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Immunotherapy in pediatric malignancies: current status and future perspectives

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Introduction

Treatment of childhood cancer has been a flagship for international collaboration through cooperative clinical trials and experimentation in multiple treatment modalities, like chemotherapy, radiation and surgery. Advances in our basic understanding of tumor immunology and in genomic sequencing of cancers has led to a wealth of information that invites development of new pharmacologic drugs for cancer, and the identification of new tumor-associated antigens that can be targeted by immune cells or biologics. The ability to expand immune cells into large quantities, as well as the availability of clinical grade cytokines, antibodies and genetically engineered proteins therapeutics, is now making both cell-based and monoclonal antibody treatments a reality. Within the last 5 years, we have seen a surge of novel immune-based therapies that are changing the landscape of how pediatric oncologists treat children with some of the more deadly cancers. In this review, we will discuss what immunotherapies are being developed and tested (if registered with clinicaltrials.gov), barriers to widespread application, and the future of immuno-oncology for childhood cancer.

Monoclonal Antibodies

Recent clinical trials have demonstrated that monoclonal antibodies (moAbs) show anti-tumor responses in a variety of childhood cancers[1–26]. MoAb technology has the capability to create distinct agents that can bind to virtually any antigen on the tumor cell surface, including sugars, lipids, proteins, gangliosides, etc, and either mark that cell for destruction by the patient's immune system (e.g. antibody dependent cellular cytotoxicity or ADCC) or carry a toxin or radionuclide capable of killing the cell directly (e.g. immunotoxins and radioimmunoconjugates). In addition, moAbs can either act as an agonist (e.g. death receptor) or antagonist (e.g. growth receptor) to a given receptor on the tumor thereby facilitating cytotoxicity or growth arrest (Figure 1). Ideally, the antigen recognized by an immunotherapeutic antibody is preferentially expressed in high quantities on the tumor as compared to normal tissues, with little cross-reactivity to antigens on normal tissues. Occasionally the use of antibodies that target tumor antigens present on "dispensable tissue", like B cells, is acceptable if that tissue is replaceable, or not essential for health. One of the appeals of monoclonal antibody therapies in general is that they are an "off the shelf" reagent, meaning they are more tumor-specific than patient-specific, and can be easily stored in pharmacies at hospitals and clinics at multiple centers for immediate administration when

indicated. There is no need for expertise in cell culture, expansion and activation, in order to create an individualized therapeutic product for each patient. In some instances, investigators are combining moAbs with cytokines that activate and recruit immune cells to the moAb-coated tumor cells in order to enhance ADCC[3, 21, 25]. We will discuss the usage of moAbs targeting pediatric solid tumors followed by leukemias and lymphomas.

MoAb Therapy for Pediatric Solid Tumors

Metastatic solid tumors remain one of the most significant challenges in pediatric oncology, with survival rates ranging from 40% to less than 5% depending on the tumor type and location of the metastatic disease. Fortunately survival for one solid tumor, metastatic neuroblastoma, has improved through development of the moAb ch14.18, a chimeric moAb against the disialoganglioside GD2[27]. GD2 is restricted to neuroectodermal tissues, expressed in high density on neuroblastoma, and is not shed from the cell surface. Recent results from a randomized, phase III study showed that 2 year event-free survival of children with metastatic neuroblastoma improved from 44% to 64% when these patients were given infusions of ch14.18 along with 13-cis-retinoic acid (CRA), interleukin (IL)-2 and granulocyte monocyte-colony stimulating factor (GM-CSF) after standard multimodality therapy[25]. The addition of IL-2 and GM-CSF to ch14.18 moAb therapy is believed to enhance ADCC by lymphocytes, neutrophils and activated macrophages. Because of these data, this ch14.18 regimen is now offered as standard of care for children with metastatic neuroblastoma, and demonstrates that immunotherapy can be incorporated with traditional treatment modalities to enhance survival.

In addition, other anti-GD2 moAbs are in development, and several have already shown efficacy in the clinic. The immunocytokine hu14.18-IL2, a humanized 14.18 moAb that is conjugated to IL-2, has shown activity in phase II trials in children with relapsed/refractory neuroblastoma[21]. Treatment with the anti-GD2 moAb 3F8 when combined with GM-CSF and CRA has improved overall survival in patients with metastatic neuroblastoma treated at a single institution in a retrospective analysis of consecutive trials[3]. 3F8 conjugated to the radionuclide ^{131}Iodine (I-131) has also shown efficacy in treatment of CNS/leptomeningeal metastases of neuroblastoma in a phase I study[10], and has shown activity in a phase I trial of advanced stage neuroblastoma patients when combined with an oral beta glucan, which prime leukocyte dectin and complement receptor 3[13]. Thus patients with advanced neuroblastoma have multiple options in terms of moAb therapy (Table 1). Perhaps utilizing moAbs in conjunction with other immunotherapies under development may allow for further synergy against this aggressive disease.

Targeting essential signaling or growth pathways on the surface of pediatric solid tumor cells, or on the tumor stroma supporting tumor growth, such as endothelial cells, has led to promising results. The moAb bevacizumab inhibits vascular endothelial growth factor (VEGF), a signaling pathway presumed to be critical for vascular supply to solid tumors, and has shown activity as a single agent in some studies of children with relapsed astrocytoma[2, 8], neuroblastoma and rhabdomyosarcoma[2] but not in other studies[28]. When combined with irinotecan, objective responses have been observed in multiply recurrent low grade gliomas[5, 16, 18] and medulloblastoma[1]. When compared to adult

patients, efficacy is lower for high grade gliomas[5, 14, 29]. Minimal to no efficacy was reported in recurrent ependymomas[30], malignant gliomas and brainstem gliomas[31] in phase II studies. Combination of bevacizumab with sorafenib and low dose cyclophosphamide led to disease responses in rhabdomyosarcoma, rhabdoid tumor and medulloblastoma in a phase I study[15]. Although the combination of vincristine, oral irinotecan and temozolomide has shown antitumor activity in children, the benefit of adding bevacizumab was unclear in a pilot trial that showed responses in Ewing sarcoma[24] but encouraging in another phase I study in terms of responses in Wilms tumor, medulloblastoma and hepatocellular carcinoma[23]. Thus bevacizumab seems to show activity across a variety of tumor types, but we have yet to optimize how to incorporate it with standard chemotherapy.

Many moAbs have been developed against the insulin growth factor-1 receptor (IGF-1R), a growth pathway used by select pediatric solid tumors, but anti-tumor activity has been sparse and variable. AMG 479 is a fully human moAb against IGF-1R that showed responses in Ewing sarcoma, including a complete response of 28 months, and in neuroendocrine tumors[32]. Figitumumab is a fully human IgG2 moAb against IGF-1R that showed objective responses with Ewing sarcoma in a phase I expansion cohort study[17]. R1507, another anti- IGF-1R antagonist moAb, did not show objective responses in a phase I study[33], whereas a 10% response rate was observed in a multicenter phase II study of Ewing sarcoma[19]. While responses can be striking and long lasting, the overall low response rates with IGF-1R moAbs may be partially explained by the lack of biomarkers that help clinicians select which patients will benefit from this treatment.

Combining irinotecan with cetuximab, a moAb against the epidermal growth factor receptor (EGFR), led to responses in CNS tumors in a phase I study[22]. Further work is clearly needed with moAbs targeting the EGFR pathway in pediatric tumors. Antibodies can also induce cell death if they crosslink a cell surface receptor that can initiate a downstream death cascade. Lexatumumab is a moAb against tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor 2 that did not cause tumor responses, but led to improvement of clinical symptoms, changes in PET activity and decreased biomarkers in a phase I study[12]. Because of the association of HER2 expression and worse survival in osteosarcoma, trastuzumab (an anti HER2 moAb) has recently been used in conjunction with standard chemotherapy for HER2 -positive osteosarcoma. There was no significant difference in event-free or overall survival between HER2-positive and HER2-negative groups, with inferior outcomes reported in both groups[34]. Because HER2 expression in osteosarcoma does not result from gene amplification, as it does in breast carcinoma, interrupting HER2 signaling may not result in death in this tumor. However, this still leaves open the possibility to use trastuzumab to induce ADCC for HER2-positive patients by combining the moAb with ADCC enhancing cytokines, such as IL2 or GM-CSF.

