Molecularly Targeted Therapies in Pediatric Cancer

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Pediatric Development of Molecularly Targeted Cancer Drugs and FDARA 2017

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Cancer Drug Development for Children and Adolescents

• Well recognized, long-standing unique considerations- scientific, societal, economic
• Accepted off label use as part of standard of care and research
• Improved outcomes and misperception of unmet clinical need for new drugs
• Unique practice model- integration of clinical research and management
• Lag in evolution of cancer drug development paradigm in pediatrics
• Broadly leverages adult drug discovery/development- highly regulated, limited opportunities for extrapolation and limited pre-clinical testing in pediatric models
FDA Advisory Committee Consensus Statement

**Pediatric** oncology drug development should generally be **coordinated** with oncology drug development for **adults**, as part of an **overall drug development plan**.
## U.S. Legislation and Pediatric Drug Development

<table>
<thead>
<tr>
<th>PREA</th>
<th>BPCA</th>
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<tr>
<td>□ Drugs and biologics</td>
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<td>□ <strong>Mandatory</strong> studies</td>
<td>□ <strong>Voluntary</strong> studies</td>
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<tr>
<td>□ Requires studies <strong>only on indication(s) under review</strong></td>
<td>□ Studies relate to entire moiety and <strong>may expand indications</strong></td>
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<td>□ <strong>Orphan indications exempt</strong> from studies</td>
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Current FDA Initiatives

• Increased role in promoting collaborative approach to timely pediatric drug development

• Optimizing regulatory authority of BPCA: Written Requests (WR) only since PREA of no relevance to oncology: 62 WRs

  21 exclusivity, 7 approvals, 17 labeling info., 25 current

  Multiple novel drugs approved in past 5 years for indications common to adults and children delayed due to Orphan designation

• Proactive identification of promising new treatments and engagement with industry/academia/advocacy groups to study these products earlier: BPCA Pediatric Oncology Working Group and Pediatric Subcommittee of ODAC

• Providing technical advice on key legislative initiatives

• Harnessing regulatory science to meet drug development challenges: design, age eligibility, pediatric cohorts in appropriate trials
Evolving Landscape of Cancer Drug Development

• Result of expanded understanding of the genetic epidemiology and molecular etiology of cancer
• Genomic/proteomic profiling of human cancers and identification of highly specific targeted agents
• Large treatment effects observed in small subsets of patients; seamless, adaptive study designs leading to drug approvals in defined cohorts
• Precision Cancer Medicine
• Transformative: NSCLC, Breast, Melanoma, AML
Opportunities for Pediatrics

• Embryonal tumors with low mutation frequency
• Genetic and epigenetic evidence base for driver gene mutations differ between adult and pediatric cancers
• Multiple demonstrations of actionable gene aberrations in pediatric tumors provide proof of principle that inhibition of some of the same molecular targets may result in vulnerability of select childhood cancers
• Insufficient development opportunities in children requires a paradigm shift in approaches to early pediatric evaluation of potentially promising new agents
RACE for Children Act:

• Incorporated as Title V of the FDA Reauthorization Act (FDARA), enacted August 18, 2017

• **Requires** evaluation of new molecularly targeted drugs and biologics “intended for the treatment of adult cancers and directed at a **molecular target** substantially relevant to the growth or progression of a pediatric cancer.”

• **Molecularly targeted pediatric cancer investigation:** clinically meaningful study data, “using appropriate formulations, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling.” [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)].

• Elimination of **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets.
Implications for FDA

• Establish with NCI, update regularly, and post on FDA website a list of “relevant” targets (1 year)

• Establish and post a list of non-relevant targets leading to waivers for pediatric studies (1 year)

• Work with NCI, Pediatric Subcommittee of ODAC, PeRC, investigators, sponsors, experts, and advocates

• Convene an open public meeting to refine/generate lists (1 year)

• Issue guidance on implementation (2 years)
Current FDA Planning

• Open Public meetings:
  1) April 20, 2018 at FDA - Review molecular target lists.
  2) Pediatric Subcommittee of ODAC, June 18/19, 2018 - review/comment on lists and considerations for application of target lists; process for prioritizing including same in class agents-working with external constituents (multi-stakeholder)

• International collaboration.coordination in light of global drug development and non-alignment of international regulatory agency requirements/processes/timelines
  – avoid duplication and competition

• Planning and implementation coordinated with internal FDA programs- OPT, DPMH, ORP, and OCC

• Advising sponsors of new conditions and requirements for iPSPs for new applications with planned submission dates after 8/18/2018
Successful Implementation

• Recognize/address anticipated, potentially adverse consequences
• Transparency with all stakeholders in implementation
• Expand pediatric pre-clinical testing initiatives - effective Industry-Academic collaboration when necessary
• Recognize/anticipate emerging scientific discovery
• Focus on early investigation of novel agents rather than individual patient access
• International collaboration in designation of relevance and prioritization
Today

• Forum for scientific **discussion** and multi-stakeholder exchange

• **Consider a framework for defining pediatric “relevance”** for current and future molecular targets

• **Address additional factors and some anticipated consequences which may impact decision-making**

• Discussions not focused on specific diseases or strategies for therapeutic investigation in a single disease area

• **No regulatory policy decisions**

• Anticipate and respect disparate perspectives

• **Focus on objective: accelerating pediatric research**
Panel 1 Discussion:
Molecular Targets in Pediatric Cancers: Classification and Criteria
Framework to Define Potential Relevance of Molecular Targets

Malcolm A. Smith, MD, PhD
Molecular targets

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.

