Topic 2: Development of Biosimilars for Breast Cancer

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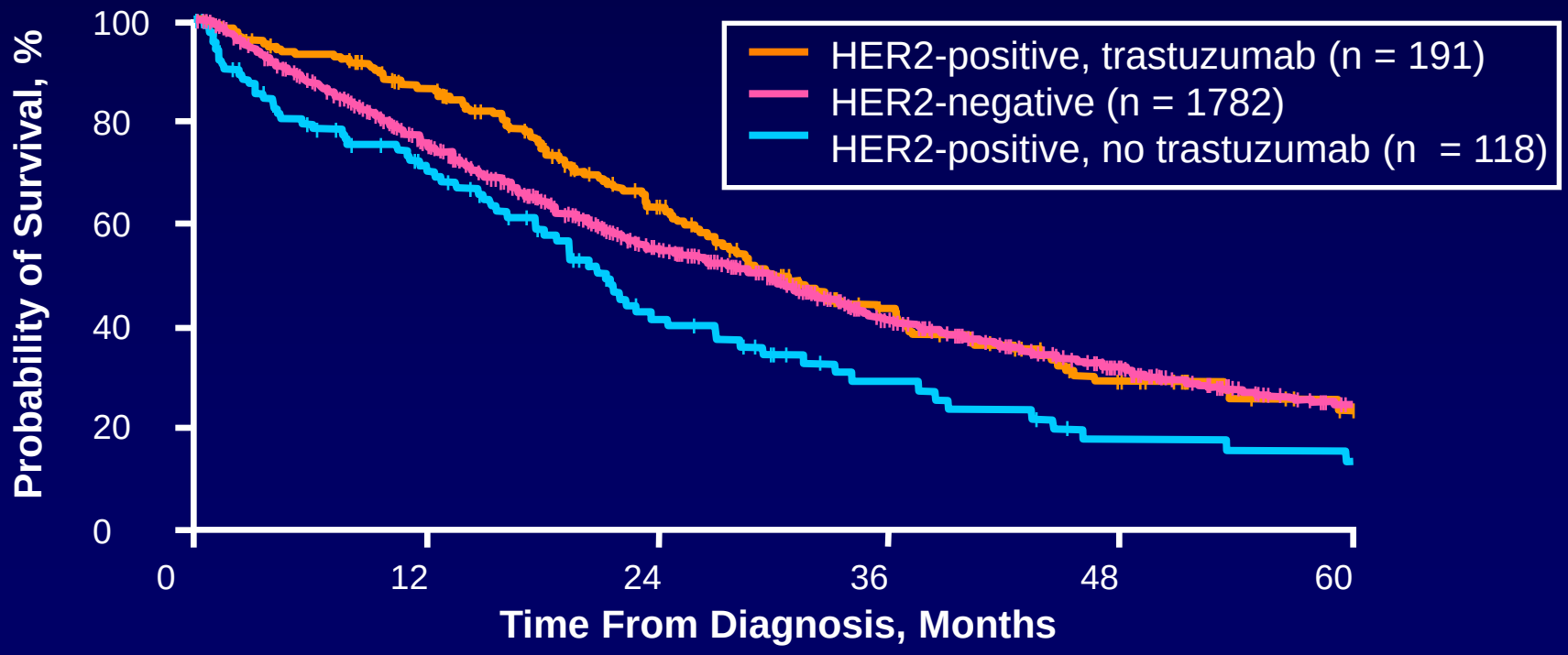
Trastuzumab Has Changed the Course of HER2-Positive Breast Cancer



Dawood S, et al. *J Clin Oncol*. 2010;28(1):92-98.

Trastuzumab—A Long Way to Approval

Identification of the HER-2 neu oncogene (Schechter et al)

Humanization of an anti HER-2 MoAb = trastuzumab (Carter et al)

2014 Patent exclusively rights expire

HERA 2y results at ESMO

Anti-HER-2 MoAb inhibits neu-transformed cells (Drebin et al)

Phase II trial as monotherapy in MBC (Baselga et al)

Pivotal phase III trial in MBC (Slamon et al)

HannaH tratuzumab sc at EBCC

BCIRG 006 (Slamon et al)

1984 1985 1986 1987 1992 1994 1996 1998 1999 2005 2010 2011 2012

Correlation of HER-2/neu amplification and prognosis (Slamon et al)

Phase II trial in MBC, in combination with chemo (Pegram et al)

Neoadjuvant NOAH (Gianni et al)

ToGA gastric trial (Van Cutsem et al)

