Update of AYA
Acute Lymphoblastic Leukemia (A.L.L.)

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Archie Bleyer, M.D.

Annual Texas AYA Oncology Conference
San Antonio, Texas
February 20-22, 2020

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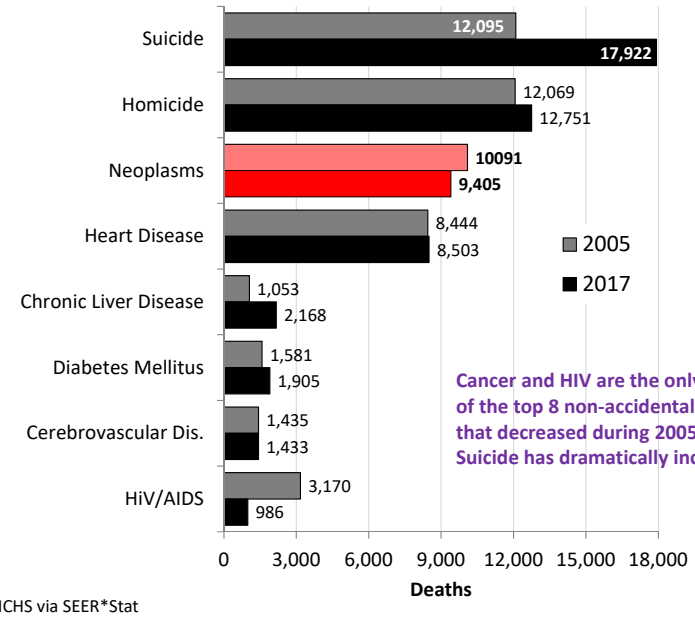
Number of Deaths of Top 8 Most Common Causes in AYAs (Age 15-39), excluding Accidents, U.S., 2005 and 2017

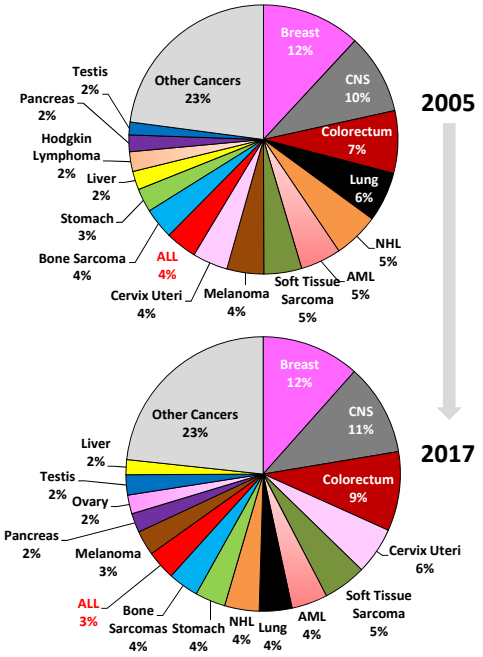


Cancer and HIV are the only causes of the top 8 non-accidental causes that decreased during 2005-2017. Suicide has dramatically increased.

Data Source: NCHS via SEER*Stat

2

Cancer Death Distribution, U.S. by Type



The Major Increases
- Colorectal Cancer
- Cervical Cancer
- Gastric Cancer
- Pancreas Cancer

Other Increases
- CNS Tumors
- Ovary Cancer

The Major Decreases
- Lung
- NHL
- Melanoma

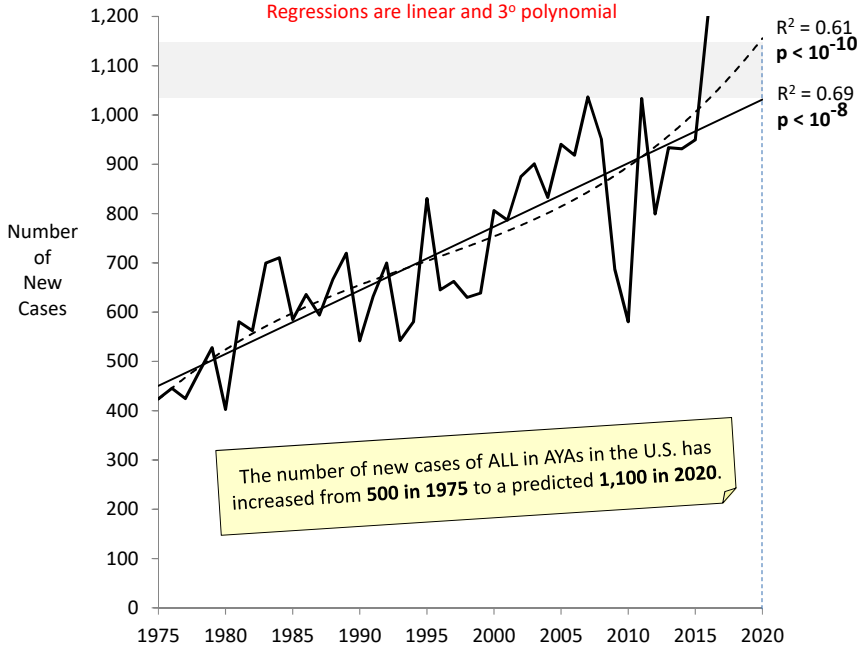
Other Reductions
- ALL
- AML

Data Source: NCHS via SEER*Stat

3

Annual Number of New Cases of ALL in AYAs (Age 15-39), 1975-2016, U.S.

Regressions are linear and 3º polynomial



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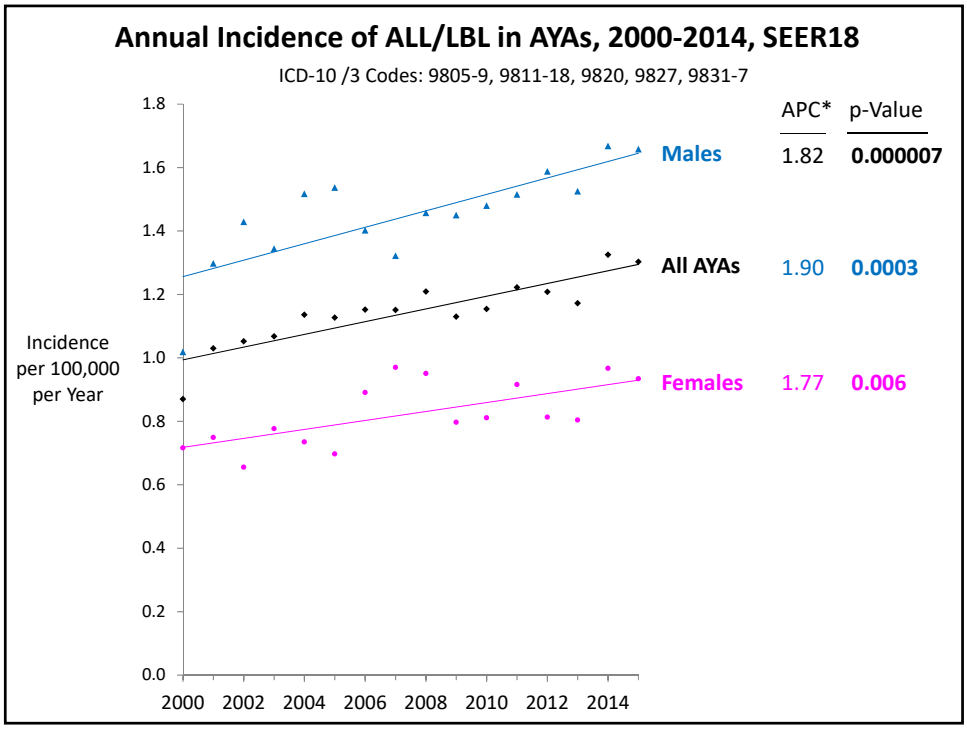

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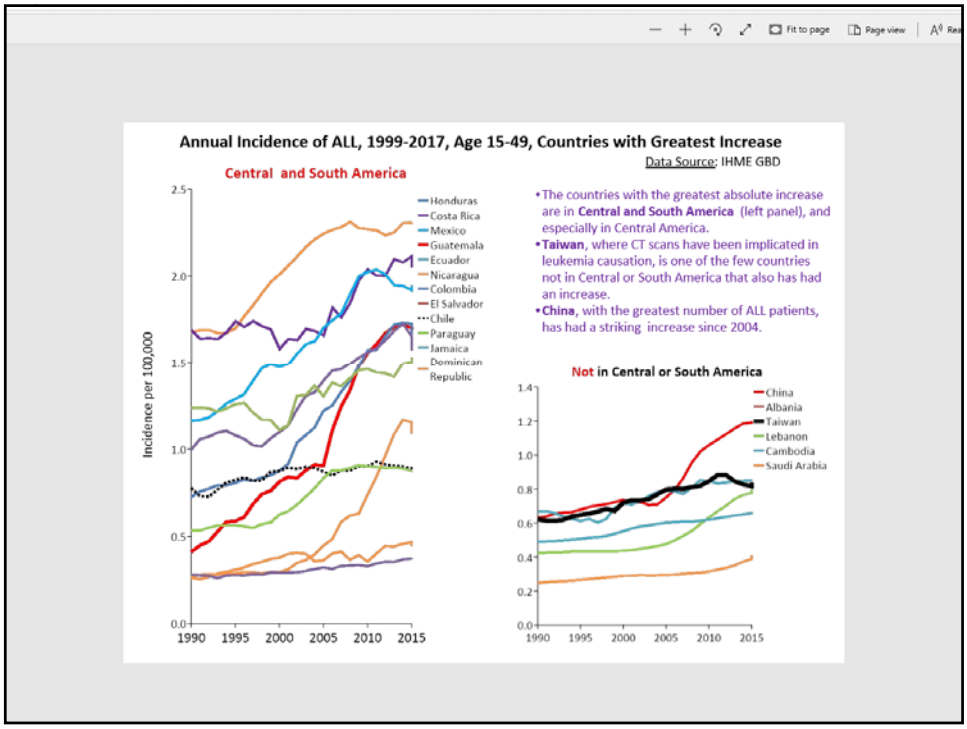

