

# Trastuzumab Biosimilars in the Therapy of Breast Cancer – “Real World” Experiences from four Bavarian University Breast Centres

## Trastuzumab-Biosimilars in der Therapie des Mammakarzinoms – „Real World“-Erfahrungen aus 4 bayerischen universitären Brustzentren



### Authors

Anna Hester<sup>1</sup>, Paul Gaß<sup>2</sup>, Peter A. Fasching<sup>2</sup>, Anne Katrin Krämer<sup>3</sup>, Johannes Ettl<sup>3</sup>, Joachim Diessner<sup>4</sup>, Achim Wöckel<sup>4</sup>, Tobias Egger<sup>5</sup>, Katja Stock<sup>6</sup>, Jutta Redlin<sup>7</sup>, Monika Andraschko<sup>8</sup>, Nadia Harbeck<sup>1</sup>, Rachel Würstlein<sup>1</sup>

### Affiliations

- 1 Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Brustzentrum und CCC München, Klinikum der Universität München, LMU München, München
- 2 Frauenklinik des Universitätsklinikums Erlangen, Erlangen
- 3 Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe der Technischen Universität München und CCC München, München
- 4 Frauenklinik und Poliklinik des Universitätsklinikums Würzburg, Würzburg
- 5 Apotheke des Universitätsklinikums Würzburg, Würzburg
- 6 Apotheke des Universitätsklinikums Erlangen, Erlangen
- 7 Krankenhausapotheke des Klinikums Rechts der Isar der Technischen Universität, München
- 8 Apotheke des LMU Klinikums, München

### Key words

HER2, breast cancer, trastuzumab, biosimilar, pCR

### Schlüsselwörter

HER2, Mammakarzinom, Trastuzumab, Biosimilar, pCR

received 29.6.2020

accepted after revision 22.7.2020

### Bibliography

DOI <https://doi.org/10.1055/a-1226-6666>  
 Geburtsh Frauenheilk 2020; 80: 924–931 © Georg Thieme  
 Verlag KG Stuttgart · New York | ISSN 0016-5751

### Correspondence

Dr. med. Anna Hester  
 Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe,  
 Brustzentrum und CCC München, Klinikum der Universität  
 München, LMU München  
 Marchioninistraße 15, 81377 München, Germany  
[anna.hester@med.uni-muenchen.de](mailto:anna.hester@med.uni-muenchen.de)



Deutsche Version unter:

<https://doi.org/10.1055/a-1226-6666>

Supporting Information:

<https://doi.org/10.1055/a-1226-6666>

### ABSTRACT

**Introduction** With the introduction of the first trastuzumab biosimilar in the summer of 2018, biosimilar antibodies for breast cancer have found their way into the area of gynaecological oncology. The switch of anti-human epidermal growth factor receptor 2 (HER2) therapy from the reference drug Herceptin® to a biosimilar has presented challenges to the clinics. In addition to structural and organisational measures, training of employees as well as patient briefing and acceptance were major challenges. The study presented here records – within the context of quality assurance – how the switch to a trastuzumab biosimilar was implemented at four Bavarian university clinics in the Purchasing Association of Bavarian University Pharmacies.

**Materials/Methods** Questionnaires on treatment figures and the switching process were sent to breast centres and pharmacies of four Bavarian university clinics between July and December 2019. The neoadjuvant, adjuvant and metastasised anti-HER2 therapy with trastuzumab with or without pertuzumab was recorded, evaluated and summarised.

**Results** In the anti-HER2-therapy, trastuzumab was used intravenously (i.v.) and subcutaneously. Between July and December 2018, all four clinics in the Purchasing Association switched the i.v. trastuzumab therapy from the reference drug (Herceptin) to a biosimilar (for 2018: Kanjinti®). Over 200 patients were treated with trastuzumab i.v. in each of the two half-years of 2018 (before and after the switch). The spectrum of side effects and pCR rates under therapy with the biosimilar were comparable to the experiences made with the reference drug. Three out of four clinics provided training to

employees and informed patients by means of a defined information leaflet. Patient acceptance was high.

**Summary** The anti-HER2 therapy could be switched successfully and safely to trastuzumab biosimilars at the Bavarian university hospitals. This may serve as guideline for the further implementation of biosimilars. The structures necessary for this initial switching process have been prepared with trastuzumab as an example.

## ZUSAMMENFASSUNG

**Einleitung** Mit Einführung der ersten Trastuzumab-Biosimilars im Sommer 2018 haben biosimilare Antikörper beim Mammakarzinom Einzug in die gynäkologische Onkologie gehalten. Die Umstellung der Anti-„human epidermal growth factor receptor 2“- (HER2-)Therapie vom Referenzarzneimittel Herceptin® auf ein Biosimilar hat die Kliniken vor Herausforderungen gestellt. Neben strukturellen und organisatorischen Maßnahmen waren Schulung von Mitarbeitern sowie Patientenaufklärung und -akzeptanz wichtige Herausforderungen. Die vorliegende Studie erfasst im Rahmen der Qualitätssicherung, wie die Umstellung auf ein Trastuzumab-Biosimilar an 4 bayerischen Universitätskliniken im Einkaufsverbund Bayerischer Universitätsapotheken durchgeführt wurde.

