



Are Regulatory Age Limits in Pediatric Melanoma Justified?

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Introduction

The incidence of pediatric melanoma depends on the age range used to define it. There is only vague consensus about age limits; ages in the literature range from ≤ 10 to ≤ 21 years.^{1,2} The number of patients available for recruitment into a clinical trial is small and also depends on whether conventional melanoma is differentiated from other subtypes by genome-based methods^{3,4} and the number of new, life-prolonging treatments, beyond early tumor excision, being studied.^{5–7} Legal/regulatory attempts to improve pediatric drug treatment^{8–10} are based on the assumption that children are therapeutic orphans.¹¹ The US Food and Drug Administration (FDA) offers rewards for voluntary pediatric melanoma studies. The European Medicines Agency (EMA) demands pediatric investigation plans (PIPs) for new drugs unless the targeted disease is PIP-exempted; pediatric melanoma is not. The FDA has issued several written requests (WRs) that offer patent extension for pediatric studies, including 1 for ipilimumab.¹² The EMA has issued 12 melanoma PIPs.^{10,13} WR/PIP-demanded studies compete for the same, small number of pediatric patients with melanoma.

This article reviews justification and design of pediatric melanoma trials, inter-relationship between pediatric melanoma WR/PIP-related trials, and alternative approaches to advancing pediatric melanoma treatment.

Methods

The background and interactions between the FDA ipilimumab WR and EU melanoma PIPs were examined through a review of FDA and EMA documents and WR/PIP-related pediatric melanoma studies listed in ClinicalTrials.gov and/or ClinicalTrialsRegister.eu. This review focused only on pediatric studies, and did not include company-sponsored adult cancer drug studies that also allow(ed) adolescents aged ≥ 15 or ≥ 16 years to enroll. Studies were analyzed to see whether they make/made medical sense, were/are feasible, and their potential to improve or harm any individual patient.

Published ipilimumab studies were identified by a PubMed search using the terms *ipilimumab* and *children*. FDA and EMA decisions were identified by searches of the agencies' websites and by Google searches.

Results

The FDA ipilimumab WR

Companies can propose a voluntary pediatric study program to the FDA for patent-protected drugs. If accepted, the FDA issues a WR. Once/if the company has performed the requested studies, it gets Pediatric Exclusivity, which keeps generic drug copies off the market for 6 months.⁸ Only the ipilimumab WR was found on the Internet,¹² although WRs were also issued for dabrafenib, cobimetinib, and nivolumab.¹⁴ The ipilimumab WR states that there is “no approved treatment for pediatric patients with metastatic melanoma,” mentions that prepubescent patients appear to have different disease characteristics, acknowledges that adolescents

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Table 1
Food and Drug Administration-requested ipilimumab written request studies.

Study	Abbreviated study description	Age, y
1	Open-label dose escalation study in pediatric patients with refractory cancers	1–21
2	Pharmacokinetics and safety study in patients with unresectable or metastatic melanoma	12–17
3	Antitumor activity in relapsed or treatment-refractory solid tumors other than melanoma	12–17
4	If further evaluation of ipilimumab is warranted based on results of studies 1, 2, or 3, or 1 or more safety and efficacy studies in specific pediatric indications	1–17, if appropriate

Table 2
Ipilimumab melanoma pediatric investigation plan-demanded studies.¹⁸

Study	Study description
1	Open-label, dose escalation clinical trial of intravenously administered ipilimumab in children from ages 3–<18 y (and adults) with untreatable, refractory, or relapsed solid malignant tumors to evaluate pharmacokinetics and safety
2	Open-label, multicenter, single-arm clinical trial of intravenously administered ipilimumab in children aged 12–<18 y with untreated or previously treated advanced/metastatic melanoma to evaluate efficacy and safety
3	Open-label randomized active-controlled study of adjuvant ipilimumab anti-CTLA4 therapy vs high-dose interferon α -2b in children aged 12–<18 y (and adults) with resected high-risk melanoma to evaluate efficacy, safety, and tolerability

Table 3
Written request/pediatric investigation plan-related completed/terminated melanoma studies listed in ClinicalTrials.gov.

