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CCR Perspectives in Drug Approval

Clinical Cancer Research

Is the European Pediatric Medicine Regulation Working for Children and Adolescents with Cancer?

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Abstract

The European Pediatric Medicine Regulation was launched in 2007 to provide better medicines for children. Five years later, the number of new anticancer drugs in early development in the pediatric population remains low, and most children with cancer are still largely denied access to innovative drugs in Europe, as compared with the United States. We analyzed individual pediatric investigation plan (PIP) and waiver decisions for oncology drugs and all oncology drugs that have been approved for marketing authorization since 2007 in Europe. Among the 45 approved PIPs, 33% concern leukemias and lymphomas, 29% solid tumors, 13% brain tumors, and 20% a drug for supportive care. No specific PIP exists for life-threatening diseases such as high-risk neuroblastoma, whereas there are several PIPs in extremely rare malignancies in children and adolescents such as gastrointestinal stromal tumor, melanoma, thyroid cancer, and chronic myeloid leukemia. This paradoxical situation is due to approval of a PIP being driven by the adult indication. Twenty-six of 28 authorized new oncology drugs have a potentially relevant mechanism of action for pediatric malignancies, but 50% have been waived because the adult condition does not occur in children. The most striking example is crizotinib. Implementation of the pediatric regulation should no longer be driven by the adult indication but should be guided instead by the biology of pediatric tumors and the mechanism of action of a drug. This change will be achievable through voluntary PIPs submitted by Pharma or revocation of the oncology class waiver list. *Clin Cancer Res; 19(6); 1315–25. ©2013 AACR.*

Introduction

On January 26, 2007, the Pediatric Medicine regulation was launched in Europe to provide better medicines for children (1). This regulation is based on rewards, incentives, and obligations for pharmaceutical companies.

In brief, the marketing-authorization application for a new medicinal product (or a new indication, new pharmaceutical form, or new route of administration) must include the results of studies conducted in the pediatric population in compliance with an agreed pediatric investigation plan (PIP). The development can be deferred until sufficient data are available to show the efficacy and safety of the product in adults (deferral). Waivers may be granted when a pediatric development is not needed or not appropriate (for example, when a disease, such as Alzheimer disease, does not occur in the pediatric age group). Once authorization is obtained and study results are included in the product information, even when results are negative, the medicine is eligible for a 6-month supplementary protection certificate (SPC) extension.

The regulation was expected to facilitate access to anticancer drugs that are in development in adults and to increase significantly the number of those drugs in clinical development for children and adolescents in Europe (2). As a result, in the pediatric oncology community, there was great anticipation and hope for children suffering with cancer. Despite major improvements in the treatment of pediatric malignancies (up to 80% of children with cancer can be cured with current therapies; ref. 3), cancer remains the most common cause of death by disease in children over the age of 1 year. Each year, 3,000 children and adolescents die of cancer in Europe (4). Thus, an urgent need remains for new effective and safe drugs.

After nearly 5 years of the regulation being in place (as of June 2012), 45 PIPs have been approved for 43 oncology drugs (5). Oncology has the second highest number of PIPs after endocrinology (6).

However, the number of new oncology drugs in pediatric early-phase trials remains low in Europe, and most pediatric patients with a relapsed or refractory disease unlikely to be cured with conventional therapy are still denied access to an innovative drug in clinical trials. This situation raises major safety, ethical, and societal concerns. When a new drug is not available in a clinical trial, European pediatric oncologists are often compelled to prescribe it off-label.

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Moreover, many parents are tempted to go to the United States to have their child participate in a clinical trial with innovative drugs that may represent a "last hope" for many families. Possibly as a result of the National Cancer Institute—Clinical Therapy Evaluation Program (NCI-CTEP), a publicly funded academic program to develop drugs that are provided free by pharmaceutical companies, a significantly larger number of drugs are being investigated in early trials in the United States than in Europe. Parents often make major sacrifices to cover the cost for such treatments, feeling that they "need to have done everything possible" before accepting a palliative outcome.

What are the reasons for this paradoxical situation: a reasonable number of oncology PIPs approved but no significant increase in new drugs in clinical development in Europe? The purpose of this article is to analyze current publicly available information about PIPs and waivers for oncology drugs to answer this question and to propose solutions to improve the current situation.

