GaBiJournal
Generics and Biosimilars Initiative Journal

SPECIAL REPORT

Overview of the patent expiry of (non-)tyrosine kinase inhibitors approved for clinical use in the EU and the US

Subramanian Venkatesan[1], MSc; Associate Professor Martine Lamfers[1], PhD; Professor Sieger Leenstra[1], MD, PhD; Professor Arnold G Vulto[2], PharmD, PhD, FCP

Kinase inhibitors form the largest class of novel anticancer drugs. To date, more than 20 kinase inhibitors have been approved for clinical use. Lengthy patent rights keep the cost of these new anticancer drugs high. In order to anticipate the introduction of generics we have reviewed the patent expiry and the indications of kinase inhibitors approved for use in Europe and the US. Most of these drugs are currently used in the treatment of several types of leukaemia and their patent protection will only expire after more than a decade.

Keywords: Anticancer drugs, kinase inhibitors, market exclusivity, patent expiry, targeted therapies

Introduction

Protein kinases are enzymes that add a phosphate group to a protein, and can modulate its function. Protein kinase inhibitors are enzyme inhibitors that block the action of one or more protein kinases. The phosphate groups are usually added to serine, threonine, or tyrosine amino acids on the protein. Most kinases act on both serine and threonine, whereas a smaller proportion acts on tyrosine.

Today's detailed understanding of cell biology is revealing the fundamental changes that result in cancer. Tyrosine kinase inhibitors (TKIs) are effective in the targeted treatment of various malignancies. Imatinib was the first of this class and was approved in 2001.

The price of progress

A major concern in contemporary health care is the soaring cost of (innovative) medicines. Due to patents and other mechanisms of market protection, innovative medicines benefit from a market monopoly for up to 20 years. When market exclusivity is over, more affordable generic medicines enter the market, as was shown in a previous study [1]. For example, in The Netherlands, temozolomide, an important drug for treating brain cancer, was used by approximately 1,200–1,300 patients at a cost of about 10 million Euros per year to the healthcare system, at the time its patent expired. Before the end of market exclusivity, the annual cost per Defined Daily Dose (DDD), was 23,000 Euros [1]. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. However, when market exclusivity ceased, the cost for almost the same number of patients decreased by 80% to two million Euros per year. It is, therefore, important for healthcare planning decisions and drug purchasing contracts, to be aware of expiring patents. For instance, the UK Medicines Information of the National Health Service periodically publishes a document entitled *Prescribing Outlook: New Medicines* [2].

When we tried to search a list of patent expiry dates for TKIs, we noticed that such a list was not readily available, in contrast to expiry dates of a selection of biological medicines [3]. For this reason we set out to compile an overview of patent expiry dates of the current clinically approved oral TKIs in the European Union (EU) and in the US. We chose this group of cancer medicines as it is growing quickly and TKIs are often very expensive so great savings can be realized by healthcare systems once their patents have expired.

Protein kinase deregulation is one of the most characteristic traits of cancer biology. Large genomic sequencing studies show that mutations in genes encoding protein kinases are often present [4]. Currently, kinase inhibitors form the largest class of new anticancer drugs [5]. A race between pharmaceutical companies to license new kinase inhibitors has led to a wave of patents contributing to an intricate web of intellectual property rights [6]. The pharmaceutical industry gains exclusivity rights for marketing a drug when the first patents are granted by EU or US patent offices. The protected period is often extended as a reward for reaching certain licensing milestones (e.g. additional six months for paediatric indications).

Competition can be held off by either exclusivity rights or patent rights of the originator drug. Once both have expired, the introduction of generics or, in the case of biological medicines, biosimilars, is allowed and sales of the originator drug usually plummet. Therefore, drug companies try to stretch their exclusivity rights or patent rights in order to keep generics off the market.

By April 2015, 21 TKIs and three serine/threonine kinase inhibitors have been approved for clinical use. In this paper, we will provide an overview of current kinase inhibitors approved for clinical use and their indications. Furthermore, we will address when their patents are due to expire.

Author for correspondence: Professor Arnold G Vulto, PharmD, PhD, FCP, Department of Hospital Pharmacy, Erasmus MC, 80 Wytemaweg, NL-3015 CN Rotterdam, The Netherlands

Submitted: 9 December 2016; Revised: 2 March 2017; Accepted: 2 March 2017; Published online first: 15 March 2017

Material and methods

An overview of all clinically approved kinase inhibitors, including their indications and date of approval in Europe and the US, was generated by searching the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) databases. The patent expiry dates were collected from various online databases and from various sources in the pharmaceutical industry, see author's note at the end of this paper.

