Convening Experts in Oncology to Address Children’s Health

Quarterly Collaboration Meetings in Pediatric Oncology

December 14, 2022 | Virtual Meeting

Reviewed Targets:
- B7H3
- PD-(L)1 Combinations:
  - PD(L)-1 Plus CD73
  - PD-(L)1 Plus LAG3
  - PD-(L)1 Plus TIGIT

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## Acronym Definitions

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<tr>
<td>AACR</td>
<td>American Association for Cancer Research</td>
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<tr>
<td>ADC</td>
<td>antibody drug conjugates</td>
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<td>ADCC</td>
<td>antibody-dependent cellular cytotoxicity</td>
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<td>AE</td>
<td>adverse event</td>
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<td>ALL</td>
<td>acute lymphocytic leukemia</td>
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<td>AML</td>
<td>acute myeloid leukemia</td>
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<tr>
<td>APC</td>
<td>adenomatous polyposis coli</td>
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<td>ARMS</td>
<td>alveolar rhabdomyosarcoma</td>
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<td>ATR</td>
<td>ataxia telangiectasia</td>
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<td>ATRT</td>
<td>atypical teratoid rhabdoid tumor</td>
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<td>AUC</td>
<td>area under the curve</td>
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<td>AURKA</td>
<td>aurora kinase A</td>
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<td>B7H3</td>
<td>B7 homolog 3</td>
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<tr>
<td>BiTE</td>
<td>bi-specific T-cell engager</td>
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<tr>
<td>CAR-NK</td>
<td>chimeric antigen receptor natural killer-cell</td>
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<td>CAR-T</td>
<td>chimeric antigen receptor T-cell</td>
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<tr>
<td>CCR2</td>
<td>chemokine receptor type 2</td>
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<tr>
<td>CD73</td>
<td>cluster of differentiation 73</td>
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<td>CDX</td>
<td>cell line-derived xenograft</td>
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<td>CLL</td>
<td>chronic lymphocytic leukemia</td>
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<td>CMMRD</td>
<td>congenital mismatch repair deficiency</td>
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<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CNV</td>
<td>copy number variation</td>
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<td>COACH</td>
<td>Convoking Experts in Oncology to Address Children’s Health</td>
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<tr>
<td>CR</td>
<td>complete response</td>
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<td>cytokine release syndrome</td>
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<td>CTL</td>
<td>cytotoxic T lymphocyte</td>
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<td>DepMap</td>
<td>Dependency Map</td>
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<tr>
<td>DHAP</td>
<td>dexamethasone, high-dose cytarabine, and cisplatin/platinum</td>
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<tr>
<td>DIPG</td>
<td>diffuse intrinsic pontine glioma</td>
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<tr>
<td>DLBCL</td>
<td>diffuse large B cell lymphoma</td>
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<tr>
<td>DLT</td>
<td>dose limiting toxicity</td>
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<tr>
<td>DSRCT</td>
<td>desmoplastic small round cell tumor</td>
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<td>EAE</td>
<td>experimental autoimmune encephalomyelitis</td>
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<td>EBV</td>
<td>Epstein Barr Virus</td>
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<td>EFS</td>
<td>event-free survival</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>EMT</td>
<td>epithelial-mesenchymal transition</td>
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<td>embryonal rhabdomyosarcoma</td>
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<tr>
<td>EwS</td>
<td>Ewing sarcoma</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>GBM</td>
<td>glioblastoma multiforme</td>
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<td>GPC2</td>
<td>glypican 2</td>
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<td>GVHD</td>
<td>graft-versus-host disease</td>
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<tr>
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<td>Definition</td>
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<tr>
<td>HDAC</td>
<td>histone deacetylase</td>
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<td>high-grade glioma</td>
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<td>HIF1A</td>
<td>hypoxia inducible factor 1-alpha</td>
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<td>Hodgkin’s lymphoma</td>
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<td>HSC</td>
<td>hematopoietic stem cell</td>
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<td>ICI</td>
<td>immune checkpoint inhibitor</td>
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<td>IDH</td>
<td>isocitrate dehydrogenase</td>
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<td>IFNγ</td>
<td>interferon gamma</td>
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<td>IHC</td>
<td>immunohistochemical</td>
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<td>IL-6</td>
<td>interleukin 6</td>
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<td>ITCC-P4</td>
<td>Paediatric Preclinical Proof of Concept Platform</td>
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<tr>
<td>kg</td>
<td>Kilogram</td>
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<tr>
<td>LAG3</td>
<td>lymphocyte-activation gene 3</td>
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<tr>
<td>LSECtin</td>
<td>liver sinusoidal endothelial cell lectin</td>
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<tr>
<td>M</td>
<td>Molar</td>
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<tr>
<td>mAb</td>
<td>monoclonal antibody</td>
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<tr>
<td>mCR</td>
<td>maintained complete response</td>
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<tr>
<td>mCRPC</td>
<td>metastatic castration-resistant prostate cancer</td>
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<td>MHC</td>
<td>major histocompatibility complex</td>
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<td>MMR</td>
<td>mismatch repair</td>
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<td>MOG35-55</td>
<td>myelin oligodendrocyte glycoprotein</td>
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<td>MPNST</td>
<td>malignant peripheral nerve sheath tumor</td>
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<td>MRL</td>
<td>Murphy Roths Large</td>
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<td>MRT</td>
<td>malignant rhabdoid tumor</td>
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<td>NAMPT</td>
<td>nicotinamide phosphoribosyltransferase</td>
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<td>Nanoemulsion</td>
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<td>nHL</td>
<td>non-Hodgkin’s lymphoma</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>NK</td>
<td>natural killer cell</td>
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<td>NSCLC</td>
<td>non-small cell lung cancer</td>
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<td>ODAC</td>
<td>Oncologic Drugs Advisory Committee</td>
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<td>ORR</td>
<td>overall response rate</td>
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<tr>
<td>OS</td>
<td>overall survival</td>
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<tr>
<td>PBD</td>
<td>Pyrrolobenzodiazepine</td>
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<td>PD-(L)1</td>
<td>programmed death-(ligand) 1</td>
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<td>patient-derived xenograft</td>
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<td>PFS</td>
<td>progression-free survival</td>
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<td>PIK3α</td>
<td>phosphatidylinositol 3-kinase alpha</td>
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<td>PIVOT</td>
<td>Pediatric Preclinical In Vivo Testing</td>
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<td>PPP</td>
<td>public-private partnership</td>
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<td>PPTC</td>
<td>Pediatric Preclinical Testing Consortium</td>
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<td>PRISM</td>
<td>Profiling Relative Inhibition Simultaneously in Mixtures</td>
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<tr>
<td>PVR</td>
<td>poliovirus receptor</td>
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<tr>
<td>PXA</td>
<td>pleomorphic xanthoastrocytoma</td>
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<td>RMS</td>
<td>rhabdomyosarcoma</td>
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<tr>
<td>RTK</td>
<td>receptor tyrosine kinase</td>
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<td>SCCHN</td>
<td>squamous cell carcinoma of head and neck</td>
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<td>ScFv</td>
<td>single-chain variable fragment</td>
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<td>SCLC</td>
<td>small cell lung cancer</td>
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<tr>
<td>siRNA</td>
<td>small interfering RNA</td>
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<td>SMARCA4</td>
<td>switch/sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin A4</td>
</tr>
<tr>
<td>SMARCB1</td>
<td>switch/sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin B1</td>
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<td>SME</td>
<td>subject matter expert</td>
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<td>SSM</td>
<td>simple somatic mutation</td>
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<tr>
<td>SV</td>
<td>structural variations</td>
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<tr>
<td>Tcon</td>
<td>conventional T cell</td>
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<tr>
<td>TIGIT</td>
<td>T cell immunoreceptor with immune globulin and immunoreceptor tyrosine-based inhibitor motif domains</td>
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<tr>
<td>TIL</td>
<td>tumor-infiltrating lymphocyte</td>
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<tr>
<td>TMB</td>
<td>tumor mutational burden</td>
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<tr>
<td>TME</td>
<td>tumor microenvironment</td>
</tr>
<tr>
<td>TNBC</td>
<td>triple-negative breast cancer</td>
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<tr>
<td>topo-cyclo</td>
<td>topotecan-cyclophosphamide</td>
</tr>
<tr>
<td>Treg</td>
<td>regulatory T cell</td>
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Executive Summary

Despite advances in therapeutic development for adult cancers, developing treatment regimens for pediatric cancers poses unique challenges, in part, because effective adult treatments are not always readily translatable to the pediatric population due to distinct differences between adults and children, even those with the same cancer diagnosis. In addition, pediatric cancer patient populations are quite small, which complicates study design and sufficient powering for pediatric clinical trials. Convening Experts in Oncology to Address Children’s Health (COACH) assembles subject matter experts (SMEs) from diverse fields to review research landscapes for therapeutic targets of potential interest for pediatric oncology indications and offer recommendations regarding preclinical research activities to further develop therapeutics for use in pediatric populations. On December 14, 2022, COACH convened the Third Quarterly Collaboration Meeting—with SMEs 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 discuss and provide recommendations regarding preclinical research required to develop the following drug targets for early phase pediatric clinical trials: programmed cell death 1/programmed cell death ligand 1 (PD-(L)1), in combination with cluster of differentiation 273 (CD73), lymphocyte-activation gene 3 (LAG3), or T cell immunoreceptor with immune globulin and immunoreceptor tyrosine-based inhibitor motif domains (TIGIT), as well as B7 homolog 3 (B7H3) alone.

