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An overview of patents on therapeutic monoclonal antibodies in Europe: are they a hurdle to biosimilar market entry?

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ABSTRACT

As patents on many high-selling biological medicines are expiring, non-innovator versions, such as biosimilars, may enter this multi-billion dollar market. This study aims to map patents and patent applications for innovator as well as biosimilar monoclonal antibodies in Europe, and investigates legal challenges associated with patenting the innovator product and alleged infringing activities, focusing on consequences for biosimilar developers. Via an exploratory literature review in PubMed and a database analysis in Darts-ip, Derwent Innovation, and Espacenet, an overview of basic patents and exclusivity rights for some of the best-selling biologicals is given, supplemented with a detailed analysis of patents taken during the medicine's life cycle via three specific case studies (trastuzumab, bevacizumab, cetuximab). Case law was used to determine which patents were viewed by biosimilar developers as blocking market entry. For the selected monoclonal antibodies, the key protection instruments appeared to be the basic patent and the additional protection provided by a supplementary protection certificate. We observed that additional patents filed after the basic patent are hard to obtain and often insufficient in blocking market entry of biosimilars, but can in some cases be a substantial hurdle for biosimilar developers to overcome in patent litigation cases or to invent around, creating uncertainty on the launch date of a biosimilar on the market. These hurdles, however, seem to be surmountable, given that many cases were won by biosimilar developers. Also, biosimilars can be protected by filing new patents and these mainly pertain to new formulations.

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1. Introduction

In return for innovation, pharmaceutical companies can be rewarded different intellectual property (IP) rights. Different types of IP rights exist that can be used by pharmaceutical companies to secure a period of exclusivity to recover investments from a long and costly research and development program, i.e., patents, copyrights, design rights, trademarks, and other IP protection mechanisms such as trade secrets.^{1,2} Patents, which are territorial and temporally exclusive rights for inventions that are new, inventive, and industrially applicable, are considered the main instruments for protecting IP related to pharmaceuticals.³⁻⁵ In return for this exclusivity, the invention shall be disclosed to the public in a sufficiently clear and complete way.⁵

In Europe, a patent can be applied for at a national level, with the aim to obtain a patent in one country, or a single central application can be filed at the European Patent Office (EPO) with the aim to obtain a European patent that can be valorized in the countries of interest indicated in the European patent.² The basis for patent law in Europe is provided by the enactment of the European Patent Convention (EPC).⁵ As indicated in Article 2 of the EPC, a European patent shall in each of the Contracting States act as a national patent. The patentability of biotechnological

inventions, including biotechnological medicines, is further regulated by Chapter V of the EPC (Rules 26–34) that integrates Directive 98/44/EC on the legal protection of biotechnological inventions.^{6,7} The patent (application) grants its owner the right to exclude third parties from commercial exploitation of the invention without its consent. In Europe, a patent has a maximal duration of 20 y from the filing date of the application, though after fulfillment of specific criteria, an additional period of protection can be obtained for a market authorized product via a national supplementary protection certificate (SPC). A divisional patent application can be filed as long as the parent application is pending, and is often filed when the parent application does not comply with the concept of ‘unity of invention’.⁸ The divisional application should not extend the scope of the subject matter of the parent patent (Article 76 of the EPC). The scope of protection of a patent is determined by its claims and its validity can be challenged via opposition procedures at the European level up to 9 months after publication of the mention that the patent has been granted by the EPO; at a later stage the validity can be challenged nationally in a law suit before a national court.⁹ Decisions on granting or opposition made by the EPO can be challenged by those affected by the decision via appeal procedures at the EPO level.

In general, in the course of a medicine's life cycle, developers of medicines can try to protect their product in different ways. At the start, if the medicine is based on a new and inventive compound found to be the invention, this compound can be considered for patenting as such, often first via a more generic structure covering a group of structurally related compounds. Later, a selection invention can be claimed if a specific form of the active compound can be demonstrated to be in some way superior over the previously claimed group of compounds. Also, new salt forms, compounds with a different crystal structure or with a reduced particle size may be deemed patentable, provided that they possess unexpected advantages over existing compounds.⁹ A novel and inventive synthetic process that is used to produce the active compound, and different steps of the manufacturing process of a medicine may be patented if they comply with the patentability criteria. Even if the compound is known or previously patented, a patent can also be applied for on a specific formulation of the medicine, or on the combination with one or more other active pharmaceutical ingredients, provided that unexpected properties can be demonstrated. Later in the development process, novel and inventive administration routes, dosage regimens, and indications can possibly be patented.^{2,5} A "method of treatment" as such is however excluded from patentability to guarantee that physicians are not obstructed in providing care.

These same principles apply to the patenting of therapeutic antibodies although some specifics to the patenting of antibodies must be taken into consideration. More generic protection for antibodies has been sought in several ways, i.e., based on reference to its target specificity, by target-independent functional properties, by epitope, by target-dependent functional properties, or as the result of a process (product-by-process claim).¹⁰ Where protection is to be limited to one specific monoclonal antibody with particular properties, this can be characterized by its sequence, or by reference to the deposit of the hybridoma that produces it.¹⁰ Patentability of an antibody highly depends on whether the antigen it binds or a similar antibody (in generic, polyclonal, or monoclonal form) is part of the prior art.¹¹ Many therapeutically interesting targets are already known and the mere production of an antibody against such a target is now no longer considered inventive by the EPO.¹² A new characteristic, leading to unexpected advantages over previously described antibodies, would then be needed to claim an inventive step.^{11,12} Broad patent protection can be sought via functional claims, but even if granted by the EPO, these are more easily challenged by competitors.^{12,13} Structural claims on the other hand offer narrow protection, but can still effectively prevent the entry of non-innovator copies to the market.^{12,13}

Obtaining a patent or other exclusivity rights on a medicine does not entitle the patent holder to commercialize this medicine. For this, it also has to comply with, for instance, regulatory requirements such that a marketing authorization for the medicine is obtained, followed by a successful market access phase. As developing a new, innovative drug may cost up to US\$ 2.6 billion¹⁴ and time to market of a medicine from first patenting can take 10 y or

longer, valuable time to receive a return on the investment is often substantially reduced. Therefore, upon receiving marketing authorization of a medicine, 8 y of data exclusivity and additional 2 y of market exclusivity are granted, during which the company may stop producers of generic or biosimilar medicines from referring to their data file and entering the market, respectively.^{15,16}

In addition to data and market exclusivity for a registered pharmaceutical product, where the product is covered by a patent, an SPC can be applied for by the patent holder to extend protection of the active pharmaceutical ingredient after expiry of the basic patent. While in Europe this is not a patent extension, an SPC will confer to the specific-registered medicine the same rights as the initial patent.¹⁷ The SPC can only be granted for products that are at the moment of application protected by a patent and authorized for use in the European Union, and the duration of the SPC is determined by Article 13 of the SPC Regulation to be equal to the period between the filing date of the patent and the date of first marketing authorization of the product minus 5 y, with a maximum duration of SPC protection of 5 y in total.¹⁸ A one-time extension of 6 months can be granted when submitting results from studies included in the pediatric investigation plan (Article 13(3) of the SPC Regulation).

Balancing access to innovation and sustainability of the healthcare system are ongoing concerns for many European countries.¹⁹ As shown by Urquhart,²⁰ monoclonal antibodies dominated the top 10 best-selling medicines in 2017, and a continued increase in both market share and expenditure can be expected.²¹ However, patents on many high-selling biological medicines are expiring or have expired, opening this multi-billion market to competitors. Competition from biosimilar medicines, which are similar to a reference product in terms of quality, safety, and efficacy,²² may reduce treatment costs and help healthcare systems to sustain limited healthcare budgets or increase patient access to treatment.²³ Since the development of a legal and regulatory framework for marketing authorization of biosimilars in 2005, already more than 50 biosimilars in different therapeutic classes have been approved for use in the European Union, including epoetins and insulins.^{16,24,25} Since 2013, originator monoclonal antibodies have also been exposed to competition from biosimilars.²⁶ Authorization dates of innovator and biosimilar monoclonal antibodies and fusion proteins in Europe are shown in Table 1.