Materials and Methods

The European Medicine Agency's (EMA) decision on a PIP, a waiver, or a modification of an agreed PIP is publicly available on the EMA website for each individual product (5). For each PIP, the decision describes the pediatric conditions and indications, the subset(s) of the pediatric population required by the pediatric development (mainly age ranges), and the titles of the studies to be conducted. The start of some of these studies may be deferred. The need for long-term follow-up and the date for completion of the PIP are stated.

We analyzed all individual decisions for oncology drugs and drugs for supportive care to assess whether these PIPs meet the needs of children with cancer.

A waiver for development in children can be issued when a drug is (i) likely to be ineffective or unsafe in part or all of the pediatric population, (ii) intended for conditions that occur only in adult populations, or (iii) does not represent a significant therapeutic benefit over existing treatments for pediatric patients. To facilitate and speed up the process, a list of conditions that occur only in the adult population has been adopted by the Pediatric Committee (class waiver list; Table 1), and all drugs intended to treat these conditions are exempt from the requirement for a PIP.

When analyzing individual decisions on a waiver as published on the website, it seems that information was not available about drugs that were known to be class waived. Because any drug approved after 2006 must have an agreed PIP or a waiver at the time of filing for marketed authorization, we analyzed the status of all oncology drugs approved since 2007 using information publicly available on the EMA website, and we cross-analyzed with the list of products with a PIP or a known waiver. This was an attempt to identify which drugs were likely to be class waived before filing for a marketed authorization in adults.

Results

As of June 2012, 45 PIPs had been approved for 43 oncology drugs (Table 2). These included 15 PIPs (33%) for the treatment of leukemias and/or lymphomas, 13 PIPs (29%) for malignant solid tumors, and 6 PIPs (13%) for the treatment of brain tumors. Nine PIPs (20%) concerned a medicine for supportive care to treat such symptoms or conditions as nausea and vomiting, secondary thrombopenia and anemia, tumor-lysis–related hyperuricemia, and mobilization of hematopoietic stem cells. The median duration of a PIP was 6 years, with a range from 1.5 to 26 years. The start had been deferred for 82% of these PIPs. No information is available on the current status of all PIPs. As of June 2012, 8 PIPs were supposed to be completed, whereas the remaining 37 PIPs still had a median of 73% of their duration to run.

PIPs have been approved for extremely rare malignancies in children such as chronic myeloid leukemia (CML), metastatic melanoma, gastrointestinal stromal tumor (GIST), and thyroid cancer. In some cases (e.g., CML), more than one drug has been approved for subsequent pediatric investigation. Indeed, these drugs have shown activity in these diseases in adults. This raises the issue of feasibility, in particular when several PIPs have to be run in parallel in malignancies occurring extremely rarely in children. The implementation of 6 PIPs (L-asparaginase, anti-Bcl2 ABT 263, pralatrexate, rituximab, SGN35, and pixantrone) for non-Hodgkin lymphomas may prove to be challenging as well. The current cure rate in non-Hodgkin lymphomas is high (more than 90%), and patients with relapsed or refractory disease eligible for new drug trials are rare. Only one PIP (approved in December 2008) has been successfully completed, leading to a full-marketed authorization. Everolimus (Votubia) was authorized in September 2011 for the treatment of subependymal giant cell astrocytoma associated with tuberous sclerosis complex in patients over the age of 3 years.

From July 2007 until June 2012, the marketed authorization of 28 new oncology drugs (generic compounds and drugs for supportive care excluded) has been approved by the EMA (Table 3). Only 2 drugs have a mechanism of action that is not relevant to a pediatric malignancy. Abiraterone is an androgen-biosynthesis inhibitor. Tegafur is 5-fluorouracil prodrug, and we know that 5-fluorouracil has little or no activity in pediatric malignancies. Among the 26 drugs with a potentially relevant mechanism of action, 4 drugs (15%) have been approved for use in children, namely everolimus, nelarabine, thiotepa, and an oral suspension of 6-mercaptopurine. At least one PIP has been approved for 8 of these drugs (30%). However, 14 drugs with a potentially relevant mechanism of action (50%) have been waived, with the vast majority having been class waived.

