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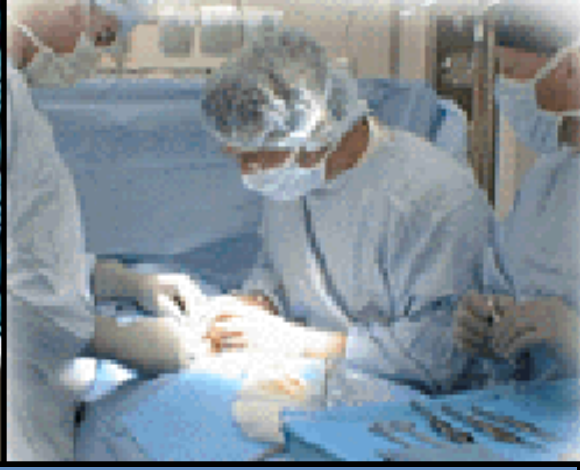

Pediatric Oncology Update

June 24, 2014

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

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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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??

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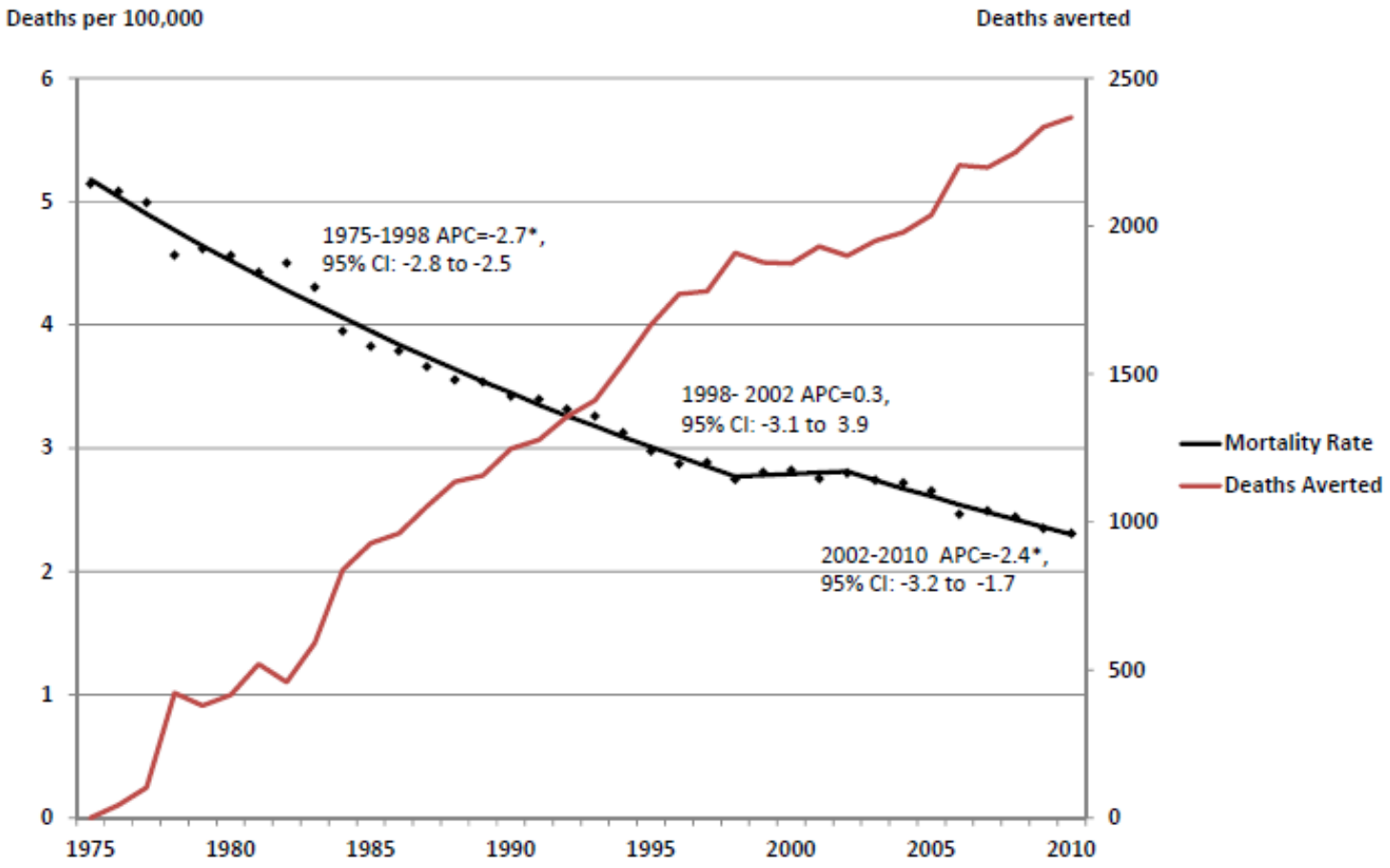
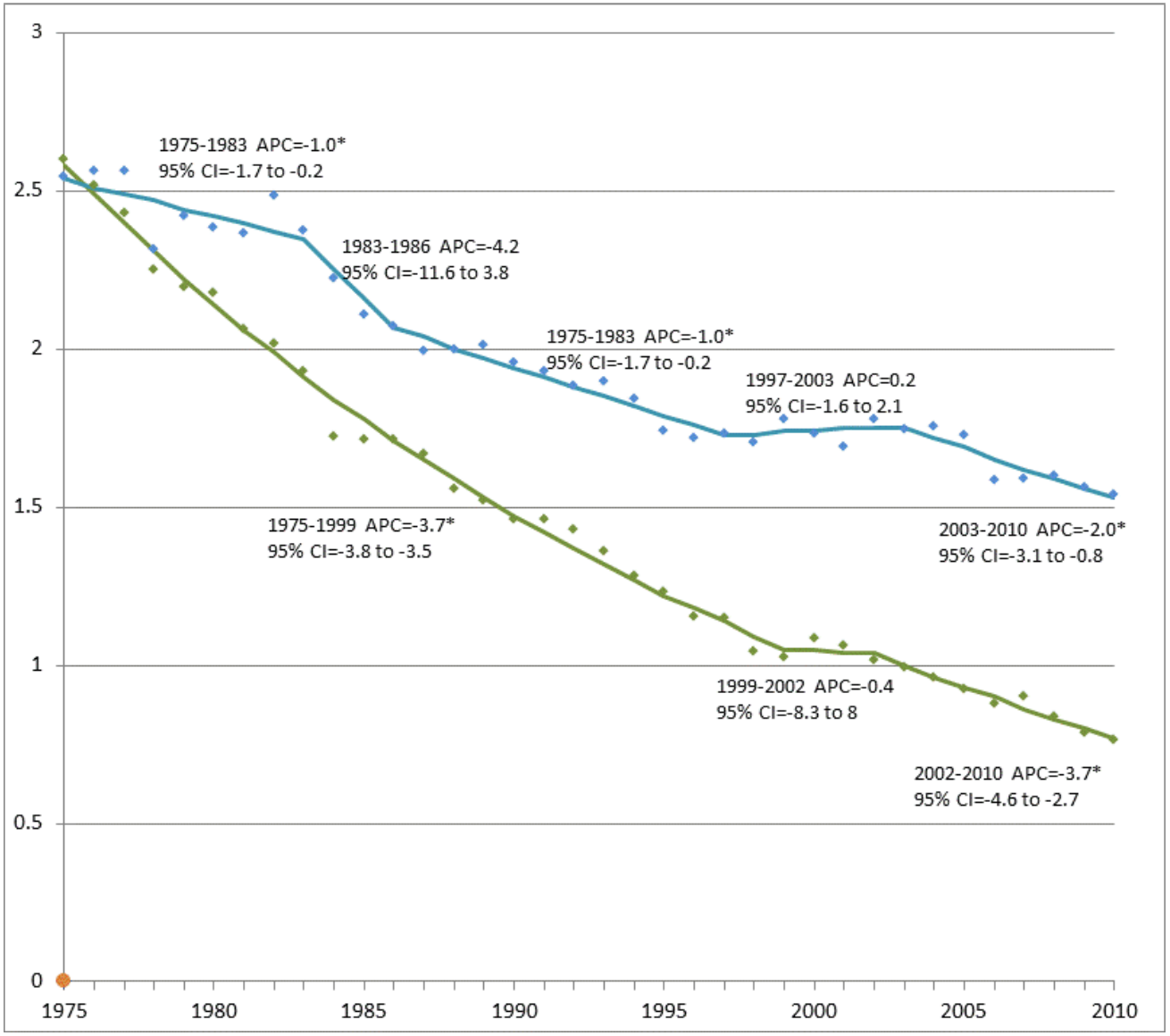
Mortality for All Malignant Cancer s (Age < 20 years): 1975 to 2010



Smith, et al. Cancer (2014)

National Cancer Institute

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



Smith, et al. Cancer (2014)

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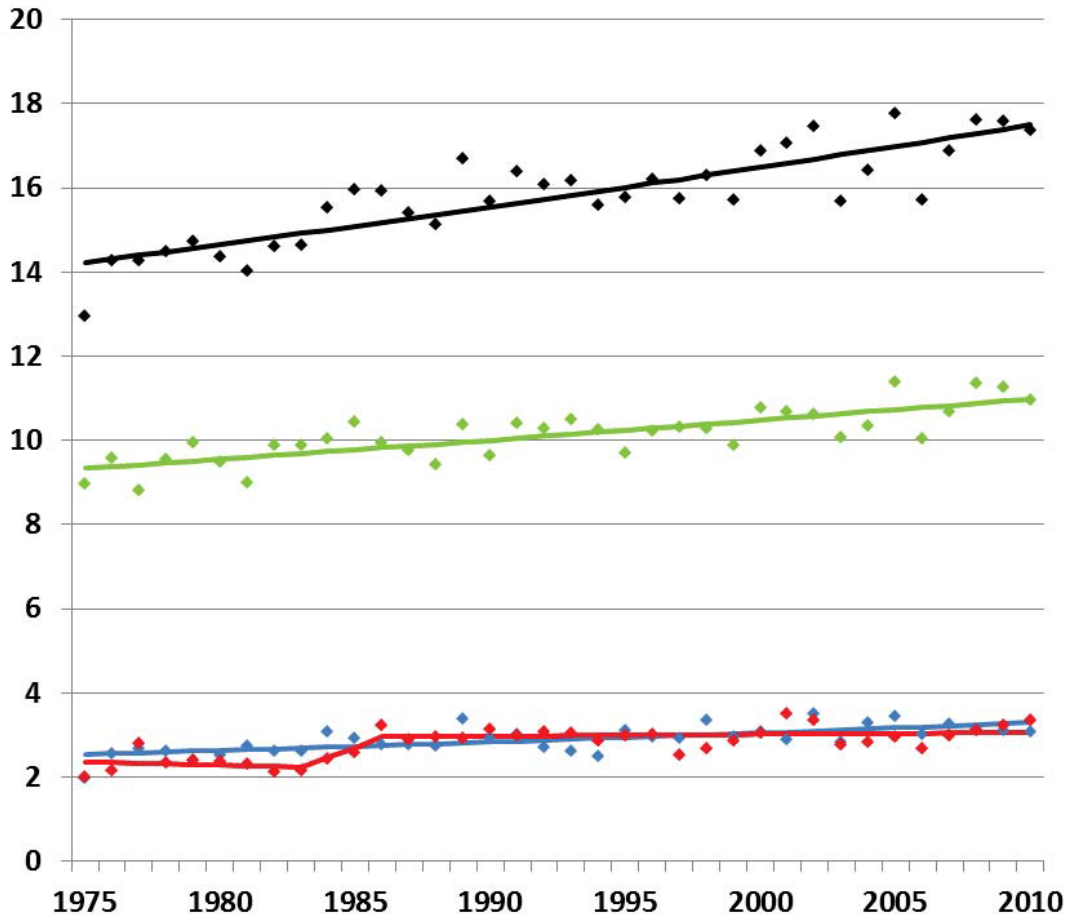
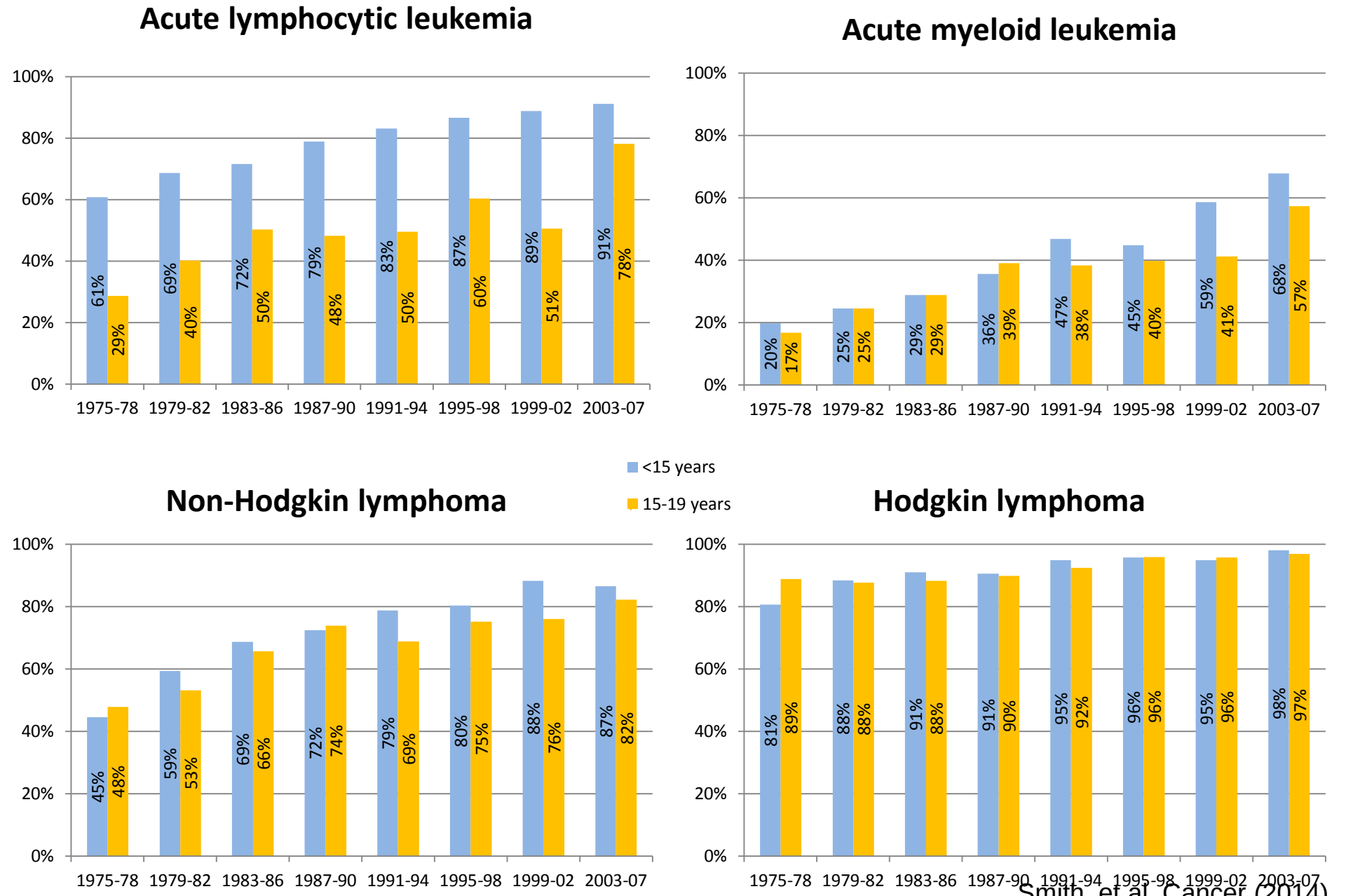
Childhood Cancer Incidence (< 20 years, SEER 9 registries from 1975 – 2010)



Smith, et al. Cancer (2014)

5-Year Relative Survival for Hematopoietic Cancers



Smith, et al. Cancer (2014)

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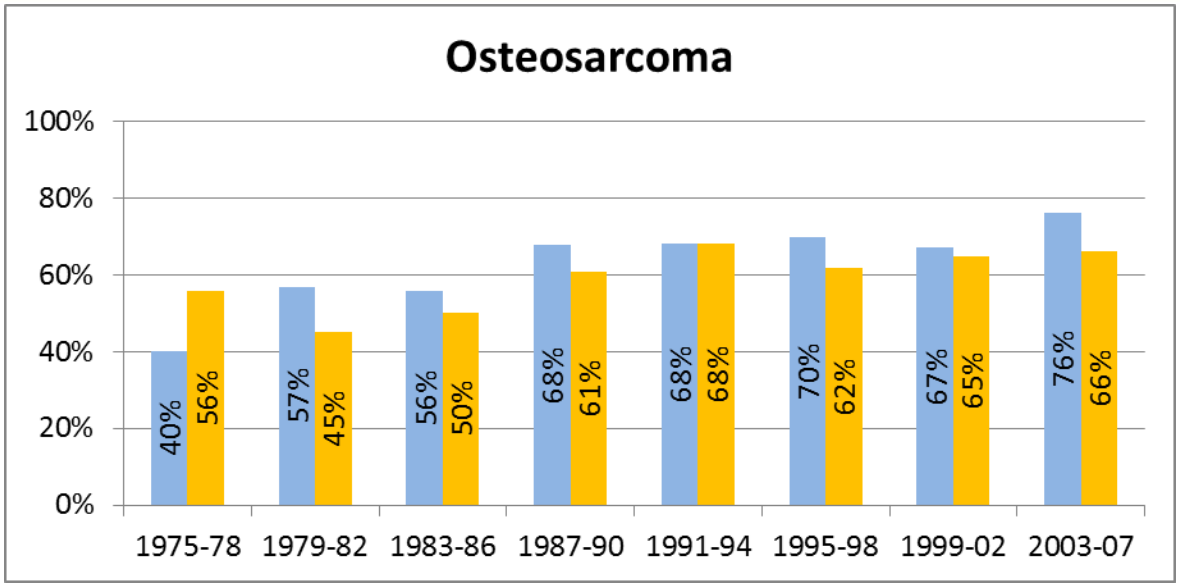
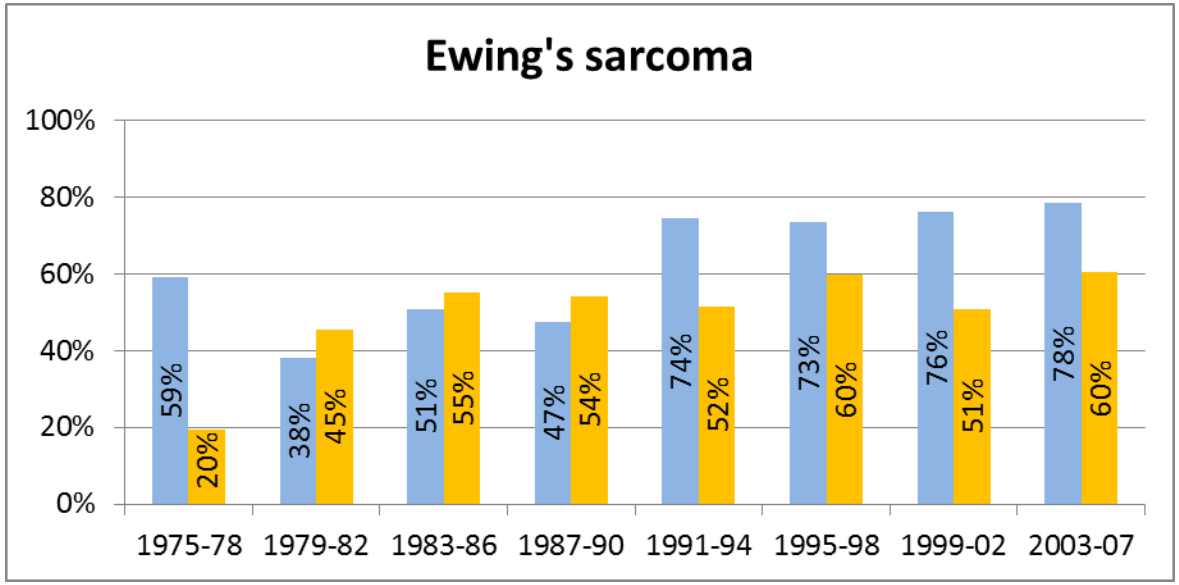
Five-year Relative Survival for Bone Sarcomas





