patients have access to treatment
Innovative therapies unaffordable	→	Biosimilars free up budget to buy innovative medicines
Budgets for certain therapy areas are inadequate	→	Additional budget can be directed to areas of unmet need

Ref: [1] Adapted from Henry D, Taylor C. Semin Oncol 2014;41(Suppl 3):S13–20

Societies and organisations recognise the importance of biosimilars for a sustainable healthcare system

Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers

Tabernero J, Vyas M, Giuliani R, Arnold D, Cardoso F, Casali PG, Cervantes A, Eggermont AMM, Eniu A, Jassem J, Pentheroudakis G, Peters S, Rauh S, Zielinski CC, Stahel RA, Voest E, Douillard J-Y, McGregor K, Ciardello F

European Society for Medical Oncology (January 2017)
"Biosimilars (similar versions of the originator biologics) present a necessary opportunity for physicians, patients and healthcare systems. If properly developed clinically, manufactured to the correct standards and used appropriately (with both the physician and patient being well informed), they can positively impact the financial sustainability of healthcare systems, globally."

Spanish Society of Medical Oncology (February 2015)
"When it comes to initiating a biological treatment in oncology (biosimilar or reference), the medical oncologist must have freedom of prescription, considering sustainability criteria and available evidence."

SEOM

Sociedad Española de Oncología Médica
Posicionamiento SEOM sobre los anticuerpos biosimilares

1. Properly developed clinically
2. Manufactured to the correct standards
3. Used appropriately with both the physician and patient being well informed

Tabernero J, et al. ESMO Open 2016;1:e000142;
SEOM. Posicionamiento SEOM sobre los anticuerpos biosimilares, 2015

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MoAb biosimilari in Oncologia – maggiore complessità

1. Molti studi di fase I – safety, PK, PD, immunogenicità

2. Alcuni studi di fase III: Endpoint clinici complessi – e non sempre valutabili nel breve-termine:
   1. risposta radiologica vs Soprevvivenza
   2. Safety

Anti-cancer biosimilars

Biosimilar	Available Data
Trastuzumab*	
Myl-1401O	Phase III (*HER2*-positive MBC): equivalent ORR at week 24 in combination with taxanes and comparable safety (N = 500)[17]
CT-P6	Phase III (*HER2*-positive MBC): similar ORR and TTP in combination with paclitaxel (N = 475)[18] Phase III (*HER2*-positive neoadjuvant): similar pCR rates and comparable safety (N = 549)[19]
BCD-022	Phase III (*HER2*-positive MBC): noninferiority to trastuzumab in combination with paclitaxel; similar safety, tolerability, and immunogenicity (N = 126)[20]
SB3	Phase III (*HER2*-positive neoadjuvant): equivalence by ratio of breast pCR rates; similar safety, pharmacokinetics, and immunogenicity (N = 800)[21]
Bevacizumab‡	
BCD-021	Phase III (nonsquamous NSCLC): similar ORR, safety, and immunogenicity in combination with carboplatin plus paclitaxel (N = 138)[25]
ABP-215	Phase III (nonsquamous NSCLC): no clinically meaningful differences with regard to efficacy or safety in combination with carboplatin plus paclitaxel (N = 642)[26]
Cetuximab§	
STI-001	Phase III (colorectal cancer): press release reported positive results from a Chinese trial, but data not yet published[27]

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Trastuzumab

Trastuzumab biosimilars are currently undergoing regulatory review

Company	Biosimilar	Submitted to EMA	Submitted to FDA
Amgen	ABP 980	✓	✓
Biocon/Mylan	MYL-1401O	✓ (withdrawn)	✓
Celltrion	CT-P6	✓	✓
Samsung Bioepis	SB3	✓	
Biocad	BCD-022	Approved by the Ministry of Health of the Russian Federation	

Adapted from Gabi Online. Biosimilars of trastuzumab. Updated July 2017. Available at: http://www.gabionline.net/Biosimilars/General/Biosimilars-of-trastuzumab; Celltrion press release. July 2017. Available at: https://www.celltrion.com/en/pr/reportDetail.do?seq=440; Biocon press release. November 2013. Available at: http://www.biocon.com/biocon_press_releases_261113.asp; Amgen press release. July 2017. Available at http://www.amgen.com/media/news-releases/2017/07/amgen-and-allergan-submit-biosimilar-biologics-license-application-for-abp-980-to-us-food-and-drug-administration/; All websites accessed August 2017.

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

JAMA. doi:10.1001/jama.2016.18305
Published online December 1, 2016.

Hope S. Rugo, MD; Abhijit Barve, MD, PhD, MBA; Cornelius F. Waller, MD; Miguel Hernandez-Bronchud, MD, PhD; Jay Herson, PhD; Jinyu Yuan, PhD; Rajiv Sharma, MBBS, MS; Mark Baczkowski, MS, RPh; Mudgal Kothekar, MD; Subramanian Loganathan, MD; Alexey Manikhas, MD; Igor Bondarenko, MD; Guzel Mukhametshina, MD; Gia Nemsadze, MD, PhD; Joseph D. Parra, MD; Maria Luisa T. Abesamis-Tiambeng, MD; Kakhaber Baramidze, MD, PhD; Charuwan Akewanlop, MD; Ihor Vynnychenko, MD; Virote Sriuranpong, MD; Gopichand Mamillapalli, MS, MCh; Sirshendu Ray, MS; Eduardo P. Yanez Ruiz, MD; Eduardo Pennella, MD, MBA; for the Heritage Study Investigators

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

Summary

Background CT-P6 is a proposed biosimilar to reference trastuzumab. In this study, we aimed to establish equivalence

Lancet Oncol 2017

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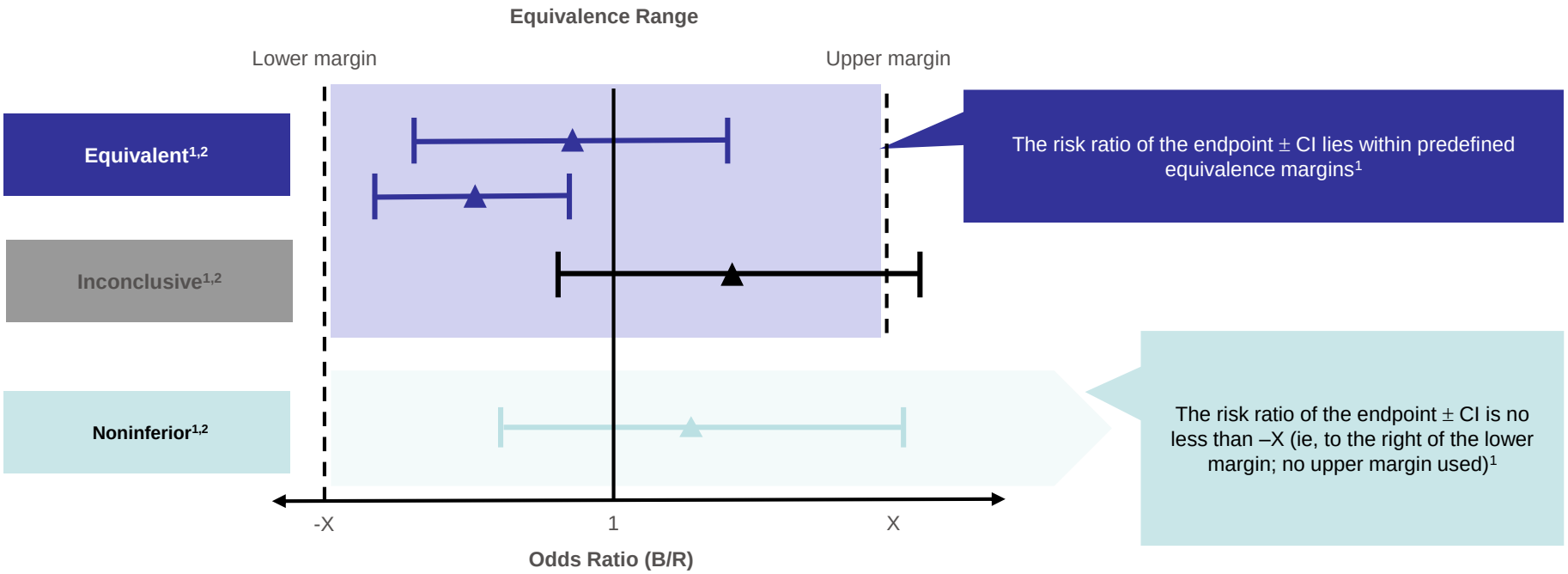
Equivalence Studies Are Designed to Demonstrate No Clinically Meaningful Differences Between the Biosimilar (B) and Reference (R) Product[1]



X is the predefined acceptable equivalence margin.

