Checkpoint Proteins in Pediatric Brain and Extracranial Solid Tumors: Opportunities for Immunotherapy
Eric K. Ring1, James M. Markert2, G. Yancey Gillespie2, and Gregory K. Friedman1

Abstract

Pediatric brain and extracranial solid tumors are a diverse group of malignancies that represent almost half of all pediatric cancers. Standard therapy includes various combinations of surgery, cytotoxic chemotherapy, and radiation, which can be very harmful to a developing child, and survivors carry a substantial burden of long-term morbidities. Although these therapies have improved survival rates for children with solid tumors, outcomes still remain extremely poor for subsets of patients. Recently, immunosuppressive checkpoint molecules that negatively regulate immune cell function have been described. When found on malignant cells or in the tumor microenvironment, they contribute to immune evasion and tumor escape. Agents designed to inhibit these proteins have demonstrated significant efficacy in human adult solid tumor studies. However, there is limited research focusing on immune checkpoint molecules and inhibitors in pediatric solid tumors. In this review, we examine the current knowledge on immune checkpoint proteins with an emphasis on cytotoxic T lymphocyte antigen-4 (CTLA-4); programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1); OX-2 membrane glycoprotein (CD200); and indoleamine 2,3-dioxygenase (IDO). We review T-cell signaling, the mechanisms of action of these checkpoint molecules, pediatric preclinical studies on checkpoint proteins and checkpoint blockade, pediatric checkpoint inhibitor clinical trials conducted to date, and future immunotherapy opportunities for childhood cancers.

Introduction

Pediatric solid tumors are a heterogeneous group of malignancies that represent approximately 50% of pediatric cancers (1). They can be divided into extracranial solid tumors and central nervous system (CNS) tumors, which are the most common solid tumors in children, accounting for 20% to 25% of childhood malignancies. Neuroblastoma, Wilms tumor, and sarcomas, including rhabdomyosarcoma, osteosarcoma, and Ewing sarcoma, represent the most common extracranial solid tumors in childhood. The mainstay of therapy includes various combinations of surgery, cytotoxic chemotherapy, and radiation, which can be toxic, impair normal development, and result in long-term morbidities. Although these therapies have improved survival rates for children with solid tumors, outcomes are extremely poor for subsets of patients such as those with high-grade, refractory, or metastatic disease. Novel, targeted therapies are being developed to improve outcomes and lessen toxicities from conventional therapies.

Recently, immunosuppressive checkpoint molecules that negatively regulate immune cell function and enable local tumor escape have been described in adult malignancies (2, 3). These molecules exert their immunosuppressive effects by downregulating the normal T-cell response and increasing FoxP3+ regulatory T cell (Treg) numbers and activation. These checkpoint molecules are normally expressed on a variety of cells in the body and likely play a crucial role in peripheral immune tolerance and regulation. When found on malignant cells or in the tumor microenvironment, they can contribute to immune evasion and tumor escape. Agents designed to inhibit these proteins have been developed and have shown significant efficacy in human adult solid tumor studies, with several agents approved by the FDA (4–10). Table 1 provides a summary of checkpoint inhibitors advanced to clinical trials and approved for human use. There is limited research focusing on immune checkpoint molecules and the potential benefit of checkpoint blockade in children with solid tumors. In this review, we examine immune checkpoint proteins with an emphasis on cytotoxic T lymphocyte antigen-4 (CTLA-4); programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1); OX-2 membrane glycoprotein (CD200); and indoleamine 2,3-dioxygenase (IDO). We review their mechanism of action, pediatric preclinical studies related to these checkpoint proteins, pediatric checkpoint inhibitor clinical trials, and future immunotherapy opportunities.

