

Game changers in pediatric cancer

Jane de Lartigue, PhD

Although there have been significant improvements in patient outcomes for some forms of pediatric cancer, progress has been painfully slow for others. An increasing understanding of pediatric cancers is highlighting the unique molecular drivers and challenging the assumption that drugs developed in adults can be applied to children and young adults. Here, we discuss game-changing therapeutic advances and a shifting view of childhood cancers.

Unique genomic background

Although pediatric cancers are rare, representing just 1% of all new cancers diagnosed annually in the United States, they are the second leading cause of death in children aged 1 to 14 years. There are many different histological tumor types under the umbrella of childhood cancers, of which the most common are leukemias, central nervous system tumors, and lymphomas (Figure 1).^{1,2}

Significant progress has been made in the treatment of certain pediatric cancers in recent decades, exemplified by pediatric acute lymphoblastic leukemia (ALL), which has been transformed from a virtually incurable cancer to one in which 5-year survival rates now reach up to 90%. In other forms of pediatric cancer, however, survival rates have stagnated and little progress has been made in the development of effective new therapies.³

Because of their rarity, pediatric cancers are difficult to study and adequate enrollment of children in clinical trials can be chal-

lenging. Pharmaceutical companies are often hesitant to test drugs in the pediatric population in patients who often cannot advocate for themselves. As a result, the activity of drugs developed in adult patients has often been inferred in pediatric patients with the same tumor type or molecular aberrations. However, as researchers have gathered more information about pediatric cancers, there has been increasing recognition of their unique attributes and the need for dedicated clinical trials in this patient population.

Pediatric cancers tend to be found in the developing mesodermic tissue, whereas adult cancers are more prevalent in the epithelial tissues. Genome sequencing studies have revealed a much lower

