Biosimilars in Oncology and Hematology: A Brave New World of Cancer Treatment

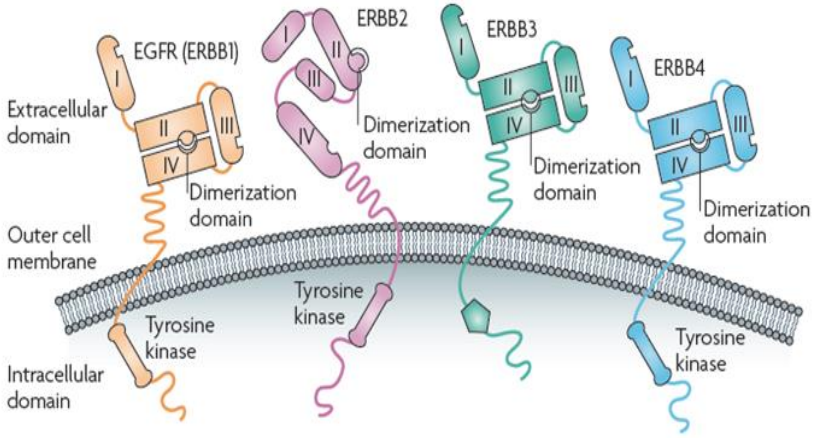
How Do We Incorporate Biosimilars into Breast Cancer Care?

Francisco J. Esteva, MD, PhD
Professor of Medicine, NYU School of Medicine
Director, Breast Medical Oncology
Associate Director of Clinical Investigation
Laura and Isaac Perlmutter Cancer Center
New York University Langone Medical Center

Outline

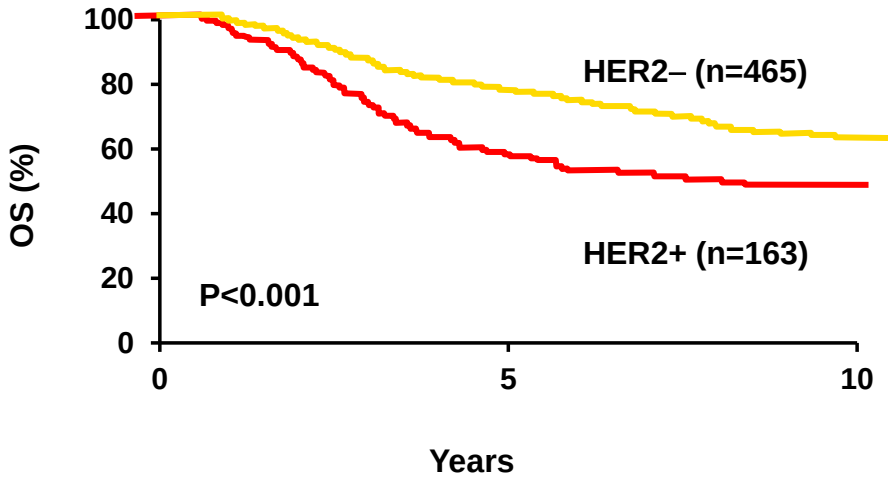
- Introduction (HER2, Trastuzumab)
- Biosimilars currently in development for the treatment of breast cancer
- Extrapolation between different indications

EGF Receptor Family



Baselga & Swain. Nat Rev Cancer 2009;9:463-75

Worse Survival of Patients With HER2+ Primary Breast Cancer



Adapted from Pritchard et al. N Engl J Med 2006;354:2103

Milestones of HER2 Targeted Therapy in Breast Cancer

1982 — neu oncogene discovery Weinberg

1985 — Her2 cloned Schechter, Hung, …, Ullrich, Coussens

1985 — Her2 amplification in breast cancer King, Kraus, Aaronson

1987 — Amplification of Her2/neu correlates with shorter survival Slamon

1998 — FDA approves single agent trastuzumab for 2nd line and in combination with paclitaxel for 1st line MBC

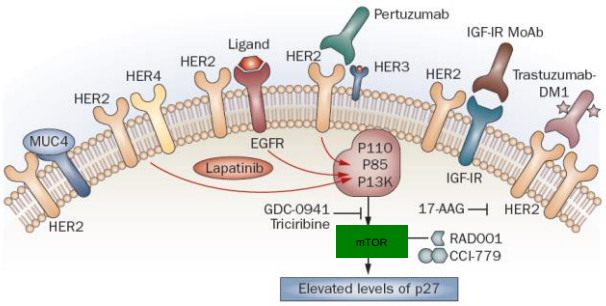
2006 — FDA approves trastuzumab in adjuvant setting

