SciMedCentral

Annals of Breast Cancer Research

Review Article

Trastuzumab Biosimilars Setting the Pace for the Provision of a Cost Effective Oncological Care: Regulatory and Clinical Issues

Viale G[1,2] and Irshad S[3]*

[1]*Department of Oncology and Hemato-Oncology, Univesity of Milan, Italy*
[2]*New Drugs and Early Drug Development for Innovative Therapies Division, European Institute of Oncology IRCCS, Italy*
[3]*School of Cancer and Pharmaceutical Sciences, Kings Health Partners, Guy's & St Thomas NHS Trust, UK*

***Corresponding author**
Sheeba Irshad, School of Cancer and Pharmaceutical Sciences, Kings Health Partners, Guy's & St Thomas NHS Trust, UK , Email: sheeba.irshad@kcl.ac.uk

Submitted: 09 October 2018

Accepted: 26 October 2018

Published: 29 October 2018

Keywords

- Biosimilars; Trastuzumab; Anticancer treatment costs; Breast cancer; HER2

Abstract

Anti-HER2 directed treatment has become the standard of care among patients with early and advanced HER2-positive breast cancer. Owing to the associated treatment costs, barriers such as insurance coverage and availability prevent its use in neoadjuvant, adjuvant or metastatic settings in many developing countries. In 2017, the patent for intravenous trastuzumab (Herceptin) expired across Europe, promoting the development of trials with trastuzumab biosimilars. Biosimilars are products that are developed to be highly similar in terms of safety, purity and potency to existing approved biologics. They may represent a potential opportunity to lower the cost of treatment and increase patient accessibility to important drugs. Four trastuzumab biosimilars have already been approved for routine use in Europe with others likely to follow. Here, we provide a detailed review of trastuzumab biosimilars; and discuss important regulatory and clinical considerations that must be addressed and appreciated as these agents enter routine cancer care.

INTRODUCTION

Breast cancer is a highly heterogeneous disease, with human epidermal growth factor receptor 2 (HER2) overexpression observed in about 15-20% of tumors. Anti-HER2 directed treatment changed the natural history of this disease, both in early and metastatic setting [1]. Trastuzumab - trade name Herceptin® (Genentech, South San Francisco, CA,USA/F. Hoffmann-La Roche Ltd, Switzerland) -is a recombinant humanized monoclonal antibody targeting HER2, approved for the treatment of HER2-overexpressing breast cancer either early or advanced [2]. Data from randomized clinical trials in women with HER2 positive (HER2+) breast cancer showed that adjuvant treatment with trastuzumab led to a significant improvement in disease free survival (DFS) and overall survival (OS) with a 33% reduction in the risk of death compared with chemotherapy alone [3-6]. Evidence from clinical studies supported the concurrent administration of the monoclonal antibody and taxanes [7,8] and subsequent administration of trastuzumab alone for a total period of up to 1 year [9]. In the neoadjuvant setting, the addition of trastuzumab to chemotherapy provided positive results in terms of pathological complete response (pCR) rate and improvement of DFS [10,11]. Likewise, the addition of trastuzumab to standard first-line chemotherapy in patients with metastatic HER2+ breast cancer resulted in a prolonged time to disease progression and improved OS [12]. More recently, the CLEOPATRA trial showed that dual HER2 blockade with trastuzumab and pertuzumab in combination with docetaxel significantly prolonged progression free survival (PFS) and OS in women with HER2+breast cancer not previously treated [13,14]. Continuous blockade of HER2 signaling was demonstrated to play a key role in improving OS in metastatic HER2+ breast cancer and it is recommended even beyond progression [15-18].

However, the cost of adjuvant trastuzumab therapy for 1-year, as well as the cost associated with its indefinite use in a metastatic setting have raised questions and concerns of patient access to this life-saving therapy. Trastuzumab belongs to the class of biologics, drugs at least partially derived from living organisms such as yeast, plant or bacteria usually obtained by recombinant DNA technology. This class comprise an increasing number of therapies and cancer drugs and account for more than half of the total spending on medical care in developed countries. Trastuzumab sales were up by 15.98%, to reach global revenue of USD 7.55 billion in 2017 and continues to be among the top 20 global products sales [19] ; placing a significant economic burden. The high cost limits patient access to trastuzumab, and this may partly explain the marked difference in survival rates observed in less developed countries [20]. Indeed, a physician survey investigating access to trastuzumab in different countries showed that some barriers, including cost of treatment prevent its extensive use in neoadjuvant, adjuvant or metastatic setting, but its use could be increased could instead be increased with the availability of a lower cost biosimilar to trastuzumab [21]. Thus,

the use of biosimilars may expand access to newest therapies by offering a comparable, more affordable alternative and a potential solution to the increasing costs of cancer treatment.

Biosimilar is a product that is developed to be highly similar, in terms of safety, purity and potency, to an existing licensed reference biologic product, notwithstanding minor differences in clinically inactive components [22,23]. Biosimilars represent a potential opportunity to lower the cost of treatment and increase patient accessibility to biologics. The cost saving generated with the introduction of trastuzumab biosimilars is estimated to be 20–30% lower compared to the cost of the reference product [24]. Even with a discount as low as 15%, the cost savings from the introduction of biosimilar trastuzumab would reach 0.26 million in the first year [25]. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have encouraged competition in the biologics market and implemented specific pathways of development and regulatory approval of these agents, on the basis of equivalence evidence from preclinical and clinical endpoints. Four trastuzumab biosimilars have already been approved for routine use in Europe, as shown in Figure 1, with others likely to follow. We identified trastuzumab biosimilars approved by EMA and FDA and reviewed preclinical and clinical data leading to their approval. We also searched trastuzumab biosimilars undergoing clinical evaluation on Pubmed and on clinicaltrial.gov. Here, we provide a detailed review of these trastuzumab biosimilars; and discuss important regulatory and clinical considerations needed to help the introduction of biosimilar medicines into routine cancer care.