T-cell Signaling

T-cell signaling plays a critical role in the adaptive immune system. T cells first recognize foreign antigens associated with the major histocompatibility complex (MHC) on antigen-presenting cells (APC) through the CD3 T-cell receptor (TCR). Second, CD28 on T cells interacts with CD80 (B7-1)/CD86 (B7-2) on APCs, resulting in amplification of TCR signaling, production of IL2, and growth and expansion of T cells while preventing the death of
Activated T cells (11). Checkpoint molecules can result in down-regulation of this T-cell response (Fig. 1). Myeloid-derived suppressor cells (MDSC) and FoxP3+ Tregs normally work to provide signals for the physiologic termination of the immune response but can also be upregulated in various malignancies (12). Tumor-infiltrating Tregs are often associated with a poor clinical outcome, likely by limiting antitumor immune responses and promoting immunologic tolerance to cancer cells (13). Tregs mediate...
immune regulation through direct cytolytic activity, metabolic disruption, suppression of dendritic cells, and secretion of soluble or membrane-bound immunosuppressive molecules (12). Increased Treg numbers and activation are associated with expression of CTLA-4, PD-1/PD-L1, CD200, and IDO (14–17).

**CTLA-4**

CTLA-4 is a cell surface homodimeric glycoprotein belonging to the human immunoglobulin gene superfamily found on CD4+ and CD8+ T cells, as well as Tregs. It shares 30% homology with CD28 and binds the B7 family of proteins with very high affinity. The molecule is predominantly expressed within the intracellular compartment of T cells and can be exported to the cell surface in response to constitutive T-cell activation and high levels of IL2 (18, 19). Once on the cell surface, the extracellular domain of CTLA-4 competes with CD28 by interacting with CD80 (B7-1)/CD86 (B7-2), resulting in inhibition of IL2, IFNγ, IL4 production, IL2 receptor expression, and cell-cycle progression, thereby decreasing activation and expansion of T cells and accelerating death of activated T cells (11).

Human germline mutations in the CTLA-4 gene are associated with severe immune dysregulation and lymphoproliferative infiltration of target organs (20). CTLA-4 knockout mice developed profound lymphoproliferation and succumbed to early death (21). CTLA-4 may be critical for circulating Tregs to maintain immunologic self-tolerance and homeostasis. Spontaneous development of systemic lymphoproliferation occurred when Tregs were deficient in CTLA-4 (22). In colon adenocarcinoma models, anti–CTLA-4 antibodies mediated a rapid and dramatic reduction of Tregs and expansion of CD8+ T cells at the tumor site (23). The combination of direct enhancement of effector T-cell function and inhibition of Treg activity are essential for mediating the full therapeutic effects of anti–CTLA-4 antibodies (14).

Although preclinical studies in adult malignancies have demonstrated increased CTLA-4 expression and significant responses to anti–CTLA-4 antibodies, few pediatric studies exist (24–26). Patients with newly diagnosed or relapsed osteosarcoma and Ewing sarcoma had increased expression of peripheral blood TILs (27). Although the significance of CTLA-4 expression on tumor cells has not been fully elucidated, cytoplasmic and surface expression of CTLA-4 in pediatric neuroblastoma, rhabdomyosarcoma, and osteosarcoma cell lines has been reported (28). See Table 2 for summary of checkpoint protein expression by pediatric tumor type. In vitro treatment of human CTLA-4–expressing osteosarcoma cell lines with recombinant forms of the CTLA-4-ligands B7-1 and B7-2 induced caspase-dependent tumor cell apoptosis, suggesting that tumor surface CTLA-4 may be targetable. Genetic polymorphisms in the CTLA-4 gene have been shown to influence T-cell activation and susceptibility to malignancies; the presence of CTLA-4 +49G>A (rs231775) polymorphism, which results in greater affinity of CTLA-4 to bind the B7-1 molecule leading to increased inhibition of T-cell activation, is associated with increased risk of malignant bone tumors, including osteosarcoma and Ewing sarcoma (29, 30).