2007-2014 — FDA approves lapatinib, pertuzumab, trastuzumab-DM1

2014 — Main trastuzumab patent expires in Europe*

Trastuzumab Biosimilars

Innovation Continues



*www.evidence.nhs.uk

Adapted from Esteva FJ, et al. *Nat Rev Clin Oncol*. 2010;7(2):98-107

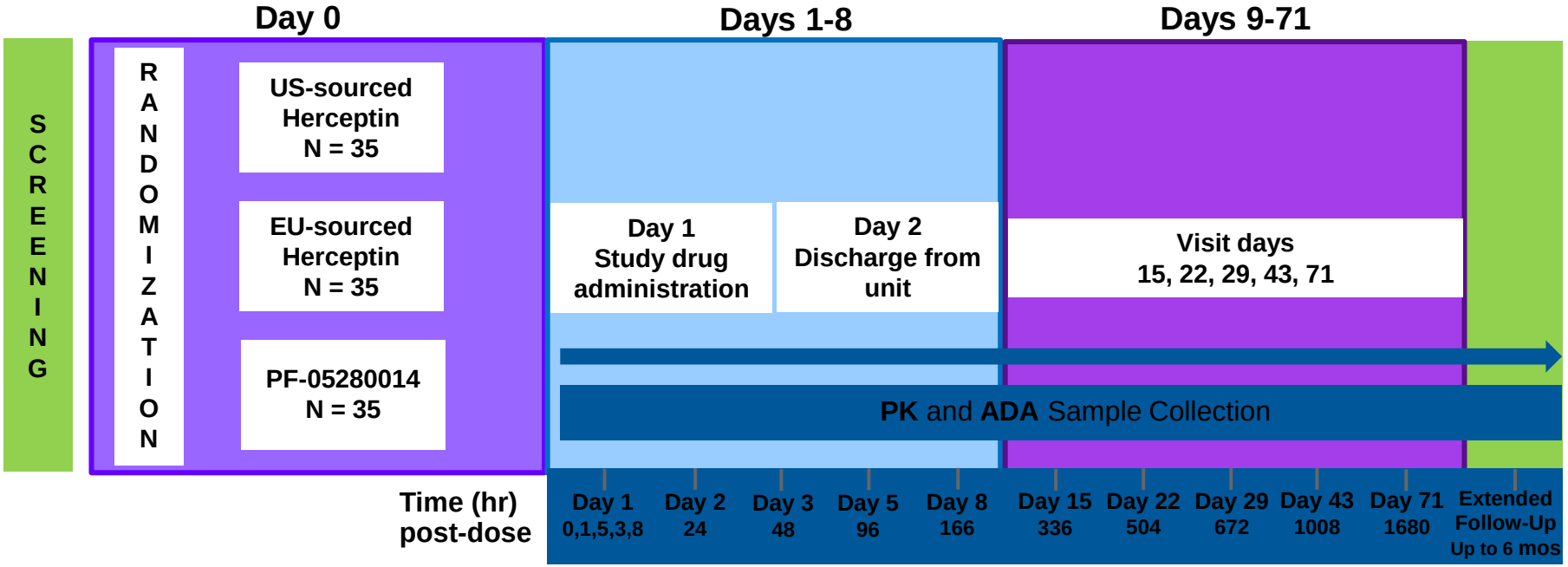
Trastuzumab biosimilars in late phase clinical development for breast cancer

Company name	Product name	Stage of development
Pfizer, USA	PF-05280014	Phase III trial ongoing
Celltrion, South Korea	CT-P6	Marketed in South Korea for metastatic breast cancer, following approval in Jan 2014 (Herzuma). Phase III in early-stage breast cancer ongoing
Amgen, USA	ABP-980	Phase III trial ongoing
Biocad, Russia	BCD-022	Phase III trial ongoing

www.clinicaltrials.gov, accessed 11/2/14

A Phase I Pharmacokinetics Trial Comparing PF-05280014 and Herceptin® in Healthy Volunteers

- In this double-blind, randomized, 3-arm trial, 105 healthy male volunteers aged 18-55 were randomized to receive a single 6 mg/kg dose of **PF-05280014**, **Herceptin**-US, or **Herceptin**-EU

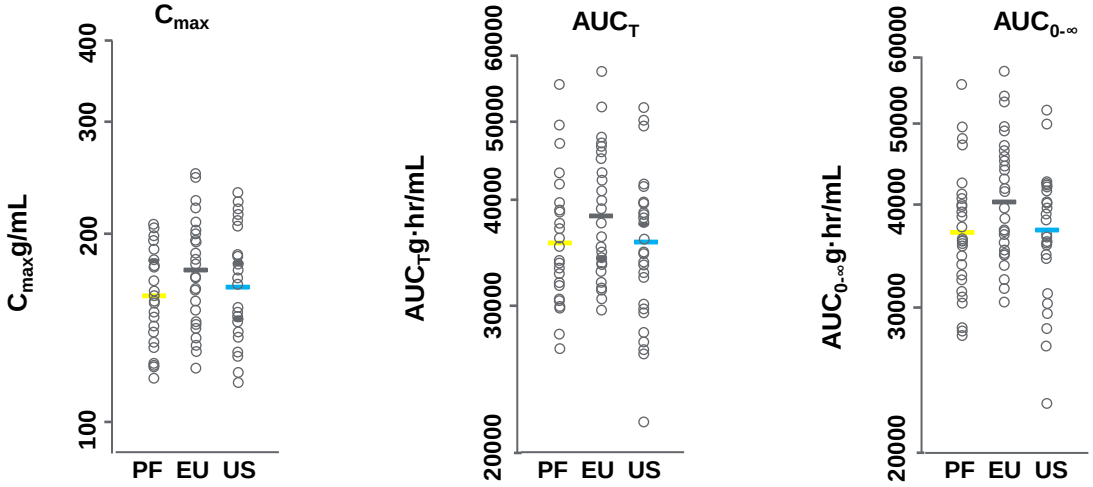


- Primary endpoints
  - Maximum serum concentration (C_{max}) of the administered mAb
  - Area under the serum concentration-time curve (AUC) from time 0 to the last time point with measurable concentration of the administered mAb (AUC_T)

Yin D, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 612.

