Childhood Cancer Data Initiative Webinar Series

Pre-clinical Evaluation of Targeted Therapies for Pediatric Cancer

Carol J. Bult, Ph.D. & Malcolm A. Smith, M.D., Ph.D.

NIH NATIONAL CANCER INSTITUTE

May 13, 2025

Today's Speakers

Carol J. Bult, Ph.D.
Professor and Knowlton Family Chair at the Jackson Laboratory & Principal Investigator at the PIVOT Coordinating Center

Malcolm A. Smith, M.D., Ph.D.
Associate Branch Chief, Pediatric Oncology at the National Cancer Institute & Program Director for PIVOT

Pediatric Cancers Are Rare

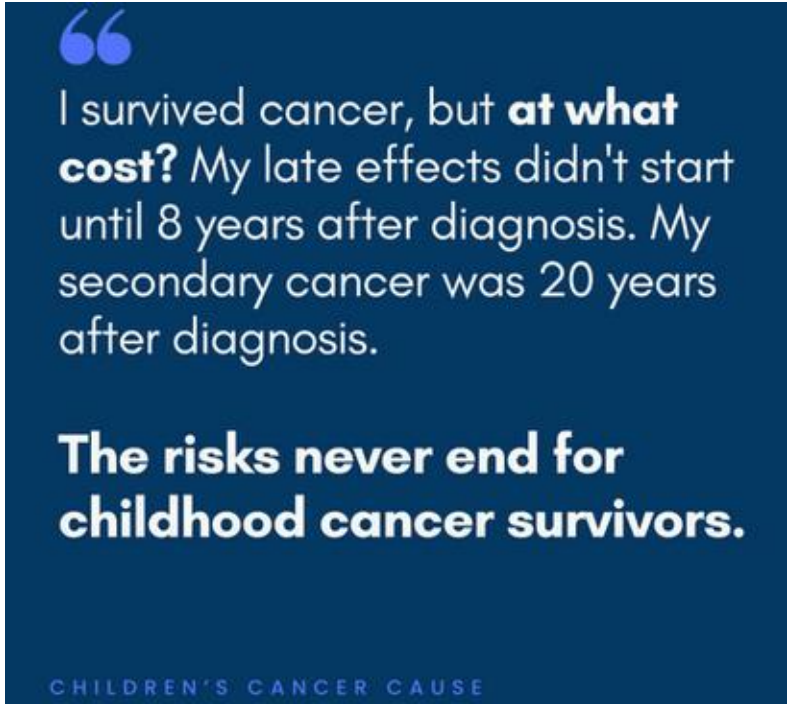
- 1 in 6,500 children and adolescents (under 20) diagnosed with cancer annually in the U.S.
- Leading cause of death by disease in children >1 year old (in U.S.)

Survival has improved significantly over the years

- Current 5-year survival following cancer diagnosis is ~85%
- ~500,000 survivors of childhood and adolescent cancer alive today in the US

https://www.cancer.org/cancer/types/cancer-in-children/key-statistics.html

https://www.cancer.gov/types/childhood-cancers/child-adolescent-cancers-fact-sheet



60% to more than 90% of survivors develop one or more chronic health conditions

https://www.cancer.gov/types/childhood-cancers/late-effects-hp-pdq#:~:text=20%25%20to%2080%25%20of%20survivors,life%2Dthreatening%20complications%20during%20adulthood

https://www.childrenscancercause.org/2023-survey-results

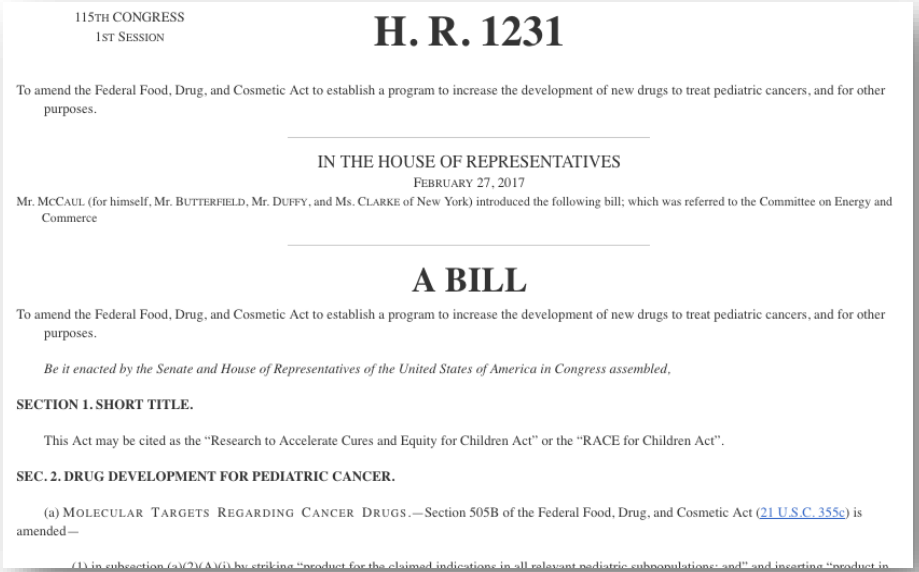
Molecularly Targeted Pediatric Cancer Treatment Options Are Limited

Challenges

- Large number of candidate agents
- Small number of patients
- Multiple cancer subtypes

https://www.aacr.org/blog/2023/04/28/annual-meeting-2023-the-past-present-and-future-of-targeted-therapies-for-pediatric-cancer/

Research to Accelerate Cures and Equity (RACE) for Children Act



115TH CONGRESS
1ST SESSION

H. R. 1231

To amend the Federal Food, Drug, and Cosmetic Act to establish a program to increase the development of new drugs to treat pediatric cancers, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES
FEBRUARY 27, 2017

Mr. MCCAUL (for himself, Mr. BUTTERFIELD, Mr. DUFFY, and Ms. CLARKE of New York) introduced the following bill; which was referred to the Committee on Energy and Commerce

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to establish a program to increase the development of new drugs to treat pediatric cancers, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Research to Accelerate Cures and Equity for Children Act" or the "RACE for Children Act".

SEC. 2. DRUG DEVELOPMENT FOR PEDIATRIC CANCER.

(a) MOLECULAR TARGETS REGARDING CANCER DRUGS.—Section 505B of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355c) is amended—

2017, enacted in August 2020

2007-2017[1]

- 78 adult cancer drugs approved by FDA
- 17 (21.8%) drugs received pediatric labeling information

…modern cancer drugs target molecular pathways that may be shared by pediatric and adult cancers.[2]

[1]Hwang et al. 2019. J Natl Cancer Inst 112(3):224–228
[2]Liu et al., 2024. Pediatrics

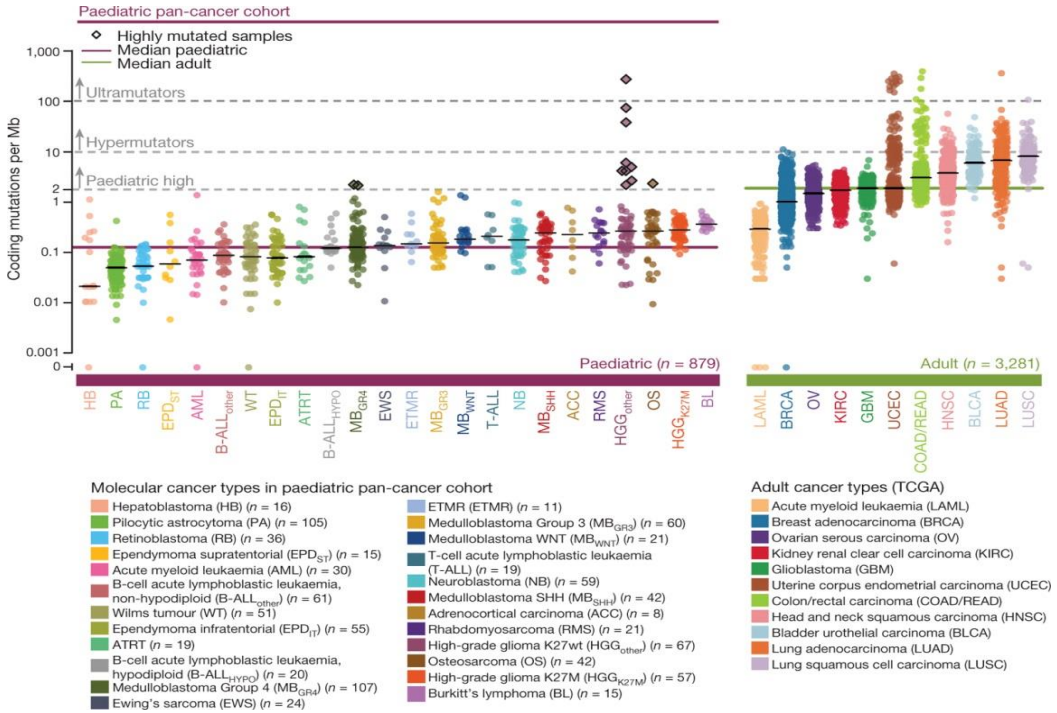
~200 Molecular Targets with Relevance to Pediatric Cancer

CATEGORY	TARGET	GENE/PATHWAY ALTERATION
A) Gene Abnormality	ABL1, ABL2	ABL1/ABL2 gene fusions (BCR-ABL1, etc.)
A) Gene Abnormality	ACVR1	ACVR1
A) Gene Abnormality	ALK	ALK and ALK gene fusions
A) Gene Abnormality	ASCL1	ASCL1
A) Gene Abnormality	BRAF	BRAF and BRAF gene fusions
A) Gene Abnormality	CCND1, CCND2	CCND1, CCND2
A) Gene Abnormality	CDK12	EWSR1-FLI1
A) Gene Abnormality	CSF1R	CSF1R gene fusions
A) Gene Abnormality	CTNNB1	CTNNB1
A) Gene Abnormality	DDX3X	DDX3X
A) Gene Abnormality	DOT1L	KMT2A (MLL) gene fusions
A) Gene Abnormality	EED	EED
A) Gene Abnormality	EGFR	EGFR
A) Gene Abnormality	ETS gene fusions	ETS gene fusions (ERG, FLI1, ETV1)
A) Gene Abnormality	EWSR1-FLI1	EWSR1-FLI1
A) Gene Abnormality	EZH2	SMARCB1, SMARCA4
A) Gene Abnormality	FGFR	FGFR and FGFR gene fusions
A) Gene Abnormality	FLT3	FLT3
A) Gene Abnormality	Gamma secretase	NOTCH1, FBXW7
A) Gene Abnormality	GFI1	GFI1
A) Gene Abnormality	GFI1B	GFI1B
A) Gene Abnormality	Histone H3	H3K27M, H3G34R/V
A) Gene Abnormality	IDH1	IDH1
A) Gene Abnormality	IDH2	IDH2
A) Gene Abnormality	JAK1, JAK2, JAK3	JAK1, JAK2, JAK3
A) Gene Abnormality	KIT	KIT
A) Gene Abnormality	KMT2A (MLL)	KMT2A (MLL) gene fusions (KMT2A-AFF1
A) Gene Abnormality	LIN28B	LIN28B
A) Gene Abnormality	MAP2K1 (MEK1), MAP2K2 (MEK2)	BRAF and BRAF gene fusions, MAP2K1,
A) Gene Abnormality	MAPK3 (ERK1), MAPK1 (ERK2)	BRAF, MAP2K1
A) Gene Abnormality	MDM2	MDM2, TP53
A) Gene Abnormality	MEN1 (menin)	KMT2A (MLL) gene fusions
A) Gene Abnormality	MET	MET and MET gene fusions
A) Gene Abnormality	MTOR	TSC1, TSC2

https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

https://vagabondnetwork.com/blog/pediatric-vs-adult-cancers-why-are-children-not-just-small-adults/

