

Precision Oncology in Pediatric Cancer Surgery



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KEYWORDS

- Precision oncology • Precision medicine • Pediatric cancer • Molecular profiling
- Gene sequencing • Targeted therapy • Basket trial

KEY POINTS

- Large-scale ongoing “basket trials” recruit pediatric patients and allocate targeted therapies based on molecular alterations, as opposed to tumor type, increasing access to clinical trials and providing a framework for clinical implementation.
- Pediatric precision oncology offers a promising treatment option for recurrent and treatment-refractory pediatric solid tumors, where prognosis remains dismal despite exhaustive multimodal therapy (chemotherapy, radiotherapy, and surgery).
- Although uncommon, immunotherapy and small molecule inhibitors are associated with impaired wound healing, coagulopathy, and spontaneous gastrointestinal perforation in children.
- Future research focuses on optimizing targeted treatment efficacy (eg, combination therapy) and improving biopsy strategies (eg, “liquid biopsy”).

INTRODUCTION

Overview of Precision Medicine in Pediatric Population

Precision medicine incorporates the unique genetic alterations of a patient's disease to guide their therapy. One of the earliest well-known examples of precision medicine in the pediatric population is the targeted treatment of children with G551D-CFTR mutation positive cystic fibrosis with the CFTR potentiator ivacaftor, which led to improved lung function.¹ Within pediatric oncology, the strong link between genetic aberrations, tumorigenesis, and cancer biology creates an ideal model for the application of precision medicine—aptly termed precision oncology. Precision oncology is a developing multidisciplinary approach to personalized cancer treatment where therapies target specific molecular or genetic alterations (Fig. 1). In this article, the authors

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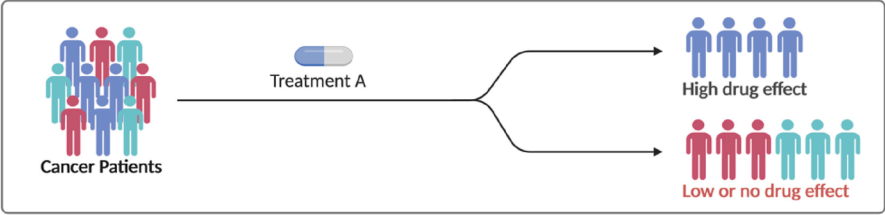
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Conventional Therapy



Precision Cancer Therapy

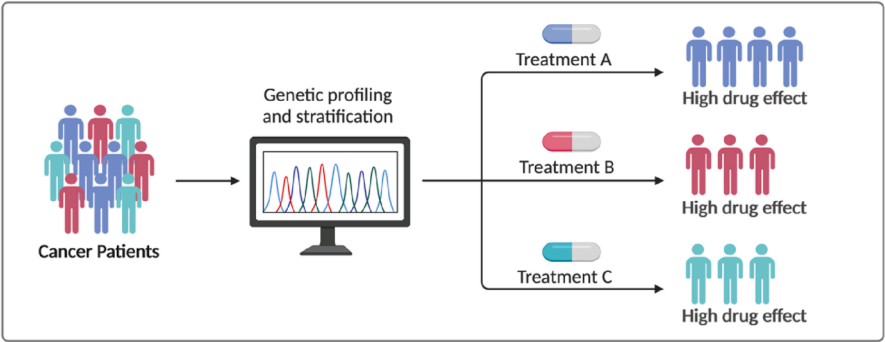


Fig. 1. Precision oncology process. (Created in BioRender. Lee, W. (2026) <https://BioRender.com/9b52v15>.)

review the current role of precision oncology in the treatment of pediatric cancer—with a focus on pediatric solid tumors—and the surgical implications of these novel targeted therapies.

Overview of Pediatric Oncology

Cancer is one of the leading causes of non-accidental death in children after infancy ultimately leading to death in 20% of all children diagnosed with cancer.^{2,3} Although improvements in local treatment and cytotoxic chemotherapy have drastically improved 5-year survival from 58% in the 1970s to 85% in 2022, progress has plateaued and prognosis remains dismal for patients with recurrent/refractory disease or particular high-risk biological features (eg, high-risk neuroblastoma [HR-NB]).^{4,5} In addition, posttreatment morbidity among cancer survivors is especially common in the pediatric population due to longer life expectancy relative to their adult counterparts. Survivors of pediatric cancer are susceptible to an increased risk for end-organ damage from cytotoxic therapies (eg, ototoxicity, cardiomyopathy, nephropathy, and impaired fertility), impaired growth and development, decreased quality of life, and increased rates of secondary malignancies.⁴ Thus, the goals of pediatric precision oncology are to use targeted therapies to not only increase survival but also decrease the long-term toxicity and morbidity associated with current cytotoxic therapies.

Although there is significant overlap between pediatric and adult oncology, there are many unique characteristics of pediatric cancers that limit the crossover from adult precision oncology to the pediatric world. In contrast to adult cancers, pediatric cancers and their subtypes are rare and often characterized by single driver mutations with relatively few somatic mutations.^{6–10} In addition to a lower mutational burden, only 30% to 45% of known pediatric cancer mutations overlap with adult cancer

mutations, which have limited the adoption of established targeted therapies currently being used for adult cancers.^{11,12} Thus, fewer targetable somatic mutations have led to fewer available therapies and active clinical trials for pediatric patients, which highlights the need for ongoing pediatric-specific precision oncology studies to identify targetable genomic alterations.

IMPACT OF DISCOVERY SEQUENCING STUDIES IN PEDIATRIC ONCOLOGY

Overview of Genomic Alterations

Genomic alterations can occur due to single-nucleotide variations (eg, base pair insertions, deletions, or substitutions), copy number variation (eg, deletions or duplications of genomic segments), structural alteration (eg, chromoplexy, chromothripsis), loss of heterozygosity, or gene fusion products. Epigenetic modifications can also occur, such as chromatin remodeling, DNA methylation, or histone modification, which can affect downstream gene expression.¹³ Next-generation sequencing (NGS), such as whole genome sequencing (WGS) or whole exome sequencing (WES), has allowed us to begin to understand the complexity of tumorigenesis and disease progression. The addition of transcriptomics (ie, RNA sequencing [RNAseq]) and proteomics has also allowed us to elucidate the downstream effects and identify potential targets or pathways for intervention. Although commercially available gene panels can be used to detect known deleterious mutations (eg, OncoPrint Dx, FoundationOne CDx, and TruSight), discovery sequencing studies are increasingly combining tumor-specific gene sequencing panels with RNAseq or epigenetic studies to identify clinically actionable mutations.

Discovery Sequencing Studies

Discovery sequencing studies aim to identify recurrent mutations within a specific cancer type. Association of these recurrent mutations with clinical outcomes data can provide prognostic relevance and lead to further molecular risk stratification (eg, *MYCN* amplification and HR-NB). They may also provide a therapeutic target for an available FDA-approved or investigational drug currently being used for a different indication. This is particularly useful in refractory or difficult-to-treat rare tumors where no effective therapy exists. Thus, over the past 2 decades, a multitude of discovery sequencing studies in pediatric oncology have been performed to achieve these aims (Table 1).

Prior discovery sequencing studies have provided insight into the heterogeneity of genomic alterations that exist across pediatric cancers. Sequencing of tumors sampled at different time points has shown that mutational events can change with increasing age¹⁴ and with variable retention of targetable mutations at later time points.^{6,15} For example, in HR-NB, genomic alterations in the anaplastic lymphoma kinase (ALK) gene occurred in 10.5% of cases at diagnosis, but increased by 70% at the time of relapse.¹⁶ In the setting of low somatic mutational burden, even in high-risk cancer subtypes, germline mutations, mutations of upstream regulators (ie, hijacking),¹⁷ gene fusions,¹⁸ and epigenetic modifications have also been identified as significant events in tumorigenesis.^{19–22}

More importantly, these studies have demonstrated the feasibility of performing precision oncology in the clinical setting by translating biopsy samples into clinically actionable data that have been used to alter or refine diagnoses, identify and apply targeted therapies, and detect increased familial risk. Most of these studies are being performed on recurrent or refractory cancers and use multiple methods of genomic analysis. Although a limitation of these studies is their varied definition of a “clinically actionable mutation,” the majority agrees that it is defined by the detection of a known

Table 1
Summary of discovery sequencing studies in pediatric oncology (2015–2023)

Study Name	Country	Year Published	Successful Samples Analyzed (No)	Tumor Types	Method of Genomic Analysis	Study Definition of Actionable Mutation	Actionable Mutations (%)	Actionable Mutation with Available Targeted Drug (%)	Genomic Analysis Altered Diagnosis (%)
Peds-MiOncoSeq	USA	2015	91	Relapsed/refractory, primary high-risk, rare	WES, RNAseq	Targetable with current drug, altered diagnosis or risk stratification, altered plan for patient/family counseling	46	23	2
ClinOmics	USA	2016	59	Relapsed/refractory	WES, RNAseq, SNP array	Known pathogenic mutation, altered diagnosis, targetable with an approved/ investigational drug	51	41	7
BASIC3	USA	2016	121	Relapsed/refractory, primary high risk	WES	Established clinical utility (known diagnostic or prognostic value, or therapeutic target), potential utility (within known targetable cancer pathway)	39	NR	NR
iCAT	USA	2016	89	Relapsed/refractory	NGS panel, aCGH	Targetable with an approved/ investigational drug	31	31	3
PMTB	USA	2016	39	Primary high risk	Hybrid capture-based DNA sequencing assay, RNAseq, WES, NGS panel	Targetable with an approved/ investigational drug	73	73	NR

