



Early Evaluation of Molecularly Targeted Therapies for Childhood and Adolescent Cancer

Discussion Document for use during Friends of Cancer Research's meeting on February 20, 2018

Disclaimer:

Friends of Cancer Research prepared this discussion document with input from a multi-stakeholder working group representing a broad cross-section of the pediatric cancer community. This document does not reflect consensus views, opinions, or positions of the working group members or the institutions they represent. This document is meant to facilitate open discussion among different stakeholders.

Background

The Pediatric Research Equity Act (PREA) requires sponsors of new drug applications (NDA) or biologics license applications (BLA) (or supplements to applications) for a new active ingredient, indication, dosage form or dosing regimen, or route of administration, to submit *assessments** (Federal Food, Drug and Cosmetic Act (FD&C Act) Sec. 505B (a)(2), 21 USC 355c (a)(2), amended in the Food and Drug Administration Safety and Innovation Act (FDASIA) Public Law 112-144). The assessment consists of data gathered using appropriate formulations for each age group that are adequate to assess the safety and effectiveness of the drug or biological product for that indication, and support dosing and administration for each pediatric subpopulation for which the drug or biological product is safe and effective. When sponsors have data to demonstrate that assessments in the pediatric population are not feasible, they can obtain a waiver or deferral for completing the assessments in all or some of the *pediatric age groups*.

Until the passage of Title V of the FDA Reauthorization Act (FDARA) of 2017 (FD&C Act Sec. 505B (a)(3), 21 USC 355c (a)(3), Public Law 115-52), PREA had not been an effective mechanism to establish a requirement for the development of drugs for *pediatric cancers*, as most of the oncology drugs approved have been for treating cancers that occur in adults and not in children (e.g., cancers of the lung, prostate and breast). Therefore, drug sponsors would obtain waivers for conducting assessments of these drugs in pediatric patients. Additionally, drugs developed for rare cancer indications, which may occur in both adult and pediatric populations, are granted orphan drug designation and are thus exempted from PREA required studies.

*Italics indicate words defined in the Glossary of Terms (page 11).

While there was limited obligation to study investigational therapies in pediatric oncology, incentives have been put into place to promote the development of oncology products for pediatric cancer when these agents are in development or already approved for adult use. The Best Pharmaceuticals for Children Act (BPCA) is a voluntary mechanism which provides incentives in the form of six months of exclusivity for marketing to sponsors upon the completion and submission of pediatric studies that meet the terms of a written request from FDA (FD&C Act Sec. 505A, 21USC 355a, reauthorized in the FDA Amendments Act (FDAAA) Public Law 110-85). BPCA also allows FDA to request studies that cannot be realized under PREA because the applications or supplements are not subject to the requirements of PREA. To date, BPCA has been the primary mechanism used to develop oncology products for the treatment of malignancies in children and adolescents. Recent legislation (FDARA) has created a mechanism to further encourage the development of novel medicines that address the high unmet need in the pediatric population.

Molecularly targeted agents developed for adult cancers have greatly advanced the concept of precision medicine in oncology. As malignancies occurring in children and adolescents can harbor molecular abnormalities similar to those found in adult cancers, these agents may be relevant to the treatment of pediatric patients with cancer. Although large scale sequencing efforts, such as TARGET¹ and the Pediatric Cancer Genome Project (PCGP)² have provided evidence that the genetic and epigenetic repertoires of driver gene aberrations often differ between adult and pediatric cancers, a growing body of evidence suggests that genetic and other molecular biological vulnerabilities of certain adult cancers may recapitulate opportunities for the use of targeted therapies in select pediatric tumors^{3,4}.

Therefore, timely investigation of signals of activity of potentially useful targeted drugs and biologic agents under development and of their toxicities relative to the unique growth and developmental considerations of pediatric patients is often warranted for pediatric populations with cancer.