Study	Compound	Abbreviated study description	NCT #	Age, y
1	Ipilimumab	S&E in treatment-resistant cancer	NCT01445379	2–21
2	Ipilimumab	Previously treated or untreated unresectable stage III or IV melanoma	NCT01696045	12–17
3	Vemurafenib	Stage IIIC or IV melanoma harboring BRAFV600 mutations	NCT01519323	12–17

are comparable to adults regarding primary tumor characteristics, and requests the studies listed in Table 1. The ipilimumab WR was preceded by a National Cancer Institute-conducted pediatric melanoma study NCI7458 that started in 2008,¹⁵ which is identical to study 1 in Table 1 and is listed on ClinicalTrials.gov.¹⁵

Ipilimumab PIP studies

The EMA approved 2 ipilimumab PIPs, 1 for malignant neoplasms other than melanoma; nervous system, hematopoietic, and lymphoid tissue tumors; and 1 exclusively for melanoma.¹⁶ The studies required in the 2011 melanoma PIP are listed in Table 2. The first 2 correspond to the WR-studies listed in Table 1.

Phase I clinical trial of ipilimumab in pediatric patients with advanced solid tumors

This publication included 33 patients aged 2 to 21 years with different solid malignant tumors. It corresponds to study 1, Table 1, and study 1, Table 2. In ClinicalTrials.gov, 29 completed patients were reported, including 12 melanoma patients, but their ages were not given.¹⁵ The ClinicalTrials.gov study description claimed that ipilimumab was considered an experimental drug because it had not been tested in children, adolescents, or young adults.^{15,16} The principal investigator listed in ClinicalTrials.gov is the publication's first author.¹⁷

Completed/terminated WR/PIP-requested pediatric melanoma studies

Table 3 lists pediatric melanoma studies found in ClinicalTrials.gov or ClinicalRegister.eu that are related to WRs or PIPs.¹⁰ Studies 1 and 2 in Table 3 correspond to studies 1 and 2 in Tables 1 and 2, respectively; that is, to the first 2 ipilimumab studies requested in both the ipilimumab WR¹ and in the first ipilimumab melanoma PIP.¹⁸

Two pediatric melanoma studies terminated in 2016

The second ipilimumab study listed in Tables 1 and 2 is discussed in the FDA clinical review,¹⁹ led to FDA ipilimumab

approval in patients aged ≥ 12 years,²⁰ and is discussed in an academic publication.²¹ Conducted globally in 2013–2016, it originally planned to recruit 40 patients. When terminated, 14 patients had been enrolled, of whom 12 were treated with ipilimumab. It closed early due to both poor recruitment, because data on clinical benefit in adults treated with ipilimumab plus nivolumab emerged, and because pediatric trials of combination therapy had opened.¹⁹ The academic publication states that the study was terminated due to slow accrual and due to registration of ipilimumab in adults²¹; however, it does not mention that in the meantime combination treatment of ipilimumab plus nivolumab had been FDA-approved, a treatment with superior efficacy in comparison to ipilimumab monotherapy. The vemurafenib study (study 3, Table 3)²² recruited in 2012–2016 and was terminated due to slow recruitment. It corresponds to the study described in the vemurafenib PIP.⁸ The median age of the 6 recruited patients was 15.8 years.^{9,10,22}

Ongoing pediatric monotherapy studies in melanoma and other solid tumors

Four PIP-demanded international studies on systemic monotherapy with pembrolizumab,²³ dabrafenib,²⁴ paclitaxel,²⁵ and cobimetinib²⁶ are currently treating patients with solid malignancies, including melanoma.¹⁰ Furthermore, the PIP-demanded talimogene laherparepvec study (EMA-001251-PIP01-11-M03) recruits for intralesional administration in advanced malignant noncentral nervous system tumors. All ongoing pediatric melanoma studies are listed in Table 4.

PIP modifications

The ipilimumab melanoma PIP was modified 7 times. Table 5 shows the latest clinical study requirements.²⁷ The FDA had released the developer from the WR obligation to perform study 3 (Table 1)²⁸; the modified PIP reflects their agreement with this FDA decision. Studies 4 and 5 in Table 5 were recently added.

Table 4
Ongoing pediatric investigation plan-related industry-sponsored pediatric studies.