Risk ratio and 90% or 95% CI.

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CI = confidence interval.

1. Isakov L. Am J Ther 2016;23:e1903–10; 2. Pater C. Curr Control Trials Cardiovasc Med 2004;5:8.

Equivalence margins: how similar is similar enough?

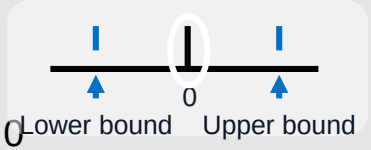
- ‘Minimal Clinically Important Difference’ (MCID)

ORR difference (OD)

Confidence interval for the **absolute difference** in primary endpoint between biosimilar and reference product

% biosimilar – % reference product

•If drugs have same efficacy, ORR difference = 0



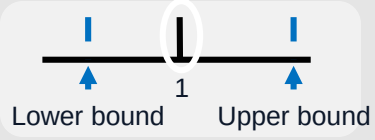
EMA
European Medicines Agency

Odds ratio (OR)

Confidence interval for the **ratio** of primary endpoint for biosimilar versus reference product

$$\frac{\%\ \text{biosimilar}}{\%\ \text{reference product}}$$

•If drugs have same efficacy, odds ratio = 1



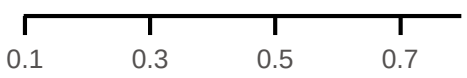
FDA
US Food and Drug Administration

EMA. ICH Topic E 9 statistical principles for clinical trials, 1998. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf;
FDA. Guidance for industry statistical approaches to establishing bioequivalence, 2001. Available at: http://www.fda.gov/downloads/Drugs/Guidances/ucm070244.pdf. Accessed August 2017.

Results

Historical Results of Trastuzumab Studies

Reference	Treatment	N	pCR rate (95% CI)[a]
Untch 2011	Trastuzumab	217	0.39 (0.32, 0.46)
Dawood 2007	Trastuzumab	40	0.55 (0.38, 0.71)
Mittendorf 2009	Trastuzumab	142	0.51 (0.42, 0.59)
Untch 2010	Trastuzumab	426	0.40 (0.35, 0.45)
Holmes 2011	Trastuzumab	33	0.55 (0.36, 0.72)
Guarneri 2012	Trastuzumab	36	0.25 (0.12, 0.42)
Bayraktar 2012	Trastuzumab	235	0.58 (0.52, 0.65)
Roche 2012	Trastuzumab	298	0.41 (0.35, 0.46)
Untch 2012	Trastuzumab	307	0.45 (0.39, 0.50)
Buzdar 2007	Trastuzumab	45	0.60 (0.44, 0.74)
Gianni 2010	Trastuzumab	117	0.38 (0.30, 0.48)



pCR rate

[a]Calculated using exact method

von Minckwitz et al. ESMO 2017, Poster discussion 151 PD

Studio Heritage

JAMA | Original Investigation

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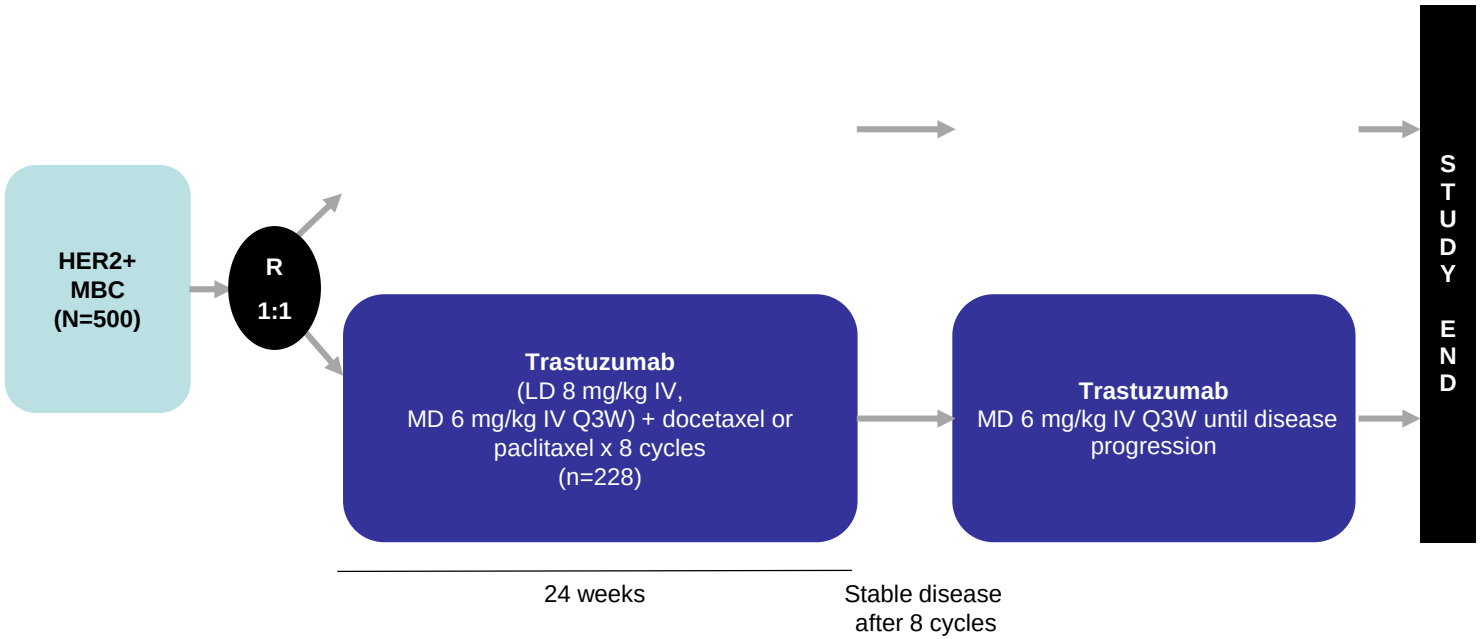
MYL-1401O vs trastuzumab: Phase 3 equivalence study in HER2+ MBC (HERITAGE)



Primary endpoints

- Part 1: ORR (CR or PR) at Week 24: ITT population
  - 90% CI for risk ratio: 0.81–1.24
  - 95% CI for risk difference: -15%; +15%
- Part 2: safety, tolerability and immunogenicity

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Rugo HS, et al. JAMA 2017;317:37–47.