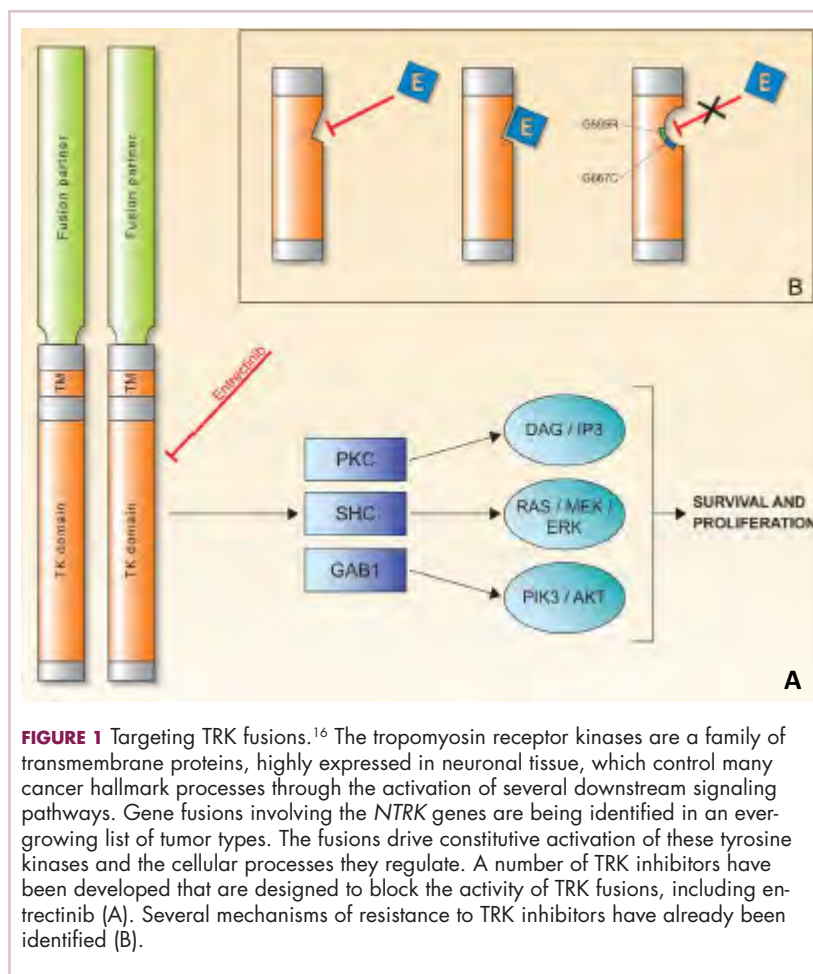


FIGURE 1 Targeting TRK fusions.¹⁶ The tropomyosin receptor kinases are a family of transmembrane proteins, highly expressed in neuronal tissue, which control many cancer hallmark processes through the activation of several downstream signaling pathways. Gene fusions involving the *NTRK* genes are being identified in an ever-growing list of tumor types. The fusions drive constitutive activation of these tyrosine kinases and the cellular processes they regulate. A number of TRK inhibitors have been developed that are designed to block the activity of TRK fusions, including entrectinib (A). Several mechanisms of resistance to TRK inhibitors have already been identified (B).

TABLE 1 Recent US Food and Drug Administration approvals in pediatric cancer

Drug	Manufacturer	Mechanism of action	Approved pediatric indication
Tisagenlecleucel (Kymriah)	Novartis	CD19-targeted CAR T-cell therapy	Relapsed/refractory B-cell ALL after 2 or more prior treatments
Pembrolizumab (Keytruda)	Merck	PD1-targeted mAb	Relapsed/refractory cHL after 3 or more prior treatments Relapsed/refractory dMMR/MSI-high solid tumors Relapsed/refractory PMBCL after 2 or more prior treatments
Nivolumab (Opdivo)	Bristol-Myers Squibb	PD1-targeted mAb	Relapsed/refractory dMMR/MSI-high mCRC after failure of chemotherapy (alone or in combination with ipilimumab)
Ipilimumab (Yervoy)	Bristol-Myers Squibb	CTLA4-targeted mAb	Metastatic melanoma
Blinatumomab (Blincyto)	Amgen	CD19-targeted BiTE	Relapsed/refractor B-cell ALL regardless of Philadelphia chromosome status
Dasatinib (Sprycel)	Bristol-Myers Squibb	Multitargeted kinase inhibitor	Chronic phase Philadelphia chromosome-positive CML
Nilotinib (Tasigna)	Novartis	Multitargeted kinase inhibitor	Chronic phase Philadelphia chromosome-positive CML
Gemtuzumab ozogamicin (Mylotarg)	Pfizer	CD33-targeted ADC	Relapsed/refractory CD33-positive AML
Dinutuximab (Unituxin)	United Therapeutics	GD2-targeted mAb	High-risk neuroblastoma

ADC, antibody-drug conjugate; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; cHL, classical Hodgkin lymphoma; CML, chronic myeloid leukemia; CTLA-4, cytotoxic T lymphocyte antigen-4; dMMR, defective mismatch repair; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; PD-1, programmed cell death protein-1; PMBCL, primary mediastinal large B-cell lymphoma

mutational burden in pediatric cancers and the mechanisms of oncogenesis are also quite different; adult tumors can develop from a series of acquired gene mutations, but pediatric tumors tend to develop from a single catastrophic event.^{4,5}

Even the same type of cancer in a pediatric and adult patient can be quite different, with very different underlying molecular mechanisms. In a recent genomic analysis of different types of pediatric cancer by researchers at St Jude's Children's Research Hospital, less than half of the identified mutated genes were found to be similar to those found in adult patients.⁶

A 'magic bullet'?

Chromosomal rearrangements are common in pediatric cancers. This type of molecular abnormality can result in a fusion of 2 different genes when the chromosome breaks apart and the pieces join back together in a muddled order. If the genetic code fuses in a manner that is "readable" by the cell, then it can drive aberrant activation of one or both genes.⁷ Gene fusions often involve kinase enzymes that are essential players in cell signaling pathways regulating hallmark cancer processes, such as unchecked cell proliferation. The fusion drives the constitutive activation of the kinase and, thus, these downstream signaling pathways.