Study	Drug	Patients	Study description	NCT #	Centers	Countries	Age
1	Pembrolizumab	310	Advanced melanoma or advanced R/R PDL1-positive solid tumors or lymphoma	NCT02332668	47	United States, Australia, Brazil, Canada, European Union, Israel, South Korea, New Zealand, Sweden	6 mo–17 y
2	Dabrafenib	86	Advanced BRAF V600 mutation-positive solid tumors	NCT01677741	25	United States, European Union, Israel	1–17 y
3	Paclitaxel	134	R/R solid tumors	NCT01962103	21	United States, Canada, European Union, Switzerland	6 mo–≤ 8 y (Ph1) 2–≤24 y (Ph2)
4	Cobimetinib	50	Previously treated solid tumors	NCT02639546	41	European Union, United States, United Kingdom, Israel, Switzerland	6 mo–17 y (DES Ph) 6–30 y (EXT Ph)
5	Talimogene Laherparepvec	18	S of intralesional administration in advanced non-CNS tumors	NCT02756845	18	United States, Canada, France, Spain, Switzerland	2–21 y

DES=dose escalation; EXT Ph=extension phase; Ph1=Phase I; Ph2=Phase II; R/R=relapsed/resistant; S=safety.

Table 5

Clinical studies demanded by the ipilimumab pediatric investigation plan EMEA-000117-PIP02-10-M07.²⁷

Study	Study description
1	OL DES PK and S of i.v. ipilimumab in untreatable, R/R solid malignant tumors
2	OL MC E&S study of i.v. ipilimumab in patients aged 12–17 y with untreated or previously treated a/m melanoma
3	Deleted in procedure EMEA-000117-PIP02-10-M07
4	Population PK analysis of ipilimumab in adult and pediatric cancer patients
5	Model-based simulation to determine a dose regimen for adolescent melanoma patients

a/m=advanced/metastatic; DES=dose escalation; E&S=efficacy & safety; i.v.=intravenous; MC=multicenter; OL=open label; PK=pharmacokinetics; R/R=relapsed/resistant; S=safety.

Discussion

Medicine, law, therapeutic orphans, and pediatric melanoma studies

The FDA statement that “no approved treatment for pediatric patients with metastatic melanoma” exists is legally correct, but medically wrong.⁹ Qualified physicians can prescribe ipilimumab regardless of patient age. The FDA is disallowed by law from telling physicians what to do.^{29,30} Pediatric patients with melanoma are human beings, not another species. Medicine is a profession of physicians, not lawyers.^{31,32} Medically, there is approved treatment for pediatric patients with metastatic melanoma.

Shirkey claimed children were “therapeutic orphans” when in fact the legislation used only “human beings” without differentiating adults from children.³³ However, the 1962 Act also transferred jurisdiction over the advertising of prescription drugs to the FDA,³⁴ which prompted companies to insert pediatric warnings into drug labels as protection against damage lawsuits. The American Academy of Pediatrics claimed the use of drugs inadequately studied in children created potential dangers of drug toxicities in children of all ages,³⁵ and pediatric clinical pharmacologists pointed to “continued pediatric therapeutic disasters,”³⁶ but the clinical cases used to support these claims were in newborns rather than older children or adolescents.^{35,36} The therapeutic orphans concept was founded on exaggerated alarmist statements. The American Academy of Pediatrics support and the FDA’s desire to resolve the therapeutic orphans problem eventually led to US legislation requiring separate pediatric registration studies based on chronological age.⁹ A legal rather than a physiologic definition of childhood was used in a medical context. Although this appeals to society’s protective instincts, it is problematic. The date of birth is appropriate for administrative uses (eg, for marriage, a drivers’ license, and contracts), but not to define physiological maturity.⁹

When no life-prolonging treatment was available, patient age was mainly an academic/semantic issue. Emerging opportunities to drastically modify disease progression^{5–7} and increasing ability to differentiate between different forms of melanoma make the use of chronological age limits alone to select melanoma

treatment questionable. Genomic analyses have shown that conventional melanoma is comparable in pediatric, adolescent, and adult patients; therefore, the same treatment is indicated. This is not true for Spitz nevus, Spitzoid melanoma, or melanoma arising in a giant congenital nevus.^{3,4}

Ipilimumab pediatric dose escalation study

FDA- and EMA documents^{16,19} focus on the need to find a cure for various cancer types, express the firm belief that all pediatric patients need separate adult-style proof-of-safety and efficacy trials, and suggest that the only hope of finding a so-called golden bullet is by exposing various pediatric cancer patients to new compounds such as is done in adults. But this approach may not work in minors, especially when the total number of patients is much smaller.