Discussion

Article 12 of the European regulation states that a waiver can be adopted when the disease or indication for which a drug is developed does not exist in children. The oncology class waiver list includes more than 20 adult malignancies that do not occur in children, such as breast cancer

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Table 1. List of class waiver: malignancies not occurring in children [from the EMA website (5)]

- Treatment of adenocarcinoma of the colon and rectum
- Treatment of adenocarcinoma of the pancreas
- Treatment of basal cell carcinoma
- Treatment of breast carcinoma
- Treatment of cervix and corpus uteri carcinoma
- Treatment of chronic lymphocytic leukemia
- Treatment of endometrial carcinoma
- Treatment of fallopian tube carcinoma (excluding rhabdomyosarcoma and germ cell tumors)
- Treatment of follicular lymphoma
- Treatment of gastric adenocarcinoma
- Treatment of gastric carcinoids
- Treatment of gastroenteropancreatic neuroendocrine tumors (excluding neuroblastoma, neuroganglioblastoma, and pheochromocytoma)
- Treatment of hairy cell leukemia
- Treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma, and rhabdoid tumors of the kidney)
- Treatment of liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma)
- Treatment of lung carcinoma (small cell and non–small cell carcinoma)
- Treatment of melanoma (from 0 to less than 12 years old)
- Treatment of primary myelofibrosis
- Treatment of mesothelioma
- Treatment of melanoma (from 12 to less than 18 years old; revoked July 14, 2008)
- Treatment of multiple myeloma
- Treatment of oropharyngeal, laryngeal, or nasal epithelial carcinoma (excluding nasopharyngeal carcinoma or lymphoepithelioma)
- Treatment of ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumors)
- Treatment of peritoneal carcinoma (excluding blastomas and sarcomas)
- Treatment of prostate carcinoma (excluding rhabdomyosarcoma)
- Treatment of ureter and bladder carcinoma
- Treatment of vaginal and vulvar carcinoma (excluding rhabdomyosarcoma and soft tissue sarcoma)
- Treatment of vulvar intraepithelial neoplasia

and kidney cancer (Table 1). A waiver can be claimed for any drug submitted for the treatment of these cancers in adults, even though its target or targeted pathway may have been established as potentially relevant for a pediatric malignancy.

The regulation seems to have simply ignored the fact that more than 90% of anticancer drugs used in pediatric malignancies to cure children are also used in adults but in different cancers. As an example, neuroblastoma is a pediatric malignancy of the sympathetic nervous system that occurs in young children. With current intensive multiagent chemotherapy and surgery, only 40% of children with a high-risk neuroblastoma are cured, and there is a major need for innovative therapies (7). Among the drugs used are anthracyclines, cyclophosphamide, cisplatin, and carboplatin, all of which are approved for breast, ovarian, or lung cancer. If the pediatric regulation would have been running for the past 30 years, a class waiver could potentially have been obtained and none of these drugs would have been studied in pediatric malignancies, including neuroblastoma. Fortunately, large academic phase III trials have been run in Europe and in the United States to establish standard treatments for high-risk neuroblastoma using those chemotherapy drugs that are not licensed in this disease, a practice widespread in pediatric medicine (8, 9). We cannot afford to allow the good intentions of the Pediatric Medicine regulation to hamper this academic endeavor.

In the United States, the Best Pharmaceuticals for Children Act (since 1997) is an incentive-based regulation that provides a patent extension for pharmaceutical companies providing information for the use of medicines in the pediatric population (1). This is a voluntary process based on an approved written request. The vast majority of oncology drugs with a written request were cytotoxic compounds, very few were innovative-targeted agents. In 2003, the Pediatric Research Equity Act (PREA) was passed to mandate the pediatric development of a medicine (excluding biologics) when relevant (1). However, the PREA refers only to drugs used for treatment of the same condition in adults and children. This is very much the same situation as the European class waiver list.