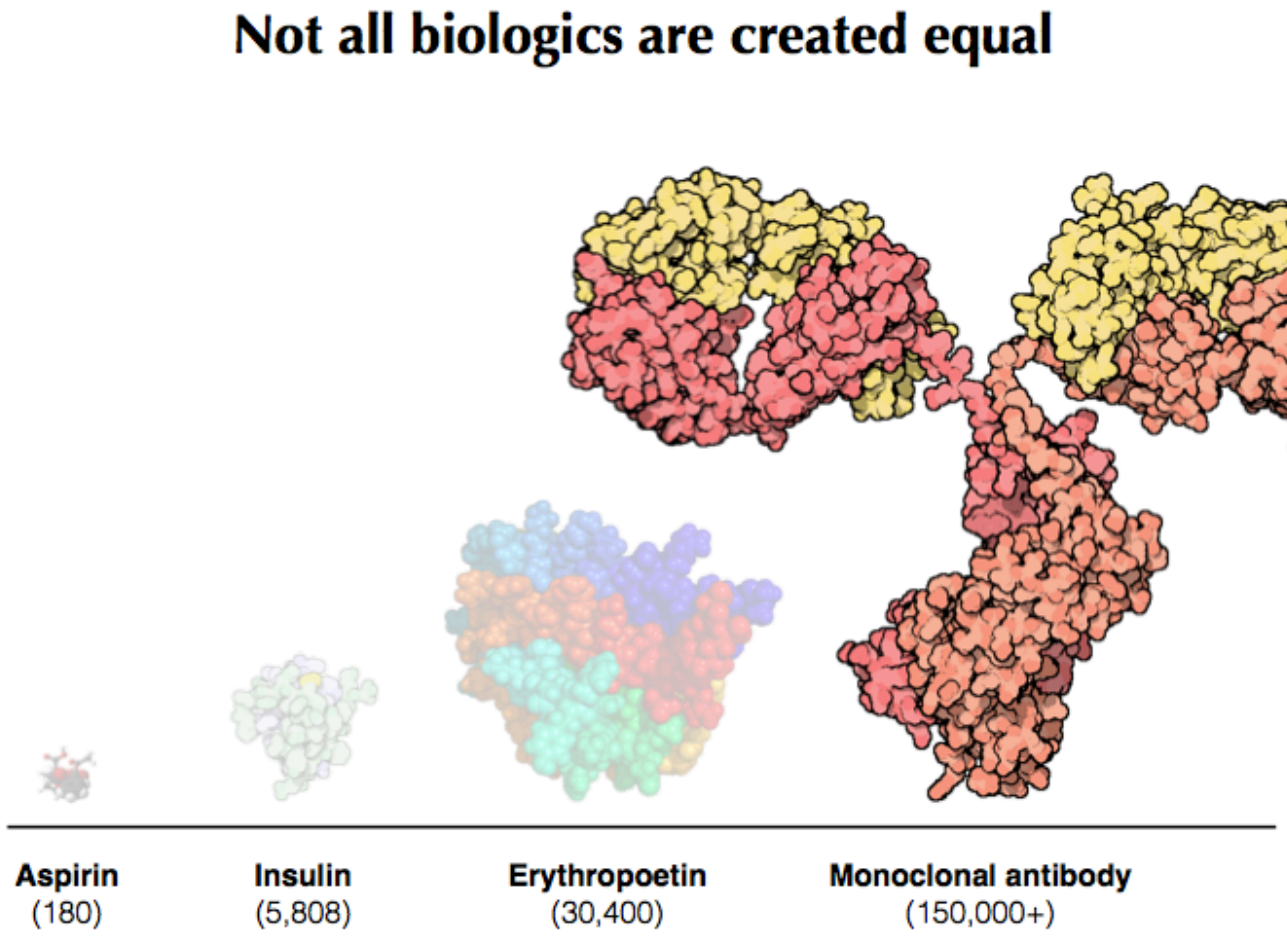
Cloning of HER-2 (Semba et al, Coussens et al)

Herceptin®-enhanced chemosensitivity: impressive synergy in pre-clinical models (Pietras et al)

Adjuvant trials: NSABP B-31, NCCTG-N9831 (Ramon et al) **HERA** (Piccart et al)

Biologics are complex drugs that are derived from living organisms such as bacterial and eukaryotic cells.

Generics, Biosimilars, & Biosimilar Antibodies
Differences in Size and Complexity



Revers, L. & Furczon, E. (2010) An introduction to biologics and biosimilars. Part I: Biologics: What are they and where do they come from? *Can. Pharm. J.* **143**:134.

Biosimilars

- The goal of biosimilar testing is not therapeutic equivalence, but rather comparability
- Biosimilars must demonstrate comparability with the reference product in quality (physicochemical and biological), nonclinical, and clinical testing.
- Biosimilars have already been approved in Europe, such as erythropoietin and filgrastim,
- However, erythropoietin and filgrastim have relatively simple structures, and accepted surrogate efficacy markers (ie, hemoglobin levels, neutrophil counts)

Thill M, *Expert Rev Anticancer Therapy*. In submission.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 May 2012
EMA/CHMP/BMWP/403543/2010
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues

European Medicines Agency. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. Accessed 25 September 2014.

Regulatory Conditions:
Shortened Approval for Biosimilar Antibodies

Classic approval for originators

Proof of **"patient benefit"**

Shortened approval for biosimilar antibodies

Proof of **"similarity"**

European Medicines Agency (EMA): Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues . Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. Accessed 25 September 2014.

