



Pediatric Oncology Update

June 24, 2014

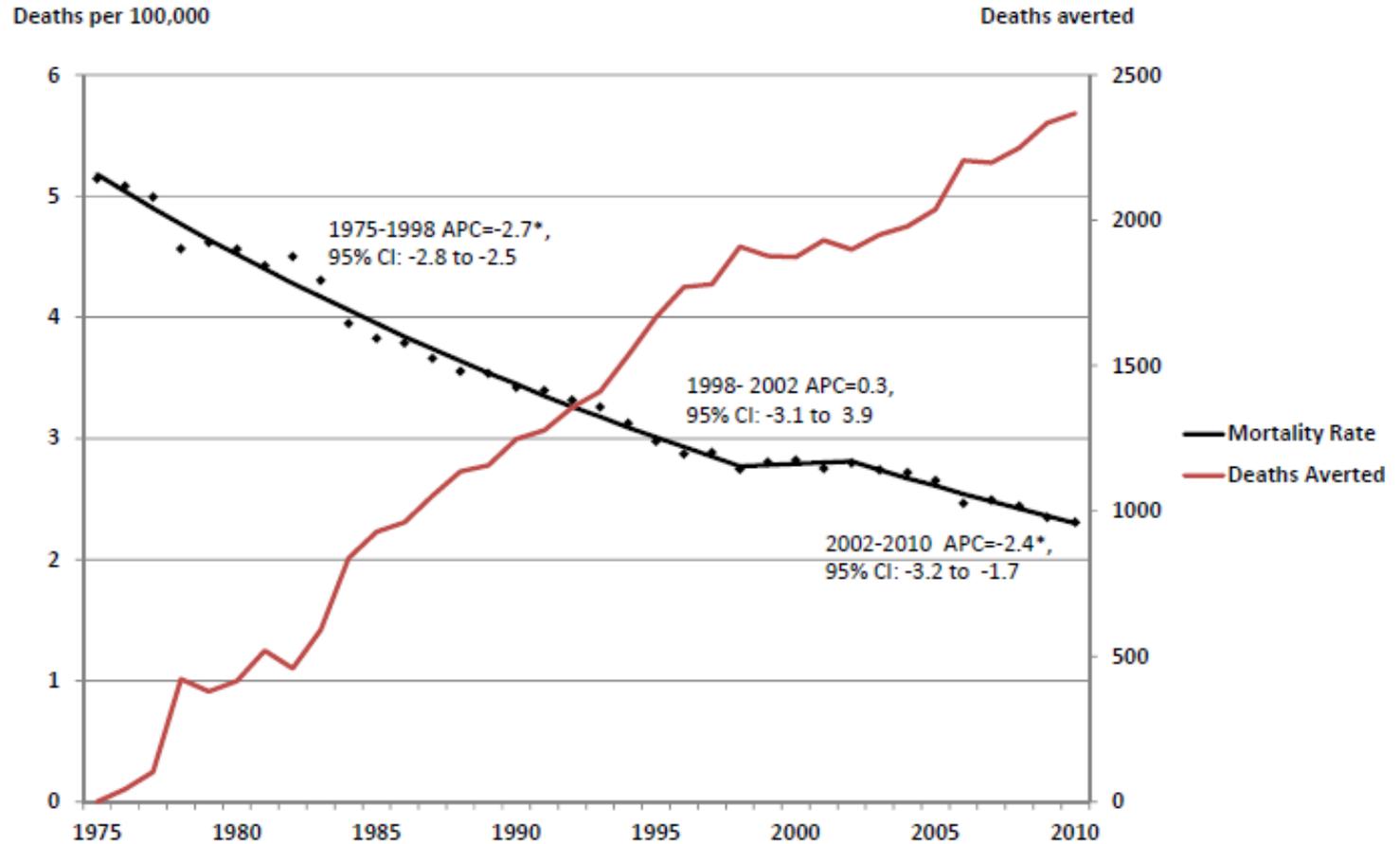


Malcolm A. Smith, MD, PhD
Cancer Therapy Evaluation Program
National Cancer Institute, U.S.A.

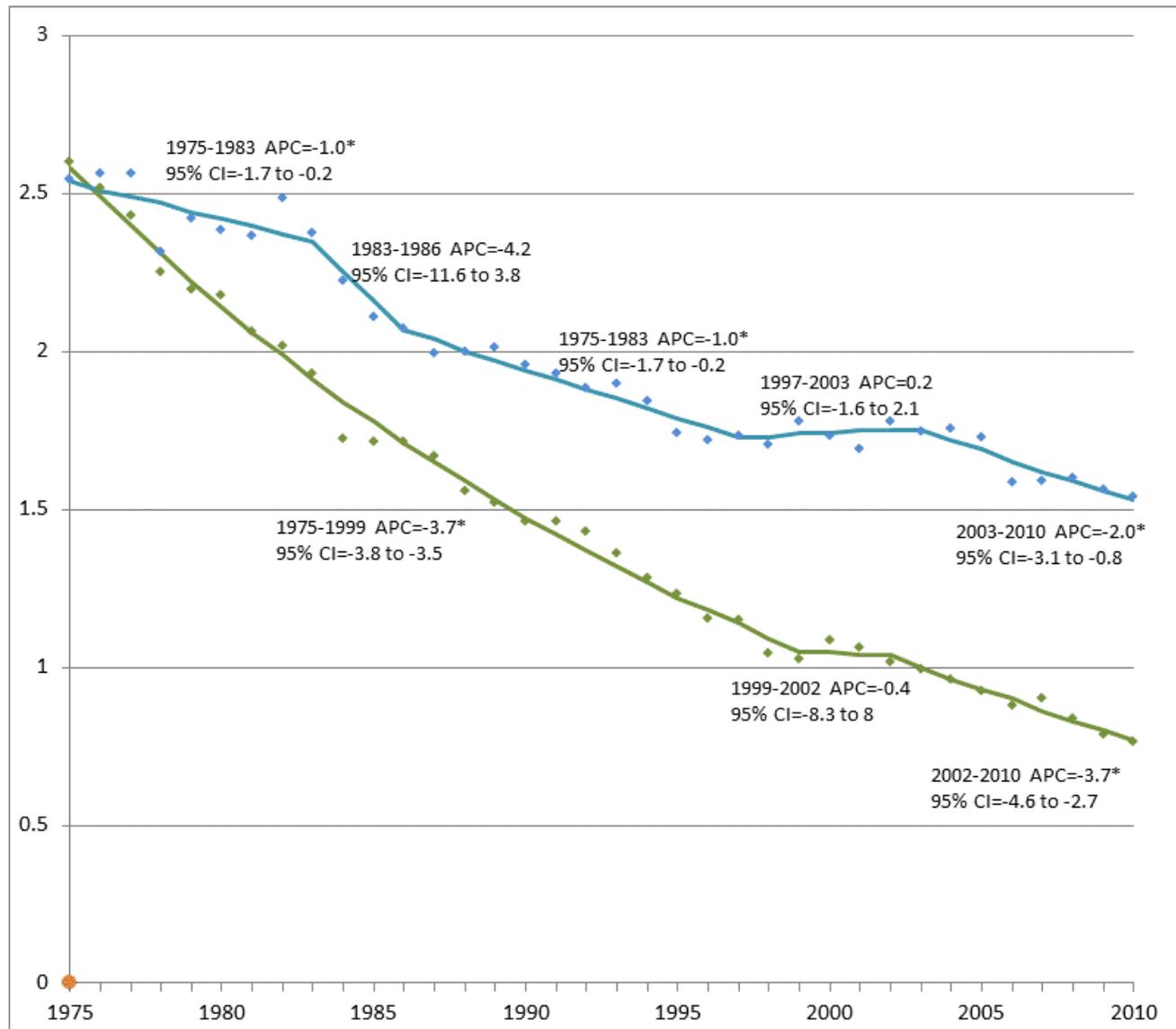
Outline

- Childhood cancer incidence, survival, and mortality
- NCI research programs for children with cancer
- TARGET update
- How to move forward and identify more effective treatments??

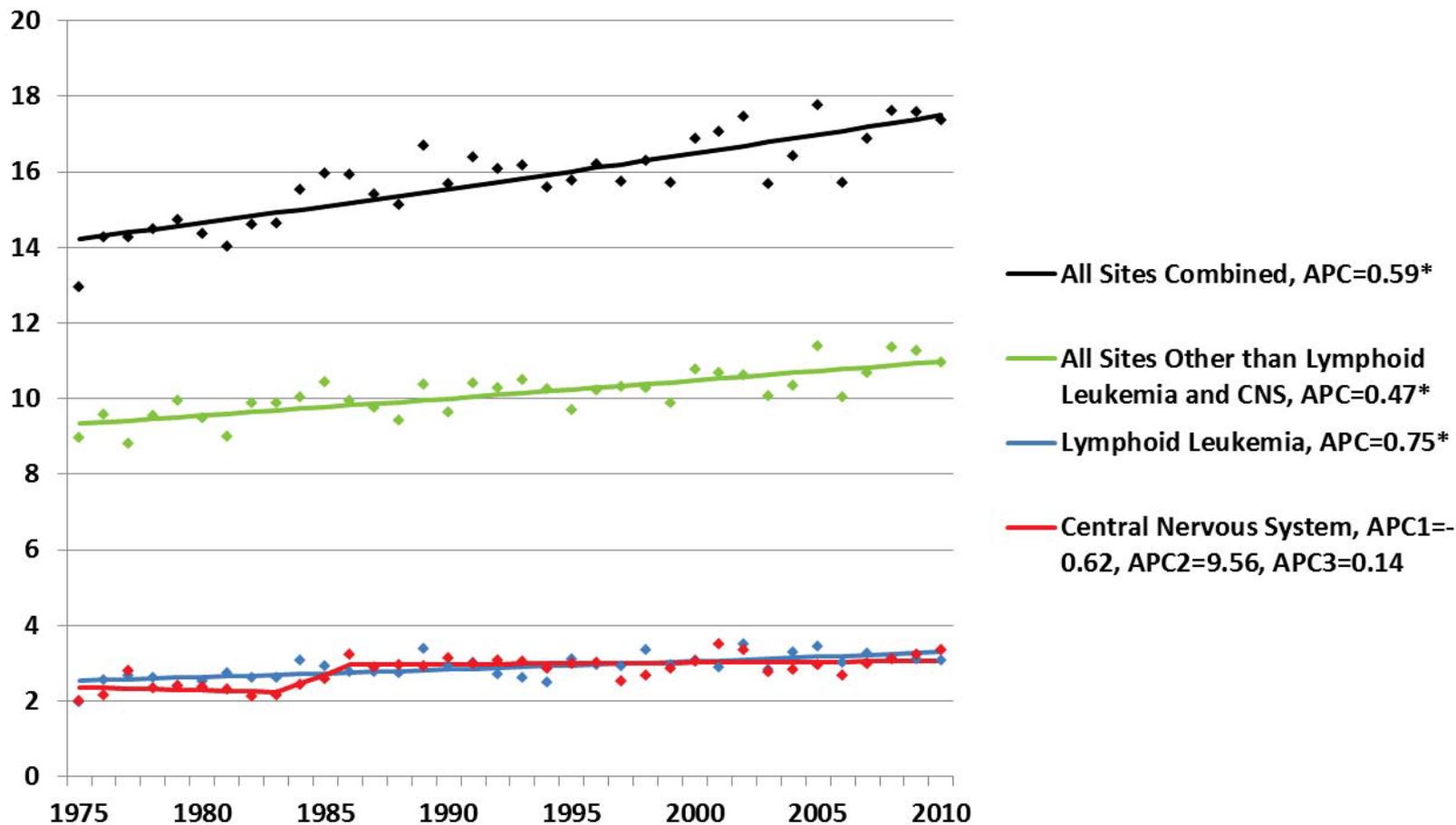
Mortality for All Malignant Cancer s (Age < 20 years): 1975 to 2010



Mortality for All Leukemia/Lymphoma versus Other Cancer s (Age < 20 years): 1975 to 2010

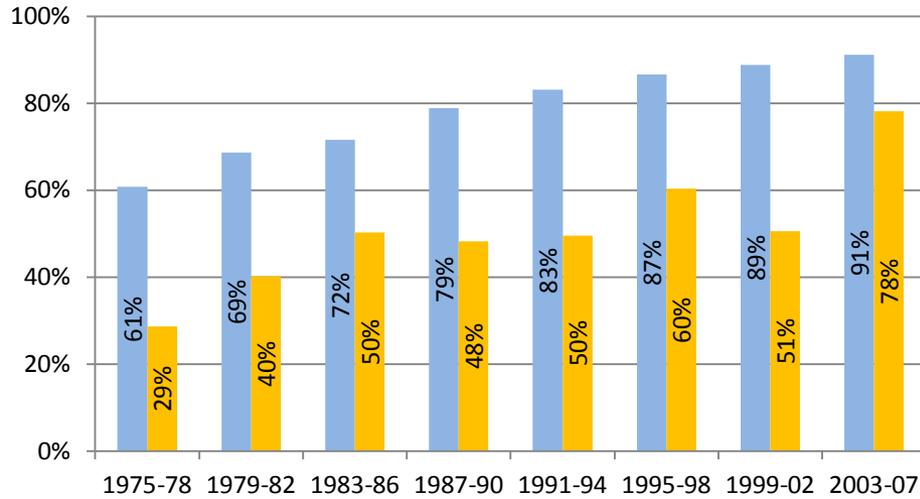


Childhood Cancer Incidence (< 20 years, SEER 9 registries from 1975 – 2010)

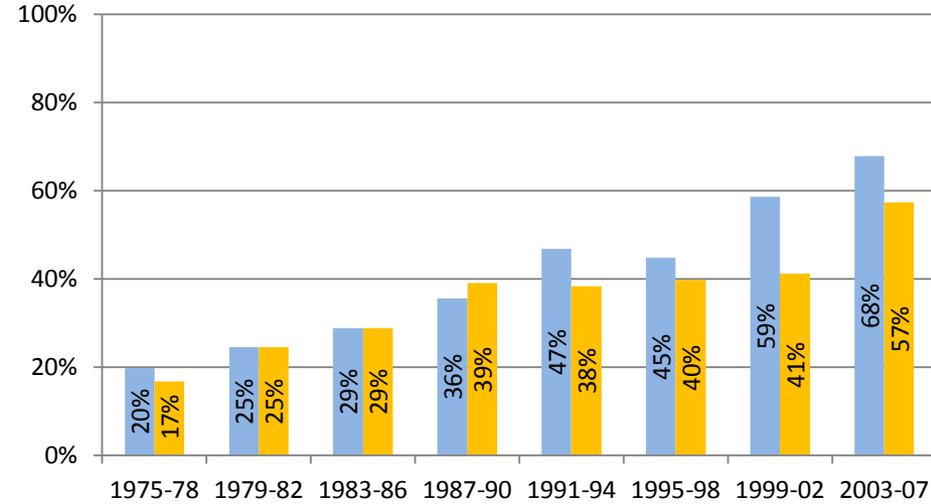


5-Year Relative Survival for Hematopoietic Cancers

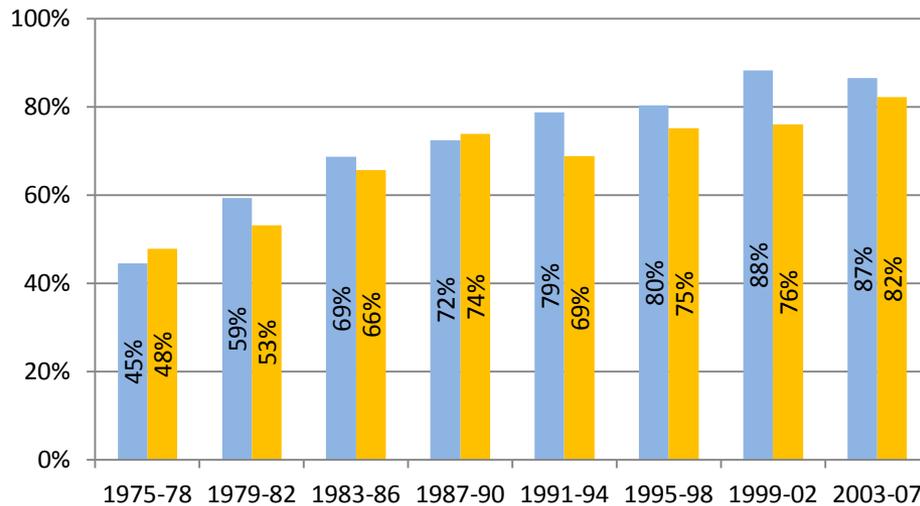
Acute lymphocytic leukemia



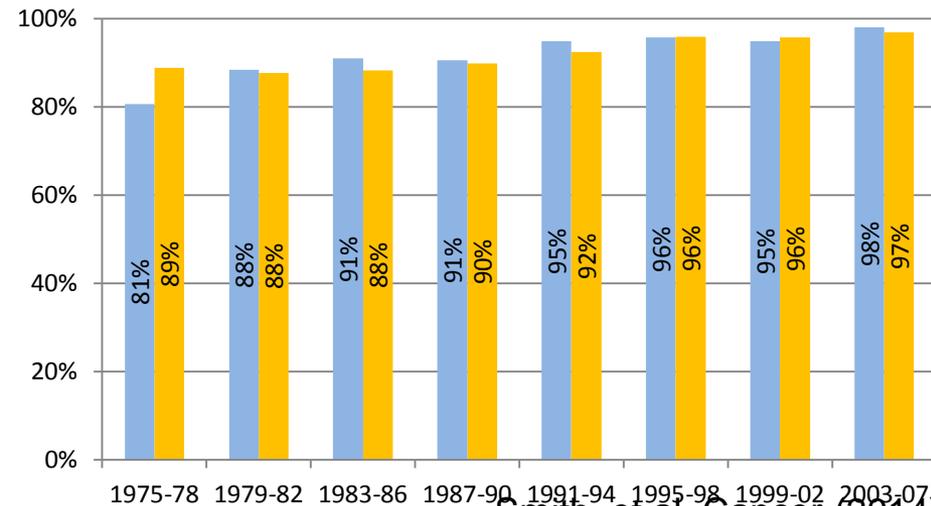
Acute myeloid leukemia



Non-Hodgkin lymphoma

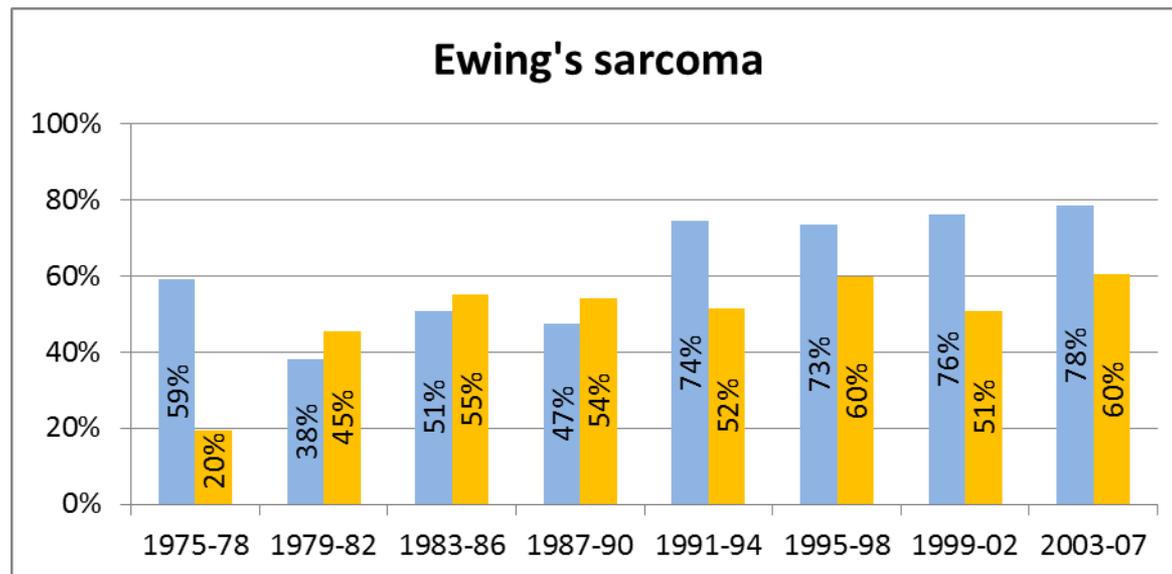
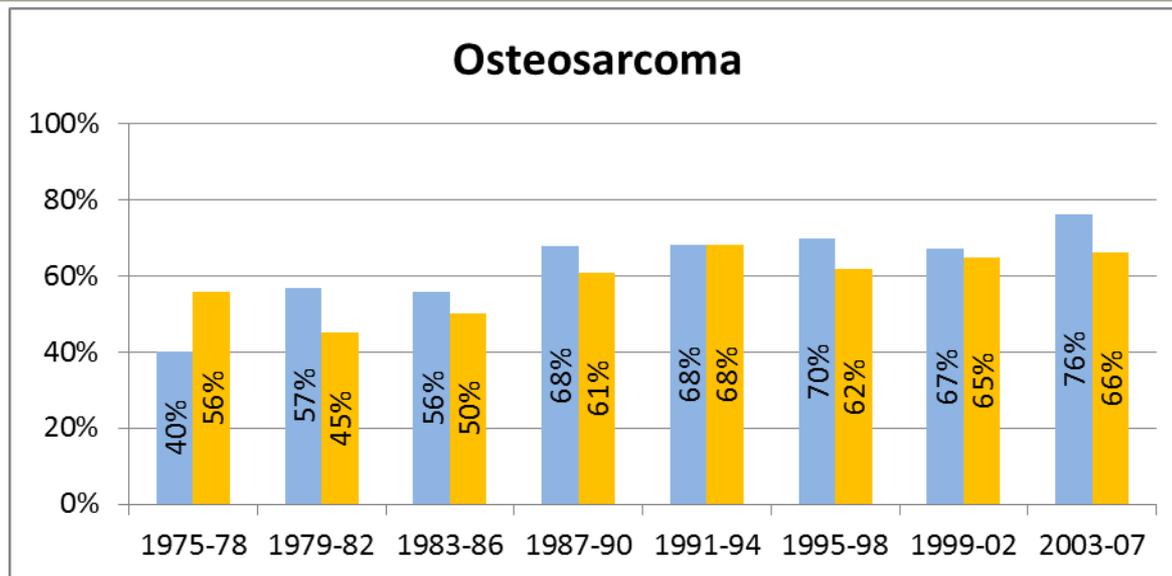