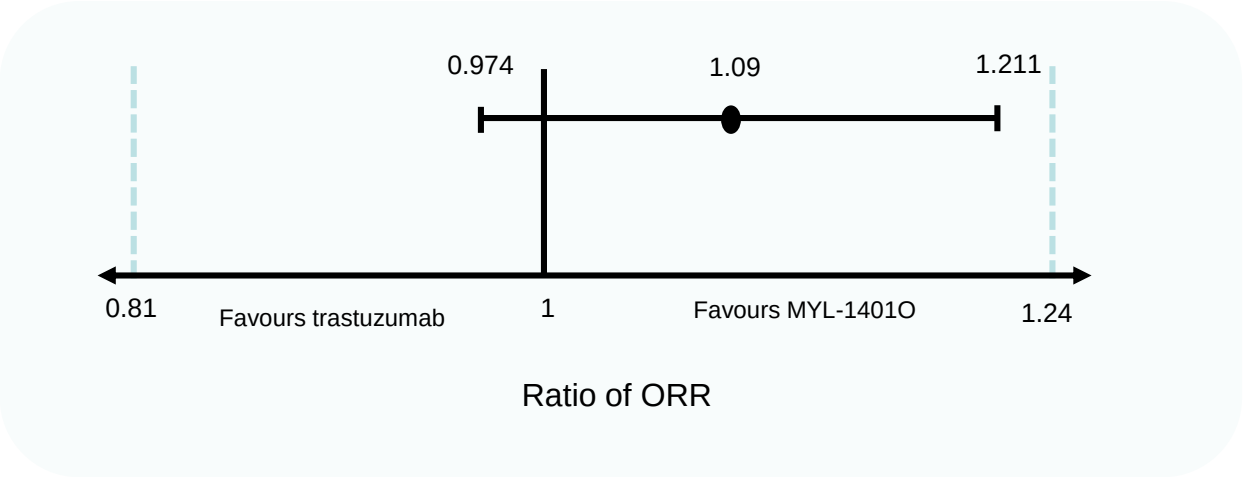
CR, complete response; LD, loading dose; MD, maintenance dose; ORR, overall response rate; PR, partial response.

Methods

- Trastuzumab (Herceptin; Roche Pharma AG) or the proposed biosimilar (MYL-1401O;Mylan) iv every 3 weeks.
  - initial 8-mg/kg loading dose, 90 minutes
  - 6mg/kg over 30 minutes.
- Investigator decision, at each study site to all patients
  - Docetaxel 75 mg/m2 every 3 weeks
  - paclitaxel at 80 mg/m2 weekly (Paclitaxel could be omitted by investigator choice for 1 week every 4 weeks)

MYL-1401O vs trastuzumab in HER2+ MBC: Primary endpoint at Week 24

Primary endpoint	MYL-1401O (n=230)	Trastuzumab (n=228)
ORR (ITT), %	69.6	64.0
Risk ratio* (90% CI)	1.09 (0.974, 1.211)	
Risk difference (95% CI)	5.53 (-3.08, 14.04)	



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Rugo HS, et al. JAMA 2017;317:37–47.

*Primary endpoint.

MYL-1401O vs trastuzumab in HER2+ MBC: Secondary outcomes at Week 48

	MYL-1401O (n=230)	Trastuzumab (n=228)	P value
Time to tumour progression			
Events, % patients	41.3	43.0	0.68
Kaplan-Meier estimate, months Median (95% CI)	11.1 (8.83–11.20)	11.1 (8.88–11.20)	
PFS			
Events, % patients	44.3	44.7	0.84
Kaplan-Meier estimate, months Median (95% CI)	11.1 (8.81–11.20)	11.1 (8.60–11.20)	
OS			
Events, % patients*	10.9	14.9	0.13

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Rugo HS, et al. JAMA 2017;317:37–47.

*Kaplan-Meier estimate was not estimable.
OS, overall survival; PFS, progression-free survival.

AEs

Serious Adverse Events[b]			
≥1 Serious adverse event	94 (38.1)	89 (36.2)	183 (37.1)
CTCAE preferred term			
Neutropenia	68 (27.5)	62 (25.2)	130 (26.4)
Neutropenia with fever	11 (4.5)	10 (4.1)	21 (4.3)
Leukopenia	4 (1.6)	12 (4.9)	16 (3.2)
Pneumonia	4 (1.6)	5 (2.0)	9 (1.8)

[b] Serious adverse events, defined by the investigator as grade 4 or requiring hospitalization, by week 24 in at least 2% of patients in either treatment group, in descending order of frequency in the overall safety population.

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Cardiac Function

Table 5. Descriptive Statistics for Cardiac Function (LVEF Values) by Visit in the Safety Population

	LVEF, %			
	Proposed Biosimilar + Taxane (n = 247)		Trastuzumab + Taxane (n = 246)	
Visit and Statistic	Observed	Change From Baseline	Observed	Change From Baseline
Baseline[a,b]	(n = 246)		(n = 244)	
Mean (95% CI)	64.0 (63.3 to 64.7)		64.1 (63.4 to 64.8)	
Median (range)	64.0 (51 to 82)		63.0 (51 to 84)	
Week 12[b]	(n = 212)	(n = 212)	(n = 209)	(n = 207)
Mean (95% CI)	63.3 (62.4 to 64.1)	−1.0 (−1.7 to −0.2)	63.4 (62.6 to 64.2)	−0.8 (−1.5 to −0.2)
Median (range)	63.0 (28 to 79)	−1.0 (−29 to 14)	63.0 (52 to 82)	0.0 (−16 to 14)
Week 24[b]	(n = 148)	(n = 148)	(n = 140)	(n = 138)
Mean (95% CI)	63.6 (62.8 to 64.4)	−0.6 (−1.5 to 0.2)	63.2 (62.2 to 64.2)	−0.9 (−1.8 to −0.1)
Median (range)	63.5 (50 to 81)	−1.0 (−13 to 21)	63.0 (41 to 82)	−1.0 (−19 to 13)

Abbreviation: LVEF, left ventricular ejection fraction.

[a] Screening visit, prior to the first dose of study drug.

[b] Sample sizes are the numbers of patients with available data within the treatment group.

Adiuvante CT-P6

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

Summary

Background CT-P6 is a proposed biosimilar to reference trastuzumab. In this study, we aimed to establish equivalence

Lancet Oncol 2017

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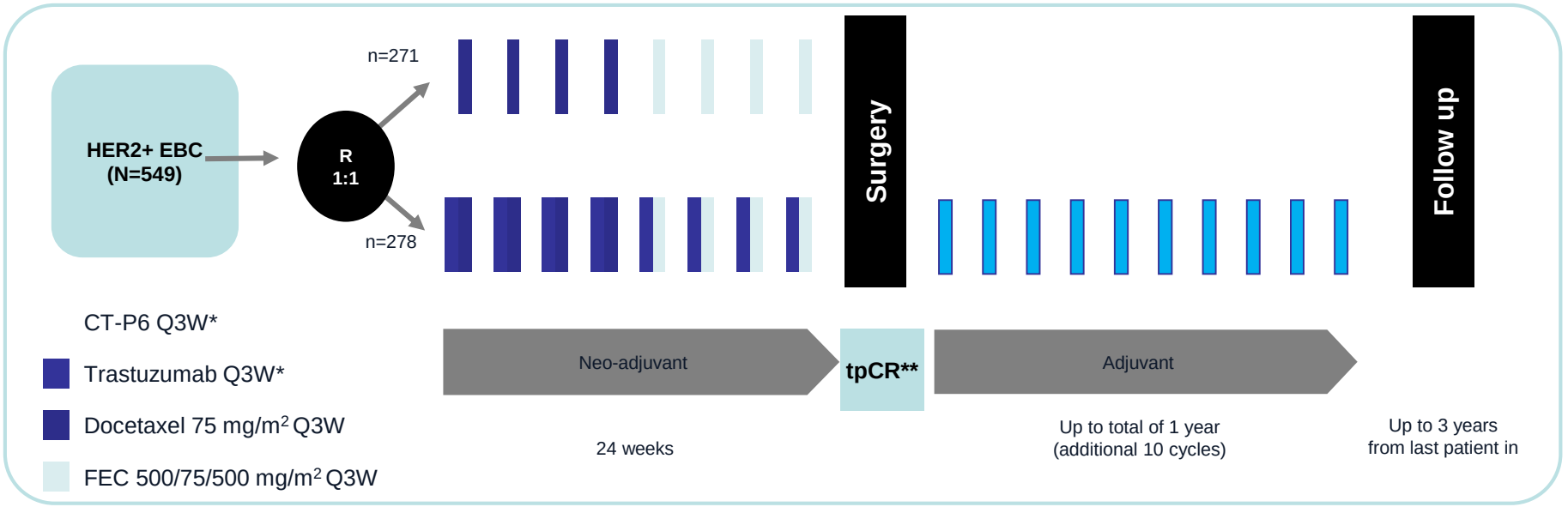
CT-P6 vs trastuzumab: Phase 3 equivalence study in HER2+ EBC



