The Global Need for a Trastuzumab Biosimilar for Patients With HER2-Positive Breast Cancer

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Abstract

Trastuzumab improves survival outcomes for patients with HER2-positive (HER2$^+$) breast cancer, yet not all such women receive this important therapy. Trastuzumab was approved by the US Food and Drug Administration in 1998 and the European Medicines Agency in 2000 as treatment for HER2$^+$ metastatic breast cancer (MBC). Observational studies between 2000 and 2015 in patients with HER2$^+$ MBC suggest that nearly 12% in the United States, 27% to 54% in Europe, and 27.1% to 49.2% in China did not receive trastuzumab or any other HER2-targeted agent as first- and/or later-line for treatment of metastatic disease. In 2006, both agencies approved trastuzumab as adjuvant therapy for patients with HER2$^+$ early breast cancer (EBC). Observational studies on real-world treatment patterns for HER2$^+$ EBC between 2005 and 2015 suggest that 19.1% to 59.5% of patients across regions of North America, Europe, Australia, New Zealand, and China did not receive (neo)adjuvant trastuzumab. Data suggest that some patient subgroups, including older patients, those with HER2$^+$/hormone receptor-positive disease, and women with small and/or node-negative HER2$^+$ tumors, were less likely to receive anti-HER2 therapy. Barriers to accessing trastuzumab are multifactorial and include issues related to drug funding and high treatment costs for patients that have been reported worldwide. Herein, we review available literature on the use of, and barriers to, treatment with trastuzumab in patients with HER2$^+$ breast cancer. We also discuss how the availability of safe and effective biosimilars might increase access to trastuzumab and allow greater use of anti-HER2 therapy, potentially improving patient outcomes.

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Introduction

Between 15% and 20% of patients with breast cancer have HER2-positive (HER2$^+$) disease.[1,2] Trastuzumab, a recombinant humanized monoclonal antibody against HER2, was approved by the US Food and Drug Administration (FDA) in 1998 and the European Medicines Agency (EMA) in 2000 for use in patients with HER2$^+$ metastatic breast cancer (MBC).[3,4] Subsequently, trastuzumab was approved by the EMA and FDA as adjuvant therapy (2006) and by the EMA as neoadjuvant therapy (2011) for patients with HER2$^+$ early breast cancer (EBC).[3,4] Furthermore, in 2015, trastuzumab was added to the World Health Organization (WHO) Model List of Essential Medicines.[5]

Targeted therapy with trastuzumab and/or other currently available HER2-directed agents, including pertuzumab, lapatinib, and ado-trastuzumab emtansine (T-DM1), is standard treatment for patients with HER2$^+$ breast cancer, and clinical guidelines recommend trastuzumab-based chemotherapy (along with pertuzumab) as (neo)adjuvant treatment for HER2$^+$ EBC and in the metastatic setting.[6-10] Although trastuzumab was initially evaluated and used in the first-line metastatic setting,[11] in some countries it became common practice to continue trastuzumab at progression, which improves patient outcomes.[12] However, multiple lines of HER2 blockade, as well as combinatorial treatment strategies, have significant cost implications for patients and health care systems.

Patents for several biologic drugs, including trastuzumab, have recently expired or will soon expire,[13] which has stimulated the development of biosimilars. Biosimilars are biologic products that are highly similar to a licensed biologic (ie, the reference or originator product), "notwithstanding minor differences in clinically inactive components," and have no clinically meaningful differences in safety, purity, or potency compared with the reference product.[14-16]

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Biosimilars might increase access to biologics. For example, use of granulocyte colony-stimulating factor in the United Kingdom increased more than 30% in the first 2 years after the introduction of biosimilar filgrastim.[17] Cost savings from the use of a biosimilar also might allow for expanded access to other novel therapies, indirectly leading to better overall health outcomes. For example, a study calculated that the potential cost savings generated by switching 100,000 patients in Germany, France, Italy, Spain, and the United Kingdom from originator epoetin to biosimilar epoetin could support an additional 9770 to 12,913 rituximab, 3912 to 5171 bevacizumab, or 3713 to 4908 trastuzumab treatments.[18]

Access to trastuzumab might be limited for various reasons such as lack of drug funding or because of treatment costs,[19-21] and real-world data show that not all patients with HER2$^+$ breast cancer receive trastuzumab.[22-44] This review discusses the use of, and barriers to, treatment with trastuzumab in patients with HER2$^+$ breast cancer, and how the introduction of trastuzumab biosimilars might address the needs of patients and the wider health care system.

Patterns of Trastuzumab Use Worldwide

Patterns of Use in EBC

In a 2011 international physician survey, 92% of respondents (N = 151) indicated that they routinely recommend 1 year of adjuvant trastuzumab; however, 47% reported having at least 1 case within the previous year in which trastuzumab was recommended but treatment could not be started.[19] Failure to start recommended trastuzumab was more commonly reported by physicians from low- and middle-income countries (75%) than high-income countries (40%; $P = .005$) and most often cited by respondents from Africa (100%), Asia (89%), and Latin America (80%).[19] Observational studies on real-world treatment patterns in patients diagnosed with and/or treated for HER2$^+$ EBC between 2005 and 2015 suggest that 19.1% to 59.5% in the United States, Canada, Australia, New Zealand, United Kingdom, The Netherlands, Germany, and China did not receive neoadjuvant or adjuvant trastuzumab (Table 1).[23-25,30-32,34-37,39-41,44,45] Use of trastuzumab was somewhat less in patients with small (≤1 cm) and/or node-negative HER2$^+$ tumors,[28,30,40,41,44] in whom the benefits of adjuvant trastuzumab therapy are somewhat controversial.[7,9,10]

Several studies conducted between 2006 and 2013 also suggest that older patients with HER2$^+$ EBC and patients with HER2$^+$/hormone receptor (HR)-positive disease were less likely to receive trastuzumab-based therapy (Table 1).[24,30,34,35,39,41] Of these patients, approximately 50% of those aged 65 years or older in the United States, 47.1% (32 patients) older than 69 years in Germany, and 67% (176 patients) older than 70 years in Australia and New Zealand did not receive trastuzumab-based therapy (Table 1).[34,35,39,41] Lesser use of trastuzumab in older patients might reflect, in part, increased comorbidities. However, among women of this older age group in the United States, those who resided in impoverished neighborhoods or who were black were less likely to receive trastuzumab-based therapy (Table 1).[35,39] Similar to the overall population, older women with more favorable disease characteristics, including those with HR$^+$ tumors, small tumors, or no lymph node involvement, were also less likely to receive adjuvant trastuzumab.[35,39]

Patterns of Use in MBC

A prospective, US-based observational cohort study (registHER) that enrolled patients with HER2$^+$ MBC between 2003 and 2006 reported that approximately 12% (121 patients) did not receive first-line trastuzumab-based systemic therapy (Table 2).[22,26,27,29,33,38,42,43,45] The percentage of registHER patients with HER2$^+$ MBC who did not receive trastuzumab-based therapy as first- or later-line treatment was somewhat greater among patients with HR$^+$ tumors (17%, 90 patients), older patients (75 years or older; 23%, 15 patients), and those with central nervous system metastases (approximately 32%, 119 patients; Table 2).[22,29,38] Similarly, preliminary results from another US-based, observational cohort study in patients diagnosed with HER2$^+$ MBC between 2009 and 2011 showed that approximately 45% (34 patients) of those with brain metastases did not receive first-line treatment with trastuzumab.[33] This might reflect concerns regarding the penetration of trastuzumab, although recent data with T-DM1 as well as etirinotecan (a pegylated irinotecan) show that macromolecules can be effective treatment against brain metastases.[46,47]

An observational study of patients in China with HER2$^+$ invasive breast cancer who received hospitalized therapy between 2010 and 2015 reported that 27.1% of those with metastatic disease did not receive trastuzumab at any time after diagnosis and 49.2% did not receive trastuzumab in the first-line setting.[45] An analysis of drug utilization among patients with HER2$^+$ breast cancer in Sweden estimated that approximately 27% of those with metastatic disease did not receive trastuzumab in 2004.[42] However, this estimate was only 4 years after trastuzumab was approved in Europe, during which time trastuzumab use rose from 11% (2000) to 73% (2004).[42] A European-based, observational cross-sectional study of patients diagnosed with or treated for MBC in 2008 showed that approximately 54% (712 patients) of those with HER2$^+$ tumors in France, Germany, Spain, Italy, and the United Kingdom did not receive HER2-targeted or trastuzumab-based systemic therapy as part of their most recent regimen (Table 2).[27] Consistent with US data, treatment differences according to HR status were also evident in Europe. For example, approximately 61% (491 patients) with HER2$^+$/HR$^+$ and 44% (221 patients) with HER2$^+$/HR$^-$ tumors did not receive HER2-targeted therapy as part of their most recent regimen (Table 2).[27] Another study that investigated treatment patterns according to HR and HER2 status in those same 5 European countries and during a similar time frame (2008 and 2010) also showed less frequent use of anti-HER2 therapy among patients with HER2$^+$/HR$^+$ than those with HER2$^+$/HR$^-$ tumors.[26] Overall, across countries, approximately 36% to 74% of patients with HER2$^+$/HR$^+$ and 25% to 49% of those with HER2$^+$/HR$^-$ tumors did not receive anti-HER2 therapy as first-line treatment in the metastatic setting.[26]