**Material/Methoden** Fragebögen zu Behandlungszahlen und Umstellungsprozess wurden an Brustzentren und Apotheken

4 bayerischer Universitätskliniken zwischen Juli und Dezember 2019 versandt. Die neoadjuvante, adjuvante und metastasierte Anti-HER2-Therapie mit Trastuzumab mit oder ohne Pertuzumab wurde erfasst und zusammenfassend ausgewertet.

**Ergebnisse** In der Anti-HER2-Therapie wurde Trastuzumab intravenös (i. v.) und subkutan eingesetzt. Alle 4 Kliniken stellten die i. v. Trastuzumab-Therapie zwischen Juli und Dezember 2018 im Einkaufsverbund vom Referenzarzneimittel (Herceptin) auf ein Biosimilar (für 2018: Kanjinti®) um. In beiden Halbjahren 2018 (vor und nach Umstellung) wurden jeweils über 200 Patientinnen mit Trastuzumab i. v. behandelt. Nebenwirkungsspektrum und pCR-Raten waren unter Therapie mit dem Biosimilar vergleichbar mit den Erfahrungen beim Referenzarzneimittel. An 3/4 Kliniken wurden die Mitarbeiter im Rahmen von Fortbildungen geschult und die Patientinnen mittels eines definierten Aufklärungsbogen informiert. Es lag eine hohe Patientenakzeptanz vor.

**Zusammenfassung** Die Anti-HER2-Therapie konnte an den bayerischen Universitätskliniken erfolgreich und sicher auf Trastuzumab-Biosimilars umgestellt werden. Dies kann als Leitfaden für weitere Biosimilar-Implementierungen dienen. Der erste Umstellungsprozess am Beispiel von Trastuzumab hat die Strukturen vorbereitet.

---

## Introduction

Biological drugs (biologics) have become increasingly important in medicinal therapy in recent years. Biologics are large and complex biologically active molecules, which are produced biotechnologically as drugs from living cells. Owing to their size and complexity, complete molecular-genetic characterisation of biologics is often not achievable [1, 2].

As soon as patent protection for a biologic expires, the drug may also be produced and marketed by other pharmaceutical companies. These biologic-equivalents (biosimilars) are structurally similar to the original drug and produce an identical effect in the human body. Since the production of these complex molecules occurs in living cells, biosimilars are however, depending on the production process, not fully identical in structure to the reference product. Likewise, different batches of the same product may show a certain structural variability. This represents the difference between biosimilars and chemically-synthesised, easily characterised generics. For marketing authorisation for a biosimilar, proof is required of identical biological characteristics, identical efficacy and identical safety [1, 5]. The American and European regulatory authorities describe the marketing authorisation concept for biosimilars as “Totality of Evidence”: This represents the entirety of all analytical, preclinical and clinical studies necessary for the marketing authorisation of a biosimilar. The concept follows a stepwise approach: The essential first step lies in the functional and analytical testing to demonstrate, at the molecular level, the similarity of the biosimilar to the reference drug. The pre-clinical testing may then be shortened in comparison to the mar-

keting authorisation process for new drugs and focuses on potential uncertainties arising from the qualitative analyses. Phase I studies must demonstrate the equivalence with regard to pharmacodynamics and kinetics; Phase III data on safety in clinical use must be collected in at least one indication. Once all the evidence has been provided, marketing authorisation of the biosimilar may occur in this indication. If it is demonstrated that the mechanism of action of the biosimilar in an additional indication is the same as in the indication studied (and if the above-mentioned data on pharmacokinetics, immunogenicity, efficacy and safety are available) marketing authorisation for this additional indication may be granted. This is termed the concept of extrapolation [3, 4, 6, 7].

The first authorised biosimilar in Europe was the somatotropin biosimilar Omnitrope® in 2006. Biosimilars – for example, the active substance filgrastim – have been in use for years in oncology and gynaecology. Biosimilar monoclonal antibodies found their way into gynaecological oncology with the marketing authorisation and availability of the first trastuzumab biosimilar for the therapy of HER2-positive breast cancer on 02 May 2018 [8].

Clinical equivalence to the reference product was demonstrated for the trastuzumab biosimilar Kanjinti in the neoadjuvant and adjuvant setting [9], for Trazimera® in the metastatic setting [10] and for Herzuma® in the neoadjuvant setting [11]. The corresponding marketing authorisation was then granted for neoadjuvant, adjuvant and metastatic therapy of breast and stomach cancer.

The costs for oncologic therapies increased by 41% between 2011 and 2015 [12]. Most recently, in 2018, costs for oncologic therapies further increased by 6% when compared to 2017 [13].

Oncologics are among the active substances with the highest turnovers; according to the BARMER-drug report 2019, trastuzumab ranked 7th in turnover in 2018 [13]. It is estimated that the introduction of biosimilars could save 50–100 billion euros in therapy costs in the European Union and the USA in 2020 [14, 15].

Nevertheless, the introduction of biosimilars presents challenges to the treating physicians. During the first years after their introduction on the market biosimilars were used only hesitantly in Germany. Both physicians and patients were uncertain with regard to efficacy, safety and exchangeability of these drugs [16, 17]. A survey in the USA showed that over 30% of oncologists had concerns with regard to safety of biosimilars [18]. This emphasises the need for briefing and training on biosimilars within the medical profession. Physicians must also be briefed thoroughly on the concept of extrapolation [5, 17].