One of the first chromosomal rearrangements linked to cancer, BCR-ABL1 – more commonly known as the Philadelphia chromosome – results in aberrant activation of the ABL1 kinase. It is present in nearly all cases of

chronic myeloid leukemia (CML) and 3% to 5% of patients with ALL, and thus became the central focus of targeted drug development. Imatinib was initially approved by the US Food and Drug Administration (FDA) in 2001 for the treatment of adult patients with CML and had such a significant impact on the treatment landscape that it made the cover of Time magazine as a "magic bullet" in the war on cancer.⁸

Approval was expanded into pediatric patients in 2006 and for pediatric patients with ALL in 2013. However, as with the use of most kinase inhibitors, tumors can evolve under the selective pressure of treatment, developing additional molecular abnormalities that drive resistance.⁹

Next-generation multikinase inhibitors that more potently inhibit the BCR-ABL1 fusion protein have been developed to provide additional treatment options for patients who become resistant to imatinib. Dasatinib and nilotinib are among several drugs that have recently been approved for pediatric cancer therapy (Table 1). Both therapies were approved to treat children with Philadelphia chromosome-positive CML in the chronic phase in either the front- or second-line setting after failure of imatinib.

The approval of dasatinib was based on data from 97 patients across 2 trials, 51 of whom were newly diagnosed and 46 previously treated with imatinib. Most of the patients were treated with dasatinib 60 mg/m² once daily. After 2 years of follow-up, more than 95% of newly diagnosed patients and 82.6% of relapsed/refractory patients had complete cytogenetic response.¹⁰

TABLE 2 Ongoing clinical trials of targeted therapies in pediatric cancers

Drug	Developer	Mechanism of action	Most advanced stage of clinical development in the pediatric setting (ClinicalTrials.gov identifier)
Larotrectinib (LOXO-101)	Loxo	TRK inhibitor	Phase 1/2 in relapsed/refractory solid or primary CNS tumors (NCT02637687)
Entrectinib (RXDX-101)	Ignyta	TRK inhibitor	Phase 1 in relapsed/refractory solid or primary CNS tumors (NCT02650401)
LOXO-195	Loxo	TRK inhibitor	Phase 1/2 in relapsed/refractory NTRK fusion-positive cancers (NCT03215511)
Vemurafenib (Zelboraf)	Genentech	BRAF inhibitor	Phase 1 in relapsed/refractory BRAF-mutant gliomas (NCT01748149)
Dabrafenib (Tafinlar)	Novartis	BRAF inhibitor	Phase 2 + trametinib in relapsed/refractory glioma (NCT02684058)
Trametinib (Mekinist)	Novartis	MEK inhibitor	Phase 2 in relapsed/refractory glioma or neurofibroma (NCT03363217)
Selumetinib (AZD6244)	AstraZeneca	MEK inhibitor	Phase 1/2 in relapsed/refractory BRAF-mutant glioma (NCT01089101)
Erdafitinib	Janssen	Pan-FGFR inhibitor	Phase 2 in relapsed/refractory solid tumors, NHL, or histiocytic disorders with FGFR mutations (NCT03210714)
Crizotinib (Xalkori)	Pfizer	ALK/MET/ROS1 inhibitor	Phase 2 + combination chemotherapy in newly diagnosed ALCL (NCT01979536)
Ceritinib (Zykadia)	Novartis	ALK inhibitor	Phase 1/2 + brentuximab vedotin in ALK-positive ALCL (NCT02729961)
Lorlatinib	Pfizer	ALK/ROS1 inhibitor	Phase 1 in relapsed/refractory ALK-positive neuroblastoma (NCT03107988)
Dasatinib (Sprycel)	Bristol-Myers Squibb	Multi-targeted kinase inhibitor	Phase 3 in newly diagnosed ALL (NCT03020030)
Nilotinib (Tasigna)	Novartis	Multi-targeted kinase inhibitor	Phase 1/2 + vinblastine in relapsed/refractory low-grade glioma (VINILO; NCT01884922/NCT01887522)

