FDARA 2017 and the RACE for Children Act: Implications for Pediatric Cancer Drug Development

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Disclaimer

- I have no financial interests to disclose
- I will not be presenting the off label use of any approved drugs

Outline

- Brief summary of U.S. legislation related to drug development for children
- Move from indication to MOA-based trigger for PREA requirements for pediatric studies: Voluntary to Mandatory
- Legislative mandates of FDARA to implement new pediatric provisions Title V
- Update on current plans
- Potential global implications: strategies for coordination

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

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

Current FDA Initiatives

- Increased role in promoting **collaborative** approach to timely pediatric drug development
- Optimizing regulatory authority of **BPCA**: Written Requests only since **PREA** of no relevance to oncology
- **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

Delayed Pediatric Cancer Drug Development Due to Orphan Exemption

- brentuximab vedotin (ADCETRIS)
- blinatumomab (BLINCYTO)
- inotuzumab ozogamycin (BESPONSA)
- liposomal cytarabine/DNR (VYXEOS)
- enasidenib (IDHIFA)
- midostaurin (RYDAPT)
- olaratumab (LARTRUVO)
- ipilumimab (YERVOY)
- pembrolizumab (KAYTRUDA)

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 from pediatric studies** for cancer drugs directed at relevant molecular targets.

Implications

- 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)

Status

- Introductory workshop planning in progress (February 20, 2018): Developing a framework for target selection/designation
- Target classification and criteria for determining relevance, process for updating lists, and additional considerations for decision-making for pediatric evaluation: Friends of Cancer Research
- Open Public meeting: 1)April 19, 2018 at FDA- Review molecular target lists. 2) Pediatric subcommittee of ODAC, June 18/19, 2018- review/comment on lists and considerations; process for prioritizing same in class agents- working with external constituents
- 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

Molecular Target

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.

Strategies for Identification

- Gene sequencing
- Expression profiling
- CMA
- Focused proteomics
- Pathway/phenotypic analysis
- Functional screening(siRNA, shRNA, CRISPR)
- *In vitro* or *in vivo validation*

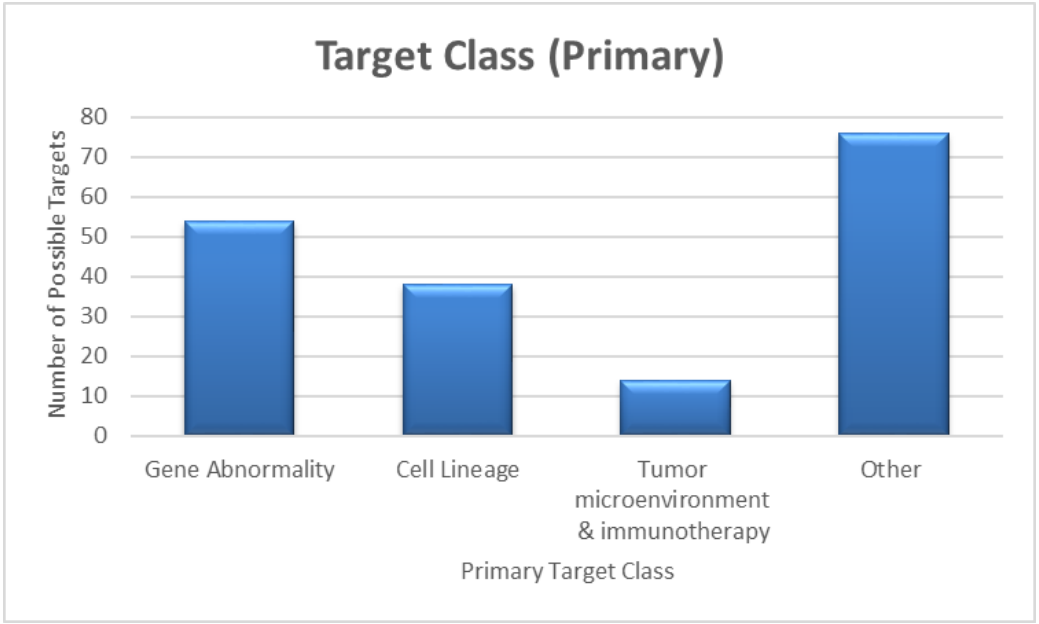
Target Classification

- Resulting from specific gene abnormalities; present in a critical biologically related pathway or exhibit a synthetic, lethal relationship to a gene abnormality
- Intrinsic to cancer cell lineage or developmental stage
- Contributing to functional aspects of tumor micro-environment (stroma, infiltrating immune cells)
- Essential elements of cancer (and normal) cells

Factors Related to Relevance

- Identification of the target in a pediatric cancer (gene defect, intrinsic or differential expression by cancer cell)
- Target function relevant to etiology or progression
- Effect of target modulation; in vivo, in vitro, synergy in biologic/rational combination
- Clinical experience; adult and pediatric
- Existence of predictive biomarkers
- Cell surface access of immune-directed targets

- About 182 possible targets identified thus far.



Considerations for Application of Target List to Product Development for Children

- Biologic plausibility
- Evidence of serious, deleterious (lethal) effects on critical developmental processes
- Risk: benefit analysis
- Toxicity profile
- Formulation issues
- Pre-clinical studies and access to product
- International coordination: global development

Successful Implementation

- Transparent process
- Respect/anticipate emerging scientific discovery
- International collaboration in designation and prioritization
- Recognize/address anticipated, potentially adverse consequences
- Global coordination/collaboration