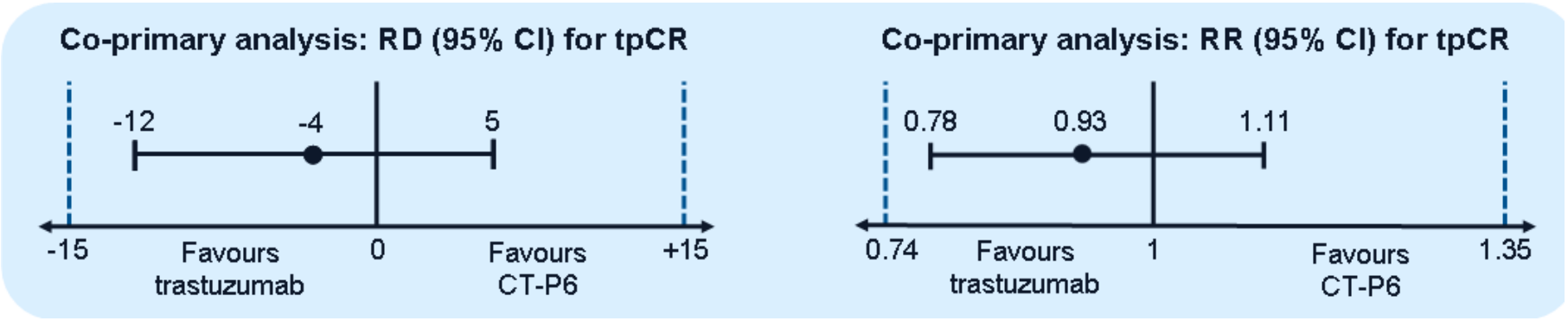
- **Primary endpoint**
  - tpCR (breast and lymph; ypT0/is ypN0) after neoadjuvant therapy and surgery (up to 30 weeks)†; per protocol set
  - Pre-defined equivalence margins: 95% CI for risk ratio 0.74–1.35; 95% CI for risk difference +/-15%
- Secondary endpoints
  - Efficacy: breast pCR (ypT0/is), pCR without DCIS (ypT0 ypN0), ORR, breast conservation rate, DFS, PFS, OS
  - Other: PK, PD, biomarkers and safety

*Subjects who go through neoadjuvant period completely (24 weeks) will receive surgery within 3–6 weeks after last treatment of neoadjuvant period. **pCR in breast and axillary lymph nodes.
†Loading dose 8 mg/kg IV, maintenance dose 6 mg/kg IV.
Stebbing J, et al. Lancet Oncol 2017; June 2017 (epub ahead of print).

DCIS, ductal carcinoma in situ; DFS, disease-free survival.

CT-P6 vs trastuzumab in HER2+ EBC: Primary efficacy analysis

Per-protocol set	CT-P6 n=248	Trastuzumab n=256
tpCR rate*† % (95% CI)	46.8 (40.4, 53.2)	50.4 (44.1, 56.7)
Risk ratio (95% CI)	0.93 (0.78, 1.11)	
Risk difference (95% CI)	-4 (-12, 5)	



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*pCR in breast and axillary lymph nodes.
†After neoadjuvant therapy and surgery (up to 30 weeks).
Stebbing J, et al. Lancet Oncol 2017; June 2017 (epub ahead of print).

Safety

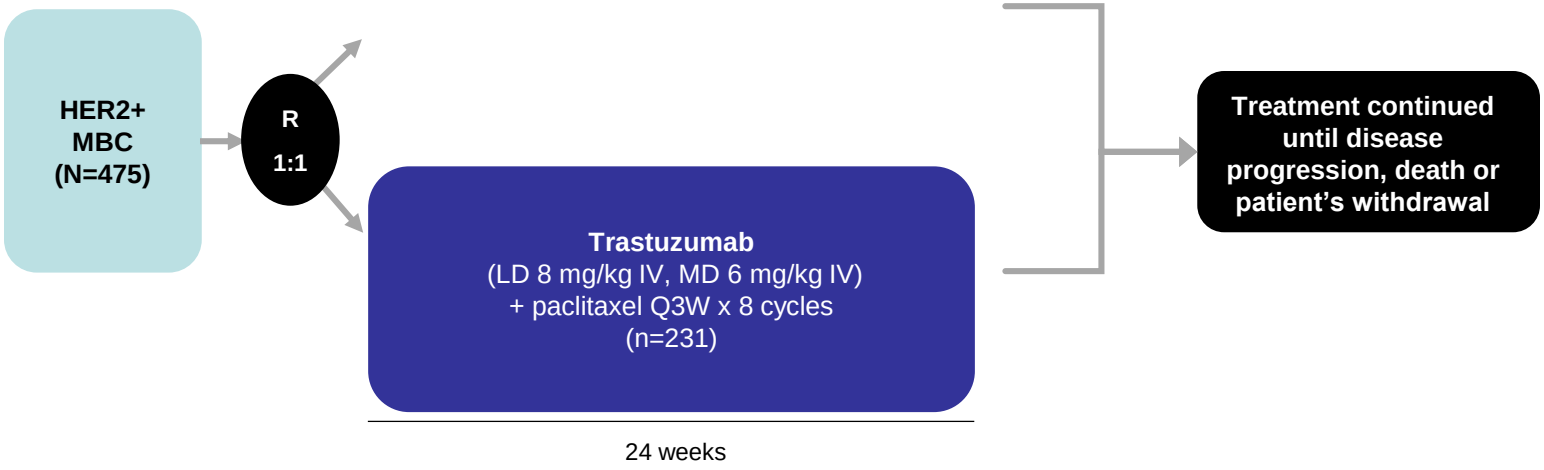
CT-P6 vs trastuzumab:
events of interest during the neoadjuvant phase[2]

Event of interest, n (%)	CT-P6 (n=271)	Trastuzumab (n=278)
Cardiac disorders	17 (6%)	18 (6%)
Infections	12 (4%)	11 (4%)
Infusion-related reactions	14 (5%)	14 (5%)

Biosimilari trastuzumab

Altri studi di fase III

CT-P6 vs trastuzumab: Phase 3 equivalence study in HER2+ MBC



Primary endpoint

- ORR (CR or PR) at 6 months, assessed by independent committee
  - 95% CI for risk difference: -15%; +15%

Secondary endpoints

- Safety, TTP

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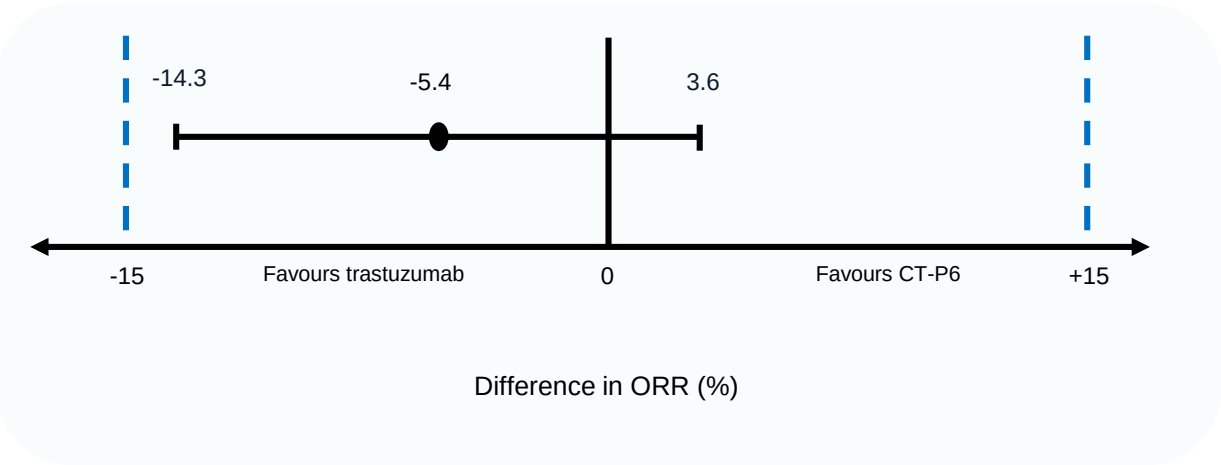
Im YH, et al. ASCO 2013; Abstract 629 and poster presentation;
NCT01084876. Available at: https://clinicaltrials.gov/ct2/show/NCT01084876. Accessed April 2017.