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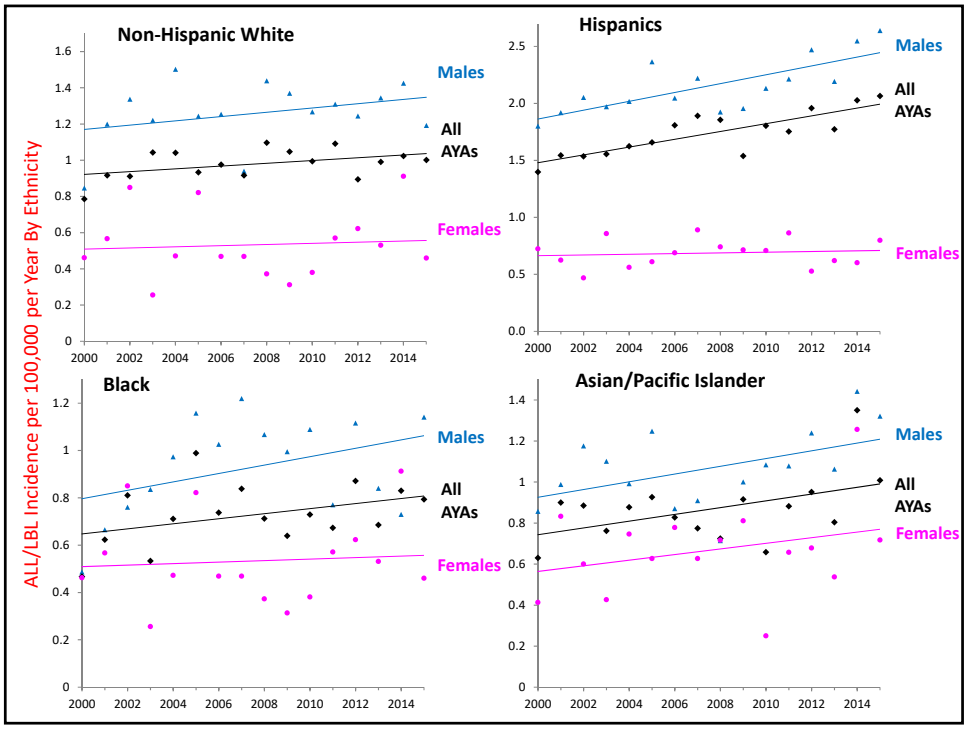

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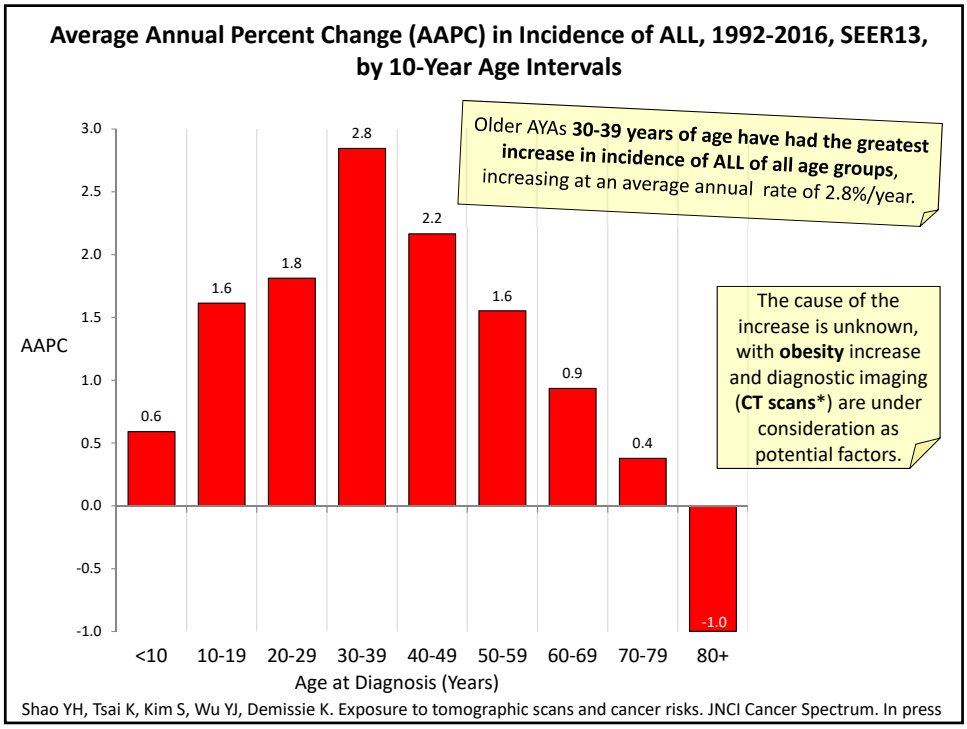

Shao YH, Tsai K, Kim S, Wu YJ, Demissie K. Exposure to tomographic scans and cancer risks. JNCI Cancer Spectrum. In press

8

Increasing Incidence:

- Males > Females
- Race/Ethnicity Population Trends:
  Blacks & Hispanics > Asians > Non-Hispanic Whites

Why Increasing Incidence?

- Increasing obesity (Incidence ∝BMI)
- Race/Ethnicity Population Trends:
  Blacks & Hispanics › Asians › Non-Hispanic Whites
- ? CT Scans?

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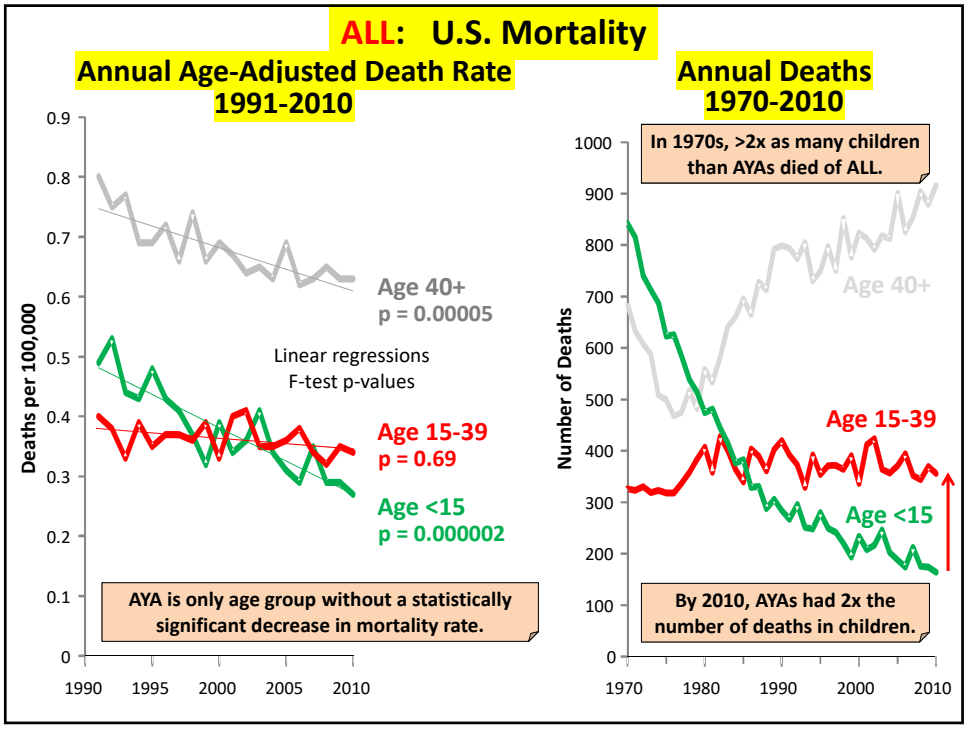

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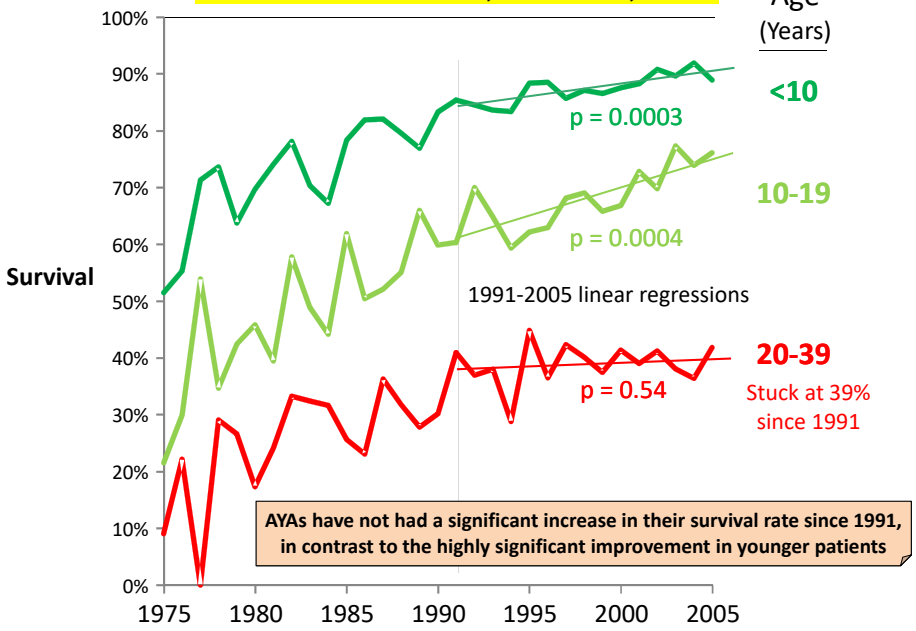
ALL: Survival

Annual 5-Year Survival, 1975-2005, SEER



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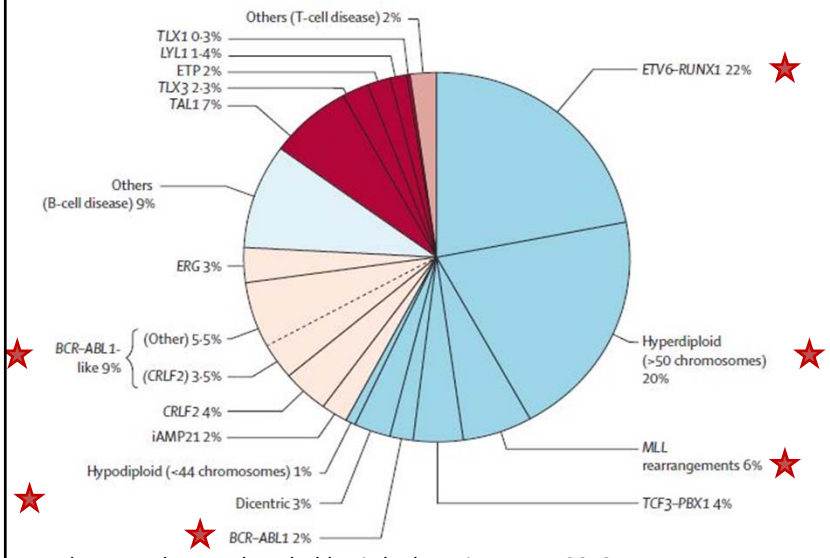
Molecular Abnormality in A.L.L.



