Pediatric Phase I / Pilot Consortium

Malcolm A. Smith, MD, PhD
Cancer Therapy Evaluation Program
November 2011
Pediatric Phase I / Pilot Consortium – Children Are Different

- Multi-institutional studies required:
  - Substantial infrastructure required for site training, for study monitoring, and for implementing PK/PD/Imaging studies
- Ethical issues limit risks to children participating in correlative research studies
  - Direct impact on type of PD studies that can be performed
- Pharmaceutical interest is limited →
  - Limited non-NIH funding stream for pediatric drug development
  - NCI plays unique role in supporting teams of experienced investigators to safely & efficiently conduct multi-institutional “first-in children” studies
US childhood mortality trends for lymphoma and leukemia, and all other cancer sites combined

- 1975-1996, APC = -1.9*
  95% CI, -2.1 to -1.7
- 1996-2006, APC = -0.3
  95% CI, -1.1 to 0.5
- 1975-1998, APC = -3.6*
  95% CI, -3.8 to -3.5
- 1998-2006, APC = -2.2*
  95% CI, -3.1 to -1.2
Strategy for Discovering Effective New Treatments for Children with Cancer

TARGET Discovery Programs

PPTP Preclinical Evaluation

COG Phase 1 Clinical Trial

COG Definitive Clinical Trial
• History of NCI support:
  – Pediatric phase 1 clinical trials resource supported by NCI since 1992
  – COG Phase 1 Consortium supported since 2002
  – NCI continues providing primary support for pediatric phase 1 trials in children with cancer in North America

• Ongoing need:
  – Approximately 20% of children for whom current treatments not sufficiently effective. Continued need for NCI support of an experienced team of investigators to conduct first-in-children studies for new anticancer agents with novel mechanisms of action and molecular targets
Consortium Contributions

• Phase 1 evaluations of targeted agents building on genomic and preclinical discoveries:
  – ALK inhibitor crizotinib phase 1 study focusing on patients with neuroblastoma and ALCL and other tumors with ALK mutations.
  – JAK inhibitor ruxolitinib (INCB018424) phase 1 study following up on discovery of JAK mutations in high-risk B-precursor ALL.
  – Aurora A kinase inhibitor MLN8237 phase 1 study following up on PPTP findings of high activity for MLN8237 against ALL and neuroblastoma preclinical models.
  – NTX-010 (Seneca Valley Virus, SVV-001) oncolytic virus phase 1 study focusing on patients with neuroendocrine tumors

• COG Phase 1 Consortium conducts phase 1 studies with intensive monitoring and PK / PD evaluations

• COG builds on Consortium phase 1 studies by developing phase 2 and subsequently phase 3 clinical trials using dose/schedule/PK data generated by the Consortium.
JAK mutations in “BCR-ABL1-like” ALL

- JAK2 (n=16): 10 R683G; 3 non-R683G pseudokinase domain; 3 kinase domain
- JAK1 (n=3): 3 pseudokinase domain
- JAK3 (n=1): uncertain functional consequences

• Phase 1 trial of JAK inhibitor ruxolitinib (INCB18424) in Sept 2010 in collaboration with Incyte.

• Ruxolitinib in development for adults with myelofibrosis (MF):
  – JAK2 mutations common for this condition
  – NDA filed in June 2011

• Eventual COG plan for combining JAK inhibitor for JAK-mutant ALL in same way that imatinib has been added to standard chemotherapy for BCR-ABL ALL.
ALK is an Oncogenic Kinase in Neuroblastoma

- Co-discovery of ALK as the familial neuroblastoma gene (Mosse, Nature 2008) and frequent somatic amplification and mutation (TARGET)
  - Amplification: 31/599 (5.2%)
  - Focal gain: 102/599 (17.0%)
  - Mutations in kinase domain: 43/552 (7.2%)
  - Mutations in extracellular domain: Present, frequency still be defined

![Diagram showing MYCN, ALK, Somatic Mutations, and Germline Mutations]
ALK-mutated (translocated) tumors are highly sensitive to ALK inhibitors

• PF-02341066 in the Karpas299 xenograft model (NPM-ALK ALCL).
• 1st cycle of treatment initiated on day 11 through day 23 (except the 100 mg/kg group, which was treated through day 28).
• A 2nd cycle of treatment initiated on day 62 - 76 for the 100 mg/kg/d group after tumor regrowth.
• COG Phase 1 Consortium initiated phase 1 trial of ALK inhibitor crizotinib (PF-02341066) Sept 2009.
Consortium Contributions

- Phase 1 evaluations of targeted agents building on genomic and preclinical discoveries:
  - ALK inhibitor crizotinib phase 1 study focusing on patients with neuroblastoma and ALCL and other tumors with ALK mutations.
  - JAK inhibitor ruxolitinib (INCB018424) phase 1 study following up on discovery of JAK mutations in high-risk B-precursor ALL.
  - Aurora A kinase inhibitor MLN8237 phase 1 study following up on PPTP findings of high activity for MLN8237 against ALL and neuroblastoma preclinical models.
  - NTX-010 (Seneca Valley Virus, SVV-001) oncolytic virus phase 1 study focusing on patients with neuroendocrine tumors