TRASTUZUMAB BIOSIMILARS APPROVED IN THE EUROPEAN UNION

In 2017, the patent for Herceptin expired across Europe, thus promoting the development of trials with trastuzumab biosimilars. All drugs approved or in phase II/III of clinical development are summarized in Table 1. Currently four trastuzumab biosimilars have obtained authorization for routine use in Europe by the EMA: Ontruzant (SB3, Samsung Bioepis, Incheon, R.O.K.), Kanjinti (ABP-980, Amgen, Thousand Oaks, CA, U.S.A.), Trazimera (PF-05280014, Pfizer, New York, NY, U.S.A.) and Herzuma (CT-P6, Celltrion Healthcare, South Korea/Hospira, USA) [26-29]. The clinical indications for all four agents are that of reference trastuzumab: HER2+ breast cancer either in the early or the metastatic setting and metastatic gastric cancer, in combination with cisplatin and capecitabine/fluorouracil.

Ontruzant (SB3, Samsung Bioepis, Incheon, R.O.K)

SB3 (Ontruzant) was the first biosimilar of the reference anti-HER2 antibody trastuzumab to obtain the marketing authorisation in the European Union,and is currently under review by FDA. A randomised phase I pharmacokinetic study of healthy males demonstrated similarity in terms of pharmacokinetic equivalence [30], resulting in a phase III trial being conducted to compare SB3 and EU-sourced reference trastuzumab in patients with early or locally advanced HER2-positive breast cancer treated with neoadjuvant therapy [31]. The study recruited 875 patients and confirmed equivalence for the efficacy of the two drugs, based on pCR rates of 51.7% and 42.0% in the SB3 and trastuzumab groups. The overall response rates were 96.3% and 91.2% for the SB3 and trastuzumab respectively. The incidence of treatment related adverse events was comparable between treatment arms [32]. The median follow-up was approximately 11 months in the two groups, highlighting the need for caution in interpretation of the safety data. However, a collateral study investigating the long-term cardiac safety in patients treated with SB3 (NCT02771795) is currently underway. It is noteworthy that no previous or new studies are investigate its use in the metastatic setting, despite it already having been approved by EMA for the same indications as reference trastuzumab (early and metastatic HER+ breast cancer and HER2 overexpressing gastric cancer). Given as the mechanism of action of trastuzumab is similar in different conditions such as early and metastatic HER2-positive breast cancer, HER2-positive gastric cancer and based on the above comparability studies, extrapolation to the other indications has been allowed.

Herzuma (CT-P6, Celltrion Healthcare, South Korea/ Hospira, USA)

CT-P6, trading name Herzuma, granted a marketing authorisation valid throughout the European Union in February 2018, whereas FDA has requested supplementary information about the product. CT-P6 in combination with paclitaxel demonstrated comparability to reference transtuzumab plus paclitaxel in a pooled analysis of data from a phase I/IIb pharmacokinetics study [33]. A subsequent phase III study (NCT01084876) of 475 women with HER2+ metastatic breast cancer demonstrated similar efficacy and safety profile of CT-P6 to reference transtuzumab [34]. The objective response rate (ORR) during the first 8 cycles of treatment, primary endpoint of the study, was similar: 57% and 62% respectively in the CT-P6 and trastuzumab groups, with a 5% difference (CI: -0.14, 0.04) that met the predefined criteria for equivalence. Secondary efficacy endpoints (median time to progression and median time to response) also supported the equivalence of the two drugs (11.07 months vs. 12.52 months for CT-P6 vs Herceptin respectively).In a more recent phase III, double-blind, equivalence trial (ClinicalTrials.gov #NCT02162667), 549 patients with HER2+ early breast cancer were randomly allocated 1:1 to receive neoadjuvant CT-P6 or Herceptin in combination with docetaxel (75mg/mq) and FEC (fluorouracil 500 mg/mq, epirubicin 75mg/mq, and cyclophosphamide 500 mg/mq) chemotherapy [35]. The primary endpoint of the study, pCR, was similar with CT-P6 and reference trastuzumab (46.8% (95% CI 40.4–53.2) and 50.4% (95% CI 44·1–56·7) respectively); the 95% CI of the estimated treatment outcome difference was within the equivalence margin. After a 3-years follow up, toxicity profile was consistent with reference product; long-term safety and efficacy monitoring is ongoing.

Trazimera (PF-05280014, Pfizer, New York, NY, U.S.A.)

PF-05280014 (Trazimera), was approved for use in the European Union in May 2018, following its rejection from the FDA in April 2018, which included a request for additional technical information.

Comparative non-clinical assessments of PF-05280014 and reference trastuzumab demonstrated PF-05280014 biosimilar has the same primary amino-acid sequence as the licensed

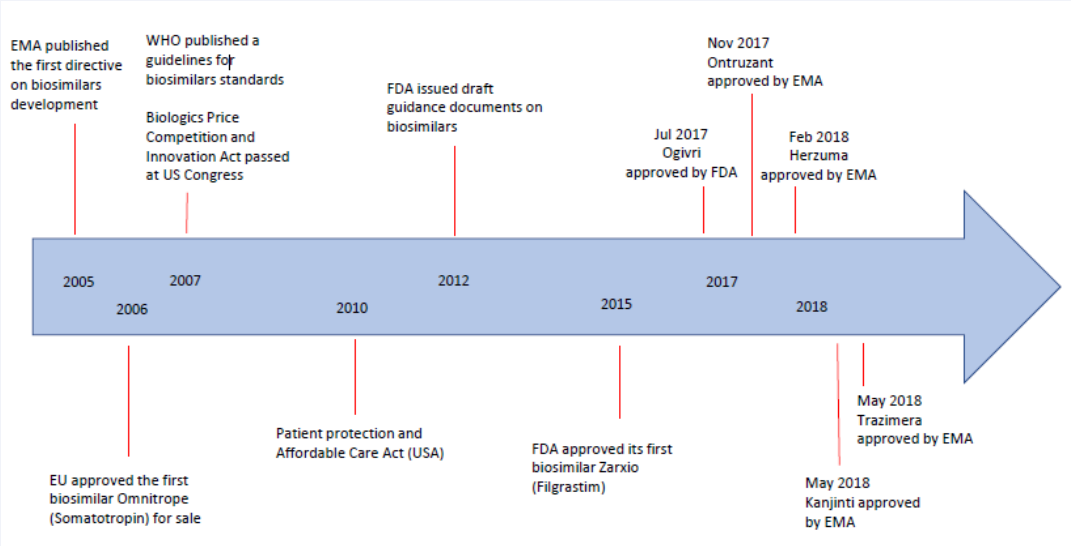

Figure 1 Four trastuzumab biosimilars.