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; CNS, central nervous system; FGFR, fibroblast growth factor receptor; MEK, mitogen-activated protein kinase; NHL, non-Hodgkin lymphoma; TRK, tropomyosin receptor kinase

Nilotinib was approved on the basis of findings from 2 clinical trials including 69 patients – 1 trial involving patients who were refractory to or relapsed after dasatinib and imatinib treatment, and 1 that included both relapsed/refractory and newly diagnosed patients. Patients received nilotinib 230 mg/m² twice daily, rounded to the nearest 50-mg dose, in 28-day cycles. By cycle 12, the cumulative major molecular response rate (MMR) was 47.7% in patients with relapsed/refractory disease, and 64% in newly diagnosed patients.¹¹ Clinical trials of both drugs in the pediatric setting are ongoing.

Other prominent gene fusions

Gene fusions involving the anaplastic lymphoma kinase (ALK) occur in patients with non–small-cell lung cancer and ALK inhibitors have provided an effective new treatment option for patients whose tumors display this abnormality.

ALK fusions are also a prominent feature of several kinds of pediatric cancers and ALK inhibitors offer promise in this setting.^{7,12} An *NPM-ALK* fusion is found in 90% of pediatric anaplastic large cell lymphoma (ALCL)

cases,¹³ whereas a variety of ALK fusions are found in up to half of patients with inflammatory myofibroblastic tumor (IMT), a rare form of soft tissue sarcoma.¹⁴ ALK inhibitors are being tested in a variety of clinical trials in pediatric patients (Table 2).

The results of a small phase 1 study of crizotinib in pediatric patients with ALK-positive ALCL (n = 26) or IMT (n = 14) were recently published. ALCL patients received crizotinib at a dose of 165 mg/m², while IMT patients were given 100, 165, or 280 mg/m². For the latter, the results were presented as a pooled cohort since safety and efficacy data were similar across dose levels. The overall response rate (ORR) was 83% for patients with ALCL and 86% for those with IMT. Grade 3/4 adverse events occurred in 83% and 71% of patients, respectively, and most commonly involved reduced neutrophil count.¹⁵

Most recently and perhaps most promisingly, fusions involving the neurotrophic tropomyosin receptor kinase (*NTRK*) gene have generated significant buzz. There are 3 *NTRK* genes, *NTRK1*, 2, and 3, which encode the TRKA, TRKB, and TRKC proteins, respectively.

To date, 22 different partner genes have been identified that can fuse with the *NTRK* genes and, as with other kinase fusions, drive constitutive activation of the receptor proteins and downstream oncogenic signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway (Figure 2).

NTRK fusions are being identified in an ever-growing number of cancer types, but are typically found in a small percentage of patients. However, in certain rare pediatric tumors, including congenital infantile fibrosarcoma and papillary thyroid cancer, they are found at much higher frequencies.

TRK inhibitors have been developed to target the fusion proteins and, given the spread of *NTRK* fusions across different types of cancers, they offer the most substantial promise as the next tumor agnostic cancer therapy – to treat patients based on the shared presence of a molecular aberration, irrespective of the type of cancer.¹⁶

The ongoing SCOUT trial is evaluating larotrectinib (LOXO-101) in pediatric patients. Among 24 patients (17 with *NTRK* fusions and 7 without) with infantile fibrosarcoma (47%), soft tissue sarcoma (41%) or papillary thyroid cancer (12%), the ORR was 93%, including complete response (CR) in 13% of patients.¹⁷