Molecular Biology Tumor Board (MBB)	France	2016	58	Relapsed/refractory, primary high risk (poor prognosis at time of diagnosis)	NGS panel, aCGH	Targetable with an approved/ investigational drug	40	40	NR
MOSCATO-01	France	2017	69	Relapsed/refractory	aCGH, NGS panel, WES, RNAseq	Targetable with an approved/ investigational drug	61	61	4
PIPseq	USA	2017	50	Relapsed/refractory	WES, RNAseq	Led to change in assessment or management of patient (diagnosis, prognosis, therapeutic plan, genetic counseling plan)	90	80	34
TARGET	Australia	2017	27	Primary high risk (expected survival <30%)	NGS panel, RNAseq	Known pathogenic mutations	59	41	NR
UCSF	USA	2017	31	Central nervous system tumors with uncertain diagnosis or treatment	NGS panel	Known pathogenic mutation, altered diagnosis, targetable with an approved/ investigational drug	81	61	19
TRICEPS	Canada	2019	62	Relapsed/refractory, primary high-risk	WES, RNAseq	Targetable, biomarker useful for MRD detection, prognostic risk stratification, change diagnosis	87	87	22
PNOC003	Transnational	2019	15	Primary diffuse intrinsic pontine glioma (DIPG)	WES, WGS, RNAseq	Targetable with an approved/ investigational drug	100	100	NR

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Table 1
(continued)

Study Name	Country	Year Published	Successful Samples Analyzed (No)	Tumor Types	Method of Genomic Analysis	Study Definition of Actionable Mutation	Actionable Mutations (%)	Actionable Mutation with Available Targeted Drug (%)	Genomic Analysis Altered Diagnosis (%)
SMC	South Korea	2019	53	Relapsed/refractory	NGS panel	Targetable with an approved/ investigational drug	36	36	NR
SMPAEDS	United Kingdom	2019	209	Relapsed/refractory	Hybrid capture-based NGS panel	Targetable with an approved/ investigational drug	51	51	NR
ProFILER	France	2020	43	Relapsed/refractory, Rare	NSG panel, aCGH	Targetable with an approved/ investigational drug	23	23	NR
ZERO Childhood Cancer	Australia	2020	252	Relapsed/refractory, primary high risk	WGS, RNAseq, DNA methylation analysis	Targetable with an approved/ investigational drug	71	71	5
PROFYLE	Canada	2020	100	Relapsed/refractory, rare	NGS panel, WGS, RNAseq	Potential to alter diagnosis, risk stratification, prognosis, or treatment plan	82	71	NR
DCOG-iTHER	The Netherlands	2020	80	Relapsed/refractory	WES, IcWGS, RNAseq, DNA methylation analysis	Targetable with an approved/ investigational drug	59	34	NR

INFORM	Germany	2021	926	Relapsed/refractory, primary high risk	WES, lcWGS, DNA methylation analysis, RNAseq	Targetable with an approved/ investigational drug	85	48	7
MAPPYACTS	France	2022	787	Relapsed/refractory	WES, RNAseq, NGS panel	Targetable with an approved/ investigational drug	69	30	NR
MATCH	USA	2022	1000	Relapsed/refractory	NGS panel, IHC	Targetable with an approved/ investigational drug	34	31	NR
KiCS	Canada	2023	264	Relapsed/refractory, rare, suspected genetic cancer predisposition	NGS panel, RNAseq, WGS	Targetable with an approved/ investigational drug	54	54	NR

Abbreviations: aCGH, array comparative genomic hybridization; IHC, immunohistochemistry; lcWGS, low coverage whole genome sequencing; NGS, next-generation sequencing; NR, not reported; RNA-seq, ribonucleic acid sequencing; SNP, single-nucleotide polymorphism; WES, whole exome sequencing; WGS, whole genome sequencing.

mutation that can be directly or indirectly targeted with an approved or investigational drug; rates vary from 31% to 100% (see [Table 1](#)).

These studies continue to accrue data worldwide and range from single-center studies to transnational multicenter collaborations (see [Table 1](#)). Publicly available data repositories also have allowed for data sharing across multiple centers and data pooling to strengthen analytical power ([Box 1](#)).

ESTABLISHED THERAPEUTIC TARGETS IN PEDIATRIC ONCOLOGY

Cell Surface Targets

Ideal therapeutic targets are diffusely expressed by cancer cells with little-to-no expression on noncancerous cells. Targets can be found on the cell surface (eg, GD2, PD-1) or within the cell (eg, phosphoinositide 3-kinase [PI3K]/mammalian target of rapamycin [mTOR] pathway) but ideally are targetable with available FDA-approved drugs or agents that are under investigation in the clinical or preclinical settings ([Table 2](#)). As recurrent molecular alterations are discovered across difficult-to-treat pediatric tumors, the overlap in molecular targets between adult and pediatric tumors has allowed for the repurposing of established targeted therapies for off-label use in pediatric oncology (see [Table 2](#)). Prominent examples include the use of immune checkpoint inhibitors (ICIs) targeting PD-1 and CTLA-4 for Hodgkin lymphoma,²³ melanoma,²⁴ and microsatellite instability (MSI) high tumors,²⁵ anti-CD20 monoclonal antibody (rituximab) for non-Hodgkin lymphoma, and ALK inhibitors (crizotinib, ceritinib) for ALK-positive tumors including lymphoma and NB.^{26–28} This has not only increased the therapeutic options for refractory disease but has also improved response rates and overall survival (OS) when combined with cytotoxic therapy.²⁹

In addition to discovering new indications for existing drugs, ongoing research aims to discover novel therapeutic targets. The discovery of the cell surface marker, tumor-associated disialoganglioside GD2, expressed uniformly by NB tumor cells is a pivotal example of targeted therapy development in pediatric oncology ([Fig. 2](#)).³⁰ This led to the development of dinutuximab, an anti-GD2 monoclonal antibody, which demonstrated significant improvement in event-free survival (EFS) ($66 \pm 5\%$ vs $46 \pm 5\%$, $P = .01$) and OS ($86 \pm 4\%$ vs $75 \pm 5\%$, $P = .02$) at 2 years in patients with HR-NB.²⁹ Dinutuximab is currently FDA-approved for use in children with HR-NB and is used as salvage immunotherapy in children with refractory disease.³¹ Thus, the discovery of recurrent mutations in difficult-to-treat pediatric cancers has increased therapeutic options and subsequently improved survival through the utilization of existing drugs or the development of novel therapies.

APPLICATIONS OF PRECISION ONCOLOGY IN THE DIAGNOSIS AND TREATMENT OF PEDIATRIC CANCERS

Precision Trials in Pediatric Oncology

Early pediatric precision oncology studies highlighted the value of evaluating multiple refractory tumor types to identify clinically actionable mutations among the most

Box 1

List of sequencing data repositories in pediatric oncology

St Jude Cloud (<https://pecan.stjude.cloud/>)

Gabriella Miller Kids First Data Resource Portal (<https://kidsfirstdrc.org/>)

R2 Genomics Analysis and Visualization Platform (<http://r2.amc.nl/>)

Table 2 Molecular targets in pediatric oncology		
Molecular Target	Available Drug/Agent(s)	Tumor Types
Cell Surface Targets		
GD2	Dinutuximab	Neuroblastoma
CD20	Rituximab	NHL
ALK	Crizotinib, ceritinib	Anaplastic large cell lymphoma, inflammatory myofibroblastic tumor, neuroblastoma
CD33	Gemtuzumab ozogamicin	AML
PD-1	Pembrolizumab, nivolumab	Hodgkin lymphoma, MSI-H colorectal cancer
CTLA-4	Ipilimumab	Melanoma
SMO	Vismodegib	Medulloblastoma
FGFR	Ponatinib, dovitinib	Rhabdomyosarcoma
Intracellular Targets		
ABL1 kinase	Imatinib, ruxolitinib, dasatinib	ALL, CML
VEGFR/PDGFR kinases	Pazopanib	Rhabdomyosarcoma (PAX3-FOXO1 fusion) (Singh 2022)
PARP1	Olaparib, talazoparib	Ewing sarcoma (EWSR1-FLI1 fusion), medulloblastoma, Wilms tumor
PI3K/mTOR	Everolimus, temsirolimus, rapamycin	Osteosarcoma, subependymal giant cell astrocytoma
MEK	Trametinib, selumetinib	Glioma, neurofibroma, juvenile myelomonocytic leukemia
BRAF	Vemurafenib, dabrafenib	Melanoma, glioma, astrocytoma
NTRK 1/2/3	Larotrectinib	Infantile fibrosarcoma, soft tissue sarcoma, congenital mesoblastic nephroma, thyroid cancer, melanoma, breast cancer
CDK 4/6	Palbociclib, ribociclib	Neuroblastoma
BET	JQ1, IBET726, OTX015	Neuroblastoma, medulloblastoma
AURKA	Alisertib	Neuroblastoma
KDM4B	QC6352	Rhabdomyosarcoma (PAX3-FOXO1 fusion)

Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MSI-H, microsatellite instability-high; NHL, non-hodgkin lymphoma.