Table 1: Clinical studies evaluating trastuzumab biosimilars.

Drug name	Phase/ trial status	NCT number	Setting and comparator	Primary endpoint and results	Drug status
ABP-980 (Kanjinti) Amgen (Thousand Oaks, CA, U.S.A.)	III C	NCT01901146	**Early BC** Neoadjuvant EC followed by ABP-980/trastuzumab plus paclitaxel	**pCR** 47.8% and 41.8% (ABP-980 vs trastuzumab) risk difference 5.8%, [90% CI -0.5 to 12.0]	Approved by EMA in May 2018, not approved by FDA
CT-P6 (Herzuma) Celltrion Healthcare (Incheon, R.O.K.)	I C	NCT02665637	Single dose CT-P6/trastuzumab in healthy male volunteers	PK parameter (AUC)	
	I/IIb ANR	NCT01084863	First line CT: paclitaxel + trastuzumab/CT-P6	PK parameter	
	III ANR	NCT02162667	**Early BC** Neoadjuvant CT (Docetaxel and FEC) + trastuzumab/CT-P6	**pCR** 46.8% vs. 50.4% (CT-P6 vs. trastuzumab) Risk difference 5%; −0·04 [95% CI −0·12 to 0·05]	Approved by EMA in February 2018; FDA requested supplementary information
	III ANR	NCT01084876	**mBC** First line CT: paclitaxel + trastuzumab/CT-P6	**24 weeks ORR** 57% vs 62% (CT-P6 vs Herceptin) Risk difference: 5%; [95% CI: -0.14, 0.04]	
PF-05280014 (Trazimera) Pfizer (New York, NY, U.S.A.)	I C	NCT02015156 (REFLECTIONS B327-06)	Single dose PF-05280014/trastuzumab in healthy male volunteers	Incidence of pyrexia	
	I C	NCT01603264 REFLECTIONS B327-01	Single dose PF-05280014/ trastuzumab-EU/trastuzumab-US in healthy male volunteers	PK parameters (AUC; Cmax)	Approved for use in the European Union in May 2018, rejected by FDA in April 2018 with a request for additional technical information
	III	NCT01989676	**mBC**	**25 weeks ORR**	

	ANR	(REFLECTIONS B327-02)	First line paclitaxel + trastuzumab/ PF-05280014	Risk ratio ORR: 0.940 over trastuzumab [95% CI 0.842–1.049]	
	I/II/III C	NCT02187744 (REFLECTIONS B327-04)	**Early BC** Neoadjuvant docetaxel and carboplatin + PF-05280014/ trastuzumab	**Cycle 5 Ctrough >20 µg/ml** 92.1% vs 93.3% (PF-05280014 vs Herceptin)	
SB3 (Ontruzant) Samsung Bioepis Co., Ltd (Incheon, R.O.K.)	I C	NCT02075073	Single dose SB3/ trastuzumab-EU/trastuzumab-US in healthy male volunteers	PK parameters (AUC; Cmax; AUClast)	
	III C	NCT02149524	**Early BC** Neoadjuvant docetaxel and FEC +trastuzumab/SB3	**pCR:** 51.7% vs. 42.0% (SB3 vs. trastuzumab) Adjusted ratio: 1.259 [95% CI, 1.085 to 1.460]	Approved by EMA in November 2017, under review by FDA
	III ANR	NCT02771795	trastuzumab/SB3 (observational)	Cardiac safety (CHF incidence/ LVEF decrease) Data not available	
MYL-1401O (Ogivri) Mylan (Canonsburg, PA, U.S.A.)	III C	NCT02472964 (HERITAGE STUDY)	**mBC** First line CT: taxane (docetaxel or paclitaxel)+ trastuzumab/MYL-1401O	**24 weeks ORR** 69.6% vs. 64% (MYL vs Herceptin) HR: 1.09 [95% CI: 0.95 to 1.24]	Approved by FDA in July 2017; application withdrawal in EU
BCD-022 (HERtiCAD) CJSC BIOCAD (San Petersburg, Russia)	III C	NCT01764022	**mBC** First line CT: paclitaxel + trastuzumab/ BCD-022	**ORR after 3 and 6 cycles** 53.57% vs 53.70% (BCD-022 vs Herceptin)	Received authorization from the Russian regulatory body in January 2016
CMAB302 (Cipterbin) Shanghai CP Guojian Pharmaceutical	II C	NCT01439191	**mBC** Cipterbin +/- vinorelbine	**24 weeks ORR** Data not available	
Co.,Ltd	III C	NCT01291667	**mBC** Cipterbin + vinorelbine simultaneously or sequencely in metastatic breast cancer	**PFS** Data not available	
HLX02 (Shanghai Henlius Biotech)	III R	NCT03084237	**mBC** HLX02/ trastuzumab + docetaxel in metastatic breast cancer	**24 weeks ORR** Data not available	
DMB-3111 (Meiji Seika Pharma Co., Ltd.)	I C	NCT02100917	Single dose DMB-3111/trastuzumab in healthy male volunteers	PK parameters (AUC; Cmax)	

ANR: Active, Not Recruiting; AUC: Area Under the Curve; AUClast: Area Under the Concentration-time Curve From Time Zero to the Last Quantifiable Concentration; CHF: congestive heart failure; Cmax: Maximal Concentration; mBC: metastatic breast cancer; ORR: objective response rate; pCR: pathological Complete Response; PFS: Progression Free Survival; PK: Pharmacokinetic.

trastuzumab, with similar in vitro functional properties and in vivo pharmacokinetics, antidrug antibody (ADA) responses and tolerability [36]. Its phase I clinical trial confirmed the pharmacokinetic similarity, safety and immunogenicity between PF-05280014 and trastuzumab in healthy male volunteers (NCT01603264 and NCT02015156) [37].