PF-05280014 Phase I: Pharmacokinetics

Individual and Mean Estimates of C_{max}, AUC_T, and $AUC_{0-\infty}$ of PF-05280014, Herceptin®-EU, and Herceptin®-US



$AUC_{0-\infty}$, area under the concentration-time curve from time 0 extrapolated to infinte time; AUC_T, area under the concentration-time curve from time 0 to last measurable administered monoclonal antibody; C_{max}, maximum serum concentration; EU, trastuzumab EU; PF, PF-05280014; US, trastuzumab-US

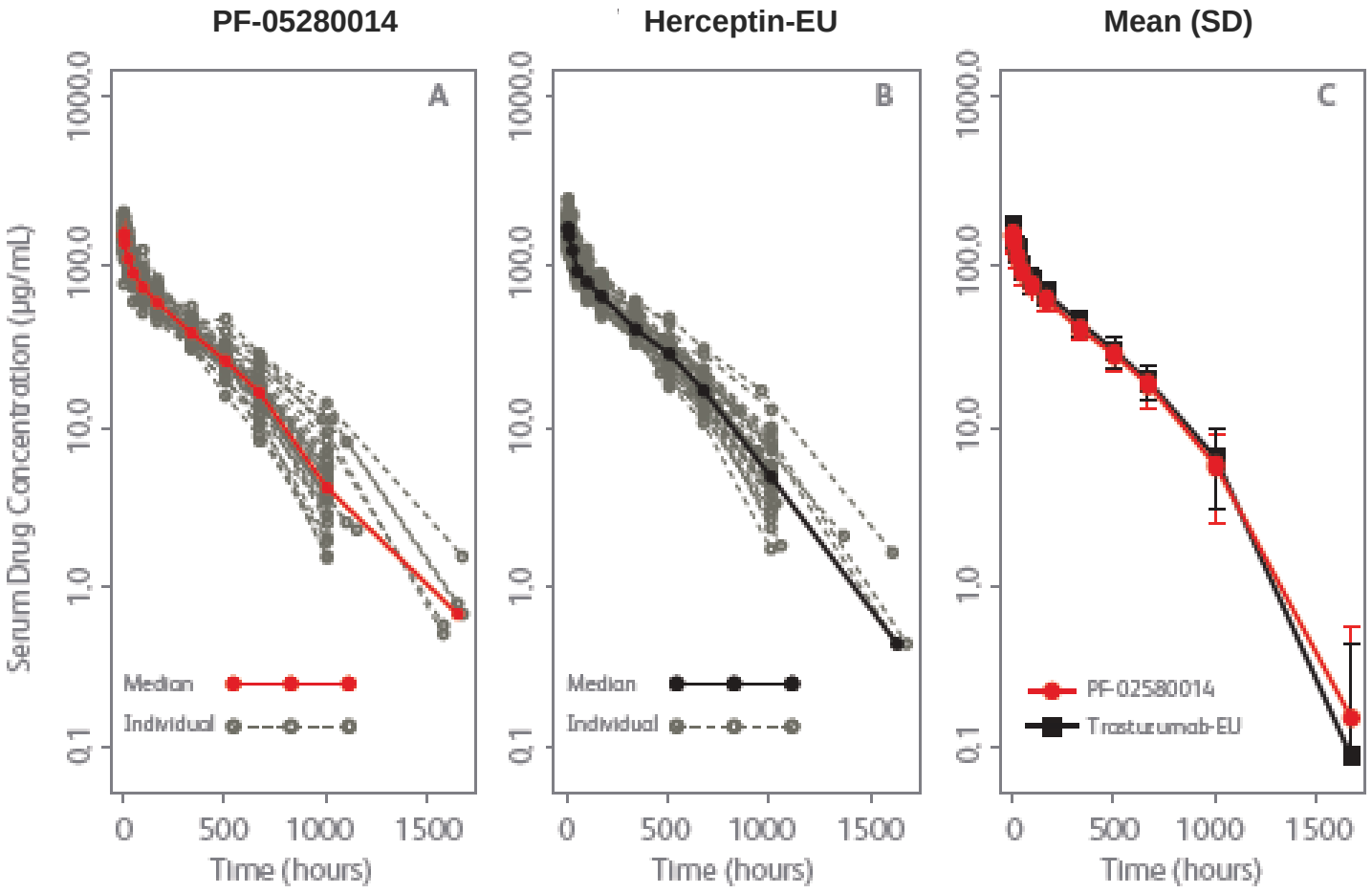
Statistical Comparison of PK Exposure Parameters Between Test and Reference Products

			Geometric Mean			
Test	Reference	Parameter*	Test	Reference	Ratio, %†	90% CI, %
PF-05280014	Trastuzumab-US	C_{max}	157	161	97.41	90.71-104.62
		AUC_T	35210	35230	99.94	93.08-107.31
		$AUC_{0-\infty}$	36650	36710	99.83	93.06-107.09
PF-05280014	Trastuzumab-EU	C_{max}	157	171	91.49	85.32-98.09
		AUC_T	35210	38000	92.66	86.44-99.34
		$AUC_{0-\infty}$	36650	39770	92.15	86.03-98.69
Trastuzumab-EU	Trastuzumab-US	C_{max}	171	161	106.48	99.20-114.30
		AUC_T	38000	35230	107.85	100.50-115.75
		$AUC_{0-\infty}$	39770	36710	108.34	101.05-116.16

*C_{max}, AUC_T and $AUC_{0-\infty}$ were in units of g/mL, g·hr/mL, respectively. †Test/reference ratio of adjusted geometric means.

Yin D, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 612.

PF-05280014 Phase I: Pharmacokinetics



SD= standard deviation

Ewesuedo R, et al. San Antonio Breast Cancer Symposium, December 10–14, 2013 (poster OT1–1–03)

PF-05280014 Phase I Safety

Treatment-Emergent Adverse Events Regardless of Causality Occurring in ≥5% of Total Subjects (Modified ITT Population)