Smith, et al. Cancer (2014)

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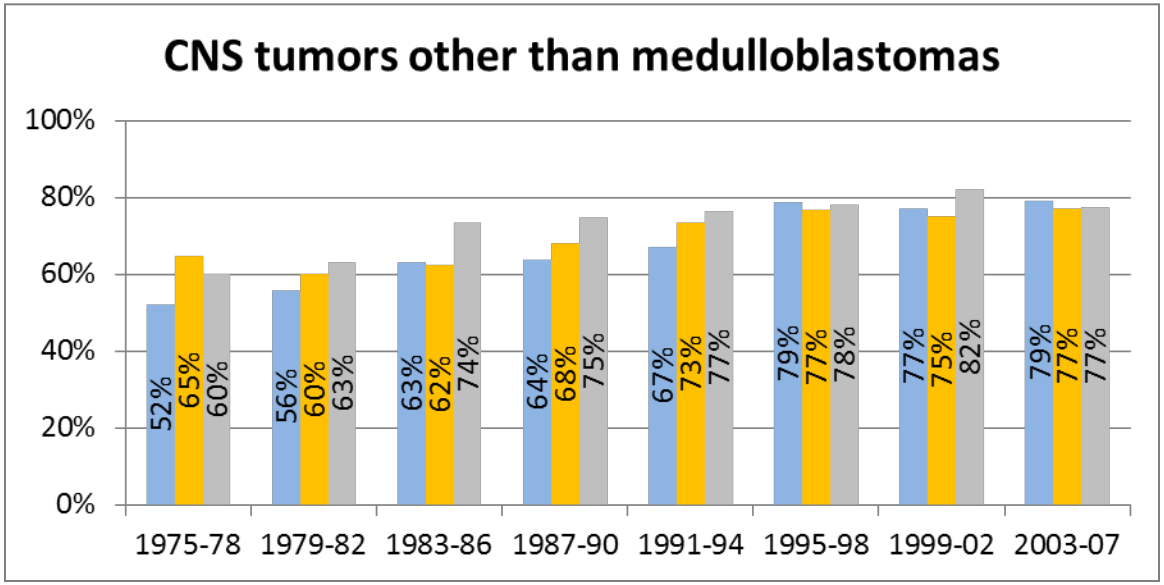
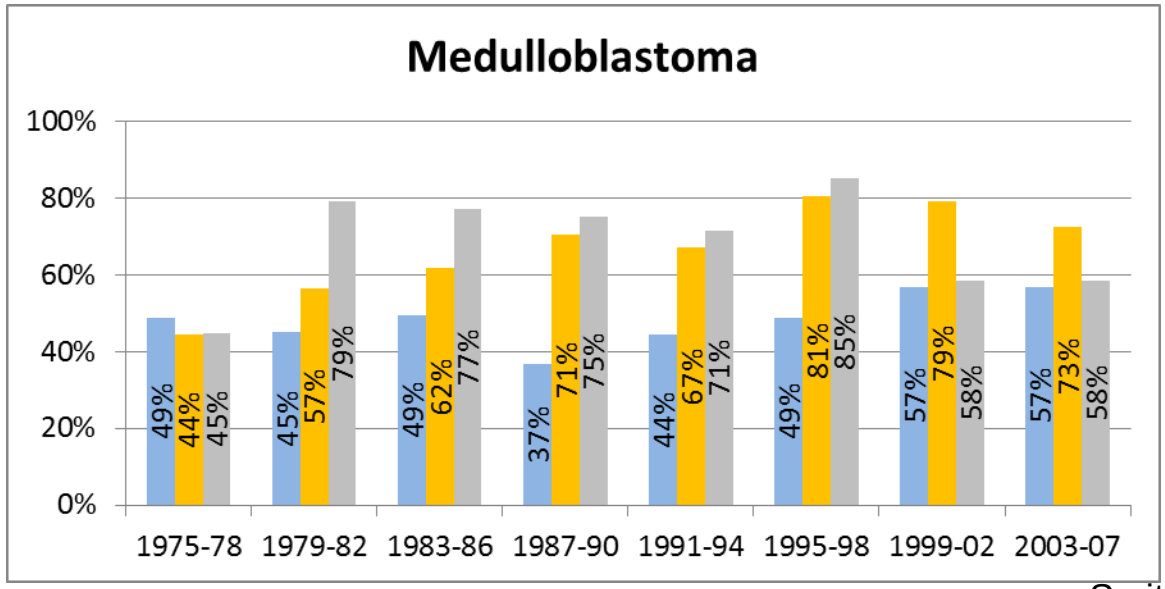
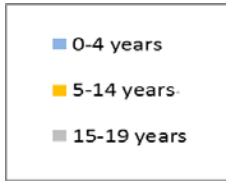
Five-year Relative Survival for CNS Cancers







Smith, et al. Cancer (2014)

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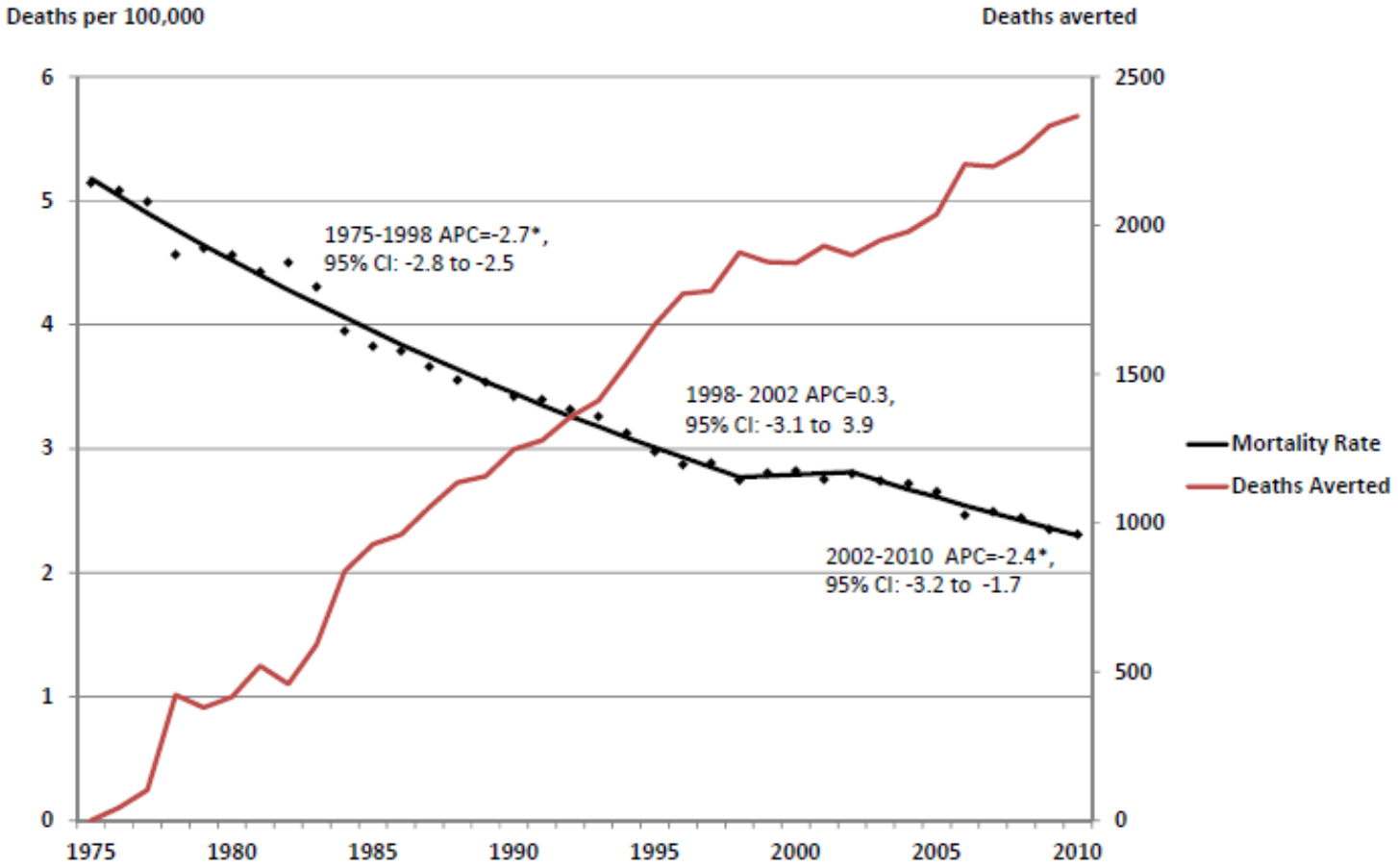
Mortality for All Malignant Cancer s (Age < 20 years): 1975 to 2010

> 45,000 deaths averted since 1975



Smith, et al. Cancer (2014)

Children’s Oncology Group

CHILDREN'S ONCOLOGY GROUP

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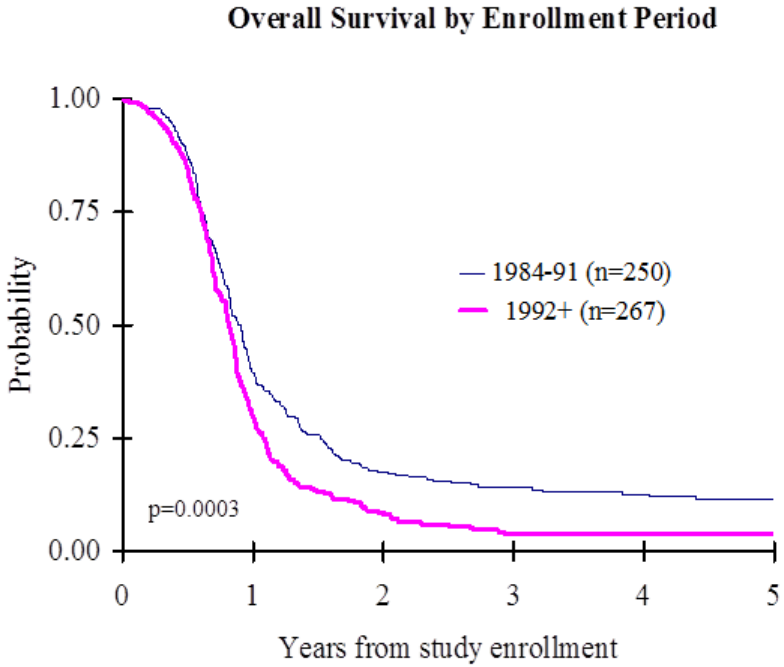
Overall survival mask cancers for which outcome remains highly unfavorable

- 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.



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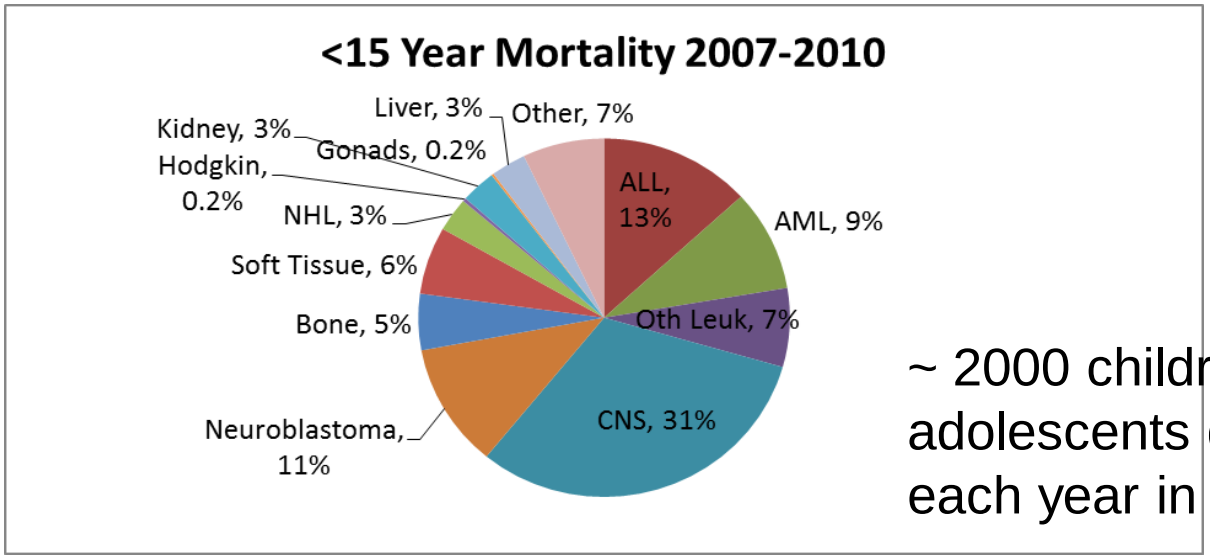
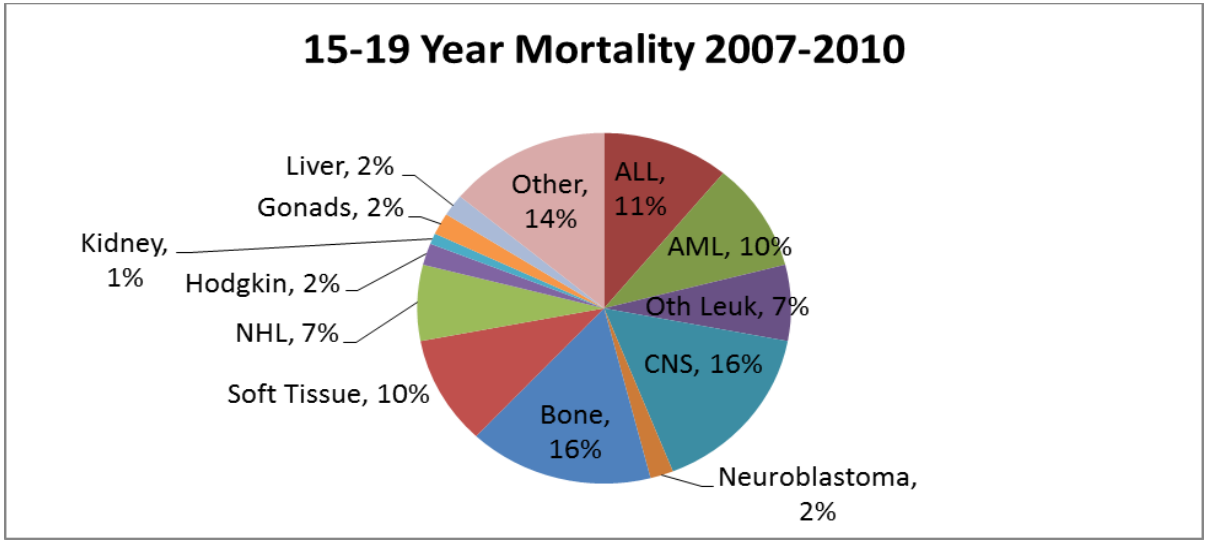
Causes of Childhood Cancer Mortality



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



Smith, et al. Cancer (2014)

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Childhood Cancer Survivor Study (CCSS)

- Retrospectively ascertained cohort of survivors of pediatric cancer diagnosed between1970-1986:
  - 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

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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

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Brief Update

target.cancer.gov

BSA/NCAB
Bethesda MD
June 24, 2014

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Comprehensive Characterization

Disease	Patient Data	Case # (Relapse)	Chip-based				Sequencing			
			Expression	Chr. copy #	Methyl-ation	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]

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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 Lympho-blastic Leukemia	**750**	Y	1500
Osteosarcoma	**200**	Y	TBD

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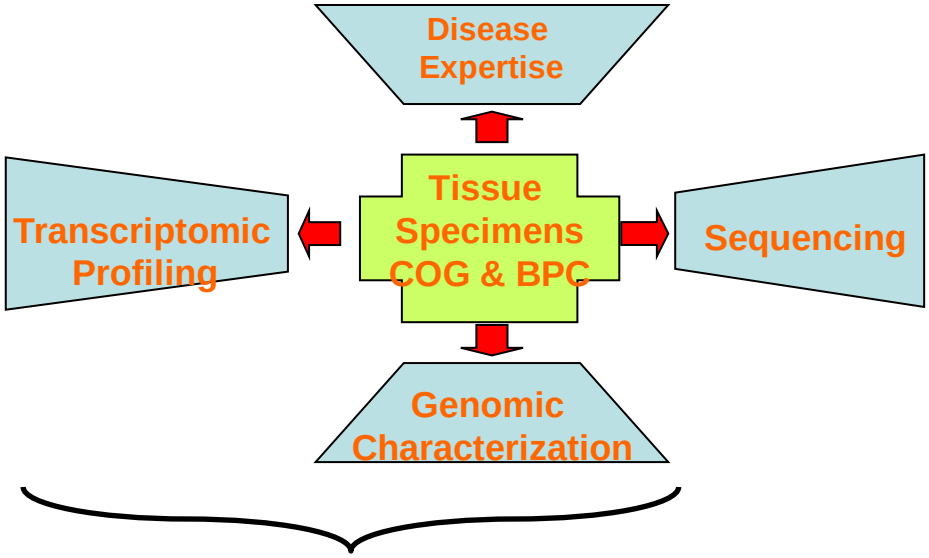
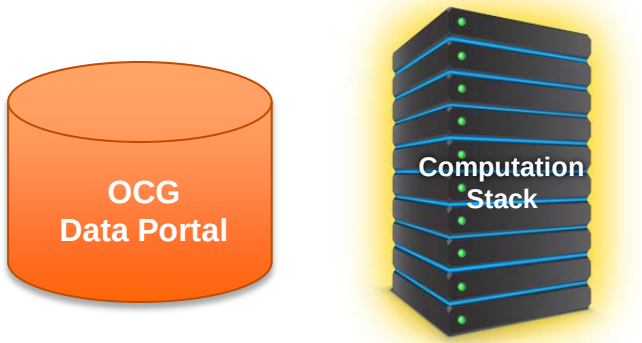
TARGET Initiative:



All data types except raw sequence files are stored the DCC



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Selected Vignettes

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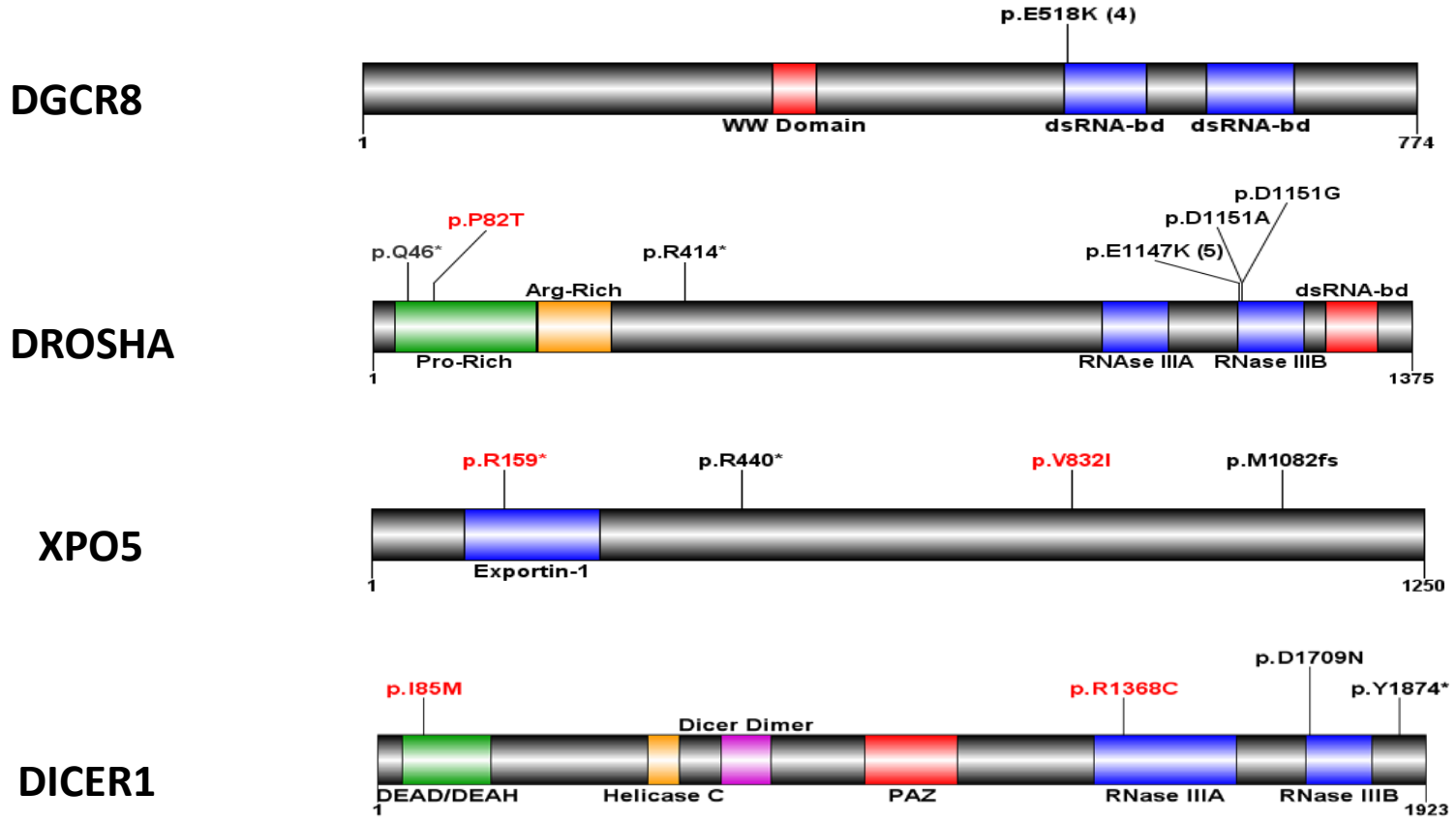
Favorable Histology Wilms Tumors: Mutations in miRNA Processing Genes

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



Black = Somatic Mutation
Red = Germline Mutation

E. Perlman & WT PT, unpublished

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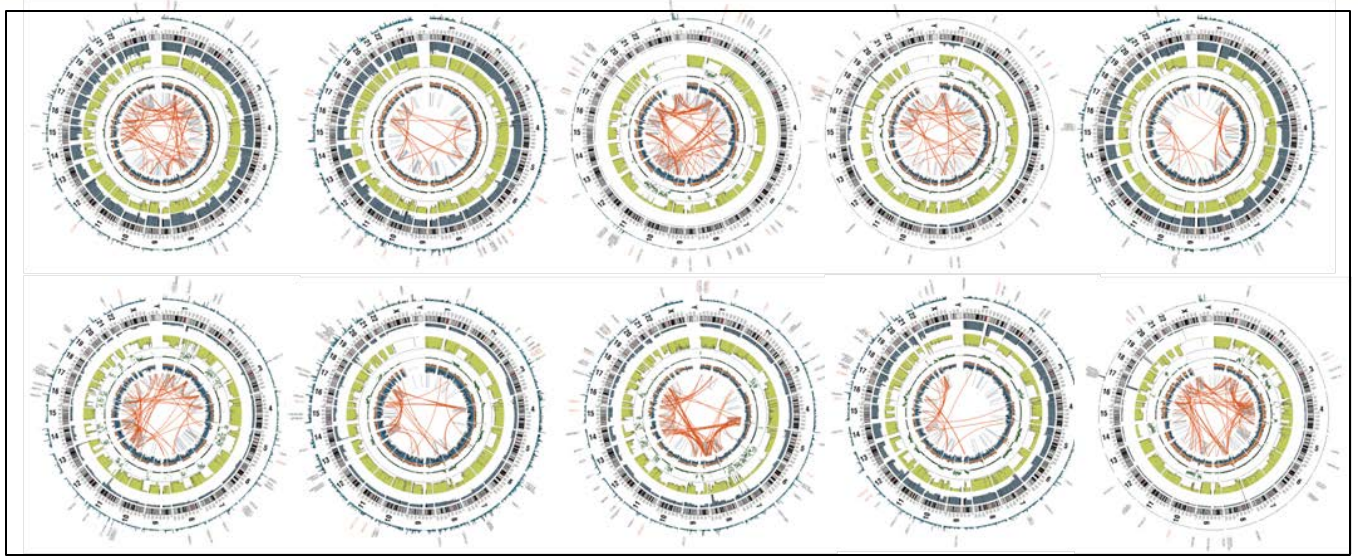
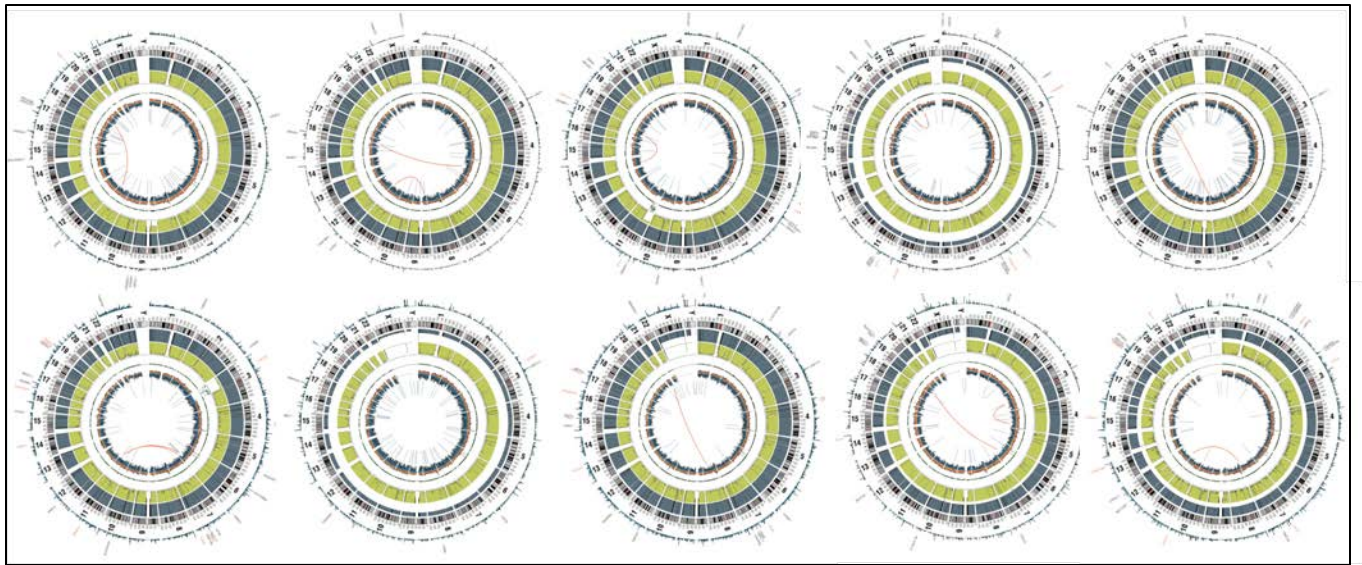
Osteosarcoma Genomes Are Mostly Rearranged



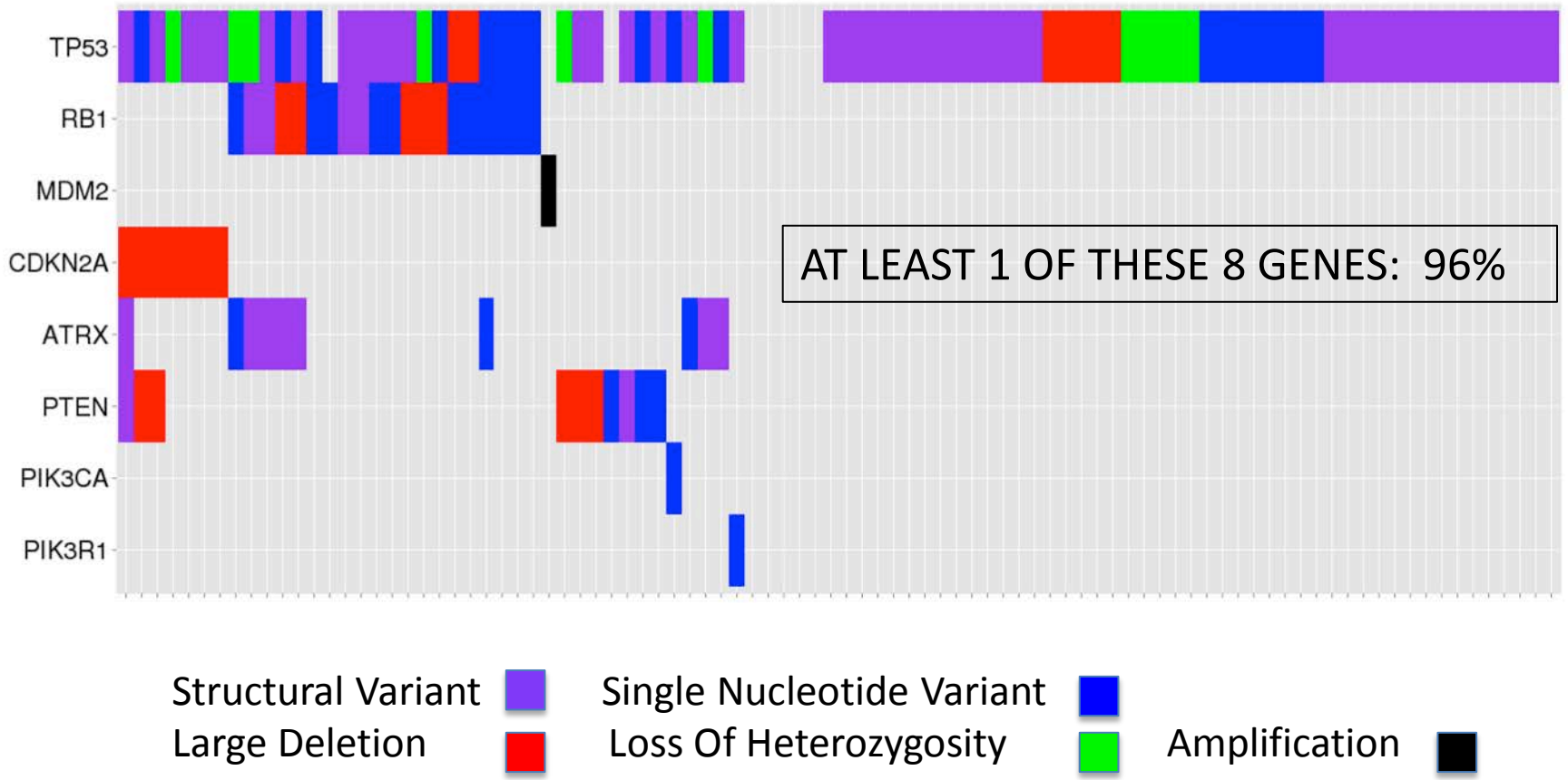
OS



AML

Integrated Genomics of Osteosarcoma

Mutations in 92 tumors



C. Lau, P. Meltzer & OS PT, unpublished

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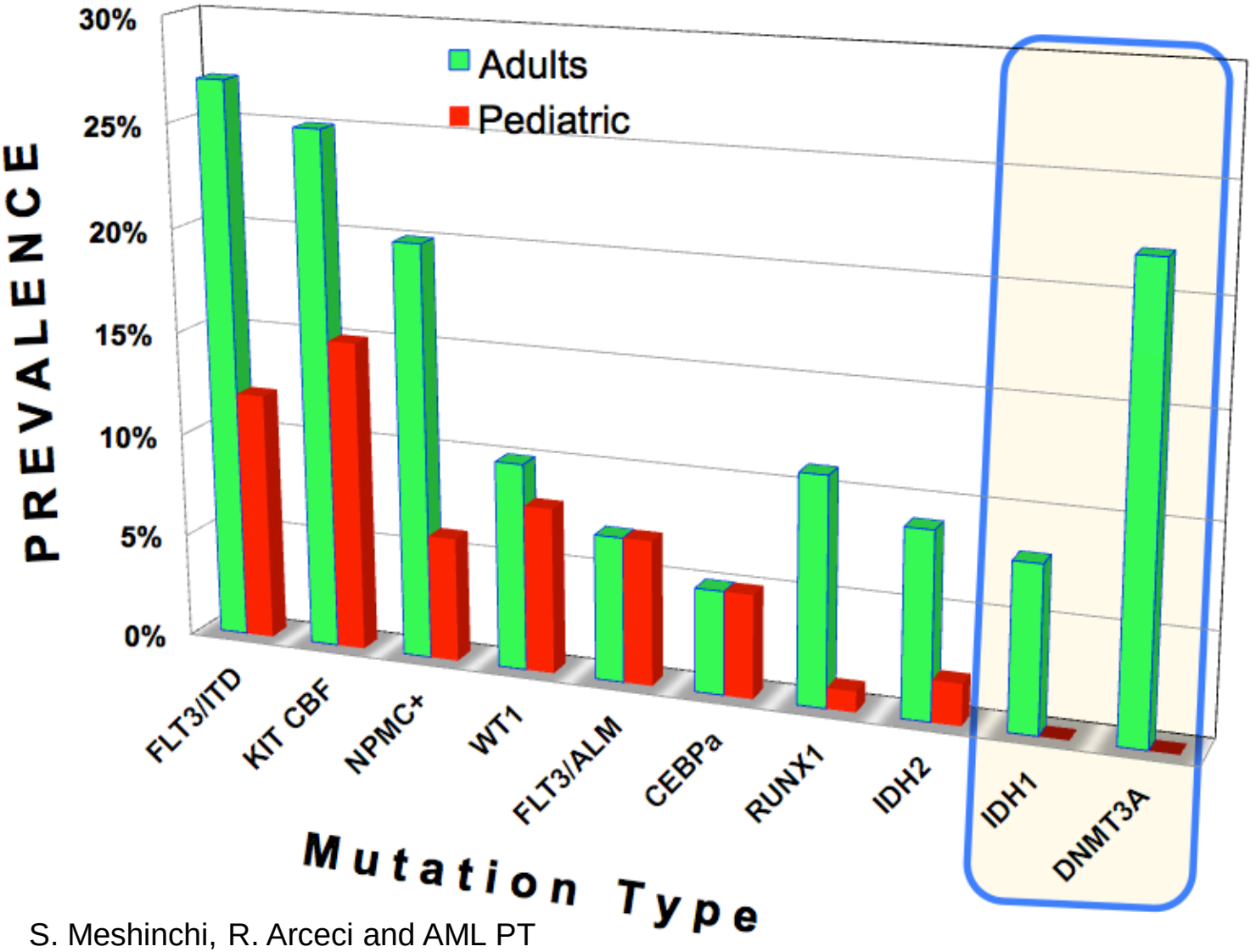
Gene Mutations are Different in Children vs. Adults with Acute Myeloid Leukemia



S. Meshinchi, R. Arceci and AML PT

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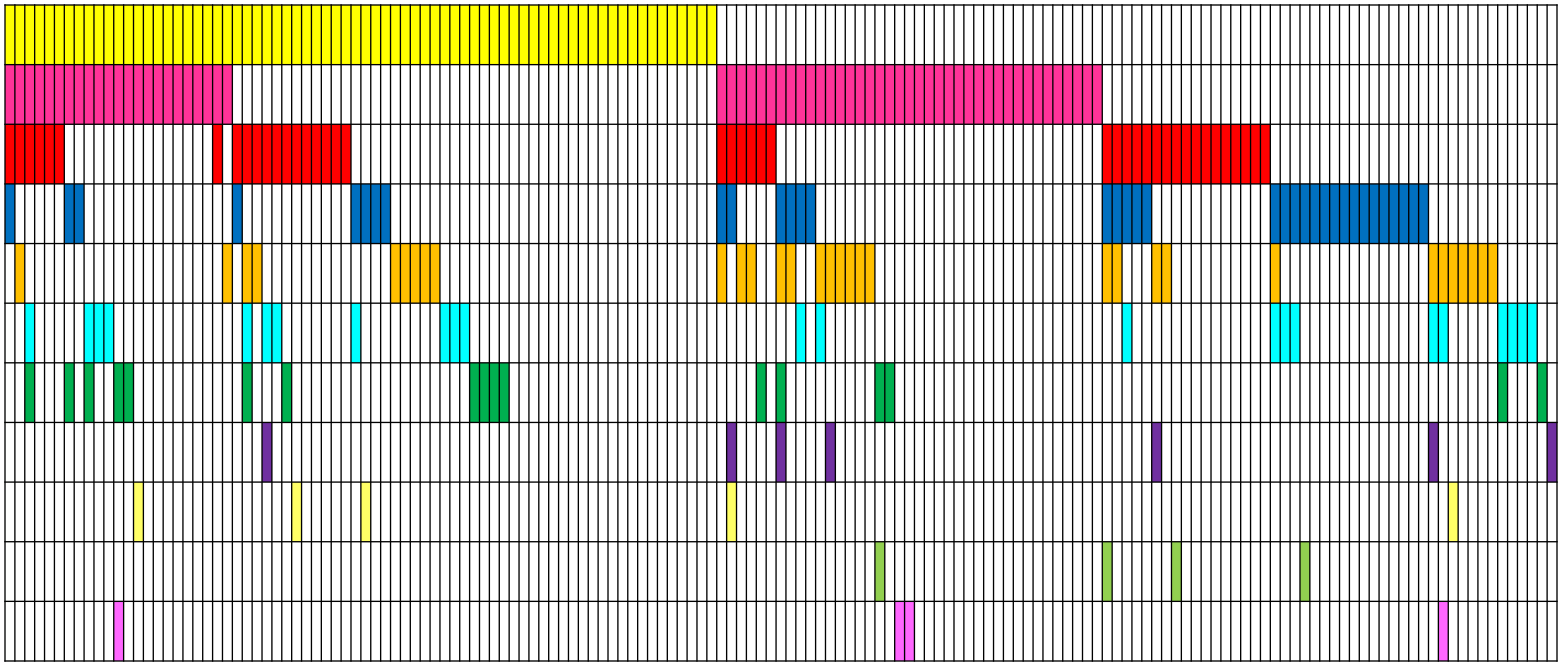
83% of Acute Myeloid Leukemia Cases Have Mutations in 11 Functional Categories



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

S. Meshinchi, R. Arceci & AML PT, unpublished

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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)

S. Hunger, M. Loh, C. Mullighan, J. Zhang & ALL PT

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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	*IGH@-CRLF2*	
PAKKCA		*EBF1-PDGFRB*
PAKKXB	*IGH@-CRLF2*	
PAKTAL		*STRN3-JAK2*
PAKVKK		*NUP214-ABL1*
PAKYEP		*BCR-JAK2*
PALETF		NONE
PALIBN		*IGH@-EPOR*
PALJDL		NONE
PAMDRM	*IGH@-CRLF2*	
PANNGL		*PAX5-JAK2*
PANSFD		*ETV6-ABL1*
PANEHF		*RCSD1-ABL1*
SJBALL085		*NUP214-ABL1*
SJBALL010		*RANBP2-ABL1*