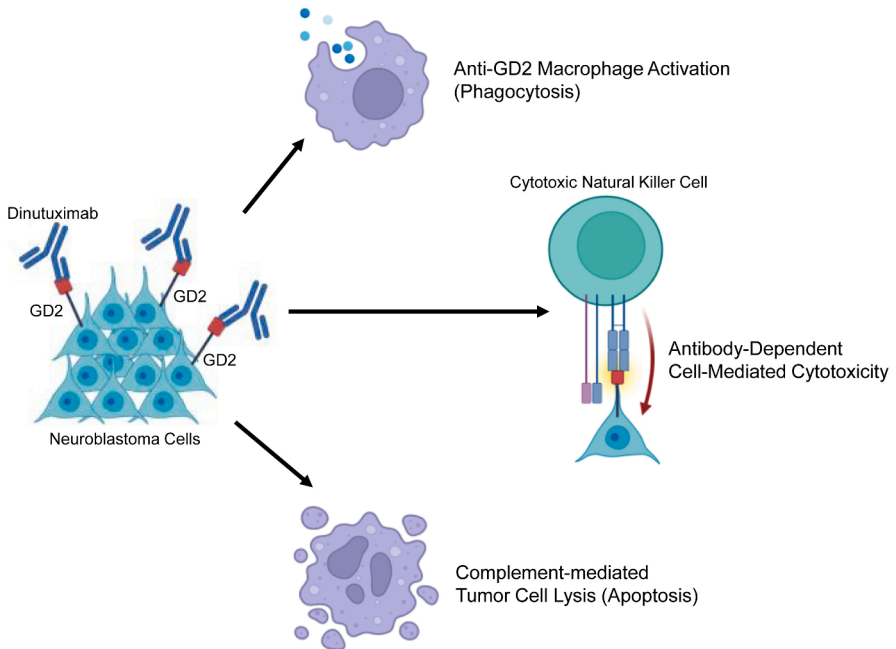


Fig. 2. Targeting of the cell surface marker, GD2, on neuroblastoma cells leads to tumor cell death via multiple mechanisms including antibody-dependent cell-mediated cytotoxicity, complement-mediated cell lysis/apoptosis, and macrophage activation/phagocytosis. (Created in BioRender. Lee, W. (2026) <https://BioRender.com/09ciko9>.)

difficult-to-treat cancers (see [Table 1](#)). However, in these early studies, the number of participants that actually received matched targeted therapy or reported clinical follow-up was low.^{32–34} Although conventional tumor-specific clinical trials provided a framework for evaluating the efficacy of novel therapeutic agents, the low (or often unknown) frequency of genomic variants in rare pediatric cancers⁶ and our limited understanding of their therapeutic response created unique challenges in applying this framework to pediatric precision oncology.³⁵

“Basket trials” provide a solution by recruiting multiple cancer types and allocating participants to treatment arms based on their targetable genomic alteration. Thus, creating a framework to increase access to molecular screening and molecular targeted therapies for cancers with low numbers (ie, refractory or rare tumors) while also evaluating treatment safety and efficacy. At present, the largest ongoing pediatric precision oncology “basket trials” are the National Cancer Institute–Children’s Oncology Group Pediatric Molecular Analysis for Therapy Choice (MATCH) trial (NCT03155620, APEC1621) and the Secured Access–European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors (AcSe’-ESMART) trial (NCT02813135, EUDRACT:2016–000133–40) ([Table 3](#)).

The Pediatric MATCH trial began recruitment in 2017 and is actively recruiting patients aged 1 to 21 years from Children’s Oncology Group institutions with treatment-refractory or recurrent solid tumors, non-Hodgkin lymphoma, or histiocytic disorders.³⁶ This basket trial uses a centralized system which obtains tumor samples after recurrence or disease progression (except in high-grade glioma), performs targeted NGS amplicon sequencing, RNAseq, and immunohistochemistry, and

Table 3
Comparison of ongoing basket trials in pediatric oncology

Trial Name	Clinical Trial ID	Sponsor	Sequencing Method(s)	Method of Treatment Matching	Treatment Arms
Pediatric-MATCH	NCT03155620	National Cancer Institute– Children’s Oncology Group	Uniform gene panel (amplicon DNA sequencing, RNAseq, IHC)	Automated	Monotherapy
AcSe-ESMART	NCT02813135	Gustave Roussy Cancer Campus, Grand Paris	Decentralized advanced molecular testing (WES/ WGS ± RNAseq)	Multidisciplinary tumor board	Agent combined with chemotherapy

automatically assigns patients to one of 13 treatment arms previously agreed on by the trial’s Target and Agent Prioritization committee (Table 4).³⁷ Of the first 1000 patients enrolled, the majority had non-central nervous system (CNS) solid tumors (72.3%)—primarily sarcomas (50.5%)—and 31.5% were identified to have actionable mutations. Out of those with actionable mutations, 90.2% were matched to a treatment arm, but only 41.6% were ultimately enrolled in a Phase II sub-trial.³⁶ This study highlights several ongoing challenges in treatment allocation (eg, genomic alterations not yet targetable such as *TP53*, *MYCN*, and *CTNNB1*) as well as patient enrollment (eg, inability for younger patients to take pills, competing non-precision oncology trials).³⁶ However, this ongoing trial is the first “basket trial” in the United States to

Table 4 National Cancer Institute–Children’s Oncology Group pediatric MATCH trial treatment arms			
Arm	Actionable Mutation	Drug	Drug Mechanism of Action
A	NTRK 1/2/3 fusion	Larotrectinib	TRK inhibitor
B	FGFR 1/2/3 mutation/fusion; FGFR4 mutation	Erdafitinib	FGFR kinase inhibitor
C	SMARCB 1/4 mutation/loss	Tazemetostat	EZH2 inhibitor
D	TSC 1/2, mTOR, or PIK3CA mutation; PTEN mutation/loss	Samotolisib	Dual PI3K/mTOR inhibitor
E ^a	BRAF mutation/fusion; NRAS, KRAS, HRAS, NF1, ARAF, GNAQ, GNA11 mutation	Selumetinib	Selective MEK inhibitor
F	ALK mutation/fusion; ROS1 fusion	Ensartinib	ALK inhibitor
G ^a	BRAF V600 mutation	Vemurafenib	BRAF V600 E inhibitor
H	BRCA 1/2, ATM, RAD51 C/D mutation	Olaparib	PARP inhibitor
I	CDK 4/6, CCND 1/2/3 amplification	Palbociclib	Selective CDK inhibitor
J ^a	BRAF mutation/fusion; NRAS, KRAS, HRAS, NF1, ARAF, GNAQ, GNA11, MAP2K1 mutation	Ulixertinib	ERK inhibitor
K	IDH1 R132 mutation	Ivosidenib	IDH1 inhibitor
M ^a	HRAS mutation	Tipifarnib	Farnesyl transferase inhibitor (blocks Ras activation)
N	RET mutation/fusion	Selpercatinib	RET inhibitor

Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, V-raf murine sarcoma viral oncogene homolog B1; CDK, cyclin-dependent kinase; ERK, extracellular signal-regulated kinase; EZH2, enhancer of zeste homolog 2; FGFR, fibroblast growth factor receptor; IDH1, isocitrate dehydrogenase 1; mTOR, mammalian target of rapamycin; PARP, Poly(ADP-ribose)-polymerase; PI3K, phosphoinositide 3-kinase; RET, rearranged during transfection; TRK, tropomyosin receptor kinase.

^a Arms involved in targeting of mitogen-activated protein kinase (MAPK, MEK signaling pathway).

demonstrate the feasibility of a centralized nationwide screening and treatment allocation framework.

The AcSe'-ESMART trial began in 2016 led by the Gustave Roussy Cancer Campus, Grand Paris and the Innovative Therapies for Children with Cancer Precision Cancer Medicine Program. This trial is also continuing active enrollment of patients less than 18 years of age with life expectancy ≥ 3 months and hematologic or solid tumors with progression despite standard therapy or no known effective standard therapy.³⁸ In contrast to the Pediatric MATCH trial, this uses a decentralized sequencing framework and obtains sequencing results (WES or WGS $\pm$ RNAseq), as opposed to tumor samples, and determines treatment allocation based on centralized multidisciplinary tumor board (MTB) consensus (see [Table 3](#)).³⁸ This study also differs from its US counterpart by combining targeted therapy with chemotherapy in its treatment arms, in contrast to targeted monotherapy (see [Table 3](#)). Although both "basket trials" are ongoing, they demonstrate the potential variation in trial design and the feasibility of expanding pediatric precision oncology into clinical practice.

TARGETED THERAPIES IN PEDIATRIC SOLID TUMORS

As surgical resection is a key component in the management of high-risk and difficult-to-treat pediatric solid tumors, the development of targeted therapies for pediatric solid tumors is of particular interest.^{39,40} Molecular testing of recurrent or refractory solid tumors has allowed for molecular risk stratification and treatment allocation,⁴¹ whereas extensive preclinical research has also identified recurrent tumor-specific molecular alterations which has provided the rationale for Phase I/II clinical trials ([Table 5](#)).⁴² Targeted therapies can be classified into serving one of two primary functions (1) inhibition of a key tumorigenic pathway (eg, tyrosine kinase inhibitors [TKIs], histone deacetylase [HDAC] inhibitors): or (2) tumor-directed immune system activation (eg, monoclonal antibodies, chimeric antigen receptor T-cell [CAR-T] therapy, DNA vaccines) (see [Table 5](#)). The following sections review the targeted therapies currently in-use or under investigation among the most common extracranial pediatric solid tumors.