Mechanism of action and clinical indication of tyrosine kinase inhibitors

Targeting breakpoint cluster region-Abelson (BCR-ABL)

The treatment of leukaemia has benefited most from the advent of kinase inhibitors. The first clinically successful TKI was imatinib, which inhibits the product of the Philadelphia chromosome (Ph+) in chronic myelogenous leukaemia (CML), BCR-ABL. Currently, several different TKIs have been developed which target an array of tyrosine kinases of which BCR-ABL is a common denominator. These drugs are often used interchangeably after drug resistance has occurred in CML or acute lymphoblastic leukaemia (ALL).

Bosutinib (Bosulif)

Bosutinib is used in the treatment of CML in which the BCR-ABL fusion gene is present. It is indicated when CML is resistant to treatment with the TKIs imatinib, nilotinib and dasatinib [7, 8]. It was authorized by EMA in March 2013 and the EU patent is expected to expire on September 2024. FDA approved it on September 2012, and the US patent is expected to expire in November 2026. Interestingly, market exclusivity to recoup investment in the US is almost four years longer than in the EU.

Dasatinib (Sprycel)

Dasatinib is used to treat CML and Ph+ ALL patients who do not respond to other treatment [9, 10]. It was authorized by EMA in November 2006 and the EU patent is expected to expire in November 2019. FDA authorized dasatinib in June 2006, and the US patent is expected to expire in October 2025, providing more than 19 years of market exclusivity to recoup the investment.

Imatinib (Gleevec/Glivec)

Imatinib is used in the treatment of multiple diseases, namely CML, Ph+ ALL, myelodysplastic or myeloproliferative diseases (MD/MPD), advanced hypereosinophilic syndrome or chronic eosinophilic leukaemia (HES/CEL), gastrointestinal stromal tumours (GIST) and dermatofibrosarcoma protuberans (DFSP), see EMA Summary of Product Characteristics (SmPC).

It is used against Ph+ CML and ALL since these cancers are mostly dependent on the oncogenic activity of BCR-ABL [11]. In MP/MPD, imatinib is used in patients with platelet-derived growth factor receptor (PDGFR) gene rearrangements [12] and in HES/CEL it is used for patients who have a FIP1L1 and PDGFRα rearrangement [13]. In GIST, imatinib is used in unresectable or metastatic cases and in cases with risk of recurrence after resection [14]. In DFSP, imatinib is used in unresectable or metastatic cases [15]. It was authorized by EMA in November 2001 and the EU patent expired in December 2016. Whereas imatinib was authorized by FDA in May 2001, the same year as in the EU, the US patent is only expected to expire in June 2022. The US patent grants a record market exclusivity of 21 years.

Nilotinib (Tasigna)

Nilotinib is used in CML after the development of resistance to imatinib or as a first-line therapy [16]. It was authorized by EMA in November 2007 and the patent is expected to expire in December 2028, providing a record 21-year EU market exclusivity. Nilotinib was authorized by FDA around the same time (October 2007): the US patent is expected to expire five years earlier than in the EU (July 2023).

Ponatinib (Iclusig)

Ponatinib is used for CML and Ph+ ALL patients who do not respond to dasatinib, nilotinib or imatinib. This situation could, for example, occur due to a resistance-inducing *BCR-ABL1 (T315I)* point mutation [17]. It was authorized by EMA on July 2013 and the EU patent is expected to expire in June 2028. Ponatinib was authorized by FDA slightly earlier (December 2012) and the US patent is expected to expire in December 2026.

Targeting Bruton's tyrosine kinase (BTK)

BTK expression is restricted to B cells and has been found to be responsible for constitutively active B cell–receptor signalling in some cases of chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma (MCL).

Ibrutinib (Imbruvica)

Ibrutinib is indicated in relapsed MCL [18] and CLL [19]. In addition, CLL patients who have a 17p deletion or *TP53* mutation are also eligible for treatment with this drug. It was authorized by EMA in October 2014 and the EU patent is expected to expire in December 2026. Ibrutinib was authorized by FDA almost a year earlier (November 2013) and has a similar US patent expiry (December 2026).

Targeting epidermal growth factor receptor (EGFR/ERBB1)

EGFR is one of the most intensely investigated oncogenes. Glioblastoma and lung cancer are among the tumours with the most frequent EGFR alterations, ranging from 60% to 15% respectively [20, 21]. Multiple kinase inhibitors have been approved to target EGFR; they are mainly used for the treatment of lung cancer. Despite progress in drug development, resistance to EGFR inhibition remains a major problem, contributing to relapses.

