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Biosimilars in oncology: A decade of experience with granulocyte colony-stimulating factor and its implications for monoclonal antibodies

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ABSTRACT

Biosimilars offer the potential for improved sustainability of cancer care. In oncology, granulocyte colony-stimulating factor and erythropoiesis-stimulating agent biosimilars have been available for almost a decade, with biosimilars of monoclonal antibodies a more recent development. Sandoz biosimilar filgrastim was approved based on Phase III confirmatory studies conducted in patients with breast cancer experiencing chemotherapy-induced neutropenia, with other indications granted based on extrapolation. Despite the fact that extrapolation is a well-established scientific principle in regulation of biological medicines, it is a commonly misunderstood part of the biosimilar concept. Broad experience from almost a decade of use of Sandoz biosimilar filgrastim includes >21 million patient-days exposure and >9 years of real-world clinical evidence, indicates extrapolation successfully at work. Together, this can help reassure oncologists that extrapolation is based on sound scientific principles. Efforts to improve understanding of extrapolation are critical to ensure the acceptance of future oncology biosimilar monoclonal antibodies.

1. Breast cancer and the development of targeted treatments

Cancer is a leading cause of morbidity and mortality, with 14 million new cancer cases reported worldwide in 2012 (Cancer Today, 2018), including more than 2.6 million cases in Europe (EU) and 4.8 million in the United States (US) (GLOBOCAN, 2012a). The burden of cancer is rising, with 21 million new cancer cases and 13 million deaths expected annually by 2030 (Heymach et al., 2018). Globally, breast cancer is the second most common cancer and is the most frequent cancer in women with approximately 1.67 million new cases diagnosed and 522,000 related deaths in 2012 - an increase in breast cancer incidence and related mortality of almost 18% since 2008 (GLOBOCAN, 2012b; Tao et al., 2015). Although breast cancer cases and their associated mortality are rising, survival rates in early breast cancer have improved. This improvement in survival has been driven (at least in part) by the development and approval of targeted treatments. For example, the addition of pertuzumab (the first drug to receive accelerated approval based on pathological complete response as a surrogate end point) to adjuvant trastuzumab plus chemotherapy has improved outcomes in patients with resected high-risk HER2 positive (HER2+) breast cancer (Perez-Garcia and Cortes, 2018). Also, improved outcomes have been achieved through the addition of capecitabine to standard adjuvant chemotherapy in patients with a poor prognosis and no response to neoadjuvant therapy (Perez-Garcia and Cortes, 2018). Other notable advances are the addition of cyclin-dependent kinase 4/6 inhibitors to metastatic ER positive breast cancer treatment and the use of poly ADP ribose polymerase inhibitors in patients with triple-negative breast cancer (Perez-Garcia and Cortes, 2018; The Lancet, 2017).

Given with paclitaxel or docetaxel, trastuzumab has long been the standard of care in patients with HER2+ breast cancer (Loibl and Gianni, 2017). Findings of the five pivotal trials - performed in women with HER2+ operable breast cancer receiving adjuvant treatment with trastuzumab - showed a significant improvement in disease-free survival that translated into a significant improvement in overall survival (Slamon et al., 2011; Perez et al., 2011, 2014; Piccart-Gebhart et al., 2005; Romond et al., 2005). Survival benefits reported with trastuzumab and other targeted treatments available for HER2+ breast cancer, such as lapatinib, pertuzumab, trastuzumab emtansine and neratinib, show that targeted medicine has changed the course of HER2+ disease; however, many patients with HER2+ breast cancer still die, highlighting a need for early diagnosis, development of new targeted treatments and evaluation of combinations of currently available targeted treatments (Loibl and Gianni, 2017). These approaches, however, have cost implications, highlighting the need for effective solutions for the sustainability of cancer care.

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2. Biosimilars in oncology

Oncology biologic medicines are placing an increasing financial burden on healthcare systems (Renwick et al., 2016), with eight of the 10 most expensive drugs on the market used in cancer treatment (Lyman et al., 2018). Over the next few years, several major biologics used in oncology, including in patients with breast cancer, will lose their patent exclusivity, providing an opportunity for the development of biosimilars. A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized reference biological medicinal product (European Medicines Agency, 2014a). Biosimilars offer the potential for improved sustainability of cancer care (Lyman et al., 2018; Rak Tkaczuk and Jacobs, 2014; Tabernero et al., 2017) since they foster competition and affordability, and may therefore help increase access to biological treatments for patients, offering improved clinical outcomes (Bennett et al., 2014; National Cancer Policy Forum, 2014). In the EU, the first biosimilar medicine was approved in 2006 (Omnitrope®, Sandoz) and 39 biosimilars are currently approved. In the US, the Food and Drug Administration (FDA) approved its first biosimilar, Sandoz biosimilar filgrastim (Zarxio®, Zarzio®, EP2006), in 2015 and nine other biosimilar medicines have received FDA approval since (US Food and Drug Administration, 2018). In oncology, G-CSF and erythropoiesis-stimulating agent (ESA) biosimilars have been available for almost a decade, with biosimilars of monoclonal antibodies (MAbs) a more recent development (Table 1).