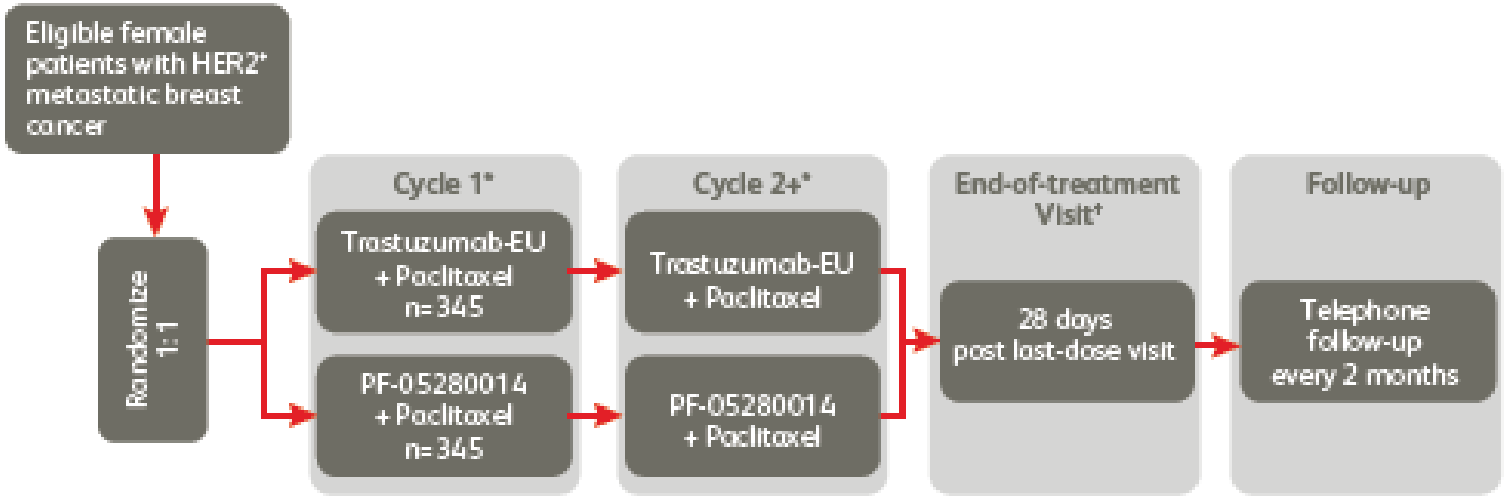
	PF-05280014 n = 35	Herceptin®-EU n = 35	Herceptin®-US n = 35
Subjects with any AE n (%)	28 (80.0)	29 (82.9)	29 (82.9)
Eye disorders, n (%)			
Conjunctival hyperemia	4 (11.4)	1 (2.9)	2 (5.7)
Gastrointestinal disorders, n (%)			
Diarrhea	3 (8.6)	2 (5.7)	1 (2.9)
Nausea	5 (14.3)	5 (14.3)	3 (8.6)
General disorders and administration site conditions, n (%)			
Pyrexia	10 (28.6)	3 (8.6)	2 (5.7)
Chills	9 (25.7)	7 (20.0)	5 (14.3)
Fatigue	3 (8.6)	3 (8.6)	3 (8.6)
Infections and infestations, n (%)			
Nasopharyngitis	3 (8.6)	3 (8.6)	2 (5.7)
Pharyngitis	1 (2.9)	4 (11.4)	2 (5.7)
Injury, poisoning and procedural complications, n (%)			
Infusion-related	13 (37.1)	10 (28.6)	7 (20.0)
Musculoskeletal and connective tissue disorders, n (%)			
Myalgia	2 (5.7)	2 (5.7)	2 (5.7)
Nervous system disorders, n (%)			
Headache	10 (28.6)	12 (34.3)	8 (22.9)
Dizziness	1 (2.9)	4 (11.4)	2 (5.7)
Respiratory, thoracic and mediastinal disorders, n (%)			
Cough	1 (2.9)	4 (11.4)	1 (2.9)

Yin D, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 612.

PF-05280014 Phase I trial
Summary of Results

- Similarity in terms of pharmacokinetic properties for PF-05280014 compared to both Herceptin® sourced from the US and Herceptin® sourced from the EU, and of trastuzumab-US compared to trastuzumab-EU for a single intravenous administration of the drugs.
- Equivalent pharmacokinetic properties
  - Maximum observed serum concentration (C_{max})
  - Area under the curve (AUC) from day 1 to day 71
- The three study drugs showed similar immunogenicity and safety profiles.

A Study of PF-05280014 [Trastuzumab-Pfizer] or Herceptin®-EU plus Paclitaxel in HER2 Positive First Line Metastatic Breast Cancer Treatment (REFLECTIONS B327-02)



*Cycle Day	1	8	15	22
Trastuzumab or PF-05280014	X	X	X	X
Paclitaxel	X	X	X	

690 patients (345/arm)

Dosage:

PF-05280014 or trastuzumab-EU: 4 mg/kg loading dose Cycle 1; 2 mg/kg weekly maintenance. After Week 33 or confirmed response, regimen may be changed to 6 mg/kg every 3 weeks.

Paclitaxel: 80 mg/m^2, with provision for dose reduction, for a minimum of 6 cycles.

* See Cycle Day table below study algorithm.