Roberts et al. *Cancer Cell* 2012;22:153

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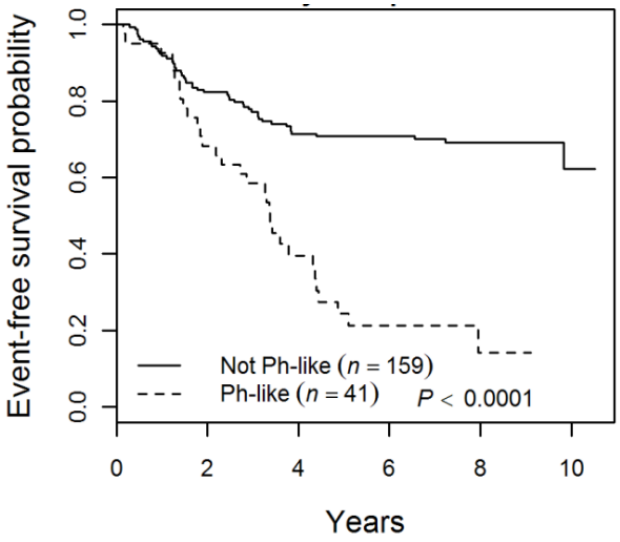
Results: Poor outcome of Ph-like ALL

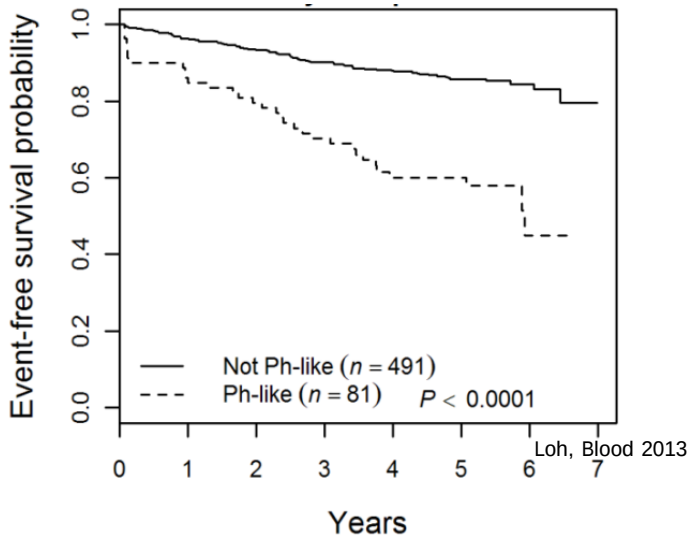
Childhood high risk ALL

COG P9906



Adolescent

COG AALL0232



Loh, Blood 2013

Young adult

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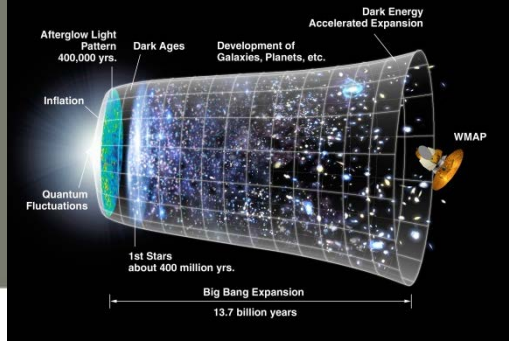
Acknowledgements



- **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**

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Precision Medicine: Following the Adult Paradigm

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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

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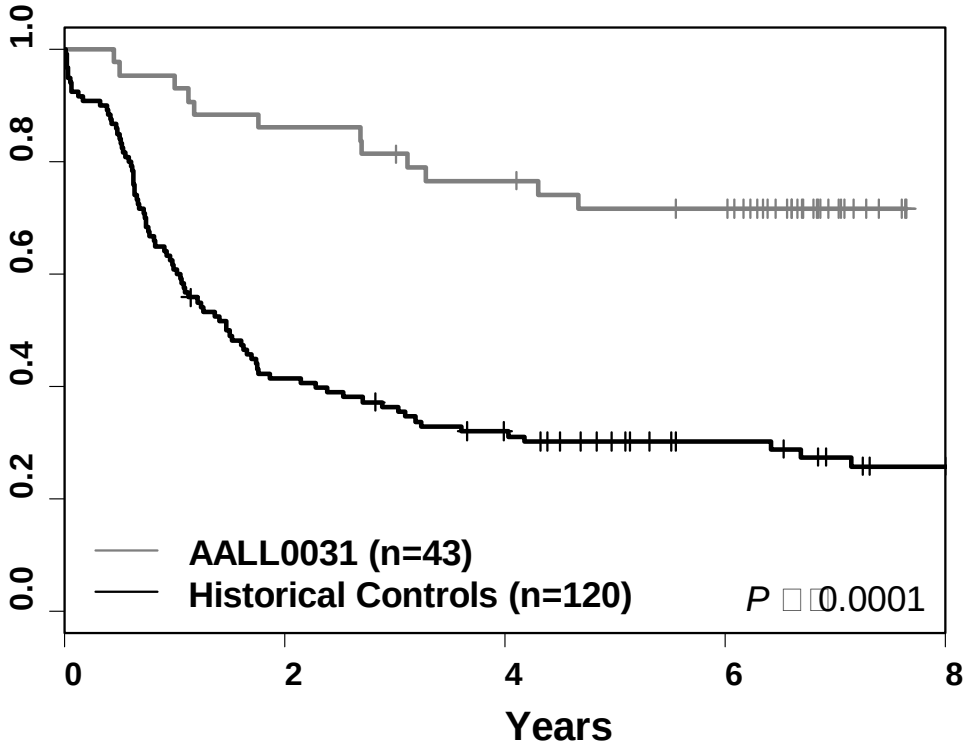
Impact of Imatinib added to standard chemotherapy for Ph+ ALL (AALL0031)

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



Schultz, K. R. et al. J Clin Oncol; 27:5175-5181 2009
Schultz K. R., Leukemia 2014

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Anaplastic Large Cell Lymphoma

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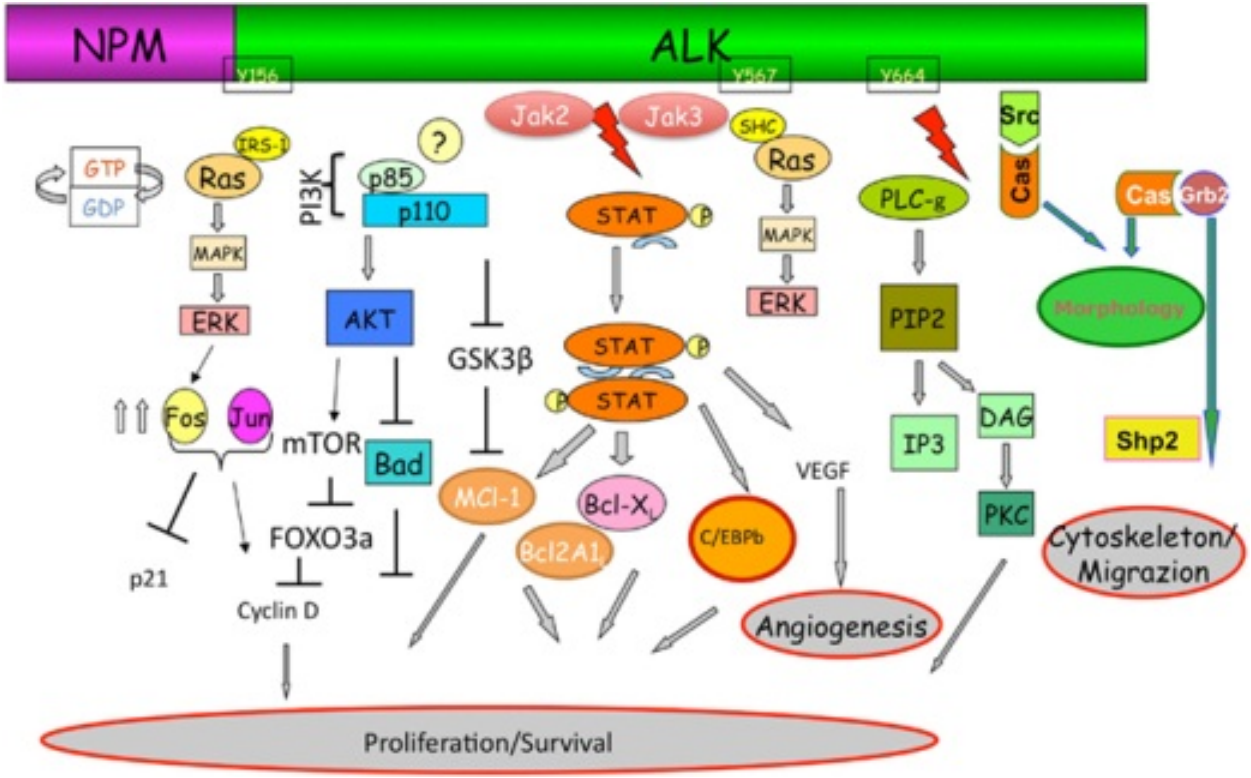
Anaplastic Large Cell Lymphoma in Children

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



Tabbo F, et al. Frontiers Oncol 2012:2:41

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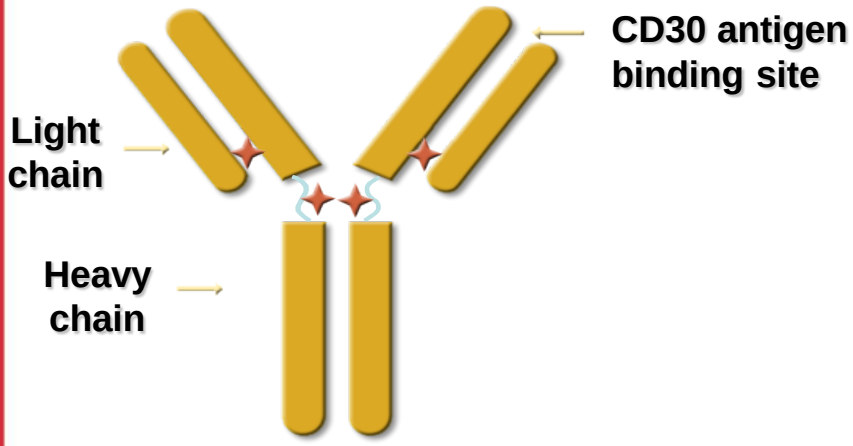
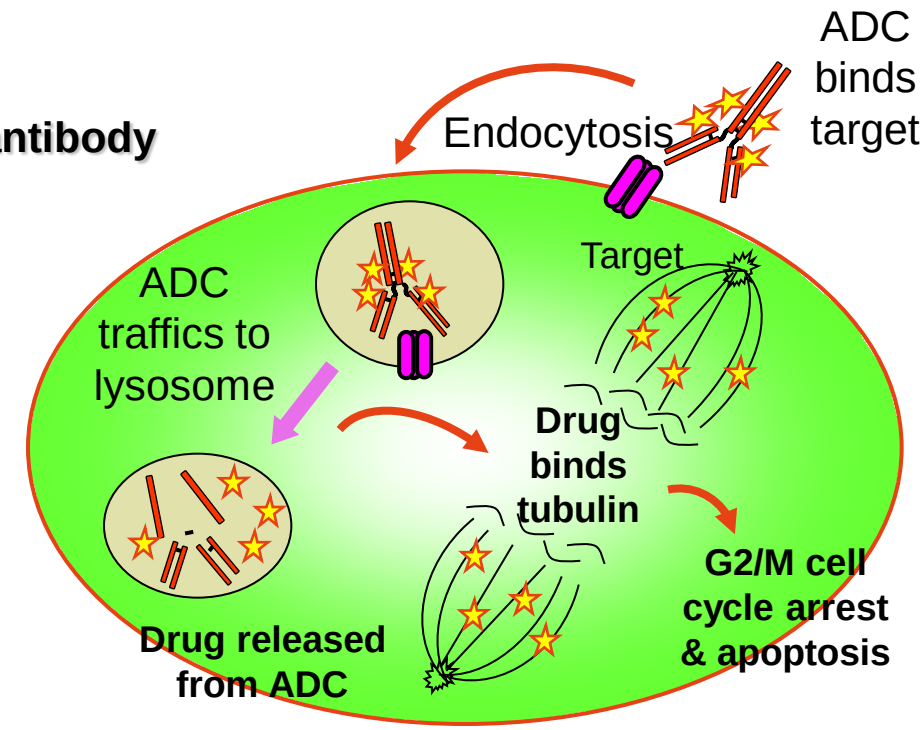
Brentuximab Vedotin (SGN-35): CD30 Targeted Antibody-Drug Conjugate



Auristatin derivative:
average of 4 molecules per antibody



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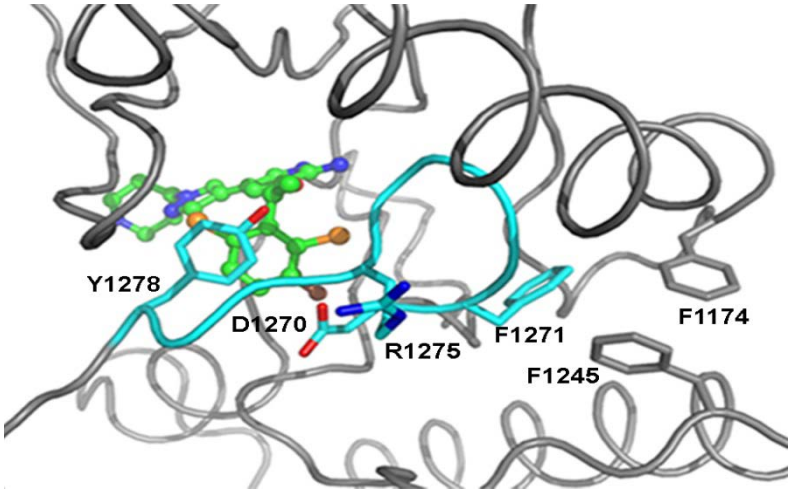
Crizotinib (MET and ALK inhibitor)

- >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



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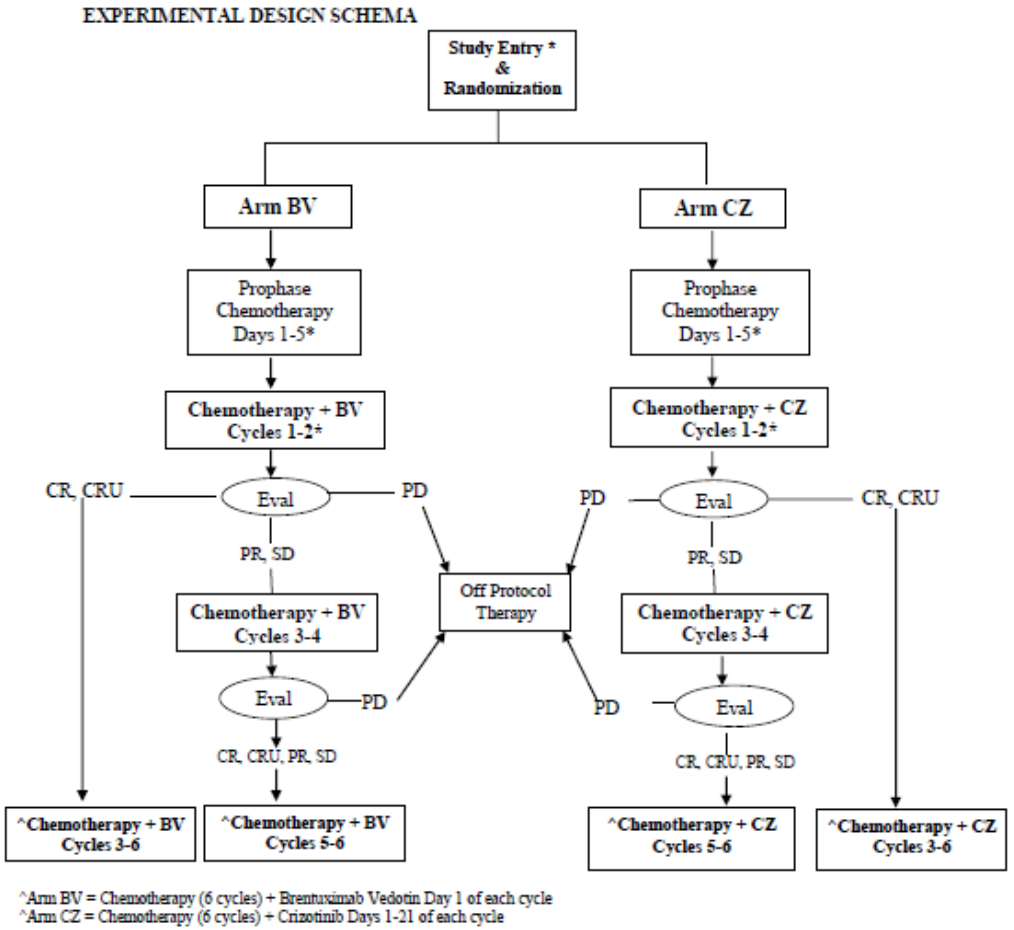
ANHL12P1: Comparison of standard chemotherapy + either brentuximab vedotin or crizotinib

Brentuximab vedotin



Crizotinib

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

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Ph-Like Acute Lymphoblastic Leukemia (ALL)

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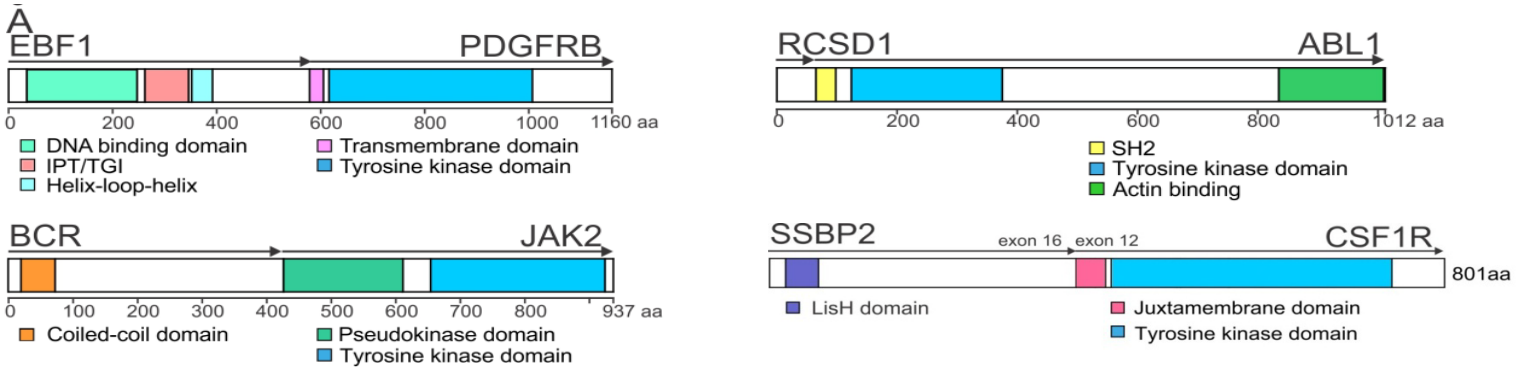
Ph-like (BCR-ABL1-like) B-ALL

- 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 ± JAK mutations
  - Remainder have variety of gene fusions targeting ABL1, ABL2, CSF1R, PDGFRB, JAK2 and other kinase genes