Inaba H, et al. Acute lymphoblastic leukaemia. Lancet 2013.

12

Advance Access publication on March 24, 2011.

Unique Characteristics of Adolescent and Young Adult Acute Lymphoblastic Leukemia, Breast Cancer, and Colon Cancer

James V. Tricoli, Nita L. Seibel, Donald G. Blair, Karen Albritton, Brandon Hayes-Lattin

Table 1. Special features of cancers in adolescent and young adult (AYA) patients

Features of acute lymphocytic leukemia in AYA patients compared with children
- Higher incidence of poor prognostic cytogenetic features such as t(9;22) (Philadelphia Chromosome) or hypodiploidy
- Lower incidence of favorable cytogenetic features associated with a favorable outcome such as high hyperdiploidy and t(12;21) ETV6-RUNX1 translocation
- More likely to be associated with aberrant gene promoter methylation

Features of breast cancer in AYA patients compared with adults
- Lower survival rate
- Worse outcome independent of stage, extent, or type
- Higher incidence of more aggressive triple-negative form
- More likely to be higher grade, poorly differentiated, and less hormone-sensitive
- More frequent spread to greater number lymph nodes

Features of colorectal cancer in AYA patients compared with adults
- More advanced disease and poorer prognosis at diagnosis
- Less responsive to treatment
- More mucinous histology and greater frequency of signet ring cells
- Greater frequency of microsatellite instability
- Lower frequency of loss of heterozygosity at 17p and 18q

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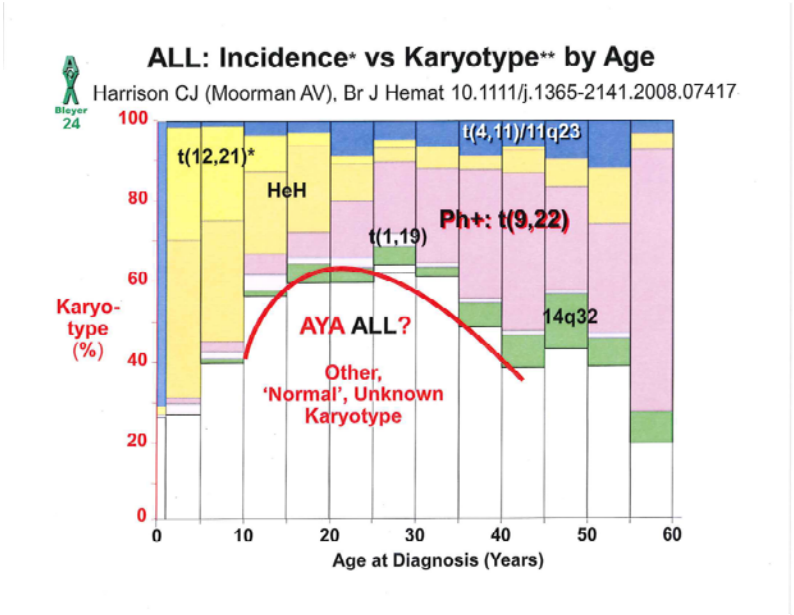

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Philadelphia chromosome–like acute lymphoblastic leukemia

Sarah K. Tasian,[1,2] Mignon L. Loh,[3,4] and Stephen P. Hunger[1,2]

[1]Department of Pediatrics, Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Philadelphia, PA; [2]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; and [3]Department of Pediatrics, UCSF Benioff Children's Hospital and [4]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA

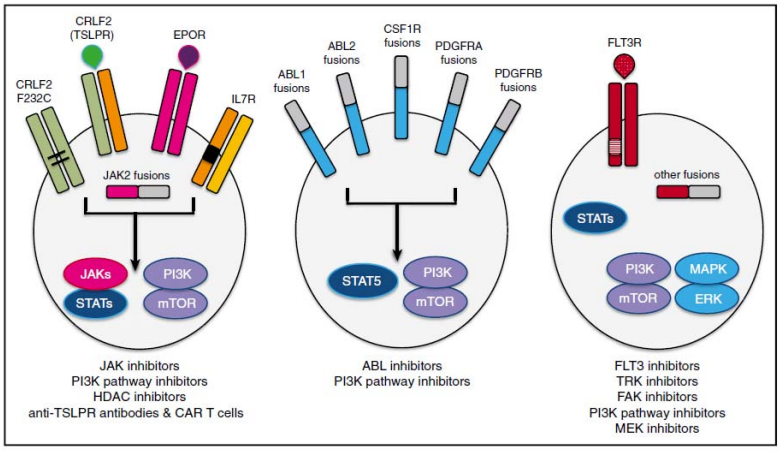

Figure 3. Schema of activated kinase signaling in Ph-like ALL. Kinase fusions and other alterations in Ph-like ALL activate oncogenic signal transduction and may be targetable by specific kinase inhibitors and other therapeutic agents.

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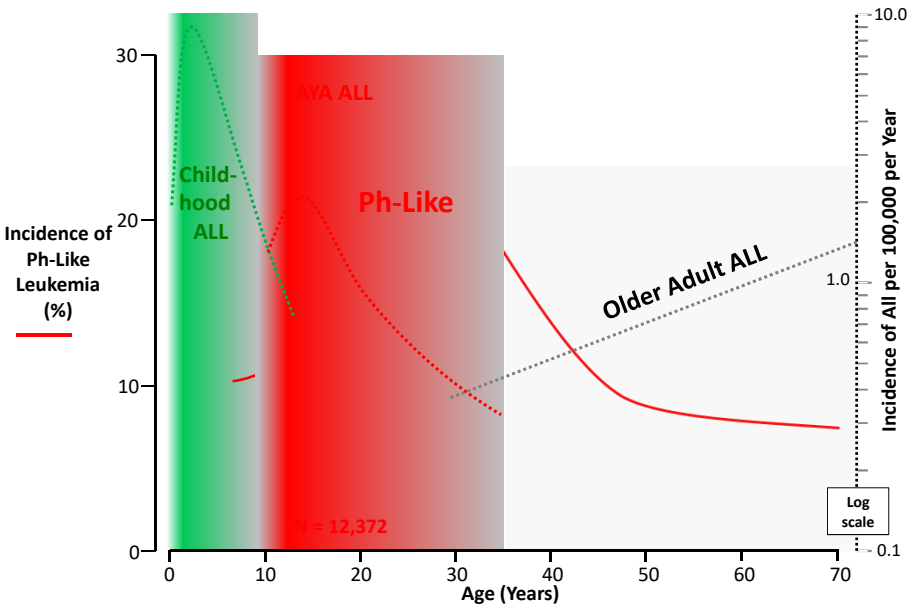
Comparison of the Incidence of All and Ph-Like Subtype



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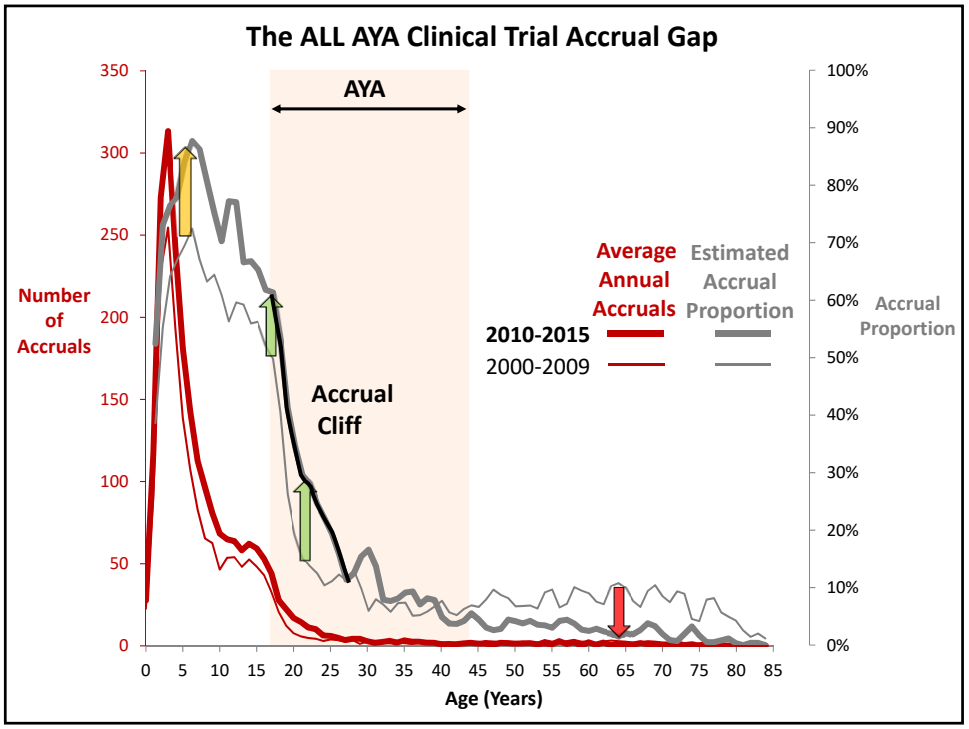

