Bevacizumab biosimilars: scientific justification for extrapolation of indications

Barbara Melosky^{*,1}, David A Reardon², Andrew B Nixon³, Janakiraman Subramanian⁴, Angel H Bair⁵ & Ira Jacobs⁵

¹Medical Oncology, British Columbia Cancer Agency, University of British Columbia, Vancouver, BC V5Z 4E6, Canada

²Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA

³Department of Medicine/Medical Oncology, Duke University School of Medicine, Durham, NC 27710, USA

⁴Division of Oncology, Saint Luke's Cancer Institute, Kansas City, MO 64111, USA

⁵Pfizer Inc., New York, NY 10017, USA

*Author for correspondence: BMelosky@bccancer.bc.ca

The first biosimilar of bevacizumab was approved by the US FDA; other potential biosimilars of bevacizumab are in late-stage clinical development. Their availability offers opportunity for increased patient access across a number of oncologic indications. The regulatory pathway for biosimilar approval relies on the totality of evidence that includes a comprehensive analytical assessment, and a clinical comparability study in a relevant disease patient population. Extrapolation of indications for a biosimilar to other eligible indications held by the originator, in the absence of direct clinical comparison, frequently forms part of the regulatory judgment. Herein, we consider the evidence required to demonstrate biosimilarity for bevacizumab biosimilars, with particular focus on the rationale for extrapolation across oncologic indications.

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Bevacizumab (Avastin[®]; Roche, Welwyn Garden City, UK; Genentech, CA, USA) is a monoclonal antibody directed against VEGF. It is approved in Europe and the USA for the treatment of a range of cancers, including metastatic or recurrent nonsquamous non-small-cell lung cancer (NSCLC), metastatic renal cell carcinoma, metastatic colorectal cancer (CRC), cervical cancer, and platinum-resistant or platinum-sensitive recurrent epithelial ovarian, fallopian tube and primary peritoneal cancers [1,2]. In addition, in the USA, Japan, and many other countries, bevacizumab is indicated for the treatment of patients with glioblastoma. In Europe, it is also authorized for use in metastatic breast cancer and in combination with erlotinib for the first-line treatment of advanced, metastatic nonsquamous NSCLC with EGF receptor-activating mutations [3]. Randomized Phase III trials have shown that progression-free survival (PFS) and/or overall survival (OS) in patients with these cancers is prolonged with treatment combining bevacizumab with standard chemotherapy (Table 1) [4–12]. Nonetheless, patient access to bevacizumab may be limited.

Barriers to bevacizumab use stem from factors such as insurance coverage and cost of treatment, manufacturing and supply and uncertainty as to its cost-effectiveness in some clinical settings [13–15]. A survey conducted by the European Society of Medical Oncology Consortium found budget constraints, affordability and issues related to the manufacture and assured supply of the product were cited most frequently as reasons for access to bevacizumab to be considered suboptimal [13]. Oncologists who were surveyed in the USA, Europe and in some emerging market countries (Brazil, Mexico and Turkey) stated the major barriers to prescribing bevacizumab were the high out-of-pocket costs for patients and a lack of reimbursement. These barriers were commonly cited as reasons for reducing the number of drug treatment cycles that were planned for patients [15].

Protein-based biologics, such as bevacizumab, are produced in living cells rather than by chemical synthesis, and are large and structurally complex [16]. Their structure and activity are influenced by events that occur during biosynthesis, including post-translational modifications, such as the covalent addition of functionality (including

Table 1. Key clinical studies supporting approved indications for bevacizumab.

