Pediatric Oncology Drug Development: A Time of and for Change

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The Challenge

• Improve cure rates

• Diminish acute toxicity

• Minimize risk for late effects
Cure Rates

5-year survival [%]

Treatment year

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Curing Cancer

5-year survival [%]

AML 1960s: 0, 1990s: 90
High Risk NB 1960s: 0, 1990s: 80
Brain Stem Glioma 1960s: 0, 1990s: 10

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PEDIATRIC CANCER U.S. Incidence (S.E.E.R. Program)

- Adult:Pediatric
  - 125-150:1

- Rate 1 in 7,000 in children 0-15 years
  - 9,000 cases/yr Ages 0-15 y
  - 3,700 cases/yr Ages 15-19 y
  - 1,500 cases/yr Ages 19-21 y
  - 14,200

- Cancer Deaths
  - 2,500-2,800/yr
Realities of Pediatric Cancer Research

- Relatively low incidence: study population
- Sub-classification and risk groups
- Mandates multi-center and multi-disciplinary clinical trials
- Improved outcome, accrual rates, integration of biology - evidence of success of NCI Cooperative Group Program
• Children’s Oncology Group
  • ~ 200 research sites throughout United States
  • Clinical trials opportunities for ~ 90% of children diagnosed with cancer in the US
Evolving and Changing Landscape of Cancer Drug Development

- Result of expanded understanding of the genetic epidemiology and molecular etiology of cancer
- Genomic/proteomic profiling of human cancers and identification of highly specific targeted agents
- Tissue/histology agnostic drug development
- Large treatment effects observed in small subsets of patients; seamless, adaptive study designs leading to drug approvals in defined cohorts
- **Precision Cancer Medicine**
  - Transformative: NSCLC, Breast, Melanoma, AML, and rare cancers
  - Target vulnerabilities extend to pediatric cancers.
Potentially Druggable Alterations

### Examples of Pediatric Precision Oncology Trials

<table>
<thead>
<tr>
<th>Trial type</th>
<th>Examples of precision trials</th>
<th>Sponsor</th>
<th>ClinicalTrials ID</th>
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<tbody>
<tr>
<td>Basket in relapsed/refractory cancers across multiple diagnoses</td>
<td>NCI–COG Pediatric MATCH&lt;br&gt;AcSé-ESMART</td>
<td>COG/NCI&lt;br&gt;Gustave Roussy</td>
<td>NCT03155620&lt;br&gt;NCT02813135</td>
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<td>Disease-specific umbrella in patients with progressive disease</td>
<td>Ruxolitinib or Dasatinib with Chemotherapy in Ph-Like ALL&lt;br&gt;NEPENTHE (Neuroblastoma)</td>
<td>MD Anderson&lt;br&gt;CHOP</td>
<td>NCT02420717&lt;br&gt;NCT02780128</td>
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<td>Single-agent targeted therapy in advanced cancers</td>
<td>Larotrectinib in NTRK Fusion Positive Tumors&lt;br&gt; EZH2 Inhibitor Tazemetostat in INI-1 Negative tumors&lt;br&gt; Crizotinib for Tumors with an ALK, MET or ROS1 alternation&lt;br&gt; LDK378 (Ceritinib) in ALK-activated Pediatric Tumors&lt;br&gt; Dabrafenib with Trametinib for BRAF V600 Positive Tumors&lt;br&gt; Afatinib in Pediatric Tumors with ErbB Pathway Deregulation</td>
<td>LOXO Oncology&lt;br&gt;Epizyme&lt;br&gt;UNICANCER&lt;br&gt;Novartis&lt;br&gt;Novartis&lt;br&gt;Boehringer Ingelheim</td>
<td>NCT02637687&lt;br&gt;NCT02601937&lt;br&gt;NCT02034981&lt;br&gt;NCT01742286&lt;br&gt;NCT02684058&lt;br&gt;NCT02372006</td>
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<td>Disease-specific trials in newly diagnosed patients</td>
<td>Total Therapy XVII JAK/STAT Mutations in ALL and Lymphoma&lt;br&gt;Addition of Dasatinib for ALL with TKI-targetable Fusions&lt;br&gt; Combination Therapy Plus Dasatinib for Ph-Like B-ALL&lt;br&gt; Clinical and Molecular Risk-Directed Therapy (Medulloblastoma)&lt;br&gt; BIOMEDE (DIPG)</td>
<td>St. Jude&lt;br&gt;DFCI&lt;br&gt;COG/NCI&lt;br&gt;St. Jude&lt;br&gt;Gustave Roussy</td>
<td>NCT03117751&lt;br&gt;NCT03020030&lt;br&gt;NCT02883049&lt;br&gt;NCT01878617&lt;br&gt;NCT02233049</td>
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**ALL**, acute lymphoblastic leukemia; AcSé-ESMART, Secured Access Program of the French National Cancer Institute (INCa); COG, Children’s Oncology Group; ESMART, European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors in Children; MATCH, Molecular Analysis for Therapy Choice; NCI, National Cancer Institute; NEPENTHE, Next Generation Personalized Neuroblastoma Therapy; Ph-like, Philadelphia chromosome-like.
Larotrectinib: FDA Approved in Pediatrics

