Biosimilaires : Nouveaux enjeux

Pr. X. Pivot

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EDITORIALS

Trastuzumab in the Treatment of Breast Cancer

Gabriel N. Hortobagyi, M.D.

"Clearly, the results reported in this issue of the Journal are not evolutionary… but revolutionary."

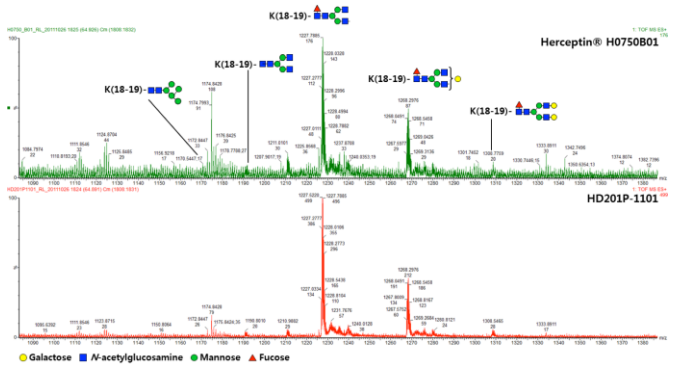
G Hortobagyi

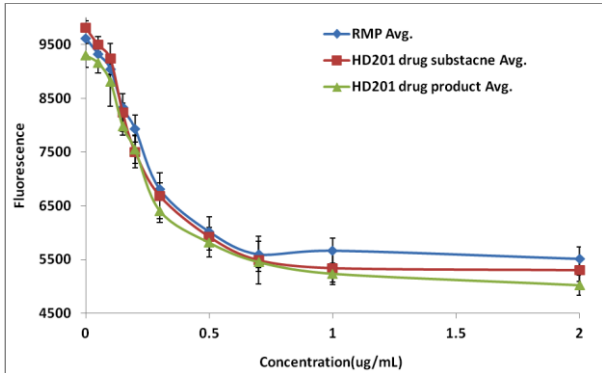
Trastuzumab biosimilars are currently undergoing regulatory review

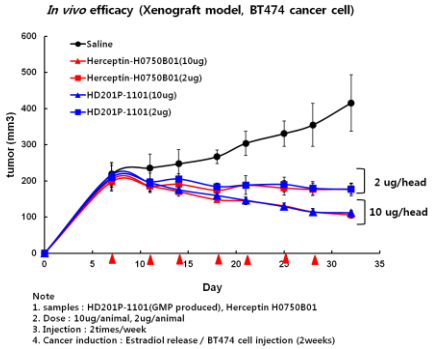
Company	Biosimilar	Submitted to EMA	Submitted to FDA
Amgen	ABP 980	March 2017	July 2017
Biocon/Mylan	MYL-1401O	August 2016	November 2016
Celltrion	CT-P6	October 2016	July 2017
Samsung Bioepis	SB3	August 2016*	
Pfizer	PF-05280014	July 2017	Submitted (date unknown)

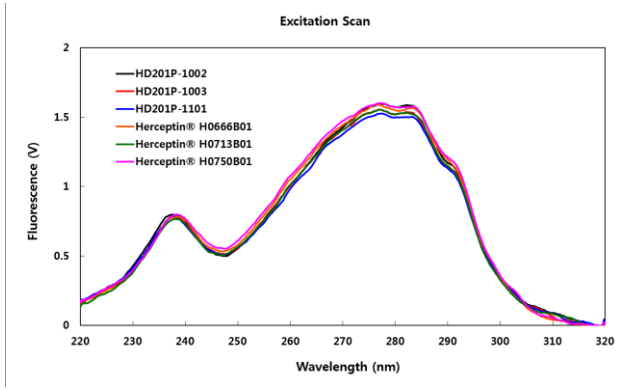
EMA, European Medicines Agency; FDA, Food and Drug Administration
EMA and FDA submission information available from company press releases (see notes page for citation details)

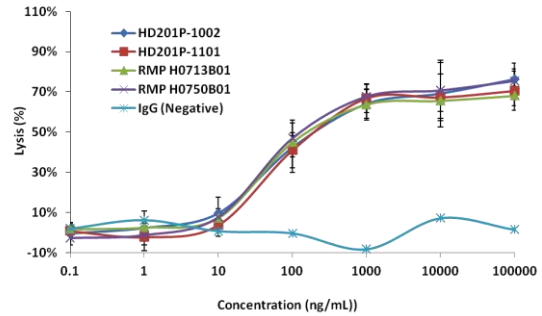
*Positive CHMP opinion received September 15, 2017
ABP 980 is an investigational product





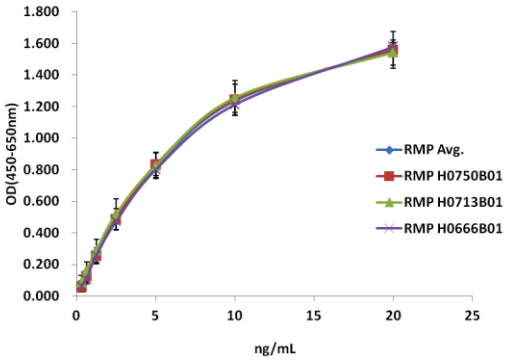


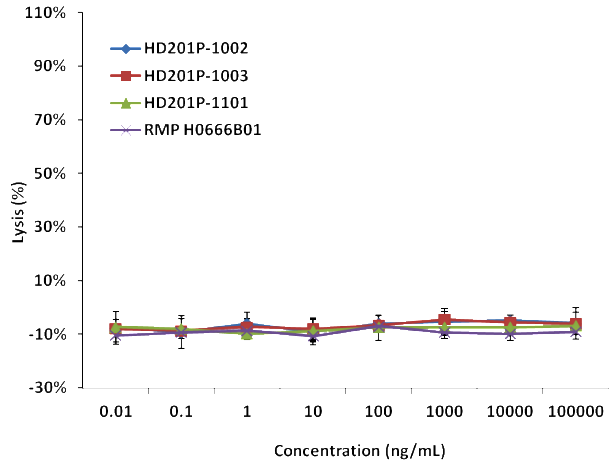


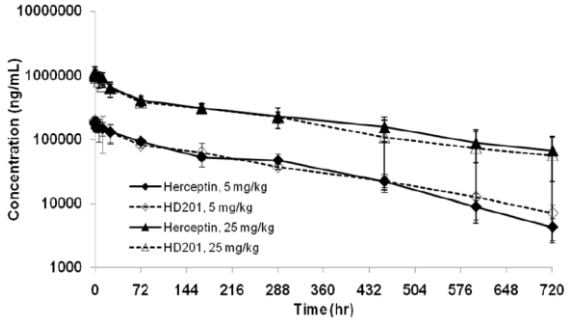


Mean (±SD) Pharmacokinetic Parameters for Herceptin® and HD201 in Female Monkeys after an Intravenous Dose

K Parameter	Sample/Dose			
	Herceptin® 5 mg/kg IV	Herceptin® 25 mg/kg IV	HD201 5 mg/kg IV	HD201 25 mg/kg IV
AUC0-∞ hr·µg/mL)	31400±6020	198000±60900	32300±6160	181000±74200
AUC0-720 hr·µg/mL)	30700±5750	173000±41800	30500±5220	156000±46200



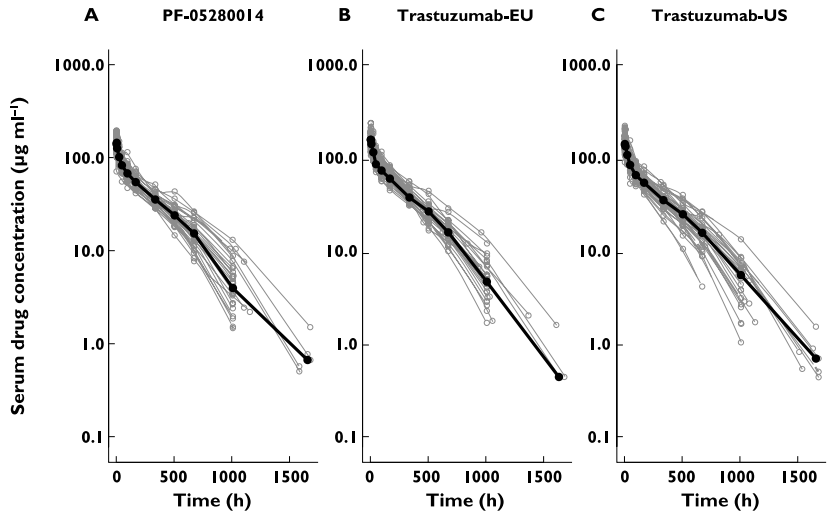




X. Pivot et al. Clin Ther 2018

Phase 1 PK studies of trastuzumab biosimilars in healthy volunteers

Randomised Phase 1 PK trial comparing potential biosimilar PF-05280014 with trastuzumab in healthy volunteers (REFLECTIONS B327-01)[1]



	PF-05280014	Trastuzumab-EU	Trastuzumab-US
Subjects (*n*)	34	35	32
C_{max} (µg ml^{-1})	159 ± 26	174 ± 31	164 ± 31
$AUC_{(0,t_{last})}$ (µg ml^{-1} h)*	35700 ± 6287	38510 ± 6569	35870 ± 6878
$AUC_{(0,\infty)}$ (µg ml^{-1} h)	37130 ± 6305	40330 ± 6994	37310 ± 6728
CL (ml h^{-1} kg^{-1})	0.166 ± 0.026	0.153 ± 0.025	0.166 ± 0.032
V_{ss} (ml kg^{-1})	56.1 ± 8.2	51.7 ± 6.9	55.7 ± 8.8
$t_{1/2}$ (h)	213 ± 42	220 ± 42	212 ± 47