Lastly, agonist moAbs targeting T cell co-stimulatory molecules like CD40[35–37], 4-1BBL[38] and OX40[39] , or antagonist moAbs against T cell inhibitory checkpoints like CTLA4[40–44], PD-1[44–48] and PDL-1[49], have had dramatic effects in adult solid cancers, and clinical trials using these agents in children are either underway or in

development (Table 2). Clinical moAbs against other promising tumor antigens in pediatric solid tumors have also been proposed[50, 51].

MoAb Therapy for Pediatric Leukemia and Lymphoma

Leukemias and lymphomas combined are the most common malignancies observed in children. Fortunately, they express a variety of antigens that can be targeted by moAbs with efficacy. A new class of moAbs, called bi-specific antibodies, are molecules that recognize 2 distinct antigenic targets . Blinatumomab is one such agent, that targets CD19 on B cell malignancies (and normal B cells) and CD3 on normal T cells. By bringing the CD19-expressing cancer physically next to a T cell, and simultaneously activating the T cell through its CD3 molecule, the T cell recognizes the cancer and eliminates it, resulting in dramatic remissions in patients with a high burden of disease[6, 52, 53]. A multi-center phase 2 clinical trial in children is already underway through the Children's Oncology Group (COG).

Other moAbs have been conjugated to toxins (immunotoxins), including RFT5-SMPT-dgA, a moAb conjugated to ricin that targets CD25 on Hodgkin lymphoma[54–56]. BL22[57] and moxetumomab pasudotox[58] are moAbs conjugated with pseudomonal exotoxin that targets CD22 on acute lymphoblastic leukemia (ALL). Combotox is a 1:1 mixture of 2 immunotoxins against CD19 and CD22 that has also produced complete remissions in children with B cell ALL[7].

Conjugating moAbs to radionuclides has been used to increase anti-tumor efficacy and potency. An anti-CD25 moAb conjugated to I-131, CHT-25, has shown success in children with Hodgkin lymphoma[59], while the anti-CD20 moAb conjugated to ^{90}Yttrium, ibritumomab, has shown activity in pediatric non-Hodgkin's lymphoma[4]. Because these therapies result in prolonged cytopenias, they may need to be undertaken in the setting of autologous stem cell rescue.

Conjugating moAbs to drugs has been an effective method of delivering toxic therapy with greater specificity to tumors. In 2000, the Food and Drug Administration (FDA) approved gemtuzumab ozogamicin, an anti-CD33 moAb conjugated with the drug calicheamicin for treatment of elderly patients with AML. The agent was withdrawn from the US market in 2010 after concerns of hepatic veno-occlusive disease (VOD) were described and clinical benefit was not documented in an adult AML phase 3 trial (SWOG S0106). However, recent data has led to renewed interest in this moAb and clinical trials are currently available for children with refractory AML[26]. As gemtuzumab ozogamicin was approved based on its activity in advanced AML in adults, this renewed interest is focusing on alternative ways to integrate this agent into initial treatment regimens in order to improve efficacy and reduce toxicity. Interestingly, using gemtuzumab ozogamicin with busulfan and cyclophosphamide as a conditioning regimen for poor-risk CD33+ pediatric AML did not increase the risk of VOD[60]. In 2011, the FDA approved Brentuximab vedotin, an anti-CD30 moAb conjugated to monomethyl auristatin E, a drug that inhibits microtubules, after demonstrating responses in Hodgkin lymphoma and anaplastic large cell lymphoma[61, 62]. Lastly, inotuzumab ozogamicin is an anti-CD22-calecheamicin conjugate that has shown activity in phase II studies in children with B cell leukemia[9].

Unconjugated moAbs can be potent in of themselves. Epratuzumab is a moAb that targets CD22, and has been combined with chemotherapy to induce remissions in B cell leukemia[20]. Ipilimumab, an anti-CTLA4 moAb, has shown activity in adults with B cell malignancies[63], and is currently being explored in pediatric cancers. Rituximab has a long track record as a moAb against CD20, which is expressed on mature B cells and B cell lymphomas. Rituximab showed a 96% overall response rate in one phase II trial for lymphocyte-predominant Hodgkin lymphoma, with 75% remaining in remission after one year[64]. Another phase II trial showed similar results[65]. Activity has also been reported in children with Burkitt lymphoma and diffuse large B cell lymphoma and EBV-associated post-transplant lymphoproliferative disease (PTLD) [11].

Lastly, some moAbs that have demonstrated activity in adult hematologic malignancies may warrant expanded study in childhood cancers. The anti-CD19 moAb conjugated to a mayatansine derivative SAR3419[66], the anti B cell lactosamine moAb mAb216[67] and the anti-CD37 IgG fusion protein TRU-016[68] may be promising reagents for pediatric B cell ALL. For B cell lymphomas, other potential “second generation” anti-CD20 moAbs that could be tested besides rituximab include AME-133v[69], veltuzumab[70], obinutuzumab[71], ocrelizumab[72] or ofatumumab[73]. For adult T cell leukemias/ lymphomas, the anti-CCR4 moAb mogamulizumab and the anti-CD4 moAb zanolimumab[74] have had activity and thus warrant investigation in children with these cancers[75]. For pediatric AML, the anti-inhibitory killer immunoglobulin-like receptor (KIR) moAb IPH-2101[76], or the novel anti-CD33 moAbs AVE9633[77] and the alpha particle bismuth-213-lintuzumab[78] also warrant investigation. While there is no shortage of moAbs that could be tested in children (Table 3), because of the rarity of pediatric cancers, prioritization and coordination between centers and cooperative groups will be critical in developing multi-institutional phase II studies to accrue enough patients of a given tumor type.

Chimeric Antigen Receptors

Advances in transfusion medicine and cell culture technologies, along with the availability of clinical grade cytokines and artificial antigen presenting cells, has allowed for the ex vivo growth and expansion of high numbers of immune effector cells, like T cells or natural killer (NK) cells, that can be potentially reinfused to the patient in order to treat pediatric tumors. In addition to being able to generate large quantities of these cells, advances in genetic engineering have allowed scientists to manipulate the quality of these cells. In particular, it is now possible to genetically modify lymphocytes by transfecting them with a vector that produces in them a “chimeric antigen receptor”. These receptors are often single chain Fv fragments of a moAb (that recognizes a tumor antigen) fused to the signaling chain of the T cell receptor (1^{st} generation CAR). In addition, one can fuse one co-stimulatory molecule, like CD28 (2^{nd} generation CAR), or two co-stimulatory signals, like CD28 and CD137 (3^{rd} generation CAR), to enhance the T cell activation signal (Figure 2). This technology has led to the creation of cells that have the targeting properties of moAbs but the killing capacity of effector cells[79]. T lymphocytes bearing these chimeric antigen receptors (CARs) have had dramatic results in early clinical studies, and could revolutionize how we treat both newly diagnosed and relapsed cancers (Table 4).

CARs for Pediatric Solid Tumors

Clinical experience with CARs in solid tumors with children or adults has been very limited thus far. While many clinical trials involving solid tumors are ongoing, limited but promising data has emerged. Children with refractory neuroblastoma were treated with autologous activated T cells or Epstein Barr virus specific T cells that were engineered to express a first generation CAR against GD2 in a phase I, dose escalation study. Half of the subjects were observed to have tumor regressions or necrosis[80]. A follow up analysis showed 27% of patients with active disease at the time of GD2 CAR infusion eventually achieved a complete response[81]. It is important to note that since the investigators used a first generation CAR, which lacks costimulatory molecules, anti-tumor responses and in vivo persistence of the CARs may be even better with second or third generation GD2 CARs, that can have a single or multiple co-stimulatory molecules to enhance T cell persistence and activity.

The interleukin-13 receptor alpha (IL-13Rα) is expressed on gliomas and medulloblastomas but otherwise not expressed within the central nervous system. CAR T cells have been engineered to express a membrane-tethered IL-13, rather than a moAb, to target the CARs to the IL-13Rα on gliomas, creating CARs that have been designated as IL13-zetakine[82]. While a phase I study is ongoing, 3 patients with glioblastoma multiforme have been treated and transient responses were obtained[83]. In addition to IL-13Rα, there is interest in targeting the epidermal growth factor receptor variant III (EGFRvIII) since it is also expressed on gliomas[84], as well as CD276 (B7H3) which is expressed on gliomas and other solid tumors[85]. Clinical trials are ongoing for both IL-13Rα and EGFRvIII CARs for high grade gliomas.

