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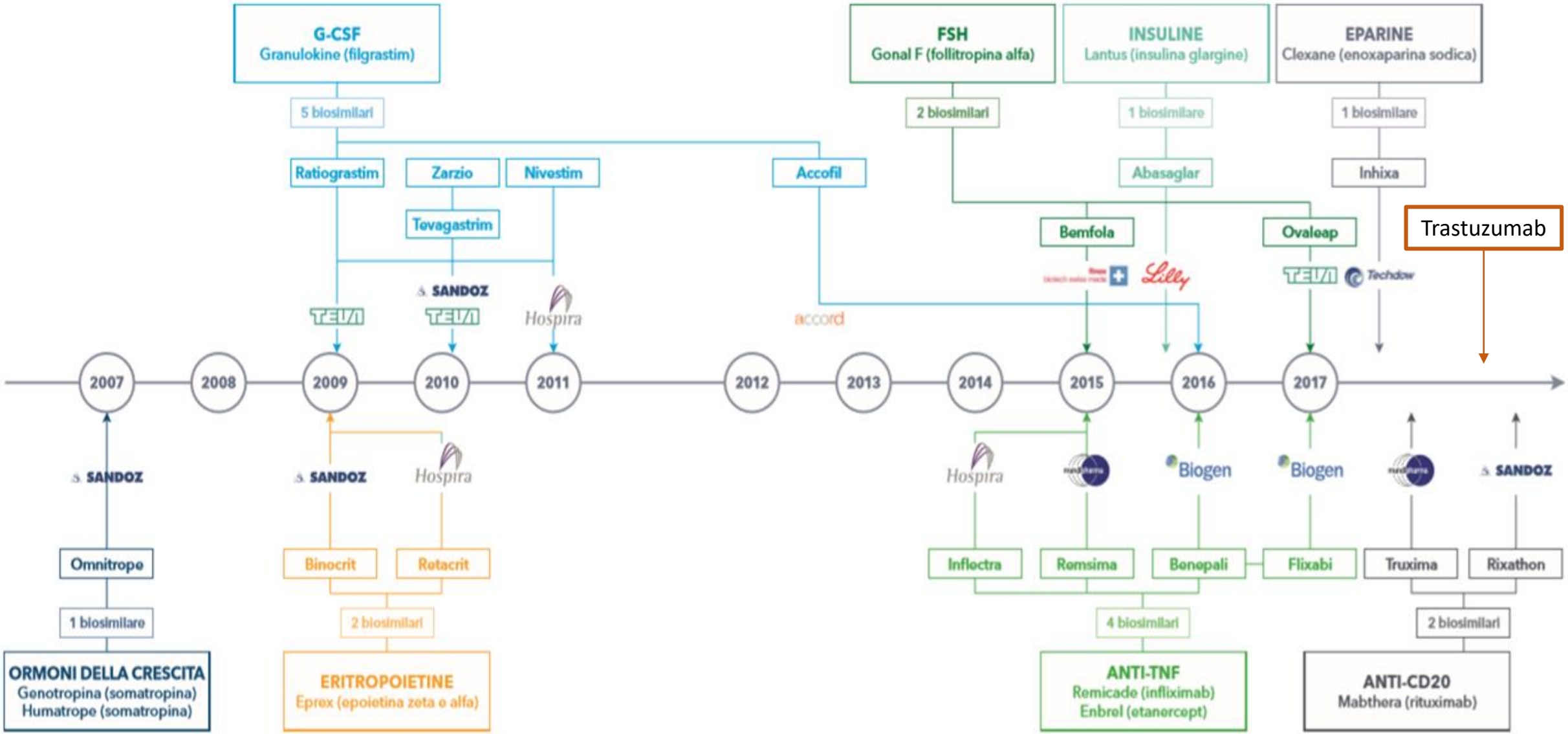
Farmaci in sviluppo

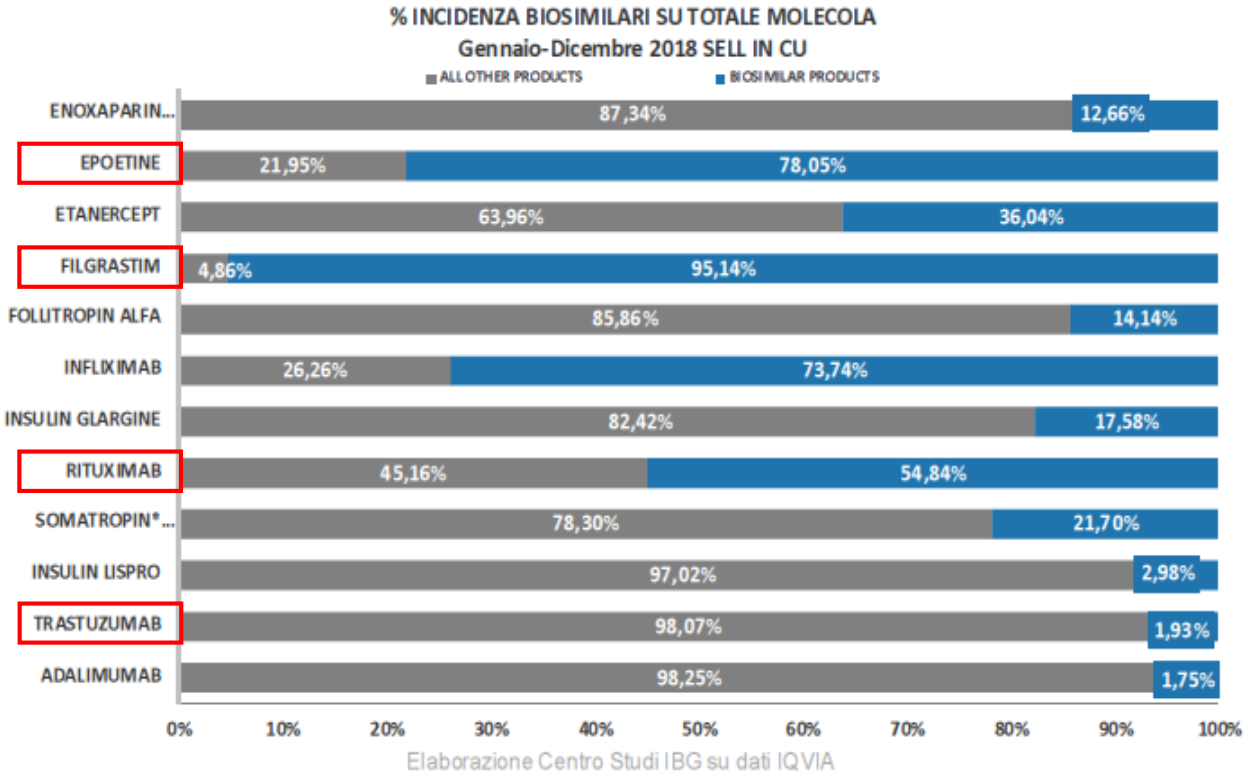
Rank	Product	Generic Name	Company	Pharmacological Class	WW Product Sales ($m) 2017	2024	CAGR
1.	**Humira**	adalimumab	AbbVie + Eisai	Anti-tumour necrosis factor alpha (TNFa) MAb	18,922	15,233	-3%
2.	**Keytruda**	pembrolizumab	Merck & Co + Otsuka Holdings	Anti-programmed cell death-1 (PD-1) MAb	3,823	12,686	+19%
3.	**Revlimid**	lenalidomide	Celgene + BeiGene	Immunomodulator	8,191	11,931	+6%
4.	**Opdivo**	nivolumab	Bristol-Myers Squibb + Ono Pharmaceutical	Anti-programmed cell death-1 (PD-1) MAb	5,725	11,247	+10%
5.	**Eliquis**	apixaban	Bristol-Myers Squibb	Factor Xa inhibitor	4,872	10,535	+12%
6.	**Imbruvica**	ibrutinib	AbbVie + Johnson & Johnson	Bruton's tyrosine kinase (BTK) inhibitor	3,196	9,557	+17%
7.	**Ibrance**	palbociclib	Pfizer	Cyclin-dependent kinase (CDK) 4 & 6 inhibitor	3,126	8,284	+15%
8.	**Dupixent**	dupilumab	Sanofi	Anti-IL-4 & IL-13 MAb	247	8,058	+64%
9.	**Eylea**	aflibercept	Regeneron Pharmaceuticals + Bayer + Santen Pharmaceutical	Vascular endothelial growth factor receptor (VEGFr) kinase inhibitor	6,282	6,827	+1%
10.	**Stelara**	ustekinumab	Johnson & Johnson	Anti-IL-12 & IL-23 MAb	4,011	6,466	+7%

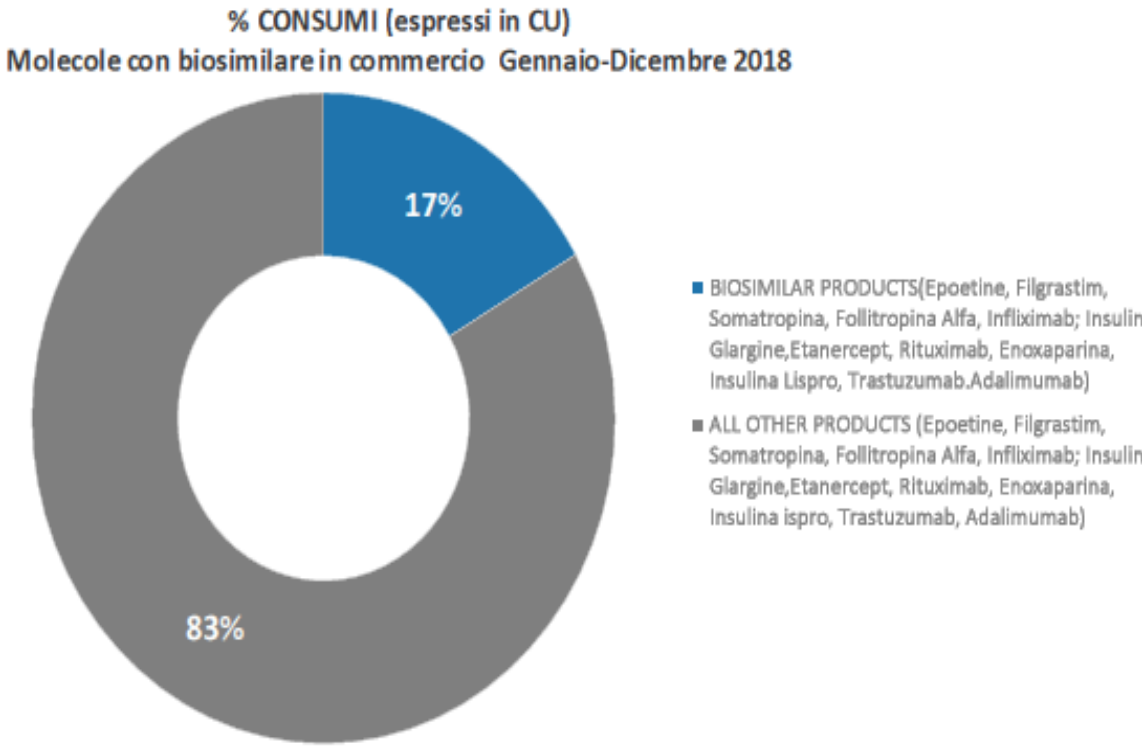
Fonte: EvaluatePharma World Preview 2018 report, May 2018

Scala del tempo.....



