Ospedaletto di Pescantina (VR)

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L’arrivo del trastuzumab biosimilare

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The principle of biosimilarity

To establish that there is **not likely** to be any **clinically significant difference** between the reference product and the test product.

- But the key concept to demonstrate **biosimilarity is not only a therapeutic equivalence trial** (because this would be insensitive to differences) rather, the concept is to perform a **comparability exercise**

- Clinicians and regulators often view this issue differently

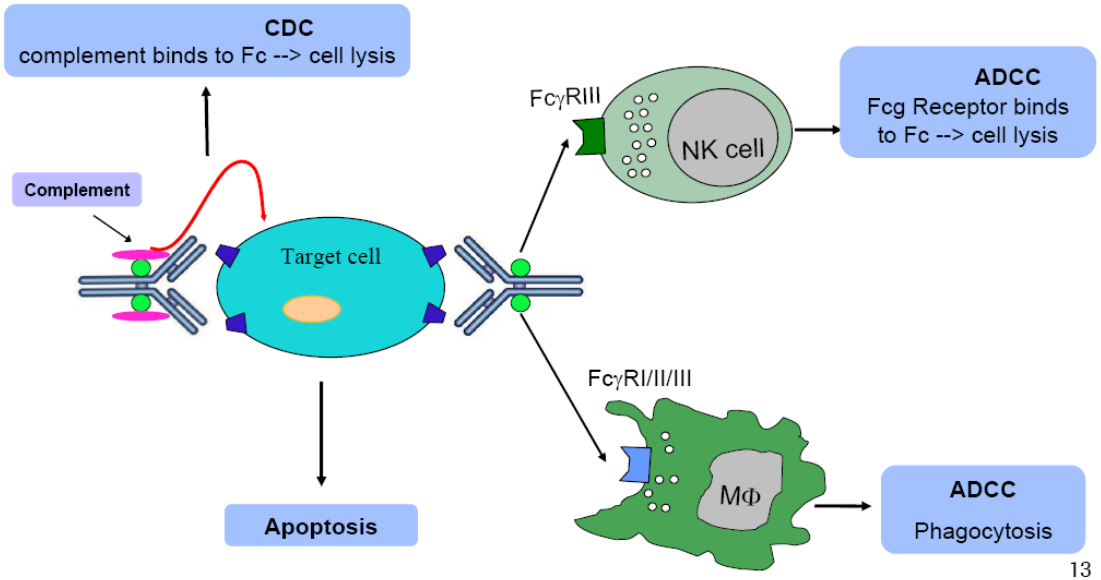
Biosimilar mAbs

Biosimilar monoclonal antibodies: the clinical issues are not different but……

Very complex mechanism of action

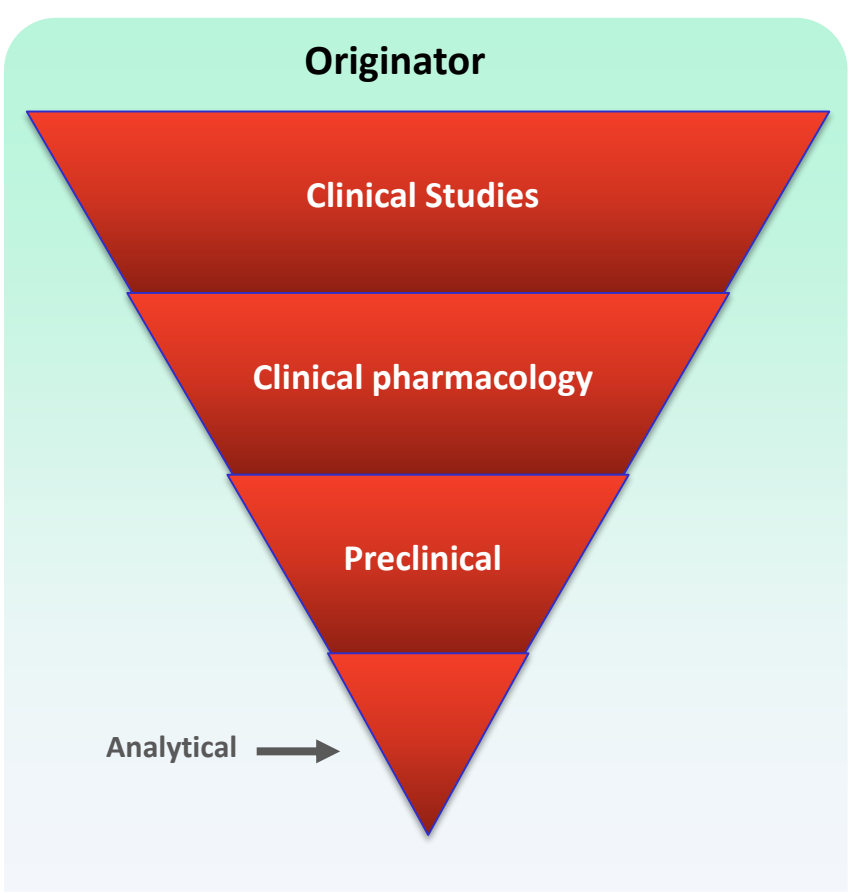
Very complex production

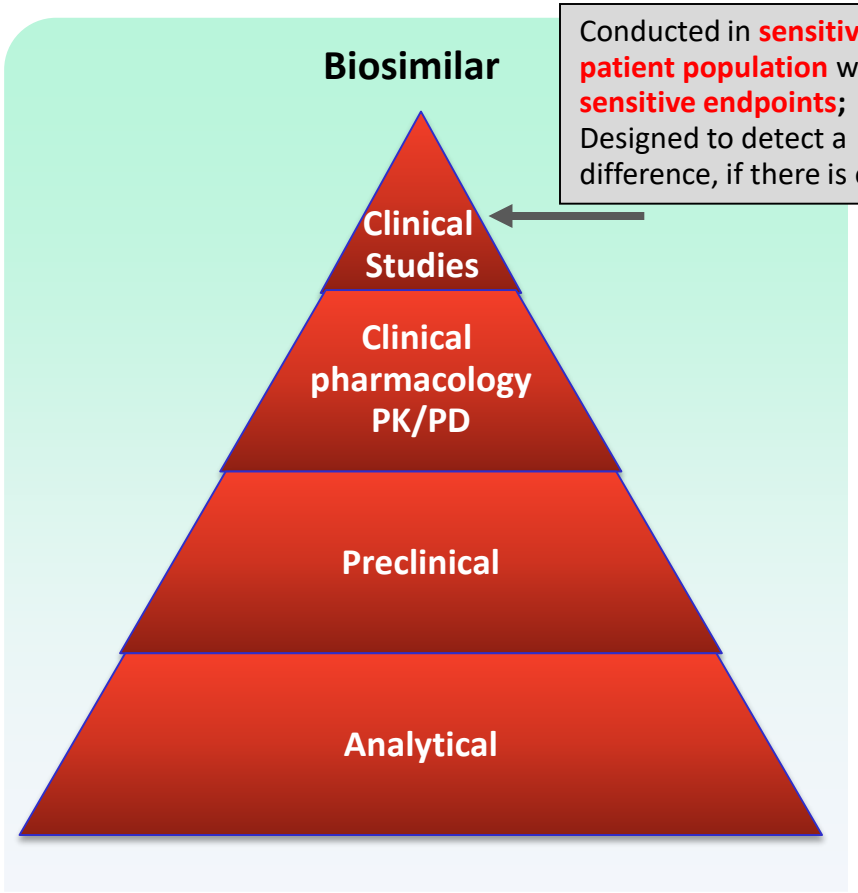
Complex (oncology) indications



Biosimilar Development Program Objective:

establish biosimilarity based upon totality of evidence, *not re-establish benefit*





Key differences in requirement and study design for biosimilar and innovator Clinical Trials

	Biosimilar	Innovator
Patient Population	**Sensitive and homogeneous patient population**	**Any**
Clinical Design	**Comparative vs innovator**	**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**

Clinical efficacy of Biosimilars

For erythropoietic agents or G-CSFs, endpoints are easy to measure

For monoclonal antibodies activity, endpoint is efficacy, which is not reproducible and often difficult to assess

- 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

Why is Neoadjuvant/Adjuvant a Sensitive Population to Study Similarity of Herceptin and Biosimilar Trastuzumab?