Trastuzumab has an established status in the therapy of the early and metastatic breast cancer [19–21]. The Association of Gynaecological Oncology (AGO) has recommended the use of trastuzumab biosimilars since 2018 [22]. In the summer of 2018, all breast centres of the Bavarian universities within the Purchasing Association of the Bavarian University Pharmacies (EBU) implemented the switch of trastuzumab therapy from the reference drug to the biosimilar. Extended organisational and structural decisions and measures were linked to this decision for a biosimilar.

The work presented here summarises the organisational aspects and clinical experiences from four Bavarian university breast centres (which are affiliated in the EBU) during the switch to a biosimilar. The pathological complete remission rate (pCR) of the neoadjuvant anti-human epidermal growth factor receptor 2- (HER2-) therapy was recorded as the outcome parameter for oncological safety of the biosimilar therapy. These experiences may serve as guidelines for the future introduction of further biosimilars.

## Materials and Methods

This study recorded the switch of targeted anti-HER2 therapy of early and metastatic, HER2-positive breast cancer at four Bavarian university clinics (Technical University of Munich, Ludwig-Maximilian University of Munich, Julius-Maximilian University of Würzburg, Friedrich-Alexander University of Erlangen) within the context of measures for quality assurance. The pharmacies of the four university clinics are affiliated in the EBU. A consistent biosimilar in the EBU was chosen; access to this biosimilar was granted to the four university clinics simultaneously starting in July 2018. Since Regensburg University Hospital belongs to a different purchasing association, it was not included in the survey.

## Procedure

The breast centre of the LMU clinic generated two questionnaires (see below for content). These were sent to the pharmacies and the management department of the breast centres of the other university clinics in July 2019. The questionnaires were completed by employees of the respective breast centres and pharmacies. One breast centre did not supply any treatment figures and is therefore considered in the following evaluation only with regard to the switching processes but not to the figures. The content of

the returned questionnaires were summarised under anonymised conditions. An updated set of pCR rates was obtained again in December 2019.

## Questionnaires

The questionnaires used in this study are attached as Supporting Information.

### Breast centres

The questionnaire directed to the breast centres consisted of two main parts. The first part recorded the anti-HER2 therapies established as standard therapies at the breast centres before the trastuzumab biosimilar became available and the side effects that occurred. The centres were asked from what point in time onwards and in what kind of therapeutic situations (only in newly initiated therapies versus ongoing therapies in the neoadjuvant, post-adjuvant, adjuvant or metastatic therapy situation) the therapy was switched to which biosimilar. In addition, the treatment figures were recorded: The treatment figures for anti-HER2 therapies within the 1st and 2nd half of 2018 (before and after the switch to the biosimilar) were collected for patients receiving neoadjuvant, post-neoadjuvant, adjuvant and metastatic treatment (in each case with or without pertuzumab). In order to examine the oncological safety, the pCR rates of the primary cases from 2018 (therapy could extend into 2019), who had received neoadjuvant anti-HER2 therapy, were recorded and the pCR rates of patients receiving treatment with the reference drug Herceptin only, partly reference drug/partly biosimilar and the biosimilar only (all in combination with pertuzumab) were compared.

The second part surveyed organisational aspects of the switching process. Participants were asked who was responsible for the coordination of the switch, how physician employees, nurses and patients were informed about the switch and whether there were queries or difficulties encountered by the respective occupational groups. In addition, it was asked in more detail whether patients rejected the biosimilar or whether there were side effects and how much extra time was required per patient.

### Pharmacies

The questionnaire directed at the pharmacies initially asked general questions about the anti-HER2 therapy. Here, it was recorded how many doses of the reference drug or the biosimilar were dispensed per month during the first and the second half of 2018, as well as which biosimilar was used from what time point onwards. In the second part of the switching process, it was also asked who was responsible for the decision to use a biosimilar and who coordinated the switching process. It was also recorded more precisely which biosimilars were under consideration and the factors that led to the decision for the biosimilar currently in use. In addition, questions were asked on the technical aspects of the product and on the formalities concerning billing and documentation. Furthermore, questions were also asked on information and queries from medical employees, nurses and patients directed to the pharmacies.

## Analysis

The contents of the questionnaires were analysed under anonymised conditions and summarised in the following work. This project serves as quality assurance for the centres. In consultation with the ethics committee this project is considered a measure of quality assurance. Since it is a purely retrospective analysis of experiences, there was no impact on the course of the therapies of individual patients. The answers from the questionnaire do not allow inferences to individual patients or centres.

## Results

### Standards of the participating breast centres in the anti-HER2 therapy of early and metastatic breast cancer *before* the availability of the trastuzumab biosimilar

All clinics regularly provide neoadjuvant, post-neoadjuvant, adjuvant and metastatic treatment to patients with HER2-positive breast cancer. Depending on the clinic, the proportion of subgroups in relation to total anti-HER2 therapies differed in the first half of 2018. A total of approx. 250 patients were treated with intravenous (i. v.) trastuzumab during the first half of 2018. Pertuzumab in combination with the reference drug was used in all clinics – at different proportions, depending on the therapeutic indication (► **Table 1**, left). One clinic did not provide treatment figures and is therefore not included in all following tables.

