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► **To cite this version:**

Marc Peeters, David Planchard, Mark Pegram, João Gonçalves, François Bocquet, et al.. Biosimilars in an era of rising oncology treatment options. *Future Oncology*, 2021, 17 (29), pp.3881-3892. 10.2217/fon-2021-0546 . hal-03635306

HAL Id: hal-03635306

<https://hal.science/hal-03635306>

Submitted on 31 Oct 2022

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Biosimilars in an era of rising oncology treatment options

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New diagnostic technologies, including molecular profiling, have enabled advances in treatments of various cancers; this has significantly improved clinical outcomes, including overall survival. However, the high cost of biologic drugs may prevent patients from having access to optimal treatment. Introduction of lower priced biosimilar agents into the therapeutic armamentarium brings the potential to ease the burden on healthcare expenditure and facilitate better access to effective cancer treatments. Oncology biosimilars have shown comparable efficacy and safety based on clinical evidence and physicochemical quality data as well as in real-world settings. This paper aims to review changes in the management of oncology treatment and their implication with respect to biosimilars.

First draft submitted: 2 May 2021; Accepted for publication: 9 June 2021; Published online: 30 June 2021

Keywords: biologics • biosimilars • breast cancer • colorectal cancer • lung cancer • molecular profiling • monoclonal antibodies • oncology treatment

Recent advances in the identification of molecular targets and the development of companion molecular diagnostics have paved the way for targeted therapies in cancer medicine [1,2]. Indeed, new advances in medicinal chemistry and antibody engineering have resulted in better clinical outcomes in major tumor types, such as lung, colorectal and breast cancer [1].

In the early 2000s, platinum-based chemotherapy was the mainstay of treatment for non-small-cell lung cancer (NSCLC), with an overall survival (OS) of around 8–9 months for patients with advanced disease [3–5]. Subsequently, the combination of paclitaxel/carboplatin and bevacizumab was shown to significantly extend OS compared with platinum-based chemotherapy in patients with advanced non-squamous NSCLC, where the median OS reached about 14 months [6]. In the maintenance setting with bevacizumab, the median OS from the start of induction has reached about 17 months [7]. Significant advances have been made in lung cancer treatment driven by personalized therapeutic approaches in advanced NSCLC. The targets can be: proteins that are expressed at high levels in cancer cells, such as HER2 and MET; mutant proteins that drive cancer progression, such as mutant EGFR, MET, HER2 kinase and the cell growth signaling protein BRAF; or fusion genes resulting from chromosomal translocations, involving genes, such as *ALK*, *ROS1*, *RET* and *NTRK* [15]. Since 2010, new immunotherapy drugs have led to a paradigm shift in cancer therapy by targeting immune cells to trigger the immune system to eradicate tumor cells [1,8]. Major advances were based on immune checkpoint inhibitors targeting the programmed cell death protein 1 (PD-1) or its ligand (PD-L1); for example, nivolumab and pembrolizumab (anti-PD-1 monoclonal antibodies) and atezolizumab (an anti-PD-L1 monoclonal antibody).

As in the case of NSCLC, patients with colorectal cancer are benefiting from personalized therapeutic strategies derived from a more precise determination of disease subtypes. As an example, *BRAF* mutations are found in a small fraction (8–12%) of patients with metastatic colorectal cancer (mCRC), mostly those with primary lesions located in the right side of the colon [9]. In a Phase III trial, doublet targeted therapy including a BRAF inhibitor and an anti-

EGFR monoclonal antibody cetuximab significantly improved OS and objective response rate (ORR) compared with chemotherapy plus cetuximab in patients with mCRC with the *BRAF*^{V600E} mutation [10]. Another example is microsatellite instability-high or mismatch repair-deficient mCRC. Data from a study have shown pembrolizumab monotherapy in the first-line setting in patients with microsatellite instability-high mCRC demonstrated meaningful benefits in progression-free survival (PFS) in comparison with the standard-of-care chemotherapy with or without bevacizumab or cetuximab [11].