Requirements for Biosimilar Antibody Clinical Trials

Clinical Trials of Biosimilars Are Different From Those of Originators

	Biosimilar	Originator
Patient Population	**Sensitive and homogeneous patient population**	**Any**
Clinical Design	**Comparative versus innovator (equivalence studies)**	**Superiority versus 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**

Biosimilar Antibody Clinical Trials

- The guiding principle is to **demonstrate similar efficacy and safety** compared to the reference medicinal product, not patient benefit
- Therefore, the most sensitive patient population and clinical endpoint is preferred
- Comparability should be demonstrated in scientifically appropriately sensitive clinical models and study conditions

European Medicines Agency (EMA): Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues . Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. Accessed 25 September 2014.

What Is a Sensitive and Homogenous Study Population?

- **Biosimilar 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 in breast cancer, the most sensitive population is adjuvant/neoadjuvant disease**
  - **For biosimilar rituximab in lymphoma, the population is harder to identify because lymphomas are not homogenous**

Sensitive Endpoints for Biosimilar Antibody Clinical Trials

- EMA guidelines identify response as a sensitive endpoint for clinical trials of biosimilar antibodies
- The EMA does not accept overall survival as an appropriately sensitive endpoint for biosimilar antibody clinical trials
- As overall response rate (ORR) does not always correlate with survival, this is a controversial endpoint for clinicians
  - Current clinical trials of biosimilar trastuzumab and biosimilar rituximab use ORR as primary endpoints
  - For trastuzumab, pathologic complete response (pCR) in the neoadjuvant setting may be the most sensitive endpoint
  - Long-term survival may be used as a secondary endpoint

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

Topic	Metastatic Population	Neoadjuvant/Adjuvant Population
PK	✘ Affected by patient's health status & tumor burden	✓ Homogeneous population can be selected ✘ Variability is also observed
	✓ Healthy Volunteers	
PD	✘ Clinically validated PD marker not available	
Clinical efficacy/safety	✘ • Difficult to select homogeneous group • Need to control and stratify for multiple factors (eg, 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

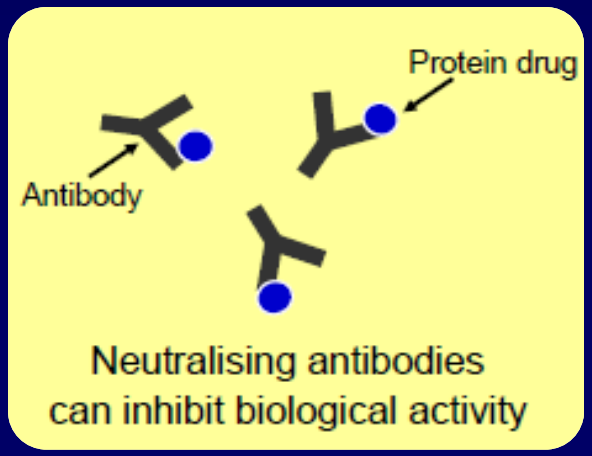
Immunogenicity: Important Component of the Safety Profile and Clinical Trial of a Biosimilar Antibody

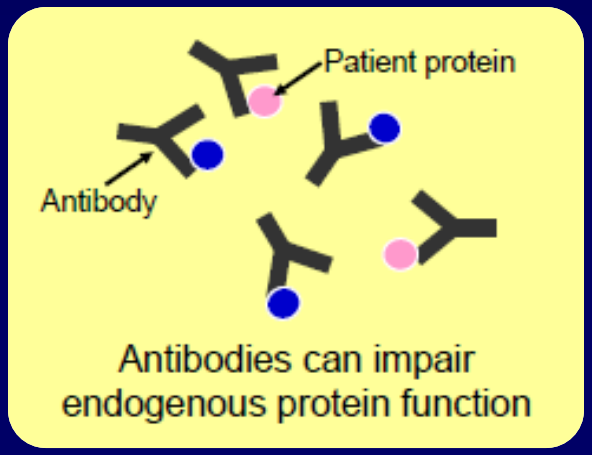
- **Biopharmaceutical substances (ie, monoclonal antibody) can cause immune reactions that lead to anti-drug antibody (ADA)**

- **Possible effects of ADA:**
  - **ADAs can influence, reduce or even neutralize efficacy of monoclonal antibodies and lead to a loss of efficacy and a developed resistance to the reference product**
  - **ADAs can cause autoimmune illnesses, examples: pure red cell aplasia (PRCA), autoimmune thrombocytopenia (ITP)**

Immunogenicity: Important Component of the Safety Profile and Clinical Trial of a Biosimilar Antibody

- Immune response can be triggered by product/process-related factors (eg, product instability, manufacturing process)
- Immunogenicity in humans can not be predicted from animal data -> absolute need for comparative clinical trials including test for neutralizing Abs and PK/PD data