Neuroblastoma

NB originates from neural crest cells and is the most common extracranial pediatric solid tumor—accounting for 7% of childhood cancers and 15% of all childhood cancer deaths.⁴³ NB is stratified from very low risk to high risk based on the presence or absence of various prognostic factors such as disseminated disease, histologic differentiation, and molecular alterations (eg, *MYCN* oncogene amplification, chromosomal copy number variation).⁴⁴ Tumor behavior is also heterogeneous ranging from spontaneous regression in low-risk disease to refractory metastatic disease in HR-NB. Although survival in low-risk disease reaches 90%, 5-year survival remains dismal in HR-NB despite multimodal therapy—with 50% of children ultimately succumbing to this disease.⁴⁵ In addition, approximately 50% of HR-NB patients do not respond to first-line therapy, or they relapse within the first 2 years of treatment initiation.⁴⁶ The poor prognosis in HR-NB is attributed to posttreatment minimal residual disease or microscopic treatment-refractory disease that proliferates and metastasizes without an effective treatment. Thus, significant work is focused on identifying recurrent molecular alterations that can be targeted in HR-NB.

The discovery of the cell surface marker, disialoganglioside GD2, and the development of the anti-GD2 monoclonal antibody, dinutuximab, is a leading example of targeted therapy development in pediatric precision oncology. GD2 is present in the

Table 5
Precision oncology clinical trials for pediatric solid tumors

Trial ID	Sponsor	Phase	Ages Included	Tumor Type	Disease State	Target	Treatment	Targeted Treatment Type	Targeted Treatment Mechanism of Action	Trial Status
NCT04308330	New York Medical College	1	1–30 y	Solid tumors (including CNS)	Recurrent, refractory	Histone deacetylase (HDAC)	Vorinostat + chemotherapy	Small molecular inhibitor	HDAC inhibitor	Recruiting
NCT02644460	Emory University	1	2–25 y	Solid tumors (including CNS)	Recurrent, refractory	CDK 4/6	Abemaciclib	Small molecular inhibitor	Selective CDK 4/6 inhibitor	Recruiting
NCT04928677	Memorial Sloan Kettering Cancer Center	1	1–21 y	GPC3-expressing extra-cranial solid tumors	Recurrent, refractory	GPC3	Codrituzumab	Monoclonal antibody	Anti-GPC3 monoclonal antibody	Recruiting
NCT04851119	COG	1/2	1–30 y	Non-CNS solid tumors (including desmoid tumors) with Wnt pathway aberrations	Recurrent, refractory	Wnt pathway	Tegavivint	Small molecular inhibitor	Inhibits transducin b-like protein 1 (TBL1) binding b-catenin (Wnt pathway)	Recruiting
NCT04897321	St Jude Children's Research Hospital	1	<21 y	Non-CNS solid tumors	Recurrent, refractory	B7-H3	B7-H3 CAR-T cells	CAR-T cell	B7-H3 CAR-T cell therapy	Recruiting
NCT04634357	Eureka Therapeutics Inc	1/2	1–21 y	HLA-A2 positive, liver tumor	Recurrent, refractory	AFP, HLA-A2	ET140203 CAR-T Cells	CAR-T cell	AFP-HLA-A2-CAR T-cell therapy	Recruiting
NCT03107988	New Approaches to Neuroblastoma Therapy Consortium	1/2	1–99 y	ALK-mutated high-risk neuroblastoma	Recurrent, refractory	ALK	Lorlatinib ± chemotherapy	Small molecular inhibitor	ALK inhibitor	Recruiting
NCT02559778	Wake Forest University Health Services	1	<22 y	High-risk neuroblastoma	Primary or recurrent	ALK, receptor tyrosine kinases, HDAC	Ceritinib, dasatinib, sorafenib, or vorinostat ± DFMO	Small molecular inhibitor	Tyrosine kinase inhibitor, HDAC inhibitor	Recruiting
NCT05272371	Jagiellonian University	1/2	1–18 y	High-risk neuroblastoma	Recurrent, refractory	GD2	Dinutuximab + chemotherapy	Monoclonal antibody	Anti-GD2 monoclonal antibody	Recruiting

NCT02914405	University Hospital Southampton NHS Foundation Trust	1	1–18 y	High-risk neuroblastoma	Recurrent, refractory	GD2, PD-1R	Dinutuximab + nivolumab	Monoclonal antibody	Anti-GD2 and anti-PD-1R monoclonal antibody	Recruiting
NCT03363373	Y-mAbs Therapeutics	2	>1 y	High-risk neuroblastoma	Refractory	GD2	Naxitamab (hu3F8)	Monoclonal antibody	Anti-GD2 monoclonal antibody	Recruiting
NCT03373097	Bambino Gesù Hospital and Research Institute	1/2	1–25 y	GD2-positive tumors	Recurrent, refractory	GD2	GD2-CART01	CAR-T cell	GD2-CAR T-cell therapy	Recruiting
NCT04049864	Belarusian Research Center for Pediatric Oncology	1	1–20 y	Neuroblastoma	Recurrent	NB-associated antigens (TH, Phox2B, survivin, MAGEA 1/3, PRAME)	DNA vaccine	DNA vaccine	Anti-NB DNA vaccine	Recruiting
NCT04936529	Memorial Sloan Kettering Cancer Center	2	All ages	High-risk neuroblastoma	Complete remission	NB-associated antigens	Bivalent DNA vaccine	DNA vaccine	Anti-NB DNA vaccine	Recruiting
NCT05429502	Novartis Pharmaceuticals	1/2	1–21 y	Neuroblastoma, medulloblastoma, high-grade glioma, malignant rhabdoid tumor, rhabdomyosarcoma	Recurrent, refractory	Cyclin-dependent kinase 4/6 (CDK 4/6)	Ribociclib + chemotherapy	Small molecular inhibitor	Selective CDK 4/6 inhibitor	Recruiting
NCT01858168	Massachusetts General Hospital	1	≥16 y	Ewing sarcoma, rhabdomyosarcoma	Refractory	Poly(ADP-ribose) polymerase (PARP)	Olaparib + chemotherapy	Small molecular inhibitor	PARP inhibitor	Recruiting
NCT04299113	Jonsson Comprehensive Cancer Center	1	≥13 y	rhabdomyosarcoma	Recurrent, refractory	HDAC	Mocetinostat + chemotherapy	Small molecular inhibitor	HDAC inhibitor	Recruiting
NCT04417062	Dana-Farber Cancer Institute	2	12–40 y	Osteosarcoma	Recurrent, refractory	PARP, ATR	Olaparib + ceralasertib	Small molecular inhibitor	PARP inhibitor, ATR inhibitor	Recruiting
NCT04833582	K-Group, Beta, Inc.	1/2	≥12 y	Osteosarcoma	Recurrent, refractory	Wee-1	ZN-c3 + chemotherapy	Small molecular inhibitor	Wee-1 inhibitor	Recruiting
NCT02502786	Memorial Sloan Kettering Cancer Center	2	13 months–30 years	Osteosarcoma	Recurrent, refractory	GD2	Humanized 3F8	Monoclonal antibody	Anti-GD2 monoclonal antibody	Recruiting

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Table 5
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Trial ID	Sponsor	Phase	Ages Included	Tumor Type	Disease State	Target	Treatment	Targeted Treatment Type	Targeted Treatment Mechanism of Action	Trial Status
NCT04294511	Sun Yat-sen University	2	14–65 y	Osteosarcoma	Primary or recurrent	PD1	Camrelizumab + chemotherapy	Monoclonal antibody	Anti-PD1 monoclonal antibody	Recruiting
NCT03628209	H Lee Moffitt Cancer Center	1/2	<39 y	Osteosarcoma	Recurrent, refractory	PD1	Nivolumab ± chemotherapy	Monoclonal antibody	Anti-PD1 monoclonal antibody	Recruiting
NCT03811886	Case Comprehensive Cancer Center	1/2	5–30 y	Pulmonary metastatic osteosarcoma	Refractory	a4b1-integrin	Natalizumab	Monoclonal antibody	Anti-a4b1-integrin monoclonal antibody	Recruiting
NCT03277924	Grupo Espanol de Investigacion en Sarcomas	1/2	12–80 y	Sarcoma (bone, soft tissue)	Refractory	Receptor tyrosine kinases (VEGFR, PDGFR, c-KIT, RET, CD114, CD135), PD1	Sunitinib ± nivolumab + chemotherapy	Small molecular inhibitor, monoclonal antibody	Tyrosine kinase inhibitor, anti-PD1 monoclonal antibody	Recruiting
NCT03462316	Sun Yat-sen University	1	14–70 y	Sarcoma (bone, soft tissue)	Refractory	NY-ESO-1	NY-ESO-1-specific T-cell receptor T-cell therapy	TCR-T therapy	Anti-NY-ESO-1 TCR transduced T-cell therapy	Recruiting
NCT01121588	Pfizer	1	≥15 y	ALK-mutated tumors (excluding NSCLC)	Primary or recurrent	ALK	Crizotinib	Small molecular inhibitor	ALK inhibitor	Active, not recruiting
NCT02909777	Dana-Farber Cancer Institute	1	1–21 y	Solid tumors (including CNS), lymphoma	Recurrent, refractory	PI3K, HDAC	Fimepinostat (CUDC-907)	Small molecular inhibitor	PI3K class 1 inhibitor, HDAC inhibitor	Active, not recruiting
NCT02867592	NCI	2	2–30 y	Solid tumors (including CNS)	Recurrent, refractory	Receptor tyrosine kinases	Cabozantinib-S-Malate	Small molecular inhibitor	Tyrosine kinase inhibitor	Active, not recruiting
NCT05093322	HUTCHMED	1/2	2–21 y	Non-CNS solid tumors, lymphoma	Recurrent, refractory	VEGFR, FGFR1, CSFR1	Surufatinib + chemotherapy	Small molecular inhibitor	VEGF, FGF, CSF inhibitor	Active, not recruiting
NCT05071209	NCI	1/2	1–30 y	Non-CNS solid tumors, lymphoma	Recurrent, refractory	Ataxia telangiectasia receptor (ATR)	Elimusertib	Small molecular inhibitor	Selective ATR inhibitor	Active, not recruiting