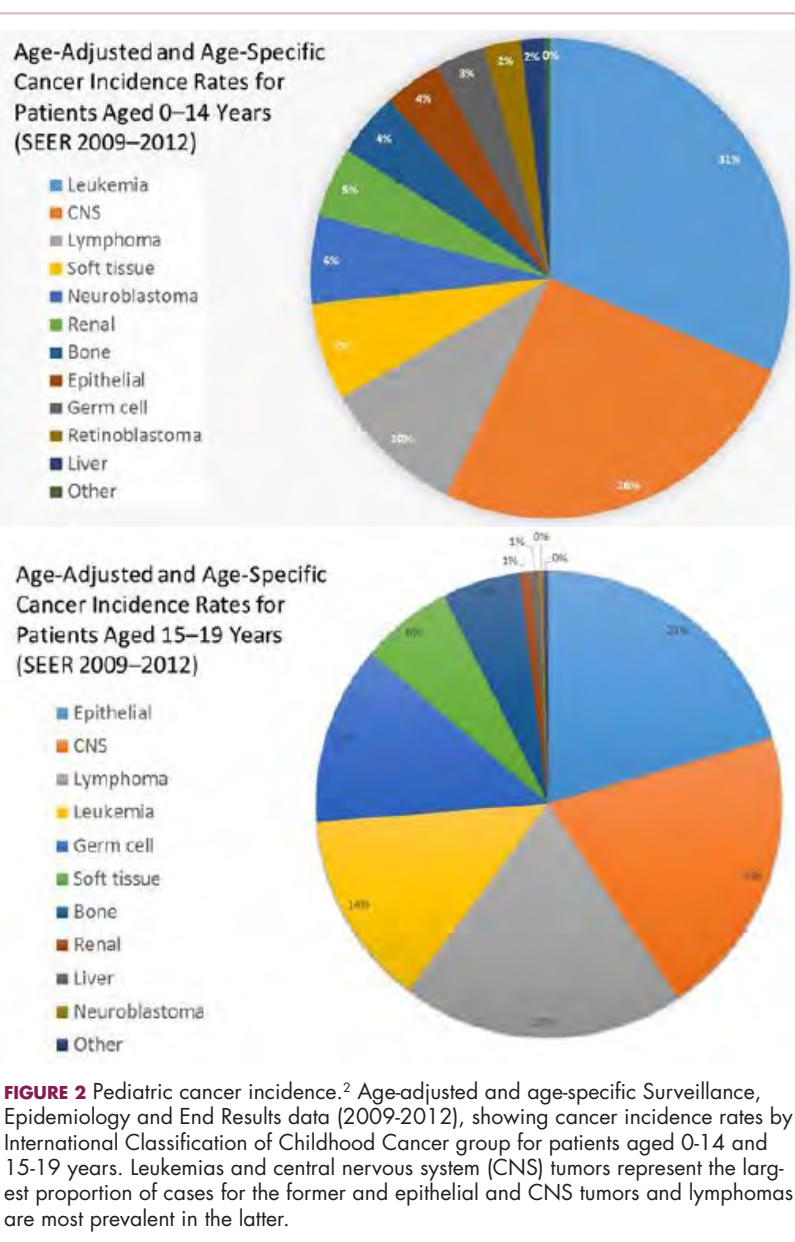
Preliminary results from an ongoing phase 1/2 study of entrectinib in pediatric patients with extracranial solid tumors were also recently presented at the annual meeting of the American Society for Clinical Oncology (ASCO). Among 15 evaluable patients enrolled to date, 3 have *NTRK* fusions and all experienced an objective response, with 1 (a patient with IMT) ongoing at 10 months.¹⁸

CAR T cells transformative in ALL

A variety of different types of immunotherapy have been tested in patients with pediatric cancers. In general, immunotherapy has proved less effective than in adult cancers, possibly because of the lower tumor mutation burden in pediatric cancers, which means there are likely fewer cancer antigens to provoke an anti-tumor immune response.