Randomised Phase 1 PK study comparing biosimilar candidate SB3 and trastuzumab in healthy male subjects[2]

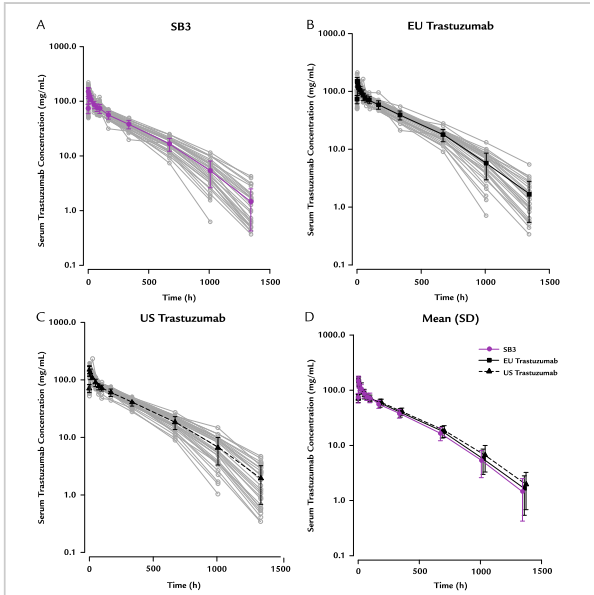


Table II. Summary statistics of pharmacokinetic parameters after a single dose of 6 mg/kg in healthy male subjects.*

Statistic	SB3 (n = 36)	EU Trastuzumab (n = 36)	US Trastuzumab (n = 36)
$AUC_{0-\infty}$, µg · h/mL	34,783 (5614)	35,890 (5761)	37,370 (5620)
AUC_{0-last}, µg · h/mL	34,321 (5349)	35,368 (5524)	36,690 (5342)
C_{max}, µg/mL	154 (28)	153 (25)	156 (26)
T_{max}, median (range), h	1.58 (1.52–95.95)	1.61 (1.53–48.07)	1.57 (1.53–24.03)
$t_{1/2}$, h	196 (45)	198 (42)	215 (53)
CL, mL/h	13.83 (2.10)	13.52 (2.43)	12.82 (2.24)
C_{day21}, µg/mL†	23.4 (4.6)	25.0 (5.7)	25.0 (6.4)

Yin D, et al. Br J Clin Pharmacol 2014;78:1281–9;
Pivot X, et al. Clin Ther 2016;38:1665–1673.e3

Challenges in the implementation of trastuzumab biosimilars: an expert panel's recommendations

1. Choosing a valid clinical endpoint is critical and challenging for the assessment of trastuzumab biosimilars
2. What should the comparison criterion be between trastuzumab biosimilars and their reference medicinal products?
3. Are safety events of particular importance during follow-up of trastuzumab biosimilars?

Pivot, X. Aulagner, G. Blay, J. Y. Fumoleau, P. Kaliski, A. Sarkozy, F. Limat, S.. Anticancer Drugs 2015;26:1009–1016

1. Choosing a valid clinical endpoint is critical and challenging for the assessment of trastuzumab biosimilars

Patient criteria[1,2]

- Overall survival (OS)

Disease criteria[1–3]

- Objective response rate (ORR)
- Disease-free survival (DFS)
- Disease-free progression (PFS)
- Pathological complete response (pCR)

Sensitive endpoints are recommended for biosimilar clinical trials[4–6]

– Clinically relevant, objective measure, able to detect differences

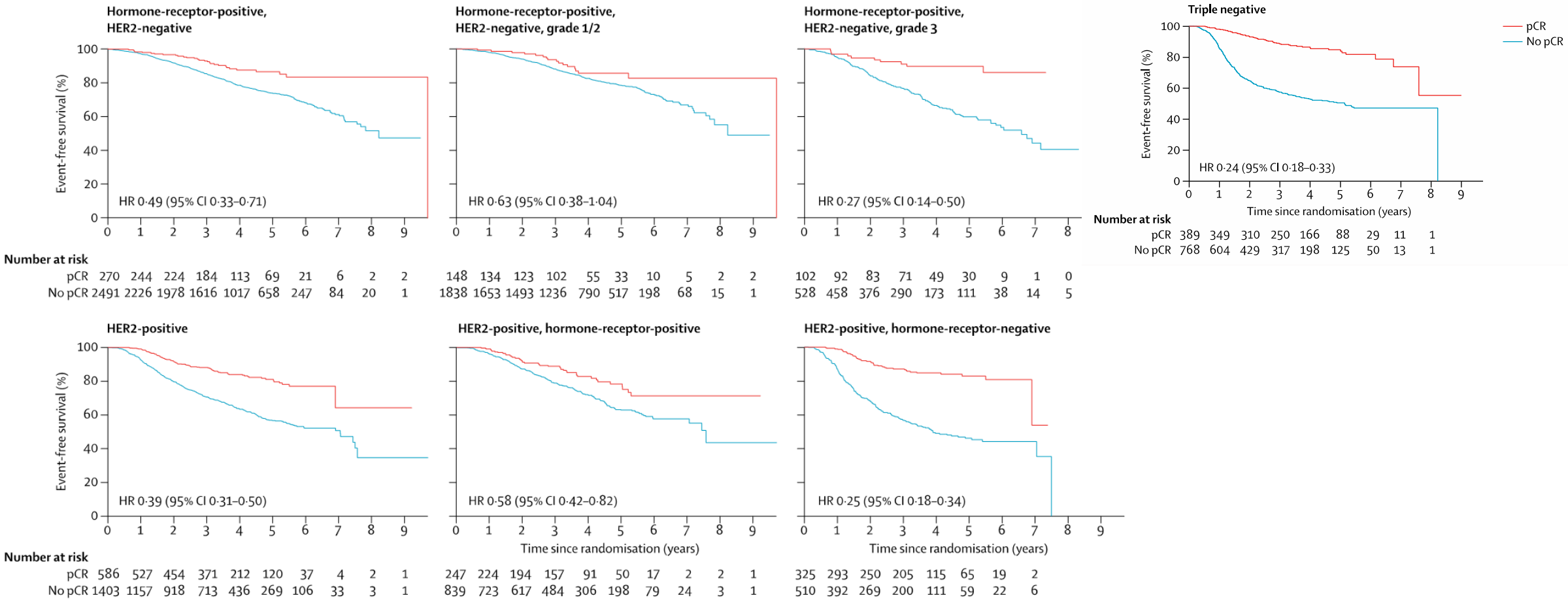
– Continuous endpoints may be preferred over binary endpoints

– Length of study should be sufficient to allow for adequate safety and immunogenicity assessment

1. Gourgou-Bourgade S, et al. Ann Oncol 2015;26:873–879; 2. Fiteni F, et al. J Visc Surg 2014;151:17–22; 3. Pivot X, et al. Cancer J 2009;15:361–365; 4. WHO. Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs), 2016; 5. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, 2014; 6. He K, et al. Clin Cancer Res 2016;22:5167–5170

pCR and long-term survival in clinical trials of neoadjuvant treatment of early breast cancer

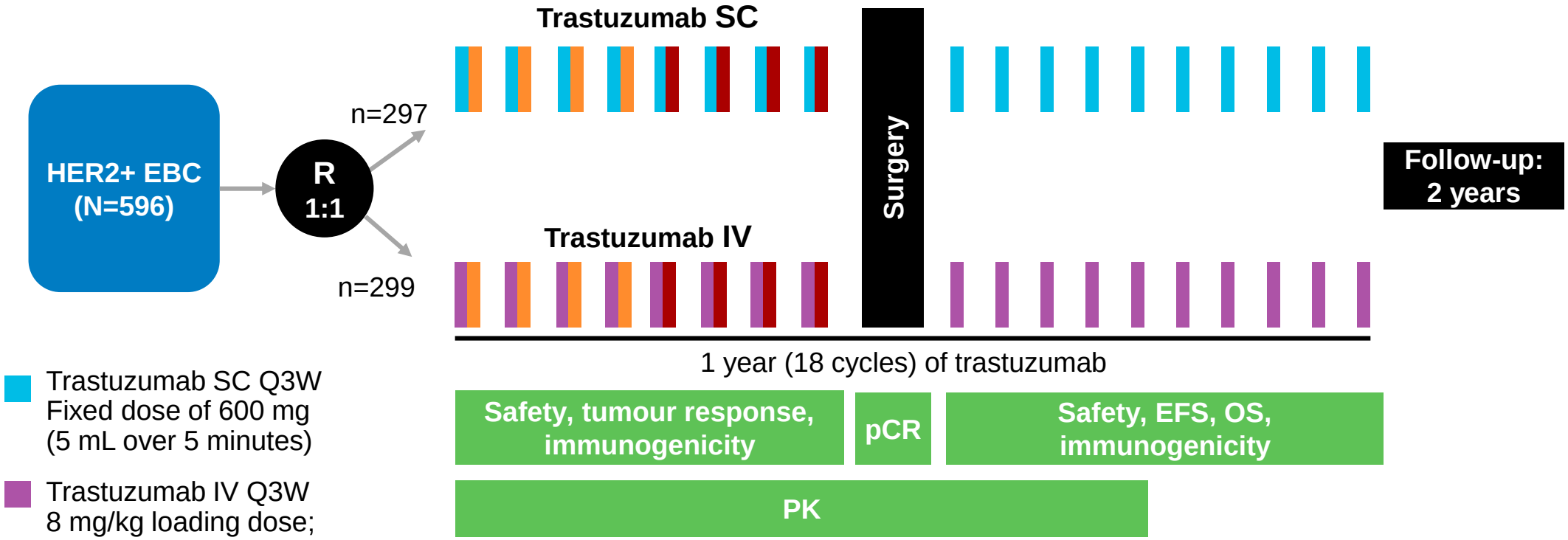
Relationship between pCR and EFS by breast cancer subtype
CTNeoBC pooled analysis