Roberts KG, et al. Cancer Cell 2012:22(2):153-166

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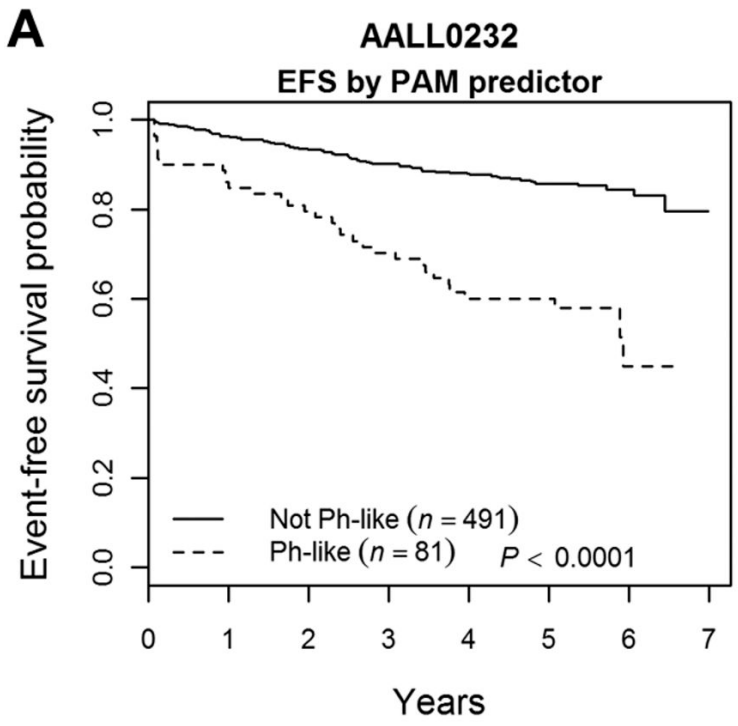
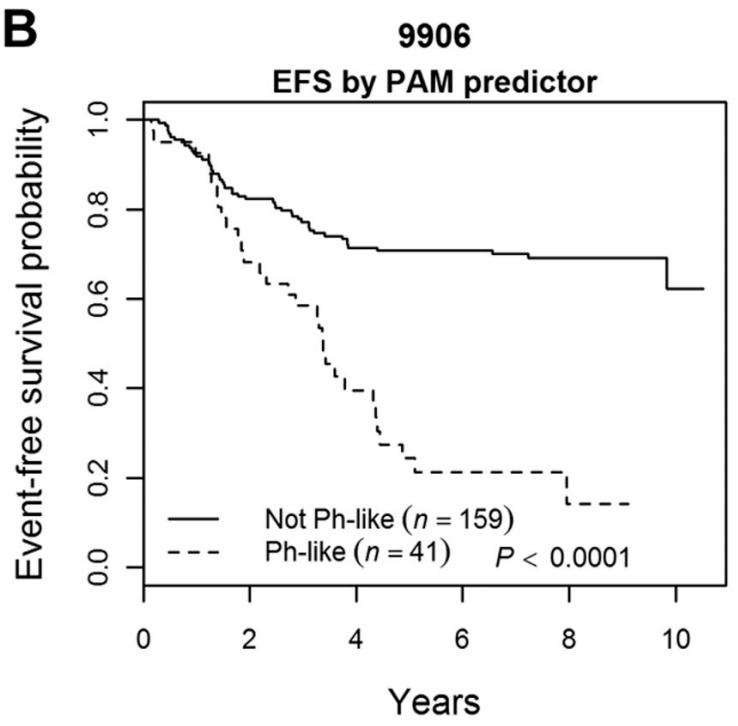
Prognosis for Children with Ph-Like ALL

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





Loh M L et al. Blood 2013;121:485-488

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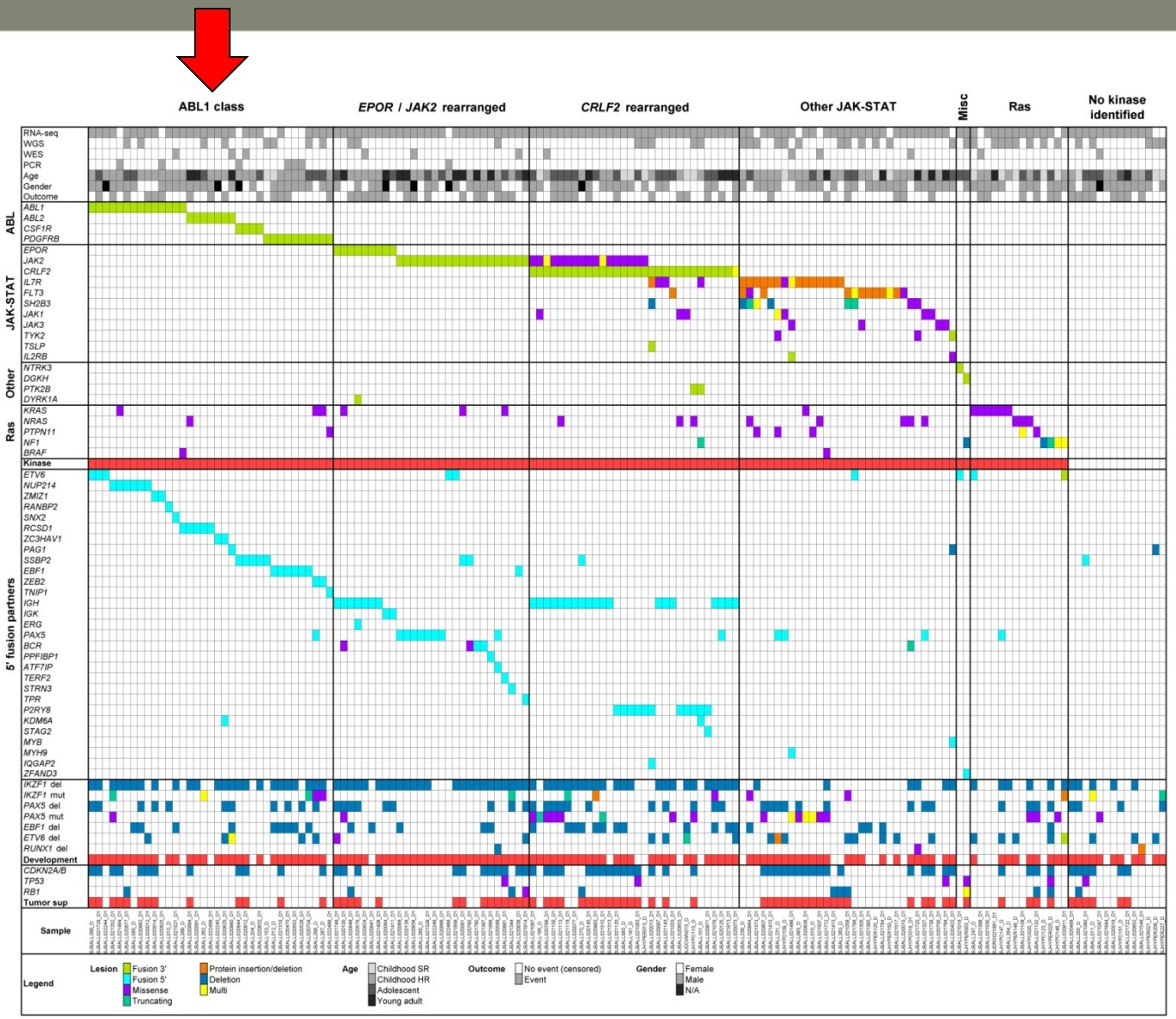
The Genomic Landscape of Ph-Like ALL



Roberts et al, AACR 2014

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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

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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/PDGRFB/CSF1R fusion positive:
Add dasatinib in prospective phase and compare outcome to that of pts from retrospective phase

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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)

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Precision Medicine: Following the Adult Paradigm

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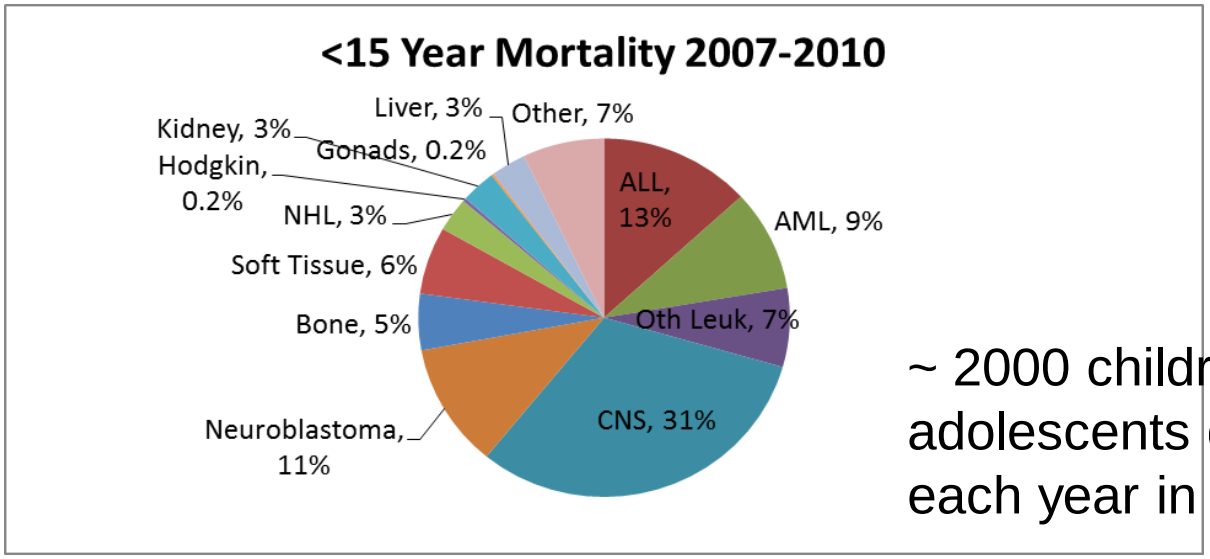
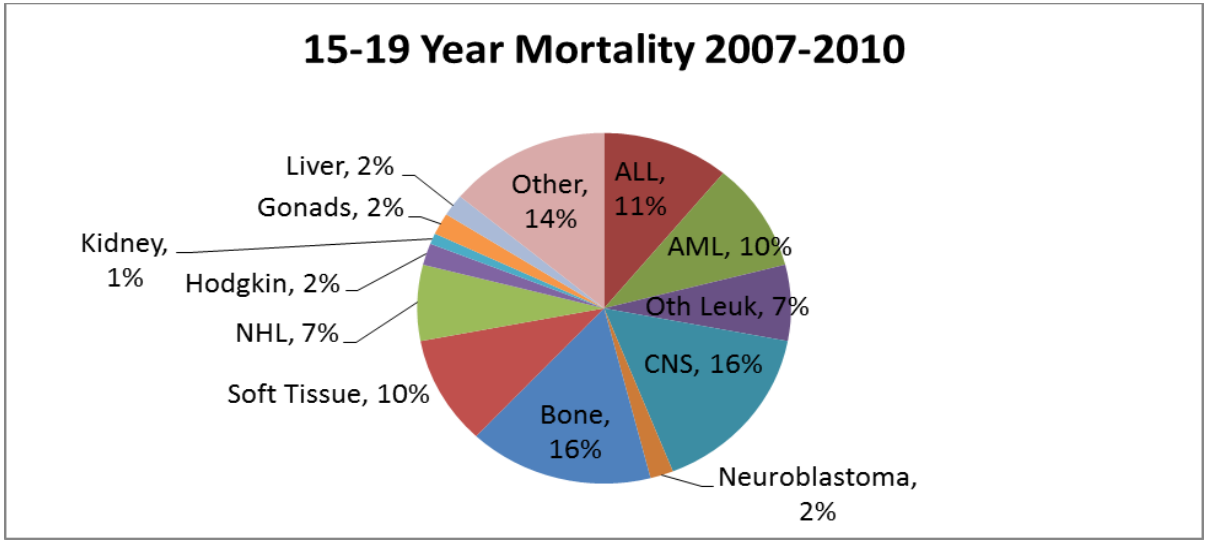
Causes of Childhood Cancer Mortality



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



Smith, et al. Cancer (2014)

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Children Are not Just Little Adults

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

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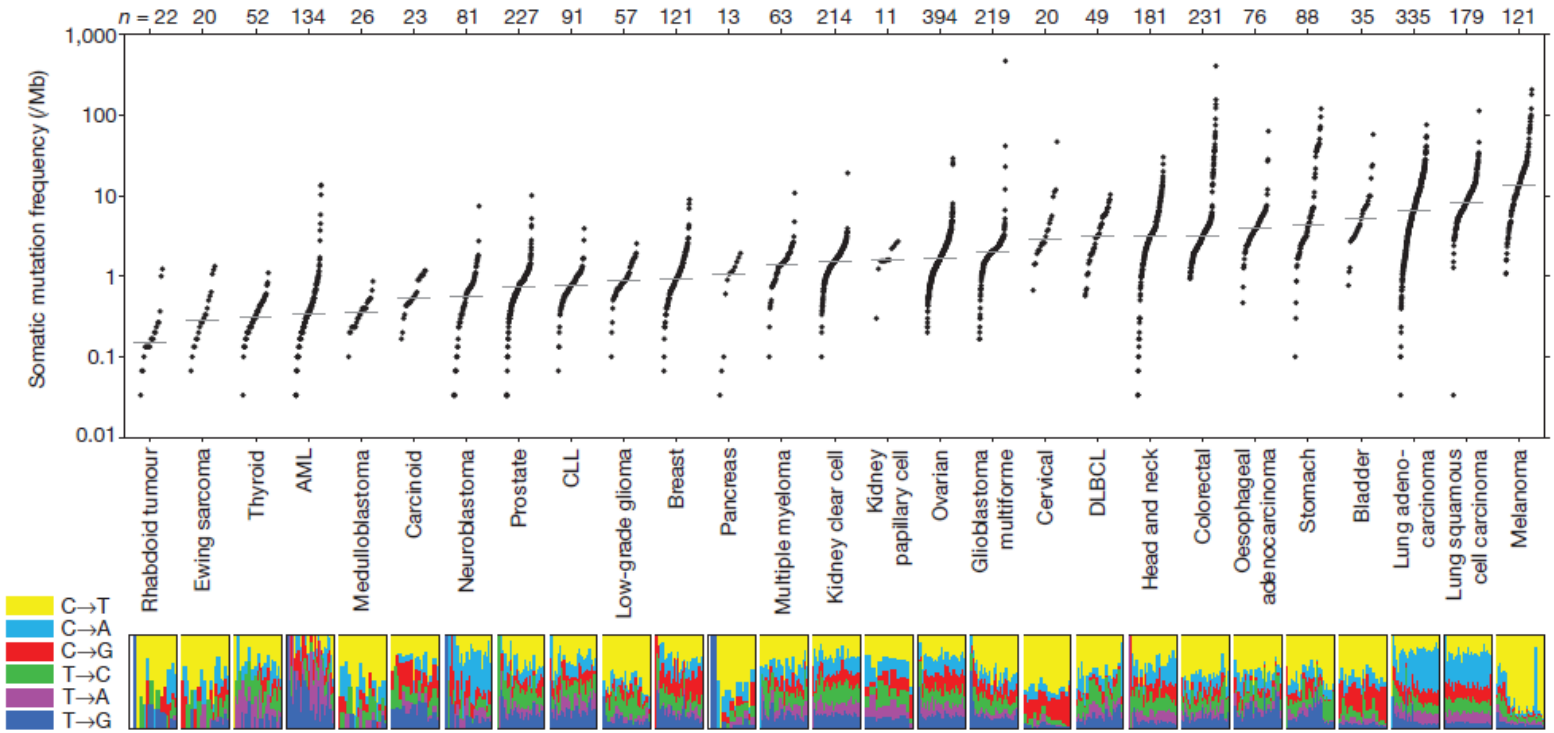
Childhood Cancers Show Lower Mutation Rates Compared to Adult Cancers



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

Lawrence MS, et al. Nature 2013:499(7457):214-218

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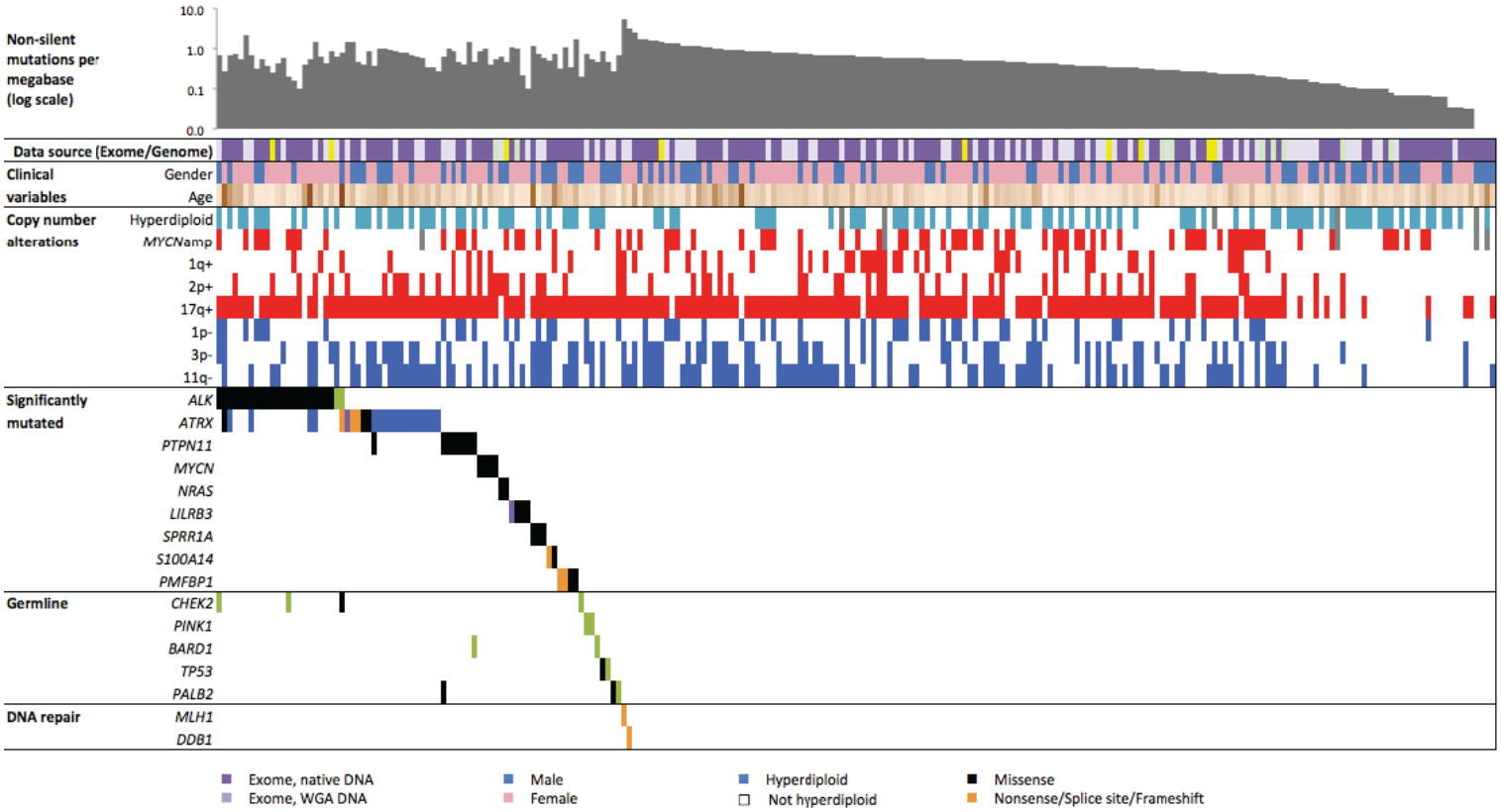
The Genomic Landscape of High-Risk Neuroblastoma



