Lessons Learned from Failed Pediatric Trials:

Failed Trials and Design Considerations in Pediatric Oncology

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Cure Rates

5-year survival [%]

Treatment year

SEER: Adamson
Curing Cancer

Side Effects
- Severe
- Moderate
- Mild
- Fatal
- Life Threatening

Late Effects
- Vision
- Brain
- Hearing
- Lungs
- Kidneys
- Digestive System
- Skin

Organ Systems
- Endocrine
- Heart
- Liver
- Fertility
- Bones
Ultimate Challenges in Pediatric Oncology

- Improve cure rates
- Decrease acute toxicity
- Minimize risks for late effects
Strategies to Prioritize Drugs For Pediatric Development

- Biology: Molecular target identification, drug mechanism of action, micro-environment vs tumor effects
- Drug availability and formulation
- Pre-clinical data: Cell lines, validated in vivo models
- Clinical data: Relevant adult trials
Pre-clinical Data

• Cell lines
  • Readily available for most pediatric cancers
  • Can investigate and understand targets, large screens quickly and relatively inexpensive
  • No understanding of host factors, dose exposure considerations may not reflect in vivo, genetic drift

• Animal Models
  • Issues of immunodeficient mice if using xenografts/PDX
  • Orthotopic vs alternative site: microenvironment issues
  • Dose/schedule/toxicity: labor and resource intense
  • Genetically engineered models may not truly reflect genetic complexity of childhood cancer
## New Drug Development in RMS

**Xenograft to Phase III Clinical Trials**

### Xenograft model

#### Phase II Window

- **Melphalan** + vincristine: Active
- **Ifosfamide** + etoposide: Active
- **Ifosfamide** + doxorubicin: Active
- **Topotecan** (IRS V): Single agent Active
- **Topotecan** + cyclophosphamide (D9501): Active

#### Definitive Phase III Study

- Too toxic
- IRS IV
- Intermediate-Risk (D9803) No improvement in FFS

*Cancer Chemother Pharmacol. 1995;36(5):393-403*

*J Clin Oncol 2001;19:213-9*

*J Clin Oncol 2004;22:1398-403*

*J Clin Oncol 2006;24:3415-22*

*J Clin Oncol 2009;27:5182-8*
**mTOR Inhibitor, VEGFR Inhibition and Chemotherapy in Rhabdomyosarcoma**

- Vinorelbine and cyclophosphamide are active in relapsed Rhabdomyosarcoma  
  Casanova M, Cancer 2002; Kuttesch JF, PBC 2009; Casanova M, Cancer 2004

- Complete inhibition of RMS xenograft growth and neovascularization with VEGF blockade

### RAPAMYCIN + VINCRISTINE

- Pediatric Phase 1 trial of bevacizumab completed with no DLT

- Increased mTOR pathway activation in RMS associated with decreased survival  
  PPTP demonstrated activity of Rapamycin in RMS

### RAPAMYCIN + CYCLOPHOSPHAMIDE

- Temsirolimus tested in Pediatric Phase 1 trial  
Randomized Phase 2 Trial: Bevacizumab and Temsirolimus in combination with Vinorelbine (V) and Cyclophosphamide (C) for First Relapse/Disease Progression of Rhabdomyosarcoma (RMS)

COG: Mascarenhas

- Randomized selection design: early end point of 6 month EFS

- 6 month EFS: Regimen **A 54%** (95% CI 38%, 65%), Regimen **B 67%** (95% CI 50%, 79%)

- 1 year EFS: Regimen **A 12%** (95% CI 3%, 30%), Regimen **B 43%** (95% CI 26%, 59%)

- Temsirolimus has been selected by COG for further investigation in newly diagnosed intermediate RMS patients randomized with VAC/VI backbone

- Still to come biological correlates of response
Eribulin and Osteosarcoma

- FDA approved as a single agent for metastatic breast cancer

- Phase 2 activity in adults with soft tissue sarcomas

- Moved to a phase 2 study in osteosarcoma at RP2D based on preclinical data

- 0/19 patients had response

- ?? What predicated response in preclinical model
- ?? How strong a pre-clinical signal do you need
- ?? What about combination strategies

Parp Inhibition and Ewing Sarcoma

- Drug screen demonstrated highly significant association between *EWS-FLI1* rearrangement and sensitivity to the PARP1 inhibitor olaparib

- Ewing sarcoma cell line assays confirmed sensitivity discovered in drug screen
  

- Phase 2 study single agent failed in adults with Ewing
  
  BMC Cancer. 2014 Nov 5;14:813

- Parp inhibition sensitizes to DNA damage prevents repair

  Cell Rep 2014;9(3):829-41
  Pediatr Blood Cancer 2015;62:91-8
  Mol Cancer Ther 2015;14:2818-30
Novel Phase 1/2 Study
ADV1411: Talazoparib with Temozolomide

Part A: dose finding with required PK
Of both Talazoparib and Temozolomide

Part B: Ewing Sarcoma phase 2
Simon 2 stage design
Tissue and biomarker evaluation
(PARP-1 and DNA repair markers)