Depending on the clinic, i. v. application of trastuzumab was primarily used (in this case up to 145 doses per month), or in part intravenous and in part subcutaneous (s. c.) (approx. 40 i. v. therapies and 30 subcutaneous doses per month) or predominantly trastuzumab s. c. (approx. 65 s. c. doses and 4 i. v. therapies per month).

All four clinics had no adverse drug reactions except occasionally those cited in the Summary of Product Characteristics.

### Switch of anti-HER2 therapy to trastuzumab biosimilar in the 2nd half of 2018

The EBU chose the biosimilar Kanjinti for use in the participating clinics. The first doses of the biosimilar were dispensed depending on the clinic between July and December of 2018 (18.07.2018, 01.08.2018, 06.08.2018, 12/2018).

In three out of four clinics, both ongoing as well as newly initiated i. v. trastuzumab therapies in all therapeutic indications were switched from the reference drug to the biosimilar (now up to 158 i. v. therapies per month or 50–60 i. v. therapies and 15 s. c. therapies per month). Use of the reference drug continues only in the case of participation in a clinical trial or in exceptional individual cases (side effects). In one clinic, the biosimilar was only used in newly initiated i. v. therapies, whereas ongoing s. c. and i. v. therapies were continued with the reference drug (now approx. 100 doses of the reference drug s. c. and 10 doses of the biosimilar i. v. per month).

In the 2nd half of 2018, approx. 210 patients were treated with the biosimilar. After switching to the biosimilar, the percentage distribution to the different therapy indications (neoadjuvant, post-neoadjuvant, adjuvant, metastatic) remained more or less the same as in the 1st half year before switching. Likewise, pertuzumab was still being used. Comparison of the figures of both half years with regard to the use of pertuzumab in post-neoadjuvant and adjuvant therapy is only possible to a limited extent, since the marketing authorisation for pertuzumab in this therapy situation was granted in June 2018 (► **Table 1** right).

### Comparison of pCR rates with the reference drug and the biosimilar to investigate the oncological safety of the biosimilar

To investigate the oncological safety of the biosimilar, the pCR rates after neoadjuvant therapy were recorded as outcome parameter. In this case, data was collected separately from patients who, in the neoadjuvant therapy, had only received the reference

► **Table 1** Treatment figures from three Bavarian university clinics in the therapy of HER2-positive breast cancer (in one clinic with > 90% proportion of Herceptin s. c. treatment, figures were not recorded).

Treatment figures HER2-positive breast cancer 2018	Patient numbers in 2018 before introduction of biosimilar (1st half of 2018, n = 288)		Patient numbers in 2018 since introduction of biosimilar (2nd half of 2018, n = 242)		
	Herceptin i. v.	Herceptin s. c.	Biosimilar	Herceptin i. v.	Herceptin s. c.
neoadjuvant total (% of all patients)	59 (20%)	1 (< 1%)	58 (24%)	1 (< 1%)	0 (0%)
▪ of which + pertuzumab (%)	57 (97%)	0 (0%)	58 (100%)	1 (100%)	0 (0%)
post-neoadjuvant total (% of all patients)	65 (23%)	20 (7%)	44 (18%)	2 (1%)	10 (4%)
▪ of which + pertuzumab (%)	21 (32%)	1 (5%)	31 (70%)	1 (50%)	1 (10%)
adjuvant total (% of all patients)	38 (13%)	2 (1%)	32 (13%)	0 (0%)	1 (< 1%)
▪ of which + pertuzumab (%)	8 (21%)	0 (0%)	11 (34%)	0 (0%)	0 (0%)
metastatic total (% of all patients)	91 (32%)	12 (4%)	77 (32%)	4 (2%)	11 (5%)
▪ of which + pertuzumab (%)	61 (67%)	0 (0%)	52 (68%)	2 (50%)	0 (0%)
<b>total</b>	<b>253 (88%)</b>	<b>35 (12%)</b>	<b>211 (87%)</b>	<b>9 (4%)</b>	<b>22 (9%)</b>
▪ of which + pertuzumab (%)	146 (58%)	1 (3%)	152 (72%)	4 (44%)	1 (5%)

► **Table 2** pCR rates after neoadjuvant anti-HER2 therapy in patients with early HER2-positive breast cancer from three participating clinics. Two patients from centre 1, who received only Herceptin neoadjuvant, were treated within the scope of the TP2 study. Of note is the smaller number of cases of the 1st group, which is due to the inclusion time interval. All primary cases of the year 2018 with continuation of the therapy also into 2019 were included.

Therapeutic schedule for the neoadjuvant therapy	Primary cases HER2-positive breast cancer of the year 2018					
	neoadjuvant only Herceptin + pertuzumab		neoadjuvant in part Herceptin + pertuzumab, in part biosimilar + pertuzumab		neoadjuvant only biosimilar + pertuzumab	
	pCR	non-pCR	pCR	non-pCR	pCR	non-pCR
Number of patients (%)	5 (33%)	10 (67%)	13 (54%)	11 (46%)	22 (55%)	18 (45%)

drug, both the reference drug and the biosimilar or only the biosimilar. Almost all patients received pertuzumab in addition to trastuzumab. Due to small number of cases, marked fluctuations in pCR rates between the clinics are sometimes observed. The therapy with only the reference drug + pertuzumab had a pCR rate of 33% summed up over all clinics with an overall small number of cases in this group. The therapy with in part biosimilar/in part reference drug as well as only the biosimilar (each in combination with pertuzumab) had a pCR rate of 54 and 55% respectively (► **Table 2**).

