Industry Perspective on Master Protocols and Platforms

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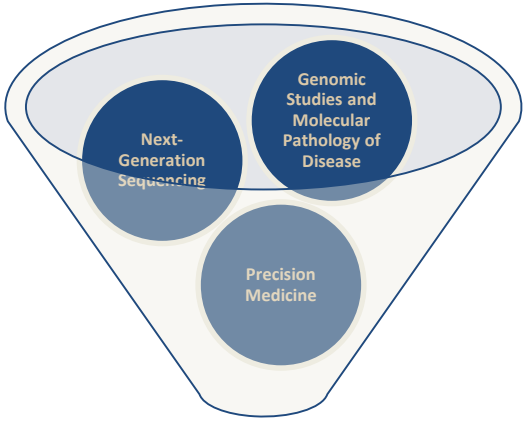
Presentation Outline

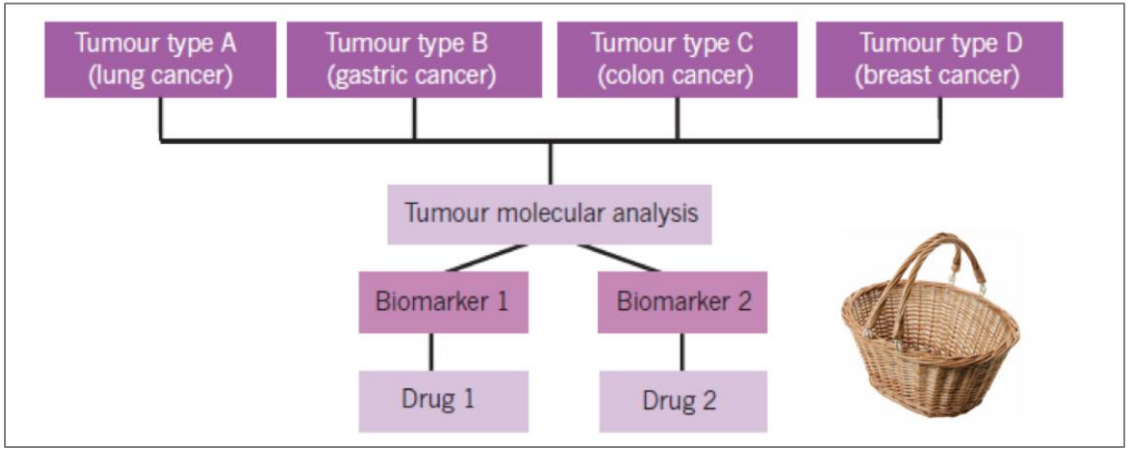
- Why Master Protocols?
- Challenges in Pediatric Oncology Drug Development
- Mechanism-of-Action Based Drug Development in Pediatric Oncology
- The iMATRIX Trial Concept and Its Master Protocol
- Opportunities & Challenges

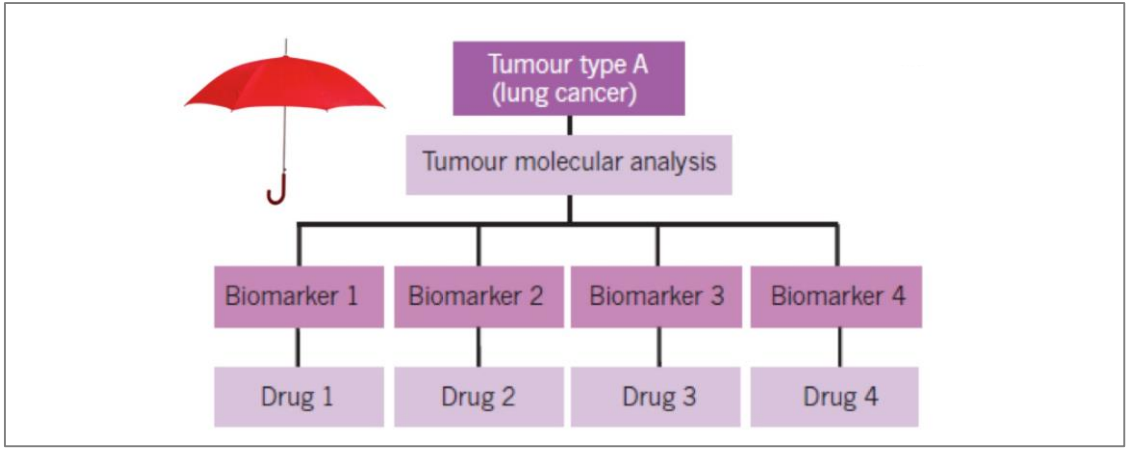
Master trials: finding the right trial for the patient