Subsequent phase III randomized double-blind, REFLECTIONS B327-04 study (NCT02187744) compared pharmacokinetics, efficacy, safety and immunogenicity of PF-05280014 and trastuzumab. Neoadjuvant trastuzumab or the biosimilar product were given in combination with docetaxel and carboplatin in 226 patients with operable HER2+ breast cancer. The primary objective to determine whether neoadjuvant treatment with PF-05280014 was non-inferior to trastuzumab was met. The study demonstrated non-inferiority pharmacokinetics for PF-05280014 versus trastuzumab in the percentage of patients with

trough plasma concentration (Ctrough) >20 µg/ml at Cycle 5 (Cycle 6 predose) with 92.1% vs 93.3% Cycle 5 Ctrough >20 µg/ml for PF-05280014 vs transtuzumab respectively. Efficacy endpoints included pCR and ORR; for both these secondary endpoints, rates were comparable between PF-05280014 and Herceptin (pCR 47.0% vs 50.0% and objective response 88.1% vs 82.0% respectively) [38].

An additional, distinct comparative safety and efficacy study (NCT01989676) evaluating PF-05280014 versus trastuzumab, each administered in combination with paclitaxel, as first-line treatment for 707 patients with HER2+ metastatic breast cancer waspresented at the 2017 ESMO Congress. It confirmed thesimilarity of PF-05280014 and Herceptin in terms of efficacy, safety, immunogenicity, and pharmacokinetic in the metastatic setting. ORR, the primary endpoint of the study, was comparable between the two agents. Accordingly, 1-year PFS (56% vs 52% respectively) and 1year OS (88.84% vs 87.96% respectively) were similar between PF-05280014 and Herceptin, as well as the safety profile of the two drugs [39].

Kanjinti (ABP-980, Amgen, Thousand Oaks, CA, U.S.A)

The fourth trastuzumab biosimilar approved by EMA in May 2018 is ABP-980 (Kanjinti); again, this drug has not been yet approved by FDA. Positive results from a phase I pharmacokinetic study [40], led to the development of a phase III trial comparing ABP-980 and reference transtuzumab in the neoadjuvant setting. The LILAC study (NCT01901146) randomized 725 patients with histologically confirmed HER2-positive invasive early breast cancer to receive, after anthracycline-based chemotherapy, neoadjuvant and adjuvant ABP 980 (n=364), neoadjuvant and adjuvant trastuzumab (n=190), or neoadjuvant trastuzumab and adjuvant ABP 980 (n=171) with concomitant paclitaxel [41]. The primary endpoint, pCR in the breast and axilla after neoadjuvant treatment and surgery was seen in 172 (48%) of 358 patients who received ABP 980 and 137 (41%) of 338 who received trastuzumab, yielding a risk difference of 7.3% (90% CI 1.2–13.4) and relative risk (RR) of 1.188 (1.033–1.366), falling within the predefined equivalence margin (risk difference 5.8%, 90% CI −0.5 to 12.0, and RR 1.142, 0.993 to 1.312). ABP 980 and Herceptin had similar safety outcomes in both the neoadjuvant and adjuvant phases of the study [41,42]. It is noteworthy as a weakness of the study that only 696 of 725 randomised patients were evaluable for pathological complete response after surgery. No data about the outcomes, characteristics, or allocated treatment of the patients who did not reach surgery were provided. There is an argument to have these lost to follow up patiens included in the intention-to-treat analysis and their responses classified where possible (eg, those who did not reach surgery due to progressive disease could have been classified as non-pathological complete response). The effect of these few patients on the overall results is unknown.

TRASTUZUMAB BIOSIMILARS CURRENTLY NOT APPROVED IN THE EUROPEAN UNION

In the recent multicenter Heritage clinical trial, Rugo and colleagues evaluated the efficacy in terms of overall response and safety of a proposed trastuzumab biosimilar, Ogivri (MYL-1401O; Mylan/Biocon Ltd) compared with the standard trastuzumab [43], supported by previous results [44]. A total number of 458 patients with HER2 positive metastatic breast cancer from developing countries in Asia, Africa, Eastern Europe, and South of America were randomized to receive first line taxane based schemotherapy (docetaxel or paclitaxel) in combination with either trastuzumab or the biosimilar drug [43]. Pertuzumab was not administered since the Heritage Study began before its approval as first-line treatment of HER2-positive metastatic breast cancer; moreover, this antibody was not available worldwide. In addition, only few patients (< 10%) had previously received adjuvant trastuzumab. The overall response rate at 24 weeks was 69.6% (95% CI, 63.62% to 75.51%) in patients receiving the proposed biosimilar plus taxane compared with 64.0% (95% CI, 57.81% to 70.26%) achieved with trastuzumab plus a taxane. The ORR ratio (1.09 [90% CI, 0.97 to 1.21]) and ORR difference (5.53 [95% CI, −3.08 to 14.04]) were consistent with the predefined statistical therapeutic equivalence between biosimilar and trastuzumab. The 48-week exploratory findings of the secondary efficacy analysis showed overlapping results in the two groups of patients: no statistical difference in time to tumor progression, PFS nor OS were observed. Importantly, the toxicity profile of the two drugs was analogue; trastuzumab and its biosimilar showed also comparable pharmacokinetics and an identically low immunogenicity profile. Supported by these results, FDA approved in July 2017 Ogivri in the same indications as Herceptin; this drug was the first trastuzumab biosimilar approved by FDA. However the European CHMP required some clarifications and a more detailed documentation (lack of a valid certificate confirming that the manufacturing facility of the product complies with good manufacturing practice requirements). In August 2017 Mylan withdrew its application for a marketing authorisation for Ogivri, withdrew its application for a marketing authorisation for Ogivri, owing to the lack of required documentation.