Table 2. Summary of checkpoint protein expression by pediatric tumor type

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>CTLA-4</th>
<th>PD-1/PD-L1</th>
<th>CD200</th>
<th>IDO</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extracranial solid tumors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>ND</td>
<td>−/+++/+++</td>
<td>ND</td>
<td>ND</td>
<td>(38–40)</td>
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<tr>
<td>Hodgkin lymphoma</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>+++</td>
<td>(77)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>++</td>
<td>−/+++</td>
<td>ND</td>
<td>ND</td>
<td>(40)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>+++</td>
<td>−/+++</td>
<td>+++</td>
<td>+++</td>
<td>(28, 38, 42, 45, 58, 63)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>+++</td>
<td>+++/+++</td>
<td>ND</td>
<td>+++</td>
<td>(28, 38, 47, 69)</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>ND</td>
<td>+++</td>
<td>ND</td>
<td>ND</td>
<td>(44)</td>
</tr>
<tr>
<td>Alveolar RMS</td>
<td>ND</td>
<td>+++</td>
<td>ND</td>
<td>ND</td>
<td>(38)</td>
</tr>
<tr>
<td>Embryonal RMS</td>
<td>++</td>
<td>+++</td>
<td>ND</td>
<td>ND</td>
<td>(28, 38)</td>
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<tr>
<td>Wilms, favorable</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>(41)</td>
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<tr>
<td>Wilms, anaplastic</td>
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<td>+</td>
<td>ND</td>
<td>ND</td>
<td>(41)</td>
</tr>
<tr>
<td><strong>Intracranial solid tumors</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>Ependymoma</td>
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<td>ND</td>
<td>+++</td>
<td>ND</td>
<td>(59)</td>
</tr>
<tr>
<td>Germinoma</td>
<td>ND</td>
<td>+++</td>
<td>ND</td>
<td>ND</td>
<td>(42)</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>ND</td>
<td>+++</td>
<td>ND</td>
<td>ND</td>
<td>(40)</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>ND</td>
<td>−/+++</td>
<td>ND</td>
<td>ND</td>
<td>(40)</td>
</tr>
</tbody>
</table>

NOTE: Checkpoint protein expression was graded as follows: −, no expression; +, 1–19% of tumors tested; ++, 20–59% of tumors tested; ++++, 60–100% of tumors tested. Table 2. Summary of checkpoint protein expression by pediatric tumor type.
PD-1/PD-L1

PD-L1 (B7-H1) is a member of the B7 family of costimulatory molecules involved in the regulation of cellular and humoral immune responses through the PD-1 receptor. PD-L1 exists as a 40 kDa type I transmembrane cell surface glycoprotein on hematopoietic and parenchymal cells (34). Interaction of PD-1 with PD-L1 dramatically inhibits T-cell receptor–mediated proliferation and production of IL2 and IFNγ. PD-1 regulates peripheral tolerance and autoimmunity; PD-1–deficient mice develop features of lupus-like disease and dilated cardiomyopathy (35).

PD-L1 expressed on the surface of malignant cells can suppress the antitumor immune response, leading to tumor growth and immune escape (2). Studies in adult malignancies have indicated that increased PD-L1 expression is associated with increased disease stage, presence of metastases, and refractory or relapsed disease (36, 37). Several studies have examined PD-L1 expression in pediatric solid tumors by IHC (Table 2; refs. 38–42). Results have been variable, likely due to a lack of standardized methods for scoring and reporting stains, and because there are over a dozen PD-L1 antibodies that differ in their targeted epitope, isotype, source, and binding affinity (43). Despite these limitations, moderate-to-high PD-L1 expression was seen in pediatric sarcomas, whereas expression in Wilms tumor was low; however, expression was more likely to occur in anaplastic Wilms and was associated with an increased risk of recurrence in favorable histology tumors (38, 39, 41, 42). Importantly, pediatric patients whose tumors had the highest proportion of PD-L1 positivity showed the poorest survival (38).

In pediatric preclinical studies, PD-L1 expression was upregulated to response to immunogenic stimuli in retinoblastoma and neuroblastoma cells (44, 45). PD-L1 antibody treatment enhanced T-cell activation and proliferation, implicating PD-L1 in the negative regulation of the antitumor immune response. In a murine neuroblastoma model, targeting PD-1/PD-L1 with blocking antibodies was insufficient to control tumor growth alone; however, combining PD-1/PD-L1 blockade with a selective colony-stimulating factor-1 receptor inhibitor (BLZ945) that blocks induction of suppressive MDSCs resulted in significant tumor responses, suggesting that combined immunotherapy approaches may be necessary (46).