There are notable exceptions among the disappointments, however, and most exciting is the development of chimeric antigen receptor (CAR) T cells. CAR T cells fall into a category of immunotherapy known as adoptive cell therapy (ACT), in which immune cells are harvested from a patient and grown outside the body to increase their numbers before being reinfused into the patient.

In the case of CAR T-cell therapy, the cells are genetically engineered to express a CAR that endows them with tumor-targeting capabilities. To date, the development of CAR T cells has focused on the use of the CD19 antigen



as a target, which is highly expressed on a variety of B-cell malignancies, including several of the most common forms of pediatric cancer. ASCO shined the spotlight on CAR T-cell therapy this year, naming it the Advance of the Year for 2018, saying that the treatment is “poised to transform childhood ALL.”¹⁹

Two CD19-targeted CAR T-cell therapies – tisagenlecleucel and axicabtagene ciloleucel – were brought to market in 2017. Only tisagenlecleucel is approved in the pediatric ALL population, however, having been awarded approval for the treatment of patients aged up to 25 years whose disease is refractory to or relapsed after receiving at least 2 prior therapies. In the pivotal trial, complete responses were observed in more than 60% of patients.²⁰

TABLE 3 Select ongoing clinical trials of immunotherapy in pediatric cancers

Drug	Developer	Mechanism of action	Most advanced stage of clinical development in the pediatric setting (ClinicalTrials.gov identifier)
Ibrutinib (Imbruvica)	Pharmacyclics/Janssen	BTK Inhibitor	Phase 3 in relapsed/refractory NHL (NCT02703272)
Blinatumomab (Blincyto)	Amgen	CD19-targeted BiTE	Phase 1 + immune checkpoint inhibitors in B-cell leukemias/lymphoma (NCT02879695, NCT03605589)
Brentuximab vedotin (Adcetris)	Seattle Genetics	CD30-targeted ADC	Phase 3 + combination chemotherapy in high-risk cHL (NCT02166463)
Inotuzumab ozogamicin (Besponsa)	Wyeth	CD22-targeted ADC	Phase 3 + chemotherapy in newly diagnosed B-cell ALL (NCT03150693)
Pembrolizumab (Keytruda)	Merck	PD1-targeted mAb	Phase 3 in metastatic melanoma (KEYNOTE-716; NCT03553836)
Nivolumab (Opdivo)	Bristol-Myers Squibb	PD1-targeted mAb	Phase 2 +/- ipilimumab in high-grade primary CNS malignancies (NCT03130959)
Durvalumab (Imfinzi)	AstraZeneca	PDL1-targeted mAb	Phase 1 in relapsed/refractory solid tumors, lymphoma and CNS tumors (NCT02793466)
Tisagenlecleucel (Kymriah)	Novartis	CD19-targeted CAR T-cell therapy	Phase 2 in NHL (BIANCA; NCT03610724)
Axicabtagene ciloleucel (Yescarta)	Kite	CD19-targeted CAR T-cell therapy	Phase 2 in B-cell ALL (ZUMA-4; NCT02625480)
CD22 CARs	Various	CD22-targeted CAR T-cell therapy	Phase 2 in relapsed/refractory B-cell NHL (NCT03196830)
Bispecific CARs	Various	CD19 and CD22 dual-targeting CAR T-cell therapy	Phase 1/2 in relapsed/refractory B-cell malignancies (NCT03289455, NCT03287817, NCT03468153, NCT03098355, NCT03185494, NCT03614858)
GD2 CARs	Various	GD2-targeted CAR T-cell therapy	Phase 2 in neuroblastoma (4SCAR-GD2; NCT02765243)
GD2-targeting NK CARs	Baylor College of Medicine	NK cells expressing CARs targeting GD-2	Phase 1 in neuroblastoma (GINAKIT2; NCT02765243)
CD30 CARs	UNC Lineberger Comprehensive Cancer Center	CD30-targeted CAR T-cell therapy	Phase 1/2 in relapsed/refractory CD30-positive HL and NHL (NCT02690545)
HER2 CARs	Seattle Children's Hospital	HER2-targeted CAR T-cell therapy	Phase 1 in relapsed/refractory CNS tumors (NCT03500991)
EGFR CARs	Seattle Children's Hospital	EGFR806-targeted CAR T-cell therapy	Phase 1 in relapsed/refractory solid and CNS tumors (NCT03638167, NCT03618381)
Glypican-3 CARs	Baylor College of Medicine	Glypican-3-targeted CAR T-cell therapy	Phase 1 in solid tumors (NCT02932956)
Dinutuximab (Unituxin)	United Therapeutics	Anti-GD2 mAb	Phase 2 + 131I-MIBG in relapsed/refractory neuroblastoma (NCT02932956)
Hu3F8	Y-mAbs Therapeutics	Anti-GD2 mAb	Phase 1/2 in high-risk neuroblastoma (NCT02650648, NCT01757626)
NK cells	Various	Adoptive cell therapy using donor NK cells	Phase 1/2 in relapsed/refractory AML (NCT03068819, NCT02763475), solid tumors (NCT01807468*, NCT03420963, NCT02100891), neuroblastoma (NCT02573896)