A phase 1 CAR trial targeting HER2 positive tumors has also been initiated[86], with potential applicability for osteosarcoma and some cases of medulloblastoma. One adult patient who received a high dose of HER2 CAR cells unexpectedly died of immune mediated toxicity; it has been hypothesized that this toxicity potentially reflected HER2 CAR recognition of cross reactivity with low levels of HER2 on lung or cardiac epithelium[87]. There were two important lessons gleaned from this unfortunate complication. First, it suggested that CAR-modified T cells do not necessarily safely target antigens that are safely targeted by moAbs. Second, the dose of T cells utilized was much higher than used in other CAR studies, and suggests that a dose escalation strategy may be necessary when designing future CAR trials.

Clearly, other targets on pediatric solid tumors will have to be validated and tested. Promising antigens include the fibroblast growth factor receptor 4[88, 89] and IGF-1R, but others will come to light as more results of cDNA microarray and whole genome sequencing of pediatric tumors become available[51, 90–95].

CARs for Pediatric Leukemias and Lymphomas

Undoubtedly the most exciting data regarding CARs has come from trials involving B cell malignancies. By targeting CD19, a marker present on normal B cells and B cell leukemias/lymphomas, adults with advanced follicular lymphoma[96, 97], splenic marginal zone

lymphoma[97], B cell ALL[98, 99] and refractory chronic lymphocytic leukemia (CLL)[97, 99, 100] have attained sustained complete remissions at 4 different centers after infusion of independently designed CD19 CARs. In one phase I trial, the CD19 CAR-modified T cells expanded more than 1000 fold in vivo, were found 6 months after infusion. Based on the striking clinical remissions induced by infusions of a relatively small number of CAR T cells, it has been calculated that a single CD19 CAR-modified T cell (and its progeny) was estimated to kill 1000 CLL cells in vivo [101]. Some of these remissions have lasted at least a year without further therapy.

Because B cell ALL is the most common leukemia observed in children, studies with CD19 CAR in pediatric ALL were performed with similarly dramatic responses. In the first phase I study, two children with refractory B cell ALL developed complete remissions, with one child ongoing remission at 11 months after treatment and the other child relapsing with CD19 negative disease 2 months after treatment.[102] Similar to adults, CD19 CAR-modified T cells expanded more than 1000 fold in vivo, and were detectable even in the cerebral spinal fluid, a common site of B cell leukemia relapse. Both children developed a cytokine release syndrome that was reversible. In another phase I study using CD19 CAR-modified multivirus specific T cells, 2 children with B cell ALL were treated after allogeneic hematopoietic stem cell transplant. One child had leukemia at the time of infusion and ultimately died of relapse, while the other child was treated in remission and remained in remission 2 months thereafter, with follow up still ongoing[99]. The relapse of a CD19 negative clone in the first study is informative in that the child was previously treated with blinatumomab, which may have selected for CD19 negative clones, and indicates that targeting other antigens in addition to CD19 may be warranted.

With that notion in mind, CARs against lymphoid antigens like CD22[103], CD30[104] and ROR1[105], myeloid antigens like CD33[106] and CD123[107, 108], stress ligands like NKG2DLs[109] and B7-H6[110], and signaling pathways like VEGF receptor-1[111] have been developed and demonstrated efficacy in preclinical models.

NK Cell Infusions

NK cells are lymphoid cells that eliminate virally infected cells and tumor cells, and with proper expansion and activation, have shown potent activity against pediatric tumors[112–114]. Because of data demonstrating that when the inhibitory killer immunoglobulin-like receptors (KIRs) on NK cells are mismatched to host HLA after alloHSCT, there is improved survival in adults with AML[115] and in pediatric patients with ALL[116], groups have initiated studies by either infusing KIR mismatched NK cells to children with refractory cancer or infusing KIR mismatched NK cells after alloHSCT to also take advantage of the high levels of homeostatic cytokines (e.g. IL-15) present in the early transplant period that are favorable for NK cell expansion. A pilot study of haploidentical NK cell infusions administered to children with AML in remission showed no evidence of graft-versus-host-disease (GVHD) and maintained remission 2–3 years after infusion[117]. In a separate phase I/II trial after haploidentical HSCT, IL-2 activated NK cell infusions given to children with high risk leukemia/tumors at day +3, +40 and +100 caused a temporary elimination of host immune cells and an increase in various cytokines/

chemokines when compared to unstimulated NK cells[118]. Ongoing studies are exploring NK cell infusions in children with leukemia (Table 5).

Because of the preclinical data showing that NK cells can recognize and lyse pediatric solid tumors, some studies have focused on infusing NK cells to children with high-risk neuroblastoma or sarcomas. In an ongoing phase I/II trial, allogeneic IL-2 activated haploidentical NK cells have been used for high-risk neuroblastoma and help remove levels of soluble MHC class I chain-related gene A (MICA)[119], which is secreted by tumors to neutralize circulating NK cells. In a pilot study of children with refractory solid tumors, haploidentical HSCT led to 50% survival at 14 months, with KIR mismatch correlating with complete and partial remissions[120], and in a separate study, resolution of lung metastases in a child with rhabdomyosarcoma[121]. Ongoing trials are exploring NK cell infusions in children with refractory solid tumors (Table 5). The optimal parameters for using NK cell infusions have still not been defined. Although still somewhat controversial, NK cells do not seem capable of immunologic memory (at least not in the same way memory T cells retain specificity). For this reason it is likely that several NK cell infusions may be needed for optimal anti-tumor effects. With the development of cytokines like IL-15, there may opportunities to expand NK cells in patients after infusion, improving anti-tumor activity further. In addition, the availability of several active tumor moAbs in the clinic could be combined with NK cell infusions as a means of promoting ADCC.

Tumor Vaccines

In order to augment existing T cell responses to tumor-associated antigens, vaccines have been explored for decades as a means of directing T cells towards tumors. However, prior usage of vaccines in cancer has been more successful in the setting of minimal residual disease than with bulky tumors[122]. With the FDA approval of sipuleucel-T for prostate cancer in 2010, and promising data for Biovax-ID from phase III trials in B cell lymphoma, there is now precedent for successfully moving cell based vaccines to the clinic and demonstrating activity in patients with metastatic bulky disease.

Vaccines for Pediatric Solid Tumors

Because of the relative rarity of most pediatric solid tumors, creating a broadly applicable cancer vaccine therapy strategy will be complex. As there are clear biologic differences between different subtypes of histologically similar tumors, identifying a universal tumor antigen for a given histologic type will be difficult. Furthermore, as the T cells activated by a vaccine will need to recognize that vaccine's epitope as presented by the patients own HLA antigens, the vast polymorphisms of HLA within our species will make the selection of a vaccine "cocktail" that might contain epitopes that can be presented by the HLA repertoire of most individuals, quite complex. Nevertheless for neuroblastoma, scientists have used peptides derived from the MYCN oncogene, which is amplified in a fraction of high-risk patients, and have shown that these peptides can induce immune responses that are able to lyse tumor cells in children with HLA $A1^{+}$ tumors[123]. Dendritic cells (DCs) pulsed with overlapping peptides derived from full length cancer-testis antigens like MAGE-A1, MAGE-A3, and NY-ESO-1 were given along with decitabine into neuroblastoma patients in a phase I study, with one patient harboring residual bone marrow disease after standard

therapy reported to achieve a complete remission[124]. In one pilot trial, DCs pulsed with peptides generated from translocation breakpoints in Ewing sarcoma and alveolar rhabdomyosarcoma have been administered with continuous infusion IL-2 to children with refractory disease, but no clinical responses were observed[125]. When this approach was combined with autologous T cell infusions, the 5-year survival was 43% in those patients that successfully completed immunotherapy, which is favorable compared to historical controls for these very high risk patients[126]. Pulsing monocytes with RNA derived from autologous tumor, and using this as a vaccine, has the theoretical advantage of presenting peptides from whatever immunogenic epitopes might be expressed by the tumor. This approach, pulsing monocytes with RNA from a child's tumor, has been used in neuroblastoma patients after completing chemotherapy, but none of the patients showed a response[127]. One child with a pleomorphic xanthoastrocytoma showed a partial response when this approach was used for brain tumors[128].