Prior to the availability of targeted therapy, HER2-positive breast cancer had a rather poor prognosis [12]. Survival outcomes have significantly improved in this cancer type [13], prevalent in 15–20% of breast cancers [14,15], with the advent of trastuzumab, a humanized monoclonal antibody targeting subdomain 4 of the HER2 extracellular domain [16,17]. Trastuzumab was approved in 1998 by the US FDA and has since significantly improved clinical outcomes, including disease-free survival [18]. More recently, other HER2-targeted agents have been introduced as the standard of care. Pertuzumab, a recombinant humanized monoclonal antibody that binds to the extracellular domain of HER2, is used in combination with trastuzumab for the treatment of advanced local or metastatic HER2-positive breast cancer [19]. In the CLEOPATRA trial, a statistically significant improvement in PFS was shown in the PERJETA-treated group compared with the placebo-treated group (hazard ratio [HR]: 0.62; 95% CI: 0.51–0.75; $p < 0.0001$), as well as an increase in median PFS of 6.1 months (median PFS of 18.5 months in the PERJETA-treated group vs 12.4 months in the placebo-treated group) [20]. Furthermore, in the NeoSphere trial, statistically significant improvements in pathological complete response (pCR) rates were observed in patients receiving pertuzumab plus trastuzumab and docetaxel compared with those receiving trastuzumab plus docetaxel in patients with operable, locally advanced or inflammatory HER2-positive breast cancer [21]. Additionally, in the neoadjuvant setting, the TRYPHAENA trial confirmed cardiac safety in patients treated with the dual HER2 blockage [22]. Based on the results of the APHINITY trial, conducted in patients with HER2-positive early breast cancer who had their primary tumor excised, pertuzumab is used in combination with trastuzumab for patients with nodal involvement. A recently published 6-year follow-up for the trial showed invasive disease-free survival benefit from adding pertuzumab in node-positive patients [23].

Other HER2-targeted agents, including TDM-1 (or ado-trastuzumab emtansine), an antibody–drug conjugate, and tucatinib, a small-molecule tyrosine kinase inhibitor, have been added to subsequent lines of therapy for patients with metastatic HER2-positive breast cancer who are resistant to treatment with trastuzumab [24,25]. Adding further to the treatment options is trastuzumab deruxtecan, or DS-8201, which was approved by the FDA under accelerated approval for treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting, based on results in the DESTINY-Breast01 trial [26,27]. Other studies using this antibody–drug conjugate are ongoing to test its efficacy and safety for use in other indications and in combination with other drugs [28].

While biologic therapies have revolutionized cancer treatment and dramatically improved outcomes, the economic impact of these costly medicines has imposed a financial burden. Such financial toxicity often limits drug access and treatment options for patients [29]. The introduction of multiple biosimilars upon the expiration of patents of some of these biologics has been shown to offset part of this cost burden, albeit at different ranges depending on the various policies in different regions and depending on other factors such as physician and patient acceptance [30]. Biosimilars have the potential to reduce healthcare costs and increase accessibility without compromising safety, efficacy or quality [31]. Regulatory approval of biosimilars is based on a stepwise approach to build ‘totality of evidence’ to demonstrate that the biosimilar is ‘highly similar’ to the reference product based on sophisticated analytical and clinical assessments [32]. Furthermore, the quality attributes investigated by biosimilar manufacturers have raised concerns for pharmacovigilance and post-market surveillance, which have resulted in improvements in industry practice [33]. As more biosimilars become available, clinical data generated in the real-world setting have accumulated, providing further reassurance.

Accessibility & cost–effectiveness of cancer therapies

Despite the advances in the cancer treatment, according to WHO estimates worldwide cancer cases are expected to increase by approximately 60% over the next few decades, from 18.1 million in 2018 to 29.5 million by 2040 [34]. Spending on all medicines used in the treatment of cancer patients reached nearly \$150 billion in 2018 and is forecast to reach nearly \$240 billion by 2023, growing by 9–12% per year [35]. Cost and accessibility barriers create disparities in cancer treatments and the resulting clinical outcomes. Many of the most promising and efficacious drugs in the oncology space are biologics, and they are expensive, which in turn may prohibit patients’ access to effective biologic

therapies [36]. Based on 2019 sales, monoclonal antibody-based biologics, including pembrolizumab, nivolumab, rituximab, bevacizumab and trastuzumab, ranked among the top-selling cancer drugs [37]. These biologic agents were expensive and, at least in part, contributed to the rising cost of cancer treatment. However, biosimilars are now available for some of these biologic agents and have contributed to decreases in treatment costs by bringing about price competition between the reference product and its biosimilar competitors [38].