Hodgkin lymphoma



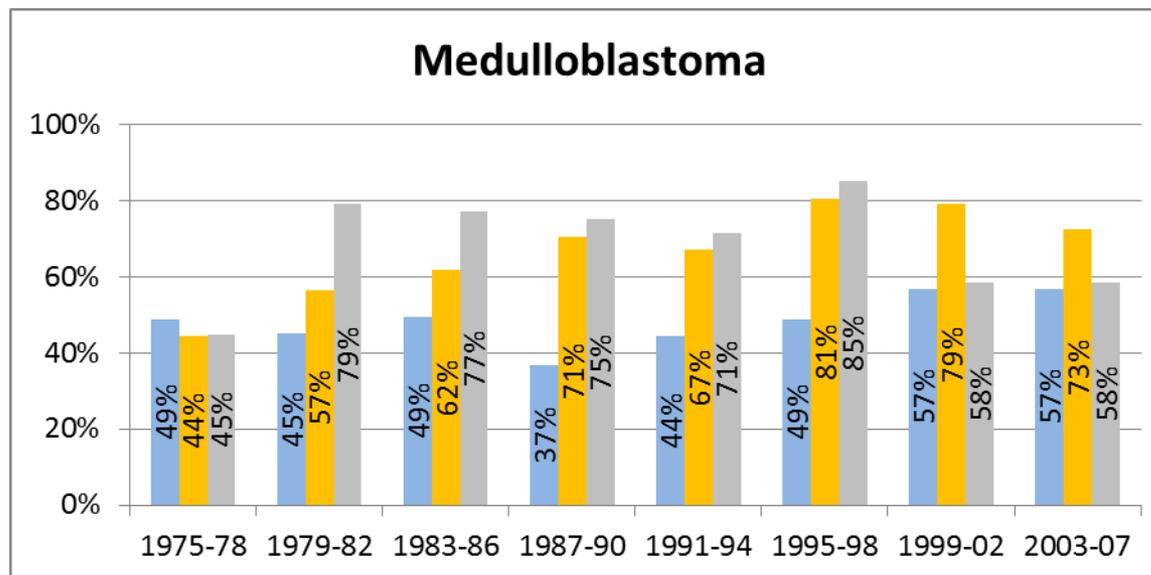
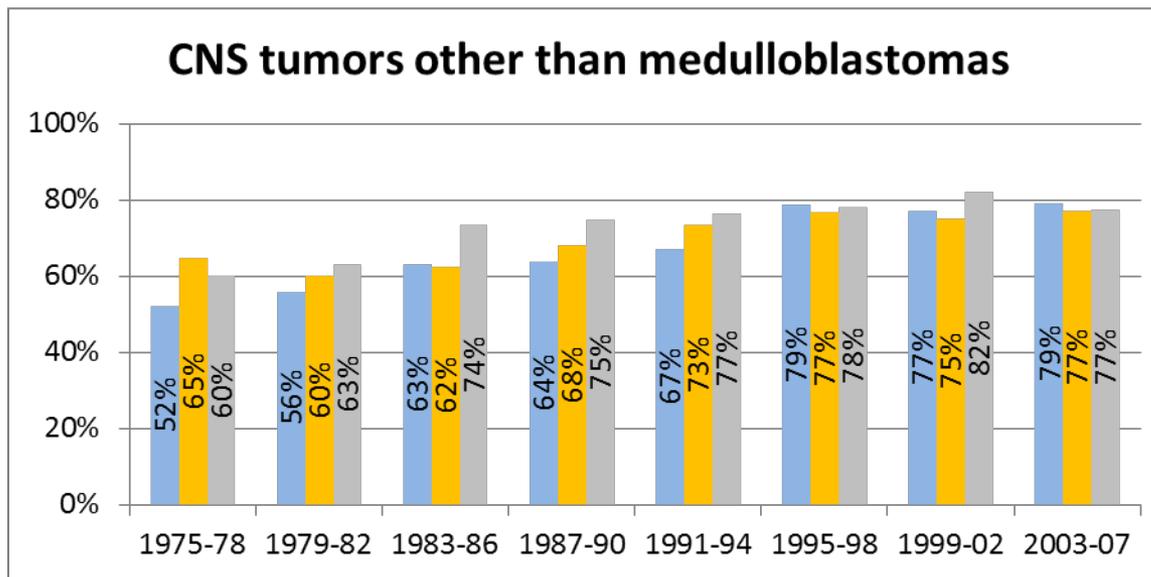
■ <15 years
■ 15-19 years

Five-year Relative Survival for Bone Sarcomas



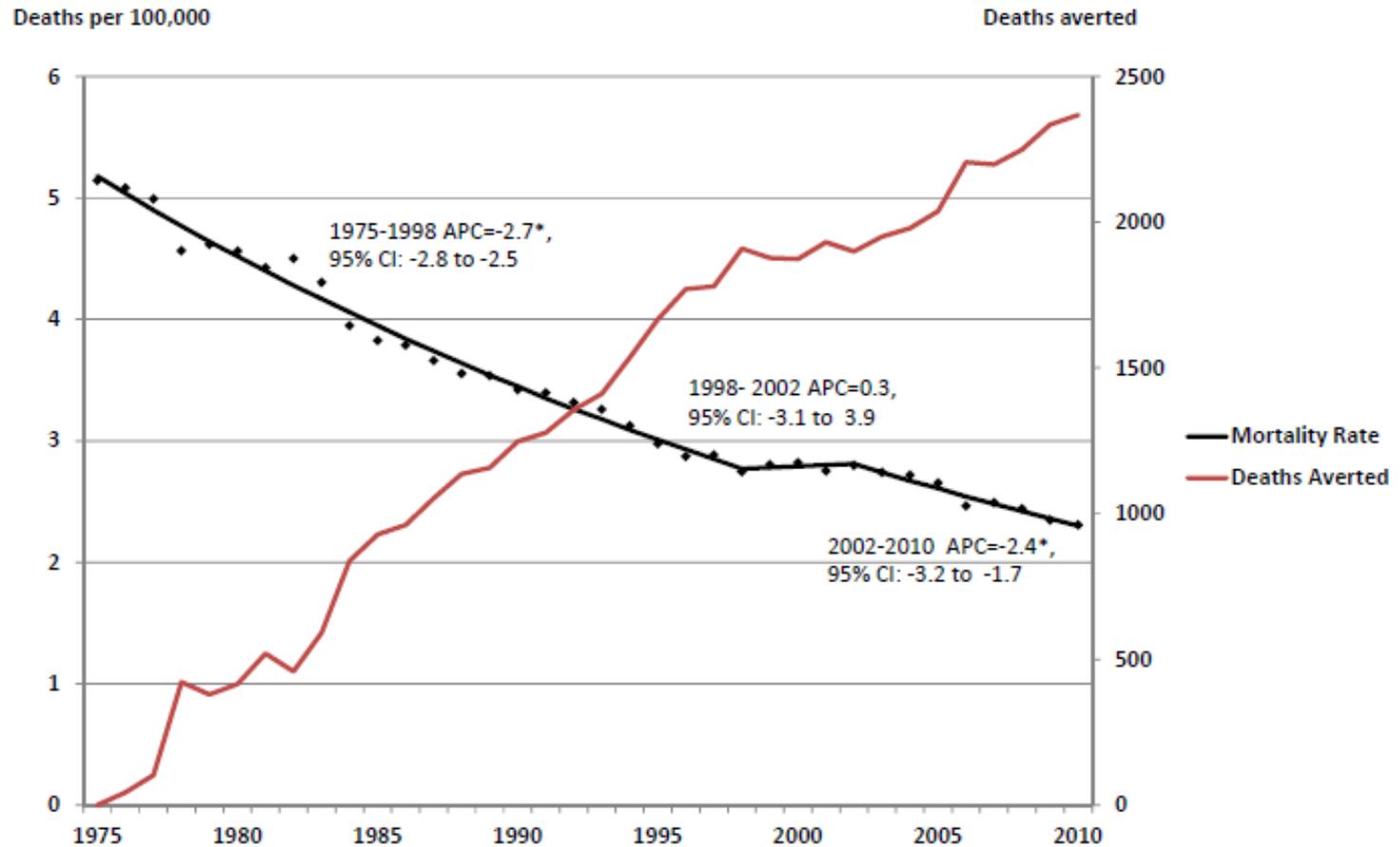
■ <15 years
■ 15-19 years

Five-year Relative Survival for CNS Cancers



Mortality for All Malignant Cancer s (Age < 20 years): 1975 to 2010

> 45,000 deaths averted since 1975



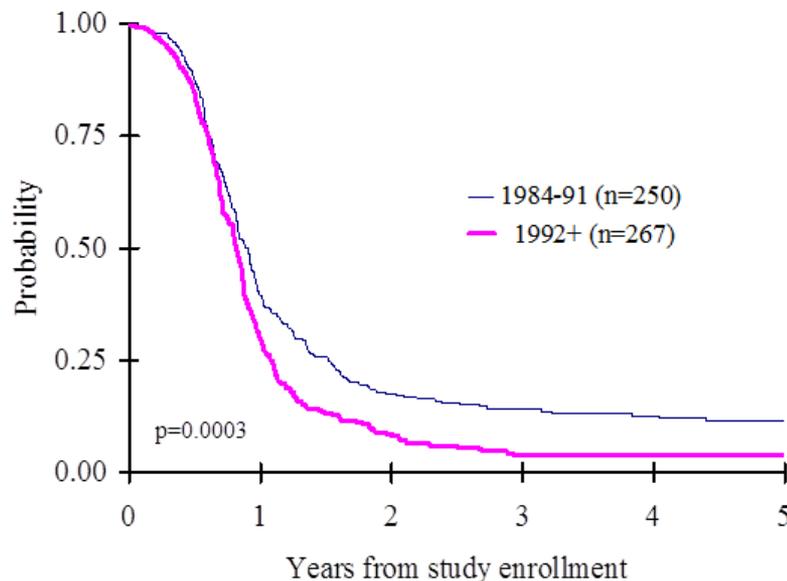
Children's Oncology Group



Overall survival mask cancers for which outcome remains highly unfavorable

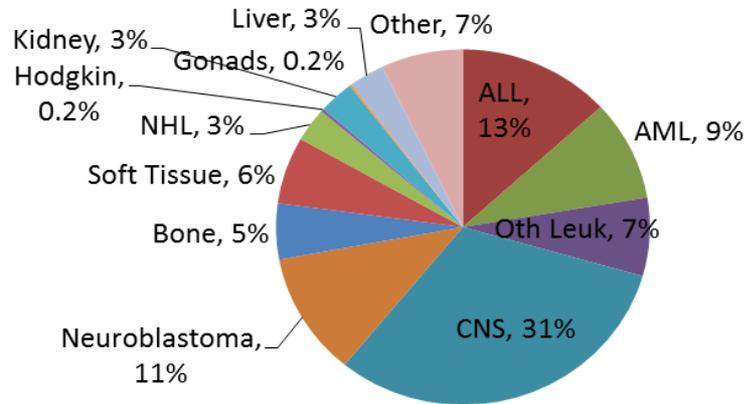
- For some brain cancers (e.g., DIPG & supratentorial high-grade gliomas), outcome has not improved over the past 3 decades.
 - Note: the poorer outcome in the more recent period is the result of more precise diagnosis of DIPG and exclusion of brainstem low-grade gliomas.

Overall Survival by Enrollment Period



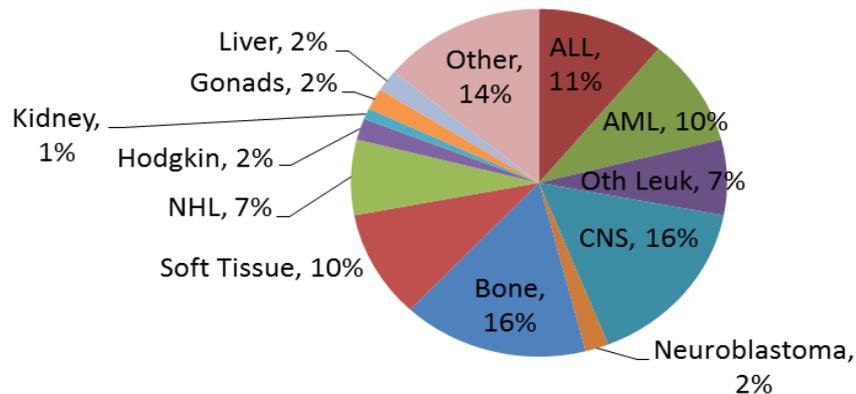
Causes of Childhood Cancer Mortality

<15 Year Mortality 2007-2010



~ 2000 children and adolescents die of cancer each year in the US

15-19 Year Mortality 2007-2010



Childhood Cancer Survivor Study (CCSS)

- Retrospectively ascertained cohort of survivors of pediatric cancer diagnosed between 1970-1986:
 - Cohort initiated with first CCSS award in 1994
 - 14,370 long-term (five-year or more) survivors of childhood cancer diagnosed between 1970 and 1986
 - 3,737 sibling controls recruited for comparison purposes
- Data collected:
 - Clinical data on malignancy and treatment abstracted from medical records
 - Self-reported data on risk factors (e.g., family history), and health and psychosocial outcomes data collected via baseline and follow-up questionnaires
- Biospecimens; second cohort (1987-1999); intervention studies, public use dataset

NCI's Investment in Pediatric Cancer Research

- The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative
- The Pediatric Preclinical Testing Program (PPTP)
- COG Phase 1 / Pilot Consortium
- Pediatric Brain Tumor Consortium
- NCI intramural program
- Children's Oncology Group (COG)
- Childhood Cancer Survivorship Study (CCSS)
- Investigator-initiated research projects
- Other research



TARGET

Therapeutically Applicable Research
to Generate Effective Treatments



Brief Update

target.cancer.gov

*BSA/NCAB
Bethesda MD
June 24, 2014*

Comprehensive Characterization

Disease	Patient Data	Case # (Relapse)	Chip-based				Sequencing			
			Expression	Chr. copy #	Methylation	miRNA	WGS	WXS	Transcriptome	Other
Acute Lymphoblastic Leukemia (P-I)	Y	189 (0)	Y	Y			<Y		mRNA-seq	Targeted
Acute Lymphoblastic Leukemia (P-II) (ALL)	Y	184 (84)	Y	Y	<Y		Y	<Y	m/miRNA-seq	
Acute Myeloid Leukemia	Y	200 (100)	Y	Y	Y		<Y	<Y	m/miRNA-seq	
Induction Refractory Acute Myeloid Leukemia	Y	30 (25)			Y		Y		<m/miRNA-seq	
Neuroblastoma (NBL)	Y	180 (9)	Y	Y	Y	Y	<Y	>Y	mRNA-seq	Targeted
Osteosarcoma	Y	92 (0)	Y	Y	Y		<Y	<Y	mRNA-seq	
Wilms Tumor	Y	113 (5)	Y	Y	Y		<Y	<Y	m/miRNA-seq	
Clear Cell Carcinoma of the Kidney	Y	13 (0)	Y	Y	<Y		Y		mRNA-seq	
Rhabdoid Tumor (kidney)	Y	40 (0)					Y	ChIP-seq	m/miRNA-seq	Methyl-seq
Pediatric Preclinical Testing Program	L	131	Y	Y				Y		
ALL Xenografts	Y	33 [244]	Y	Y			Y			
NBL Models	L	7 [27]					Y	Y		

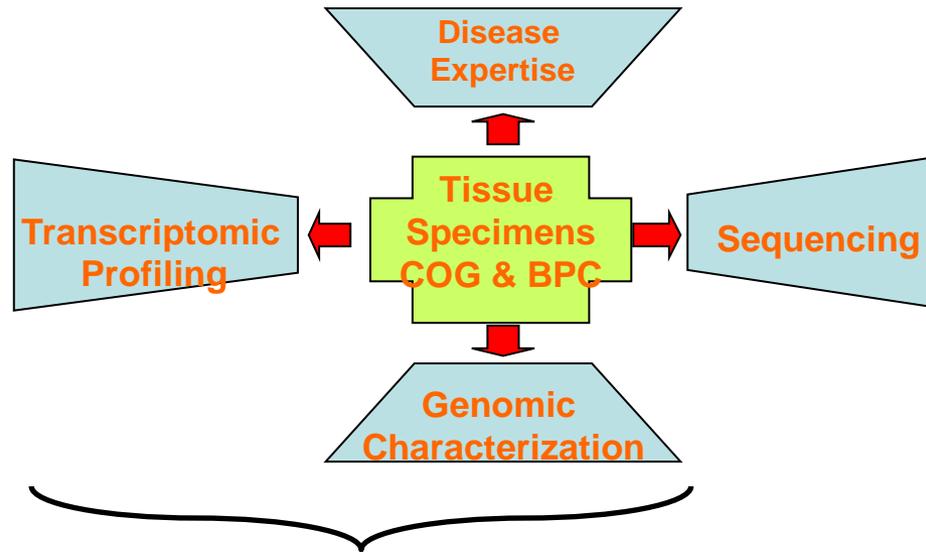
L=Limited
 [# of samples]

Validation in New Cohorts, in progress

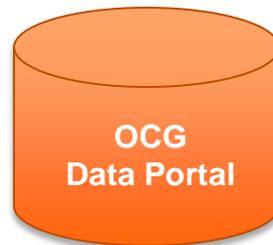
~400 genes to 500X coverage			
Disease	Cases	Patient Data	Samples
Acute Myeloid Leukemia	800	Y	1597
Neuroblastoma	500	Y	1000
Wilms Tumor	570	Y	670

Planned			
Acute Lymphoblastic Leukemia	750	Y	1500
Osteosarcoma	200	Y	TBD

TARGET Initiative:



All data types except raw sequence files are stored the DCC





TARGET

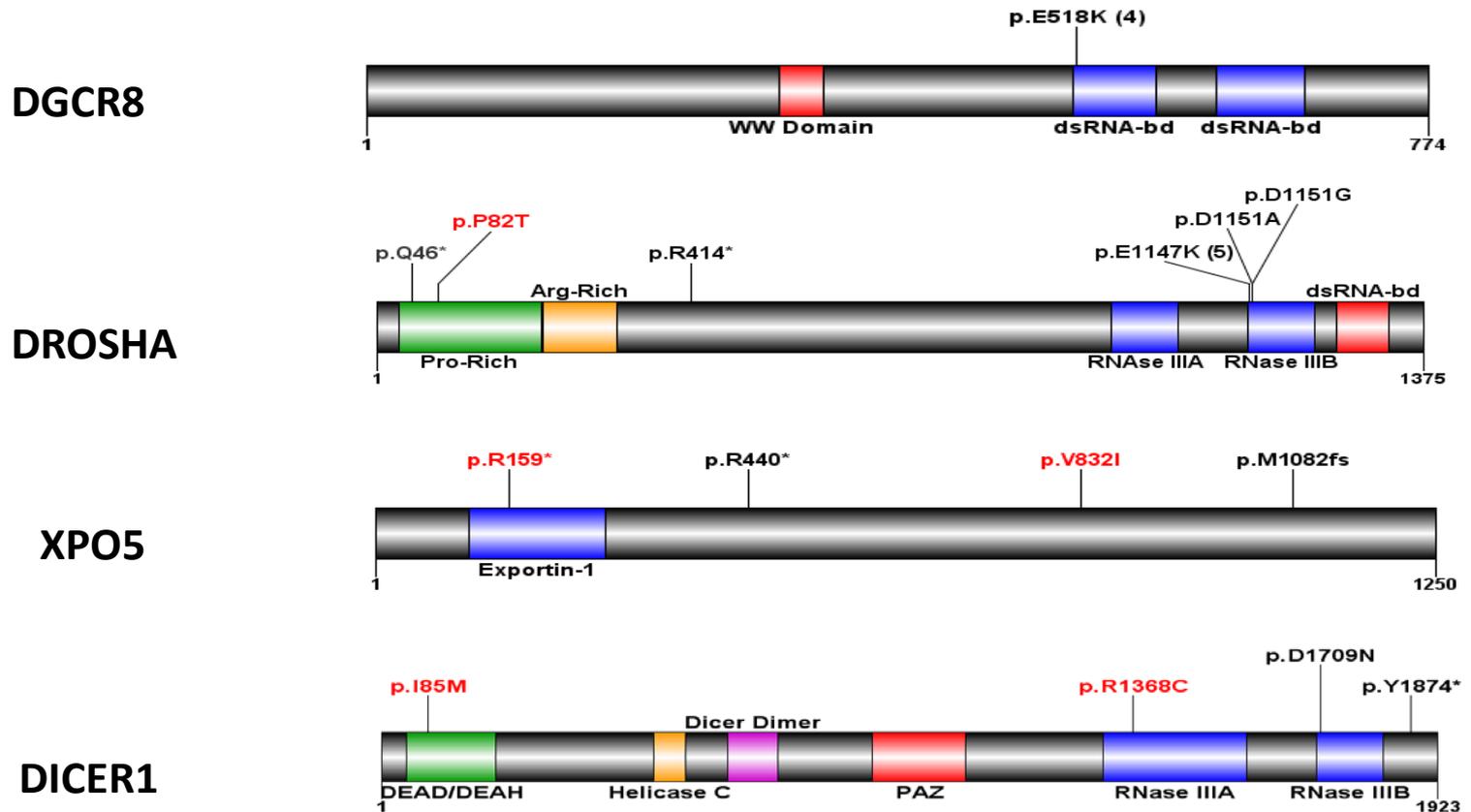
Therapeutically Applicable Research
to Generate Effective Treatments



Selected Vignettes

Favorable Histology Wilms Tumors: Mutations in miRNA Processing Genes

- ❖ 15 / 79 cases somatic
- ❖ 5 / 79 cases germline

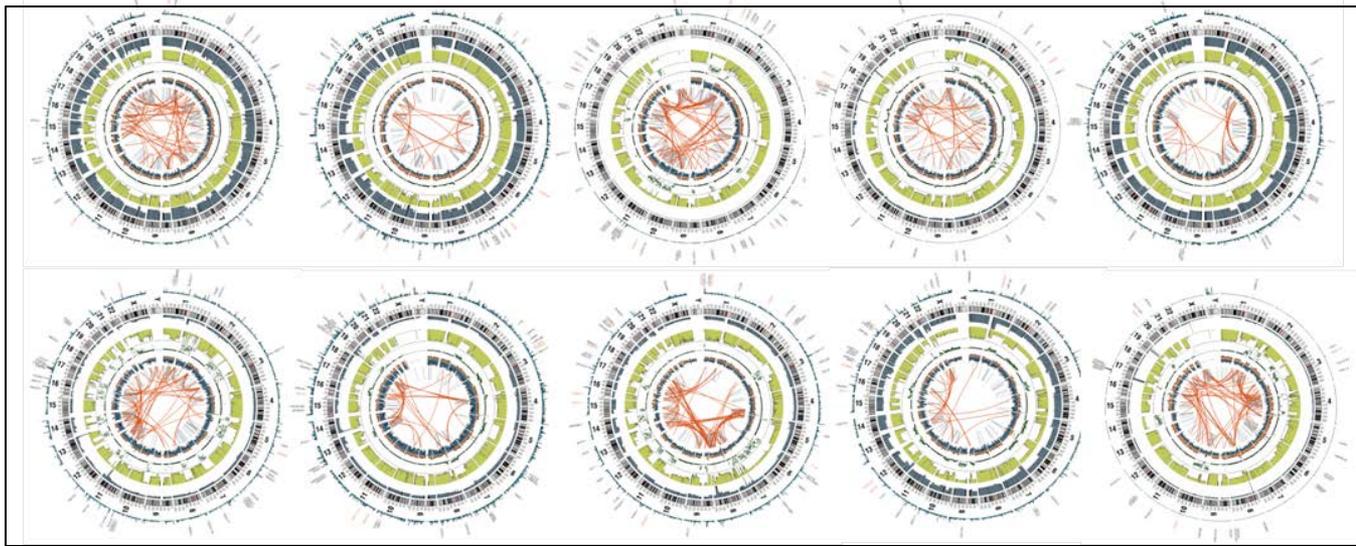


Black = Somatic Mutation

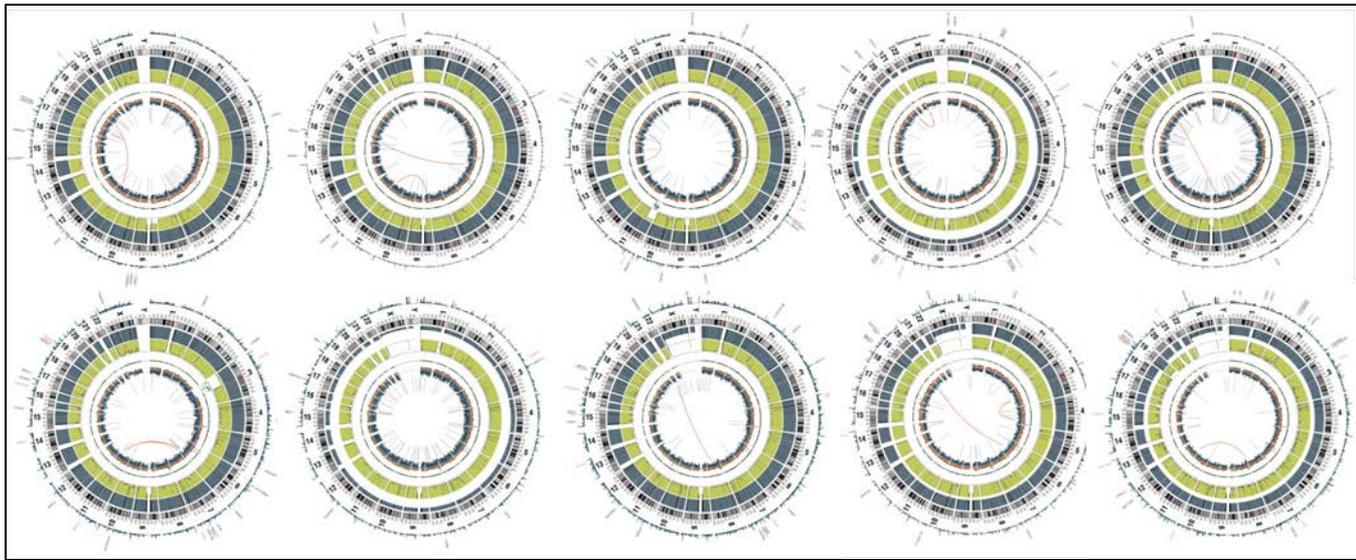
Red = Germline Mutation

E. Perlman & WT PT, unpublished

Osteosarcoma Genomes Are Mostly Rearranged



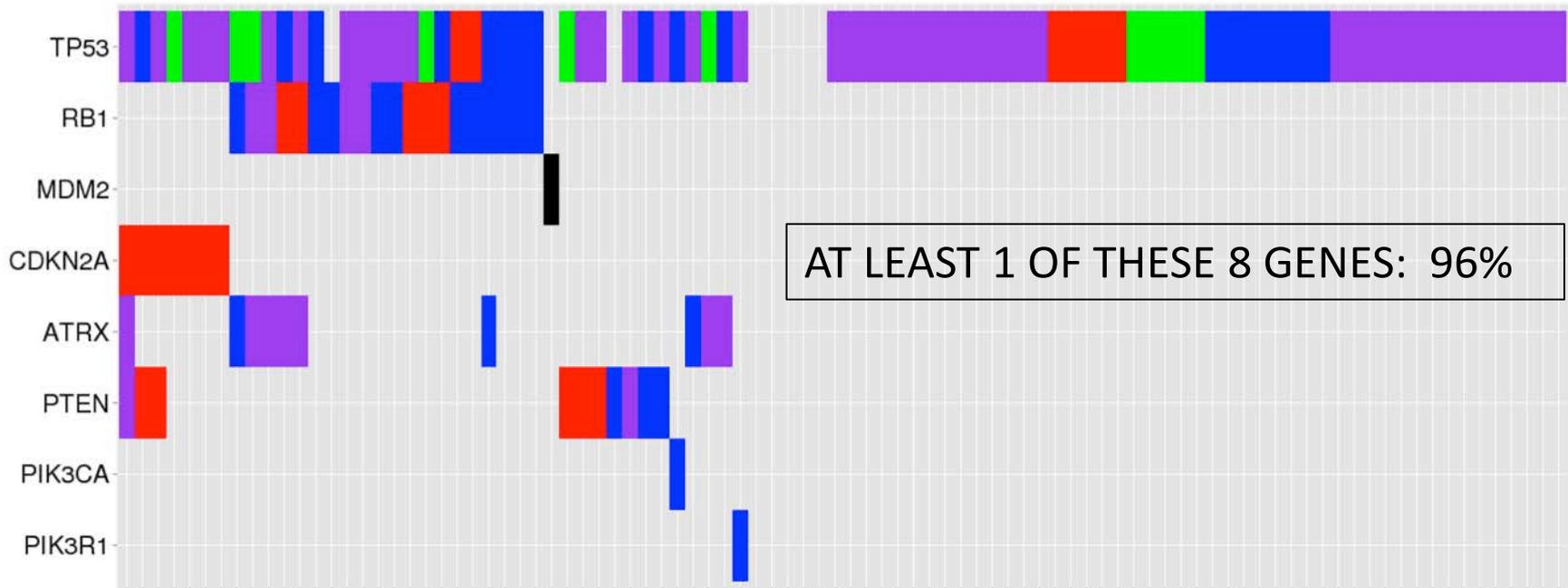
OS



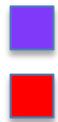
AML

Integrated Genomics of Osteosarcoma

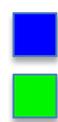
Mutations in 92 tumors



Structural Variant
Large Deletion



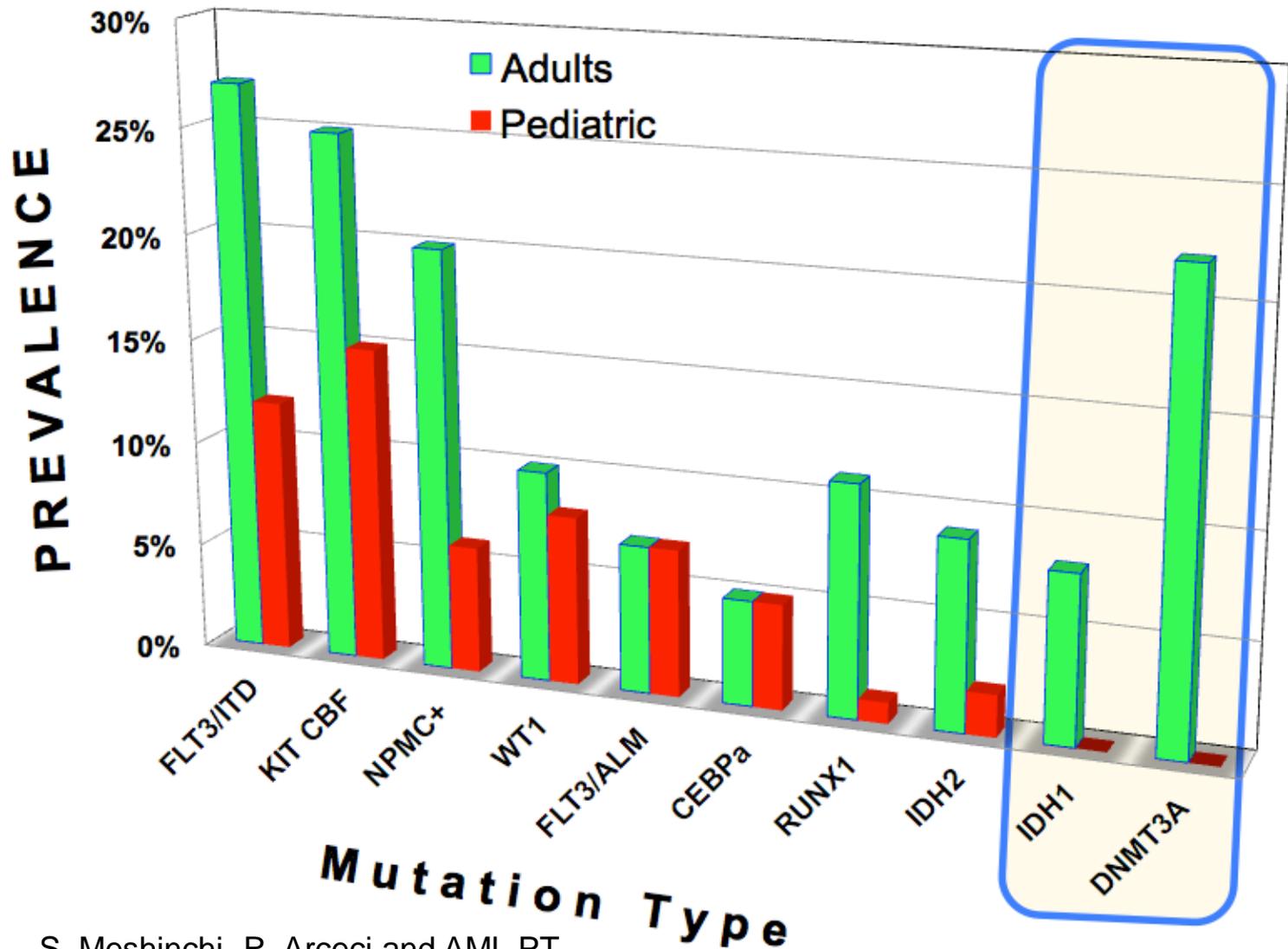
Single Nucleotide Variant
Loss Of Heterozygosity



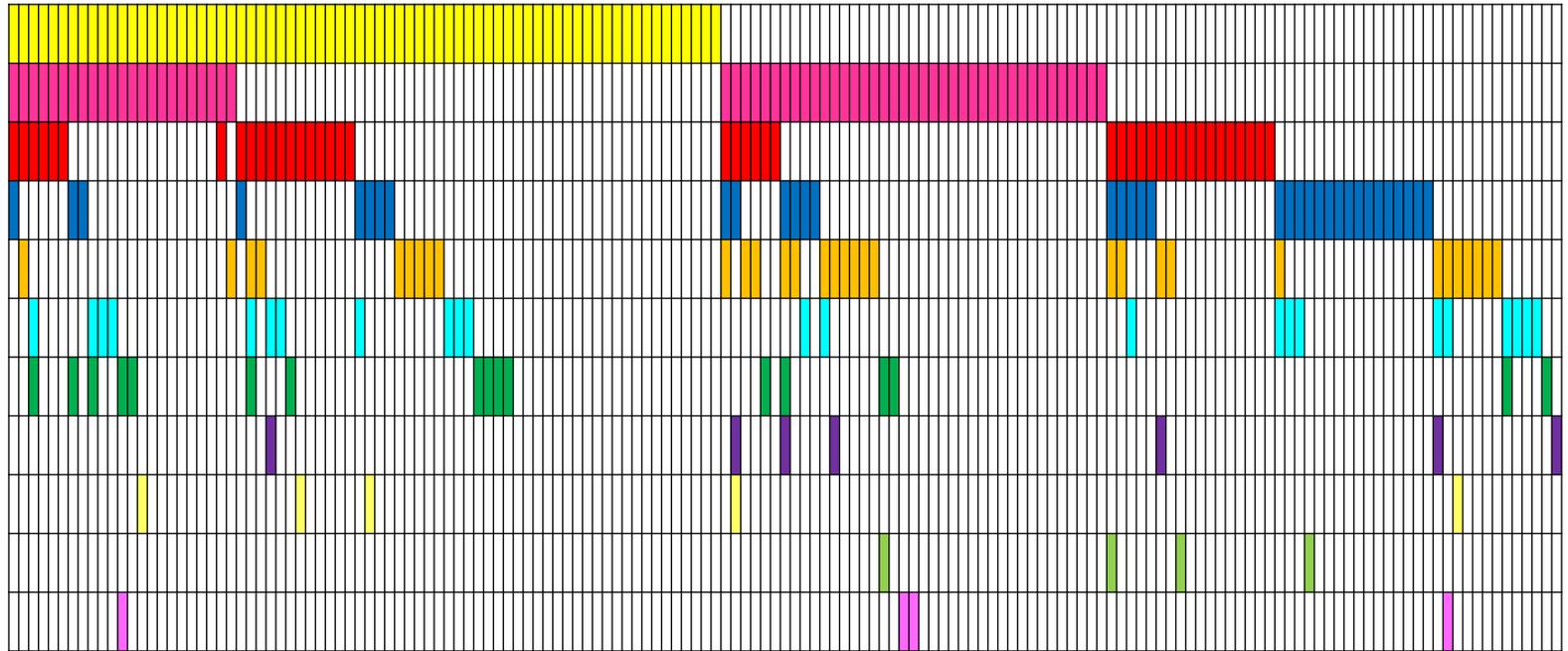
Amplification



Gene Mutations are Different in Children vs. Adults with Acute Myeloid Leukemia



83% of Acute Myeloid Leukemia Cases Have Mutations in 11 Functional Categories



Tyrosine Kinases	Transcription Factors	Tumor Suppressors	RAS family	Protein Phosphatases	Epigenetic Modifiers	Nuclear Transport	Spliceosome	ETS	Cohesin	Oncogenes
0.38	0.33	0.23	0.19	0.17	0.12	0.09	0.04	0.03	0.02	0.02

Publications from the ALL Team

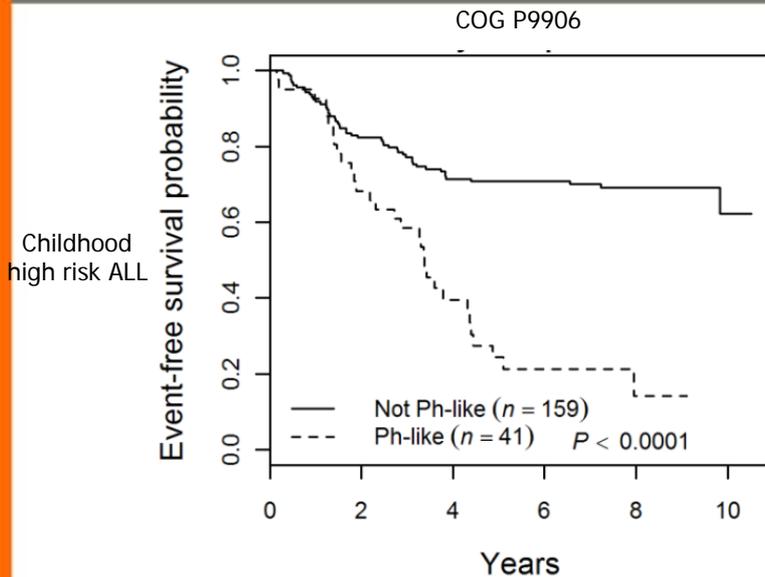
- **Ph-like ALL, IKZF1 deletions and mutations** (Mullighan, NEJM 2009)
- **JAK mutations in HR-ALL** (Mullighan, PNAS 2009)
- **CRLF2 genomic alterations in HR and Down syndrome ALL** (Mullighan, Nature Genetics 2009; Harvey, Blood 2010; Chen Blood 2012)
- **Expression profiles-supervised** (Kang, Blood 2010)
- **Expression profiles-unsupervised (R8 group)** (Harvey, Blood 2010)
- **Recurrent mutations in 4 key pathways in HR ALL** (Zhang, Blood 2011)
- **Kinase activating lesions** (Roberts, Cancer Cell 2012) **but no point mutations** (Loh, Blood 2013) **in Ph-like ALL**
- **GATA3 SNPs and risk of Ph-like ALL** (Perez Andreu Nature Genetics 2013)
- **Comprehensive genomics of Ph-like ALL** (Roberts, submitted)