Cortazar P, et al. Lancet 2014;384:164–172

EFS, event-free survival; pCR, pathological complete response

HannaH: Phase 3 trial to demonstrate non-inferiority of trastuzumab SC vs IV in terms of PK and efficacy



Primary endpoints

- Non-inferiority of trastuzumab SC vs IV based on co-primary endpoints:
  - PK: observed trastuzumab C_{trough} pre-dose at Cycle 8 (presurgery)
  - Efficacy: pCR (breast only)

Ismael G, et al. Lancet Oncol 2012;13:869–878

FEC, fluorouracil, epirubicin and cyclophosphamide; IV, intravenous; Q3W, once every 3 weeks; R, randomisation; SC, subcutaneous

European Journal of Cancer 62 (2016) 62–75

Available online at www.sciencedirect.com

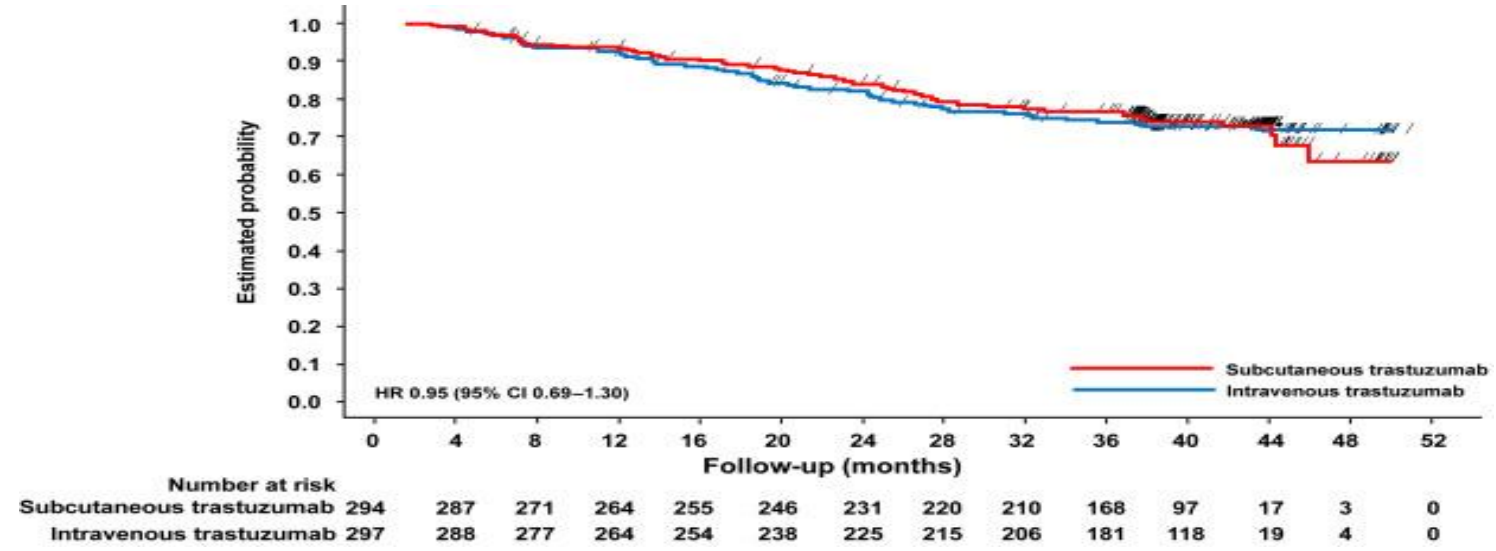
ScienceDirect

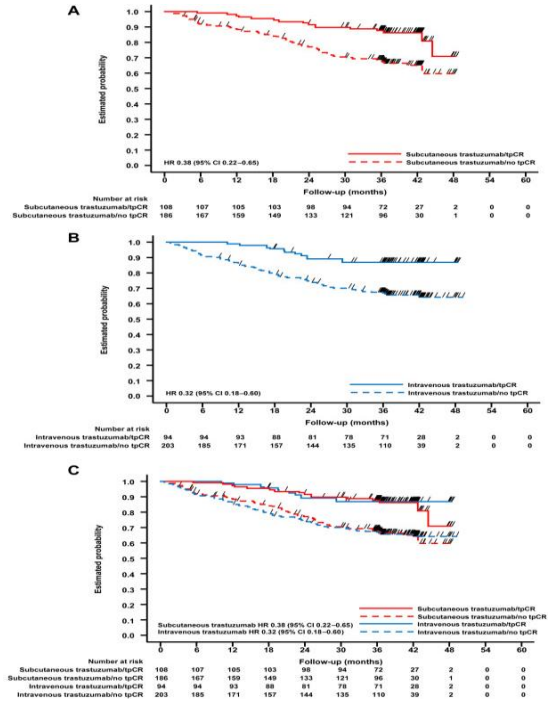
journal homepage: www.ejcancer.com

Clinical Trial

HannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant–adjuvant trastuzumab after 2 years of treatment-free follow-up

Christian Jackisch [a,*], Roberto Hegg [b], Daniil Stroyakovskiy [c], Jin-Seok Ahn [d], Bohuslav Melichar [e], Shin-Cheh Chen [f], Sung-Bae Kim [g], Mikhail Lichinitser [h], Elżbieta Starosławska [i], Georg Kunz [j], Silvia Falcon [k], Shou-Tung Chen [l], Aulde Crepelle-Fléchais [m], Dominik Heinzmann [m], Mona Shing [n], Xavier Pivot [o]





Neo-adjuvant setting has become the first choice for the assessment of new strategies

“It allows for evaluation of innovative therapies an evaluation in a homogeneous population with rare confounding factors, and the relationship between pathological complete response (pCR) and survival outcomes is an early indicator of efficacy.”

X. Pivot, DG Cox. A new era for early development in HER2-positive breast cancer *Lancet Oncology* 2018

2. Equivalence margins: how similar is similar enough?

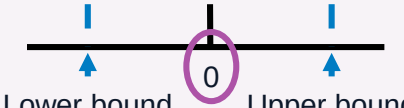
- ‘Minimally Clinically Important Difference’ (MCID)

Risk difference (RD)

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

% biosimilar – % reference product

- If drugs have same efficacy, risk difference = 0



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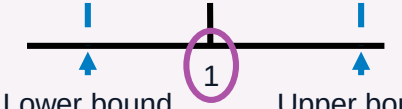
Risk ratio (RR)

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

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

- If drugs have same efficacy, risk ratio = 1



FDA

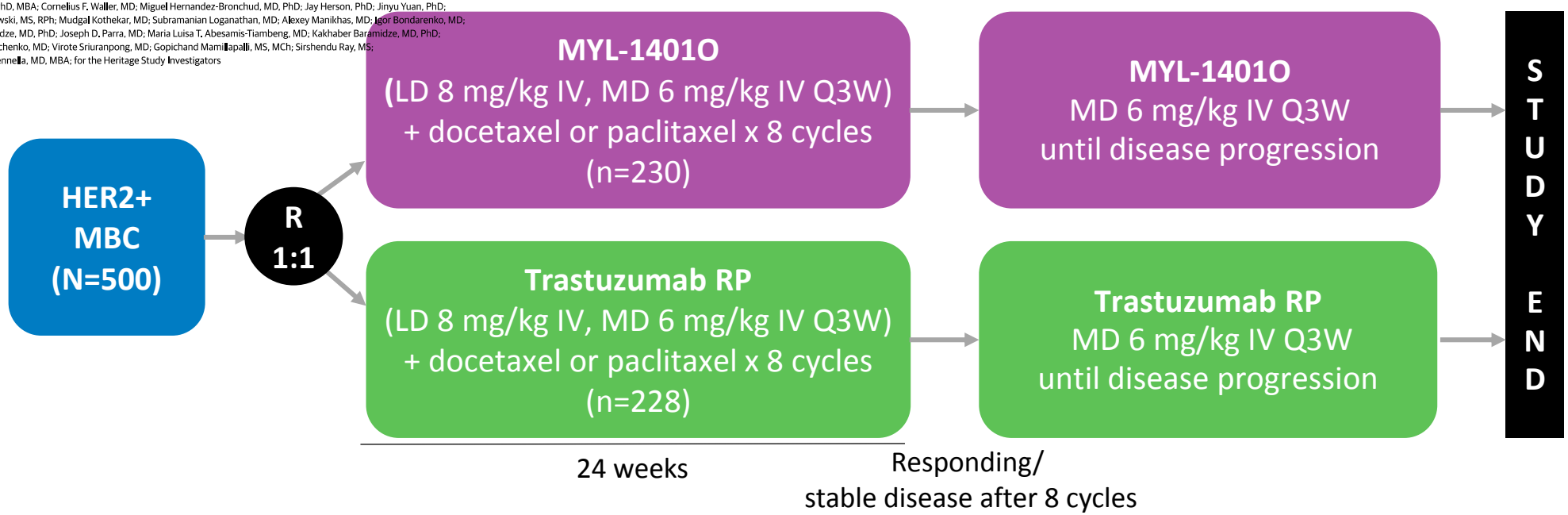
EMA. ICH Topic E 9 statistical principles for clinical trials, 1998. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf;
FDA. Guidance for industry statistical approaches to establishing bioequivalence, 2001. Available at: http://www.fda.gov/downloads/Drugs/Guidances/ucm070244.pdf.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