Reasons for Patients Not Receiving Anti-HER2 Therapy

Few studies in patients with EBC, and none in patients with MBC, reported reasons for patients not receiving anti-HER2 therapy.[23,25,30,32,36,37,40,44] Furthermore, it is not clear how often HER2 blockade is continued in multiple lines of systemic therapy for metastatic disease. In the adjuvant setting (Table 1), trastuzumab was withheld from patients because of advanced age (11%-23%), increased risk of cardiac toxicity (15%-46.4%), or other comorbidities (approximately 12%).[23,25,36,37,40] In other cases,

Table 1 Observational Studies of Real-World Treatment Patterns in Patients With HER2$^+$ EBC: Use of Neoadjuvant and Adjuvant Trastuzumab

Reference (Country)	Patient Population (Setting)	Study Observation Period	Patients With HER2$^+$ BC, n	Patients Received Trastuzumab, %	Patients Did Not Receive Trastuzumab, %	Reasons for Withholding Trastuzumab
Overall Population						
Kurian et al[30] (US)	Stage I-III BC (adjuvant)	Dx 2004-2007; Tx within 1 year of Dx	287[a]	68.3	31.7	NR
Stenehjem et al[37] (US)	Women with stage I-IIIA BC (adjuvant)	Dx January 2005 to December 2012; follow-up until April 2013 or death, whichever occurred first	245	75.9[b]	24.1	Low risk of recurrence: 30.5% Unknown: 18.6% Age or comorbidity: 16.9% Loss to follow-up: 15.3% Patient declined: 11.9% Patient relocated: 6.8%
DaCosta Byfield et al[24] (US)	Commercially insured (aged ≥18 years) with HER2$^+$ stage I-III BC (neoadjuvant or adjuvant)	Dx January 2008 to August 2013	915	72[c]	28	NR
			HR$^+$: 662	69	31	
			HR$^-$: 253	80	20	
				$P < .01$[d]		
Noonan et al[32] (CA)	HER2$^+$ stage I-III BC (adjuvant)	Dx January 2005 to January 2010; median follow-up 25 months	148	76	24	Small tumor size (T1a), comorbidities, and patient preference
Zurawska et al[44] (CA)	Women (≥18 years) with stage I-III invasive BC (adjuvant)	Dx January 2005 to December 2006; median follow-up 62 months (range, 17 days to 85 months)	94	80.9	19.1	Subcentimeter tumors (presumably reason for withholding trastuzumab): 55.5% No reason provided: 27.8% Declined systemic Tx: 16.7%
Coulson et al[23] (UK)	Nonmetastatic BC (adjuvant)	Dx September 2007 to August 2008	199	67	33	Age >75 years: 23% Patient refusal: 20% Clinician recommend/unfavorable risk-benefit ratio: 19% High cardiac risk: 15% Other comorbidities: 12% General frailty/poor PS: 6% Unfit for surgery/primary endocrine therapy: 6%
Webster et al[40] (UK)	HER2$^+$ stage I-III BC (adjuvant)	Dx January 2005 to December 2008	338	70.7	29.3	Not treated with CTX (n = 71; 71.7%): reasons for withholding trastuzumab not reported
						Treated with CTX (n = 28; 28.3%): Cardiac comorbidity: 46.4% Patient refusal: 25.0% Lack of funding in period before NICE approval: 10.7% Clinician recommendation/perceived low recurrence risk: 10.7% Disease recurrence before trastuzumab: 7.4%

Table 1 Continued

Reference (Country)	Patient Population (Setting)	Study Observation Period	Patients With HER2$^+$ BC, n	Patients Received Trastuzumab, %	Patients Did Not Receive Trastuzumab, %	Reasons for Withholding Trastuzumab
de Munck et al[25] (NL)	Women with invasive nonmetastatic BC (adjuvant)	Dx September 2005 to January 2007	1928	55	45	NR
			Received adjuvant CTX: 1114	94	6	No reason given: 36% Cardiac toxicity: 29% Patient refusal: 21% Age: 11% Other: 3%
Seferina et al[36] (NL)	Stage I-III invasive BC (adjuvant)	Dx January 2005 to December 2007; follow-up to October 2011	476	48.3	51.7	NR
			Eligible for adjuvant trastuzumab per guidelines: 251	78.1	21.9	Cardiac comorbidities: 33% Borderline indication for trastuzumab: 20% Patient preference: 15% Not yet prescribed by hospital (Dx before March 1, 2005): 13% Other comorbidities: 11% Early stop of CTX because of side effects: 7% Other disease characteristics: 2%
Liebrich et al[31] (GE)	BC (neoadjuvant, adjuvant, palliative)	Dx in 2007; follow-up data up to May 2009	Invasive BC: 785	61	39	NR
			Eligible for adjuvant trastuzumab per guidelines: 433	77	23	NR
Peters et al[34] (GE)	Women with nonmetastatic invasive BC (adjuvant)	Dx and biopsy in 2006-2011; follow-up data up to 2013	331	77	23	NR
Whitfield et al[41] (AU and NZ)	Invasive BC (adjuvant)	Tx January 2006 to December 2008	Tx in 2008: 908	74	26	NR
Li et al[45] (CN)	HER2$^+$ invasive BC (neoadjuvant or adjuvant)	Tx January 1 2010 to October 30 2015	1017	40.5	59.5	NR
Older Patients						
Reeder-Hayes et al[35] (US)	Women (≥65 years) with HER2$^+$ stage I-III invasive BC (neoadjuvant or adjuvant)	Dx in 2010 and 2011; Tx within 1 year of Dx	1362	49	51	NR
			White: 1162	50	50	
			Black: 104	40	60	
			Other minority: 96	52	48	
Vaz-Luis et al[39] (US)	Women (≥66 years) with HER2$^+$ stage IB-III invasive BC without history of CHF (adjuvant)	Dx in 2010-2011; Tx within 9 months of Dx	770	55.6	44.4	NR
			66-70 years: 252	71.0	29.0	
			71-75 years: 170	68.8	31.2	
			76-80 years: 152	47.4	52.6	

Table 1 Continued

Reference (Country)	Patient Population (Setting)	Study Observation Period	Patients With HER2$^+$ BC, n	Patients Received Trastuzumab, %	Patients Did Not Receive Trastuzumab, %	Reasons for Withholding Trastuzumab
			≥80 years: 196	30.6	69.4	
					$P < .001$[d]	
			Non-Hispanic white: 620	56.5	43.6	
			Non-Hispanic black: 45	35.6	64.4	
			Hispanic/other/unknown: 105	59.1	40.9	
					$P = .02$[d]	
			HR$^+$: 557	51.9	48.1	
			HR$^-$: 213	65.3	34.7	
					$P < .001$[d]	
Peters et al[34] (GE)	Women with nonmetastatic invasive BC (adjuvant)	Dx and biopsy 2006-2011; follow-up data up to 2013	<50 years: 75	93.3	6.7	NR
			50-69 years: 188	79.3	20.7	
			>69 years: 68	52.9	47.1	
				$P < .001$[d]		
Whitfield et al[41] (AU and NZ)	Invasive BC (adjuvant)	Tx January 2006 to December 2008	≤70 years: 1741	75	25	NR
			>70 years: 264	33	67	
				$P < .001$[d]		
Patients With Small and/or Node-Negative Tumors						
Zurawska et al[44] (CA)	Women (≥18 years) with stage I-III invasive BC (adjuvant)	Dx January 2005 to December 2006; median follow-up 62 months (range, 17 days to 85 months)	Node-negative tumors <1 cm: 13	23.1	76.9	NR
Webster et al[40] (UK)	HER2$^+$ stage I-III BC (adjuvant)	Dx January 2005 to December 2008	Node-negative tumors ≤1 cm: 25	28	72	NR
Whitfield et al[41] (AU and NZ)	Invasive BC (adjuvant)	Tx January 2006 to December 2008	Tx in 2008, node-positive: 450	84	16	NR
			Tx in 2008, node-negative tumors >1 cm: 326	71	29	NR
			Tx in 2008, node-negative tumors ≤1 cm: 132	43	57	NR

Abbreviations: AU = Australia; BC = breast cancer; CA = Canada; CHF = congestive heart failure; CN = China; CTX = chemotherapy; Dx = diagnosis; EBC = early breast cancer; GE = Germany; HR = hormone receptor; NICE = National Institute for Health and Clinical Excellence; NL = The Netherlands; NZ = New Zealand; PS = performance status; Tx = treatment; UK = United Kingdom; US = United States.