A biosimilar is a biologic medicine that is highly similar in quality, efficacy and safety to an existing biologic reference product [39]. Lower-priced biosimilars may also help save costs for the healthcare system. One projection estimates that \$250 billion may be saved between 2014 and 2024 in the USA if 11 biosimilars, including Avastin[®] (bevacizumab), Herceptin[®] (trastuzumab) and Rituxan[®] (rituximab), were to enter the market [40]. According to a report from the IQVIA Institute, cost savings from biosimilars in the EU5 countries (France, Germany, Italy, Spain and UK) alone are estimated to amount to more than €10 billion in the period 2016–2020 [41]. In this regard, biosimilars could potentially play an important role in increasing patient access to biologic therapies. The lower price of biosimilars has the potential to reduce healthcare expenditure and provide better access to biologic therapy for cancer. In the case of monoclonal antibody biosimilars, currently the cost ratio of biosimilar to reference product ranges from 59.4 to 86.0% [38]. Furthermore, the expected cost saving of using monoclonal antibody biosimilars for one patient for 1 month is about \$322–7424, whereas the expected saving for the entire treatment course per patient is about \$17,517–38,923 [38]. This price reduction not only helps relieve the financial burden, but also leads to an increase in prescription of drugs.

The launch of the filgrastim biosimilar caused a 104% increase in filgrastim uptake in the UK, and with the availability of epoetin biosimilars from 2007 to 2014, treatment volume increased by 263% and price decreased by 50% in three European countries (Romania, Bulgaria and the Czech Republic) [42,43].

The launch of oncology biosimilars & their economic impact

Major patents for some of the oncology biologics have expired, and several biosimilars for these drugs have been approved. According to the EMA, as of May 2021 39 biosimilars of filgrastim, bevacizumab, trastuzumab, pegfilgrastim and rituximab have been approved [44].

Since the first trastuzumab biosimilars launched in Europe in 2018 a total of six trastuzumab biosimilars have been approved by the EMA (as of May 2021) [45]. In terms of clinical development, there were some differences in clinical study design across Phase III trials of different trastuzumab biosimilars. In the case of ABP 980 (Kanjinti[®]; Amgen), CT-P6 (Herzuma[®]; Celltrion) and SB3 (Ontruzant[®]; Samsung Bioepis), Phase III trials were conducted in HER2-positive *early* breast cancer (using pCR as a primary end point), whereas MYL-1401O (Ogivri[®]; Mylan), PF-05280014 (Trazimera[®]; Pfizer) and HLX02 (Zercepac[®]; Shanghai Henlius Biotech) Phase III trials were conducted in the first-line metastatic breast cancer setting, with ORR as the primary clinical end point [46,47]. Study indications, primary end points and prespecified equivalence margins for each trastuzumab biosimilar development campaign are shown in Table 1.

As of May 2021, nine bevacizumab biosimilars – ABP 215 (Mvasi[®]; Amgen), PF-06439535 (Zirabev[®]; Pfizer), SB8 (Aybintio[®] and Onbevzi[®]; Samsung Bioepis), FKB238 (Equidacent[®]; Centus Biotherapeutics Europe Ltd), MB02 (Alymsys[®] and Oyavas[®]; mAbxience and STADA) and MYL-1402O (Abevmy[®] and Lextemy[®]; Mylan) – have been approved for the same types of cancer as the bevacizumab reference product in the EU.

Several budget impact analyses estimate that the launch of these oncology biosimilars will generate significant budget savings. For example, in the case of trastuzumab biosimilars, it was estimated that switching from reference to trastuzumab biosimilar would lead to budget savings of €0.91 billion–2.27 billion over 5 years, which would allow an additional 3503–7078 patients to be treated with trastuzumab [48]. Another study estimated the savings of introducing trastuzumab biosimilar for the treatment of breast cancer in Croatia to range from €0.26 million–0.69 million in the first year after introduction [49]. Regarding bevacizumab, a study of a hypothetical 10-million-member health plan estimated that 503 patients would be treated with bevacizumab reference product or biosimilar in year 1 and 676 patients in year 3. Switching from reference product to bevacizumab biosimilar was projected to be associated with a total cost saving of \$3,430,967 in year 1 and \$14,731,112 in year 3, with more than half associated with patients with colorectal cancer [8]. Based on these types of projections, oncologic biosimilars may help ease the burden of increasing treatment costs, facilitating greater access to important biologic therapies as treatments for cancer.

Table 1. Comparison of approved trastuzumab biosimilars.