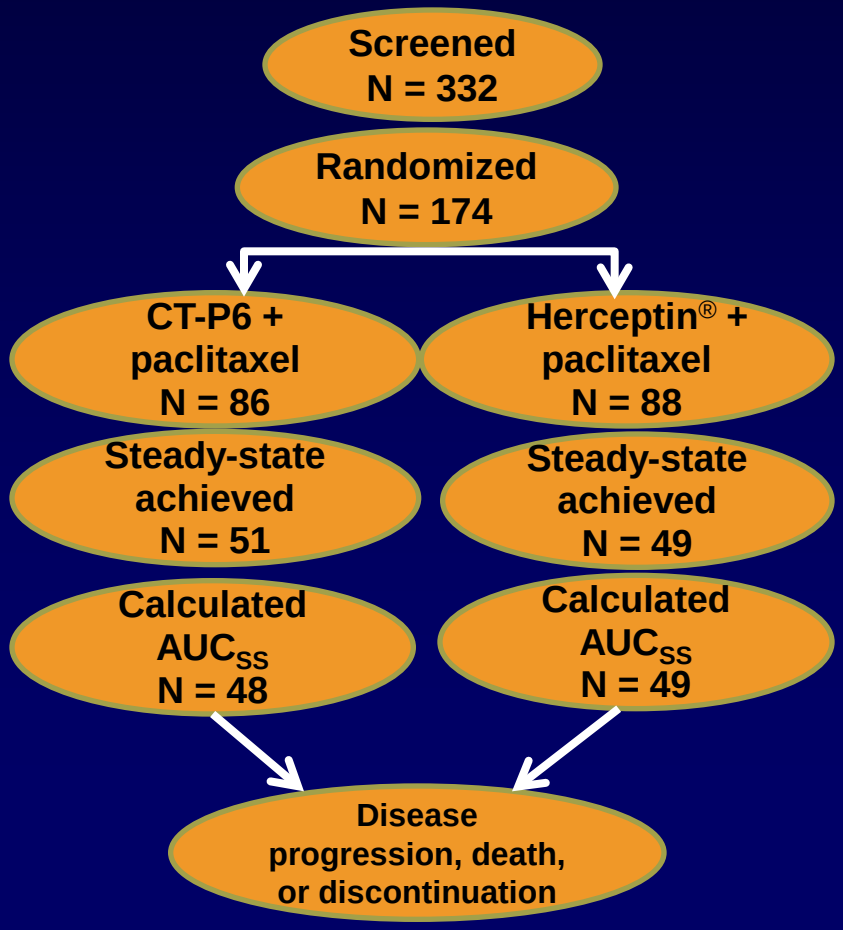
Clinical Trials of Biosimilar Trastuzumab

- **CT-P6***
- **PF-05280014***

*Not auhorized by the European Medicines Agency

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

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

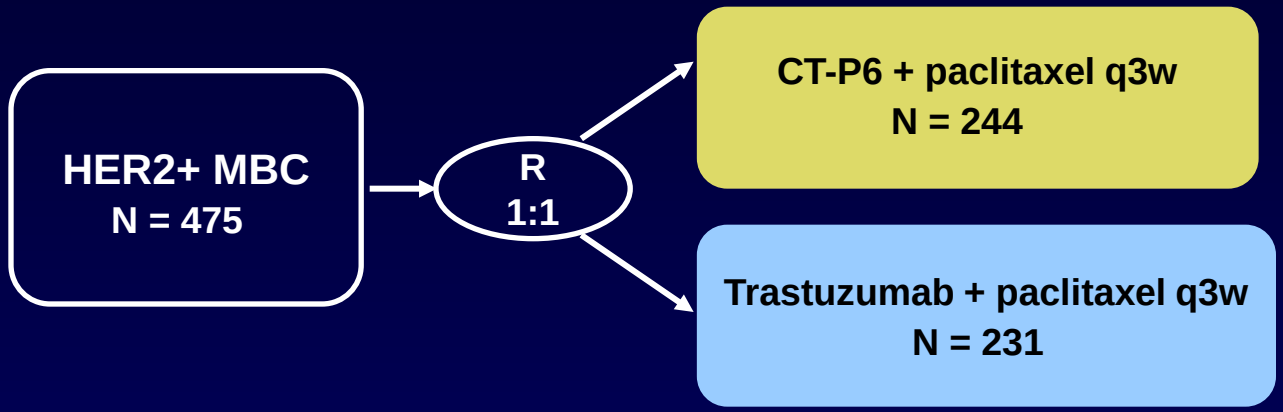
Parameter	Treatment	N	Geometric mean	% CV	Ratio, %	90% CI	*P* value
AUC_{SS} (µgh/mL)	CT-P6	48	32,000	43.5	104.57	93.64, 116.78	.5029
	Herceptin	49	30,600	30.9			
$C_{trough\ SS}$ (µg/mL)	CT-P6	51	19.5	37.0	101.35	87.94, 116.82	.8754
	Herceptin	49	19.2	39.6			

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.