## Switching process to trastuzumab biosimilar

### Decision process and logistics

The pharmacies and management departments of the breast centres were responsible for coordinating the switch. The EBU led the contract negotiations. All available trastuzumab biosimilars were discussed. The decision for the biosimilar Kanjinti was influenced by various factors. According to the participating pharmacies, these comprise cost/benefit analysis, authorisation data, stability data, efficacy, safety, security of supply, galenics, handling, pack size, logistics, labelling, shelf life and supplier rating. No specific difficulties were encountered in the coordination of the switching process. A prior intensive consultation between the pharmacies and all participating clinics, as well as good patient communication, were important. Furthermore, it was essential that the therapy protocols were activated in the cytostatics ordering systems at the target date and that the name of the biosimilar was clearly distinguishable from the reference drug in the ordering system. This guaranteed traceability. Technical difficulties in the production of the biosimilar infusion solutions were not encountered. The larger volume of the bottle (420 mg content instead of 150 mg for the reference drug) facilitated handling. The ready-to-use application solution can be kept for 7 days. No difficulties arose with regard to billing and documentation.

### Briefing and communication with physicians and nursing staff

The team of physicians and the nursing staff were informed in all participating clinics by the management department of the breast centres or the day clinics. The information was communicated via e-mail, information letters (exact course of action/time point of the switch) as well as via personal discussions and team meetings. In addition, internal clinic training for switching to biosimilars took place in three clinics. There were no specific difficul-

ties encountered on the physicians' side (in total approx. 2–3 queries to the pharmacies since the switch). The additional time required for briefing the patients is estimated at 5–10 minutes per patient. One clinic estimates that about 5% of the patients required additional time due to the briefing and patient queries. Only in cases where there were extended queries or rejections by patients, was the necessary time expenditure clearly increased. Care staff occasionally also directed questions to the pharmacies on the administration of the biosimilar.

### Patient briefing and side effects

In three of the participating clinics, patients were informed on the use of the biosimilar in a personal discussion with the physician. This discussion was documented in writing in the patient file. In two clinics the patients were additionally required to confirm their consent to the use of the biosimilar by signing a defined informed consent form. In addition, patients received standardised information material from the EMA. One clinic did not conduct a dedicated patient briefing. However, here, the s.c. therapy with trastuzumab was continued in >90% of cases and the switch to the biosimilar thus only affected a small fraction of all treated patients. Patients had occasional queries, directed in part to the physicians in part to the pharmacies. The queries concerned mostly equivalence of efficacy, the difference between generic and biosimilar, production site and production process (since the tradename sounded "Chinese") as well as drug safety with regard to the expected side effects. There were fears of being a "test object", of receiving poorer-quality medications for cost reasons as well as, as a patient insured by the public health system, not receiving the same medications as private patients. These fears were expressed especially by patients who had already received long-term trastuzumab for metastatic breast cancer. All queries were answered by the participating pharmacists or physicians in detailed personal discussions.

The observed side effects of the trastuzumab biosimilar essentially corresponded to the side effects specified in the Summary of Product Characteristics, the reporting obligation is fulfilled. General discomfort and diffuse symptoms (nausea, stomach cramps, muscle pain), flu-like symptoms, fever, subjectively painful skin as well as tinnitus were described. With the exception of tinnitus these side effects are also specified in the Summary of Product Characteristics of the biosimilar [23]. Sometimes the side effects ceased after repeated administration, in other cases premedication with dimetindene and paracetamol was administered. If side

effects persisted, the therapy was switched back to the reference drug administered s.c or i.v. In total, 12 patients were reported from the surveyed clinics to have definitely rejected the administration of the biosimilar by the time the survey was conducted.

## Discussion

The introduction of a trastuzumab biosimilar at the Bavarian university clinics in summer of 2018 was the first time an antibody therapy was switched to a biosimilar in all gynaecology clinics on a large scale. This work shows which points in such a switching process should absolutely be considered, where difficulties might arise and which structures are important and may thus serve as a guideline for future switching processes.

The treatment figures of the participating clinics show that introducing the biosimilar into the oncology therapy did not result in any significant shifts in the treatment figures. Within the scope of this survey, no patient changed over to a different centre due to rejection of the biosimilar therapy. In both halves of 2018 more than 200 patients were treated with trastuzumab – this demonstrates the high relevance of this topic for a relevant proportion of our oncology patients.