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



Primary endpoints

- ORR (CR or PR) at Week 24; ITT population
- Pre-defined equivalence margins: 90% CI for RR 0.81–1.24; 95% CI for RD +/-15%*

Secondary endpoints

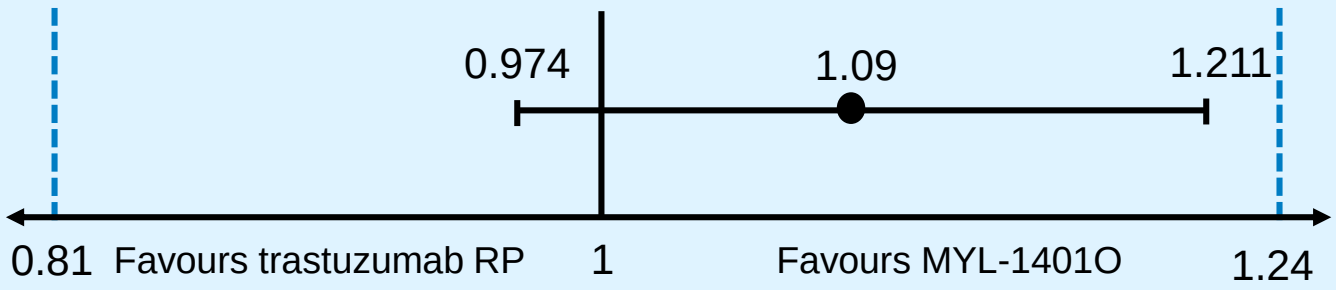
- TTP, PFS, OS at Week 48
- AEs, LVEF, and immunogenicity at Week 48; PK

ed by the EMA. AE, adverse event; CR, complete response; ITT, intention-to-treat; LD, loading dose; LVEF, left ventricular ejection fraction; MD, maintenance dose; ORR, overall response rate; PR, partial response; TTP, time to progression

Mylan/Biocon (MYL-1401O) vs trastuzumab RP in HER2+ MBC: primary efficacy results

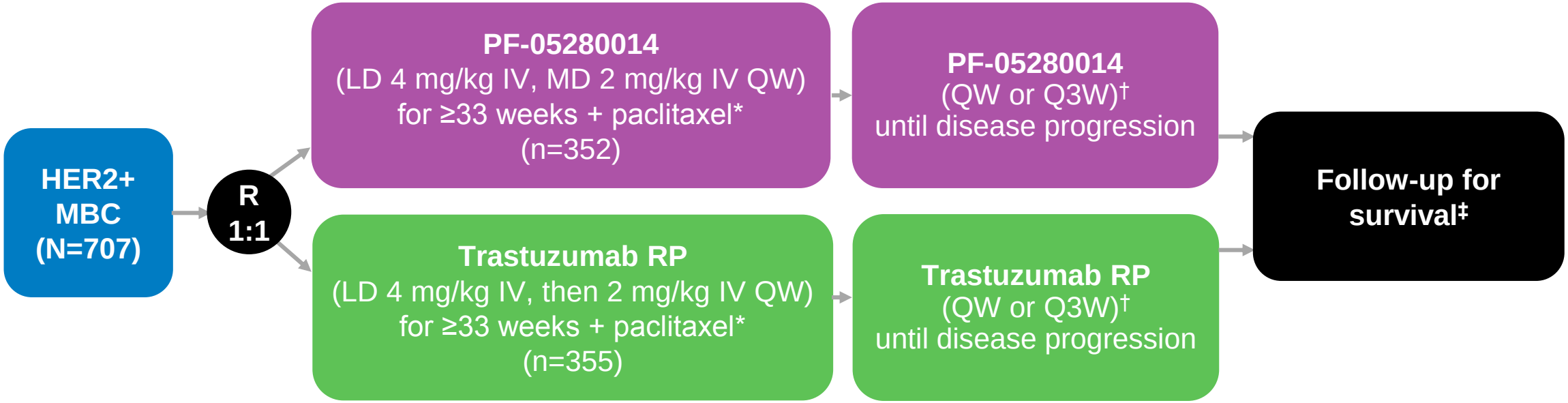
Efficacy at Week 24 (ITT population)	MYL-1401O + taxane (n=230)	Trastuzumab RP + taxane (n=228)
ORR, % (95% CI)	69.6 (63.62, 75.51)	64.0 (57.81, 70.26)
Risk ratio (90% CI)	1.09 (0.974, 1.211)	
Risk difference (95% CI)	5.53 (-3.08, 14.04)	

Primary analysis: RR (90% CI) for ORR



Rugo HS, et al. JAMA 2017;317:37–47

Pfizer (PF-05280014) vs trastuzumab RP in HER2+ MBC: Phase 3 equivalence study



Primary endpoint

- ORR (CR or PR by Week 25, confirmed at Week 33); ITT population
- Pre-defined equivalence margins: 95% CI for RR 0.8–1.25

Secondary endpoints

- DOR, PFS and OS rates at 1 year; PK; safety; immunogenicity

*80 mg/m^2 (with provision for dose reduction) D1, 8, 15 x ≥6 4-week cycles or until maximal benefit of response

†Following completion of the paclitaxel administration period and beginning no earlier than Week 33 of the study, the PF-05280014 or trastuzumab RP regimen may be changed at the discretion of the investigator to 6 mg/kg Q3W

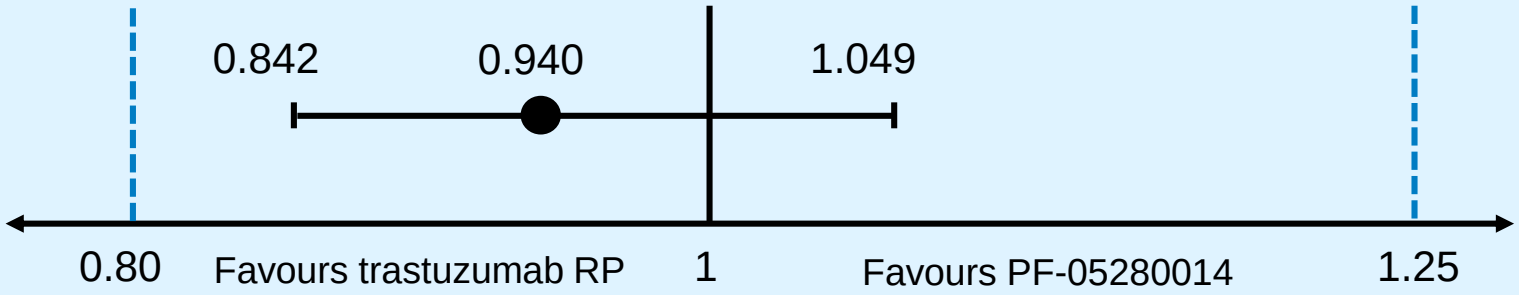
‡Until death or 1 year from randomisation ≥6 months following last dose of study drug, whichever was longer. QW, once every week

Pegram M, et al. ESMO 2017; Poster 238PD

Pfizer (PF-05280014) vs trastuzumab RP in HER2+ MBC: primary efficacy results

Efficacy by Week 25 (confirmed at Week 33) (ITT population)	PF-05280014 (n=352)	Trastuzumab RP (n=355)
ORR (ITT), % patients (95% CI)	62.5 (57.2, 67.6)	66.5 (61.3, 71.4)
Risk ratio* (95% CI)	0.940 (0.842, 1.049)	
CR, %	2.8	3.7
PR, %	59.7	62.8

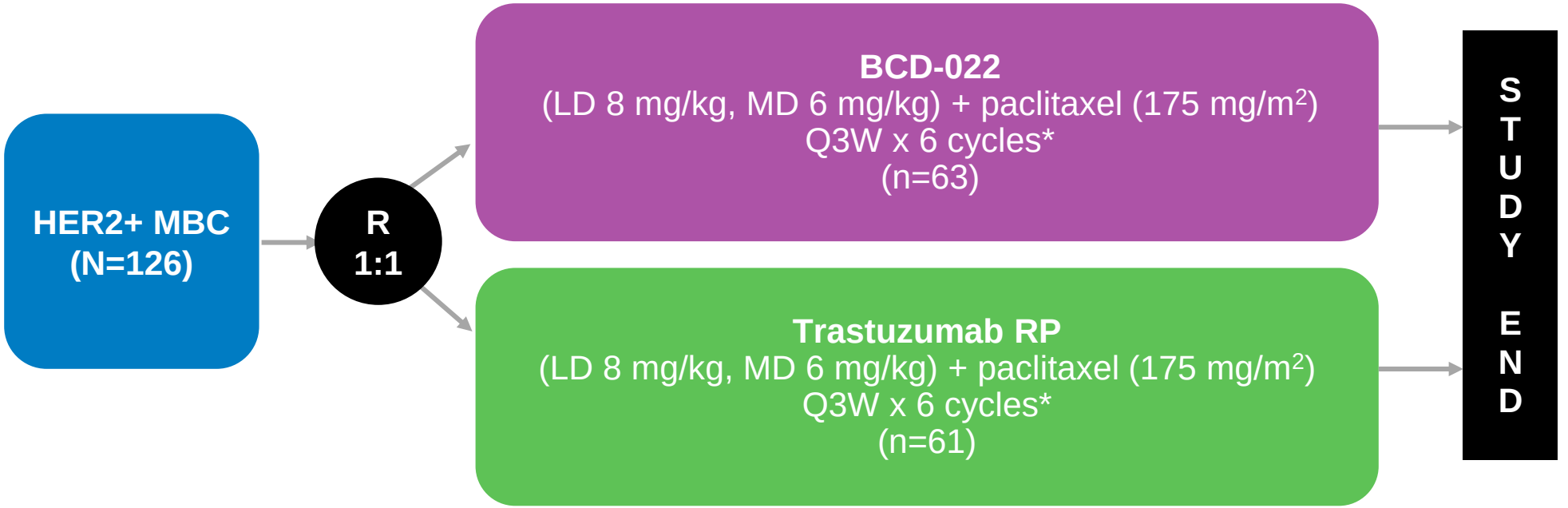
Primary analysis: RR (95% CI) for ORR



Pegram M, et al. ESMO 2017; Poster 238PD

*RR and associated 95% CI based on the Miettinen and Nurminen method

Biocad (BCD-022) vs trastuzumab RP in HER2+ MBC: Phase 3 non-inferiority study



Primary endpoints

- ORR at Day 127; pre-defined non-inferiority margin for RD of -20% (lower 95% CI)
- AUC after the first test drug administration (PK substudy)