Gene Fusions Discovered in BCR-ABL1-like Acute Lymphoblastic Leukemia

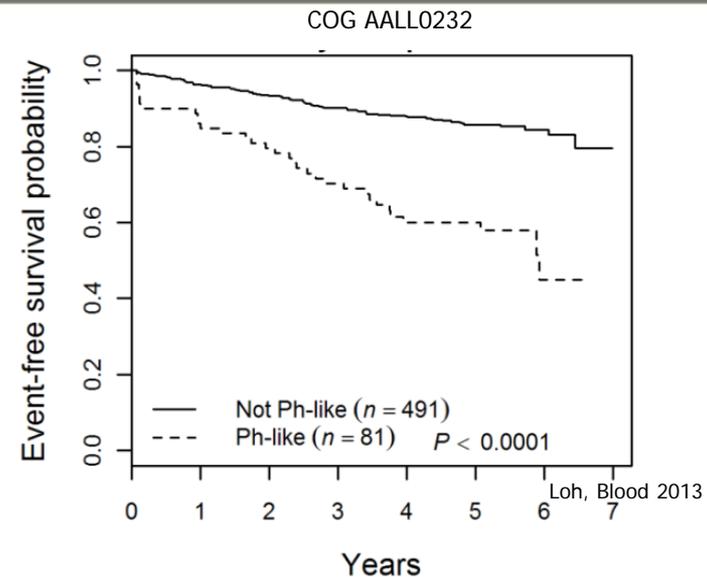
- ❖ Unsupervised analysis of gene expression data identified a Ph+ like “signature” without BCR-ABL1 fusion transcript
- ❖ Sequence analysis of kinase genes found mutations in RAS (~30%), JAK2, but nothing which would explain the expression profile
- ❖ mRNA-seq identified at least one chimeric transcript in most of these cases

Sample ID	Known fusions	New fusions
PAKHZT	<i>IGH@-CRLF2</i>	
PAKKCA		<i>EBF1-PDGFRB</i>
PAKKXB	<i>IGH@-CRLF2</i>	
PAKTAL		<i>STRN3-JAK2</i>
PAKVKK		<i>NUP214-ABL1</i>
PAKYEP		<i>BCR-JAK2</i>
PALETF		NONE
PALIBN		<i>IGH@-EPOR</i>
PALJDL		NONE
PAMDRM	<i>IGH@-CRLF2</i>	
PANGL		<i>PAX5-JAK2</i>
PANSFD		<i>ETV6-ABL1</i>
PANEHF		<i>RCSD1-ABL1</i>
SJBALLO85		<i>NUP214-ABL1</i>
SJBALLO10		<i>RANBP2-ABL1</i>

Results: Poor outcome of Ph-like ALL

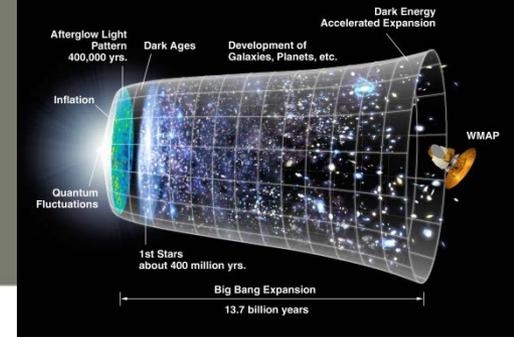


Adolescent



Young adult

Acknowledgements



❖ CTEP

Malcolm A. Smith MD. Ph.D. – *Associate Branch Chief*

❖ OCG

Jaime M. Guidry Auvil, Ph.D. – *Scientific Program Manager*

Martin Ferguson, Ph.D. – *Consultant*

Shannon Behrman, Ph.D. – *Science Communications Manager*

Jessica Mazerik, Ph.D. – *Health Communications Fellow*

❖ OCG Data Coordinating Center

Tanja M. Davidsen, Ph.D. – *Bioinformatics Program Manager*

Patee Gesuwan – *Senior Bioinformatics Engineer*

Leandro C. Hermida – *Bioinformatics Scientist / Software Engineer*

❖ Leidos (SAIC) Support

Jeanne Lewis – *Senior Contract Specialist*

Ellen Miller -- *COTR*

❖ TARGET Project Team Members

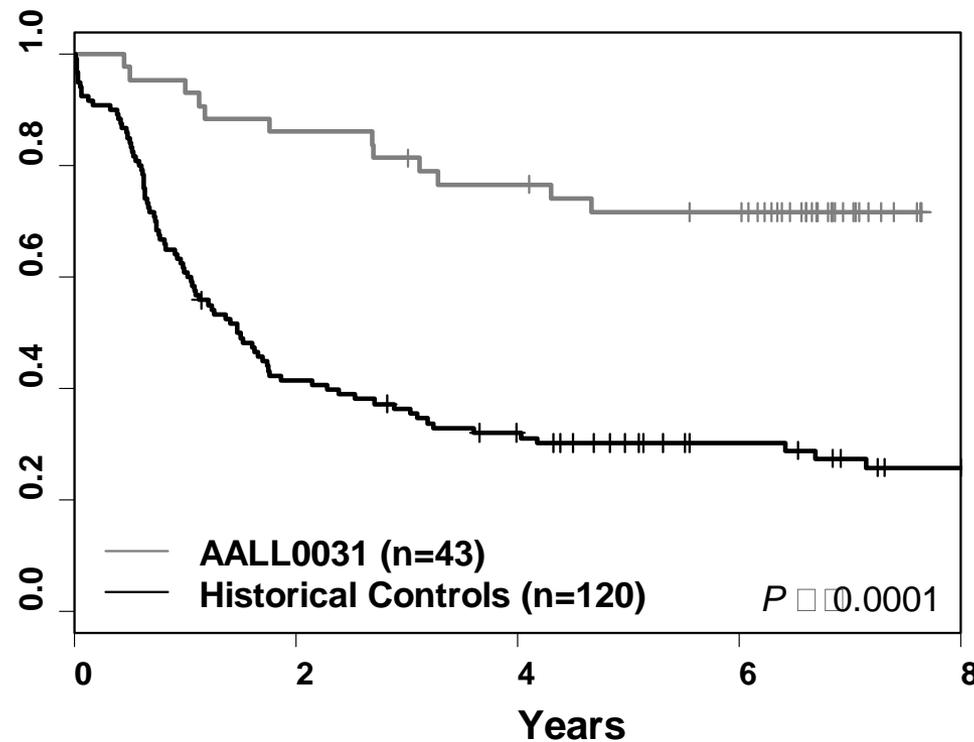
Precision Medicine: Following the Adult Paradigm

Precision Medicine: Following the Adult Paradigm

- Ph⁺ acute lymphoblastic leukemia (ALL)
- ALK⁺ anaplastic large cell lymphoma (ALCL)
- BRAF mutations in pilocytic astrocytoma and high-grade gliomas
- Ph-like ALL

Impact of Imatinib added to standard chemotherapy for Ph⁺ ALL (AALL0031)

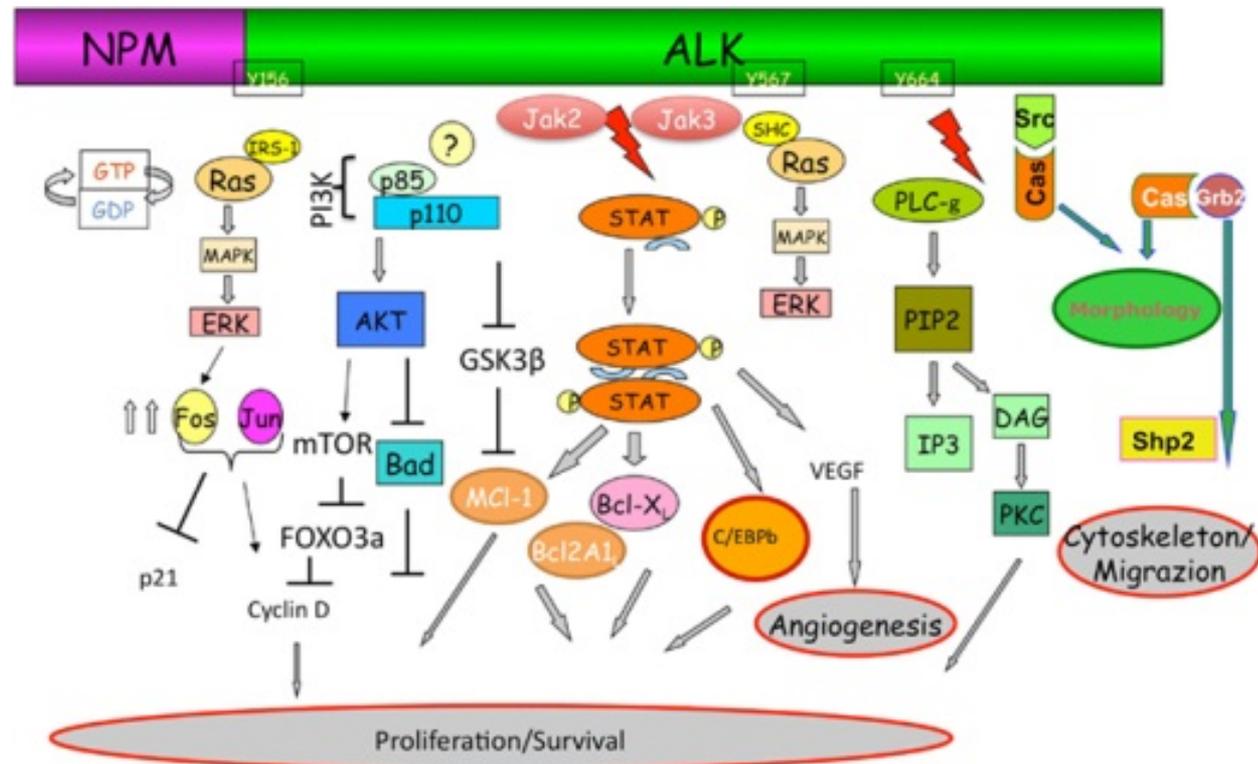
- Adding imatinib to standard chemotherapy more than tripled EFS for Ph⁺ ALL in COG AALL0031
- 7-yr EFS of 71.7% vs. 21.4%



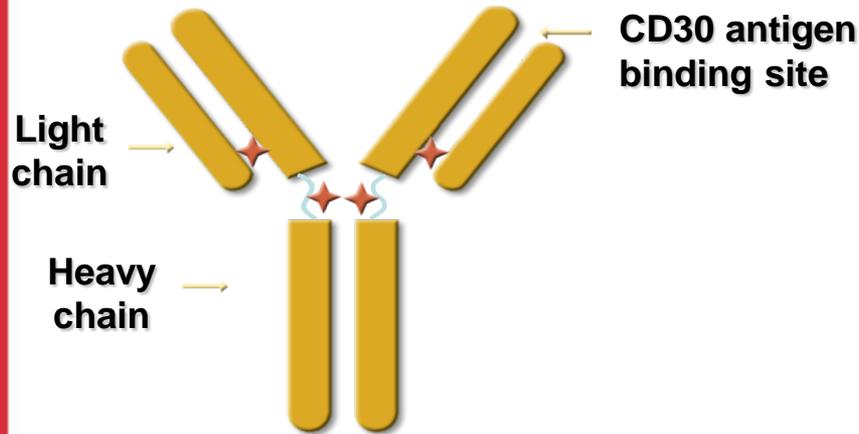
Anaplastic Large Cell Lymphoma

Anaplastic Large Cell Lymphoma in Children

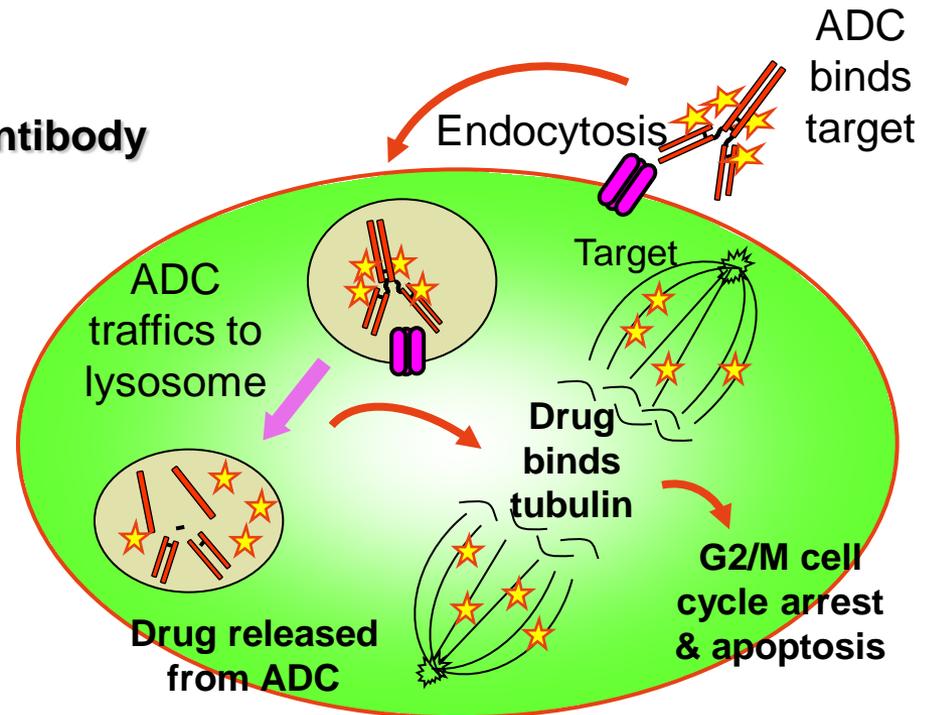
- Approximately 15% of childhood NHL cases.
- NPM-ALK is oncogenic driver.
- CD30 is uniformly expressed at high levels.



Brentuximab Vedotin (SGN-35): CD30 Targeted Antibody-Drug Conjugate



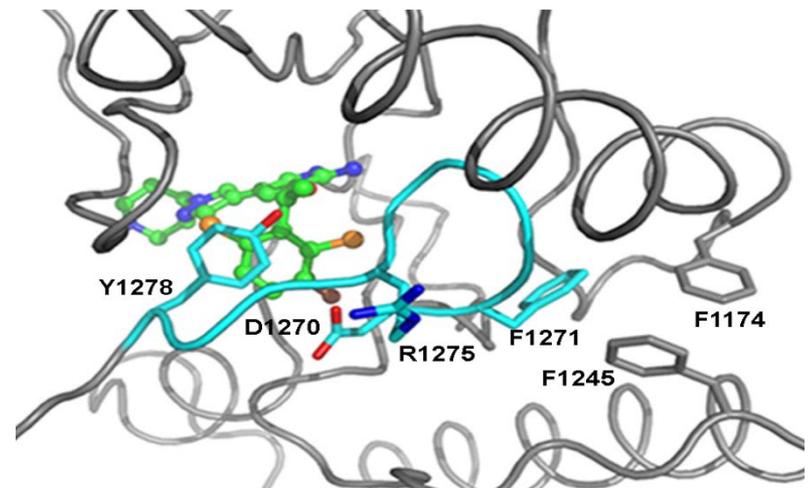
**Auristatin derivative:
average of 4 molecules per antibody**



Crizotinib (MET and ALK inhibitor)

- >95% of pediatric ALCL are ALK+
- ALK translocations in ALCL include:
 - t(2;5) – NPM/ALK – 85%
 - t(1;2) – TPM3/ALK – 3%
 - Inv (2) – ATIC/ALK
 - t(2;3) – TFG/ALK
 - t(2;17) – CLTC/ALK
 - t(2;X) – MSN/ALK
 - t(2;19) – TPM4/ALK
 - t(2;22) – MYH9/ALK
 - t(2;17) – ALO17/ALK

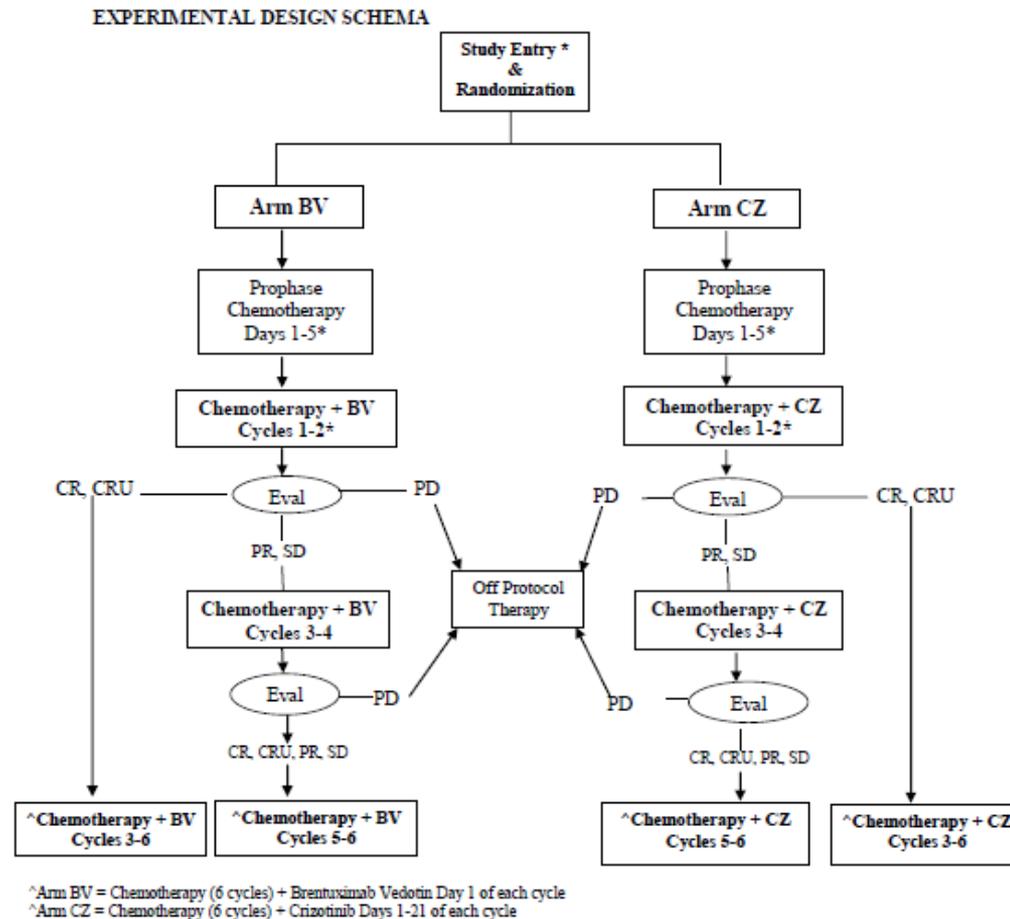
ALK with Crizotinib



ANHL12P1: Comparison of standard chemotherapy + either brentuximab vedotin or crizotinib