By way of an example, we can use crizotinib, a MET–ALK inhibitor, which proved to be an active treatment of lung cancer with an EML4–ALK translocation (10). The relevance to pediatrics is that NPM–ALK translocations are found in more than 60% of cases of anaplastic large cell lymphoma

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Table 2. Approved PIPs in pediatric oncology (as of June 2012)

Condition	Agent	Company	Pediatric indication	Date
Brain tumors	Cediranib	AstraZeneca	High-grade glioma	June 2, 2010
	Cilengitide	Merck KGA	High-grade glioma	August 30, 2011
	Bevacizumab	Roche	High-grade glioma	March 11, 2011
	AdenoTK	ARK Therapeutics	High-grade glioma	May 23, 2008
	Veliparib	Abbot	High-grade glioma	April 8, 2011
	Everolimus	Novartis	Subependymal astrocytoma	December 5, 2008
Leukemias and lymphomas	L-Asparaginase erythro	ERYtech Pharma	ALL	October 29, 2010
	Imatinib	Novartis	ALL	December 2, 2009
	6-Mercaptopurine	Stallegernes	ALL	April 20, 2009
	Elacytarabine	Clavis Pharma	Acute myeloid leukemia	February 28, 2012
	Decitabine	Jansen-Cilag	Acute myeloid leukemia	March 4, 2011
	Midostaurin	Novartis	Acute myeloid leukemia	January 3, 2011
	Nilotinib	Novartis	Chronic myeloid leukemia	March 27, 2009
	Bosutinib	Wyeth	Chronic myeloid leukemia	September 3, 2010
	Dasatinib	Bristol-Myers Squib	Chronic myeloid leukemia and Philadelphia$^+$ ALL	November 3, 2009
	L-Asparaginase	Medac	ALL and non-Hodgkin lymphoma	February 1, 2008
	ABT263 (anti-bcl2)	Abbot	ALL and non-Hodgkin lymphoma	December 14, 2009
	SGN-35	Takeda	Hodgkin and non-Hodgkin lymphoma	February 21, 2011
	Pralatrexate	Allotherapeutics	Non-Hodgkin lymphoma	December 2, 2010
	Rituximab	Roche	Non-Hodgkin lymphoma	July 14, 2009
	Docetaxel	Sanofi-Aventis	Nasopharyngeal carcinoma	May 16, 2008
Solid tumors	Sunitinib	Pfizer	GIST	February 24, 2009
	Ipilimumab	Bristol-Myers Squib	Melanoma	June 8, 2011
	Vemurafenib	Roche	Melanoma	April 8, 2011
	Dabrafenib	GlaxoSmithKline	Melanoma and solid tumors	February 27, 2012
	Trametinib	GlaxoSmithKline	Melanoma and solid tumors	February 28, 2012
	Ombrabuline	Sanofi-Aventis	Rhabomyosarcoma	June 7, 2011
	IGF-IR MoAb	Roche	Ewing tumors	April 20, 2009
	Pazopanib	GlaxoSmithKline	Rhabdomyosarcoma and Ewing tumors	January 3, 2011
	Bevacizumab	Roche	Rhabdomyosarcoma	October 1, 2008
	Linifanib (ABT869)	Abbot	Solid tumors	July 15, 2009
	Ipilimumab	Bristol-Myers Squib	Solid tumors	November 3, 2008
	Deforolimus	Merck Sharpe Dome	Solid tumors	January 25, 2010
	Vandetanib	Bristol-Myers Squib	Thyroid cancer	November 3, 2008
Mixed conditions	Cyclophosphamide	Keocyt	Malignant diseases	January 27, 2012
	Pixantrone	CTI Life	Non-Hodgkin lymphoma and solid tumors	January 16, 2010
	Treosulfan	Medac	Hematopoietic stem cell transplantation conditioning	June 7, 2011
Supportive care	Darbopoietin	Amgen	Anemia	March 11, 2011
	Denosumab	Amgen	Bone metastasis	October 14, 2008
	Plerixafor	Genzyme	Mobilization of hematopoietic stem cells	February 23, 2009
	Pegloticase	Savient Pharmaceuticals	Hyperuricemia	January 28, 2011
	Elthrombopag	GlaxoSmithKline	Secondary thrombopenia	September 30, 2011
	Casopitant	GlaxoSmithKline	Vomiting	January 27, 2009
	Aprepitant	Merck Sharpe Dome	Vomiting	November 3, 2008
	Fosaprepitant	Merck Sharpe Dome	Vomiting	July 15, 2009

Abbreviations: ALL, acute lymphoblastic leukemia; IGF-IR, insulin-like growth factor I receptor; MoAb, monoclonal antibody.