Laetsch TW et al. *Lancet Oncol*. 2018

*Figure 2: Swimmer plot of all enrolled patients (n=24) by NTRK fusion status*
Many Challenges Applying the Precision Approach to Pediatric Oncology

- Limited understanding of the spectrum of biologically and clinically-relevant alterations
- Limited number of pre-clinical models
- Limited experience with clinical application of genomic sequencing technologies
- Challenges of clinical trial design
  - Small numbers of patients with each tumor subtype
  - Biopsies of refractory tumors often not performed
- **Limited number of available drugs**
Average of 6.5 yrs to Start Pediatric Trial

Median = 6.5 yr

Neel DV et al. Eur J Cancer. 2019
RACE for Children Act:

• 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.
Factors Related to Relevance

- Identification of the target in a pediatric cancer
- Target function related to etiology or resistance
- Effect of target modulation- *in vivo, in vitro*; synergy in biologic/rational combination
- Clinical experience: adult and pediatric
- Availability of predictive and response biomarkers
Biology and Pre-clinical Data

- Valid and relevant cell lines and models limited in pediatric oncology
- Many ‘targets’ evaluated late
  - eg Alk and crizotinib
- Limited relevant human tumor data
  - Different tumors
  - Relative rarity
Target/Drug Selection

• Pediatric pre-clinical data to suggest possible role in a pediatric tumor
  • To justify a phase ½ trial or expansion cohort minimal data required
    • Cell lines
    • Pathway knowledge
    • Broad mechanism e.g. immune check point

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Drug Formulation

• IV is easy
  • All ages eligible
• Oral
  • May limit based on size to allow for dosing in pediatrics but wouldn’t base on age but size and the available strengths/formulation
• Currently most companies delay development until an adult indication is clear: RACE Act may help change this
Key Considerations

Pediatric formulation requirement

• 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)].

• Importance of early development of pediatric formulations:
  eg: larotrectinib vs entrectinib in NTRK oncofusion positive cancer

• Impact on accuracy and feasibility of drug administration to children

• Develop pediatric appropriate formulation in stages
  Start with existing formulation and concurrently develop pediatric appropriate formulation as data emerge
Key Considerations

• Clinical benefit: risk analysis
• Safety and toxicity profile
  • Pre-clinical
    • Growth and development
  • Clinical
    • Toxicities from adults
Key Considerations
Rare target patient populations require collaboration
• International clinical trial collaboration
• Coordination of regulatory requirements

Adequate safety and dosing data in children and adolescents
• Age of eligibility and appropriate formulations
• FDA recommendation on adolescent cohorts  *Chuk et al Clin Cancer Res 2017 23:9-12*

Impact on trial design
• Master protocols
• Rolling 6 design with expansions to ensure adequate toxicity and PK data
• Starting dose based on adult recommended phase 2 dose
• Limit pediatric dose finding
Changing the Future of Pediatric Oncology Drug Development

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<tr>
<th>TRIAL ASPECT</th>
<th>PAST</th>
<th>FUTURE</th>
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<tr>
<td>Timeline for trials in pediatrics</td>
<td>First-in-child occurs several years after first-in-human</td>
<td>Adolescents enrolled in trials concurrent with adults</td>
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<tr>
<td></td>
<td>0</td>
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<td></td>
<td>FDA approval</td>
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Plan for trials in children in place early in drug development
Development of new agents to improve the outcome of children and adolescents with cancer requires:

- Coordination of pre-clinical, clinical, and biologic resources
  - Improved understanding of the tumor/host/drug factors
  - Development of Biomarkers and standardized genomic testing
  - Access to agents of interest
- Collaboration
  - NCI/Academia/Industry
  - International