Another trastuzumab biosimilar, BCD-022 (JSC BIOCAD, Russia), was investigated in a multicenter randomized phase III clinical trial in association with paclitaxel as first-line treatment for HER2-positive metastatic breast cancer patients (NCT01764022); this study enrolled 126 patients, mainly in Belarus, India, Russian Federation, Ukraine. No statistically significant differences were observed in ORR, the primary endpoint of the study (53.57% (95% CI 40.70 – 65.98%) in BCD-022 group and 53.70% (95% CI 40.60 – 66.31%) in Herceptin group). In addition no significant differences were noticed between the two groups for all other efficacy parameters and the safety profiles were equivalent. Given these and other evidence supporting the non inferiority of the drug to Herceptin, BCD-022 under the trade name of HERtiCAD, was the first trastuzumab biosimilar to receive authorization from the Russian regulatory body in January 2016 [45].

BIOSIMILARS AT EARLIER STAGES OF DEVELOPMENT

Other candidate biosimilars are at earlier stages of development [46,47]. The Chinese trastuzumab biosimilar Cipterbin (CMAB302, Shanghai CP Guojian Pharmaceutical Co., Ltd) has been evaluated in a recent phase I dose escalation study and showed an acceptable safety profile in Chinese

metastatic breast cancer patients [48]. Subsequent phase II and III trials are currently ongoing in China to investigate the use of Cipterbin in combination with vinorelbine in the metastatic setting (NCT01439191, NCT01291667). Another trastuzumab biosimilar, HLX02 (Shanghai Henlius Biotech), after showing pharmacokinetic equivalence to Herceptin in a phase I Chinese trial (NCT02581748) is currently under investigation in a phase III trial enrolling metastatic breast cancer patients in Ukraine, Poland, Philippines (NCT03084237). Similarly, HD201 (trade name Hervelous; Prestige BioPharma/ Alvogen) is under evaluation in a phase III trial in patients with early breast cancer in the neoadjuvant setting (NCT03013504, TROIKA study), planning to enroll a total of 500 patients in Western and Eastern Europe.

A phase I trial showed the bioequivalence of a trastuzumab biosimilar (DMB-3111, developed by Meiji Seika Pharma-Japan and Dong-A Socio Holdings-Korea) and Herceptin; both displayed similar efficacy and safety profiles in healthy Japanese adult males (NCT02100917) [49]. Initial efforts are also directed to the identification of biosimilars for other anti-HER2 agents. A preclinical study recently aimed to identify a potential biosimilar of trastuzumab emtansine (Kadcyla®) and extensively characterized their physicochemical, immunological, and biological profiles [50].

CHALLENGES TO BIOSIMILAR DRUG DEVELOPMENT

Development of biosimilars for cancer patients is becoming a high priority and their use is expected to increase in the near future with impending patent expiration of a number of biological agents. Trastuzumab is a cornerstone treatment for HER2 positive breast cancer and likewise their biosimilars are proving to be the front-runners again in changing the landscape of targeted therapies in oncology by proving a cost-effective treatment alternative. In being the trend setters, they have highlighted several unaddressed issues on the correct use of biosimilars in clinical practice, triggering key discussions between both the care-providers and consumers on the regulatory pathways in place for biosimilar approvals.

In 2004–05, the EMA/European Commission (EC) was the first major regulatory authority to introduce a framework for the marketing authorization of biosimilars. Subsequently, the EMA Committee for Medicinal Products for Human Use (CHMP) released product-specific guidelines, outlining the data requirements and studies necessary to demonstrate similarity [51-55]. Due to the natural variability and more complex manufacturing of biosimilars, the generic approach which involves demonstration of bioequivalence with a reference medicine, applicable to most chemically-derived medicines, is not sufficient to demonstrate the similarity of biological-derived products. In addition to comparative pharmacokinetic and pharmacodynamic studies, clinical trials must report an acceptable degree of similarity in clinical efficacy and safety to the reference product [56].

Specific to the development of transtuzumab biosimilars, biosimilar antibodies are “generic” versions of “innovator” (or “originator”) antibodies with the same amino acid sequence, but produced from different clones and manufacturing processes. However, monoclonal antibodies (mAb) are complex in structure and function compared to non-mAb proteins. As a consequence, biosimilar mAbs may include possible differences in glycosylation and other microvariations, raising concerns whether small (undetectable) differences might lead to unexpected immunogenicity in patients. Similarity testing between originator mAbs and biosimilar mAbs, including their physicochemical characterization, in vitro functioning, in vivo safety and immunogenicity, is more challenging. EMA and FDA have acknowledged the difficulty in assessing similarity between mAb products, and in 2012 EMA published specific guidelines for similarity and immunogenicity testing of biosimilar mAbs. Extensive comparative quality studies that include sensitive analytical techniques able to detect minor differences between the biosimilar and the reference product, in terms of primary structure analysis, conformation, folding, purity, concentration and biological activity (cell inhibition, antibody-dependent cellular cytotoxicity activity and antigen binding affinity and avidity) are required.