Patient population	Treatments	Efficacy (primary end point)	Safety	Ref.
Previously untreated metastatic CRC	IFL plus (BEV or PBO)	Median survival: 20.3 and 15.6 months in the IFL + BEV and IFL + PBO groups, respectively (HR for death: 0.66 [$p < 0.001$])	Grade 3 hypertension: 11.0 and 2.3% in the IFL + BEV treatment and IFL + PBO arm, respectively	[4]
Recurrent or advanced NSCLC (stage IIIB or IV)	PTX and carboplatin with or without BEV	Median survival: 12.3 and 10.3 months in the chemotherapy + BEV group and chemotherapy alone group, respectively (HR for death: 0.79 [$p = 0.003$])	Clinically significant bleeding: 4.4 and 0.7% for the chemotherapy + BEV and chemotherapy alone groups, respectively ($p < 0.001$) Fifteen treatment-related deaths in the chemotherapy + BEV group, including five from pulmonary hemorrhage	[5]
Previously untreated metastatic RCC	IFN + (BEV or PBO)	Median PFS: 10.2 and 5.4 months in the BEV + IFN group and PBO + IFN control group, respectively (HR: 0.63 [95% CI: 0.52–0.75]; $p = 0.0001$)	(Grade ≥ 3 AEs) fatigue: 12 and 8%; asthenia 10 and 7%; in the BEV + IFN and PBO + IFN control group, respectively Deaths due to AEs: eight (2%) patients who received ≥ 1 doses of BEV; seven (2%) of those who did not receive BEV	[6]
Initial treatment for metastatic breast cancer	PTX alone or with BEV	Median PFS: 11.8 and 5.9 months for PTX + BEV and PTX alone, respectively (HR: 0.60; $p < 0.001$)	Grade 3/4 hypertension: 14.8 and 0.0% ($p < 0.001$); proteinuria: 3.6 and 0.0% ($p < 0.001$); headache: 2.2 and 0.0% ($p = 0.008$); cerebrovascular ischemia: 1.9 and 0.0% ($p = 0.02$); infection: 9.3 and 2.9% ($p < 0.001$) in the PTX + BEV and PTX alone groups, respectively Overall, febrile neutropenia was $<1\%$	[7]
Recurrent glioblastoma	BEV alone or in combination with irinotecan	Estimated 6-month PFS rates: 50.3 and 42.6% in the BEV + irinotecan and BEV alone groups, respectively. ORR was 37.8 and 28.2%, respectively	Most common grade ≥ 3 AEs were convulsion (13.9%), neutropenia (8.9%) and fatigue (8.9%) in the BEV + irinotecan group (65.8% of patients); hypertension (8.3%) and convulsion (6.0%) in the BEV alone group (46.4% of patients)	[8]
Recurrent, persistent or metastatic cervical cancer	Chemotherapy (cisplatin + PTX) or (topotecan + PTX) each with or without BEV	Overall survival: 17.0 and 13.3 months for the BEV + chemotherapy and chemotherapy alone groups, respectively (HR for death: 0.71 [98% CI: 0.54–0.95]; $p = 0.004$)	Hypertension of grade ≥ 2 : 25 and 2%; thromboembolic events of grade ≥ 3 : 8 and 1%; GI fistulas of grade ≥ 3 : 3 and 0%; in the BEV + chemotherapy and chemotherapy alone groups, respectively	[9]
Platinum-resistant ovarian cancer	Single-agent chemotherapy (PEGylated liposomal doxorubicin, PTX or topotecan) alone or with BEV	Median PFS: 6.7 and 3.4 months with chemotherapy in combination with BEV and single-agent chemotherapy alone, respectively (HR: 0.48 [95% CI: 0.38–0.60]; $p < 0.001$)	Grade ≥ 2 hypertension and proteinuria were more common in patients receiving a BEV-containing regimen GI perforation occurred in 2.2% of BEV-treated patients	[10]
Previously untreated, incompletely resectable stage III or any stage IV epithelial ovarian, primary peritoneal or fallopian tube cancer	PTX + carboplatin for cycles 1 through 6 with either PBO (cycles 2–22), BEV (cycles 2–6) and PBO (cycles 7–22) or BEV (cycles 2–22)	Median PFS: 14.1, 11.2 and 10.3 months in the BEV-throughout, BEV-initiation and control group, respectively (HR relative to control group for progression or death: 0.717 [95% CI: 0.625–0.824]; $p < 0.001$ with BEV-throughout; 0.908 [95% CI: 0.795–1.040]; $p = 0.16$ with BEV-initiation)	Hypertension requiring medical therapy: 22.9, 16.5 and 7.2%; GI-wall disruption requiring medical intervention: 2.6, 2.8 and 1.2% in the BEV-throughout, BEV-initiation and control group, respectively	[11]
Platinum-sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer	GC with (PBO or BEV)	Median PFS: 12.4 and 8.4 months for the GC + BEV arm and GC + PBO arm, respectively (HR: 0.484; [95% CI: 0.388–0.605]; $p < 0.0001$)	Grade ≥ 3 hypertension: 17.4 and $<1\%$; proteinuria: 8.5 and $<1\%$; in the GC + BEV and GC + PBO arm, respectively Rates of neutropenia and febrile neutropenia were similar between groups	[12]

5-FU: Fluorouracil; AE: Adverse events; BEV: Bevacizumab; CRC: Colorectal cancer; GC: Gemcitabine and carboplatin; GI: Gastrointestinal; HR: Hazard ratio; IFL: Irinotecan, 5-FU and leucovorin; IFN: Interferon- $\alpha 2a$; NSCLC: Non-small-cell lung cancer; ORR: Objective response rates; PBO: Placebo; PFS: Progression-free survival; PTX: Paclitaxel; RCC: Renal cell carcinoma.

glycosylation, lipidation, hydroxylation, phosphorylation) and proteolytic cleavage of regulatory subunits or selective degradation, as well as during purification, formulation or storage [17]. Therefore, due to the complexity in terms of their structure and the methods used in their manufacture, some level of heterogeneity exists between batches of the same biologic product [18]. Although it is not possible to generate an exact copy of a biologic, a 'biosimilar' can be produced [19]. A biosimilar is similar in terms of its safety, purity and potency to an originator or reference biologic product that has already been licensed [19–21]. Biosimilars of originator biologic medicines, such as bevacizumab, offer the possibility of increasing patient access to treatments, from which improved clinical outcomes across healthcare systems may follow.