When ipilimumab was in early development, it was still unknown in which cancer types it would work. The meanwhile completed ipilimumab study started in 2008.¹⁵ The developing company was involved in study planning and the PIP negotiations, as reflected in study 1 Tables 1 and 2, respectively.^{12,17–19} Ipilimumab was FDA-approved in 2011 for unresectable or metastatic melanoma. After this date, studies were no longer Phase I; ipilimumab was no longer an experimental treatment. The patients in the pivotal FDA registration study were aged 18 to 84 years.³⁶ The study rationale^{15,17} was no longer true from 2011 on when data for patients aged ≥18 years were publicly available.³⁷ The continuing recruitment of young adults into a so-called pediatric dose escalation study of an FDA-approved drug³⁷ became ethically questionable. This is especially problematic because the study included an initial dose below the accepted adult dose; which would expose older adolescent patients to suboptimal dosing. This raises questions about the adequacy of the consent used to recruit subjects. Some information beyond the publication¹⁷ was found in the FDA clinical review. Seven melanoma patients were aged <12 years, but 5 were aged ≥12 years; it does not indicate whether the melanoma patients had so-called conventional melanoma. None of the PIPs, WR, or published study rationale differentiated between

melanoma types.³ Reports also do not indicate what the ages of the older than age 12 years melanoma patients were. This is especially important since the FDA uses age 16 years as an age cutoff, and the EMA PIPs age 18 years. It is also not reported whether the young adults in the study had melanoma or other tumors. This publication has often been quoted by the scientific community.^{1,13,38–54} With 1 exception,¹³ there were no comments about these missing data. The danger of inappropriately designed pediatric studies is likely to be underestimated. Part of the most basic information for a pediatric trial study report should include the patients' age distribution to avoid giving a trial the label of pediatric when a relevant part of the study population were no longer children; information missing from the ipilimumab study report.¹⁷

Melanoma and PIP-exempted diseases

In 2008, the EMA removed melanoma from the list of PIP-exempted diseases. As a result, as of September 2017 there were 12 PIPs requiring pediatric trials in either melanoma only or in pediatric (age <18 years) patients with either melanoma or other solid malignancies.¹⁰ The flawed rationale for this removal has been discussed elsewhere.^{55,56} Furthermore, these PIPs do not distinguish between melanoma types.^{3,4}

Feasibility, ethics, and clinical usefulness of the terminated melanoma studies

Both studies were clearly unfeasible when they were designed. The number of adolescents with unresectable or metastasized melanoma is very small; about one-tenth of the number that the EMA used in its justification for removing the melanoma class waiver.^{55,56} A warning about such unfeasible pediatric melanoma studies first appeared in 2014.⁵³ Also the FDA overestimated the number of available adolescent melanoma patients.¹⁹ Studies that cannot recruit adequate subjects to produce scientifically valid results cannot be ethically or medically justified.

These 2, unfeasible WR/PIP-triggered adult-style ipilimumab/vemurafenib trials could not provide any clinical benefit to adolescent or older melanoma patients. For physiologically mature adolescents, adult doses are appropriate. Even for those very rare conventional melanomas in young children there was no question about the efficacy of ipilimumab in combination with nivolumab. The question that needed to be addressed was the appropriate dose. Such pediatric dosing information could and should instead be generated using practical, prioritized, modern, nonadult, developmental-appropriate methods, including opportunistic trials, modeling and simulation, and registries.^{9,57} The academic publication fails to address this flaw of the study.²¹ But it advocates in the conclusion to consider inclusion of children and adolescents into adult trials of promising new drugs or their combinations - an argumentation with which we agree; however, the logic of this argumentation allows doubts if this study should have been initiated at all; it also allows doubts about the concept of pediatric versus adult cancer that is the base of FDA/EMA pediatric study requirements.

Ongoing pediatric studies in melanoma and other tumors

The ongoing monotherapy studies in patients with solid malignancies, including melanoma,^{23–26} are ethically questionable. Why expose a pediatric melanoma patient to a monotherapy when there are already FDA-approved combination treatments for melanoma available?^{19,58,59} There are also other promising pediatric melanoma trials being performed worldwide¹⁰ that such patients could enroll in. The PIP-related studies listed in [Table 4](#) aim to recruit altogether 596 patients in >100 centers globally. For the

conventional melanoma patients already recruited into these trials, the fact that there are better treatments available suggests recruited patients may be unaware of this. If true, they are being mistreated. For patients with other cancer types in these studies, use of chronological age <18 years is inappropriate whenever effective adult treatments already exist. Such trials need urgent re-examination by the responsible institutional review boards/ethics committees for their possible suspension.