Secondary endpoint

- Rates of CR, PR, SD and PD

Shustova M, et al. ESMO 2016; 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.
PD, progressive disease; SD, stable disease

Biocad (BCD-022) vs trastuzumab RP in HER2+ MBC: primary efficacy results

Efficacy (Day 127)	BCD-022 + paclitaxel (n=54)	Trastuzumab RP + paclitaxel (n=56)	P*
ORR, % 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)		

Primary analysis: RD (lower 95% CI) for ORR

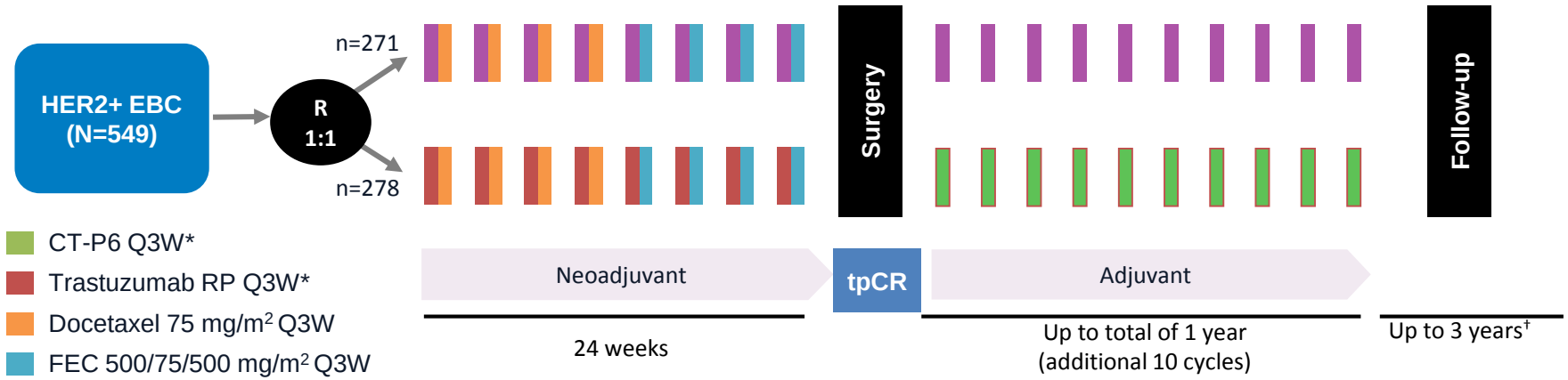
Shustova M, et al. ESMO 2016; Abstract 224 (and corresponding poster presented by Burdaeva et al.);
NCT01764022. Available at: https://clinicaltrials.gov/ct2/show/NCT01764022?term=BCD-022&rank=1. Accessed August 2017

*Yates-corrected Pearson's test

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

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

Lancet Oncol 2017; 18: 917–28



Primary endpoint

- tpCR** after neoadjuvant therapy and surgery (up to 30 weeks); per-protocol population
- Pre-defined equivalence margins: 95% CI for RR 0.74–1.35; 95% CI for RD +/-15%

Secondary endpoints

- Efficacy: pCR (breast only), tpCR (without DCIS), ORR, breast conservation rate, DFS, PFS, OS
- Other: PK, PD, biomarkers and safety

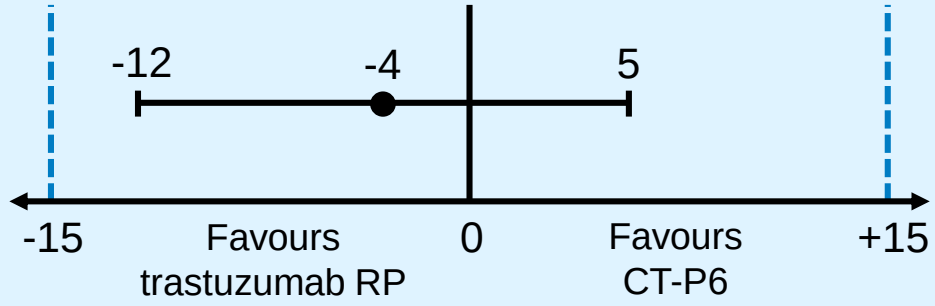
*Initial dose of 8 mg/kg IV, then 6 mg/kg for remaining cycles. **pCR in breast and axillary lymph nodes. †From the date of last patient enrolment. DCIS, ductal carcinoma in situ

Stebbing J, et al. Lancet Oncol 2017;18:917–928; Esteva FJ, et al. ESMO 2017; Poster 152PD

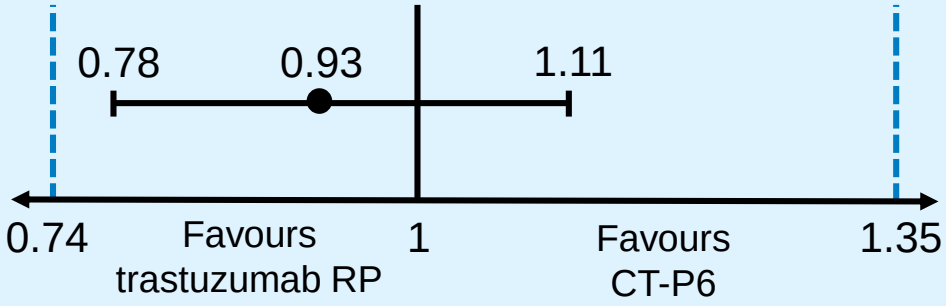
Celltrion (CT-P6) vs trastuzumab RP in HER2+ EBC: primary efficacy results

Efficacy up to 30 weeks (Per-protocol population)	CT-P6 (n=248)	Trastuzumab RP (n=256)
tpCR rate,* % (95% CI)	46.8 (40.4, 53.2)	50.4 (44.1, 56.7)
Risk difference (95% CI)	-4 (-12, 5)	
Risk ratio (95% CI)	0.93 (0.78, 1.11)	

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



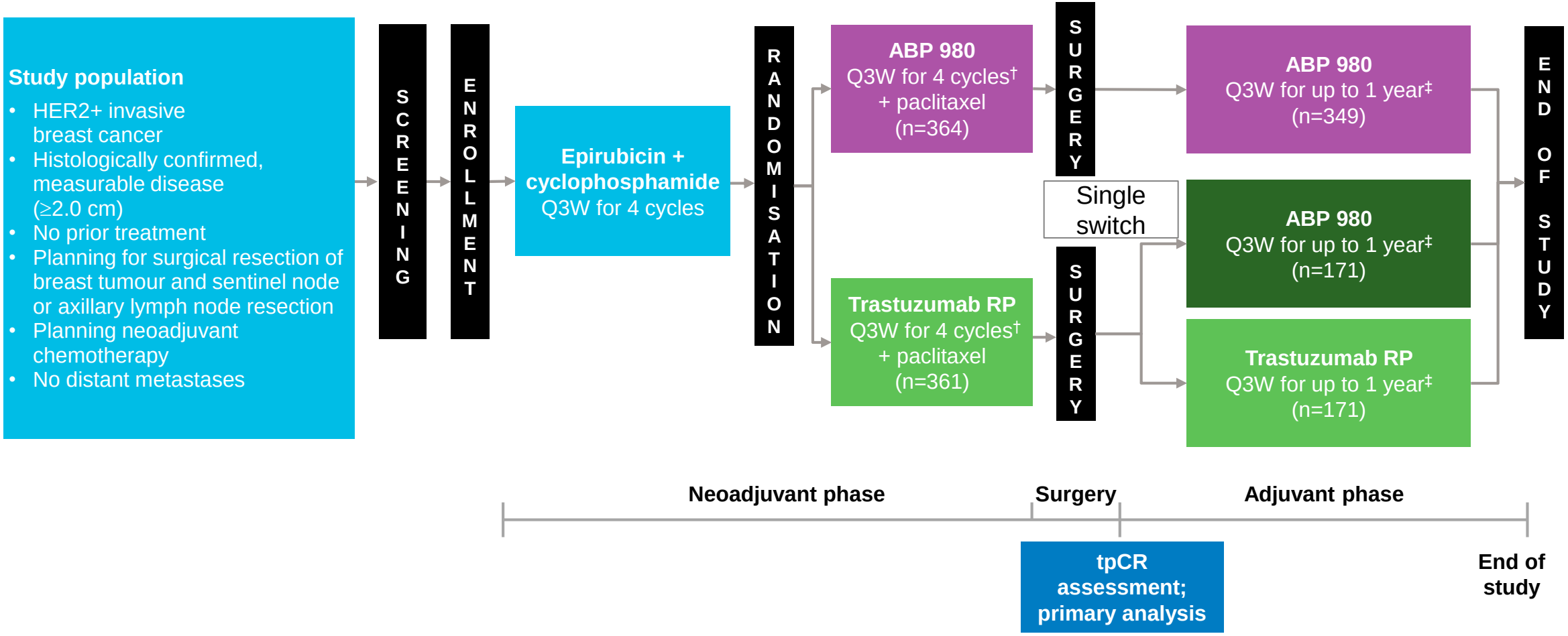
Co-primary analysis: RR (95% CI) for tpCR