Biosimilar (manufacturer)	Patient number	Study indication	Primary end point	Equivalence margin		Primary end point (BS vs RP) %	Result	
				Risk difference	Risk ratio		Risk difference	Risk ratio
ABP-980 (Amgen)	725	Early	Total pCR	(-13%, 13%)	(0.759, 1.318)	48 vs 41	7.3 (90% CI: 1.2–13.4)	1.188 (90% CI: 1.033–1.366)
CT-P6 (Celltrion)	549	Early	Total pCR	(-15%, 15%)	(0.74, 1.35)	46.8 vs 50.4	-0.04 (95% CI: -0.12 to 0.05)	0.93 (95% CI: 0.78–1.11)
SB3 (Samsung Bioepis)	875	Early	Breast pCR	(-13%, 13%)	(0.785, 1.546)	51.7 vs 42.0	10.7 (95% CI: 4.13–17.26)	1.259 (95% CI: 1.085–1.460)
MYL1410 (Mylan)	500	Metastatic	ORR (24 weeks)	(-15%, 15%)	(0.81, 1.24)	69.6 vs 64.0	5.53% (95% CI: -3.08 to 14.04)	1.09 (90% CI: 0.974–1.211)
PF-05280014 (Pfizer)	707	Metastatic	ORR (25 weeks)	N/A	(0.8, 1.25)	62.5 vs 66.5	-0.76 (95% CI: -8.02 to 6.49)	0.94 (95% CI: 0.842–1.049)
HLX02 (Shanghai Henlius Biotech)	649	Metastatic	ORR (24 weeks)	(-13.5%, 13.5%)	N/A	71.0 vs 71.4	-0.4 (95% CI: -7.4 to 6.6)	N/A

BS: Biosimilar; N/A: Not applicable; ORR: Objective response rate; pCR: Pathological complete response; RP: Reference product.
Created using data from [46,47].

Quality aspects of biologics

Biologic medicines, unlike conventional generic drugs, are structurally complex with natural variability (e.g., due to posttranslational modifications); thus making an exact replication at a molecular level is inherently impossible [39,50]. To ensure desired quality attributes, the quality control metrics of these drugs depend on physicochemical or biologic features associated with the reference product, termed critical quality attributes (CQAs) [51]. Variability may exist for all biologics, and alterations in the CQAs of an antibody may change efficacy or safety of the drug [33,50–52]. For example, the efficacy of trastuzumab against breast cancer xenografts was largely dependent on Fc- γ receptor (Fc- γ R) binding in preclinical studies, and glycosylation patterns showed a correlation with antibody-dependent cellular cytotoxicity (ADCC) [53]. It is also important to understand the concept of batch variation and its implications for clinical effect, because the variation in product quality may lead to change in clinical outcome [54]. As an example of the variation in batches, 154 lots of trastuzumab reference products marketed in the EU and USA were extensively analyzed using state-of-the-art assays over 8 years; as a result, drifts in glycosylation patterns, Fc receptor binding and ADCC activity were identified in lots with expiry dates between August 2018 and December 2019 [55].

In the case of the trastuzumab biosimilar SB3, the proportion of patients achieving a breast pathological complete response (bpCR) was 51.7 versus 42.0% for the SB3 and reference trastuzumab treatment groups, respectively – an absolute difference of 10.70% (95% CI: 4.13%–17.26%) [23]. However, an analysis by ADCC status showed that the proportion of patients achieving bpCR in the subgroup that had never been exposed to ADCC-shifted lots of reference trastuzumab was 44.1%, while that of patients achieving bpCR in the subgroup exposed to ADCC-shifted lots of reference trastuzumab was 40.1% [23]. The shift is considered as a contributing factor for the observed difference, and the European Public Assessment Report concluded it was likely that the differences were confounded by the apparent shift in terms of ADCC activity for certain batches of reference trastuzumab, and thus SB3 is not considered to be superior to reference trastuzumab [23].

Similarly, the reason why the upper border of the prespecified margin of $\pm 13\%$ in a Phase III trial of another trastuzumab biosimilar, ABP 980, was crossed was thought also to be due to changes in ADCC found for some lots of reference trastuzumab used in the study [56]. As with SB3, the European Public Assessment Report acknowledged that the higher variability in ADCC activity in the reference trastuzumab lots could have contributed to the reasons why the primary end point, the pCR, in a Phase III study of ABP 980 was not met; the residual uncertainty does not question the biosimilarity between ABP 980 and reference trastuzumab [56,57].