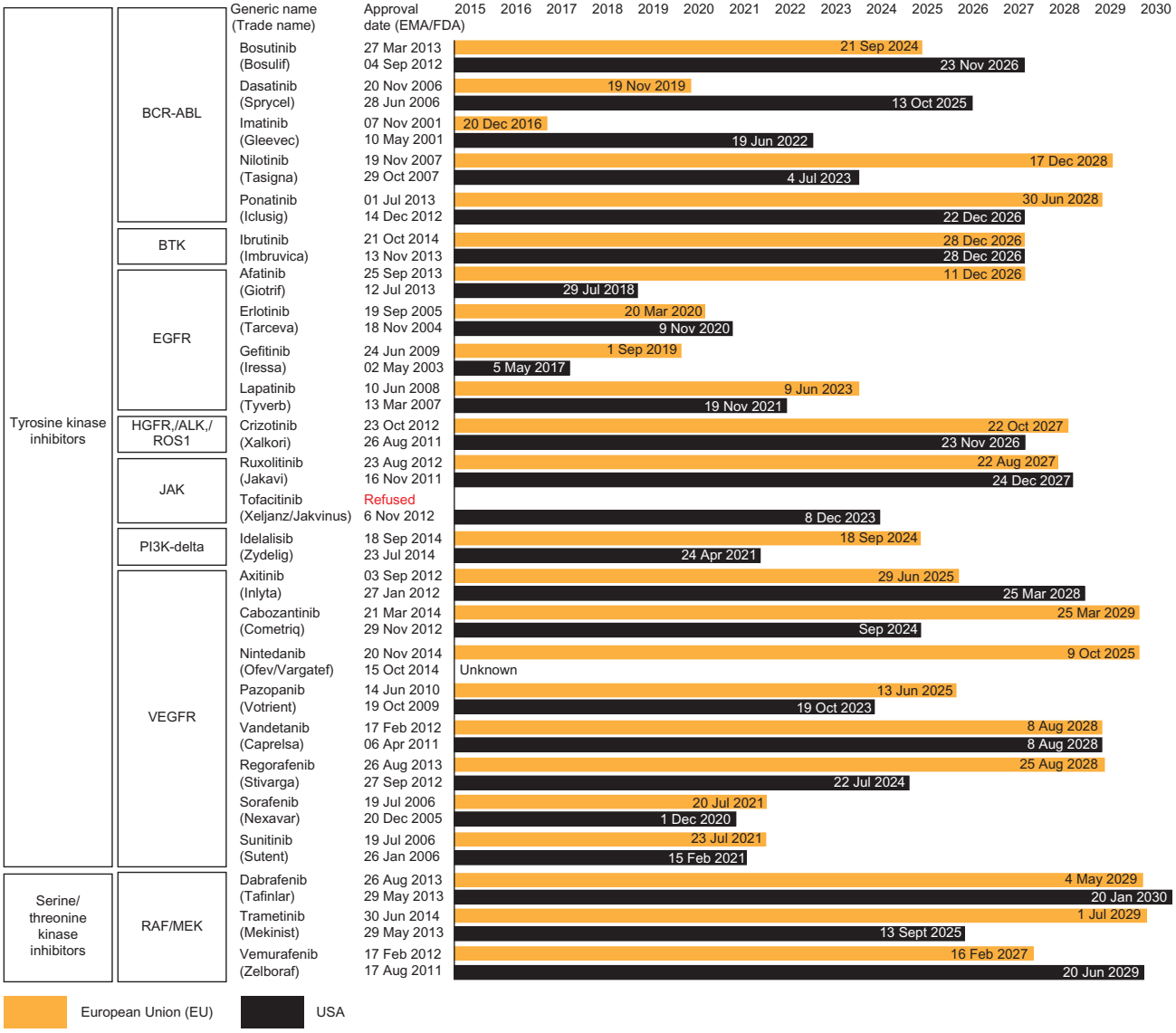
Afatinib (Giotrif)

Afatinib is used against advanced or metastatic non-small-cell lung cancer (NSCLC) with an activating EGFR mutation (exon 19 deletion, L858R, G719X or L861Q) [22-24]. It is only indicated in adult patients who have not been previously treated with TKIs. It was authorized by EMA in September 2013 and the patent is expected to expire in December 2026. Although afatinib was authorized by FDA in the same year, the US patent is expected to expire much earlier (July 2018), with an eight-year shorter market exclusivity.

Erlotinib (Tarceva)

Erlotinib is used against EGFR mutant-driven NSCLC [25]. It is also used against metastatic pancreatic adenocarcinoma [26]. It

Figure 1: EMA/FDA approved kinase inhibitors (cut-off date for approval before January 2015)



BCR-ABL: Breakpoint cluster region-Abelson; BTK: Bruton's tyrosine kinase; EGFR/ERBB1: Epidermal growth factor receptor; EMA: European Medicines Agency; FDA: US Food and Drug Administration; HGFR/MET: Hepatocyte growth factor receptor; ALK: anaplastic lymphoma kinase and ROS1: C-Ros Oncogene 1; JAK: Janus Kinase; PI3K-delta: Phosphoinositide 3-kinase delta; VEGFR: Vascular endothelial growth factor receptor; RAF/MEK: Raf-1 Proto-Oncogene, Serine/Threonine Kinase/Mitogen-Activated Protein Kinase Kinase.

was authorized by EMA in September 2005 and the patent is expected to expire in March 2020. Erlotinib was authorized by FDA in November 2004 and the US patent is expected to expire in November 2020.