Conflicts of interest and costs

Although everyone involved in pediatric trials claims to represent the patients' best interests, the rarity of pediatric melanoma results in competition for patients that creates conflicts of interest for the clinicians who do the research to build careers, the companies that need regulatory approval for their new melanoma drugs, the contract research organizations that run the trials, the regulatory authorities who control drug approval, whereas the patients and their parents are fighting for their life.

WRs for US pediatric exclusivity make economic sense to companies. If a company fails to recruit for WR studies, it will not get the economic reward it wants. The situation is worse in the European Union. Companies must execute the PIP-demanded studies, or they risk nonapproval of their adult drugs, a death sentence for research-based companies. For clinicians such studies offer networking, prestige, publications, and funding. Not all of these clinicians fully understand the WR/PIP processes. Patients and parents looking for cures or improved quality of life can be exposed to sub-optimal or medically senseless treatment and thus become therapeutic hostages of regulatory authorities driven by the therapeutic orphans dogma.⁶⁰

For pharmaceutical companies, WR-rewards and EU-approvals represent enormous financial incentives. From a business point of view, it makes no difference if such studies make medical sense: They must and will be performed. This creates competition for patients and can expose patients to studies that are medically senseless at best or prevent more effective treatment of a lethal disease at worst. This creates conflicts of interest and exposes pharmaceutical companies, clinical research organizations, responsible institution review boards/ethics committees and clinicians to potentially disastrous damage lawsuits.

Classical conflicts of interest involve industry employees and clinicians who are paid by industry to issue biased statements but these are not the only conflicts. Pediatric drug regulations have created additional conflicts for regulators. Employees of EU regulatory authorities have claimed that "lack of availability of appropriate medicines for children is an extensive and well known problem,"⁶¹ that there is "neglect of children in the development of effective and safe medicinal products,"⁶² and regarding oncology that "no application for marketing authorization was made to the authorities. Therefore, no assessment was made to provide reliable information and guidance to prescribers and the public."⁶³ Clinically, these statements are misleading at best. Who doubts the PIP-independent therapeutic successes of neonatology,⁶⁴ pediatric cardiology,⁶⁵ or pediatric oncology?⁶⁶ The conflicts creating these statements become more obvious when one considers that the authors' professional positions are closely linked to the EU pediatric legislation.^{61–63} There are also financial implications for society in such claims.

The EU Commission estimates the costs per PIP for industry at roughly €20 million.⁶⁷ With the number of approved PIPs having passed 1000, this represents roughly €20 billion. These amounts represent potentially huge conflicts of interest to all of us involved in pediatric trials that produce pediatric data and publications that support careers in pharmaceutical industry, clinical research, and regulatory administration worldwide.

Medicine and politics

The number of underage patients with cancer is very small compared with adult cancer patients, for melanoma as well as other solid malignancies. Accusations have been made that not enough focus has been given to these patients.⁶⁸ The EU parliament has adopted a declaration that asks for tougher measures to force pharmaceutical companies to investigate more pediatric malignancies,⁶⁹ and the FDA asks in its 2016 report for the power to enforce pediatric trials of new adult anticancer drugs.⁷⁰ Proof is lacking that such approaches are either needed or likely to be effective. Pediatric melanoma demonstrates why chronological age alone is inappropriate to decide about the need for pediatric trials and how the uncritical acceptance of the therapeutic orphans dogma can result in ethically questionable clinical trials reminiscent of historical examples.^{71,72}

Conclusions

FDA pediatric melanoma WRs and related EMA PIP-demanded studies should incorporate improved diagnostic techniques, focus on physiologic maturity rather than chronological age, and use more ethically justified study designs. The research community and institutional review boards/ethics committees should consider these alternatives when deciding whether to approve or suspend PIP-related melanoma studies.

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Potential conflicts of interest

Dr. Rose consults on pediatric drug development, teaches, organizes scientific conferences, edits books, and publishes. Dr. Walson has provided fee-for-service consultation to the pharmaceutical industry and contract research organizations as well as to US and EU not-for-profit government-funded research organizations (eg, Eunice Kennedy Shriver National Institute of Child Health and Human Development, FP7 health projects, and the Innovative Medicines Initiative) and has been paid for participation in numerous conferences devoted to pediatric clinical trials and drug development. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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