Molecular target lists

- 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: 21 USC 355c (m)(1)(A)

- Molecular targets considered “not relevant”

- There will be molecular targets awaiting determination that are not on either list
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<th>Framework Factors for Substantially Relevant Targets</th>
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### Presence of target

The target has been identified in at least one case of a pediatric cancer.

### Function/Mechanism

- **Target class: Gene abnormality**
  - Presence of target: The gene abnormality has been identified in at least one case of a pediatric cancer.
  - Function/mechanism: The biological function of the target is relevant to the etiology and growth of the childhood cancer.
  - In vitro activity: Modulation of the affected gene product or of a critical downstream pathway or correction/deletion of the affected gene defect adversely affects cancer cells.
  - In vivo activity: The presence of the gene abnormality creates a synthetic lethal relationship with another cellular pathway.
  - Lack of in vitro or in vivo activity: The target is intrinsically and differentially expressed in the cancer of interest compared to normal site-specific tissues.

### Non-clinical evidence

- Non-clinical evidence supports relevance of target in one or more pediatric cancers.

### In vitro activity

Target modulation shows *in vitro* 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.

### In vivo activity

Target modulation shows *in vivo* 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).

### 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.
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Use of framework structure

- Not a checklist
- A tool to organize the totality of evidence available
- Final determination of whether a target is substantially relevant to pediatric cancer is the responsibility of FDA in consultation with
  - National Cancer Institute
  - Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee
Suggested categorization of molecular targets

- Gene abnormality-based targets
- Cancer cell lineage-based targets
- Non-cancer cell targets (e.g., immune cell targets)
- Other targets
Gene abnormality-based targets
Gene abnormality-based targets

- Highly credentialed molecular targets
- Examples of targets with drugs available
  - ALK fusion genes (lung cancer, anaplastic large cell lymphoma)
  - EGFR activating mutations (lung cancer)
  - NTRK fusion genes (multiple histologies)
- Examples of targets without drugs available
  - MLL fusion genes (ALL and AML)
  - EWS fusion genes (Ewing sarcoma and other pediatric cancers)
  - PAX-FOXO1 fusion (rhabdomyosarcoma)
Gene abnormality-based targets

- **Presence of target**
  - Ubiquitously present in all cancer cells of a specific pediatric cancer because it is the initiating genomic alteration (note exceptions)

- **Function/mechanism and non-clinical evidence**
  - Modulation leads to reduced cancer cell growth and survival
  - Agents directed at target show selective activity dependent upon target presence

- **Predictive biomarkers**
  - Presence of gene abnormality
  - Genomic databases support evaluations for the presence of genomic abnormalities within childhood cancers (e.g., NCI Genomic Data Commons and SJCRH PeCan Data Portal)
Gene abnormality-based targets (3)

- Effective agents may target:
  - The protein product of the genomic abnormality
  - A downstream effector of the genomic abnormality
  - A gene product with a synthetic lethal relationship to the genomic abnormality
Cancer cell lineage-based targets
Cell lineage-based targets

- **Presence**: The target is intrinsically and differentially expressed in the cancer of interest because of the cell lineage of the cancer
- Genomic abnormality **not** required
- Cell lineage-based targets that can be modulated
  - Androgen receptor
  - Estrogen receptor
  - Glucocorticoid receptor
- Cell lineage-based targets that can be therapeutically addressed by immunotherapy agents (e.g., antibody based therapies and cellular-based therapies targeting CD19, CD20, GD2, etc.)
Framework characteristics for cell lineage-based targets

Modulated cell lineage targets

- **Function and Non-clinical evidence**: Modulation leads to reduced cancer cell growth and survival
- Androgen receptor and estrogen receptor are potential examples of "biologically implausible" targets because the cancer cell lineage in which they play oncogenic role is not represented among pediatric cancers.