Gefitinib (Iressa)

Similar to erlotinib, gefitinib is used in the treatment of EGFR mutant-driven NSCLC [27]. It was authorized by EMA in June 2009 and the EU patent is expected to expire in September 2019. Gefitinib was authorized by FDA six years earlier (May 2003) but the US patent is only expected to expire a little earlier (May 2017).

Lapatinib (Tyverb)

Lapatinib is indicated in progressive HER2-positive breast cancer [28]. It was authorized by EMA in June 2008 and the EU patent is expected to expire in June 2023. Although lapatinib was authorized by FDA one year earlier (March 2007), the US patent is expected to expire one and a half years earlier (November 2021).

Targeting the hepatocyte growth factor receptor (HGFR/MET), anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1)

NSCLCs contain in approximately 2%, 5% and 20% of the cases genetic alterations in respectively *ROS1, ALK* and *MET* [29, 30].

Table 1: Indication of clinically approved kinase inhibitors

Common name (brand name)	Target	Indication
Tyrosine kinase inhibitors		
Breakpoint cluster region-Abelson (BCR-ABL)		
Bosutinib (Bosulif)	BCR-ABL, SRC	CML
Dasatinib (Sprycel)	BCR-ABL, EPHR, PDGFRα, PDGFRß, SRC	CML, Ph+ ALL
Imatinib (Gleevec)	BCR-ABL, PDGFRα, PDGFRß, SCFR	CML, DFSP, GIST, HES/CEL, MP/MPD, Ph+ ALL
Nilotinib (Tasigna)	BCR-ABL, EPHR, PDGFRα, PDGFRß, SCFR	CML
Ponatinib (Iclusig)	BCR-ABL, FGFR, FLT3, RET, SCFR	CML, Ph+ ALL
Bruton's tyrosine kinase (BTK)		
Ibrutinib (Imbruvica)	BTK	CLL, MCL
Epidermal growth factor receptor (EGFR/ERBB1)		
Afatinib (Giotrif)	ERbB1, ERbB3, ErbB4	NSCLC
Erlotinib (Tarceva)	ERbB1	NSCLC, pancreatic adenocarcinoma
Gefitinib (Iressa)	ERbB1	NSCLC
Lapatinib (Tyverb)	ERbB1, ERbB2	Breast cancer
Hepatocyte growth factor receptor (HGFR/MET), anaplastic lymphoma kinase (ALK) and C-Ros Oncogene 1 (ROS1)		
Crizotinib (Xalkori)	HGFR, ALK, ROS1	NSCLC
Janus Kinase (JAK)		
Ruxolitinib (Jakavi)	JAK1, JAK2	Myelofibrosis
Tofacitinib (Xeljanz/Jakvinus)	JAK3	Rheumatoid arthritis
Phosphoinositide 3-kinase delta (PI3K-delta)		
Idelalisib (Zydelig)	PI3K-delta	CLL, follicular lymphoma
Vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and rearranged during transfection (RET)		
Axitinib (Inlyta)	VEGFR1, VEGFR2, VEGFR3	RCC
Cabozantinib (Cometriq)	HGFR, RET, VEGFR2	Medullary thyroid cancer
Nintedanib (Ofev/Vargatef)	PDGFRα, PDGFRß, FGFR1, FGFR2, FGFR3, VEGFR1, VEGFR2, VEGFR3	Idiopathic pulmonary fibrosis, NSCLC
Pazopanib (Votrient)	PDGFRα, PDGFRß, VEGFR1, VEGFR2, VEGFR3	RCC, sarcoma
Vandetanib (Caprelsa)	ERbB1, RET, VEGFR1	Medullary thyroid cancer
Regorafenib (Stivarga)	FGFR, PDGFRα, PDGFRß, RET, SCFR,VEGFR1, VEGFR2, VEGFR3, BRAF, BRAF V600E	Colorectal cancer
Sorafenib (Nexavar)	FLT3, SCFR, VEGFR2, VEGFR3, PDGFRß	HCC, RCC
Sunitinib (Sutent)	PDGFRα, PDGFRß, VEGFR1, VEGFR2, VEGFR3	GIST, pNET, RCC
Serine/threonine kinase inhibitors		
Dabrafenib (Tafinlar)	BRAF V600	Melanoma
Trametinib (Mekinist)	MEK1, MEK2	Melanoma
Vemurafenib (Zelboraf)	BRAF V600	Melanoma
Growth factor entrapment		
Aflibercept (Eylea)	PIGF, VEGFA, VEGFB	Age-related macular degeneration, macular oedema
Aflibercept (Zaltrap)	PIGF, VEGFA, VEGFB	CRC