In addition to these criteria, FDA has defined a particular category of biosimilars, the interchangeable biosimilars products. In January 2017, FDA released draft guidance for industries containing detailed consideration in demonstrating interchangeability with a reference product [57]. The guide proposes a dedicated switching study design, with a lead-in period of treatment with the reference product, followed by a randomized two-arm period—with one arm incorporating switching between theproposed interchangeable product and the reference product (switching arm) and the other remainingas a non-switching arm receiving only the reference product. In the US, only the biosimilars approved as interchangeable can be automatically substituted for their reference product at the pharmacy level. As no interchangeable biosimilar has been approved in the US so far, any switch of the reference medicine with a biosimilar or between biosimilars must require the treating physicians’ consent. Although most European countries recommend switching under the supervision of the prescriber, the EMA does not put any restrictions on interchangeability and delegate this to each single EU member state. The differing positions between the EMA and FDA have triggered concerns with both the patients and physicians. Efforts to harmonize regulatory processes for biosimilars approval and post marketing surveillance are warranted to: 1) Increase confidence of healthcare professionals and patients about the clinical impact of switching [58]; 2) Decrease the costs of development and repetition of clinical trials for evaluation of biosimilar products and 3) Improve pharmacovigilance of biosimilars available in clinical practice. Analyses performed in Europe and in the United States showed that current pharmacovigilance frameworks do not always allow for proper adverse events registration and assignment to specific biosimilar products [59]. Moreover, the lack of awareness of health care professionals about the structural complexity of these products may lead to an inappropriate substitution practice, although comprehensive review by regulatory authorities may mitigate these concerns. Networks of electronic healthcare records and administrative databases, potentially linkable to clinical charts and registries may rapidly assess frequency and benefit-risk profile of different switching

patterns in routine care at different levels, thus integrating and strengthening pre-marketing evidence.

Controversy also exists on the possible approval of the candidate biosimilar for other clinical indications of the original drug by extrapolation; this is an important question that has to be addressed by clinical studies: would trastuzumab biosimilars be used in all indications branded trastuzumab have once the candidate drug has showed bio-equivalence with trastuzumab in a particular setting? Extrapolation is a well establish scientific and regulatory principle that allows the approval of a biosimilar for use in an indication held by the reference product but not directly studied in a comparative clinical trial with a biosimilar [60]. Extrapolation of efficacy and safety data from one setting/indication to another may be considered once bioequivalence to the reference product has been shown in terms of pharmacokinetic, immunogenicity, and ultimately safety and efficacy. This frequently misunderstood principle helps avoiding studies unnecessary for regulatory approval and reduce development costs, thereby making biosimilars potentially more accessible to patients. However comprehensive pharmacovigilance is needed for monitoring the marketed biosimilars and ensuring their safety and efficacy. Likewise, the combination of trastuzumab biosimilars with other reference products, be investigated further; studies are warranted to evaluate dual blockade with pertuzumab and trastuzumab biosimilar in HER2+ early and metastatic breast cancer [61]. Moreover, efforts to identify and develop potential biosimilar of new HER2+ directed treatments, including trastuzumab emtansine (Kadcyla®) and pertuzumab, are awaited.

Selecting endpoints for biosimilar development is also not that easy [62]. For original products, endpoints in clinical trials must show benefits to patients, such as progression-free survival, disease-free survival, or overall survival, whereas for biosimilars, surrogate end points, such as the proportion of patients with pathological response in breast cancer neoadjuvant trials are often used. It is thought that the preferred endpoint to establish patient benefit such as progression free/disease free survival or overall survival may not be feasible or sensitive enough for establishing biosimilarity to a reference product since they may be influenced by various factors not attributable to differences between the biosimilar and the reference products themselves, but by factors like tumor burden, performance status, previous lines of treatments, underlying clinical conditions, subsequent lines of treatment [55]. Generally, it should be used the clinical endpoint which is most sensitive in detecting product-related differences and in reducing as much as possible patient and disease-related factors to increase precision. Moreover, survival endpoints might not be sensitive enough when considering comparability and the sample size required for adequate statistical analysis would be prohibitively large. Neoadjuvant setting is in many ways an ideal setting to investigate biosimilars with pCR as a surrogate endpoint for survival [63]. In addition, it is not always true that continuous endpoints are more sensitive to detect differences in clinical effects; sometimes, discrete endpoints are more adequate. Therefore, it is essential to select endpoints according to disease indications and pre-discuss them with the regulatory agencies. Competences of different endpoint measurements are important thoughts for sponsors, while regulatory agencies should care more of study reliability [56].

Finally, to trastuzumab biosimilars entry in routine daily practice, the impact in terms of cost savings should be assessed. Pharmacoeconomic evaluations have been conducted for different biosimilars to estimate their potential savings and effect in different countries. However, to date, only 1 budget impact analysis has been conducted for biosimilar trastuzumab [25]. They reported that 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. The potential effect of biosimilars on health care budgets is not as simple as being only dependent on drug price. For example, trastuzumab was first introduced as an intravenous formulation, but in 2013 a subcutaneous formulation was approved by the EMA for treatment of HER2+ breast cancer; based on noninferiority clinical data. Subcutaneous trastuzumab is administered over a shorter period of time than intravenous trastuzumab (5minutes vs. 30-90 minutes). Savings associated with use of subcutaneous administration of originator trastuzumab need to be assessed alongside those of switching to a biosimilar. In recent years, seven randomized clinical trials investigated whether a shorter regimen of adjuvant trastuzumab might have comparable efficacy to the standard 1-year trastuzumab, but with fewer side effects and reduced costs. Among these, PERSEPHONE trial was the largest non inferiority demonstrating that 6 months of adjuvant trastuzumab is non-inferior to 12 months [64]. This result may mark the first steps towards reduction of treatment duration for this patient population; pharmaceutical companies developing the biosimilars may need to re-assess the cost effectivenessof manufacturing these drugs to possible new standard of care.

CONCLUSION

Monoclonal antibodies (mAbs) such as trastuzumab have become important yet expensive components of systemic oncological treatment across a variety of disease sites; adding a significant cost burden to health care systems. With continuing expiring patents, it is expected that use of biosimilar medicines will continue to rise, reducing the costs of treatment and increasing the accessibility of patients to the biological therapy, with a positive impact on public health. However, many regulatory and clinical issues still remain. Although no clinically meaningful differences in safety, efficacy, and immunogenicity have been reported, the use biosimilars should continue to involve careful patient monitoring, active adverse event reporting with comprehensive post-marketing pharmacovigilance studies encouraged.