Consumi GEN – DIC 2018
INCIDENZA % CONSUMO BIOSIMILARE





Obiettivi

- ✓ La presa di coscienza in tema di sostenibilità
- ✓ Quanto ne sappiamo?
- ✓ Aspetti metodologici e perpelssità e scarsa fiducia
- ✓ Caratteristiche degli studi registrativi
- ✓ Switch
- ✓ AE

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Biosimilars Have the Potential to Lower Healthcare Costs

Range of Estimates on the Cost Savings That Could Be Realized by Healthcare Systems With The Availability of Biosimilars

Source	Estimated Biosimilar Savings
CBO[1]	Savings of **$25 billion** during 2009-2018 in US following implementation of bill S. 1695
PCMA[2]	Medicare Part B: **$14 billion** over 10 years
EGA[3]	**€1.6 billion,** assuming a 20% discount for just 6 biologic drugs
IGES Institut GmbH[4]	**€11.8 to €33.4 billion** between 2007-2020 in 8 EU countries

CBO, Congressional Budget Office; EGA, European Generic Medicines Association; PCMA, Pharmaceutical Care Management Association.

1. Congressional Budget Office. S. 1695 - Biologics Price Competition and Innovation Act of 2007. June 25, 2008; 2. Engel and Novitt, LLP. Report to PCMA on Potential Medicare Savings. January 2, 2007; 3. European Generic Medicines Association. The Future of Pharmaceuticals: Generic Medicines Enhancing Pharmaceutical Competition and Ensuring Healthcare Sustainability. Brussels, Belgium: EGA; 2007; 4. Haustein R, et al. GaBI J. 2012;1(3-4):120-126.

BreastCare
Multidisciplinary Journal for Research, Diagnosis and Therapy

Review Article

Breast Care
DOI: 10.1159/000496834

Published online: February 13, 2019

What Does the Pipeline Promise about Upcoming Biosimilar Antibodies in Oncology?

Antonia Busse Diana Lüftner

	Europe	US
Adcetris®/brentuximab – vedotin	August 2023	2015–2031
Avastin®/bevacizumab	January 2022	July 2019
Arzerra®/ofatumumab	data not available	December 2018
Campath®/alemtuzumab	May 2021	July 2021
Cyramza®/ramucirumab	May 2023	November 2025
Darzalex®/daratumumab	May 2026	February 2025
Erbitux®/cetuximab	June 2014	February 2016
Gazyvaro®, Gazyva®/obinutuzumab	November 2024	January 2035
Herceptin®/trastuzumab	August 2015	June 2019
Kadcyla®/trastuzumab emtansine	June 2020	September 2026
Keytruda®/pembrolizumab	June 2028	November 2036
Mabthera®, Rituxan®/rituximab	November 2013	September 2016
Opdivo®/nivolumab	May 2026	June 2027
Perjeta®/pertuzumab	May 2023	June 2024
Prolia®, Xgeva®/denosumab	June 2022	February 2025
Tecentriq®/atezolizumab	September 2027	May 2028
Vectibix®/panitumumab	2018	April 2020
Yervoy®/ipilimumab	2021	2023

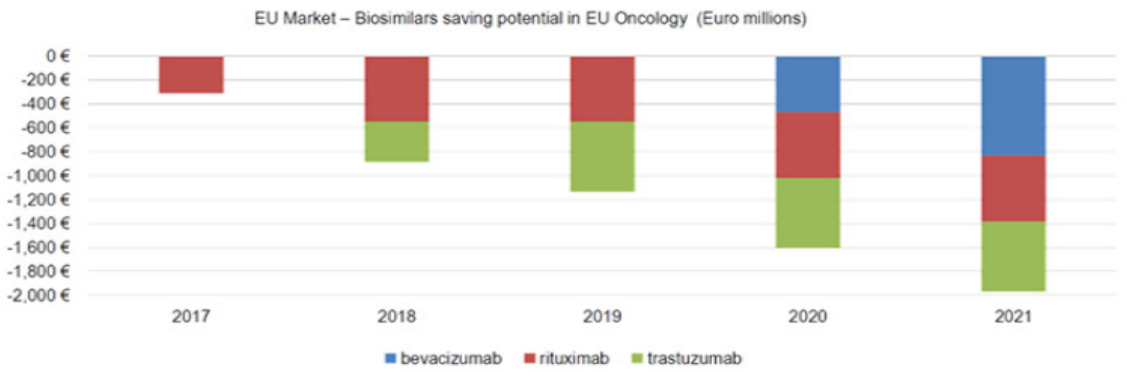
BENTHAM SCIENCE

The Ecstacy of Gold: Patent Expirations for Trastuzumab, Bevacizumab, Rituximab, and Cetuximab

Tasha R. Serna-Gallegos[1], Christopher J. La-Fargue[1] and Krishnansu S. Tewari[2,*]

[1]*Department of Obstetrics and Gynecology, University of California, Irvine-Medical Center, Orange, CA, USA and* [2]*Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of California, Irvine-Medical Center, Orange, CA, USA*

In the base case scenario, introduction of biosimilars could result in almost €2 billion of savings in 2021



Aitken M, et al. ESMO 2017

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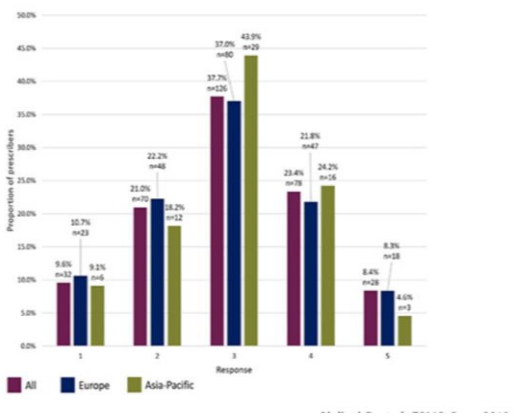
ESMO Open
Cancer Horizons

Check for updates

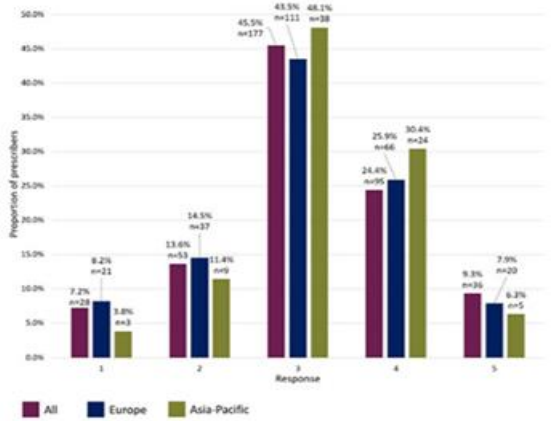
Knowledge and use of biosimilars in oncology: a survey by the European Society for Medical Oncology

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

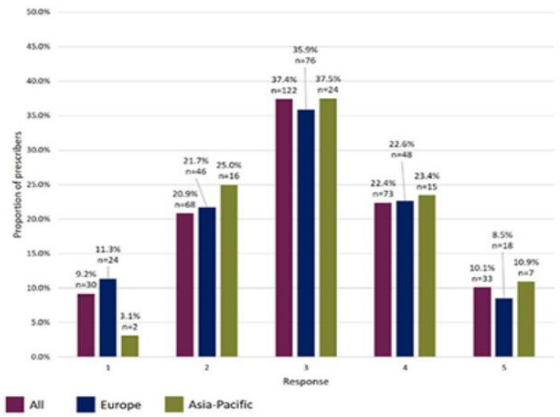
Rate of knowledge / understanding biosimilars development process and threshold of clinical evidence required for approval



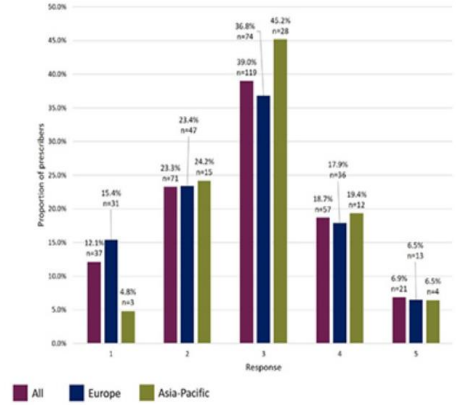
Rate of knowledge / understanding of biosimilars overall



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



Rate of knowledge / understanding requirements needed to be met for extrapolation of indications to be granted for a biosimilar



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

Prescribers' responses rating the importance and sensitivity of different data types in determining the suitability of a biosimilar for use

	Importance			Sensitivity		
Type of data (weighted average)	All	Europe	Asia-Pacific	All	Europe	Asia-Pacific
Physicochemical data demonstrating structural similarity	7.23	7.05	7.30	7.24	7.07	7.56
In vitro and in vivo data demonstrating similarity in biological activity	7.76	7.74	7.66	7.58	7.46	7.82
PK and PD data demonstrating similarity	7.94	7.85	8.10	7.83	7.75	8.10
Clinical study data demonstrating similar efficacy	8.65	8.56	8.72	8.61	8.57	8.75
Clinical study data demonstrating similar safety	8.80	8.78	8.83	8.75	8.72	8.79
Clinical study data demonstrating similar immunogenicity	8.24	8.24	8.10	8.30	8.23	8.41
Clinical study data demonstrating the ability to switch from reference to biosimilar and vice versa without impairing safety or efficacy	8.07	8.02	8.27	8.11	8.02	8.36

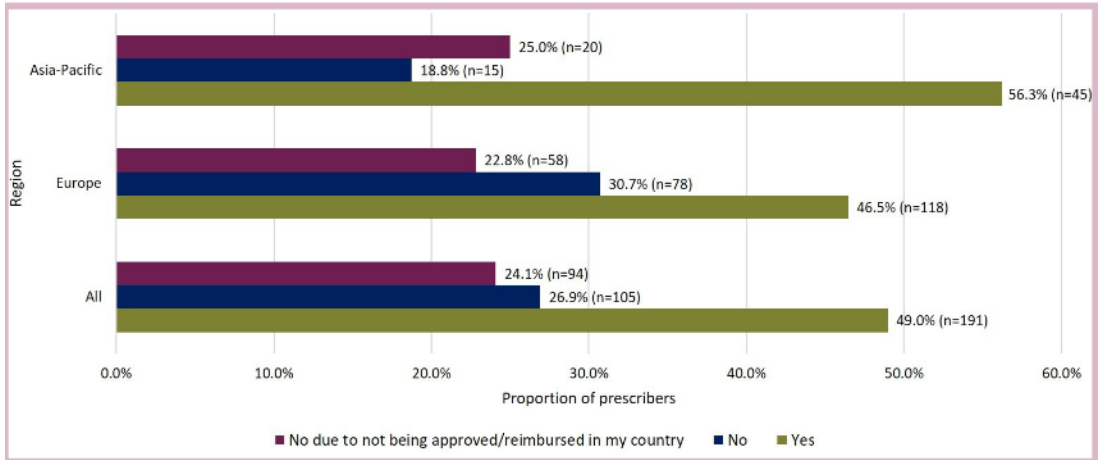


Figure 2 Level of routine use of biosimilars by prescribers in clinical practice to treat patients.

Table 2 Prescribers' responses rating their concern of potential consequences when switching a patient's treatment from a reference biologic to a biosimilar or vice versa

Potential consequence (weighted average)	All	Europe	Asia-Pacific
Potential loss of clinical efficacy	3.29	3.23	3.30
Potential for adverse events	3.35	3.32	3.35
Potential for increased risk of immune reactions	3.35	3.39	3.17

Weighted average of prescribers' responses, by region, on a scale of 1 (not at all) to 5 (very).