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Table 3. Status of new oncology drugs approved by the EMA since 2007 with regard to their development in children and adolescent

Common name	Medicine name	Marketing authorization holder	Year	Indication in adults	Approved for use in children	PIP	Pediatric indication in the PIP	Published waiver	Comment	Is the mechanism of action potentially relevant for pediatric malignancies?
Everolimus	Votubia	Novartis Europharm Ltd.	2011		1	1	SEGA associated with tuberous sclerosis complex	0	Drug authorized for treatment of patients ages 3 years and older; authorization was based on the completion of a PIP	1
Nelarabine	Atriance	Glaxo Group Ltd.	2007		1	0	T-cell ALL and T-cell lymphoblastic lymphoma	0	Drug indicated in children for the treatment of the same condition	1
Thiotepa	Tepadina	Adienne Srl	2010		1	0	HPCT in hematologic diseases and solid tumors in adult and pediatric patients	0	Drug indicated in children for the treatment of hematologic malignancies and malignant solid tumors	1
6-Mercaptopurine monohydrate	Xaluprine	Nova Laboratories Ltd.	2012		1	0	ALL in adults, adolescents and children.	0	First oral suspension of 6-mercaptopurine	1
Ipilimumab	Yervoy	Bristol-Myers Squibb Pharma EEIG	2011	Advanced melanoma	0	2	Melanoma; solid tumors	0		1
Everolimus	Afinitor	Novartis Europharm Ltd.	2009	Neuroendocrine tumors and renal cell carcinoma	0	1	SEGA associated with tuberous sclerosis complex	2	Waiver in neuroendocrine tumors and renal cell carcinoma; a PIP was approved for SEGA	1

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Table 3. Status of new oncology drugs approved by the EMA since 2007 with regard to their development in children and adolescent (Cont'd)

Common name	Medicine name	Marketing authorization holder	Year	Indication in adults	Approved for use in children	PIP	Pediatric indication in the PIP	Published waiver	Comment	Is the mechanism of action potentially relevant for pediatric malignancies?
Nilotinib	Tasigna	Novartis Europharm Ltd.	2007	Philadelphia-chromosome-positive chronic myelogenous leukemia	0	1	Chronic myelogenous leukemia	0		1
Plerixafor	Mozobil	Genzyme Europe B.V.	2009	Mobilization of hematopoietic stem cells	0	1	Mobilization of hematopoietic stem cells	0		1
Pazopanib	Votrient	Glaxo Group Ltd.	2010	Renal cell carcinoma	0	1	Soft tissue sarcomas	0	A class waiver was issued for renal cancer. Then a PIP was approved when the drug was developed in adult sarcomas	1
Pixantrone dimaleate	Pixuvri	CTI Life Sciences Ltd.	2012	Non-Hodgkin B-cell lymphoma	0	1	NHL leukemia	0		1
Vemurafenib	Zelboraf	Roche Registration Ltd.	2012	BRAF V600 mutation-positive unresectable or metastatic melanoma	0	1	BRAF V600 mutation-positive metastatic melanoma	0	Pediatric tumors other than melanoma have B-RAF mutations	1
Vandetanib	Caprelsa	AstraZeneca AB	2012	Thyroid cancer	0	1	Thyroid cancer		Vandetanib targets are altered in pediatric malignancies other than thyroid cancer	1
Lenalidomide	Revlimid	Celgene Europe Ltd.	2007	Multiple myeloma	0	0		2	Immunomodulating agent; ongoing pediatric development	1