The patents on originator bevacizumab in Europe and the USA are near to expiry. The first bevacizumab biosimilar, ABP 215 (Mvasi[®]; Amgen, CA, USA) has been approved by the US FDA for all eligible indications

(i.e., not covered by regulatory exclusivity) authorized for the originator product [22]; other potential bevacizumab biosimilars are currently in development [23].

Many biologics, including bevacizumab, have multiple indications. Regulatory agencies permit extrapolation of data for a biosimilar, allowing approval for its use in an eligible indication for which the originator is authorized without the need for a comparative clinical trial. However, adequate scientific justification and the ‘totality of evidence’ demonstrating biosimilarity are required to support approval of extrapolation [19,21,24].

This review provides an overview of bevacizumab and its mechanism of action across indications, and examines the totality of evidence approach used to support the approval of biosimilars, as well as the science underlying the concept of extrapolation.

VEGF & bevacizumab mechanism of action

VEGF plays a central role in tumor angiogenesis and has been implicated in both tumor vascularization and metastases [25,26]. In addition to the angiogenic process, the VEGF/VEGF receptor (VEGFR) pathway may be involved in a direct tumor-promoting pathway [27] and VEGF inhibition may have direct cytotoxic effects [28]. VEGF expression is associated with poorer prognosis or more aggressive disease in NSCLC [29], CRC [30], glioblastoma [31] and ovarian cancer [32]. In NSCLC, VEGF expression is associated with metastatic nodal involvement, decreased OS and PFS and increased tumor neovascularization [33]. In CRC, VEGF is significantly elevated in patients with liver metastases compared with healthy controls and patients without liver metastases, as well as in patients with node-positive CRC compared with those with node-negative CRC [34]. VEGF is often overexpressed in ovarian cancer, which is associated with an increased risk of metastatic disease and poor prognosis [35,36].

Bevacizumab binds a continuous epitope in VEGF *in vitro* and prevents binding of VEGF with VEGFR on the surface of endothelial cells [37], thereby preventing ligand-receptor interaction and downstream signaling [38]. Bevacizumab acts via inhibition of VEGF signaling and may exert its antitumor effects through inhibition of new vessel growth, regression of newly formed vessels, normalization of the vasculature to facilitate the delivery of cytotoxic chemotherapy and direct effects on tumor cells [39,40]. *In vitro*, bevacizumab inhibits VEGF-induced effects, including cell growth, increased permeability, nitric oxide production and cell migration [41,42]. Indirect clinical evidence from patients supports the hypothesis that bevacizumab has primarily cytostatic effects, indicating it inhibits the growth of new blood vessels [40].

Pharmacodynamic (PD) biomarkers, such as circulating VEGF and PGF (a VEGF family member), demonstrate a consistent effect in different tumor types after bevacizumab administration, in that circulating levels increase in response to anti-VEGF treatment of patients with various malignancies [43]. Overall, data support a consistent mechanism of action for bevacizumab, targeting VEGF and angiogenesis across various tumor types.

Demonstrating biosimilarity

In contrast with the development of a new biologic medicine, the goal of biosimilar drug development is not to establish efficacy and safety in one or more disease indications, since these are already established for the originator. Instead, the goal is to establish similarity of the biosimilar to the originator in terms of quality, safety and efficacy, thereby providing assurance there should be no meaningful clinical difference between them [44,45]. Because of the complexities and proprietary nature of the manufacturing conditions for biologics, it is not possible for the originator to be duplicated exactly and some level of heterogeneity will exist between the biosimilar and the originator [46]. Thus, regulatory agencies such as the EMA and FDA, as well as the WHO, have issued specific guidelines for the development and approval of biosimilars [19–21]. Although minor differences exist between the guidelines, demonstrating structural, functional and clinical similarity to the originator product is a requirement in all cases [19–21]. Regulatory authorities have not provided a definitive battery of analyses that need to be conducted, and each potential biosimilar is developed and approved on an individual basis. Biosimilar approval is granted on evaluation of the totality of evidence, encompassing the comparative analytical, nonclinical, pharmacokinetic (PK)/PD and clinical data [46,47]. Thus, the development pathway and requirements for approval for biosimilars differ from those of new biologic medicines, and from those for generic versions of chemically synthesized small-molecule drugs (Figure 1).

Biosimilarity is established through a rigorous, stepwise comparison of the proposed biosimilar and the reference product [19–21]. The foundation of biosimilarity rests on the demonstration of similarity in structure and function. Analytical assessments are performed that compare the originator product and potential biosimilar, to confirm similarity in primary sequence, higher-order protein structure, post-translational modifications, biochemical quality

Figure 1. Development pathways for originator biologics, biosimilars and generic versions of small-molecule drugs.

PK/PD: Pharmacokinetic/pharmacodynamic.