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

Pugh TJ, et al. Nature Genetics 2013:45(3):279-284

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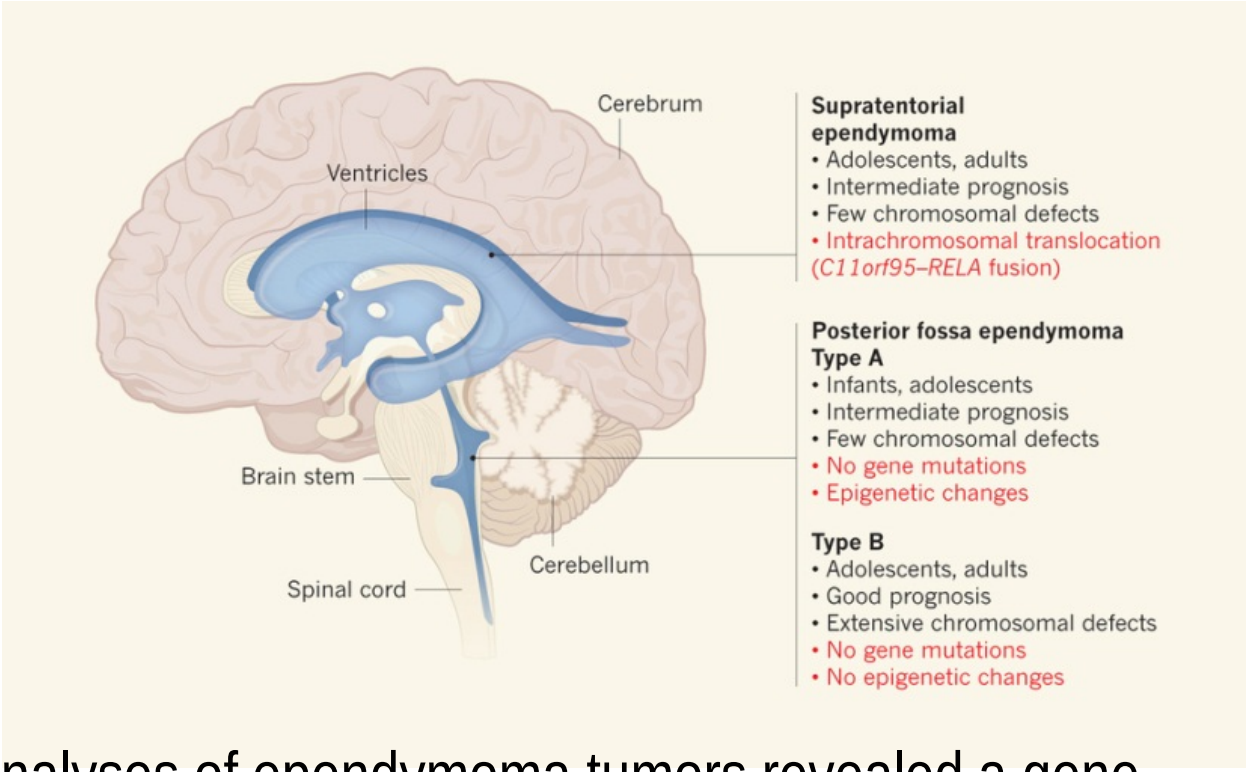
The Genomic Landscape of Ependymoma



- 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

Versteeg R. Nature 2014:506(7489):438-439

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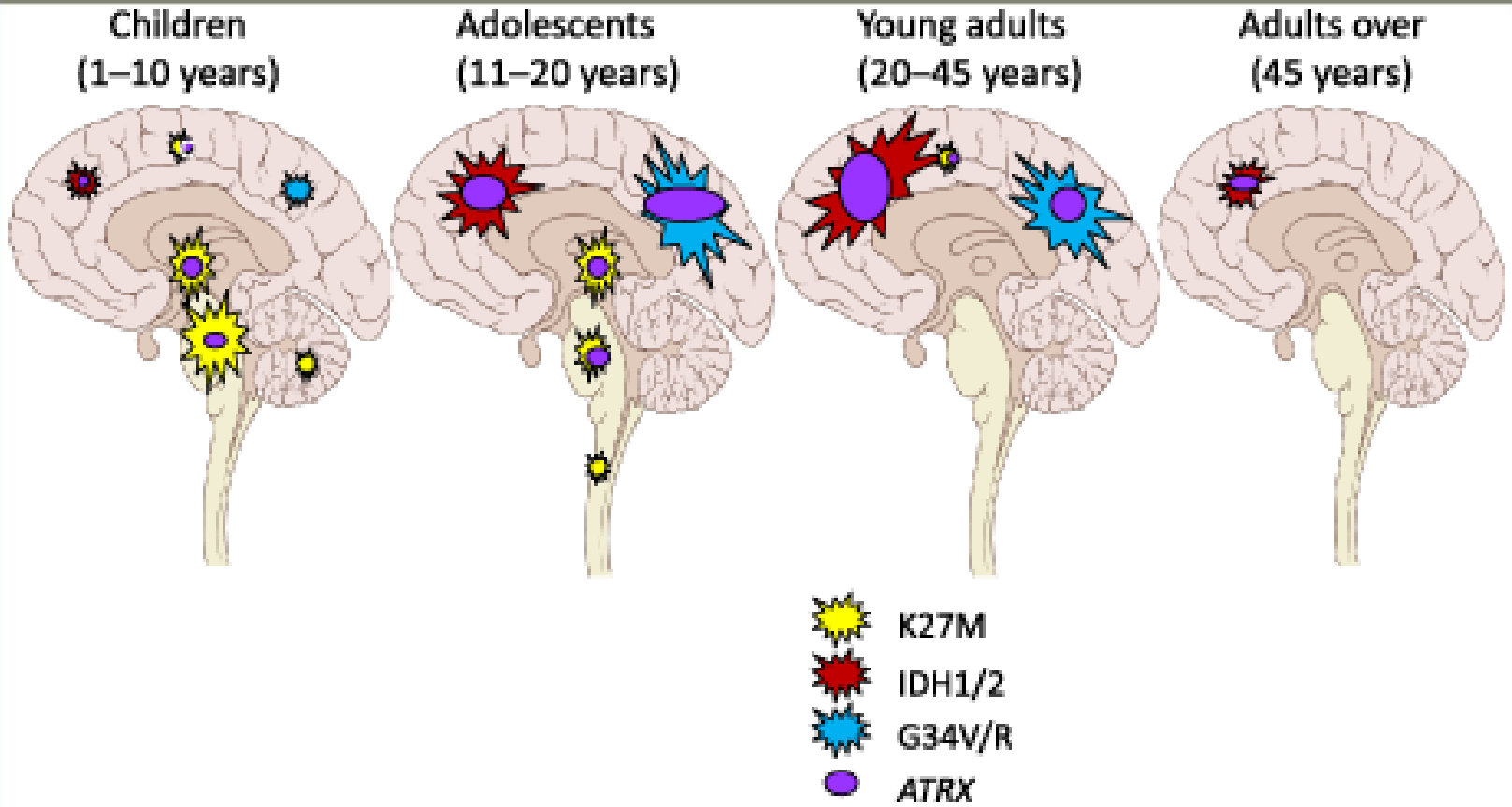
Chromatin Remodeling Defects in Pediatric and Young Adult Glioblastoma



- 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).

Fontebasso AM, et al. Brain Pathol 2013:23(2):210-216.

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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

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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

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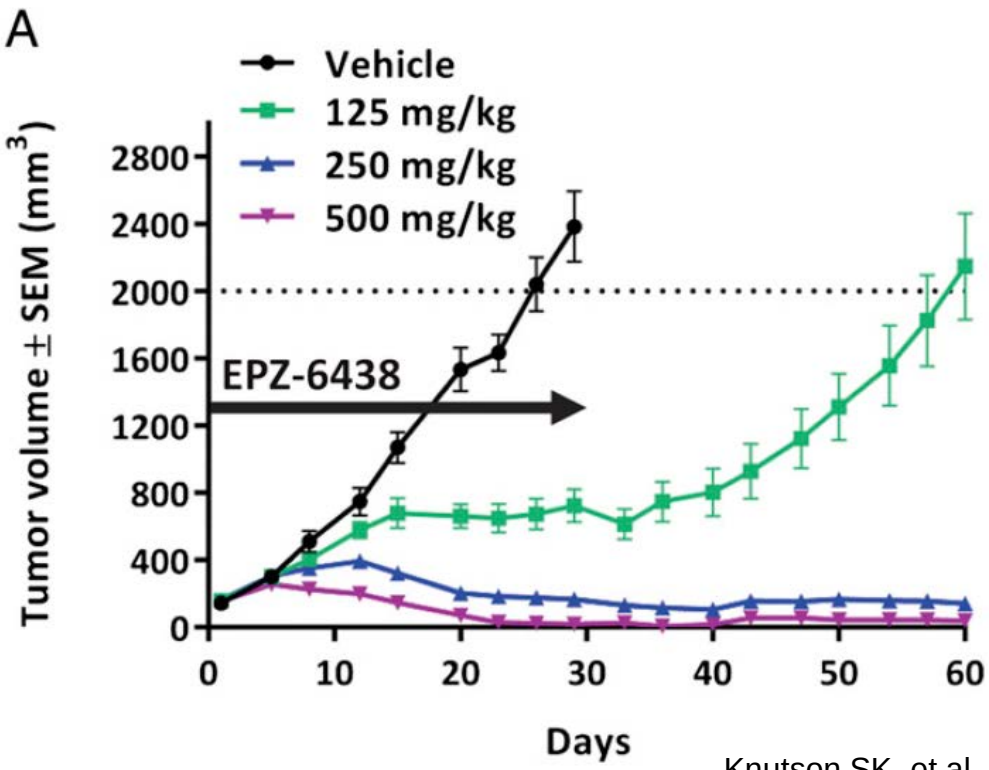
Rhabdoid tumors and EZH2 inhibition

- 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



Knutson SK, et al. PNAS 2013:110(19):7922-7927

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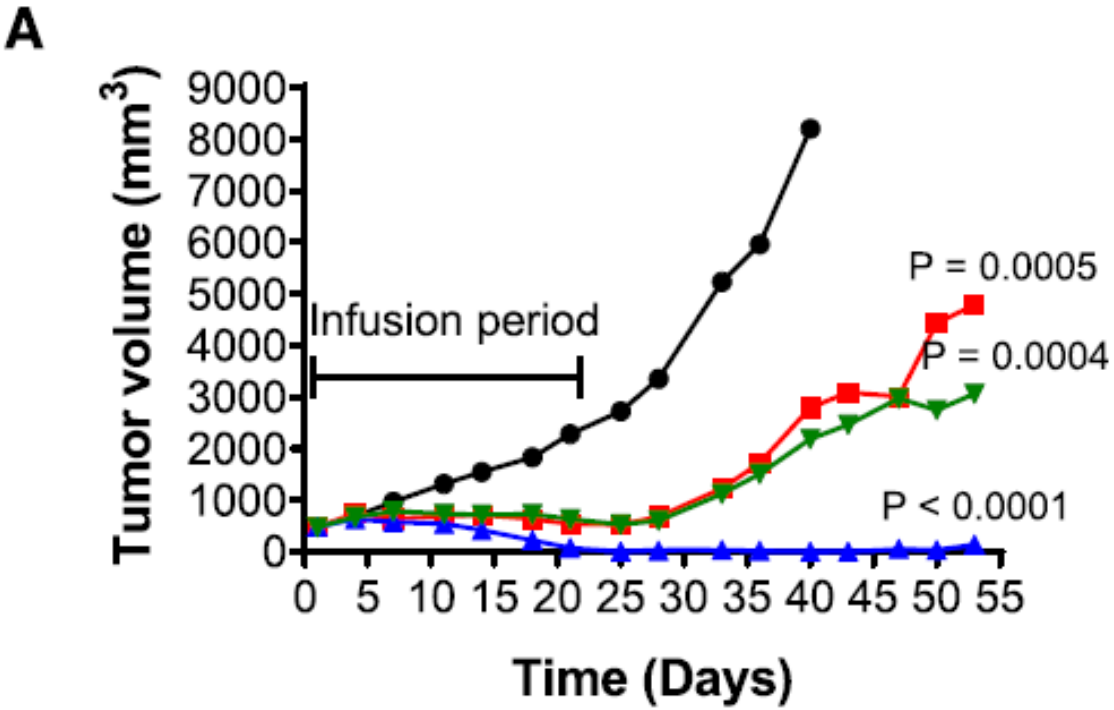
MLL Leukemia and DOT1L Inhibition

- 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



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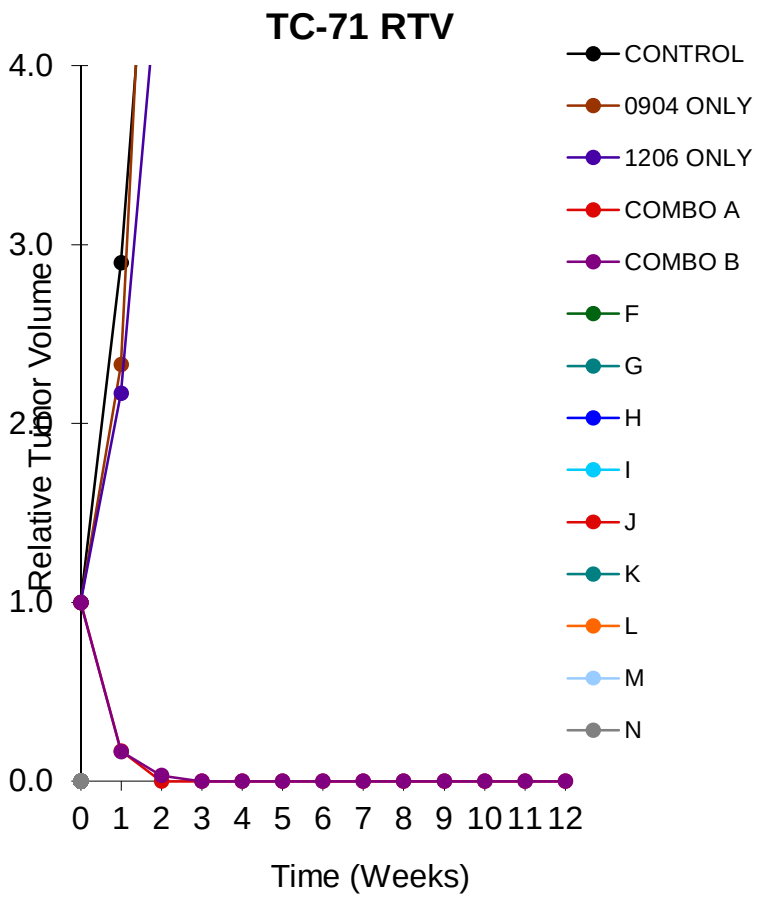
Ewing Sarcoma and PARP Inhibition

- 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



Smith, et al. AACR-NCI-EORTC Mol Targets, 2013

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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

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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

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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

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Back-up Slides

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

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

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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

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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

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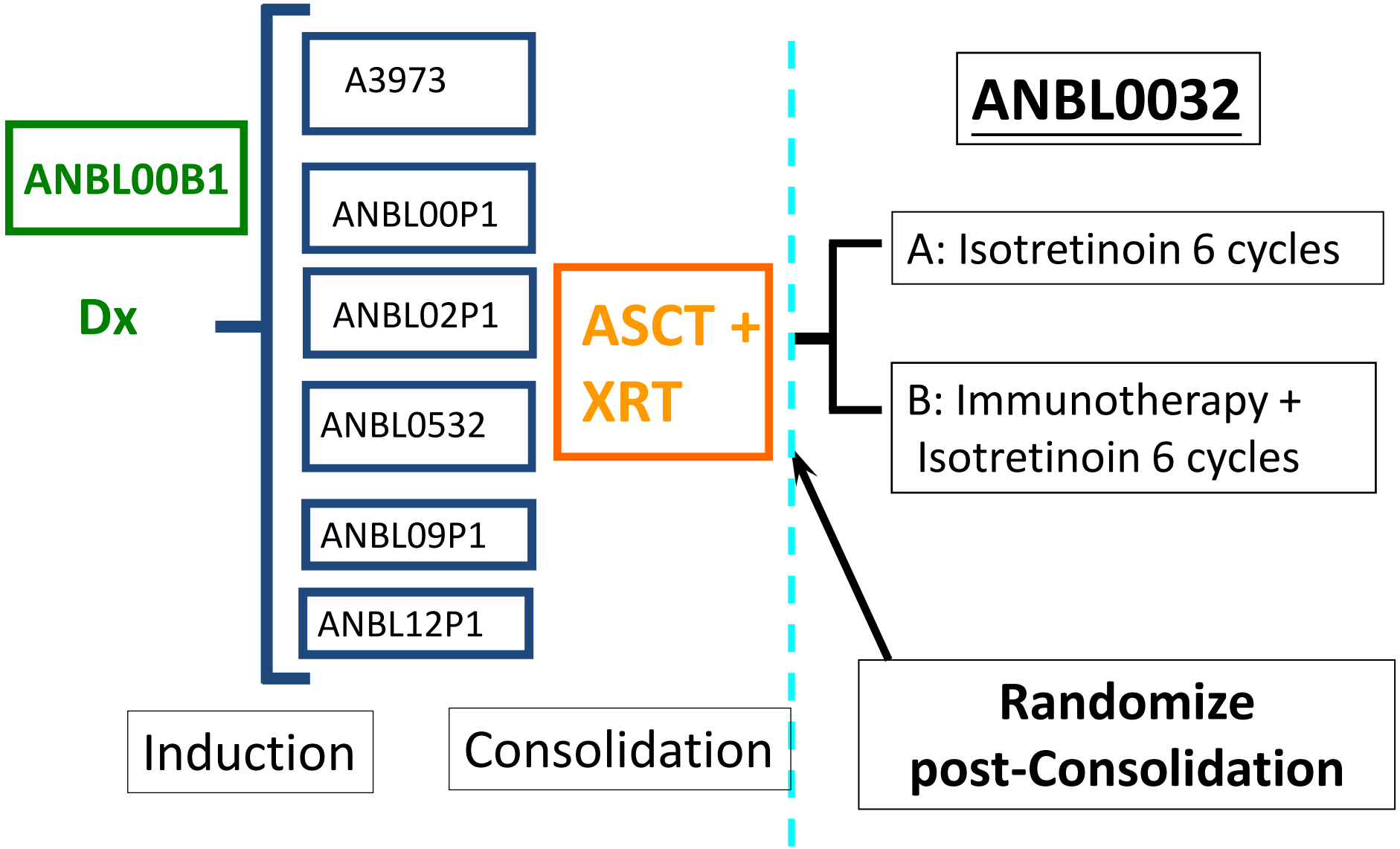
The Development of ANBL0032: phase 3 evaluation of ch14.18

- 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

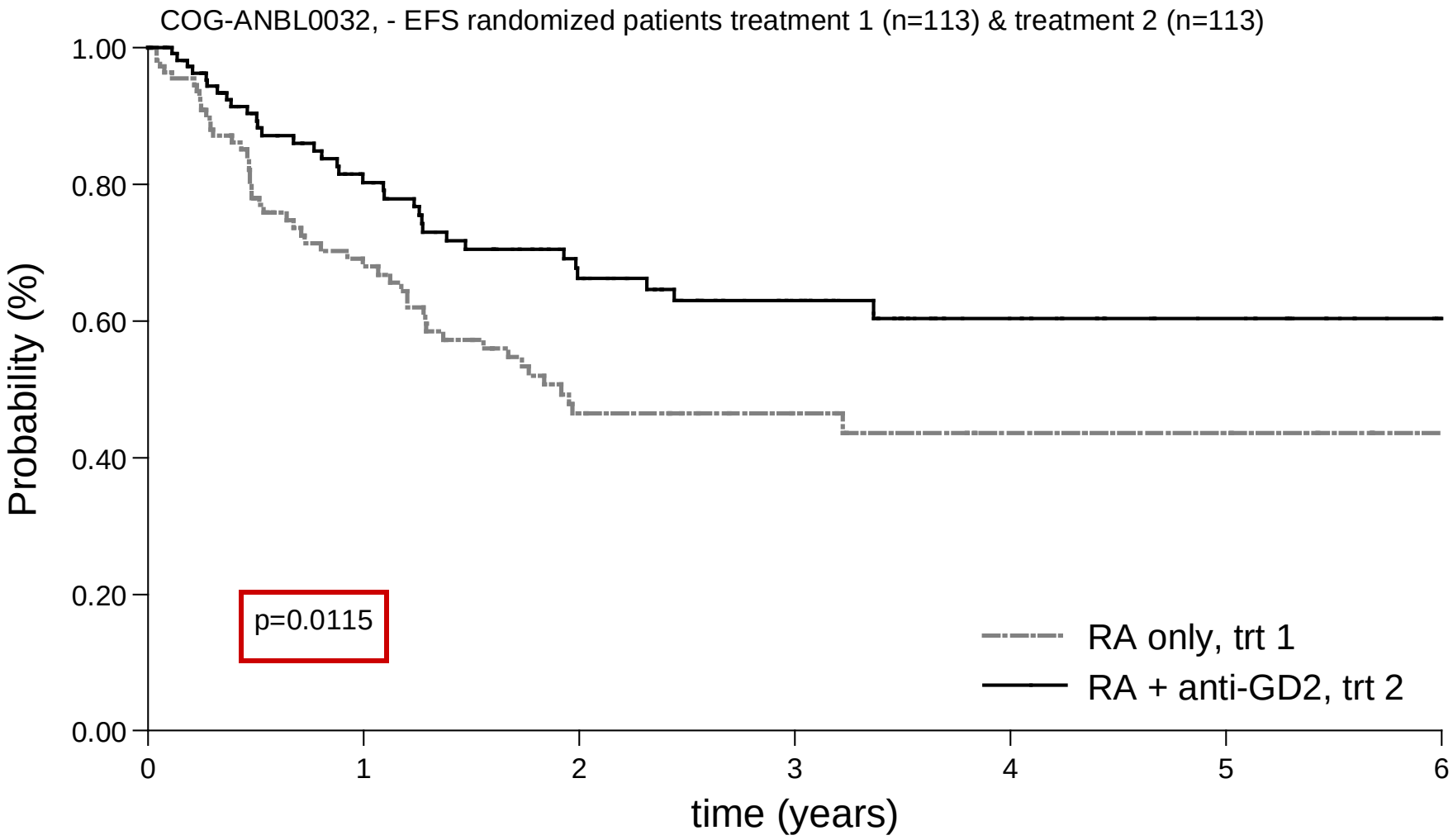
Isotretinoin (cis-RA) x 2 weeks q 4 weeks X 6 courses