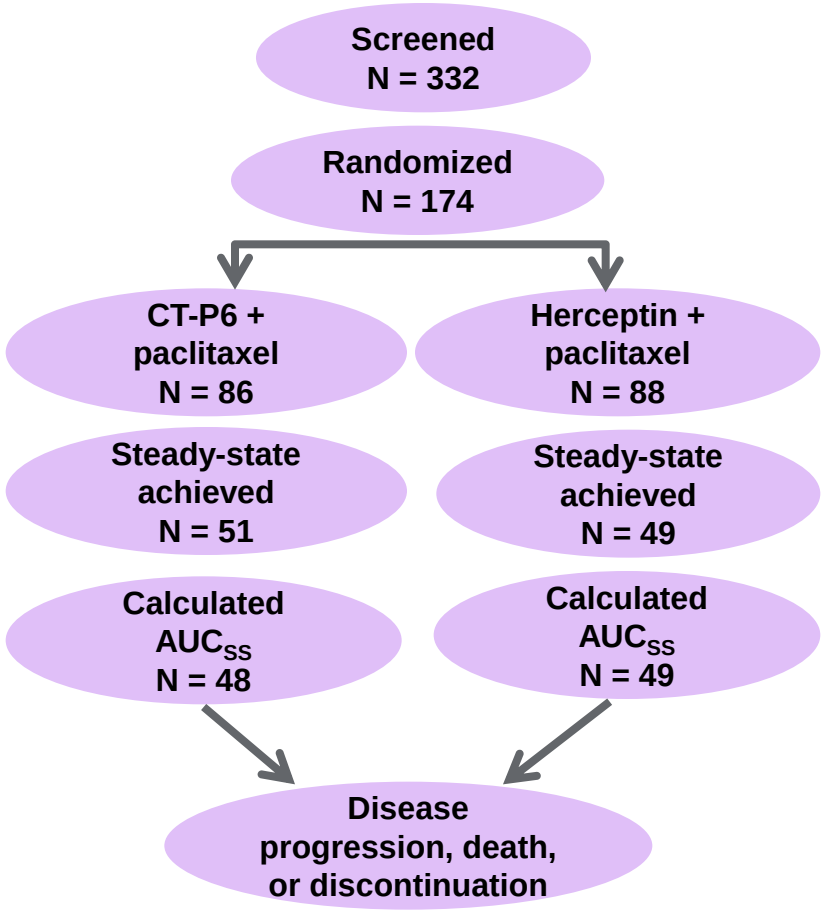
† Study treatment to continue until disease progression or investigator's decision to end treatment.

HER2+=human epidermal growth factor receptor 2–positive

Ewesuedo R, et al. San Antonio Breast Cancer Symposium, December 10–14, 2013 (poster OT1–1–03)

Phase I/IIb Randomized Clinical Trial Comparing PK and Safety of Herceptin® and its Biosimilar CT-P6 in Metastatic Breast Cancer

- **MBC, HER2 FISH+ with measurable disease, no prior trastuzumab and CT for MBC, > than 12 months from adjuvant/ neoadjuvant trastuzumab and CT**



Primary Endpoint:
- Area under the curve at steady state (AUC_{ss})

Secondary Endpoint:
- Trough concentration at steady state ($C_{trough\ ss}$)

Tertiary Endpoints:
- Average concentration ($C_{av,ss}$)
- Minimum concentration (C_{min})
- Maximum concentration (C_{max})
- Peak to trough fluctuation ratio (PTF)
- Clearance at steady state (CL_{ss})
- Terminal elimination rate constant (λ_z)
- Mean residence time at steady state (MRT_{ss})
- Terminal half life ($t_{½}$)
- Apparent volume of distribution at steady state (Vz_{ss})

Safety Objectives: Cardiotoxicity, Infusion reaction /hypersensitivity

Im Y, et al. Presented at 13th St Gallen International Breast Cancer Conference; 13-16 March 2013; St Gallen, Switzerland. Poster 268.

Phase I/IIb Trial Comparing Herceptin® and its Biosimilar CT-P6 in MBC: Results

- **Multicenter trial: Korea, Russia, Ukraine, Latvia, Serbia**

Parameter	Treatment	N	Geometric mean	% CV	Ratio (%)	90% CI	*P* value
AUC_{SS} (µgh/mL)	**CT-P6**	48	32,000	43.5	104.57	93.64, 116.78	.5029
	Herceptin®	49	30,600	30.9			
$C_{trough\ SS}$ (µg/mL)	**CT-P6**	51	19.5	37.0	101.35	87.94, 116.82	.8754
	Herceptin®	49	19.2	39.6			

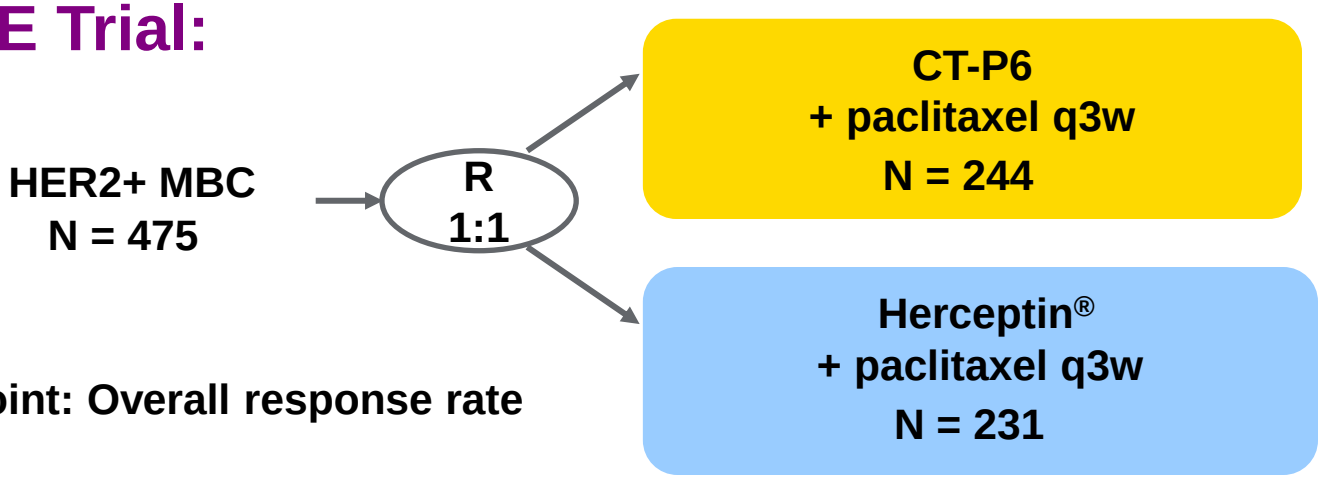
Conclusions of the study:

- **CT-P6 demonstrated equivalent PK profile to Herceptin**
- **CT-P6 well tolerated with a comparable safety profile to Herceptin**
- **(infusion-related reaction, cardiotoxicity, and infection)**

Im Y, et al. Presented at 13th St Gallen International Breast Cancer Conference; 13-16 March 2013; St Gallen, Switzerland. Poster 268.