[a]Analysis of trastuzumab use was limited to 2006-2007 because adjuvant trastuzumab was not approved by the US Food and Drug Administration until 2006.

[b]Includes 1 patient who received adjuvant lapatinib.

[c]Includes 4 patients who received adjuvant lapatinib in addition to trastuzumab.

[d]Statistically significant difference.

Table 2 Observational Studies of Real-World Treatment Patterns in Patients With HER2$^+$ MBC: Use of Anti-HER2 Therapy[a]

Reference (Country)	Patient Population (Setting)	Study Observation Period	Patients With HER2$^+$ MBC, n	Patients Did Receive HER2-Targeted Therapy	Patients Did Not Receive HER2-Targeted Therapy
Yardley et al[43] (US)	HER2$^+$ MBC (first-line)	Enrolled December 2003 to February 2006; followed until death, disenrollment, or study end (June 2009)	De novo: 327	88.1%	11.9%
			Recurrent: 674	87.8%	12.1%
Kaufman et al[29] (US)	HER2$^+$ MBC (first-line)	Enrolled December 2003 to February 2006; followed until death, disenrollment, or study end (June 2009)	<65 years: 792	85%	15%
			65-74 years: 144	81%	19%
			≥75 years: 65	77%	23%
Tripathy et al[38] (US)	HER2$^+$ MBC (first-line)	Enrolled December 2003 to February 2006; followed until death, disenrollment, or study end (June 2009)	HR$^+$: 530	83%	17%
Patt et al[33,b] (US)	HER2$^+$ MBC (first-line)	Dx January 2009 to December 2011; follow-up through November 2014	Brain metastases and systemic Tx: 75	54.7%	45.3%
Brufsky et al[22] (US)	HER2$^+$ MBC (first- or later line)	Enrolled December 2003 to February 2006; followed until death, disenrollment, or study end (June 2009)	CNS metastases: 377	68.4%	31.6%
Wilking et al[42] (SE)	HER2$^+$ MBC (first- or later line)	Last quarter 2000 through end of 2004[c]	2000: 190	11%	89%
			2001: NR	19%	81%
			2002: NR	33%	67%
			2003: NR	47%	53%
			2004: NR	73%	27%
Gao et al[27] (FR, GE, IT, SP, UK)	Women (≥21 years) with MBC (first- or later line)	Dx or Tx at any time during 2008	1311	46%	54%
			HR$^+$: 809	39%	61%
			HR$^-$: 502	56%	44%
DeKoven et al[26]	Patients (≥21 years) with MBC (first-line)	First Dx or relapse of MBC in July 2008 and June 2010			
FR			HR$^+$: 4887	63.8%	36.1%
			HR$^-$: 3356	74.9%	25.1%
GE			HR$^+$: 9491	40.5%	59.5%
			HR$^-$: 5417	57.9%	42.1%
IT			HR$^+$: 5294	37.4%	62.6%
			HR$^-$: 3464	65.5%	34.5%
SP			HR$^+$: 2106	35.5%	64.5%
			HR$^-$: 1162	67.8%	32.2%
UK			HR$^+$: 5382	26.5%	73.5%
			HR$^-$: 3471	51.3%	48.7%
Li et al[45] (CN)	HER2$^+$ invasive BC first-line	Tx January 1, 2010 to October 30, 2015	720	50.8%	49.2%
	Overall			72.9%	27.1%

Abbreviations: BC = breast cancer; CN = China; CNS = central nervous system; Dx = diagnosis; FR = France; GE = Germany; HR = hormone receptor; IT = Italy; MBC = metastatic breast cancer; NR = not reported; SE = Sweden; SP = Spain; Tx = treatment; UK = United Kingdom; US = United States.
[a]HER2-targeted therapy consisted of trastuzumab in 7 studies,[29,33,38,42,43,45] trastuzumab and/or lapatinib in 3 studies.[22,26,27]
[b]Preliminary results of a study presented at the 2016 American Society of Clinical Oncology Quality Care Symposium.[33]
[c]Percentages of patients who received trastuzumab was calculated using drug sales data received from the Retail Drug Supplier in SE, treatment recommendations by the Swedish Breast Cancer Group, cancer and death statistics received from the National Board of Health and Welfare, general statistics (eg, population) obtained from Statistics Sweden, an estimated frequency of HER2 positivity of 25%, a treatment duration of 38 weeks, and an estimated use of 1 unit of trastuzumab per patient per week.

patients declined systemic therapy or specifically refused trastuzumab (11.9%-25%) or their oncologist advised against its use because of a perceived low risk of recurrence or unfavorable risk–benefit ratio (10.7%-30.5%).[23,25,32,36,37,40,44]

Less frequently (2%-15.3%), trastuzumab was withheld because of other patient-related factors (eg, loss to follow-up, general frailty/poor performance status) or disease characteristics (Table 1).[23,25,36,37,40] In 1 United Kingdom-based study conducted

between 2005 and 2008, 10.7% (3 patients) did not receive adjuvant trastuzumab because they were treated before National Institute of Clinical Excellence approval of trastuzumab in 2006 made funding for trastuzumab in this setting widely available.[40] Finally, 18.6% (11 patients) in 1 US-based study, 27.8% (5 patients) in 1 Canadian-based study, and 36% (24 patients) in 1 European-based study (The Netherlands) did not receive trastuzumab for unknown or undocumented reasons.[25,37,44]

Summary

Observational studies suggest that, in the past, up to approximately 60% of patients with HER2$^+$ breast cancer might not have received anti-HER2 therapy at some point during their course of treatment. Interpretation of these findings might be limited by the accuracy of data reporting, and the analysis does not consider use of anti-HER2 therapy in countries where trastuzumab is approved but data for treatment patterns are not available. Additionally, estimates of trastuzumab use at the time of data collection or reporting might not be reflective of current treatment patterns or guidelines. It should also be noted that several studies in patients with EBC reported findings on the basis of data from patients who were diagnosed and/or treated between 2005 and 2008 (Table 1),[23,25,30,31,36,40,41,44] which might not have captured or been sufficient to fully characterize trastuzumab use after expanded approvals for adjuvant or neoadjuvant therapy.

Furthermore, the decision not to treat patients with trastuzumab might have been appropriate in some situations, such as in patients at increased risk of cardiac toxicity or other comorbidities.[3,4] Indeed, evidence suggests that up to nearly one-half of patients with HER2$^+$ EBC who did not receive adjuvant trastuzumab might not have been eligible because of cardiac or other comorbidities.[23,25,36,40] In addition, the prevalence of cardiovascular disease might be associated with demographic factors (eg, age or race),[48] which could explain, at least in part, why certain patient subgroups appeared less likely to receive HER2-targeted therapy. Nevertheless, real-world data show that not all patients with HER2$^+$ breast cancer receive HER2-targeted agents, suggesting there might be opportunities for increasing access to optimal anti-HER2 therapy.