Regimen B: immunotherapy

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

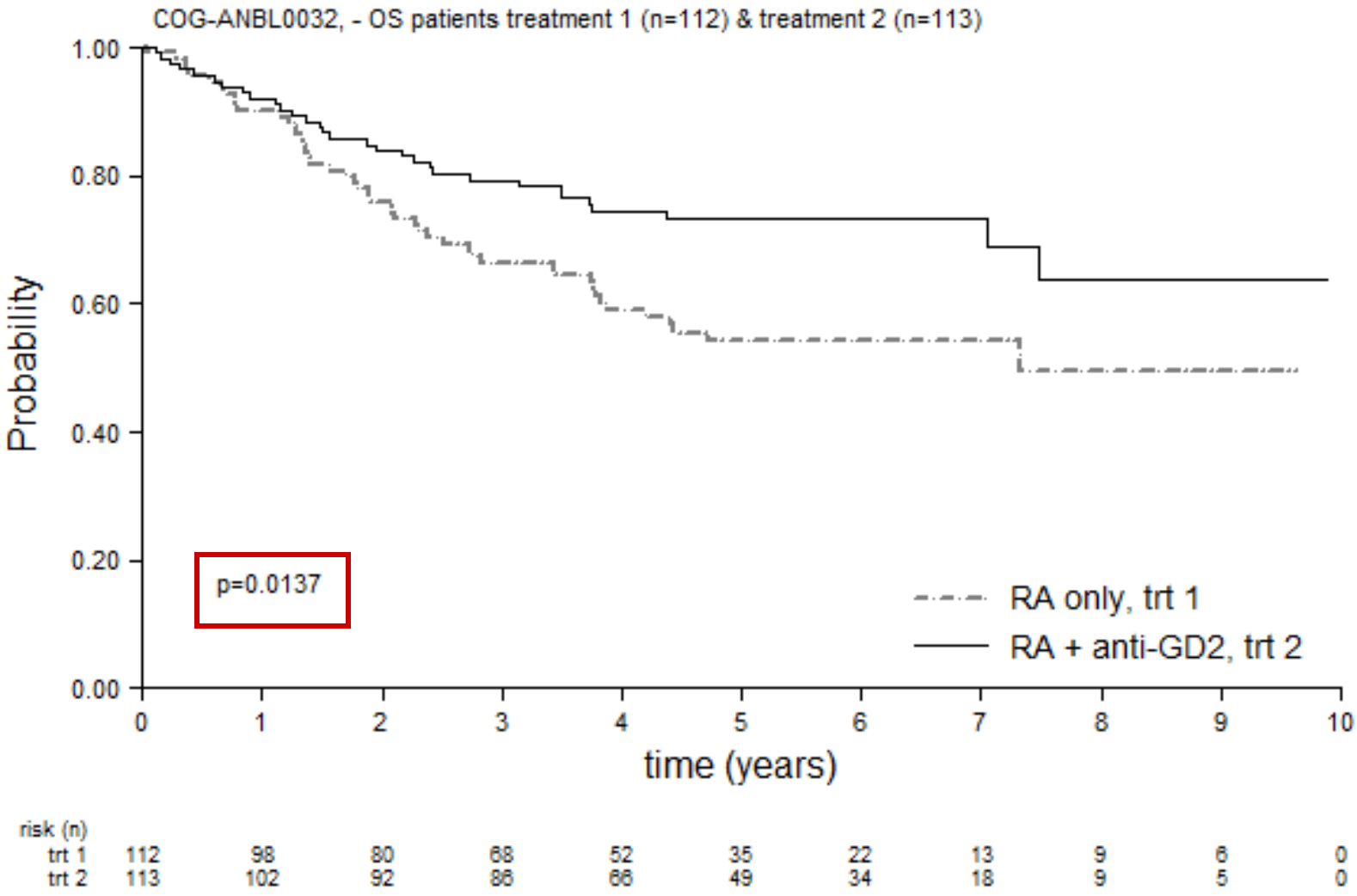
Course 1	Course 2	Course 3	Course 4	Course 5	Course 6
Ch14.18	Ch14.18	Ch14.18	Ch14.18	Ch14.18	
GM-CSF	IL2	GM-CSF	IL2	GM-CSF	
Cis-RA	Cis-RA	Cis-RA	Cis-RA	Cis-RA	Cis-RA

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



Yu, et al. NEJM 2010

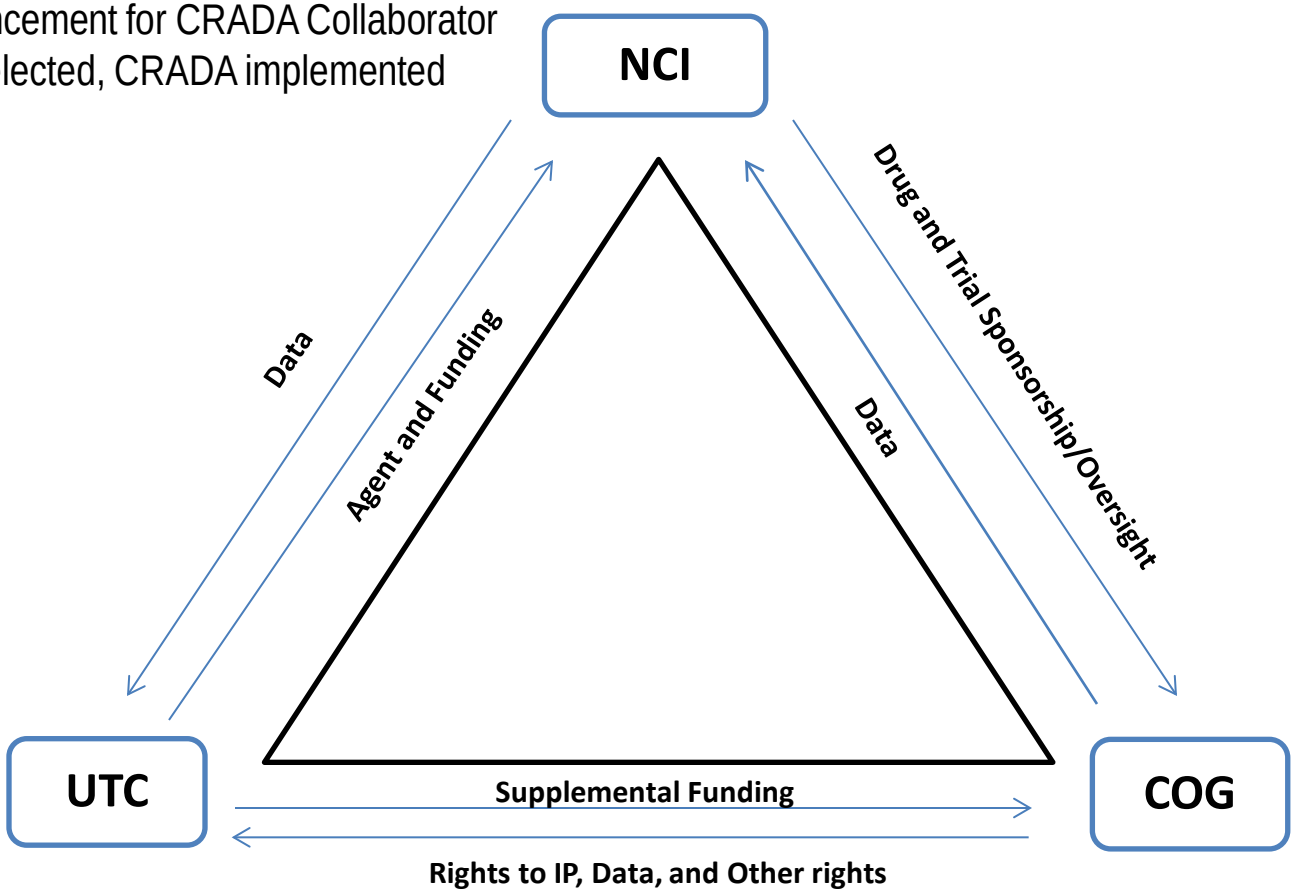
Ch14.18 + Cytokines Improves Overall Survival for High Risk Neuroblastoma (2012)



- 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.

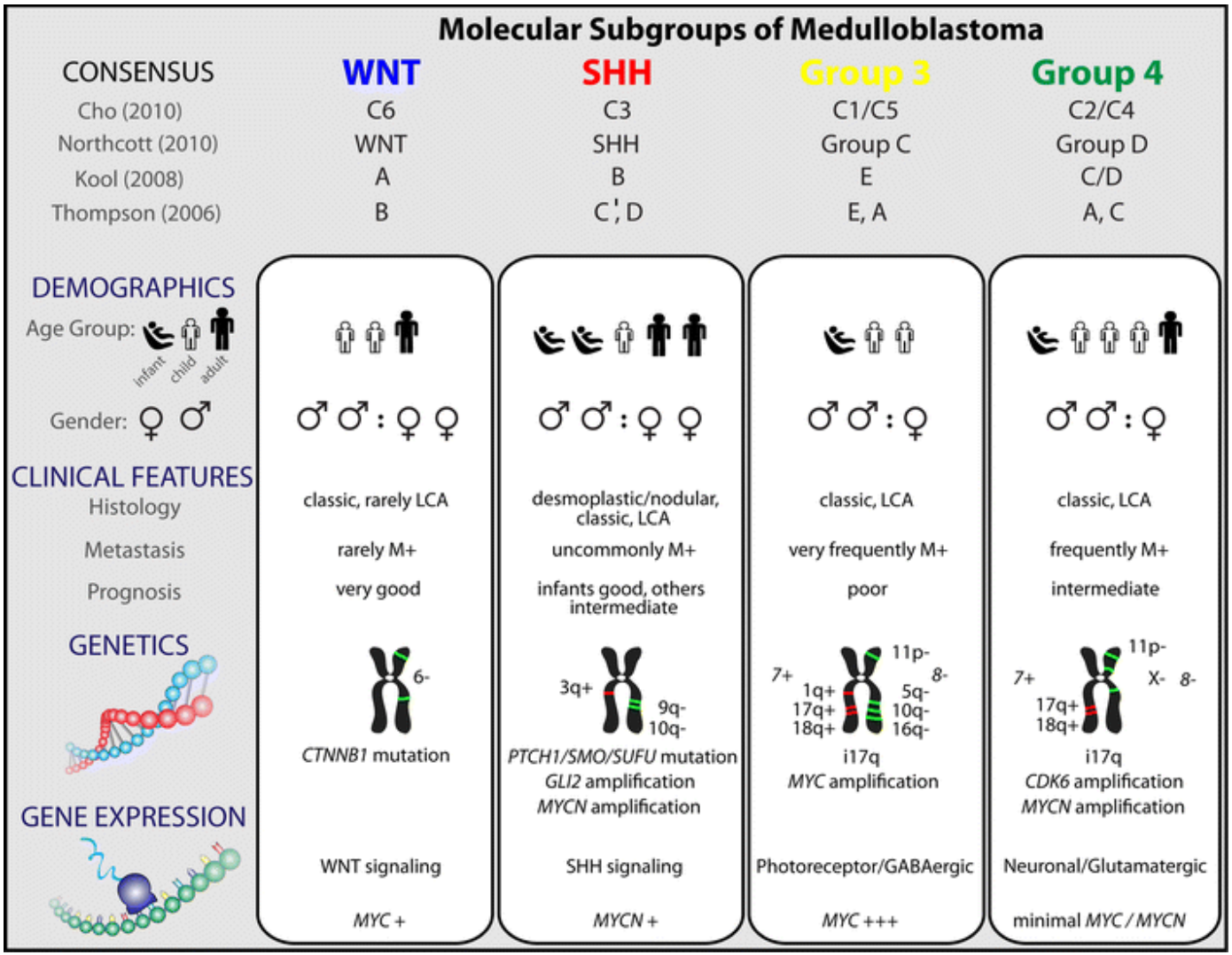
Collaborative Development of ch14.18 for Children with High-Risk Neuroblastoma

2001 – ANBL0032 initiated
2009 – ANBL0032 randomization stopped
2009 – Announcement for CRADA Collaborator
2010 – UTC selected, CRADA implemented

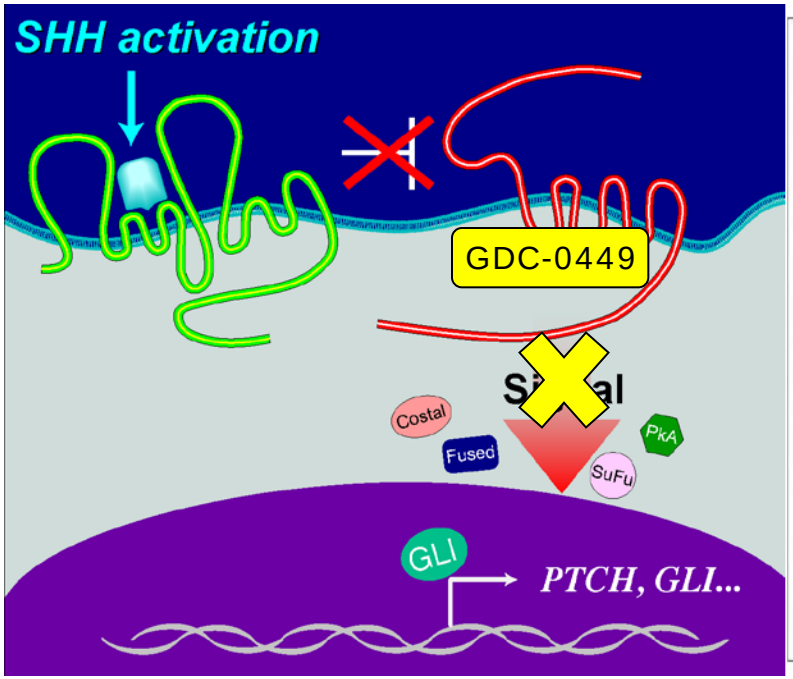


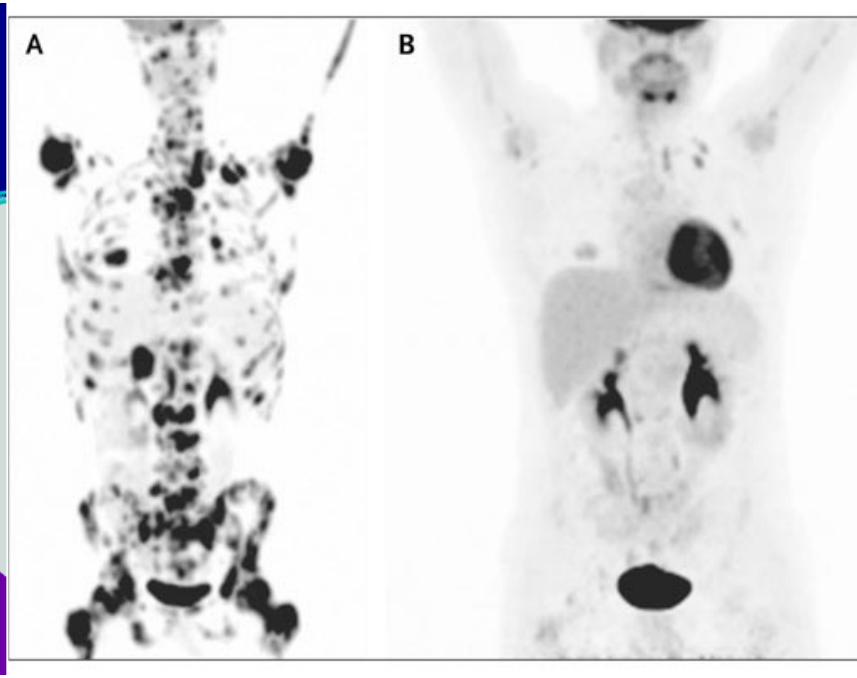
UTC

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



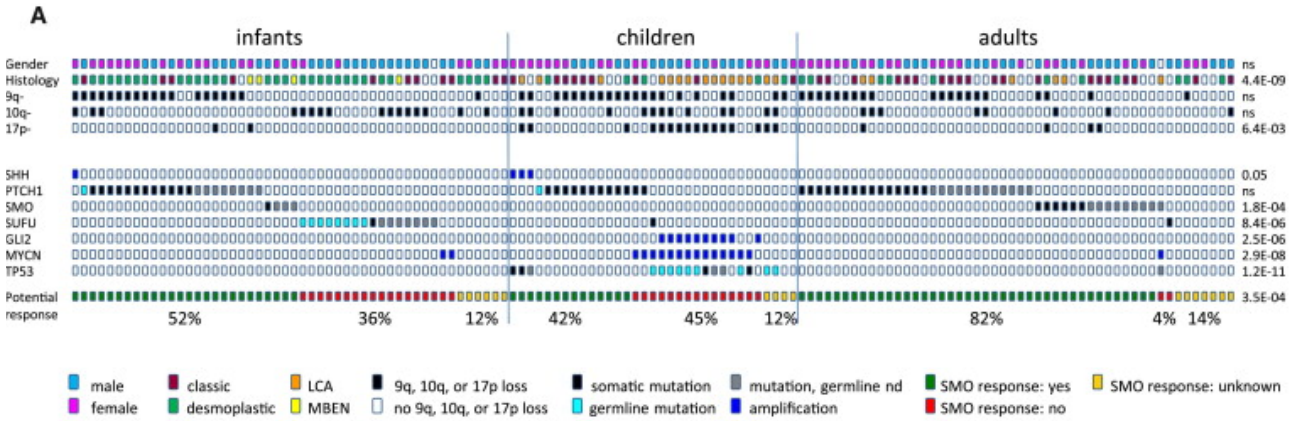
Taylor MD, et al. Acta neuropathologica 2012:123(4):465-472

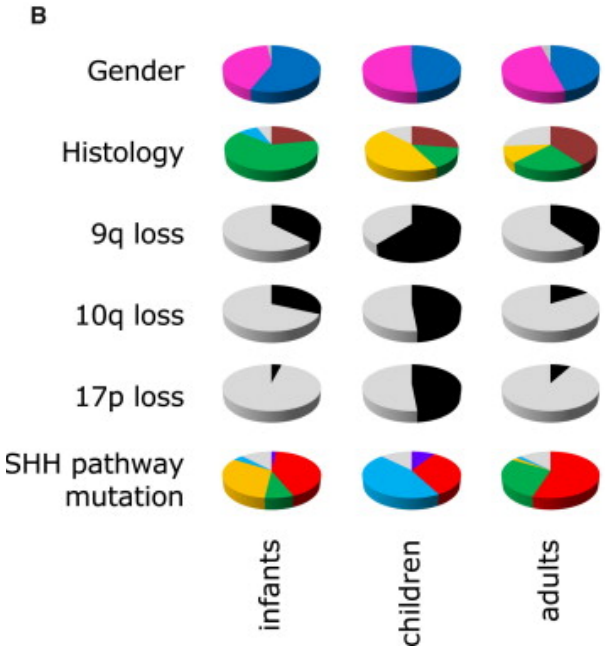


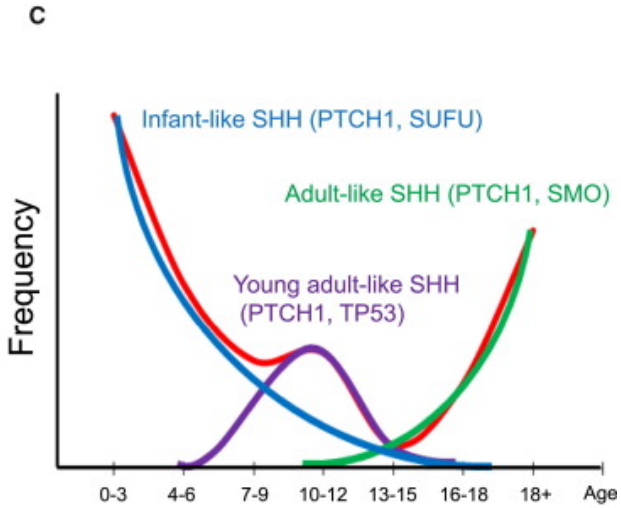


Rudin, et al. NEJM 361:1173-78, 2009

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.