	MBC Aim: Palliate	Neoadjuvant/Adjuvant Aim: Cure
PK	Affected by patients' status and tumor burden	Homogeneous population can be selected
PD	Clinically validated PD marker not available	Clinically validated PD marker not available
Clinical Efficacy/Safety	Population with heterogeneous characteristics affecting final clinical outcome. Need to control and stratify for multiple factors (eg, prior use of chemotherapy, performance status). Difficult to select a homogeneous group	Baseline patient characteristics allow selection of homogeneous populations not confounded by external factors Subgroup of patients with higher responses could be identified (ie, hormone receptor negative)
Immunogenicity	Immune system compromised by previous lines of treatment, concomitant medications	Immune system impaired during chemotherapy cycles, but would likely recover to normal status after treatment is completed

EMA Guideline: Extrapolation of Indication

Extrapolation of clinical efficacy and safety data to other indications of the reference mAb not specifically studied during the clinical development of the biosimilar mAb is possible based on the overall evidence of comparability provided with adequate justification

Is extrapolation of indication possible with Biosimilar Trastuzumab?

Early and the metastatic patient populations are different regarding disease burden, CT regimens, concomitant medications, immune response

Extrapolation of immunogenicity/efficacy/safety data obtained in the early breast cancer population to the metastatic population is possible while extrapolation from the metastatic population to the early breast cancer population may represents a risk for the patients

Equivalence margins: how similar is similar enough?