Other highly regulated markets have also approved biosimilars, such as the Republic of Korea where eight biosimilar medicines are available, including two trastuzumab biosimilars and one rituximab biosimilar (GaBI, 2014). Biosimilar G-CSF, such as Sandoz biosimilar filgrastim, is used to prevent chemotherapy-induced neutropenia (CIN) in oncological patients as supportive therapy. This is in addition to other indications that were granted on the basis of extrapolation. Use of G-CSF reduces neutropenic complications associated with chemotherapy and may improve survival by minimizing dose reductions and treatment delays (Lyman et al., 2010, 2013, 2017). Of note, guidelines on myeloid growth factors include biosimilar medicines in their recommendations. Biosimilars of filgrastim are strongly recommended by ASCO, EORTC, and NCCN, and the latest ESMO clinical practice guidelines for management of anemia and iron deficiency in patients with cancer include European Medicines Agency (EMA) approved biosimilars of ESAs (Smith et al., 2015; Aapro et al., 2011; National Comprehensive Cancer Network, 2018; Aapro et al., 2018).

MAb biosimilar medicines used for curative intent in breast cancer are also becoming increasingly available for treatment of the most common breast cancer subtypes. For example, trastuzumab biosimilars (Ogivri™, Mylan; Ontruzant®, Samsung Bioepis) are approved for the treatment of HER2+ early breast cancer in the neoajuvant setting and in HER + metastatic breast cancer. Biosimilar bevacizumab is also now available as a biosimilar in both the EU and US (Mvasi™, Amgen), offering another treatment option in metastatic breast cancer.

3. Biosimilar development

The development of a biosimilar involves an extensive series of comparisons performed between the proposed biosimilar medicine and the reference biologic. These include analytical assessment of the physico-chemical and functional characteristics of the two medicines, performed using state-of-the-art technology and highly sensitive methods, in order to identify any potential differences (Holzmann et al., 2016). This involves identification of critical quality attributes that are considered to have a potential impact on clinical outcomes, and thus must be kept within narrow limits to ensure the consistent quality and consistent clinical properties of the medicine (Holzmann et al., 2016). Once the analytical comparisons are complete, regulatory requirements for any biosimilar (including MAbs) will include a comparison of the pharmacokinetics (PK) and, if applicable, also pharmacodynamics (PD) properties in a Phase I study. Finally, biosimilar development typically includes a Phase III study, which is considered confirmatory to resolve any potential residual uncertainty regarding biosimilarity following the analytical and PK/PD comparisons. Biosimilar regulation is designed so that patients and physicians can expect that the efficacy, safety and immunogenicity are the same for the reference and the biosimilar medicine (European Commission, 2017).

Regulatory bodies, including the EMA, FDA, and the Republic of Korea's Ministry of Food and Drug Safety, stipulate that Phase III confirmatory studies are performed in a sensitive population in which potential clinically meaningful differences between the two medicines

Table 1
List of oncology biosimilars that have been approved or received positive review/recommendation from EMA and FDA.

Active substance	Approved medicine	Authorization status
Filgrastim	Accofil (Accord Healthcare)	Approved by EMA September 2014
	Filgrastim Hexal (Sandoz)	Approved by EMA February 2009
	Grastofil (Apotex)	Approved by EMA October 2013
	Nivestim (Hospira)	Approved by EMA June 2010
	Ratiograstim (Ratiopharm)	Approved by EMA September 2008
	Tevagrastim (Teva Generics)	Approved by EMA September 2008
	Zarzio (Hexal AG)	Approved by EMA February 2009
	Zarxio (Sandoz Inc.)	Approved by FDA March 2015
Pegfilgrastim	Fulphila (Mylan)	Approved by FDA June 2018
	CHS-1701 (Coherus)	Approved by EMA July 2018
	Lapelga (Apotex)	Approved by EMA July 2018
	B12019 (Cinfa)	Approved by EMA September 2018
	Ziextenzo/LA-EP2006 (Hexal AG)	Approved by EMA September 2018
Bevacizumab	Mvasi (Amgen)	Approved by EMA January 2018
		Approved by FDA September 2017
Rituximab	Blitzima (Celltrion)	Approved by EMA July 2017
	Ritemvia (Celltrion)	Approved by EMA July 2017
	Rituzena (Celltrion)	Approved by EMA July 2017
	Rixathon (Hexal AG)	Approved by EMA June 2017
	Riximyo (Hexal AG)	Approved by EMA June 2017
	Truxima (Celltrion)	Approved by EMA February 2017
Trastuzumab	Herzuma (Celltrion)	CHMP positive opinion December 2017
	Ogivri (Mylan)	Approved by FDA December 2017
	Ontruzant (Samsung Bioepis)	Approved by EMA November 2017

Table 2
Regulatory body definitions of 'biosimilar' and 'sensitive population', as well as requirements to conduct Phase III clinical trials.