Differences in PD-L1 expression and response to PD-L1 blockade were seen in primary versus metastatic tumors and within different subtypes of the same tumor (47, 48). Human metastatic osteosarcomas, but not primary tumors, expressed PD-L1, and CD8+ tumor-infiltrating lymphocytes in metastatic osteosarcoma expressed PD-1, suggesting that PD-L1+ tumors are immunogenic but able to tolerate infiltrating T cells within the tumor microenvironment through this pathway (47). An anti–PD-L1 antibody significantly increased survival and improved function of infiltrating lymphocytes in a metastatic murine osteosarcoma model. Group 3 murine medulloblastoma had a higher percentage of CD8+/PD-1− T cells and were
more sensitive to PD-1 blockade than Shh murine tumors (48). These studies indicate that immunologic differences within the tumor microenvironment may exist and can be leveraged for therapeutic benefit.

There are several FDA-approved anti–PD-1/anti–PD-L1 mAbs that have improved survival in multiple adult malignancies (Table 1; refs. 6–10). Importantly, PD-L1 expression correlated with response to treatment, but PD-L1 negativity did not preclude a treatment response, and PD-L1 tumor expression was neither prognostic nor predictive in efficacy endpoints in trials using anti–PD-L1 antibodies (10, 49). The irAEs seen with PD-1/PD-L1 inhibition were similar to those seen with CTLA-4 blockade, with skin, gastrointestinal, hepatic, and endocrine toxicities occurring most frequently (6–10). Grades 3 to 4 toxicities occurred in 16% of adult melanoma patients treated with nivolumab (PD-1 inhibitor) alone; however, this rate increased to 55% when nivolumab was combined with ipilimumab (7).

Although no completed pediatric studies exist, several studies are ongoing, and a recent report of significant responses to nivolumab in two young siblings with recurrent multifocal glioblastoma and biallelic mismatch repair deficiency suggests the potential of PD-1/PD-L1 blockade in children (50). A safety/efficacy study to assess the dose-limiting toxicities and define a recommended phase II dose of pembrolizumab (PD-1 inhibitor) in children with recurrent or refractory high-grade glioma and diffuse intrinsic pontine glioma (DIPG) is active through the Pediatric Brain Tumor Consortium (NCT02359565). Initial starting dose is at the recommended dose in adults (2 mg/kg every 3 weeks). Secondary objectives include correlating potential biomarkers (PD-L1 and PD-1 tumor expression, patient immunophenotype, cytokine expression profiles, RNA signature profile, and tumor gene expression profile) with outcomes and exploring whether quantitative magnetic resonance spectroscopy and diffusion-weighted imaging can predict early tumor response and differentiate between progressive disease and pseudoprogression.

As discussed above, a pediatric phase I/II trial investigating the safety of nivolumab alone and with ipilimumab is ongoing. This study will explore whether correlations exist between PD-L1 tumor expression levels and antitumor effects of nivolumab alone and in combination with ipilimumab. A phase II study of neoadjuvant nivolumab in patients >1 year old with primary or recurrent glioblastoma is currently recruiting patients in Spain (NCT02550249). Patients who require surgery will receive neoadjuvant nivolumab 3 mg/kg i.v. every 2 weeks. Changes in PD-L1 expression on tumor cells and lymphocytes will be assessed at baseline, and response rate will be measured. Finally, two other trials are exploring combination approaches. A European basket trial that is stratifying patients ≤18 years old with relapsed or refractory tumors based on tumor molecular anomalies includes an arm combining nivolumab and cyclophosphamide with and without radiation (NCT02813135), and a Canadian phase II clinical trial testing the safety of durvalumab and tremelimumab in 16 years and older with advanced rare tumors is planned (NCT02879162).