Rather than having the scientist select the appropriate tumor antigen for vaccination, approaches using tumor lysates or tumor lysate-pulsed DCs have also been employed to allow the patient's immune system to select the most immunogenic antigen. In a phase I trial, tumor-lysate pulsed DCs were given to children with relapsed solid tumors with a 20% response rate[129], including a significant regression in a patient with metastatic fibrosarcoma[130]. Vaccination with tumor lysate-pulsed IL-12 secreting DCs showed a mixed response in adrenocortical carcinoma[131]. Vaccines of tumor lysate-pulsed DCs have also been used in children with high grade gliomas, with sustained remissions achieved in some patients treated at a time of minimal disease[132]. Genetically-modified neuroblastoma cells encoded with IL-2[133–135] or IL-2 and the chemokine lymphotactin[136–138], as a means of attracting immune cells to the vaccine, have been used in phase I/II trials with mixed results; responses were seen in some trials but not in others.

Vaccines for Pediatric Leukemias and Lymphomas

There is limited experience using vaccines for pediatric leukemias and lymphomas at this time, partly due to the fact that most very high-risk patients go onto allogeneic hematopoietic stem cell transplant (alloHSCT). For Epstein Barr virus-positive lymphomas, manipulating the tumor to overexpress LMP2 has led to clinical responses. The Wilms tumor-1 (WT1) antigen is a transcription factor that is expressed on leukemia cells and is being explored as a potential vaccine to augment the graft-versus-leukemia (GVL) effect after alloHSCT[139]. For myeloid leukemias, there is also interest in vaccinating against PR1, an epitope that is shared by proteinase-3 and elastase. T cell specific responses against both WT1 and PR1 have been associated with improvement in GVL effects in adult leukemias[140, 141], but definitive data is still lacking in children.

As was stated earlier in identifying targets for moAbs and CARs, further work is needed in determining the optimal antigens for vaccination. Whether tumor vaccines should be used to treat bulky disease or in the setting of minimal residual disease, or even while in remission to prevent recurrence, remains to be determined (Table 6).

Strategies to Enhance Immune-Based Therapies

While moAbs and adoptive cell therapies have shown potent efficacy in their own right, developing clinical grade reagents that could be given concurrently to enhance these effects would be highly desirable. For example, the success of the moAb ch14.18 was contingent on combining it with GM-CSF and IL-2 to recruit and activate immune cells capable of initiating ADCC. In addition, the preliminary anti-tumor effects of alpha interferon has made this agent a candidate drug to treat children with melanoma and brain tumors.

Interleukins and cytokines

IL-2 is in the gamma (c) cytokine family and is FDA approved for adults with malignant melanoma and renal cell carcinoma. It was one of the first cytokines studied in children, with no anti-tumor responses observed as a single agent therapy. More recently, other clinical grade gamma (c) cytokines have been developed and tested in adults, namely IL-7, IL-15, and IL-21[142], with potential promise in children. A recent pilot trial using a modified DC vaccine for pediatric sarcomas has incorporated IL-7 to enhance immune reconstitution and hopefully increase the number of tumor-reactive T cells (NCT00526240).

Tumor necrosis factor alpha (TNF-α) and dactinomycin was first administered to children in phase I trials over 20 years ago, with some antitumor responses observed in metatstatic Ewing sarcoma, non-Hodgkin's lymphoma and Wilms tumor, [143, 144]. In a more recent phase II study of TNF-α and dactinomycin for recurrent Wilms tumor, 15.8% of patients had complete responses but unfortunately the study terminated early because the TNF-α was no longer available[145].

IFN-α2a is approved by the FDA for the adjuvant therapy of adults with stage III melanoma, hairy cell leukemia, Kaposi sarcoma and chronic myelogenous leukemia, all of which are very rare in pediatrics. An ongoing clinical trial is examining the use of IFN-α2a in children with melanoma. Ongoing phase I trials are also exploring the role of pegylated IFN-α2a for plexiform neurofibromas and brain tumors in children.

IFN-α2b is FDA approved in adults for hairy cell leukemia, malignant melanoma and Kaposi sarcoma. One pilot study reported some benefit in children with recurrent craniopharyngioma[146], while a phase I trial showed responses in children with plexiform neurofibromas[147]. A phase II trial showed a delay in time to progression in children with diffuse intrinsic pontine glioma, but no improvement in 2-year survival[148].

Toll like receptors

In regards to adoptive cell therapies, activating toll like receptors (TLRs) is one potential strategy to further stimulate immune effector cells and/or directly cause anti-tumor effects. TLRs are part of our innate immunity and allow cells to be activated by damage associated molecular patterns (DAMPs) or from microbes (MAMPs) (e.g. DNA, RNA or lipopolysaccharide [LPS]). In fact, the FDA has already approved the TLR2 and TLR4 agonist Bacillus Calmette-Guerin cell wall skeleton (BCG-CWS) for the treatment of adults with bladder cancer, the TLR4 agonist monophosphoryl lipid A as an adjuvant for the human papilloma virus vaccine and the TLR7 agonist imiquimod for basal cell cancer[149].

The TLR4 agonist Mifamurtide demonstrated improved overall survival in patients with nonmetastatic osteosarcoma[150], but is only approved in Europe. The TLR3 agonists Ampligen, Hiltonol, and polyadenylic polyuridylic acid; TLR4 agonists LPS and Picibanil; TLR5 agonist CBLB502; TLR7 and TLR8 agonists Resiquimod, 852A, and VTX-2337; TLR9 agonists Agatolimod, GNKG168, and CpG-28; and poly TLR agonists Immuvac and IMM-101 have been safely given to adults with advanced cancers[151].

Elimination of immunosuppressive cell subsets

It is now evident that the tumor microenvironment is conducive toward attenuating or abrogating immune responses, thus targeting immunosuppressive cell subsets present in pediatric tumors may enhance the effectiveness of adoptively transferred T or NK cells. For example, M2 macrophages localize into the hypoxic regions of tumors and secrete immunosuppressive cytokines. Because pediatric tumors are infiltrated with macrophages[152] that may negatively influence outcome[153], therapies should be developed and explored that selectively deplete this population to prepare the patient for further immunotherapy. Regulatory T cells (Tregs) in the tumor also produce immunosuppressive cytokines like IL-10 and transforming growth factor-beta, suppressing effector cell function. Tregs have been described in the peripheral blood[154] and in metastases of children with solid tumors[155]. Because Tregs express the high affinity IL-2 receptor, CD25, and clinical grade moAbs against CD25 are available, combining Treg depletion with immunotherapies is an attractive concept[156, 157]. Lastly myeloid-derived suppressor cells (MDSCs) cause a reduction in arginine levels within the tumor, increasing nitric oxide, which inhibits T cell activation. MDSCs also produce a tryptophan metabolite called indoleamine-2,3-oxygenase that suppresses immune function. A subset of MDSCs, called fibrocytes, have recently been described in pediatric cancers[158]. Thus therapies that either differentiate MDSCs, like all trans retinoic acid[159], or that inhibit MDSCs, like Polyphenon E[160] or cyclooxygenase-2 inhibitors[161, 162], may be advantageous in enhancing immunotherapies by eliminating this suppressor cell subset.

Overview of Immunotherapy Support and Infrastructure Barriers

Advancements in developing novel and/or improved immunotherapies for pediatric cancer are occurring at a rapid pace. Discoveries are occurring in academic, industrial and government laboratories. Scientific exchange and collaborations in the field of immunotherapy are being fostered by multiple scientific and clinical societies in North America, Europe and Asia. Most promising therapies are being tested initially at the single institutional level through phase I trials, although in childhood cancer there is precedent for moving the most exciting therapies to multi-institutional phase I, phase II, and even phase III, trials through the Children’s Oncology Group. In addition, more focused consortiums such as New Agents for Neuroblastoma Therapy, Pediatric Blood and Marrow Transplant Consortium and the “Pediatric Cancer Dream Team” sponsored by Stand Up to Cancer and the St. Baldrick’s Foundation, are available to test various immunotherapies in defined populations of childhood cancer. Another potential avenue, the Cancer Immunotherapies Trials Network, with support from the National Cancer Institute, is testing clinical grade biologics in adults, but there may be opportunities for pediatric cancer patients through this

mechanism as well. Funding in the United States is being driven at the federal level by both traditional grant mechanisms and translational research initiatives like Production Assistance for Cellular Therapies from the National Heart, Lung, and Blood Institute. Because of flat NIH budgets and sequestration, research support for preclinical and clinical research cannot keep up with inflation or the need to expand, and thus support from industry partners and private charitable foundations focused on childhood cancer are becoming increasingly important.