NCT02308527	University of Birmingham	2	1–21 y	High-risk neuroblastoma	Recurrent, refractory	VEGF	Bevacizumab + chemotherapy	Monoclonal antibody	Anti-VEGF monoclonal antibody	Active, not recruiting
NCT03294954	Baylor College of Medicine	1	1–21 y	High-risk neuroblastoma	Recurrent, refractory	GD2	GD2-CAR expressing natural killer T cells	CAR-T cell	GD2-CAR NK T-cell therapy	Active, not recruiting
NCT02998983	Laboratorio Elea Phoenix SA	2	1–12 y	High-risk neuroblastoma	Recurrent, partial remission	N-glycolyl GM3	Racotumomab	Monoclonal antibody	Anti-N-glycolyl GM3 monoclonal antibody	Active, not recruiting
NCT04095221	Memorial Sloan Kettering Cancer Center	1/2	≥1 y	Rhabdomyosarcoma, desmoplastic small round cell tumor	Recurrent, refractory	Checkpoint kinase CHEK 1/2	Prexasertib + chemotherapy	Small molecular inhibitor	CHEK 1/2 inhibitor	Active, not recruiting
NCT04154189	Eisai Inc.	2	2–25 y	Osteosarcoma	Recurrent, refractory	Receptor tyrosine kinases (CEGFR, FGFR, CSFR1, RAF-1, RET, KIT)	Chemotherapy ± lenvatinib	Small molecular inhibitor	Tyrosine kinase inhibitor	Active, not recruiting
NCT04803877	Sarcoma Alliance for Research through Collaboration	2	≥5 y	Osteosarcoma	Recurrent, refractory	Receptor tyrosine kinases (CEGFR, FGFR, CSFR1, RAF-1, RET, KIT), PD1	Regorafenib + nivolumab	Small molecular inhibitor, monoclonal antibody	Tyrosine kinase inhibitor, anti-PD1 monoclonal antibody	Active, not recruiting
NCT01459484	Italian Sarcoma Group	2	<40 y	ABCBI/P-glycoprotein overexpressing high-grade Osteosarcoma	Non-metastatic, primary or recurrent	n/a	Mifamurtide	Muramyl dipeptide (immunostimulant)	Immunostimulant via NOD2 activation	Active, not recruiting
NCT03006848	St Jude Children's Research Hospital	2	12–49 y	Osteosarcoma	Recurrent, refractory	PDL1	Avelumab	Monoclonal antibody	Anti-PDL1 monoclonal antibody	Active, not recruiting
NCT02484443	NCI	2	<29 y	Osteosarcoma	Recurrent, refractory	GD2	Dinutuximab	Monoclonal antibody	Anti-GD2 monoclonal antibody	Active, not recruiting

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Table 5
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Trial ID	Sponsor	Phase	Ages Included	Tumor Type	Disease State	Target	Treatment	Targeted Treatment Type	Targeted Treatment Mechanism of Action	Trial Status
NCT01953900	Baylor College of Medicine	1	All ages	Osteosarcoma, neuroblastoma	Recurrent, refractory	GD2, varicella zoster	iC9-GD2-CAR-VZV-CTL	CAR-T cell	Anti-GD2-VZV-CAR T-cell therapy	Active, not recruiting
NCT01502410	NCI	2	2–30 y	RMS, liver tumors, renal tumors (including Wilms tumor), thyroid tumors	Recurrent, refractory	Raf kinase	Sorafenib tosylate	Small molecular inhibitor	Multi-kinase inhibitor (Raf/BRAF, ERK, MEK), Anti-angiogenic (VEGF, PDGF)	Completed
NCT01598454	Laboratorio Elea Phoenix SA	1/2	1–10 y	Solid tumors (including CNS)	Recurrent, refractory	N-glycolyl GM3	Racotumomab	Monoclonal antibody	Anti-N-glycolyl GM3 monoclonal antibody	Completed
NCT00831844	NCI	2	7 months–30 years	Non-CNS solid tumors	Recurrent, refractory	IGF-1R	Cixutumumab	Monoclonal antibody	Anti-insulin-like growth factor-1 receptor (IGF-1R) monoclonal antibody	Completed
NCT02982941	MacroGenics	1	1–35 y	Non-CNS solid tumors	Recurrent, refractory	B7-H3	Enoblituzumab	Monoclonal antibody	Anti-B7-H3 monoclonal antibody	Completed
NCT02452554	COG	2	1–30 y	Non-CNS solid tumors	Recurrent, refractory	CD56	Lorvotuzumab mertansine (IMGN901)	Monoclonal antibody	Anti-CD56 monoclonal antibody	Completed
NCT04385277	COG	2	<31 y	High-risk neuroblastoma	Post-consolidation therapy, non-progressive	GD2	Dinutuximab + chemotherapy	Monoclonal antibody	Anti-GD2 monoclonal antibody	Suspended (met accrual goal)
NCT04751383	NCI	1	2–35 y	Osteosarcoma, neuroblastoma	Recurrent, refractory	CD47, GD2	Magrolimab + dinutuximab	Monoclonal antibody	Anti-CD47 and anti-GD2 monoclonal antibodies	Suspended (unacceptable toxicity)
NCT01236586	NCI	2	1–21 y	Solid tumors (including CNS), lymphoma	Recurrent, refractory	Gamma secretase (notch signaling)	RO4929097	Small molecular inhibitor	Gamma secretase inhibitor (notch pathway)	Withdrawn

majority of human NB cell lines, retaining its expression in recurrent disease, and is rarely expressed in normal human tissues—thus making it an ideal target.⁴⁷ After extensive preclinical testing and safety evaluation, Phase III investigation of dinutuximab (with granulocyte-macrophage colony-stimulating factor and interleukin-2) in 226 patients with HR-NB demonstrated a clear long-term improvement in 5-year EFS ($56.6 \pm 4.7\%$ vs isotretinoin alone $46.1 \pm 5.1\%$; $P = .042$) and 5-year OS ($73.2 \pm 4.2\%$ vs isotretinoin alone $56.5 \pm 5.1\%$; $P = .045$).⁴⁸ Since FDA approval in 2015, dinutuximab has become the first FDA-approved targeted immunotherapy for HR-NB as part of a first-line multi-agent regimen. Current studies aim to use dinutuximab to augment standard-of-care salvage chemotherapy regimens in refractory disease⁴⁹ and mitigate the toxicity profile with the development of a humanized anti-GD2 monoclonal antibody, naxitamab.⁵⁰ In addition, bivalent vaccines and CAR-T therapy are also being explored to target HR-NB via the GD2 cell surface marker (NCT03294954, NCT03373097).⁵¹

In contrast to GD2, MYCN is another potential target in NB that has proved challenging thus far. MYCN is a disordered protein hidden within the cell nucleus which is involved in normal cell proliferation by binding with MAX to act as a transcription factor. However, MYCN amplification can lead to uncontrolled cancer cell proliferation, survival, immune evasion, and metastasis.⁵² Although MYCN amplification occurs in 20% to 30% of NB cases, it is highly correlated with aggressive disease, poor survival, and its presence is a defining factor of high-risk disease.⁵³ Since the 1990s, MYCN has been identified as a potential target in HR-NB. Approaches to MYCN targeting include blocking MYCN-MAX dimerization or subsequent DNA binding,⁵⁴ inhibition of MYCN stabilizer proteins⁵⁵ or chaperone molecules,⁵⁶ and targeting epigenetic modifications to downregulate MYCN expression.⁵⁷ However, the crossover from preclinical to clinical studies has been limited, with the first-in-human Phase I trial of an MYCN inhibitor, PeptoMYC, currently underway (NCT04808362). PeptoMYC preferentially binds MAX to form PeptoMYC-MAX heterodimers, subsequently blocking MYCN oncogene activation.^{58,59} Preliminary results seem to demonstrate safety with mild infusion-related reactions reported and eight patients with stable disease (SD, 47.1%) in the first 17 patients enrolled.⁶⁰

Early Phase I/II clinical trials are also investigating the efficacy of targeting key tumorigenic pathways in NB (Table 6). Targeting of the ALK signaling pathway with receptor TKIs (eg, crizotinib, lorlatinib)⁶¹ and the PI3k/Akt/mTOR pathway with Akt inhibitors (eg, perifosine)⁶² has demonstrated safety with ongoing evaluation of efficacy (see Table 5). Preclinical research has also identified additional targets with potential for clinical translation in the Wnt signaling pathway,^{63,64} Ras-mitogen-activated protein kinase (MAPK) signal transduction pathway,⁶⁵ and P53-MDM2 pathway.^{66,67} For example, with more than 98% of NB expressing wild-type P53,⁶⁸ targeted inhibition of the P53 inhibitor (MDM2) with nutlin-3a has led to P53 accumulation and downstream reactivation of P53-dependent apoptotic pathways decreasing tumor cell proliferation in vitro and tumor growth in preclinical murine models.^{69–72} These preclinical findings elucidate the mechanistic understanding of these targetable pathways and provide the rationale for further clinical translation.