ADC, antibody-drug conjugate; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BiTE, bispecific T-cell engager; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; cHL, classical Hodgkin lymphoma; CNS, central nervous system; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MIBG, meta-iodobenzylguanidine; NHL, non-Hodgkin lymphoma; NK, natural killer; PD-1, programmed cell death protein-1

Clinical trials of both CAR T-cell therapies in pediatric ALL and non-Hodgkin lymphoma are ongoing (Table 3).

CD19 has also proven to be a promising target for other forms of immunotherapy, including a new type of antibody known as a bispecific T-cell engager (BiTE). In 2014, blinatumomab became the first BiTE to receive regulatory approval, for the treatment of adult patients with relapsed/refractory ALL. Blinatumomab also targets the CD3 protein on T cells and helps to bring cancer cells and cytotoxic immune cells into close enough proximity that an immunological synapse can be formed between the two, facilitating tumor cell killing.²¹

In 2016, the approved indication was expanded into the pediatric population based on the results of a phase 1/2 study in which the safety and efficacy of blinatumomab were evaluated in 93 pediatric patients with relapsed/refractory ALL. Among the 70 patients who received the recommended dose of 5 μ g/m² a day for the first 7 days, followed by 15 μ g/m² a day thereafter, 51% achieved complete remission within the first 2 cycles, 52% of whom achieved minimal residual disease (MRD).²² Most recently, the FDA expanded the indication for blinatumomab to include patients (both adults and children) who are in remission, but MRD positive.²³

Despite the dramatic responses, many patients relapse after treatment with CD19-targeted CAR T cells, and researchers have uncovered numerous mechanisms of resistance. Among them is the loss of the CD19 antigen on the surface of target cells, such that a CD19-positive tumor becomes CD19-negative after treatment, driving relapse.²⁴⁻²⁶

Several strategies for overcoming CD19-negative relapse are already being investigated, including the development of CD22-targeted CAR T cells and bispecific CAR T cells that target both CD19 and CD22. The results of a first-in-human trial of anti-CD22 CAR T-cell therapy were recently published. Among 21 pediatric and adult patients with relapsed/refractory B-cell ALL who were treated with either 3 x 10⁵ cells/kg, 1 x 10⁶ cells/kg, or 3 x 10⁶ cells/kg, complete responses were observed in 57%.²⁷

Results from 15 pediatric patients enrolled in a trial evaluating CD22-targeted CAR T cells as salvage therapy for those who relapse after CD19-targeted CAR T cell therapy were presented at the recent Congress of the European Hematology Association in Stockholm, Sweden. Patients who had undergone a stem cell transplant received the CAR T cells at a dose of 0.9 x 10⁵ cell/kg and those who had not undergone a transplant received a dose of 8.2 x 10⁵ cells/kg. At 30 days after CAR T cell infusion, the CR rate was 80% and the treatment was well tolerated.²⁸

More immunotherapy approvals

The immune checkpoint inhibitors, which work by blocking inhibitory receptors on the surface of T cells, have also had recent approvals in pediatric patient populations.