Organisation	Definition of a biosimilar	Definition of sensitive population	Requirement to conduct Phase III clinical trial
European Medicines Agency (EMA)	*"A biological medicinal product that contains a version of the active substance of an already* authorised *original biological medicinal product (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established."* (European Medicines Agency, 2014b)	*"The study population should generally be representative of approved therapeutic indication (s) of the reference product and be sensitive for detecting potential differences between the biosimilar and the reference. Occasionally, changes in clinical practice may require a deviation from the approved therapeutic indication, e.g. in terms of concomitant medication used in a combination treatment, line of therapy, or severity of the disease. Deviations need to be justified and discussed with regulatory authorities."* (European Medicines Agency, 2014b)	*"It is usually necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference medicinal product in adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blind, by using efficacy endpoint."* (European Medicines Agency, 2014b)
US Food & Drug Administration (FDA)	*"The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,"* and that *"there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."* (US Food and Drug Administration, 2015a)	*"In choosing which condition of use to study that would permit subsequent extrapolation of clinical data to other conditions of use, FDA recommends that a sponsor consider choosing a condition of use that would be adequately sensitive to detect clinically meaningful differences between the two products."* (US Food and Drug Administration, 2015a)	*"FDA expects a sponsor to conduct comparative human PK and PD studies (if there is a relevant PD measure(s)) and a clinical immunogenicity assessment […] If residual uncertainty about biosimilarity remains after conducting these studies, an additional comparative clinical study or studies would be needed to further evaluate whether there are clinically meaningful differences between the two products."* (US Food and Drug Administration, 2015a)
Ministry of Food and Drug Safety (MFDS) (Republic of Korea)	*"A biological product that is comparable to already marketed reference products in terms of quality, safety and efficacy."* (Ministry of Food and Drug Safety, 2015)	*"It would be mandatory to examine potential differences between the biosimilar product and the reference product using a sensitive, well-established experimental model."* (Ministry of Food and Drug Safety, 2015)	*"Similar efficacy of the biosimilar product and the reference product should be demonstrated in an adequately powered, randomized, and parallel group clinical trial (equivalence trials). Such clinical studies should preferably be double-blinded or at a minimum observer-blinded. In the absence of any blinding, careful justification is required to prove that trial results are free from significant bias."* (Ministry of Food and Drug Safety, 2015)
Pharmaceuticals and Medical Devices Agency (PMDA) (Japan)	*"A 'follow-on' biologic is a biotechnological drug product developed to be comparable in regard to quality, safety and efficacy to an already approved biotechnology-derived product (hereinafter "original biologic") of a different company. A follow-on biologic can generally be developed on the basis of data that demonstrate the comparability with the original biologic with respect to quality, safety and efficacy, or other relevant data. […] 'Follow-on Biologics' in this guideline is a synonym for 'Biosimilars'."* (Pharmaceuticals and Medical Devices Agency, 2009)	*"Depending on the original biologic and/or target disease, it may be appropriate to conduct a clinical study in healthy adults, while a clinical study enrolling patients is sometimes more appropriate"* and *"It is necessary to determine the necessary and adequate number of patients to be enrolled, and pre-specify the margins defining clinical comparability (comparability margin) using clinically established endpoints."* (Pharmaceuticals and Medical Devices Agency, 2009)	*"It is required to design such a clinical study that is necessary and appropriate to evaluate the comparability of the follow-on biologic with the original biologics in terms of efficacy and safety, taking into account comprehensive information including literature on the original biologic."* (Pharmaceuticals and Medical Devices Agency, 2009)
Health Canada	*"A biologic drug that obtains market authorization subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug."* (Health Canada, 2016)	*"PK studies should be carried out in healthy subjects when appropriate as they are usually considered to be a homogeneous and sensitive population."* (Health Canada, 2016)	*"The study should be conducted using a clinically relevant and sensitive endpoint to show that there are no clinically meaningful differences between the biosimilar and reference biologic drug. […] In all cases, an acceptable comparability margin should be defined taking into account the smallest effect size that the reference biologic drug would reliably be expected to have based on publicly available historical data."* (Health Canada, 2016)
Therapeutic Goods Administration (TGA) (Australia)	*"A biosimilar medicine is a version of an already registered biological medicine (the reference medicine)."* (Therapeutic Goods Administration, 2018)	*"TGA has adopted a number of European guidelines that outline the quality, nonclinical and clinical data requirements specific to biosimilar medicines."* (Therapeutic Goods Administration, 2018) See European Medicines Agency (EMA) definition.	*"TGA has adopted a number of European guidelines that outline the quality, nonclinical and clinical data requirements specific to biosimilar medicines."* (Therapeutic Goods Administration, 2018) See European Medicines Agency (EMA) definition.

can best be identified (Table 2).

Sensitive indications typically are homogenous, have a large effect size for the chosen endpoint to allow detection of even small differences in efficacy, and involve an immunocompetent population to detect differences in immunogenicity.

Once biosimilarity has been established by comprehensive analytical and clinical comparisons, the biosimilar may be approved for all licensed indications of the reference medicine without the need to perform individual clinical trials in each patient subpopulation, provided there is scientific justification. Such an extrapolation of the totality of all data is a key concept of biosimilar regulation (European Medicines Agency, 2014b). It should be noted that clinical studies alone may be the least sensitive method for detecting differences between a proposed biosimilar and its reference biologic (Holzmann et al., 2016). As such, the structural and functional characteristics are the foundation for extrapolation to other indications of the reference biologic, since

two medicines shown to be highly similar would be expected to behave in the same way in all patient populations (Holzmann et al., 2016).