Double-Blind, Randomized, Parallel Group, Phase III Study to Demonstrate Equivalence in Efficacy and Safety of CT-P6/Paclitaxel vs Herceptin®/Paclitaxel in MBC

COMPARE Trial:



Primary Endpoint: Overall response rate (ORR)

Inclusion Criteria:

- MBC with measurable lesions
- HER2 + IHC or FISH centrally confirmed
- No prior trastuzumab and/or chemo Tx in metastatic setting
- >12 months since prior adjuvant or neoadjuvant trastuzumab and/or chemo
- ECOG 0 or 1

Exclusion Criteria:

- Prior chemo for MBC
- CNS metastases
- Baseline LVEF ≤50% or history of CHF

Im YH, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 629.

Patient Characteristics	CT-P6 + Paclitaxel (n = 244)	Trastuzumab + Paclitaxel (n = 231)
Age (years)		
Median (range)	54 (31-75)	53 (25-78)
≥65 years	34 (13.9)	22 (9.5)
<65 years	210 (86.1)	209 (90.5)
Ethnicity, no (%)		
Caucasian	158 (64.8)	141 (61.0)
Asian	86 (35.2)	90 (39.0)
Prior neoadjuvant or adjuvant therapy, n (%)	130 (53.3)	121 (52.4)
Trastuzumab	8 (3.3)	8 (3.5)
Taxane	33 (13.5	31 (13.4)
Anthracycline	111 (45.5)	106 (45.9)
Baseline ECOG PS score, n (%)		
Score 0	128 (52.5)	116 (50.2)
Score 1	115 (47.1)	115 (49.8)
Disease status		
Initial metastatic	90 (36.9)	84 (36.4)
Recurrence	154 (63.1)	147 (63.6)
Disease-free interval, months (range)	23.8 (0.9-148.2)	20 (0.5-384.9)

Im YH, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 629.

Safety

	CT-P6 + Paclitaxel		Herceptin® + Paclitaxel		*P* value	
	All	≥G3	All	≥G3	All	≥G3
Total serious adverse events	33	28	28	24	.6477	.7048
All adverse events	224	110	214	107	.7336	.7865
Hematologic events						
Anemia	187	10	180	4	.7388	.1274
Neutropenia	142	81	140	82	.5931	.5975

Im YH, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 629.

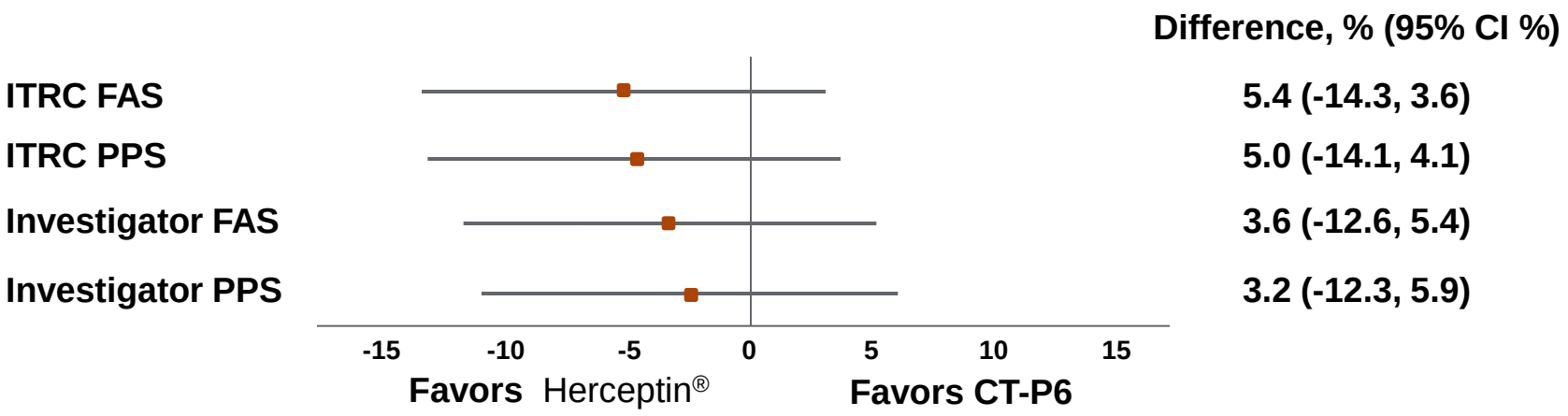
Nonhematologic Adverse Events

	CT-P6 + Paclitaxel		Trastuzumab + Paclitaxel		*P* Value	
	All	≥G3	All	≥G3	All	≥G3
Cardiotoxicity	15	6	14	3	.9684	.3539
Hypersensitivity	118	11	127	11	.1492	.8954
Peripheral neuropathy						
Sensorimotor	4	3	5	1	.6748	.3423
Sensory	48	7	50	4	.5954	.4101
Unspecified	63	14	56	13	.6917	.9587
Nausea / Vomiting	48	2	44	2	.8633	.9561
Fatigue and/or Asthenia	73	5	63	3	.5238	.5252
Diarrhea	34	1	41	1	.2545	.9690
Stomatitis	14	0	16	0	.5945	NE
Alopecia	122	0	127	3	.2775	.0741
Myalgia	47	1	52	2	.3836	.5307
Pain in extremity	22	2	29	6	.2132	.1323
Arthralgia	21	0	30	0	.1232	NE
Infections	57	10	46	8	0.3622	.7171

Im YH, et al. *J Clin Oncol*. 2013;31(suppl): Abstract 629.

