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

**PD-(L)1 + CD73/LAG3/TIGIT:**

**Immune Checkpoint Inhibitor Combination Therapies**
- Inhibition of PD-(L)1 blocks inhibition of tumor-targeting T cells, enabling destruction of tumor cells via the immune system.
- Tumors with high mutational burden are more likely to respond to PD-(L)1 inhibitors.
- Other therapies are administered as combinations with PD-(L)1 inhibitors, leveraging those antitumor mechanisms.
  - High expression of CD73 in tumors increases extracellular adenosine production to suppress immune-mediated tumor cell eradication.
  - High expression of LAG3 in T cells suppresses antitumor activities.
  - High expression of TIGIT in immune cells inhibits T cell and natural killer cell antitumor activities.

**Key Considerations**
- PD-(L)1 plus CD73/LAG3/TIGIT inhibitors may be effective only in very rare pediatric tumor subtypes.
- Preclinical studies of PD-(L)1 plus CD73/LAG3/TIGIT inhibitors suggest potential intolerable toxicities for pediatric patients.
- Efficacy of PD-(L)1 plus CD73/LAG3/TIGIT inhibitors in adult patients, limited to immunogenic tumors. Conversion of tumors from non-immunogenic to immunogenic may sensitize tumors to PD-(L)1 plus CD73/LAG3/TIGIT inhibition.

**Key Considerations**
- B7H3 expression in tumor cells can have co-stimulatory or co-inhibitory immune system effects on T and NK cells, as well as stimulate epithelial-mesenchymal transition, proliferative, and metabolic reprogramming.
- B7H3 inhibition of T cells inhibits destruction of tumor cells via the immune system.

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**Recommendations**
- Develop immunocompetent pediatric preclinical models to study PD-(L)1 plus CD73/LAG3/TIGIT inhibitor combinations.
- Extrapolate adult preclinical and clinical data to pediatric indications based on levels of immunogenicity, use to identify strategies to convert non-immunogenic tumors to immunogenic tumors.
- Identify other tumor characteristics that may predict sensitivity to PD-(L)1 plus CD73/LAG3/TIGIT inhibition, use to develop biomarkers.

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  - Inhibition of B7H3 enables destruction of tumor cells via the immune system.

**Recommendations**
- Avoid prematurely limiting B7H3 agents for further development.
- Enable studies prioritizing agents that perform best in adult clinical settings.
- Focus preclinical efforts on identifying rational B7H3 combination strategies.