Relevant Molecular Targets for Cancer Drug Development for Children

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Cancer Drug Development for Children and Adolescents

- Well recognized, long-standing challenges- biologic, clinical, societal, and economic
- Widely leverages adult drug discovery/development- Delay inevitable for pediatric development
- Limited opportunities for extrapolation; limited pre-clinical testing in pediatric models; limited access to Precision Medicine
- **Impact of legislative initiatives, most notably Pediatric Research Equity Act (PREA) which support pediatric drug development has been markedly less obvious in Oncology than in other clinical areas.**
- Many targeted agents likely applicable to cancers in children
- **Research to Accelerate Cures and Equity for Children Act (RACE) essentially amends PREA**

U.S. Legislation and Pediatric Drug Development

PREA

- Drugs and biologics
- **Mandatory** studies
- Requires studies **only on indication(s) under review**
- **Orphan indications exempt** from studies
- Pediatric studies must be labeled

Best Pharmaceuticals for Children Act (BPCA)

- Drugs and biologics
- **Voluntary** studies with incentive
- Studies relate to entire moiety and **may expand indications**
- Studies may be **requested** for orphan indications
- Pediatric studies must be labeled

RACE for Children Act:

- Incorporated as Title V Sec. 504 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 Federal Food, Drug, and Cosmetics Act (FD&C Act) Sec. 505B (a)(3)(A)].
- Elimination of **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets.

Molecular Target Definition

- 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 addressing the target with a small molecule, biologic product, or other intervention, a desired therapeutic effect is produced resulting in the alteration of the disease process

Current Implementation Status

- Planning and implementation coordinated with internal FDA programs- Office of Hematology and Oncology Products **(OHOP**)/Oncology Center of Excellence (**OCE**), Office of Pediatric Therapeutics (**OPT**), Office of Clinical Pharmacology (**OCP**), Division of Pediatric and Maternal Health (**DPMH**), Office of Regulatory Policy (**ORP**), and Office of the Chief Counsel (**OCC**)

- Open Public meetings:
  1. **April 20, 2018 at FDA - Review candidate molecular target lists.**
  2. **Pediatric Subcommittee of ODAC, June 20, 2018** - **finalize lists**; considerations for application of target lists to decision-making re. early evaluation; process for prioritization including same in class agents (multi-stakeholder); processes to support **international collaboration/coordination-** Global drug development and non-alignment of regulatory requirements/timelines.

Current Implementation Status Cont'd.

- Lists posted on OCE website Pediatric Oncology Program (https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/default.htm
- Advising sponsors of new conditions and requirements for initial Pediatric Study Plan (iPSPs) for **new** applications with planned submission dates after 8/18/2020
- Guidances in clearance; anticipate draft publication.

Framework for Defining Relevance

- Presence of target in one or more pediatric cancers- not prevalence-dependent
- Target function- etiology, drug resistance, lethality
- Non-clinical evidence- general and pediatric-specific-that target inhibition affects tumor growth
- Adult clinical experience
- Availability of predictive/response biomarkers
- Localization for immunotherapy-directed targets
- Therapeutic agent available/in development

Target Lists

- Statutory requirement to purportedly address regulatory uncertainty for Industry and **guide (not dictate)** decision-making re. early evaluation of and iPSP submission for a specific agent as an amended PREA requirement
- **Designation as relevant neither an absolute nor exclusive requirement for decisions related to pediatric evaluation:** studies of new products may be required if directed at a target **not** on the list and waivers may be justified for products directed at targets considered relevant
- **Not envisioned to restrict authority or flexibility**
- **Candidate** Target List constructed by OCE with the National Cancer Institute (NCI) and input from international content experts in a open public meeting
- Published, peer-reviewed literature, abstracts, public databases
- No pre-specified **minimum evidence base**

Relevant Target Lists

- Targets associated with specific gene abnormalities
- **Targets associated with cell lineage determinants**
- **Targets on normal immune cells and cells within the Tumor Microenvironment**
- Other Targets: Pathways and Functional Mechanisms

Publishing and Updating Lists

- Semi-annual public workshops
- Enabling on-going recommendations for addition/deletion: internal and external advice panels
- Lists posted on FDA's OCE website Pediatric OncologyProgram- https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/default.htm
- Open docket for comments- https://www.regulations.gov/document?D=FDA-2018-N-3633-0001

Table 1: Targets Associated with Specific Cell Lineage Determinants

Target Symbol			
AKR1C3	CD70	GPNMB	PTEN
BCOR	CD79b	ERBB2 (HER2/Neu)	SYK
BTK	CD123/IL3RA	IL6	WT1
CD7	CD276 (B7-H3)	IL13RA2	YAP1
CD19	Cereblon CBL (E3 Ubiquitine protein ligase)	LRRC15	
CD20	DLL3	MAGE-A3	
CD22	DLK1	MSLN (mesothelin)	
CD30	EGFRvIII	NR5A1 (Steroidogenic factor-1)	
CD33	EPHA2	NY-ESO-1	
CD37	GD2	Olig2	
CD38	GPC2	PIK3CD (PI3 kinase delta)	
CD56	GPC3	PRAME	

Table 2: Targets on Normal Immune Cells and Cells in the Tumor Microenvironment

Target Symbol	
B7H3	OX40
CD40	PD-1/PD-L1
CD47	RELA
CD52	RIG-I
CXCR4	STEAP1
CXCL10	STING
CTLA4	TIM3/TIM4
GM-CSF	VEGF
IDO1	VEGFR
IFN-gamma	
IL-2	
LAG3	