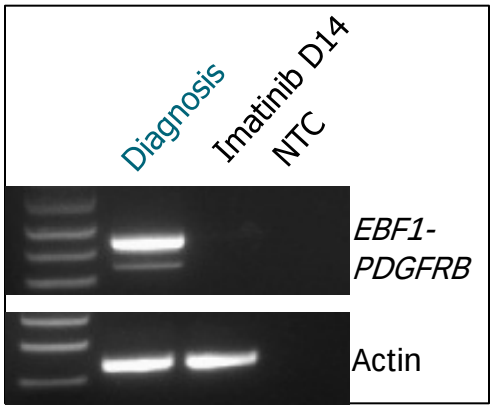






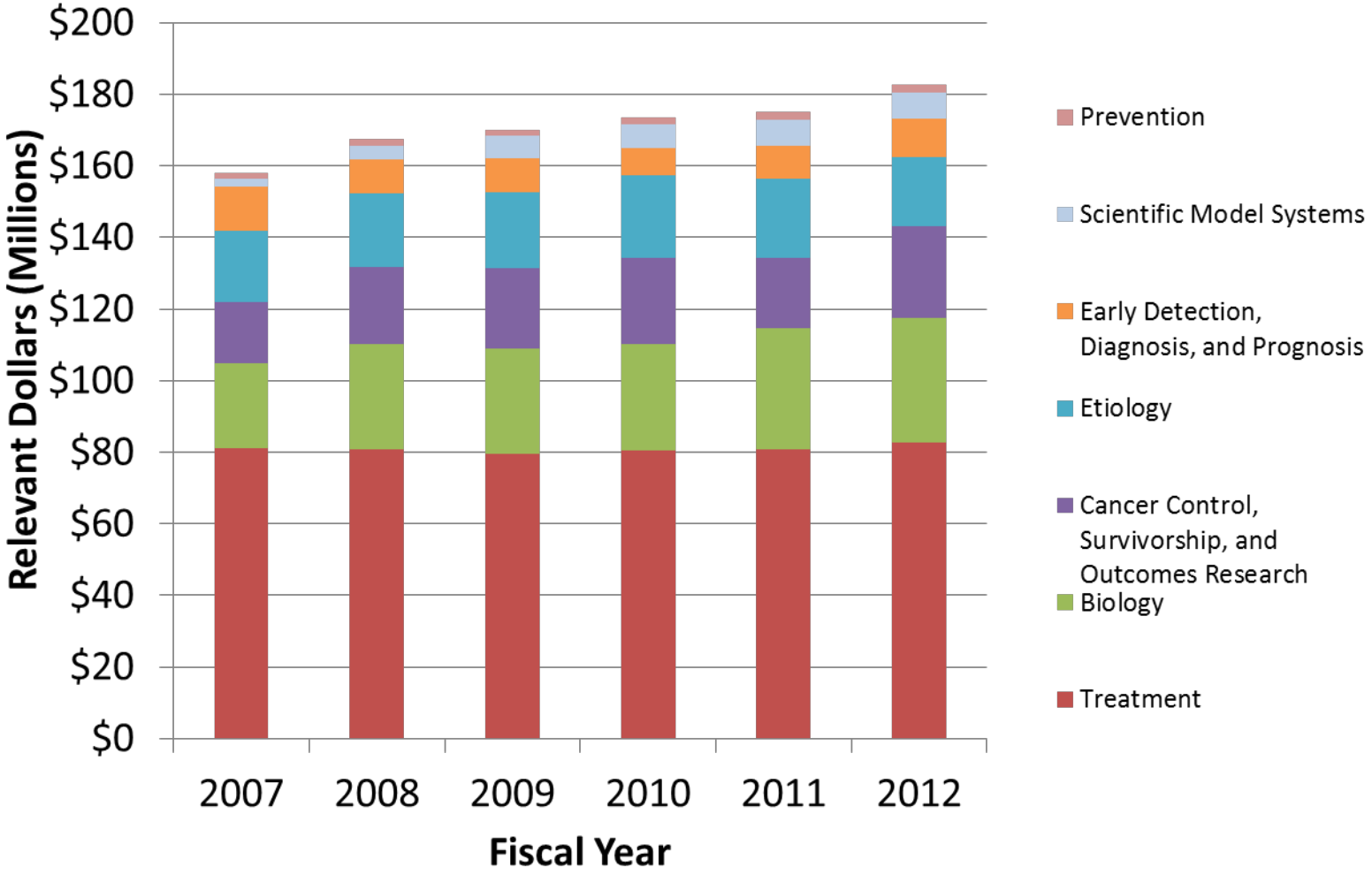
Kool M, et al. Cancer Cell 2014:25(3):393-405

- 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



RT-PCR

Weston BW, et al. J Clin Oncol 2013:31(25):e413-416


$200
$180
$160
$140
$120
$100
$80
$60
$40
$20
$0
Relevant Dollars (Millions)
2007
2008
2009
2010
2011
2012
Fiscal Year
Prevention
Scientific Model Systems
Early Detection, Diagnosis, and Prognosis
Etiology
Cancer Control, Survivorship, and Outcomes Research
Biology
Treatment

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BRAF Mutated Pediatric Low-Grade Astrocytomas

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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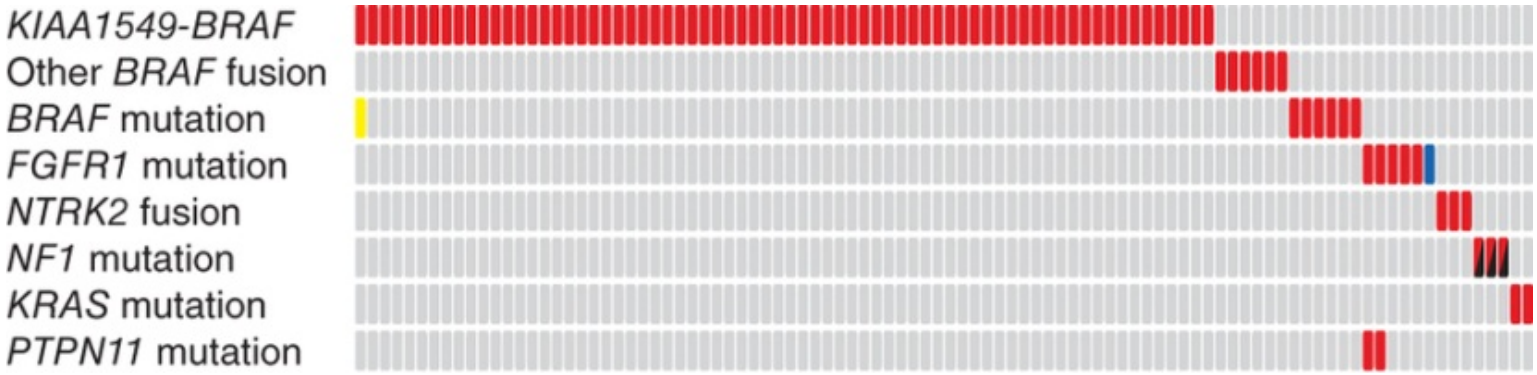
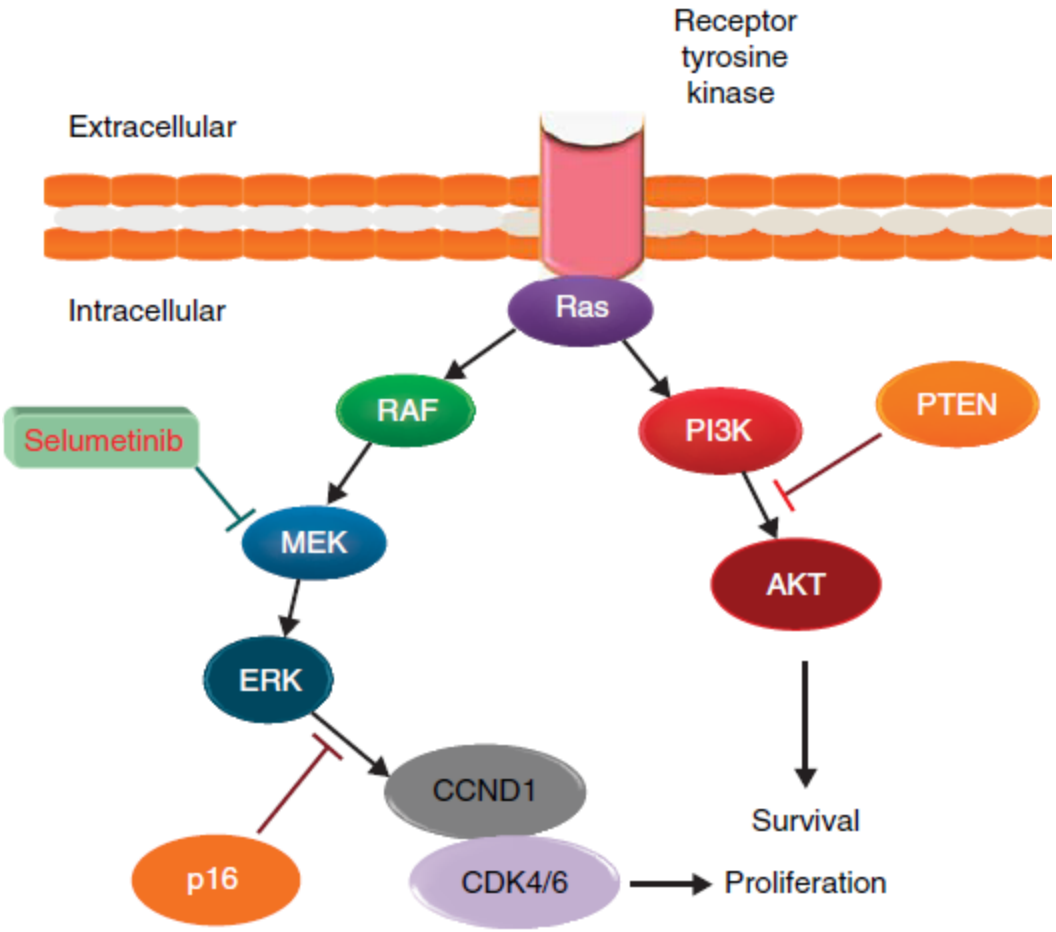
- ~80% with BRAF fusion proteins and ~5% with BRAF mutations (primarily V600E)



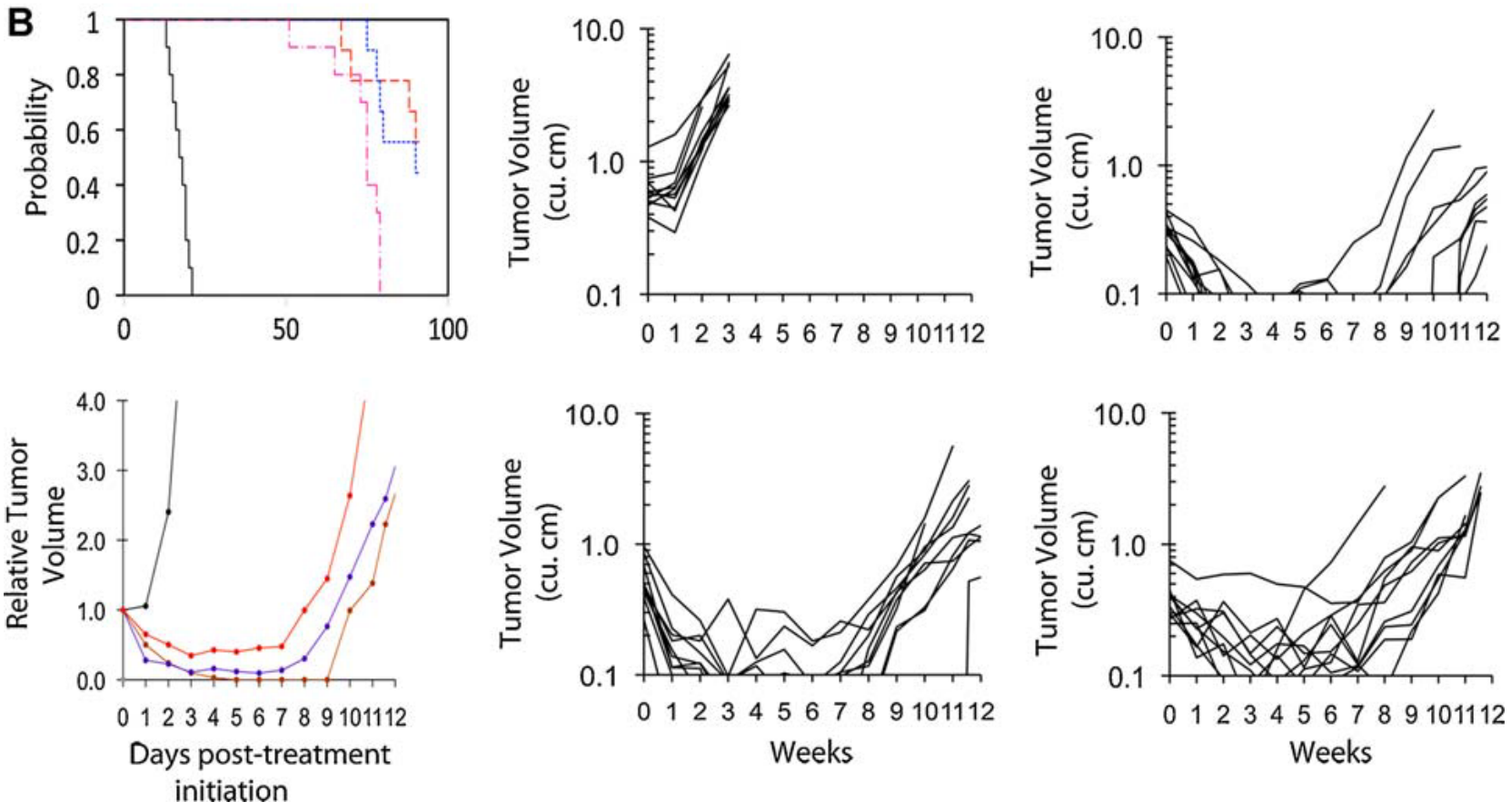
Jones, et al. Nature Genetics 2013:45(8):927-932

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

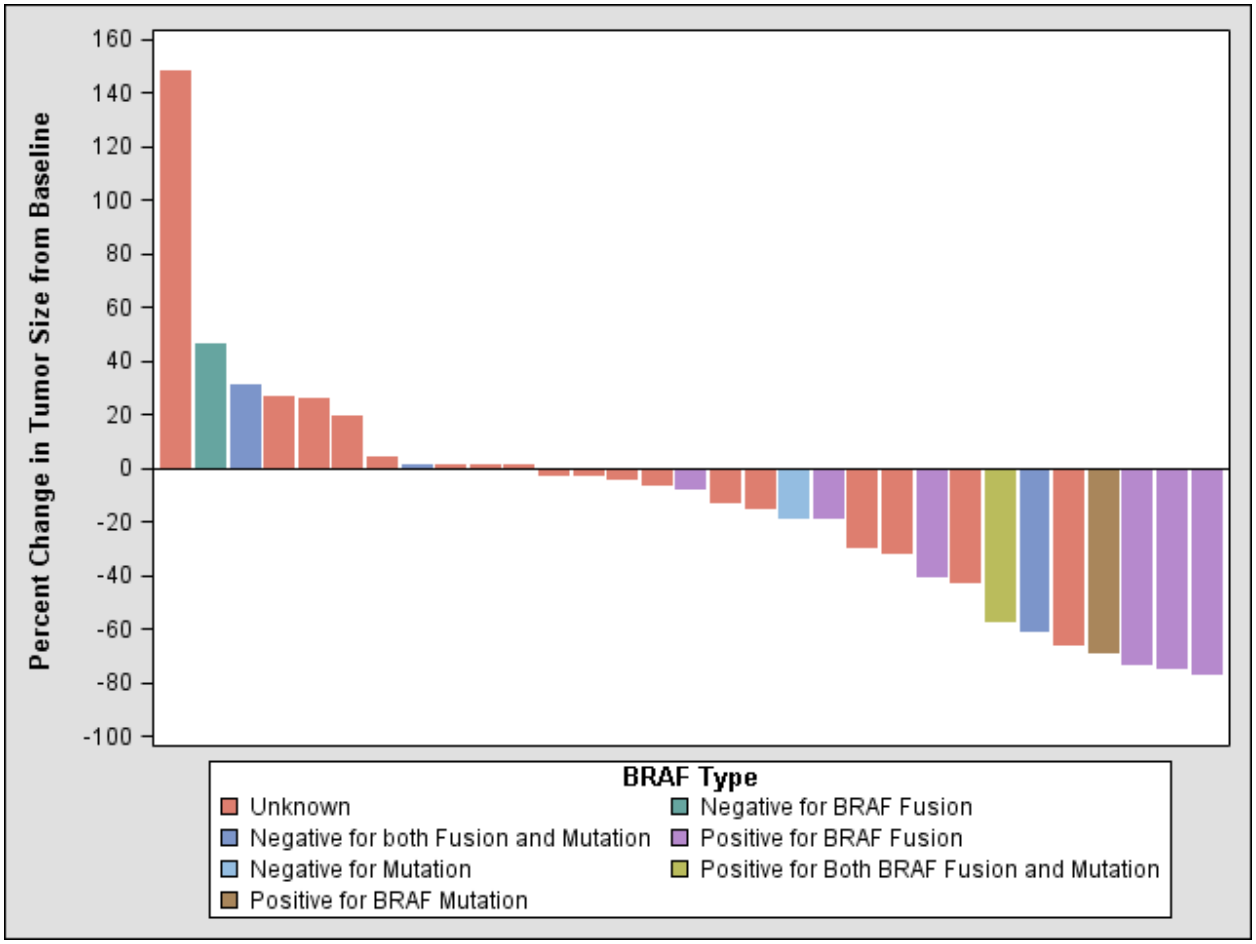


Miller CR, et al. Gyn Oncol 2014:133:128-137

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



Kolb EA, et al. Pediatr Blood Cancer. 2010;55(4):668-77



- All patients with BRAF genomic alterations showed tumor shrinkage.

Banerjee A, et al. J Clin Oncol 2014:32:5s, (suppl; abstr 10065)