**CD200**

CD200 is a type I transmembrane protein related to the B7 family of costimulatory receptors involved in T-cell signaling. It is normally expressed on lymphoid and neuronal tissue (51); its receptor, CD200R, is expressed on APCs and T cells. Interaction of CD200 with CD200R inhibits monocyte/macrophage production of IL2 and IFNγ (52, 53) and downregulates the T-cell–mediated immune response through augmented production of Tregs (54, 55). CD200-deficient mice demonstrate myeloid dysregulation and autoimmune inflammation (52, 53). CD200 can be expressed on the surface of malignant cells and result in tumor immune escape (54, 56). In adult acute myeloid leukemia (AML), expression of CD200 correlated with lower natural killer (NK) cell numbers, increased frequency of Tregs, and a worse prognosis (16, 57).

Few preclinical studies in pediatric cancers exist. Two neuroblastoma samples expressed surface CD200, and Th1 cytokines that are necessary for efficient cytotoxic T-cell function, IL2 and IFNγ, were downregulated when CD200-expressing but not CD200-negative tumor cell lines were added to mixed lymphocyte reactions (58). Inclusion of an anti-CD200 antibody restored Th1 cytokine responses, suggesting that CD200 suppresses anti-tumor immune responses. In a murine glioma model, mice treated with a CD200 antagonist with OVA–poly-ICLC, which induces an antigen-specific cellular immune response, had prolonged survival compared with untreated mice. Treated mice had increased numbers of antigen-specific T cells and production of TNFα and IFNγ, implicating CD200 in suppressing the immune response (59). Several pediatric brain tumor types, including ependymoma, medulloblastoma, and DIPG, had higher CD200 expression by Western blot analysis, as compared to normal brain tissue (59). Increased CD200 mRNA expression was seen in supratentorial compared with posterior fossa ependymoma and in group 4 compared with Shh or group 3 medulloblastoma. Further research is needed to elucidate the cause of immunologic differences seen between tumor types and within tumor subtypes.

There is one reported clinical trial of the monoclonal anti-CD200 antibody samalizumab in 26 adults with advanced B-cell chronic lymphocytic leukemia (B-CLL) or multiple myeloma (60). Samalizumab was well tolerated; the most common adverse events were fatigue, fever, and rash, and grade ≥3 events included neutropenia and infections. The drug exhibited a dose-dependent effect on CD200+/B-CLL, CD4+ T cells, and Tregs. Some patients showed disease stabilization, and two patients who received >9 cycles had a reduced tumor burden. There are currently no active adult or pediatric clinical trials targeting CD200.

**IDO**

IDO is an intracellular enzyme that catalyzes the initial and rate-limiting step in the kynurenine pathway, which is the major pathway of L-tryptophan catabolism in mammals (61). The kynurenine pathway produces many metabolites, including L-kynurenine, kynurenic acid (KYNA), quinolinic acid (QUIN), 3-hydroxykynurenine (3-HK), and picolinic acid (PIC). QUIN is a potent NMDA receptor agonist, and QUIN, L-kynurenine, and PIC inhibit T- and NK-cell proliferation (62). 3-HK has immunomodulatory properties indirectly by the production of free radicals. T and NK cells are also inhibited by the depletion of available tryptophan, which occurs in the presence of high levels of IDO. IFNγ induces IDO in monocytes and tumor cells, which suggests that IDO is upregulated in the setting of inflammation, likely to quell the inflammatory cascade (63). IDO is expressed in a wide variety of normal cells and likely plays a fundamental role in immunosuppression and peripheral tolerance (64, 65). IDO is expressed in the placenta early in pregnancy and has been published online.
implicated in the prevention of allogenic fetus rejection (66). Mucosal biopsies of patients with inflammatory bowel disease revealed IDO overexpression, suggesting that IDO has an anti-inflammatory mechanism to counterbalance the tissue-damaging effects of activated T cells (67).

Many adult tumors constitutively express IDO, and increased IDO expression correlated with aggressive tumor growth and resistance to T-cell–targeting therapies due to the recruitment and activation of MDSCs through a Treg-dependent mechanism (17, 68). Expression of IDO in immunogenic murine tumor cells prevented rejection by mice preimmunized with tumor antigen and resulted in decreased T-cell accumulation at the tumor site (68). Furthermore, IDO inhibition with 1-methyl-tryptophan (1MT) significantly slowed tumor progression.