Recent data from a 4-year follow-up Phase III trial of SB3 showed that 4-year event-free survival (EFS) rates were 83.4% for SB3 and 80.7% for reference trastuzumab (HR: 0.77; 95% CI: 0.47–1.27) and that 4-year OS rates were 94.3% for SB3 and 89.6% for reference trastuzumab (HR: 0.53; 95% CI: 0.24–1.16), but the difference in both cases was not statistically significant (Figures 1 & 2) [58]. In addition, a *post hoc* analysis was conducted in subgroups including the drifted reference trastuzumab group for patients who were exposed to at least one vial

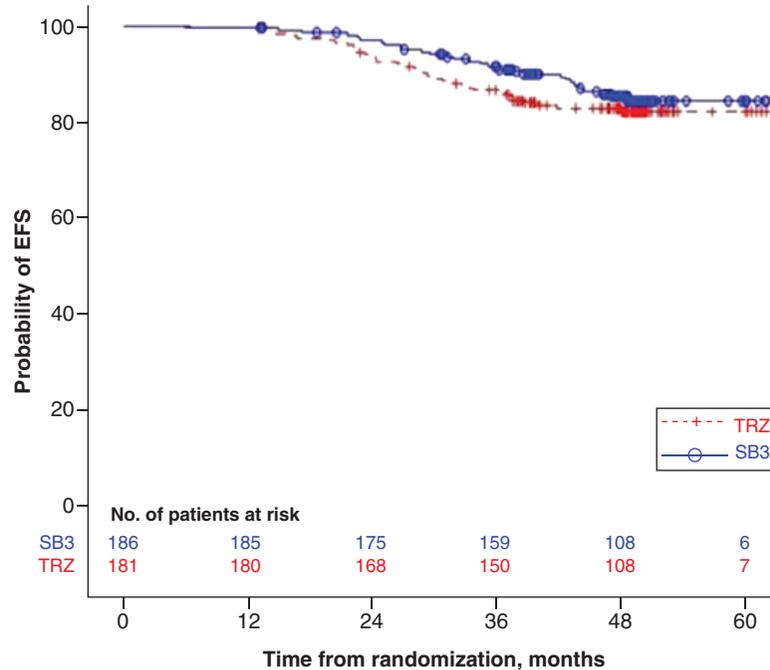


Figure 1. Kaplan–Meier plot of event-free survival comparing SB3 and reference trastuzumab.
 EFS: Event-free survival; HR: Hazard ratio; TRZ: Reference trastuzumab.
 Data taken from [58].

Summary of EFS		
	No. of events (%)	HR
SB3 (n = 186)	29 (15.59%)	0.77 [0.47, 1.27] p = 0.3055
TRZ (n = 181)	35 (19.34%)	

from a drifted trastuzumab lot and the non-drifted reference trastuzumab group for those who were never exposed to any drifted vials [58]. This analysis showed no difference in EFS and OS between SB3 and non-drifted reference trastuzumab; however, there was an apparent difference in EFS and OS between drifted reference trastuzumab and non-drifted reference trastuzumab [58].

This was an important lesson in drug development, demonstrating how very careful analytical characterization of trastuzumab biosimilars has resulted in improved understanding of variability in glycosylation characteristics, which can impact Fc-dependent immune mechanisms of action, resulting in measurable differences in clinical outcome. Given that batch-to-batch variation naturally occurs during the manufacturing of complex biologic therapeutics, CQAs must be monitored over time to assure the safety and efficacy of reference products as well as biosimilars. This is reflected in the good vigilance practice guidelines set forth in Europe for biologic drugs; these guidelines capture immunogenicity, manufacturing variability, stability and cold chain management, transport and traceability [59]. Pharmacovigilance concerns raised by the quality attributes investigated by biosimilar manufacturers have raised the bar for the whole field of biologics manufacture [33].

The totality of evidence for biosimilar drug approval

The regulatory approval pathway for biosimilars is based on the totality of evidence [32]. This is a stepwise approach, starting with the foundation of analytical studies, moving on to preclinical animal studies and clinical pharmacokinetics (and pharmacodynamics studies where possible), followed by a clinical immunogenicity assessment and clinical studies demonstrating equivalent efficacy compared with the reference biologic product in a randomized Phase III head-to-head comparison trial [46]. At each step, regulators evaluate the totality of evidence determining whether further studies are needed at any step along the way to eliminate any residual uncertainty between the biosimilar and the reference biologic in order to demonstrate similarity between the biosimilar and the reference product [32]. Based upon the rigor with which the totality of evidence leads to regulatory approval for the biosimilar drug, guidelines committees such as the National Comprehensive Cancer Network have acknowledged that ‘an FDA-approved biosimilar is an appropriate substitute for trastuzumab’ [60], an example underscoring the confi-