integrate predictive biomarkers, enable simultaneous study of multiple targeted agents across different tumor types in small populations of patients



Modern Oncology Drug Development



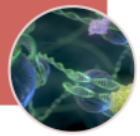


Master trials have multiple potential advantages

increased access for patients, optimized and cost-effective study conduct

Efficiency of screening

- Large population of patients screened
- Up-front screening for multiple biomarkers
- Common platforms for biomarker assessment
- Reduced screen failure rate



Expanded patient eligibility

- Access to many options
- Higher chance of being placed into a treatment arm (among many)
- Availability of treatments for uncommon-rare genotypes/ subsets

Increased speed of drug development

- Flexibility of closing and opening studies
- Single protocol
- Require fewer patients to be enrolled
- Vast clinical trial networks
- Shared control groups (recruitment time)
- Faster trial activation

Reduced cost of drug development

- Shared cost
- Cost savings from common trial infrastructure and single screening process
- Failures are early and cheap
- Shared control groups (trial costs)

Greater/better options for patients

- Sponsors can pursue disease areas of interest not supported by internal programs
- Patients are more likely to receive treatments that deliver meaningful benefit (See I-SPY 2)

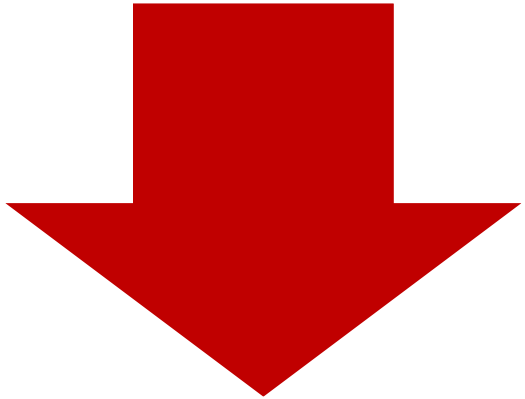
Accelerated drug approval

- Harmonized regulatory processes (e.g., single IND, etc.)
- Expedited review processes

Key reference: Seminars in Oncology: October 2015, 42(5), 724–730

Children with cancer also need access to new and more efficacious therapeutic options

Challenges



High **attrition rate in adult drug development** contributes to lack of early access to investigational drugs.

Pediatric oncology drug development is largely based on adult drug development programs. The majority of **pediatric tumors are rare and distinct entities** from those seen in adults

Multiple programs compete for **a limited patient pool** and for academic collaborators

Reactive obligatory vs proactive voluntary approach.

Limited market incentives

Leverage **pediatric expertise**

Match and prioritize molecules for pediatric cancers based on **target or mechanism of action** of the drug

