Implementing FDARA 2017 Provisions: Facilitating Precision Cancer Medicine for Children

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Cancer Drug Development for Children and Adolescents

- Well recognized, long-standing challenges- biologic, societal, economic
- **Widely leverages adult drug discovery/development- limited opportunities for extrapolation and limited pre-clinical testing in pediatric models**
- **Impact of legislative initiatives 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

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The landscape of genomic alterations across childhood cancers

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LETTER

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Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours

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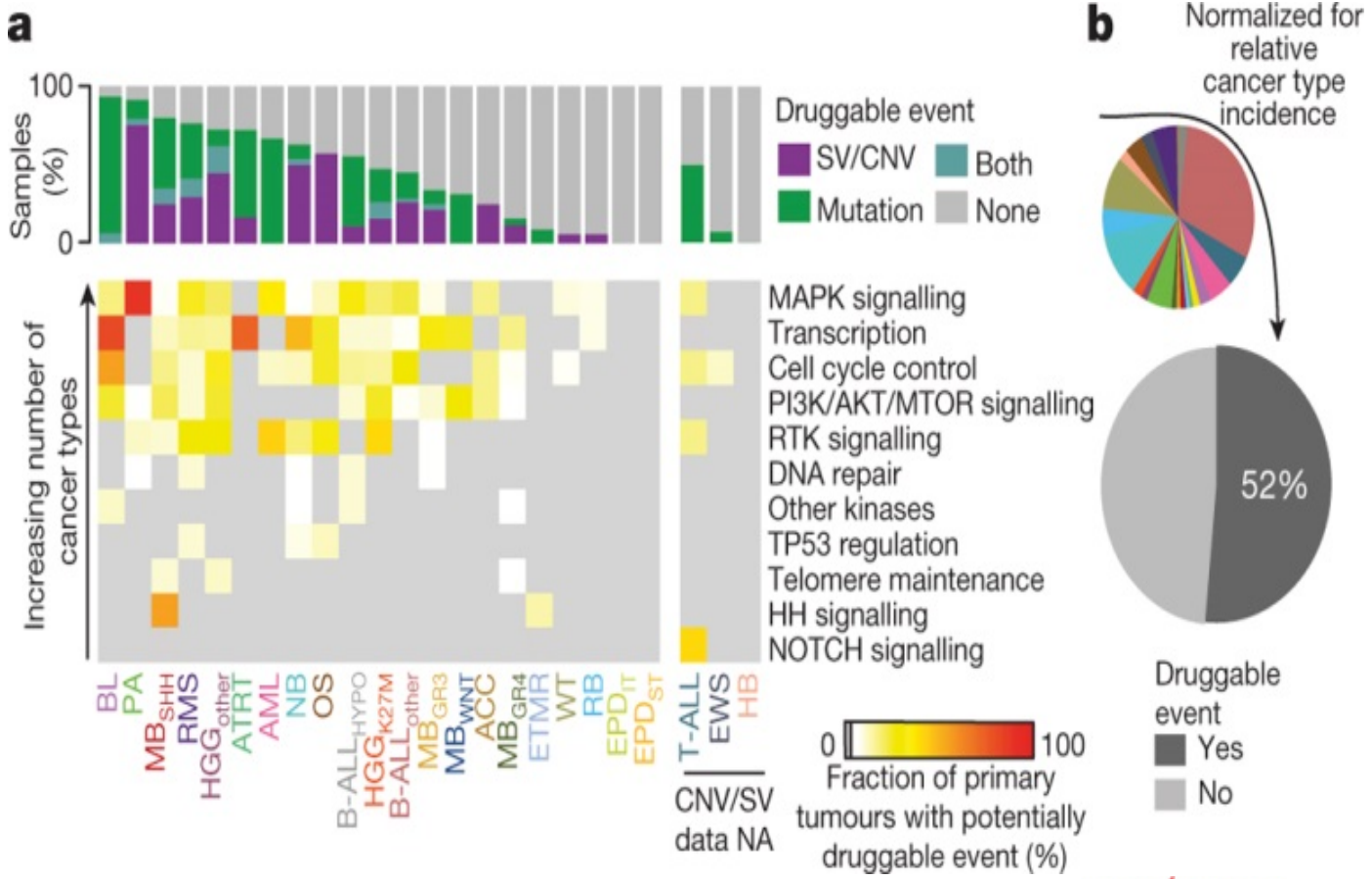
Potentially druggable events in pediatric cancers



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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

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 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.