4. Extrapolation

Extrapolation is not a new concept, but a well-established scientific principle in the regulation of biological medicines (European Commission, 2017). For instance, once an innovator medicine has demonstrated efficacy and safety in randomized clinical trials and has been approved, use of the new medicine in patients with the same indication in the real-world is an accepted example of extrapolation. Patients included in randomized controlled clinical trials (RCTs) are subject to stringent entry criteria that may exclude certain types of patients (*e.g.* elderly patients who have concomitant comorbidities and receive multiple medications). Thus, there is an unavoidable disparity between the population in which the medicine was initially/primarily evaluated, and the patients who receive it after approval. Randomized controlled trials are considered the most powerful study design in clinical trials (Sullivan, 2011); however, this difference in patients included in RCTs and those in real-world practice highlights the need for post-approval surveillance to monitor drug safety in everyday use in different patient types.

Extrapolation is also well known and accepted for changes in the manufacturing process of biologic medicines (European Commission, 2017; Weise et al., 2014). Regulatory bodies require that the manufacturer conducts rigorous comparisons to demonstrate that the biologic remains the same, following changes to the manufacturing process (Krendyukov and Schiestl, 2018). It is of note that even when manufacturing changes are extensive, regulatory bodies may not request clinical data in each indication (Weise et al., 2014; Krendyukov and Schiestl, 2018). This same process is followed when a biosimilar is approved for the same indications as the reference biologic. All biological medicines show a certain degree of variability due to their cell-based production (Lamanna et al., 2018); however, strict manufacturing quality systems and multi-layered regulatory controls are in place for both reference biologics and biosimilars to maintain consistency over time and ensure that the inherent variability is kept within acceptable limits and has no impact on efficacy, safety, and immunogenicity (Lamanna et al., 2018). The evidence suggests that these controls are effective for routine manufacturing, including manufacturing changes, since only one verifiable case of 'clinical drift' (*i.e.* changes over time in the biologic that result in changes in safety or effectiveness) resulting in suspension of the market authorization has been reported since the first biologic medicine was approved 35 years ago (Lyman et al., 2018; Lamanna et al., 2018).

Despite its acceptance in these examples, extrapolation is a commonly misunderstood part of the biosimilar concept (Krendyukov and Schiestl, 2018), with several medical societies initially expressing concerns regarding extrapolation with biosimilars (Weise et al., 2014; Danese, 2013). The term 'extrapolation' may itself lead to misinterpretation of the concept. In mathematical terms, extrapolation refers to projecting unknown values from trends in known data (Krendyukov and Schiestl, 2018); however, in biosimilar terms, extrapolation is based on evidence from the series of comparisons performed to demonstrate biosimilarity to the reference medicine (Krendyukov and Schiestl, 2018). Recognising this misconception, Health Canada recently removed the term 'extrapolation' in the latest update of their biosimilar guideline, instead referring to what it means exactly, namely the authorization of indications for the biosimilar (Health Canada, 2016).

There is also a need for oncologists to understand that extrapolation is from the reference biologic to the biosimilar (*i.e.* molecule to molecule), rather than from the sensitive indication in which the biosimilar has been studied to other indications. A biosimilar is not automatically granted approval for each indication of the reference medicine. Indeed, each extrapolated indication must have scientific justification and undergoes a separate assessment by regulators. Factors that are considered in this thorough assessment include mechanism of action and target receptors involved in mediating the response, clinical evidence with the reference biologic, any potential differences in safety and immunogenicity between indications, and the demonstrated level of analytical similarity of the molecules (Weise et al., 2014). Approval of the proposed biosimilar for all indications of the reference medicine will only be granted once all of these considerations have been reviewed, and each indication is considered scientifically justified (European Commission, 2017).

Depending on the specific complexity of the biological medicines, it may become less common in future for regulatory bodies to require that a manufacturer of a proposed biosimilar performs a Phase III confirmatory study. The guidelines in the EU and US are already open to more targeted approaches and the EMA recently accepted the application for Cinfa's proposed biosimilar pegfilgrastim without a Phase III confirmatory study (GaBI, 2017). This example may reflect improved understanding of biosimilars since the first biosimilar approvals, driven by improvements in analytical technology, the sensitivity of the clinical PK/PD comparison, and the product understanding. The general acceptance of biosimilars in the medical community may be facilitated by the growing body of published data on biosimilar use (including real-world evidence and over a decade of clinical experience with biosimilars in oncology supportive care), efforts by regulatory bodies to address misconceptions regarding biosimilars (Kurki and Bielsky, 2014), and recent positioning statements by oncology societies such as ASCO and ESMO providing guidance on biosimilar use in the cancer setting (Lyman et al., 2018; Tabernero et al., 2017). It should be noted that clinical confirmation of PK/PD either in healthy volunteers or, if necessary, in patients, will remain mandatory.

One good example of experience is biosimilar G-CSFs which have now been approved by the EMA for nearly 10 years (Table 3).

5. Experience of extrapolation

In the example of Sandoz biosimilar filgrastim, the Phase III confirmatory studies were conducted in patients with breast cancer experiencing CIN (Gascón et al., 2010; Blackwell et al., 2015), with other indications granted on the basis of extrapolation (Gascón et al., 2013). Since approval, data and clinical experience have demonstrated the safety and efficacy of Sandoz biosimilar filgrastim in extrapolated indications (Gascón et al., 2013). Data in patients with CIN also includes real-world evidence in 1,447 patients with different tumor types, such as diffuse large B-cell lymphoma (Gascón et al., 2018) and non-small cell lung cancer (Aapro et al., 2017b), and in elderly patients (Aapro et al., 2017a). Safety signals have been in line with those reported for reference filgrastim (Green et al., 2003; Holmes et al., 2002). A large body of data is also available from formal studies for stem cell mobilisation in both the autologous and allogeneic settings (Schmitt et al., 2016, 2014). Additionally, real-world evidence is also emerging in this setting (Agrawal et al., 2018; Lefrère et al., 2011; Taylor and Seddon, 2017), including data from a study with the largest donor cohort (n = 244) of mobilisation reported to date (Becker et al., 2016).