Compare: Overall Response Rate

	ITRC		Investigator	
	CT-P6 + Paclitaxel (n = 244)	Herceptin® **+ Paclitaxel (n = 231)**	**CT-P6 + Paclitaxel (n = 244)**	Herceptin® **+ Paclitaxel (n = 231)**
Complete response	**9 (3.7%)**	**4 (1.7%)**	**12 (4.9%)**	**6 (2.6%)**
Partial response	**129 (52.9%)**	**139 (60.2%)**	**146 (59.8%)**	**152 (65.8%)**
Stable disease	**49 (20.1%)**	**38 (16.5%)**	**61 (25.0%)**	**56 (24.2%)**
Overall response rate	**138 (56.6%)**	**143 (61.9%)**	**158 (64.8%)**	**158 (68.4%)**
Difference, % [95% CI]	**5.4 [-14.3, 3.6]**		**3.6 [-12.6, 5.4]**	



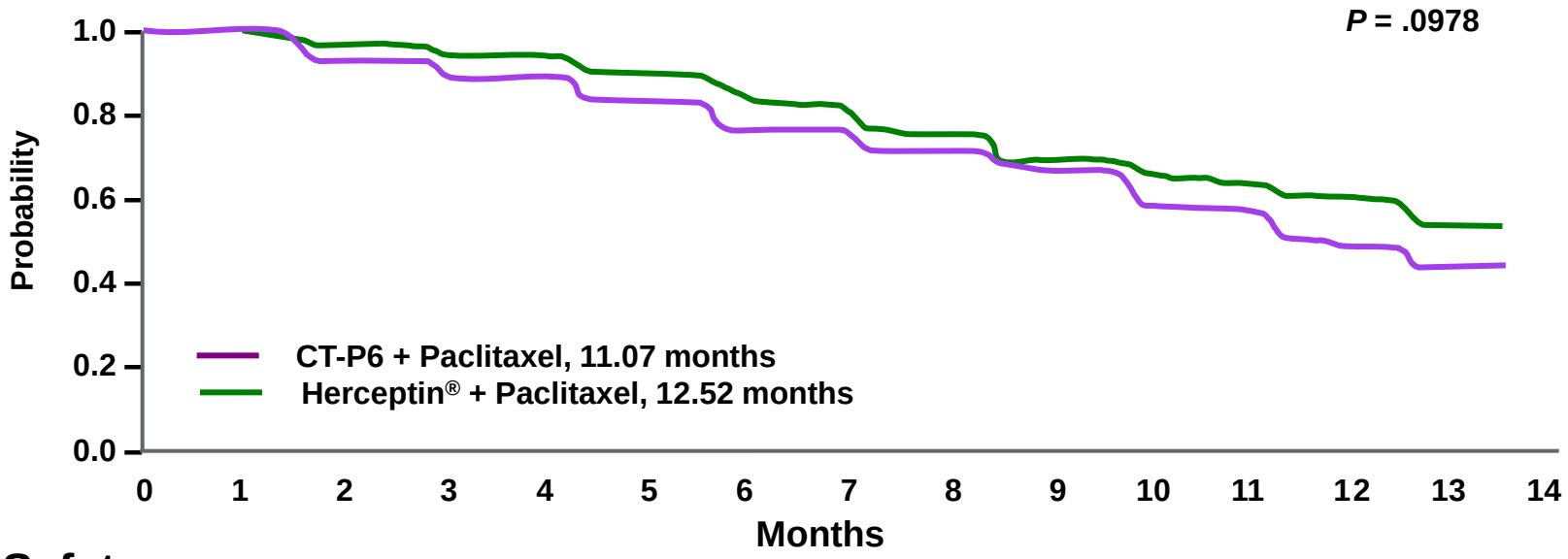
FAS, Full analysis set; PPS, per protocol patient set

Difference in proportion of complete response or partial response. Confidence interval estimated using the exact method.

Im YH, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 629.

Compare: Time to Progression

Time to progression in the responder group by independent review committee (full analysis set, 1 year data)



- **Safety**
  - **CT-P6 was well tolerated with a safety profile comparable to Herceptin**
  - **No immunogenicity data available**

Im YH, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 629.

CT-P6 in Metastatic Breast Cancer
Summary of Results

CT-P6 (trastuzumab biosimilar) is similar to Herceptin® in terms of pharmacokinetic properties, safety and efficacy

What is the most “Sensitive and Homogenous Population” in Breast Cancer?

- Biosimilar monoclonal antibodies should be studied in the population of patients in whom, *if there is a difference between the biosimilar and the reference product*, that difference will most easily be detected.

- This population will vary for each antibody and each disease in which the antibody is used
  - **With biosimilar trastuzumab, the most sensitive population is early-stage breast cancer in the neoadjuvant setting**

The neoadjuvant setting is the most sensitive population to study similarity of Herceptin® and Trastuzumab biosimilar

Topic	Metastatic Population	Neoadjuvant population
PK	✘ Affected by patient's health status & tumor burden	✓ Homogeneous population can be selected ✘ Variability is also observed
PD	✘ Clinically validated PD marker not available	
Clinical efficacy/safety	✘ • Difficult to select homogeneous group • Need to control and stratify for multiple factors (e.g., prior use of chemotherapy, performance status) • Population with heterogeneous characteristics affecting final clinical outcome	✓ • Populations less likely to be confounded by baseline characteristics and external factors • Sub-group of patients with higher responses could be identified (eg, hormone-receptor negative patients)
Immunogenicity	✘ Immune system affected by performance status and concomitant chemotherapies received	✓ Immune system impaired during chemotherapy cycles, but likely to recover to normal status thereafter

Phase III Trials of Neoadjuvant Trastuzumab Biosimilars in Early-Stage Breast Cancer

	SB-3 (Samsung Bioepis)	ABP-980 (Amgen)	CT-P6 (Celltrion)
Trial identifier	NCT02149524	NCT01901146	NCT02162667
Trial design	Randomized double-blind	Randomized double-blind	Randomized double-blind
Comparator	Herceptin®	Herceptin®	Herceptin®
Disease	EBC	EBC	EBC
Chemo	?	Epirubicin, Cyclophosphamide, Paclitaxel	docetaxel followed by FEC (5-fluorouracil, epirubicin and cyclophosphamide)
Primary Endpoint	pCR (breast)	pCR (breast)	pCR (breast/LN)
No of pts	498	556	532
Status	Ongoing	Ongoing	Planning to start in 2014

www.clinicaltrials.gov, accessed 11/2/14

Is Extrapolation across Indications Possible using Trastuzumab Biosimilars?