Giuliani R, at al ESMO Open 2019; 4:e000460

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- ✓ AE

Review

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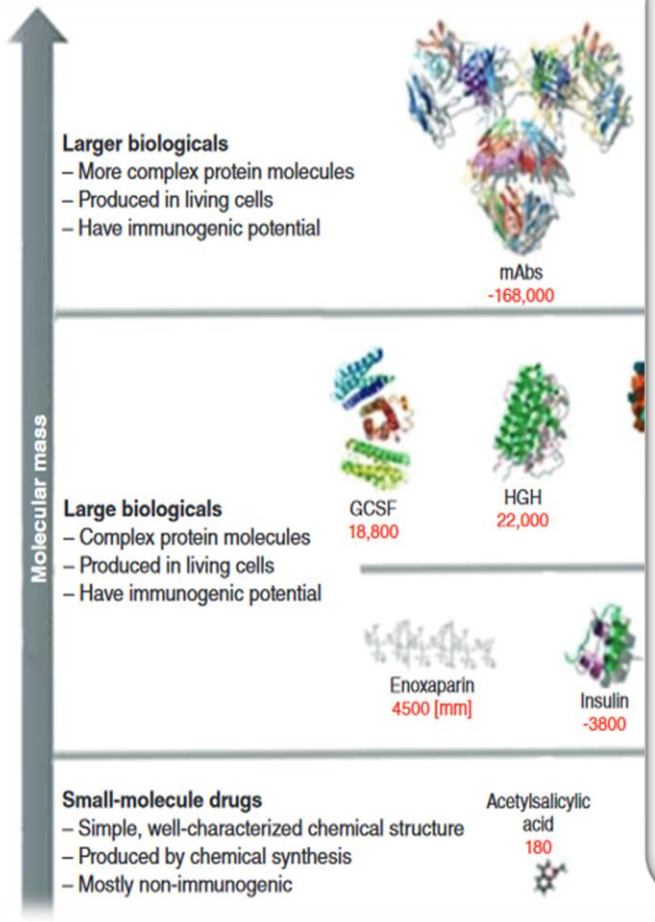
Biosimilars: what the oncologist should know

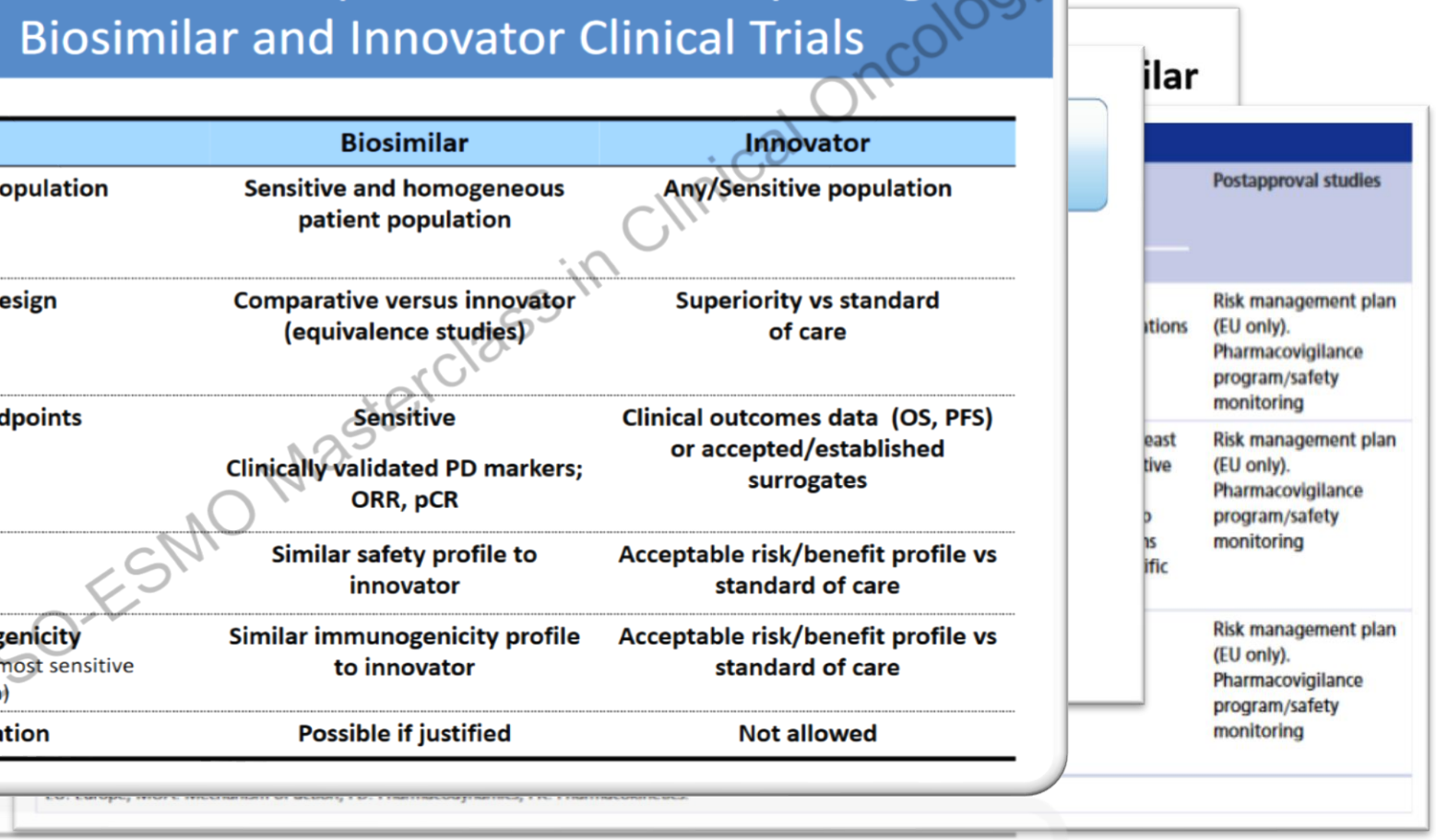
Marc Thill*,[1], Nicholas Thatcher[2], Vladimir Hanes[3] & Gary H Lyman[4]

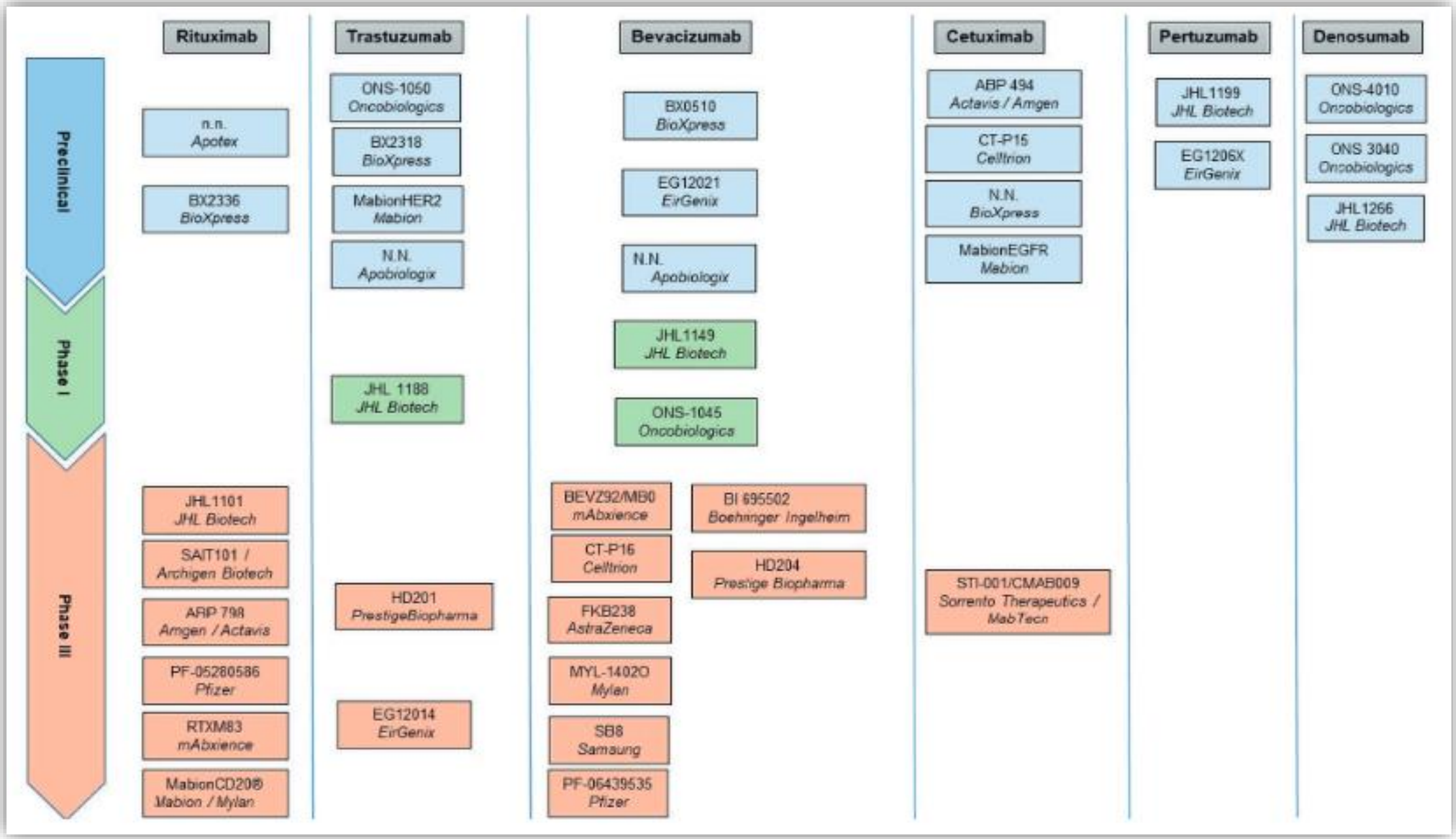
[1]Department of Gynecology and Gynecological Oncology, Agaplesion Markus Hospital, Frankfurt am Main, Germany
[2]Department of Medical Oncology, The Christie Hospital, Manchester, UK
[3]Amgen, Inc, Thousand Oaks, CA 91320, USA



Key Differences in Requirement and Study Design for Biosimilar and Innovator Clinical Trials

	Biosimilar	Innovator
Patient population	**Sensitive and homogeneous patient population**	**Any/Sensitive population**
Clinical design	**Comparative versus innovator (equivalence studies)**	**Superiority vs standard of care**
Study endpoints	**Sensitive** **Clinically validated PD markers; ORR, pCR**	**Clinical outcomes data (OS, PFS) or accepted/established surrogates**
Safety	**Similar safety profile to innovator**	**Acceptable risk/benefit profile vs standard of care**
Immunogenicity (tested in most sensitive population)	**Similar immunogenicity profile to innovator**	**Acceptable risk/benefit profile vs standard of care**
Extrapolation	**Possible if justified**	**Not allowed**

