In September 2022, COACH convened its second meeting with representatives from the National Cancer Institute (NCI), Food and Drug Administration (FDA), European Medicines Agency (EMA), advocacy groups, and organizations, including the Pediatric Preclinical Proof of Concept Platform (ITCC-P4), and the Pediatric Preclinical In Vivo Testing (FNIT) consortium to assess three cancer-associated targets that could be potential entities for development of life-saving drugs for pediatric indications.

Hallmarks of Cancer

**MEN1:** Scaffold for chromatin remodeling
- Mutations in MEN1, the gene that encodes menin protein, result in uncontrolled cell division and tumorigenesis.
- Inhibition of MEN1 results in increased non-homologous end-joining DNA repair.
- Mutations in MEN1, the gene that encodes menin protein, may play a role in tumorigenesis.

Key Considerations
- Menin inhibitors may be effective for several tumor types, and preclinical research may identify additional menin inhibitor resistance mechanisms.
- Use of chemotherapy and kinase inhibitors may help mitigate differentiation syndrome that arises due to menin inhibition.
- Electrolyte control may help prevent menin inhibitor-associated cardiac toxicities.

Recommendations
- Perform pharmacokinetic studies to aid future pediatric clinical trial design.
- Identify menin inhibitor combination therapies, including novel therapeutics and existing chemotherapies.
- Use future Phase I adult clinical trials data to determine whether to pursue, and how to design, menin inhibitor pediatric clinical trials.

**IL-2:** Immune system activator
- Mutations in IL-2 are rare in tumor genomes.
- Drugs that stimulate IL-2, S. 2, activity induces immune responses that can target tumors.

Key Considerations
- T-cell receptors targeted by IL-2 agents may preclude pediatric clinical trials.
- Results from adult clinical trials of new IL-2 agents will determine the relevance of IL-2 for pediatric populations.
- Results from preclinical models can be used to evaluate new IL-2 agents that are successful in adult clinical trials.
- IL-15 has a lower toxicity profile compared to IL-2.

Recommendations
- Use future results from adult clinical trials of new IL-2 agents and combination therapies to decide whether to preclinically pursue these therapies in pediatric patient populations.
- Consider using s. IL-5 agents instead of IL-2 agents to augment monomeric antibody, chimeric antigen receptor T cell, and natural killer cell therapies.

**PARP:** Repairer of single-strand DNA breaks
- Mutations in BRCA, PALB2, and other homologous repairer of single-strand DNA breaks are associated with increased non-homologous end-joining DNA repair.
- Mutations in BRCA, PALB2, and other homologous repairer of single-strand DNA breaks may result in increased replication errors, triggering cytotoxicity in tumor cells with high genomic instability.

Key Considerations
- Schizotypal 1 expression in tumors may be a useful biomarker for sensitivity to PARP inhibition.
- Patient-derived xenograft (PDX) mouse models can be used to predict a patient’s response to PARP inhibitors.
- PARP inhibitors are associated with hematologic and gastrointestinal toxicities.
- Combinations of PARP inhibitors with liposomal doxorubicin are effective in preclinical models with lower toxicity and are undergoing pediatric clinical testing.

Recommendations
- Conduct additional preclinical studies to identify biomarkers of PARP inhibitor sensitivity.
- Test additional agent reformulations and synergistic/treatment combinations to increase the PARP inhibitor therapeutic window for pediatric use.
- Consider using IL-15 agents instead of IL-2 agents to augment monoclonal antibody, chimeric antigen receptor T cell, and natural killer cell therapies.

**Clinical Development Status**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved Drug(s)</th>
<th>Target Therapies</th>
<th>Approved as Targeted Therapy</th>
<th>Approval Status</th>
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<tbody>
<tr>
<td>COACH</td>
<td>Approved drugs, all targeting S. 2, 6, 24a</td>
<td>31 drugs in active development, with 8 drugs in Phase III clinical trials</td>
<td>Approved outside the U.S.</td>
<td>November 18, 2022</td>
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