PD-(L)1-Based Monotherapies
PD-(L)1 monoclonal antibodies (mAbs) are a class of immune checkpoint inhibitors (ICIs) that block the inhibition of tumor targeting T cells, enabling immune destruction of tumors. Due to inherent differences between adult and pediatric tumors, PD-(L)1 inhibitors have had less broad success in pediatric patients compared to adults. Pediatric tumors often have low expression of PD-1 and PD-L1 and low tumor mutational burden (TMB), which, based on adult tumor data, predicts low sensitivity to PD-(L)1 inhibitors. Pediatric tumors with mutations correlated with high TMB (e.g., those arising in the setting of congenital mismatch repair deficiency [CMMRD]) and tumors with loss of function of switch/sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin B1 (SMARCB1) or switch/sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin (SMARCA4) may be sensitive to PD-(L)1 inhibitors. The latter group includes some pediatric chordoma, epithelioid sarcoma, and malignant rhabdoid tumor (MRT) subtypes. Most pediatric preclinical data for PD-(L)1 inhibitors are limited to indications with available immunocompetent models. These inhibitors have been mostly studied in in vivo models of gliomas and osteosarcomas.

There are 6 FDA-approved PD-(L)1 therapeutics, another 14 in pipeline development globally, and 144 planned or ongoing clinical trials involving PD-(L)1 inhibition in adult and pediatric patients. Data from Phase I/II pediatric clinical trials indicate that PD-(L)1 drugs may be most beneficial for pediatric Hodgkin’s lymphoma (HL). Some patients with SMARCB1-deficient
tumors had partial responses to PD-(L)1 inhibition, but treatment of most pediatric embryonal tumors and sarcomas resulted in progressive disease.

**PD-(L)1 Combination Therapies**

**PD-(L)1 Plus CD73**
Dual inhibition of PD-(L)1 and CD73 is hypothesized to increase the body’s immune response to tumors, enhance tumor cell clearance, and decrease tumor growth. CD73 autonomously supports tumor growth and produces extracellular adenosine to suppress immune-mediated tumor cell eradication. Inhibiting CD73 is hypothesized to reverse the suppression of immune-mediated tumor cell eradication. CD73 expression in tumors varies and may predict outcomes in pediatric acute lymphocytic leukemia (ALL) patients. While no studies examining the inhibition of both CD73 and PD-(L)1 have been conducted in models relevant to pediatric indications, preclinical evidence suggests that targeting CD73 alone can sensitize tumors to immune-mediated tumor cell eradication, and a small number of relevant preclinical studies inhibiting both PD-(L)1 and the adenosine pathway support potential efficacy for PD-(L)1 plus CD73 inhibition.

No CD73 therapies have been approved by the FDA, but 7 of 35 CD73 products in development are in Phase II/III clinical trials in combination with PD-(L)1 inhibitors for adult solid tumor indications. One non-industry sponsored trial is studying the efficacy of a PD-(L)1 inhibitor combined with a CD73 inhibitor for osteosarcoma. Positive adult clinical trial results suggest that the efficacy of CD73 inhibition may only be effective against immunogenic tumors, such as lung cancers.

**PD-(L)1 Plus LAG3**
Combination inhibition of PD-(L)1 and LAG3 is thought to increase the body’s immune response to tumors, but further studies are needed to determine relevant tumor types and subtypes. LAG3—an immune checkpoint receptor with established roles in suppression of T cell antitumor activity—is expressed by antigen-stimulated T cells and strongly correlates with T cell inhibition. LAG3 ligand interactions with major histocompatibility complex (MHC) II downregulate cytokine secretion and proliferation of CD4+ T cells. Reduced T cell number and activity enables tumor cell proliferation and reduces tumor cell clearance. Several pediatric tumor types significantly express LAG3, but preclinical data are lacking on combinations of LAG3 and PD-(L)1 inhibition in pediatric models. Adult preclinical data suggest that LAG3 coordinates with PD-(L)1 to suppress antitumor activity. Data from preclinical knockout models suggest that dual inhibition of LAG3 and PD-(L)1 may result in intolerable autoimmune-related side effects.

Bristol Myers Squibb’s relatlimab is the only FDA-approved LAG3 inhibitor, and it was approved in March 2022 for use in combination with the PD-1 inhibitor nivolumab for adult and pediatric patients 12 years of age and older with unresectable or metastatic melanoma (Tawbi et al., 2022). Of the 35 LAG3 therapies of all agents types in development globally, 13 are in Phase II/III clinical trials, being tested in combination with PD-(L)1 inhibitors. Most of these Phase II/III trials are for only adult indications, but Bristol-Myers Squibb is sponsoring two clinical trials that
include pediatric patients, for the nivolumab plus relatlimab combination in HL and non-Hodgkin’s lymphoma (nHL).

**PD-(L)1 Plus TIGIT**

Dual inhibition of PD-(L)1 and TIGIT increases tumor antigen-specific CD8+ T cell expansion and promotes tumor rejection by the immune system in preclinical models. TIGIT is a potent suppressor of T cell immunity, potently inhibits innate and adaptive immunity, and is expressed by many different immune cell populations. High TIGIT expression was reported to be associated with lower survival in a pediatric ALL cohort. TIGIT expression was found to be elevated in a pediatric high-grade glioma cohort in comparison to low-grade gliomas, and expression was inversely associated with survival for the high-grade glioma cohort.

No TIGIT therapies are FDA-approved, and there are few relevant pediatric clinical trials. Of 56 TIGIT therapies of all agents types in development globally, 12 are in Phase II/III clinical trials with PD-(L)1 inhibitors, mainly for non-small cell lung cancer (NSCLC). However, Phase III results for tiragolumab (i.e., TIGIT inhibitor) in combination with PD-(L)1 inhibition in NSCLC and small cell lung cancer (SCLC) have not shown significant efficacy to date. A Phase I/II study for dual blockade of PD-(L)1 and TIGIT is currently evaluating safety and preliminary efficacy in pediatric cancer patients with loss-of-function mutations in SMARCB1 or SMARCA4.

**Key Considerations**

- PD-(L)1 inhibitors, as well as doublet combination strategies (i.e., dual inhibition of PD-(L)1 and other targets) with CD73, LAG3, or TIGIT, may be effective only in very rare pediatric tumor subtypes (e.g., MRTs, SMARCB1-deficient tumors, SMARC4A-deficient tumors).
- Based on preclinical studies, PD-(L)1 inhibition in combination with CD73 or LAG3 suggest the potential for these inhibitor combinations to have intolerable toxic effects in pediatric patients, while combined inhibition of PD-(L)1 and TIGIT may have milder toxic effects.
- The lack of immunocompetent pediatric preclinical models limits studies of PD-(L)1 inhibitor combination strategies. Public-private partnerships (PPPs) may help accelerate the development of useful immunocompetent models.
- PD-(L)1 inhibitor and doublet combination strategies have shown efficacy in some adult tumor preclinical models. Efficacy is limited mostly to immunogenic tumors (i.e., hot tumors); however, most pediatric tumors are non-immunogenic (i.e., cold tumors).
- Conversion of cold pediatric tumors to hot tumors may sensitize them to PD-(L)1 inhibition and doublet combinations with CD73, LAG3, or TIGIT; however, strategies for cold tumor conversion have not been identified for neither pediatric nor adult tumors.
- Effective extrapolation of adult preclinical and clinical data to pediatric indications requires careful comparison of tumors with similar immunogenicity (i.e., cold adult tumors to cold pediatric tumors).
- Other tumor characteristics, in addition to factors such as TMB as a surrogate for immunogenicity, may predict PD-(L)1 sensitivity.
Next Steps

- PD-(L)1 inhibition and dual inhibition of PD-(L)1 plus CD73, LAG3, and TIGIT are low to moderate priority for further preclinical research as reviewed by COACH.
- Preclinical researchers should wait for additional results from adult clinical trials and extrapolate these data to pediatric tumors with similar levels of immunogenicity or underlying mechanisms of reduced immunogenicity.
- A more thorough understanding of the immune response in tumors may help researchers identify strategies for converting cold tumors to hot tumors.
- Development of better immunocompetent preclinical models of pediatric cancer to study these and future agents.

B7H3

B7H3-targeted immunotherapies show strong promise for pediatric cancer indications. B7H3 has unclear immunoregulatory functions but is highly expressed in many cancers. Depending on context, B7H3 can have co-stimulatory or co-inhibitory effects on T cells and natural killer (NK) cells, as well as protumor intrinsic effects, including stimulation of epithelial-mesenchymal transition (EMT), proliferation, and metabolic reprogramming. Between 80 and 90 percent of pediatric solid and brain tumors express B7H3, but expression is low in ALL and acute myeloid leukemia (AML) patients. In osteosarcomas, high B7H3 expression is positively correlated with patient survival. Preclinical studies of B7H3-targeted therapies showed antitumor activity in embryonal tumors (e.g., neuroblastoma and Wilms tumor), sarcomas, and central nervous system (CNS) tumors. B7H3 chimeric antigen receptor T cell (CAR-T) therapy is active against osteosarcoma in xenograft models. In addition, two B7H3 antibody drug conjugates demonstrated high efficacy in preclinical models of solid tumors.

Of the 32 B7H3-targeted therapies in development globally, only 13 are in clinical development. Current pediatric clinical trials focus on B7H3 CAR-T therapies in CNS tumors. A Phase I pediatric clinical trial of Macrogenics’ B7H3 mAb showed no antitumor activity, but tumor sample staining provided important data about B7H3 expression in different tumor types.