REFERENCES

1. Loibl S, Gianni L. HER2-positive breast cancer. Lancet. 2017; 389: 2415-2429.
2. Genentech. Herceptin US prescribing information.
3. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005; 353: 1659-1672.
4. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005; 353: 1673-1684.

5. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011; 365: 1273-1283.

6. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017; 389: 1195-1205.

7. Perez EA, Suman VJ, Davidson NE, Gralow JR, Kaufman PA, Visscher DW, et al. Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. J Clin Oncol. 2011; 29: 4491-4497.

8. Perez EA, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer CE Jr, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014; 32: 3744-3752.

9. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013; 382: 1021-1028.

10. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010; 375: 377-384.

11. Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 2005; 23: 3676-3685.

12. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001; 344: 783-792.

13. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015; 372: 724-734.

14. Baselga J, Swain SM. CLEOPATRA: a phase III evaluation of pertuzumab and trastuzumab for HER2-positive metastatic breast cancer. Clin Breast Cancer. 2010; 10: 489-491.

15. Von Minckwitz G, Schwedler K, Schmidt M, Barinoff J, Mundhenke C, Cufer T,et al. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. Eur J Cancer. 2011; 47: 2273-2281.

16. Gelmon KA, Boyle FM, Kaufman B, Huntsman DG, Manikhas A, Di Leo A, et al. Lapatinib or trastuzumab plus taxane therapy for human epidermal growth factor receptor 2-positive advanced breast cancer: final results of NCIC CTG MA.31. J Clin Oncol. 2015; 33:1574-1583.

17. Blackwell KL, Burstein HJ, Storniolo AM, Rugo HS, Sledge G, Aktan G, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012; 30: 2585-2592.

18. Rimawi MF, Niravath PA, Wang T, Rexer B, Forero A, Wolff AC, et al. TBCRC023: a randomized multicenter phase II neoadjuvant trial of lapatinib plus trastuzumab, with endcorine therapy and without chemotherapy, for 12 vs. 24 weeks in patients with HER2 overexpressing breast cancer. Cancer Res. 2015; 75: S6-02.

19. IMS Health. Top 20 global products 2015. December 2015.

20. Cancer control WHO Guide for effective Programs.

21. Lammers P, Criscitiello C, Curigliano G, Jacobs I. Barriers to the Use of Trastuzumab for HER2+ Breast Cancer and the Potential Impact of Biosimilars: A Physician Survey in the United States and Emerging Markets. Pharmaceuticals. 2014; 7: 943-953.

22. Zelenetz AD, Ahmed I, Braud EL, Cross JD, Davenport-Ennis N, Dickinson BD, et al. NCCN biosimilars white paper: Regulatory, scientific, and patient safety perspectives. J Nat Compr Canc Netw. 2011; 9: S1-S22.

23. Cai X, Wake A, Gouty D. Analytical and bioanalytical assay challenges to support comparability studies for biosimilar drug development. Bioanalysis. 2013; 5: 517-520.

24. Blackwell K, Gligorov J, Jacobs I, Twelves C. The global need for a trastuzumab biosimilar for patients with HER2-positive breast cancer. Clin Breast Cancer. 2018; 18: 95-113.

25. Cesarec A, Likic R. Budget impact analysis of biosimilar trastuzumab for the treatment of breast cancer in Croatia. Appl Health Econ Health Policy. 2017; 15: 277-286.

26. European Medicines Agency (2017) EPAR Summary for the Public: Ontruzant (Trastuzumab).

27. European Medicines Agency (2018) EPAR Summary for the Public: Kanjinti (Trastuzumab).

28. European Medicines Agency (2018) EPAR Summary for the Public: Trazimera (trastuzumab).

29. European Medicines Agency (2018) EPAR Summary for the Public: Herzuma (trastuzumab**).**

30. Pivot X, Curtit E, Lee YJ, Golor G, Gauliard A, Shin D, et al. A Randomized Phase I Pharmacokinetic Study Comparing Biosimilar Candidate SB3 and Trastuzumab in Healthy Male Subjects. Clin Ther. 2016; 38: 1665-1673.

31. Pivot X, Bondarenko I, Nowecki Z, Dvorkin M, Trishkina E, Ahn JH, et al. Phase III, randomized, double-blind study comparing the efficacy, safety, and immunogenicity of SB3 (trastuzumab biosimilar) and reference trastuzumab in patients treated with neoadjuvant therapy for human epidermal growth factor receptor 2-positive early breast cancer. J Clin Oncol. 2018; 36: 968-974.

32. Pivot X, Bondarenko I, Nowecki Z, Dvorkin M, Trishkina E, Ahn JH, et al. A phase III study comparing SB3 (a proposed trastuzumab biosimilar) and trastuzumab reference product in HER2-positive early breast cancer treated with neoadjuvant–adjuvant treatment: final safety, immunogenicity and survival results. Eur J Cancer. 2018; 93: 19-27.

33. Esteva FJ, Stebbing J, Wood-Horrall RN, Winkle PJ, Lee SY, Lee SJ. A randomised trial comparing the pharmacokinetics and safety of the biosimilar CT-P6 with reference trastuzumab. Cancer Chemother Pharmacol. 2018; 81: 505-514.

34. Im Y-H, Odarchenko P, Grecea D, Komov D, Anatoliy CV, Gupta S, et al. Double-blind, randomized, parallel group, phase III study to demonstrate equivalent efficacy and comparable safety of CT-P6 and trastuzumab, both in combination with paclitaxel, in patients with metastatic breast cancer as first-line treatment. J Clin Oncol. 2013; 31: Poster 62.

35. Stebbing J, Baranau Y, Baryash V, Manikhas A, Moiseyenko V, Dzagnidze G, et al. CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial. Lancet Oncol. 2017; 18: 917-928.

36. Hurst S, Ryan AM, Ng CK, McNally JM, Lorello LG, Finch GL, et al. Comparative nonclinical assessments of the proposed biosimilar PF-

05280014 and trastuzumab (Herceptin). BioDrugs. 2014; 28: 451–459.