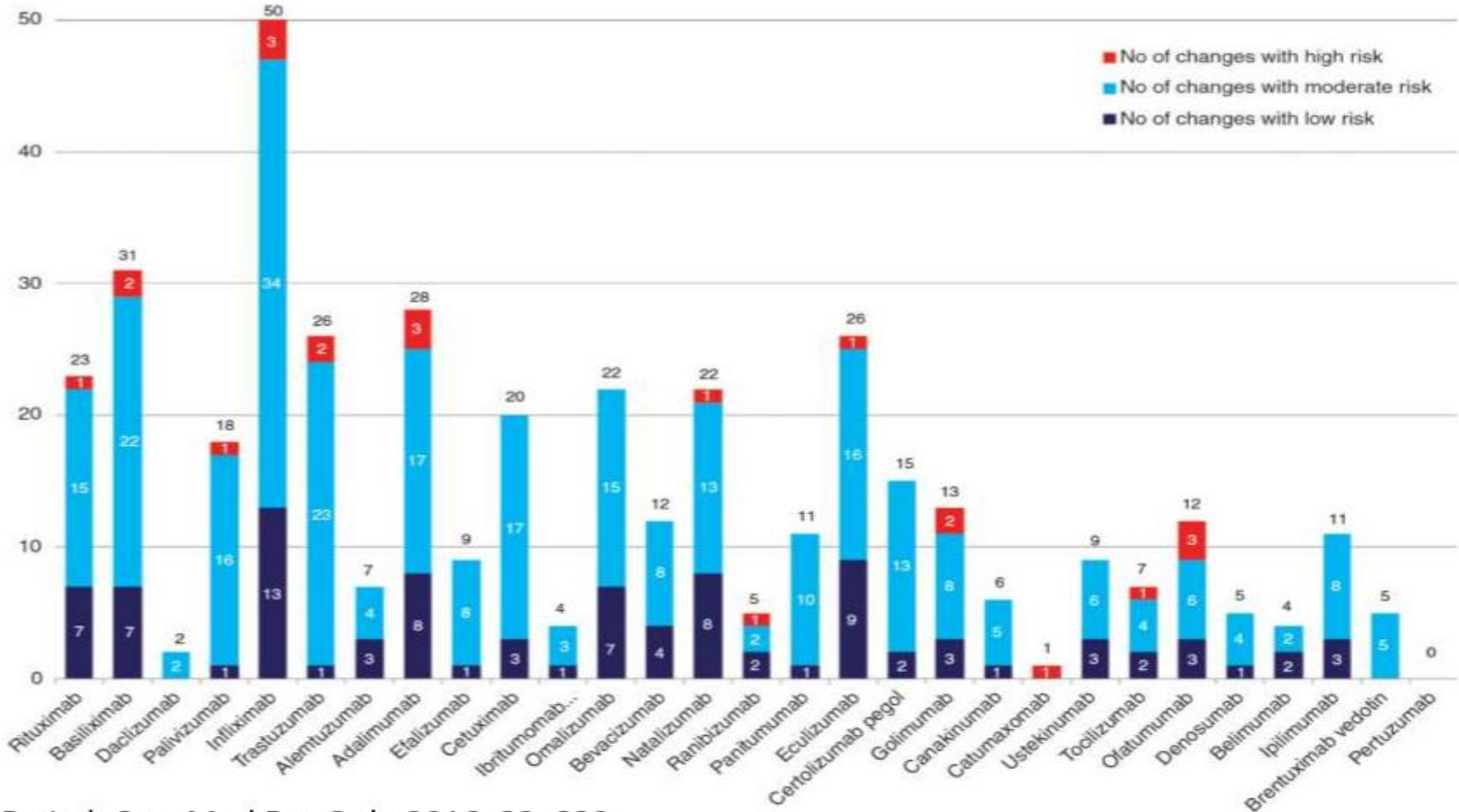



Preclinical
Phase I
Phase III
Rituximab
n.n.
Apotex
BX2336
BioXpress
JHL1101
JHL Biotech
SAIT101 /
Archigen Biotech
ARP 798
Amgen / Actavis
PF-05280586
Pfizer
RTXM83
mAbxience
MabionCD20®
Mabion / Mylan
Trastuzumab
ONS-1050
Oncobiologics
BX2318
BioXpress
MabionHER2
Mabion
N.N.
Apobiologix
JHL 1188
JHL Biotech
HD201
PrestigeBiopharma
EG12014
EirGenix
Bevacizumab
BX0510
BioXpress
EG12021
EirGenix
N.N.
Apobiologix
JHL1149
JHL Biotech
ONS-1045
Oncobiologics
BEVZ92/MB0
mAbxience
CT-P16
Celltrion
FKB238
AstraZeneca
MYL-1402O
Mylan
SB8
Samsung
PF-06439535
Pfizer
BI 695502
Boehringer Ingelheim
HD204
Prestige Biopharma
Cetuximab
ABP 494
Actavis / Amgen
CT-P15
Celltrion
N.N.
BioXpress
MabionEGFR
Mabion
STI-001/CMAB009
Sorrento Therapeutics /
MabTecn
Pertuzumab
JHL1199
JHL Biotech
EG1206X
EirGenix
Denosumab
ONS-4010
Oncobiologics
ONS 3040
Oncobiologics
JHL1266
JHL Biotech

BIOSIMILARI IN ONCOLOGIA

Position Paper 2018

Changes in manufacturing process during originator biologic's life

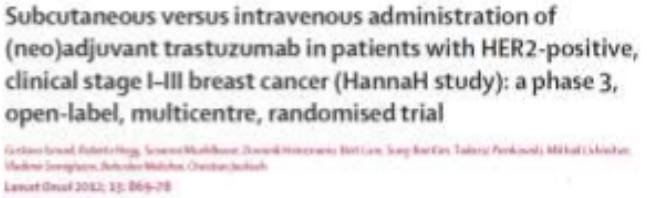


Vezer B et al. Curr Med Res Opin 2016; 32, 829

Trastuzumab sottocute: 2012

- (EMA/CHMP/751770/2012/corr1)

  Esercizio di comparabilità (analitica e clinica) richiesto per valutare efficacia e sicurezza della formulazione sc (con maggior rischio immunogenicità) e contenente ialuronidasi umana ricombinante (rHuPH20) per aumentare assorbimento dei farmaco.
- Efficacia, sicurezza e immunogenicità:
  - Studio randomizzato in aperto in pazienti con carcinoma mammario NON metastatico. 235 trastuzumab IV vs 234 trastuzumab SC in PP population (primary analysis population).
  - Enpoint principale: pCR, pathological complete response.
  - Non Inferiorità dimostrata se il limite inferiore dell'intervallo di confidenza al 95% 2 code per la differenza in pCR %(SC-IV) non oltrepassava –12·5%.
- Risultati
  - La differenza tra i due gruppi (SC-IV) = 4.7% (95% CI –4·0 to 13·4); il valore inferiore dell'IC era maggiore di -12.5%, il margine di non inferiorità pre-specificato.
  - Analisi a 20 mesi ritenute soddisfacenti per l'immissione in commercio nonostante la richiesta di dati aggiuntivi a supporto di efficacia e sicurezza a 60 mesi
- Estrapolazione:
  - indicazione nei pazienti con carcinoma mammario metastatico


Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I–III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial

Obiettivi

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Chissà da dove vengono? India, Cambogia?

Chissà se dentro c'è la dose giusta e il farmaco giusto?

Ce li propinano per rispamiare !

Soldi soldi soldi!***

Thanks to Dr G. Rosti

Trials di fase III sull'utilizzo del trastuzumab biosimilare

Agent	Company	Phase	n	Indi-cation	Endpoint	Study design	Trial status	Results	Drug status
CT-P6 (Herzuma®)	Celltrion Healthcare (Incheon, ROK)/ Teva Pharmaceuticals (Petach Tikwa, Israel)	pooled I/ IIB–III	475	first line mBC	ORR	equivalence	completed	CT-P6 vs. trastuzumab RPa: ORR 57 vs. 62%; mTTP 11.07 vs. 12.52 months [14]	marketed in South Korea following approval in January 2014; submitted to FDA in July 2017 and rejected in April 2018; resubmitted to FDA in May 2018
		III	549	eBC (NAT)	pCR	equivalence	completed	non-inferior pCR (ypt0/is ypN0): 46.8% (95% CI 40.4–53.2) vs. 50.4% (95% CI 44.1–56.7) (CT-P6 vs. trastuzumab RP); 95% CI of the estimated treatment outcome difference (−0.04 (95% CI −0.12 to 0.05)) was within the equivalence margin, RR 0.92 [15]	
PF-05280014 (Trazimera®)	Pfizer (New York, NY, USA)/Hospira (Lake Forest, IL, USA)	III	707	mBC	ORR	equivalence	completed	RR 0.940 (95% CI 0.842–1.049) over trastuzumab; 95% CI within the prespecified equivalence margin of 0.80–1.25; ORR 62.5% (95% CI 57.2–67.6%) for PF-05280014 vs. 66.5% (95% CI 61.3–71.4%) for trastuzumab RP; PFS (median 12.16 months for PF-05280014 vs. 12.06 months for trastuzumab; 1-year rate 54 vs. 51%) or OS (median: not reached in either group; 1-year rate 89.31 vs. 87.36%) [16]	phase I study completed; phase III study ongoing, expected to be completed March 2018; positive phase III results reported in November 2016 and September 2017; submitted to EMA and FDA for approval in September 2017; rejected by FDA in April 2018; approved by EMA in June 2018
		III	226	eBC (NAT)	PK endpoints	non-inferiority	completed	PF-05280014 vs. trastuzumab RP: non-inferior pCR 47 vs. 50%; lower limit of 95% CI (−8.02, 6.49%) for the stratified difference between groups was above the non-inferiority margin (−12.5%) (NCT02187744) [17]	
ABP980 (Kanjinti®)	Amgen (Thousand Oaks, CA, USA)	III	827	eBC (NAT)	pCR	equivalence	completed	non-inferior pCR 48% (95% CI 43–53) for ABP 980 41%, (95% CI 35–46) for trastuzumab RP (RD 7.3, 90% CI 1.2–13.4; RR 1.188, 90% CI 1.033–1.366); central assessed pCR 48 vs. 42% (RD 5.8, 90% CI −0.5 to 12.0 and RR 1.142, 90% CI 0.993–1.312) [18]	approved by EMA in March 2018; submitted to FDA for approval in July 2017; rejected by FDA in June 2018
SB3 (Ontruzant®, EU; Samfenet®, R.O.K.)	Samsung Bioepis (Biogen/Samsung) (Incheon, ROK)/ Daewoong Pharmaceuticals (Seoul, ROK)/Merck (MSD) (Kenilworth, NJ, USA)	III	875	eBC	pCR	equivalence	completed	SB3 vs. trastuzumab RP: equivalent bpCR 51.7 and 42% with SB3 and trastuzumab RP; adjusted ratio of bpCR: 1.259 (95% CI 1.085–1.460), within the predefined equivalence margins; adjusted difference: 10.70% (95% CI 4.13–17.26%), with the lower limit contained within and the upper limit outside the equivalence margin; tpCR: 45.8 and 35.8% ORR 96.3% for SB3 vs. 91.2% for trastuzumab RP, adjusted ratio 1.259 (95% CI 1.085–1.460) [19]; EFS: comparable between groups, HR (SB3/trastuzumab RP) 0.94 (95% CI 0.59–1.51); 12-month EFS 93.7% for SB3 vs. 93.4% for trastuzumab RP; final analysis after 438 days: EFS rate for SB3 (92.2%) vs. trastuzumab RP (91.6%) [20]	approved by EMA in November 2017; approved by Korea's MFDS in November 2017; submitted to FDA for approval in December 2017
MYL-1410 (Ogivri®)	Mylan (Canonsburg, PA, USA)/Biocon (Bangalore, India)	III	458	mBC	ORR	equivalence	completed	MYL-1410 vs. trastuzumab RP: non-inferior ORR: 69.6 vs. 64% (HR 1.09; 95% CI 0.95–1.24); ORR difference (5.53; 95% CI −3.08 to 14.04) 48-week PFS (44.3 vs 44.7%; −0.4%; 95% CI −9.4 to 8.7%), OS (89.1 vs. 85.1%; 4.0%; 95% CI −2.1 to 10.3%; p = 0.13) [21]	received approval from FDA December 2017; submitted to EMA for approval in November 2016; withdrawn from EMA August 2017; resubmitted to EMA for approval in December 2017; received approval from Russian regulatory body January 2016
BCD-022 (HERtiCAD®)	Biocad (Saint Petersburg, Russia)	III	126	mBC	ORR	non-inferiority	completed	BCD-022 vs. trastuzumab RP: ORR 53.6 vs. 53.7%; progression rate not different: 21.45 vs. 20.4%)	

*Genentech, San Francisco, CA, USA.