Genomes of Pediatric and Adult Cancers Have Different Properties

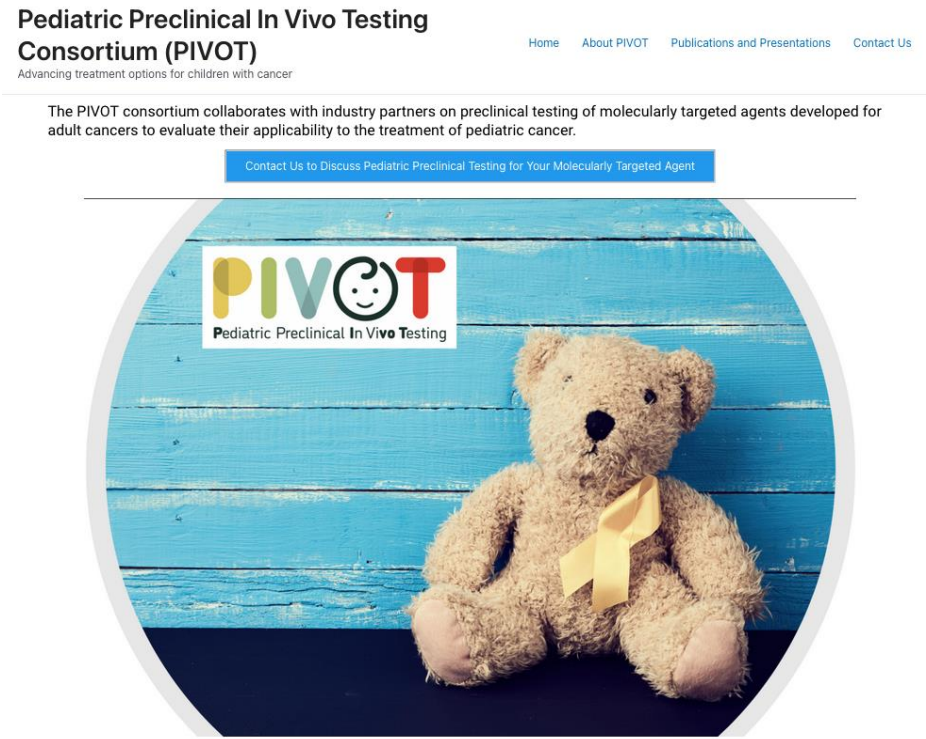


S N Gröbner *et al. Nature* **555**, 321–327 (2018) doi:10.1038/nature25480

PIVOT Program

NCI Pediatric Preclinical in Vivo Testing Program

A program funded by the National Cancer Institute of the National Institutes of Health



https://preclinicalpivot.org/

- **2004-2014**
  Pediatric Preclinical Testing Program (PPTP)
- **2015-2021**
  Pediatric Preclinical Testing Consortium (PPTC)
- **2022-**
  Pediatric Preclinical In Vivo Testing (PIVOT)

PIVOT Consortium Members

Coordinating Center

The Jackson Laboratory
Leading the search for tomorrow's cures

Carol J. Bult, PhD
Jeff H. Chuang, PhD
Emily Jocoy, PhD

Sarcomas, Kidney, Liver

UT Health San Antonio
Greehey Children's Cancer Research Institute

Peter J. Houghton, PhD
Raushan Kurmasheva, PhD

Neuroblastoma

The Children's Hospital *of* Philadelphia®

Yael Mossé, MD
John M. Maris, MD

Childhood Leukemia

Children's Cancer Institute

Richard Lock, PhD

Brain Tumors

Ann & Robert H. Lurie Children's Hospital of Chicago®

Xiao-Nan Li, MD, PhD

Osteosarcoma

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Children's Cancer Hospital®

Richard G. Gorlick, MD

Soft Tissue Sarcomas

St. Jude Children's Research Hospital
Finding cures. Saving children.

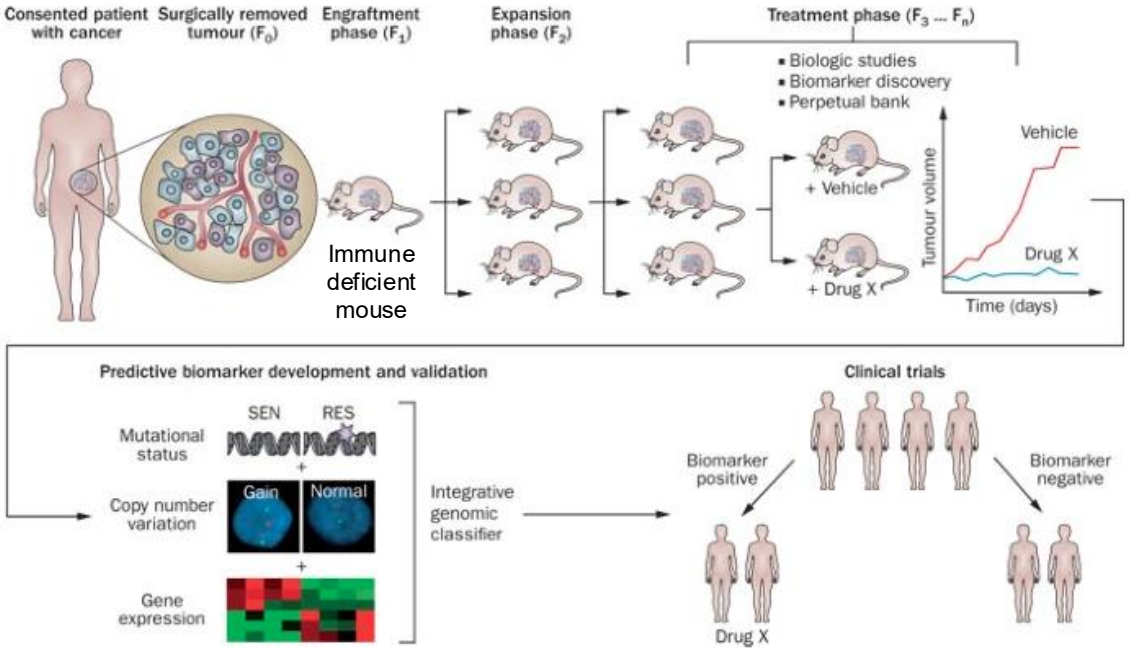
Michael A. Dyer, PhD
Elizabeth Stewart, MD

Sarcomas, Kidney, Rare Tumors

1884
Memorial Sloan Kettering Cancer Center

Andrew Kung, MD, PhD
Filemon Dela Cruz, MD

PIVOT Uses Patient Derived Xenografts (PDXs) as Preclinical Models



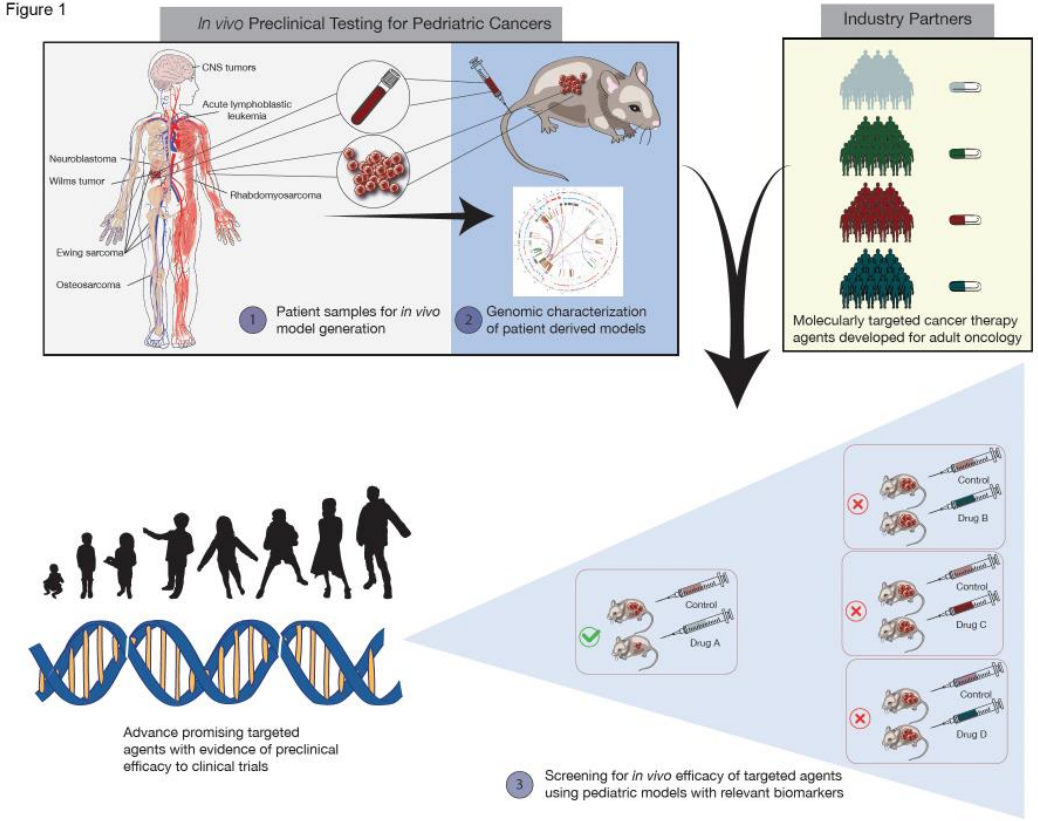
Tentler *et al*. 2012. *Nat Rev Clin Oncol* 9, 338–350.

Key Features of PIVOT

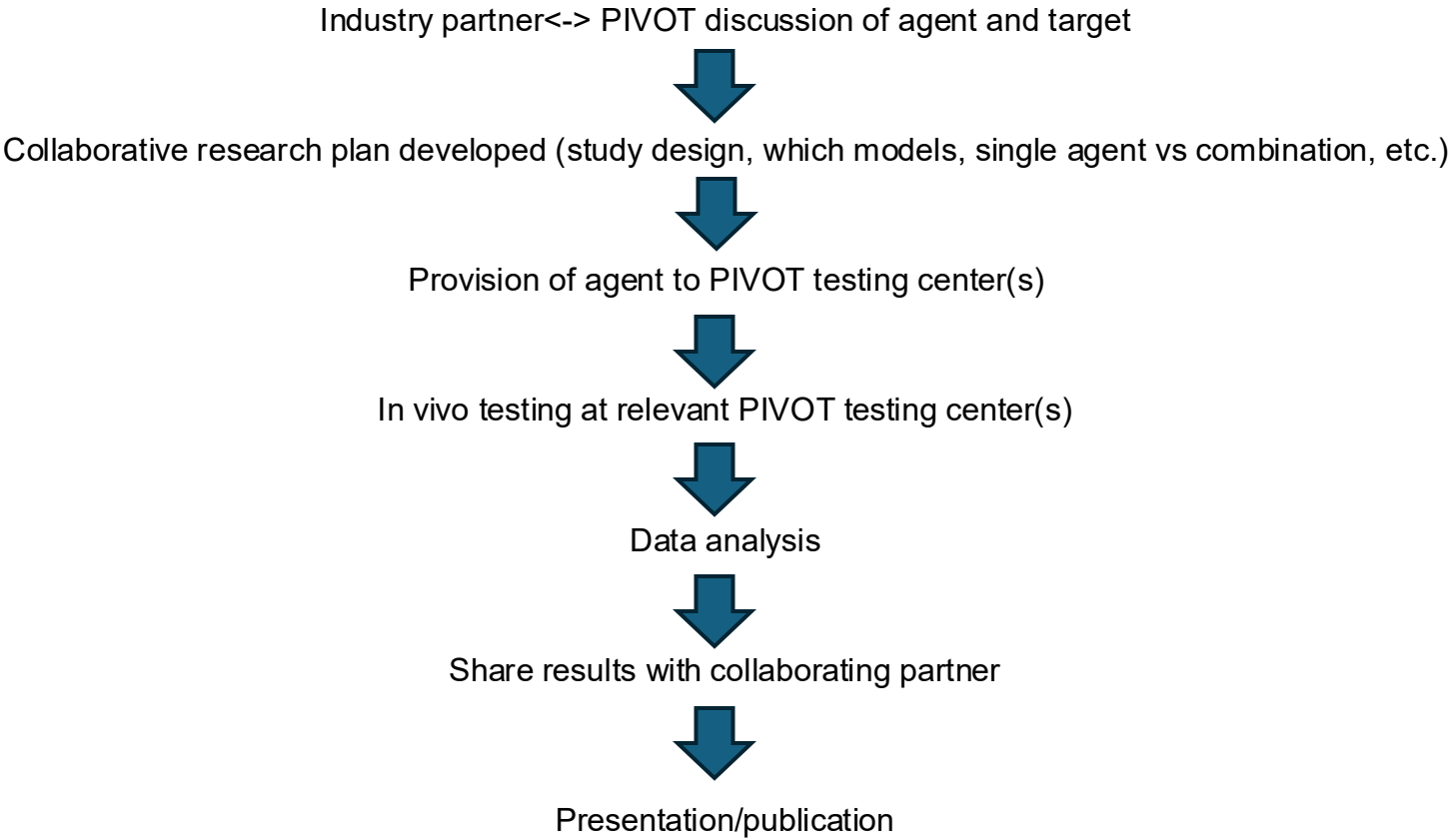
PIVOT
Pediatric Preclinical In Vivo Testing