Adapted with permission from Future Medicine Ltd[©] (2017) [48].

attributes and biologic activity [49–51]. The sensitivity of *in vitro* assays provides the greatest likelihood of detecting minor differences between the proposed biosimilar and the originator product. Structural assessments are required to establish that the proposed biosimilar and originator share the same amino acid composition and primary sequence [52]. In addition, results of analytical tests should show high similarity between the products in terms of post-translational modifications, product isoforms, product purity, higher-order structure and protein-folding. Functional activity characterization is conducted to confirm the proposed biosimilar has a similar mechanism of action to the originator product, as well as to resolve any remaining uncertainty arising from the structural analyses as to whether any minor differences identified are likely to have clinically meaningful effects [20,21]. Since biologics typically depend on specific binding to the target antigen and potential follow-on effector function(s) to achieve their clinical effects [53], demonstrating similarity in functional activity of the proposed biosimilar and the originator product also serves as the basis for extrapolation. For monoclonal antibodies, functional assessments typically include those that evaluate antigen binding (Fab biologic function) and Fc effector biologic functions, including antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity activity [54]. Although the primary sequence and higher-order structure of the Fc region of bevacizumab are important for VEGF binding, this does not induce complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity activity [42]. This finding is consistent with a mechanism of antitumor activity via neutralization of secreted VEGF activity involving the Fab region of bevacizumab, and it is essential that this aspect is reflected in the analytical similarity plan for a proposed biosimilar. Comparative assessment of the functional activity of a proposed biosimilar and the originator should be capable of establishing that any differences in quality attributes are unlikely to be clinically relevant, as well as to provide a rationale for the approach to *in vivo* and clinical evaluation [21,55]. Regulatory agencies appear to be moving away from requiring nonclinical *in vivo* evaluations. This development is because the extensive *in vitro* analytical characterization establishes the core aspects of biosimilarity, and it is therefore unlikely that *in vivo* nonclinical studies would identify new safety signals [56,57]. Consequently, biosimilar developers and regulatory authorities are in discussions surrounding the relevance of *in vivo* nonclinical studies [56].

The goal of comparative clinical studies is to demonstrate that clinically meaningful differences between the originator product and proposed biosimilar do not exist, in terms of PK/PD, therapeutic effect or safety, including immunogenicity [19–21]. Demonstration of PK similarity in a head-to-head study, typically in healthy subjects, is an essential requirement to support biosimilarity, and is the first step of a biosimilar clinical program [19–21]. Once PK similarity has been demonstrated, generating the data to directly compare the efficacy, safety and immunogenicity of the potential biosimilar to the originator in patients in a clinical study (or studies) is the final step in establishing biosimilarity. A product can only be approved as a biosimilar by following rigorous assessment

of the totality of evidence, comprising analytical structural and nonclinical functional assessments, clinical PK and efficacy data [19–21].

Principles of extrapolation

Extrapolation of data is a well-established principle that is based on applying the conclusions from a study conducted in one population to make inferences for another population, and is widely accepted by regulatory bodies. Extrapolation is intended to avoid clinical trials conducted unnecessarily, and to help ensure the most efficient allocation of clinical research resources.

Extrapolation of indications for biosimilars is governed by specific guidelines [20,21] and figures highly in the deliberations of regulatory authorities, since it often forms part of licensing applications for biosimilars. However, extrapolation of data is not unusual and regulatory bodies have shown they are comfortable in applying this principle by doing so between one originator biologic and another. For instance, the initial approval of the monoclonal antibody trastuzumab (Herceptin®; Roche) was for use of an intravenously administered formulation for infusion, which is now indicated for the treatment of patients with early and metastatic HER2-positive breast cancer and in metastatic gastric cancer [58]. However, a fixed-dose formulation for subcutaneous administration was subsequently developed [59]. In an open-label, two-part, Phase I/Ib study in healthy male subjects and female patients with HER2-positive early breast cancer, a subcutaneous trastuzumab dose of 8 mg/kg was found to result in exposure comparable to an intravenous trastuzumab dose of 6 mg/kg [60]. A single pivotal study, using pathological complete response (pCR) as the coprimary efficacy end point, demonstrated that a fixed-dose trastuzumab subcutaneous formulation was noninferior, since the lower limit of the 95% CI (-4.0–13.4) for the difference in pCR between groups (4.7%) was greater than the prespecified margin of -12.5%, and had a similar safety profile to the established intravenous formulation, in patients with nonmetastatic, HER2-positive, locally advanced or inflammatory breast cancer treated with neoadjuvant chemotherapy [61,62]. Noninferiority between treatments in the PK coprimary end point was also demonstrated in that the geometric mean ratio of the trough concentration (C_{trough}) at predose cycle 8 before surgery was 1.33 (90% CI: 1.24–1.44), with the lower limit of the two-sided 90% CI greater than the prespecified noninferiority margin of 0.8 [61]. Extrapolation of the efficacy data to the metastatic breast cancer setting was considered acceptable [63].