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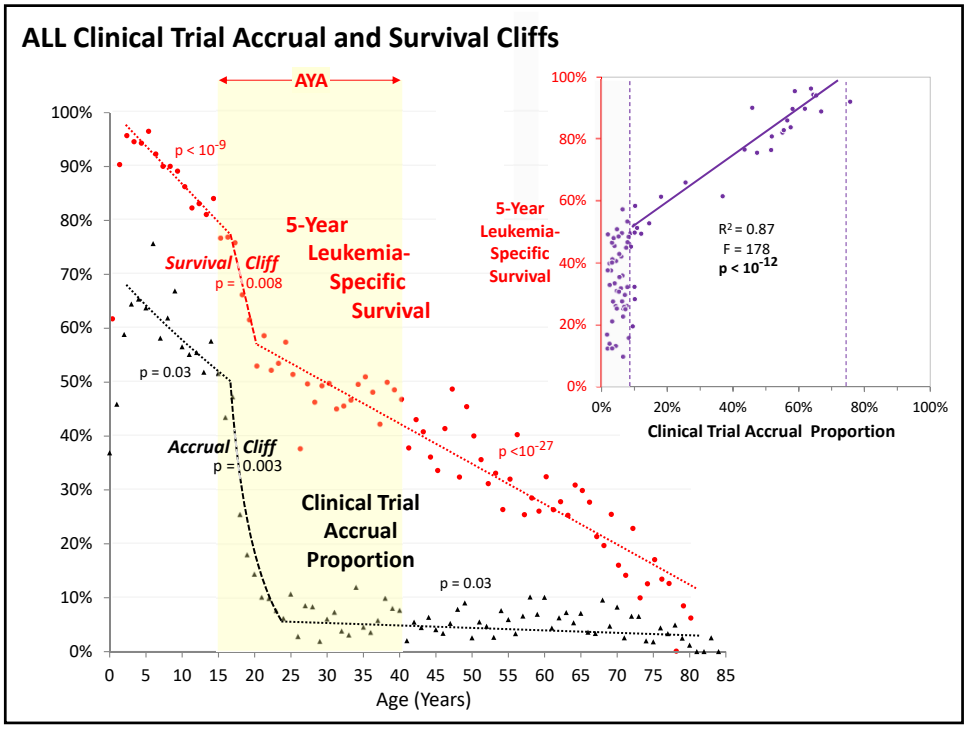

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Blood consult: Therapeutic Strategy and complications in the adolescent and young adult with acute lymphoblastic leukemia
Taizo A. Nakano and Stephen P. Hunger

Table 1. Clinical features and common complications of AYA patients with ALL

Features	Complications
Treatment toxicity	Steroid-induced hyperglycemia, avascular necrosis
	Asparginase-induced fatigue, weakness, pancreatitis, thrombosis
	Liver dysfunction
Cytogenetic abnormalities	Increased prevalence of high-risk features
	Ph+ ALL (*BCR-ABL1*)
	iAMP21
	MLL rearrangements
	Decreased prevalence of lower-risk features
	High hyperdiploidy and/or trisomies of chromosomes 4 and 10
	ETV6-RUNX1
Social	Poor medical compliance
	Underinsured
	Low enrollment in clinical trials

AYA indicates adolescent and young adult; and ALL, acute lymphoblastic leukemia.

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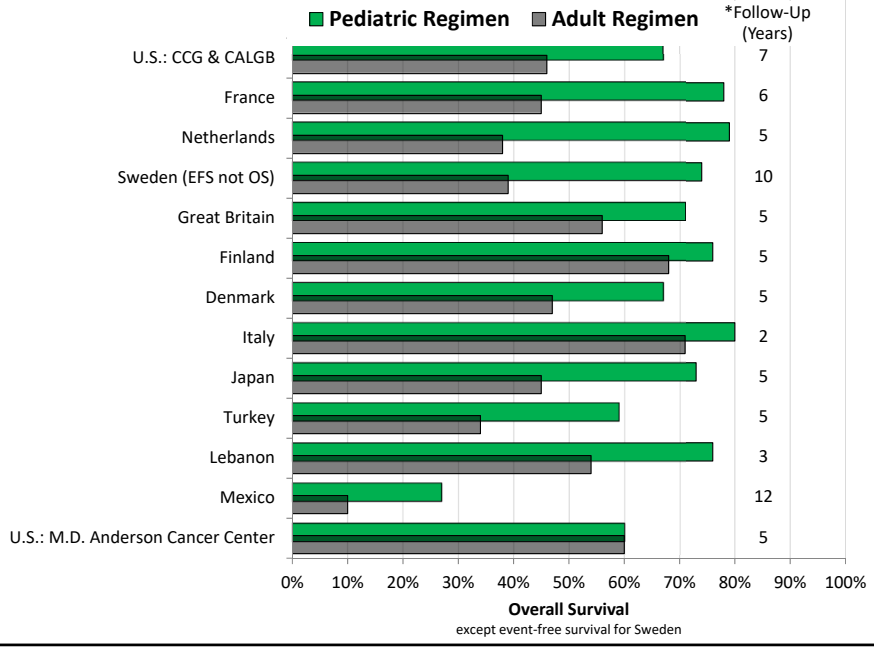
Older Adolescent and Adult ALL: Overall Survival at 2-12* Years after Diagnosis
Reports Comparing Pediatric and Adult Regimen Outcomes in AYAs after Same Follow-Up Interval*



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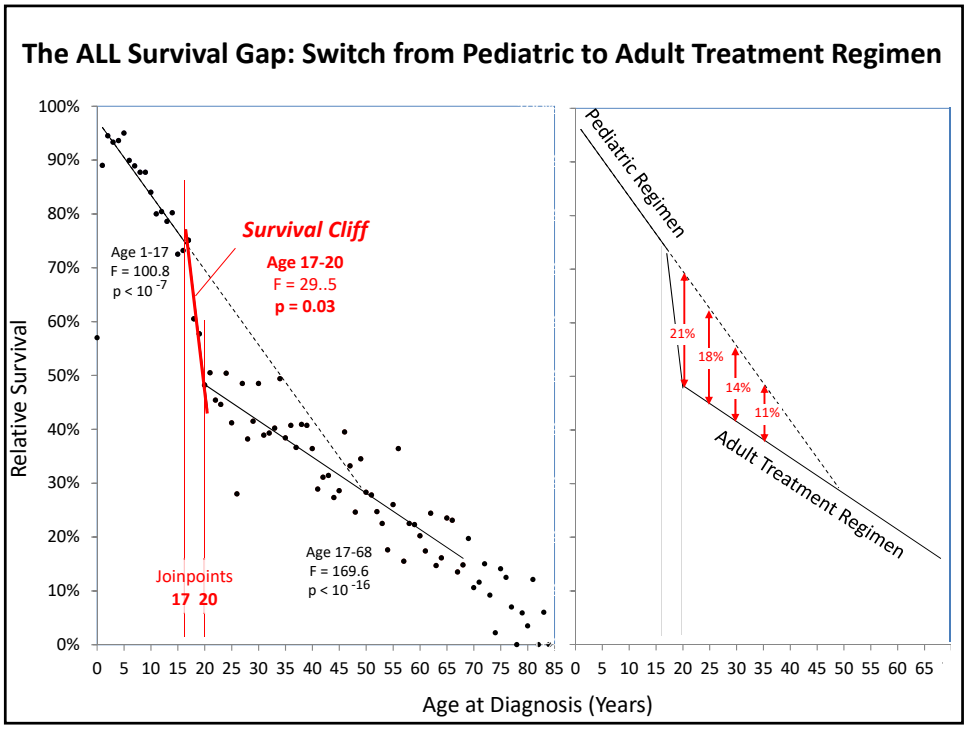

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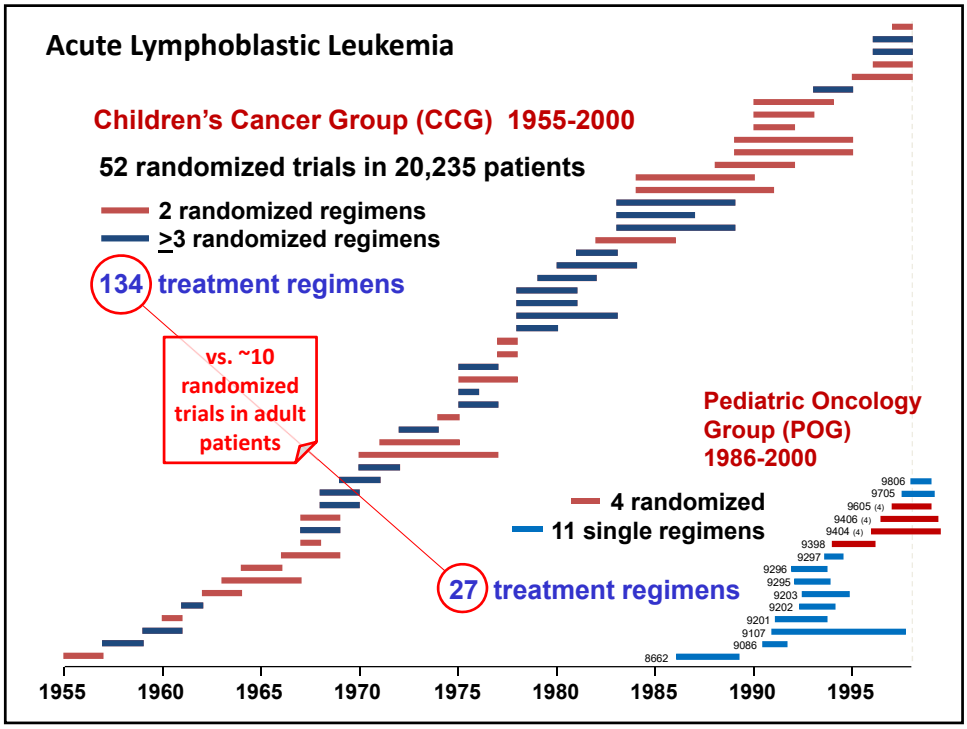