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



Primary Endpoint: Overall Response Rate (ORR)

Inclusion Criteria:

- MBC with measurable lesions
- HER2 + IHC or FISH centrally confirmed
- No prior trastuzumab and/or chemotherpy 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

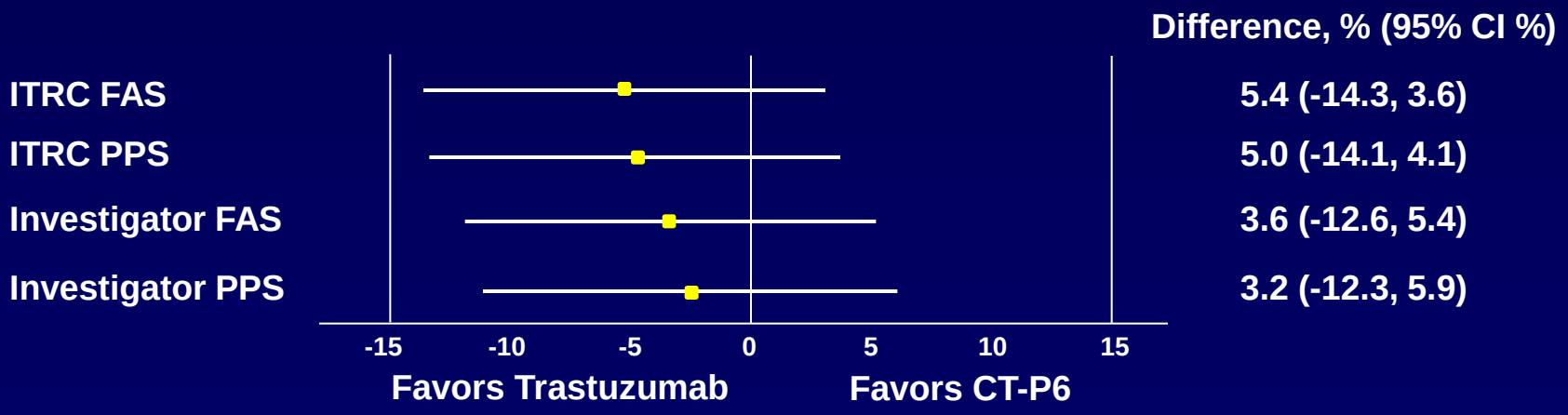
Im YH, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 629.

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.

Compare: Overall Response Rate

	ITRC		Investigator	
	CT-P6 + Paclitaxel (n = 244)	Trastuzumab + Paclitaxel (n = 231)	CT-P6 + Paclitaxel (n = 244)	Trastuzumab + 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]	

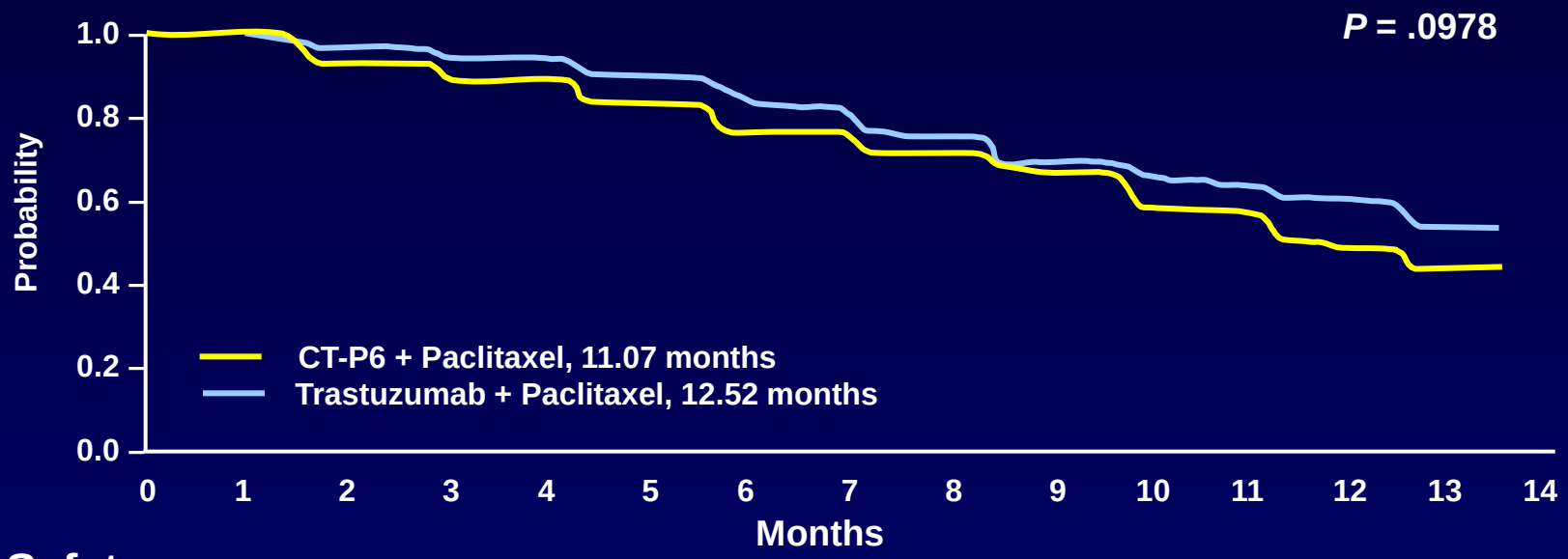


FAS, Full analysis set; PPS, per protocol patients set
Difference in proportion of complete response or partial response. Confidence interval estimated using the exact method.

