Tumor Panel I:
Rare and Pediatric Cancers
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Moderator:

Mike Rice, MS, MBA, Senior Consultant, Defined Health

Panelists:

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- Meredith K. Chuk, MD, Scientific Liaison for Sarcoma, Medical Officer, FDA
- Carlos Rodriguez-Galindo, MD, Associate Professor, Department of Pediatrics, Harvard Medical School; Medical Director, Pediatric Oncology Clinical Trials, Pediatric Oncology, Dana-Farber Cancer Institute; Director, Solid Tumor Program, Pediatric Oncology, Dana-Farber Cancer Institute
- Maoxia Zheng, PhD, Global Development Team Leader, Pediatric Oncology, Genentech
- Peter Sandor, MD, MBA, Vice President, Global Marketing Oncology, Amgen Inc.
Pediatric Cancers Largely Treated by Evidence Based / Off-Label Use of FDA Approved Drugs Tested in Adults

- As of 2003, there were only 15 oncology drugs specifically labeled for use in children (Table 1).
- The NCI lists 410 FDA approved oncology therapeutic and supportive care drugs.
- Today, only approximately 20 are FDA approved for pediatric use.
  - Only 3 were first approved in children.
- According to Adis R&D Insight, there are 67 drugs in development for pediatric oncology indications; which if successful could significantly impact the management of childhood cancers.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Asparaginase</td>
<td>Leukemias, lymphomas, neuroblastoma, retinoblastoma</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Acute nonlymphocytic leukemia in adults and children</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Wilm’s tumor, rhabdomyosarcoma, choriocarcinoma, testicular carcinoma, Ewing’s sarcoma, sarcoma botryoides</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Acute lymphocytic leukemia in adults and children</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Wilm’s tumor, neuroblastoma, soft tissue sarcomas, Hodgkin’s disease, other malignant lymphomas, acute lymphocytic leukemia, acute myelogenous leukemia</td>
</tr>
<tr>
<td>Lomustine</td>
<td>Brain tumors, Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>Acute lymphocytic leukemia in adults and children</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Acute lymphocytic leukemia, meningeal leukemia, osteosarcoma, non-Hodgkin’s lymphomas</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Thioguanine</td>
<td>Acute Non-lymphocytic leukemia</td>
</tr>
<tr>
<td>Teniposide</td>
<td>Refractory childhood acute lymphocytic leukemia</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>Acute promyelocytic leukemia</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Histiocytoses, testicular germ cell carcinomas, Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Vinoreistine</td>
<td>Acute leukemias, lymphomas, Wilm’s tumor, rhabdomyosarcoma, neuroblastoma</td>
</tr>
</tbody>
</table>

Source: Journal of Clinical Oncology, Vol 21, No 6 (March 15), 2003: pp 1066-1073, Adis R&D Insight
### Only 3 Drugs First FDA Approved in Children – Significant Lag for Access to Most Oncology Drugs Approved in Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pediatric Indication</th>
<th>Pediatric Approval Date</th>
<th>Adult Indication</th>
<th>Adult Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unituxin (dinutuximab)</strong></td>
<td>Neuroblastoma</td>
<td>Mar-15</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Clolar (clofarabine)</strong></td>
<td>R/R ALL</td>
<td>Jan-05</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Vumon (teniposide)</strong></td>
<td>R/R ALL</td>
<td>Jul-92</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Arranon (nelarabine)</strong></td>
<td>R/R T-ALL</td>
<td>Oct-05</td>
<td>R/R T-ALL</td>
<td>Oct-05</td>
</tr>
<tr>
<td><strong>Oncaspar (pegaspargase)</strong></td>
<td>Front-Line ALL</td>
<td>Jul-06</td>
<td>R/R ALL</td>
<td>Feb-94</td>
</tr>
<tr>
<td><strong>Gleevec (imatinib)</strong></td>
<td>Ph1+ ALL</td>
<td>Sep-06</td>
<td>CML</td>
<td>May-01</td>
</tr>
</tbody>
</table>
Despite Limited Innovation in Treating Pediatric Cancers – Incremental Improvements in Protocols Has Reduced Pediatric Mortality By 50%

- Cancer is a leading cause of death in children, second only to accidents. (annual 10,450 new cases)

Figure 5. U.S. Pediatric Cancer 5-Year Survival by Site, Ages 0–19

- Hodgkin lymphoma
- Wilms tumor
- Leukemia
- Non-Hodgkin lymphoma
- All Sites
- Neuroblastoma
- Soft Tissue sarcoma
- Brain/ONS
- Bone and joint

NCI - An Analysis of the National Cancer Institute’s Investment in Pediatric Cancer Research, 2013
Outcomes Transformed Through Both Trial and Error and Rationally Designed Transformative Therapies

Improvement in patient outcomes can be rapid with rationally designed transformative therapies, or incremental advances in treatment standards.

Then and Now: Age of Onset Compared to Overall Survival

Trial and error incremental advancement

SEER database; scientific literature
Why is it Important to Understand Pediatric Cancer and Prioritize Child Centric Drug Programs?

- Cancers in children are distinct diseases compared to those observed in adults
- Compared to adults, children respond differently to therapies and have unforeseen adverse effects:
  - Differences in mutational drivers, relatively few secondary mutations compared to adults
  - Childhood growth and development lead to different toxicities than seen in adult clinical studies (short stature, infertility, cardiotoxicity, cognitive impairment, bone conditions and secondary malignancies)
  - Late effects are different than adults and with median diagnosis at age 6, survivors have >70 years of expected life to deal with sequelae of disease / treatment
- For example, unmet needs in Acute Lymphoblastic Leukemia (ALL) are considerably different depending on age
Aging Formulary of Pediatric Oncology Drugs - How to Incentivize Pediatric Drug Development?

- Most drugs available to children were developed for adult diseases and half the drugs used for pediatric cancer treatment are over 25 years old.
  - The FDA has approved only three new drug expressly developed for a pediatric cancer in the past 25 years.
  - NCI spends 96% of its budget on adult cancers and only 4% of its budget on children’s cancers.
- Pharmaceutical companies currently lack the financial incentives to develop new drugs because the market for drugs for rare pediatric diseases is so small.
  - Research and development for new drugs from pharmaceutical companies comprises 60% of funding for adult cancer drugs – almost negligible for childhood cancers.

- NCI’s investment in pediatric cancers research was $185.1 million in fiscal year (FY) 2013.

Figure 10. NCI’s Childhood Cancer Projects by Cancer Site

NCI - An Analysis of the National Cancer Institute’s Investment in Pediatric Cancer Research, 2013
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