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New Drugs

A clinician's guide to biosimilars in oncology

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ABSTRACT

Biological agents or "biologics" are widely used in oncology practice for cancer treatment and for the supportive management of treatment-related side effects. Unlike small-molecule generic drugs, exact copies of biologics are impossible to produce because these are large and highly complex molecules produced in living cells. The term "biosimilar" refers to a biological product that is highly similar to a licensed biological product (reference or originator product) with no clinically meaningful differences in terms of safety, purity, or potency. Biosimilars have the potential to provide savings to healthcare systems and to make important biological therapies widely accessible to a global population. As biosimilars for rituximab, trastuzumab, and bevacizumab are expected to reach the market in the near future, clinicians will soon be faced with decisions to consider biosimilars as alternatives to existing reference products. The aim of this article is to inform oncology practitioners about the biosimilar development and evaluation process, and to offer guidance on how to evaluate biosimilar data in order to make informed decisions when integrating these drugs into oncology practice. We will also review several biosimilars that are currently in development for cancer treatment.

Introduction

New agents for the treatment and supportive care of cancer have markedly improved therapeutic options and outcome for many malignancies. Biologics include monoclonal antibodies (mAbs) targeted to critical pathways involved in cancer pathogenesis and growth factors to reduce or ameliorate treatment-related hematological toxicity. Unfortunately, access to potentially life-saving biologics is limited in many areas of the world [1–3]. As the patent expiry of several drugs approaches, there has been intense interest in developing biosimilar agents to introduce cost savings for healthcare systems and to widen global access to key biological therapies [1,2,4].

A biosimilar drug is a biological product that is highly similar, but not identical, to a licensed biological product (the reference or originator product) [5–7]. Unlike small-molecule generic drugs that are typically chemically synthesized and easy to replicate, it is impossible to make exact copies of reference products because biosimilars (as biologics) are large and highly complex molecules produced in living cells. Structural differences to the reference product may arise due to variations in post-translational modification (such as glycosylation patterns), which could have impact upon drug efficacy or safety [5–7]. The development of biosimilars therefore involves extensive evaluation and a detailed, comprehensive manufacturing process to ensure that there are no clinically meaningful differences in purity, safety, or potency [5–7]. As is the case for any new therapeutic agent, the evaluation process and approval requirements for a proposed biosimilar may differ between regulatory agencies, leading to differential access based on geographic location.

Drugs for supportive care were the first biosimilars to gain approval for use, with the European Union (EU) approval in 2007 of epoetin alfa and filgrastim [8]. The first biosimilar approved in the United States (US) was filgrastim in 2015 [9]. Patents for several biologic mAbs for cancer treatment have recently expired in the EU and will soon expire in the US (see Table 1 for products and patent expiration dates). This has instigated multiple biosimilar development programs and regulatory approval requests for newly developed biosimilar agents. Biosimilars for rituximab,

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Table 1
Biosimilar mAbs with registered phase III clinical trials for oncology.[a]