Identify **new targets** in pediatric cancer

Increase efficiencies with **innovative trial designs**

Greater multi-stakeholder **collaboration** and sharing of information

Opportunities

Mechanism of action or target-based drug development in pediatric oncology

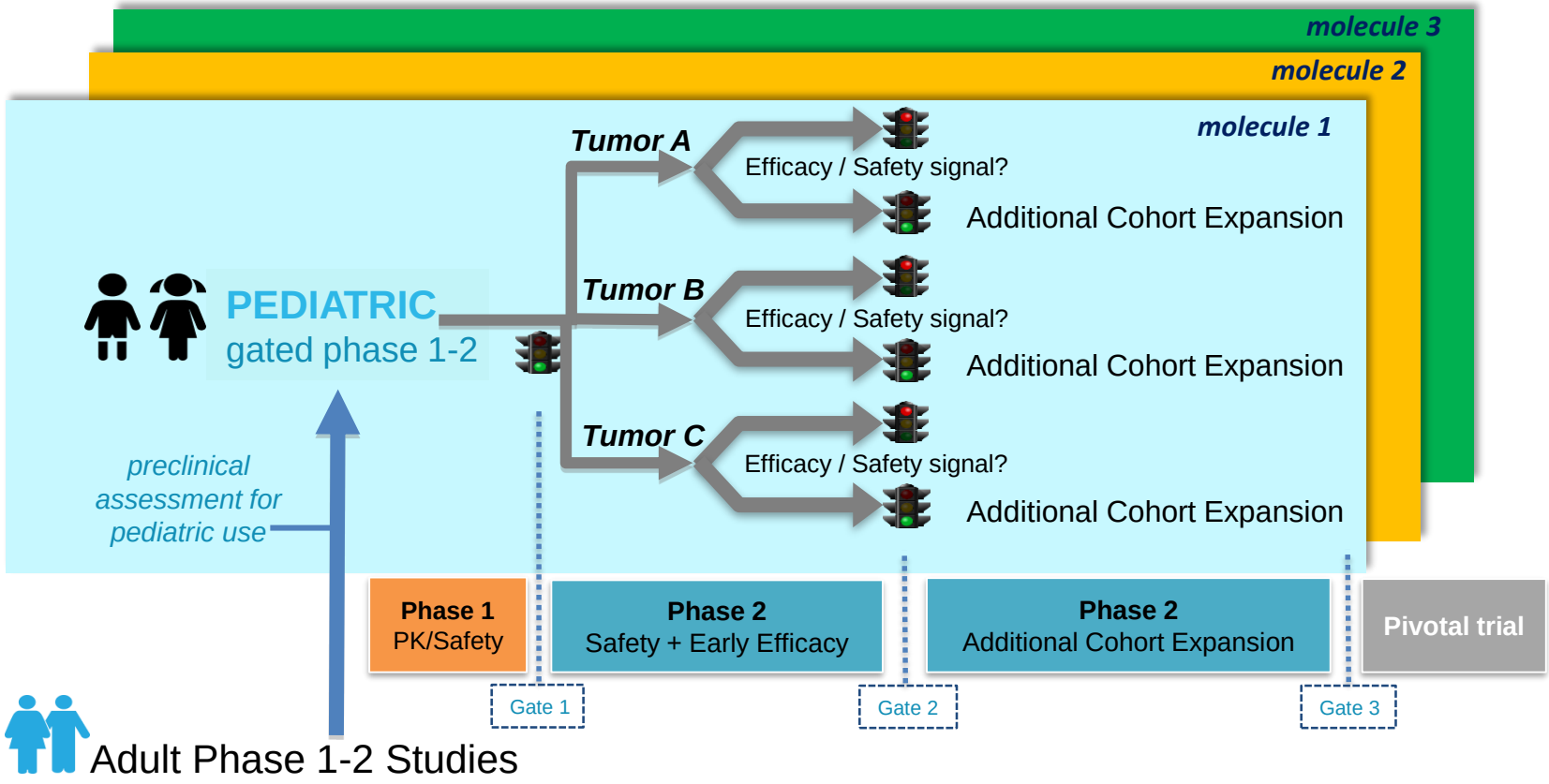
- Target-based drug development has largely benefited adult oncology patients. Drug development in children need to **keep pace with advances in science**
- **Adjust the focus of pediatric oncology drug development to the many pediatric diseases for which there are no adult counterparts**, rather than exclusively on the tumor types being investigated in adults
- Limit initial plan proposals to early phase pediatric clinical research, and defer discussion of pivotal trials until early-phase pediatric data is available
- Greater cooperation and collaboration between stake-holders to **prioritize new molecules based on mechanism of action or target of the drug**
- **Standardize** targeted approaches to ensure consistent interpretation by health authorities and industry for widespread adoption and sustainability
- Ultimately, **preserve and match children with rare tumors to the most promising therapies**