Clinical evidence with Sandoz biosimilar filgrastim also includes the first study in oncology patients to report data on switching between a reference biologic and a biosimilar (Aapro et al., 2018; Blackwell et al., 2015). The PIONEER study reported no clinically meaningful differences regarding efficacy, safety or immunogenicity when patients were switched from reference to Sandoz biosimilar filgrastim, or vice versa (GaBI, 2017; Blackwell et al., 2018).

This broad experience from almost a decade of use includes over 21 million patient-days exposure and more than 9 years of real-world clinical evidence (Nakov et al., 2018; Harbeck et al., 2016), indicating extrapolation successfully at work. Together, the decade of evidence and experience with biosimilar filgrastim can help reassure oncologists that the concept of extrapolation is based on sound scientific principles.

Table 3
Approved filgrastim and proposed pegfilgrastim biosimilar medicines: examples of Phase I PK/PD and Phase III confirmatory studies in a sensitive population of patients with breast cancer.

G-CSF	Biosimilar/proposed biosimilar	Phase I/III studies
Filgrastim	Accofil (Accord Healthcare)/Grastofil (Apotex)	Phase I: 36 healthy volunteers in randomized, two-way crossover study assessing PK and PD parameters [KWI-300-1 01] (Jilma et al., 2014). Phase I: 73 volunteers in randomized, double-blind, two-way crossover study assessing PK and PD parameters [KWI-300-1 02] (Jilma et al., 2014). Phase I: 78 healthy volunteers in randomized, double-blind, active and placebo-controlled, parallel group study assessing PD of repeat dose [KWI300-1 03] (Jilma et al., 2014). Phase I: 48 healthy volunteers in randomized, double-blind, active-controlled, comparative three-way crossover PK and PD study of apo-filgrastim and EU and US filgrastim [GCSF-SUI-N-05SB01-3FA] (Jilma et al., 2014). Phase III: non-comparative, multicenter, repeat dose safety study. 120 patients with breast cancer receiving TAC [KWI-300-I 04] (Jilma et al., 2014).
	Nivestim (Hospira)	Phase I: 44 evaluable healthy volunteers in open-label, randomized, active comparator-controlled (Neupogen, Amgen) two-way crossover study in each of two parallel groups of subjects; randomized to IV or SC and further randomized to order of treatment administration [GCF061] (Waller et al., 2010a). Phase I: 48 evaluable healthy volunteers in randomized, double-blind, multiple-dose, active comparator-controlled (Neupogen, Amgen), two-way crossover study; randomized to 5 or 10 μg/kg and further randomized to order of treatment administration. Multiple doses, 5 injections over 5 consecutive days [GCF062] (Waller et al., 2010b). Phase III: multicenter, randomized, double-blind therapeutic equivalence study; randomized (2:1) to 5 μg/kg PLIVA/Mayne filgrastim or 5 μg/kg reference (Neupogen, Amgen). Followed for 28 days after last dose and at 6 months. 250 evaluable patients with invasive breast cancer [GCF071] (Waller et al., 2010c)
	Ratiograstim (Ratiopharm)/Tevagrastim (Teva Generics)	Phase I: 56 healthy male Caucasian volunteers in randomized, two-period crossover, two-arm study assessing PK and PD profiles of XM02 and reference (Neupogen, Amgen); randomized to either SC 5 or 10 μg/kg of the study drugs [XM02-01-LT] (Lubenau et al., 2009a). Phase I: 144 healthy Caucasian volunteers in randomized, two-period crossover study of PK and PD characteristics of IV or SC XM02 and reference (Neupogen, Amgen) at 5 or 10 μg/kg [XM02-05-DE] (Lubenau et al., 2009b). Phase III: multinational, multicenter, randomized, controlled study. 348 patients with BC receiving docetaxel/doxorubicin chemotherapy randomized to daily SC 5 μg/kg/day XM02 (n = 140), reference (Neupogen, Amgen) (n = 136) or placebo (n = 72) [XM02-02-INT] (del Giglio et al., 2008). Phase III: multinational, multicenter, randomized, controlled study. 240 SCLC or NSCLC patients, randomized to XM02 or reference (Neupogen, Amgen) at 2:1 in first CTX cycle. In subsequent cycles, all patients received XM02 [XM02-03-INT] (Gatzemeier et al., 2009). Phase III: multinational, multicenter, randomized, controlled study in CTX-naïve patients with aggressive NHL undergoing CTX (n = 92). Randomized to XM02 or reference (Neupogen, Amgen) at 2:1 in the first CTX cycle. In subsequent cycles, all patients received XM02 [XM02-04-INT] (Engert et al., 2009).
	Sandoz biosimilar filgrastim (Zarzio/Zarxio, Hexal AG/Sandoz Inc.), Filgrastim Hexal (Sandoz)	Phase I: 32 healthy volunteers in a randomized, double-blind, multiple-dose, two-way cross-over study to compare the PK, PD, and safety of Sandoz biosimilar filgrastim and EU-approved reference (Neupogen, Amgen) following single and multiple 10 μg/kg SC doses [EP06-101] (US Food and Drug Administration, 2015b). Phase I: 26 healthy volunteers in a randomized, double-blind, two-way crossover, single center study to compare the PK, PD, and safety of Sandoz biosimilar filgrastim and EU-approved reference (Neupogen, Amgen) administered at a single 5 μg/kg IV dose [EP06-102] (Gascón et al., 2010). Phase I: 56 healthy volunteers in a randomized, double-blind, multiple-dose, two-way cross-over study to determine the PK and PD of Sandoz biosimilar filgrastim and EU-approved reference (Neupogen, Amgen) at two dose levels administered to two groups (2.5 and 5 μg/kg) as single and multiple SC injections (EP06-103) (US Food and Drug Administration, 2015b). Phase I: 24 healthy volunteers in a randomized, double-blind, two-way cross-over study to determine the PK and PD of Sandoz biosimilar filgrastim and EU-approved reference (Neupogen, Amgen) administered at a single 1 μg/kg SC dose [EP06-105] (US Food and Drug Administration, 2015b). Phase III: open phase III single-arm study. 170 patients with BC undergoing four cycles of chemotherapy (doxorubicin and docetaxel) receiving Sandoz biosimilar filgrastim (300 or 480 μg) for prevention of CIN. Safety, efficacy and immunogenicity assessed (Gascón et al., 2010). Phase III: randomized, double-blind, parallel-group, multicenter, study comparing efficacy and safety of Sandoz biosimilar filgrastim and US licensed reference (Neupogen, Amgen). 218 patients with breast cancer receiving TAC. Received 5 μg/kg/day filgrastim over six chemotherapy cycles; randomized 1:1:1:1 into four arms. Two arms received only one product (nonalternating), biosimilar or reference, and two arms (alternating) received alternating treatments during each cycle (biosimilar then reference or vice versa) (Blackwell et al., 2015).