Key Considerations

- B7H3 is highly expressed in many pediatric solid tumors and not expressed in most essential healthy tissues.
- Preclinical studies demonstrated efficacy of B7H3 targeting against many tumor indications relevant to pediatric patients, including osteosarcoma, rhabdomyosarcoma (RMS), Ewing sarcoma (EwS), neuroblastoma, medulloblastoma, glioblastoma, Wilms tumor, and some leukemias.
- Preclinical studies of B7H3 loss suggest that B7H3 inhibition in pediatric patients may negatively affect bone development.
- Multiple strategies to target B7H3 are being pursued, including antibody drug conjugates and CAR-T therapies.
• B7H3 CAR-T therapy has been fairly tolerable in limited pediatric patient cohorts; cytokine release syndrome (CRS), with a maximum grade of 2, was the only adverse event (AE) type reported.
• Preclinical and adult clinical data on B7H3 inhibition support progression to early-phase pediatric clinical trials.

Next Steps
• B7H3 was determined to be a low to moderate priority for further preclinical research as reviewed by COACH, given the already ongoing clinical research.
• The research community should avoid prematurely limiting strategies targeting B7H3 and enable studies prioritizing agents that perform best in the clinical setting.
• Companies with B7H3-targeted therapies that are effective in preclinical pediatric models and have adult dosing recommendations should proceed with pediatric clinical trials for safety and early efficacy.
• Preclinical researchers should continue to study different B7H3-targeted therapies and consider investigating rational combination strategies.
Meeting Summary

Review of Meeting Objectives
Stacey Adam, PhD, Foundation for the National Institutes of Health (FNIH)

Dr. Stacey Adam welcomed meeting participants and reiterated that the goal of Convening Experts in Oncology to Address Children’s Health (COACH) is to provide expert recommendations regarding drug target prioritization and salient preclinical steps to either clarify the priority of a specific drug target or to prepare the drug target for pediatric cancer clinical trials. If meeting participants identify a target as high priority, they will specify preclinical testing needed to advance agents to pediatric clinical trials or clarify existing clinical challenges. If meeting participants identify a target as low priority, they will determine whether additional preclinical data are required to advance the target to higher priority or declare it as not relevant for pediatric cancer indications. Meeting participants should also consider whether preclinical testing is needed to clarify targets currently inconclusive for relevance in pediatric cancer. Dr. Adam reminded meeting participants that proprietary data for reviewed agents should not be discussed within COACH, unless private sector partners choose to disclose this information, and that COACH discussions should focus on drug targets and not agents.

Pediatric Cancer Drug Target Data
Stacey Adam, PhD, Foundation for the National Institutes of Health (FNIH)

Dr. Adam presented data on relevant genetic alterations, transcriptomic expression, patient survival, and in vitro and in vivo dependency for relevant drug targets and combinations: programmed death-ligand 1 (PD-(L)1) in combination with cluster of differentiation 273 (CD73), lymphocyte-activation gene 3 (LAG3), and T cell immunoreceptor with immune globulin and immunoreceptor tyrosine-based inhibitor motif domains (TIGIT), as well as B7 homolog 3 (B7H3) alone, as well as data on in vitro and in vivo drug sensitivity and clinical response rates for their respective therapeutics. To address limitations associated with each of these data types, meeting participants considered these data in combination, identifying pediatric indications that may be sensitive to the target therapeutics. The presence of alterations in a drug target within a given tumor type does not necessarily indicate that target would be an effective therapeutic target. In addition, a therapeutic formulated to inhibit a differentially expressed protein in a specific tumor type may not result in any significant therapeutic effect. While there are limitations to in vitro dependency data, they can provide scientific rationale to support further preclinical assessments. However, in vitro dependency may not always reflect in vivo drug sensitivity.

Data types for each drug target were compiled from different databases, as well as scientific literature. Data on genomic alterations in clinical tumor samples data, compiled from cBioPortal and PedcBioPortal cohorts, included simple somatic mutations (SSMs), copy number variations (CNVs), and structural variations (SVs). Adult patient Expression data from tumor samples were compiled from CCDI Molecular Targets Platform and XenaBrowser, and pediatric expression...
data were included when available. *In vitro* dependency data were obtained from **Dependency Map** (DepMap) and presented using Chronos scores, a normalized metric of cell viability after gene deletion. A Chronos score of 0 indicates gene is non-essential, while score of -1 is comparable to the median of all pan-essential genes. *In vitro* sensitivity data were represented with Profiling Relative Inhibition Simultaneously in Mixtures (PRISM) scores (i.e., area under the curve [AUC] derived from eight-point dose-response curve ranging from 10µM to 610pM) from DepMap. PRISM score of 1 indicates complete lack of response at all concentrations, whereas score of 0 indicates complete loss of viability at all concentrations. *In vivo* dependency and drug sensitivity data were aggregated from relevant scientific literature.

Research landscape data included federal grant spending, publications, and general commercial activity relevant to each target. Federal grant data obtained from the National Institutes of Health (NIH) were further classified by subtopics and federal agency administrators. Publication data were analyzed using PubTator. Commercial activity was summarized from Citeline’s **PharmaProjects** and **Trialtrove** databases.

**PD(L)-1-Based Monotherapies**

*Stacey Adam, PhD, Foundation for the National Institutes of Health*

PD-(L)1 proteins are immune checkpoint proteins that limit tumor immunity by inhibiting T cell responses. PD-L1 is expressed by tumor cells and is recognized by the PD-1 receptor expressed on T cells. PD-(L)1 antibodies are a class of immune checkpoint inhibitors (ICIs) that block inhibition of tumor-targeting T cells, enabling destruction of tumor cells via the immune system. The efficacy of these antibodies requires targetable antigens to be presented by tumors and for T cells to recognize those antigens. The anti-tumor immune response is partially dependent on the mutational burden of tumor cells that results in the expression of neo-antigens (i.e., proteins translated from mutated genes that T cells recognize as foreign).

**Relevant Genetic Alterations, Transcriptomic Expression, and Patient Survival**

**PD-(L)1 Expression**

PD-(L)1 is not highly expressed in pediatric tumors, but there is a positive association between PD-L1 expression and survival in glioma and osteosarcoma. Of 451 pediatric tumors tested, 39 stained positive for PD-L1 above a 1 percent threshold, with samples of Burkitt lymphoma, which is virally driven, showing the highest rate of PD-L1 positivity. PD-L1 expression was also assessed in adult patients in a Phase II study of atezolizumab (PD-L1 monoclonal antibody [mAb]); samples from a subset of Hodgkin’s lymphoma (HL) patients had the greatest proportion of high PD-L1-expressing tumors. In addition, immunohistochemical (IHC) analysis identified 8 membranous PD-L1-positive rhabdoid tumors from a total of 16 samples. A threshold level of PD-L1 can be used to indicate response to PD-(L)1 therapies. Some tumors with PD-L1 amplification—common only in HL and mediastinal B-cell lymphoma—exhibit strong responses to ICIs, including those targeting PD-(L)1, but genetic alterations in PD-(L)1 genes are not generally consistent predictors of ICI response (Goodman et al., 2018).
**Tumor Mutational Burden**

Tumors with a higher tumor mutational burden (TMB) are more likely to express immunogenic neoantigens and respond to ICIs (Wang et al., 2021). Because mutations that disrupt DNA repair mechanisms (e.g., DNA mismatch repair [MMR] genes, polymerase proofreading genes) increase TMB, these mutations are predictive of response to PD-(L)1 therapies and other ICIs. However, pediatric tumors usually have low TMB and neoantigen levels—except for tumors with specific mutations in DNA repair genes—compared to adult tumors, and rarely respond to ICIs (2.8% overall response rate [ORR], excluding HL) (Gröbner et al., 2018; Pearson et al., 2020).

**SMARCB1/SMARCA4 Mutations**

Objective responses to ICIs have been observed in multiple tumor types containing mutations in either switch/sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin B1 or A4 (SMARCB1 or SMARCA4), such as: small cell carcinoma of the ovary (hypercalcemia type), thoracic sarcoma, renal medullary carcinoma, epithelioid sarcoma, poorly differentiated chordoma, and rhabdoid tumors, including atypical teratoid rhabdoid tumors (ATRTs). Despite having a low TMB, tumors with these mutations exhibit increased immunogenicity and ICI response. In a study of 24 tumors containing SMARCB1 alterations, 12 contained two-copy deletions, 5 had single-copy deletions, 5 had two inactivating alterations, and 2 had single nonsense mutations. These SMARCB1-deficient tumors showed increased PD-L1 expression.

A study of 140 malignant rhabdoid tumors (MRTs) and 161 ATRTs—tumors typically driven by SMARCB1 loss—detected similarities between extracranial MRTs and MYC-positive ATRTs, including global DNA hypomethylation as well as overexpression of Hox genes and genes involved in mesenchymal development. These MRTs and ATRTs were categorized based on DNA methylation patterns into five subgroups, three of which (e.g., ATRT-MYC-like, receptor tyrosine kinase [RTK]-like, and extra-renal MRT-like) exhibited cytotoxic T lymphocyte (CTL) infiltration and expression of PD-(L)1. A subset of tumor-infiltrating lymphocytes (TILs) expressed PD-1, indicating interaction between TILs and tumor cells expressing PD-L1. This interaction with the immune system is consistent with increased response to ICIs, including PD-(L)1 inhibitors.

**Dependency and Drug Sensitivity**

Preclinical studies of PD-(L)1 inhibition are limited by the availability of immunocompetent, syngeneic mouse models for different tumor types, including glioma, osteosarcoma, leukemias, lymphomas, and MRTs.