Conclusions

For some childhood cancers, like ALL and Wilms tumor, we have seen great strides with cure rates pushing 90%. Yet for many other tumors, like metastatic sarcomas and high grade brain tumors, survival has plateaued despite advances in surgical techniques, chemotherapy and radiation therapy treatments. Especially in the last 5 years there have been significant strides in moving novel immune-based therapies from the lab to the clinic with bona fide responses, and prolonged survival documented in children with certain high-risk cancers. Treatment strategies, like the combination of ch14.18, IL-2 and GM-CSF, demonstrate that immune-based therapies can be incorporated into standard multimodality regimens, and improve survival, as demonstrated in randomized trials. Similar observations were made with mifamurtide for osteosarcoma. The last decade has shown us just a sample of what is evolving into a true paradigm shift in the care for children with cancer – the dawn of immunotherapy.

However, as fast as discoveries in the lab are moving to the clinic, we still have much to learn about how to properly use immunotherapies safely and effectively in patients. For example, we have learned that these therapies are different from traditional pharmaceuticals drugs, in that many cell-based therapies can increase in number and potency in vivo, rather than be metabolized and have decreased potency over time. We also learned, in the setting of CARs, that effects predicted from moAbs do not necessarily predict effects observed when the scFv from the same moAb is attached to a highly activated T cell. Lastly, the pace of publishing data showing efficacy in preclinical models, moving to early phase testing in patients and then to large scale phase III trials is difficult, expensive and too slow. While advancements in technology will help speed discoveries into the clinic, changes in the political and regulatory climate will be equally necessary to help the science continue to be translated into better clinical outcomes, hopefully with less long term treatment-related side effects.

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Executive summary

Monoclonal Antibodies

- The improvement of survival for children with metastatic neuroblastoma with ch14.18 in a phase III study demonstrates that immunotherapy can be successfully incorporated into traditional treatment approaches.
- Checkpoint stimulators and inhibitors are being explored in several adult solid tumors, and warrant investigation in pediatric solid tumors.
- Bispecific moAbs bring T cells and B cell malignancies physically together, leading to tumor lysis and in some cases, dramatic remissions.
- Immunotoxins, radionuclide-conjugated moAbs, antibody-drug conjugates and unconjugated moAbs are all available that target tumor-associated antigens.

Chimeric Antigen Receptors

- CD19 CAR modified T cells have induced dramatic, sustained remissions in children with chemorefractory disease, with a reversible cytokine release syndrome noted.
- GD2 CAR modified T cells have induced complete responses in some children with neuroblastoma.
- Clinical trials with EGFRvIII CARs and IL-13 zetakine are underway for adults with brain tumors, and should be explored in children as well.

NK Cell Infusions

- Haploidentical NK cell infusions have been shown to maintain remissions in children with AML.
- In pilot data from children with chemorefractory solid tumors, KIR mismatch correlated with complete and partial remissions.

Tumor Vaccines

- Tumor lysates or tumor lysate-pulsed DCs have had a modest response rate in some pediatric solid tumors, with better results noted in children with minimal disease burden.
- There is limited experience using vaccines for children with hematologic malignancies, but clinical experiences with vaccines targeting LMP2, WT1 and PR1 in adults warrant investigation in children.

Strategies to Enhance Immune-Based Therapies

- Clinical grade interleukins, cytokines, and toll like receptor agonists need to be further expanded in childhood cancers.
- The TLR4 agonist Mifamurtide demonstrated improved overall survival in a randomized trial of patients with nonmetastatic osteosarcoma, but is only approved in Europe for this disease.

- Eliminating immunosuppressive cell subsets, like Tregs, MDSCs and M2 macrophages, may be necessary to improve efficacy of immunotherapies.

Overview of Immunotherapy Support and Infrastructure Barriers

- Immunotherapies are being developed in academic, government and industrial laboratories around the world at a rapid pace, and the availability of multinational cancer consortiums will allow testing of childhood cancers, which are relatively rare, to occur at a faster rate than any one center can achieve.
- Because of flat NIH budgets, “fiscal cliffs” and “sequestration” in the U.S., maintaining financial support for childhood cancer research has been extremely challenging, and will require engagement with an evolving political and regulatory landscape to continue moving these exciting, paradigm shifting therapies to the clinic.

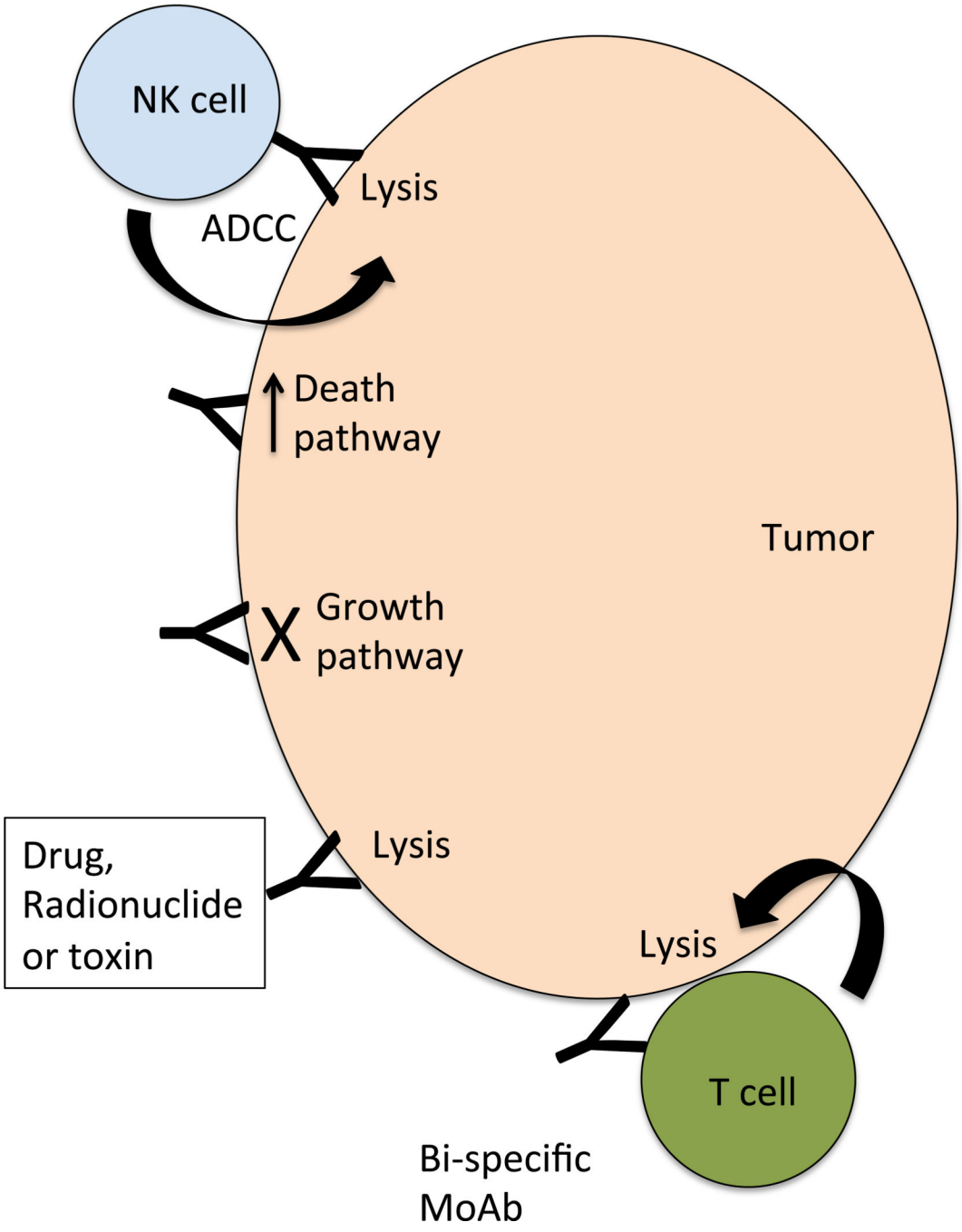

Figure 1. Mechanisms of tumor destruction by monoclonal antibodies

Antibodies can mark the tumor for lysis by antibody dependent cellular cytotoxicity (ADCC), act as an agonist for a death pathway (e.g. TRAIL), inhibit an essential tumor growth pathway (e.g. IGF-1 receptor), deliver a toxin/radionuclide/drug that lyses the tumor, or bring a T cell adjacent to the tumor.