Brentuximab vedotin

Crizotinib

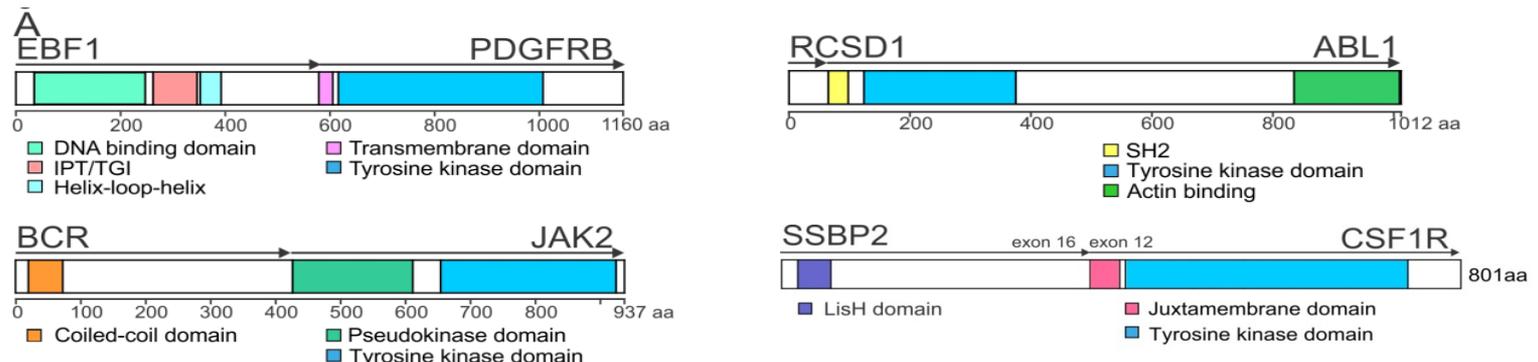


- Target is 64 eligible patients per arm.
- Compare each arm to historical control: 70% EFS

Ph-Like Acute Lymphoblastic Leukemia (ALL)

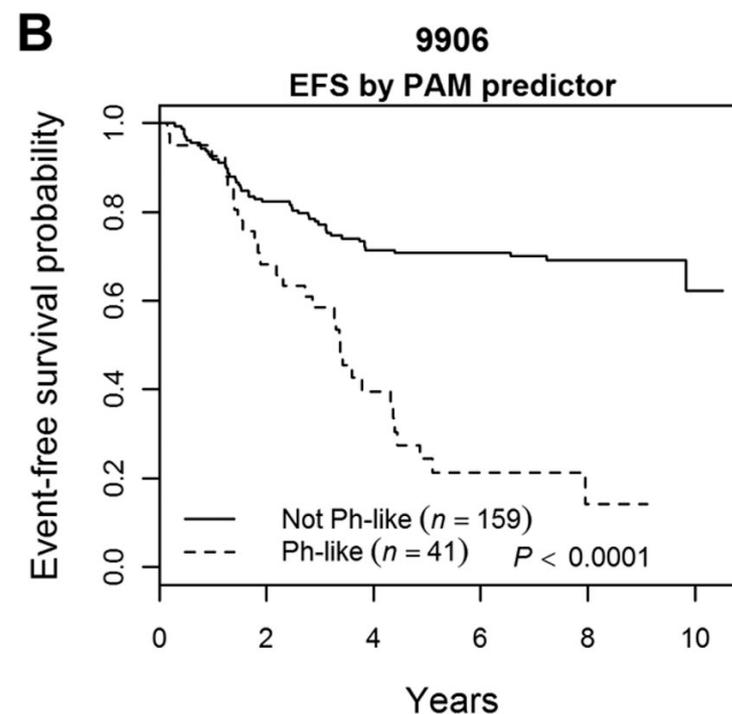
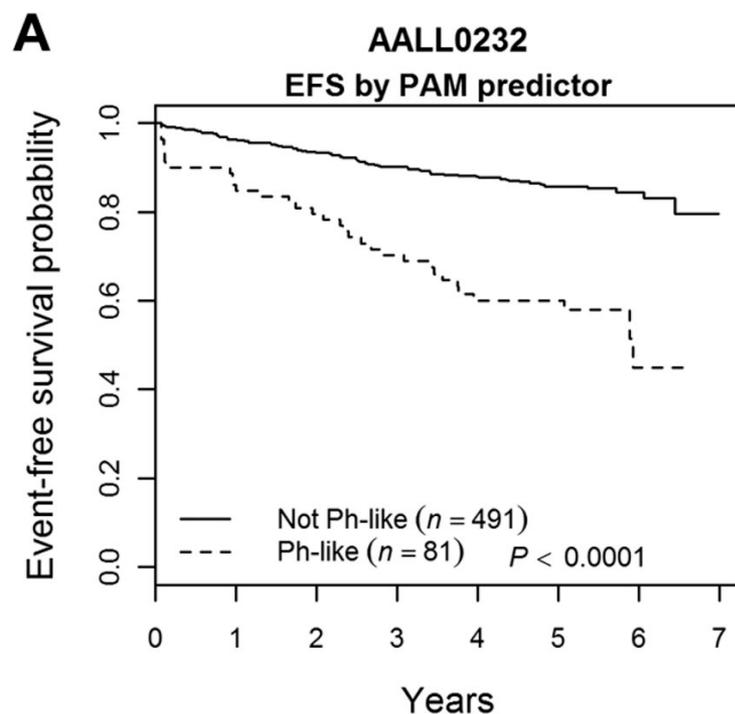
Ph-like (BCR-ABL1-like) B-ALL

- Cases with a gene expression profile similar to that of Ph⁺ ALL (but without BCR-ABL1 fusion) (Mullighan NEJM 2009; Den Boer Lancet Onc 2009; Harvey Blood 2010; Roberts Cancer Cell 2012)
- Genomics of Ph-like ALL (as defined by COG)
 - 50% have CRLF2 alterations \pm JAK mutations
 - Remainder have variety of gene fusions targeting ABL1, ABL2, CSF1R, PDGFRB, JAK2 and other kinase genes

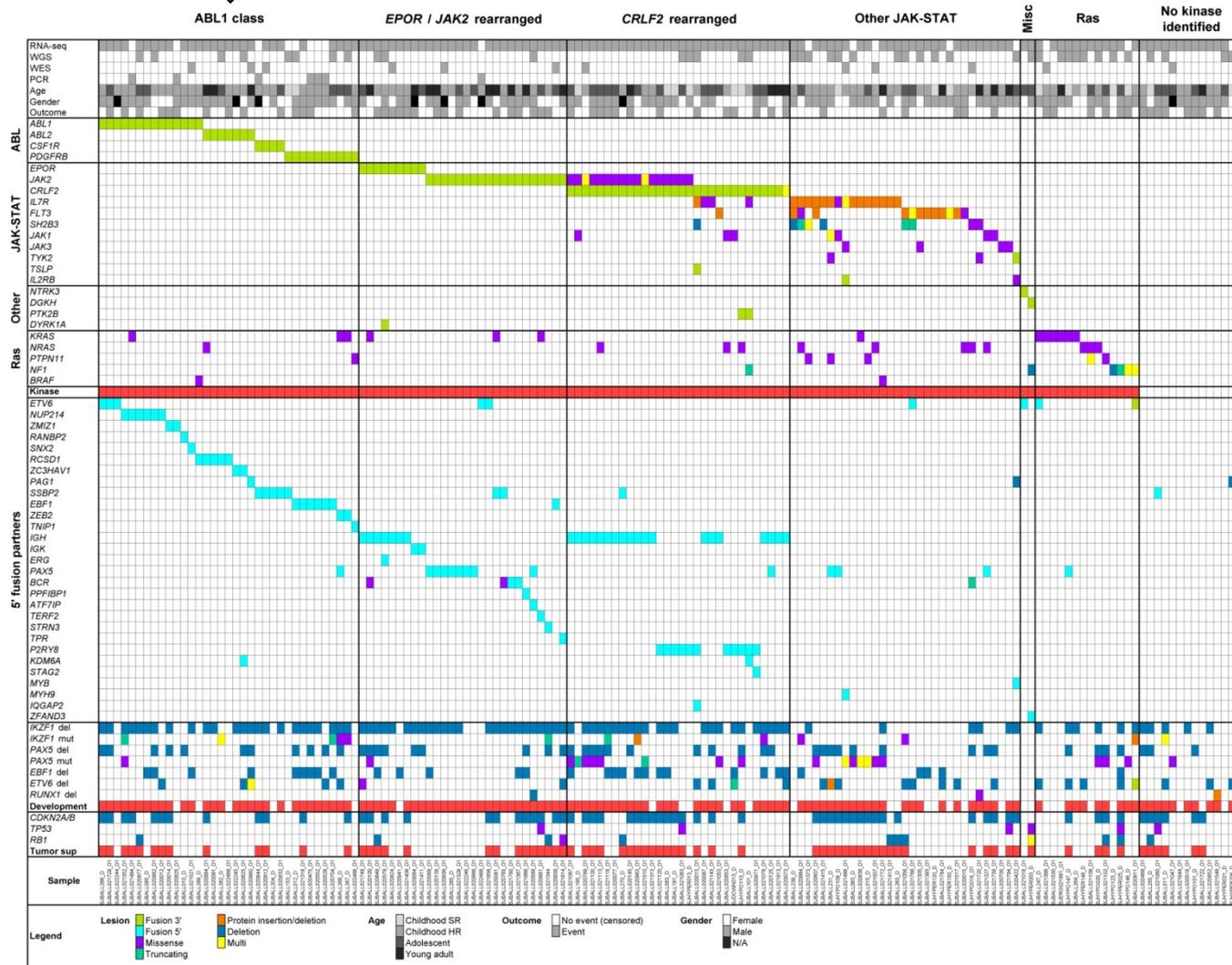
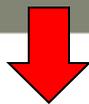


Prognosis for Children with Ph-Like ALL

- Ph-like ALL patients have greatly increased risk of treatment failure and death



The Genomic Landscape of Ph-Like ALL



Ph-Like ALL Team

- NCH
 - Julie Gastier Foster
 - Shalini Reshmi
 - Eileen Stonerock
- SJCRH
 - Charles Mullighan
 - Kathryn Roberts
 - Jinghui Zhang
- UCSF
 - Mignon Loh
- U Colorado
 - Stephen Hunger
- UF
 - Mini Devidas
- UNM
 - Cheryl Willman
 - Rick Harvey
 - Iming Chen

Identification & Treatment of Ph-Like ALL

Identify Ph-like ALL by LDA Card



Candidate testing

Fusions: RT-PCR
CRLF2 alterations: FISH/PCR
JAK/IL7RA/SH2B3 mutation



RNA-seq

If candidate screens negative



WGS

If above negative

Retrospective phase (Year 1)

Assay all cases enrolled on:
AALL1131: 1420 pts

Ph-like: N=230

ABL1/PDGFRB/ABL2/CSF1R fusions: N=58

No changes in therapy

Prospective phase (Years 2-4)

AALL1131: 2821 pts

Ph-like: N=456

ABL1/PDGFRB/ABL2/CSF1R fusions: N=114

Change therapy based on results

**ABL1/ABL2/PDGFRB/CSF1R fusion positive:
Add dasatinib in prospective phase and compare
outcome to that of pts from retrospective phase**

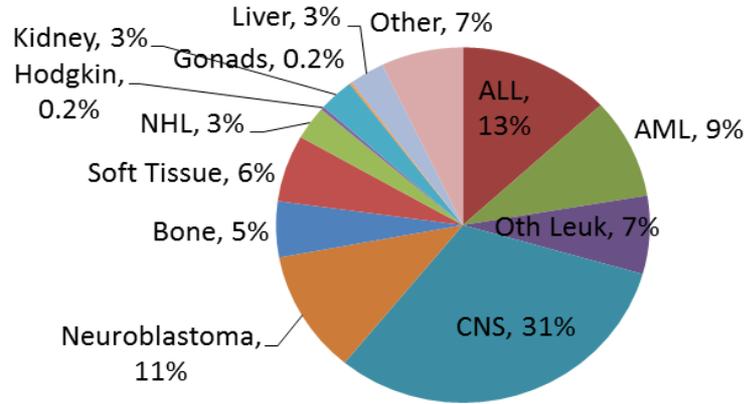
Grants to Support Ph-Like Clinical Translation

- SBF Consortium grant (Hunger et al); 7/1/13-6/30/16
- LLS SCOR (Carroll) Project 1 (Hunger/Mullighan); 10/1/13-9/30/18
- SPECS II (Willman/Hunger); 4/1/11-3/31/16
- Children's Oncology Group Operations and Statistical awards (Adamson, Devidas)

Precision Medicine: Following the Adult Paradigm

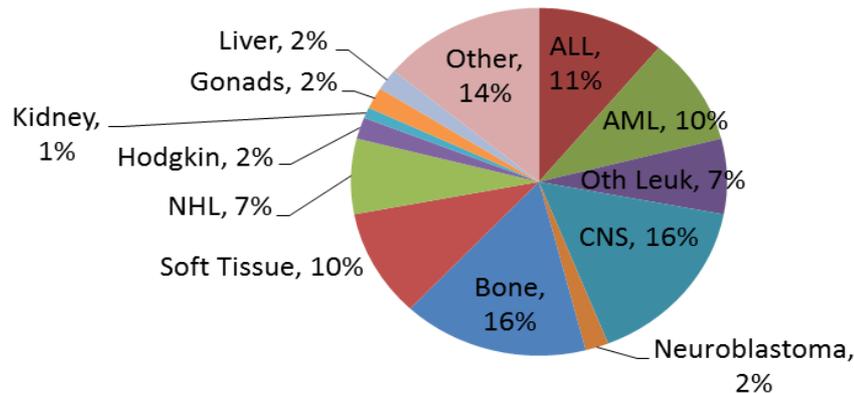
Causes of Childhood Cancer Mortality

<15 Year Mortality 2007-2010



~ 2000 children and adolescents die of cancer each year in the US

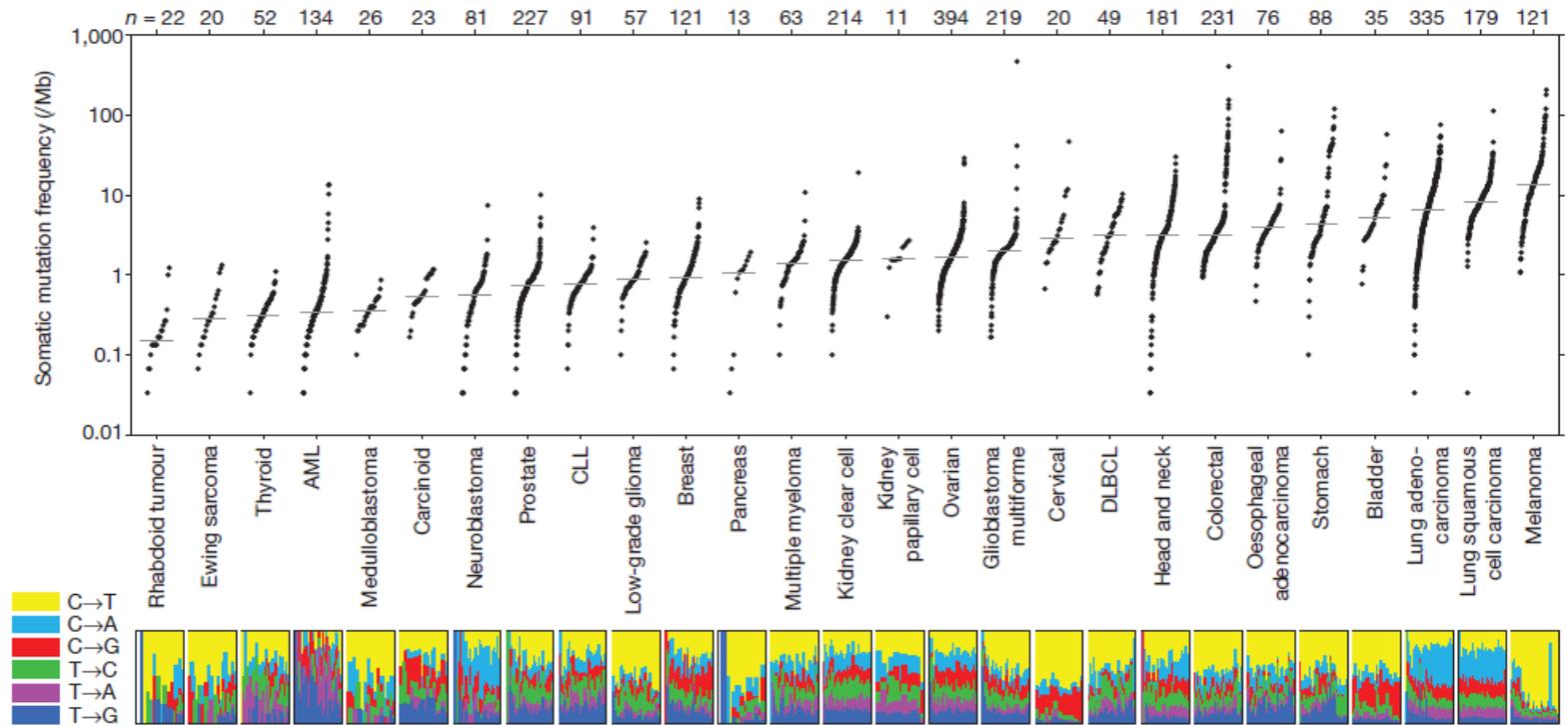
15-19 Year Mortality 2007-2010



Children Are not Just Little Adults

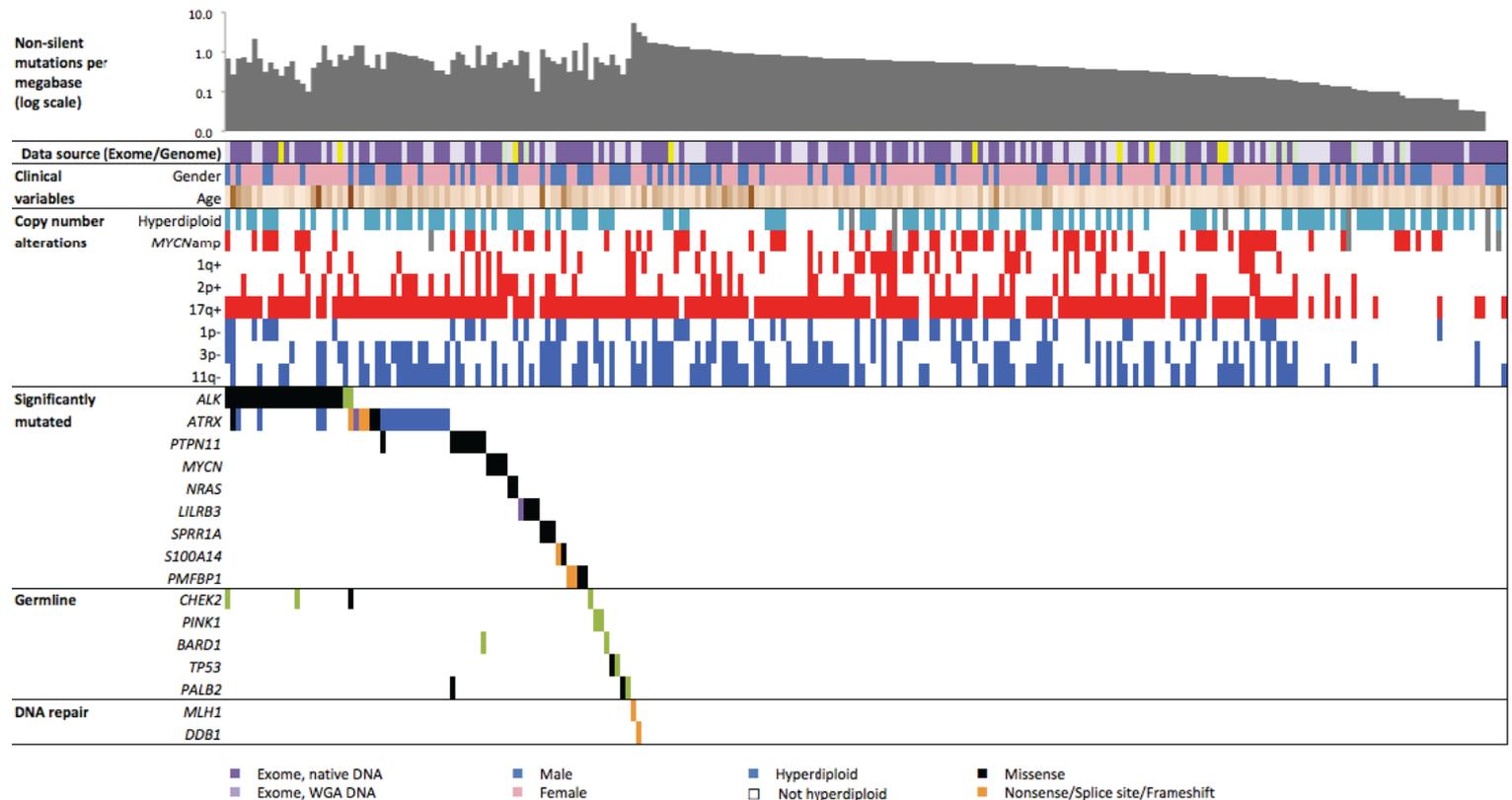
- And childhood cancers aren't just early-developing adult cancers