**Glioma:** PD-1 therapy alone resulted in significantly increased survival in a mouse isocitrate dehydrogenase (IDH)-mutant glioma model, and this survival rate can be improved with chemotherapy or IDH inhibition (Kadiyala et al., 2021). However, IDH-mutant gliomas are rare in pediatric populations, with a 0 to 17 percent incidence rate in adolescents older than 14 years of age (Ryall et al., 2020).
PD-(L)1 monotherapy studies in the GL261 immunocompetent glioma model have provided mixed results, but effective combination therapies with PD-(L)1 therapies have been identified:

- Nicotinamide phosphoribosyltransferase (NAMPT) inhibition acts synergistically with anti-PD-1 therapy by increasing tumor PD-L1 expression and recruiting T cells to the tumor site (Li et al., 2020).
- Depletion of IL-6 has also resulted in a synergistic effect with PD-(L)1 therapies, leading to long-term survival (Lamano et al., 2019).
- A dendritic cell vaccine administered in combination with anti-PD-1 therapy also resulted in improved treatment efficacy (Antonios et al., 2016).

**Osteosarcoma:** The K7M2 immunocompetent, syngeneic murine model of osteosarcoma is used extensively to study PD-(L)1 therapies. Downregulation of MYC with JQ-1 inhibitor reprograms the tumor microenvironment (TME) to facilitate T cell infiltration and increases sensitivity to anti-PD-1 therapy (Jiang et al., 2022). In addition, some metastatic osteosarcomas may exhibit heightened expression of PD-L1 and sensitivity to PD-(L)1 inhibition (Lussier et al., 2015).

**Leukemias:** PD-(L)1 monotherapy is effective in preclinical models of acute lymphocytic leukemia (ALL), but it is ineffective in acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL) models. Relapsed pediatric B-cell ALL models respond to pembrolizumab, with an additional synergistic effect in combination with blinatumomab (i.e., CD19-directed bispecific T-cell engager [BiTE]) (Wunderlich et al., 2021). In addition, loss of interleukin 6 (IL-6) strengthens anti-PD-L1 efficacy in B-cell ALL models (Bent et al., 2021). While CLL is normally nonresponsive to PD-(L)1 monotherapy, CLL can be sensitized to PD-(L)1 therapy when treated with avadomide, an E3 ligase modulator (Ioannou et al., 2021).

**Lymphomas:** Preclinical studies in non-Hodgkin’s lymphoma (nHL) models have provided mixed results, with successful combination therapies identified in nHL subtypes that are rare in children. Anti-PD-1 therapy alone prevents tumor growth in a model of diffuse large B cell lymphoma (DLBCL) and results in complete regression and long-term survival when administered in combination with dexamethasone, high-dose cytarabine, and cisplatin/platinum (DHAP) chemotherapy (Zhang et al., 2020). In a peripheral T-cell lymphoma model, anti-PD-L1 therapy alone was ineffective but demonstrated some synergy with aurora A kinase (AURKA) inhibition (Islam et al., 2017).

**Rhabdoid Tumors:** Anti-PD-1 monotherapy was highly effective in MYC rhabdoid tumor syngeneic mouse models, inducing complete tumor regression, and subsequent prolonged survival, in 67 to 80 percent of treated mice.

**Additional Tumor Types:** PD-(L)1 monotherapies are ineffective against medulloblastoma and neuroblastoma in preclinical models. However, chemokine receptor type 2-positive (CCR2+) hematopoietic stem cell (HSC) transfer can sensitize medulloblastomas to PD-1 therapy by stimulating tumors to generate adenomatous polyposis coli (APC) protein (Flores et al., 2018).
**PD-(L)1 Inhibition Safety Studies**

PD-(L)1 knockout models have been used to assess potential safety issues associated with PD-(L)1 inhibition. PD-1 knockout mice are viable, fertile, and exhibit no obvious developmental defects (Nishimura et al., 1998). However, these mice develop osteoporosis and increased osteoclast numbers, indicating altered bone homeostasis (Greisen et al., 2022).

Loss of PD-(L)1 mildly alters baseline immune functions, increases inappropriate T cell infiltration, and increases susceptibility to infection. Knockout of PD-1 in Murphy Roths Large (MRL) mice resulted in fatal myocarditis due to T cell infiltration (Wang et al., 2010). Increased T cell numbers have been observed in the spleen and pancreas of PD-1 knockout mice but not PD-L1 knockout mice (Pauken et al., 2013). After neonatal thymectomy, PD-1 knockout mice develop fatal hepatitis due to T cell infiltration (Kido et al., 2008). Chronic inflammation and spontaneous activation of T cells in PD-1 knockouts also triggers neuroinflammation and autoimmune diabetes (Jiang et al., 2016). In addition, PD-1 knockout mice show increased susceptibility to *Mycobacterium tuberculosis* and *Toxoplasma gondii* (Barber et al., 2011; McBerry et al., 2014) and exhibit a fatal T cell immunopathology after infection with lymphocytic choriomeningitis virus (Frebel et al., 2012).

**Clinical Trial Development**

Pediatric clinical trial indications with the highest ORRs for anti-PD-(L)1 therapies include HL, mesothelioma, and SMARCB1-deficient tumors. Most pediatric neuroendocrine tumors and sarcomas continued to progress during anti-PD-(L)1 treatment. Atezolizumab (i.e., PD-L1 mAb) was recently approved for alveolar soft part sarcoma—a tumor type rare in the pediatric population. Notably, anti-PD-1 and anti-PD-L1 therapies may have differential effects from one another in the same cancer type, but this initial analysis generalized effects of both therapies.

**Research and Development Landscape**

Many drugs targeting PD-(L)1 have been approved, and trials in both adult and pediatric indications are ongoing. PD-1 clinical research is more mature than PD-L1 research, with a higher percentage of drugs in Phase III trials. In addition, the number of planned and ongoing pediatric PD-1 trials is approximately three times that of PD-L1 trials, which is similar in the adult oncology market landscape. Both drug targets are feasible candidates for further development for pediatric indications.

**PD(L)-1 Combination Therapies**

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**PD(L)-1 Plus CD73**

CD73 is a cell surface ecto-5′-nucleotidase that supports immunosuppressive tumor environments by catalyzing the conversion of AMP to extracellular adenosine, which suppresses immune-mediated tumor cell eradication and supports tumor growth. In hypoxic tumor environments, CD73 expression increases due to the stabilization of its upstream transcription factor (hypoxia inducible factor 1-alpha [HIF1A]). As a result, tumors often contain high levels of
extracellular adenosine, which suppresses immune-mediated tumor cell eradication and supports tumor growth (Ohta et al., 2006; Wilson et al., 2009).

**Relevant Genetic Alterations, Transcriptomic Expression, and Patient Survival**

Patient Expression of CD73 is highly variable across tumor types and may predict patient outcomes in certain pediatric populations. High CD73 expression is correlated with poor survival outcomes in adult ALL, but pediatric cohorts have shown mixed outcomes. Although early studies in pediatric patient suggested that CD73 expression correlated with poorer outcomes, a more recent study conducted in over 400 children found no predictive value of CD73 expression for patient outcomes (Pieters et al., 1992; Wieten et al., 2011). Notably, CD73 expression is high in Ewing sarcomas (EwSs), gliomas, and malignant peripheral nerve sheath tumors (MPNSTs) compared to other tumor types.

**Dependency and Drug Sensitivity**

No pediatric preclinical studies of PD-(L)1 and CD73 inhibition have been performed to date. However, preclinical evidence suggests that targeting CD73 alone can sensitize tumors to immune-mediated tumor cell destruction. In multiple studies, CD73 knockout mice exhibited suppressed tumor growth, including smaller and less invasive glioblastomas (Yan et al., 2019). In addition, nasal administration of a nanoemulsion (NE)-small interfering RNA (siRNA) targeting CD73 in a rat glioma model reduced tumor size by 80 percent (Azambuja et al., 2020).

Very few preclinical studies targeting PD-(L)1 and the adenosine pathway have been performed in key indications relevant to pediatric cancer. Combined targeting of PD-1 and adenosine pathways in the GL261 glioma model did not produce synergistic effects on survival; however, this combined targeting has resulted in synergistic effects in preclinical models of melanoma and other adult indications (Ott et al., 2020).

**CD73 Inhibition Safety Studies**

CD73 knockout models have been used to assess potential safety issues associated with CD73 inhibition. CD73 knockout mice are viable, fertile, and exhibit no obvious developmental defects, but these mice do develop cardiac, renal, and pulmonary system defects over time (Thompson et al., 2004). CD73 knockout mice show no significant differences from wildtype mice in systolic blood pressure, ejection fraction or cardiac output, but they do develop fulminant vascular leakage in hypoxic environments (Koszalka et al., 2004; Thompson et al., 2004). These mice also have aortic valve dysfunction similar to that induced by high-fat diet, suggesting a role for CD73 in maintaining heart valve integrity (Zukowska et al., 2017). In addition, bleeding time after tail tip resection was shorter in CD73 knockout mice compared to wildtype (Koszalka et al., 2004); CD73 knockout mice exhibit spontaneous proteinuria and deterioration of renal function (Blume et al., 2012); and CD73 knockout mice develop inflammation and fibrosis following lung injury that results in increased mortality (Ehrentraut et al., 2013). While the cellularity and composition of lymphoid organs appear normal in CD73 knockout mice, loss of CD73 in a hyperoxic lung injury model led to inflammation and inappropriate infiltration of macrophages and lymphocytes (Li et al., 2017).
**Clinical Trial Development**
The MD Anderson Cancer Center is sponsoring the only trial for PD-(L)1 and CD73 combination therapy for pediatric cancer. This Phase II study of oleclumab and durvalumab includes a cohort enrolling patients 12 years and older with recurrent or metastatic osteosarcoma with measurable disease who have received at least one prior systemic therapy but have not received prior ICI therapy. The trial’s primary efficacy endpoint is event-free survival (EFS) rate after four months. As of January 2022, 7 patients have initiated study treatment (NCT04668300).