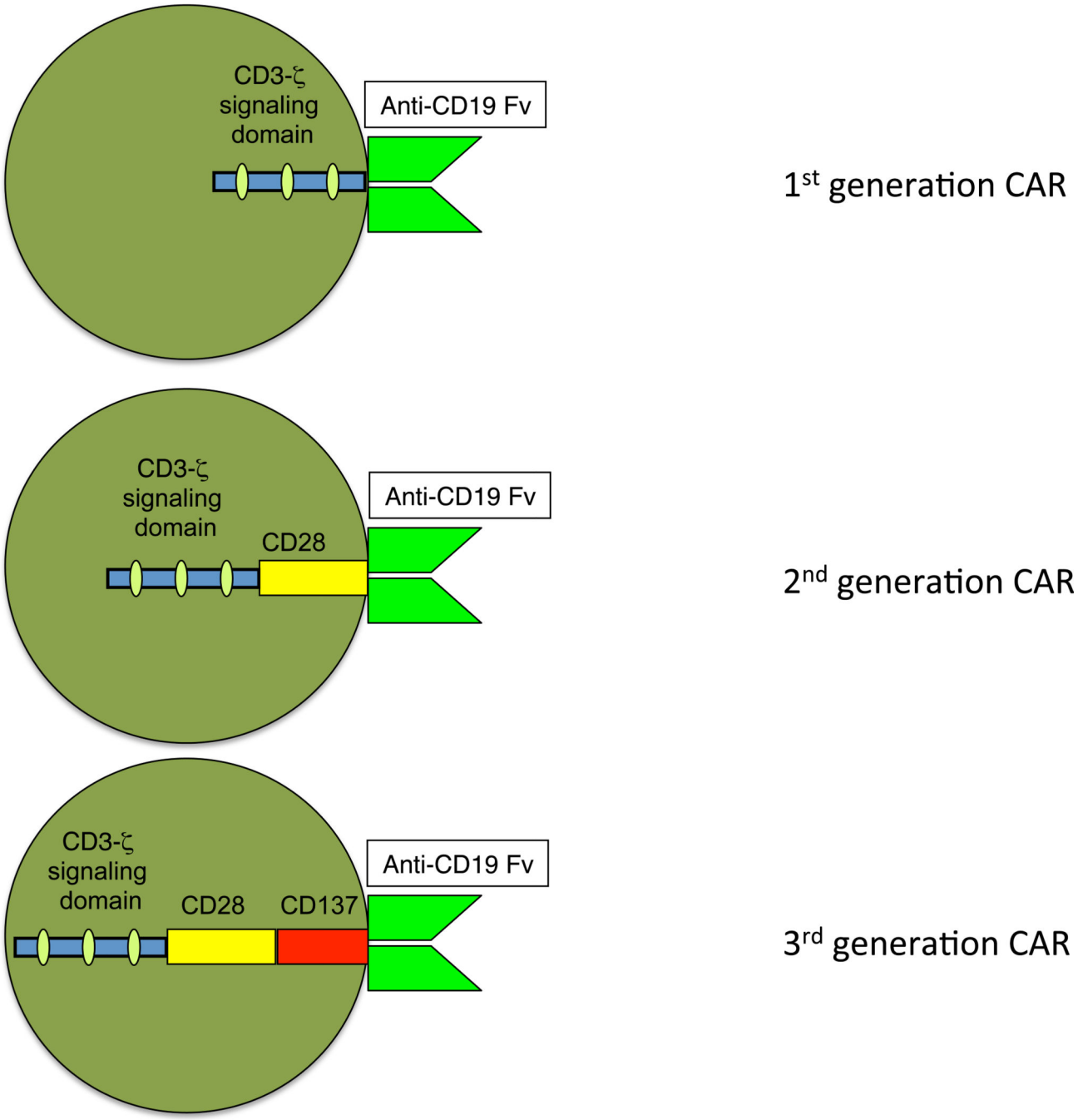

Figure 2. Anatomy of a CAR

First generation CARs consist of an Fv fragment against a tumor-associated antigen (e.g. CD19 on B cell malignancies) linked to the CD3-zeta signaling chain. Second generation CARs incorporate a co-stimulatory signal (e.g. CD28) to enhance T cell activation and cytotoxicity. Third generation CARs incorporate two co-stimulatory signals (e.g. CD28 and CD137) to theoretically provide additional T cell activation. To date, each generation of CAR has not been compared head to head.

Table 1

Open Pediatric Trials using anti-GD2 Monoclonal Antibodies

Clinical trial number	Title	Sponsor
NCT01767194	Irinotecan Hydrochloride and Temozolomide With Temsirolimus or Monoclonal Antibody Ch14.18 in Treating Younger Patients With Refractory or Relapsed Neuroblastoma	National Cancer Institute
NCT00026312	Isotretinoin With or Without Monoclonal Antibody, Interleukin-2, and Sargramostim Following Stem Cell Transplantation in Treating Patients With Neuroblastoma	National Cancer Institute
NCT01711554	Lenalidomide and Monoclonal Antibody With or Without Isotretinoin in Treating Younger Patients With Refractory or Recurrent Neuroblastoma	National Cancer Institute
NCT01526603	High Dose Chemotherapy and Autologous Transplant for Neuroblastoma	Masonic Cancer Center, University of Minnesota
NCT01419834	Humanized 3F8 Monoclonal Antibody (Hu3F8) in Patients With High-Risk Neuroblastoma and GD2-Positive Tumors	Memorial Sloan-Kettering Cancer Center
NCT01662804	Humanized 3F8 Monoclonal Antibody (Hu3F8) When Combined With Interleukin-2 in Patients With High-Risk Neuroblastoma and GD2-positive Solid Tumors	Memorial Sloan-Kettering Cancer Center
NCT00877110	Anti-GD2 3F8 Antibody and Allogeneic Natural Killer Cells for High-Risk Neuroblastoma	Memorial Sloan-Kettering Cancer Center
NCT01183429	High-Dose 3F8/GM-CSF Immunotherapy Plus 13-Cis-Retinoic Acid for Consolidation of First Remission After Non-Myeloablative Therapy in Patients With High-Risk Neuroblastoma	Memorial Sloan-Kettering Cancer Center
NCT01757626	Combination Therapy of Antibody Hu3F8 With Granulocyte- Macrophage Colony Stimulating Factor (GM-CSF) in Patients With Relapsed/Refractory High-Risk Neuroblastoma	Memorial Sloan-Kettering Cancer Center
NCT01183897	High-Dose 3F8/GM-CSF Immunotherapy Plus 13-Cis-Retinoic Acid for Primary Refractory Neuroblastoma in Bone Marrow	Memorial Sloan-Kettering Cancer Center
NCT01183884	High-Dose 3F8/GM-CSF Immunotherapy Plus 13-Cis-Retinoic Acid for Consolidation of Second or Greater Remission of High-Risk Neuroblastoma	Memorial Sloan-Kettering Cancer Center
NCT00445965	Iodine I 131 Monoclonal Antibody 3F8 in Treating Patients With Central Nervous System Cancer or Leptomeningeal Cancer	Memorial Sloan-Kettering Cancer Center
NCT01704716	High Risk Neuroblastoma Study 1 (1.5) of SIOP-Europe (SIOPEN)	St. Anna Kinderkrebsforschung, Austria
NCT01701479	Long Term Continuous Infusion ch14.18/CHO Plus s.c. Aldesleukin (IL-2) (LTI)	St. Anna Kinderkrebsforschung, Austria
NCT01576692	A Safety/Feasibility Trial of the Addition of the Humanized Anti-GD2 Antibody (hu14.18K322A) With and Without Natural Killer Cells to Chemotherapy in Children and Adolescents With Recurrent/Refractory Neuroblastoma (GD2NK)	St. Jude Children's Research Hospital
NCT00743496	A Phase I Trial Of The Humanized Anti-GD2 Antibody In Children And	St. Jude Children's Research Hospital