According to research by Rader *et al.*,²⁸ patents are the main determinant for innovators to guarantee market exclusivity, at the same time blocking market entry of biosimilars. Previous research also shows that patent disputes between companies may cause uncertainty on the validity of an innovator's patent, and may at the same time influence the launch date of the biosimilar, as companies will not risk a product launch until disputes are resolved.²⁶ The launch date is also influenced by strategies for prolongation of exclusivity rights of the company that developed the innovator product, such as filing a patent for a new indication, formulation, or dosage regime.¹⁰ Biosimilar developers can, however, use new production techniques to efficiently produce their product, which may be patentable. Patenting a new formulation may also be

Table 1. Innovator monoclonal antibodies and fusion proteins for which biosimilars are being developed (selection) or authorized in the European Union (March 2020), and patent and other exclusivity rights' expiry dates in the European Union.^{25,27}

Active substance	Brand name innovator	MAH innovator	Date of authorization innovator	Patent and exclusivity expiry EU	Brand name biosimilar	MAH biosimilar	Date of authorization biosimilar
Adalimumab	Humira®	AbbVie	08/09/2003	2018	Amgevita®	Amgen	22/03/2017
					Imraldi®	Samsung	24/08/2017
					Halimatoz®/Hefiya®/Hyrimoz®	Bioepis	26/07/2018
					Hulio®	Sandoz	16/09/2018
Bevacizumab	Avastin®	Roche	12/01/2005	2022	Kromeya®/Idacio®	Mylan	01/04/2019
					Fresenius Kabi	12/02/2020	
Etanercept	Enbrel®	Pfizer	02/02/2000	2015	Mvashi®	Amgen	15/01/2018
					Zirabev®	Pfizer	13/02/2019
Infliximab	Remicade®	Janssen Biologics	13/08/1999	2015*	Benepali®	Samsung	14/01/2016
					Erelzi®	Bioepis	23/06/2017
					Remsima®	Sandoz	18/05/2018
					Inflectra®	Celltrion	17/02/2017
Rituximab	MabThera®	Roche	02/06/1998	2013	Rixathon®/Riximyo®	Sandoz	15/06/2017
					Ritemvia®/Rituzena®/Blitzima®	Celltrion	13/07/2017
					Ontruzant®	Samsung	15/11/2017
					Herzuma®	Bioepis	09/02/2018
Trastuzumab	Herceptin®	Roche	28/08/2000	2014	Kanjinti®	Amgen	16/05/2018
					Trazimera®	Pfizer	26/07/2018
Cetuximab	Erbix®	Merck KGaA	29/06/2004	2014	Ogivri®	Mylan	12/12/2018
Eculizumab	Soliris®	Alexion	20/06/2007	2020	-	-	-
Ranibizumab	Lucentis®	Novartis	22/01/2007	2022	-	-	-

*: In some European countries, biosimilar infliximab was launched in 2013.

MAH: Marketing authorization holder; EU: European Union; -: Patent and other exclusivity rights are not yet expired for these products.

possible. The European Medicines Agency (EMA) does not require the formulation of the biosimilar to be identical to that of the reference product.²⁹

In this study, we had two objectives. First, we wanted to map both patents and patent applications for a selection of biological molecules that currently represent (off-patent) innovator as well as biosimilar monoclonal antibodies in Europe. Second, we aspired to investigate legal challenges associated with patenting the innovator product and alleged infringing activities, specifically focusing on consequences for developers of biosimilar medicines.

This is the first study that provides an overview of basic patents and exclusivity rights for some of the best-selling biological products, and that carries out a detailed analysis of patenting along the medicine's life cycle via specific case studies to determine which patents were effectively used to hinder companies developing a biosimilar.

2. Results

Results of the literature review and database analysis are structured in two parts. First, an overview is given on the basic patent and other exclusivity protections of the molecules that are included in Table 1. Second, a detailed analysis of patents and their legal challenges are presented for the innovator product in chronological order and throughout its life cycle for three cases: trastuzumab, bevacizumab, and

cetuximab. These case studies were selected as patent filing strategies for adalimumab, etanercept, infliximab, and rituximab were already discussed in the literature,³⁰⁻³² and ranibizumab and eculizumab were found less relevant to study since both molecules are still patent-protected and have no approved biosimilars. We focus on the most crucial patents, i.e., the basic patent and patents that were the subject of a patent litigation case with a company that we believe was developing a biosimilar. A more complete overview of identified patents for each case study can be consulted in the Appendices. Reference is made to possibilities of biosimilar developers to protect their product via patents.

2.1. Overview of basic patents and other exclusivity protections

For a selection of nine molecules, Table 2 lists regulatory market exclusivities, basic patents, relevant SPCs, other exclusivity rights, the date of end of protection, and the total years that the product was protected since marketing authorization. Listed SPCs are valid for the United Kingdom (UK), Germany, and/or France. In case different expiry dates were found (a difference of 1 d may occur, depending on calculations by national patent offices), the latest date is shown.

Protected years since the approval of the selected molecules (covering both patent protection and regulatory exclusivity rights) range from 10 y for cetuximab to 17 y for

Table 2. Basic patent and other exclusivity protections on selected therapeutic monoclonal antibodies.^{10,31-37}

Brand name	Active substance	Regulatory market exclusivity	Basic patent	SPC*	SPC extension	End of protection*	Protected years since approval
Humira®	adalimumab	08.09.2003–08.09.2013	EP0929578 (10.02.1997–10.02.2017) EP0666868 (28.10.1992–28.10.2012)	10.02.2017 to 16.04.2018 On EP0451216: 28.12.2009 to 28.12.2014 On EP1325932: 03.04.2018 to 16.12.2019	+ 6 m (ped)	Oct 16, 2018	15 years
Avastin®	bevacizumab	12.01.2005–12.01.2015	EP0939121 (31.08.1990–31.08.2010) EP0610201 (18.03.1992–18.03.2012) EP0669836 (12.11.1993–12.11.2013) EP0590058 (15.06.1992–15.06.2012)	On EP0451216 (28.12.2014) + 6 m (ped) on EP1325932 (16.06.2020) + 6 m (ped)	Jan 23, 2022 [†]	17 years	
Enbrel®	etanercept	02.02.2000–02.02.2010	EP0939121 (31.08.1990–31.08.2010) EP0610201 (18.03.1992–18.03.2012) EP0669836 (12.11.1993–12.11.2013) EP0590058 (15.06.1992–15.06.2012)	31.08.2010 to 31.01.2015	+ 6 m (ped)	Aug 1, 2015	15,5 years
Remicade®	infliximab	13.08.1999–13.08.2009	EP0939121 (31.08.1990–31.08.2010) EP0610201 (18.03.1992–18.03.2012) EP0669836 (12.11.1993–12.11.2013) EP0590058 (15.06.1992–15.06.2012)	18.03.2012 to 24.08.2014 (UK), 13.08.2014 (Germany, France) /	+ 6 m (ped)	Feb 24, 2015 (UK), Feb 13, 2015 (Germany, France) Nov 12, 2013	15,5 years
MabThera®	rituximab	02.06.1998–02.06.2008	EP0939121 (31.08.1990–31.08.2010) EP0610201 (18.03.1992–18.03.2012) EP0669836 (12.11.1993–12.11.2013) EP0590058 (15.06.1992–15.06.2012)	/	/	July 29, 2014	14 years
Herceptin®	trastuzumab	28.08.2000–28.08.2010	EP0939121 (31.08.1990–31.08.2010) EP0610201 (18.03.1992–18.03.2012) EP0669836 (12.11.1993–12.11.2013) EP0590058 (15.06.1992–15.06.2012)	15.06.2012 to 29.07.2014 On EP0451216: 28.12.2009–29.07.2014	/	Sept 14, 2014	10 years
Erbitux®	cetuximab	29.06.2004–29.06.2014	EP0359282 (15.09.1989–15.09.2009) EP0758904 (01.05.1995–01.05.2015)	On EP0667165: 15.09.2009 to 14.09.2014 01.05.2015 to 01.05.2020	/	May 1, 2020	13 years
Soliris® (Orphan drug)	eculizumab	PNH: 20.06.2007–20.06.2017 + 2 years as pediatric reward (2019) aHUS: 29.11.2011–29.11.2021 + 2 years as pediatric reward (2023) MG: 17.08.2017–17.08.2027	EP0940468 (15.06.1992– withdrawn)	On EP0451216: 28.12.2009 to 27.12.2014 On EP0973804: 03.04.2018 to 24.01.2022	/	Jan 24, 2022	15 years
Lucentis®	ranibizumab	22.01.2007–22.01.2017	EP0940468 (15.06.1992– withdrawn)	On EP0451216: 28.12.2009 to 27.12.2014 On EP0973804: 03.04.2018 to 24.01.2022	/	Jan 24, 2022	15 years

SPC: supplementary protection certificate; ped: extension for results of pediatric plan; PNH: paroxysmal nocturnal hemoglobinuria; aHUS: atypical hemolytic uremic syndrome; MG: myasthenia gravis

* The exact date might differ with one day in the different European Member States, depending on calculations by national patent offices.

[†]This date is mentioned in many (web) articles as the date when biosimilars for bevacizumab may enter the market, and is seemingly linked to the end of the SPC protection on ranibizumab, an antibody fragment derived from the same murine monoclonal antibody as bevacizumab.

bevacizumab. Average protection on the market seems to be around 15 y. Except for rituximab, all molecules were granted an SPC in UK, Germany, and/or France. As the development time from patent filing to marketing authorization of rituximab was only 5 y, the calculation of a potential SPC period would give zero additional years of protection.

2.2. Case study on trastuzumab

Trastuzumab is a humanized monoclonal antibody used in the treatment of breast and gastric cancer, where tumor cells overexpress the protein human epidermal growth factor receptor 2 (HER2, or also named HER2/neu, ErbB2 or c-ErbB-2).³⁸ In Europe, trastuzumab has been marketed by Roche under the trade name Herceptin® since 2000. Patent and regulatory exclusivities on Herceptin® as an intravenous formulation expired on July 29, 2014. Since 2017, several trastuzumab biosimilars have been approved for use in the European Union, i.e., Ontruzant® (Samsung Bioepis, 2017), Herzuma® (Celltrion, 2018), Kanjinti® (Amgen, 2018), Trazimera® (Pfizer, 2018), and Ogivri® (Mylan, 2018).²⁵

The development of trastuzumab by Genentech (since 2009 part of Roche) builds on the earlier patent of Protein Design Labs, now called PDL BioPharma, on a method for producing humanized antibodies, i.e., EP0451216, filed on December 28, 1989. Later, Protein Design Labs agreed to a license on the granted patent to Genentech for the development and commercialization of, amongst others, Herceptin®,^{39,40} in return for royalties on the sales. Also, Genentech itself was at that time actively performing research in this field; as early as 1984 Genentech applied for a European patent claiming mouse-human chimeric antibodies (Genentech's Cabilly patent family, EP0125023). This patent was granted in 1991 and was eventually maintained in amended form in 2002 after opposition by several companies, including Protein Design Labs, on grounds of lack of novelty, lack of inventive step, insufficient disclosure, and added subject matter.