Childhood Cancers Show Lower Mutation Rates Compared to Adult Cancers



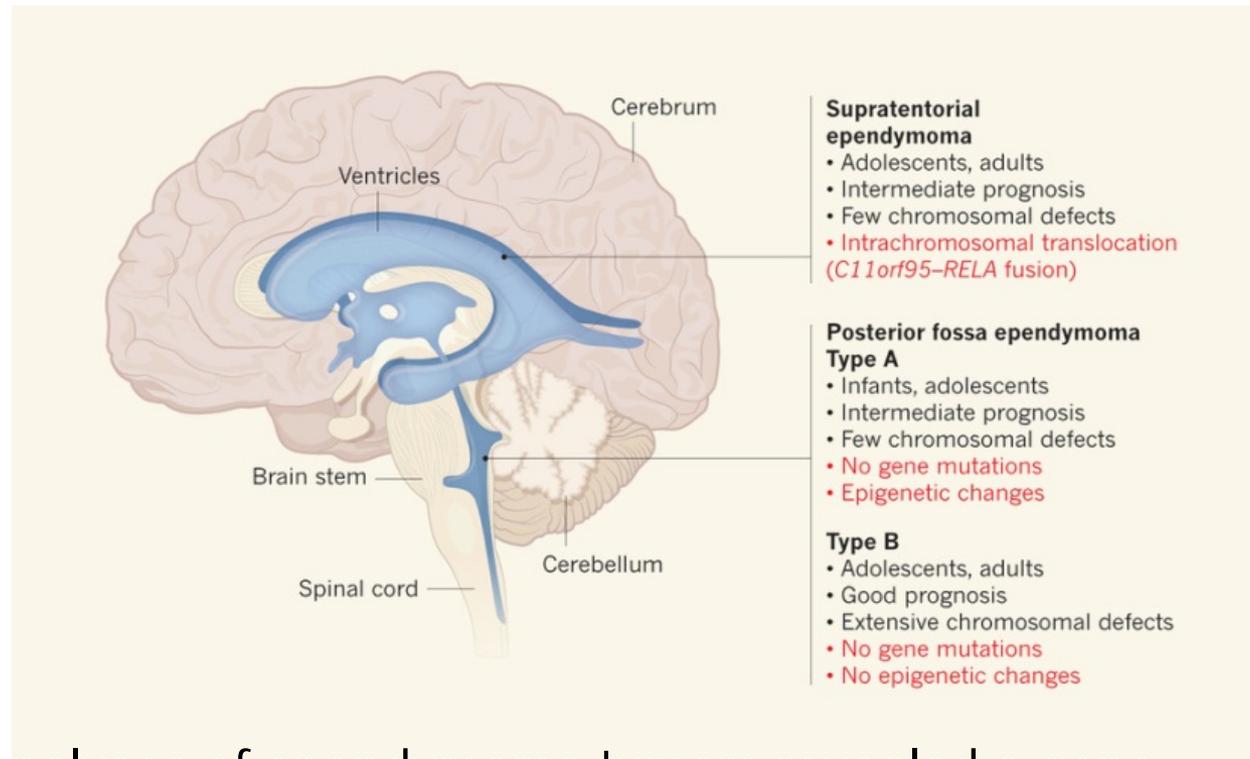
- Somatic mutation frequencies observed in exomes from 3,083 tumor–normal pairs

The Genomic Landscape of High-Risk Neuroblastoma



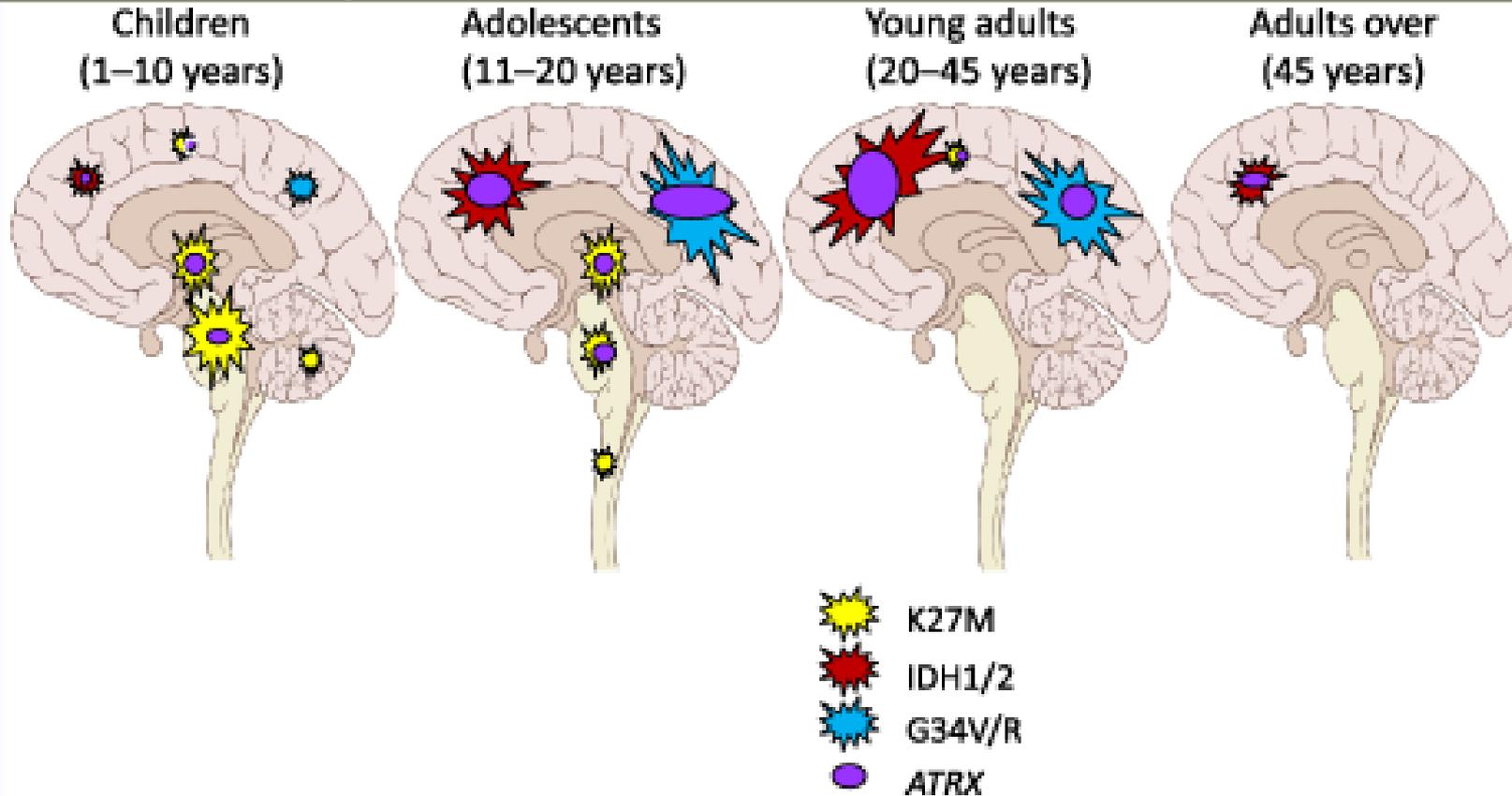
- 240 matched tumor and normal pairs (age > 18 mos and Stage 4 disease) by WES (221 cases), WGS (18 cases), or both (1 case)

The Genomic Landscape of Ependymoma



- Analyses of ependymoma tumors revealed a gene rearrangement in 1 subtype, but no recurring DNA mutations in 2 others:
 - Parker M, et al. Nature 2014:506(7489):451-455
 - Mack SC, et al. Nature 2014:506(7489):445-450

Chromatin Remodeling Defects in Pediatric and Young Adult Glioblastoma



- K27M-H3.3 or H3.1 (yellow stars) occur mainly in brainstem HGA and K27M-H3.3 mainly thalamic HGA (70%–80% of all GBM in these locations).

Genomic Landscapes of Other Childhood Cancers

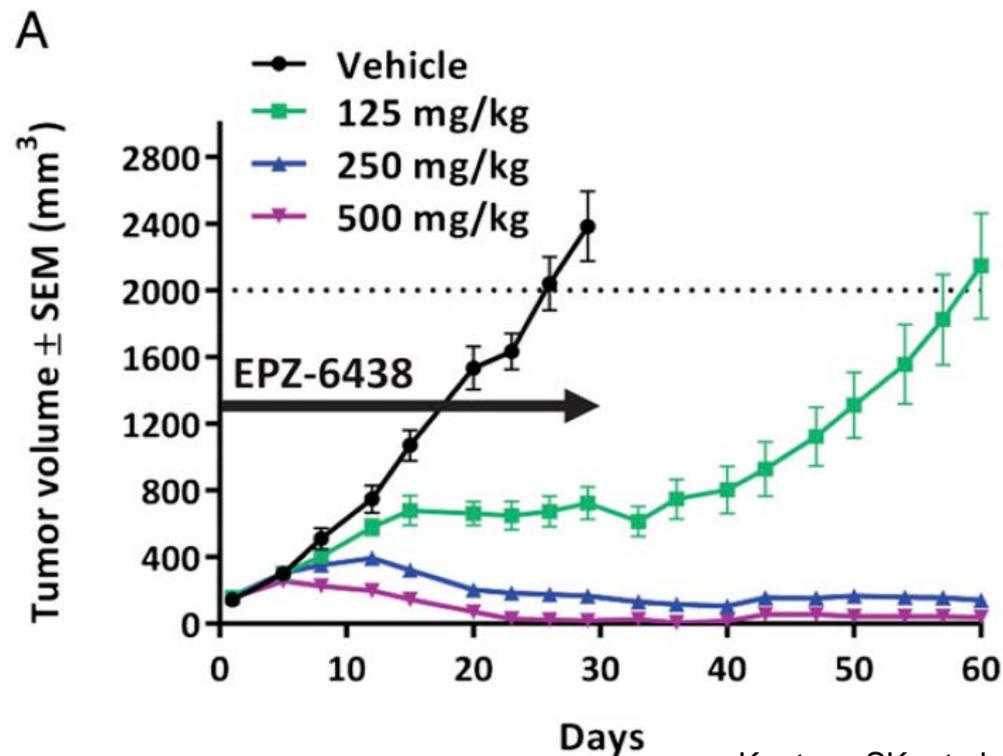
- Osteosarcoma
 - Chen X, et al. Cell Reports 2014;7:104-112
- Ewing sarcoma
 - Crompton, et al. Proc AACR 2014: Abstr #999
- Rhabdomyosarcoma
 - Chen X, et al. Cancer Cell 2013;24(6):710-724
 - Shern JF, et al. Cancer Discovery 2014;4:216-231
- Rhabdoid tumor
 - Lee RS, et al. J Clin Invest 2012;122:2983-298

A Strategy for Pediatric Precision Medicine

- Focusing on liabilities created by the primary genomic lesion or liabilities associated with the cell of origin, for example:
 - Rhabdoid tumors: SMARCB1 mutation/deletion
 - MLL leukemias: MLL gene rearrangement
 - Ewing sarcoma: EWS-FLI1
 - Alveolar rhabdomyosarcoma: PAX-FKHR
 - DIPG: Histone 3.3 K27M mutation

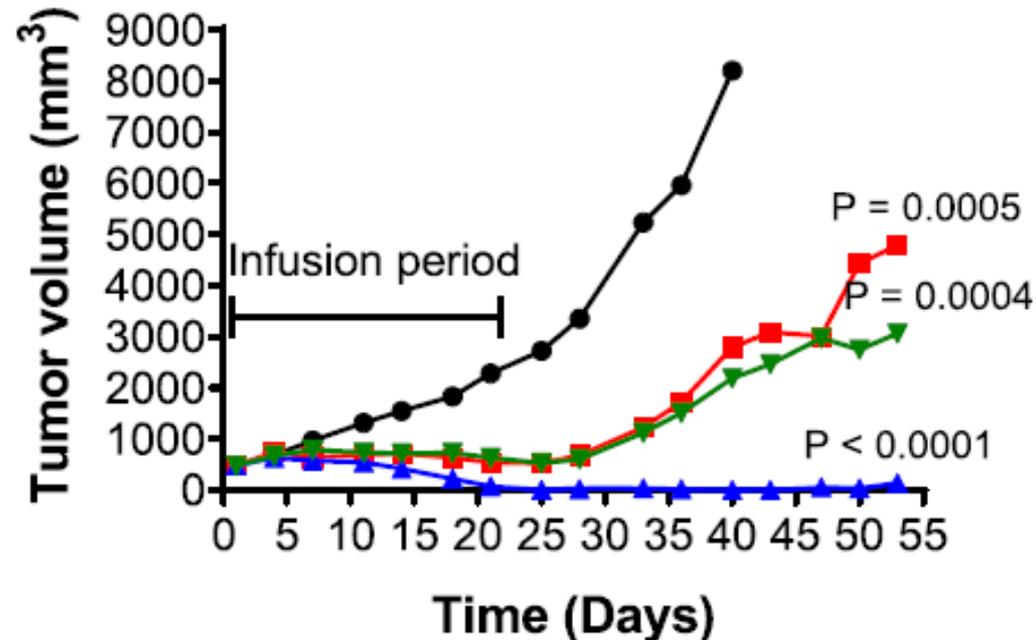
Rhabdoid tumors and EZH2 inhibition

- Knockout of EZH2 completely blocked the growth of SMARCB1 mutant cancers but had no effect on osteosarcomas driven by p53/Rb loss.
 - Wilson BG, et al. Cancer Cell 2010;18(4):316-328



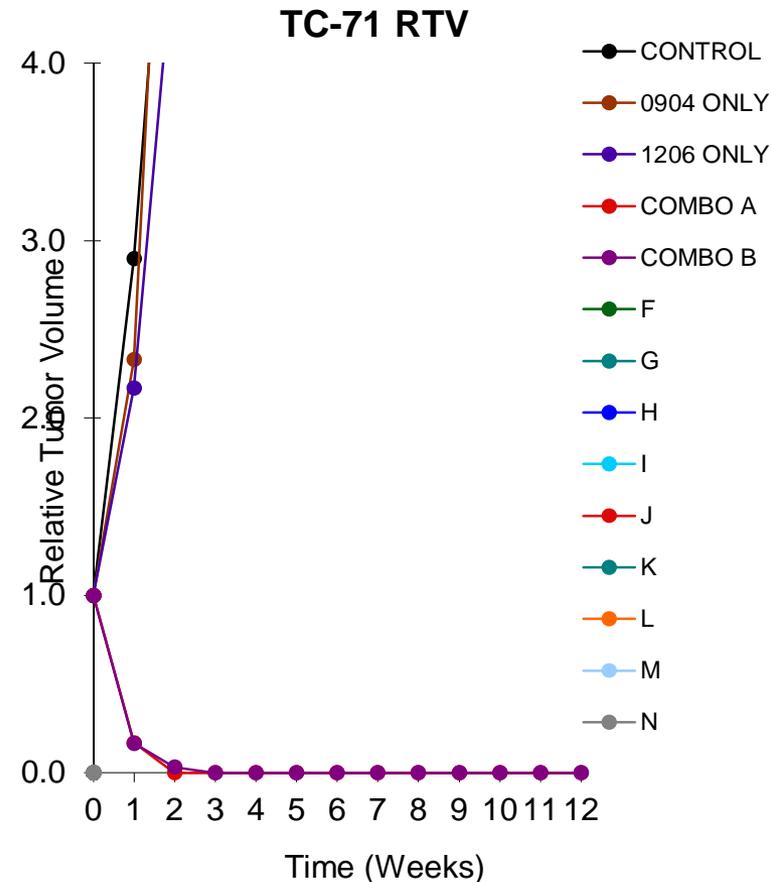
MLL Leukemia and DOT1L Inhibition

- MLL-rearranged leukemia is dependent on aberrant H3K79 methylation by Dot1L
 - Bernt KM, et al. Cancer Cell 2011;20(1):66-78
- Effect of EPZ-5676 administration on MV4-11 xenograft tumors implanted SC in immunocompromised rats
 - Daigle SR, et al. Blood 2013;122(6):1017-1025

A

Ewing Sarcoma and PARP Inhibition

- Reports of sensitivity of EWS-FLI1 expressing tumors to PARP inhibition.
 - Garnett MJ, et al. Nature 2012;483 :570-575
 - Brenner JC, et al. Cancer Res 2012;72:1608-1613
- PPTP identified dramatic synergy for the PARP inhibitor BMN 673 and low-dose temozolomide
- COG Phase 1 trial ongoing: NCT02116777



A Strategy for Pediatric Precision Medicine

- Focusing on liabilities created by the primary genomic lesion or liabilities associated with the cell of origin, including:
 - Rhabdoid tumors: SMARCB1 mutation/deletion
 - MLL leukemias: MLL gene rearrangement
 - Ewing sarcoma: EWS-FLI1
 - Alveolar rhabdomyosarcoma: PAX-FKHR
 - DIPG: Histone 3.3 K27M mutation

Other Priority Clinical Research Areas

- CAR T-cell therapy (e.g., targeting CD19+ ALL)
- Bispecific T-cell engaging antibodies (e.g., blinatumomab targeting CD19+ ALL)
- Immune checkpoint inhibitors
- GD2-targeted therapies for neuroblastoma

Children Are not Just Little Adults

- And childhood cancers aren't just early-developing adult cancers
- A pediatric-specific approach to precision medicine is needed
- Crucial to identify susceptibilities created by childhood cancer oncogenic drivers
- National and international clinical trials will be essential given the small sizes of genomically defined subgroups
- NCI has a critical role to play

Back-up Slides

Chimeric 14.18 (ch14.18) for High-Risk Neuroblastoma

Illustrating a public-private partnership
strategy for pediatric drug development.

