In March 2023, COACH convened its fourth meeting with representatives from the National Cancer Institute (NCI), Food and Drug Administration (FDA), European Medicines Agency (EMA), advocacy groups, the pharmaceutical industry, Pediatric Preclinical Testing Consortium (PPTC), and the Pediatric Preclinical In Vivo Testing (PIVOT) consortium to assess three cancer-associated targets that could be potential entities for development of life-saving drugs for pediatric indications.

**P3KCA: PI3K/AKT Signaling Kinase**

- **Development**: 17 drugs in active development, most of which are now clinical trials; 1 pediatric clinical trial is either ongoing or pending.
- **Clinical Status**: 3 drugs in development, 17 drugs in active development, with 1 in Phase III clinical trials.

- **Key Considerations**
  - Based on tumor attributes,
  - HDAC1-3 inhibitors may have synergistic impacts with PI3K inhibitors.
  - HDAC1-3 inhibitor-related cardiac side-effect profiles may also have synergistic toxicities.
- **Recommendations**
  - Perform mechanistic studies to better understand CNS toxicities are needed.
  - HDAC1-3 inhibitor treatment strategies should be effective in treating brain tumors.

**ATR: Sensor for DNA Damage**

- **Clinical Status**: 33 drugs in active development, most of which are new chemical entities (NCEs). 1 approved drug for PIK3CA-related overgrowth spectrum (PROS) patients treated with alpelisib.

- **Key Considerations**
  - HDACs deacetylate histones to regulate gene expression, which can trigger anticancer activity.
  - Accurate biomarkers for ATR inhibitor response will require appropriate dosing to minimize toxic effects.
- **Recommendations**
  - Review results from ongoing adult clinical trials that may provide insights into potential pediatric applications as well as rational treatment combinations.
  - Identify ATR combination treatment strategies that include HDAC1-3 inhibitors with the exception of T-cell immunotherapies.

**HDAC1-3: Regulating Gene Expression**

- **Clinical Status**: 6 drugs in development, with 1 in clinical trials.

- **Key Considerations**
  - The Pediatric Preclinical Testing Consortium (PPTC) determined that HDACs are druggable targets.
  - The Pediatric Preclinical In Vivo Testing (PIVOT) consortium to assess three cancer-associated targets that could be potential entities for development of life-saving drugs for pediatric indications.

- **Recommendations**
  - Perform high throughput screening for potential HDAC1-3 inhibitors.
  - Identify HDAC1-3 inhibitors that may be effective in treating brain tumors.
  - Determine ATR combination treatment strategies that include HDAC1-3 inhibitors with the exception of T-cell immunotherapies.

**Clinical Trials**

- 17 drugs in active development, with 1 in Phase III clinical trials.