Barriers to Accessing Trastuzumab

Physicians might decide not to prescribe anti-HER2 therapy in situations where such treatment has regulatory approval but is not funded or reimbursed. A survey of oncologists in the United States and emerging markets (Brazil, Mexico, Turkey, and Russia) showed that most physicians reported "always" or "frequently" prescribing trastuzumab for patients with HER2$^+$ breast cancer (neoadjuvant, 73%; adjuvant, 92%; metastatic, 92%). However, 31% (between 10% in the United States and 76% in Russia) of physicians in these countries reported there had been at least 1 instance in which they had to cancel or delay treatment because of reimbursement issues, although it was not stated how often this precluded trastuzumab use.[21] Furthermore, among the small percentage of respondents who reported "not so often," "rarely," or "never" prescribing trastuzumab, between 37% and 49% considered lack of drug funding a barrier to use in the neoadjuvant, adjuvant, and metastatic settings.[21] Reimbursement of anti-HER2 therapy also varies across Europe, which might create disparities in accessing trastuzumab.[20] For example, trastuzumab is on formulary and available at low or no out-of-pocket cost to patients with HER2$^+$ breast cancer throughout Western Europe; however, in several Eastern European countries it is not reimbursed or as highly subsidized as in Western Europe, leaving patients responsible for up to the full cost of treatment.[20]

Reimbursement decisions are complex and might be influenced by several factors.[49] In many countries, cost-effectiveness information is considered when making decisions about drug funding and reimbursement. Economic evaluations of trastuzumab-based adjuvant systemic therapy performed in high-income countries show that trastuzumab is a highly cost-effective intervention for most patients.[50-52] However, trastuzumab-based adjuvant systemic therapy is not considered cost-effective in several Latin American countries[53] and, like many therapeutic options, uncertainties remain regarding its cost-effectiveness in the metastatic setting.[54] This might be of particular relevance to patients who receive multiple lines of HER2 blockade for treatment of metastatic disease, because the most clinically effective sequence might not be considered cost-effective and, therefore, might not be reimbursed.[55] Controversies surrounding the cost-effectiveness of trastuzumab might contribute to its limited accessibility in some patients and regions.

Another consideration for reimbursement is off-label regulations.[49] Public and/or private payers might not reimburse off-label indications or might provide coverage of off-label indications only when there is sufficient evidence to support that use.[49] This might be relevant to certain subpopulations of patients with HER2$^+$ breast cancer. For example, guidelines recommend trastuzumab-based adjuvant chemotherapy as an option for patients with small node-negative HER2$^+$ tumors, because this patient population remains at higher risk of recurrence than those with node-negative HER2$^-$ tumors of the same size.[7,9,10] However, direct evidence for efficacy of trastuzumab in small, node-negative HER2$^+$ breast cancer is lacking, reflecting the design of registration studies, and trastuzumab is not approved for use in this setting.[3,4,7,9,10]

As a result of reimbursement strategies, some patients might face greater economic burden, which might create a barrier to accessing treatment.[19-21] Among surveyed oncologists in the United States and emerging markets who reported that they "not so often," "rarely," or "never" use trastuzumab, 34% (of 137 respondents) and 42% (of 41 respondents) cited "high out-of-pocket treatment cost for patient" as a barrier to use in the neoadjuvant and adjuvant settings, respectively.[21] In an international survey of physicians (N = 151) conducted in 2011, 27% of respondents who reported at least 1 instance within the previous year in which adjuvant trastuzumab was recommended to a patient who ultimately did not receive it cited cost as the reason for withholding treatment.[19] Furthermore, cost was more often cited by physicians in low- and middle-income countries (73%) than in high-income countries (7%; $P < .0001$) as a reason for withholding adjuvant trastuzumab.[19]

Biosimilars: A Pathway to Increasing Trastuzumab Access in HER2$^+$ Breast Cancer Worldwide

Overview of Biosimilar Development

Traditional pharmaceutical agents are small, low molecular-weight drugs with structures that are readily defined and that can

be exactly replicated using chemical synthesis to create generic copies.[56] Biologics such as trastuzumab are high molecular-weight proteins, often containing post-translational modifications, with complex 3-dimensional structures that are difficult to fully characterize.[56] Unlike small-molecule drugs, biologics are produced in living systems through a series of biological reactions that are inherently variable and sensitive to manufacturing and environmental conditions.[56] Because this has been long recognized, biologic manufacturing is characterized by heterogeneity of the same biologic product produced by different manufacturers and within/between batches from the same manufacturer.

Manufacturers of an originator biologic have extensive knowledge about the manufacturing process of their product.[57] This information is considered proprietary and confidential; therefore, it is not accessible to biosimilar manufacturers. For this reason, and because of their complexity and heterogeneity, biologics cannot be exactly replicated, so the concept of a generic equivalent and regulatory approval requirements for small-molecule generics cannot be applied to biologics.[14,16] Therefore, regulatory agencies such as the EMA and FDA, as well as the WHO, have issued guidelines for the approval of biosimilars.[14-16] All agencies require a rigorous stepwise approach to comparing biosimilar and reference products that begins with extensive structural and functional characterization (Figure 1).[14-16,58] Depending on the outcome of analytical (structural) and in vitro functional assessments, nonclinical in vivo testing might be conducted to further evaluate drug safety,[14-16] if deemed necessary. Animal toxicity studies should show high similarity between the proposed biosimilar and reference products in terms of their pharmacokinetics (PK) and pharmacodynamics (PD).[15,16] These studies might also include immunogenicity assessments to support the interpretation of nonclinical results.[15,16,59] Nonclinical assessments are followed by a limited number of comparative clinical trials that are designed to show a high degree of pharmacologic (PK/PD) and clinical (safety, efficacy, and immunogenicity) similarity to the reference product.[14-16,59]

In the United States, biosimilars are approved following a pathway established by the Biologics Price Competition and Innovation Act of 2009, which places greater emphasis on findings from analytical and functional assessments than a full reference or originator biologics application.[15,60] When analytical and functional similarity are established, biosimilar approval might rely, in part, on the safety and efficacy data that supported the approval of its reference product, thereby reducing the extent of clinical testing compared with that required for originator biologics.[16,60] The need for clinical testing to demonstrate similarity in drug safety and efficacy between the proposed biosimilar and reference product also distinguishes the biosimilar pathway from that of small-molecule generics.

Factors to Consider When Evaluating Trastuzumab Biosimilars

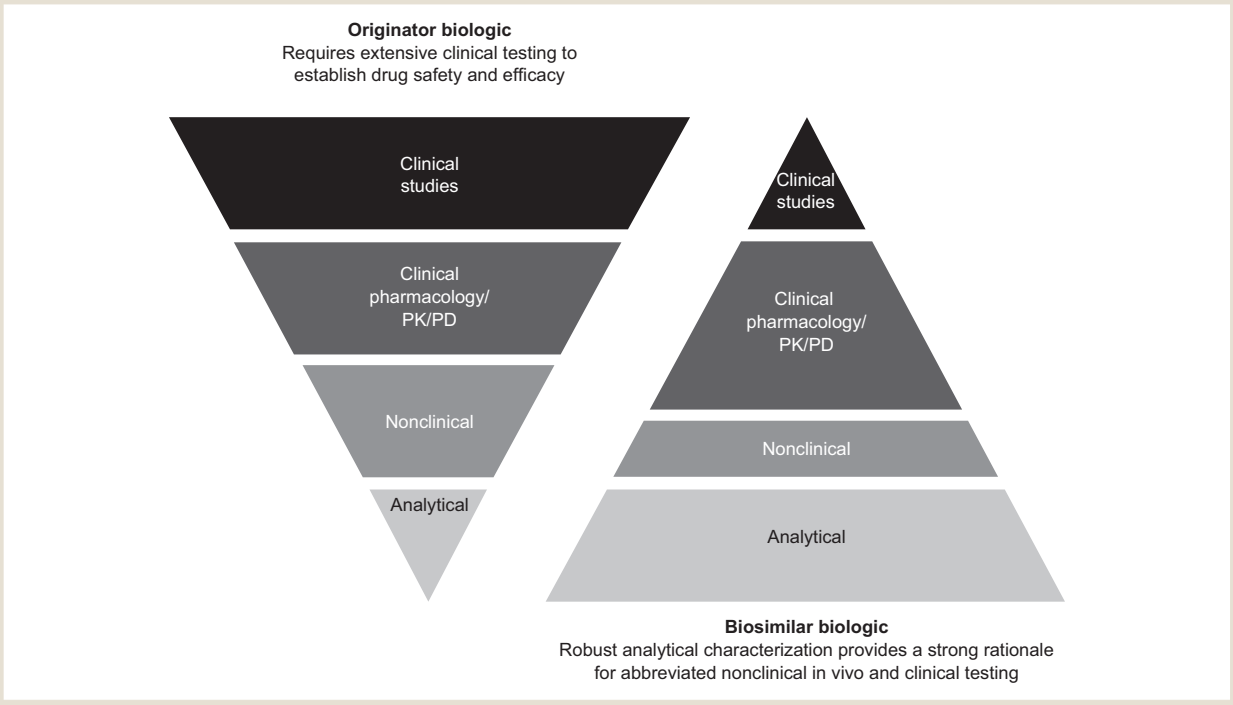
The key to developing high-quality biosimilars rests on a demonstration of physicochemical and functional similarity.[14-16] The large size and complex structure of trastuzumab, as well as differences in manufacturing processes, create the potential for heterogeneous biologic products. Therefore, comparative physicochemical analyses should be selected to detect differences in primary (ie, amino acid sequence), secondary, and higher-order structures, post-translational modifications, product isoforms, and product-related impurities (eg, protein aggregates; Figure 2).[14-16,61,62] To evaluate differences in biologic activity, in vitro studies that measure target binding, tumor cell growth inhibition, and antibody-dependent, cell-mediated cytotoxicity should be selected.[16,63]

