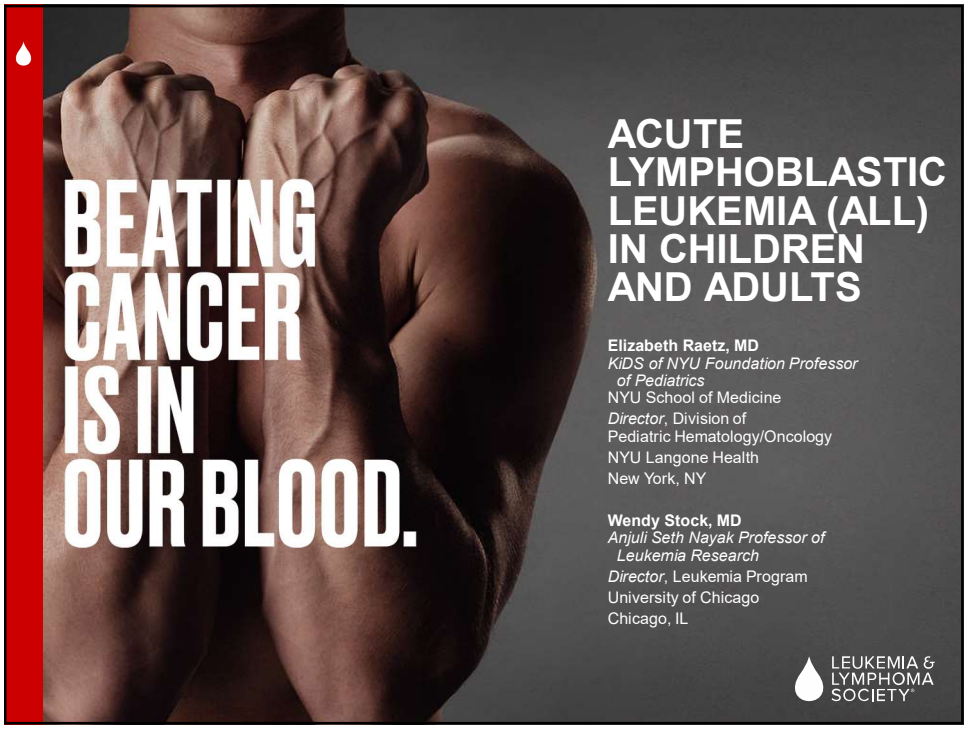
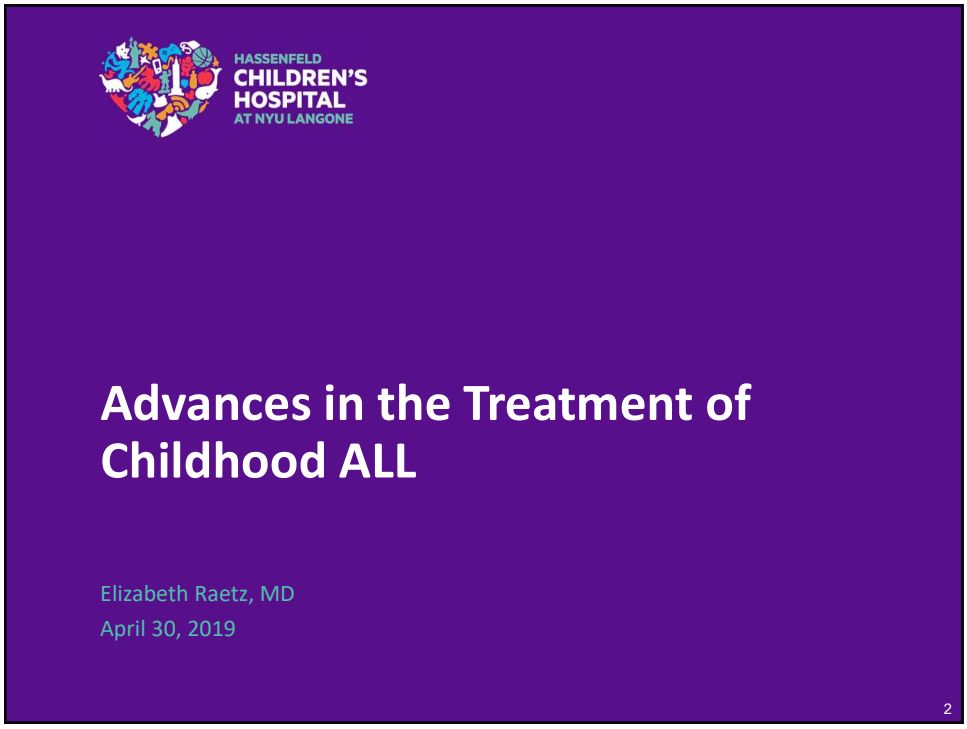