Extrapolation, as it applies to biosimilars, is the scientific rationale that bridges all the data collected from one indication of the biosimilar to other eligible approved indications of the originator [24]. Importantly, extrapolation reduces or eliminates the need for repeating indication-specific clinical studies that have established the safety and efficacy for the originator product [19–21,24,45]. The extent of data required for the scientific justification of extrapolation may vary somewhat among regulatory authorities [64]. Nonetheless, consideration of extrapolation by the EMA and FDA requires that demonstration of biosimilarity with the originator must be shown across a comprehensive comparability exercise, encompassing the evaluation of efficacy, safety and immunogenicity in an indication involving a clinically relevant mechanism of action and receptors [19–21]. The overriding consideration in the selection of the patient population's disease is that it should be sufficiently sensitive to identify a difference with respect to the potential biosimilar versus the originator, should one exist [19–21].

The FDA guidance stipulates that the scientific justification for extrapolation should address the following key aspects, which bevacizumab satisfies. First, the mechanism of action in each condition should be understood, as evidenced by: target/receptors, receptor binding, dose/concentration response, pattern of molecular signaling upon engagement of the target/receptors, relationships between product structure and target/receptor interactions, and location and expression of target/receptors [21,65]. Overall, bevacizumab has a consistent mechanism of action across indications, targeting VEGF and angiogenesis in various tumor types.

Also, the PK and biodistribution of the originator product in the condition where the proposed biosimilar was tested and in the extrapolated indication should be understood. Similarly, the immunogenicity and expected toxicities in each condition of use and patient population should be known [21]. A population PK analysis was conducted on data from eight clinical trials of bevacizumab in patients ($n = 491$) with solid tumors, with treatment dose ranging from 1 to 20 mg/kg [66]. The majority (79%) of patients received bevacizumab in combination with various chemotherapy regimens. Bodyweight and gender were the most significant covariates to explain interpatient variability for both clearance and central compartment volume of distribution. The effect of chemotherapy on bevacizumab clearance was minimal. Since more than 98% of the circulating VEGF is predicted to be bound with bevacizumab at the clinical dose rates in CRC (2.5 mg/kg per week) and in breast cancer and NCSLC

(5 mg/kg per week), covariate effects were considered unlikely to significantly influence efficacy. The PK properties of bevacizumab are acknowledged as being consistent across the approved indications [65].

Bevacizumab biosimilars: considerations for development & approval

Data from the comprehensive functional assessments that were performed for ABP 215 were described in the briefing document submitted as part of the Biologics License Application [65], and illustrate the type of studies used to assess similarity of a bevacizumab biosimilar with the originator. Functional similarity to originator bevacizumab was examined in multiple preclinical pharmacologic assessments [67]. Because bevacizumab targets VEGF, assessment of the biologic activity included comparative binding studies to VEGF and VEGF isoforms by surface plasmon resonance and to cell-surface expressed neonatal Fc receptor and to Fc gamma receptor-IIIa by chemiluminescent immunoassay. A human umbilical vein endothelial cell-based assay was used to compare the inhibitory effects on proliferation and VEGFR2 phosphorylation. Antitumor activity in terms of inhibition of both tumor growth and tumor-associated vasculature was compared in two tumor xenograft models [67]. Across multiple functional assessments, ABP 215 was similar to bevacizumab [65]. The PK similarity of ABP 215 to both bevacizumab from the USA (bevacizumab-US) and bevacizumab from the EU (bevacizumab-EU) and of bevacizumab-US to bevacizumab-EU was demonstrated in a randomized, single-blind, single-dose study in healthy male subjects [68]. In a Phase III study in patients with nonsquamous NSCLC, the primary end point was met since the two-sided 90% CI of the risk ratio of the objective response rate (ORR; 0.93 [90% CI: 0.80–1.09]) was within the prespecified margin (0.67–1.50), supporting clinical equivalence of bevacizumab and ABP 215 [69]. Safety aspects and immunogenicity were also comparable to bevacizumab.

Additional insight into the assessment of a potential bevacizumab biosimilar is found in the studies that evaluated the structural and functional similarity of PF-06439535 to bevacizumab-EU and bevacizumab-US [70]. Peptide mapping demonstrated the amino acid sequence of PF-06439535 was identical to that of bevacizumab-EU and bevacizumab-US. N-linked oligosaccharide profiling identified similar levels of N-linked oligosaccharides in the products. Imaged capillary electrophoresis demonstrated that predominant charge isoforms were similar. Biologic activity, measured via inhibition of VEGF-induced cell proliferation in human umbilical vein endothelial cells and binding to the four major VEGF isoforms, was similar [70]. In addition, comparative *in vivo* nonclinical animal studies have evaluated the potential biosimilar bevacizumab in terms of toxicokinetics and potential toxicity [70].

The PK similarity of PF-06439535, bevacizumab-EU and bevacizumab-US, and between bevacizumab-EU and bevacizumab-US, following a single intravenous dose were compared in 102 healthy male subjects [71]. The three study drugs exhibited similar PK profiles, as the 90% CIs for the ratios of maximum serum concentration, area under the serum concentration–time curve from time zero to time of last quantifiable concentration and zero to infinity were all within 80.00–125.00% bioequivalence acceptance window for the comparisons of PF-06439535 to bevacizumab-EU or bevacizumab-US, and of bevacizumab-EU to bevacizumab-US. The numbers of subjects testing positive for antidrug antibodies were similarly low across treatment arms; none tested positive for neutralizing antibodies. The reporting of treatment-related adverse events in the PF-06439535 (15.2% of subjects), bevacizumab-EU (25.7%) and bevacizumab-US (18.2%) arms indicated comparable safety profiles between treatments [71].