On the basis of the totality of the evidence from the preceding steps, a comparative clinical pharmacology (PK/PD) study and a comparative clinical efficacy trial (or trials), including clinical immunogenicity and safety assessments, are conducted to investigate whether there are clinically meaningful differences between a proposed biosimilar and reference product.[14-16,59] This is in contrast to new drug approvals, which require that large phase III clinical trials are conducted in each indication for which licensure is sought. In some cases, efficacy end points that are selected for biosimilar clinical trials will differ from those used in pivotal trials that led to approval of the originator. Furthermore, whereas phase III trials to support new drug approvals are designed to establish "significant" benefit over a comparative agent, which is usually the current standard treatment, biosimilarity studies are designed to show that differences between treatment groups are not clinically meaningful (ie, are small enough that the biosimilar is considered neither superior nor inferior to the reference product and vice versa).[16,64] To this end, the most suitable design for biosimilarity studies is a statistically driven equivalence trial in which equivalence is shown when a given parameter (eg, the confidence interval [CI]) falls within the lower and upper limits of a predetermined equivalence margin.[64]

Regulatory guidelines for biosimilar development recommend using patient populations, treatment settings, and clinical end points that are adequately sensitive to detect all clinically meaningful differences in efficacy, safety, and immunogenicity between a biosimilar and reference product.[15,16,59,63] Furthermore, clinical end points that measure activity (eg, tumor response), or PD measures that correlate with clinical outcome, should be used in a homogenous study population.[16,63] The clinical setting (eg, neoadjuvant or metastatic) and end points (eg, pathologic complete response [pCR] and progression-free survival or objective response rate [ORR] in the neoadjuvant and metastatic settings, respectively) used to establish biosimilarity in $HER2^+$ breast cancer might vary between different trastuzumab biosimilar clinical development programs. However, regulatory agencies will require adequate scientific justification for choice of these and other study design elements.[15,16,59] It is unclear to what extent study design might affect the choice of biosimilars in clinical practice.

Regulatory agencies might also approve a biosimilar for use in other indications for which it has not been studied in a comparative clinical trial with the reference product but for which the reference product is approved; this is known as "extrapolation."[14,16,65] For example, extrapolation of data from comparative clinical studies that establish biosimilarity in $HER2^+$ EBC (eg, neoadjuvant setting) or in patients with metastatic disease could support the approval of trastuzumab biosimilars for use in other indications of trastuzumab. However, extrapolation of data must be scientifically justified on the basis of the totality of the data from all stages of biosimilar development and other evidence that shows the reference product has

Figure 1 The Development of Originator Biologics Versus Biosimilars



Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics.
Adapted from Kozlowski S. Biosimilar biological products: overview of approval pathway under the biologics price competition and innovation act of 2009. Available at: https://c.ymcdn.com/sites/casss.site-ym.com/resource/resmgr/WCBP_Speaker_Slides/2013_WCBP_Kozlowski_Steven.pdf.

similar therapeutic effects in the studied and extrapolated indications. This concept of extrapolation is consistent with the objective of biosimilar development, because it reduces or eliminates the need for duplicative clinical studies. However, it is in contrast to the development of originator drugs, for which specific clinical trial data are required for each indication for which licensure of the product is sought. It is unclear how receptive clinicians will be to the concept of extrapolation.

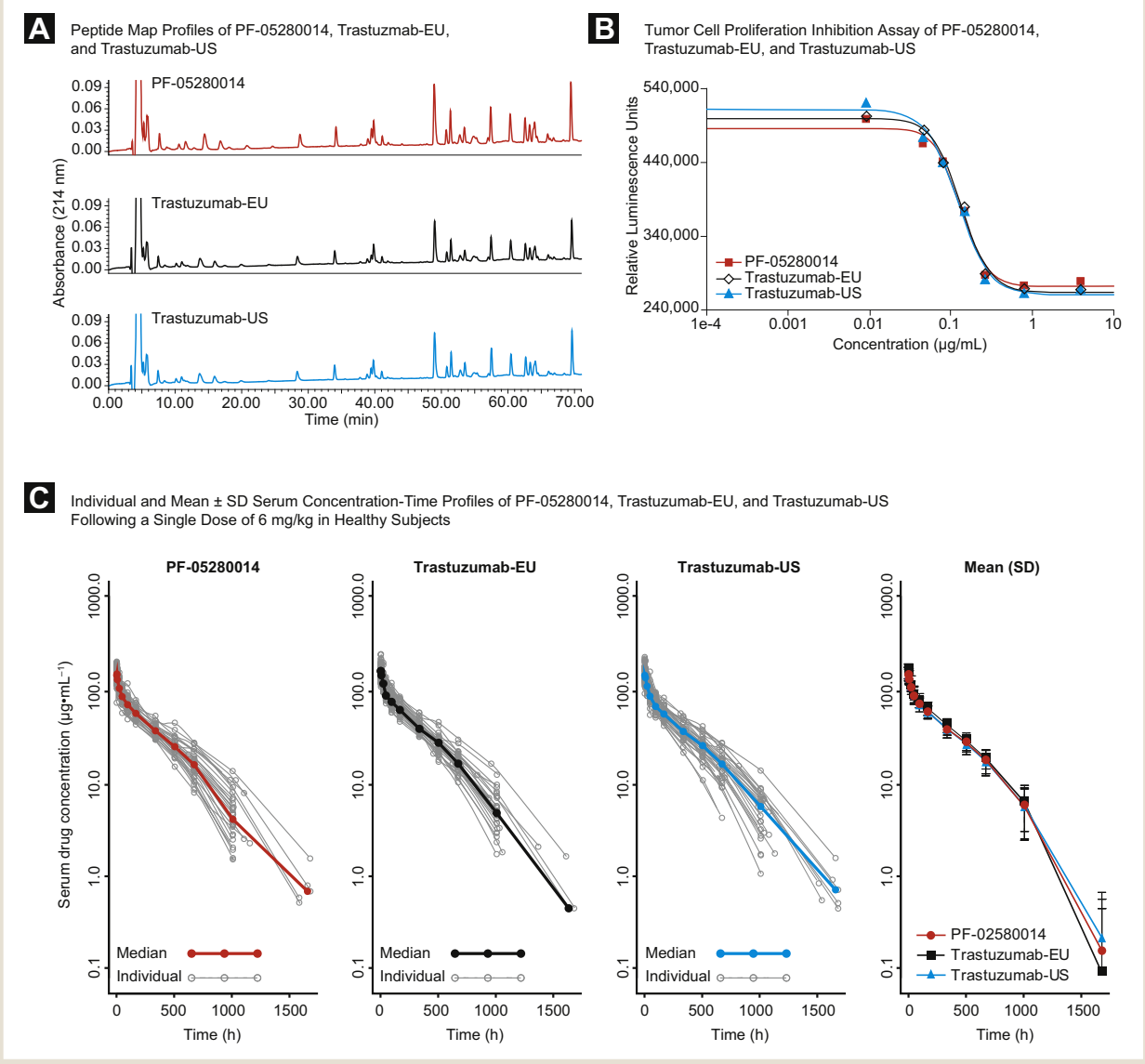
Although the EMA and FDA guidelines for regulatory approval of biosimilars continue to evolve, products that have been approved using this pathway have undergone rigorous comparative assessments to show similarity to a licensed biologic at all stages of the development process, including in a clinical study or studies. In contrast, oncologists should be aware of "noncomparable biotherapeutic products," also known as "intended copies," that have been introduced as biosimilars in some countries (eg, Russia, China, and India) where stringent regulatory pathways for biosimilar approval had not yet been established or were under development at the time these agents were approved.[66-68] Intended copies are not truly biosimilars in the context of this review or widely accepted regulatory perspectives, because they have not met EMA, FDA, or WHO requirements for establishing biosimilarity.[67] In other words, regulatory approval for intended copies did not follow a comparative development pathway with the reference biologic and/or the scientific and clinical evidence used to support the approval is incomplete or absent.[67] Therefore, intended copies might represent a risk to patient safety and drug efficacy because the quality and clinical profile of these products have not been as fully characterized as would be a true biosimilar.