Children and adolescents are not smaller adults, and the efficacy, dosage form, and dosing regimen of targeted drugs developed for malignant disease, which develop in adults, cannot simply be extrapolated to different indications in the pediatric population. Thus, there is a need to more expediently identify and evaluate new anti-cancer agents which may be appropriate for investigation in pediatric cancers earlier in drug development programs. Title V of FDARA amended PREA to support the early evaluation of potentially effective drugs by requiring pediatric investigation of appropriate new drugs intended for adults with cancer. The investigations that FDA may require by statute are referred to as *molecularly targeted pediatric cancer investigations*. These investigations may include clinical studies designed to yield clinically meaningful pediatric study data, gathered using appropriate *formulations* for each age group for which the study is required, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling [FDARA Title V Sec 504 (a)(3)(A), FD&C Act Sec. 505B (a)(3)(A), 21 USC 355c(a)(3)(A)]. Importantly, Title V of FDARA also specifies that the requirement for early pediatric investigations of drugs directed at *molecular targets* considered substantially relevant to the growth or progression of a pediatric cancer be applied, even when the adult indication

has received an orphan designation, or when the adult cancer indication does not occur or is biologically different in the pediatric population (e.g., breast cancer).

The law directs the FDA, in collaboration with the NCI, to establish, publish, and regularly update a list of molecular targets considered on the basis of data the Agency determines to be adequate, to be substantially relevant to the growth or progression of pediatric cancers, and that may trigger the requirement for pediatric investigations [21 USC 355c (m)(1)(A)]. Molecular targets that are considered “not relevant” to the growth or progression of pediatric cancers will be placed on a second list [21 USC 355c (m)(1)(B)].

The FDA is mandated to convene a public meeting no later than one year after the date of the enactment of FDARA, to solicit views of physicians, academic researchers (including pediatric oncologists and rare disease specialists), patient advocates, industry, and other stakeholders for the establishment of the molecular targets lists [21 USC 355c (m)(2)(1)]. Future public meetings are planned for later in the year at the meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC).

In order to facilitate an early, informal opportunity for stakeholders to discuss the molecular targets list, Friends of Cancer Research (*Friends*) will convene a public meeting to discuss approaches for developing, updating, and applying the molecular target list. Friends has invited several stakeholders, including FDA, NCI, industry, academic researchers, clinical investigators, and patient advocates to discuss the implementation of the FDARA provisions. The objective of this document, which will be presented at the *Friends* meeting, is to discuss numerous ways to develop transparent and scientifically sound processes that address the following provisions:

1. Developing the molecular target lists: Forming frameworks of factors that may guide the definition of molecular targets as substantially relevant or not relevant to the growth or progression of one or more pediatric cancers
2. Updating the lists of molecular targets: Defining mechanisms and timelines by which such updates may occur
3. Applying the molecular target lists: Addressing key considerations in the application of the lists to pediatric cancer drug development

Framework of factors to consider for the development of a pediatric cancer molecular target list

Although there may be variations in the way “molecular target” is defined, for the purposes of this discussion document, we refer to a molecular target as a molecule in human cells that is intrinsically associated with a particular disease process, such as etiology, progression, and/or drug resistance. To be referred to as a target, there must be evidence that by engaging the target, either with a targeted small molecule, biologic product, or other treatment intervention, a desired therapeutic effect is produced that results in the alteration of the disease process. In other words, a molecule would not be referred to as a molecular target if there is no evidence to inform the hypothesis that its modulation (i.e. inhibition or activation) alters the disease.

In this discussion document, we are focusing on molecular targets in cancer, which can be further classified by subtype. One set of targets can be classified by whether they represent the result of specific gene abnormalities, are present in a critical biologically-related pathway of a gene abnormality, or exhibit a synthetic lethal relationship to a gene abnormality (*gene abnormality-based targets*). Targets can also be intrinsic to the cancer cell lineage or developmental stage (*cancer cell lineage-based targets*), or they may be identified in non-cancer cells, such as normal immune cells or supporting cells contributing to the tumor micro-environment (*non-cancer cell targets*). A final category is targets present in the cancer cells as well as non-cancer cells that do not show cancer-specific genetic alterations, such as tubulin or heat-shock proteins (*other targets*).