Immunotherapy cell lineage targets

- **Function**: ideally contributes to growth and survival, which minimizes risk of resistance due to loss of expression
- **Non-clinical evidence**: in vitro and in vivo activity in pediatric preclinical models
- **Location**: cell surface for antibody-based and CAR T-cell therapies.
Non-cancer cell targets
Framework characteristics for non-cancer cell targets (e.g., immune cell targets)

- Checkpoint inhibitors and immune-activating agents
- Other agents targeting tumor microenvironment
- *Predictive biomarkers*: tumor mutational burden, immune cell-infiltrate, PD-L1 expression
- Multiple challenges in assessing pediatric relevance
  - Large number of immuno-oncology targets and agents under development
  - Most childhood cancers have low tumor mutational burden
  - Limited pediatric model systems for *non-clinical testing*
Other targets
Applying framework to “other targets”

- Cancer cell targets not associated with genomic abnormality or with specific cell lineage
  - Examples
    - Tubulin
    - Topoisomerases
    - Chaperone proteins (Hsp90)
  - Function: Modulation leads to reduced cancer cell growth and survival

Other framework factors
- Non-clinical evidence in pediatric models is important
- Adult clinical experience can be informative
- Predictive biomarkers very useful when available
## Framework Factors for Substantially Relevant Targets

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## Framework

### Factors for Not Relevant

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Molecular Targets in Pediatric Cancers: Classification and Criteria

Panelists:
• Malcolm Smith, NCI (moderator)
• Scott Armstrong, Dana-Farber Cancer Institute
• Nancy Goodman, Kids V Cancer
• Katherine Janeway, Dana-Farber Cancer Institute
• Gregory Reaman, U.S. FDA
• Martina Uttenreuther-Fischer, Boehringer Ingelheim

Molecularly Targeted Therapies in Pediatric Cancer
#ProgressForPatients
Panel 2 Discussion:
Processes for Updating the Molecular Target List
Panel 2: Processes for Updating the Molecular Target List
Objective

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
Opportunity 1

- FDA will convene and preside over a public annual workshop for all stakeholders
  - FDA
  - NCI
  - Industry
  - Academic and clinical investigators
  - Patient advocates

- Input from individual stakeholders on advances in relevant scientific evidence that may impact the inclusion of 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 ODAC
Opportunity 2

• Nomination mechanism to occur during or prior to meetings of the Pediatric Subcommittee of the ODAC

• Clinical investigators as well as researchers in academia and industry have the opportunity to suggest changes to the list based on substantial scientific evidence that demonstrate:
  – emerging relevant targets, or
  – no relevance in pediatric disease
Opportunity 3

• Clinical investigators or sponsors may 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 relevant or non-relevant which could result in changes to the lists
Process

Opportunity 1

Opportunity 2

Opportunity 3

Assessment by FDA with input from the Pediatric Subcommittee of the ODAC to determine whether there is substantial new evidence to change the status of the target of interest

Updated target list is published on the FDA’s website
For Discussion

1. Develop a transparent mechanism for nominating targets
2. Considerations in ensuring a continuous review process
3. Examples of evidence required for updating target list
4. Mechanisms to request interaction with the FDA
5. Incentives to investigate targets that have insufficient evidence for determination of relevance
   • Open-access crowd-sourcing approaches
Panel 2 Discussion:
Processes for Updating the Molecular Target List

Panelists:
• Peter Ho, Boston Pharmaceuticals (moderator)
• Albert J Allen, Eli Lilly and Company
• Martha Donoghue, U.S. FDA
• Danielle Leach, St. Baldrick’s Foundation
• Rajen Mody, University of Michigan School of Medicine
• Nita Seibel, NCI

Molecularly Targeted Therapies in Pediatric Cancer
#ProgressForPatients
Panel 3 Discussion:
Considerations for the Application of a Molecular Target List to Cancer Drug Development for Pediatrics

#ProgressForPatients  WiFi Code: frc18
Applying the Molecular Target List to Cancer Drug Development for Pediatrics

Brenda Weigel, MSc, MD
University of Minnesota
Focus on Application

• Once the list is created, what are some other factors (clinical, scientific, etc) that need to be considered?

• Key question: When to start pediatric clinical trial?
  • Based on pre-clinical data
  • Formulation
  • Clinical information
Key Considerations

• Clinical benefit: risk analysis

• Safety and toxicity profile
  • Pre-clinical
  • Clinical
Key Considerations

• Pediatric formulation requirement
  • Importance and timing of development of these pediatric formulations (early)
  • Impact on administration to children
    • Phased formulation development
Key Considerations

• Patient population

• Need for collaboration to increase number of patients

• Impact on trial design
  • Master protocols
  • Adolescent cohorts
  • Age of eligibility
Key Considerations

• International Collaborations
  • PIP requirements
    • Commitment to phase 2 and 3 development early
  • FDA requirements
    • Early phase development
Discussion
Questions

• 1. What is the ‘optimal’ time to initiate a pediatric phase 1 trial of a targeted agent?
• 2. Are there trial designs that should be considered to expedite pediatric drug development?
• 3. How do we implement international collaborations to meet FDA and EMA/PIP requirements?
Panel 3 Discussion:
Considerations for the Application of a Molecular Target List to Cancer Drug Development for Pediatrics

Panelists:
• Brenda Weigel, University of Minnesota (moderator)
• Peter Adamson, Children’s Hospital of Philadelphia
• Jo Lager, Sanofi
• Charles Mullighan, St. Jude Children’s Research Hospital
• Susan Weiner, Children’s Cause for Cancer Advocacy
• Lynne Yao, U.S. FDA