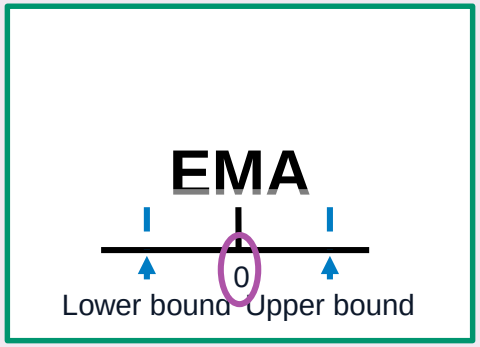
‘Minimally Clinically Important Difference’ (MCID)

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**

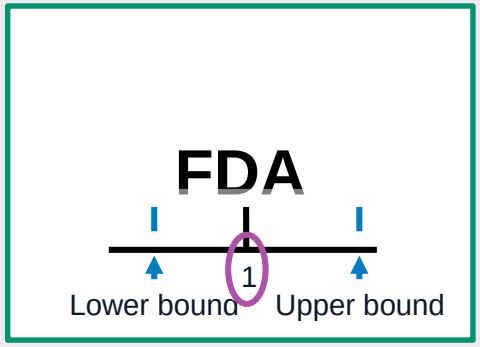


Risk ratio (RR)

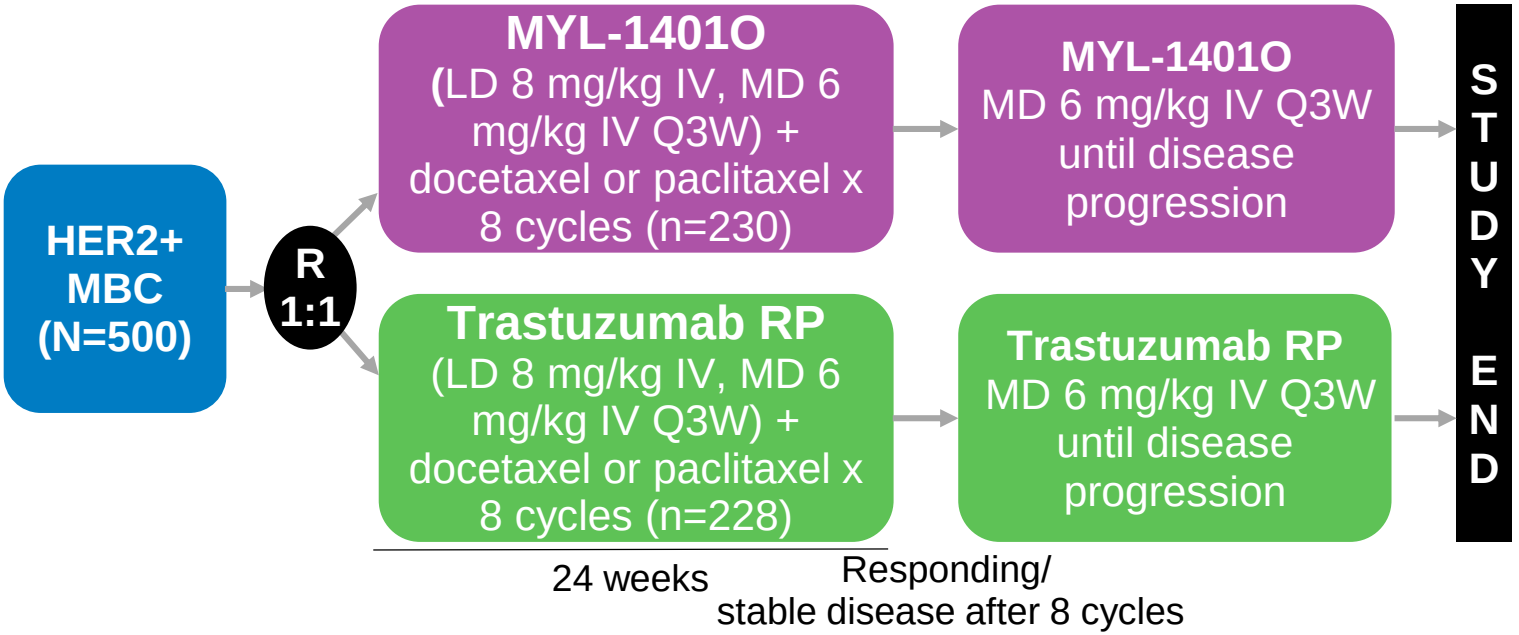
Confidence interval for the **ratio** of primary endpoint for biosimilar versus reference product

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

- **If drugs have same efficacy, risk ratio = 1**



Mylan/Biocon (MYL-1401O) vs Trastuzumab RP in HER2+ MBC: Phase 3 equivalence study (HERITAGE)



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

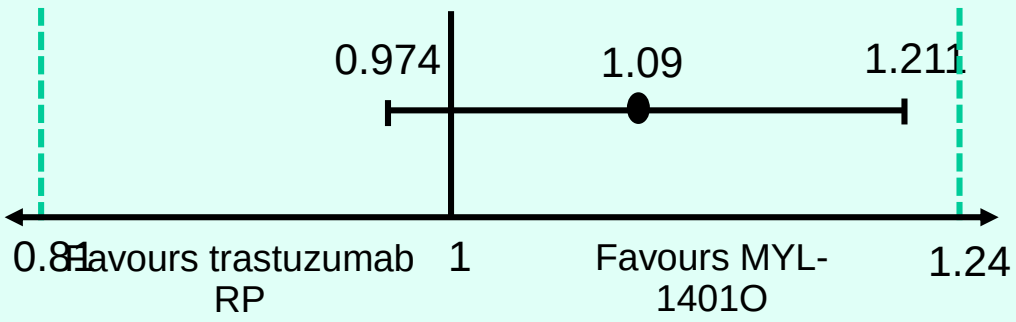
- TTP, PFS, OS at Week 48
- AEs, LVEF, and immunogenicity at Weeks 24 and 48; PK

