FDARA Implementation:
Future Pediatric Cancer Drug Development

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PREA

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

BPCA

- Drugs and biologics
- **Voluntary** studies
- 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: Changing the Paradigm

- 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."
- **Amends PREA:** requirement for pediatric assessment based on MoA rather than clinical indication.
- **Molecularly targeted pediatric cancer investigation**: "dosing, safety and **preliminary** efficacy to inform potential pediatric labeling."
- Elimination of **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets

Why the PREA amendments are important

- Extends precision oncology to children
- Genomic/proteomic profiling of human cancers has led to the identification of highly specific targeted agents
- Some molecular abnormalities in pediatric cancers are similar to those found in adult cancers
- PREA amendments support early evaluation of novel therapies relevant to pediatric cancer

Implications for FDA

- Establish with NCI, update regularly, and post on FDA website a **list of "relevant" targets** (1 year)
  - *Completed and posted*
- 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)
  - *Initial open public meetings have been held (4/20/2018 & 6/18-19/2018)*
- Issue guidance on implementation (2 years)
  - *Two guidances are in clearance in the Office of Chief Counsel*

Target lists

- Statutory requirement to address regulatory uncertainty for Industry and **guide** decision-making
- Designation as relevant not an absolute requirement for decisions related to pediatric evaluation
- Not envisioned to define or restrict authority of FDA
- Molecular targets of interest: independent of agent and/or biomarker availability
- **Candidate** Target List constructed by OHOP with NCI and input from content experts and stakeholders
- Published peer-reviewed literature, abstracts, public databases
- No pre-specified minimum evidence base

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
- Adult clinical experience
- Predictive/response biomarkers availability
- Accessibility for immunotherapy-directed targets
- Therapeutic agent available/in development
- **Focus on facilitating appropriate initial pediatric evaluations early in development timeline not increasing number of pediatric phase 1 studies**

Target lists, cont'd

- Target lists are not concrete and will change over time
- Processes in place to encourage flexibility
- Lists posted on OCE website for the Pediatric Oncology Program: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/default.htm

Question

- How many targets are currently included in the relevant target lists?
  - A: 154
  - B: 28
  - C: 103
  - D: 205

Target list examples:
Targets associated with specific gene abnormalities

Target Symbol		Gene Abnormality
ABL1/2	*	ABL1/2 gene fusions (BCR-ABL1, etc.)
ACVR1		ACVR1
ALK	*	ALK and ALK gene fusions
ASCL1		ASCL1 gene
BRAF	*	BRAF
BRD3-NUTM1		BRD3-NUTM1
BRD4-NUTM1		BRD4-NUTM1
CCND1,2		CCND1,2
CDK12		EWSR1-FLI1
c-KIT or KIT	*	c-KIT or KIT
CSF1R		CSF1R gene fusions
CTNNB1 (β-catenin)		CTNNB1

Target Symbol		Gene Abnormality
DDX3X		DDX3X
DOT1L		MLL gene fusions
EGFR	*	EGFR
ERK	*	BRAF, MAP2K1
ETS gene fusions		ETS fusions (ERG, FLI1, ETV1)
EWSR1-FLI1		EWSR1-FLI1
EZH2	*	SMARCB1, SMARCA4
FGFR	*	FGFR and FGFR gene fusions
FLT3	*	FLK2, STK1, CD135
Gamma secretase		NOTCH1 and FBXW7
GFI1		GFI1
GFI1B		GFI1B

Target list examples:
Targets associated with cell lineage determinants

Target Symbol (1)	Target Symbol (2)	Target Symbol (3)	Target Symbol (4)
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	

Target list examples:

Targets on immune cells and cellular components of the tumor microenvironment

Target Symbol (1)	
B7H3	
CD40	
CD47	
CD52	
CXCR4	
CXCL10	
CTLA4	*
GM-CSF	
IDO1	*
IFN-gamma	
IL-2	
LAG3	

Target Symbol (2)	
OX40	
PD-1/PD-L1	*
RELA	
RIG-I	
STEAP1	
STING	
TIM3/TIM4	
VEGF	*
VEGFR	*

Target list examples:

Other targets: pathways and functional mechanisms

Target Symbol (1)	Target Symbol (2)	Target Symbol (3)	Target Symbol (4)
AKT *	BMPR	DNA-PK	LSD1
ATM *	Brd1	DNMT (DNA methyl transferase)	MCL1
ATR	Brd4	FAK	MCT1 (monocarboxylate transporter 1)
ATRX	CDK4/6 *	FOLR1 (folate receptor 1)	MEK *
AURKA (Aurora kinase A)	CHK1	GSK-3	MIZ1
AURKB (Aurora kinase B)	CDK2	HDAC	MGMT
AXL	CDK7	HIF1A	MLL5
A1/BFL	CDK9	Hippo pathway (YAP, TAZ, TEADs)	MYST3 (MYST histone acetyltransferase (monocytic leukemia)
BAK	CK1	Hsp90 *	NAMPT
BAX	CK2 (casein kinase 2)	IAPs (inhibitor-of-apoptosis)	NEDD8 activating enzyme (NAE)
BCL2 family members (Bcl-2, Bcl-XL, Mcl-1, A1/BFL, BAK, BAX) *	CREBBP/EP300	IGFR-1 *	PARP *
BET bromodomain family *	DNA (alkylators)	KDM4A	PDK-1 (3-phosphoinositide-dependent protein kinase 1)

Non-relevant targets leading to waivers

Target Symbol
AR
ESR1
ESR2
GnRHR
PSA/PSCA/PSMA

Answer

- D: There are currently **205** targets included in the relevant target lists!

Publishing and updating lists

- Semi-annual public workshops
- Enabling ongoing recommendations for addition/deletion
- Opened FDA docket for comments on existing targets and suggestions for additions/deletions
- Planned review of “Immune/Tumor Micro-environment” targets:
  - June 2019 at Pediatric Subcommittee of ODAC meeting

Successful implementation

- Transparency with all stakeholders in implementation
- Recognize/address anticipated, potentially adverse consequences
- Expand pediatric pre-clinical testing initiatives
  - Effective industry-academic collaboration
- 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
  - Global drug development and non-aligned regulatory requirements and timelines.

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ADMINISTRATION

Back-up slides

Deferral considerations for agents directed at relevant targets

- Insufficient data to define relevance until such time that evidence provides a biologic rationale for study in children
- Lack of reasonable evidence of clinical activity associated with inhibition of target or pathway
- Uncertainty re. single agent activity until one or more biologically rational combinations demonstrate treatment effect
- Appropriate formulation development

Waiver considerations for agents directed at relevant targets

- Serious developmental toxicity: consideration for full or age dependent partial waivers
- Second or third “in class” product (**single agent**) without compelling evidence of substantial differences in efficacy, safety, PK profiles, or formulation to warrant additional pediatric studies
- Age group-specific partial waivers for formulation concerns
- Feasibility and practicability due to small study populations potentially addressed by limited study requirements and innovative study design and conduct: embedded pediatric trials, expansion cohorts, histology-agnostic development