A "similar biologic" was approved by the Drugs Controller General of India in 2013 as a trastuzumab biosimilar and is marketed under the brand name CanMAb (Biocon Ltd, Bengaluru, India), but this product should be considered an intended copy because it was not evaluated using strict criteria for showing biosimilarity to originator trastuzumab.[69] The WHO has issued recommendations for regulatory risk assessment of biologic products licensed following a generic pathway or with limited analytical, nonclinical, and/or clinical evidence.[70] These guidelines might help address concerns regarding the safety and efficacy of intended copies.

Current Development Status of Biosimilar Trastuzumab

Several trastuzumab biosimilars are in development and comparative clinical PK studies in healthy volunteers have shown pharmacologic equivalence and similar immunogenicity and safety profiles between ABP 980 (Amgen, Thousand Oaks, CA), Hercules/Myl-1401O (Mylan NV, Canonsburg, PA), PF-05280014 (Pfizer Inc, New York, NY), and SB3 (Samsung Bioepis Co, Incheon, South Korea) and their respective trastuzumab reference products.[61,71-74] Comparative clinical studies have also shown PK similarity of BCD-022 (Biocad, Saint-Petersburg, Russia)

Figure 2 Examples of Analytical, Functional, and Nonclinical Data to Show Biosimilarity Between a Proposed Biosimilar and Originator Biologic Product. (A) Peptide Map Profiles of PF-05280014, Trastuzumab-EU, and Trastuzumab-US. (B) Tumor Cell Proliferation Inhibition Assay. Functional Similarity of PF-05280014, Trastuzumab-EU, and Trastuzumab-US Was Determined Using an In Vitro Tumor Cell Proliferation Inhibition Assay (CellTiter Glo; Promega, Inc, Madison, WI) With a HER2-Overexpressing Metastatic Breast Carcinoma Cell Line. (C) Individual and Mean ± SD Serum Concentration-Time Profiles of PF-05280014, Trastuzumab-EU, and Trastuzumab-US After a Single Dose of 6 mg/kg in Healthy Subjects



Abbreviations: SD = standard deviation; trastuzumab-EU = trastuzumab sourced from the European Union; trastuzumab-US = trastuzumab sourced from the United States.
Panels A and B adapted with permission from Hurst et al. Comparative nonclinical assessments of the proposed biosimilar PF-05280014 and trastuzumab (Herceptin). BioDrugs 2014; 28:451-9. Panel C reproduced with permission from Yin et al. A randomized phase 1 pharmacokinetic trial comparing the potential biosimilar PF-05280014 with trastuzumab in healthy volunteers (REFLECTIONS B327-01). Br J Clin Pharmacol 2014; 78:1281-90.

and CT-P6 (Celltrion, Incheon, South Korea), each given in combination with paclitaxel, to originator trastuzumab, also in combination with paclitaxel, in patients with HER2$^+$ MBC.[75,76]

Clinical trials comparing safety and efficacy of these proposed or approved trastuzumab biosimilars in patients with EBC or MBC are ongoing (Table 3).[77-100] Primary end points include measures of tumor response, such as pCR in the neoadjuvant setting and ORR in the metastatic setting. Secondary end points vary, but include additional measures of efficacy, such as event-free, progression-free, and overall survival, as well as measures of safety and immunogenicity (ie, antidrug and neutralizing antibodies).

To date, results from some of these trials have only been disclosed at international oncology congresses.[78,82,84,94,95,98,99] A study in patients with HER2$^+$ EBC comparing neoadjuvant treatment with the proposed trastuzumab biosimilar ABP 980 and originator trastuzumab, each after run-in anthracycline-based chemotherapy,

Table 3 Proposed Biosimilars of Trastuzumab With Registered Phase III Clinical Trials for Breast Cancer

Biosimilar (Manufacturer), Brand Name (if approved)	Patient Population (Setting)	Intervention	Primary End Points	Secondary and Other End Points	ClinicaTrials.Gov Identifier	Key Efficacy and Safety Results (Where Available)	Regulatory Filing Status (If Known)
ABP 980 (Amgen, Thousand Oaks, CA)[77,78]	$HER2^+$ EBC (neoadjuvant and adjuvant)	Epi and Cy → ABP 980 and Pac	pCR	EFS, OS, LVEF, AEs, ADA, NAb	NCT01901146	pCR, local review: 48.0% pCR, central independent review: 47.8% ≥1 AE: 80.2% Grade 3+ AE: 14.8% Most common AEs were arthralgia (17.3%), asthenia (14.8%), neutropenia (14.6%), peripheral neuropathy (13.7%) and anemia (11.0%)	Submitted to EMA, 2017[79]; submitted to FDA, 2017[80]
		Epi and Cy → Trast and Pac				pCR, local review: 40.5% RD (90% CI): 7.3% (1.2%-13.4%)[a] RR (90% CI): 1.19 (1.033-1.366)[a] pCR, central independent review: 41.8% RD (90% CI): 5.8% (−0.5% to 12.0%)[b] RR (90% CI): 1.14 (0.993-1.312)[b] ≥1 AE: 79.5% Grade 3+ AE: 14.1% Most common AEs were arthralgia (15.2%), asthenia (16.3%), neutropenia (12.5%), peripheral neuropathy (11.9%), and anemia (10.2%)	
BCD-022 (Biocad, Saint-Petersburg, Russia)[81,82]	$HER2^+$ MBC (first-line)	BCD-022 and Pac	ORR, PK	CR, PR, stabilization rate, progression rate, AEs, CTX cycles postponed because of AEs, DC due to AEs, ADA, PK	NCT01764022	ORR (95% CI): 53.57% (40.70-65.98) CR: 5.36% PR: 48.21% SD: 25.0% Progression rate: 21.43% NAb: 1 patient	
		Trast and Pac				ORR (95% CI): 53.70% (40.60-66.31) CR: 3.70% PR: 50.0% SD: 25.93% Progression rate: 20.37% NAb: 1 patient	
						Lower limit of 95% CI for ORR difference between groups (−19.83%) did not exceed the noninferiority margin No statistically significant differences between groups for all other efficacy end points, or in rate of AEs (including severe AEs)	

Table 3 Continued

Biosimilar (Manufacturer), Brand Name (if approved)	Patient Population (Setting)	Intervention	Primary End Points	Secondary and Other End Points	ClinicaTrials.Gov Identifier	Key Efficacy and Safety Results (Where Available)	Regulatory Filing Status (If Known)
CT-P6 (Celltrion Incheon, South Korea), Herzuma[83-86]	$HER2^+$ EBC (neoadjuvant and adjuvant)	CT-P6 and Doc → CT-P6 and F and Epi and Cy	pCR	ORR, PK, PD, and safety	NCT02162667	pCR (95% CI): 46.8% (40.4-53.2) ORR (95% CI): 88.3% (83.6-92.0) ≥1 SAE: 7.4% Withdrew treatment because of significant LVEF decrease: 3 patients IRR: 11.4%	Approved by EMA, 2018[87]; submitted to MHLW in Japan, 2017[88]; submitted to FDA, 2017[80]
		Trast and Doc → Trast and F and Epi and Cy				pCR (95% CI): 50.4% (44.1-56.7) ORR (95% CI): 89.5% (85.0-92.9) ≥1 Treatment-emergent SAE: 11.9% Withdrew treatment because of significant LVEF decrease: 3 patients IRR: 10.4%	
						pCR treatment difference (95% CI): −0.0362 (−0.1238 to 0.0516)[c] ORR treatment difference (95% CI): −0.0115 (−0.0990 to 0.0764)	
	$HER2^+$ MBC	CT-P6 and Pac	ORR	Safety and efficacy	NCT01084876	ORR: 57% Median TTP: 11.07 mo Median TTR: 1.38 mo SAEs: 13.5% IRR: 15.6% Cardiotoxicity: 3.3%	
		Trast and Pac				ORR: 62% Median TTP: 12.52 mo Median TTR: 1.38 mo SAEs: 12.1% IRR: 26.0% Cardiotoxicity: 4.3% ORR treatment difference (95% CI): 5% (−0.14 to 0.04)[c] TTP; $P = .10$ TTR; $P = .37$	
Hercules/Myl-14010 (Biocon, Bengaluru, India/Mylan, Canonsburg, PA), Ogivri[89]	$HER2^+$ MBC (first-line)	Hercules/Myl-14010 and Pac or Doc	24-Week ORR	Secondary: TTP, PFS, and OS at 48 weeks; Other: AEs, laboratory assessments, LVEF, immunogenicity	NCT02472964	24-Week ORR (95% CI): 69.6% (63.62-75.51) 48-Week PFS: 44.3% 48-Week OS: 89.1% TEAE: 96.8% ADA: 2.4%	Application resubmitted to EMA, 2017[90]; approved by FDA, 2017[91]
		Trast and Pac or Doc				24-Week ORR (95% CI): 64.0% (57.81-70.26) 48-Week PFS: 44.7% 48-Week OS: 85.1% TEAE: 94.7% ADA: 2.8%	
						ORR ratio (90% CI): 1.09 (0.974-1.211)[d] ORR difference (95% CI): 5.53 (−3.08 to 14.04)[e] PFS difference (95% CI): −0.4% (−9.4 to 8.7; $P = .84$)[f] OS difference (95% CI): 4.0% (−2.1 to 10.3; $P = .13$)[f]	