Rugo HS, et al. JAMA 2017;317:37–47

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

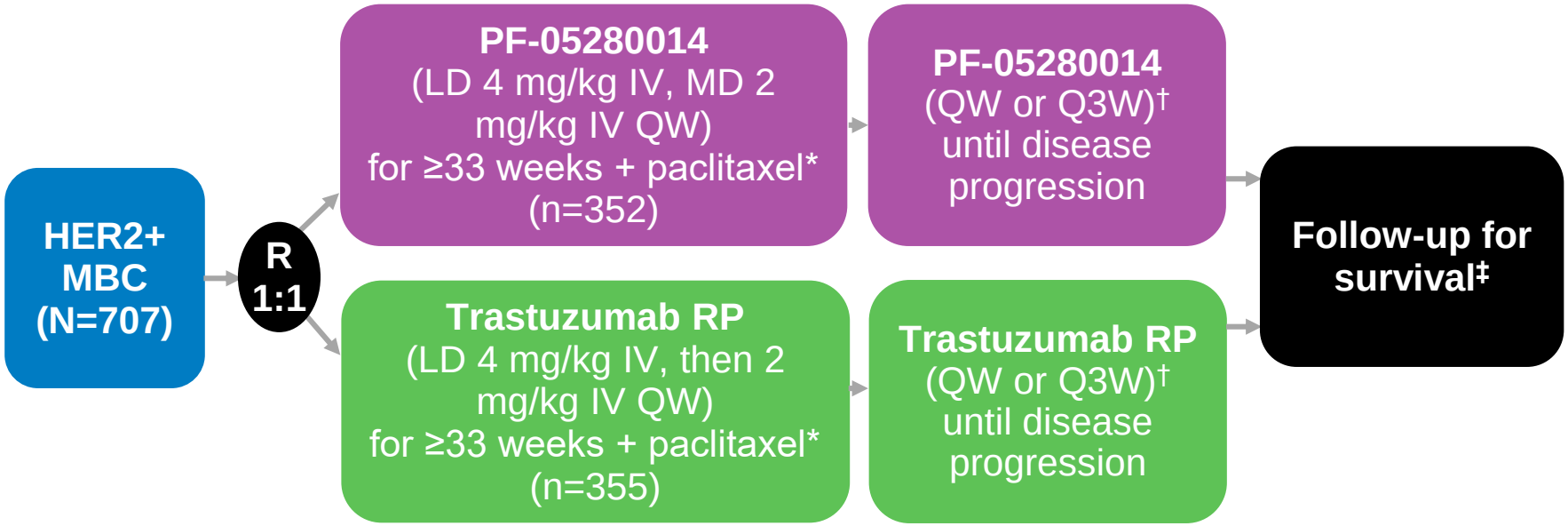
Efficacy at Week 24 (ITT population)	MYL-1401O + taxane (n=230)	Trastuzumab RP + taxane (n=228)
ORR, % (95% CI)	69.6 (63.62, 75.51)	64.0 (57.81, 70.26)
Risk ratio (90% CI)	1.09 (0.974, 1.211)	
Risk difference (95% CI)	5.53 (-3.08, 14.04)	

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

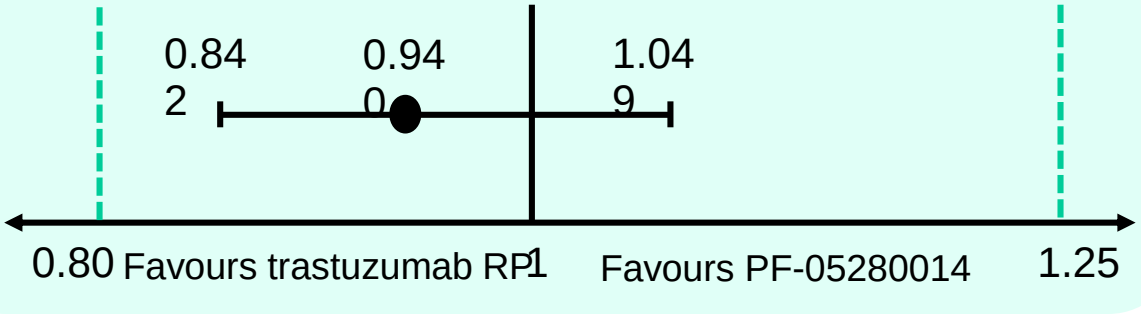
- DOR, PFS and OS rates at 1 year; PK; safety; immunogenicity