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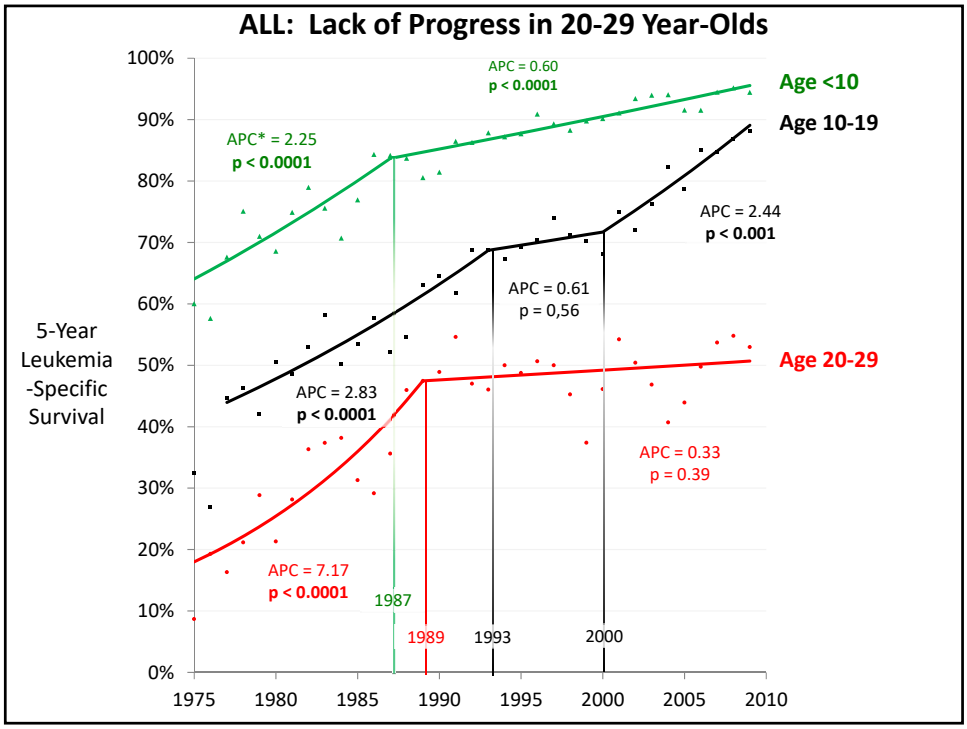

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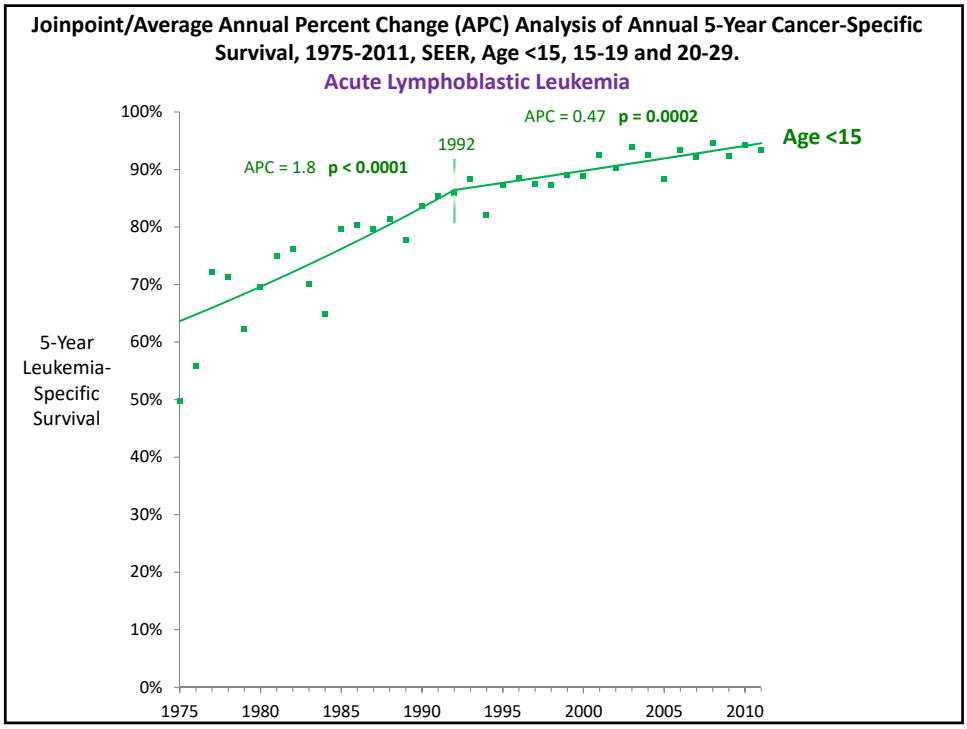

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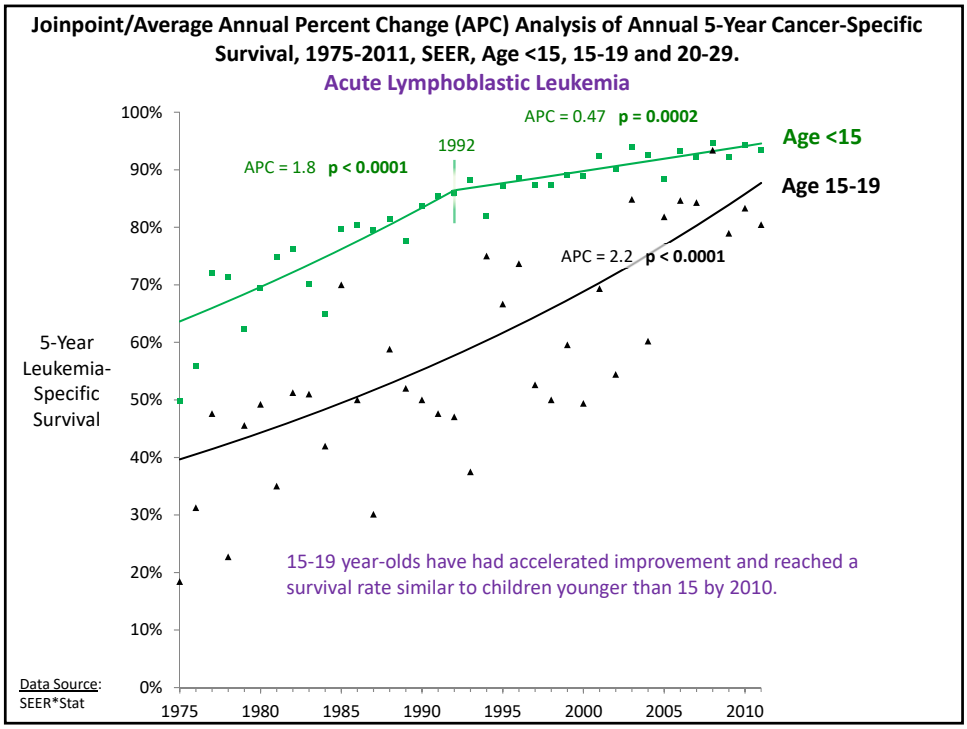

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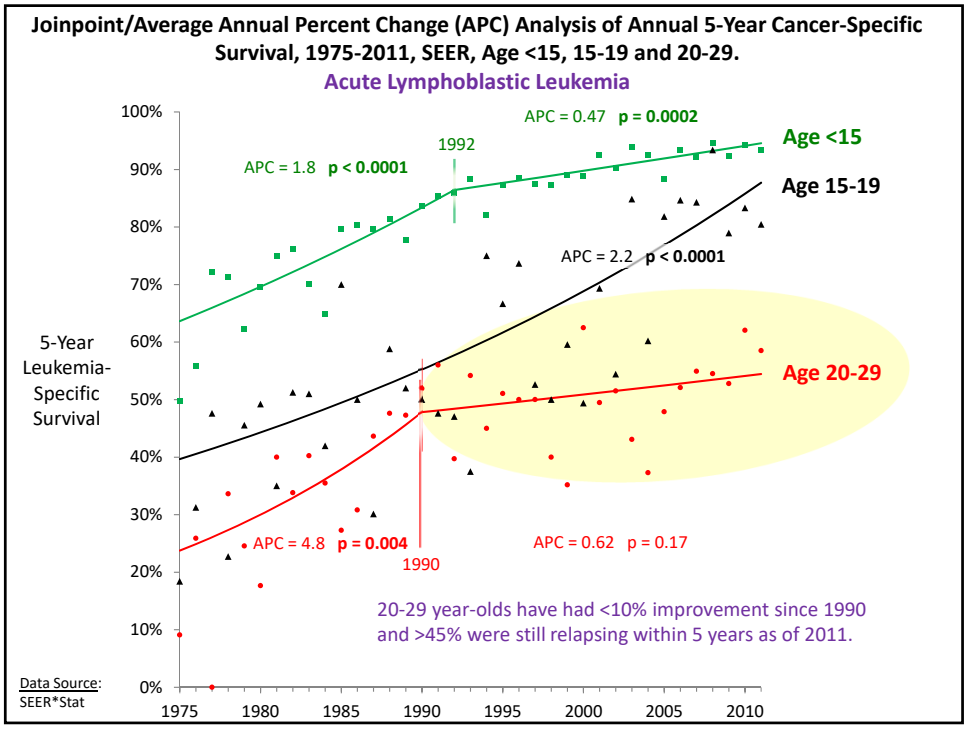