As a parameter for the oncological safety, the pCR rate of the therapy with the biosimilar and the experiences with the reference drug were comparable. However, this statement is subject to some constraints due to low number of cases and due to the retrospective nature of the survey without adjustment for patient specific confounders. Due to the stipulated inclusion period, the group of patients who only received the reference drug was however small: Primary cases of the year 2018 were included – following diagnosis of HER2-positive breast cancer, neoadjuvant therapy generally however begins with 8–12 weeks of anthracycline chemotherapy and the anti-HER2 therapy is only administered after a time interval. This meant that for patients with a first diagnosis in the year 2018 there was barely enough time to have completed the neoadjuvant therapy exclusively with the reference drug before the introduction of the biosimilar and only a small group achieved this. Additionally and outside the common project the pCR rate at the LMU was surveyed again for comparison when additional patients who had only received the reference drug and who had had their first diagnosis as early as 01.10.2017 were included. In this instance the pCR rate was 57% and was thus comparable to the “in part reference drug/in part biosimilar” or the “biosimilar only” group from this survey (54 or 55% respectively). With very low case numbers, these figures agree with the data on comparable efficacy and represent additional real world evidence for the use of the biosimilars [24].

The expert associations do not provide clear recommendations on the optimal time point for the switch (e.g. in neoadjuvant therapy concepts, it would be possible to switch to the biosimilar during the ongoing neoadjuvant therapy or only postoperatively during the adjuvant stage). Within the scope of this survey, we could not identify any disadvantages through an immediate switch. Logistically it is easiest to switch all patients at the target date regardless of their therapeutic regimen.

There were no technical or billing difficulties at any of the participating clinics. It is important to thoroughly assess potential

products beforehand with regard to these factors as was done in this case. An important point concerns furthermore the use of trastuzumab in clinical studies. It must be determined reliably whether the respective study allows for the use of a biosimilar or whether the reference drug, administered i.v. or s.c., must be used. All German study groups still opened their studies for all suitable substances in 2018.

The detailed briefing of physicians and nurses, partly through training events, resulted in relatively few queries arising on the topic of biosimilars. All professional groups appeared well informed about the concept. Good provision of information to the treating team is extremely important to, on the one hand, counter the, partly unfounded scepticism of physicians and nursing staff towards biosimilars [17, 18], however, on the other hand, also to be able to inform the patients sufficiently.

Thorough briefing of patients, ideally with defined written information leaflets, represents an essential part of the switching process. Scepticism and fears of the patients mostly arose with regard to possibly receiving poorer-quality therapies for cost reasons, as is also described in other patient surveys on biosimilars [25]. It was evident in our patient collective that especially those patients who had received long-term trastuzumab therapy, who had good experiences with therapy with few side effects and a long, stable disease process, met the therapy switch with the most scepticism. However, renewed detailed discussions with the respective patients about the mechanism of action, medical background, marketing authorisation situation, decision process and oncological safety led to broad acceptance. This shows that a good patient education can contribute considerably to the success of such a switching process, without complications. A large survey with over 3,000 patients (partly also oncology patients) as well as with healthy controls in Europe and the USA revealed that the general knowledge and awareness of biosimilars in the general population is low and that persons with a disease have a slightly better knowledge [26]. A patient educational measure performed in the USA with printed information on biosimilars was subsequently evaluated via an online survey. This showed that subsequently almost 80% of the oncology patients were able to answer correctly questions regarding marketing authorisation, reporting of side effects and cost management of biosimilars [27]. The German Society for Haematology and Oncology (DGHO) recommends dedicated briefing by the treating physician [28]. The European Society for Medical Oncology (ESMO) emphasizes the necessity of educating the prescribing physicians, nursing staff and patients in the use of biosimilars [14].

Since biosimilars are similar to the reference drug but – like different batches of the reference drug – are not identical, new side effects may arise. For example, increased immunogenicity caused by altered glycosylation or an increase in neutralising antibodies may occur [28]. In our surveyed centres, side effects with the biosimilar therapy essentially corresponded to the adverse drug reactions described in the Summary of Product Characteristics. According to our experiences side effects may cease to occur after repeated administration. If they persist, a premedication e.g. with antihistamines and paracetamol or in individual cases renewed administration of the reference drug may be considered. To ensure constant clinical evaluation, it is essential to report possible

side effects that occurred also with biosimilars, via the Medicines Commission of the German Medical Association [29]. The German Society for Haematology and Oncology (DGHO) also recommends the close monitoring of efficacy and safety of a new drug, especially in patients with comorbidities or in cases of extended co-medication. The American and European Medicines Control Agencies as well as the Medicines Commission of the German Medical Association issued statements on the safety and efficacy and on the implementation of biosimilars in the clinical practice [30–32]. An independent registry to record side effects might be helpful [28]. The modern ordering systems of the clinics ensure traceability of substance switching.

In the near future, further challenges will arise in gynaeco-oncology: With expiry of the patents for bevacizumab in the summer of 2020 and pertuzumab in 2023, new biosimilars are expected for these biologics. In summary, the following recommendations may be given for future switching processes to biosimilars (► **Table 3**).

► **Table 3** Recommendations for future switching processes to biosimilars.