On June 15, 1992, Genentech filed EP0590058, the basic patent related to trastuzumab, which claims several sequences of humanized heregulin antibodies and was later complemented with additional protection via an SPC. Two divisional applications were filed off of this patent: EP1400536, claiming a method for making humanized antibodies, and EP0940468, claiming a humanized antibody variable domain, but both applications were withdrawn by the company just before the 20-y patent term expired.

Genentech also investigated stable monoclonal antibody formulations and filed on July 23, 1996 a patent application for a specific freeze-dried formulation of, amongst other monoclonal antibodies, trastuzumab, which can be used for subcutaneous administration after reconstitution, i.e., EP0845997. However, the application was withdrawn after the Examining Division of the EPO instructed Genentech to address the EPO requests via changes to one of the divisional applications. Two divisional applications were filed: EP1516628, claiming a specific freeze-dried formulation of, amongst other monoclonal antibodies, trastuzumab, and EP2275119, claiming a specific freeze-dried formulation of an anti-HER2 antibody used in the treatment of cancer where tumor cells overexpress the HER2 receptor. These

divisional patents were granted in August and September 2013, respectively, and were both subject to opposition, which was rejected for each in 2016 and the patents were maintained with only a few months left before patent expiry. However, earlier, in 2015, the Norwegian counterpart of the first-mentioned divisional EP1516628, NO323557, had already been invalidated by biosimilar developer Hospira (since 2015 part of Pfizer). Also in the UK, Hospira successfully invalidated the two divisional patents in 2016 based on lack of inventive step (obviousness).

The use of trastuzumab for the treatment of malignant breast cancer characterized by overexpression of ErbB2 (HER2) in combination with a taxoid, for example paclitaxel or docetaxel, was patented by Genentech in EP1037926 on December 10, 1998. The grant of this patent was opposed by several parties that were of the opinion that the invention was not new, inventive or sufficiently disclosed. After rejection of an appeal filed by Genentech to the negative decision of the Opposition Division of the EPO, the patent was revoked based on grounds of lack of inventive step on February 7, 2018, only 10 months before the end of patent term. Shortly after the start of the appeal procedure in August 2016, Pfizer, which was developing a trastuzumab biosimilar, started a patent litigation case in Belgium with the aim to invalidate the patent. However, the proceedings were suspended, pending the decision of the EPO in the appeal procedure. On the other hand, Hospira was successful in invalidating the patent in the UK based on lack of inventive step on November 30, 2016. Several divisional patent applications (EP1947119, EP2275450, and EP2277919) were filed from this application, each of which was later abandoned.

On May 3, 1999, EP1075488 was filed by Genentech, proposing a protein purification method via ion exchange chromatography. The patent was granted but opposed by Novo Nordisk on grounds of lack of novelty, lack of inventive step and insufficiency of disclosure, and was maintained in an amended form. Two divisional applications had been filed. The first one is EP1308455, claiming a composition comprising anti-HER2 antibodies with a certain amount of acidic variants (obtained after an ion exchange chromatography step), which is viewed as a patent on a formulation, and seen by many biosimilar developers as a potential threat to market entry. The EPO revoked this patent in opposition based on lack of novelty, but the decision was overturned in appeal and the patent was maintained in unamended form in 2015. However, in 2014, Hospira had already obtained an invalidation of the UK patent at the UK High Court of Justice based on lack of novelty and lack of inventive step, at the same time receiving a declaration of non-infringement for their trastuzumab formulation. In 2018, in a court case in Belgium against Pfizer (developer of Trazimera®), the patent was deemed invalid based on lack of novelty. Also in 2018, the German court decided that a biosimilar of Celltrion, Herzuma® (marketed by Mundipharma), did not infringe Genentech's patent. In 2019, the Dutch and the Belgian court were of the same opinion. Also in 2019, Samsung Bioepis (Ontruzant®) and Amgen (Kanjinti®) invalidated the German counterpart based on lack of novelty and inventive step. MSD, which is marketing trastuzumab biosimilar Ontruzant®, developed by South Korean company Samsung Bioepis, was ruled not to infringe Genentech's patent in

Sweden and Finland in 2019. A second divisional application filed off of EP1075488 was EP1308456, claiming antibody purification by ion exchange chromatography, and claiming, in contrast to the parent patent, a specific amount of antibody to be loaded onto the resin. No opposition was filed against the granted patent.

On May 9, 2000, Genentech claimed the use of an anti-ErbB2 antibody in the treatment of cancer where tumor cells overexpress the ErbB2 protein, before or after surgical removal of the tumor (EP1187632). This patent was revoked based on lack of inventive step after successful opposition of Teva, which was co-developing trastuzumab biosimilar Herzuma[®] with Celltrion, and subsequent rejection of the appeal from Genentech.

Later that year, on August 25, 2000, Genentech claimed in EP1210115 a dosing schedule for the treatment of breast cancer with anti-ErbB2 antibodies. This patent was revoked in 2016 on the grounds of lack of sufficient disclosure of the invention after opposition of several biosimilar developers. In 2015, the England and Wales Court of Appeal had already decided to dismiss the appeal of Genentech to the invalidation of the patent in a court case against Hospira (Pfizer) on grounds of lack of inventive step, and thus the patent was declared invalid for the UK. Two divisional applications were filed: 1) EP2111870 (the application was withdrawn in 2018 in an appeal against the decision of the Examining Division to refuse the application based on grounds of lack of inventive step, insufficient disclosure, and extension beyond the content of the parent patent), and 2) EP2110138 (the application was withdrawn in 2015 after a negative communication from the Examining Division, in which they stated that this application involved double patenting and in addition lacked sufficient disclosure).

On May 18, 2001, Genentech filed EP1282443 on the use of an anti-HER2 antibody for cancer patients tested to have an amplified her2 gene and HER2 overexpression on tumor cells. The patent was revoked in 2016 after an opposition procedure by BioGeneriX and Teva, active in the development of biosimilars, and the appeal of Genentech was subsequently rejected when it withdrew all claim requests, stating that it no longer approved the text of the granted patent. One divisional application had been filed, EP2116262, claiming a method to identify patients who are likely to respond to treatment with an anti-HER2 antibody, but this application was withdrawn by the applicant in 2019, after a warning from the Examining Division that the application would be refused based on grounds of lack of inventive step and insufficient disclosure.

In addition to the patents previously discussed, a patent on a subcutaneous formulation and two more patents on protein purification and prevention of disulfide bond reduction were found relevant for Herceptin[®] and can be consulted in [Table A1](#).

As detailed earlier, companies developing biosimilars may also seek protection of inventions via patents. Patents on new formulations of trastuzumab have been identified. On April 16, 2015, Mylan and partner Biocon filed an application on stable protein formulations comprising a molar excess of sorbitol, which includes trastuzumab (EP3131584). This application is still under examination. On August 12, 2016, Amgen filed a patent application on the production of an aqueous solution

for trastuzumab and other molecules, and specifically including biosimilars thereof, which mentions different methods, for example filtration (EP3334747). This application is also currently under examination. Amgen filed several international applications as well for a liquid pharmaceutical composition for trastuzumab and on a lyophilized pharmaceutical formulation for trastuzumab and other molecules (WO2018201064, WO2018200533, and WO2019055357).

2.3. Case study on bevacizumab

Bevacizumab is a humanized monoclonal antibody used in the treatment of colon, rectum, breast, lung, kidney, ovary, and cervix cancer due to its ability to attach to and inhibit the biological activity of vascular endothelial growth factor (VEGF), a protein responsible for the growth of blood vessels.⁴¹ In Europe, bevacizumab has been marketed by Roche under the trade name Avastin[®] since 2005. Patent and regulatory exclusivities on Avastin[®] in Europe will protect the product until at least June 2020, but possibly even longer (23rd of January 2022). Already in 2018, a biosimilar to bevacizumab was approved for use in the European Union, i.e., Mvasi[®] (Amgen), and also more recently, in February 2019, Zirabev[®] (Pfizer) was approved.²⁵ Marketing of these biosimilars will be delayed until relevant patents and regulatory exclusivities have expired.

As was the case for trastuzumab, also the discovery of bevacizumab is related to Genentech's patent on chimeric antibodies (EP0125023, filed on April 6, 1984) and PDL Biopharma's patent on humanized antibody production (EP0451216, filed on December 28, 1989). For the latter, Genentech again received a license from PDL Biopharma, now for its development of bevacizumab.

The basic patent on bevacizumab, EP0666868, claiming the use of anti-VEGF monoclonal antibodies for the treatment of cancer, was filed on October 28, 1992 by Genentech, and maintained in amended form in 2006 after an opposition procedure, where the opponent asked the revocation of the patent based on lack of novelty and inventive step, insufficiency of disclosure and added subject matter. Three divisional applications were filed off of the basic patent, of which one was related to the use of a human VEGF antagonist for the treatment of non-neoplastic diseases where excessive neovascularization plays a role and was the subject of several patent litigation cases with Bayer and Regeneron's VEGF antagonist, aflibercept, for treatment of age-related macular degeneration of the eye. All cases were eventually settled. Already on March 28, 1996, Genentech also claimed the use of a human VEGF antagonist in the treatment of age-related macular degeneration (EP817648). However, the claimed indication has never been added to the label of Avastin[®], although locally injected bevacizumab is known to be used off-label for this indication.⁴² A next-generation product, ranibizumab (Lucentis[®]), which is an antibody fragment derived from the same murine monoclonal antibody as bevacizumab, was developed specifically for the treatment of age-related macular degeneration.