CT-P6 vs trastuzumab in HER2+ MBC: Primary endpoint at Week 24

Primary endpoint	CT-P6 (n=244)	Trastuzumab (n=231)
ORR at 6 months (ITRC), %	56.6	61.9
Risk difference*, % (95% CI)	-5.4 (-14.3, 3.6)	



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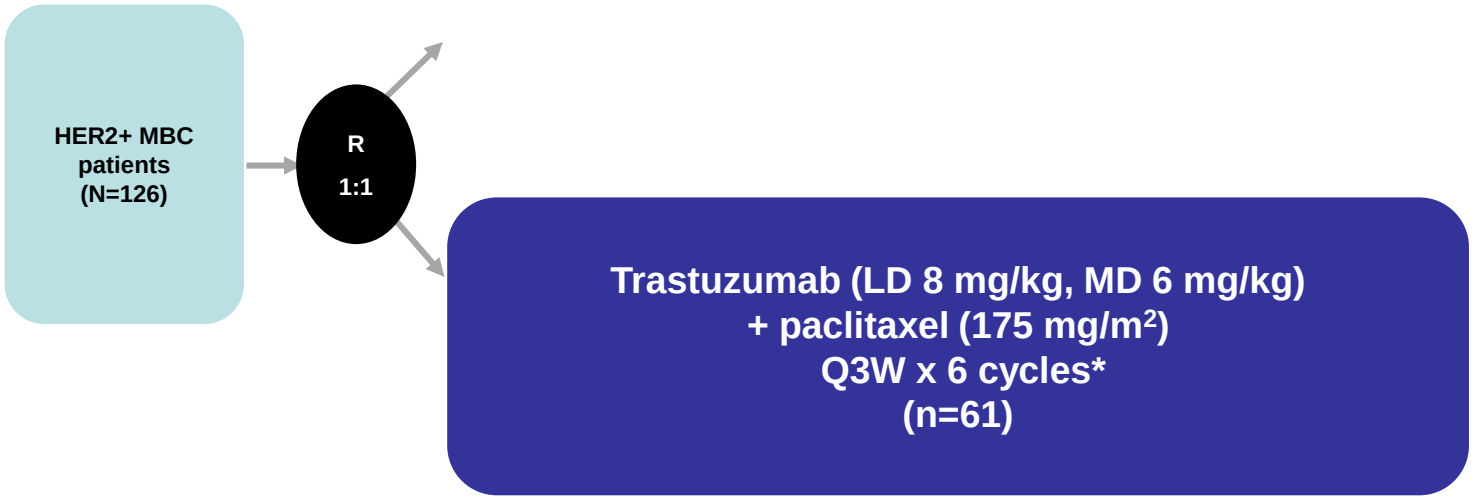
Im YH, et al. ASCO 2013; Abstract 629 and poster presentation.

*Difference in proportion of complete response or partial response.
ITRC, Independent Tumour Review Committee.

BCD-022 vs trastuzumab in HER2+ MBC Non-inferiority study



Primary endpoints

- ORR at Day 127, assessed by independent committee
  - Pre-specified non-inferiority margin for difference in ORR: -20%
- AUC after the first test drug administration (PK substudy)

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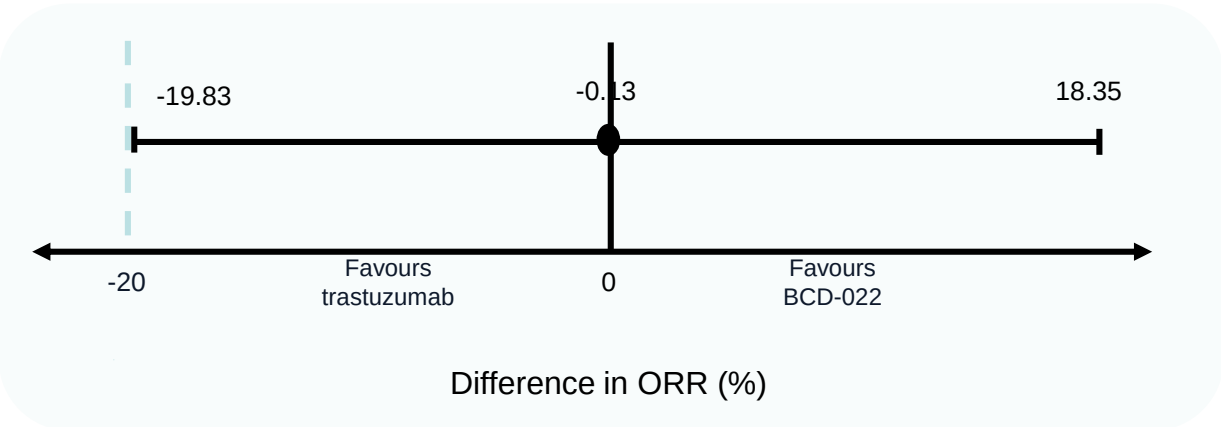
Shustova M, et al. Ann Oncol 2016;27(Suppl 6):vi68–vi99; Abstract 224 (and corresponding poster presented by Burdaeva et al.);
NCT01764022. Available at https://clinicaltrials.gov/ct2/show/NCT01764022?term=BCD-022&rank=1. Accessed August 2017. *Or until progression or unbearable toxicity.

BCD-022 vs trastuzumab in HER2+ MBC
Primary efficacy analysis

	BCD-022 (n=54)	Trastuzumab (n=56)	P*
ORR (Day 127), % patients (95% CI)	53.6 (40.7, 66.0)	53.7 (40.6, 66.3)	0.862
Difference in ORR, % (95% CI)	-0.13 (-19.83, 18.35)		