BEATING
CANCER
IS IN
OUR BLOOD.
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN CHILDREN AND ADULTS
Elizabeth Raetz, MD
KiDS of NYU Foundation Professor of Pediatrics
NYU School of Medicine
Director, Division of Pediatric Hematology/Oncology
NYU Langone Health
New York, NY
Wendy Stock, MD
Anjuli Seth Nayak Professor of Leukemia Research
Director, Leukemia Program
University of Chicago
Chicago, IL
LEUKEMIA & LYMPHOMA SOCIETY


HASSENFELD CHILDREN'S HOSPITAL AT NYU LANGONE
Advances in the Treatment of Childhood ALL
Elizabeth Raetz, MD
April 30, 2019
2

DISCLOSURES

Acute Lymphoblastic Leukemia (ALL) in Children and Adults

Elizabeth Raetz, MD, has affiliations with

Pfizer *(Grant Support)*

Wendy Stock, MD has no affiliations to disclose

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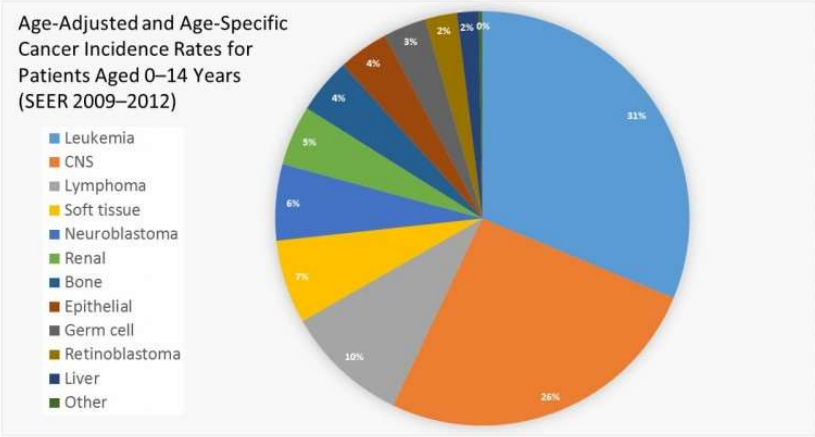
LEUKEMIA & LYMPHOMA SOCIETY®

3

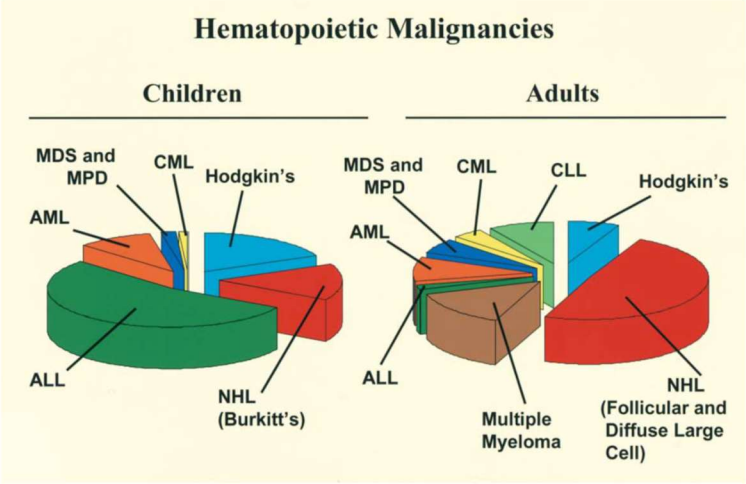
Leukemia is the Most Common Childhood Cancer