ALL: acute lymphoblastic leukaemia; BRAF: proto-oncogene, serine/threonine kinase; CLL: chronic lymphocytic leukaemia; CML: chronic myelogenous leukaemia; CRC: colorectal cancer; DFSP: dermatofibrosarcoma protuberans; EPHR: Ephrin receptor; ERbB1: Epidermal growth factor receptor; FGFR: fibroblast growth factor receptor; FLT: Fms Related Tyrosine Kinase 3; GIST: gastrointestinal stromal tumours; HCC: Hepatocellular carcinoma; HES/CEL: hypereosinophilic syndrome or chronic eosinophilic leukaemia; MCL: mantle cell lymphoma; MEK: Mitogen-Activated Protein Kinase Kinase; MP/MPD: myelodysplastic or myeloproliferative diseases; NSCLC: non-small-cell lung cancer; Ph+: Philadelphia chromosome; Pnet: pancreatic neuroendocrine tumours; RCC: renal cell carcinoma; SCFR: KIT Proto-Oncogene Receptor Tyrosine Kinase; SRC: SRC Proto-Oncogene, Non-Receptor Tyrosine Kinase; VEGFA: vascular endothelial growth factor A; VEGFB: vascular endothelial growth factor B.

ROS1 and *ALK* usually undergo gene rearrangements, whereas *MET* is often amplified.

Crizotinib (Xalkori)
Crizotinib is used against previously treated *ALK*-positive metastatic NSCLC [31]. It was authorized by EMA in October 2012 and the EU patent is expected to expire in October 2027, whereas crizotinib was authorized by FDA in August 2011 and the US patent is expected to expire in November 2026.

Targeting Janus kinase (JAK)
The *JAK2* V617F mutation leads to a persistently active *JAK2/STAT3* pathway, which is frequently present in myeloproliferative diseases such as polycythaemia vera (PV).

Ruxolitinib (Jakafi)
Ruxolitinib targets *JAK1/2* and is used against the forms of myelofibrosis that cause splenomegaly, namely primary myelofibrosis, post-polycythaemia vera myelofibrosis and post-essential thrombocythaemia myelofibrosis [32]. It was authorized by EMA in August 2012 and the EU patent is expected to expire in August 2027. Ruxolitinib was authorized likewise by FDA in November 2011 and the US patent is expected to expire in December 2027.

Tofacitinib
Tofacitinib inhibits *JAK3* and is used in the treatment of patients with moderately to severely active rheumatoid arthritis who have not responded adequately to methotrexate. It has been refused by EMA due to concerns about the risk and type of serious infections seen with its use. However, FDA approved tofacitinib in November 2012 and the US patent is expected to expire in December 2023.

Targeting phosphoinositide 3-kinase delta (PI3K delta)
PI3K delta is one of the four isoforms of this enzyme and is specifically expressed in leukocytes. It is critical for the proliferation and survival of B lymphocytes. Hyperactivation of PI3K delta signalling is one of the main drivers for the malignant transformation of B lymphocytes.

Idelalisib (Zydelig)
Idelalisib is used in combination with rituximab for the treatment of adult patients with CLL who are refractory to therapy, or in patients with a 17p deletion or *TP53* mutation. Furthermore, idelalisib is also indicated for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior therapeutic lines of treatment, see EMA SmPC. It was authorized by EMA in September 2014 and the EU patent is expected to expire in September 2024. Whereas idelalisib was authorized by FDA around the same time (July 2014), the US patent is expected to expire two years earlier (April 2021).

Targeting vascular endothelial growth factor receptor (VEGFR), PDGFR and Ret Proto-Oncogene (RET)
Mutant RET is believed to mediate migration of the tumour cells whereas VEGFR and PDGFR are thought to mediate angiogenesis. Several multi-targeted tyrosine kinase inhibitors have been developed to simultaneously inhibit these kinases.

Axitinib (Inlyta)
Axitinib is used in advanced renal cell carcinoma (RCC) after resistance to sunitinib or cytokine-based therapy [8, 33, 34]. It was authorized by EMA in September 2012 and the EU patent is expected to expire in June 2025. Although axitinib was authorized by FDA six months earlier (January 2012), the US patent is expected to expire almost three years later (March 2028).