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 trastuzumab (Herceptin)**
  - **No immunogenicity data available**

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

Safety

	CT-P6 + Paclitaxel		Trastuzumab + 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

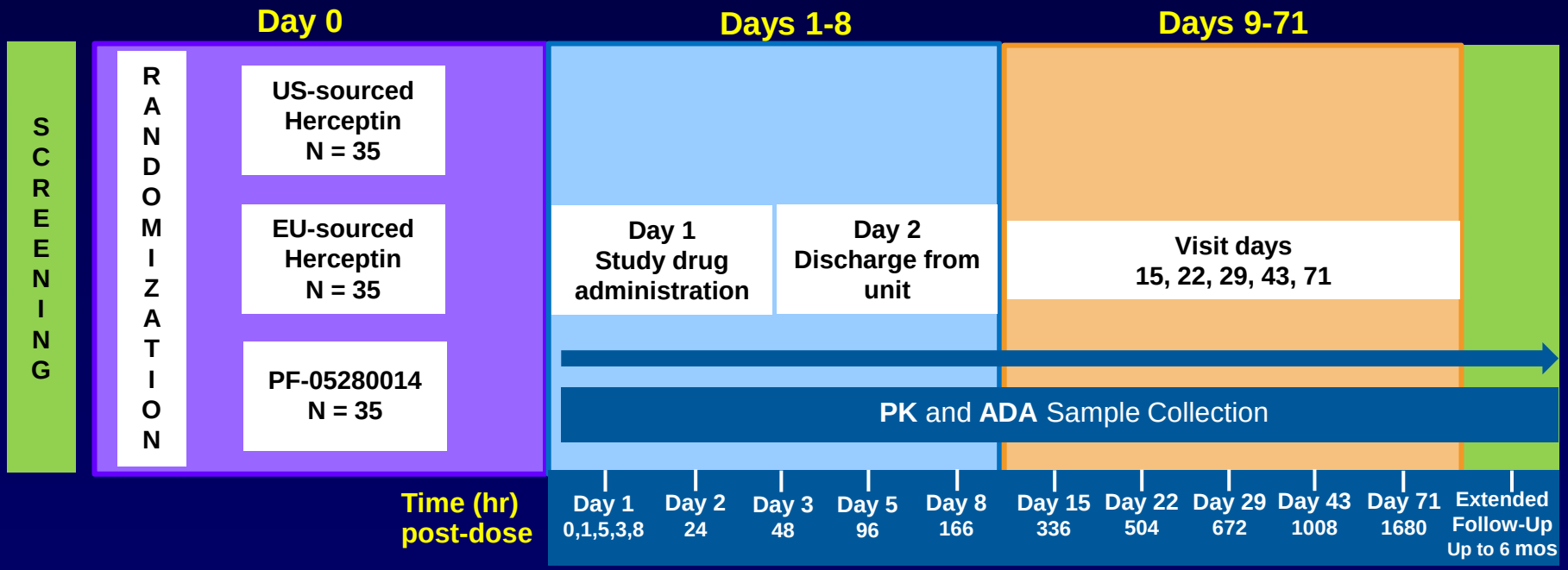
Im YH, et al. *J Clin Oncol*. 2013;31(suppl): Abstract 629.

Current Status: CT-P6

- CT-P6 (branded Herzuma) has been approved by the Korean Ministry of Food and Drug Safety for all indications of Herceptin®, including gastric cancer
- No application has been submitted to the EMA or other regulatory bodies
- Phase III trial of CT-P6 vs Herceptin® in 532 women with HER2+ early breast cancer is planned (NCT02162667)
  - Primary endpoint: pathologic complete response after surgery and 8 cycles neoadjuvant therapy
  - Current status: Planned, not yet enrolling

A Phase I Pharmacokinetics Trial Comparing PF-05280014 and Trastuzumab 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, trastuzumab-US, or trastuzumab-EU

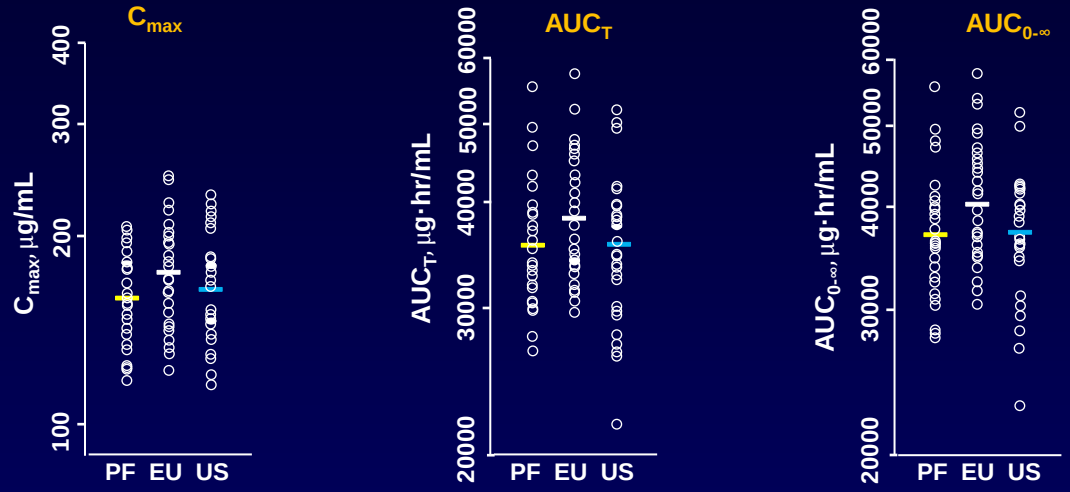


- Primary endpoints
  - Maximum serum concentration (C_{max}) of the administered mAb
  - Area under the serum concentration-time curve (AUC) from time 0 to the last time point with measurable concentration of the administered mAb (AUC_T)