1	Regular communication with the pharmacy
2	Definition and preparation of the target date set for the switch
3	Preparation of the ordering system
4	Training of nurses and physicians
5	Definition of the patient briefing methods
6	Documentation and reporting of side effects

## Conclusion

The switching process from a biologic to a corresponding biosimilar is a major challenge. The work presented here confirms as a real world experience the similarity of a trastuzumab biosimilar (in this case Kanjinti) to the reference drug Herceptin by means of clinical experiences (pCR rates) in the switch year 2018. Overall the switch of the anti-HER2 therapy could be implemented successfully in all four participating clinics and without major problems. With regard to future switching processes, it is also of future importance that the new product is selected based on clearly defined criteria. Continuous communication between pharmacies and all participating clinics is essential as is the timely and in-depth informing and training of all concerned professional groups, in particular also of the oncology specialist care staff. It must be ensured that guidelines concerning the administration and ordering for the target date are adequately known and the change of the therapy protocols in the ordering software has been implemented. General stipulations on how the patients are to be informed are helpful and should, especially in large departments, be implemented by a standardised process. Conveying information by means of a short personal discussion and the use of a written information leaflet would be a candidate approach. If patients have been clearly informed as to content by trained physicians and care staff, patient acceptance is high. Implementation of the

trastuzumab biosimilar may lead to the development of good structures for expected future switching processes.

## Conflict of Interest

Anna Hester received honoraria for lectures and advisory boards from Roche as well as honoraria for lectures and reimbursement of training costs from Pfizer.

Peter A. Fasching received research support from Novartis and BioNTech and honoraria from Novartis, Roche, Pfizer, Celgene, Daiichi-Sankyo, Teva, AstraZeneca, Puma, Eisai, Merck Sharp & Dohme, MSD and Myelo Therapeutics.

Johannes Ettl received honoraria for consultancy work from Eli Lilly, Novartis, Pfizer Inc, AstraZeneca and Roche as well as honoraria and travel support from Celgene, Eli Lilly, Novartis, Pfizer Inc, Roche, Teva, AstraZeneca and Tesaro.

Anne Katrin Krämer received honoraria for advisory boards from Novartis, honoraria for lectures from Teva and reimbursement of training and travel expenses from Celgene, Novartis, IGEA and MSD. Achim Wöckel received honoraria for consultancy work, lectures and support for expert training from Amgen, AstraZeneca, Aurikamed, Celgene, Eisai, Lilly, Novartis, Pfizer, Roche, Tesaro, Sirtex, MSD and Genomic Health.

Nadia Harbeck received honoraria for lectures and/or consultancy work from Amgen, AstraZeneca, Celgene, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Samsung and Sandoz.

Rachel Würstlein received honoraria for consultancy work as well as support for travel expenses from Agendia, Amgen, Aristo, AstraZeneca, Boeinger Ingelheim, Carl Zeiss, Celgene, Clinsol, Daiichi-Sankyo, Eisai, Genomic Health, Glaxo Smith Kline, Hexal, Lilly, Medstrom Medical, MSD, Mundipharma, Nanostring, Novartis, Odonate, Paxman, Palleos, Pfizer, Pierre Fabre, Puma Biotechnology, Riemser, Roche, Sandoz/Hexal, Seattle Genetics, Tesaro Bio, Teva.

All other authors indicate that there are no conflicts of interest.

## References

- [1] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products. CHMP/437/04 Rev 1. London, 23 October 2014. Online: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2014/10/WC500176768.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf); last access: 10.08.2019
- [2] Weise M, Bielsky MC, De Smet K et al. Biosimilars: what clinicians should know. *Blood* 2012; 120: 5111–5117. doi:10.1182/blood-2012-04-425744
- [3] Kolberg H-C, Colleoni M, Santi P et al. Totality of Scientific Evidence in the Development of ABP 980, a Biosimilar to Trastuzumab. *Target Oncol* 2019; 14: 647–656. doi:10.1007/s11523-019-00675-z
- [4] Markus R, Liu J, Ramchandani M et al. Developing the Totality of Evidence for Biosimilars: Regulatory Considerations and Building Confidence for the Healthcare Community. *BioDrugs* 2017; 31: 175–187. doi:10.1007/s40259-017-0218-5
- [5] Thill M, Thatcher N, Hanes V et al. Biosimilars: what the oncologist should know. *Future Oncol* 2019; 15: 1147–1165. doi:10.2217/fon-2018-0728
- [6] Services USDoHaH. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry. 2015. Online: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>; last access: 08.08.2020
- [7] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. Online: [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-monoclonal-antibodies-non-clinical\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-monoclonal-antibodies-non-clinical_en.pdf); last access: 08.07.2020