When there is evidence of effectiveness for a drug or biologic directed at a molecular target in an adult cancer, and the target has been identified as substantially relevant for the growth or progression of a pediatric cancer, there may be a rationale for the agent's evaluation in the pediatric cancer population, regardless of similarity to the histologically-defined cancer found in the adult. Although not an absolute requirement, it is beneficial for sponsors of an agent such as this to have associated *in vitro* and *in vivo* data using pediatric non-clinical models to provide increased confidence for the role of the target in growth or progression of specific cancers. These data may help guide pediatric clinical development of the agent.

Here, we propose two frameworks, one that outlines factors that may be useful when determining whether a target is substantially relevant in pediatric cancer and may trigger the requirement for pediatric investigations. The second framework outlines factors to consider when assessing the available data that may help determine there is insufficient evidence of relevance, and that the target is hence "not relevant."

Factors to consider for defining a target as substantially relevant for the growth or progression of pediatric cancer

The FDA in collaboration with the NCI is tasked with determining whether a molecular target is considered substantially relevant to the growth or progression of pediatric cancer, or whether there is evidence that the target is not relevant to pediatric cancer. It is solely the prerogative of the FDA to determine whether adequate evidence is available to define a target as substantially relevant that triggers a requirement for pediatric investigations. Thus, defining "adequate evidence" is beyond the scope of this document. However, several factors may support a scientifically-based and data-driven decision-making approach. These factors are not meant to be either inclusive or prescriptive, as there may be additional factors for some specific targets and some of the listed factors may not be required for all targets within a class. Indeed, specific considerations related to the framework factors may have different applicability depending upon the target class. The framework (Table 1) is meant to guide discussion on the types of evidence available that will support the determination of whether a molecular target is substantially relevant to the growth or progression of pediatric cancers. The framework is not meant to be read as a checklist. It is important to note that the totality of evidence available may

be considered when guiding discussions to determine target relevance. The presence of a single factor or a particular combination of factors may not be sufficient to trigger relevance.

Table 1: Framework of factors and characteristics that may guide the determination of whether molecular targets are **substantially relevant** in the growth or progression of pediatric cancer

Factors	Considerations
Presence of target	The target has been identified in at least one case of a pediatric cancer
Target class: Gene abnormality	The gene abnormality has been identified in at least one case of a pediatric cancer
Target class: Cancer cell lineage	The target is intrinsically and differentially expressed in the cancer of interest compared to normal site-specific tissues
Function/Mechanism	The biological function of the target is relevant to the etiology and growth of the childhood cancer
Target class: Gene abnormality	Modulation of the affected gene product or of a critical downstream pathway or correction/deletion of the affected gene defect adversely affects cancer cells
Target class: Cancer cell lineage	The presence of the gene abnormality creates a synthetic lethal relationship with another cellular pathway
Target class: Cancer cell lineage	The target is associated to cancer cell development, growth, and survival
Non-clinical evidence	Non-clinical evidence supports relevance of the target in one or more pediatric cancers
<i>In vitro</i> activity	Target modulation shows <i>in vitro</i> selectivity for cancer cell lines containing/expressing the molecular target (pediatric or adult cell lines if target is known to be shared by multiple cancer types regardless of patient population) compared to the sensitivity of cell lines not containing/expressing the target
<i>In vivo</i> activity*	Target modulation shows <i>in vivo</i> activity manifested as tumor stabilization or regression in models of pediatric cancers with the molecular target of interest (or adult cancer models containing/expressing the target)
Lack of <i>in vitro</i> or <i>in vivo</i> activity	For targets for which target modulation does not show <i>in vivo</i> or <i>in vitro</i> activity, support for relevance may be found in evidence for supra-additive or synergistic activity when target modulation is used in biologically rational combinations
Adult clinical experience	Target modulation by investigational agents known to affect the target, shows clinical activity in specific cancers in adults
Predictive biomarkers	Biomarkers that predict responses to target modulation may be useful in the selection of appropriate pediatric study populations
Location	For immunotherapy targets, the target is expressed on the cell surface (excepting immunotherapies that target intracellular antigens that are displayed as peptides by MHC proteins on the cell surface)
Agent under development	There is an agent in development or proceeding to development that addresses the specific target

*The *in vivo* activity should be observed at drug exposures that are relevant to the clinical setting if there is clinical experience with the agent. Prolonged stable disease may be relevant, particularly for agents that induce their anticancer effect through mechanisms other than cancer cell apoptosis.