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

PF-05280014 Phase I Results

Individual and Mean Estimates of C_{max}, AUC_T, and $AUC_{0-\infty}$ of PF-05280014, Trastuzumab-EU, and Trastuzumab-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 µg/mL, µg·hr/mL, respectively. †Test/reference ratio of adjusted geometric means.

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

PF-05280014 Safety

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

	PF-05280014 n = 35	Trastuzumab-EU n = 35	Trastuzumab 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.

Current Status: PF-05280014

- **Two phase III trials of PF-05280014 in breast cancer are planned**
  - **Trial B327002 of PF-05280014 vs Herceptin® in 690 women with metastatic breast cancer (NCT01989676)**
    - **Concomitant therapy: Paclitaxel**
    - **Primary endpoint: ORR**
    - **Current status: Enrolling**
  - **Trial B327-04 of PF-05280014 vs Herceptin® for the neoadjuvant treatment of women with operable HER2+ breast cancer (NCT02187744)**
    - **Concomitant therapy: Docetaxel and paclitaxel**
    - **Primary endpoint: Percentage of patients with steady-state drug concentrations >20 µg/mL**
    - **Current status: Planned, not yet initiated**

Some Ongoing Phase III Trials of Trastuzumab Biosimilars

	ABP-980 (Amgen)	BCD-022 (Biocad)	SB3 (Samsung)
Trial identifier	NCT01901146	NCT01764022	NCT02149524
Trial design	Randomized double-blind	Randomized	Randomized double-blind
Comparator	Herceptin	Herceptin	Herceptin
Disease	EBC	MBC	EBC
Chemo	Epirubicin, Cyclophosphamide, Paclitaxel	Paclitaxel	NA
Endpoints	pCR	RR, PK Safety, Immunogenicity	pCR
No of pts	588	110	498
Status	Ongoing	Ongoing	Ongoing

Ongoing Trials of Trastuzumab Biosimilars

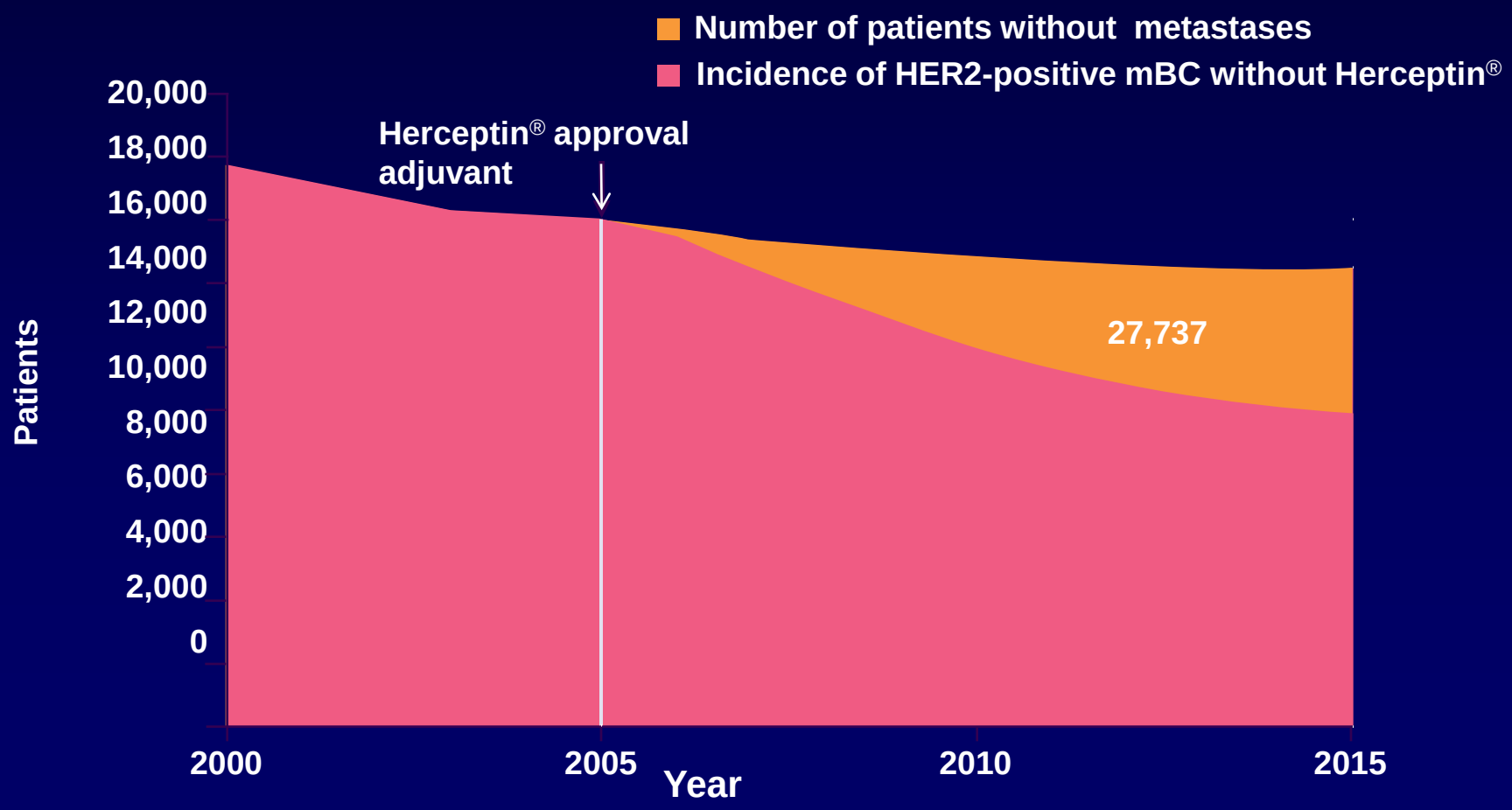
Companies Developing Trastuzumab Biosimilars