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 treatment intervention, a desired therapeutic effect is produced resulting in the alteration of the disease process

Statutory Requirements 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 targets (non-relevant) leading to waivers** of pediatric studies (1 year)
- Work with NCI, Pediatric Subcommittee of ODAC, Pediatric Review Committee (PeRC), investigators, sponsors, experts, and advocates on implementation and required studies
- Convene an open public meeting to generate/finalize lists (1 year)
- Issue guidance on implementation (2 years)

Current FDA Efforts: Implementation

- Open Public meetings:

  1)April 20, 2018 at FDA - Review candidate molecular target lists.
  2)Pediatric Subcommittee of ODAC, June 20, 2018 - final review/comment on lists and considerations for **application of target lists**; process for **prioritization** including same in class agents- working with external constituents (multi-stakeholder); a process to support **international collaboration/coordination-** Global Drug Development and non-alignment of regulatory requirements/timelines
- Planning and implementation coordinated with internal FDA programs- Office of Hematology & Oncology Products/ Oncology Center of Excellence (OHOP/OCE), Office of Pediatric Therapeutics (OPT), Office of Clinical Pharmacology (OCP), Division of Pediatric & Maternal Health (DPMH), Office of Regulatory Programs (ORP), and Office of Chief Counsel (OCC)
- Focus on **accelerating** appropriate initial pediatric evaluations not increasing number of pediatric phase 1 studies
- Advising sponsors of new conditions and requirements for Initial Pediatric Study Plans (iPSPs) for **new** applications with planned submission dates after 8/18/2020

Friends of Cancer Research Workshop

- Forum for scientific **discussion and multi-stakeholder exchange**
- Consider a **framework** for defining pediatric **"relevance"** for current and future molecular targets and **classification**: tool to organize totality of evidence
- Address additional factors which may impact decision-making and some anticipated consequences
- Discussions not focused on specific diseases or strategies for therapeutic investigation in a single disease area
- No regulatory policy decisions other than focus on accelerating initial evaluation rather than increasing number of pediatric phase 1 studies

Target Lists

- Statutory requirement to purportedly address regulatory uncertainty for Industry and **guide (not dictate)** early decision-making
- **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 likely for products directed at targets considered relevant
- **Not envisioned to restrict authority or flexibility**
- Relevant molecular targets- independent of agent and/or biomarker availability
- **Candidate** Target List constructed by OCE with NCI and input from international content experts (Investigators)
- Published, peer-reviewed literature, abstracts, public databases
- No pre-specified **minimum evidence base**
- Further recommendations received via National Cancer Institute Request For Information (NCI RFI) through May 30, 2018

Gene Abnormality

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
CDK12	EWSR1-FLI1
CSF1R	CSF1R gene fusions
CTNNB1 (β-catenin)	CTNNB1
DDX3X	DDX3X
DOT1L	MLL gene fusions
EGFR	EGFR
ERK	BRAF, MAP2K1

Target Symbol	Gene Abnormality
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
Histone 3 G34R/V	Histone 3 G34R/V
Histone 3 K27M	Histone 3 K27M
IDH1 and IHD2	IDH1 and IDH2
JAK1, 2, and 3	JAK1, 2, and 3
LIN28B	LIN28B

Gene Abnormality

Target Symbol	Gene Abnormality
MDM2	MDM2, TP53
MEK	BRAF and BRAF gene fusions, MAP2K1, NF1
Menin	MLL gene fusions
MET	MET
MLL	MLL gene fusions
mTOR	TSC1, TSC2
MYC	MYC translocations and amplification
MYCN	MYCN amplification
Neoantigens	MSH2, MLH1, MSH6, PMS2 POLE, and POLD1
NFkappaB	RELA fusion
NOTCH1	NOTCH1, FBXW7
NT5C2	NT5C2

Target Symbol	Gene Abnormality
NTRK	NTRK gene fusions
ODC1	MYC target gene
PARP	BRCA1/2, PALB2, ATM, BRIP1, CHEK2, RAD51, etc.
PAX-FOXO1	PAX-FOXO1
PDGFRA/B	PDGFRA/B gene fusions
PI3Kα	PIK3CA
PPM1D (WIP1)	PPM1D (WIP1)
RAS	RAS
RET	RET
SH2B3	SH2B3
SHP2	SHP2
Smoothened	PATCH1, SMO