RP, reference product; PK, pharmacokinetics; RD, risk difference; RR, risk ratio; pCR, pathologic complete response; bpCR, breast pathologic complete response; tpCR, total pathologic complete response; eBC, early breast cancer; mBC, metastatic breast cancer; EFS, event-free survival; HR, hazard ratio; CI, confidence interval; ORR, overall response rate; OS, overall survival; mTTP = median time to progression; ROK, Republic of Korea; EU, European Union; FDA, Federal Drug Administration; EMA, European Medicines Agency; MFDS, Ministry of Food and Drug Safety; NAT, neoadjuvant treatment; PFS, progression-free-survival.

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

	ABP 980 (n=364)	Trastuzumab (n=190)	Switched from adjuvant trastuzumab to ABP 980 (n=171)
Age (years)	53·0 (46·0-60·0)	53·0 (45·0-60·0)	53·0 (44·0-62·0)
Ethnicity			
White	331 (91%)	175 (92%)	158 (92%)
Black or African American	10 (3%)	2 (1%)	2 (1%)
Other	23 (6%)	13 (7%)	11 (6%)
Weight (kg)	70·6 (61·60-81·00)	70·2 (62·00-79·00)	73·3 (62·20-81·30)
Geographical region			
Eastern Europe	271 (75%)	141 (74%)	132 (77%)
Western Europe	43 (12%)	24 (13%)	22 (13%)
Other	50 (14%)	25 (13%)	17 (10%)
ECOG performance status score			
0	298 (82%)	163 (86%)	149 (87%)
1	66 (18%)	27 (14%)	22 (13%)
Tumour stage			
<T4	282 (78%)	147 (77%)	134 (78%)
T4	82 (23%)	43 (23%)	37 (22%)
Axilla lymph node involvement			
Yes	277 (76%)	136 (72%)	130 (76%)
No	87 (24%)	54 (28%)	41 (24%)
Hormone receptor status			
Positive for ER, PR, or both	265 (73%)	140 (74%)	128 (75%)
Negative for ER and PR	99 (27%)	50 (26%)	43 (25%)
Histological grade			
1	8 (2%)	1 (1%)	0
2	174 (48%)	93 (49%)	80 (47%)
3	120 (33%)	67 (35%)	65 (38%)
Unknown	62 (17%)	29 (15%)	26 (15%)
Left ventricular ejection fraction (%)	65 (61·0-68·0)	65 (60·0-68·0)	65 (60·0-68·0)

Data are median (IQR) or n (%). Percentage values might not total 100% because of rounding. ECOG=Eastern Cooperative Oncology Group. ER=oestrogen receptor. PR=progesterone receptor.

Table 1: Baseline characteristics of safety population

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

Table 1. Patient Demographic and Baseline Clinical Characteristics According to Treatment Arm (full analysis set)

Characteristic	SB3 (n = 437)	TRZ (n = 438)
Median age, years (range)	51 (24-65)	50 (22-65)
Race		
White	294 (67.3)	289 (66.0)
Asian	134 (30.7)	138 (31.5)
IIA	65 (14.9)	62 (14.2)
IIB	150 (34.3)	146 (33.3)
IIIA	85 (19.5)	99 (22.6)
IIIB	103 (23.6)	86 (19.6)
IIIC	33 (7.6)	45 (10.3)
IV	1 (0.2)	0

Double-blind RCTs comparing biosimilars to trastuzumab as neoadjuvant (and adjuvant) therapy for HER2 + breast cancer

Presenter	N	Neoadjuvant cycles (chemio)	biosimilar	Endpoints
Von minckwitz	725	4 (paclitaxel) after 4 x AC	ABP 980	pCR
Esteva	549	8 (4Doc→4FEC)	CT-P6	pCR
Pivot	875	8 (4Doc→4FEC)	SB3	pCR & EFS (12mos)
Lammers	226	6 (Doc/carbo)	PF-05280014	pK (cycle 5 trought) & pCR

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

Hope S. Rugo, MD; Abhijit Barve, MD, PhD, MBA; Cornelius F. Waller, MD; Miguel Hernandez-Bronchud, MD, PhD; Jay Herson, PhD; Jinyu Yuan, PhD;

Table 1. Patient Demographic Characteristics, Disease History, and Baseline Characteristics in the Intention-to-Treat Population

Characteristic	Proposed Biosimilar + Taxane (n = 230)	Trastuzumab + Taxane (n = 228)
Age		
Mean (SD), y	54.3 (10.97)	52.9 (11.22)
Median (range), y	55.0 (26-79)	54.0 (26-82)
<50 y, No. (%)	74 (32.2)	86 (37.7)
≥50 y, No. (%)	156 (67.8)	142 (62.3)
≥15 ng/mL	162 (70.4)	172 (75.4)
Missing	8 (3.5)	10 (4.4)
Time from initial diagnosis to metastatic disease, No. (%)		
<2 y	146 (63.5)	153 (67.1)
≥2 y	75 (32.6)	71 (31.1)
Missing	9 (3.9)	4 (1.8)
No. of metastatic sites, No. (%)		
1	58 (25.2)	61 (26.8)
2	87 (37.8)	67 (29.4)
3	44 (19.1)	57 (25.0)
≥4	41 (17.8)	43 (18.9)

(continued)

Table 1. Patient Demographic Characteristics, Disease History, and Baseline Characteristics in the Intention-to-Treat Population (continued)

Characteristic	Proposed Biosimilar + Taxane (n = 230)	Trastuzumab + Taxane (n = 228)
Presence of visceral metastases, No. (%)		
Yes	172 (74.8)	185 (81.1)
No	58 (25.2)	43 (18.9)
NS as first site of metastasis, o. (%)		
Yes	1 (0.4)	2 (0.9)
No	229 (99.6)	226 (99.1)

obreviations: ADA, antidrug antibody; CNS, central nervous system; D, extracellular domain; ECOG, Eastern Cooperative Oncology oup; ER, estrogen receptor; LVEF, left ventricular ejection fraction; , progesterone receptor.

ample sizes are the numbers of patients with available data within the reatment group.

he titer value corresponds to the highest dilution of a sample that yields a ositive result in the assay.

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

	Neoadjuvant treatment		Adjuvant treatment		
	ABP 980 (n=364)	Trastuzumab (n=361)	ABP 980 (n=349)	Trastuzumab (n=171)	Switched from adjuvant trastuzumab to ABP 980 (n=171)
Total number of doses of investigational product administered					
Neoadjuvant					
1–3	7 (2%)	9 (3%)	0	0	0
4	357 (98%)	352 (98%)	0	0	0
Adjuvant					
1–10	0	0	41 (12%)	12 (7%)	17 (10%)
11–13	0	0	308 (88%)	159 (93%)	154 (90%)
Weight-based average dose (mg/kg)*	6·5 (6·5–6·5)	6·5 (6·5–6·5)	6·2 (6·17–6·18)	6·2 (6·15–6·17)	6·2 (6·15–6·18)
Weight-based cumulative dose (mg/kg)*	26·0 (26·0–26·0)	26·0 (26·0–26·0)	74·0 (68·0–76·0)	74·0 (74·0–80·0)	74·0 (70·0–80·0)
Total cumulative dose (mg)*†	1820·0 (1605·5–2106·0)	1830·0 (1612·0–2080·0)	5106·0 (4399·6–5920·0)	5200·0 (4440·0–5920·0)	5208·0 (4514·00–6142·00)

Data are number (%) or median (IQR). Percentage values might not total 100% because of rounding. *For visits where partial loading or reloading doses were indicated on the electronic case report form, 4 mg/kg was given, and for visits where maintenance doses were indicated on the form, 3 mg/kg was used. †Calculated with use of the patient's weight at screening.

Table 2: Investigational product exposure in the safety analysis population

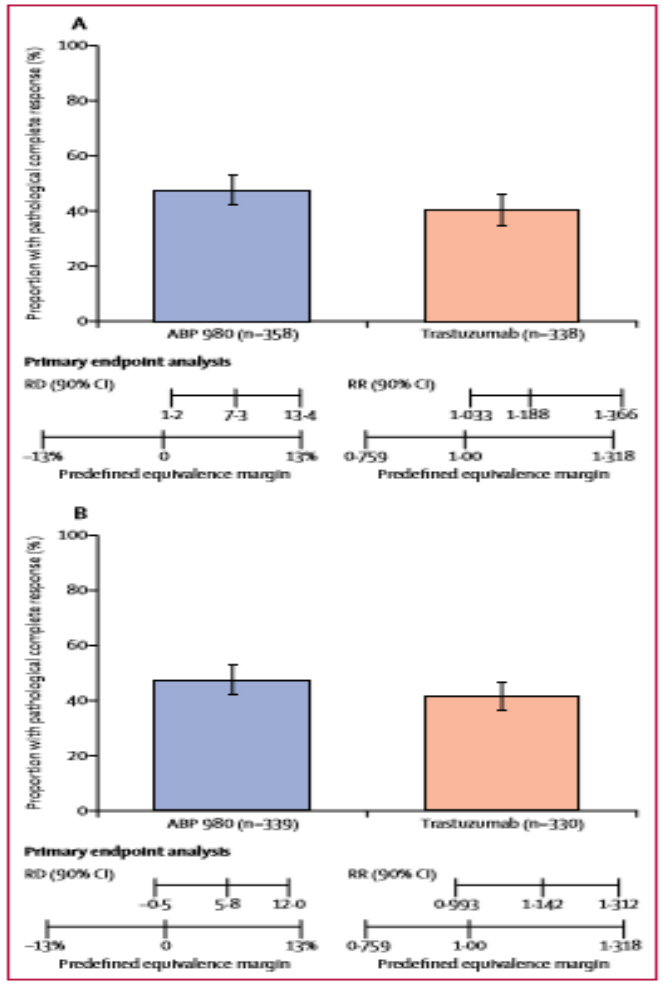

Figure 2: Proportions of patients with pathological complete responses (A) Local laboratory review. (B) Central laboratory review. Data are percentages and the error bars represent 95% CIs. RD=risk difference. RR=risk ratio.

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

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

Table 2. Primary Outcome: Ratio and Difference of Overall Response Rate at Week 24 in the Intention-to-Treat Population

Response[a]	Proposed Biosimilar + Taxane (n = 230)	Trastuzumab + Taxane (n = 228)	Difference, %	Rate Ratio
Response type, No. (%)				
Complete	3 (1.3)	0		
Partial	157 (68.3)	146 (64.0)		
Stable disease	48 (20.9)	49 (21.5)		
Progressive disease	9 (3.9)	20 (8.8)		
Not evaluable	13 (5.7)	13 (5.7)		
Overall response rate				
Overall response, No. (%)[b]	160 (69.6)	146 (64.0)	5.53[c]	1.09[d]
90% CI, %	64.57 to 74.56	58.81 to 69.26	−1.70 to 12.69	0.974 to 1.211
95% CI, %	63.62 to 75.51	57.81 to 70.26	−3.08 to 14.04	0.954 to 1.237

Table 3. Secondary Outcomes: Time to Tumor Progression, Progression-Free Survival, and Overall Survival at Week 48 in the Intention-to-Treat Population

Outcome	Proposed Biosimilar + Taxane (n = 230)	Trastuzumab + Taxane (n = 228)	Log-Rank *P* Value	Unstratified		Stratified[a]	
				Hazard Ratio (95% CI)[b]	*P* Value	Hazard Ratio (95% CI)[b]	*P* Value
Time to Tumor Progression[c]							
Events, No. (%)	95 (41.3)	98 (43.0)	.68	0.94 (0.71-1.25)	.69	0.92 (0.69-1.23)	.58
Censored events, No. (%)[d]	135 (58.7)	130 (57.0)					
Kaplan-Meier estimate, median (95% CI), mo	11.1 (8.83-11.20)	11.1 (8.88-11.20)					
Progression-Free Survival[e]							
Events, No. (%)	102 (44.3)	102 (44.7)	.84	0.97 (0.74-1.28)	.85	0.95 (0.71-1.25)	.69
Censored events, No. (%)[d]	128 (55.7)	126 (55.3)					
Kaplan-Meier estimate, median (95% CI), mo	11.1 (8.81-11.20)	11.1 (8.60-11.20)					
Overall Survival[f]							
Events, No. (%)	25 (10.9)	34 (14.9)	.13	0.67 (0.40-1.13)	.13	0.61 (0.36-1.04)	.07
Censored events, No. (%)[d]	205 (89.1)	194 (85.1)					
Kaplan-Meier estimate, median (95% CI), mo	Not estimable	Not estimable					

[a] Stratified by assigned taxane, tumor progression, and tumor endocrine status. The sample size for both the proposed biosimilar and trastuzumab groups was 220.