Stebbing J, et al. Lancet Oncol 2017;18:917–928

*After neoadjuvant therapy and surgery (up to 30 weeks)

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



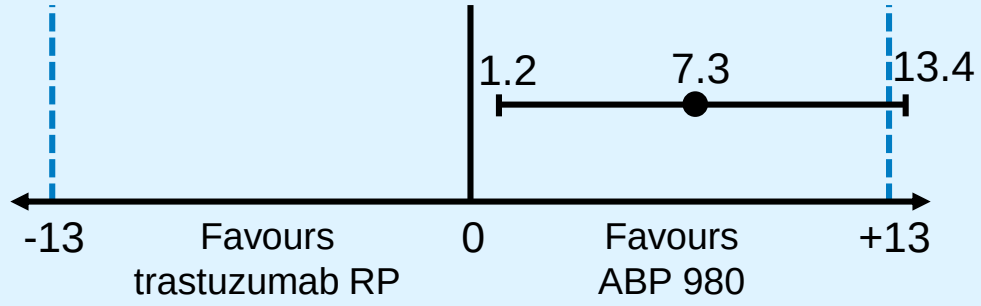
†Initial dose of 8 mg/kg IV then 6 mg/kg for remaining cycles;
‡Total of up to 1 year from the first day of ABP 980/trastuzumab RP administered in the neoadjuvant phase
tpCR, total pathological complete response absence of invasive tumour cells in the breast tissue and axillary lymph node[s] regardless of residual ductal carcinoma in situ).
ABP 980 is an investigational product

von Minckwitz G, et al. ESMO 2017; Poster 151PD; Kolberg H-C, et al. SABCS 2017; Poster PD3-10; von Minckwitz, G et al. SABCS 2017; Poster P5-20-13

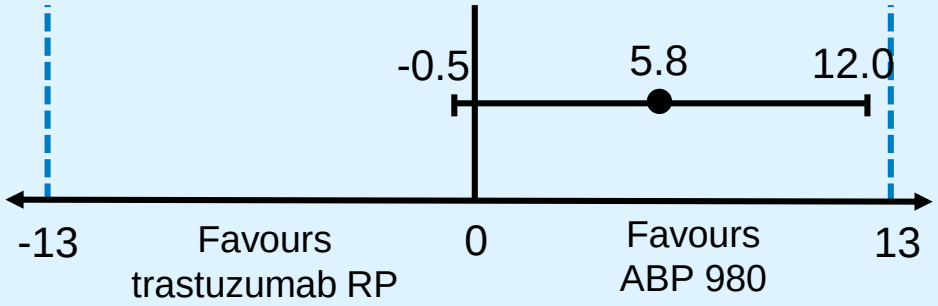
Amgen (ABP 980) vs trastuzumab RP in HER2+ EBC: primary efficacy results

Efficacy	Co-primary analysis (local pathology assessment)		Sensitivity analysis (central pathology assessment)	
tpCR* evaluable population	ABP 980 (n=358)	Trastuzumab RP (n=338)	ABP 980 (n=339)	Trastuzumab RP (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)	

Co-primary analysis: RD (90% CI) for tpCR



Sensitivity analysis: RD (90% CI) for tpCR



von Minckwitz G, et al. ESMO 2017; Poster 151PD

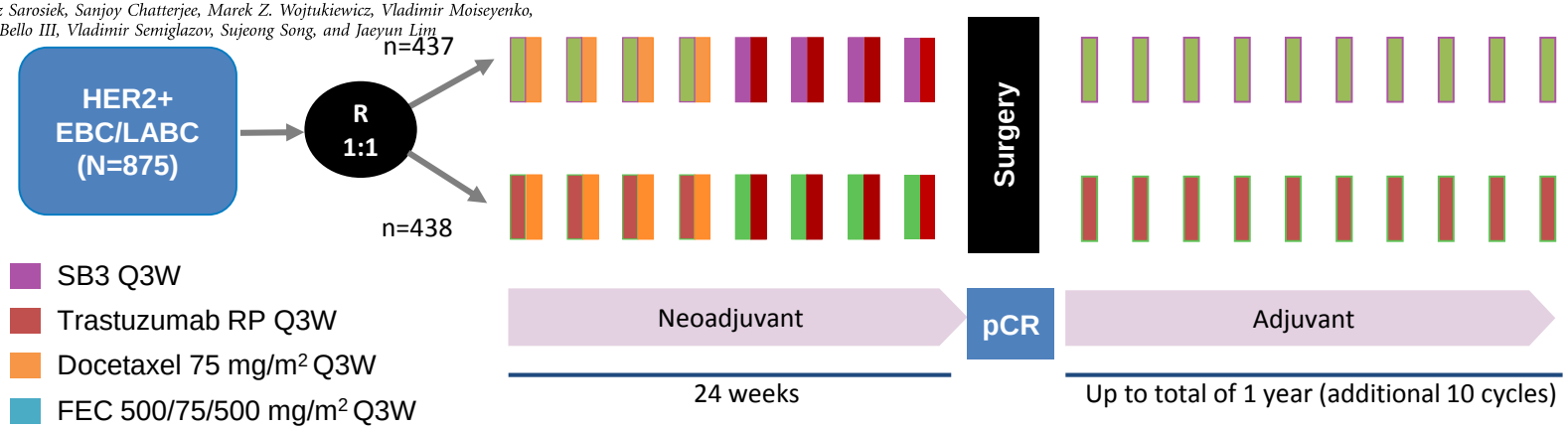
*pCR in breast and axillary lymph nodes.
ABP 980 is an investigational product

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

DOI: 10.1200/JCO.2017.74.0126



Primary endpoint

- pCR (breast only) after neoadjuvant therapy and surgery; per-protocol population
- 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