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Table 3 (*continued*)

G-CSF	Biosimilar/proposed biosimilar	Phase I/III studies
Proposed Pegfilgrastim	Sandoz proposed biosimilar pegfilgrastim (Hexal AG)	Phase 1: 185 healthy volunteers in single-dose, randomized, double-blind, two-way crossover study. Randomized to receive Sandoz proposed biosimilar pegfilgrastim followed by reference pegfilgrastim (biosimilar/reference) and 93 subjects were randomized to receive reference pegfilgrastim followed by Sandoz proposed biosimilar pegfilgrastim (reference/biosimilar) (Nakov et al., 2018). Phase III: randomized, double-blind trial. 316 women receiving chemotherapy for breast cancer, randomized to Sandoz proposed biosimilar pegfilgrastim or reference (Neulasta, Amgen) (Harbeck et al., 2016). Phase III: randomized, double-blind trial. 308 patients with early-stage breast cancer receiving TAC, randomized to Sandoz proposed biosimilar pegfilgrastim or reference pegfilgrastim (Neulasta, Amgen) (Blackwell et al., 2016).
	Lapelga (Apotex)	Phase I: 66 healthy adults. single-dose, randomized, assessor-blinded, two-way crossover, active-controlled PK/PD study. Subjects randomized to either Apotex's proposed pegfilgrastim biosimilar (6 mg/0.6 ml prefilled syringe) or the reference (Neulasta, Amgen; 6 mg/0.6 ml prefilled syringe) (Desai et al., 2016).
	DA-3031 (Dong-A ST)	Phase III: randomized, multi-center, open-label, study. 74 patients with breast cancer receiving TAC; randomized to daily SC filgrastim 100 μg/m2/day for up to 10 days or a single SC injection of DA-3031 at fixed doses of 6 mg on day 2 of each chemotherapy cycle (Park et al., 2017).
	MYL-1401H (Biocon/Mylan)	Phase I: 216 healthy volunteers. Single-center, randomized, double-blind, 3-period, 3-treatment, 3-way crossover trial assessing PK and PD. Randomized to one of the six possible treatment sequences to receive a single SC injection (2 mg) of either MYL-1401H and EU-reference and US-reference (Neulasta, Amgen) (Waller et al., 2016a). Phase III: multicenter, randomized, double-blind, parallel-group trial. 194 newly diagnosed patients with breast cancer eligible to receive docetaxel, doxorubicin, and cyclophosphamide, were randomized (2:1) to receive 6 mg/0.6 ml of either MYL-1401H or EU-reference (Neulasta, Amgen) on Day 2 of each cycle (Waller et al., 2016b).
	B12019 (Cinfa Biotech)	Phase I: 161 healthy volunteers. Single-dose, randomized, double-blind, two-way crossover study assessing PK and PD equivalence (Roth et al., 2016). Phase I: 96 healthy volunteers. Multiple-dose, randomized, double-blind, three-period, two-sequence cross-over study assessing immunogenicity and PD comparability of B12019 and reference (Neulasta, Amgen) at a reduced dose (3 mg) (Roth et al., 2017).
	CHS-1701 (Coherus)	Phase I: 122 health volunteers. multi-center, randomized, single-blind, 3-sequence, crossover study assessing PK and PD. Subjects were randomized to 1 of 3 treatment sequences; each included 1 dose of CHS-1701 (6-mg) and 2 doses of pegfilgrastim (6- mg) separated by ≥28 days (Glaspy et al., 2017).