It is essential that comparative clinical studies are conducted in an appropriate population and with a clinical end point capable of detecting potential differences between treatments. In particular, the potential for variability in outcomes due to disease- or patient-related factors should be minimized, so any observed differences can be ascribed to the drug itself and not the patient population [72]. Biosimilar manufacturers usually engage with regulators to select the most appropriate study population, which is based on evaluation of historical studies of the originator product, practical considerations and input from clinicians in order to address advances in clinical practice and reflect the latest knowledge of the disease [20,21]. The impact of comedication or previous therapy should be understood, with limited potential for having a confounding influence on outcomes. In particular, when considering the most sensitive population in which to conduct comparative studies in oncology, the indication where the originator is approved for first-line treatment may be for use with or without concomitant chemotherapy. Another consideration in the design of a comparative clinical study is selection of a suitable end point [73–75]. End points should be appropriate to the disease state and sensitive enough to detect clinically relevant differences in efficacy and safety, if any exist, between the potential biosimilar and the originator. A clinical end point measuring activity (such as ORR) may be preferred by regulatory authorities to a survival-based end point (typically used when evaluating novel biologics for oncology indications) for clinical comparisons of a potential biosimilar [75];

Table 2. Clinical studies comparing potential (and an approved) biosimilars[†] with bevacizumab in patients with advanced nonsquamous non-small-cell lung cancer.

Product (manufacturer)	Trial registration ID	Design	n	Primary end point		Status	Completion	Outcome
				Measure	Time frame			
ABP 215 (Mvasi) [‡] (Amgen)	NCT01966003	Randomized, DB parallel group	642	ORR	≤19 weeks	Completed	July 2015 (primary) [§]	Similar efficacy, safety and IG between ABP 215 and BEV [69,81]
BCD-021 (Biocad)	NCT01763645	Randomized, DB parallel group	138	ORR	day 127	Active, not recruiting	December 2014 (primary) [§]	Similar efficacy, safety and IG between BCD-021 and BEV [82]
BI 695502 (Boehringer Ingelheim)	NCT02272413	Randomized, DB parallel group	671	ORR	≤18 weeks	Ongoing, not recruiting	June 2017 (primary) [§]	–
FKB238 (Centus Biotherapeutics)	NCT02810457	Randomized, DB, parallel group	est. 730	ORR	≤12 months	Recruiting	June 2019 (est.) [§]	–
PF-06439535 (Pfizer)	NCT02364999	Randomized, DB parallel group	719	ORR	≤19 weeks	Ongoing, not recruiting	May 2017 (primary) [§] [80]	–
SB8 (Samsung Bioepis)	NCT02754882	Randomized, DB parallel group	est. 678	ORR	≤24 weeks	Active, not recruiting	June 2018(est.) [§]	–

[†] Only those potential biosimilars with trials in patients with nonsquamous non-small-cell lung cancer that are registered at ClinicalTrials.gov are included here; other potential biosimilars may be in development.
[‡] Approved by the US FDA (14 September 2017) [22].
[§] Primary completion date refers to the final data collection for the primary outcome measure. Table last updated in December 2017.
 BEV: Bevacizumab; DB: Double-blind; est: Estimated; ID: ClinicalTrials.gov identifier; IG: Immunogenicity; NCT: National Clinical Trial; ORR: Objective response rate.

particularly, since the latter end point can be influenced by factors other than product-related differences between products [20]. Use of a survival-based end point may require a larger patient population and with longer follow-up, and may not be amenable to assess the impact of switching. For instance, equivalence of ORR was chosen as the primary end point in a pivotal comparative efficacy and safety study of the rituximab biosimilar GP2013 (Rixathon[®]; Sandoz, Kundl, Austria) and rituximab in patients (n = 627) with previously untreated advanced follicular lymphoma [76]. Similarity was demonstrated as the entire 95% CI (-5.94–5.14) for the difference in ORR (-0.40%) between the two treatments was within the prespecified equivalence margin of ±12%. Median follow-up for the primary analysis was 11.6 months. PFS and OS were included descriptively as secondary efficacy objectives; however, the power to show equivalence based on PFS was calculated to be less than 1%, for the number of patients enrolled and a median estimated PFS of 36 months. At data cut-off, patients in either group did not reach the estimated median PFS or OS, highlighting the unsuitability of time-dependent survival-based end points for biosimilarity trials.

The goal of a comparative clinical trial is to demonstrate the potential biosimilar is equivalent to the originator; therefore, studies are conducted using an equivalence design (i.e., where the difference in efficacy or safety between the potential biosimilar and originator product is less than a prespecified margin of clinical equivalence) [73–75]. Bearing in mind that response rate (i.e., lack of demonstrable treatment effect) is preferable as a primary end point in biosimilar trials [55], not all patient populations in which the originator is indicated as a first-line therapy (particularly in oncology indications) may be considered suitably sensitive to detect differences, should they exist.