On April 3, 1998, EP0973804 was filed by Genentech on a variant of an earlier developed anti-VEGF antibody, which is claimed to have stronger binding affinity. No opposition to

this patent was filed. Later, an SPC for Lucentis® (ranibizumab) was obtained on this patent. Six divisional applications were filed, of which, EP1325932, claiming humanized anti-VEGF antibodies with specific properties, was extended on a national level with an SPC for Avastin®.

On August 17, 2007, Roche filed EP2056874, claiming the use of bevacizumab for prevention and reduction of metastasis in a patient with relapsed HER2 positive breast cancer. One divisional application was filed: EP2441472. Both patents were revoked based on grounds of lack of inventive step after opposition proceedings from what we assume are companies that were at that time developing a biosimilar.

On November 20, 2009, Roche filed EP2361085, claiming the use of bevacizumab for the treatment of recurrent or metastatic breast cancer, together with chemotherapy. The patent was maintained in amended form in 2018 after the opposition of Pfizer, amongst others. Two divisional applications were filed, which seem to contain similar claims. For the first divisional application, EP2752189, an appeal procedure is ongoing against the decision to revoke the patent based on grounds of lack of inventive step after opposition from 10 opponents, including Pfizer. For the second divisional application, EP3178478, examination is still in progress.

For Avastin®, a number of patent applications have also been filed, which may or may not be granted, on humanizing anti-VEGF antibodies, the combination of bevacizumab with an anti-neoplastic composition, protein purification, prevention of disulfide bond reduction, prediction of the risk on a cardiovascular event, monitoring and diagnostic methods, aqueous formulations, the use in treatment of (platinum resistant) ovarian, peritoneal, and fallopian tube cancer, and the use in treatment of (proneural subtype) glioblastoma together with chemo and radiotherapy (Table A2).

Biosimilar developers are also seeking protection for incremental innovation. On August 12, 2016, Amgen filed EP3334747, claiming a method for the production of an aqueous solution for, amongst other molecules, bevacizumab and its biosimilars, which can be obtained via filtration (cfr. trasuzumab). Examination of this application is in progress.

2.4. Case study on cetuximab

Cetuximab is a chimeric (mouse/human) monoclonal antibody used in the treatment of colon, rectum, and head and neck cancer, due to its affinity for epidermal growth factor receptor (EGFR), a protein involved in cell growth and present on the cell surfaces of many colorectal and squamous cell cancers.⁴³ In Europe, cetuximab has been marketed by Merck KGaA under the trade name Erbitux®. Patents and regulatory exclusivity rights on this product have expired since September 14, 2014. To date, no biosimilars to cetuximab have been approved for use in the European Union.²⁵

On September 15, 1989, Rorer International filed EP0359282, claiming a monoclonal antibody that binds to EGFR, compositions that effectively inhibit human tumor cell growth (when these cells express human EGFR), and potential combinations with an anti-neoplastic agent, such as doxorubicin or cisplatin. In addition, a method of producing the monoclonal antibody and therapeutic compositions thereof is claimed. Based on the

parent application, divisional application EP0667165 was filed, owned by Rhône-Poulenc Rorer International holdings (after a merger of Rorer with Rhône-Poulenc). The independent claim specifically relates to the combination of a monoclonal antibody that inhibits the growth of tumor cells that express EGFR with an anti-neoplastic agent. After the publication of grant of the patent on March 27, 2002, several parties (YM BioSciences, The Scripps Research Institute, Amgen and Abgenix) filed opposition against this patent based on lack of novelty, lack of inventive step, insufficient disclosure, and added subject matter. In May 2004, proceedings were stayed because the ownership of the patent (EP0667165) was challenged by Yeda, the commercialization arm of the Weizmann Institute of Science. In 2004, Yeda filed an action in Germany to challenge ownership of the patent in a case against Imclone (licensee), Rhône Poulenc Rorer, and Aventis (formed after a merger of Rhône Poulenc Rorer and Hoechst). Yeda argued that the named inventors on the patent, who were previously working for the Weizmann Institute of Science, but moved to Meloy (later Rorer), are not the inventors of the patent because they were not involved in later steps and that the actual invention of the synergistic effect of the combination of an anti-EGFR monoclonal antibody with an anti-neoplastic agent was made by ‘the Weizmann scientists’.⁴⁴ Furthermore, Yeda accused Rorer of using a draft publication of the Weizmann Institute of Science to file its patent application. However, the action was dismissed in Germany and an appeal of Yeda was rejected. This was also the case in the UK, where Yeda had also started an action relating to ownership. On December 7, 2007, they settled to resolve all litigation matters, i.e., ongoing actions in the United States (where Yeda had won its action related to ownership), Austria, the United Kingdom, France, and Germany. The settlement agreement also concluded that Sanofi (formed after a merger with Aventis in 2004) and Yeda share ownership of the European patent and shall jointly seek protection from an SPC, and specifies license agreements of Yeda with Merck KGaA and Amgen. Imclone, which already had a license from Rorer, also received a license from Yeda. Sublicenses from Imclone to Bristol-Myers Squibb and Merck KGaA also stayed valid. As part of the agreement, Yeda received a single lump sum payment from Imclone and Sanofi of US\$ 60 million each, and continued to receive royalties on the sales of Erbitux®. The opposition procedure at the EPO was closed in 2011 after withdrawal of opposition by the opponents.

Yeda and Aventis sought protection for cetuximab with an SPC on EP0667165. In France, an SPC was approved already in 2005 and was valid from the expiry of patent until September 14, 2014.⁴⁵ In the Netherlands and the UK, the application was refused based on Article 3 of the SPC Regulation (Regulation (EC) No 469/2009). The courts concluded that the product of the marketing authorization (Erbitux® – cetuximab), is not the product of the basic patent, in which a combination of cetuximab with an anti-neoplastic agent is claimed. An appeal from Yeda and Aventis was rejected in both countries. The court of appeal (England & Wales) referred the issue to the Court of Justice of the European Union (CJEU), which answered that the issue should indeed be interpreted as concluded by the national court.

Merck KGaA also filed several patent applications for (concentrated) liquid and lyophilized formulations of cetuximab, a crystal form of cetuximab, and prediction methods for patients' response and side effects (Table A3).

Companies developing cetuximab biosimilars have applied for patent protection of inventions related to cetuximab. Amgen is linked to the development of a cetuximab biosimilar⁴⁶ and several patent applications for formulations can be found. On October 5, 2007, Amgen filed EP2081553 on a liquid formulation with increased stability consisting of a buffer, a sugar, or polyol and, for example, cetuximab. Also, on October 5, 2007, Amgen filed EP2094247 on a solution with increased stability consisting of a buffer, a divalent cation, a sugar, or polyol and, for example, cetuximab. Later, on August 12, 2016, EP3334747 was filed by Amgen, which claims a production method for an aqueous formulation obtained via a charged depth filter, which mentions several antibodies, including bevacizumab and cetuximab, and biosimilars of these molecules. The examination of these three applications is in progress.

3. Discussion

This study focused on European patent applications on selected therapeutic monoclonal antibodies. An overview of effective market protection of nine monoclonal antibodies was provided in Table 2, followed by more detailed case studies on trastuzumab, bevacizumab, and cetuximab, while patent filing strategies for tumor necrosis factor (TNF) inhibitors adalimumab, etanercept and infliximab, and anti-CD20 monoclonal antibody rituximab were already covered in the literature.³⁰⁻³² The added value of our study lies, in addition to the inclusion of new molecules, in providing examples of patents on biosimilars, and especially, in its focus on consequences of innovator patent filing strategies for developers of biosimilar medicines. Furthermore, in the discussion section, the results of our overview are compared with findings for therapeutic monoclonal antibodies earlier discussed in the literature.

The results of this study have shown that the duration of effective market protection between the selected molecules is rather large (10 to 17 y), and is determined by the basic patent and SPC with possibly an extension via pediatric exclusivity rights. An average market protection of 15 y for the different molecules in this study is in line with the SPC Regulation, which states that *“the holder of both a patent and a certificate should be able to enjoy an overall maximum of 15 years of exclusivity from the time the medicinal product in question first obtains authorization to be placed on the market in the Community”*.¹⁸ Only when the development time of a molecule since the filing date of the (basic) patent exceeds 10 y, for example for cetuximab, this exclusivity period will be shorter than 15 y, since the maximum duration of the SPC is limited to 5 y, starting from the patent expiry date. Also, in the case of the molecules in Table 2, the 10 y of regulatory market exclusivity that are provided by the European Commission at the moment of marketing authorization did not seem to play a role in extending market protection provided by patents and SPCs, except for eculizumab (Soliris®), an orphan medicinal product. Furthermore, the three case

studies illustrate the diversity of intellectual property strategies applied to each molecule throughout its life cycle, with not only patents on the antibody itself, but also patents on indications, dosages, formulation/administration routes, and biomarker testing. The development of combination products and next-generation products was not explicitly covered in the results section but is elaborated on as a potential competition strategy further in the discussion. It should be noted that for the three case studies, multiple patent applications filed after the basic patent were either not upheld by the EPO in opposition procedures or granted patents were successfully challenged by competitors in national patent litigation cases.