GD2: Disialoganglioside

- Over 99% of neuroblastoma expresses GD2
- Reactivities of anti-GD2 to normal tissues is confined mostly to tissues of neuroectodermal origin, e.g., skin and brain tissue
- GD2 is also expressed by selected other tumors, including melanoma and osteosarcoma

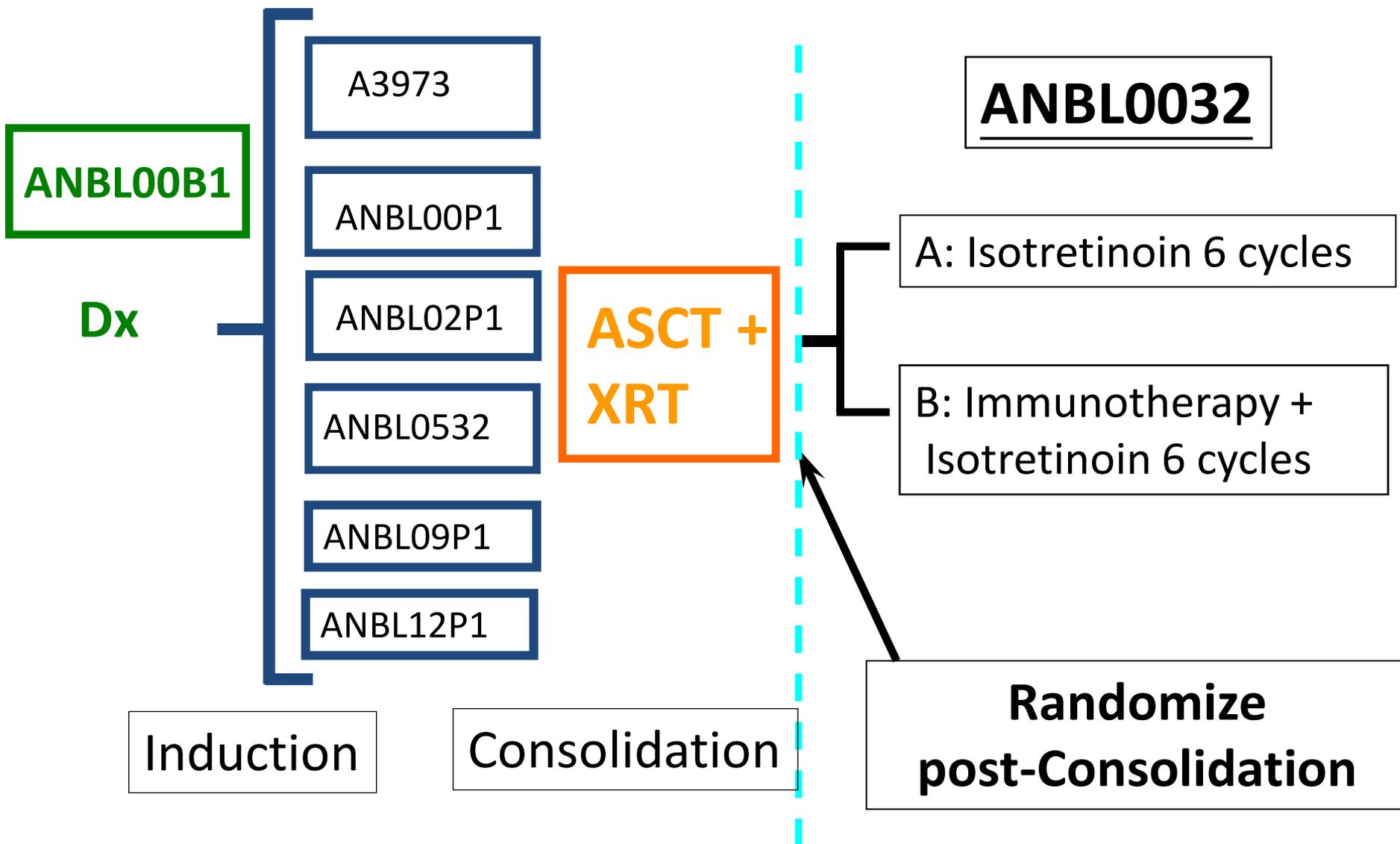
ch14.18 characteristics

- Initially developed as a murine IgG3 mAb, 14.18, that bound GD2.
- ch14.18 produced by combining cDNA sequences encoding the variable portions of 14.18 with the constant regions of the human heavy chain IgG1 and light chain κ .
- ch14.18 has potent ADCC and CDC activity

The Development of ANBL0032: phase 3 evaluation of ch14.18

- **1990's:** Phase I and II clinical trials of ch14.18
 - ch14.18, pilot study of ch14.18+GM-CSF:Yu
 - Phase II study of ch14.18+ GM-CSF (POG9347):Yu
 - Pilot study of ch14.18 +GM-CSF/IL2 in MRD (CCG0935)
- **1998:** Agreement to conduct “intergroup” phase 3 trial by CCG + POG. NCI agrees to manufacture agent for the trial.
- **1998:** Concept Proposal submitted by COG for CTEP review
- **2000:** Protocol submitted by COG for CTEP review
- **2001:** ANBL0032 activated
- **2009:** Positive results for ANBL0032 identified
- **2009:** ANBL0032 continues as single arm study with all patients receiving ch14.18 plus cytokines
- **2009:** ANBL0931 activated
- **2010:** United Therapeutics announced as NCI CRADA partner

COG High-Risk Neuroblastoma Studies 2001 - 2014



ANBL0032

Regimen A: standard therapy

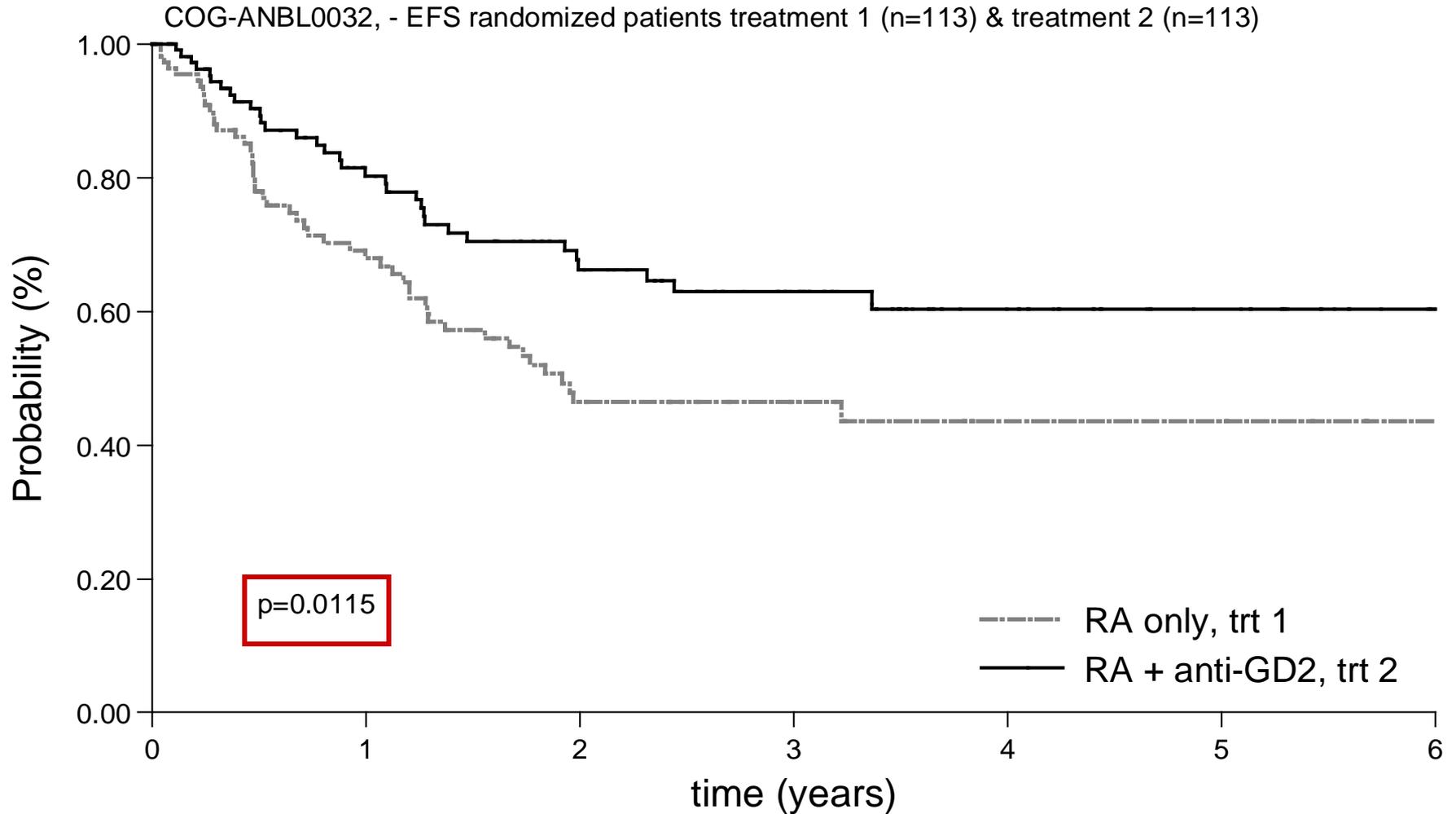
Isotretinoin (cis-RA) x 2 weeks q 4 weeks X 6 courses

Regimen B: immunotherapy

Schema for administration of ch14.18 + cytokines + cis-RA

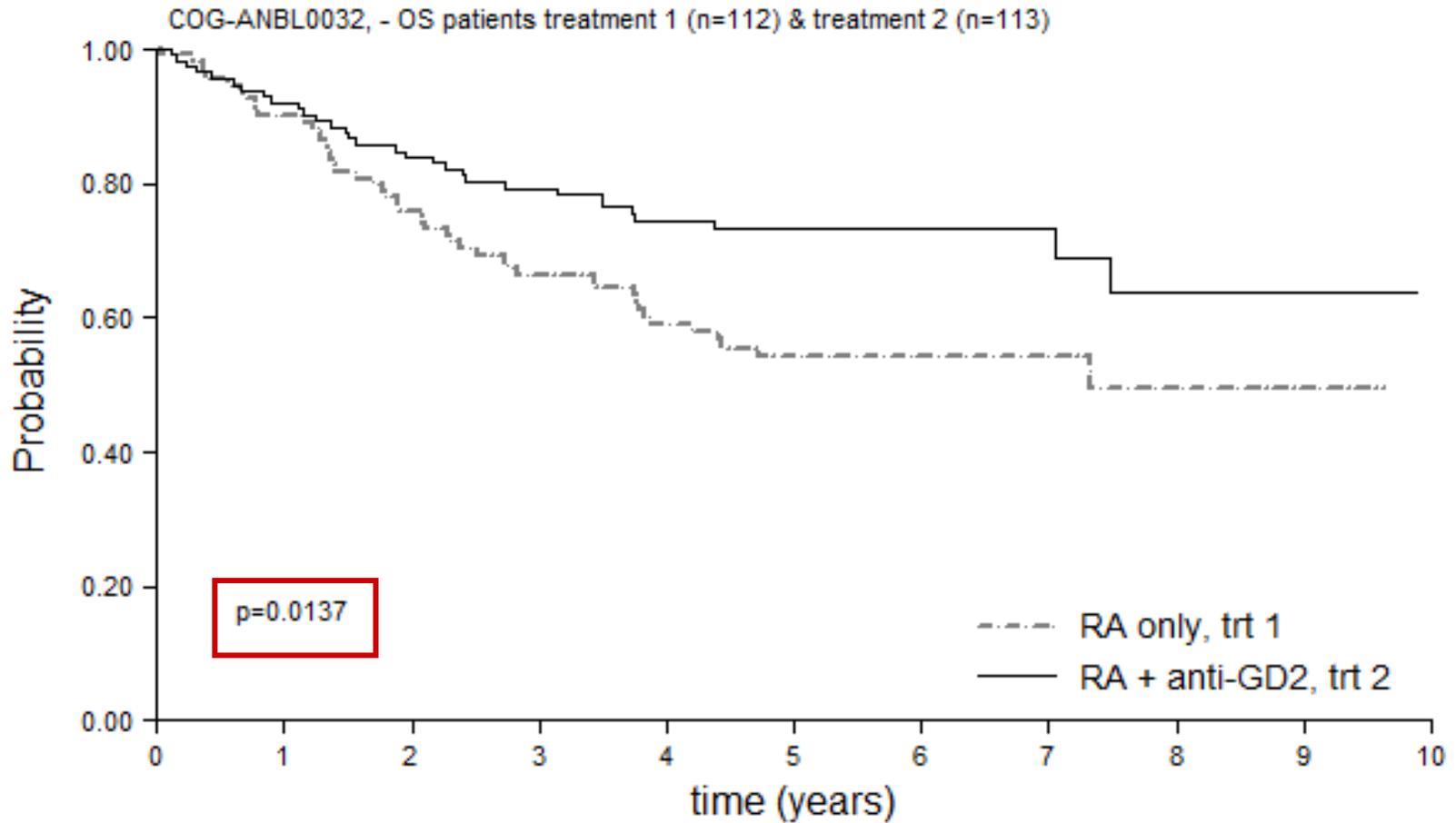
Course 1	Course 2	Course 3	Course 4	Course 5	Course 6
Ch14.18	Ch14.18	Ch14.18	Ch14.18	Ch14.18	
GM-CSF	IL2	GM-CSF	IL2	GM-CSF	
Cis-RA	Cis-RA	Cis-RA	Cis-RA	Cis-RA	Cis-RA

Ch14.18 + Cytokines Improves Event-free Survival for High Risk Neuroblastoma (2009)



risk (n)	0	1	2	3	4	5	6
trt 1	113	59	32	20	10	8	1
trt 2	113	69	47	29	15	9	3

Ch14.18 + Cytokines Improves Overall Survival for High Risk Neuroblastoma (2012)



risk (n)	0	1	2	3	4	5	6	7	8	9	10
trt 1	112	98	80	68	52	35	22	13	9	6	0
trt 2	113	102	92	86	66	49	34	18	9	5	0

- Public funds promote basic research for target identification
- Public funds support initial clinical work through existing clinical trials infrastructure
- Public funds support manufacturing of agent for proof-of-principle clinical trials.
- Once sufficient risk removed from agent's development, then pharmaceutical involvement can successfully occur.

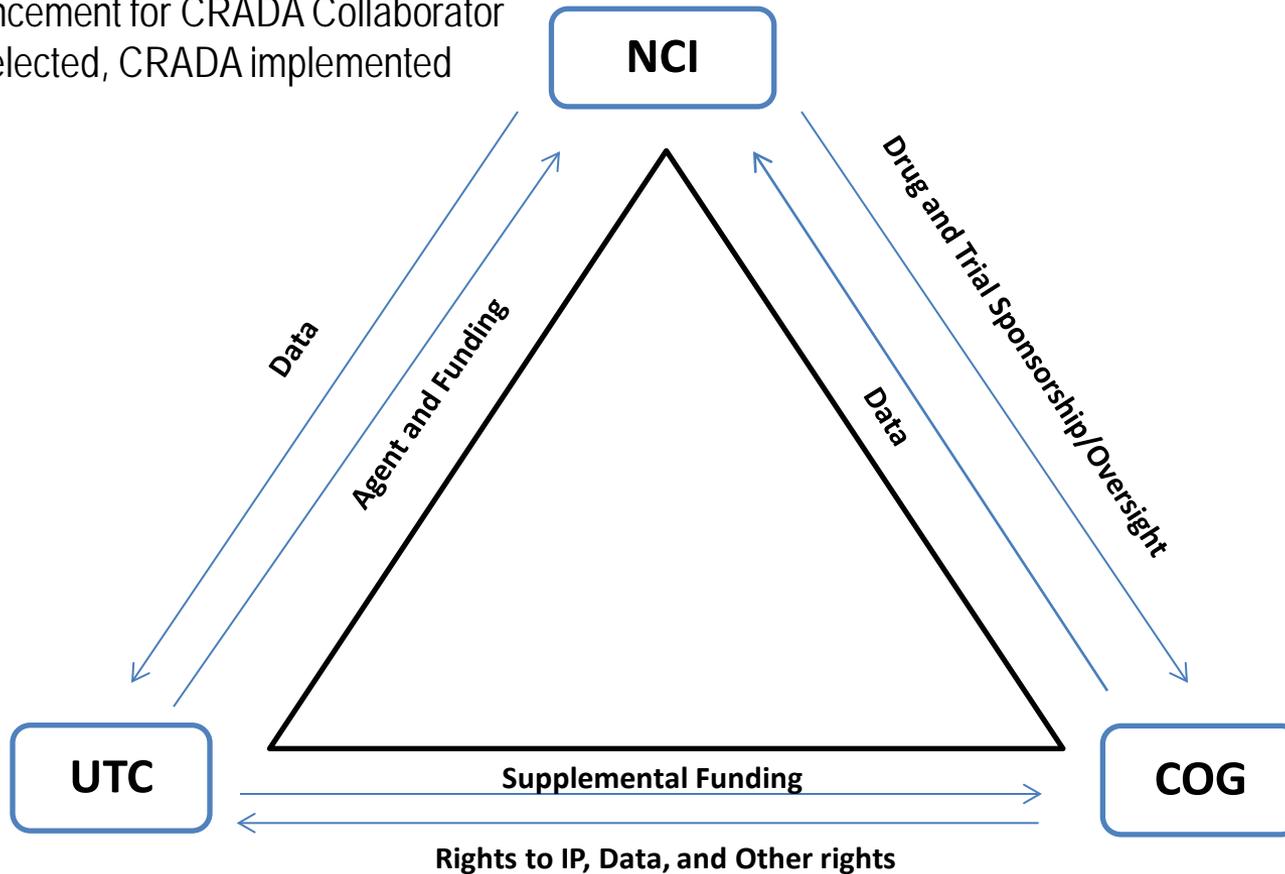
Collaborative Development of ch14.18 for Children with High-Risk Neuroblastoma

2001 – ANBL0032 initiated

2009 – ANBL0032 randomization stopped

2009 – Announcement for CRADA Collaborator

2010 – UTC selected, CRADA implemented



UTC

- Scale up and make ch14.18 → to NCI → COG
- Conduct additional clinical trials as needed
- Submit BLA

Molecular Subgroups of Medulloblastoma

CONSENSUS

Cho (2010)
Northcott (2010)
Kool (2008)
Thompson (2006)

WNT

C6
WNT
A
B

SHH

C3
SHH
B
C', D

Group 3

C1/C5
Group C
E
E, A

Group 4

C2/C4
Group D
C/D
A, C

DEMOGRAPHICS

Age Group:  infant, child, adult

Gender: ♀ ♂

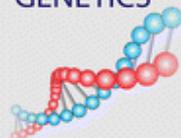
CLINICAL FEATURES

Histology

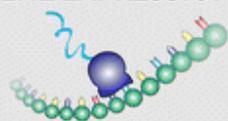
Metastasis

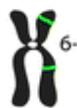
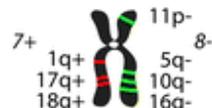
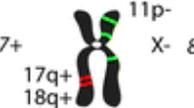
Prognosis

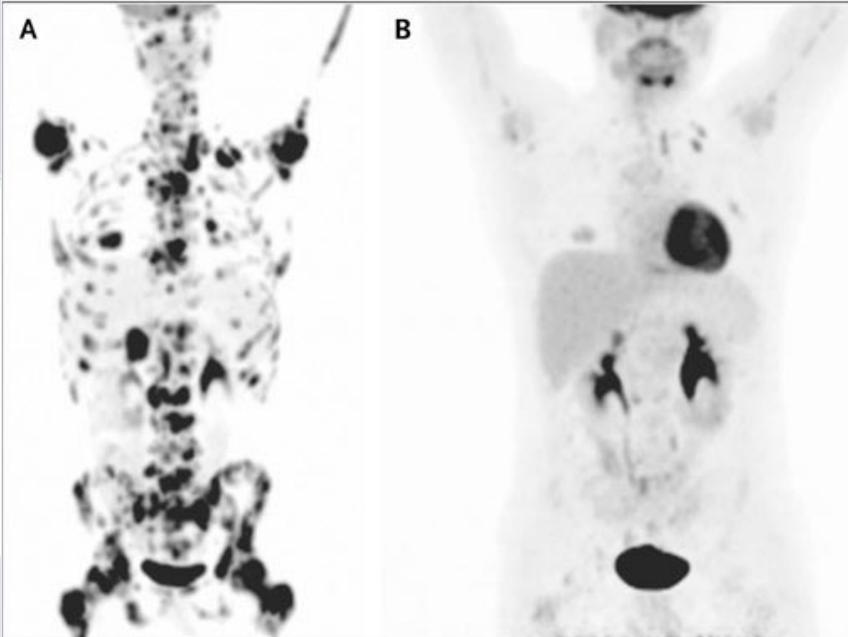
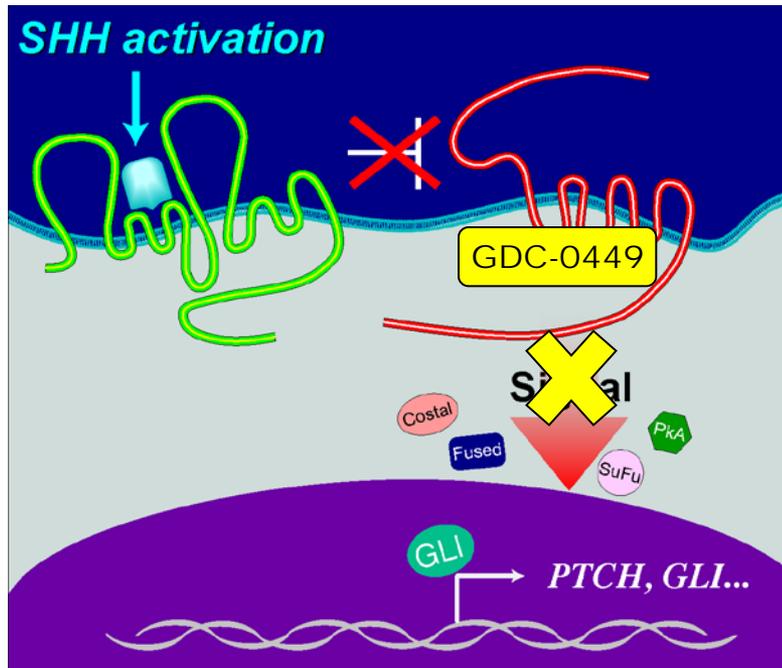
GENETICS