Pivot X, et al. JCO 2018

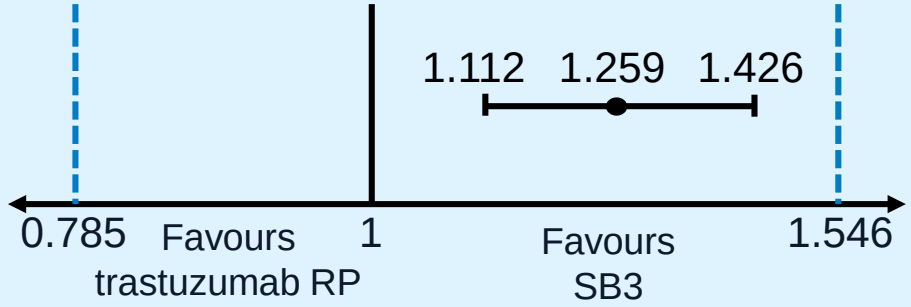
LABC, locally-advanced breast cancer

Samsung Bioepis (SB3) vs trastuzumab RP in HER2+ EBC: primary efficacy analysis

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

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 X, et al. JCO 2018

European Journal of Cancer 93 (2018) 19–27

Available online at www.sciencedirect.com

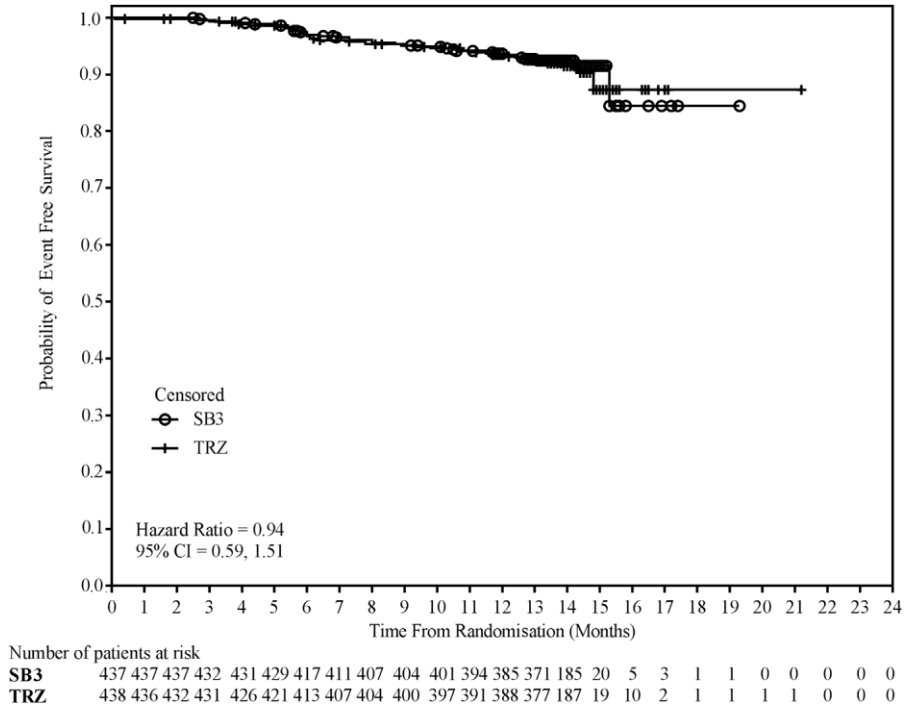
ScienceDirect

journal homepage: www.ejcancer.com

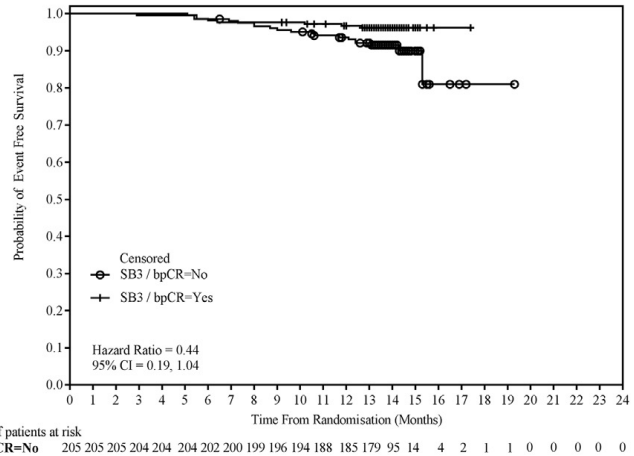
Original Research

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

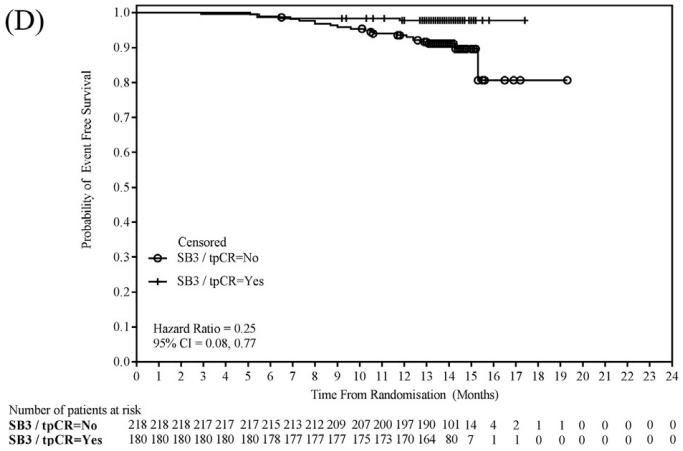
X. Pivot [a,*,1], I. Bondarenko [b], Z. Nowecki [c], M. Dvorkin [d], E. Trishkina [e], J.-H. Ahn [f], S.-A. Im [g], T. Sarosiek [h], S. Chatterjee [i], M.Z. Wojtukiewicz [j], Y. Shparyk [k], V. Moiseyenko [l], M. Bello III [m], V. Semiglazov [n], Y. Lee [o], J. Lim [o]



(A)



(D)



MABS
2017, VOL. 9, NO. 4, 704–714
http://dx.doi.org/10.1080/19420862.2017.1305530

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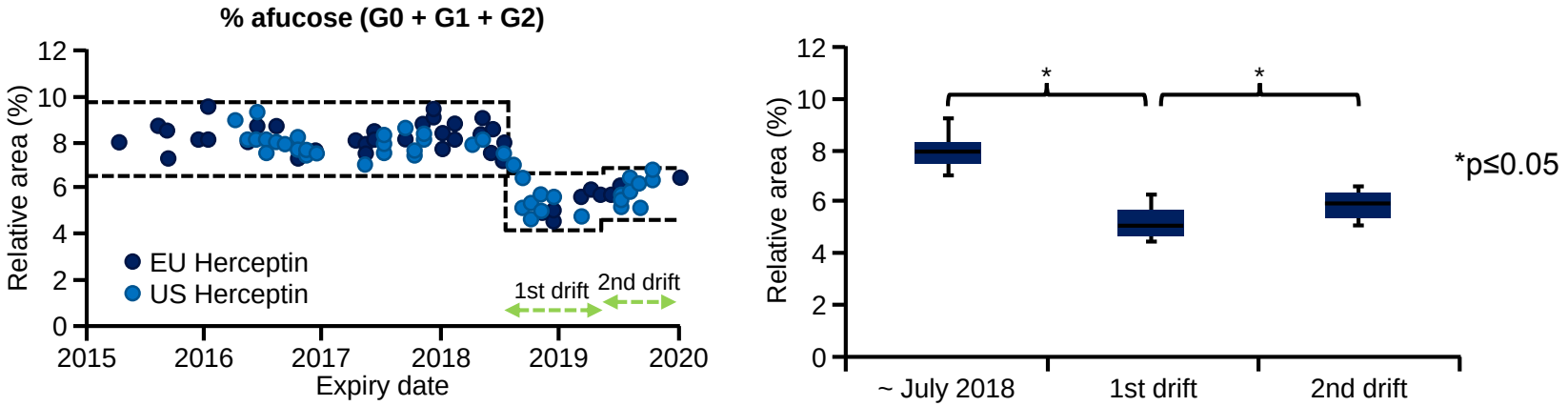
REPORT

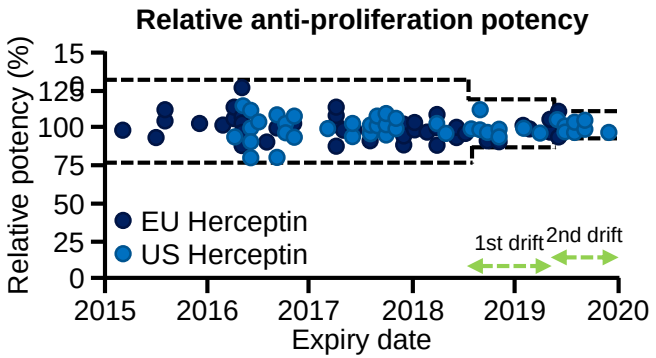
OPEN ACCESS

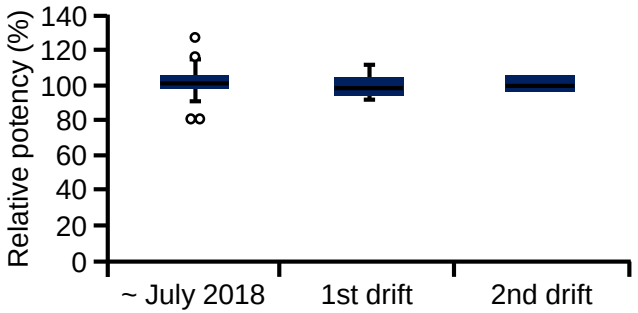
Drifts in ADCC-related quality attributes of Herceptin®: Impact on development of a trastuzumab biosimilar

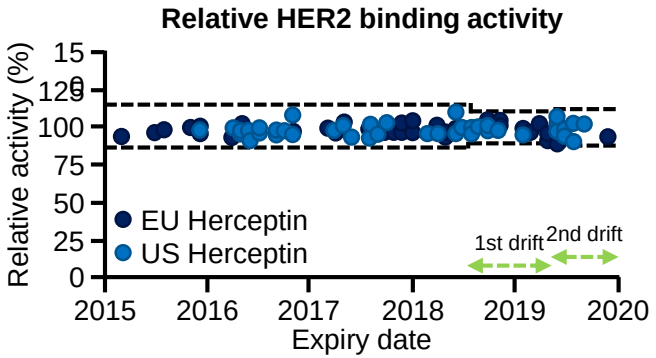
Seokkyun Kim*, Jinsu Song*, Seungkyu Park, Sunyoung Ham, Kyungyeol Paek, Minjung Kang, Yunjung Chae, Heewon Seo, Hyung-Chan Kim, and Michael Flores