Because of the importance of non-clinical evaluation in determining relevance of molecular targets, every effort should be made to ensure sponsors expedite early non-clinical

investigation, which could be in collaboration with academic research teams with pediatric expertise in non-clinical testing. The creation of these collaborations and/or partnerships should be explored further as they will be crucial for early testing of non-clinical models, such as xenograft mouse models.

Biomarkers that are identified as predictive for the activity of adult cancer targeted agents should also be evaluated for distribution and potential utility across pediatric cancers. Sponsors are strongly encouraged to test samples from pediatric cancers to determine relevance, especially when an assay to identify a target is developed in conjunction with the investigational agent and is not available for use on patients by investigators other than the sponsors.

Factors to consider that will help identify targets that are not relevant to the growth or progression of pediatric cancer

There may be evidence available that demonstrates a molecular target is not relevant in pediatric cancers that would prevent it from being added to the substantially relevant molecular target list. The factors listed in Table 2 highlight considerations that may guide the determination of whether a molecular target is not relevant to the growth or progression of pediatric cancer. Again, it is solely the FDA’s responsibility to determine what is the evidence necessary to determine whether a molecular target is considered not relevant in pediatric cancer, and thus this document does not attempt to define what “adequate evidence” refers to in this context.

Table 2: Framework of factors and characteristics to consider that may guide the determination of whether molecular targets are **not relevant** to the growth or progression of pediatric cancer[#]

Factors	Considerations
Biologically implausible	Molecular targets for which available evidence supports no role for the targets in pediatric cancers (e.g. endocrine/autocrine sex steroid hormonal pathways that are known to be drivers of specific adult cancer types but are very rarely to never observed in pediatric cancers)
Non-clinical evidence	Evidence of lack of activity of an agent in development against a specific target in non-clinical systems could be a component of the evidence base used to determine that a specific molecular target may not be relevant to the growth or progression of a pediatric cancer
Adult clinical evidence	Evidence of lack of clinical activity of an agent in development against a specific target could be a component of the evidence base used to determine that a specific molecular target may not be relevant to the growth or progression of a pediatric cancer

[#]There may be agents that are relevant to the growth or progression of disease but that would not be considered for development because of their association with developmental processes such that their inhibition would raise concerns about irreversibly deleterious developmental effects and subsequent growth-related toxicities (see *Additional Considerations* section below).

Targets with insufficient evidence

Molecular targets for which sufficient evidence to make a determination of “substantially relevant” or “not relevant” may not yet be available and will not be included in either list.

Decisions regarding relevance of these targets to the growth or progression of pediatric cancers could be made when there is an adequate evidence base to make such a determination. Sponsors and investigators are strongly encouraged to investigate the potential relevance of new and currently unlisted targets as expeditiously as possible, especially when there are early non-clinical or clinical signals of activity.

Mechanisms to update the molecular targets lists

To ensure the molecular targets lists are updated with the most relevant evidence available in light of the rapid pace at which scientific advances occur, three distinct opportunities are discussed.

The first opportunity includes an annual public workshop at which all stakeholders, including but not limited to members of the FDA, NCI, industry, academic and clinical investigators and patient advocates, will discuss potential changes to the molecular targets lists. The FDA will be responsible for convening and presiding over this annual meeting, which may occur following a national or international scientific meeting. This meeting will seek input from individual stakeholders on advances in relevant scientific evidence that may impact the inclusion of one or more molecular targets on the current published lists, including potential relevance of unlisted targets. Final decisions related to the lists will require input from the Pediatric Subcommittee of the ODAC.

The second opportunity consists of a transparent nomination mechanism to occur during or prior to meetings of the Pediatric Subcommittee of the ODAC. This mechanism could include, but is not limited to, clinical investigators as well as researchers in academia and industry, who will have the opportunity to suggest targets to be added to or removed from the list based on substantial scientific evidence that demonstrate emerging relevant targets, or that demonstrate no relevance in pediatric disease, respectively.