- Testing is performed by seven highly qualified research programs that focus on specific childhood cancers
  - Agent provided by industry partner
  - No cost to the industry partner for testing
  - Collaboration model with presentation/publication of results expected
- PIVOT Coordinating Center at The Jackson Laboratory coordinates studies with industry partners and testing centers and performs data management/analysis for the consortium
- NCI provides scientific, technical, and regulatory assistance, advice, and oversight
  - The NCI Program Director for PIVOT is Dr. Malcolm Smith, Cancer Therapy Evaluation Program (CTEP)
  - Dr. Beverly Teicher is the NCI representative on the PIVOT Steering Committee

Figure 1

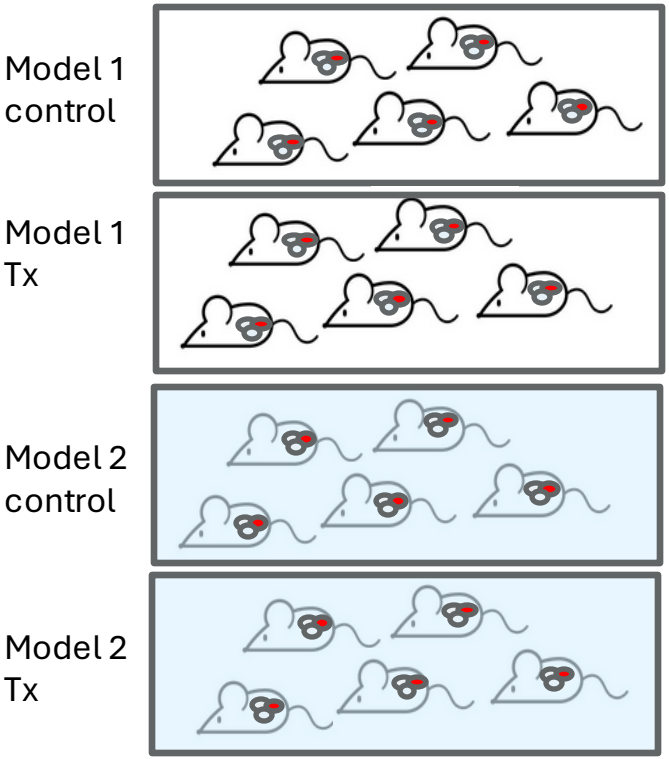

In vivo Preclinical Testing for Pediatric Cancers
CNS tumors
Acute lymphoblastic leukemia
Neuroblastoma
Wilms tumor
Rhabdomyosarcoma
Ewing sarcoma
Osteosarcoma
1 Patient samples for in vivo model generation
2 Genomic characterization of patient derived models
Industry Partners
Molecularly targeted cancer therapy agents developed for adult oncology
Advance promising targeted agents with evidence of preclinical efficacy to clinical trials
Control
Drug A
Drug B
Drug C
Drug D
3 Screening for in vivo efficacy of targeted agents using pediatric models with relevant biomarkers

General PIVOT Workflow

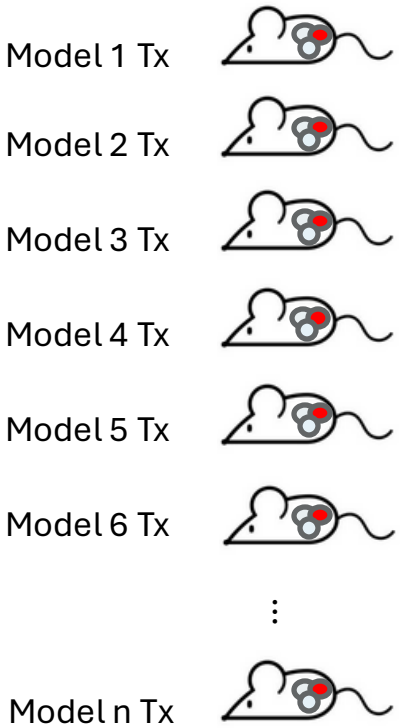


Experimental Design

Cohort design
Fewer models, more animals per model



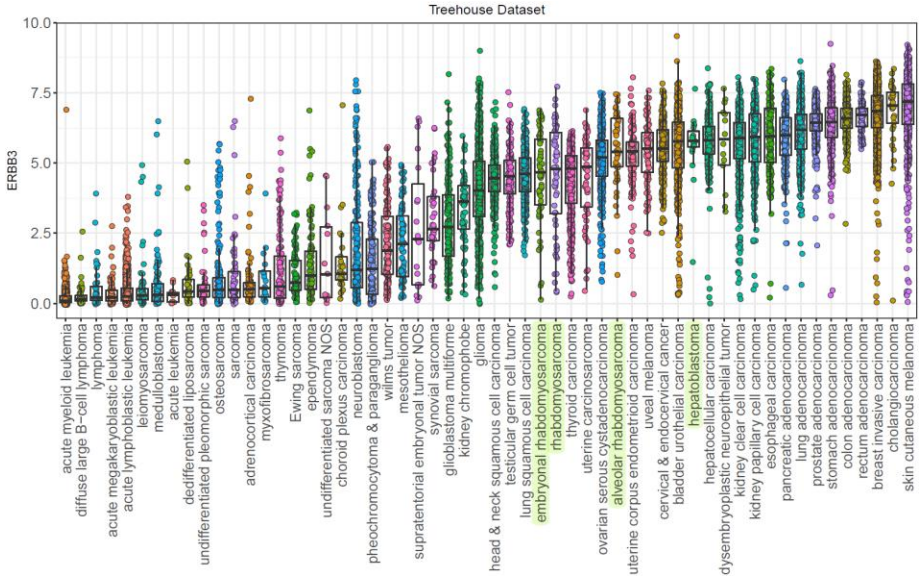
Single mouse trial (SMT)
More models, fewer mice per model



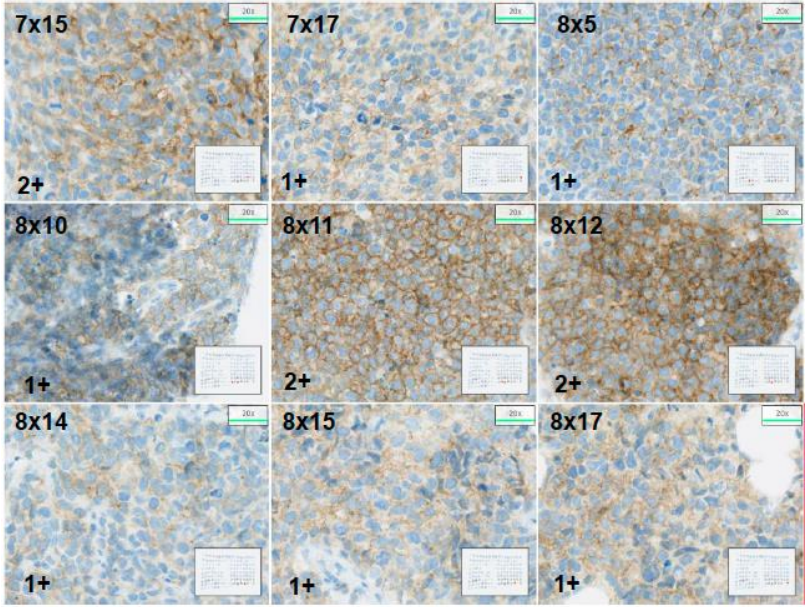
Tumor

Model Selection

Gene expression for *ERBB*3 (aka *HER3*)



IHC for *ERBB*3 on PDX sarcoma tumors



Data from Treehouse Childhood Cancer Initiative

Presented at AACR 2023

Evaluating and Classifying Treatment Response

Solid tumors

- Event = 4X tumor volume from day 0
- Event Free Survival (EFS)
- Relative tumor volume change (RTV)

Blood cancers

- Event = >25% huCD45+ cells in peripheral blood
- Event Free Survival (EFS)
- % HuCD45 in blood cancers

ORM	ORM Code	Criteria
Progressive Disease	PD	**< 50%** tumor regression **throughout** study **> 25%** tumor growth at **end of study**
Progressive Disease 1	PD1	**PD** the mouse's **time-to-event ≤ 200%** the **median time-to-event in control group**
Progressive Disease 2	PD2	**PD** the mouse's **time-to-event is > 200%** the **median time-to-event in control group**
Stable Disease	SD	**< 50%** tumor regression **throughout** study **≤ 25%** tumor growth at **end of study**
Partial Response	PR	**≥ 50%** tumor regression at **any point during study** but **measurable tumor** throughout study period
Complete Response	CR	**disappearance** of measurable tumor mass during the study period
Maintained Complete Response	MCR	**no measurable tumor mass** for at **least 3 consecutive weekly** readings at any time after treatment has been completed

Houghton et al. 2007. Pediatric Blood and Cancer 49(7):928-940

Tumor Regression, Not Slowing of Tumor Growth, Is PIVOT's Definition of an Active Agent

Objective Response Rate (ORR) Categories

1. Maintained Complete Response (MCR),
2. Complete Response (CR), and
3. Partial Response (PR)

Progressive Disease Categories

1. Progressive disease 1 (PD1): less than 2-fold prolongation to time of event
2. Progressive disease 2 (PD2): greater than 2-fold prolongation in time to event relative to vehicle controls

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journal homepage: www.elsevier.com/locate/pharmthera

Lessons learned from 20 years of preclinical testing in pediatric cancers

Malcolm A. Smith [a,*], Peter J. Houghton [b], Richard B. Lock [c], John M. Maris [d], Richard Gorlick [e], Raushan T. Kurmasheva [b], Xiao-Nan Li [f], Beverly A. Teicher [a], Jeffrey H. Chuang [g], Filemon S. Dela Cruz [h], Michael A. Dyer [i], Andrew L. Kung [h], Michael W. Lloyd [j], Yael P. Mossé [d], Timothy M. Stearns [j], Elizabeth A. Stewart [i], Carol J. Bult [j], Stephen W. Erickson [k]

https://pubmed.ncbi.nlm.nih.gov/39510293/

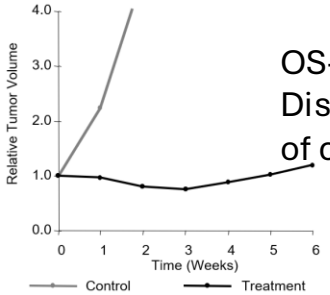
Lesson 1:

VEGF pathway inhibitors slow tumor growth but rarely cause objective responses in pediatric preclinical models, consistent with their clinical effect