37. Yin D, Barker KB, Li R, Meng X, Reich SD, Ricart AD, 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: 1281-1290.

38. Lammers PE, Dank M, Masetti R, Abbas R, Hilton F, Coiro J, et al. Neoadjuvant PF-05280014 (a potential trastuzumab biosimilar) versus trastuzumab for operable HER2+ breast cancer. Br J Cancer. 2018; 119: 266-273.

39. Pegram M, Tan-Chiu E, Freyman A, Vana A, Hilton F, Zacharchuk C, et al. A randomized, double blind study of PF-05280014 (a potential trastuzumab biosimilar) vs trastuzumab, both in combination with paclitaxel, as first-line treatment for HER2-positive metastatic breast cancer. Ann Oncol. 2017; 28: 74-108.

40. Hanes V, Born T, Chow V. Comparative similarity of ABP 980 and trastuzumab: Results of functional similarity and human pharmacokinetic assessment. In: Proceedings of the Thirty-Eighth Annual CTRC-AACR San Antonio Breast Cancer Symposium: 2015 Dec 8-12; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res, 2016; 76: P6-13-12.

41. Von Minckwitz G, Ponomarova O, Morales S, Zhang N, Hanes V. Efficacy and safety of biosimilar ABP 980 compared with trastuzumab in her2 positive early breast cancer. Ann Oncol. 2017; 28:37-43.

42. Von Minckwitz G, Colleoni M, Kolberg HC, Morales S, Santi P, Tomasevic Z, et al. Efficacy and safety of ABP 980 compared with reference trastuzumab in women with HER2-positive early breast cancer (LILAC study): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2018; 19: 987-998.

43. Rugo HS, Barve A, Waller CF, Hernandez-Bronchud M, Herson J, Yuan J, et al. Effect of a proposed trastuzumab biosimilar compared with trastuzumab on overall response rate in patients with ERBB2 (HER2)–positive metastatic breast cancer: a randomized clinical trial. JAMA. 2017; 317: 37-47.

44. Mylan Inc. Internal reports including results from Study MYL-Her-1001 and MYL-Her-1002. Presented at: Pharmacology 2015 Meeting of the British Pharmacological Society; December 15-17, 2015; London, England.

45. Shustova M, Burdaeva O, Alexeev S, Shelepen K, Khorinko A, Mukhametshina G, et al. Efficacy and safety of BCD-022, trastuzumab biosimilar candidate, compared to herceptin: Results of international multicenter randomized double blind study in patients with HER2+ mBC. Anns Oncol. 2016; 27: 68-99.

46. López-Morales CA, Miranda-Hernández MP, Juárez-Bayardo LC, Ramírez-Ibáñez ND, Romero-Díaz AJ, Piña-Lara N, et al. Physicochemical and biological characterization of a biosimilar trastuzumab. Biomed Res Int. 2015; 2015: 427235.

47. Wisman LA, De Cock EP, Reijers JA, Kamerling IM, Van Os SH, de Kam ML, et al. A phase I dose-escalation and bioequivalence study of a trastuzumab biosimilar in healthy male volunteers. Clin Drug Investig. 2014; 34: 887-894.

48. Zhou X, Yu J, Wang W, Song G, Wan X, Ren J, et al. A phase I dose-escalation study of a biosimilar trastuzumab in Chinese metastasis breast cancer patients. Springerplus. 2015; 4: 803.

49. Morita J, Tanaka M, Nomoto M, Matsuki S, Tsuru T, Matsuguma K, et al. Pharmacokinetic Bioequivalence, Safety, and Immunogenicity of DMB-3111, a Trastuzumab Biosimilar, and Trastuzumab in Healthy Japanese Adult Males: Results of a Randomized Trial. BioDrugs. 2016; 30: 17-25.

50. Chen L, Wang L, Shion H, Yu C, Yu YQ, Zhuet L, et al. In-depth structural characterization of Kadcyla® (ado-trastuzumab emtansine) and its biosimilar candidate. Mabs. 2016; 8: 1210-1223.

51. European Medicines Agency. Guideline on similar biological medicinal products. 2005.

52. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. 2006.

53. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2006.

54. European Medicines Agency. Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins. 2007.

55. European Medicines Agency. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. 2012.

56. Zhang N, Chi E. Statistical considerations for the development of biosimilar products. GaBI Journal. 2014; 3: 21-25.

57. US FDA. Biological Product Definitions.

58. Trifirò G, Marcianò I, Ingrasciotta Y. Interchangeability of biosimilar and biological reference product: updated regulatory positions and pre- and post-marketing evidence. Expert Opin Biol Th. 2018; 18: 309-315.

59. Grampp G, Felix T. Pharmacovigilance considerations for biosimilars in the USA. BioDrugs. 2015; 29: 309-321.

60. Krendyukov A, Schiestl M. Extrapolation concept at work with biosimilar: a decade of experience in oncology. ESMO Open. 2017; 3: 00319.

61. Baker H. Trastuzumab biosimilar shows potential for breast cancer. Lancet Oncol. 2017; 18: e4.

62. Nixon NA, Hannouf MB, Verma S. The evolution of biosimilars in oncology, with a focus on trastuzumab. Curr Oncol. 2018; 25: S171-S179.

63. Jackisch C, Scappaticci FA, Heinzmann D, Bisordi F, Schreitmüller T, Minckwitz Gv, et al. Neoadjuvant breast cancer treatment as a sensitive setting for trastuzumab biosimilar development and extrapolation. Future Oncol. 2015; 11: 61-71.

64. Earl HM, Hiller L, Vallier AL, Loi S, Howe D, Higgins HB, et al. PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): Randomised phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results. J Clin Oncol. 2018; 36: 506.

Cite this article

Viale G, Irshad S (2018) Trastuzumab Biosimilars Setting the Pace for the Provision of a Cost Effective Oncological Care: Regulatory and Clinical Issues. Ann Breast Cancer Res 3(1): 1014.