3.1. Competition strategies

To supplement protection from the basic patent, competition strategies that were identified in earlier research can also be found in this analysis, such as patent filings on a new indication, new formulation, or new dosage regimen, and developing and patenting combination and next-generation products.^{10,47} These strategies are further elaborated in the following paragraphs, together with a comparison with patent filing strategies for molecules not included as a detailed case study, for example, adalimumab (Humira®, AbbVie), infliximab (Remicade®, J&J), etanercept (Enbrel®, Pfizer) and rituximab (MabThera®, Roche). An extensive patent filing strategy was used by AbbVie to protect best-selling product Humira® (adalimumab), with patents on formulations, dosages, new indications, and the use of many divisional applications.³¹ A report by I-MAK has found that more than 70 European patent applications have been filed for Humira®.⁴⁸ Many applications have been observed to be withdrawn, refused, or revoked, as was also the case in our study for trastuzumab, bevacizumab, and cetuximab. Patent filing strategies for Remicade® (infliximab), Enbrel® (etanercept) and MabThera® (rituximab) are considered to be less extensive but still follow the expected strategies.^{30,32}

3.1.1. Applying for patent protection on a new indication

A first strategy to extend protection for a product involves the patenting of new indications. For instance, in addition to the indication of cancer which was already clear in the basic patent for bevacizumab, the use of bevacizumab for the treatment of age-related macular degeneration, and specific cancers such as ovarian cancer, breast cancer, and glioblastoma were patented over time.

This strategy can also be observed for rituximab, for which first the use for non-Hodgkin lymphoma was patented, and later patents were filed on its use for chronic lymphocytic leukemia and rheumatoid arthritis.³⁰ Also, for adalimumab, various second medical use patents were filed.³¹ It seems that patents for new indications are often filed in combination with a new dosage regimen or co-treatments.

3.1.2. Applying for patent protection on a new formulation/administration route

A patent strategy may also be driven by development hurdles such as formulation challenges. For instance, for cetuximab, many efforts were made to find a stable formulation, with

multiple patent applications filed. For the other molecules, this seems to be limited to one per administration form. Precedents demonstrate that patents on formulations of medicines are often ruled to be invalid due to lack of an inventive step.² We noticed in the analysis that indeed few formulation patents applied for in the three case studies have been granted or are active until the end of the 20-y patent protection term. AbbVie has been successfully using this strategy to switch patients on Humira® to a new formulation with less injection pain, even though in Europe the patent for this formulation was revoked after an opposition procedure.

Formulation patents for a new administration route can also be of interest, such as for the later developed subcutaneous versions of trastuzumab and rituximab. Developing a subcutaneous version of a medicine is typically more patient-friendly, as it can be administered by the patient at home, and an inconvenient physician visit can thus be avoided. Also, administration times are shortened, which is beneficial for patients and healthcare providers.⁴⁹ A patent-protected subcutaneous version of trastuzumab was approved for use in the European Union in 2013,⁵⁰ the year before the expiry of market protection on intravenously administered trastuzumab and possible entry of biosimilars to the market. A subcutaneous version of rituximab was developed as well, which led to increased overall MabThera® market shares (when summing market shares of both intravenously and subcutaneously administered MabThera®) even though the entry of biosimilars in 2017 negatively influenced the market shares of intravenously administered rituximab.⁵¹ The development of a subcutaneous version of an initially intravenously administered medicine thus seems to be an effective defense strategy. This strategy is now also employed by biosimilar developers, with Celltrion receiving a positive EMA opinion for its subcutaneously administered infliximab biosimilar in September 2019.⁵²

3.1.3. Applying for patent protection on a new dosage regimen

A new dosage regimen can be claimed when having unexpected advantages over prior art regimens. Although there is the possibility to leave the patented dosage regimen out of the label of the biosimilar, still, biosimilar developers prefer to rely on the dosage regimen as authorized for the reference product.⁵³ For Humira® (adalimumab), two patents for dosage regimens for rheumatoid arthritis, as well as Crohn's disease and ulcerative colitis, were active at the moment of the loss of basic protection on Humira®. Eventually, the patent litigation cases that were started by several biosimilar developers were settled, ensuring market entry of biosimilars in October 2018.

3.1.4. Filing divisional patent applications

The filing of divisional patent applications increases the complexity of the product's patent portfolio by adding new patent applications that need to be taken into consideration and leads to uncertainty of launch dates for competitor products, even though the duration of patent protection is not extended (and often the scope is even more limited). The use of many divisional applications can be seen in the case studies on

trastuzumab and bevacizumab, both products of Roche, but less in the case study on cetuximab (Merck KGaA).

AbbVie has made extensive use of this strategy to increase complexity for its competitors.³¹ Furthermore, they have repeatedly withdrawn patents related to adalimumab before a decision in a patent litigation case was taken, while replacing the content (claims) of the original patent by several divisional patents to spread the risk for losing protection for one or another claim. In 2017, the UK High Court has under special circumstances taken a decision even after patents on Humira® were withdrawn by AbbVie, and granted declarations to Fujifilm Kyowa Kirin Biologics and Biogen that "*their products were obvious and/or anticipated at the claimed priority dates of certain of AbbVie's patents*" ([2017] EWHC 395 (Pat)).

3.1.5. Development and applying for patent protection of combination therapies

For treatment of cancer, combination therapies are often used to improve efficacy in this heterogeneous disease.⁵⁴ This is as well reflected in the patent filing strategies of the selected case studies relating to anti-cancer compounds, with, for example, combinations with chemotherapy. Additionally, combinations with other monoclonal antibodies are patented, for example trastuzumab and pertuzumab (both from Roche), trastuzumab and bevacizumab (both from Roche), and cetuximab and matuzumab (both from Merck KGaA). This last combination has not been commercialized, as the development of matuzumab was stopped when clinical trial outcomes were not as promising as expected.⁵⁵ These limited examples might indicate that companies are in the first instance looking for in-house combination therapies. The TNF inhibitors and rituximab are for their use as treatments for rheumatoid arthritis often combined with methotrexate, and also patented as such.

3.1.6. Development and applying for patent protection of next-generation products

Although development and patenting of next-generation products, which are created via modifying the structure of a previously developed molecule, are distinct from the patent strategy for the innovator molecule itself, it can be seen as an element in a competitive strategy for the company that developed the innovator product to protect its market share. Next-generation products might have an improved efficacy and safety profile but can come with a premium price relative to standard therapy.⁴⁷

Since the development and approval of Herceptin® (trastuzumab), Roche has worked on several new products related to anti-HER2 antibodies, to protect its position in the oncology area. One of these products is pertuzumab (Perjeta®), a humanized mouse monoclonal antibody, which was granted marketing authorization in the European Union on March 4, 2013 for treatment of early-stage and metastatic breast cancer in combination with trastuzumab and docetaxel or traditional chemotherapy.⁵⁶ Another product of Roche is trastuzumab emtansine (Kadcyla®), an antibody–drug conjugate approved for use in the European Union since November 15, 2013 for the treatment of breast cancer, after treatment with trastuzumab and a taxane.⁵⁷ This medicine can be regarded both as a next-generation product and combination treatment.

Furthermore, following the development of Avastin® (bevacizumab), Roche patented ranibizumab for age-related macular degeneration (which is not on the label of Avastin®).

3.2. Biosimilars

As the data in Table 1 indicate, the market entry of biosimilars either did not happen for a number of years following the expiry of market protection on the innovator product (for trastuzumab, etanercept, rituximab) or did not yet happen (for cetuximab). Regardless of barriers arising from patent strategies, this may also be due to a number of factors, such as the complexity of the manufacturing process (a market access barrier for biosimilar monoclonal antibodies cited in the literature)²⁶ or, in the case of Erbitux® (cetuximab), the fact that it is not a top 10 biological medicine by global sales.

Although it seems that mainly the basic patent and subsequent SPC protection play a role in delaying market entry of biosimilars, further patenting in addition to the basic patent might influence competition with companies developing a biosimilar, as is shown by different patent litigation cases. Table 3 summarizes whether biosimilar market entry is hindered (delayed) by secondary patents for each of the three case studies (trastuzumab, bevacizumab, and cetuximab) and the four monoclonal antibodies discussed in previous articles (adalimumab, etanercept, infliximab, and rituximab). In our case studies, the hurdle arising from secondary patents was in particular clear for the case of trastuzumab, where Pfizer actively pursued different patent litigation cases against Genentech/Roche. Except for one patent on trastuzumab where the decision to reject the patent was overturned in appeal, biosimilar developers have won all identified opposition and national patent litigation cases. This indicates that some patents on trastuzumab were seen as a real hurdle for biosimilar entry, but that biosimilar developers can challenge these patents and win. For trastuzumab, eventually, all identified hurdles related to patents were cleared, albeit for some patents later than the expiry of basic patent protection in 2014, and this might explain why biosimilars were not immediately available. On the other hand, the first marketing authorization for a trastuzumab biosimilar was only granted in 2017, so development hurdles might have also played a role. Only one active patent on Herceptin® without an ongoing challenge by third parties can be identified, i.e., for the subcutaneous version of trastuzumab (until 2030), and this patent does not block market entry for intravenously administered versions. Patents that would potentially protect Avastin® longer than the basic protection have also been under attack by developers of biosimilars. The only active patent identified claims the use in the treatment of recurrent or metastatic breast cancer together with chemotherapy (until 2029). Biosimilar developers will probably

have to market their product without this indication on the label. Patents on other new indications have also been recently granted for Avastin®, but opposition was still possible at the time of the study (May 2019). As far as we can assess, for Erbitux® (cetuximab) no patent litigation cases were held with companies developing a biosimilar. The only patents found that are still active, are one on a lyophilized formulation (until 2022) and one on a clinical prediction method (until 2030). The delayed entry of cetuximab biosimilars does not seem to be related to IP issues.