Targeting of epigenetic modifications, such as (HDACs and bromodomain and extraterminal (BET) proteins, has also shown promise in the targeted treatment of NB. In a Phase I trial aiming to identify the maximum tolerated dose of the HDAC inhibitor, vorinostat, in refractory pediatric solid tumors, one patient with NB experienced a complete response (CR).⁷³ Thus, the recognition of recurrent epigenetic modifications in NB has expanded the therapeutic potential of small molecule inhibitors that can alter tumor cell DNA transcription and ultimately tumor cell survival.⁷⁴

Table 6 Current challenges in pediatric precision oncology	
Limitations in immunotherapy	Immature or depleted immune system Lack of biomarkers to predict response of immunotherapy Potential for acute and/or late toxicity Potential for immune system overactivation
Potential resistance to targeted therapies	Tumor and tumor microenvironment heterogeneity Mutations of the target itself Activation of alternate pathways (eg, upstream, downstream, parallel) Tumor microenvironment cross talk
Lack of access to targeted therapies	Limited overlap with adult tumor molecular targets Small number of patients with rare or difficult-to-treat tumors Safety concerns in pediatric use
Prohibitive cost	Sequencing Data analysis Targeted therapy
Lack of logistical infrastructure	Lengthy turnaround time (biopsy to matched therapy initiation) Lack of unified framework for pediatric precision oncology
Ethical impact of identifying incidental germline mutations	Unknown implications of incidental germline mutations Potential for unnecessary further invasive and/or noninvasive diagnostic testing in healthy individuals

Future directions in molecular therapy development include targeting of cancer exosomes containing oncogenic microRNAs (miRNA)⁷⁵ and DNA vaccines to prevent NB recurrence (NCT04049864).

Wilms Tumor

Wilms tumor (WT), or nephroblastoma, is the most common renal malignancy and the second most common abdominal solid tumor in childhood. Although 5-year survival is favorable at greater than 90% with surgery, chemotherapy, and radiotherapy, survival rates decline with advanced disease (metastatic, recurrent).^{76,77} The need for alternative therapies in this difficult-to-treat subpopulation, as well as the known toxicity of standard therapeutic regimens (eg, cardiotoxicity from anthracyclines), has driven targeted therapy development for WT.⁷⁸

WTs with an unfavorable prognosis are characterized by an increased ratio of anti-inflammatory (M2) macrophages and low levels of tumor-infiltrating lymphocytes (TILs), which creates an immunologically “cold” environment—protecting the tumor from the immune system.^{79,80} This also creates a challenge in the development of targeted immunotherapies against WT. Unlike lymphoma, pediatric solid tumors—especially WTs—express the lowest level of traditional immunotherapy targets, such as immune checkpoint ligands (eg, PD-1, PD-L1)^{81–83} and a suboptimal

response to ICIs. This was demonstrated by the KEYNOTE-051 study where response to pembrolizumab occurred in only 5.9% of solid tumors as compared with 60% in the lymphoma group.⁸⁴ Thus, alternative novel targets are currently being explored.

B7 homolog 3 protein (B7-H3) is an immunoregulatory molecule in the PD-1 pathway that has been linked to cancer cell immune evasion and metastasis. Unlike PD-1, B7-H3 is highly expressed in pediatric solid tumors—with one study observing positive expression in 100% of WT tumor samples.⁸⁵ This seems to be a promising target with ongoing studies targeting B7-H3 with CAR-T therapy (NCT04897321) and monoclonal antibody therapy (enoblituzumab; NCT02982941).

Other promising targets include N-glycolyl GM3 and WT 1 (WT1), which demonstrate overexpression in WT. N-glycolyl GM3 is a ganglioside on the outer cell membrane and found in up to 88% of WT tumor samples with low-to-absent expression in normal kidney tissue—making it an ideal therapeutic target.⁸⁶ Early investigation of an anti-N-glycolyl GM3 monoclonal antibody, racotumomab, was shown to be safe, but it did not alter disease progression with 12 of 14 patients experiencing disease progression and the other two patients with SD.⁸⁷ Similarly, targeting of WT1 with tumor-associated antigen cytotoxic T-cells demonstrated safety and led to disease stability in two of seven patients while increasing 6-month progression-free survival (PFS) from 38% to 73% compared with prior therapy. Additional WT1-targeted therapies are also being explored in adult tumors such as CUE-102 (NCT05360680), an immunogenic fusion protein to mobilize the immune system against WT1, and ASP7517 (NCT04837196), an artificial WT1-loaded artificial immunogenic vector cell. In sum, targeted therapies for WT remain under early investigation but have shown to be safe with early promise with regard to efficacy.

Additional studies also aim to induce cellular apoptosis of tumor cells with the use of recombinant tumor necrosis factor-alpha in combination with actinomycin D.^{88,89} Phase II study of combination therapy in 19 patients with recurrent or refractory WT led to 3 patients (15.6%) with a CR, 5 (26.3%) with SD, and 11 (57.9%) with progressive disease (PD). However, widespread adoption remains limited by notable toxicities including thrombocytopenia (40.7%), liver transaminitis (23.7%), neutropenia (20.3%), and leukopenia (13.6%).⁸⁸

Hepatoblastoma

Hepatoblastoma (HB) is the most common primary liver malignancy of childhood with the fastest rising incidence among childhood malignancies in children less than 5 years of age.⁹⁰ Advances in cisplatin-based chemotherapy and surgery (resection, liver transplantation) have increased 5-year OS to 82% but similar to NB and WT; recurrent metastatic disease is often refractory to available therapies with poor outcomes.⁹¹ The association of HB with genetic syndromes, such as familial adenomatous polyposis or Beckwith–Wiedemann, suggests potential targetable molecular alterations and pathways.^{92,93} However, relative to other pediatric solid tumors, HB retains one of the lowest exon mutational burdens—averaging 2.0 to 3.9 coding mutations per tumor.⁹⁴ Despite this, progress in molecular and epigenetic profiling has allowed for disease risk stratification^{95,96} and identification of potential therapeutic targets.

One of the major aberrant pathways in HB is the Wnt/ β -catenin signaling pathway which is often accompanied by YAP activation leading to cancer cell proliferation and differentiation into cancer stem cells.⁹⁷ Targeting of *CTNNB1* (gene encoding for β -catenin) and β -catenin itself have demonstrated therapeutic efficacy in preclinical models of hepatocellular cancers which led to the development of small molecule inhibitors of this pathway.⁹⁸ Tegavivint is a small molecule inhibitor of β -catenin which

was initially developed for desmoid tumors. By selectively disrupting of β -catenin and transducing β -like protein 1 binding, β -catenin nuclear translocation is inhibited leading to β -catenin degradation. This has shown promise in other tumors with Wnt/ β -catenin signaling overactivation and is a promising therapy under investigation for refractory HB (NCT04851119). Other promising preclinical targets include TERT promoter regions⁹⁴ and receptor tyrosine kinases involved in this pathway.⁹⁹ Sorafenib is a multi-kinase inhibitor which has been shown to decrease tumor cell viability and inhibit tumor progression in combination with cisplatin in preclinical studies¹⁰⁰ and has been adopted as adjunct therapy in unresectable disease in the ongoing Phase III Pediatric Hepatic International Tumor Trial (NCT03017326). Additional targeted therapies being evaluated in-human are anti-glypican-3 immunotherapy (monoclonal antibody, CAR-T; NCT04928677) and ICLs (NCT05322187).

The PI3K/Akt/mTOR pathway is also dysregulated in HB and a potential targetable pathway.¹⁰¹ Preclinical research has demonstrated decreased tumor growth, increased tumor cell apoptosis, and reduced serum alpha fetoprotein (AFP) levels with the inhibition of PI3K,¹⁰² mTOR,¹⁰³ and PIM kinases.¹⁰⁴ Additional pathways under preclinical investigation include the TGF- β /SMAD¹⁰⁵ and JAK/STAT signaling pathways.¹⁰⁶

Epigenetic modifications leading to genetic alterations have also been identified in HB, such as DNA methylation, histone modification, and long non-coding RNAs, with particular interest in HDAC inhibitors for recurrent/refractory HB (NCT04308330). In addition, ongoing preclinical research has identified additional novel therapies (eg, PLK1 inhibitors, PARP1 inhibitors, MDM4 inhibitors, anti-CD326 monoclonal antibodies) which halt tumor growth in combination with cytotoxic therapy.^{107–110} Thus, although HB contains a relatively low mutational burden, advances in genomic profiling have identified promising preclinical targets and targetable pathways providing rationale for inclusion in ongoing clinical trials.