In the rapidly growing biosimilar market, many oncology biosimilar medicines are under development and likely to be approved in the near future (Table 4).

Taking the example of trastuzumab, published Phase III confirmatory trials are now available for approved trastuzumab biosimilars, and those under development in both the setting of patients with early breast cancer receiving (neo)adjuvant treatment (Stebbing et al., 2017; Pivot et al., 2018a, b; von Minckwitz et al., 2017), and in women with metastatic disease (Im et al., 2013; Rugo et al., 2017; Pegram et al., 2017). This example highlights that there may be more than one breast cancer patient population with suitable sensitivity for development of a biosimilar and extrapolation based on totality of evidence. Approval of these biosimilars offers the potential for improved access to trastuzumab, allowing more patients to benefit.

6. Interchangeability of biosimilar and reference medicines

Availability of biosimilars in oncology increases the therapeutic armamentarium and may ultimately lead to important clinical considerations regarding switching or interchangeability between biologics. Switching is the decision by the prescribing physician to exchange one medicine with another medicine with the same therapeutic intent in a given patient (Kurki et al., 2017; European Commission, 2013) (Table 5). Switching is frequently performed between biologic medicines in everyday clinical practice (Ebbers et al., 2012). A recent systematic review of 90 switching studies including over 14,000 patients and healthy volunteers across 14 indications concluded that there is little risk of immunogenicity or treatment-related adverse events, or changes in efficacy when switching between reference biologics and biosimilars (Cohen et al., 2018). This indicates that switching from reference biologic to biosimilar, or vice versa, may be performed safely under the supervision of the prescribing physician (Blackwell et al., 2018; Kurki et al., 2017).

Substitution refers to the practice of dispensing one medicine instead of another equivalent medicine at the pharmacy level without the consultation of the prescribing physician [European Commission]. Several EU countries have rules against the automatic substitution of biosimilars and reference products by a pharmacist without the consultation of the prescriber (Thimmaraju et al., 2015). However, in the US, the Biologics Price Competition and Innovation Act (BPCI Act) includes an additional approval stage for a product to be designated as an “interchangeable biosimilar”, permitting switching from the reference at the discretion of the pharmacist (Lyman et al., 2018; Braun and Kudrin, 2016; Faccin et al., 2016). This interchangeability status includes confirmed biosimilarity, and is distinct from designation as a biosimilar. It has the aim of demonstrating that efficacy, safety and immunogenicity are the same in switched patients as in patients receiving the reference product continuously (US Food and Drug Administration, 2015c). In January 2017 the FDA released draft guidance that sponsors should submit data from a switching study in order to apply for interchangeability status (US Food and Drug Administration, 2017) but as yet no “interchangeable biosimilars” have been approved in the US.

7. Potential for sustainability of cancer care

Although access to MAb biosimilars, including trastuzumab, offers great opportunities, their use and potential for sustainability of cancer care will largely depend on clinician and patient understanding of biosimilars. Knowledge gaps remain that must be overcome, including the need for oncologists to understand extrapolation as a fundamental concept for biosimilar development. Prescribers from Europe, Asia and

Table 4
Approved and proposed trastuzumab biosimilar medicines: examples of Phase I PK/PD and Phase III confirmatory studies in a sensitive population of patients with breast cancer.