G. Vassal et al., *New drugs for children and adolescents with cancer: the need for novel development pathways,* The Lancet Oncology 14 (3), e117-124 (March 2013)

Robin Norris & Peter Adamson, *Challenges and opportunities in childhood cancer drug development,* Nature Reviews Cancer 12, 776-782 (November 2012)

The iMATRIX trial concept: preserve and match children with rare tumors to the most promising therapies

An innovative **pediatric** oncology clinical trial platform to **investigate several drugs in multiple tumor types**



The ultimate goal is to allow for molecule & disease prioritization within the regulatory framework

Disease	Molecule 1	2	3	4
A	√	√	x	√
B	x	√	x	x
C	N/A	x	x	x
D	x	x	x	√
E	√	x	N/A	x

Objective: one sponsored pivotal study per molecule in one disease supported by clinical evidence and feasibility assessment (extensive consultation with Academic Community and HAs)

Advance to pivotal trial | Available for supported research | No further development

iMATRIX trial status update

rapid accrual across a number of pediatric tumor types

- **Single molecule clinical studies** for atezolizumab and cobimetinib in several pediatric cancer tumor types have been initiated

- **Master Trial proposal** is currently being evaluated by the FDA and EMA
  - Joint FDA and EMA *Parallel Scientific Advice* and EMA Qualification procedure meeting on 31st August, 2016
  - Strong encouragement from the agencies to continue with the iMATRIX Trial efforts

- **Outreach Efforts for future Multi-Sponsor Master Trial** collaborations to enable industry to fulfill its mission of addressing unmet need for children with cancer and to provide rare patients with the most promising therapies

iMATRIX Master Protocol and Drug-specific appendices

An open-label, multi-center, Phase I/II Study, to evaluate the PK, safety, tolerability and efficacy of drugs in the treatment of relapsed or refractory pediatric tumors with known or expected pathway involvement

Study 1
iMATRIX Master IND/CTA

Study 2
New IND/CTA for Pivotal Study(ies)

Master IND/CTA for multiple drugs in multiple tumor types

Master Protocol +
Drug A appendix

IND/CTA amendments to add or remove drugs

- Drug B appendix
- Drug C appendix
- Drug D appendix
- Drug “n” appendix

best molecule: tumor match

The iMATRIX trial and its master protocol

an ongoing experiment with obvious opportunities… and some remaining challenges

Challenges

- New concept in pediatrics for national HAs and IRBs, lack of centralized review process may impact **review timelines**
- Complex design and quality oversight may complicate protocol & amendment **authoring and study start up**
- Operational benefits may only be seen when **a critical number of molecules** are available on the iMATRIX
- **Combinations** may require separate IND/CTA
- Ultimately, **actionable molecular targets may be rarer in children** compared to adults, limiting the impact of predictive biomarkers

Opportunities

- Target true **unmet needs** in childhood cancer
- **Evidence-based** identification of optimal tumor type(s) for each molecule
- **Consistency** of data collection, analysis, and interpretation
- **Operational efficiency** of trial conduct: same sites, accelerated implementation, optimization of costs
- Ultimately, provide a **standardized framework** for patient-centric development that preserves study participants and matches children with rare cancer to the most promising therapies **across industry's portfolio**

Paradigm shifts are urgently needed in pediatric drug development

Isolated development	Harmonized across industry
Reactive, late	Proactive, early
“Stick and carrot”	Pediatric-centric
Molecule-based in disease context	Mechanistic, biomarker-based in disease and molecule context

Doing Now What Patients Need Next