Trastuzumab is used in different ways across tumor types and disease settings

- In combination with different chemotherapies, Pertuzumab, hormonal therapies, and as single agent (maintenance)
- Neoadjuvant and adjuvant Herceptin® in breast cancer
- Herceptin® in metastatic breast cancer
- Herceptin® in metastatic gastric cancer

Challenges to Incorporate Trastuzumab Biosimilars into Breast Cancer Care

- Residual uncertainties and differences
- Lack of reliable disease and product specific PD markers and complex non-linear pharmacokinetics
- Conflicting and inconsistent historical clinical data with the reference product (e.g., variable ORR or pCR rates with Herceptin)
- Extrapolation issues
  - Regulatory and prescribers' hesitation
  - Difficulties in extrapolation of safety and long-term immunogenicity
- Operational execution of global clinical studies

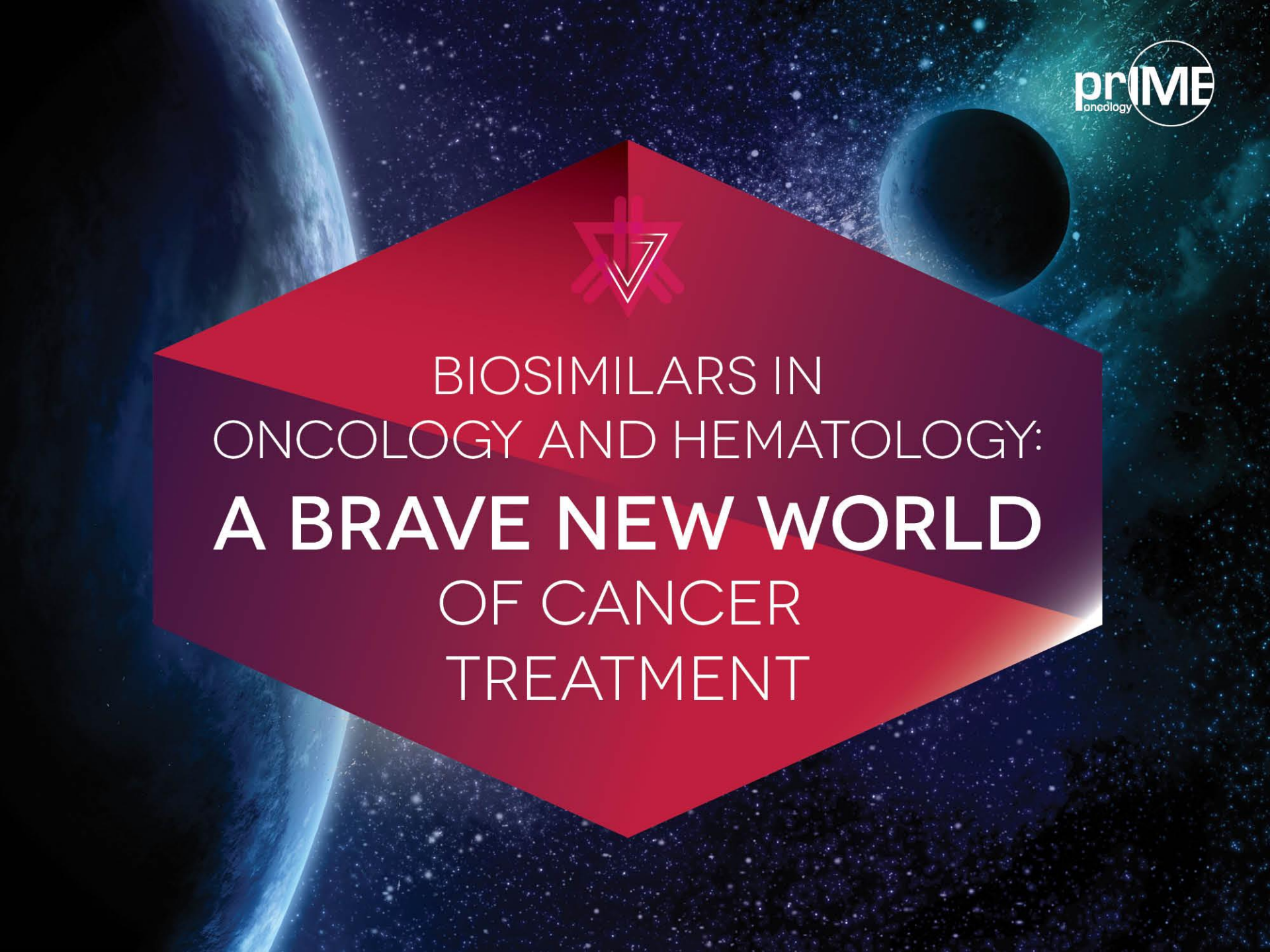
Conclusions

- Biosimilar ≠ Identical
- Phase III randomized trials of trastuzumab biosimilars are ongoing (global studies)
- Incorporation of trastuzumab biosimilars into breast cancer care will require equivalence trials in the metastatic and early-stage settings
- The neoadjuvant setting provides the most sensitive and homogeneous population
- How trastuzumab biosimilars are tested in clinical trials will determine how they are used in the clinic

NYU Langone Medical Center

Thank You!

Francisco.Esteva@nyumc.org


prIME oncology
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