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

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

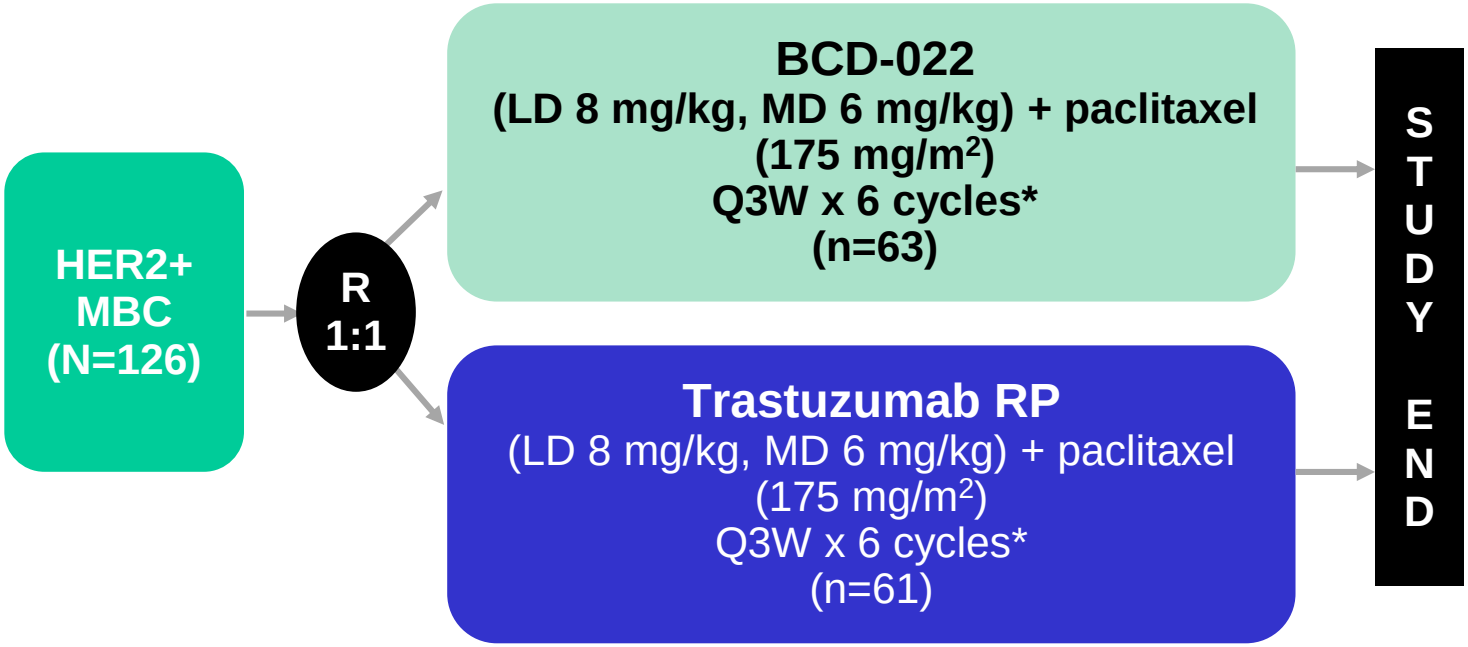
Efficacy by Week 25 (confirmed at Week 33) (ITT population)	PF-05280014 (n=352)	Trastuzumab RP (n=355)
ORR (ITT), % patients (95% CI)	62.5 (57.2, 67.6)	66.5 (61.3, 71.4)
Risk ratio* (95% CI)	0.940 (0.842, 1.049)	
CR, %	2.8	3.7
PR, %	59.7	62.8

Primary analysis: RR (95% CI) for ORR



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

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



Primary endpoints

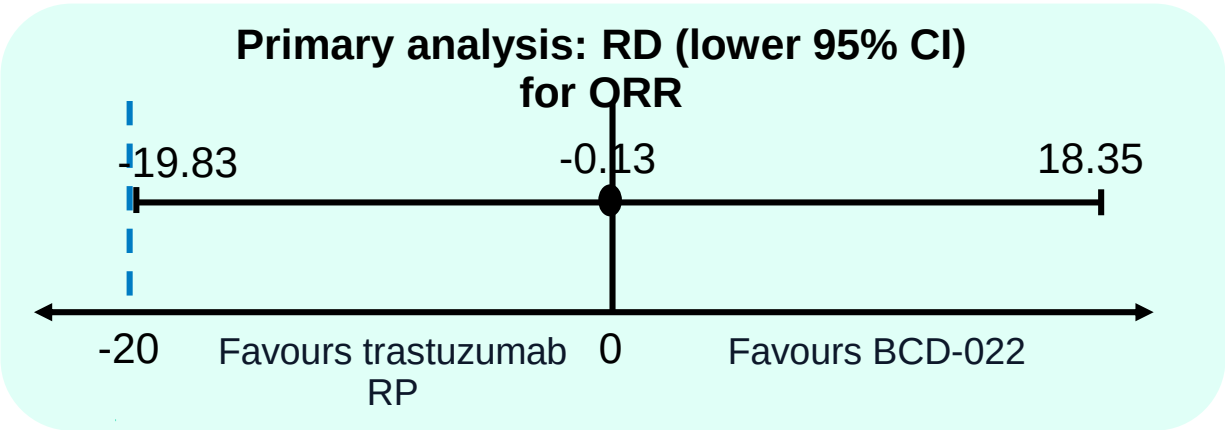
- ORR at Day 127; pre-defined non-inferiority margin for RD of -20% (lower 95% CI)
- AUC after the first test drug administration (PK substudy)