The third opportunity would create a transparent process for clinical investigators or sponsors to request a meeting at any time with the FDA to discuss new scientific data related to a new or existing molecular target, which may warrant a change in that target's status as substantially relevant or non-relevant and could result in changes to the lists.

Data gathered from any and all sources could then be assessed by the FDA with input from the Pediatric Subcommittee of the ODAC in order to determine whether there is substantial new evidence to change the status of the target of interest. It is important to note that even if agents under development addressing molecular targets for adult indications are added to the "substantially relevant in pediatric cancer" list late in the development paradigm for the adult indication, those targets will not be exempted from the requirement for pediatric investigation.

Continuous review of nominations for potential targets of relevance obtained through any of the opportunities listed may be accomplished by a transparent mechanism where members of the Pediatric Subcommittee of the ODAC review nominations on an ad hoc basis to inform the

FDA as to a target's potential relevance. Changes made to the list after nomination review could be made immediately and not wait for the next meeting of the Pediatric Subcommittee of the ODAC. As mandated by law the resulting lists will be published on the internet website of the FDA [21 USC 355c (m)(1)].

Additional considerations for the potential application of the molecular target list

Additional considerations may potentially arise when seeking to apply the list of molecular targets. In this section we will highlight a few factors that could influence the application of the list, such as balancing clinical benefit and risk, the availability of pediatric formulations, and the size of the patient population when conducting clinical trials. These factors will play different roles in each scenario but discussing and brainstorming potential approaches with several key stakeholders in the pediatric cancer community is imperative to help accelerate the availability of life-saving therapies for children and adolescents with cancer.

1. Clinical benefit: risk analysis

As with any clinical study, investigations in pediatric patients must be scientific and ethically justified, taking into consideration the prospect of direct benefit to individual children and adolescents with cancer. Regulatory requirements for pediatric clinical research are provided in 45 CFR part 46, with subpart D specifically addressing the categories of allowable research involving children as subjects. As per FDA's guideline, "E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population", clinical studies will assess the balance of risk and anticipated clinical benefit.

"Experimental interventions or procedures that present greater than low risk must offer a sufficient prospect of clinical benefit to justify exposure of a pediatric population to such risk. Likewise, the balance of risk and anticipated clinical benefit must be at least comparable to the available alternative treatments. There should be a reasonable expectation that a clinical benefit resulting from the clinical study can be made available to this population in the future."

Therefore, in addition to the factors in the framework outlined in this document, the requirement for sponsors to study a molecularly targeted therapy in pediatric cancer patients must be supported by the prospect of direct clinical benefit. A reasonable balance needs to be identified in a case-by-case scenario and all data need to be considered in identifying the right balance.

For example, when a target is considered to be substantially relevant to the growth or progression of pediatric cancer, yet the toxicity profile of a new agent modulating this target is known to cause irreversible adverse effects of sufficient magnitude, including those associated with a vital developmental pathway, conducting a pediatric investigation using this agent may not be justified and further development may be precluded.

2. Pediatric formulation requirements

Drugs and biologics need to be formulated to best suit a pediatric patient's age, size, physiologic condition, and treatment requirements to be studied in children and adolescents. To facilitate the availability of these *pediatric formulations* needed for the pediatric investigations outlined in Title V of FDARA, sponsors are encouraged to begin establishing a pediatric formulation early in the adult drug development process. This will help sponsors meet the requirements outlined in FDARA and provide an initial pediatric study plan (iPSP) at the conclusion of the adult Phase 2 study, which includes plans for the development of a potentially marketable pediatric appropriate formulation.

3. Patient population

A molecularly targeted pediatric cancer investigation, as required by Title V of FDARA, is designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling. Thus, a sufficient patient cohort needs to be accrued to identify proper dosing, safety concerns, and signals of preliminary efficacy. However, due to the rarity of some pediatric cancers, accruing an adequate number of pediatric patients with cancer for early clinical studies conducted at single centers may not be feasible. Collaborations among different clinical centers and between strong pediatric trial networks are encouraged in order to conduct pediatric investigations that will yield robust findings. Moreover, international collaborations for clinical trials involving rare forms of pediatric cancer may be considered to improve accrual rates. Collaborative drug development efforts are logistically, operationally, and legally complex, and as such, require increased and more transparent communication among regulatory organizations, industry, and other stakeholders.