Clinical trial number	Title	Sponsor
	Adolescents With Neuroblastoma, Osteosarcoma Or Melanoma	
NCT01857934	Therapy for Children With Advanced Stage Neuroblastoma	St. Jude Children's Research Hospital
NCT01592045	ch14.18 Pharmacokinetic Study in High-risk Neuroblastoma	United Therapeutics

Table 2

Open Pediatric Trials Incorporating Monoclonal Antibodies for Solid Tumors

Clinical trial number	Title	Sponsor
NCT01236560	Vorinostat, Temozolomide, or Bevacizumab in Combination With Radiation Therapy Followed by Bevacizumab and Temozolomide in Young Patients With Newly Diagnosed High-Grade Glioma	National Cancer Institute
NCT01055314	Temozolomide, Cixutumumab, and Combination Chemotherapy in Treating Patients With Metastatic Rhabdomyosarcoma	National Cancer Institute
NCT01217437	Temozolomide and Irinotecan Hydrochloride With or Without Bevacizumab in Treating Young Patients With Recurrent or Refractory Medulloblastoma or CNS Primitive Neuroectodermal Tumors	National Cancer Institute
NCT01222715	Vinorelbine Tartrate and Cyclophosphamide in Combination With Bevacizumab or Temsirolimus in Treating Patients With Recurrent or Refractory Rhabdomyosarcoma	National Cancer Institute
NCT01445379	Phase I Study of Ipilimumab (Anti-CTLA-4) in Children and Adolescents With Treatment-Resistant Cancer	National Cancer Institute
NCT01598454	Use of Racotumomab in Patients With Pediatric Tumors Expressing N-glycolylated Gangliosides	Laboratorio Elea S.A.C.I.F. y A.
NCT01502917	Convection-Enhanced Delivery of 124I-8H9 for Patients With Non-Progressive Diffuse Pontine Gliomas Previously Treated With External Beam Radiation Therapy	Memorial Sloan-Kettering Cancer Center
NCT01015222	Dasatinib, Bevacizumab, Paclitaxel in Patients With Advanced Malignancies	M.D. Anderson Cancer Center
NCT01552434	Bevacizumab, Temsirolimus, Valproic Acid, Cetuximab	M.D. Anderson Cancer Center
NCT00936936	High-dose Chemotherapy for Poor-prognosis Relapsed Germ-Cell Tumors	M.D. Anderson Cancer Center
NCT00761644	Doxil, Bevacizumab and Temsirolimus Trial	M.D. Anderson Cancer Center
NCT00885326	N200702:Bevacizumab, Cyclophosphamide, & Zoledronic Acid in Patients W/ Recurrent or Refractory High-Risk Neuroblastoma	New Approaches to Neuroblastoma Therapy Consortium
NCT01176461	Multiple Class I Peptides & Montanide ISA 51 VG w Escalating Doses of Anti-PD-1 ab BMS936558	H. Lee Moffitt Cancer Center and Research Institute

Table 3

Open Pediatric Trials Incorporating Monoclonal Antibodies for Hematologic Malignancies

Clinical trial number	Title	Sponsor
NCT01595048	Combination Chemotherapy With or Without Rituximab in Treating Younger Patients With Stage III-IV Non-Hodgkin Lymphoma or B-Cell Acute Leukemia	Children's Oncology Group
NCT01780662	Brentuximab Vedotin and Gemcitabine Hydrochloride in Treating Younger Patients With Relapsed or Refractory Hodgkin Lymphoma	National Cancer Institute
NCT01471782	Clinical Study With Blinatumomab in Pediatric and Adolescent Patients With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia	Amgen Research (Munich) GmbH
NCT00658658	Panitumumab Pediatric Study	Amgen
NCT01393717	Brentuximab Vedotin Before Autologous Stem Cell Transplant in Treating Patients With Hodgkin Lymphoma	City of Hope Medical Center
NCT01869803	Gemtuzumab Ozogamicin in Treating Patients With Relapsed or Refractory Acute Myeloid Leukemia or Acute Promyelocytic Leukemia	Comprehensive Cancer Center of Wake Forest University
NCT01620229	Brentuximab Vedotin After Donor Stem Cell Transplant in Treating Patients With Hematologic Malignancies	Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium
NCT01409161	Acute Promyelocytic Leukemia (APL) Treated With ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin	M.D. Anderson Cancer Center
NCT00659425	CAT-8015 in Children, Adolescents and Young Adults With Acute Lymphoblastic Leukemia or Non-Hodgkin's Lymphoma	MedImmune LLC
NCT01508312	Brentuximab Vedotin (SGN-35) in Transplant Eligible Patients With Relapsed or Refractory Hodgkin Lymphoma	Memorial Sloan-Kettering Cancer Center
NCT00672165	Targeted Atomic Nano-Generators (Actinium-225-Labeled Humanized Anti-CD33 Monoclonal Antibody HuM195) in Patients With Advanced Myeloid Malignancies	Memorial Sloan-Kettering Cancer Center
NCT01492088	Study of Brentuximab Vedotin (SGN-35) in Pediatric Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma or Hodgkin Lymphoma	Millennium Pharmaceuticals, Inc.
NCT01279707	Monoclonal Antibodies in Recurrent or Refractory B Cell Acute Lymphoblastic Leukaemia (ALL) (MARALL)	Queen Mary University of London, England
NCT01920932	Adcetris (Brentuximab Vedotin), Combination Chemotherapy, and Radiation Therapy in Treating Younger Patients With Stage IIB, IIIB and IV Hodgkin Lymphoma	St. Jude Children's Research Hospital
NCT01440179	SAR3419 in Acute Lymphoblastic Leukemia (MYRALL)	Sanofi
NCT01421667	A Study of Brentuximab Vedotin in Relapsed or Refractory	Seattle Genetics, Inc

Clinical trial number	Title	Sponsor
	Non-Hodgkin Lymphoma	
NCT01786135	A Safety Study of SGN-CD19A for B-Cell Lymphoma	Seattle Genetics, Inc
NCT01786096	A Safety Study of SGN-CD19A for Leukemia and Lymphoma	Seattle Genetics, Inc
NCT01461538	Brentuximab Vedotin in Patients With CD30-positive Nonlymphomatous Malignancies	Seattle Genetics, Inc
NCT01900496	Study of Rituximab and Brentuximab Vedotin for Relapsed Classical Hodgkin Lymphoma	Sidney Kimmel Comprehensive Cancer Center

Table 4

Open Pediatric Trials using Chimeric Antigen Receptors for Cancer

Clinical trial number	Title	Sponsor
NCT01593696	Anti-CD19 White Blood Cells for Children and Young Adults With B Cell Leukemia or Lymphoma	National Cancer Institute
NCT01822652	3rd Generation GD-2 Chimeric Antigen Receptor and iCaspase Suicide Safety Switch, Neuroblastoma, GRAIN	Baylor College of Medicine
NCT00902044	Her2 Chimeric Antigen Receptor Expressing T Cells in Advanced Sarcoma	Baylor College of Medicine
NCT01109095	CMV-specific Cytotoxic T Lymphocytes Expressing CAR Targeting HER2 in Patients With GBM (HERT-GBM)	Baylor College of Medicine
NCT01316146	Administration of T Lymphocytes for Hodgkin's Lymphoma and Non-Hodgkin's Lymphoma (CART CD30)	Baylor College of Medicine
NCT00889954	Her2 and TGFBeta CTLs in Treatment of Her2 Positive Malignancy (HERCREEM)	Baylor College of Medicine
NCT01626495	Pilot Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCRζ and 4-1BB Signaling Domains in Patients With Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma (Pedi CART-19)	Children's Hospital of Philadelphia
NCT01460901	Study of Donor Derived, Multi-virus-specific, Cytotoxic T-Lymphocytes for Relapsed/Refractory Neuroblastoma (STALLONe)	Children's Mercy Hospital Kansas City
NCT01864902	Treatment of Relapsed and/or Chemotherapy Refractory CD33 Positive Acute Myeloid Leukemia by CART-33 (CART33)	Chinese PLA General Hospital
NCT01864889	Treatment of Relapsed and/or Chemotherapy Refractory B-cell Malignancy by CART19	Chinese PLA General Hospital
NCT01860937	Autologous T-Lymphocytes Genetically Targeted to the B-Cell Specific Antigen CD19 in Pediatric and Young Adult Patients With Relapsed B-Cell Acute Lymphoblastic Leukemia	Memorial Sloan-Kettering Cancer Center
NCT01430390	In Vitro Expanded Allogeneic Epstein-Barr Virus Specific Cytotoxic T-Lymphocytes (EBV-CTLs) Genetically Targeted to the B-Cell Specific Antigen CD19 Positive Residual Or Relapsed Acute Lymphoblastic Leukemia After Allogeneic Hematopoietic Progenitor Cell Transplantation	Memorial Sloan-Kettering Cancer Center
NCT01683279	A Pediatric Trial of Genetically Modified Autologous T Cells Directed Against CD19 for Relapsed CD19+ Acute Lymphoblastic Leukemia	Seattle Children's Hospital