VEGF Pathway Inhibitors

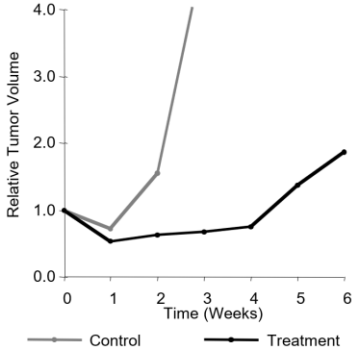
in vivo testing of multiple VEGF pathway inhibitors
(cediranib, sunitinib, sorafenib, pazopanib, regorafenib, cabozantinib)

Xenograft Line	Histology	Response (Median Score)	Midpoint Difference	Overall Group Response	Heat Map
BT-29	Rhabdoid	2.0	-3.0	PD2	
KT-16	Rhabdoid	8.0	3.0	CR	
KT-14	Rhabdoid	2.0	-3.0	PD2	
KT-10	Wilms	5.0	0.0	SD	
KT-11	Wilms	0.0	-5.0	PD1	
KT-13	Wilms	2.0	-3.0	PD2	
SKNEP	Ewings/Kidney	2.0	-3.0	PD2	
EW5	Ewings	2.0	-3.0	PD2	
EW8	Ewings	2.0	-3.0	PD2	
Rh28	ALV Rhabdomyosarcoma	2.0	-3.0	PD2	
Rh30	ALV Rhabdomyosarcoma	2.0	-3.0	PD2	
Rh30R	ALV Rhabdomyosarcoma	2.0	-3.0	PD2	
Rh41	ALV Rhabdomyosarcoma	2.0	-3.0	PD2	
Rh18	EMB Rhabdomyosarcoma	2.0	-3.0	PD2	
BT-28	Medulloblastoma	0.0	-5.0	PD1	
BT-45	Medulloblastoma	2.0	-3.0	PD2	
BT-46	Medulloblastoma	0.0	-5.0	PD1	
GBM2	Glioblastoma	1.0	-4.0	PD1	
BT-39	Glioblastoma	0.0	-5.0	PD1	
D645	Glioblastoma	2.0	-3.0	PD2	
D456	Glioblastoma	2.0	-3.0	PD2	
NB-SD	Neuroblastoma	2.0	-3.0	PD2	
NB-1771	Neuroblastoma	2.0	-3.0	PD2	
NB-1691	Neuroblastoma	0.0	-5.0	PD1	
NB-EBc1	Neuroblastoma	2.0	-3.0	PD2	
CHLA-79	Neuroblastoma	2.0	-3.0	PD2	
NB-1643	Neuroblastoma	2.0	-3.0	PD2	
OS-1	Osteosarcoma	2.0	-3.0	PD2	
OS-2	Osteosarcoma	0.0	-5.0	PD1	
OS-17	Osteosarcoma	8.0	3.0	CR	
OS-33	Osteosarcoma	4.0	-1.0	SD	
OS-31	Osteosarcoma	2.0	-3.0	PD2	
ALL-2	ALL B-precursor	0.0	-5.0	PD1	
ALL-3	ALL B-precursor	1.0	-4.0	PD1	
ALL-4	ALL B-precursor	1.0	-4.0	PD1	
ALL-7	ALL B-precursor	0.0	-5.0	PD1	
ALL-8	ALL T-cell	1.0	-4.0	PD1	
ALL-17	ALL B-precursor	0.0	-5.0	PD1	
ALL-19	ALL B-precursor	0.0	-5.0	PD1	



OS-33 "Stable Disease" to 6 weeks of cediranib

KT-10 "PD2" response with slowing of tumor growth



Maris JM, *et al*: *Pediatr Blood Cancer* 2008, **50**(3):581-587

Low ORR for in vivo testing of multiple VEGF pathway inhibitors. Tumor growth delay, but not regression for this class of agents

Mirrors responses seen in clinical trials

	Solid Tumor		Acute Lymphoblastic Leukemia	
	VEGFR2-Targeted	Non-VEGFR2-Targeted	VEGFR2-Targeted	Non-VEGFR2-Targeted
Models tested	158	2328	24	863
ORR	4%	16%	8%	38%
CR/MCR%	1%	10%	0%	30%
PD2%	41%	12%	13%	8%
PD1%	47%	65%	79%	33%
Total PD%	94%	81%	92%	60%

Lesson 2:

Agents targeted to specific gene products (e.g., mutated kinases) rarely cause regressions in the absence of specific genomic alterations associated with sensitivity to the agent

Agents that target specific genomic alterations can be effective if the specific lesion is present

Agent	Agent Target	# Tested	Objective Response Rate	Responsive Models
Dasatinib	BCR::ABL1	43	2%	*BCR::ABL1* ALL
Sunitinib	VEGFR2 & FLT3	45	9%	*FLT3*-mutated ALL
Selumetinib	MEK	46	4%	*BRAF* V600E mutated glioma
VTP-50469	Menin-KMT2A	16	38%	*KMT2A*-rearranged infant ALL
Talazoparib	PARP	44	7%	*PALB2*-mutant Wilms tumor

Agents that target specific genomic alterations are generally ineffective if the specific lesion is present

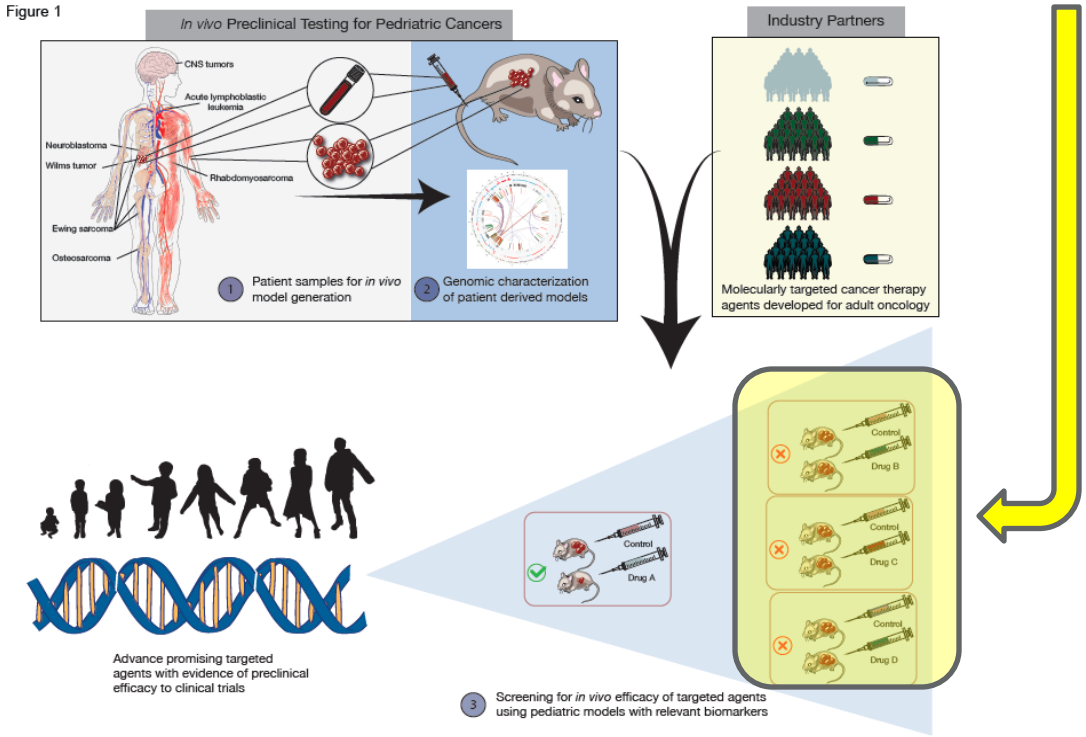
Agent	Agent Target	# Tested	Objective Response Rate	Responsive Models
Dasatinib	BCR::ABL1	43	2%	*BCR::ABL1* ALL
Sunitinib	VEGFR2 & FLT3	45	9%	*FLT3*-mutated ALL
Selumetinib	MEK	46	4%	*BRAF* V600E mutated glioma
VTP-50469	Menin-KMT2A	16	38%	*KMT2A*-rearranged infant ALL
Talazoparib	PARP	44	7%	*PALB2*-mutant Wilms tumor

Lesson 3:

Many classes of targeted agents show limited tumor-regressing activity across a broad range of pediatric cancers as exemplified by HDAC, HSP90, and proteasome inhibitors

What Have We Learned?

Preclinical *de-prioritization* of targeted agents for pediatric oncology is key



Overall Response Rates Across ~100 Agents Tested in Diverse Solid Tumors and Leukemia Preclinical Models

	Total Models	Solid Tumor	Acute Lymphoblastic Leukemia
Models tested	3382	2486	887
ORR	21%	15%	37%
CR/MCR%	15%	9%	29%
PD2%	13%	14%	9%
PD1%	56%	64%	34%
Total PD%	76%	82%	61%

Many Tested Agents Were Ineffective Across Most Models

- HDAC, HSP90, and proteasome inhibitors had limited tumor-regressing activity across a broad range of pediatric solid tumors

	HSP90 Inhibitors		HDAC Inhibitors		Proteasome Inhibitors	
	Solid Tumor	Acute Lymphoblastic Leukemia	Solid Tumor	Acute Lymphoblastic Leukemia	Solid Tumor	Acute Lymphoblastic Leukemia
Models tested	75	20	73	15	33	16
ORR	3 %	5 %	1 %	13 %	6 %	25 %
CR/MCR%	1 %	0 %	1 %	13 %	0 %	13 %
PD2 %	8 %	30 %	10 %	7 %	3 %	0 %
PD1 %	85 %	55 %	86 %	73 %	91 %	75 %
Total PD%	97 %	85 %	99 %	80 %	94 %	75 %

Objective Response Measure (ORM) results are provided for three HSP90 inhibitors [alvespimycin (17-DMAG), onalespib (AT13387), and ganetespib (STA9090)], for three HDAC inhibitors [vorinostat, quisinostat (JNJ26481585), and entinostat] and for two proteasome inhibitors (bortezomib and ixazomib). See Table 1 for a description of the ORM categories. References to primary publications for each agent are provided in the text.

- These agents had potent in vitro activity across a range of cell lines
- These agents showed little clinical activity for both pediatric and adult non-hematological cancers

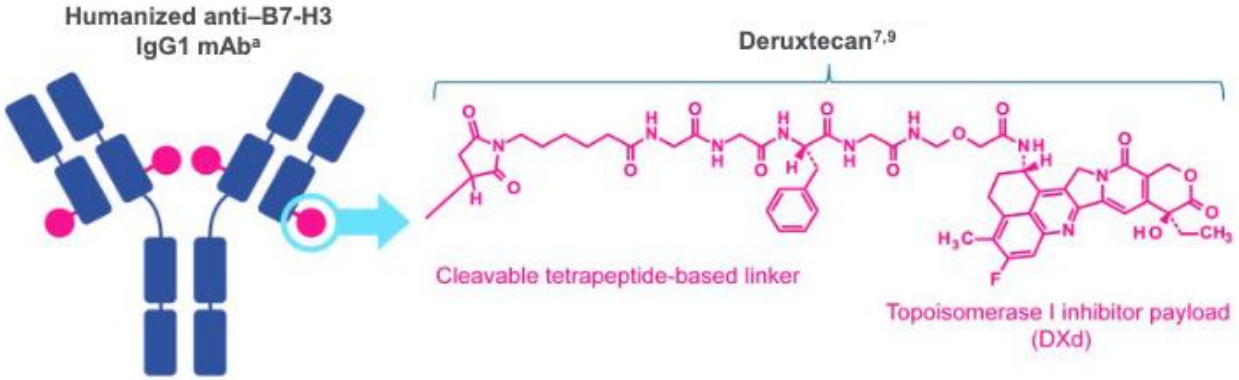
Lesson 4:

Antibody drug conjugates (ADCs) are often effective in preclinical models, but overprediction of activity occurs

Antibody Drug Conjugates (ADCs)