[b] The hazard ratio estimates were obtained from the Cox proportional hazards model. A hazard ratio less than 1.0 indicates a lower average event rate and a longer progression-free survival for the proposed biosimilar relative to trastuzumab.

[c] Defined as the time from randomization to the date of first documentation of objective progression, divided by (365.25/12).

[d] Events not occurring before the data cutoff were censored at the date of cutoff or the date of the last tumor assessment.

[e] Defined as the time from randomization to first documentation of objective progression or to death due to any cause, divided by (365.25/12).

[f] Defined as the time from randomization to the date of death due to any cause, divided by (365.25/12).

Bevacizumab biosimilar BEVZ92 versus reference bevacizumab in combination with FOLFOX or FOLFIRI as first-line treatment for metastatic colorectal cancer: a multicentre, open-label, randomised controlled trial

Alvaro Romera, Sergiy Peredpaya, Yaroslav Shparyk, Igor Bondarenko, Giovanni Mendonça Bariani, Kathia Cristina Abdalla, Enrique Roca, Fábio Franke, Felipe Melo Cruz, Anita Ramesh, Vikas Ostwal, Pradeep Shah, Sajeed Abdul Rahuman, Alexandra Paravisini, Camino Huerga, Ana Del Campo García, Susana Millán

	All treated patients		Assessable patients	
	BEVZ92 (n=69)	Reference bevacizumab (n=71)	BEVZ92 (n=55)	Reference bevacizumab (n=61)
Age, years				
Mean (SD; range)	56·3 (12·9; 29–83)	56·7 (11·6; 33–78)	57·0 (12·8; 29–83)	57·0 (12·0; 33–78)
<65	49 (71%)	51 (72%)	39 (71%)	42 (69%)
≥65	20 (29%)	20 (28%)	16 (29%)	19 (31%)
Sex				
Female	30 (43%)	32 (45%)	23 (42%)	28 (46%)
Male	39 (57%)	39 (55%)	32 (58%)	33 (54%)
Race				
White	50 (72%)	55 (77%)	38 (69%)	47 (77%)
Asian	14 (20%)	12 (17%)	12 (22%)	10 (16%)
Black	2 (3%)	3 (4%)	2 (4%)	3 (5%)
Other	3 (4%)	1 (1%)	3 (5%)	1 (2%)
TNM stage				
IVa	30 (43%)	32 (45%)	26 (47%)	29 (48%)
IVb	38 (55%)	38 (54%)	28 (51%)	31 (51%)
Missing	1 (1%)	1 (1%)	1 (2%)	1 (2%)
Months since diagnosis of metastatic colorectal cancer				
n	67	69	53	61
Mean (SD)	13·0 (14·7)	13 (17·5)	12·4 (14·5)	13·2 (17·9)
Median (IQR)	4·5 (1·6–21·4)	4·3 (1·6–17·7)	3·6 (1·6–21·0)	4·3 (1·6–21·0)
ECOG performance status				
0	7 (10%)	18 (25%)	6 (11%)	17 (28%)
1	57 (83%)	43 (61%)	45 (82%)	35 (57%)
2	5 (7%)	10 (14%)	4 (7%)	9 (15%)
Number of target lesions				
1	9 (13%)	11 (15%)	8 (15%)	10 (16%)
2	29 (42%)	31 (44%)	25 (45%)	27 (44%)
≥3	31 (45%)	29 (41%)	22 (40%)	24 (40%)
Extent of disease				
Liver only	7 (10%)	5 (7%)	7 (13%)	4 (7%)
Other	62 (90%)	66 (93%)	48 (87%)	57 (93%)
Previous treatment*				
Surgery	55 (80%)	53 (75%)	45 (82%)	46 (75%)
Radiotherapy	14 (20%)	15 (21%)	12 (22%)	12 (20%)
Chemotherapy	24 (35%)	23 (32%)	20 (36%)	18 (30%)

Data are n (%) unless otherwise specified. TNM=tumour, node, metastasis. ECOG=Eastern Cooperative Oncology Group. *Recorded at screening visit.

Table 1: Baseline characteristics in all treated patients and assessable patients

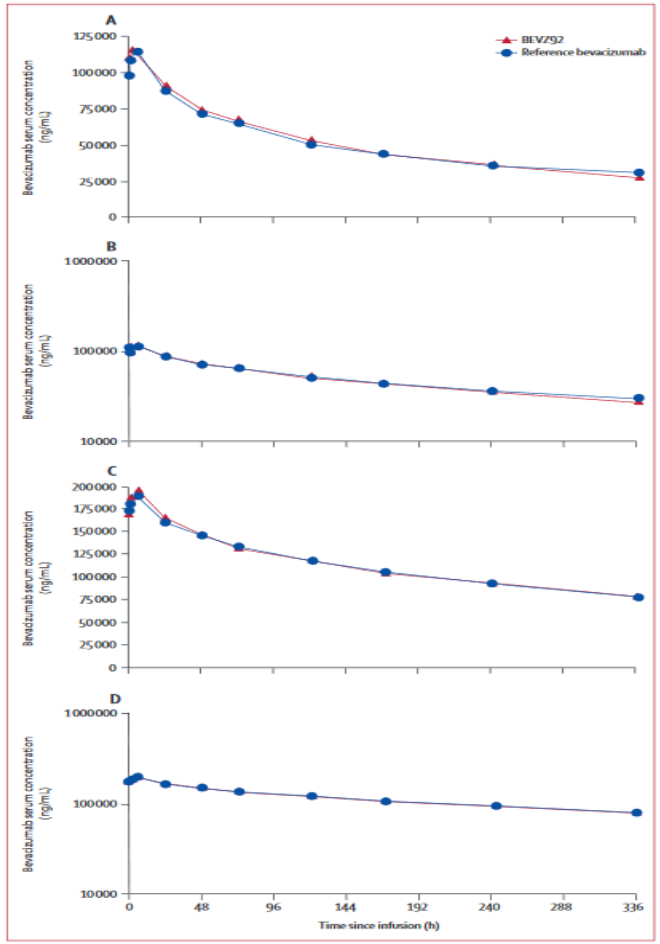

Figure 2: Serum bevacizumab concentrations during cycle 1 on a standard (A) and semi-logarithmic (B) scale and during cycle 7 on a standard (C) and semi-logarithmic (D) scale in all assessable patients in the BEVZ92 and reference bevacizumab groups

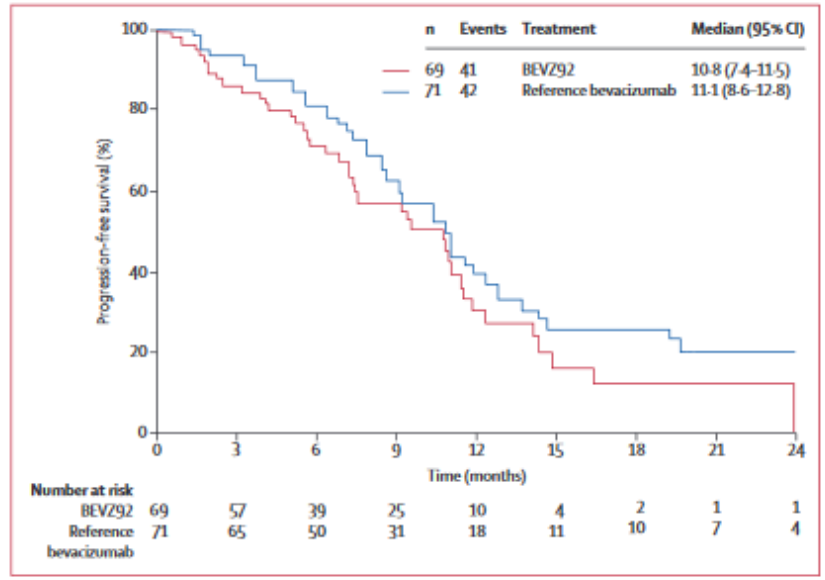

Figure 3: Progression-free survival in the BEVZ92 and reference bevacizumab groups

	BEVZ92 (n=71)	Reference bevacizumab (n=71)
Complete response	1 (1%)	3 (4%)
Partial response	34 (48%)	37 (52%)
Stable disease	27 (38%)	25 (35%)
Progressive disease	4 (6%)	2 (3%)
Unevaluable	5 (7%)	4 (6%)
Objective response*	35 (49% [37–61])	40 (56% [44–68])
Clinical benefit†	62 (87% [77–94])	65 (92% [83–97])

Data are n (%) or n (% [95% CI]). The best overall responses among all post-baseline assessments of each patient, including unscheduled assessments, are included. *Patients with a complete or partial response at any time during the study (including unscheduled assessments; patients who did not undergo any post-baseline tumour assessments were deemed non-responders); exact two-sided 95% CIs were calculated with the Clopper-Pearson method. †Patients with a complete response, partial response, or stable disease at any time during the study (including unscheduled assessments and assessments after end of treatment).

Table 3: Response to treatment in the intention-to-treat population

	BEVZ92 (n=69)	Reference bevacizumab (n=71)
Any TEAE irrespective of causality	66 (96%)	71 (100%)
Grade ≥3 TEAE	44 (64%)	49 (69%)
TEAE leading to discontinuation	13 (19%)	6 (8%)
Any treatment-related TEAE*	63 (91%)	70 (99%)
Grade ≥3 treatment-related TEAEs	37 (54%)	44 (62%)
Any serious† TEAE	19 (28%)	21 (30%)
Fatal TEAEs	8 (12%)	5 (7%)
Any bleeding event	14 (20%)	19 (27%)
Grade ≥3 bleeding events	1 (1%)	2 (3%)

Data are n (%). TEAE=treatment-emergent adverse event. *Related to any study treatment, including fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or fluorouracil, leucovorin, and irinotecan (FOLFIRI) regimens. † Any untoward medical occurrence that at any dose results in death, a life-threatening event, hospitalisation or prolongation of hospitalisation, substantial or persistent disability, a congenital anomaly or birth defect, or any other medically important condition.