Table 3 Continued

Biosimilar (Manufacturer), Brand Name (if approved)	Patient Population (Setting)	Intervention	Primary End Points	Secondary and Other End Points	ClinicaTrials.Gov Identifier	Key Efficacy and Safety Results (Where Available)	Regulatory Filing Status (If Known)
PF-05280014 (Pfizer, New York, NY)[92-95]	HER2$^+$ MBC (first-line)	PF-05280014 and Pac	ORR	DOR, 1-year PFS rate, 1-year OS rate, safety, PK, ADA, NAb	NCT01989676	1-Year PFS: 56% 1-Year OS: 88.84% ADA: 0 patients	Submitted to EMA, 2017; submitted to FDA, 2017[96]
		Trast-EU and Pac				RR for ORR (95% CI): 0.940 (0.842-1.049)[g] 1-Year PFS: 52% 1-Year OS: 87.96% ADA: 1 patient Safety profile, including incidence of SAEs, was similar between arms, and no new safety signals were identified Mean trough and peak serum concentrations were similar for both agents, up to cycle 5 day 8	
	HER2$^+$ EBC (neoadjuvant)	PF-05280014 and Doc/Carb	PK	pCR, safety, ADA, NAb, PK, ORR	NCT02187744	Patients with cycle 5 C_{trough} (pre-dose cycle 6) >20 μg/mL: 92.1% pCR (95% CI): 47.0% (36.9%-57.2%) ORR (95% CI): 88.1% (80.2%-93.7%) All-causality, Grade 3-4 TEAEs: 38.1% ADA: 0%	
		Trast-EU and Doc/Carb				Patients with cycle 5 C_{trough} (pre-dose cycle 6) >20 μg/mL: 93.3% 95% CI for stratified difference: −8.02% to 6.49%[h] pCR (95% CI): 50.0% (39.0%-61.0%) ORR (95% CI): 82.0% (72.5%-89.4%) All-causality, Grade 3-4 TEAEs: 45.5% ADA: 0.89%	
SB3 (Samsung Bioepis, Incheon, South Korea), Ontruzant[97-99]	HER2$^+$ BC (neoadjuvant)	SB3 and Doc → F and Epi and Cy	bpCR	tpCR, ORR, EFS, OS, PK, immunogenicity, safety	NCT02149524	Neoadjuvant period: bpCR: 51.7% tpCR: 45.8% ORR: 96.3% TEAE: 96.6% SAE: 10.5% Adjuvant period (1 year): TEAEs: 97.5% Grade 3+ TEAEs: 74.3% TEAEs of special interest: 11.0%[i] SAEs: 12.8% Deaths: 0.2% ADA: 0.7%	Approved by EMA, 2017; submitted to FDA, 2017[100]
		Trast and Doc → F and Epi and Cy				Neoadjuvant period: bpCR: 42.0% tpCR: 35.8% ORR: 91.2% TEAE: 95.2% SAE: 10.7%	

Table 3 Continued

Biosimilar (Manufacturer), Brand Name (if approved)	Patient Population (Setting)	Intervention	Primary End Points	Secondary and Other End Points	ClinicaTrials.Gov Identifier	Key Efficacy and Safety Results (Where Available)	Regulatory Filing Status (If Known)
						bpCR ratio (90% CI): 1.259 (1.112-1.426)[j] bpCR difference (95% CI): 10.70% (4.13-17.26)[j] PK equivalence was shown Immunogenicity was comparable (0.7% vs. 0%) between SB3 and Trast groups, respectively Adjuvant period: TEAEs: 96.1% Grade 3+ TEAEs: 71.9% TEAEs of special interest: 12.1%[i] SAEs: 13.2% Deaths: 1.1% ADA: 0.7%	

Abbreviations: ADA = antidrug antibodies; AE = adverse event; BC = breast cancer; bpCR = breast pathologic complete response; Carb = carboplatin; CI = confidence interval; CR = complete response; C_{trough} = trough plasma concentration (at end of dosing interval at steady-state); CTX = chemotherapy; Cy = cyclophosphamide; DC = discontinued; DFS = disease-free survival; Doc = docetaxel; DOR = duration of response; EBC = early breast cancer; EFS = event-free survival; EMA = European Medicines Agency; Epi = epirubicin; F = 5-fluorouracil; FDA = US Food and Drug Administration; IRR = infusion-related reactions; LVEF = left ventricular ejection fraction; MBC = metastatic breast cancer; MHLW = Ministry of Health, Labor and Welfare; NAb = neutralizing antibodies; ORR = overall response rate; OS = overall survival; Pac = paclitaxel; pCR = pathological complete response; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RD = risk difference; RR = risk ratio; SAE = serious adverse event; SD = stable disease; TEAE = treatment-emergent adverse event; tpCR = total pathological complete response; Trast = trastuzumab; Trast-EU = trastuzumab sourced from the European Union; TTP = time to progression; TTR = time to response.

[a]The upper bound of the 90% CIs for RD and RR of pCR slightly exceeded the equivalence margins (±13.0% and 0.759-1.318, respectively).

[b]The 2-sided 90% CIs for RD and RR of pCR were contained within the equivalence margins (±13.0% and 0.759-1.318, respectively).

[c]The 95% CI for the treatment difference was within the equivalence margin (±0.15).

[d]The 90% CI was within the predefined equivalence margin (0.81%-1.24%), consistent with statistical therapeutic equivalence of Hercules/Myl-1401O and Trast.

[e]The 95% CI was within the predefined equivalence margin (±15%), consistent with statistical therapeutic equivalence of Hercules/Myl-1401O and Trast, per EMA recommendation.

[f]No statistically significant difference in PFS or OS was observed between treatment groups.

[g]The 95% CI for RR of ORR was within the prespecified equivalence margin of 0.8 to 1.25.

[h]The lower limit of the 95% CI for the stratified difference between groups was above the noninferiority margin (−12.5%).

[i]Includes IRR, left ventricular systolic dysfunction, and congestive heart failure.

[j]The 90% CI for the ratio of bpCR was within the prespecified equivalence margin (0.785-1.546); the lower margin of the 95% CI for the difference between bpCR rates was contained within and the upper margin was outside of the predefined equivalence margin (±13%).

showed clinical equivalence between the 2 products on the basis of central independent review of pCR (47.8% and 41.8%, respectively), and comparable safety profiles, with 292 (80.2%) and 287 (79.5%) patients, respectively, reporting 1 or more adverse events.[78] The efficacy and safety of neoadjuvant CT-P6 and originator trastuzumab, each in combination with chemotherapy, were compared in patients with HER2$^+$ EBC.[84] The pCR rate was 46.8% for CT-P6 and 50.4% for originator trastuzumab, and the 95% CI (−0.1238 to 0.0516) for the estimate of treatment difference (−0.0362) was within the equivalence margin (±0.15), showing equivalence in efficacy between the 2 treatments.[84] CT-P6 and originator trastuzumab also had similar safety profiles (7.4% vs. 11.9% of patients, respectively, reported ≥1 serious adverse event).[84] In a study conducted in patients with HER2$^+$ MBC, the proposed trastuzumab biosimilar BCD-022 showed noninferiority in efficacy to originator trastuzumab on the basis of ORRs of 53.57% and 53.70%, respectively.[82]