Several biosimilars for adalimumab entered the European market in October 2018, after expiry of the basic patent, SPC and a 6-month pediatric extension, following a settlement agreement including a non-exclusive license on patents for dosage regimens for rheumatoid arthritis and inflammatory bowel disease.⁵⁸ Marketing in the US will have to wait until 2023 when a licensing agreement on formulation and dosage patents starts.⁵⁹ For MabThera® (rituximab), which lost basic protection in 2013, two patents on second medical uses including new dosage regimens were a substantial hurdle to overcome for biosimilar developers. An appeal to revocation of one patent is still pending in March 2020, however, biosimilars already launched in many European countries after national invalidation of the patent or after the decision by the EPO to revoke the patent during oral proceedings in June 2018. In Belgium, marketing of Sandoz's rituximab biosimilar was further delayed up to September 2019 due to an ongoing infringement action. For infliximab, later patents than the basic patent on Remicade® did not seem to influence the market entry of biosimilars in Europe, although it is suggested that a license has been given for the combination of infliximab with methotrexate.³² Also, for etanercept, no major hurdles related to secondary patents have been identified. Only a patent covering a specific formulation has to be taken into account, but this can be bypassed by biosimilar developers by making a new formulation, as has been done by Samsung Bioepis.³²

3.3. Limitations and areas for future research

This study is subject to a number of limitations. First, the study focused on product claims, including second medical use claims. Some patents with process claims are not linked to a specific product, and therefore not easy to identify. As patent claims on the molecule itself and possible indications can be considered as the most blocking for competitors, especially biosimilar products, this would probably not considerably affect the results of this study. It cannot be excluded that some patents related to the selected molecules have been overlooked. Still, the most relevant patents were most likely revealed via the search on case law. Second, it was not always clear whether licenses on a certain

Table 3. Summary of results on whether secondary patents are a hurdle to market entry of therapeutic monoclonal antibodies.

Brand name	Active substance	Secondary patents delaying market entry of biosimilars?
Humira®	adalimumab	Eventually no. All litigation cases were settled before expiry of SPC by grant of a non-exclusive licensing agreement.
Avastin®	bevacizumab	Probably no. It remains to be seen whether biosimilars launch in June 2020.
Erbitux®	cetuximab	No. Potential hurdles were not identified.
Enbrel®	etanercept	No. Potential hurdles were not identified.
Remicade®	infliximab	No. But, a licensing agreement might exist.
MabThera®	rituximab	Yes. But, these hurdles were overcome via patent litigation.
Herceptin®	trastuzumab	Yes. But, these hurdles were overcome via patent litigation.

patent were given to a third party, as this is not always made public. Third, we calculated the effective market protection since approval by the EMA in [Table 2](#), while products will also undergo a pricing and reimbursement procedure before launch on the market. However, as this is the case for all products, calculating market protection starting from the grant of marketing authorization is a valid proxy. Fourth, we did not check for each country whether an SPC was granted, and, if so, for which time period it provided exclusivity. However, we can assume that when an SPC was granted in one of the selected countries (the UK, Germany, and France), this would considerably hinder competitors. Fifth, the selection of case studies is limited to oncology products. Nevertheless, results from the general overview in [Table 2](#) and previous literature were considered when drawing conclusions. Sixth, although identifying strategies of companies based on filed patent applications may not provide a complete picture as to why these decisions were taken, an overview of identified patents nonetheless generates valuable knowledge on how patent portfolios develop in practice. Finally, the European perspective may be too narrow to analyze patent strategies, since many patent litigation cases occur in the US, where most of the revenue is made. As the IP system in the US is substantially different from that in Europe, it was not considered to be in the scope of this study.

The current analysis focused mainly on identifying patents relevant to the innovator product. Areas for future research could be to conduct a more elaborate claim analysis of the identified patents to define the scope of protection of the different molecules. Also, follow-on strategies to protect the position of the innovator company on the market, for example via next-generation products and combinations with new or existing medicines could be worked out more in detail. An in-depth study of biosimilars that are currently in development and subsequent analysis of patent applications related to these biosimilars could be of added value. In addition, a comparative analysis with the small molecule market and entry of generics could be conducted to study whether IP strategies and enforcement of patents in this market differ from the biopharmaceutical market. Finally, IP strategies other than patent strategies can be further studied, for example the use of multiple brand names for the same biosimilar product with only a difference in indications on the label to potentially work around active second medical use patents of the innovator product (i.e., ‘skinny labelling’).

4. Conclusion

For the selected monoclonal antibodies, the key protection instruments are the basic patent and the additional protection provided by the award of an SPC with possible pediatric extension, which provide for an average effective market protection of the innovator product of 15 y.

Biosimilar developers still face on a case-by-case basis substantial hurdles arising from patents taken after the basic patent, which need to be overcome in patent litigation cases on a European or national level. These hurdles, however, seem to be surmountable, given that many cases were observed to have been won by biosimilar developers and agreements were made to settle ongoing cases. For some patents on the innovator product, the biosimilar developer can invent around this

patent, for example when claiming a specific formulation, but this is often not possible for other patents, such as on a specific dosage regimen. Patent protected new indications can be ‘carved’ out of the label of the biosimilar to avoid infringement and already launch the biosimilar on the market. Also biosimilars can be protected by filing new patents and these mainly pertain to new formulations.

5. Methods

First, the basic patent (i.e., the first patent that would provide product-specific protection), SPC, and potential other exclusivity rights were identified and listed for the selected therapeutic monoclonal antibodies in Europe, which are included in [Table 1](#), alongside a calculation of the total years of protection the product has enjoyed or will have enjoyed since marketing authorization in the European Union ([Table 2](#)). The information in [Table 2](#) was constructed via relevant articles and searches for SPCs in the national patent registers of the UK, Germany and France, which can be considered as highly valued markets for pharmaceutical companies. Also, these databases are well established and publicly accessible.

Then, specific cases for a more in-depth study were chosen based on added value toward previously published papers discussing patents on monoclonal antibodies, and the total years of market protection of a product, which was calculated in the first part. More particularly, trastuzumab, with a period of protection of the reference product that seems average relative to other selected molecules (14 y), bevacizumab, with a relatively long period of protection of the reference product (17 y), and cetuximab, with a more limited period of protection of the reference product (10 y), were chosen. Patent strategies for the innovator products of adalimumab, etanercept, infliximab, and rituximab have been previously described in the literature³⁰⁻³² and were therefore not included as case studies. Also, ranibizumab and eculizumab were considered less relevant to study in-depth, as these molecules are still patent protected, and to date no biosimilars of these molecules are approved for marketing in the European Union.

Two types of strategies were analyzed in the different case studies: 1) the strategy of the innovator company to apply for and enforce their patents and defend their product and market share, and 2) the strategy of the biosimilar developer to declare a patent invalid, claim non-infringement, or to invent around patents on the reference product and potentially apply for a new patent. A list of patents on the reference product and the current status was prepared. For patents related to biosimilars, we determined whether new patents were filed and what type of inventions were claimed.

A two-step approach was used to obtain detailed information on the selected cases: 1) an exploratory literature review, and 2) a database analysis.

5.1. Exploratory literature review

An exploratory literature search in PubMed was conducted to (1) search patent landscape analyses to learn from their methodology, and (2) identify articles indicating patent numbers of monoclonal antibodies and relevant case law. The search strategy included

different combinations of the following terms: 'Patents as Topic [Mesh]', 'Biological', 'Europe', 'Antibody, monoclonal [Mesh]', and international nonproprietary and brand names of the selected molecules. Articles could be published in English or Dutch.

European Regulations and Directives, guidelines, and books known to the authors were searched for relevant information on how to patent/claim a therapeutic monoclonal antibody and possible intellectual property strategies. Case law on relevant biological products was also searched on the internet.

5.2. Database analysis

In addition to internet searches, the Darts-ip database⁶⁰ was used to search for relevant case law. Case law was studied to determine which patents have been used to hinder market access of biosimilars and which arguments are used in opposition, appeal, and national patent litigation processes. For each of the molecules included in an in-depth case study, a general patent search was performed by active ingredient and Europe as a jurisdiction.

To supplement European patent numbers that were linked to case law and found via the Darts-ip database, the Derwent Innovation patent database⁶¹ was used to search for pending patent applications and granted patents on a specific product. Also, 'dead' patents (expired, not maintained, elapsed, revoked) and withdrawn or refused patent applications were taken into consideration. Different search terms were used depending on the product investigated, e.g., the international nonproprietary name, description of function or indication, US patent number, often combined with the known applicant. Patents were also screened for reference to earlier patents. In addition, different synonyms were adopted. A template was used to make an overview of the following information: Product, title, patent number, assignee/applicant, application date, priority date, publication date, abstract, number of claims, claims, legal status, selected European Member states, and other characteristics. In addition, Espacenet, the public patent database of the EPO, and the European patent register with publicly available procedural information were consulted.^{62,63}

Searches for patents and case law were performed between December 2018 and May 2019.

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Author contribution

IH and EM developed the idea and were involved in the design of this study. EM was involved in data collection and drafted the initial version of the manuscript. IH and AV critically revised the manuscript. All authors read and approved the final manuscript.