Reference product	Patent expiration in EU/US	Biosimilar	Manufacturer	Primary endpoint	Condition	Published data[b]
Trastuzumab (Herceptin®, Genentech)	2014/2019	BCD-022	Biocad	ORR	HER2+ MBC	*Phase I:* BCD-022 showed similar PK and safety to trastuzumab in patients with HER2+ MBC [33]
		PF-05280014	Pfizer	PK, pCR (2nd) ORR	HER2+ EBC HER2+ MBC	*Preclinical:* PF-05280014 showed similar structural and functional properties, PK and immunogenicity profiles to trastuzumab [34] *Phase I:* PF-05280014 showed similar PK, safety and immunogenicity to trastuzumab in healthy volunteers [35]
		ABP 980	Amgen	ORR	HER2+ EBC	*Phase I:* ABP 980 showed comparable PK, PD, safety, tolerability and immunogenicity to trastuzumab in healthy volunteers [36]
		CT-P6	Celltrion	pCR pCR	HER2+ EBC HER2+ MBC	*Phase I/IIB:* CT-P6 showed equivalent PK and similar safety to trastuzumab in patients with HER2+ MBC [37] *Phase III:* CT-P6 showed similar efficacy (ORR) and safety to trastuzumab in combination with paclitaxel [38]
		SB3-G31-BC	Samsung Bioepis	pCR	HER2+ BC	No published data
		Hercules/ Myl1401O	Mylan GmbH	ORR	HER2+ MBC	No published data
Rituximab (Rituxan®, Genentech/Biogen Idec; MabThera®, Roche)	2013/2016	GP2013	Sandoz	ORR	FL	*Preclinical:* GP2013 showed physicochemical and functional characteristics comparable to rituximab [39] *Preclinical:* GP2013 showed similar in vitro potency and similar PK, PD, and efficacy to rituximab [40]
		BCD-020	Biocad	CD20+ count ORR	Indolent NHL	*Phase III:* BCD-020 showed equivalent PK and similar PD and safety to rituximab in patients with indolent NHL [41] *Phase III:* BCD-020 showed similar efficacy (ORR) and safety to rituximab in patients with indolent B-cell non-Hodgkin's lymphoma [42]
		PF-05280586	Pfizer	ORR	LTBFL	*Preclinical:* PF-05280586 showed similar structural and in vitro functional characteristics and similar in vivo PK and immunogenicity profiles to rituximab [43] *Phase I:* PF-05280586 showed similar PK, effectiveness, and safety to rituximab in subjects with active rheumatoid arthritis [44]
		CT-P10	Celtrion	ORR	FL	*Phase III:* CT-P10 showed equivalent PK and similar efficacy (ACR20/50/70), PD, safety [45], and immunogenicity [46] to rituximab in subjects with rheumatoid arthritis
		RTXM83	mAbxience	ORR	DLBCL	*Preclinical:* RTXM83 showed similar structural and in vitro functional characteristics and similar in vivo PK/PD profiles to rituximab [47] *Phase III:* RTXM83 showed comparable PK and safety profile (immunogenicity) to rituximab when combined with CHOP for first-line treatment of DLBCL [48]
		ABP 798	Amgen	RD, ORR	NHL	No published data
Bevacizumab (Avastin®, Genentech)	2022/2019	BCD-021	Biocad	ORR	NSCLC	*Phase I:* BCD-021 showed similar PK and safety to bevacizumab in patients with NSCLC [49] *Phase III:* BCD-021 showed similar efficacy (ORR), safety and immunogenicity to bevacizumab in patients with advanced non-squamous NSCLC [50]
		PF-06439535	Pfizer	ORR	NSCLC	*Preclinical:* PF-06439535 showed similar structure and in vitro biological activity [51] and similar in vivo toxicologic and toxicokinetic to bevacizumab [52–54] *Phase I:* PF-06439535 demonstrated PK similarity and comparable safety profiles to bevacizumab [53]
		ABP 215	Amgen	ORR	NSCLC	*Preclinical and Phase I:* ABP 215 showed similar in vitro functional characteristics and equivalent human PK to bevacizumab

DLBCL, diffuse large B-cell lymphoma; EBC, early breast cancer; FL, follicular lymphoma; HER2+, human epidermal growth factor receptor 2–positive; LTBFL, low tumor burden follicular lymphoma; MBC, metastatic breast cancer; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; ORR, overall response rate; pCR, pathological complete response; PD, pharmacodynamics; PK, pharmacokinetics; RD, risk difference.

[a] Registered on ClinicalsTrials.gov, the International Clinical Trials Registry Platform, or the European Union Clinical Trials Register.

[b] Published on PubMed, Web of Science, or congress websites.

trastuzumab, and bevacizumab are expected to reach the market in the near future, and clinicians will soon be faced with decisions to utilize biosimilars as alternatives to existing reference products. The aim of this article is to inform oncology practitioners about the biosimilar development and evaluation process, including relevant clinical trial design issues, and to enable critical appraisal of data to allow for best informed decision making when integrating biosimilars into practice.