- COG Phase 1 Consortium conducts phase 1 studies with intensive monitoring and PK / PD evaluations
- COG builds on Consortium phase 1 studies by developing phase 2 and subsequently phase 3 clinical trials using dose/schedule/PK data generated by the Consortium.
Further Clinical Evaluations of Agents Recently Studied by COG Phase 1 Consortium

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent(s)</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVL0319</td>
<td>Lenalidomide</td>
<td>Phase 2 CNS trial in children with recurrent low-grade gliomas</td>
</tr>
<tr>
<td>ADVL0413</td>
<td>Sorafenib</td>
<td>Frontline for FLT3 positive AML</td>
</tr>
<tr>
<td>ADVL0414</td>
<td>VOIT</td>
<td>Frontline COG pilot study for high risk rhabdomyosarcoma</td>
</tr>
<tr>
<td>ADVL0416</td>
<td>SAHA + Cis RA</td>
<td>Frontline PBTC trial for infants with CNS embryonal tumors</td>
</tr>
<tr>
<td>ADVL0419</td>
<td>Valproic acid</td>
<td>Frontline Texas-Oklahoma Pediatric Neuro-Oncology trial in BSG and unresectable HGG</td>
</tr>
<tr>
<td>ADVL0515</td>
<td>CBDCA + VBL</td>
<td>Under consideration by CNS tumor committee</td>
</tr>
<tr>
<td>ADVL0516</td>
<td>Dasatinib</td>
<td>Frontline COG trial for children/young adults with Philadelphia chromosome positive ALL</td>
</tr>
<tr>
<td>ADVL0517</td>
<td>Ispinesib</td>
<td>No further development; CTEP withdrew IND</td>
</tr>
<tr>
<td>ADVL0612</td>
<td>Sunitinib</td>
<td>Phase 2 COG trial for children with recurrent CNS tumors</td>
</tr>
<tr>
<td>ADVL0712</td>
<td>IMC-A12</td>
<td>Phase 2 COG trial for children with sarcomas and other solid tumors and frontline study for metastatic rhabdomyosarcoma</td>
</tr>
<tr>
<td>ADVL0714</td>
<td>VEGF Trap</td>
<td>No further pediatric development due to toxicity and PK profile</td>
</tr>
<tr>
<td>ADVL0812</td>
<td>MLN8237</td>
<td>Phase 2 COG trial in refractory/recurrent solid tumors including neuroblastoma and ALL</td>
</tr>
</tbody>
</table>
Would making the Phase 1 Consortium part of COG be a more efficient use of resources?

• The Consortium is integrated with COG in appropriate ways:
  – Clinical data management system
  – Protocol development resources
  – Shared meetings
  – Thus, no duplicative infrastructure

• Scope of clinical trials for the Consortium is very different from those of COG:
  – Intensity of monitoring and data reporting
  – Numbers of patients per trial and numbers of participating institutions
  – Emphasis on PK, PD, and imaging endpoints
  – If COG were to take responsibility for phase 1 trials, it would need to replicate the Consortium’s capabilities in these areas

• There would be little or no budgetary savings from incorporating the Consortium into COG assuming that the same scope of work was maintained
What is gained by having the Phase 1 Consortium distinct from COG?

- Focused NCI and peer review to ensure that the Consortium has the following:
  - Strong scientific leadership,
  - Data collection and management procedures that meet the high standards for granularity, accuracy, and timeliness required for phase 1 trials,
  - Appropriate integration of PK and PD
  - High productivity in developing and completing clinical trials

- Phase 1 studies would represent a small percentage of COG accrual if Consortium were merged into COG:
  - Risk that phase 1 trials would be de-emphasized because of the higher priority for COG of larger phase 2 and 3 trials
Budget Considerations

• Flat Budget relative to FY10:
  – Direct cost in Year 1 of $3 million
  – Total cost in Year 1 of $3.47 million

• Apportioning of funds:
  – Scientific Leadership (~10%)
  – Protocol Development & Regulatory (15%-20%)
  – Statistics and Data Management (~10%)
  – Imaging (15%-20%)
  – Pharmacokinetic/Biology Support (~5%)
  – Travel (4%)
  – Basic Member Institution Site Support (~40%)
Conclusions

- COG Phase 1 / Pilot Consortium is premier organization for conduct of “first in children” clinical trials for anticancer agents
- Record of accomplishment:
  - Protocols activated and completed
  - Patients enrolled
  - Publications and presentations
  - Contributions to COG PK studies
  - Mentoring junior faculty
  - Integrating new imaging methods into pediatric phase 1 trials
- Consortium is needed so that children can benefit from advances in cancer biology and drug development in coming years.