**Research and Development Landscape**
Two of the four grants supporting PD-(L)1 and CD73 combination research reference lung cancer indications. Oncology literature for this treatment combination is minimal with only 10 articles published since the first relevant publication in 2017. This literature includes the two preclinical investigations into PD-(L)1 and CD73 combination oncology targets but no studies of indications relevant to pediatric cancer. Overall, there is substantial need for additional PD-(L)1 and CD73 combination research, both for adult and pediatric indications.

No CD73 therapies have been FDA-approved, and there is limited preclinical support for future pediatric clinical trials. Seven CD73 therapies administered in combination with PD-(L)1 drugs are in Phase II or III clinical trials, including one Phase II pediatric clinical trial testing oleclumab and durvalumab in a range of sarcomas. Recent adult clinical trial results for CD73 and PD-1 combination therapies have varied, with positive results in non-small cell lung cancer (NSCLC) and negative results in triple-negative breast cancer (TNBC) (Buisseret, 2022; Herbst et al., 2022). Notably, industry is not currently sponsoring any pediatric clinical trials for CD73, which may reflect the lack of preclinical supporting research.

**PD(L)-1 Plus LAG3**
LAG3 is an immune checkpoint receptor expressed by activated T cells and has established roles in suppression of T cell anti-tumor activity. LAG3 binds major histocompatibility complex (MHC) class II molecules to downregulate cytokine secretion and reduces proliferation of CD4+ T cells (Maruhashi et al., 2022). LAG3 also binds galectin-3 and liver sinusoidal endothelial cell lectin (LSECtin) and may support normal mitochondrial function in T cells (Previte et al., 2019). Chronic antigen exposure due to long-term infections results in sustained T cell LAG3 expression (Butler et al., 2011). Similarly, TILs persistently exposed to tumor antigens express high levels of LAG3 (Gandhi et al., 2006).

**Relevant Genetic Alterations, Transcriptomic Expression, and Patient Survival**
LAG3 is expressed in several pediatric tumor types, including MPNSTs, neuroblastomas, Wilms tumors, and Hls (Mochizuki et al., 2019; Moerdler et al., 2021). Notably, LAG3-positive T cells mediate immunosuppression in HL, and Epstein Barr Virus (EBV)-associated HL patients with high LAG3 expression have worse survival outcomes than patients with lower LAG3 expression (Aoki et al., 2020; Jimenez et al., 2022).
**Dependency and Drug Sensitivity**

While no studies have published preclinical data on LAG3 and PD-(L)1 combination therapies relevant to pediatric indications, preclinical findings indicate that LAG3 coordinates with PD-(L)1 to suppress antitumor activity. LAG3 and PD-1 are expressed by TILs in mouse cancer models and this expression promotes immune escape (Woo et al., 2012). In addition, dual blockade of LAG3 and PD-1 strongly suppresses tumor burden in a CLL mouse model (Wierz et al., 2018).

**LAG3 Inhibition Safety Studies**

Although LAG3 knockout mice are viable, fertile, and have no apparent developmental or immune defects under normal conditions (Miyazaki et al., 1996), LAG3 knockout mice are susceptible to autoimmune disease and develop lethal myocarditis in combination with PD-1 loss. Moreover, LAG3-deficient conventional T cells (Tcons) induced significantly more severe graft-versus-host disease (GVHD), compared to wildtype Tcons, in response to grafting (Sega et al., 2014). In addition, LAG3 knockout in a non-obese diabetic mouse model resulted in accelerated diabetes onset with a 100 percent incidence (Bettini et al., 2011), and LAG3 knockout T cells show a delay in cell cycle arrest after stimulation with superantigen staphylococcal enterotoxin B, resulting in increased T cell expansion and splenomegaly (Jha et al., 2014). LAG3 knockout mice also exhibited increased susceptibility to mercury-induced autoimmunity (Jha et al., 2014).

LAG3;PD-1 double knockout mice develop early-onset, lethal autoimmune reactions, resulting in approximately 80 percent lethality by 10 weeks of age. Notably, non-susceptible, LAG3 single knockout mice do not develop these autoimmune reactions. Histological assessments indicated evidence for endocarditis, myocarditis, and pancreatitis. Autoimmune infiltrates were detected in multiple organs in double knockout mice, but these mice also had an increased survival rate after multiple tumor transplantations compared to wildtype mice (Okazaki et al., 2011; Woo et al., 2012).

**Clinical Trial Development**

Bristol-Myers Squibb is currently sponsoring two clinical trials for PD-(L)1 and LAG3 combination therapy. The Phase I/II trial will enroll patients 0 to 30 years of age with recurrent or refractory HL or nHL to assess safety, tolerability, drug levels, and preliminary efficacy (NCT05255601). The Phase II trial is registered through Health Canada, and eligibility criteria include both pediatric and adult patients with LAG3-positive tumors or HL; however, Bristol-Myers Squibb has not updated this trial’s status since 2018 (CA224-058).

**Research and Development Landscape**

Thirteen federal U.S. grants support PD-(L)1 and LAG3 combination research. Based on publications, interest in this combination is increasing, with 70 percent of PD-(L)1 and LAG3 articles related to oncology. Published literature relevant to PD-(L)1 and LAG3 most often references HL, nHL, AML, neuroblastoma, and glioma indications. Preclinical oncology studies in PD-(L)1 and LAG3 therapy regimens have persisted since 2016 for adult indications, but there is still a need for preclinical pediatric oncology studies.
While commercial development of LAG3 is crowded with industrial activity, there is opportunity for pursuit of additional pediatric oncology indications. Opdualog (relatlimab [LAG3 inhibitor] plus nivolumab [PD-1 inhibitor]), which was approved in March 2022, for patients 12 years of age and older with unresectable or metastatic melanoma, is the only FDA-approved therapy that inhibits LAG3 (Tawbi et al., 2022). Of the 35 LAG3 therapies in the developmental pipeline, 13 are being tested in Phase II/III trials in combination with PD-(L)1 inhibitors. Three out of four pediatric LAG3 clinical trials are PD-(L)1 combination trials, including two Phase I/II pediatric clinical trials in patients with HL, nHL, and solid tumors, and another trial in patients with melanoma and other solid tumors. Due to a lack of Phase II/III pediatric clinical trials testing this combination, future trial duration and accrual cannot be estimated.

PD-(L)1 Plus TIGIT
TIGIT is a checkpoint receptor of the immunoglobulin superfamily and a potent suppressor of T cell immunity. Although poliovirus receptor (PVR) is the major ligand for TIGIT, TIGIT also binds nectin-2 and nectin-3. TIGIT is widely expressed by different immune cell types and potently inhibits innate and adaptive immunity. Moreover, TIGIT is co-expressed with PD-1 on tumor antigen-specific CD8+ T cells and CD8+ TILs and indirectly impedes T cell function by binding PVR on dendritic cells (Chauvin et al., 2015; Yu et al., 2009). TIGIT also inhibits natural killer (NK) cell cytokine production and tumor killing activity and augments regulatory T cell (Treg) function to suppress CTL activity (Stanietsky et al., 2009). Dual blockade of PD-1 and TIGIT increases tumor antigen-specific CD8+ T cell expansion and promotes tumor rejection in preclinical modes.

Relevant Genetic Alterations, Transcriptomic Expression, and Patient Survival
TIGIT expression is low across most pediatric indications, except in ALL and glioma. Analysis of glioma subtypes suggests that high-grade gliomas (HGGs) may respond to TIGIT-based therapy. TIGIT expression is elevated in pediatric HGGs, compared to lower grade gliomas, and its expression was inversely associated with overall survival in children with HGGs (Shoger et al., 2018). In addition, pediatric HGGs have poor T cell infiltration (Robinson et al., 2020).

Dependency and Drug Sensitivity
Very few preclinical studies have targeted both PD-(L)1 and TIGIT in vivo using models of relevant indications. Combination PD-(L)1 and TIGIT therapy increased T cell function and downregulated suppressive Tregs and tumor-infiltrating dendritic cells (Hung et al., 2018). Consistent with these immune cell effects, dual blockade of PD-1 and TIGIT in the GL261 glioblastoma model resulted in improved survival and altered myeloid cell function to restore antigen-specific T cell proliferation (Raphael et al., 2021).

TIGIT Inhibition Safety Studies
Compared to knockout mice of other immune checkpoint genes, TIGIT knockout mice exhibit relatively mild autoimmune defects. TIGIT knockout mice are viable, fertile, and have no obvious developmental defects (Levin et al., 2011). However, TIGIT knockout mice respond differently to immune challenge than wildtype mice. TIGIT knockout mice exhibit augmented T cell responses after immunization, as well as deficient adaptive immune tolerance and overactivation of NK cells through increased interferon gamma (IFNγ) production (Joller et al., 2021).
In response to suboptimal myelin oligodendrocyte glycoprotein (MOG35-55) treatment, TIGIT knockout mice have an increased risk of experimental autoimmune encephalomyelitis (EAE) compared to wildtype. In a model of GVHD with lethally irradiated B10.BR mice, mice that received T cells from TIGIT knockout mice succumbed to GVHD faster compared to those receiving wildtype T cells (Levin et al., 2011). In addition, TIGIT knockout mice show impaired liver regeneration, developing chronic hepatitis and fibrosis following human immunodeficiency virus (HIV) infection (Bi et al., 2014; Zong et al., 2019).

**Clinical Trial Development**
The only PD-(L)1 and TIGIT combination therapy clinical trial in pediatrics, sponsored by the National Cancer Institute (NCI) in collaboration with Roche/Genentech to test atezolizumab (PD-L1 inhibitor) and tiragolumab (TIGIT inhibitor), is currently recruiting. This Phase I/II clinical trial will evaluate (1) the safety of tiragolumab monotherapy in patients under 18 years of age with SMARCB1 or SMARCA4 deficient tumors, including MRT, and (2) the antitumor activity of combination atezolizumab plus tiragolumab by ORR (NCT05286801).