Company	Biosimilar Name	Status
Celltrion	CT-P6	Global phase III trial completed (IM ASCO 2013 #629), approved in Korea; application pending in other countries
Biocon	CANM ab	Phase III trial completed in India, but results pending, approval in India blocked by court injunction
BIOCAD	BCD-022	Phase III trial ongoing in Russia, India, Ukraine, and Belarus
Amgen, Synthon, Actavis	ABP 980	Phase I trial complete in Europe and phase III trial recruiting
BioCND and Genor	GB221	Phase I trial completed in Australia
Pfizer	PF-05280014	Phase I REFLECTIONS B327-02 trial recruiting
Hospira	NR	Clinical studies ongoing
Dr Reddy's Laboratories	NR	Clinical studies pending
Intas	NR	Clinical studies pending
PlantForm	NR	Clinical studies expected to begin in 2014
Mylan Inc.	Hertraz	Phase III trial completed in India but approval blocked by court injunction
Samsung Bioepis Co	SB3	Phase III trial recruiting in Czech Republic
Shanghai CP Guojan Pharm Co	CMAB302	Phase II trial completed

Thill M, Expert Rev Anticancer Therapy, submitted

Monoclonal Antibody
Herceptin®

Adjuvant treatment with Herceptin® can reduce a recurrent breast cancer in 28,000 patients in the 5 biggest countries in the EU within 10 years



Weisgerber-Kriegl U, et al. *J Clin Oncol.* 2008;26(May 20 Suppl): Abstract 6589.

First-Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

	Oxford / AGO LoE	/ GR	
➢ Docetaxel + trastuzumab + pertuzumab	1b	A	++
➢ Paclitaxel + trastuzumab + pertuzumab	5	D	+
➢ T-DM 1 (relapse within 6 months after taxane and trastuzumab-pretreatment)	2b	B	+
➢ 1st-Line chemotherapy* + trastuzumab	1b	B	+
➢ Trastuzumab mono	2b	B	+/-
➢ Taxanes + lapatinib	1b[a]	B	+/-
➢ Trastuzumab + aromatase inhibitors (if ER+)	2b	B	+/-**
➢ Lapatinib + aromatase inhibitors (if ER+)	2b	B	+/-**

*Taxanes; vinorelbine; paclitaxel/carboplatin; capecitabine/docetaxel

**see Chapter Endocrine +/- targeted

Second-Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (If Pretreatment With Trastuzumab)

	Oxford / AGO LoE	/ GR	
➢ T-DM 1	1b	A	++
➢ Capecitabine + lapatinib	1b	B	+
➢ Trastuzumab + lapatinib (HR neg. disease)	2b	B	+
➢ TBP: 2nd-line chemotherapy + trastuzumab	2b	D	+
➢ Taxane + trastuzumab + pertuzumab	5	D	+
➢ Any other 2nd-line chemotherapy* + trastuzumab + pertuzumab	5	D	+/-
➢ Trastuzumab + aromatase inhibitors (if ER+)	3b	B	+
➢ Lapatinib + aromatase inhibitors (if ER+)	3b	B	+

*e.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel (toxicity!)

Conclusions

- Several biosimilars of trastuzumab are currently in development, including phase III trials
- Biosimilars are tested in a reduced clinical trial program, so special attention must be paid to the patient population and endpoints of these trials
  - A trial examining response rate in metastatic breast cancer may not be appropriately sensitive
  - Pathologic complete response as an endpoint for a clinical trial in neoadjuvant breast cancer represents a more sensitive approach
- How trastuzumab biosimilars are tested in clinical trial may determine how they are used in the clinic—a biosimilar only tested in the metastatic population might not be appropriate for the adjuvant setting

Thank You!