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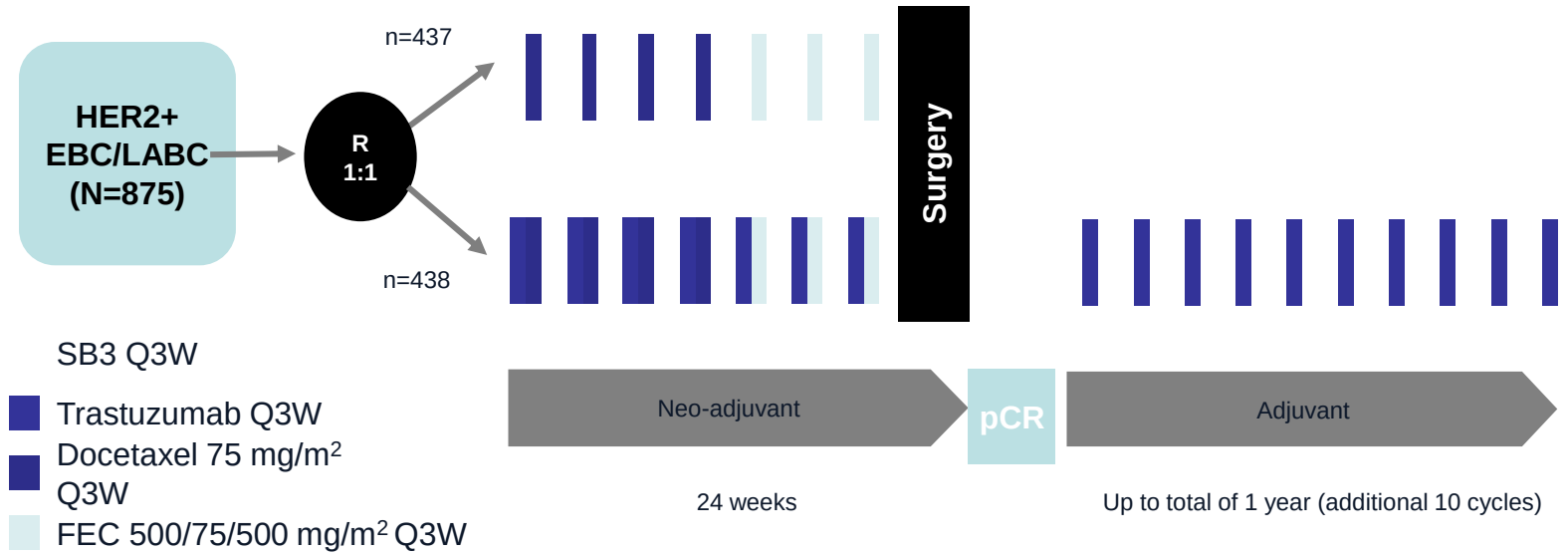
Shustova M, et al. Ann Oncol 2016;27(Suppl 6):vi68–vi99; Abstract 224 (and corresponding poster presented by Burdaeva et al.); NCT01764022. Available at https://clinicaltrials.gov/ct2/show/NCT01764022?term=BCD-022&rank=1. Accessed August 2017.

*Yates-corrected Pearson's test.

SB3 vs trastuzumab: Phase 3 equivalence study in HER2+ EBC



- **Primary endpoint**
  - Breast pCR after neoadjuvant therapy and surgery (per protocol set)
  - Pre-defined equivalence margins: 90% CI for RR 0.785–1.546; 95% CI for RD +/-13%
- Secondary endpoints
  - Efficacy: tpCR*, ORR, EFS
  - Other: PK, immunogenicity and safety

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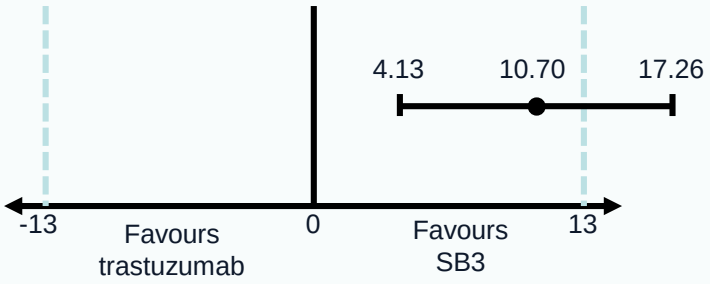
*pCR in breast and axillary lymph nodes. LABC, locally-advanced breast cancer.

Pivot XB, et al. J Clin Oncol 2017;35(Suppl): Abstract 509 and poster presentation.

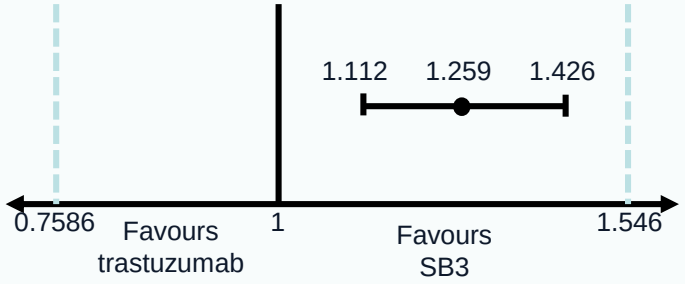
SB3 vs trastuzumab in HER2+ EBC: Primary efficacy analysis

Breast pCR: per-protocol set	SB3 n=402	Trastuzumab n=398
Breast pCR rate, % patients	51.7	42.0
Risk ratio (90% CI)	1.259 (1.112, 1.426)	
Risk difference (95% CI)	10.70 (4.13, 17.26)	

Co-primary analysis: RD (95% CI) for breast pCR



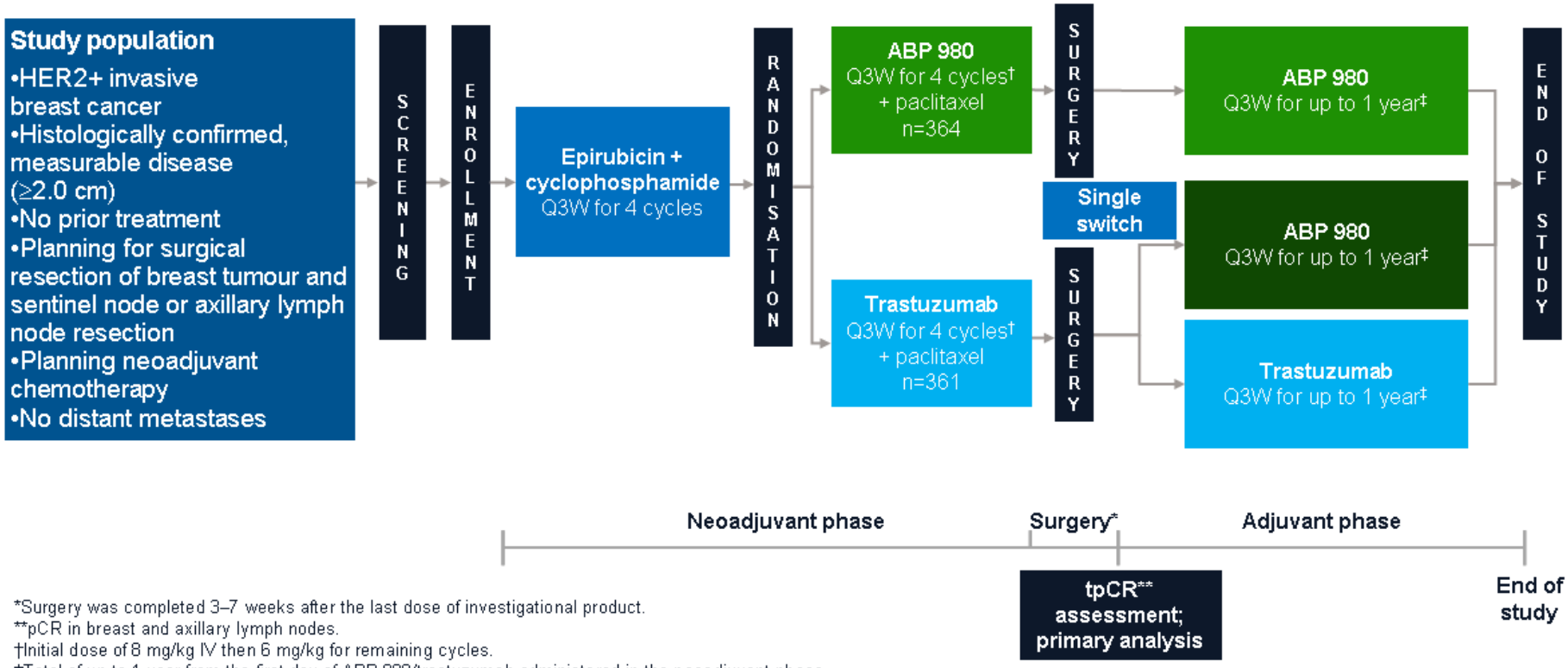
Co-primary analysis: RR (90% CI) for breast pCR



Although equivalence of efficacy was demonstrated based on the RR of breast pCR rates, the upper limit of the 95% CI for the RD was outside the pre-defined equivalence margin

Pivot XB, et al. J Clin Oncol 2017;35(Suppl): Abstract 509 and poster presentation.