**Research and Development Landscape**
More than half of PD-(L)1 and TIGIT grants are administered by NCI, and interest in PD-(L)1 and TIGIT in oncology peaked in 2020 based on publication patterns. Although 71 percent of articles relevant to both PD-(L)1 and TIGIT are oncology-related, very few (3 percent) are relevant to pediatric oncology, with references to glioma, AML, HL, nHL, and ALL.

There are no FDA-approved TIGIT therapies, but 56 are in active development, with 12 in Phase II/III clinical trials in combination with PD-(L)1 inhibitors. TIGIT and PD-(L)1 combinations in development are mostly being tested in NSCLC, but current results of a Phase III clinical trial (SKYSCRAPER-01) suggest that addition of tiragolumab does not significantly improve progression-free survival (PFS) over atezolizumab and chemotherapy alone in first-line treatment of PD-L1-high locally advanced or metastatic NSCLC; the study will continue until the co-primary endpoint—overall survival (OS)—can be assessed (NCT04294810). Another Phase III trial (SKYSCRAPER-02) demonstrated no significant improvement from the addition of tiragolumab to atezolizumab plus chemotherapy for first-line treatment of extensive stage small cell lung cancer (SCLC); interim analysis indicated that that the OS endpoint was also not met (NCT04256421). The only clinical trial relevant for pediatric patients is a Phase I/II pediatric clinical trial testing atezolizumab and tiragolumab for relapsing or recurrent SMARCB1- or SMARCA4-deficient tumors (NCT05286801). Because no pediatric Phase III trials testing TIGIT have occurred, the overall feasibility cannot be estimated for pediatric clinical development; however, the failure rate of therapies targeting TIGIT in oncology indications is relatively low compared to other oncology targets.

**Additional Considerations for Preclinical and Clinical Development**
After the conclusion of Dr. Adam’s presentation of PD-(L)1 combination targets, meeting attendees discussed predictive biomarkers, extrapolation of adult data to pediatric indications, the potential for alternative PD-(L)1 combination therapy sensitization, relevant pediatric preclinical models, and improvement of public-private research partnerships.
Extrapolation of Adult Data

Multiple meeting participants agreed that results from adult clinical trials can provide important insights into which PD-(L)1 combinations may be effective in specific pediatric populations. Drs. Andy Pearson and Eleni Venetsanakos emphasized the importance of using data from adult “cold” tumors (i.e., those with low levels of TILs) to inform future development of PD-(L)1 combination therapies for pediatric patients, who almost always have cold tumors. Dr. Stergios Zacharoulis noted adult cold tumors have not responded well to PD-(L)1 inhibitor combination treatments and suggested that if adult cold tumors continue to not respond, PD-(L)1 inhibitor combination efficacy may be limited to only rare pediatric tumor subtypes.

Biomarkers to Predict Treatment Response

Identifying biomarkers that predict treatment response to PD-(L)1 combinations is crucial for the development and success of clinical trials for pediatric indications. Dr. Ronald Bernardi noted that, for adult oncology indications, biomarker strategies to predict response to PD-(L)1 combination therapies differ across companies based on target expression levels and cutoffs used as well as cell types in which expression occurs. This is partially due to the complexities of these biomarker assays as well as the tumor environment.

Dr. Kara Davis agreed with the importance of selective biomarkers to overcome challenges analyzing findings from heterogenous patient cohorts with diverse tumor histologies. Because of this variability, she suggested using expression levels of specific combination therapy targets. Dr. Davis recalled an EwS patient who, after receiving nivolumab in combination with an epigenetic agent, has survived multiple years and achieved stable disease. Despite the success of the nivolumab combination treatment, a patient sample collected prior to first-line treatment showed very low expression of PD-L1 and limited TILs, indicating prior treatments may have changed the overall nature of the tumor and its sensitivity to PD-1 inhibition. Therefore, research partnerships are needed to reassess tumors from patients receiving multiple lines of treatment prior to the administration of a subsequent experimental treatment.

Alternative PD-(L)1 Sensitization Mechanisms in Pediatric Tumor Subtypes

Some pediatric tumor subtypes (e.g., atypical rhabdoid tumors, ATRTs) are responsive to PD-(L)1 inhibition and combination therapies despite having low TMB. Dr. Birgit Geoerger explained that apart from hot tumors being predictive of PD-(L)1 inhibitor response, at least nine other tumor parameters are associated with PD-(L)1 sensitivity. Dr. Mark Kieran added that a better mechanistic understanding of cold tumor responses to PD-(L)1 combinations could help identify relevant sensitization markers in pediatric tumors. Moreover, Dr. Bernardi noted both TIGIT and LAG3 have roles outside of the PD-(L)1 pathway, and further studies are needed to determine TIGIT and LAG3 mechanisms relevant for pediatric tumors.

Cold-to-Hot Tumor Conversion

Dr. Pooja Hingorani noted preclinical studies are pursuing combination therapies that can convert cold adult tumors into hot tumors, but success has been limited. Mouse models tend to overpredict the immunotherapy efficacy, which does not always translate to human clinical trials. Drs. Hingorani and Malcolm Smith agreed that results from preclinical and clinical studies
related to adult cold tumors will help inform research strategies and potential treatment combinations for cold pediatric tumors.

**Pediatric Preclinical Models**

*Modeling the Human Immune System in Mouse Models*

Multiple meeting participants noted that a significant challenge to preclinical research of ICIs is the lack of immunocompetent mouse models relevant to pediatric indications. For example, Dr. Smith explained that an immunocompetent model for glioblastoma (GL261) was created using traditional mutagenesis, resulting in a TMB that is much higher than those observed in pediatric tumors. The limited immunocompetent mouse models available also do not sufficiently reflect the human immune system. Thus, surrogate molecules are often required during preclinical testing to elicit a response similar to the expected human response. Dr. Bernardi noted that various research groups are developing *in vitro* tumor models that maintain immune microenvironments; however, additional assessments would be needed to determine whether these immune environments are relevant to pediatric patients.

*Prioritization of Preclinical PD-(L)1 Combination Therapy Testing*

A multitude of PD-(L)1 doublet and even triplet combination therapies are in development, but these combinations are too high in number to extensively test each in pediatric preclinical models. Dr. Bernardi indicated that the research community must determine how to prioritize combinations for testing in preclinical models of pediatric indications responsive to PD-(L)1 inhibition. Dr. John Maris noted there are well-established models of cold neuroblastomas and osteosarcomas that reflect clinical experiences with ICIs, which could be used to screen PD-(L)1 combination therapies in a systematic way. Combinations that may have relevance to pediatric indications include:

- Combinations that increase PD-(L)1 tumor expression
- Combinations that convert cold tumors to hot tumors
- Combinations that target unique biological aspects of tumor subtypes sensitive to PD-(L)1 inhibition

Dr. Maris doubted that PD-(L)1 treatment combinations would be successful in pediatric indications beyond rare tumor subtypes. His laboratory had hypothesized that PD-(L)1 inhibitor combination therapy may be useful in a relapse pediatric population with heightened TMB after years of exposure to genotoxic agents. However, he found no indication of increased TMB in pediatric relapses, with very few exceptions. However, PD-(L)1, CD73, LAG3, and TIGIT inhibitors may enhance the effects of bi-specific T cell engagers (BiTEs) or cancer vaccines on T cell activity.

*Improving Public-Private Partnerships*

Dr. Susan Weiner expressed the frustration felt by pediatric cancer patient and caregiver communities related to the lack of combination therapy studies relevant to pediatric cancers, questioning whether companies lack interest in pediatric indications due to their rarity.
compared to adult cancers. Dr. Nathalie Scholler provided insight into challenges, such as the lack of immunocompetent preclinical models, related to companies pursuing cold-to-hot tumor conversion strategies, noting companies favor positive results that enable the rapid identification of a solution, while academia may be better equipped to address the complex challenges related to pediatric cold-to-hot tumor conversion. Dr. Vicky Buenger explained that public-private partnerships could help by supporting research into more complex questions, especially those related to pediatric indications.

Dr. Scholler indicated that the lack of relevant pediatric preclinical models deters companies from pursuing pediatric indications. Current models overpredict the efficacy of immunotherapies, which presents a considerable risk when moving forward with clinical trials. Dr. Adam explained that COACH was originally part of a potential larger effort to design a clinical system that shares the risks and costs for the development of preclinical pediatric models for testing of immunotherapies, and this approach may be valuable for research progression in pediatric cancer.

Next Steps
Meeting participants indicated that PD-(L)1 and the discussed PD-(L)1 combinations are low to moderate priority targets for COACH. The completion of additional adult studies will provide critical insight into rational treatment combinations for pediatric indications as well as the mechanistic differences between cold and hot tumors. However, successful extrapolation of adult data requires comparison of pediatric tumors to adult tumors with similar immune microenvironments, as well as a more thorough understanding of hot tumors.

B7H3
Stacey Adam, PhD, Foundation for the National Institutes of Health

Overview
The immunoregulatory functions and protein interactions of B7H3—an immune checkpoint protein from the same superfamily as PD-L1—are unclear, but B7H3 is highly expressed in many cancer types. Currently, TLT-2 remains a candidate B7H3 receptor, and previous studies have implicated the B7H3 protein in both immune and non-immune signaling pathways. Depending on context, B7H3 can have co-stimulatory or co-inhibitory immune system effects on T cells and NK cells, and it can also exert pro-tumorigenic effects by stimulating epithelial-mesenchymal transition (EMT), proliferation, and metabolic reprogramming. Stimulation of monocytes, B cells, T cells, or NK cells can induce B7H3 expression in these immune cell types as well (Chapoval et al., 2001). Because of these diverse roles, B7H3 is being therapeutically targeted via many different approaches, including mAbs, small molecule inhibitors, antibody drug conjugates (ADCs), chimeric antigen receptor T-cell (CAR-T) therapies, and chimeric antigen receptor NK-cell (CAR-NK) therapies.