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Common name	Medicine name	Marketing authorization holder	Year	Indication in adults	Approved for use in children	PIP	Pediatric indication in the PIP	Published waiver	Comment	Is the mechanism of action potentially relevant for pediatric malignancies?
Temsirolimus	Torisel	Pfizer Ltd.	2007	Renal-cell carcinoma	0	0		1	mTOR is a relevant target in pediatric malignancies; ongoing pediatric development	1
Lapatinib	Tyverb	Glaxo Group Ltd.	2008	HER2-positive (ErbB2) breast cancer (ErbB2):	0	0		1	Inhibitor of EGFR and HER2-neu receptors	1
Panitumumab	Vectibix	Amgen Europe B.V.	2007	Wild-type KRAS metastatic colorectal cancer	0	0		0	Monoclonal antibody inhibiting the EGFR TK receptor	1
Trabectedin	Yondelis	Pharma Mar S.A.	2007	Advanced soft tissue sarcoma	0	0		0	Cytotoxic compound to be evaluated in children; ongoing development in children with solid malignancies	1
Nab-paclitaxel	Abraxane	Celgene Europe Ltd.	2008	Metastatic breast cancer	0	0		0	Cytotoxic compound that proved to be more active than paclitaxel	1
Thalidomide	Thalidomide Celgene	Celgene Europe Ltd.	2008	Multiple myeloma	0	0		0	Immunomodulating agent	1
Azacitidine	Vidaza	Celgene Europe Ltd.	2008	Myelodysplastic syndromes, chronic myelomonocytic leukemia, acute myeloid leukemia	0	0		0	Ongoing development in children with leukemias	1

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Common name	Medicine name	Marketing authorization holder	Year	Indication in adults	Approved for use in children	PIP	Pediatric indication in the PIP	Published waiver	Comment	Is the mechanism of action potentially relevant for pediatric malignancies?
Vinflunine	Javlor	Pierre Fabre Médicament	2009	Transitional cell carcinoma of the urothelial tract	0	0		0	Vinca-alkaloids are a major class of drugs in the treatment of several pediatric malignancies	1
Gefitinib	Iressa	AstraZeneca AB	2009	Non–small cell lung carcinoma with activating mutations of EGFR-TK	0	0		0	Ongoing development in children with solid tumors	1
Ofatumumab	Arzerra	Glaxo Group Ltd	2010	Chronic lymphocytic leukemia	0	0		0	An anti-CD20 monoclonal antibody; CD20 is expressed on B lymphocytes and B-cell tumors (CLL and NHL)	1
Cabazitaxel	Jevtana	Sanofi-Aventis group	2011	Hormone-refractroy metastatic prostate cancer	0	0		0	A taxoid that crosses blood brain barrier. Studies in children are warranted	1
Eribulin mesylate	Halaven	Eisai Europe Ltd.	2011	Metastatic breast cancer	0	0		0	Tubulin-based antimitotic drug	1
Axitinib	Inlyta	Pfizer Ltd.	2012	Renal cell carcinoma	0	0		0	Angiogenesis is a major therapeutic target in pediatric malignancies as well	1

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Common name	Medicine name	Marketing authorization holder	Year	Indication in adults	Approved for use in children	PIP	Pediatric indication in the PIP	Published waiver	Comment	Is the mechanism of action potentially relevant for pediatric malignancies?
Tegafur/gimeracil/oteracil	Teysuno	Nordic Group BV	2011	Advanced gastric cancer	0	0		0	5-Fluorouracil did not show antitumor activity in pediatric malignancies	0
Abiraterone acetate	Zytiga	Janssen-Cilag International N.V.	2011	Metastatic castration-resistant prostate cancer	0	0		0	Androgen biosynthesis inhibitor; mechanism of action is not relevant for pediatric malignancies	0

Abbreviations: EGFR, EGF receptor; HPCT, hematopoietic progenitor cell transplantation; NHL, non-Hodgkin lymphoma; SEGA, subependymal giant cell astrocytoma; TK, tyrosine kinase.

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(ALCL), and ALK mutations are found in 8% to 10% of cases of sporadic neuroblastoma (11). The drug is approved for adult lung cancer in the United States and in Europe. Because lung cancer does not exist in children, the company was issued a class waiver in 2010, and no pediatric development was started in Europe. PREA waivers in the United States would similarly have resulted in crizotinib not being investigated in children. However, Best Pharmaceuticals for Children Act legislation resulted an a written request from the U.S. Food and Drug Administration (FDA) that was issued in 2010 and led to a phase I trial of crizotinib run by the Children's Oncology Group. The preliminary results showed responses (including prolonged complete remissions) in patients with ALK-mutated neuroblastoma and in ALCL (12). We are aware of 2 families who went from Europe to the United States to get access to crizotinib for their child. This is the perfect illustration of the negative impact of the class waiver list for children in Europe.