ABP 980 vs trastuzumab: Phase 3 equivalence study in HER2+ EBC (LILAC)



*Surgery was completed 3–7 weeks after the last dose of investigational product.
**pCR in breast and axillary lymph nodes.
†Initial dose of 8 mg/kg IV then 6 mg/kg for remaining cycles.
‡Total of up to 1 year from the first day of ABP 980/trastuzumab administered in the neoadjuvant phase.
Q3W, once every 3 weeks.
NCT01901146. Available at: https://clinicaltrials.gov/ct2/show/NCT01901146. Accessed June 2017;
von Minckwitz G, et al. ESMO 2017; Abstract and poster discussion 151PD.

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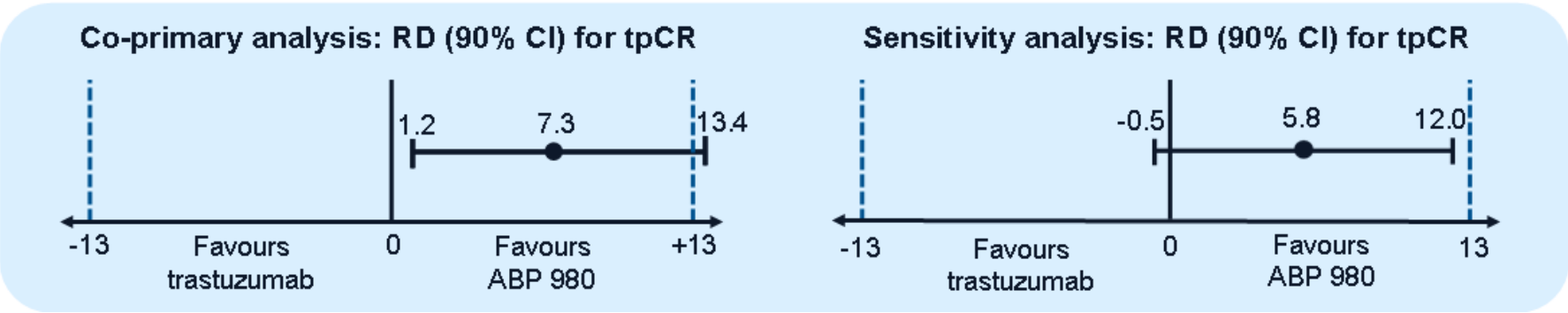
ABP 980 vs trastuzumab in HER2+ EBC: Primary efficacy analysis

	Co-primary analysis (local pathology assessment)		Sensitivity analysis (central pathology assessment)	
tpCR* evaluable population	ABP 980 n=358	Trastuzumab n=338	ABP 980 n=339	Trastuzumab n=330
tpCR rate, %	48.0	40.5	47.8	41.8
Risk ratio (90% CI)	1.19 (1.03, 1.37)		1.14 (0.99, 1.31)	
Risk difference (90% CI)	7.3 (1.2, 13.4)		5.8 (-0.5, 12.0)	



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*pCR in breast and axillary lymph nodes.
von Minckwitz G, et al. ESMO 2017; Abstract and poster discussion 151PD.

Example safety findings: AEs of special interest

ABP 980 vs trastuzumab: events of interest during the neoadjuvant phase[1]

Event of interest, n (%)	ABP 980 (n=364)	Trastuzumab (n=361)
Any EOI **Grade ≥3**	31 (8.6)	29 (8.0)
Neutropenia	21 (5.8)	21 (5.8)
Infusion reactions	7 (1.9)	7 (1.9)
Infections and infestations	7 (1.9)	2 (0.6)
Hypersensitivity	2 (0.5)	2 (0.6)
Cardiac failure	0 (0.0)	0 (0.0)
Pulmonary toxicity	0 (0.0)	0 (0.0)

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1. von Minckwitz et al. ESMO 2017, Poster discussion 151 PD; 2. Stebbing J, et al. Lancet Oncol 2017; June 2017 (epub ahead of print)

Example safety findings: anti-drug antibodies

ABP 980 vs trastuzumab: incidence of anti-drug antibodies (ADAs)

	ABP 980 (n=364)	Trastuzumab (n=361)
Patients with a post-baseline result, n	355	351
Binding antibody positive post-baseline, n (%)	2 (0.6)	2 (0.6)
Transient*, n (%)	2 (0.6)	0

No patients developed neutralising antibodies at any study time point
*Negative result at the patient's last time point tested within the study period

von Minckwitz et al. ESMO 2017, Poster discussion 151 PD

Trastuzumab biosimilar clinical development: Summary of Phase 3 designs

	Amgen ABP980[1]	Samsung Bioepis SB3[2]	Celltrion CT-P6[3,4]	Pfizer PF-05280014[5,6]	Biocon/Mylan MYL-1401O[7]
Neoadjuvant/ adjuvant	✓	✓	✓	(✓)	-
Neoadjuvant regimen	EC→T + P	T+ D→T + FEC	T+ D→T + FEC	T + DCa	
N	725	875	549	226	
Metastastic	-	-	✓	✓	✓
Regimen	-	-	T + P	T + P	T + (D or P)
N			475	707	458
Primary endpoint	tpCR	pCR breast only	EBC: tpCR MBC: ORR	(EBC: PK endpoint) MBC: ORR	ORR
Equivalence margin for efficacy (risk difference)	90% CI ±13%	95% CI ±13%	EBC: 95% CI ±15% MBC: 95% CI ±15%	MBC: 95% CI 0.8–1.25 (risk ratio)	95% CI ±15%
Switch? Y/N	Y	N	N	N	N

E, epirubicin; C, cyclophosphamide; Ca, carboplatin; D, docetaxel; FEC, fluorouracil, epirubicin, cyclophosphamide; P paclitaxel; T, trastuzumab (reference product or proposed biosimilar)

1. von Minckwitz G, et al. ESMO 2017; Abstract and poster discussion 151PD; 2. Pivot XB, et al. J Clin Oncol 2017;35(Suppl): Abstract 509 and poster presentation;
3. Stebbing J, et al. Lancet Oncol 2017; June 2017 (epub ahead of print); 4. Im YH, et al. ASCO 2013; Abstract 629 and poster presentation;
5. Lammers PE, et al. ESMO 2017, poster discussion 154PD; 6. Pegram M, et al. ESMO 2017, Poster discussion 238PD; 7. Rugo HS, et al. JAMA 2017;317:37–47.

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Bevacizumab

Cancer Chemother Pharmacol (2016) 77:839–846
DOI 10.1007/s00280-016-3001-2

ORIGINAL ARTICLE

A phase I pharmacokinetics study comparing PF-06439535 (a potential biosimilar) with bevacizumab in healthy male volunteers

Beverly Knight[1] · Danielle Rassam[2] · Shanmei Liao[3] · Reginald Ewesuedo[4]

PRP Pharmacology Research & Perspectives
Open Access

ORIGINAL ARTICLE

A phase 1 study comparing the proposed biosimilar BS-503a with bevacizumab in healthy male volunteers

Naoyuki Tajima[1], Alberto Martinez[2], Fumiaki Kobayashi[1], Ling He[3] & Peter Dewland[2]

[1]Daiichi Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
[2]Daiichi Sankyo Development Ltd., Chiltern Place, Chalfont Park, Gerrards Cross, SL9 0BG, United Kingdom
[3]Daiichi Sankyo Pharma Development, 399 Thornall Street, Edison, New Jersey 08837

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Expert Opinion on Investigational Drugs

ISSN: 1354-3784 (Print) 1744-7658 (Online) Journal homepage: http://www.tandfonline.com/loi/ieid20

A randomized, single-blind, Phase I trial (INVICTAN-1) assessing the bioequivalence and safety of BI 695502, a bevacizumab biosimilar candidate, in healthy subjects

Willem Hettema, Christopher Wynne, Benjamin Lang, Mario Altendorfer, Niklas Czeloth, Ragna Lohmann, Sandeep Athalye & Dorothee Schliephake

Cancer Chemother Pharmacol (2017) 80:755–763
DOI 10.1007/s00280-017-3416-4

ORIGINAL ARTICLE

A phase I, randomized, single-dose study evaluating the pharmacokinetic equivalence of biosimilar ABP 215 and bevacizumab in healthy adult men

Richard Markus[1] · Vincent Chow[1] · Zhiying Pan[1] · Vladimir Hanes[1]

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

LUNG CANCER—NON-SMALL CELL METASTATIC

Randomized, double-blind, phase 3 study evaluating efficacy and safety of ABP 215 compared with bevacizumab in patients with non-squamous NSCLC.