Relevant Genetic Alterations, Transcriptomic Expression, and Patient Survival
Between 60 and 90 percent of adult tumors express B7H3, whereas most essential healthy tissues either do not express B7H3 or express it at low levels (Picarda et al., 2016). B7H3 is also
highly expressed in many pediatric solid tumors; in one microarray study of 388 pediatric solid and brain tumor samples, 84 percent were positive for B7H3, with 70 percent demonstrating high-intensity B7H3 staining. Other studies, using IHC staining or mRNA expression levels to detect B7H3 in pediatric tumors, detected substantial B7H3 expression in rhabdomyosarcoma (RMS), Wilms tumor, neuroblastoma, and EwS as pediatric indications. Notably, ALL and AML cancer types have low B7H3 expression.

B7H3 expression data from preclinical pediatric models have largely reflected expression data from clinical samples. PIVOT preclinical models demonstrated the highest B7H3 expression in osteosarcoma, followed by neuroblastoma, RMS, Wilms tumor, and embryonal rhabdomyosarcoma (ERMS); ALL showed the lowest B7H3 expression of PIVOT preclinical models. B7H3 tumor microarrays of various PDX and cell line-derived (CDX) models showed that the tumor types with the highest expression were EwS, rhabdoid, ERMS, alveolar rhabdomyosarcoma (ARMS), pleomorphic xanthoastrocytoma (PXA), Wilms tumor, neuroblastoma, and osteosarcoma.

B7H3 expression levels may correlate with positive survival outcomes in specific tumor types, although this remains unclear for some tumor types due to differing results across studies. For example, 92 percent of osteosarcoma tumors show positive B7H3 IHC staining, and while some studies indicated a positive correlation between osteosarcoma B7H3 expression and survival outcomes, other studies did not detect a significant correlation between expression and survival (Wang et al., 2013). However, for neuroblastoma, high B7H3 expression was negatively correlated with survival.

**Dependency and Drug Sensitivity**

Preclinical studies of B7H3-targeted therapies have demonstrated efficacy in a variety of tumor types, including adult AML and ALL (despite low B7H3 expression in both), various sarcomas (e.g., osteosarcoma, RMS, EwS), some central nervous system (CNS) cancers (e.g., neuroblastoma, medulloblastoma, glioblastoma multiforme [GBM]), and Wilms tumor. A range of B7H3-targeted drug modalities have been tested in preclinical models, with the most common being ADCs, followed by CAR-T therapy. NCI preclinical testing programs have evaluated two B7H3 ADCs (MGC018 and DS-7300), as well as a B7H3 ADC tool compound.

**Leukemias**

Response to B7H3-targeted therapies in adult leukemias is B7H3 expression-dependent (Lichtman et al., 2021; Tyagi et al., 2022), and response to B7H3 CAR-T therapy in xenografts of NALM6 lines (i.e., B cell precursor leukemia) correlated with higher expression of B7H3 (Majzner et al., 2019). In an adult AML PDX model, inhibition of B7H3 with an mAb enhanced NK cell-mediated cytotoxicity and induced antibody-dependent cellular cytotoxicity (ADCC) in AML cancer cells (Tyagi et al., 2022). However, despite B7H3-targeted therapy success in adult preclinical models of AML and ALL, findings are not directly applicable to pediatric leukemias.
Sarcomas
Osteosarcomas, RMSs, and EwSs have all responded to B7H3-targeted therapies in preclinical models. B7H3 CAR-T therapy outperformed control CAR-T therapy, resulting in a complete response when administered to an osteosarcoma xenograft model (MG63.3), and other osteosarcoma PDX models treated with a B7H3 ADC achieved a 100 percent ORR (Kendsersky et al., 2021; Majzner et al., 2019). In addition, the B7H3-DNA topoisomerase I inhibitor ADC (DS-7300a) was highly effective in 5 of 7 osteosarcoma models tested (Gorlick et al., 2022).

For RMS, DS-7300a showed high efficacy in RMS PDX models, resulting in maintained complete response (MCR) in 15 of 22 models (Gorlick et al., 2022). In addition, 4 of 6 mouse models of RMS responded to B7H3-seco-duocarmycin hydroxybenzamide azaindole (DUBA) ADC (i.e., B7H3-targeted DNA alkylating agent) (Kurmasheva et al., 2020). MCR was also reported in three RMS PDX models receiving m276-SL-PBD—a B7H3-pyrrolobenzodiazepine (PBD) ADC (i.e., B7H3-targeted DNA crosslinking agent) (Kendsersky et al., 2021). However, because m276-SL-PBD has not been tested in humans, it is unknown if preclinical dosing is directly translatable or tolerable in humans.

Administration of B7H3 ADCs and CAR-T therapies in EwS preclinical models resulted in high CRRs. B7H3 CAR-T therapy in an EW8 xenograft model resulted in complete tumor regression and 100 percent long-term survival (Majzner et al., 2019). The DS-7300a ADC induced a significant response in 6 of 15 EwS models tested (Gorlick et al., 2022). MCR was also reported for three EwS xenograft models treated with m276-SL-PBD (Kendsersky et al., 2021).

Central Nervous System Tumors
B7H3 therapies have been moderately successful in preclinical CNS tumor models; response to these therapies may be dependent on tumor MYC status. A PIVOT study of DS-7300a reported strong response in a MYC-altered GMB model (Gorlick et al., 2022), and in neuroblastoma xenografts, DS-7300a resulted in MCR or CR in 7 of the 10 xenografts tested. Medulloblastoma models show mixed responses to B7H3-targeted therapy depending on xenograft origin. In one study, all DAOY xenografts showed CR after B7H3 CAR-T administration, while CR occurred only in 4 of 6 D425 (i.e., MYC-amplified medulloblastoma) xenograft mice (Majzner et al., 2019).

Wilms’ Tumor
Although Wilms’ tumors have been less extensively studied, results have demonstrated favorable response rates. Treatment with DS-7300a or m276-SL-PBD in two Wilms’ tumor models resulted in 100 percent MCR (Gorlick et al., 2022; Kendsersky et al., 2021).

B7H3 Inhibition Safety Studies
B7H3 knockout mice are viable, fertile, and have no obvious developmental defects. Certain aspects of the immune system also appear normal, including T, B, and NK cell populations in bone marrow, thymus, lymph node, spleen, and peripheral blood. However, B7H3 knockout mice developed EAE more rapidly than wildtype mice after exposure to myelin oligodendrocyte glycoprotein peptide (Suh et al., 2003). In addition, in a grafting model, B7H3 knockout mice exhibited increases in T cell proliferation, spleen cytokine secretion, and intraepithelial
lymphocyte inflammatory cytokines, resulting in GVHD lethality (Veenstra et al., 2015). Moreover, the effects of loss of B7H3 on bone development are particularly concerning for pediatric indications. B7H3 knockout mice have lower bone mineral density, which leads to increased susceptibility to fractures, and loss of B7H3 in calvarial cells resulted in impaired osteogenic differentiation, indicating B7H3 is required for late-phase osteoblast differentiation (Suh et al., 2004).

**Clinical Trial Development**

B7H3 mAbs (omburtamab and enoblituzumab) are well-tolerated but have demonstrated limited efficacy in clinical trials. Multiple B7H3 ADCs, radio-iodinated omburtamab (i.e., 131-iodine omburtamab), and B7H3 CAR-T therapies are in clinical development.

Pediatric clinical trials for B7H3-targeted therapies are mainly in early phases. Y-mAbs Therapeutics reported a 3-year overall survival rate of 54 percent in patients treated with 131-iodine omburtamab, compared to an external control group from a German registry with a 3-year overall survival rate of 15 percent (NCT00089245). In addition, Y-mAbs submitted data from a supplementary Phase II/III clinical trial of its therapeutic, but no patient responses were attributable to omburtamab. Based on confounding factors and interpretability challenges for the Phase II/III trial, paired with the inappropriate external control group used in the Phase I study, the FDA Oncologic Drugs Advisory Committee (ODAC) unanimously rejected Y-mAbs Therapeutics’ 131-iodine omburtamab for use in treatment of neuroblastoma.

Seattle Children’s Hospital reported safety, tolerability, and feasibility findings from two Phase I clinical trials for B7H3 CAR-T therapy in patients 26 years of age or younger with diffuse intrinsic pontine glioma (DIPG) or relapsing or recurrent non-CNS solid tumors. The first three evaluable patients in the DIPG cohort (i.e., BrainChild-03) received a total of 40 weekly infusions, each containing $10^7$ cells, with no dose limiting toxicities (DLTs) reported (NCT04185038). One of these three patients had sustained clinical and radiographic improvement through the first year of the study. For the non-CNS solid tumor cohort (i.e., STRIvE-02), three patients received 0.5 molar (M) CAR-T/kilogram (kg), and six patients received 1M CAR-T/kg. None of these patients experienced DLTs after the first infusion (NCT04483778), but cytokine release syndrome (CRS) was reported in two patients, with a maximum grade of 2.

**Research and Development Landscape**

NCI administered nine B7H3-related grants, and the overall focus on B7H3 in oncology research is increasing over time, with the number of preclinical investigations into B7H3 as an oncology target remaining steady since 2014. B7H3 published literature most often references glioma, neuroblastoma, and osteosarcoma, but considerable need remains for research on B7H3 as a pediatric oncology target.