Secondary endpoint

- Rates of CR, PR, SD and PD

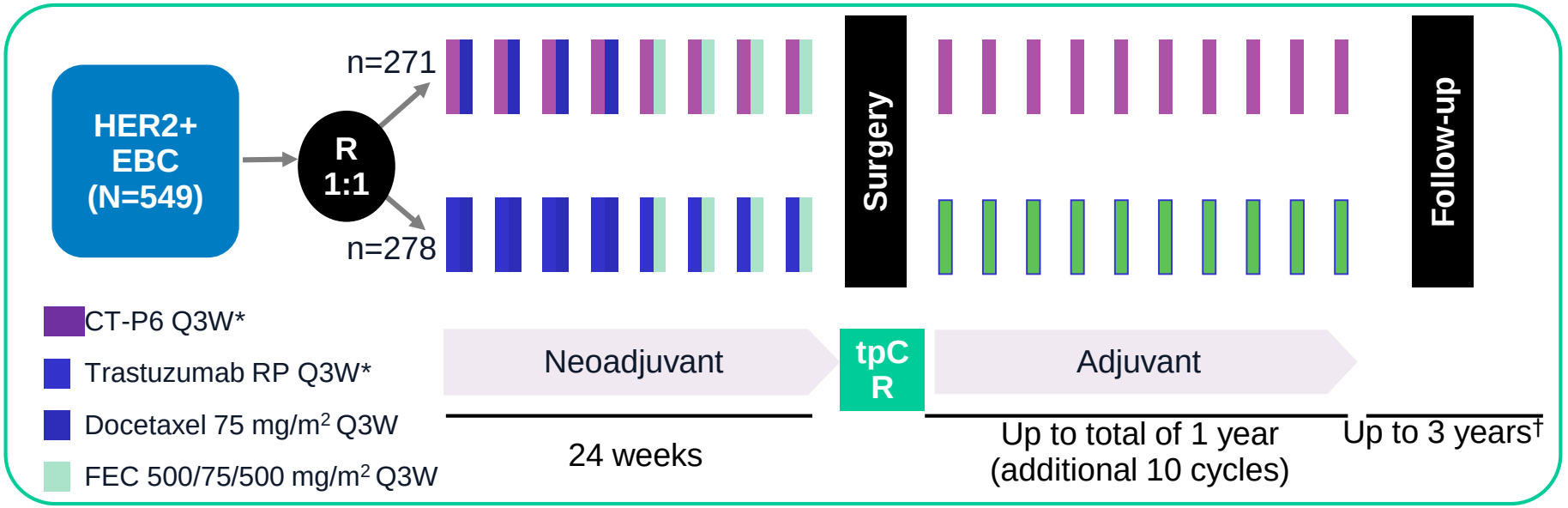
Biocad (BCD-022) vs Trastuzumab RP in HER2+ MBC:primary efficacy results

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)	



*Yates-corrected Pearson's test

Celltrion (CT-P6) vs Trastuzumab RP in HER2+ EBC Phase 3 equivalence study



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

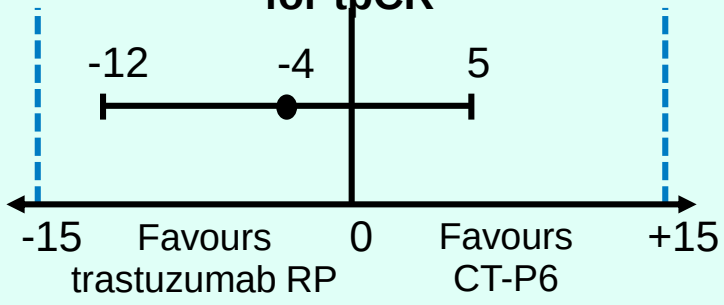
- Efficacy: pCR (breast only), tpCR (without DCIS), ORR, breast conservation rate, DFS, PFS, OS
- Other: PK, PD, biomarkers and safety

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

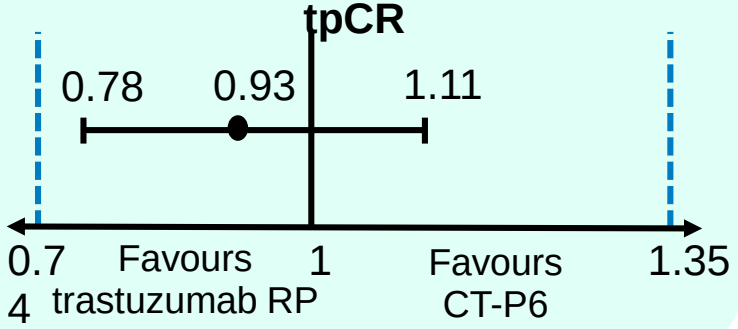
Celltrion (CT-P6) vs Trastuzumab RP in HER2+ EBC:primary efficacy results