Pembrolizumab and nivolumab, inhibitors of the programmed cell death receptor 1 (PD-1) protein, have both been approved for use in adult and pediatric patients (older than 12 years) with relapsed/refractory metastatic colorectal cancer (and other solid tumors in the case of pembrolizumab) that display defects in the mismatch repair pathway that fixes damaged DNA or in patients that have high levels of microsatellite instability. Both deficient mismatch repair and microsatellite instability-high can indicate a high mutation burden in a tumor, which may predict increased sensitivity to immunotherapy.²⁹

The approval in pediatric patients in both of those instances, however, was not based on data in pediatric patient populations but extrapolated from adult patients. Pembrolizumab is also approved for the treatment of adults and pediatric patients with classical Hodgkin lymphoma (cHL) after 3 or more previous treatments, but once again efficacy in the pediatric population was inferred from clinical trials performed in adults. Most recently, pembrolizumab was approved for the treatment of adult and pediatric patients with relapsed or refractory primary mediastinal large B-cell lymphoma.³⁰

Ipilimumab, which targets a different T cell receptor – cytotoxic T lymphocyte antigen-4 (CTLA-4) – has been approved for the treatment of pediatric patients aged 12 years and older with metastatic melanoma. This expanded indication, following on from its approval in adult patients in 2011, was based on data from 2 trials in which objective responses were observed in 2 out of 17 patients, including 1 partial response that lasted 16 months.³¹

Finally, antibody-drug conjugates (ADC), in which tumor antigen-targeting monoclonal antibodies are conjugated to cytotoxic payloads to combine the specificity of an antibody with the cell-killing potency of chemotherapy, have also generated some recent successes in pediatric cancers.

Gemtuzumab ozogamicin is an ADC that targets the CD33 protein, which is highly expressed on 85%-90% of cases of acute myeloid leukemia (AML). In 2000, it was the first ADC to be brought to market in the United States, but it was subsequently voluntarily withdrawn by the manufacturer in 2010 after confirmatory trials failed to show a survival benefit.

Recently, a meta-analysis of gemtuzumab ozogamicin trials suggested that the drug likely does improve long-term overall survival (OS) and reduce the risk of relapse and researchers developed an intermittent dosing schedule to help mitigate toxicity.³² This new dosing regimen received FDA approval in 2017 for the treatment of pediatric patients aged 2 years and older on the basis of 2 clinical trials.

In the MyloFrance-1 trial, 57 patients were administered 3 mg/m² gemtuzumab ozogamicin on days 1, 4, and 7 followed by cytarabine consolidation therapy and demonstrated a 26% CR rate and median recurrence-free survival of 11.6 months. In the phase 3 AML-19 trial, 237 patients received gemtuzumab ozogamicin at a dose of 6 mg/m² on day 1 and

3 mg/m² on day 8 or best supportive care. Gemtuzumab ozogamicin improved OS from 3.6 to 4.9 months.^{33,34}

Inotuzumab ozogamicin is a CD22-targeting ADC that has been FDA approved for the treatment of adult patients with relapsed/refractory B-cell precursor ALL since last year. The therapy has been available to pediatric patients through

a compassionate access program, but it has not been extensively evaluated in this population. The results of a retrospective analysis of pediatric patients who received at least 1 dose of inotuzumab ozogamicin were presented at ASCO in 2017. Among 29 patients with heavily pretreated disease the CR rate was 62%, 72% of whom achieved MRD negativity.³⁵

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