Similar to other checkpoint molecules, there are few studies examining IDO in pediatric tumors. Urakawa and colleagues scored IDO expression from 0 to 5 by IHC in 30 pediatric osteosarcoma patient samples. Patients with high (>4+) IDO expression had significantly lower metastasis-free survival (53% vs. 81%) and 5-year overall survival (60% vs. 92%) compared with patients with lower (<4+) expression, suggesting that the immune tolerance mediated by IDO may have an important role in the metastatic potential of osteosarcoma and may impact clinical outcome (69). IDO expression was also seen in 17 of 20 (85%) pediatric Hodgkin lymphoma patient samples and in human Ewing sarcoma grown in NOD/scid mice (70, 71).

Indoximod (1-methyl-tryptophan), an orally available IDO inhibitor, is currently being studied in several adult phase I and II trials alone; in combination with conventional chemotherapy and/or radiation; and with ipilimumab, pembrolizumab, or nivolumab. In a phase I study of indoximod in 48 adults with advanced extracranial solid tumors, an MTD was not reached, and the only irAE was grade 2 hypophysitis in three patients (6%) previously treated with other checkpoint inhibitors (72). A phase I trial using indoximod in combination with temozolomide for children with primary malignant brain tumors is currently recruiting patients 3 to 21 years old (NCT02502708). Patients will receive indoximod orally in escalating doses, beginning at 12.8 mg/kg/week daily and increasing to 22.4 mg/kg/week twice daily, along with temozolomide 200 mg/m² daily for 5 days. Primary outcome measures are incidence of regimen-limiting toxicities and objective response rate, and secondary outcomes are indoximod pharmacokinetics, progression-free survival, and overall survival.

Future Directions

On the basis of dramatic, durable responses seen in a variety of adult cancers and the initial preclinical data indicating that many pediatric solid tumors express checkpoint molecules, immune checkpoint inhibition is a promising therapy for pediatric malignancies. Adult checkpoint inhibitor studies resulted in some significant, potentially fatal autoimmune side effects, with increased toxicity seen when combining PD-1 and CTLA-4 inhibitors. Increased vigilance and aggressive treatment of these adverse events was essential to decrease morbidity and mortality. Initial pediatric checkpoint inhibitor trials have shown similar results with some autoimmune side effects. Further studies and larger clinical trials are needed to evaluate the full range of side effects in children. The short- and long-term consequences of using checkpoint inhibitors in children with naive immune systems and developing organ systems are unknown.
Checkpoint blockade may be beneficial for children with relapsed or refractory solid tumors as mono-therapy, in combination with other checkpoint inhibitors, or with standard chemotherapy or radiotherapy. The role of checkpoint molecules in immune suppression and tumor escape suggests that patients need an intact immune system to achieve maximum therapeutic benefit from these agents. Thus, checkpoint inhibitors may have less therapeutic benefit when combined with myelosuppressive chemotherapy. An ideal response from checkpoint inhibitors is likely to be achieved with the combination of a potent immunogen to activate the immune system, a cytokine to further amplify the antitumor immune response, and a checkpoint inhibitor to further amplify and sustain the immune response (Fig. 2).

Agents designed to stimulate the tumor immune response such as tumor vaccines or oncolytic viruses may be attractive therapies to combine with immune checkpoint inhibition. A phase I study using pembrolizumab (anti–PD-1) with or without talimogene laherparepvec (T-VEC; Imlygic [Amgen]), an oncolytic herpes simplex virus-1 that produces GM-CSF and is the first FDA-approved oncolytic virus, is currently recruiting patients for treatment of stages IIIB to IV melanoma (NCT02263508). Other emerging immune checkpoint molecules, such as Fibrinogen-like protein 2 (FGL2), lymphocyte activation gene-3 (LAG-3), and colony stimulating-1 receptor (CSF-1R), have shown immunomodulatory roles in human cancer and require further studies in pediatric cancers (73–75). Additional pediatric clinical trials and a more complete understanding of the tumor microenvironment and tumor-host interaction will aid in realizing the full potential of immune checkpoint blockade in pediatric cancers.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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