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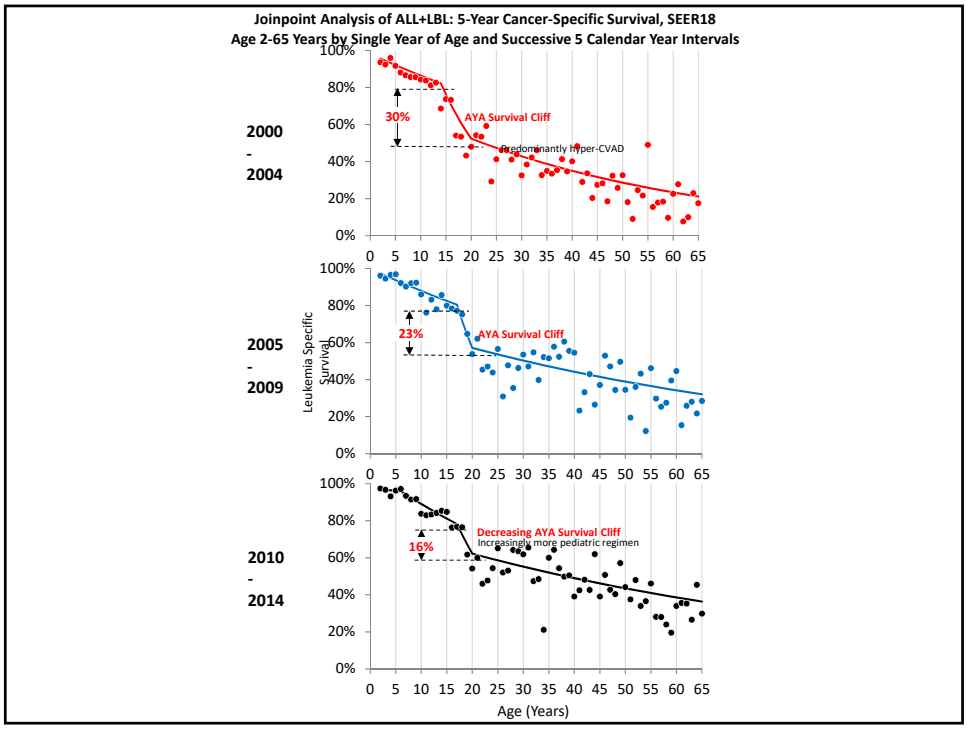

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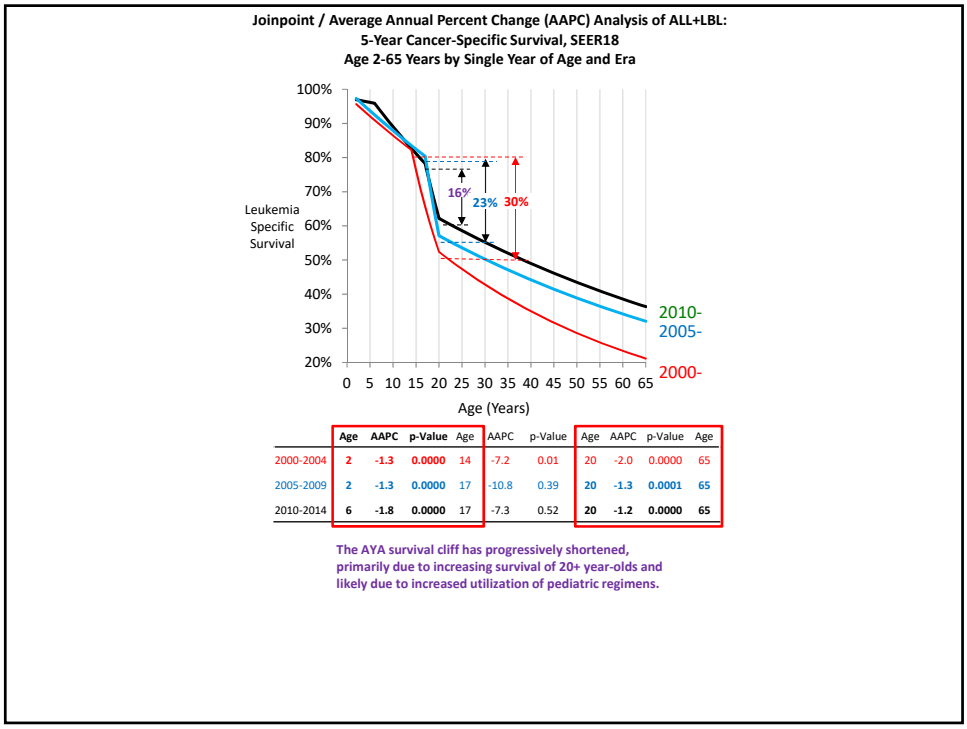

	Age	AAPC	p-Value	Age	AAPC	p-Value	Age	AAPC	p-Value	Age
2000-2004	2	-1.3	0.0000	14	-7.2	0.01	20	-2.0	0.0000	65
2005-2009	2	-1.3	0.0000	17	-10.8	0.39	20	-1.3	0.0001	65
2010-2014	6	-1.8	0.0000	17	-7.3	0.52	20	-1.2	0.0000	65

The AYA survival cliff has progressively shortened, primarily due to increasing survival of 20+ year-olds and likely due to increased utilization of pediatric regimens.

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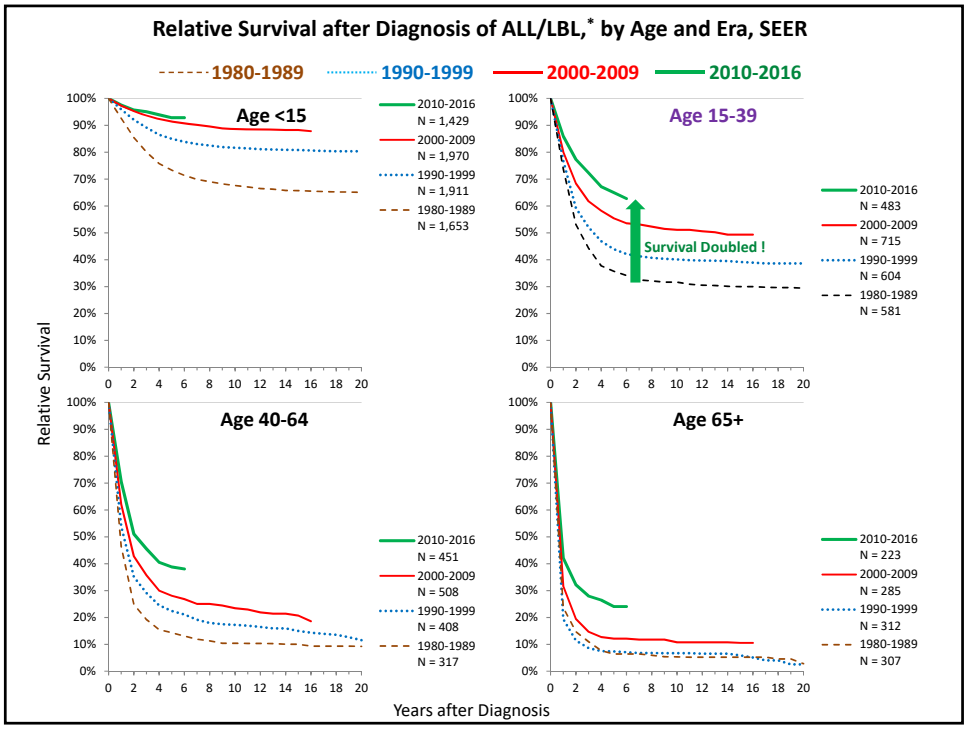

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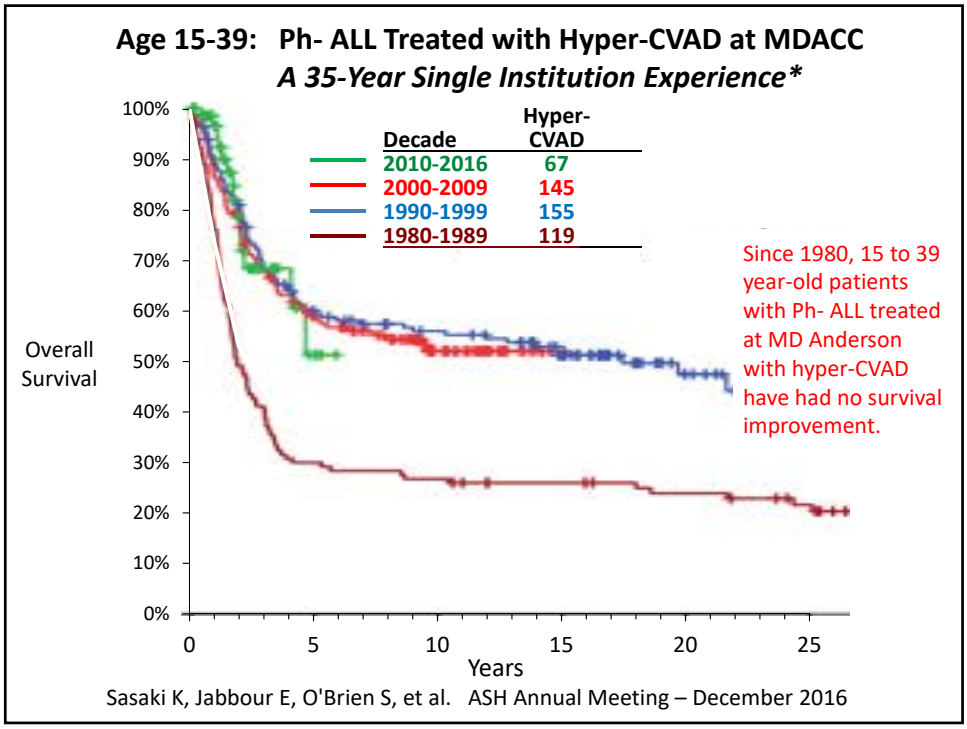