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) originates from immature mesodermal cells and is the most common soft tissue sarcoma in childhood.¹¹¹ Although 70% of patients with localized disease are able to achieve complete remission with multimodal therapy (chemotherapy, radiation, surgery), the 5-year EFS for metastatic disease is poor (<20%).¹¹² RMS is classified by histologic subtype (embryonal, alveolar, pleomorphic, spindle cell/sclerosing) but molecular classification based on the presence or absence of the *PAX-FOXO1* gene fusion may provide more prognostic value with fusion-positive RMS correlating with decreased EFS and OS.¹¹³ Sixty percent of alveolar RMS is fusion-positive and the resultant *PAX-FOXO1* fusion protein acts as an oncogenic transcription factor inducing abnormal gene expression leading to tumorigenesis.¹¹⁴ Preclinical studies targeting *PAX-FOXO1* either directly with silencing RNA or indirectly with HDAC inhibitors have demonstrated inhibition of tumor growth,^{115,116} and HDAC inhibitors are currently being evaluated for in-human use as an adjunct to chemotherapy (NCT04299113).

Molecular testing has also identified additional targetable pathways—similarly dysregulated in other types of sarcomas—which are involved in tumorigenesis and cancer cell proliferation. Targeting of the PI3K/Akt/mTOR pathway with the mTOR inhibitor, temsirolimus, is promising with disease stabilization in 41% of patients with refractory RMS.¹¹⁷ Phase II investigation of temsirolimus and bevacizumab (anti-vascular endothelial growth factor [VEGF]) in recurrent RMS was halted early due to superior outcomes with temsirolimus in 6-month EFS (69.1% vs 54.6%) and disease progression (11% vs 28%).¹¹⁸ Results are currently pending from a Phase III trial

examining the efficacy of temsirolimus with or without standard chemotherapy in patients with intermediate-risk RMS (NCT02567435).

However, inhibition of other identified pathways has led to variable outcomes. Phase II investigation of crizotinib (ALK inhibitor) in patients with metastatic RMS led to an objective response rate (ORR) in 14.3% of patients with median OS of 5.6 months, but all participants ultimately succumbed to PD.¹¹⁹ Similarly, antibody targeting the insulin-like growth factor 1 receptor (IGF-1R) with cixutumumab in 20 patients with refractory RMS led to one partial response (PR) and disease stabilization in three patients,¹²⁰ but further studies did not reveal any improvement in survival outcomes.^{121,122} Preclinical evaluation of the multi-kinase inhibitor, sorafenib, led to inhibition of xenograft tumor growth, but did not result in an objective response in a Phase II study of refractory RMS.¹²³ Thus, although prior studies have demonstrated limited success with targeted monotherapy in refractory RMS, ongoing trials indicate that future targeted therapies will likely be used as an adjunct to standard chemotherapy regimens.

Osteosarcoma

Osteosarcoma (OST) is the most common primary malignant bone tumor in children, adolescents, and young adults occurring most frequently in the metaphysis of long bones.¹²⁴ Approximately 15% to 20% of patients present with metastatic disease, most commonly to the lung, and have poor survival outcomes (5-year OS 20%).¹²⁴ Current treatment involves neoadjuvant chemotherapy, limb-sparing surgical resection of all primary and metastatic disease, and adjuvant chemotherapy, but those with a poor tumor response to neoadjuvant chemotherapy (<90% necrosis) also have poor outcomes (5-year EFS 50%–60%).¹²⁵

Genomic profiling of OST tumor samples has identified regions of localized hypermutations (ie, kataegis) in known tumorigenic genes (*TP53*, *RB1*, *ATRX*, *DLG2*), as well as differential expression of miRNAs (miR-21/221/106a) that may alter gene expression and contribute to cancer cell proliferation.^{126,127} However, structural and immunologic aspects of OST have created challenges in targeted therapy development. The dense calcified matrix intrinsic to OST limits not only the penetration of applied therapies but also contributes to immune system evasion which limits the efficacy of immunotherapy approaches.^{128,129} OST is also associated with a high density of immunosuppressive M2 macrophages and low levels of TILs which further limits the ability of targeted molecular therapies to mobilize the immune system against the tumor.¹³⁰ Despite these limitations, ongoing research aims to combine forms of targeted therapy to improve survival outcomes in recurrent/refractory OST (see [Table 5](#)).

Targeting of cell surface markers is an emerging therapeutic avenue in OST. In addition to NB, OST also highly expresses the cell surface marker, GD2, in up to 95% of OST tumor samples.¹³¹ Thus, the use of existing anti-GD2 therapies (monoclonal antibodies, CAR-T cell therapy) to treat OST is currently under investigation (NCT02502786, NCT02484443, NCT03373097). Glycoprotein NMB is also expressed by 92.5% of OST tumor samples and antibody targeting with glembatumumab has demonstrated cytotoxic effects on OST tumor cells with improvements in survival in the preclinical setting.^{132,133} Phase II investigation of glembatumumab in 22 patients with refractory OST demonstrated safety, but poor overall response with only one PR and two with disease stabilization.¹³⁴ Ongoing research aims to evaluate the utility in targeting alternative cell surface markers, such as $\alpha 4$ -integrin, CD47, and RANKL (NCT03811886, NCT04751383).¹³⁵

ICIs are of particular interest given their clinical success in adult solid tumors and preclinical efficacy in OST xenograft models. However, clinical Phase I/II trials have demonstrated safety with limited improvement in PFS and OS.¹³⁶ As monoclonal

antibody therapy relies on immune system recruitment, this poor response may be due to rapid depletion of cytotoxic T-cells and the immunosuppressive tumor micro-environment (TME) in OST. The combination of TILs and anti-PD1 antibody therapy in patients with metastatic OST led to an ORR of 33.3% and improved median PFS (5.4 months) and OS (15.2 months) compared with ICIs alone, which illustrates the potential value of combining immunotherapy with immune stimulation.¹³⁷ Ongoing clinical trials aim to evaluate the efficacy of ICIs as adjunct therapy in difficult-to-treat OST (NCT04294511, NCT03628209).

TME modulation is also being explored to alter the immunosuppressive environment and potentially facilitate improved efficacy of immunotherapies. Agents that decrease M2 macrophage activation and increase pro-inflammatory cytokines, such as mifamurtide and all-trans retinoic acid, have been shown to disrupt cancer stem cell formation and improve survival in localized OST.^{138,139} However, the use of these agents in metastatic or refractory OST has not yet been investigated. Thus, although the immunosuppressive TME and structural obstacles of OS have proven challenging in the development of effective targeted therapies for metastatic and refractory OST, the current focus on multifaceted therapeutic regimens that include tumor cell targeting, TME modulation, and immune-stimulation shows great promise.

CHALLENGES TO PRECISION ONCOLOGY IN THE PEDIATRIC POPULATION

Although pediatric precision oncology has the potential to improve survival and mitigate toxicity from current cytotoxic therapies, there are several challenges that must be overcome to make this a clinical reality (see [Table 6](#)). Here, we discuss the issues with novel targeted therapies (eg, efficacy, toxicity, access) and barriers to clinical implementation of a nationwide pediatric precision oncology program (eg, cost, logistics, ethical impact).

Challenges in Immunotherapy

During the development of novel immunotherapy approaches, it is important to consider the immune milieu of pediatric oncology patients. In addition to immune system depletion after cytotoxic induction chemotherapy, the relatively immature immune system of pediatric patients and the immunologically “cold” TME found in the majority of pediatric solid tumors may affect the efficacy of targeted monotherapy. It should also be emphasized that most of Phase I/II trials include patients who suffer from recurrent and/or treatment refractory disease. Thus, due to known aggressive and resistant tumor biology, combining targeted immunotherapy with cytotoxic chemotherapy or immune stimulation should be considered in trial design. However, this must be weighed carefully with the risk for acute and/or late toxicities from on-target/off-tumor effects from immune system modulation. For example, although rare, the anti-GD2 monoclonal antibody carries the risk of binding to GD2 present on nerve cells leading to severe neuropathic pain. This stresses the importance of careful study design and monitoring for adverse effects during Phase I/II clinical trials evaluating novel immunotherapies.

Challenges with Targeted Therapies

In addition to balancing maximizing efficacy and mitigating toxicity, the potential for resistance to targeted therapies must also be considered. Various mechanisms within known heterogeneous malignancies could lead to future resistance such as mutations in the target itself (eg, GD2 downregulation), reactivation of upstream or downstream

pathways (eg, BRAF upregulation with MEK inhibition), or activation of alternate parallel pathways (eg, MAPK signaling activation with mTOR inhibition).¹⁴⁰ This may be mitigated by optimizing therapy administration (ie, combination therapy) or adopting biopsy strategies to ensure all tumors contain the target of interest (eg, recurrent biopsies, biopsies of primary and metastatic disease, “liquid biopsy”).

Lack of Access to Novel Targeted Therapies

Relatively small numbers of patients with rare or difficult-to-treat pediatric malignancies, limited overlap with adult molecular targets, and safety concerns with off-label use of adult targeted therapies create challenges in obtaining novel targeted therapies for pediatric patients with cancer. In the United States, the Best Pharmaceuticals for Children Act attempts to address this by allowing off-patent use of drugs for pediatric conditions to assess safety and efficacy, which has improved access to developing agents in pediatric oncology.¹⁴¹ In addition, due to the Pediatric Research Equity Act, the FDA also has the authority to require testing of relevant drugs in the pediatric population during the drug development process and to accelerate approval of breakthrough drugs for first-in-human pediatric trials to evaluate potential utility.¹⁴¹ Increasing collaboration with industry and the development of “basket trials” may further increase access to molecular testing and investigational treatments.