Taking the above factors into account, patients with previously untreated, advanced NSCLC are considered a sensitive population, suitable for the evaluation of potential biosimilars to bevacizumab when combined in a treatment regimen with paclitaxel and carboplatin [75]. Comparative clinical trials in patients with NSCLC have been registered for an approved biosimilar; a number of potential biosimilars to bevacizumab are in the advanced stages of development (Table 2). In all of the studies listed, the primary end point is ORR. For instance, the potential biosimilar bevacizumab PF-06439535 was compared with bevacizumab-EU in combination with paclitaxel and carboplatin, a treatment regimen for which safety and efficacy profile in patients with advanced nonsquamous NSCLC is well understood [77]. Based on the treatment effect, using ORR as end point in clinical studies of originator bevacizumab [78], the NSCLC patient population was considered suitably sensitive to detect differences between the products should they exist [79]. In this double-blind, randomized, parallel-group clinical trial (NCT02364999), equivalence in the primary end point was demonstrated by week 19 [80], based on the 90%

CI of the relative risk of ORR of PF-06439535 versus bevacizumab-EU, which was within a prespecified margin of 76–132% [77].

Approved biosimilars

To date, the EMA has granted marketing authorization for more than 20 biosimilars within the product classes of insulin, human growth hormone, granulocyte colony-stimulating factor, erythropoiesis-stimulating agents, follicle-stimulating hormone and TNF inhibitors [83,84]. In the USA, six biosimilars are currently licensed: adalimumab, etanercept, filgrastim, infliximab and bevacizumab [85]. The introduction of biosimilars is anticipated to bring cost savings in healthcare budgets and increased patient access. In a study to identify key drivers for the uptake of biosimilars in the top 10 EU member state pharmaceutical markets, average biosimilar price discount was approximately 15%, with the discount (range: 0–32%) dependent on the product and the country [86]. A separate analysis of the impact of competition arising from the introduction of biosimilars in Europe (23 countries) found that this led to increased consumption, based on change in treatment days for biosimilars and originator products (2016, the year before biosimilar entrance), as a proxy for patient access [87]. This increase in consumption ranged from 16% for gonadotropins (follicle-stimulating hormones and luteinizing hormone) to 122% for granulocyte-colony stimulating factors. Biosimilar experience in the USA is more recent than in Europe. Considerable reductions of direct spending on biologic drugs are anticipated due to the introduction of biosimilars, with the actual cost savings hinging on the level of competition and issues around reimbursement [88].

Biosimilars to epoetin and filgrastim are approved for all indications of the originators, and more than 9 years of experience of epoetin biosimilars in Europe have illustrated that the efficacy and safety profiles of biosimilar epoetin are similar to those of the originator [89,90]. The totality of evidence, demonstrating biosimilarity of the epoetin biosimilars with originator, and the mechanism of action for epoetin judged as consistent across all approved indications support extrapolation [64]. Similarly, filgrastim biosimilars have received approval for the indications of the originator via extrapolation based on the evidence supporting similarity between the biosimilars and the originator in terms of analytical assessments, PK/PD studies, efficacy and safety in patients, and a single mechanism of action [64].

Conclusion

Bevacizumab inhibits angiogenesis and is the standard of care for a multitude of malignancies; however, patient access to bevacizumab may be limited due to a variety of factors. The availability of biosimilar versions of bevacizumab could increase access, thereby meeting the needs of patients with cancer. The development program for a potential biosimilar is more tailored, but the assessment is just as rigorous compared with those required for a new biologic medicine. The resultant savings in development costs for a biosimilar and the impact on pricing due to greater competition offer the potential of more affordable treatment options. This is achieved without compromising quality, as biosimilarity is established based on rigorous and comprehensive comparability studies, which encompass structural, functional and clinical data.

The process of extrapolation is a key element of the biosimilar approval process. By following a carefully designed and tailored development program, manufacturers can increase the availability of biologic therapies for patients. For consideration of extrapolation by regulatory authorities, biosimilarity must be shown based on a rigorous comparability assessment involving efficacy, safety and immunogenicity in a relevant indication.

Additional considerations include the mechanism of action in each indication and the target receptors involved. Since the mechanism of action of bevacizumab is well understood – namely inhibition of VEGFR-mediated endothelial cell proliferation and angiogenesis – provided the analytical assessment of a potential biosimilar shows similarity with bevacizumab, it is not necessary to conduct trials in patients with each tumor type approved for the innovator product. Ultimately, regulatory authorities will assess the available evidence for each proposed bevacizumab biosimilar on a case-by-case basis and determine whether to authorize them for additional indications via extrapolation. Significant clinical experience to date with approved and licensed biosimilars has shown, as anticipated, that biosimilars behave similarly to the originator products, including in indications that were approved through the process of extrapolation [91], and has expanded patient access to needed biologic therapies [87].