I-DXd B7-H3 (CD276) directed ADC
Ifinatamab Deruxtecan

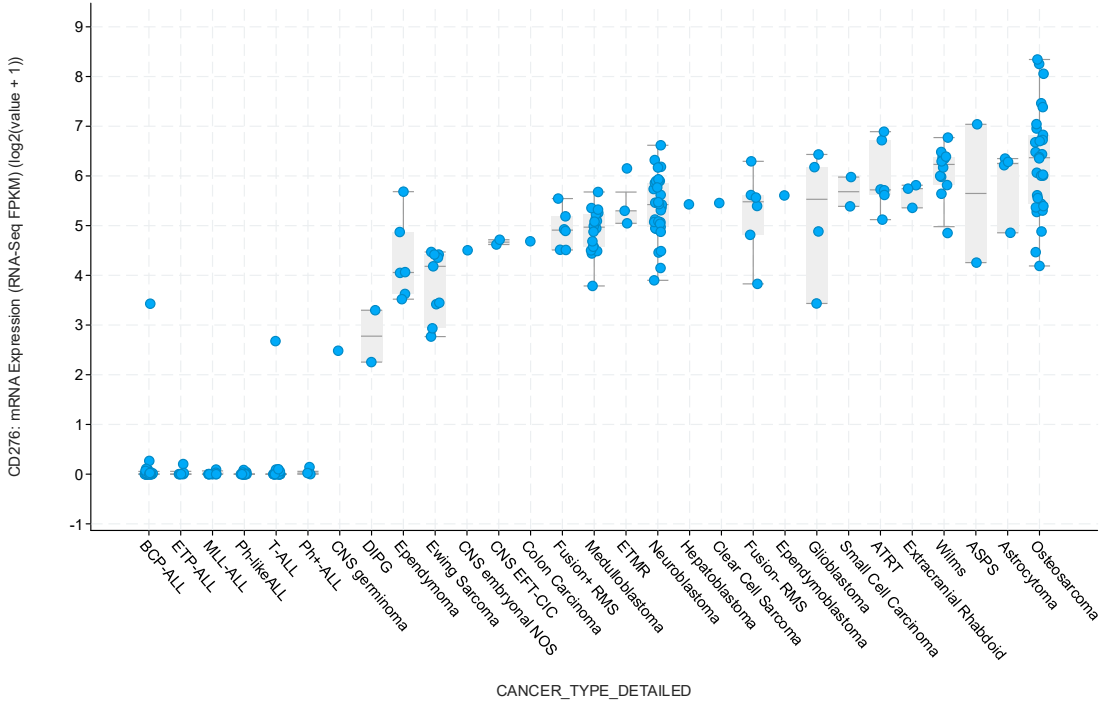
This agent has shown great promise for treating small cell lung cancer in adult patients



Antibody – Linker – Payload

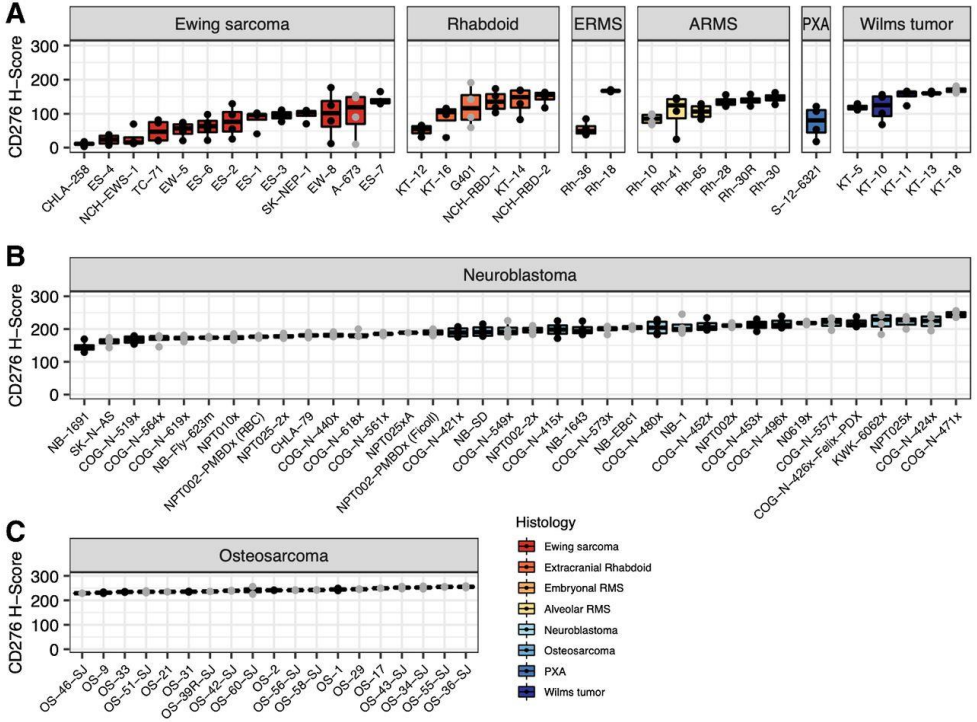
https://datasourcebydaiichisankyo.com/documents/14090001/14096298/WCLC-2023_I-DXd_Johnson_Oral_FINAL.pdf/dfc8673b-b3c3-9ed7-50d7-e48b4c9b3e5b

CD276 mRNA Is Highly Expressed in Diverse Pediatric Solid Tumors

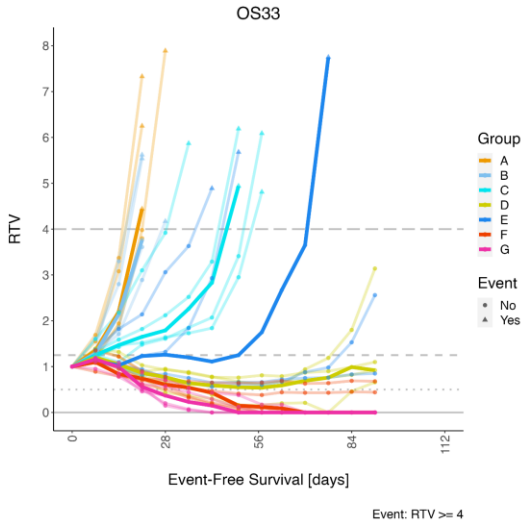


From cBioPortal

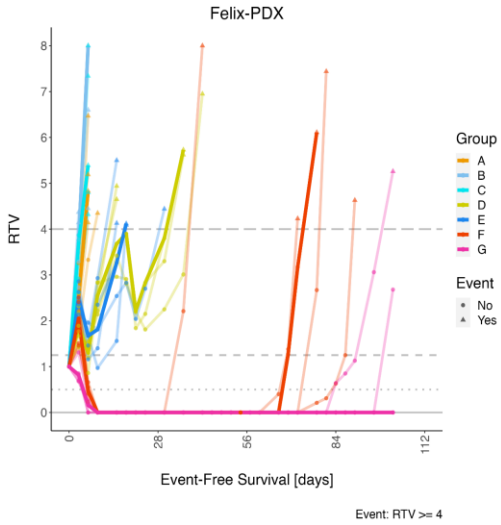
CD276 (B7-H3) Protein Is Highly Expressed in Diverse Pediatric Solid Tumors



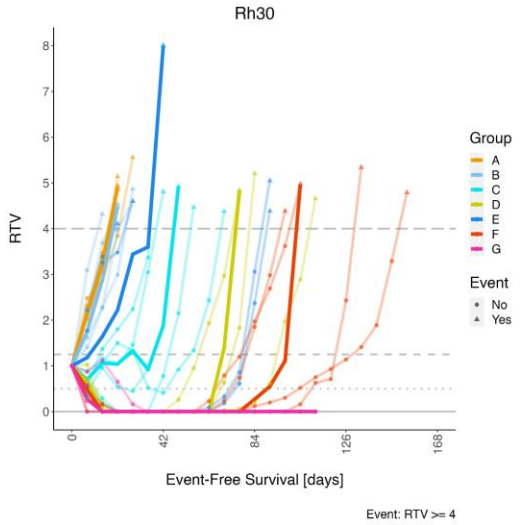
Kendsersky NM, *et al*: *Clin Cancer Res* 2021, **27**:2938-2946



Osteosarcoma



Neuroblastoma



Rhabdomyosarcoma

A: **Control (IV) vehicle, day1 and day15**
B: **Isotype control ADC (IV) 1mg/kg, day1 and day15**
C: **Isotype control ADC (IV) 3mg/kg, day1 and day15**
D: **Isotype control ADC (IV) 10mg/kg, day1 and day15**
E: **I-DXd (IV) 1mg/kg, day1 and day15**
F: I-DXd (IV) 3mg/kg, day1 and day15
G: **I-DXd (IV) 10mg/kg, day1 and day15**

Presented at AACR 2023

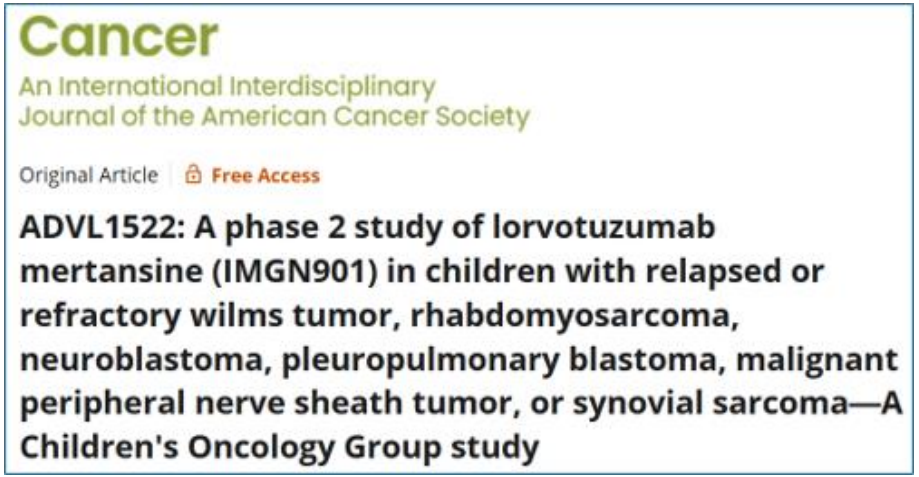
High ORR for In Vivo Testing of I-Dxd Dose-Dependent Response Shows Great Promise!

Model	Diagnosis	1 mg/kg		3 mg/kg		10 mg/kg	
		I-Dxd	IC-ADC	I-Dxd	IC-ADC	I-Dxd	IC-ADC
OS-9	Osteosarcoma	PD2	PD1	PR	PD1	MCR	PD1
OS-33	Osteosarcoma	PD2	PD1	MCR	PD1	MCR	SD
Felix	Neuroblastoma	PD2	PD1	MCR	PD1	MCR	PD2
COG-N-452X	Neuroblastoma	PD1	PD1	PD1	PD1	MCR	PD1
Rh30	Rhabdomyosarcoma	PD2	PD1	MCR	PD1	MCR	MCR
WT11	Wilms tumor	PD1	PD1	PD2	PD1	MCR	PD2

Antibody drug conjugates (ADCs) are often effective in preclinical models, but overprediction of activity occurs

Agent	Target	Tumor Types	Solid Tumor		Acute Lymphoblastic Leukemia	
			# Tested	ORR	# Tested	ORR
Coltuximab Ravtansine (SAR3419)	CD19	ALL	0	NA	3	100 %
Denintuzumab mafodotin (SGN-CD19A)	CD19	ALL	0	NA	7	71 %
Pivekimab sunirine (IMGN632)	CD123	ALL	0	NA	8	75 %
Zilovertamab vedotin (VLS-101)	ROR1	ALL, EWS	5	40 %	7	29 %
VLS-211	ROR1	ALL, EWS	5	60 %	7	43 %
Lorvotuzumab mertansine (IMGN901)	CD56	OS, RMS, NB, Rhabdoid, CNS, Wilms	25	36 %	0	NA
Glembatumumab vedotin (CDX-011)	GPNMB	OS, RMS	8	38 %	0	NA
Telisotuzumab vedotin (ABBV-399)	MET	RMS	4	0 %	0	NA
Samrotamab vedotin (ABBV-085)	LRRC15	OS	7	29 %	0	NA
Rovalpituzumab tesirine (Rova-T)	DLL3	NB	10	20 %	0	NA
ADCT-701	DLK1	NB	12	58 %	0	NA
Trastuzumab deruxtecan (DS-8201A)	HER2	OS, EWS, RMS, NB, Rhabdoid, Wilms	39	56 %	0	NA
m276-PBD	CD276 (B7-H3)	OS, EWS, RMS, NB, Rhabdoid, Wilms	59	93 %	0	NA
Vobramitamab duocarmazine (MGC018)	CD276 (B7-H3)	NB	10	30 %	0	NA
All Models Tested			**184**	**59 %**	**32**	**59 %**

The number of solid tumor and leukemia models studied as well as the objective response rates (ORR) are shown for ADCs studied by the PPTP/C for solid tumor models and for acute lymphoblastic leukemia (ALL) models. Abbreviations: OS, osteosarcoma; EWS, Ewing sarcoma; RMS rhabdomyosarcoma; CNS, central nervous system tumors; NB, neuroblastoma; NA, not applicable. References to primary publications for each agent are provided in the text.