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

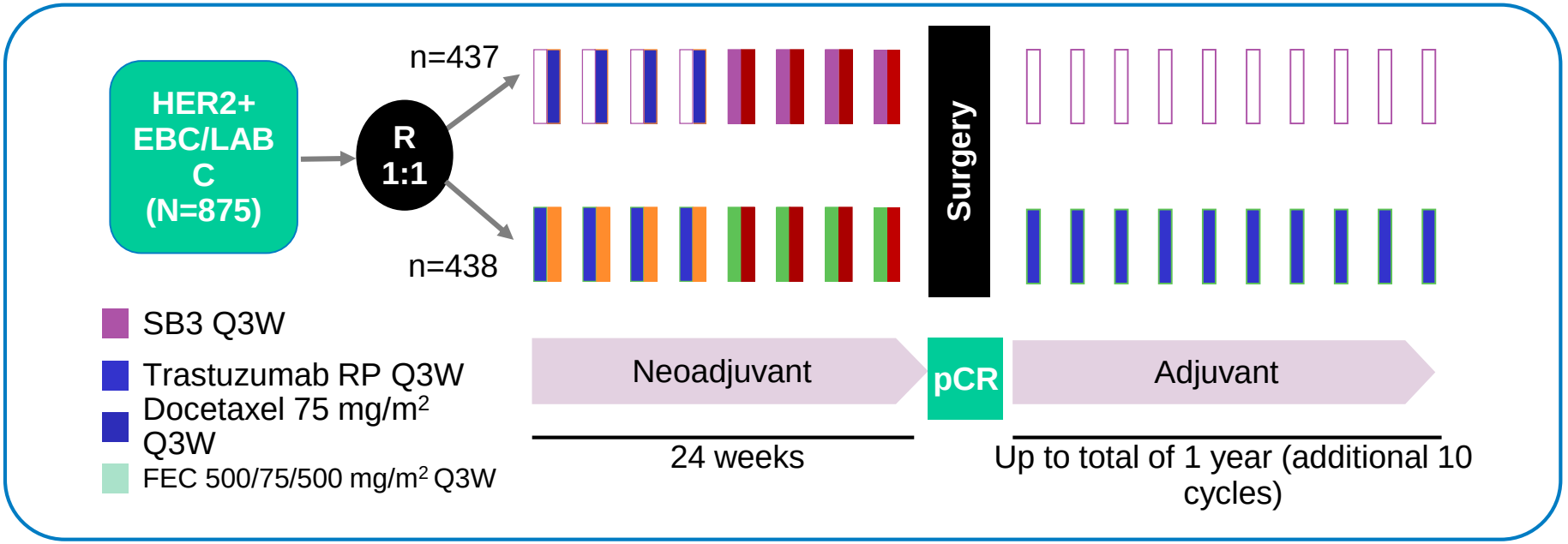


Co-primary analysis: RR (95% CI) for tpCR



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

Samsung Bioepis (SB3) vs Trastuzumab RP in HER2+ EBC: Phase 3 equivalence study



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

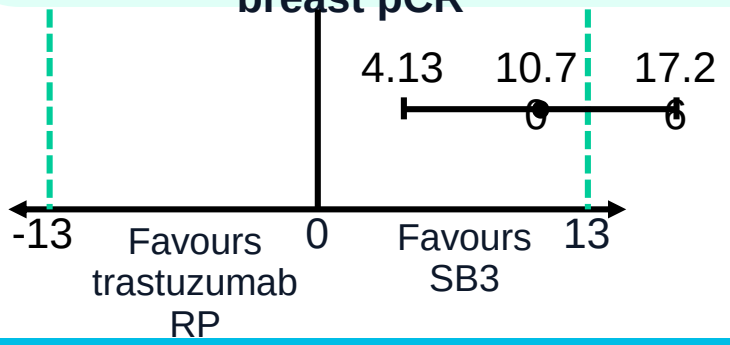
- Efficacy: tpCR, ORR, EFS
- Other: PK, immunogenicity and safety

Pivot XB, et al. ASCO 2017; Abstract 509 and poster presentation

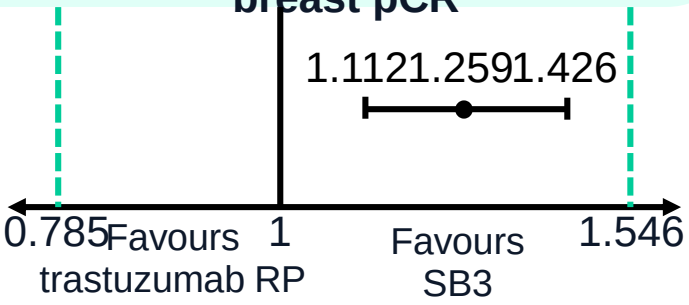
Samsung Bioepis (SB3) vs trastuzumab RP in HER2+ EBC: primary efficacy analysis