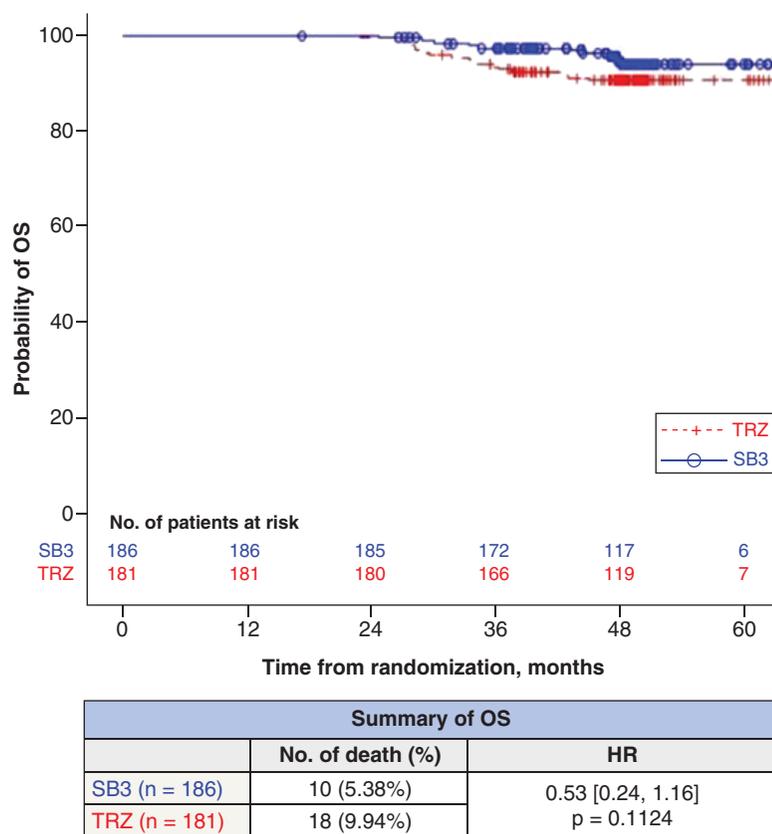


Figure 2. Kaplan–Meier plot of overall survival comparing SB3 and reference trastuzumab.

HR: Hazard ratio; OS: Overall survival; TRZ: Reference trastuzumab.

Data taken from [58].

dence with which drug indications can be extrapolated based upon the totality of evidence supporting biosimilar development.

Clinical study is the final stage in the stepwise process to demonstrate that there are no clinically meaningful differences between the biosimilar and the reference biologic product [51]. In general, the clinical efficacy study aims to confirm clinical equivalence between a proposed biosimilar and its reference product on the basis of prespecified margins, along with comparable safety and immunogenicity. Such studies do not aim to establish *de novo* efficacy and safety [51].

For example, patients with NSCLC are considered to represent a highly sensitive population for measuring differences in response rates to assess biosimilarity of bevacizumab [61], and as a result, Phase III clinical trials of all bevacizumab biosimilars, including ABP 215, PF-06439535, SB8, FK238, MB02 and MYL-1402O, were undertaken in NSCLC [61–65]. All six biosimilars have been approved in the EU, including extrapolation of indications for the treatment of patients with the same types of cancer for which the reference bevacizumab is currently indicated in the EU [61,63–66].

A large Phase III trial of SB8 was conducted in this sensitive population of NSCLC, with best ORR as the primary end point, and showed equivalence between SB8 and reference bevacizumab in patients with metastatic or recurrent NSCLC [61]. For SB8 and reference bevacizumab (Avastin), respectively, the best ORR in the Full Analysis Set population was 47.6 and 42.8%, and the best ORR in the Per Protocol population subset was 50.1 and 44.8%. The risk ratio of 1.11 (90% CI, 0.975–1.269) in Full Analysis Set population and the risk difference of 5.3% (95% CI: –2.2 to 12.9%) in the Per Protocol subset showed equivalence between the biosimilar and reference bevacizumab. (Predefined equivalence margin: [0.737–1.357] for FAS, [–12.5 to 12.5%] for PPS) Secondary end points such as PFS, OS and duration of response were also comparable between the two groups, and the safety profiles and immunogenicity of SB8 and reference bevacizumab were similar [61]. This study met its equivalence end point between SB8 and reference bevacizumab in terms of best ORR risk ratio, with comparable

Table 2. Comparison of approved bevacizumab biosimilars.