Gene Abnormality

Target Symbol	Gene Abnormality
SYT-SSX	SYT-SSX
TERT	TERT
TORC1/2 as distinct from mTOR	TORC1/2
TrkB	TrkB
TP53	TP53
TYK2	TYK2

Cell Lineage

Target Symbol (1)
AKR1C3
BCOR
BTK
CD7
CD19
CD20
CD22
CD30
CD33
CD37
CD38
CD56

Target Symbol (2)
CD70
CD79b
CD123/IL3RA
CD276 (B7-H3)
Cereblon CBL (E3 Ubiquitine protein ligase)
DLL3
DLK1
EGFRvIII
EPHA2
GD2
GPC2
GPC3

Target Symbol (3)
GPNMB
ERBB2 (HER2/Neu)
IL6
IL13RA2
LRRC15
MAGE-A3
MSLN (mesothelin)
NR5A1 (Steroidogenic factor-1)
NY-ESO-1
Olig2
PIK3CD (PI3 kinase delta)
PRAME

Target Symbol (4)
SYK
WT1
YAP1

Tumor Microenvironment & Immunotherapy

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

Others

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)

Others

Target Symbol (5)
PI3Kdelta
PIM1
PKA
PKC
PLK1
POL1
PRDM1
PRDM8
PRDM10
PRMT2
PRMT5
Proteasome

Target Symbol (6)
PTPN (protein tyrosine phosphatase)
RPA3
SHP2
SMYD3
Somatostatin Receptor
Survivin (BIRC5)
SUZ12
SWI/SNF
TET2
TGF-beta
Thymidylate synthase
Topoisomerase I/II

Target Symbol (7)
TRAIL
Tubulin
XPO1 (Exportin)
WDR5
WEE1

Automatic Waivers

Target Symbol
AR
ESR1
ESR2
GnRHR
PSA/PSCA/PSMA
VEGF
VEGFR

Waiver Considerations

- Serious developmental toxicity- consideration for full or age dependent partial waiver
- Second or third “in class” product without compelling evidence of substantial differences in efficacy, safety, PK profiles, or formulation to warrant additional pediatric studies
- Feasibility and practicability due to small study populations potentially addressed by limited study requirements and innovations in study design and conduct

Publishing and Updating Lists

- Semi-annual public workshops
- Enabling on-going recommendations for addition/deletion
- Lists posted on OCE website Pediatric Oncology Program (https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/default.htm)
- Opening FDA docket for comments on existing targets and suggestions for additions/deletions

Considerations for Decision-Making and Prioritization

- Likely variable by target class and disease
- Prevalence of target expression in a single disease or across histologies and evidence that target inhibition modulates tumor growth
- Extent of unmet clinical need or potential public health impact
- Availability of and access to agent
- Availability of predictive or response biomarkers
- Collaboration between Industry and clinical investigator community: **Multi-stakeholder input required** to inform FDA decision-making

Considerations for Decision- Making and Prioritization

- Clinical and/or pre-clinical evidence of activity
- Toxicity profile
- Potential benefit : risk assessment
- Formulation
- Multiple agents in class: transparent evaluation of selection criteria in pre-competitive space
- Rare pediatric cancers not well supported by current study platforms; innovative designs/solutions

Addressing Challenges

- Uniform international **master protocols** for biomarker-directed studies- efficient and high quality data
- Increasing **extramural** input while respecting proprietary considerations
- **Early** pipeline presentations; possible Industry collaboration
- Industry-initiated Public Private Partnership

Successful Implementation

- Transparency among all stakeholders
- Address anticipated, potentially adverse consequences
- **Initiate early pediatric pre-clinical testing initiatives - effective Industry-Academic collaboration when necessary (Public-Private Partnerships)**
- Recognize emerging scientific discovery
- **Global development requires international collaboration in designation of relevance, prioritization, and decision-making re. study feasibility and conduct**
- Robust, publicly shared, datasets-genomic, proteomic, pre-clinical testing- all require support and expansion

Global Coordination

- Priority setting of relevant targets through periodic international, multi-stakeholder workshops
- Continue Pediatric Cluster Call discussions of Pediatric Investigation Plans/initial Pediatric Study Plans (PIPs/iPSPs) and provide Common Commentary when requested and appropriate
- Plans for international expansion of the EU ACCELERATE Platform
- Support/encourage international trials when possible; avoid duplication and competition


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