Cabozantinib (Cometriq)
Cabozantinib is used against unresectable or metastatic forms of medullary thyroid cancer. Patients with a RET mutation seem to have more benefit from cabozantinib [35]. It was authorized by EMA in March 2014 and the patent is expected to expire in March 2029, granting 15 years of market exclusivity. Although cabozantinib was authorized by FDA just over a year earlier (November 2012), the US patent is expected to expire almost five years earlier (September 2024), indicating three years shorter market exclusivity in the US.

Nintedanib (Vargatef/Ofev)
Recently, nintedanib, marketed as Vargatef by Boehringer-Ingelheim, was approved for combination therapy with docetaxel for the treatment of adult patients with recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy. Subsequently, the indication was extended to the treatment of adults with idiopathic pulmonary fibrosis (IPF) for which it is marketed as Ofev, see SmPCs, by the same company. It was authorized by EMA in November 2014 and the EU patent is expected to last until October 2025; it is unknown whether this date applies to both brands. Nintedanib was also authorized by FDA in October 2014. Unfortunately, we were not able to retrieve a reliable US patent expiry date for nintedanib in the US.

Pazopanib (Votrient)
Pazopanib is used in the treatment of metastatic RCC [36] and some forms of metastatic soft-tissue sarcoma [37]. It was authorized by EMA in June 2010 and the EU patent is expected to expire in June 2025, allowing 15 years of market exclusivity. Pazopanib was authorized by FDA in October 2009 and the US patent is expected to expire in October 2023, leaving three years less market exclusivity compared with the EU.

Vandetanib (Caprelsa)
Similar to cabozantinib, vandetanib is used against unresectable or metastatic forms of medullary thyroid cancer. Patients with a RET mutation seem to have more benefit from vandetanib [38]. It was authorized by EMA in February 2012 and the patent is expected to expire in August 2028. Although vandetanib was authorized by FDA almost a year earlier (April 2011), the patent is expected to expire in August 2028, leaving a long market exclusivity of more than 17 years.

Regorafenib (Stivarga)
Regorafenib is a tyrosine and serine/threonine kinase inhibitor. In addition to inhibiting several tyrosine kinases, it also inhibits the serine/threonine kinase *BRAF*. It is used against metastatic colorectal cancer (CRC) which has previously failed treatments, such as fluoropyrimidine-based chemotherapy, anti-VEGF therapy or anti-EGFR therapy, see SmPC. Furthermore, it is also used against metastatic GIST. It was authorized by EMA in August 2013 and the patent is expected to expire in August 2028. Regorafenib was authorized by FDA almost a year earlier (September 2012), but the US patent is expected to expire in July 2024.

Sorafenib (Nexavar)
Sorafenib is used against hepatocellular carcinoma [39], refractory RCC [40] and refractory differentiated thyroid carcinoma. It received EMA authorization in July 2006 and the patent is expected to expire in July 2021. In the US sorafenib was authorized by FDA in December 2005 and the patent is expected to expire in December 2020.

Sunitinib (Sutent)
Sunitinib is used against unresectable or metastatic GIST after failure with imatinib treatment [41]. Furthermore, it is indicated in metastatic RCC [42] and unresectable or metastatic pancreatic neuroendocrine tumours (pNET) [43]. It was authorized by EMA in July 2006 and the patent is expected to expire in July 2021. Likewise, sunitinib was authorized by FDA the same year (January 2006) and the US patent is expected to expire in February 2021.

Mechanism of action and clinical indication of serine/threonine kinase inhibitor

Targeting *BRAF*

Cancer cells contain multiple genetic and epigenetic abnormalities. Despite this complexity, their growth and survival can often be impaired by the inactivation of a single oncogene. *BRAF* is a possible candidate for 'oncogene addiction' as it is known and is often mutated in codon 600 in melanoma, making it an attractive drug target.

Dabrafenib (Tafinlar)
Dabrafenib is used against unresectable or metastatic melanoma containing the *BRAF* V600E mutation, see SmPC. It was authorized by EMA in August 2013 and the EU patent is expected to expire in May 2029. Similarly, dabrafenib was authorized by FDA in May 2013 and the patent is expected to expire in January 2030, leaving almost 17 years of market exclusivity in the US as well as in the EU.

Trametinib (Mekinist)
Like dabrafenib, trametinib is used against melanomas containing the activating *BRAF* V600E or V600K point mutation [44]. It was authorized by EMA in June 2014 and the EU patent is expected to last until July 2029. However, trametinib was authorized by FDA in May 2013 and the patent is expected to expire in September 2025, resulting in three years less market exclusivity in the US.

Vemurafenib (Zelboraf)
Like the previous two drugs, vemurafenib is used against unresectable or metastatic melanoma containing the *BRAF* V600E mutation [45]. It was authorized by EMA in February 2012 and the patent is expected to expire in February 2027. Vemurafenib was authorized by FDA in August 2011 and the US patent is expected to expire in June 2029, resulting in an extended almost 18 years of US market exclusivity.