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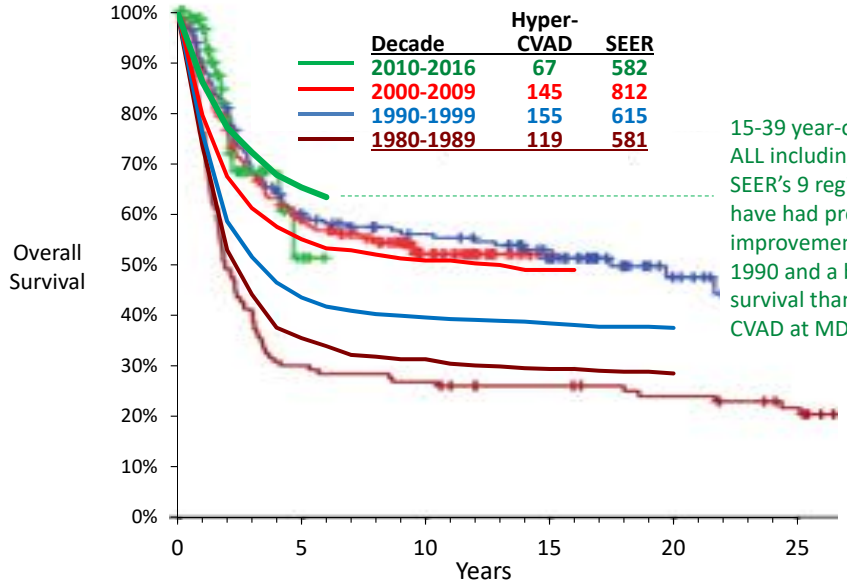
Age 15-39: Ph- ALL Treated with Hyper-CVAD at MDACC* and SEER9 Patients including Ph+ ALL



15-39 year-olds with ALL including Ph+ in SEER's 9 regions have had progressive improvement since 1990 and a better survival than hyper-CVAD at MDACC

Sasaki K, Jabbour E, O'Brien S, et al. ASH Annual Meeting – December 2016

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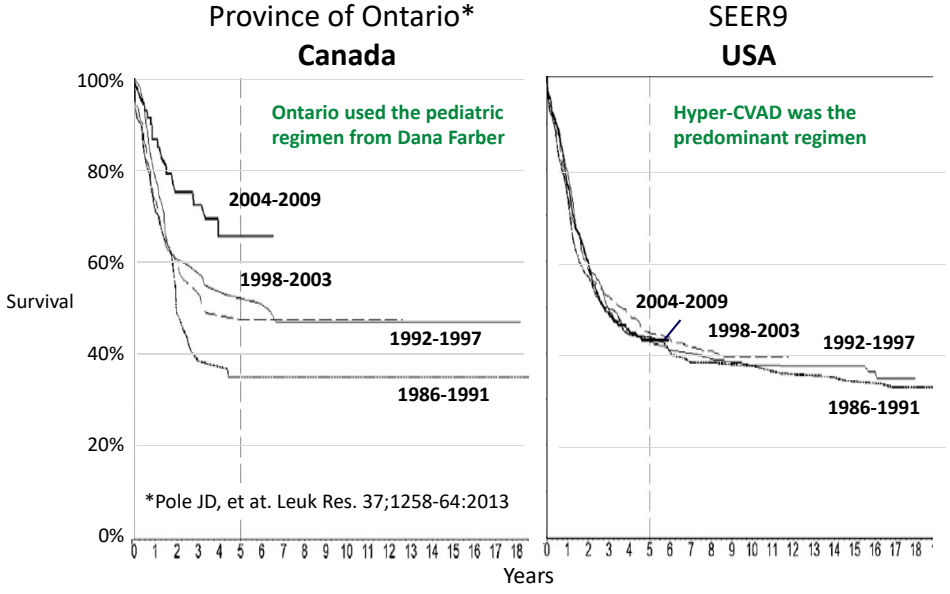
ALL Survival, Age 20-29



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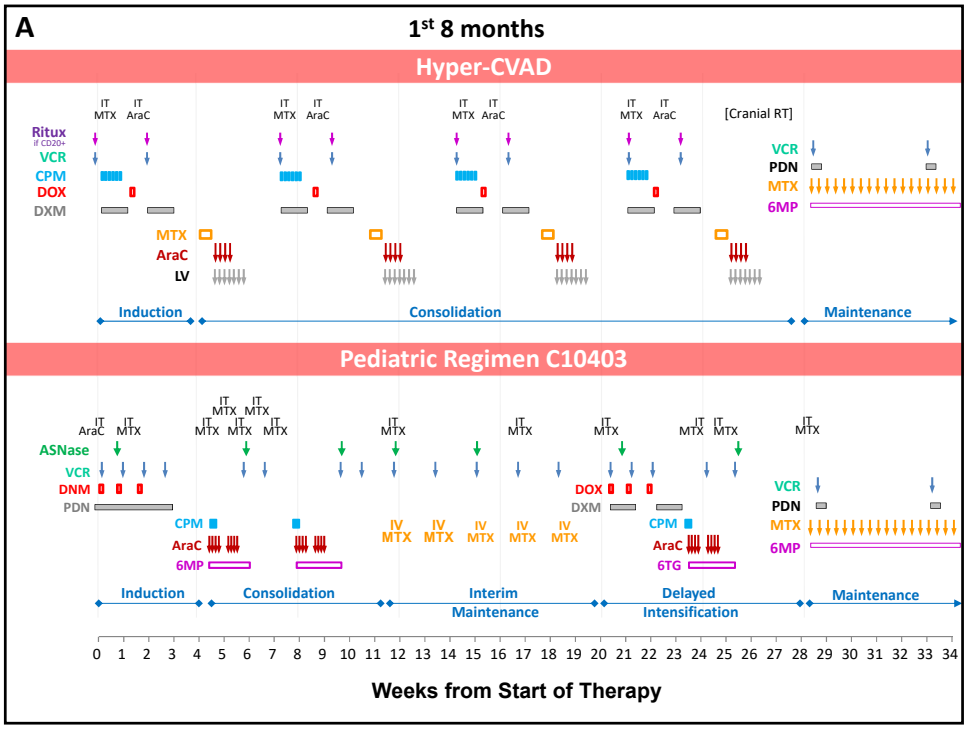

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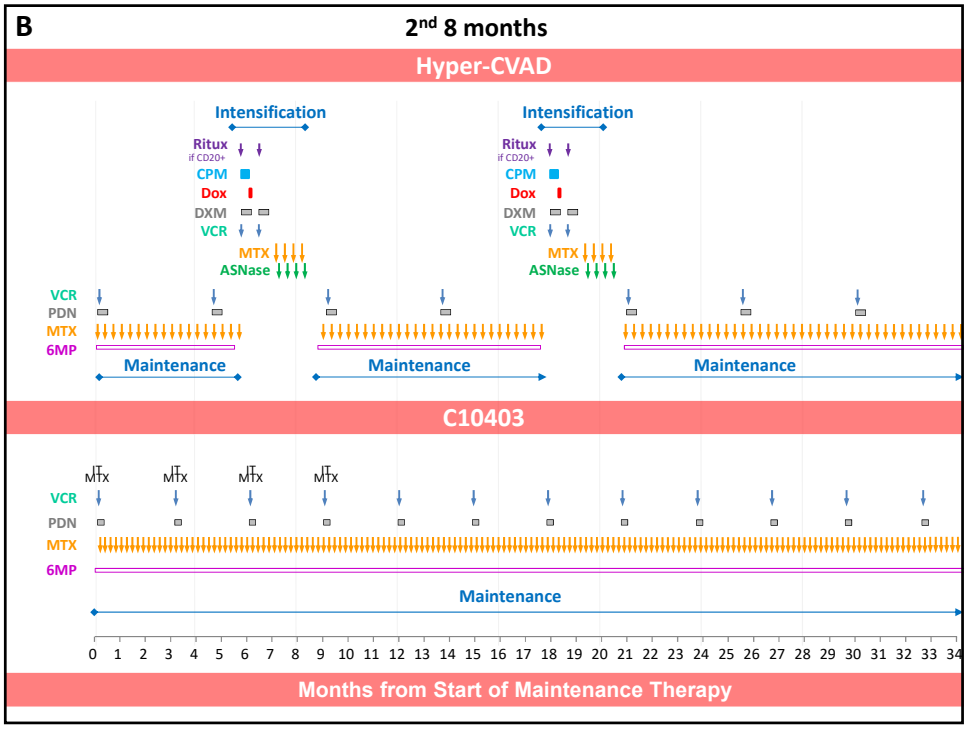

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↑ in Hyper-CVAD

↑ in Pediatric

↑ CNS Toxicity

Chemotherapy Agent	Dose Unit	Pediatric (C10403)	Hyper-CVAD [2,36]
		Total Dose	
Cyclophosphamide	mg/m²	3,000	7,200
Anthracycline (Dox Equiv)	mg/m²	158	200
Prednisone	mg	5,400	36,000
Dexamethasone	mg	70	1,280
Methylprednisolone	mg	0	1,200
Vincristine	mg	68	88
Cytarabine	mg/m²	1,800	48,000
6-Mercaptopurine	mg/m²	58,380	109,500
6-Thioguanine	mg/m²	840	0
Methotrexate PO	mg/m²	2,160	0
Methotrexate IV	mg/m²	500	5,800
Methotrexate IT	mg	132	48-192^
Cytarabine IT	mg	70	400-1600^
Hydrocortisone IT	mg	0	240
Cranial radiation	Gy	0-12^	0-30^
Asparaginase (Pegylated)	IU/m²	17,500	0* - 20,000
Rituximab (CD20+)	mg/m²	0	3,000