Biosimilars	Primary end point (full analysis set)				Primary end point (per protocol set)			
	Patient number	ORR, n (%)	Risk ratio (90% CI)	Risk difference (95% CI)	Patient number	ORR, n (%)	Risk ratio (90% CI)	Risk difference (95% CI)
PF-06439535	358	162 (45.3)	1.0146 [†] (0.8856–1.1625)	0.6531% [†] (-6.6080 to 7.9082)	351	161 (45.9)	1.0177 [†] (0.8656–1.1966)	0.7985% [†] (-6.5371 to 8.1267)
Reference bevacizumab	361	161 (44.6)			355	160 (45.1)		
ABP 215	328	128 (39.0)	0.93 (0.80–1.09)	-2.90% (-10.48 to 4.67)	281	121 (43.1)	0.94 (0.80–1.10)	-2.82% (-11.06 to 5.42)
Reference bevacizumab	314	131 (41.7)			274	125 (45.6)		
SB8	379	181 (47.6)	1.11 (0.975–1.269)	4.8% (-2.3 to 11.9)	337	169 (50.1)	1.12 (0.977–1.278)	5.3% (-2.2 to 12.9)
Reference bevacizumab	383	164 (42.8)			328	147 (44.8)		
FKB238	364	188 (51.6)	0.96 (0.86–1.08)	N/A	352	182 (51.7)	N/A	-0.02% (-0.0905 to 0.0568)
Reference bevacizumab	367	197 (53.7)			354	189 (53.4)		
MB02	315	127 (40.3)	0.910 (0.780–1.1060)	-4.02% (-10.51 to 2.47)	256	N/A	0.915 (0.787–1.065)	-4.27% (-12.92 to 4.38)
Reference bevacizumab	312	139 (44.6)			255			

[†] Unstratified result.
N/A: Data not available; ORR: Objective response rate.
Created using data from studies B7391003 [62], 20120265 [63], SB8-G31-NSCLC [61] FKB238-002 [64] and MB02-C-02-17 [65].

safety, pharmacokinetics and immunogenicity. Other bevacizumab biosimilars showed similar results compared with reference products, demonstrating their clinical equivalence (Table 2).

As biosimilars become widely available in clinical practice, more clinical data in real-world settings will also become available. A population-based study from the Danish Breast Cancer Group for 215 patients with HER2-positive early breast cancer showed that 56% of patients treated with neoadjuvant chemotherapy plus pertuzumab plus SB3 achieved pCR, which was comparable to the response rates seen in published historical clinical studies with reference trastuzumab in combination with pertuzumab [59,65,67–69]. In another real-world study of 35 female patients with HER2-positive breast cancer treated with SB3 plus pertuzumab, 24 patients (69%) were treated with this combination in the neoadjuvant setting. Two of these patients were treated for local relapse and were excluded for efficacy assessment. Of the remaining 22 patients, 11 (50%) achieved a pCR (ypT0/ypTis and ypN0), and none of the 35 patients had a decline in left ventricular ejection fraction of $\geq 10\%$, consistent with the known safety and efficacy profile of reference trastuzumab plus pertuzumab [70]. In addition, analysis of real-world data on the incidence of hypertension and proteinuria in patients treated with bevacizumab versus bevacizumab biosimilar showed no statistically significant difference between the two groups [71]. These and other real-world data on oncology biosimilars further support the similarity of biosimilars to reference products.

Conclusion

With the introduction of molecular profiling and targeted therapies in cancer treatment, the clinical outcomes of patients with specific genetic alterations have drastically improved over the past two decades. However, the high cost of targeted therapies has caused financial toxicity in the healthcare system and has limited patients' access to optimal treatment. With the expiration of major patents for oncology biologics, several biosimilars have been approved and launched in the market, creating competition among available products. These competitions, not only between biosimilars and reference products but also among biosimilars themselves, are expected to create price erosion and increase the options for patients and healthcare providers. Historically, the launch of filgrastim and epoetin biosimilars contributed to an increase in the drug uptake and a reduction of the drug price. More recently, additional budget savings have been observed, and further savings are expected from the use of oncology monoclonal antibody biosimilars, such as those of trastuzumab and bevacizumab, as evidenced from various budget impact analyses. Biosimilar drugs can be considered as one of the potential solutions to reduce the economic burden of cancer treatment globally. The rigor with which biosimilar drugs are characterized in terms of their