Two studies have compared the proposed trastuzumab biosimilar PF-05280014 and originator trastuzumab sourced from the European Union (trastuzumab-EU) in patients with HER2$^+$ MBC or EBC.[94,95] A comparative safety and efficacy study of PF-05280014 versus originator trastuzumab, each in combination with paclitaxel as first-line treatment for HER2$^+$ MBC, showed equivalence in the primary end point of ORR, with the 95% CI (0.842-1.049) for the risk ratio for ORR (0.940 for PF-05280014/trastuzumab-EU) being within the prespecified equivalence margin (0.80-1.25).[95] Rates of progression-free survival (56% for PF-05280014 vs. 52% for trastuzumab-EU) and overall survival (88.84% vs. 87.96%) at 1 year, as well as the safety profiles were also similar between groups.[95] A separate comparative PK trial of PF-05280014 versus originator trastuzumab, each in combination with docetaxel and carboplatin, in patients with HER2$^+$ EBC also met its primary end point, showing noninferiority of PF-05280014 to trastuzumab-EU in the proportion of patients with cycle 5 trough plasma concentration (pre-dose cycle 6) >20 μg/mL (92.1% vs. 93.3%, respectively).[94] Rates of pCR (47.0% for PF-05280014 vs. 50.0% for trastuzumab-EU) and ORR (88.1% vs. 82.0%), as well as incidence of all-causality Grade 3/4 treatment-emergent adverse events (38.1% vs. 45.5%), were also similar between groups.[94]

The trastuzumab biosimilar SB3 and originator trastuzumab, each given with chemotherapy, were compared as neoadjuvant treatment for HER2$^+$ EBC.[98,99] Results showed equivalence in efficacy between treatments on the basis of the ratio of breast pCR (1.259; 51.7% for SB3 vs. 42.0% for originator trastuzumab), for which the 90% CI (1.112-1.426) was within the predefined equivalence margin (0.785-1.546).[98] Furthermore, 1-year safety, immunogenicity, and survival profiles were also similar between SB3 and originator trastuzumab.[99]

Published data from a study in patients with HER2$^+$ MBC showed comparability between CT-P6 and trastuzumab, each treatment in combination with paclitaxel, with respect to ORR and the incidence of adverse events.[86] Results from a trial comparing the efficacy of Hercules/Myl-1401O versus trastuzumab, each in combination with paclitaxel or docetaxel, as first-line treatment in patients with HER2$^+$ MBC showed equivalence in efficacy and comparable safety (Table 3).[89] Reported 24-week ORR was 69.6% (160 patients) in the Hercules/Myl-1401O group and 64.0% (146 patients) in the trastuzumab group, and the incidence of patients with at least 1 treatment-emergent adverse event was 96.8% (239 patients) in the Hercules/Myl-1401O group and 94.7% (233 patients) in the trastuzumab group.[89]

An application for marketing authorization for ABP 980 was submitted to the EMA and to the FDA.[79,80] A marketing authorization application for CT-P6 was approved by the EMA, and submitted to the Ministry of Health, Labor and Welfare in Japan, and to the FDA.[80,87,88] A resubmitted application for marketing authorization for Hercules/Myl-1401O was accepted for review by the EMA; an application for marketing authorization for Hercules/Myl-1401O was approved by the FDA.[90,91] A marketing authorization application for PF-05280014 was submitted to the EMA and to the FDA.[96] Finally, a marketing authorization application for SB3 was approved by the EMA, and an application for marketing authorization for SB3 was submitted to the FDA.[100]

Economic Effect of Biosimilars

The regulatory framework for biosimilars provides a more tailored pathway for approval compared with originator biologics that relies on a rigorous assessment of similarity. As a result, biosimilars might provide a lower-cost alternative to originator biologics and have the potential to generate cost savings. Anticipated pricing for biosimilars is approximately 20% to 30% lower than originator biologics.[101] Recent studies of biosimilar pricing in Europe reported discounts generally ranging from 5% to 35% over originator biologics, although discounts of up to 75% were noted in some cases.[102-105] In general, price discounts for biosimilars might be considered modest compared with small-molecule generics, which can be priced 80% to 90% lower than the brand-name counterpart.[101-105] This difference is explained in part by the greater complexity of biosimilars in terms of their structure and manufacturing process compared with chemically synthesized, small-molecule generics, which leads to higher development costs ($100-$200 million vs. $1-$5 million) and longer development timelines (8-10 years vs. 3-5 years).[101]

A 2016 report estimated the introduction of biosimilars to generate cumulative potential savings of €49 billion (20% discount) to €98 billion (40% discount) in France, Germany, Italy, Spain, the United Kingdom, and the United States between 2016 and 2020.[106] Pharmacoeconomic evaluations have been conducted for different biosimilars to estimate their potential savings and effect in different countries. To date, only 1 budget impact analysis has been conducted for biosimilar trastuzumab.[107] In this analysis introduction of trastuzumab biosimilars in Croatia was estimated to generate potential savings varying from €0.26 million (15% price discount) to €0.69 million (35% price discount) that could be reinvested to treat an additional 14 (15% price discount) to 47 (35% price discount) patients.[107]

The extent of cost savings achieved with biosimilars will depend on many factors; thus, drug price in and of itself is not sufficient to understand the potential savings.[106,108,109] An important consideration will be future trends in biologic drug utilization.[109] Trastuzumab was first introduced as an intravenous formulation,[3,4] but in 2013 a subcutaneous formulation was approved by the EMA for treatment of early or metastatic HER2$^+$ breast cancer.[110] Subcutaneous trastuzumab has shown noninferiority in PK and efficacy

and a safety profile that is similar to intravenous trastuzumab.[111-114] Furthermore, subcutaneous trastuzumab is administered over a shorter period of time than intravenous trastuzumab (5 minutes vs. 30-90 minutes) and might be preferred by patients.[4,113] Trastuzumab biosimilars might provide a lower-cost alternative to originator trastuzumab. However, in many institutions this price reduction for biosimilars might be outweighed by savings associated with use of subcutaneous administration of originator trastuzumab, especially because budgets for drug purchase, pharmacy, and the chemotherapy suite might be independent and held separately.

The potential effect of biosimilars on health care budgets and patient access to biologic therapy is significant, including in countries where cost is already a major issue. For example, 53%, 63%, and 81% of physicians surveyed in the countries of Brazil, Mexico, and Russia reported they would increase the use of HER2 therapy for treatment of $HER2^+$ breast cancer if a lower cost trastuzumab biosimilar was available.[21] In addition, with current drug pricing trastuzumab is not considered cost-effective in several Latin American countries.[53] However, introduction of a lower-cost biosimilar to this region could make trastuzumab cost-effective and support decisions for drug funding and reimbursement, thereby improving patient access to HER2 therapy for treatment of $HER2^+$ breast cancer. Finally, many low-income countries rely on the WHO Model List of Essential Medicines to select or prioritize drugs for national essential or reimbursable medicine lists.[115] The WHO has initiated a pilot program, inviting manufacturers to submit applications for prequalification of rituximab and trastuzumab biosimilars into their Essential Medicines List.[116] Accordingly, implementation of this program might improve patient access to HER2 therapy for treatment of $HER2^+$ breast cancer.

Conclusions

Trastuzumab is standard treatment for $HER2^+$ breast cancer, but access to this drug remains limited even in some developed countries. Biosimilars offer an approach to expand access to biologic therapies by placing additional highly similar, high-quality products into clinical practice. In oncology practice, the first approved biosimilars (eg, epoetin and filgrastim) are used in supportive care, and have clinical effects that can be quickly and easily measured. Furthermore, extensive and required postapproval pharmacovigilance programs are in place to monitor for additional safety signals. This has provided clinicians with assurance about the safety and efficacy of these biosimilars. Monoclonal antibodies such as trastuzumab as anticancer drugs have effects on patient outcomes that are not as easily assessed. Understanding the scientific and regulatory aspects of biosimilar development will help clinicians be comfortable using a trastuzumab biosimilar across all clinical settings.

Trastuzumab biosimilars are in development and might soon become available. The availability of safe and effective trastuzumab biosimilars might help address the need for increased trastuzumab access for patients with $HER2^+$ breast cancer worldwide. It is likely that trastuzumab biosimilars will be used in all indications for which the originator is approved; therefore, in addition to patients treated for breast cancer, patients with $HER2^+$ metastatic gastric or gastroesophageal junction adenocarcinoma might also benefit from the availability of trastuzumab biosimilars.

The introduction of trastuzumab biosimilars will be accompanied by the expectation of cost savings, although, with a projected discount of approximately 20% to 30%,[101] the cost savings are anticipated to be lower than with generic drugs. Nevertheless, trastuzumab biosimilars might expand use of HER2-targeted and other new therapies by generating savings for health care systems. Furthermore, biosimilars might provide greater economic benefits in emerging markets,[53] and other countries where cancer drugs are less affordable.

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