The European Union regulation is driven by the adult indication. This partly explains why there are 3 PIPs approved for the treatment of CML and 4 PIPs approved in metastatic melanoma, 2 rather common malignancies in adults but extremely rare malignancies in children. On the other hand, 50% of newly approved oncology drugs in Europe (since 2007) that exhibit a potentially relevant mechanism of action for pediatric malignancies have been class waived. We conclude that the implementation of the European Union pediatric regulation in pediatric oncology should no longer be driven by the adult indication. Because a revision of the regulation will not be considered before 2017, there is an urgent need to modify its implementation.

Pharmaceutical companies can submit a voluntary PIP, for example, an investigation plan to study a drug in a pediatric cancer that is different from the adult indication. The V600 *BRAF* mutation is found in 40% to 60% of melanomas. The incidences of melanoma in children (<12 years) and adolescents (>12 years) are 7 and 13 per million, respectively, and the overall survival is more than 90% (13). In children, V600 *BRAF* has been observed in gangliogliomas, pilocytic astrocytomas, pleomorphic xanthoastrocytoma (14), and Langherans cell histiocytosis (15). Vemurafenib is approved in the United States and Europe for the treatment of V600 *BRAF*–mutated melanoma (16), and a PIP has been approved but only for pediatric patients from 12 to less than 18 years old with V600 *BRAF* mutation–positive unresectable stage IIIC or stage IV melanoma (4). This PIP was based only on the adult indication rather than on the target.

Dabrafenib is another V600 *BRAF* inhibitor in development for use in melanoma. A voluntary PIP has been recently approved for dabrafenib in the indication of advanced V600 *BRAF* pediatric solid tumors, including melanoma in children over the age of 12 years (5). Thus, children with *BRAF*-mutated tumors will have access to a relevant targeted drug, and importantly the program will define whether dabrafenib is active in tumors other than melanoma as well.

Another way of improving the PIP process in pediatric oncology would be simply to revoke the EMA class waiver list and to consider the drug mechanism of action, using widespread existing knowledge of the biology of pediatric malignancies instead of the adult condition (17). As a result, an ALK inhibitor for the treatment of lung cancer would no longer be waived for a pediatric development in children with neuroblastoma or ALCL. We ask for science-driven PIPs that meet the needs of children with cancer.

Several international cooperative groups dedicated to early drug development, such as the Innovative Therapies for Children with Cancer European network, run a biology-driven new drug development strategy for children with cancer (18). This strategy is based on identification and validation of relevant targets in pediatric malignancies to choose and prioritize drugs to be developed in children through innovative designs using biomarkers. This strategy is in line with the voluntary PIP for dabrafenib, and it may become the rule if the class waiver list is revoked. We believe that the changes we are asking for will increase the feasibility and relevance of oncology PIPs. In addition, a significant increase in cooperation is needed between the cooperative groups, the regulatory agencies and the pharmaceutical companies to run biology-driven drug development and mechanism of action–based PIP. Then the European Union pediatric regulation will meet the needs of children with cancer and safe and effective innovative drugs will be introduced in standard care.

Conclusions

Pediatric development of anticancer drugs is now being actively affected by the European Pediatric Medicine Regulation worldwide. However, the regulation failed so far to facilitate an increase of early drug trials in Europe and many children with advanced malignancies are still denied access to innovative drugs. The process whereby PIPs are driven by the adult indication rather than by the biology of tumors and the mechanism(s) of action of the drug is a major barrier. Targeted voluntary PIPs as well as the revocation of the oncology class waiver list are potentially effective solutions. In addition, an increase in the early collaboration of EMA, Pediatric Committee, and pharmaceutical companies with the Pediatric Oncology Cooperative Groups as well as parents' advocacy groups is mandatory to ensure that PIPs are feasible, scientifically robust, and most importantly, meet the needs of children with cancer.

Disclosure of Potential Conflicts of Interest

G. Vassal is a consultant/advisory board member of GSK and Roche. B. Geoerger is a consultant/advisory board member of GSK. No potential conflicts of interest were disclosed by the other author.

Authors' Contributions

Conception and design: G. Vassal, B. Geoerger, B. Morland
Development of methodology: G. Vassal, B. Geoerger
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G. Vassal, B. Geoerger
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. Vassal, B. Geoerger
Writing, review, and/or revision of the manuscript: G. Vassal, B. Geoerger, B. Morland
Study supervision: G. Vassal

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