Nick Thatcher, Michael Thomas, Luis Paz-Ares, Gyula Ostoros, Zhiying Pan, Jerome H. Goldschmidt,

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Abstract Disclosures

Abstract

9095

Background: ABP 215 is a biosimilar candidate highly similar to BEV, a VEGF inhibitor, in analytical and functional comparisons. Pharmacokinetic similarity between ABP 215 and BEV has been demonstrated in a phase 1 study. Here we

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ARTICLE CITATION

DOI: 10.1200/JCO.2016.34.15_suppl.9095
Journal of Clinical Oncology 34, no. 15_suppl (May 2016) 9095-9095.

ONCOLOGY
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LUNG CANCER—NON-SMALL CELL METASTATIC

Efficacy and safety of BCD-021, bevacizumab biosimilar candidate, compared to Avastin: Results of international multicenter randomized double blind phase III study in patients with advanced non-squamous NSCLC.

Olga Filon, Sergey Orlov, Olga Burdaeva, Mikhail V. Kopp, Bogdan Kotiv, Sergiy Alekseev...

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Abstract Disclosures

Abstract

8057

Background: BCD-021 demonstrated equivalence to Avastin in a comprehensive

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COMPANION ARTICLES

No companion articles

ARTICLE CITATION

DOI: 10.1200/jco.2015.33.15_suppl.8057
Journal of Clinical Oncology 33, no. 15_suppl (May 2015) 8057-8057.

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FDA News Release

FDA approves first biosimilar for the treatment of cancer

Mvasi, a biosimilar to the cancer drug Avastin, is approved for certain colorectal, lung, brain, kidney and cervical cancers

For Immediate Release September 14, 2017

Release

The U.S. Food and Drug Administration today approved Mvasi (bevacizumab-awwb) as a biosimilar to Avastin (bevacizumab) for the treatment of multiple types of cancer. Mvasi is the first biosimilar approved in the U.S. for the treatment of cancer.

Inquiries

Media

Angela Stark
301-796-0397

Consumers

888-INFO-FDA

Related Information

- FDA: Information on Biosimilars
- FDA: Biologics Price Competition and Innovation Act

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Beva-biosimilars phase III - BCD-021

- 138 patients - advanced non-squamous NSCLC
- BCD-021 vs Avastin - 15 mg/kg in combination with paclitaxel (175 mg/m2) and carboplatin (AUC 6 mg/ml×min) every 3 weeks up to 6 cycles
- ORR (primary endpoint)
  - 42.59 % (95% CI 30.33 – 55.83) in BCD-021 group vs 39.29% (95% CI 27.58 – 52.27%) in Avastin group.
  - lower limit of 95% CI for ORR difference between the groups (-14.96%) did not exceed the non-inferiority margin
  - CR (1.85% *vs* 1.79%), PR (40.74% *vs* 37.50%), stable disease (51.85% *vs* 51.79%) and progression rate (5.56% *vs* 8.93%) in BCD-021 vs Avastin group, respectively.
  - Rate of all observed AEs
    - neutropenia (85.29% *vs* 78,7%), anemia (88.24% *vs* 84.85%), leukopenia (79.41% *vs* 75.76%), thrombocytopenia (69.12% *vs* 62.12%), hyperglycemia (61.76 *vs* 56.06), LDH increase (48.53 *vs* 37.88), ALP increase (35.29% *vs* 30.30), ALT increase (26.47% *vs* 28.79%), alopecia (30.88% *vs* 24,24%)
  - specific for bevacizumab included:
    - arterial hypertension (26,47% *vs*22,73%), weakness (17.65 *vs* 16.67), lung bleeding (5.88% *vs* 3.03%), proteinuria (2.94% *vs* 0%), GIT perforation (0% *vs* 1.52%) VTE (0% *vs* 1.52%).
  - Binding and neutralizing antibodies: transient and detected only in 1 patient in each group

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Beva-biosimilars phase III - ABP 215

- Similar design to BCD-021
- ABP 215: n = 328 vs BEV: n = 314
- ORR
  - 39.0% (n = 128) for ABP 215 and 41.7% (n = 131) for BEV
  - RR for ORR was 0.93 (90% CI: 0.80, 1.09).
- grade ≥ 3 treatment-emergent adverse events (TEAEs)
  - 42.9% in ABP 215 group vs 44.3% in BEV group
  - TEAEs leading to IP discontinuation affected 18.8% vs 17.2% subjects
  - Pts reporting at least one serious TEAE were 26.2% in ABP 215 group vs 23.0% in BEV group.
  - TEAEs with > 10% incidence included alopecia, nausea, neutropenia, peripheral neuropathy, and hypertension.
  - Patients developing binding antibodies were 1.4% in the ABP 215 group vs 2.5% in the BEV group; no subject tested positive for neutralizing antibodies.

Cetuximab

Positive phase III results for cetuximab and infliximab copy biologicals

Posted 05/02/2016

US-based biopharmaceutical company Sorrento Therapeutics (Sorrento) announced on 11 January 2016 that its partner, MabTech had successfully completed phase III clinical trials in China for STI-001, a copy biological for cetuximab (Erbitux) and STI-002, a copy biological for infliximab (Remicade). Both STI-001 and STI-002 met their prin endpoints in confirmatory, randomized, controlled, two-part phase III studies.

The two companies entered into a deal back in August 2015, when MabTech, a company for China mAb Biotechs, in-licensed four monoclonal antibodies to S of the candidate copy biologicals had completed phase III trials in China.

Cetuximab is a chimeric (mouse/human) monoclonal antibody. It inhibits epid to treat metastatic colorectal cancer, metastatic non-small cell lung cancer and

Biosimilar	Study details	Status/published results
Cetuximab biosimilars[†]		
CMAB009 (Shanghai Zhangjiang Biotechnology)	Phase: I Indication: advanced epithelial malignancies Concomitant treatment: none n = 18 Primary end point: PK	Complete Acceptable PK profiles after single and multiple dosing. CMAB009 was well tolerated
	Phase: III Indication: KRAS WT metastatic colorectal cancer Concomitant treatment: irinotecan n = 512 Primary end point: ORR	Complete (data not yet available)
STI-001 (Sorrento Therapeutics)	Phase: III Indication: EGFR+ metastatic colorectal cancer Concomitant treatment: irinotecan/none n = 501 Primary end point: NR	STI-001 plus irinotecan was significantly more effective than irinotecan alone • ORR, 32.9 vs 12.8% • PFS, 5.6 vs 3.2 months • OS, 14.1 vs 13.4 months

STI-001 was used for treatment of EGFR-expressing metastatic colorectal carcinoma patients in combination with irinotecan versus irinotecan alone.

Overall Response Rate (ORR: 32.9% vs 12.8%)
Progress-free Survival (PFS: 5.6 vs 3.2 months)
Overall Survival (OS: 14.1 vs 13.4 months).

Open Questions

- Superare la diffidenza – in oncologia è più difficile!
- Studi di fase IV (real life) – post-marketing pharmacovigilance
- Rischio di allentare le maglie – gioco al ribasso

GRAZIE!

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