Unique elements:
• No single agent data for parp inhibitor in children needed as agent will be synergistic
• First study to have this design in children

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>BMN 673 (mcg/m²/dose)</th>
<th>Temozolomide (mg/m²/dose)</th>
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<tbody>
<tr>
<td>-1</td>
<td>400#</td>
<td>800</td>
</tr>
<tr>
<td>1*</td>
<td>400#</td>
<td>800</td>
</tr>
<tr>
<td>2</td>
<td>400&amp;</td>
<td>800</td>
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<td>3</td>
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</tr>
<tr>
<td>6</td>
<td>600&amp;</td>
<td>1000</td>
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</table>
Anaplastic Lymphoma Kinase Gene

- Originally identified in ALCL as a fusion transcript t(2;5) \((\text{Morris S et al., Science, 1994})\)

- Inflammatory Myofibroblastic Tumors (IMT) - 30-50%

- Non-small cell lung cancer (NSCLC) - 3-5%

- Neuroblastoma - mutations/amplification in 14% of HR group

- Others
  - Renal Cell Ca
  - Anaplastic Thyroid Ca
  - Rhabdomyosarcoma
  - Resistance mechanism to ALKi Rx
ALK-1 Genetic Alterations in Cancer

Mutations Amplification

Neuroblastoma
Somatic
Germline

ALK aberrations

Translocations

ALCL
Somatic unique

IMT
Somatic shared unique

NSCLC
unique

No activity
Ligand dependent
Constitutive
Constitutive
No activity

Targeted Responses to Crizotinib

Patient with ALCL- CR by FDG-PET
Pre-Cycle 1  Post-Cycle 1 (28 days)

Patient with NB-germline mutation

Pre-Cycle 1  Post-Cycle 24
On-going Learning from ALK

• Mild side effects, long term administration tolerable; single agent MTD at 280 mg/m$^2$ (almost twice the adult dose) \textit{The Lancet Oncology, 2013 May;14(6):472-80}

• Response in ALCL met phase 2 endpoint for efficacy
  – Frontline trial incorporating crizotinib has opened (ANHL12P1, \texttt{ClinicalTrials.gov} Identifier: NCT01979536)

• Crizotinib may have a role in treatment of ALK+ IMT

• Phase 2 in patients with ALK+ NB continues

**Objective:** to open a COG-wide single stage phase II trial of genomically-directed therapies for children with refractory solid tumors and lymphomas
Adult target Cmin: 60 ug/ml at 6 mg/kg
Cixutumumab: recommended phase 2 dose higher then adults

Greater variability in clearance

Higher dose to hit desired adult target concentrations

Table 4. Pharmacokinetic Parameters (mean ± standard deviation) After First Infusion

<table>
<thead>
<tr>
<th>Dose Level (mg/kg)</th>
<th>( C_{\text{min}} ) (( \mu \text{g/mL} ))</th>
<th>( C_{\text{max}} ) (( \mu \text{g/mL} ))</th>
<th>Clearance (mL/h/kg)</th>
<th>( \text{AUC}_{0-\infty} ) (hr ( \times ) mg/mL)</th>
<th>Half-Life (days)</th>
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<tbody>
<tr>
<td>6</td>
<td>59 ± 31</td>
<td>252 ± 95</td>
<td>0.25 ± 0.12</td>
<td>32.6 ± 21.1</td>
<td>4.2 ± 1.3</td>
</tr>
<tr>
<td>No. of patients</td>
<td>17</td>
<td>7</td>
<td>7</td>
<td>7</td>
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<tr>
<td>9</td>
<td>106 ± 57</td>
<td>400 ± 141</td>
<td>0.22 ± 0.08</td>
<td>46.3 ± 20.8</td>
<td>4.4 ± 1.1</td>
</tr>
<tr>
<td>No. of patients</td>
<td>17</td>
<td>14</td>
<td>9</td>
<td>9</td>
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</tr>
</tbody>
</table>

Abbreviations: \( \text{AUC}_{0-\infty} \), area under concentration versus time curve extrapolated to infinity; \( C_{\text{max}} \), peak concentration; \( C_{\text{min}} \), trough concentration.
*Trough concentration 7 days after initial infusion.

J Clin Oncol 30:256-262., 2011
Lessons Learned and Opportunities for the Future in Pediatric Cancer Trials

• Beware of pre-clinical: models, exposure comparisons, surrogate markers of response
• Some agents may need very little dose finding in pediatrics e.g antibodies, agents with minimal toxicity
• Need early decision point to move a drug into up front therapy: randomized phase 2 studies
• Combinations
  – How to evaluate for up front therapy? What data is needed?
• Molecularly guided therapy: only 10-20% of patients at best
Conclusions

• To develop new agents to enhance the care of children and adolescents with cancer:
  – Requires coordination of pre-clinical, clinical and biologic resources
    • Needs understanding of the tumor/host/drug factors
    • Requires access to agents of interest with appropriate formulations for children
  – Requires collaboration
    • NCI/Academia/Industry
    • International
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Patients, Families, Dedicated Pediatric Oncology Community