- [8] European Medicines Agency (EMA). Assessment Report: Herizuma<sup>®</sup>, EMA/44005/2018. Online: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Public\\_assessment\\_report/human/002575/WC500249108.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002575/WC500249108.pdf); last access: 11.08.2020
- [9] von Minckwitz G, Colleoni M, Kolberg HC 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. doi:10.1016/s1470-2045(18)30241-9
- [10] Pegram MD, Bondarenko I, Zorzetto MMC et al. PF-05280014 (a trastuzumab biosimilar) plus paclitaxel compared with reference trastuzumab plus paclitaxel for HER2-positive metastatic breast cancer: a randomised, double-blind study. *Br J Cancer* 2019; 120: 172–182. doi:10.1038/s41416-018-0340-2
- [11] Stebbing J, Baranau Y, Baryash V 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. doi:10.1016/s1470-2045(17)30434-5
- [12] Barmer. Barmer Arzneimittelreport 2017. Online: <https://www.barmer.de/blob/121870/5de7f930ec629f1da7e611d561ccf46a/data/dl-grafik1.jpg>; last access: 12.08.2019
- [13] Barmer. Barmer Arzneimittelreport 2019. Online: <https://www.barmer.de/blob/195962/b7b2e41d474e012dd5fba087f0c0dfb/data/barmer-arzneimittelreport-2019.pdf>; last access: 11.08.2020
- [14] Taberero J, Vyas M, Giuliani R et al. Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. *ESMO Open* 2016; 1: e000142. doi:10.1136/esmoopen-2016-000142
- [15] Aitken M. Delivering on the potential of biosimilar medicines. The role of functioning competitive markets. IMS Institute for Healthcare Informatics 2016. Online: <https://www.medicinesforeurope.com/wp-content/uploads/2016/03/IMS-Institute-Biosimilar-Report-March-2016-FINAL.pdf>; last access: 11.08.2020
- [16] Ludwig WD, Dicheva S. [Biosimilars in oncology: a therapeutic alternative to the reference products?]. *Z Gastroenterol* 2016; 54: 1223–1229. doi:10.1055/s-0042-117650
- [17] Giuliani R, Taberero J, Cardoso F et al. Knowledge and use of biosimilars in oncology: a survey by the European Society for Medical Oncology. *ESMO Open* 2019; 4: e000460. doi:10.1136/esmoopen-2018-000460
- [18] Cohen H, Beydoun D, Chien D et al. Awareness, Knowledge, and Perceptions of Biosimilars Among Specialty Physicians. *Adv Ther* 2017; 33: 2160–2172. doi:10.1007/s12325-016-0431-5
- [19] Untch M, Thomssen C, Bauerfeind I et al. Primary Therapy of Early Breast Cancer: Evidence, Controversies, Consensus. *Geburtshilfe Frauenheilkd* 2019; 79: 591–604. doi:10.1055/a-0897-6457
- [20] Kolberg H-C, Schneeweiss A, Fehm TN et al. Update Breast Cancer 2019 Part 3 – Current Developments in Early Breast Cancer: Review and Critical Assessment by an International Expert Panel. *Geburtshilfe Frauenheilkd* 2019; 79: 470–482. doi:10.1055/a-0887-0861
- [21] Janni W, Schneeweiss A, Müller V et al. Update Breast Cancer 2019 Part 2 – Implementation of Novel Diagnostics and Therapeutics in Advanced Breast Cancer Patients in Clinical Practice. *Geburtshilfe Frauenheilkd* 2019; 79: 268–280. doi:10.1055/a-0842-6661
- [22] AGO Kommission Mamma. Aktuelle Empfehlungen 2020, Version 2020.1D. Online: <https://www.ago-online.de/leitlinien-empfehlungen/leitlinien-empfehlungen/kommission-mamma>; last access: 11.08.2020
- [23] Amgen. Fachinformation KANJINTI<sup>®</sup>. Online: <https://fachkreise.amgen.de/downloads/f/1/1120/kanjinti-fachinformation.pdf>; last access: 11.08.2020
- [24] European Medicines Agency (EMA). Kanjinti (Trastuzumab). Übersicht über Kanjinti und Begründung für die Zulassung in der EU. EMA/191628/2018. Online: [https://www.ema.europa.eu/en/documents/overview/kanjinti-epar-medicine-overview\\_de.pdf](https://www.ema.europa.eu/en/documents/overview/kanjinti-epar-medicine-overview_de.pdf); last access: 14.08.2019
- [25] van Overbeeke E, De Beleyr B, de Hoon J et al. Perception of Originator Biologics and Biosimilars: A Survey Among Belgian Rheumatoid Arthritis Patients and Rheumatologists. *BioDrugs* 2017; 31: 447–459. doi:10.1007/s40259-017-0244-3
- [26] Jacobs I, Singh E, Sewell KL et al. Patient attitudes and understanding about biosimilars: an international cross-sectional survey. *Patient Prefer Adherence* 2016; 10: 937–948. doi:10.2147/ppa.S104891
- [27] Ismailov RM, Khasanova ZD, Gascon P. Knowledge and awareness of biosimilars among oncology patients in Colorado, USA. *Future Oncol* 2019. doi:10.2217/fo-2019-0194
- [28] Wörmann B, Sinn M. Position of Scientific Oncological Societies Towards Biosimilar Antibodies. *Breast Care* 2019; 14: 5–8. doi:10.1159/000495145
- [29] Arzneimittelkommission der deutschen Ärzteschaft. Bericht über unerwünschte Arzneimittelwirkungen. Online: <https://www.dcgma.org/uaw-meldung>; last access: 14.08.2019
- [30] FDA. Biosimilar and Interchangeable Biologics: More Treatment Choices. Online: <https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices>; last access: 11.08.2020
- [31] European Medicines Agency, European Commission. Biosimilars in the EU. Information guide for healthcare professionals. Online: [https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals\\_en.pdf](https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf); last access: 11.08.2020
- [32] Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ). Leitfaden der Arzneimittelkommission der deutschen Ärzteschaft. Biosimilars. 2017. Online: <https://www.akdae.de/Arzneimitteltherapie/LF/PDF/Biosimilars.pdf>; last access: 11.08.2020