G-CSF	Biosimilar/proposed biosimilar	Phase I/III studies
Approved trastuzumab biosimilar medicines	Herzuma (CT-P6) - Celltrion	Phase I: 70 healthy adult males. Single-dose, randomized, double-blind, parallel group study comparing safety and immunogenicity of CT-P6 and reference trastuzumab (Esteva et al., 2018). Phase III: randomized, double-blind, active-controlled equivalence trial. Randomly allocated 549 patients (271 [49%] to CT-P6 *vs* 278 [51%] to reference trastuzumab) with HER2-positive early-stage breast cancer (Stebbing et al., 2017). Phase III: double-blind, randomized, parallel group, study comparing CT-P6 with trastuzumab in combination with paclitaxel in patients with metastatic breast cancer as first-line treatment. 475 patients were randomized to either CP (n = 244) or TP (n = 231) (Im et al., 2013).
	Ontruzant (SB3) – Samsung Bioepis	Phase I: 109 healthy male volunteers. Randomized, double-blind, parallel group, single-dose comparative PK study. Randomized to receive a single 6-mg/kg IV dose of SB3, EU-reference, or US-reference (Pivot et al., 2016). Phase III: randomized, double-blind, parallel group, multicenter study. 875 patients with HER2-positive early breast cancer were randomized (1:1) to SB3 or reference trastuzumab for 8 cycles concurrently with chemotherapy (Pivot et al., 2018a, b).
	Ogivri (Hercules; MYL-1401O) - Mylan	Phase I: 132 healthy male volunteers. Single-center, randomized, double-blind, three-arm, parallel-group study. Randomized to either Myl-1401O, EU-reference, or US-reference as 8 mg/kg over 90 minutes IV (Waller et al., 2017). Phase III: multicenter, double-blind, randomized, parallel-group, equivalence study. 500 patients with ERBB2 (HER2)-positive metastatic breast cancer were randomized 1:1 to receive a proposed biosimilar or trastuzumab plus a taxane (Rugo et al., 2017).
Proposed trastuzumab biosimilar medicines	PF-05280014 – Pfizer	Phase I: 105 healthy male volunteers. Double-blind, randomized, parallel-group, single-dose, 3-arm, comparative PK study. Randomized 1:1:1 to receive a single 6 mg kg(-1) IV dose of PF-05280014, EU-reference, or US-reference, and evaluated for 70 days (Yin et al., 2014). Phase III: Randomized, double-blind PK study of PF-05280014 *vs* reference trastuzumab, both given with docetaxel (D) and carboplatin (C). 226 patients with operable HER2+ breast cancer; randomized 1:1 to PF-05280014 or EU-reference (8 mg/kg at Cycle 1; 6 mg/kg thereafter) (Lammers et al., 2017). Phase III: Randomized, boule-blind study of PF-05280014 *vs* trastuzumab + paclitaxel. 707 patients with HER2+ metastatic breast cancer were randomized 1:1 to PF-05280014 or EU-reference, both given with paclitaxel (Pegram et al., 2017).
	ABP 980 – Amgen	Phase I: 157 healthy male volunteers. Single-dose, PK study. Randomized 1:1:1 to a single 6 mg/kg IV ABP 980, US-reference, or EU-reference (Hanes et al., 2017). Phase III: Randomized, multicenter, double-blind study. After run-in anthracycline-based chemotherapy, 725 patients with HER2+ early breast cancer were randomized 1:1 to IV ABP 980 (n = 364) or TRAS (n = 361) ± paclitaxel Q3W for 4 cycles (von Minckwitz et al., 2017).
	DMB-3111 – Meiji Seika Pharma Co. Ltd)	Phase I: 70 healthy Japanese adult male volunteers. Randomized, double-blind, parallel-group study. Randomized 1:1 to receive either DMB-3111 or reference trastuzumab as a single IV infusion (6 mg/kg) over 90 min (Morita et al., 2016).
	FTMB – Synthon Biopharmaceuticals	Phase I: 118 healthy male volunteers. Dose-escalation and bioequivalence study of parallel design. Received single doses of 0.5, 1.5, 3.0 or 6.0 mg/kg FTMB, or placebo, in consecutive dose-escalation cohorts to assess safety. The 6 mg/kg cohort was expanded to establish bioequivalence between FTMB and reference based on an acceptance interval of 80.0-125.0 % (Wisman et al. (2014)).

Table 5
Differentiation between substitution, switching and interchangeability of biosimilars.

Switching	Substitution	Interchangeability
The decision by the prescribing physician to exchange one medicine with another medicine with the same therapeutic intent in a given patient (European Commission, 2013).	The practice of dispensing one medicine instead of another equivalent medicine at the pharmacy level without the consultation of the prescribing physician (European Commission, 2013).	US-specific regulatory term. A biosimilar designated as an "interchangeable biosimilar" may be switched from the reference at the discretion of the pharmacist (Lyman et al., 2018; Braun and Kudrin, 2016; Faccin et al., 2016). This interchangeability status is distinct from designation as a biosimilar (US Food and Drug Administration, 2015c).

Australia have expressed that they would like more educational resources and activities to be made available covering the basic concepts on biosimilars, as well as more in-depth topics such as clinical trial design, bioequivalence criteria, use of biosimilars and approval procedures, as well as the principles of pricing and reimbursement (European Society for Medical Oncology, 2017). Provision of accurate information for all stakeholders is essential to address misconceptions and improve acceptance (Tabernero et al., 2017; Schiestl and Krendyukov, 2017). In addition, there is a need for improving both patient and physician confidence in biosimilars, which requires support from medical societies to provide adequate guidance and education and address issues in understanding of biosimilars (Lyman et al., 2018; Schiestl and Krendyukov, 2017). There is also a requirement for practice guidelines to aid oncologists in biosimilar use and help inform their patients. Moreover, patient-appropriate materials developed with medical society endorsement can further aid physicians in patient education (Lyman et al., 2018). Medical societies should also emphasize the need for post-marketing safety surveillance (Lyman et al., 2018; Schiestl and Krendyukov, 2017). As with all medicines, long-term post-approval surveillance is important to monitor safety signals and support the effectiveness of the medicine (Lyman et al., 2018). This is necessary to demonstrate the value of biosimilars to stakeholders and help reassure both clinicians and patients about the use of a biosimilar medicine in extrapolated indications for which Phase III confirmatory studies were not performed (Lyman et al., 2018). Post-approval studies also inform on the optimal use of the medicine in real-world use.

Efforts now to improve understanding will be critical to ensure the acceptance of future oncology biosimilar MAbs. Several MAb biosimilars are being developed and may be approved in the near future (GaBI, 2018a, b). Some of them can be used in combination with other biologics and chemotherapy, like trastuzumab and docetaxel, to treat metastatic HER + breast cancer (Swain et al., 2015), and as neoadjuvant treatment in patients with early breast cancer (Schneeweiss et al., 2013). Future approval of MAb biosimilars would further increase the treatment options available to oncological patients for whom therapeutic alternatives are currently limited.

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Declaration of Competing Interest

Andriy Krendyukov is a former employee of Hexal AG, Holzkirchen, Germany. Martin Schiestl is an employee of Sandoz GmbH, Kundl, Austria.

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