Table 4: Participants with at least one TEAE in the safety population

Obiettivi

- ✓ La presa di coscienza in tema di sostenibilità
- ✓ Quanto ne sappiamo?
- ✓ Aspetti metodologici e perpelssità e scarsa fiducia
- ✓ Caratteristiche degli studi registrativi
- ✓ **Switch**
- ✓ AE

Clinical Therapeutics/Volume ∎, Number ∎, 2018

Monoclonal Antibody Biosimilars in Oncology: Critical Appraisal of Available Data on Switching

Paul Declerck, PharmD, PhD[1]; Georgios Bakalos, MD, PhD[2,3]; Elias Zintzaras, MSc, PhD[3,4]
Bettina Barton, MSc, PhD[2,5]; and Thomas Schreitmüller, MSc, PhD[6]

Drugs (2018) 78:463–478
https://doi.org/10.1007/s40265-018-0881-y

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SYSTEMATIC REVIEW

Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes

Hillel P. Cohen[1] · Andrew Blauvelt[2] · Robert M. Rifkin[3] · Silvio Danese[4] · Sameer B. Gokhale[5] · Gillian Woollett[6]

BioDrugs (2018) 32:27–52
https://doi.org/10.1007/s40259-017-0256-z

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SYSTEMATIC REVIEW

Biosimilarity and Interchangeability: Principles and Evidence: A Systematic Review

Ross A. McKinnon[1] · Matthew Cook[2] · Winston Liauw[3,4] · Mona Marabani[5] · Ian C. Marschner[6,7] · Nicolle H. Packer[8,9] · Johannes B. Prins[10]

Clinical Therapeutics/Volume 41, Number 1, 2019

Drug Discontinuation in Studies Including a Switch From an Originator to a Biosimilar Monoclonal Antibody: A Systematic Literature Review

Check for updates

Georgios Bakalos, MD, PhD, MPH[1,2]; and Elias Zintzaras, MSc, PhD[2,3]

Monoclonal Antibody Biosimilars in Oncology: Critical Appraisal of Available Data on Switching

Paul Declerck, PharmD, PhD[1]; Georgios Bakalos, MD, PhD[2,3]; Elias Zintzaras, MSc, PhD[3,4]; Bettina Barton, MSc, PhD[2,5]; and Thomas Schreitmüller, MSc, PhD[6]

[1]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, University of Leuven, Leuven, Belgium; [2]Global Product Development Medical Affairs, Hoffmann-La Roche Ltd, Basel, Switzerland;

Table II. Clinical studies in oncology and nononcology indications, including a switching component.

Reference Product (Manufacturer)	Biosimilar Product (Manufacturer)	Stu
Oncology indications		
Trastuzumab (Herceptin®, Roche/Genentech)	ABP 980 (Amgen)	AB
Rituximab (MabThera®, Roche; Rituxan®, Genentech/Biogen Idec)	CT-P10 (Truxima™, Celltrion)	CT
Nononcology indications		
Rituximab (MabThera®, Roche; Rituxan®, Genentech/Biogen Idec)	CT-P10 (Truxima™, Celltrion)	CT
	CT-P10 (Truxima™, Celltrion)	CT
	GP2013 (Rixathon™, Sandoz)	AS
	PF-05280586 (Pfizer)	RE
	BCD-020 (Biocad)	BC
	SAIT101 (Archigen Biotech)	RA

LTB = low tumor burden.
*From entry at clinicaltrials.gov; completion date refers to last follow-up da

Table III. Appraisal of study designs (based on available information in trial registries and published reports).

			Switching Part of the Study								
Biosimilar and Study Identifier	Indication	Patients Enrolled	Randomized	Blinded	Sensitive Population for Oncology	Switches /Patient	Control Arm(s)	Patients in Switch Group(s)	Type of Switch	Main Outcome Measures	Follow-Up
ABP 980 NCT01901146	eBC	725‡	✓	✓	✓	1	BS RP	171	RP→BS	EFS, OS, ADA, safety	~40 weeks
CT-P10 NCT02260804	LTB FL	174‡	x	Information not available	✓	1	BS	Not available (estimate: 87)	RP→BS	Information not available	52 weeks
CT-P10 NCT01873443	RA	87	x	x	x	1	BS	20	RP→BS	DAS28, EULAR, ADA, safety	56 weeks
CT-P10 NCT02149121	RA	372‡	✓†	Information not available	x	1	BS RP	109	RP→BS	DAS28, ACR, B-cell depletion, ADA, safety	24 weeks
GP2013 NCT02514772	RA	107	✓	✓	x	1	RP	53	RP→BS	ADA, safety	24 weeks
PF-05280586 NCT01643928	RA	183	✓	✓	x	1	BS	125	RP→BS	DAS28, EULAR, ACR, B-cell depletion, PK, ADA, HAQ-DI score	52–72 weeks
BCD-020 NCT01759030	RA	160‡	✓	✓	x	1	BS RP	Not available (estimate: 70)	BS→RP→BS	ACR, DAS28, safety, ADA	24 weeks
SAIT101 NCT02819726	RA	282‡	x	Information not available	x	1	BS RP	Not available (estimate: 71)	RP→BS	Safety	28 weeks

antidrug antibodies; BS = biosimilar or proposed biosimilar; ropean League Against Rheumatism response criteria; HAQ-DI ymphoma; OS = overall survival; PK = pharmacokinetics;

ot (switch group: n = 47).
ort biosimilarity.

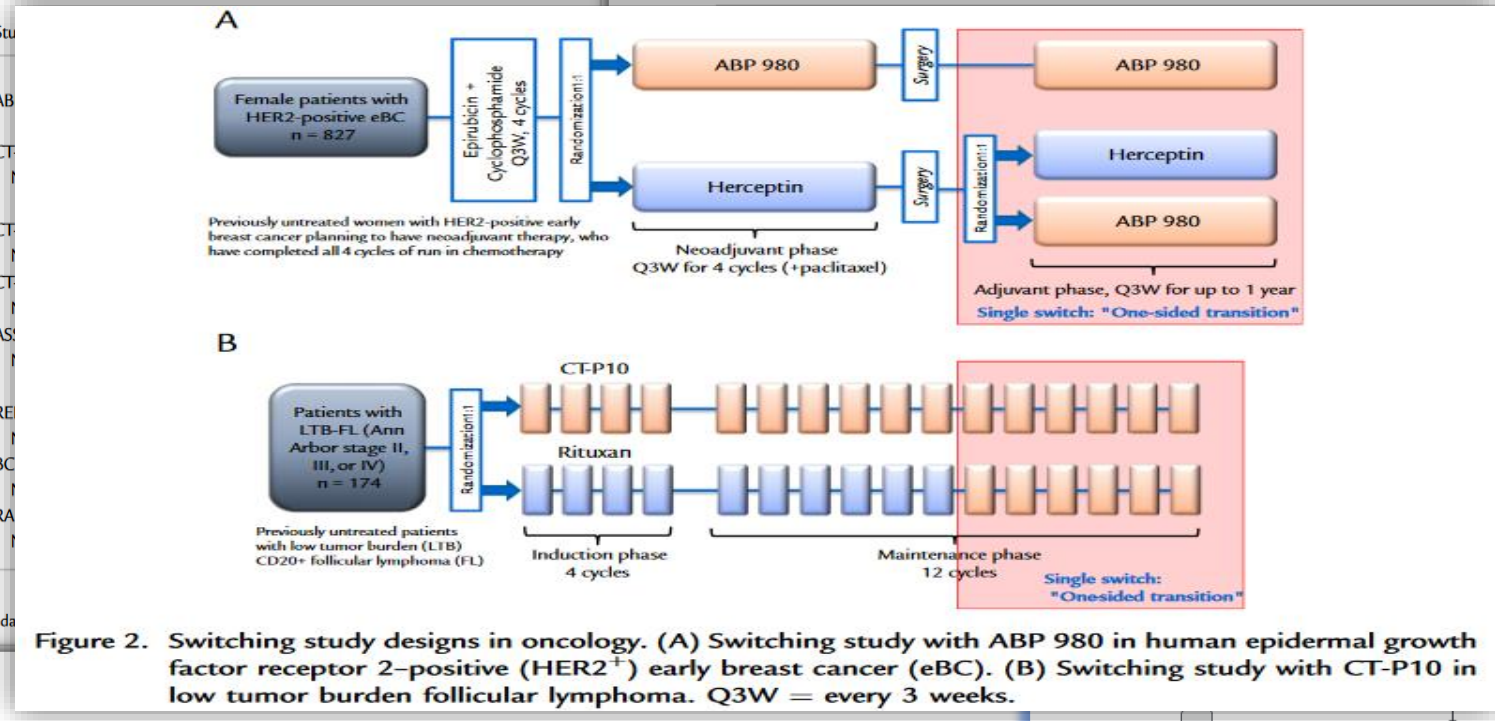

Figure 2. Switching study designs in oncology. (A) Switching study with ABP 980 in human epidermal growth factor receptor 2–positive (HER2+) early breast cancer (eBC). (B) Switching study with CT-P10 in low tumor burden follicular lymphoma. Q3W = every 3 weeks.

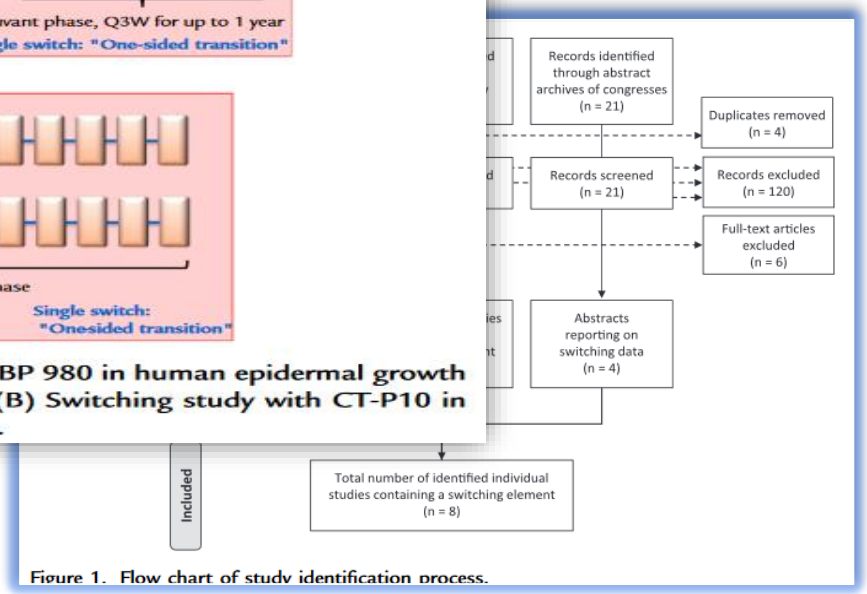

Figure 1. Flow chart of study identification process.

Obiettivi

- ✓ La presa di coscienza in tema di sostenibilità
- ✓ Quanto ne sappiamo?
- ✓ Aspetti metodologici e perpelssità e scarsa fiducia
- ✓ Caratteristiche degli studi registrativi
- ✓ Switch
- ✓ **AE**

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

	ABP 980 (n=349)			Trastuzumab (n=171)			Switched from adjuvant trastuzumab to ABP 980 (n=171)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Neutropenia	22 (6%)	2 (1%)	1 (<1%)	10 (6%)	0	0	5 (3%)	1 (1%)	0
Arthralgia	20 (6%)	0	0	9 (5%)	0	0	9 (5%)	0	0
Asthenia	17 (5%)	1 (<1%)	0	7 (4%)	0	0	10 (6%)	0	0
Anaemia	17 (5%)	0	0	7 (4%)	0	0	10 (6%)	0	0
Neuropathy peripheral	8 (2%)	0	0	3 (2%)	0	0	2 (1%)	0	0

The table shows grade 1–2 adverse events that occurred in >10% of patients in any group and grade 3 and 4 adverse events that occurred in >2% of patients in any group; none of the events were grade 5. A complete list of adverse events is provided in the appendix (pp 3–7). Adverse events were classified with Medical Dictionary for Regulatory Activities version 19.0 codes. Only treatment-emergent adverse events are summarised. Patients are only included once, even if they had multiple events in a category.