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



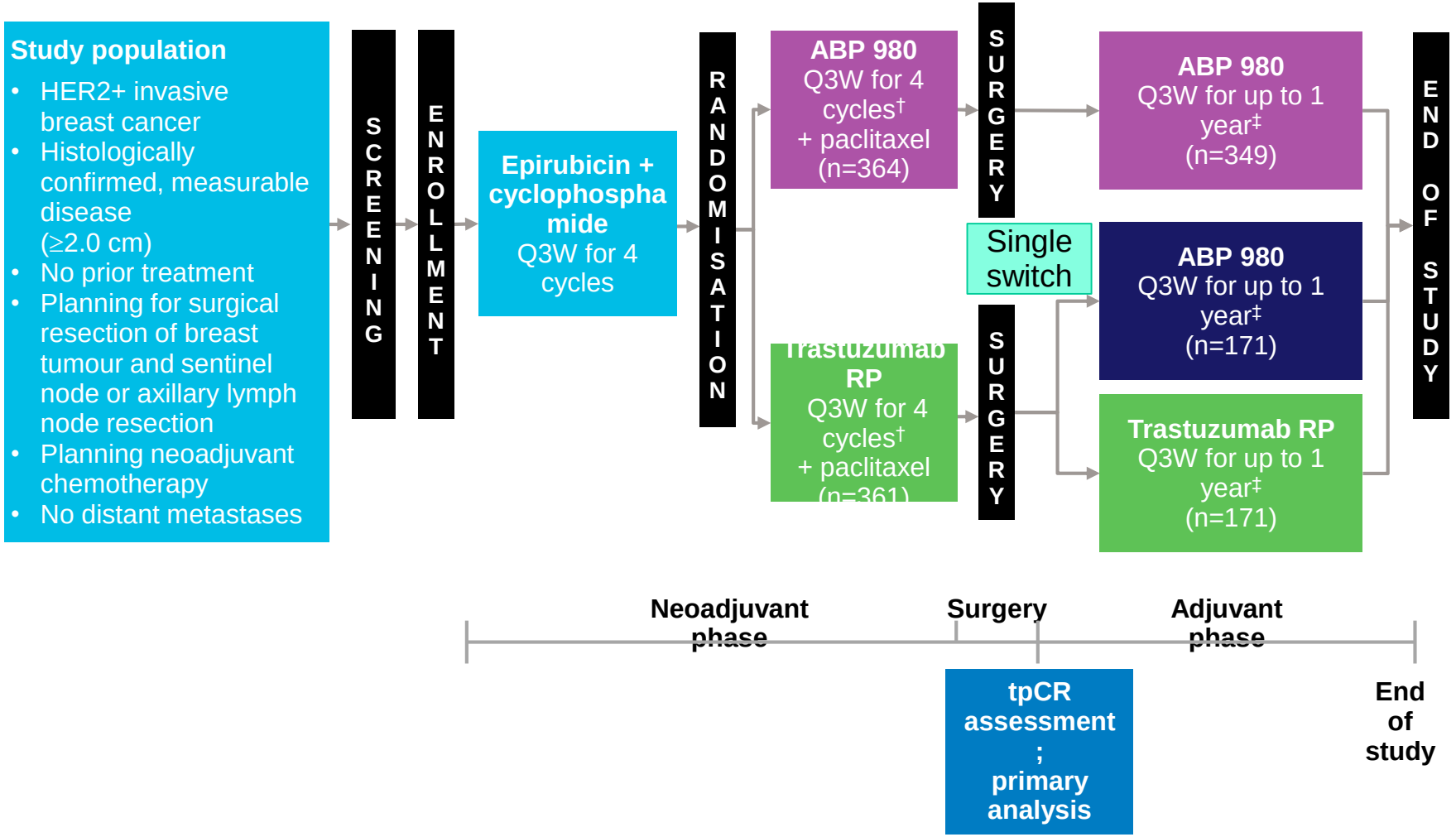
Co-primary analysis: RR (90% CI) for breast pCR



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 XB, et al. ASCO 2017; Abstract 509 and poster presentation

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

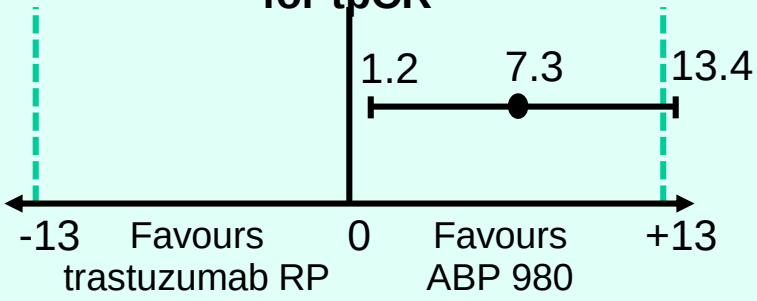


von Minckwitz G, et al. ESMO 2017; Poster 151PD; Kolberg H-C, et al. SABCS 2017; Poster PD3-10; von Minckwitz, G et al. SABCS 2017; Poster P5-20-13

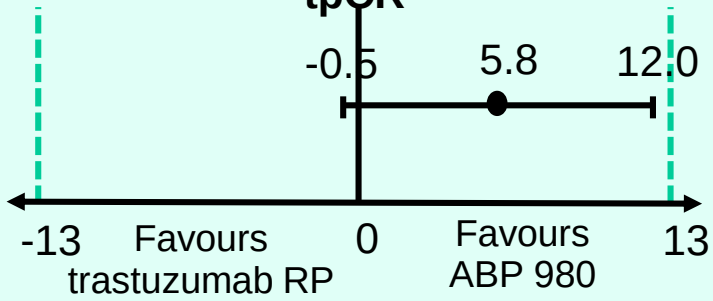
Amgen (ABP 980) vs Trastuzumab RP in HER2+ EBC:primary efficacy results

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

Conclusions

- **Biosimilars of Trastuzumab are under active development**
- **The aim of clinical trials with biosimilar Trastuzumab is to show equivalence and not patient benefit, as this was shown with Herceptin**
- **The neoadjuvant/adjuvant patient population may represent a homogeneous and sensitive population to establish similarity of biosimilar Trastuzumab to Herceptin**
- **Extrapolation of immunogenicity/efficacy/safety data obtained in the early breast cancer population to the metastatic population would be possible, but not vice versa**


BIOSIMILARS
WHAT YOU NEED TO KNOW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IN ONCOLOGIA


Biosimilars? Shouldn't you be prescribing something more BioExact?
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