GENE EXPRESSION

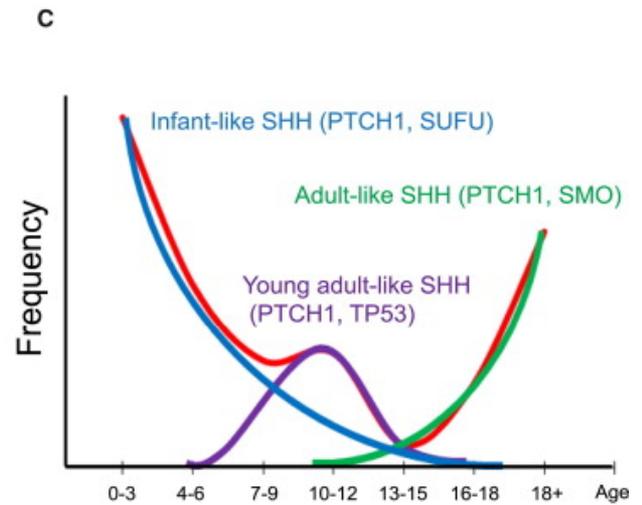
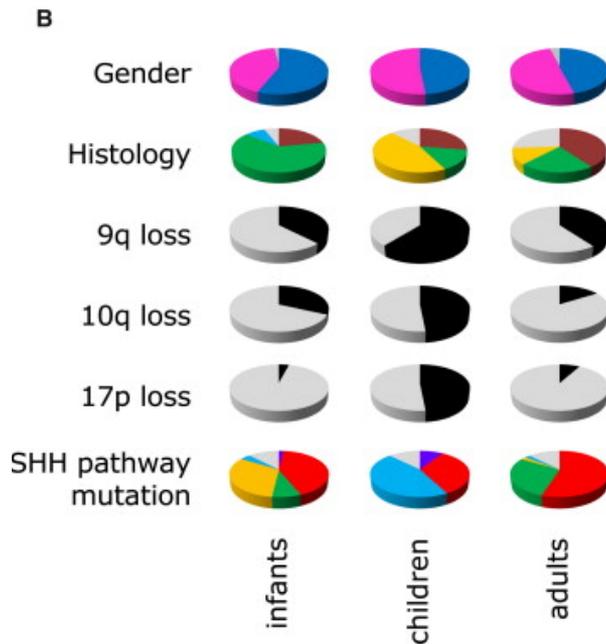
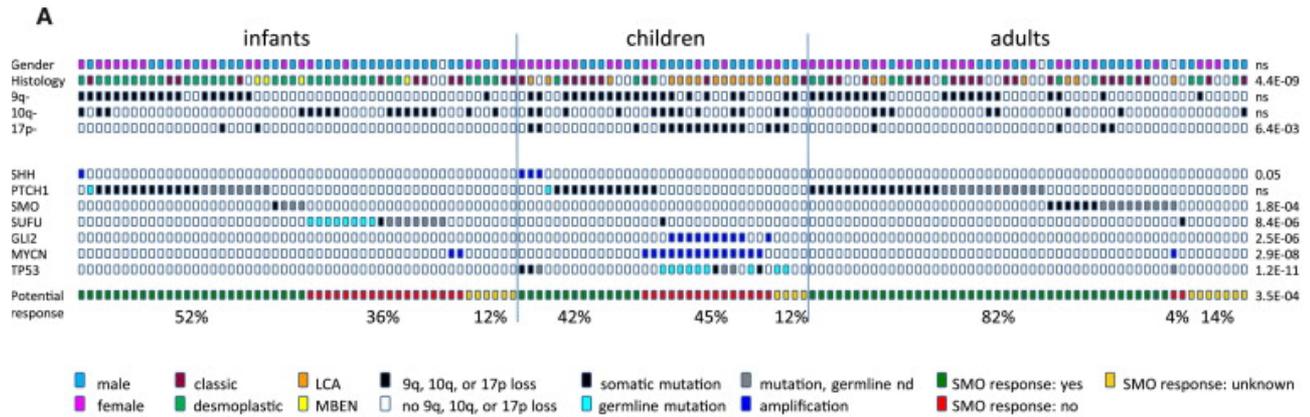


			
♂♂ : ♀♀	♂♂ : ♀♀	♂♂ : ♀	♂♂ : ♀
classic, rarely LCA	desmoplastic/nodular, classic, LCA	classic, LCA	classic, LCA
rarely M+	uncommonly M+	very frequently M+	frequently M+
very good	infants good, others intermediate	poor	intermediate
 CTNNB1 mutation	 PTCH1/SMO/SUFU mutation GLI2 amplification MYCN amplification	 i17q MYC amplification	 i17q CDK6 amplification MYCN amplification
WNT signaling	SHH signaling	Photoreceptor/GABAergic	Neuronal/Glutamatergic
MYC +	MYCN +	MYC +++	minimal MYC / MYCN

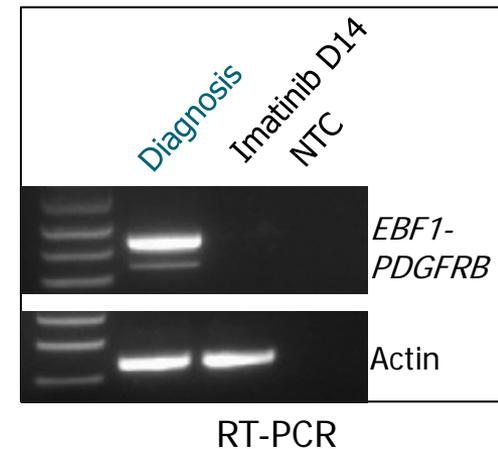


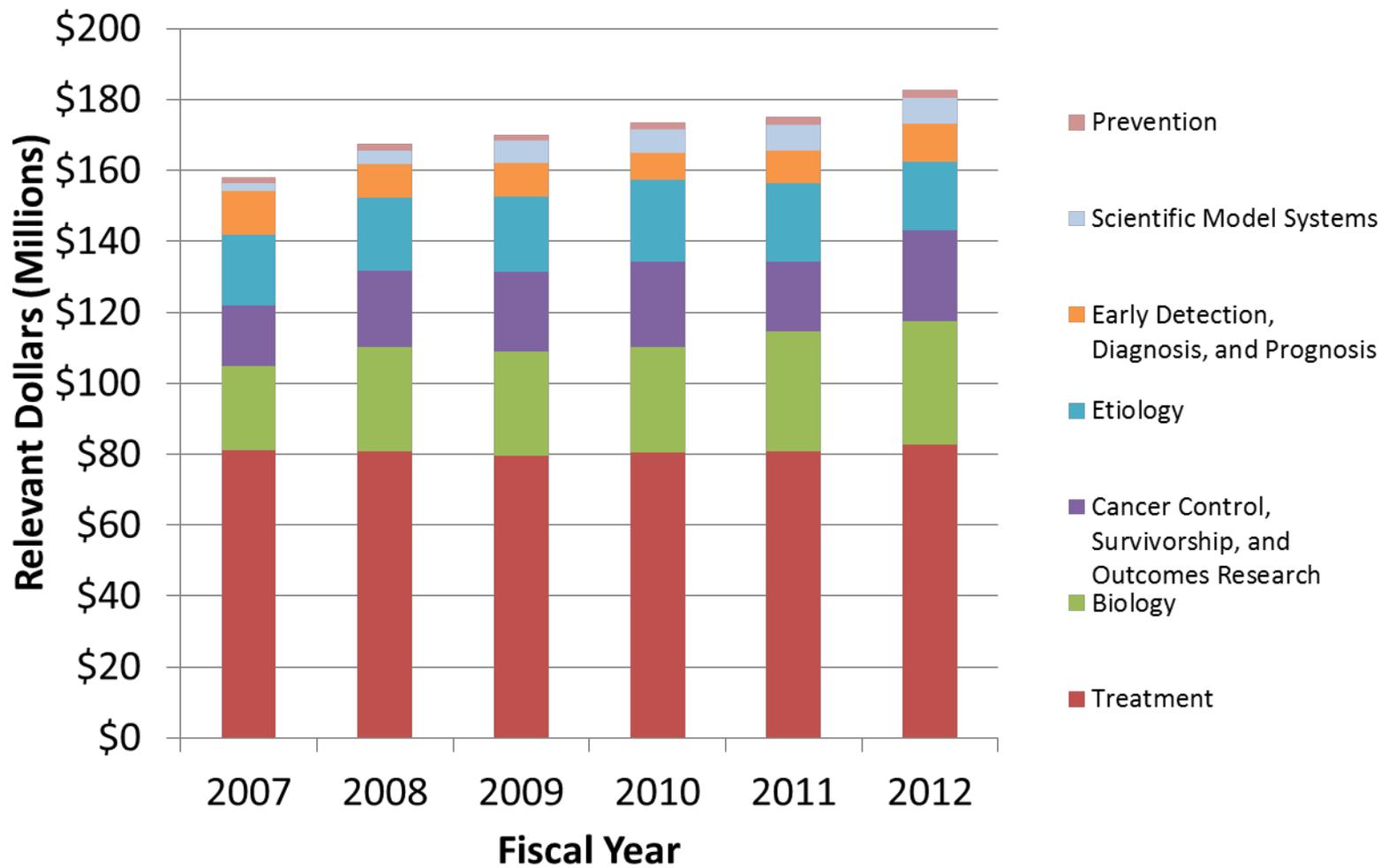
Rudin, et al. NEJM 361:1173-78, 2009

Through the PBTC, NCI supported a phase 2 clinical trial of GDC-0449 in children with recurrent medulloblastoma and a phase 2 trial in adults with recurrent medulloblastoma.



- 10 yr boy with refractory B-ALL – 70% blasts at day 29
- Cytogenetics: 5q33 deletion at PDGFRB
- Molecular testing showed EBF1-PDGFRB translocation
- Imatinib added to standard chemotherapy with immediate clinical improvement
- 1 week: morphologic remission; 2 weeks: MRD 0.017%
- Remains in remission at 2 years after imatinib initiation



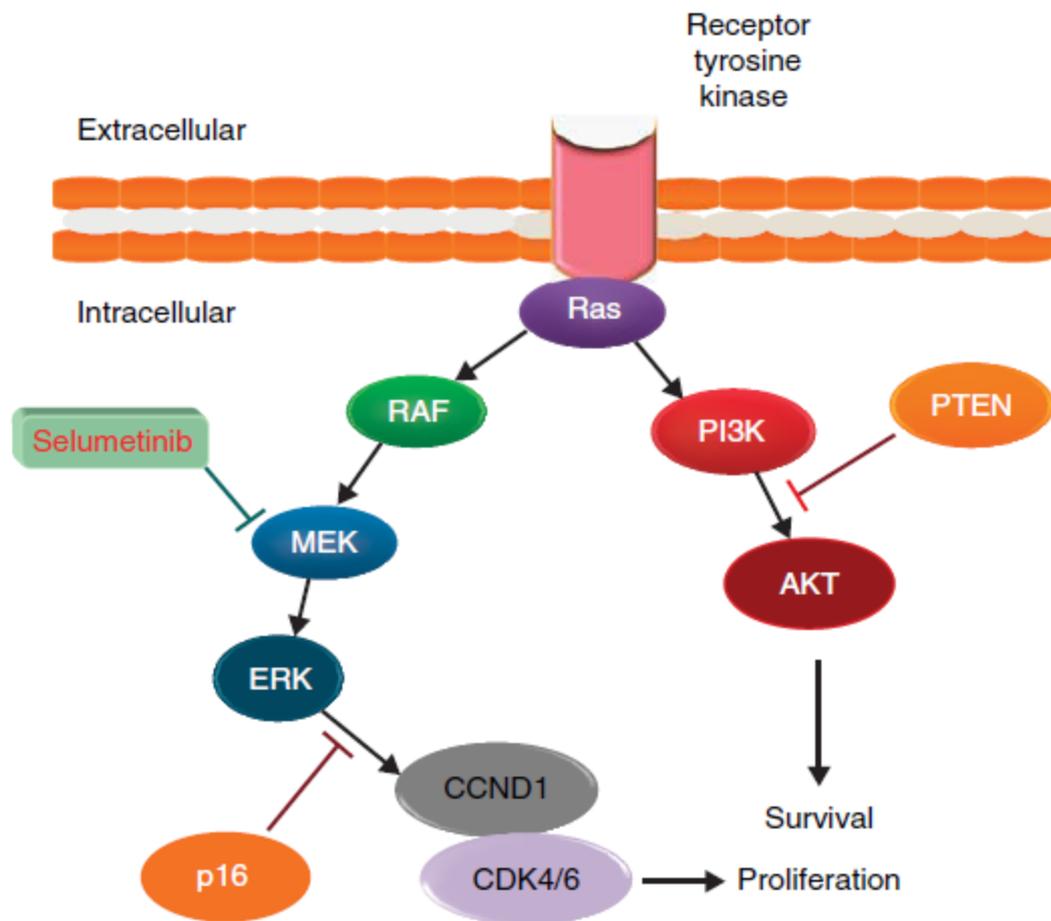


BRAF Mutated Pediatric Low-Grade Astrocytomas

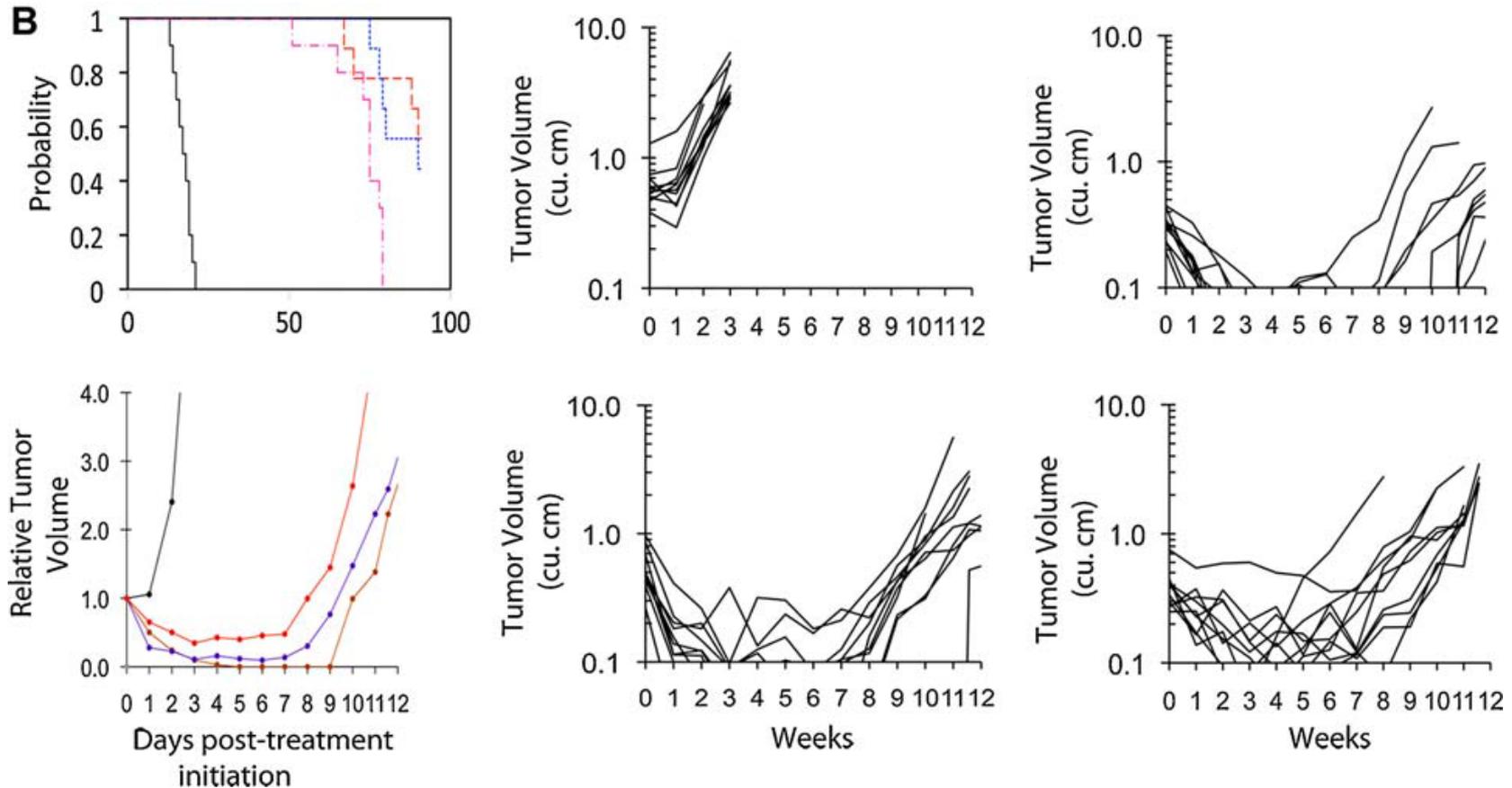
- ~80% with BRAF fusion proteins and ~5% with BRAF mutations (primarily V600E)

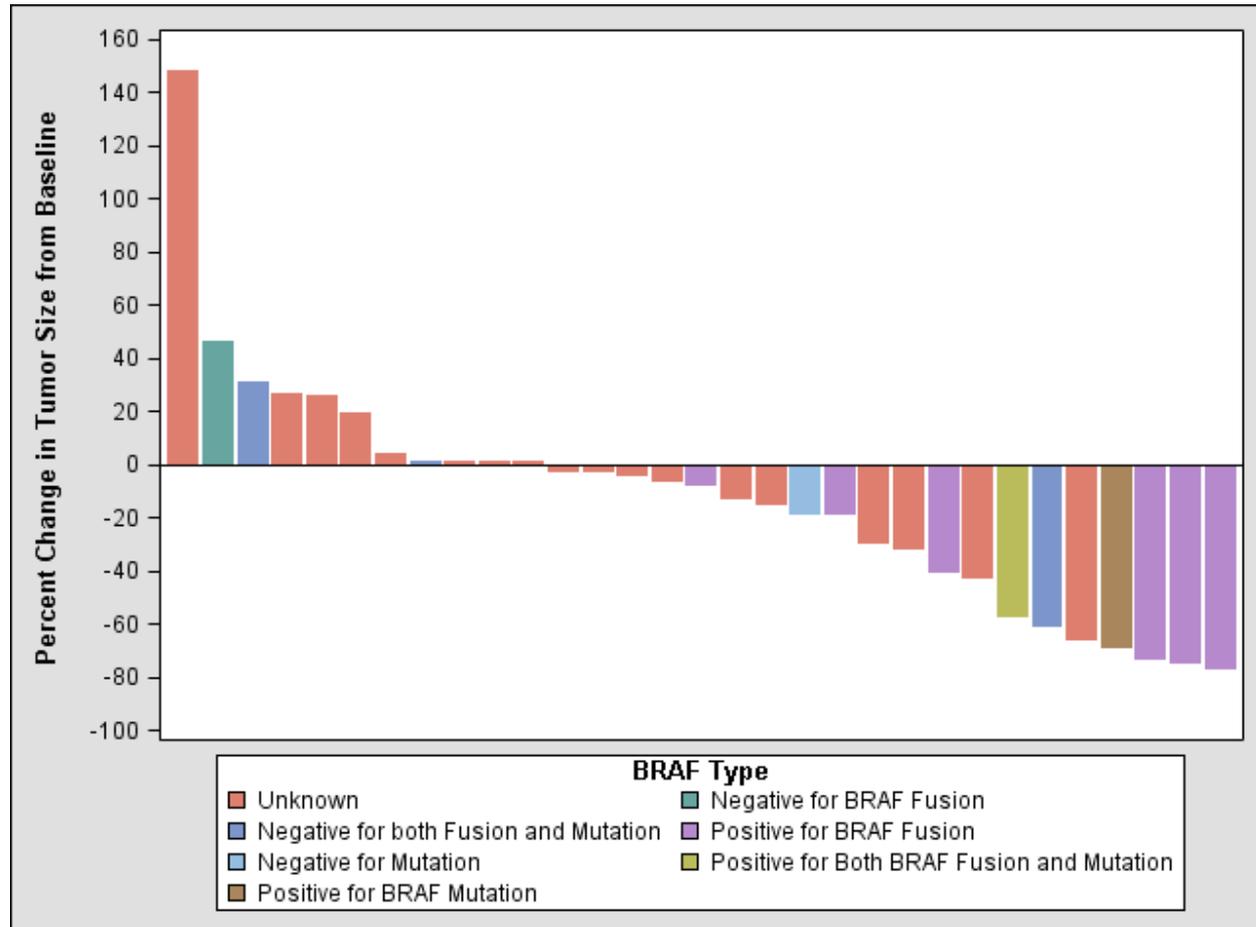


- Selumetinib: allosteric MEK inhibitor
- Under evaluation for multiple adult cancer indications.



Screening of AZD6244 against Low-Grade Astrocytoma Xenograft (BT-40) with BRAF V600E Mutation





- All patients with BRAF genomic alterations showed tumor shrinkage.