Table 4: Adverse events during adjuvant treatment in the safety analysis population

	ABP 980 (n=364)				Trastuzumab (n=361)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Infusion reactions	73 (20%)	7 (2%)	0	0	61 (17%)	7 (2%)	0	0
Neutropenia	48 (13%)	16 (4%)	5 (1%)	0	36 (10%)	15 (4%)	6 (2%)	0
Infections and infestations	44 (12%)	4 (1%)	2 (1%)	1 (<1%)	53 (15%)	1 (<1%)	1 (<1%)	0
Hypersensitivity	22 (6%)	2 (1%)	0	0	17 (5%)	2 (1%)	0	0
Cardiac failure	6 (2%)	0	0	0	1 (<1%)	0	0	0
Pulmonary toxicity	1 (<1%)	0	0	0	1 (<1%)	0	0	0

Adverse events were classified with Medical Dictionary for Regulatory Activities version 19.0 codes. Only treatment-emergent adverse events of interest are summarised. Patients are only included once, even if they had multiple events in a category.

Table 5: Adverse events of interest during neoadjuvant treatment in the safety analysis population

	ABP 980 (n=349)				Trastuzumab (n=171)				Switched from adjuvant trastuzumab to ABP 980 (n=171)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Infusion reactions	26 (8%)	2 (1%)	0	0	12 (7%)	2 (1%)	0	0	17 (10%)	2 (1%)	1 (1%)	0
Neutropenia	35 (10%)	2 (1%)	1 (<1%)	0	14 (8%)	2 (1%)	0	0	12 (7%)	1 (1%)	0	0
Infections and infestations	50 (14%)	4 (1%)	0	0	15 (9%)	2 (1%)	0	0	21 (12%)	1 (1%)	0	1 (1%)
Hypersensitivity	11 (3%)	0	0	0	7 (4%)	0	0	0	8 (5%)	0	0	0
Cardiac failure	2 (1%)	0	0	0	1 (1%)	0	0	0	0	1 (1%)	0	0
Pulmonary toxicity	4 (1%)	0	0	0	1 (1%)	1 (1%)	0	0	0	1 (1%)	0	0

Adverse events were classified with Medical Dictionary for Regulatory Activities version 19.0 codes. Only treatment-emergent adverse events of interest are summarised. Patients are only included once, even if they had multiple events in a category.

Table 6: Adverse events of interest during adjuvant treatment in the safety analysis population

	ABP 980 (n=364)			Trastuzumab (n=361)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Arthralgia	63 (17%)	1 (<1%)	0	55 (15%)	0	0
Asthenia	53 (15%)	1 (<1%)	0	59 (16%)	0	0
Neuropathy peripheral	48 (13%)	3 (1%)	0	36 (10%)	7 (2%)	0
Anaemia	38 (10%)	2 (1%)	0	35 (10%)	3 (1%)	0
Neutropenia	37 (10%)	12 (3%)	4 (1%)	25 (7%)	14 (4%)	6 (2%)

The table shows grade 1–2 events that occurred in ≥10% of patients in any group and grade 3 and 4 adverse events that occurred in >2% of patients in any group; none of the events were grade 5. A complete list of adverse events is available in the appendix (pp 3–7). Adverse events were classified with Medical Dictionary for Regulatory Activities version 19.0 codes. Only treatment-emergent adverse events are summarised. Patients are included only once, even if they had multiple events in a category.

Table 3: Adverse events during neoadjuvant treatment in the safety analysis population

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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

Mean ± SD LVEF change during overall study

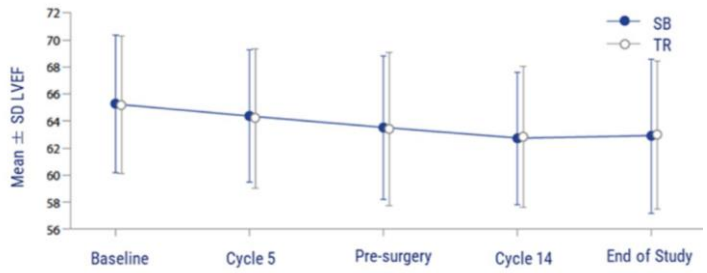

Table 4. Safety Profile According to Treatment Arm (safety set)

Adverse Event	No. of Patients (%) SB3 (n = 437)	TRZ (n = 438)
Patients with ≥ 1 TEAE	422 (96.6)	417 (95.2)
Frequently reported TEAEs (≥ 10% in both groups)		
Neutropenia	293 (67.0)	279 (63.7)
Alopecia	293 (67.0)	277 (63.2)
Nausea	136 (31.1)	133 (30.4)
Leukopenia	122 (27.9)	107 (24.4)
Diarrhea	88 (20.1)	66 (15.1)
ALT increased	81 (18.5)	76 (17.4)
Anemia	80 (18.3)	89 (20.3)
Fatigue	63 (14.4)	67 (15.3)
Myalgia	63 (14.4)	64 (14.6)
AST increased	61 (14.0)	56 (12.8)
Stomatitis	60 (13.7)	49 (11.2)
Vomiting	59 (13.5)	49 (11.2)
Neutrophil count decreased	55 (12.6)	56 (12.8)
Asthenia	51 (11.7)	48 (11.0)
TEAEs of special interest		
Infusion-related reaction	36 (8.2)	44 (10.0)
Asymptomatic LVSD	4 (0.9)	3 (0.7)
Congestive heart failure	2 (0.5)	0 (0.0)
Patients with ≥ 1 serious TEAE	46 (10.5)	47 (10.7)
Death*	1 (0.2)	3 (0.7)

Abbreviations: LVSD, left ventricular systolic dysfunction; SB3, trastuzumab biosimilar; TEAE, treatment-emergent adverse event; TRZ, reference trastuzumab.
*See main text for details.

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

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-Tiamseng, 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

Event	Participants, No. (%) Proposed Biosimilar + Taxane (n = 247)	Trastuzumab + Taxane (n = 246)	Overall (n = 493)
Treatment-Emergent Adverse Events[a]			
≥1 Treatment-emergent adverse event	239 (96.8)	233 (94.7)	472 (95.7)
CTCAE preferred term			
Alopecia	142 (57.5)	135 (54.9)	277 (56.2)
Neutropenia	142 (57.5)	131 (53.3)	273 (55.4)
Peripheral neuropathy	57 (23.1)	61 (24.8)	56 (23.9)
Diarrhea	51 (20.6)	51 (20.7)	102 (20.7)
Asthenia	54 (21.9)	40 (16.3)	94 (19.1)
Leukopenia	42 (17.0)	51 (20.7)	93 (18.9)
Nausea	49 (19.8)	34 (13.8)	83 (16.8)
Anemia	40 (16.2)	40 (16.3)	80 (16.2)
Peripheral edema	35 (14.2)	28 (11.4)	63 (12.8)
Fatigue	28 (11.3)	33 (13.4)	61 (12.4)
Pyrexia	21 (8.5)	30 (12.2)	51 (10.3)
Myalgia	23 (9.3)	23 (9.3)	46 (9.3)
Vomiting	26 (10.5)	19 (7.7)	45 (9.1)
Decreased appetite	21 (8.5)	24 (9.8)	45 (9.1)
Rash	21 (8.5)	23 (9.3)	44 (8.9)
Arthralgia	30 (12.1)	11 (4.5)	41 (8.3)
Alanine aminotransferase increased	18 (7.3)	21 (8.5)	39 (7.9)
Urinary tract infection	21 (8.5)	16 (6.5)	37 (7.5)
Nail disorder	17 (6.9)	20 (8.1)	37 (7.5)
Aspartate aminotransferase increased	13 (5.3)	22 (8.9)	35 (7.1)
Hyperglycemia	13 (5.3)	17 (6.9)	30 (6.1)
Bone pain	17 (6.9)	13 (5.3)	30 (6.1)
Headache	15 (6.1)	15 (6.1)	30 (6.1)
Cough	14 (5.7)	16 (6.5)	30 (6.1)
Dyspnea	13 (5.3)	16 (6.5)	29 (5.9)
Infusion-related reaction	17 (6.9)	11 (4.5)	28 (5.7)
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)

Bevacizumab biosimilar BEVZ92 versus reference bevacizumab in combination with FOLFOX or FOLFIRI as first-line treatment for metastatic colorectal cancer: a multicentre, open-label, randomised controlled trial

Alvaro Romera, Sergiy Peredpaya, Yaroslav Shparyk, Igor Bondarenko, Giovanni Mendonça Bariani, Kathia Cristina Abdalla, Enrique Roca, Fábio Franke, Felipe Melo Cruz, Anita Ramesh, Vikas Ostwal, Pradeep Shah, Sajeed Abdul Rahuman, Alexandra Paravisini, Camino Huerga, Ana Del Campo García, Susana Millán

	BEVZ92 (n=69)		Reference bevacizumab (n=71)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Diarrhoea	25 (36%)	6 (9%)	32 (45%)	6 (8%)
Nausea	27 (39%)	2 (3%)	29 (41%)	2 (3%)
Neutropenia	9 (13%)	14 (20%)	7 (10%)	19 (27%)
Vomiting	20 (29%)	..	20 (28%)	2 (3%)
Anaemia	16 (23%)	2 (3%)	21 (30%)	3 (4%)
Asthenia	17 (25%)	1 (1%)	18 (25%)	1 (1%)
Hypertension	7 (10%)	7 (10%)	13 (18%)	6 (8%)
Fatigue	14 (20%)	1 (1%)	14 (20%)	4 (6%)
Decreased appetite	15 (22%)	..	17 (24%)	..
Leucopenia	7 (10%)	7 (10%)	13 (18%)	3 (4%)
Peripheral neuropathy	19 (28%)	5 (7%)	22 (31%)	7 (10%)
Thrombocytopenia	6 (9%)	3 (4%)	12 (17%)	1 (1%)
Paraesthesia	5 (7%)	5 (7%)	6 (8%)	2 (3%)
Epistaxis	7 (10%)	..	10 (14%)	..
Dysgeusia	4 (6%)	..	11 (15%)	..
Stomatitis	5 (7%)	3 (4%)	6 (8%)	2 (3%)
Abdominal pain	5 (7%)	..	13 (18%)	1 (1%)
Skin hyperpigmentation	7 (10%)	..	7 (10%)	..
Weight loss	6 (9%)	..	7 (10%)	..
Increased aspartate aminotransferase	3 (4%)	..	9 (13%)	..
Proteinuria	6 (9%)	1 (1%)	5 (7%)	..
Palmar-plantar erythrodysaesthesia	3 (4%)	1 (1%)	6 (8%)	2 (3%)
Oral candidiasis	..	1 (1%)	..	2 (3%)
Urinary tract infection	..	..	1 (1%)	2 (3%)
Hypotension	..	..	1 (1%)	2 (3%)
Drug hypersensitivity	..	..	1 (1%)	2 (3%)
Sepsis	..	..	..	2 (3%)

Data are n (%). The table shows all grade 1–2 adverse events that occurred in 10% or more of patients and all grade 3–4 events that occurred in 3% or more of patients.

Table 5: **Common treatment-related treatment-emergent adverse events**

CONCLUSIONI

- ✓ **Favorire la presa di coscienza in tema di sostenibilità**
- ✓ **Implementare la formazione dei clinici in tema di farmaci biosimilari (aspetti metodologici)**
- ✓ **Incentivare l'utilizzo dei farmaci biosimilari**
- ✓ **Implementare i Registri di Monitoraggio**
- ✓ **Studi di *Real-Life***

Thanks to Dr G. Rosti

Grazie