Questions:

These questions may guide the discussion during the meeting:

1. Should the term “molecular target” only be used for molecules that already have an agent that modulates its activity and that is either fully developed or in the process of development?
2. What is considered an optimal level of evidence required for the factors presented in the framework that may guide the determination of substantially relevant to the growth or progression of pediatric cancer?
3. What level of evidence is necessary and would be considered substantial to predict direct benefit for institutional review boards to approve protocols for pediatric patients?
4. When a potential target is identified in one case of a pediatric cancer, how could a drug development strategy be defined and what are the responsibilities of each stakeholder?
5. What types of evidence inform preliminary efficacy in molecularly targeted pediatric cancer investigations and in what phase of the clinical study would these data be collected?
6. Does the validation of the drug-target relationship have to be established in pediatric non-clinical models to be considered substantially relevant to the growth or progression of a pediatric cancer?
7. The European Innovative Therapies for Children with Cancer (ITPCC)-P4 (Paediatric Preclinical Proof of Concept Platform) program and the NCI Pediatric Preclinical Testing Consortium are public-private partnerships to advance non-clinical science and enable rational drug development in pediatrics. How do these partnerships and others work, are they effective, and is there a need for additional efforts to expedite non-clinical research?
8. Would it be helpful to have a private effort that aims to create and encourage an open-access crowd-sourcing approach for the updating and maintenance of the list of relevant molecular targets?
 - i. How could this crowd-sourcing effort inform the FDA’s mandate to update the molecular targets list?
9. Could relevant data generated by international agencies and institutions be used in determining whether a molecular target is substantially relevant in pediatric cancer?
10. What considerations should be explored to facilitate international collaboration and coordination that addresses work in small patient populations?
11. Should there be a mechanism in place whereby waivers granted by the FDA are published to avert unnecessary trials for agents sharing a similar MOA?

Glossary of terms (in order of appearance):

Assessment refers to an evaluation of data gathered using appropriate formulations for each age group for which the assessment is required and that are adequate to assess the safety and effectiveness of the drug or biological product for the claimed indication in all relevant pediatric subpopulations, and support dosing and administration for each pediatric subpopulation for which the drug or biological product is safe and effective.

Pediatric age groups, according to the FDA, refers to neonates (newborns up to one month of age), infants (one month to two years of age), children (two to twelve years of age), and adolescents (twelve to sixteen years of age) (see FDA Draft Guidance "Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling," Feb. 2013). NIH policy defines "child" as individuals under 18 years old. For informed consent purposes, in clinical studies "children" refers to those under the legal age of consent.

Pediatric cancer refers to cancers arising in the pediatric population, which includes neonates, infants, children and adolescents.

Molecularly targeted pediatric cancer investigation refers to studies designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling.

Pediatric formulations refer to drugs and biologics that are formulated to best suit a pediatric patient's age, size, physiologic condition, and treatment requirements, taking into consideration the differences between adult and pediatric patients with regard to pharmacotherapy, including capabilities for drug administration, medicine-related toxicity, and taste preferences.

Molecular target refers to a molecule in human cells that is intrinsically associated with a particular disease process, such as etiology, progression, and/or drug resistance, and for which there is evidence that the resulting disease process might be addressed by a targeted, small molecule, biologic product, or other treatment intervention to produce a desired therapeutic effect.

Gene abnormality-based targets refer to targets that are the result of specific gene abnormalities or that are present in a critical biologically-related pathway of a gene abnormality or that are in a synthetic lethal relationship to a gene abnormality.

Cancer cell lineage-based targets refer to targets intrinsic to the cancer cell lineage (e.g., CD19 for B-ALL, estrogen receptor for breast cancer, and GD2 for neuroblastoma) or developmental stage.

Non-cancer cell targets refer to targets identified in non-cancer cells, such as normal immune cells or supporting cells, contributing to the tumor micro-environment

Other targets refer to targets present in cancer cells but that do not have specific genetic alterations (e.g., tubulin, HSP90, proteasome, etc.).

References:

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