The FDA has approved the first bevacizumab biosimilar [22]. Many potential biosimilars are currently in development and being tested in the clinical trial setting. The utility of response rate as an end point to demonstrate the clinical effectiveness of drug treatments in oncology is recognized and accepted by regulatory bodies. Adoption of the response rate in establishing comparability in a head-to-head trial in a relevant indication of a potential

biosimilar and originator, as part of the totality of evidence to demonstrate biosimilarity, provides the scientific justification for extrapolating data of bevacizumab biosimilars to the treatment of patients with other tumor types where the originator product is approved.

Future perspective

A number of biosimilars of bevacizumab are expected to be available in the near future, increasing the treatment options available for clinicians to consider for their patients. Bevacizumab biosimilars approved by regulatory bodies with robust and well-established pathways, for example, the FDA and EMA, will likely be authorized for most or all of the eligible indications of originator bevacizumab (i.e., not covered by regulatory exclusivity), based on extrapolation of data from a single comparative clinical trial in patients with NSCLC. Any current uncertainty by clinicians as to the basis for extrapolation of bevacizumab biosimilar data from patients with NSCLC to colorectal, and other cancers, as well as vindication of this regulatory mechanism, will be addressed with the accumulation of real-world experience of bevacizumab biosimilars in these patient populations.

Financial & competing interests disclosure

DA Reardon has participated in Speaker's Bureau for Genentech/Roche and Merck; participated in Advisory boards for Abbvie, Agenesis, Amgen, BMS, Cavion, Celldex, EMD Serono, Genentech/Roche, Inovio, Juno Pharmaceuticals, Merck, Midatech, Momenta Pharmaceuticals, Novartis, Novocure, Oncorus, Oxigene, Regeneron and Stemline Therapeutics; and received research funding from Acerta Pharma, Agenesis, Celldex Therapeutics, EMD Serono, Incyte, Inovio, Midatech and Tragara. J Subramanian has participated in Speaker's Bureau for AstraZeneca, Boehringer Ingelheim and Lilly; served as a consultant for AstraZeneca, Alexion, Pfizer, Boehringer Ingelheim and Merck; and received research funding from Biocept and Paradigm. AH Bair and I Jacobs are employees of and hold stock in Pfizer, Inc. 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.

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Executive summary

- Biosimilars of bevacizumab have the potential to increase access and to improve clinical outcomes for patients across a number of cancers.
- Regulatory agencies permit extrapolation of data for a biosimilar, allowing its approval for use for an eligible indication (i.e., not covered by regulatory exclusivity) in which the originator is authorized, without the need for a comparative clinical trial.

VEGF & bevacizumab mechanism of action

- VEGF plays a central role in tumor angiogenesis and has been implicated in both tumor vascularization and metastases.
- Bevacizumab binds to VEGF, resulting in blockade of VEGF receptor and inhibition of angiogenesis.

Demonstrating biosimilarity

- Biosimilarity is based on establishing that the quality, safety and efficacy of the biosimilar and the originator are comparable, to the extent that clinically meaningful differences should not be expected.
- Approval of biosimilars is based on the assessment of the totality of evidence, encompassing comparative analytical, nonclinical, pharmacokinetic (PK)/ pharmacodynamic (PD) and clinical data.

Principles of extrapolation

- Extrapolation is a well-established and accepted principle that is based on applying the conclusions from a study conducted in one population to make inferences for another population.
- The mechanism of action and PK of the originator should be consistent across indications, forming the basis for justification of extrapolation.
- The disease of the patient population chosen for the comparability study of the originator and potential biosimilar should be sufficiently sensitive to identify a difference, should one exist.

Bevacizumab biosimilars: considerations for development & approval

- Based on nonclinical functional assessments, there is no evidence to support a unique mechanism of action for bevacizumab across tumor types.
- The PK properties of bevacizumab are acknowledged as being consistent across the approved indications.
- Patients with non-small-cell lung cancer are considered a suitably sensitive population to detect differences between bevacizumab and a potential biosimilar, should they exist.
- Use of a response rather than survival-based end point is preferred, since the latter can be influenced by factors other than treatment-related differences, and bioequivalence can be established with a relatively shorter follow-up period.

Approved biosimilars

- The EMA and US FDA have granted marketing authorization for more than 25 biosimilars across a number of product classes.
- Some have been approved in indications for which the originator is authorized without direct clinical comparison, through extrapolation.
- Introduction of biosimilars is anticipated to bring cost savings in healthcare budgets and increased patient access.
- The first biosimilar of bevacizumab has been approved by the FDA; a number of potential biosimilars of bevacizumab are in the advanced stages of development.

Conclusion

- The process of extrapolation is a key element of the biosimilar approval process, with manufacturers required to implement development programs that are carefully designed to provide the relevant data to support it.
- Provided the totality of evidence for bevacizumab biosimilars comprises appropriate comparative analytical, nonclinical, PK/PD data as well as a clinical study, most suitably conducted in patients with non-small-cell lung cancer, extrapolation to other eligible indications, such as colorectal, and other cancers, can be scientifically justified.

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