Disclosure of potential conflicts of interest

AV is involved in consulting, advisory work, and speaking engagements for a number of companies, a.o. AbbVie, Accord, Amgen, Biogen, EGA, Pfizer/Hospira, Mundipharma, Roche, Sandoz. IH and EM declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. What is Intellectual Property?: World Intellectual Property Organization. 2018. <https://www.wipo.int/about-ip/en/>.
2. Shorthose S, Goraya T. Overview of intellectual property rights. In: Shorthose S, editor. Guide to EU pharmaceutical regulatory law. Alphen aan den Rijn: Kluwer Law International. 2015.
3. Bhattacharya S, Saha C. Intellectual property rights: an overview and implications in pharmaceutical industry. *J Adv Pharm Technol Res.* 2011;2(2):88–93. doi:10.4103/2231-4040.82952.
4. TRIPS: Agreement on Trade-Related Aspects of Intellectual Property Rights. Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization; 1994.
5. European Patent Convention 16th. München: European Patent Office - Mediengruppe Universal; 2016.
6. Directive 98/44/EC of the European parliament and of the council of 6 July 1998 on the legal protection of biotechnological inventions. *Offic J Eur Communities.* 1998;L213:13–21.
7. Chapter V – Biotechnological inventions - The European Patent Convention, Implementing Regulations: European Patent Office. 2019. https://www.epo.org/law-practice/legal-texts/html/epc/2016/e/rcii_v.html.
8. VIII. Divisional applications - Guide for applicants: How to get a European patent: European Patent Office. 2018 [Accessed 2018 Jun 29]. https://www.epo.org/applying/european/Guide-for-applicants/html/e/ga_d_viii.html.
9. Grubb PW, Thomsen PR. Patents for chemicals, pharmaceuticals, and biotechnology - fundamentals of global law, practice, and strategy 5th ed. Oxford: Oxford University Press; 2010.
10. Storz U. IP issues of therapeutic antibodies. In: Storz U, Flasche W, Driehaus J, editors. Intellectual property issues: therapeutics, vaccines and molecular diagnostics. Berlin Heidelberg: SpringerBriefs in Biotech Patents: Springer; 2012. p. 1–16.
11. Germinario C, Bertoli S, Rampinelli P, Cini M. Patentability of antibodies for therapeutic use in Europe. *Nat Biotechnol.* 2018;36(5):402–05. doi:10.1038/nbt.4134.
12. Lahrtz F. How to successfully patent therapeutic antibodies. *J Biomol Screen.* 2015;20(4):484–91. doi:10.1177/1087057114567457.
13. Gresl T, Storz U, Sandercock C. An update on obtaining and enforcing therapeutic antibody patent claims. *Nat Biotechnol.* 2016;34(12):1242–44. doi:10.1038/nbt.3735.
14. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J Health Econ.* 2016;47:20–33. doi:10.1016/j.jhealeco.2016.01.012.
15. Mistry R, Maheshwari D. Regulatory exclusivity strategies: further protection for pharmaceuticals in Us, Europe And Canada. *J Glob Trends Pharm Sci.* 2015;6:2300–10.
16. Directive 2004/27/EC of the European parliament and of the council amending directive 2001/83/EC on the community code relating to medicinal products for human use. *Offic J Eur Union.* 2004;L 136:34–57.
17. Goraya T. Supplementary protection certificates. In: Shorthose S, editor. Guide to EU pharmaceutical regulatory law. The Netherlands: Alphen aan den Rijn: Kluwer Law International; 2015. p. 201–226.

18. Regulation (EC) No 469/2009 of the European parliament and of the council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (Codified version (Text with EEA relevance). *Offic J Eur Union*. 2009;L152:1–10.
19. Godman B, Bucsecs A, Vella Bonanno P, Oortwijn W, Rothe CC, Ferrario A, Bosselli S, Hill A, Martin AP, Simoens S, et al. Barriers for access to new medicines: searching for the balance between rising costs and limited budgets. *Front Public Health*. 2018;6(328). doi:10.3389/fpubh.2018.00328.
20. Urquhart L. Market watch: top drugs and companies by sales in 2017. *Nat Rev Drug Discov*. 2018;17(4):232. doi:10.1038/nrd.2018.42.
21. Outlook for global medicines through. 2021 - balancing cost and value. New Jersey (USA): Parsippany: QuintilesIMS Institute; 2016.
22. EMA. Guideline on similar biological medicinal products 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf.
23. Delivering on the potential of biosimilar medicines - The role of functioning competitive markets. IMS institute for healthcare informatics; 2016.
24. EMA. Guideline on similar biological medicinal products 2005. https://www.ema.europa.eu/documents/scientific-guideline/guide-line-similar-biological-medicinal-products_en.pdf.
25. Download medicine data | European Medicines Agency: European Medicines Agency. 2019. <https://www.ema.europa.eu/en/medicines/download-medicine-data>.
26. Moorkens E, Jonker-Exler C, Huys I, Declerck P, Simoens S, Vulto AG. Overcoming barriers to the market access of biosimilars in the European Union: the case of biosimilar monoclonal antibodies. *Front Pharmacol*. 2016;7:193. doi:10.3389/fphar.2016.00193.
27. Derbyshire M. Patent expiry dates for biologicals: 2017 update. *Generics Biosimilars Initiative J*. 2018;7(1):29–34. doi:10.5639/gabij.2018.0701.007.
28. Rader RA. An analysis of the US biosimilars development pipeline and likely market evolution. *Bioprocess Int*. 2013;11:16–23.
29. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1). London: European Medicines Agency; 2014.
30. Storz U. Rituximab: how approval history is reflected by a corresponding patent filing strategy. *MABs*. 2014;6(4):820–37. doi:10.4161/mabs.29105.
31. Storz U. Of patents and patent disputes: the TNFalpha patent files part 1: humira. *Hum Antibodies*. 2017;25(1–2):1–16. doi:10.3233/HAB-160300.
32. Storz U. Of patents and patent disputes - the TNFalpha patent files. part 2: enbrel, remicade, cimzia and simponi. *Hum Antibodies*. 2018;26(2):49–61. doi:10.3233/HAB-170321.
33. Niazi S. Biosimilars and interchangeable biologics: strategic elements. Boca Raton (FL): Taylor & Francis Group; 2016.
34. Intellectual Property Office - Patents - SPC number: Intellectual Property Office. 2019. <https://www.ipo.gov.uk/p-find-spc.htm>.
35. DPMAregister | Patents - Beginner's search: Deutsches Patent- und Markenamt (DPMA). 2019. <https://register.dpma.de/DPMAregister/pat/einsteiger>.
36. PATENT DATABASE | Basic Search: Institut National de la Propriété Industrielle (INPI). 2019. <https://bases-brevets.inpi.fr/en/home.html>.
37. Union Register of medicinal products - Public health - European Commission: European Commission. 2019. https://ec.europa.eu/health/documents/community-register/html/index_en.htm.
38. Herceptin | European Medicines Agency: European Medicines Agency. 2019. <https://www.ema.europa.eu/en/medicines/human/EPAR/herceptin>.
39. Genentech Reports 41 Percent Increase in Year-End Net Income: Genentech. 1999. <https://www.gene.com/media/press-releases/4864/1999-01-21/genentech-reports-41-percent-increase-in>.
40. Millennium and Protein Design Labs announce agreement for humanized antibody patent rights: Pharmaceutical Online. 2001. <https://www.pharmaceuticalonline.com/doc/millennium-and-protein-design-labs-announce-a-0001>.
41. Avastin | European Medicines Agency: European Medicines Agency. 2019. <https://www.ema.europa.eu/en/medicines/human/EPAR/avastin#authorisation-details-section>.
42. Vannieuwenhuysen C, Slegers P, Neyt M, Hulstaert F, Stordeur S, Cleemput I, Vinck I. Towards a better managed off-label use of drugs. Brussels (Belgium): Belgian Health Care Knowledge Centre (KCE); 2015. Contract No.: KCE report 252.
43. Erbitux | European Medicines Agency: European Medicines Agency. 2019. <https://www.ema.europa.eu/en/medicines/human/EPAR/erbitux#authorisation-details-section>.
44. Owens J. ImClone loses Erbitux patent. *Nat Rev Drug Discov*. 2006;5(11):886. doi:10.1038/nrd2191.
45. Cetuximab - Notice FR04C0030: Institut National de la Propriété Industrielle (INPI). 2019. <https://bases-brevets.inpi.fr/en/document-en/FR04C0030.html>.
46. Biosimilars of cetuximab Mol: GaBI Online - Generics and Biosimilars Initiative. 2014. [Accessed 2018 Apr 13]. <http://gabionline.net/Biosimilars/General/Biosimilars-of-cetuximab>.
47. Moorkens E, Meuwissen N, Huys I, Declerck P, Vulto A, Simoens S. The market of biopharmaceutical medicines: a snapshot of a diverse industrial landscape. *Front Pharmacol*. 2017;8. doi:10.3389/fphar.2017.00314.
48. Overpatented, Overpriced: Special Humira Edition: Initiative for Medicines, Access and Knowledge (I-MAK). 2018. http://www.i-mak.org/wp-content/uploads/2018/09/i-mak-humira-report-final_0917.pdf.
49. Pivot X, Gligorov J, Muller V, Curigliano G, Knoop A, Verma S, Jenkins V, Scotto N, Osborne S, Fallowfield L, et al. Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, two-cohort PrefHer study. *Ann Oncol*. 2014;25(10):1979–87. doi:10.1093/annonc/mdu364.
50. Roche - Roche's new timesaving formulation of Herceptin approved in Europe for the treatment of HER2-positive breast cancer Basel: F. Hoffmann-La Roche Ltd. 2013. <https://www.roche.com/media/releases/med-cor-2013-09-02.htm>.
51. Troein P, Logendra R, Hanassab S. The impact of biosimilar competition in Europe. London (UK): IQVIA; 2018.
52. Remsima: Pending EC decision | European Medicines Agency: European Medicines Agency. 2019. <https://www.ema.europa.eu/en/medicines/human/summaries-opinion/remsim>.
53. Storz U. Extending the market exclusivity of therapeutic antibodies through dosage patents. *MABs*. 2016;8(5):841–47. doi:10.1080/19420862.2016.1180491.
54. Elloumi J, Jellali K, Jemel I, Aifa S. Monoclonal antibodies as cancer therapeutics. *Recent Pat Biotechnol*. 2012;6(1):45–56. doi:10.2174/187220812799789190.
55. Uranaka T. UPDATE 1-Merck, Takeda cancel development of cancer drug: reuters. 2008. <https://www.reuters.com/article/takeda-idUST35282120080218>.
56. Perjeta | European Medicines Agency: European Medicines Agency. 2019. <https://www.ema.europa.eu/en/medicines/human/EPAR/perjeta#authorisation-details-section>.
57. Kadcyla | European Medicines Agency: European Medicines Agency. 2019. <https://www.ema.europa.eu/en/medicines/human/EPAR/kadcyla#authorisation-details-section>.
58. AbbVie Announces Global Resolution of HUMIRA® (adalimumab) Patent Disputes with Sandoz: AbbVie. 2018. <https://news.abbvie.com/news/abbvie-announces-global-resolution-humira-adalimumab-patent-disputes-with-sandoz.htm>.
59. Dunn A With Boehringer settlement, AbbVie completes Humira sweep: bioPharma Dive. 2019. <https://www.biopharmadive.com/news/abbvie-boehringer-ingelheim-settle-humira-patent-biosimilar/554729/>.
60. Darts-ip. Brussels (Belgium): Darts-ip; 2019.
61. Derwent Innovation. Philadelphia (USA): Clarivate Analytics; 2019.
62. Espacenet - Home page: European Patent Office. 2019. <https://worldwide.espacenet.com/>.
63. Smart Search - European Patent Register: European Patent Office. 2019. <https://register.epo.org/regviewer>.