Discussion

There is no direct link between date of market authorization and date of patent expiry, beyond deducing how much market exclusivity is left. If the date of patent registration and date of submission for market authorization were recorded, one could have made assumptions on the time of product development whether relatively short or very long. The fact that a significant period of patent life is still left for most drugs leads us to conclude that the drug development time was not significantly long. An analysis of the European public assessment reports for a sample of the drugs would give one an idea of the size of the clinical trials for example, and hence, the scope of the drug discovery and development work. We believe that the patenting strategy of the originator company is the most important factor in the market exclusivity periodic sought.

Since market exclusivity for these drugs exceed 10 years, is their high price justified? It would be very difficult to find objective data for this. For some drugs market exclusivity exceeds 15 years. It could be argued that this is more than enough time to recoup their investment and make substantial profits for their investors. However, due to the rapid development of new and better TKIs, it is unlikely that all of these compounds will be in use for the full time of their market exclusivity.

Over the last two decades pharmaceutical companies have raced to introduce and patent promising kinase inhibitors. As a result of market exclusivity, the high price of these branded drugs makes cancer treatment costly and can hamper accessibility to novel cancer drugs. Therefore, it is of interest to know when patents expire and generic versions will allow real market competition.

We have provided a comprehensive overview of the clinically approved kinase inhibitors in the EU and US as of 2015. Most of the clinically approved kinase inhibitors are used to treat types of leukaemia, although indications are being expanded to other types of cancer. The last three years have seen a great rise in the clinical approval of kinase inhibitors.

Market exclusivity for almost all drugs is more than 10 years, averaging around 14–15 years. One drug (vemurafenib) could create a stunning 18 years of market exclusivity and some even beyond the 20-year patent protection limit (Nilotinib in the EU and dasatinib and imatinib in the US). It shows how important patent strategies and early access to the market are for the pharmaceutical industry.

A note of caution is warranted. Patent expiry dates are not as stable as one might expect. A patent only stands as long as it has not been challenged and overruled. The pharmaceutical industry is constantly battling over patents in the legal arena. The data we have presented in this paper is the best we, as clinical researchers, could find using publicly accessible (and sometimes confidential) resources. In addition, it is also possible that later on patents will be extended based on new data. Therefore, our data are presented without any guarantee on accuracy.

Conclusion

There are considerable differences in length of market exclusivity of this class of medicines after they enter the market. In addition, interesting differences exist between the EU and the US, although it is not possible to draw general conclusions about these differences. With the data we have generated, bodies involved in drug reimbursement may be able to better plan their negotiation and access strategies in order to optimize patient access to this important class of medicines.

Acknowledgement

Editorial assistance by Ms Judith Martin, BSc(Pharm), was highly appreciated.

Funding source
Stichting STOPhersentumoren.nl

Competing interests: The authors declare no competing financial interests in relation to this paper.

Provenance and peer review: Not commissioned; externally peer reviewed.

Author's note
This paper is neither a research article (although much research has been invested in allocating and searching sources), nor a formal systematic review. It is an attempt to collect information on duration of market exclusivity of a very cost intensive group of non-biological targeted small molecules, and to make this information available in the public domain. Due to the methodology followed, we are not able to provide 100% transparency on the sources used, because in some cases we could only retrieve the data from pharmaceutical companies on an anonymity basis, and the information is not publicly accessible. We agree this is not ideal, hence the need for this paper, but we believe this is the best you can get. In this respect, the paper is original – you cannot find this compiled information anywhere else in the public domain.

The paper finds its roots in a research project on drug repurposing (looking at new applications for existing drugs), as we noticed that it was extremely difficult to find reliable data on patent expirations for the group of TKIs. From our previous work [1], we know what happens with drug costs if the patent expires, and for the sake of allocating healthcare resources, insight in expiring patents can be relevant for formulary decisions in the hospital.

Authors
Subramanian Venkatesan[1], MSc, Research Student
Associate Professor Martine Lamfers[1], PhD
Professor Sieger Leenstra[1], MD, PhD
Professor Arnold G Vulto[2], PharmD, PhD, FCP

[1]Department of Neurosurgery
[2]Department of Hospital Pharmacy
Erasmus MC, 80 Wytemaweg, NL-3015 CN Rotterdam, The Netherlands