Geller JI, *et al*: *Cancer* 2020, **126**(24):5303-5310

- Lorvotuzumab mertansine (110 mg/m^2 per dose ≈ 3 mg/kg) was administered intravenously on days 1 and 8 of 21-day cycles.
- Diagnoses included Wilms tumor (n = 17), rhabdomyosarcoma (n = 17), neuroblastoma (n = 12), synovial sarcoma (n = 10), MPNST (n = 5), and pleuropulmonary blastoma (n = 1).
- One patient with rhabdomyosarcoma had a partial response, and 1 patient with synovial sarcoma achieved a delayed complete response.

Why the Overprediction for Clinical Activity?

Clinical translation of antibody drug conjugate dosing in solid tumors from preclinical mouse data

Baron Rubahamya[1], Shujun Dong[1], Greg M. Thurber[1,2,3]*

Antibody drug conjugates (ADCs) have made impressive strides in the clinic in recent years with 11 Food and Drug Administration approvals, including 6 for the treatment of patients with solid tumors. Despite this success, the development of new agents remains challenging with a high failure rate in the clinic. Here, we show that current approved ADCs for the treatment of patients with solid tumors can all show substantial efficacy in some mouse models when administered at a similar weight-based [milligrams per kilogram (mg/kg)] dosing in mice that is tolerated in the clinic. Mechanistically, equivalent mg/kg dosing results in a similar drug concentration in the tumor and a similar tissue penetration into the tumor due to the unique delivery features of ADCs. Combined with computational approaches, which can account for the complex distribution within the tumor microenvironment, these scaling concepts may aid in the evaluation of new agents and help design therapeutics with maximum clinical efficacy.

Rubahamya B, Dong S, Thurber GM: *Sci Adv* 2024, **10**(22):eadk1894

See also: de Goeij BE, Lambert JM: *Curr Opin Immunol* 2016, **40**:14-23

Lorvotuzumab mertansine preclinical dose 45 mg/kg/3 weeks versus ~ 6 mg/kg/3 weeks clinical dose

Learning from False Positives

- Drug exposures in mice exceeding those tolerated in humans
- ADC dosing
- Cytotoxic agent dosing (e.g., PR-104, temozolomide, etc.)
  - PR-104: Houghton PJ, *et al*: *Pediatr Blood Cancer* 2011, **57**(3):443-453
  - Temozolomide: Keir ST, *et al*: *Pediatr Blood Cancer* 2013, **60**(5):783-790
- Mitotic kinases

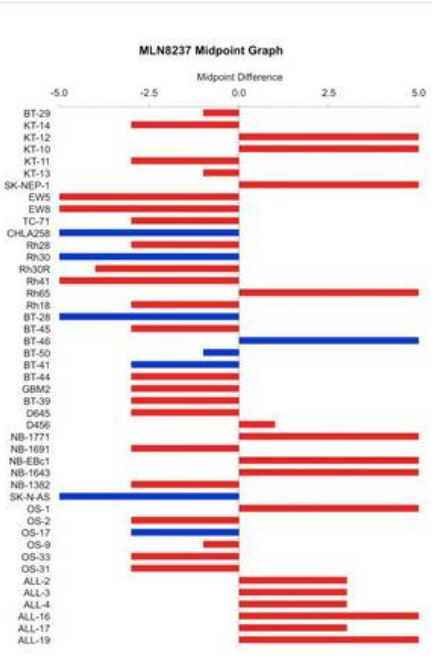
Lesson 5:

PDX models overpredict for activity of mitotic kinase inhibitors, which is likely a result of faster cell cycling times in PDX models compared to patient tumors

Mitotic Kinase Inhibitors

in vivo testing of multiple mitotic kinase inhibitors (alisertib, BSK923295A, volasertib, ispinesib)

Xenograft Line	Histology	Median Score	Midpoint Difference	Overall Group Response	Heat Map
BT-29	Rhabdoid	4.0	-1.0	SD	
KT-14	Rhabdoid	2.0	-3.0	PD2	
KT-12	Rhabdoid	10.0	5.0	MCR	
KT-10	Wilms	10.0	5.0	MCR	
KT-11	Wilms	2.0	-3.0	PD2	
KT-13	Wilms	4.0	-1.0	SD	
SK-NEP-1	Ewing	10.0	5.0	MCR	
EW5	Ewing	0.0	-5.0	PD1	
EW8	Ewing	0.0	-5.0	PD1	
TC-71	Ewing	2.0	-3.0	PD2	
CHLA258	Ewing	0.0	-5.0	PD1	
Rh28	ALV RMS	2.0	-3.0	PD2	
Rh30	ALV RMS	0.0	-5.0	PD1	
Rh30R	ALV RMS	1.0	-4.0	PD1	
Rh41	ALV RMS	0.0	-5.0	PD1	
Rh65	ALV RMS	10.0	5.0	MCR	
Rh18	EMB RMS	2.0	-3.0	PD2	
BT-28	Medulloblastoma	0.0	-5.0	PD1	
BT-45	Medulloblastoma	2.0	-3.0	PD2	
BT-46	Medulloblastoma	10.0	5.0	MCR	
BT-50	Medulloblastoma	4.0	-1.0	SD	
BT-41	Ependymoma	2.0	-3.0	PD2	
BT-44	Ependymoma	2.0	-3.0	PD2	
GBM2	Glioblastoma	2.0	-3.0	PD2	
BT-39	Glioblastoma	2.0	-3.0	PD2	
D645	Glioblastoma	2.0	-3.0	PD2	
D456	Glioblastoma	6.0	1.0	PR	
NB-1771	Neuroblastoma	10.0	5.0	MCR	
NB-1691	Neuroblastoma	2.0	-3.0	PD2	
NB-EBc1	Neuroblastoma	10.0	5.0	MCR	
NB-1643	Neuroblastoma	10.0	5.0	MCR	
NB-1382	Neuroblastoma	2.0	-3.0	PD2	
SK-N-AS	Neuroblastoma	0.0	-5.0	PD1	
OS-1	Osteosarcoma	10.0	5.0	MCR	
OS-2	Osteosarcoma	2.0	-3.0	PD2	
OS-17	Osteosarcoma	2.0	-3.0	PD2	
OS-9	Osteosarcoma	4.0	-1.0	SD	
OS-33	Osteosarcoma	2.0	-3.0	PD2	
OS-31	Osteosarcoma	2.0	-3.0	PD2	
ALL-2	ALL B-precursor	8.0	3.0	CR	
ALL-3	ALL B-precursor	8.0	3.0	CR	
ALL-4	ALL B-precursor	8.0	3.0	CR	
ALL-16	ALL T-cell	10.0	5.0	MCR	
ALL-17	ALL B-precursor	8.0	3.0	CR	
ALL-19	ALL B-precursor	10.0	5.0	MCR	
	Median	2.0			
	PD1			PR	
	PD2			CR	
	SD			MCR	



Maris et al. 2010. Pediatric Blood Cancer. 55(1):26-34.

High ORR for *In Vivo* Testing of Mitotic Kinase Inhibitors

Agent	Target	Solid Tumor		Acute Lymphoblastic Leukemia	
		# Tested	ORR	# Tested	ORR%
Ispinesib	KSP5	30	23%	8	75%
Alisertib	Aurora A kinase	41	27%	6	100%
GSK923295A	CENP-E	37	32%	6	83%
Volasertib	PLK1	34	9%	8	63%
ALL Models Tested		**142**	**23%**	**28**	**79%**

- Clinical activity limited in pediatric and adult clinical trials
- Preclinical models proliferate at faster rates than tumors in patients
- Preclinical testing using clinically relevant schedules and doses can minimize risk of over-prediction (Mosse YP, *et al*. *Clin Cancer Res* 2019, 25(11):3229-3238)

Combined Testing Lessons

Combination Testing

- **Additivity**: Explains success of most recent FDA-approved combination regimens (Hwangbo H, et al. *Nat Cancer* 2023, **4**:1693-1704)
  - Menin inhibitor and SOC agents both effective, and their combination is more effective than either used alone (AACR-NCI-EORTC 2023)
- **Rapamycin example for rhabdomyosarcoma showing *in vivo* therapeutic enhancement**
  - Rapamycin showed therapeutic enhancement for some rhabdomyosarcoma models with cyclophosphamide and vincristine (Houghton PJ, *et al*: *Molecular Cancer Therapeutics* 2010, **9**(1):101-112)
  - Little single agent activity in clinic for temsirolimus against pediatric cancers
  - Combination with SOC agents ineffective in phase 3 trial ARST1431 (Gupta AA, *et al*. Lancet Oncology 2024)
- **Supra-additivity/synergy**: highly sought characteristic but a two-edged concept
  - Talazoparib and temozolomide remarkably effective in combination for Ewing sarcoma in vivo models while neither effective as single agent (Smith MA, *et al*: *Clin Cancer Res* 2015, **21**(4):819-832)
  - Clinical testing of talazoparib and temozolomide showed synergistic effect applied strongly to normal tissue (e.g., hematopoietic cells) (Schafer ES, *et al*. *Pediatr Blood Cancer* 2020, **67**(2):e28073)

More Lessons

- PDX models are developed in immunodeficient mice, which limits their use in immunoncology studies
- Overall genomic architecture of PDX models mirrors patients…but subclonal heterogeneity may be lost and may influence testing outcomes
- Gene expression levels do not always correspond to protein abundance
- Additional –omic characterization of PDX models needed (e.g., epigenetic profiling)
- Collections of preclinical models do not always reflect the diverse ancestry of pediatric patients

Recent Results – AACR 2025

The CLK/DYRK inhibitor SM09419 shows potent efficacy across a broad panel of pediatric preclinical xenograft models: A report from the Pediatric Preclinical In Vivo Testing Consortium (PIVOT) (pdf)

Preclinical evaluation of the AKR1C3-activated alylator, OBI-3424, in hepatoblastoma- A report from the Pediatric Preclinical In Vivo Testing Consortium (PIVOT) (pdf)