Appendices

Table A1. A non-exhaustive list of patents related to Herceptin® (trastuzumab) as of May 2019.

Subject	Patent number	Date of filing	Applicant	Status
Chimeric Ab Humanized Ab production	EP0125023	06.04.1984	Genentech	Expired on 06.04.2004
	EP0451216 (parent)	28.12.1989	PDL	Expired on 28.12.2009
	EP0939127		BioPharma	Expired on 28.12.2009
	EP1477497			Expired on 28.12.2009
	EP1491556			Expired on 28.12.2009
Basic patent	EP0682040			Revoked
	EP0590058 (parent)	15.06.1992	Genentech	Expired on 15.06.2012
	EP1400536			Withdrawn
Freeze-dried formulation	EP0940468			Withdrawn
	EP0845997 (parent)	23.07.1996	Genentech	Withdrawn
	EP1516628			Expired on 23.07.2016. Invalid in Norway and UK.
Use in treatment of malignant breast cancer, with taxoid	EP2275119			Expired on 23.07.2016. Invalid in UK.
	EP1037926 (parent)	10.12.1998	Genentech	Revoked. Invalid in UK.
	EP1947119			Deemed to be withdrawn
	EP2275450			Withdrawn
Compositions	EP2277919			Withdrawn
	EP1075488 (parent)	03.05.1999	Genentech	Expired on 03.05.2019
	EP1308455			Expired on 03.05.2019. Invalid in Belgium, UK, Germany.
Use in treatment (before/after surgery)	EP1308456			Expired on 03.05.2019
	EP1187632	09.05.2000	Genentech	Revoked
Dosages	EP1210115 (parent)	25.08.2000	Genentech	Revoked. Invalid in UK.
	EP2111870			Withdrawn
	EP2110138			Withdrawn
Use in screened cancer patients	EP1282443 (parent)	18.05.2001	Genentech	Revoked
Method for purification	EP2116262			Withdrawn
	EP1648940 (parent)	24.06.2004	Genentech	Granted. Appeal to revocation ongoing.
Method for prevention of disulfide bond reduction	EP3095793			Examination in progress
	EP2188302 (parent)	08.07.2008	Genentech	Granted. Opposition procedure ongoing.
	EP2586788			Granted. Opposition procedure ongoing.
	EP3327026			Examination requested
Subcutaneous formulation	EP2459167 (parent)	28.07.2010	Roche	Active until 28.07.2030
	EP2687202			Examination ongoing

Ab, antibody.

Table A3. A non-exhaustive list of patents related to Eribitux® (cetuximab) as of May 2019.

Subject	Patent number	Date of filing	Applicant	Status
Anti-EGFR mAb	EP0359282 (parent)	15.09.1989	Rorer International	Expired on 15.09.2009
	EP0667165			Expired on 15.09.2009
Liquid formulation	EP1406658	18.06.2002	Merck	Deemed to be withdrawn
Lyophilized formulation	EP1455824	25.11.2002	Merck	Active until 25.11.2022
Aqueous composition	EP1687031	26.10.2004	Merck	Revoked
Crystal form	EP1686961 (parent)	12.11.2004	Merck	Refused
	EP1974723			Deemed to be withdrawn
Process for highly concentrated formulation	EP1713502	27.01.2005	Merck	Deemed to be withdrawn
Prediction method	EP1869208	12.04.2006	Merck	Refused
Prediction method	EP1934599 (parent)	11.10.2006	Merck	Deemed to be withdrawn
	EP2251688			Deemed to be withdrawn
Prediction method	EP2443252	15.06.2010	Merck	Active until 15.06.2030

mAb, monoclonal antibody; EGFR, epidermal growth factor receptor.

Table A2. A non-exhaustive list of patents related to Avastin® (bevacizumab) as of May 2019.

Subject	Patent number	Date of filing	Applicant	Status
Chimeric Ab	EP0125023	06.04.1984	Genentech	Expired on 06.04.2004
Chimeric Ab production	EP0451216 (parent)	28.12.1989	PDL BioPharma	Expired on 28.12.2009
	EP0939127			Expired on 28.12.2009
	EP1477497			Expired on 28.12.2009
	EP1491556			Expired on 28.12.2009
	EP0682040			Revoked
Basic patent (use of anti-VEGF antibody for treatment of cancer)	EP0666868 (parent)	28.10.1992	Genentech	Expired on 28.10.2012
	EP1167384			Expired on 28.10.2012
	EP1238986			Expired on 28.10.2012
	EP1975181			Revoked
Use in treatment of AMD	EP817648 (parent)	28.03.1996	Genentech	Expired on 28.03.2016
	EP1506787			Expired on 28.03.2016
	EP1627643			Deemed to be withdrawn
Variant anti-VEGF antibody	EP0973804 (parent)	03.04.1998	Genentech	Expired on 03.04.2018
	EP1325932			Expired on 03.04.2018
	EP1787999			Expired on 03.04.2018
	EP1650220			Expired on 03.04.2018
	EP2301580			Expired on 03.04.2018
	EP2338915			Deemed to be withdrawn
	EP2336190			Deemed to be withdrawn
Anti-VEGF antibody	EP0971959 (parent)	03.04.1998	Genentech	Expired on 03.04.2018
	EP1695985			Expired on 03.04.2018
Combination with chemo	EP1629010	28.05.2004	Genentech	Withdrawn
Method for purification	EP1648940 (parent)	24.06.2004	Genentech	Granted. Appeal to revocation ongoing.
	EP3095793			Examination in progress
Use for metastasis in breast cancer	EP2056874 (parent)	17.08.2007	Roche	Revoked
	EP2441472			Revoked
Method for prevention of disulfide bond reduction	EP2188302 (parent)	08.07.2008	Genentech	Granted. Opposition procedure ongoing.
	EP2586788			Granted. Opposition procedure ongoing.
	EP3327026			Examination requested
Prediction CV event	EP2321651	23.07.2009	Roche	Granted. Opposition procedure ongoing.
Use for breast cancer, with chemo	EP2361085 (parent)	20.11.2009	Roche	Active until 20.11.2029
	EP2752189			Granted. Opposition procedure ongoing.
	EP3178478			Examination in progress
Monitoring	EP2464744	13.08.2010	Roche	Deemed to be withdrawn
Diagnostic method	EP2478114	16.09.2010	Roche	Deemed to be withdrawn
Formulation	EP2515941	20.12.2010	Roche	Examination in progress
Use in ovarian cancer	EP2539367 (parent)	22.02.2011	Roche	Refused
	EP3064509			Examination in progress
Monitoring	EP2783015	19.11.2012	Roche	Deemed to be withdrawn
Biomarker test	EP2788769	03.12.2012	Roche	Deemed to be withdrawn
Use in treatment ovarian cancer	EP2825558	11.03.2013	Roche	Granted
Use in treatment glioblastoma	EP2882454 (parent)	06.08.2013	Roche	Granted
	EP3446709			Application published
Use in treatment glioblastoma	EP3038647	29.08.2014	Roche	Granted
Formulation	EP3193932	15.09.2015	Roche	Examination in progress
Monitoring	EP3443120	14.04.2017	Roche	Request for examination

Ab, antibody; VEGF, vascular endothelial growth factor; AMD, age-related macular degeneration; CV, cardiovascular.