References
1. Dylst P, Vulto A, Simoens S. Societal value of generic medicines beyond cost-saving through reduced prices. Expert Rev Pharmacoecon Outcomes Res. 2015;15(4):701-11.
2. Prescribing outlook – new medicines 2016. Specialist Pharmacy Service. 2016.
3. Derbyshire M. Patent expiry dates for best-selling biologicals. Generics and Biosimilars Initiative Journal (GaBI Journal). 2015;4(4):178-9. doi:10.5639/gabij.2015.0404.040
4. Greenman C, Stephens P, Smith R, Dalgliesh Gl, Hunter C, Bignell G, et al. Patterns of somatic mutation in human cancer genomes. Nature. 2007;446(7132):153-8.
5. Knight ZA, Lin H, Shokat KM. Targeting the cancer kinome through polypharmacology. Nat Rev Cancer. 2010;10(2):130-7.
6. Akritopoulou-Zanze I, Hajduk PJ. Kinase-targeted libraries: the design and synthesis of novel, potent, and selective kinase inhibitors. Drug Discov Today. 2009;14(5-6):291-7.
7. Redaelli S, Piazza R, Rostagno R, Magistroni V, Perini P, Marega M, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009;27(3):469-71.
8. Khoury HJ, Cortes JE, Kantarjian HM, Gambacorti-Passerini C, Baccarani M, Kim DW, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood. 2012;119(15):3403-12.
9. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362(24):2260-70.
10. Talpaz M, Shah NP, Kantarjian H, Donato N, Nicoll J, Paquette R, et al. Dasatinib in imatinib-resistant philadelphia chromosome-positive leukemias. N Engl J Med. 2006;354(24):2531-41.
11. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the philadelphia chromosome. N Engl J Med. 2015;344(14):1038-42.
12. Apperley JF, Gardembas M, Melo JV, Russell-Jones R, Bain BJ, Baxter EJ, et al. Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. N Engl J Med. 2002;347(7):481-7.
13. Cools J, DeAngelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1 L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med. 2003;348(13):1201-14.
14. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002;347(7):472-80.
15. McArthur GA, Demetri GD, van oosterom A, Heinrich MC, Debiec-Rychter M, Corless CL, et al. Molecular and clinical analysis of locally advanced dermatofibrosarcoma protuberans treated with imatinib: Imatinib Target Exploration Consortium Study B2225. J Clin Oncol. 2005;23(4):866-73.
16. Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362(24):2251-9.
17. Cortes JE, Kantarjian H, Shah NP, Bixby D, Mauro MJ, Flinn I, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. N Engl J Med. 2012;367(22):2075-88.
18. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507-16.
19. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369(1):32-42.
20. Brennan CW, Verhaak RG, McKenna A, Campos B, Noushmehr H, Salama SR, et al. The somatic genomic landscape of glioblastoma. Cell. 2013;155(2):462-77.
21. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer. 2007;7(3):169-81.
22. Yeh P, Chen H, Andrews J, Naser R, Pao W, Horn L. DNA-mutation Inventory to Refine and Enhance Cancer Treatment (DIRECT): a catalog of clinically relevant cancer mutations to enable genome-directed anticancer therapy. Clin Cancer Res. 2013;19(7):1894-901.
23. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327-34.
24. Mitsudomi T, Yatabe Y. Mutations of the epidermal growth factor receptor gene and related genes as determinants of epidermal growth factor receptor tyrosine kinase inhibitors sensitivity in lung cancer. Cancer Sci. 2007;98(12):1817-24.
25. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non–small-cell lung cancer. N Engl J Med. 2005;353(2):123-32.

26. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007;25(15):1960-6.
27. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004;350(21):2129-39.
28. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006;355(26):2733-43.
29. Camidge DR, Doebele RC. Treating ALK-positive lung cancer – early successes and future challenges. Nat Rev Clin Oncol. 2012;9(5):268-77.
30. Bergethon K, Shaw AT, Ou SH, Katayama R, Lovly CM, McDonald NT, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol. 2012;30(8):863-70.
31. Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, AHN Mj, De Pas T, Besse B, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013;368(25):2385-94.
32. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366(9):799-807.
33. Rixe O, Bukowski RM, Michaelson MD, Wilding G, Hudes GR, Bolte O, et al. Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. Lancet Oncol. 2007;8(11):975-84.
34. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011;378(9807):1931-9.
35. Kurzrock R, Sherman SI, Ball DW, Forastiere AA, Cohen RB, Mehra R, et al. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. J Clin Oncol. 2011;29(19):2660-6.
36. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013;369(8):722-31.
37. Sleijfer S, Ray-Coquard I, Papai Z, Le Cesne A, Scurr M, Schöffski P, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European Organisation For Research And Treatment Of Cancer–Soft Tissue and Bone Sarcoma Group (EORTC Study 62043). J Clin Oncol. 2009;27(19):3126-32.
38. Wells SA, Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012;30(2):134-41.
39. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90.
40. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356(2):125-34.
41. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368(9544):1329-38.
42. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115-24.
43. Raymond E, Dahan L, Raoul J-L, Bang Y-J, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):501-13.
44. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012;367(18):1694-703.
45. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507-16.

DOI: 10.5639/gabij.2017.0602.016