Table 5

Open Pediatric Trials using NK cell Infusions for Cancer

Clinical trial number	Title	Sponsor
NCT01287104	A Phase I Study of NK Cell Infusion Following Allogeneic Peripheral Blood Stem Cell Transplantation From Related or Matched Unrelated Donors in Pediatric Patients With Solid Tumors and Leukemias	National Cancer Institute
NCT01875601	A Phase I Study of Autologous Activated Natural Killer (NK) Cells +/− rhIL15 in Children and Young Adults With Refractory Solid Tumors	National Cancer Institute
NCT01478074	ALT-801-activated Natural Killer Cells After FLAG Induction for Acute Myeloid Leukemia	Altor Bioscience Corporation
NCT01795378	Safety and Efficacy Study of Donor Natural Killer Cells Given After Haploidentical Hematopoietic Cell Transplantation (DNKI-II)	Asan Medical Center
NCT00896701	Relationship Between Natural Killer Cells' Ability to Kill Leukemia Cells and the Outcome of Patients With Acute Myeloid Leukemia Previously Treated With Interleukin-2	Cancer and Leukemia Group B
NCT00789776	Fludarabine Phosphate, Cyclophosphamide, Total-Body Irradiation, and Donor Bone Marrow Transplant Followed by Donor Natural Killer Cell Therapy, Mycophenolate Mofetil, and Tacrolimus in Treating Patients With Hematologic Cancer	Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium
NCT01337544	Haploidentical Stem Cell Transplantation and IL-15 NK Cell Infusion for Paediatric Refractory Solid Tumours	Hospital Infantil Universitario Niño Jesús, Madrid, Spain
NCT01823198	Natural Killer (NK) Cells With HLA Compatible Hematopoietic Transplantation for High Risk Myeloid Malignancies	M.D. Anderson Cancer Center
NCT00877110	Anti-GD2 3F8 Antibody and Allogeneic Natural Killer Cells for High-Risk Neuroblastoma	Memorial Sloan-Kettering Cancer Center
NCT00526292	Chemotherapy and a Donor Natural Killer Cell Infusion in Treating Patients With Relapsed or Persistent Leukemia or Myelodysplastic Syndrome After a Donor Stem Cell Transplant	Memorial Sloan-Kettering Cancer Center
NCT01621477	T-Cell Replete Haploidentical Donor Hematopoietic Stem Cell Plus Natural Killer (NK) Cell Transplantation in Patients With Hematologic Malignancies Relapsed or Refractory Despite Previous Allogeneic Transplant	St. Jude Children's Research Hospital
NCT01576692	A Safety/Feasibility Trial of the Addition of the Humanized Anti-GD2 Antibody (hu14.18K322A) With and Without Natural Killer Cells to Chemotherapy in Children and Adolescents With Recurrent/Refractory Neuroblastoma (GD2NK)	St. Jude Children's Research Hospital
NCT00145626	HLA-Nonidentical Stem Cell and Natural Killer Cell Transplantation for Children Less the Two Years of Age With Hematologic Malignancies	St. Jude Children's Research Hospital
NCT01857934	Therapy for Children With Advanced Stage Neuroblastoma	St. Jude Children's Research Hospital

Clinical trial number	Title	Sponsor
NCT00640796	Pilot Study of Expanded, Donor Natural Killer Cell Infusions for Refractory Non-B Lineage Hematologic Malignancies and Solid Tumors	St. Jude Children's Research Hospital
NCT00995137	Genetically Modified Haploidentical Natural Killer Cell Infusions for B-Lineage Acute Lymphoblastic Leukemia	St. Jude Children's Research Hospital
NCT00703820	Clofarabine Plus Cytarabine Versus Conventional Induction Therapy And A Study Of NK Cell Transplantation In Newly Diagnosed Acute Myeloid Leukemia	St. Jude Children's Research Hospital
NCT01807611	KIR Mismatched Haploidentical Donor Hematopoietic Progenitor Cell and NK Cell Transplantation for Hematologic Malignancy	St. Jude Children's Research Hospital
NCT01700946	Therapy for Pediatric Relapsed or Refractory Precursor B-Cell Acute Lymphoblastic Leukemia and Lymphoma	St. Jude Children's Research Hospital
NCT00582816	Haploidentical Transplant With NK Cell Infusion for Pediatric Acute Leukemia and Solid Tumors	University of Wisconsin, Madison

Table 6

Open Pediatric Trials Incorporating Tumor Vaccines

Clinical trial number	Title	Sponsor
NCT01192555	Allogeneic Tumor Cell Vaccination With Oral Metronomic Cytoxan in Patients With High-Risk Neuroblastoma (ATOMIC)	Baylor College of Medicine
NCT01130077	A Pilot Study of Glioma Associated Antigen Vaccines in Conjunction With Poly-ICLC in Pediatric Gliomas	Children's Hospital of Pittsburgh
NCT01061840	Trial of Bi-shRNA-furin and Granulocyte Macrophage Colony Stimulating Factor (GMCSF) Augmented Autologous Tumor Cell Vaccine for Advanced Cancer (FANG)	Gradalis, Inc.
NCT00436930	Vaccine Therapy and GM-CSF in Treating Patients With Recurrent or Metastatic Melanoma	Hoag Cancer Institute at Hoag Memorial Hospital Presbyterian
NCT01176461	Multiple Class I Peptides & Montanide ISA 51 VG w Escalating Doses of Anti-PD-1 ab BMS936558	H. Lee Moffitt Cancer Center and Research Institute
NCT01697527	Gene and Vaccine Therapy in Treating Patients With Advanced Malignancies	Jonsson Comprehensive Cancer Center
NCT01400672	Imiquimod/Brain Tumor Initiating Cell (BTIC) Vaccine in Brain Stem Glioma	Masonic Cancer Center, University of Minnesota
NCT00338377	Lymphodepletion Plus Adoptive Cell Transfer With or Without Dendritic Cell Immunization	M.D. Anderson Cancer Center
NCT00911560	Bivalent Vaccine With Escalating Doses of the Immunological Adjuvant OPT-821, in Combination With Oral β-glucan for High-Risk Neuroblastoma	Memorial Sloan-Kettering Cancer Center
NCT01058850	Phase I Rindopepimut After Conventional Radiation in Children w/ Diffuse Intrinsic Pontine Gliomas	Paul Graham Fisher
NCT01241162	Decitabine Followed by a Cancer Antigen Vaccine for Patients With Neuroblastoma and Sarcoma	University of Louisville
NCT01803152	Dendritic Cell Vaccine With or Without Gemcitabine Pre-Treatment for Adults and Children With Sarcoma	University of Miami Sylvester Comprehensive Cancer Center
NCT01902771	Dendritic Cell Vaccine Therapy With In Situ Maturation in Pediatric Brain Tumors	University of Miami Sylvester Comprehensive Cancer Center
NCT01808820	Dendritic Cell Vaccine For Malignant Glioma and Glioblastoma Multiforme in Adult and Pediatric Subjects	University of Miami Sylvester Comprehensive Cancer Center