The B7-H3 targeting antibody-drug conjugate (ADC) Vobramitamab Duocarmazine (Vobra Duo) is potently effective against a broad panel of pediatric solid tumor xenograft models: A study from the Pediatric Preclinical In Vivo Testing (PIVOT) consortium (pdf)

https://preclinicalpivot.org/publications-and-presentations/

Cell Reports

CellPress

Volume 29, Issue 6, 5 November 2019, Pages 1675-1689.e9

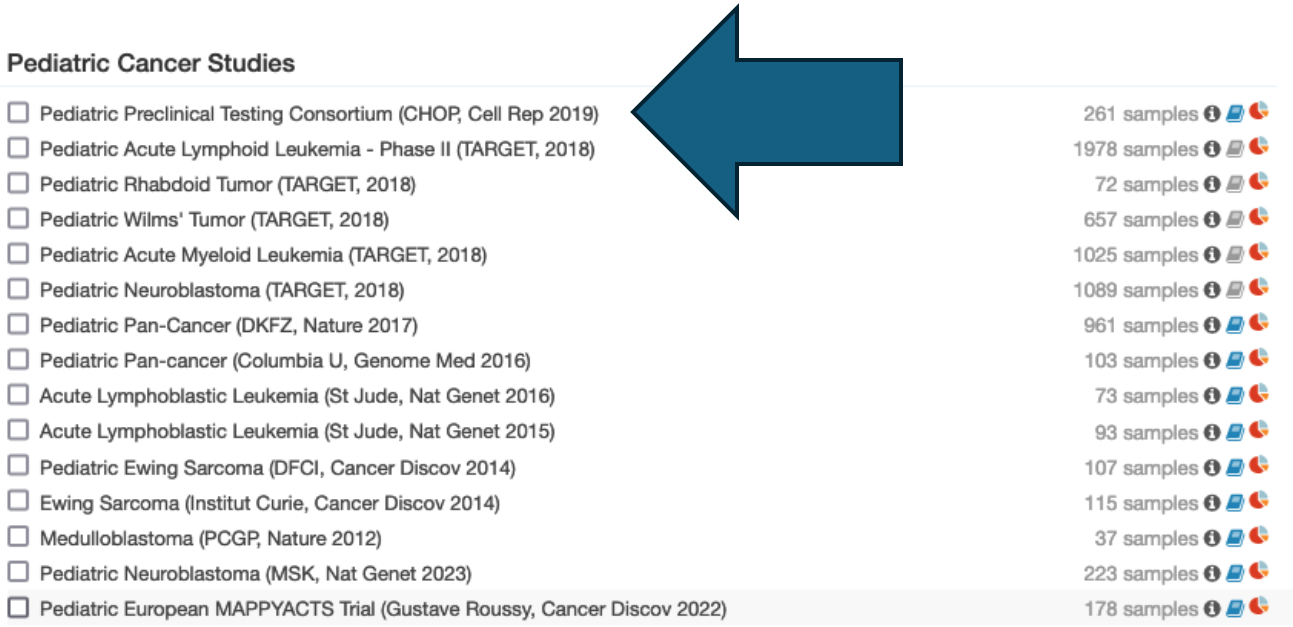
Resource

Genomic Profiling of Childhood Tumor Patient-Derived Xenograft Models to Enable Rational Clinical Trial Design

Jo Lynne Rokita [1 2 3], Komal S. Rathi [2 3], Maria F. Cardenas [4], Kristen A. Upton [1], Joy Jayaseelan [4], Katherine L. Cross [5], Jacob Pfeil [6], Laura E. Egolf [1 7], Gregory P. Way [8], Alvin Farrel [2], Nathan M. Kendsersky [1 9], Khushbu Patel [2], Krutika S. Gaonkar [2 3], Apexa Modi [1 8], Esther R. Berko [1], Gonzalo Lopez [1 2], Zalman Vaksman [2], Chelsea Mayoh [10], Jonas Nance [11], Kristyn McCoy [11]...John M. Maris [1 33]

Extensive Pediatric Tumor Genome Data Aids with Preclinical Experimental Design

Pediatric Cancer Studies	15
Bone	2
CNS/Brain	2
Kidney	2
Lymphoid	3
Myeloid	1
Other	5
Peripheral Nervous System	2
Soft Tissue	1



https://www.cbioportal.org/
https://pedcbioportal.kidsfirstdrc.org/

Pediatric Preclinical Testing Consortium (CHOP, Cell Rep 2019)

Whole-exome sequencing of 261 patient derived xenografts (PDXs) samples from high-risk childhood cancers (with no matched normals).

Cancer Type Detailed

	#	Freq
B-Lymphoblastic Leukemia/Lym…	37	14.2%
Osteosarcoma	36	13.8%
Neuroblastoma	35	13.4%
Medulloblastoma	20	7.7%
T-Lymphoblastic Leukemia/Lym…	19	7.3%
B-Lymphoblastic Leukemia/Lym…	15	5.7%
Wilms' Tumor	13	5.0%
Atypical Teratoid/Rhabdoid Tumor	12	4.6%
Acute Leukemias of Ambiguous…	10	3.8%
Ewing Sarcoma	10	3.8%
Alveolar Rhabdomyosarcoma	6	2.3%

Search...

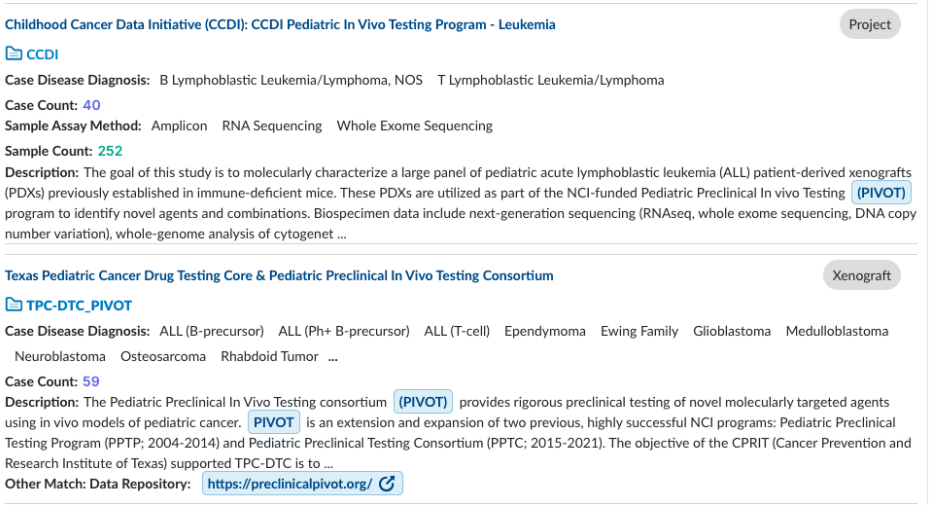
Genomic Profile Sample Counts

Molecular Profile	#	Freq
Mutations	261	100.0%
Putative copy-number alterations …	252	96.6%
mRNA Expression (RNA-Seq FPKM)	244	93.5%
Structural variants	244	93.5%
mRNA Expression z-Scores (RNA…	244	93.5%

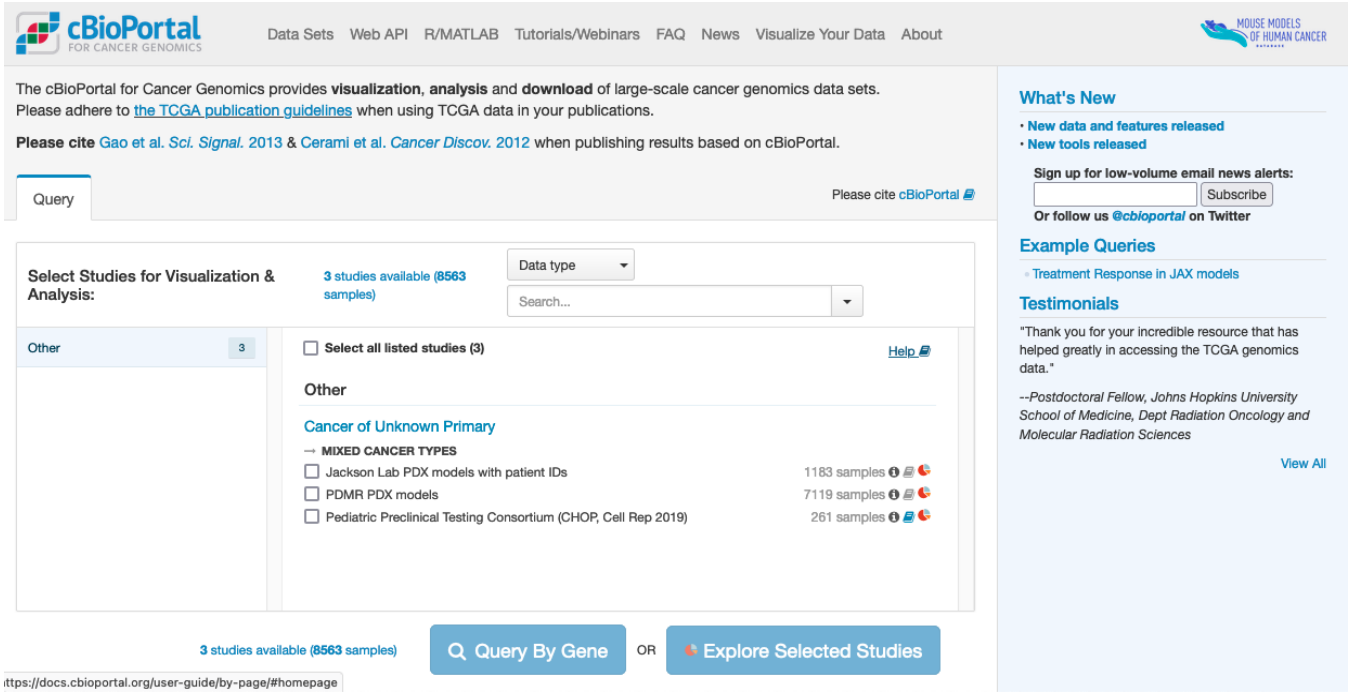
What's Next?

Genomic data for an additional 250 or so pediatric preclinical models sequenced by Alpha Hudson has just been completed

- Working on data access with NCI's Childhood Cancer Data Initiative (CCDI) team
- https://datacatalog.ccdi.cancer.gov/search?search_text=PIVOt&page=1

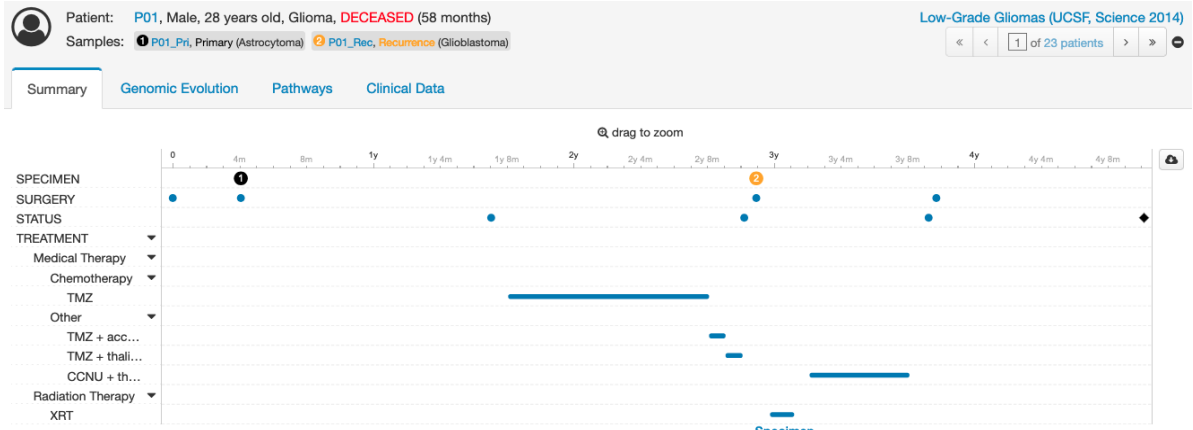


cBioPortal for PDX Genomic and Preclinical Testing Data



https://cbioportal.informatics.jax.org/

Patient Timeline in cBioPortal



Specimen

START_DATE	STOP_DATE	EVENT_TYPE	SURGERY	SAMPLE_ID
124		Specimen	Astro II Initial	P01_Pri
1063		Specimen	Glioblastoma	P01_Rec