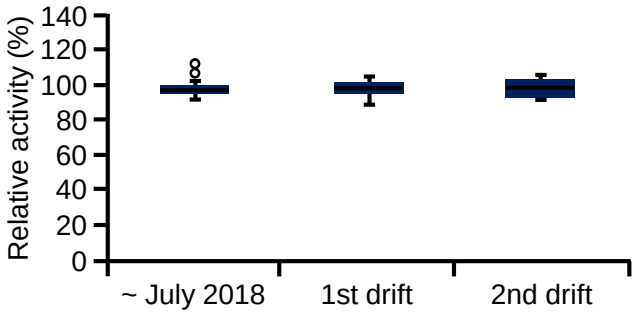


Impact of drifts on anti-proliferative potency and HER2 binding activity



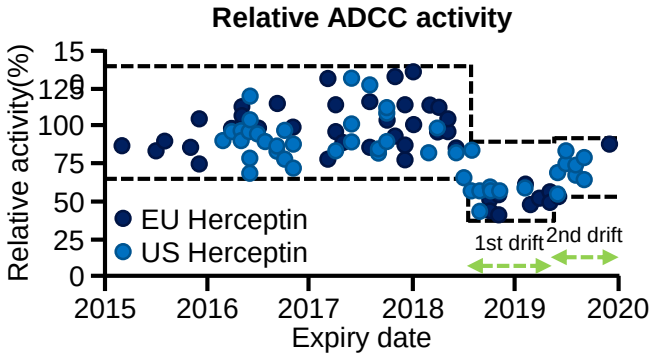


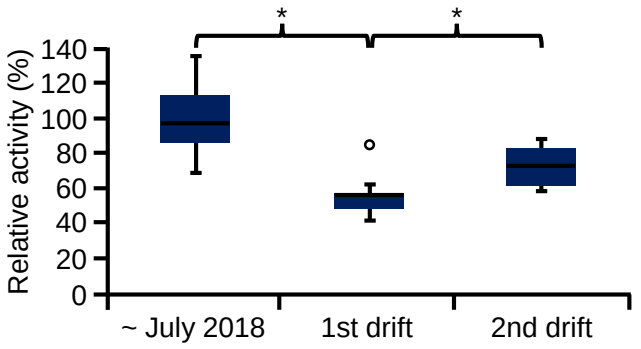




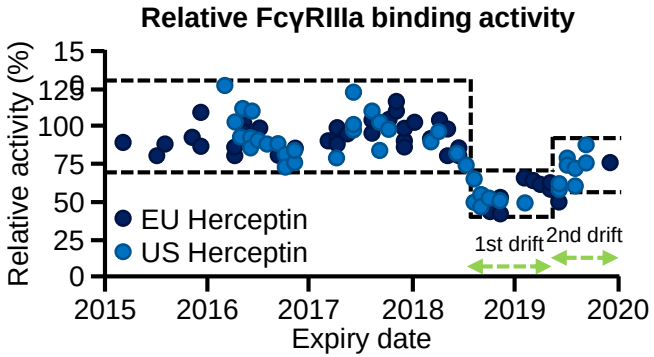
Kim S, et al. mAbs 2017

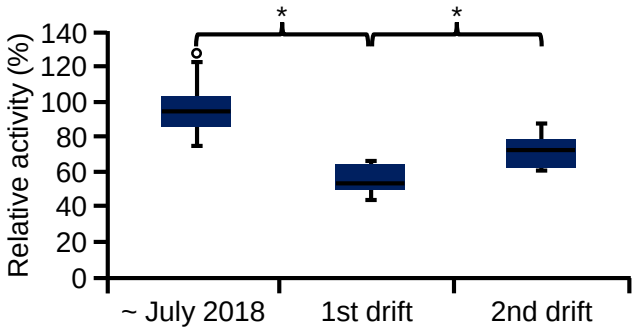
Impact of drifts on ADCC and FcγRIIIa binding





*p≤0.05





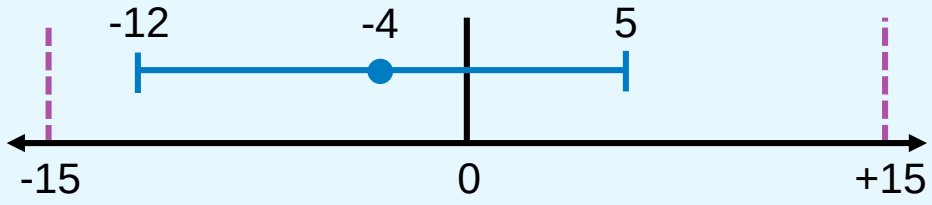
Levels of %afucose and %high mannose should be tightly monitored as critical quality attributes for biosimilar development of trastuzumab

Kim S, et al. mAbs 2017

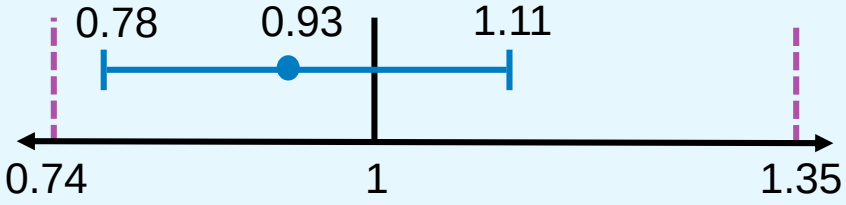
Summary: results of equivalence analyses of biosimilar vs trastuzumab in studies of HER2+ EBC

Celltrion (CT-P6)[1] (N=504)*

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

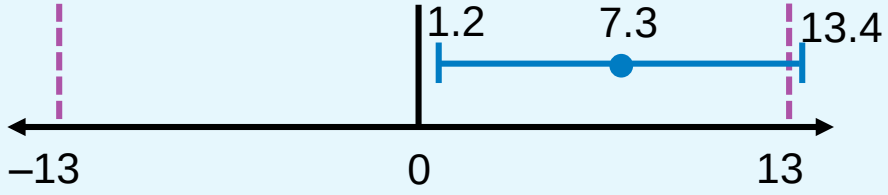


Co-primary analysis: RR (95% CI) for tpCR

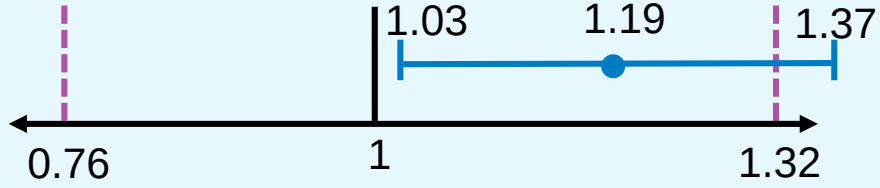


Amgen (ABP 980)[2] (N=696)†

Co-primary analysis: RD (90% CI) for tpCR

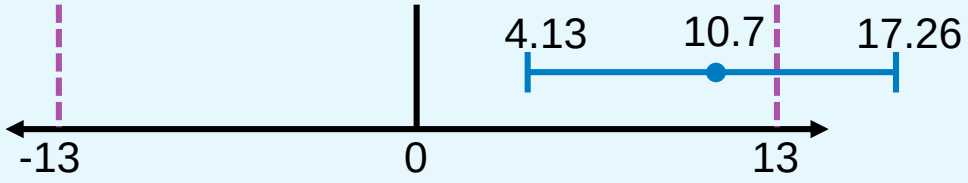


Co-primary analysis: RR (90% CI) for tpCR

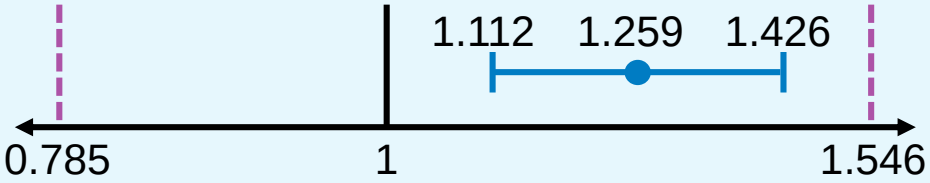


Samsung Bioepis (SB3)[3] (N=800)*

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



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



← Favours trastuzumab RP Favours biosimilar →

← Favours trastuzumab RP Favours biosimilar →

1. Stebbing J, et al. Lancet Oncol 2017;18:917–928; 2. von Mickwitz G, et al. ESMO 2017; Poster 151PD;
3. Pivot X, et al. JCO 2018

NOTE: results cannot be directly compared due to differences in study design.
*In per-protocol population. †In tpCR evaluable population. ABP 980 is an investigational product

3. Are safety events of particular importance during follow-up of trastuzumab biosimilars?

- Adverse events
- Serious adverse events
- Adverse events of special interest
- Anti-drug antibodies
- Safety following a switch from reference product

HERITAGE study: safety

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)

Table 4. Treatment-Emergent Adverse Events and Serious Adverse Events by Week 24 in the Overall Safety Population

	Participants, No. (%)		
Event	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)

Rugo HS, et al. JAMA 2017;317:37–47

Example safety findings: anti-drug antibodies (ADAs)

ABP 980 vs trastuzumab RP: development of anti-drug antibodies – by phase

	Neoadjuvant phase[1] (+ paclitaxel)		Adjuvant phase[2]		
	ABP 980 (N=364) n (%)	Trastuzumab RP (N=361) n (%)	Continued ABP 980 (N=349) n (%)	Continued Trastuzumab RP (N=171) n (%)	Trastuzumab RP/ ABP 980 (N=171) n (%)
Development of binding ADAs during the study,* n (%)	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
Development of neutralizing ADAs, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Patients with a negative or no result at baseline.

1. von Minckwitz G, et al. ESMO 2017; Poster 151 PD; 2. Kolberg H-C, et al. SABCS 2017; Poster PD3-10

ABP 980 is an investigational product

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; ; 2. Pivot X, et al. J Clin Oncol 2018:;
3. Stebbing J, et al. Lancet Oncol 2017; 4. Im YH, et al. ASCO 2013;
5. Lammers PE, et al. ESMO 2017,; 6. Pegram M, et al. ESMO 2017; 7. Rugo HS, et al. JAMA 2017;317:37–47.

Economic Burden for Cancer Drugs Threatens Patient Access

"Treatments for advanced cancer are often unavailable or available only at substantial out of pocket cost in many Eastern European countries compared to those in Western Europe"[a]

Availability and Affordability of Oncology Biologics in 27 Eastern Europe Countries

	Unavailable or Only Available at Full Cost[b,c]
Trastuzumab	**12/27**
Bevacizumab	**17/27**
Cetuximab	**12/27**

a. Cherny N, et al. *Ann of Oncology*. 2016

b. For the following indications: Trastuzumab, breast cancer and gastroesophageal cancer; Bevacizumab, non-small cell lung cancer, colorectal cancer, ovarian, renal cancer; Cetuximab: colorectal cancer

c. 27 Eastern European Countries: Albania, Armenia, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Hungary, Kazakhstan, Republic of Kosovo, Kyrgyzstan, Latvia, Lithuania, Macedonia, Malta, Montenegro, Poland, Romania, Russian Federation, Serbia, Slovenia, Slovakia, Turkmenistan, Ukraine, Uzbekistan