^depending on CNS status at diagnosis *No asparaginase for LBL patients

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TABLE 2 Comparison of potential adverse events and complications of the pediatric regimen (primarily C10403) and hyper-CVAD in AYAs with ALL

	Pediatric (eg, C10403)		Hyper-CVAD	
Hospitalization after initial diagnosis	Not required		Required for 8 cycles	
Prolonged cytopenia	±		+++	[42]
Readmission for fever and neutropenia	++	[13, 43]	++++	[5, 44]
Infections grade 3-4	++	[13]	++++	[20, 44]
Blood product support and ICU admissions	+		+++	
Hypersensitivity reactions (Asparaginase)	++	[13]	++	[20]
Pancreatitis	+/++	[13, 43, 45]	+	[20]
Hepatic dysfunction	+++	[13, 43, 45]	+++	[20]
Hyperbilirubinemia	++/+++	[13, 43, 45]	++	[20]
Hemorrhage	±	[13, 43]	+	[20]
Thrombosis	+/++	[13, 43, 45]	++	[20]
Neurotoxicity—central	+	[13]	++	
Neurotoxicity—peripheral	+/++	[13]	+/++	[20]
Infertility	±	[46, 47, 49]	++++	[48, 49]
Osteonecrosis	+	[13, 43]	+	[20]
Cardiomyopathy potential	+	[16]	++	?
Secondary malignancy potential	±	[16, 17]	++	[42, 50–52] Myelodysplasia and AML
Financial cost	Outpatient therapyall maintenance drugs oral except vincristine		13+ hospitalizations↑drug costsonly 2 oral drugs	

± rare, <1%; +, 1%-9%; ++, 10%-25%; +++, 25%-50% or moderate; ++++, >50% or severe.

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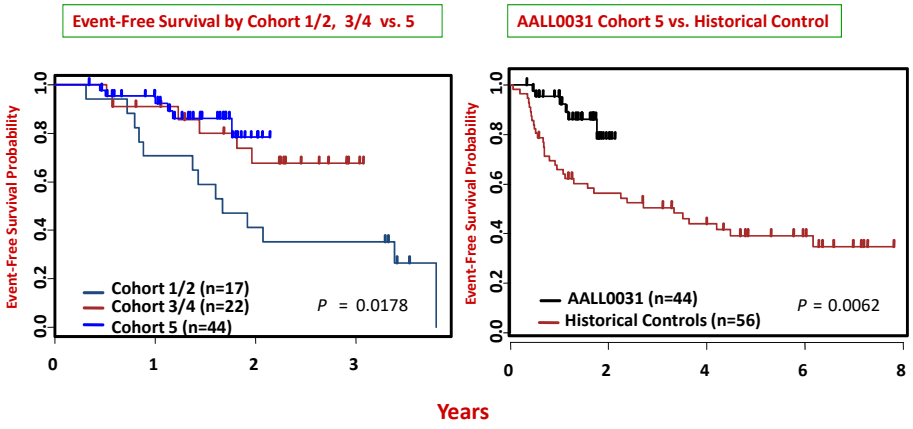
Imatinib with Chemotherapy Improves Early Outcome For Childhood Ph+ ALL (AALL0031)

Kirk Schultz, JCO



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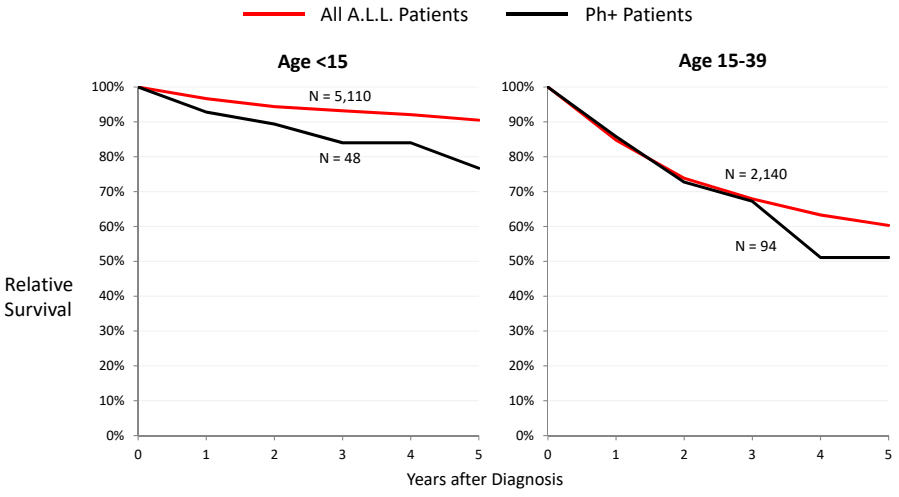
Survival during 2000-2016 of All A.L.L. Patients and Those Registered in SEER as Ph+



- Ph+ patients began to be registered in SEER in 2010 but only a fraction of them have been registered.
- As of 2016, only 4% of the ALL AYA patients in SEER18 were identified as Ph+.
- Thus, there are too few Ph+ patients to expect their exclusion to significantly change the overall ALL survival curve.
- The inclusion of Ph+ patients inflates the 5-year all-patient survival rate in comparison to rates that exclude Ph+ patients.
- Hence, the survival rates for SEER data would be higher if Ph+ patients were excluded.

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Targetable Kinase-Activating Lesions in Ph-like Acute Lymphoblastic Leukemia

K.G. Roberts, Y. Li, D. Payne-Turner, R.C. Harvey, Y.-L. Yang, D. Pei, K. McCastlain, L. Ding, C. Lu, G. Song, J. Ma, J. Becksfort, M. Rusch, S.-C. Chen, J. Easton, J. Cheng, K. Boggs, N. Santiago-Morales, I. Iacobucci, R.S. Fulton, J. Wen, M. Valentine, C. Cheng, S.W. Paugh, M. Devidas, I-M. Chen, S. Reshmi, A. Smith, E. Hedlund, P. Gupta, P. Nagahawatte, G. Wu, X. Chen, D. Yergeau, B. Vadodaria, H. Mulder, N.J. Winick, E.C. Larsen, W.L. Carroll, N.A. Heerema, A.J. Carroll, G. Grayson, S.K. Tasian, A.S. Moore, F. Keller, M. Frei-Jones, J.A. Whitlock, E.A. Raetz, D.L. White, T.P. Hughes, J.M. Guidry Auvil, M.A. Smith, G. Marcucci, C.D. Bloomfield, K. Mrózek, J. Kohlschmidt, W. Stock, S.M. Kornblau, M. Konopleva, E. Paietta, C.-H. Pui, S. Jeha, M.V. Relling, W.E. Evans, D.S. Gerhard, J.M. Gastier-Foster, E. Mardis, R.K. Wilson, M.L. Loh, J.R. Downing, S.P. Hunger, C.L. Willman, J. Zhang, and C.G. Mullighan

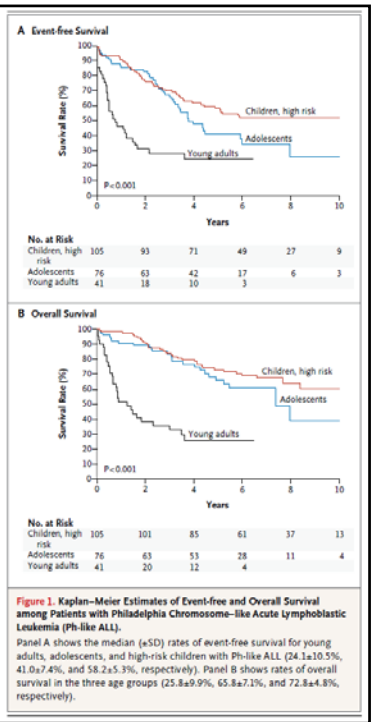

Figure 1. Kaplan–Meier Estimates of Event-free and Overall Survival among Patients with Philadelphia Chromosome–like Acute Lymphoblastic Leukemia (Ph-like ALL).

Panel A shows the median (±SD) rates of event-free survival for young adults, adolescents, and high-risk children with Ph-like ALL (24.1±10.5%, 41.0±7.4%, and 58.2±5.3%, respectively). Panel B shows rates of overall survival in the three age groups (25.8±9.9%, 65.8±7.1%, and 72.8±4.8%, respectively).

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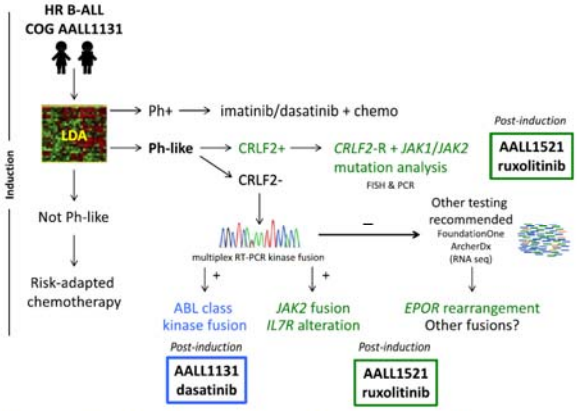

Fig. 2. Diagnostic algorithm for identifying children with Ph-like ALL in real-time. Patients with confirmed ABL class (blue) or JAK pathway (green) alterations are eligible to receive dasatinib (COG AALL1131) or ruxolitinib (COG AALL1521), respectively, in combination with chemotherapy post-induction.

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Newer Additions to AYA Acute Lymphoblastic Leukemia Therapy

- RITUXIMAB
- BLINATUMOMAB
- INOTUZUMAB
- CAR-T CELLS