Cost

Prior sequencing studies in pediatric oncology illustrated the high cost associated with precision oncology, which ranges from \$6000 to \$8000 per sample for whole exome and transcriptome sequencing.^{142,143} In addition to the cost of targeted therapy itself, the cost of tumor sample preparation, sequencing, and computational analysis all contribute to a potentially prohibitive cost. A comprehensive economic impact analysis of precision oncology in the pediatric population will be necessary to demonstrate an economic incentive for insurance company approval of molecular testing and targeted therapies.

Logistics

Although the framework for an optimal nationwide pediatric precision oncology program is still under development, current examples such as the US Pediatric MATCH trial and the European AcSe-ESMART trial demonstrate promising frameworks for clinical application. Although prior discovery sequencing studies observed lengthy turnaround times (ie, biopsy to matched therapy initiation), with data analysis alone taking up to 4 weeks, infrastructure development at participating centers, use of uniform genomic panels, and integrating data analysis with treatment matching has the potential to streamline this process further.

Ethical Impact of Incidental Germline Mutations

The ethical impact of identifying incidental germline mutations is also a key consideration to any form of genetic testing. Challenges may arise such as the interpretation of variants of unknown significance and genetic mutations that are potentially attributed to another genetic condition (ie, non-oncogenic). In addition, up to 80% of parents have expressed not wanting to receive the results of incidental germline mutations.¹⁴² Thus, genetic counselor involvement before tissue biopsy should be strongly considered, as well as an opt-in disclosure system for any identified incidental germline mutations.

SURGICAL CONSIDERATIONS

Potential Complications with Targeted Therapies

With the expanding use of novel targeted therapies in pediatric oncology, surgeons should also become familiar with the potential perioperative complications and adverse events requiring surgical intervention that are associated with targeted therapies. These include impaired healing, spontaneous gastrointestinal (GI) perforation, and increased bleeding risk.

Impaired wound healing has been previously reported with the use of anti-angiogenic agents (bevacizumab), TKIs (cabozantinib, pazopanib), and mTOR inhibitors (sirolimus). Bevacizumab was found to be associated with a major wound complication rate of 20% after soft tissue sarcoma resection. Thus, it is recommended to discontinue use for greater than 28 days pre- and post-elective surgery to allow for wound healing.¹⁴⁴ Owing to similar concerns regarding impaired wound healing, TKIs also have recommendations which vary depending on the drug itself (eg, discontinue pazopanib 1 week pre- and 2 weeks post-surgery).¹⁴⁵ Although rates of wound complications with mTOR inhibition have been reported in up to 53% of transplant cases, perioperative dose reduction (ie, omit loading dose) has been shown to reduce rates down to 7% to 8%.¹⁴⁶ Thus, knowledge of these agents and mitigating measures are important during the perioperative management of both elective and emergency cases.

In addition to impaired wound healing, increased risk for major bleeding events and spontaneous GI perforation have been associated with anti-angiogenic agents and TKIs. Systematic review of anti-angiogenic agents (bevacizumab, ramucirumab) demonstrated a significantly increased relative risk for all-grade bleeding events (RR 2.38) and high-grade bleeding events (RR 1.71) which is hypothesized to be secondary to the disruption of tumor vasculature and decreased renewal capacity of vascular endothelium.¹⁴⁷ These agents can also lead to GI perforation anywhere along the GI tract—with the stomach and colon occurring most frequently—at rates of 2% to 3% with bevacizumab.¹⁴⁵ TKIs have also been associated with GI fistula formation with tracheoesophageal fistula occurrence in 4% of patients on cabozantinib and an increased risk in patients on concomitant anti-angiogenic agents, steroids, nonsteroidal anti-inflammatory drugs, or with prior history of peptic ulcer disease.^{145,148} Therefore, although relatively uncommon, these serious adverse events are significant in a patient population with existing low physiologic reserve and require emergent surgical care to decrease subsequent morbidity and mortality.

Impact of Precision Oncology on Perioperative Management

Despite the risks of novel targeted therapies, pediatric precision oncology is a promising field with the potential to decrease surgical morbidity by shrinking tumors, as well as improving survival in difficult-to-treat and rare pediatric cancers. As precision oncology programs are implemented, the decisions surrounding when and how to obtain tumor samples for sequencing are important surgical considerations. Although most precision oncology programs agree that tumor samples should be obtained for recurrent or refractory disease, additional tissue may also be required for routine sequencing at the time of diagnosis or due to potential spatial heterogeneity of the tumor itself. Thus, the timeline and approach to surgical biopsy are key considerations in the implementation of precision oncology programs.

The timing of surgery, with regard to targeted therapy use, is also an evolving subject as few drugs have defined recommendations for discontinuation in the perioperative period. Thus, close collaboration with oncologists is paramount during surgical

planning, case scheduling, and preoperative counseling in order to safely minimize the time spent off of systemic therapy. As pediatric precision oncology rapidly develops into a clinical reality, surgeons will continue to be significant stakeholders in the care of these patients.

FUTURE DIRECTIONS

Detection of Circulating Tumor DNA (“Liquid Biopsy”)

When cancer cells undergo apoptosis or necrosis, the fragmented tumor DNA released into the bloodstream may be used as a biomarker to identify tumor recurrence, monitor treatment response, and evaluate the mutational burden.¹⁴⁹ Detection of this circulating tumor DNA (ctDNA) via peripheral blood sampling has been aptly termed “liquid biopsy.” As evolving biopsy strategies in precision oncology rely on recurrent tumor biopsies for molecular profiling and identification of actionable targets, “liquid biopsy” technology provides a promising alternative to the disadvantages associated with conventional biopsy methods (eg, procedural complications, anesthesia ± radiation exposure, pain, inpatient admission). Although its use remains limited, the FDA-approved Foundation One Liquid CDx has been used to evaluate molecular alterations in children with recurrent or refractory cancers. In 45 children, the median time to results was 13 days with targets identified in 56% of samples (eg, *TP53*, *EWS-FLI1*, *ALK*, and *MYC*) and six patients receiving targeted therapy based on these results.¹⁵⁰ Ongoing studies aim to use ctDNA to evaluate treatment response and monitor for disease recurrence or early metastasis.^{151,152}

Combining Targeted Therapies

Owing to the complex resistance mechanisms of treatment-refractory pediatric cancers, prior targeted therapy trials have demonstrated poor efficacy with use of monotherapy. Thus, current trials aim to combine targeted therapy with cytotoxic chemotherapy. Combining targeted therapies based on identified targets or aberrant tumorigenic pathways is an approach that has been successful in adult precision oncology^{153,154} but is currently being explored in the pediatric population. The INFORM2 study (NCT03838042) is evaluating nivolumab (anti-PD1) and entinostat (HDAC inhibitor) to treat refractory pediatric tumors with high PD-L1 expression and focal MYCN amplification. Dual ICI use is also being actively explored in the Pediatric MATCH “basket trial.” Given its success in adult oncology, the future of pediatric precision oncology will likely use multiple targeted therapies, in addition to cytotoxic chemotherapy, in the fight against deadly treatment-refractory disease.

SUMMARY

Pediatric precision oncology is a rapidly developing approach to personalized cancer care with the overarching goals of improving survival and minimizing the morbidity associated with existing therapies. Although ongoing large-scale Phase II clinical trials provide the framework for future clinical implementation, innovative biopsy strategies, advances in sequencing and bioinformatics technology, and increased understanding of targetable mutations/pathways will contribute to its realization. As this develops, pediatric surgical oncologists will be vital stakeholders with key considerations regarding biopsy strategies, timing and extent of surgical resection, and management of immunotherapy-related surgical complications. Multidisciplinary collaboration with oncology, radiology, medical genetics, and pharmacy will be essential in the establishment of pediatric precision oncology programs, which will ultimately provide an avenue of hope for patients with difficult-to-treat or rare pediatric malignancies.

CLINICS CARE POINTS

- Pediatric malignancies harbor low rates of somatic mutations compared with the adult population.
- The use of multiple genetic profiling methods (NGS, RNAseq, proteomics) has allowed for molecular tumor risk stratification and identification of clinically actionable targets.
- Ongoing large-scale “basket trials” (eg, National Cancer Institute–Children’s Oncology Group Pediatric MATCH) allocate treatment based on molecular alteration and provide a framework for clinical implementation of pediatric precision oncology.
- Current targeted therapies target cell surface markers (eg, anti-GD2 immunotherapy, immune checkpoint inhibitors) or dysregulated tumorigenic pathways (eg, multi-kinase inhibitors, mammalian target of rapamycin inhibitors).

Targeted therapies (anti-angiogenic agents, tyrosine kinase inhibitors) associated with impaired wound healing, increased bleeding, and spontaneous gastrointestinal perforation.

- Future research focuses on improving biopsy strategies (eg, “liquid biopsy”) and combining targeted therapies to improve efficacy in treatment-refractory tumors.

DISCLOSURE

The authors have nothing to disclose.

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