There are no FDA-approved B7H3-targeted therapies. Of the 32 B7H3-targeted therapies in development, all are in early developmental stages, and 13 are currently in clinical development. While this indicates a crowded clinical space, none of these therapies have reached Phase III clinical trials. The first in-human Phase I/II clinical trial of DS-7300 showed
high activity in patients with pretreated SCLC, squamous non-small cell lung cancer (sqNSCLC), and metastatic castration-resistant prostate cancer (mCRPC). The ADC, MGC018, is currently in Phase I/II trials in patients with mCRPC, NSCLC, TNBC, melanoma, and squamous cell carcinoma of head and neck (SCCHN). Initial results in mCRPC show activity, based on prostate-specific antigen (PSA) levels and tumor responses, and a manageable safety profile. A Phase II/III study of MGC018 in mCRPC began enrolling in November 2022 (NCT05551117). While omburtamab was rejected by the FDA for use in neuroblastoma, it is still in development for DIPG, desmoplastic small round cell tumor (DSRCT), medulloblastoma, and ependymoma.

The overall clinical feasibility for B7H3-targeted therapies is favorable due to low failure rates and short trial durations compared to other oncology targets. Moreover, pediatric B7H3 clinical trials are associated with a relatively low target accrual and short trial duration, compared to other pediatric oncology targets, indicating these trials may be both affordable and feasible.

**Additional Considerations for Preclinical and Clinical Development**

After the conclusion of Dr. Adam’s B7H3 presentation, meeting attendees engaged in further discussion of the advantages of ADCs over mAbs, treatment resistance mechanisms, combination therapies, and the impact of ODAC’s rejection of omburtamab for neuroblastoma.

**Antibody Drug Conjugates Versus Monoclonal Antibodies**

A previous trial sponsored by Macrogenics tested the B7H3 mAb from which the MGC018 ADC is derived. The initial mAb trial showed very little antitumor activity; however, data collected from this trial include B7H3 staining of patient tumor samples, for which Dr. Ken Desantes reported a 90 percent overall positivity rate for B7H3 IHC, with some B7H3-negative samples resulting from flawed testing. The only true negative specimens were from neuroblastoma patients with only marrow disease, while other neuroblastoma tumors were positive for B7H3 IHC staining. In B7H3-positive tumor samples, tumor vascular B7H3 staining was often apparent. Dr. Maris noted further work is needed to determine whether any ADCs are capable of crossing the blood brain barrier for the treatment of CNS tumors. While the mAb showed limited activity, Drs. Maris and Desantes expressed optimism about the potential efficacy of B7H3-targeted ADCs and CAR-T therapies.

**Therapeutic Resistance Mechanisms**

Resistance mechanisms for B7H3-targeted therapies have not been explored. Dr. Maris explained that loss of B7H3 in a mouse model still allows neuroblastoma cells to grow but at a slower rate, which suggests that B7H3 may have a tumor-intrinsic proliferative function. Xiao-Nan Li explained that after the administration of B7H3-targeted therapy in a preclinical model, recurrent GBM tumors still strongly expressed B7H3, which suggests that potential treatment resistance mechanisms may not occur via downregulation of B7H3. Dr. Maris indicated that more useful preclinical studies of B7H3-targeted therapy resistance mechanisms would require a more specific B7H3-targeted agent and a pediatric oncology indication.

Dr. Rosane Charlab Orbach asked whether B7H3, as a transmembrane protein, can be cleaved into a soluble fragment, potentially impacting therapeutic activity. Dr. Maris explained that it
can be cleaved but its cleavage does not interfere with preclinical model therapeutic efficacy. However, no clinical studies have measured soluble B7H3 fragment levels and compared those values to therapeutic responses. Dr. Maris added that while the prevailing hypothesis is that B7H3 inhibits T cell activity, this has not been demonstrated in most pediatric indications. Alternatively, Dr. Kieran suggested that B7H3 may serve as a targeting mechanism to deliver a conjugated therapy. Drs. Maris and Kieran agreed that B7H3 ADCs may induce immunogenic cell death as well as provide a delivery mechanism for other potent therapies; however, distinguishing between these two effects requires additional preclinical studies.

**B7H3 Combination Therapies**

Establishment of safety and single-agent efficacy for B7H3-targeted therapies is required before proceeding with preclinical studies of potential combination therapies. Assuming these therapies are successful and tolerable, Dr. Smith suggested prioritizing preclinical studies of different combination therapies. Dr. Maris cautioned that effective treatment combinations may differ depending on the type of B7H3-targeted therapy (e.g., mAb, ADC, CAR-T), as well as B7H3 single-cell expression variability. Meeting participants discussed the following B7H3-targeted treatment combination options:

- B7H3-targeted therapy simultaneously administered with standard chemotherapy (e.g., topotecan-cyclophosphamide), similar to anti-GD2 mAb plus chemotherapy combinations for neuroblastoma.
- B7H3-targeted therapy cycles between standard chemotherapy cycles to reduce platinum exposure.
- B7H3 CAR-T therapy as a maintenance cycle after chemotherapy cycles are finished.
- B7H3-targeted therapy in combination with DNA damage response inhibitors.
- B7H3-targeted therapy in combination with a MYC proteolysis-targeting chimera (PROTAC).
- B7H3 ADC therapy, which may increase TILs and calreticulin expression, followed by ICIs.

Due to the immunogenic effects of B7H3-targeted therapies, Dr. Maris suggested that inhibition of MYC could reduce any MYC-dependent immune suppression. For example, certain bromodomain inhibitors can reduce MYC transcription (Delmore et al., 2011; Mertz et al., 2011). However, current MYC inhibitors are highly toxic and may not be tolerable in combination therapies for pediatric patients. The development of a MYC PROTAC would enable more targeted MYC inhibition. Dr. Maris further suggested that if B7H3 ADCs increase TILs and calreticulin expression, these ADCs may increase ICI sensitivity, similar to research findings for a glypican 2-PBD ADC in neuroblastoma models (Pascual-Pasto et al., 2022).

Dr. Smith further suggested the development of a B7H3-topoisomerase inhibitor ADC to target the topoisomerase inhibitor to B7H3-expressing tumor cells. Dr. Maris indicated that PIVOT is currently testing something similar, but more work is required to develop the correct topoisomerase inhibitor formulation.
**Impact of the omburtamab Decision**
Dr. Buenger explained that the advocacy community was concerned about the effect that ODAC’s rejection of omburtamab would have on future research and development of B7H3-targeted therapies. Dr. Martha Donoghue clarified that this one rejection does not reflect FDA’s overall opinion of B7H3-targeted therapies, and that there is still a lot of compelling data to support the development of B7H3-targeted therapeutics. Drs. Pearson and Maris further explained that the rejected omburtamab submission did not use appropriate controls and the study design prevented interpretation of subsequent results.

**Next Steps**
Most CAR-T therapy clinical trials occur at only a single, or a few, institutions due to logistical difficulties. Therefore, there are many different efforts to develop B7H3 CAR-T therapies, providing many opportunities to identify the most effective options. In addition, many B7H3 ADCs contain different payloads (i.e., cytotoxic compounds). Due to the abundance of potential treatment options, both Drs. Maris and Smith cautioned against narrowing B7H3-targeted therapy research prematurely to ensure the identification of therapeutics that work best in the clinical setting.

Dr. Smith explained that enough information exists from preclinical models relevant to pediatric indications and adult Phase II clinical trials to support the design and execution of additional early-phase pediatric clinical trials of B7H3-targeted therapies. Pediatric preclinical data suggest strong efficacy of B7H3-targeted therapies for certain cancer indications, and dosing recommendations from adult clinical trials are already established. Thus, companies developing these B7H3-targeted therapies should be able to proceed with pediatric clinical trials.

Ultimately, Phase I pediatric clinical trials for safety and efficacy should occur in parallel with additional pediatric preclinical studies of different B7H3-targeted therapies to select lead candidates. Then, further preclinical research can test different candidate combinations.
Appendix A: Feedback

Ms. Tetyana Murza facilitated a feedback session with meeting participants to discuss pre-meeting materials, COACH meetings, and the target selection process. Dr. Maris indicated that many meeting participants may not be reading the pre-meeting materials in full, but the executive summaries provided for each target help prepare all participants for COACH meetings. In addition, while most target nominations are solicited from meeting participant companies, NCI, and FDA, Dr. Maris requested that academic participants have the opportunity to nominate targets. Therefore, Ms. Murza will include PIVOT laboratories during future nomination discussions.

The next round of target nomination and voting, for the June 2023 meeting, will begin in early January 2023. During that time, FNIH will contact COACH member organization leads via email to solicit target nominations and coordinate scheduling for the June 2023 meeting.

FNIH met with COACH members from advocacy groups on December 5, 2022, to develop a communications strategy for the release of COACH meeting summaries. Ms. Murza provided an update on the summary reports for the first three COACH meetings:

- **First meeting summary**: Expert meetings were held to solidify recommendations for targets discussed during the first meeting and these discussions will conclude on December 19. The first meeting summary will be updated with these recommendations in January and will be ready to post online shortly thereafter.
- **Second meeting summary**: Feedback was received and incorporated. The second summary meeting will be posted online in early January, prior to the first meeting summary.
- **Third meeting summary**: Reviewers will receive the third meeting summary during the middle of January 2022.

The next meeting will occur on March 15, 2023, from 10 am to 2 pm ET. The targets for this meeting are ataxia telangiectasia (ATR), histone deacetylase (HDAC), and phosphatidylinositol 3-kinase alpha (PIK3α). Ms. Murza and Dr. Adam requested that COACH members volunteer, or recommend experts in these targets, to lead data presentations and facilitate discussions.
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Appendix B 30


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