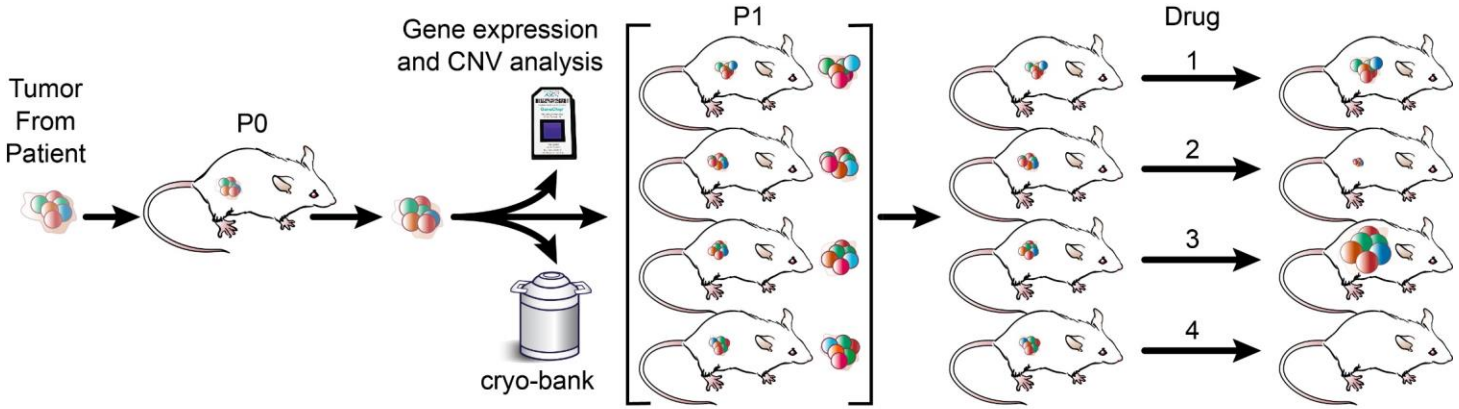
Status

START_DATE	STOP_DATE	EVENT_TYPE	STATUS
580		Status	radiographic_progression
1041		Status	radiographic_progression
1377		Status	radiographic_progression
1763		Status	DECEASED

Treatment

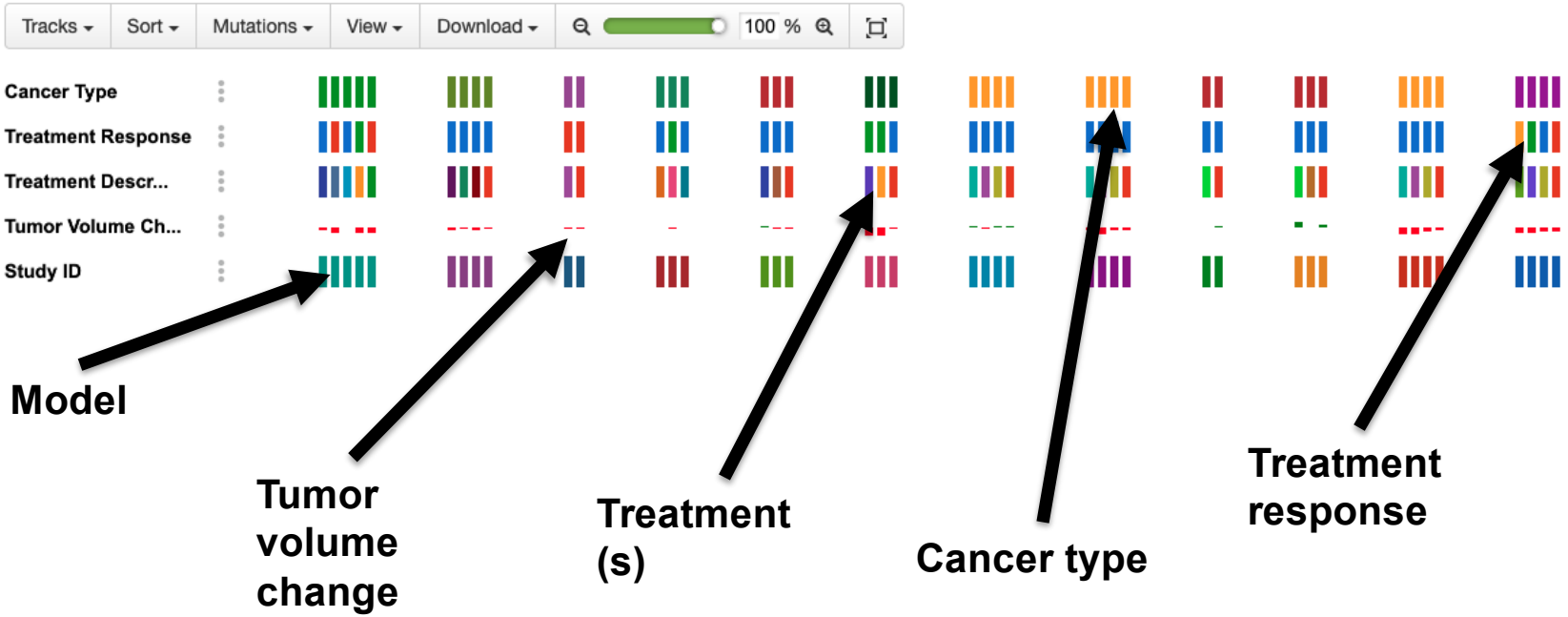
START_DATE	STOP_DATE	EVENT_TYPE	SUBTYPE	AGENT	TREATMENT_TYPE
611	977	Treatment	Chemotherapy	TMZ	Medical Therapy
977	1007	Treatment		TMZ + accutane	Medical Therapy
1007	1038	Treatment		TMZ + thalidomide	Medical Therapy
1088	1132	Treatment	XRT		Radiation Therapy
1160	1342	Treatment		CCNU + thalidomide	Medical Therapy

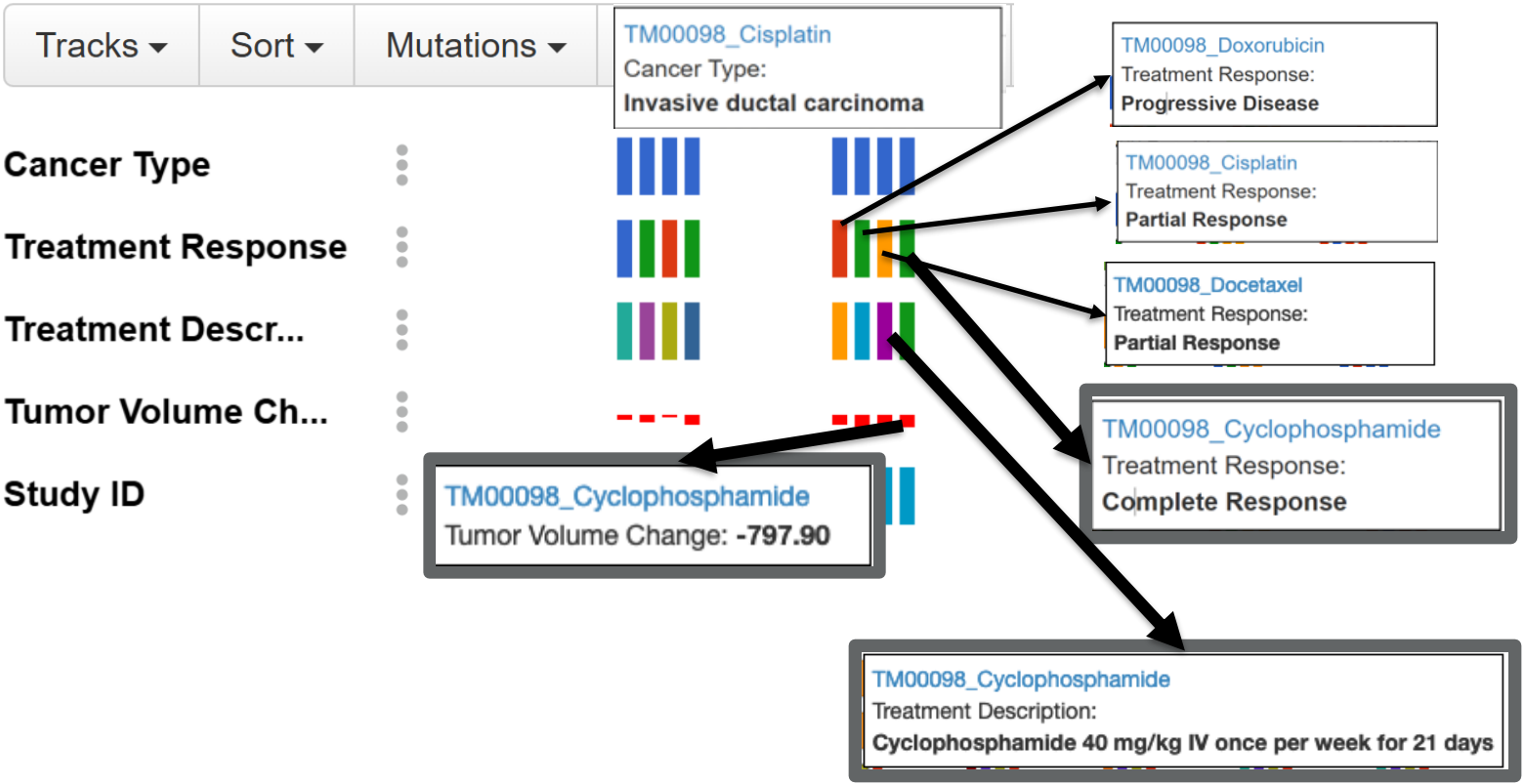
Integrating PDX Genomic and Preclinical Testing Data



A single PDX model can be evaluated for multiple treatments tested in parallel

cBioPortal Oncoprint Visualization of PDX Study Data (One Model; Many Treatments)




Tracks
Sort
Mutations
Cancer Type
Treatment Response
Treatment Descr...
Tumor Volume Ch...
Study ID
TM00098_Cisplatin
Cancer Type:
Invasive ductal carcinoma
TM00098_Doxorubicin
Treatment Response:
Progressive Disease
TM00098_Cisplatin
Treatment Response:
Partial Response
TM00098_Docetaxel
Treatment Response:
Partial Response
TM00098_Cyclophosphamide
Treatment Response:
Complete Response
TM00098_Cyclophosphamide
Tumor Volume Change: -797.90
TM00098_Cyclophosphamide
Treatment Description:
Cyclophosphamide 40 mg/kg IV once per week for 21 days

Next Steps

- Integrate recent genomic data for pediatric PDXs into cBioPortal
- Restructure PPTP/PPTC treatment response data to work with the new Oncoprint PDX treatment visualization paradigm

Acknowledgments

Coordinating Center

The Jackson Laboratory
Leading the search for tomorrow's cures

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Sarcomas, Kidney, Liver

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Greehey Children's Cancer Research Institute

Peter J. Houghton, PhD
Raushan Kurmasheva, PhD

5U01CA263981

Neuroblastoma

The Children's Hospital of Philadelphia®

Yael Mossé, MD
John M. Maris, MD

5U01CA263957

Childhood Leukemia

Children's Cancer Institute

Richard Lock, PhD

5U01CA199000

Brain Tumors

Ann & Robert H. Lurie Children's Hospital of Chicago®

Xiao-Nan Li, MD, PhD

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Osteosarcoma

The University of Texas MD Anderson Cancer Center
Children's Cancer Hospital®

Richard G. Gorlick, MD

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Soft Tissue Sarcomas

St. Jude Children's Research Hospital
Finding cures. Saving children.

Michael A. Dyer, PhD
Elizabeth Stewart, MD

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Sarcomas, Kidney, Rare Tumors

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NCI Pediatric Preclinical in Vivo Testing Program

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Q&A

How You Can Engage with CCDI

Learn about CCDI and subscribe to our monthly newsletter:
cancer.gov/CCDI

Access CCDI data and resources:
ccdi.cancer.gov

Questions? Email us at:
NCIChildhoodCancerDataInitiative@mail.nih.gov

Join Us at Our Upcoming Events

NCI Office of Data Sharing: Data Jamboree

September 29–30, 2025

Learn more and register:

https://events.cancer.gov/nci/ods-data-jamboree

2025 CCDI Symposium: Collaborate. Innovate. Transform.

October 6–7, 2025

Learn more and register:

https://events.cancer.gov/nci/ccdisymposium

Thank you for attending!

cancer.gov

cancer.gov/espanol