CQAs will give clinicians and patients the confidence they need to fully exploit the availability of biosimilars in routine clinical practice. The approval pathway for biosimilars is based on the totality of evidence, in which the similarity of a biosimilar to its reference product is demonstrated at each step of the comparison. The indications for a respective biologic product can be extrapolated based upon the rigor with which the totality of evidence leads to biosimilar drug regulatory approval. Further adding to the evidence, real-world data on the use of biosimilars are constantly emerging with the increase in available biosimilars in the market. Thus far, in real-world datasets, the clinical experience with biosimilar antibodies for oncologic indications appears to mirror that of historical data from clinical trials of reference therapeutic antibodies for both efficacy and safety signals. The clinical evidence of biosimilars, both from registrational Phase III clinical trials and in real-world settings, provides reassurance to healthcare providers and patients that biosimilars can be regarded as equivalent therapeutic options to reference products when considering multiple treatment options.

Future perspective

Cancer prevalence and treatment costs continue to increase at high rates globally. Molecularly targeted therapeutics for cancer patients with specific molecular alterations have significantly improved clinical outcomes, including OS in many instances. However, the high costs, particularly of biologic drugs, may prevent some patients from having access to optimal treatment. Cost and accessibility barriers create disparities in cancer treatment and the resulting clinical outcomes. The lower-cost biosimilars have the potential to reduce healthcare expenditure and provide better access to biologic therapy for cancer. Based on prespecified clinical efficacy equivalence margins and physicochemical quality data, oncology biosimilars have shown comparable efficacy and safety, including in real-world settings, to that seen in studies of their reference products. More oncology biosimilars will become available within the next 5–10 years. It is hoped that with reduction in the cost of effective biologic cancer treatments, patient accessibility may increase, thus mitigating against disparities and offering better treatment options to more patients.

Executive summary

Background

- Cancer prevalence and treatment costs continue to increase at high rates globally. Molecularly targeted therapeutics for cancer patients with specific molecular alterations have significantly improved clinical outcomes, including overall survival in many instances. However, the high costs, particularly of biologic drugs, may prevent some patients from having access to optimal treatment.

Accessibility & cost–effectiveness of cancer therapies

- Biosimilar oncologic therapeutics can be a potential solution for cancer treatment burden in terms of accessibility and cost.

Launch of oncology biosimilars & their economic impact

- With the expiration of major patents for oncology biologics, several biosimilars have been approved and launched in the market.
- Additional budget savings are expected for relatively recently launched oncology biosimilars, such as trastuzumab and bevacizumab biosimilars.

Quality aspects of biologics

- Pharmacovigilance concerns raised by the quality attributes investigated by biosimilar manufacturers have raised the bar for the whole field of biologics manufacture.

The totality of evidence for biosimilar drug approval

- The approval pathway for biosimilars is based on the totality of evidence, in which similarity of a biosimilar to its reference product is demonstrated at each step.
- Accumulating clinical evidence based on data from nonclinical and clinical trials as well as in real-world settings has provided assurance of biosimilars' comparable quality, safety and efficacy to those of their reference medicines.

Author contributions

All authors contributed substantially to the conception of the work, the acquisition, analysis, or interpretation of data for the work, drafting the work, revising it critically for important intellectual content, final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgments

The authors acknowledge MCI Korea and Y-J Seo for editorial support in the preparation of this manuscript, with funding from Samsung Bioepis.

Financial & competing interests disclosure

M Peeters: consulting, advisory role or lectures (Samsung Bioepis). D Planchard: consulting, advisory role or lectures (AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche, Samsung Bioepis); honoraria (AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche, Samsung Bioepis); clinical trials research as principal or coinvestigator (institutional financial interests) (AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo); travel, accommodations, expenses (AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer); data review participation (Samsung Bioepis). M Pegram: consulting (Roche/Genentech, Samsung Bioepis, Pfizer, Amgen); travel (Roche/Genentech, Samsung Bioepis, Pfizer); lectures (industry-sponsored satellite symposia at major international oncology conferences; consultant on drug development activities for biosimilar trastuzumab, and was involved in the development of the originator product; has been an invited speaker on the topic of biosimilars in oncology at several conferences (e.g., AACR, ESMO). J Gonçalves: consulting (AstraZeneca, Biogen, Novartis, Samsung Bioepis, Amgen); travel (Biogen, Amgen); was a speaker and an advisory board member of AstraZeneca, Biogen, Novartis, Samsung Bioepis and Amgen. H Jang is an employee of Samsung Bioepis. F Bocquet: no conflicts of interest. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Editorial support for manuscript preparation was funded by Samsung Bioepis.

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