https://www.cancer.gov/types/childhood-cancers/hp/unusual-cancers-childhood-pdq

4

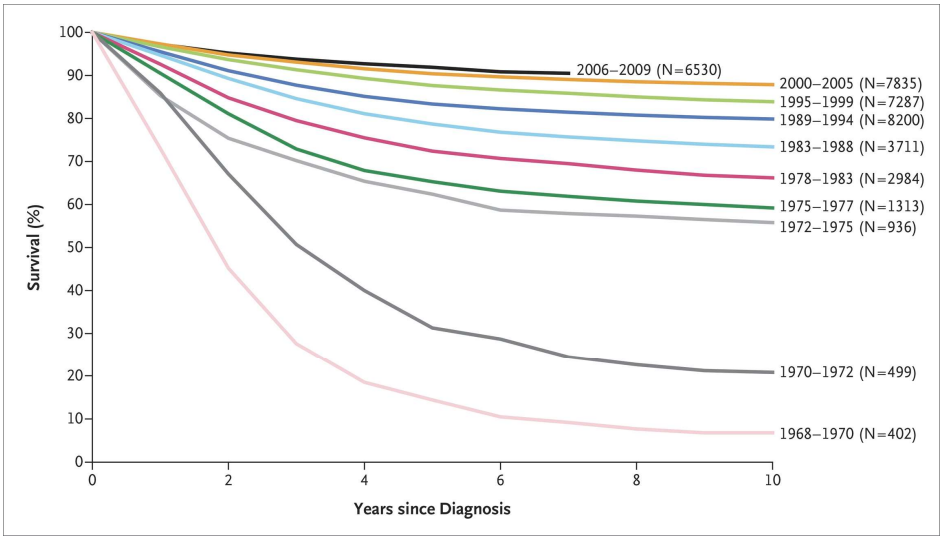
Leukemia Epidemiology: Children vs. Adults



Downing J and Shannon K. *Cancer Cell* 2002; 437-445

5

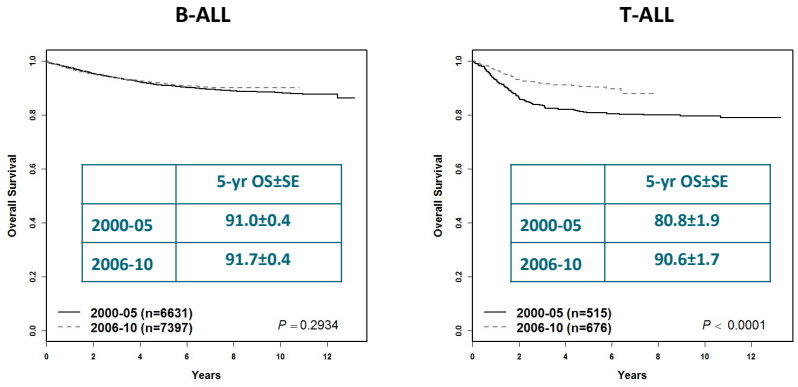
Childhood ALL Outcomes



Hunger SP, Mullighan CG. *N Engl J Med* 2015;373:1541-1552

6

Improvements in ALL Survival: 2006-10 vs. 2000-05



	5-yr OS±SE
2000-05	91.0±0.4
2006-10	91.7±0.4

	5-yr OS±SE
2000-05	80.8±1.9
2006-10	90.6±1.7

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ASPHO annual meeting, 2018

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Curative Strategies in Childhood ALL

- Delivery of multiple chemotherapy agents to prevent drug resistance
- Recognition that sanctuary sites need focused treatment (CNS)
- Identification of risk groups at diagnosis to determine intensity of therapy
  - NCI risk group and clinical features
  - Sentinel genetic lesions
  - Early response to therapy (MRD)

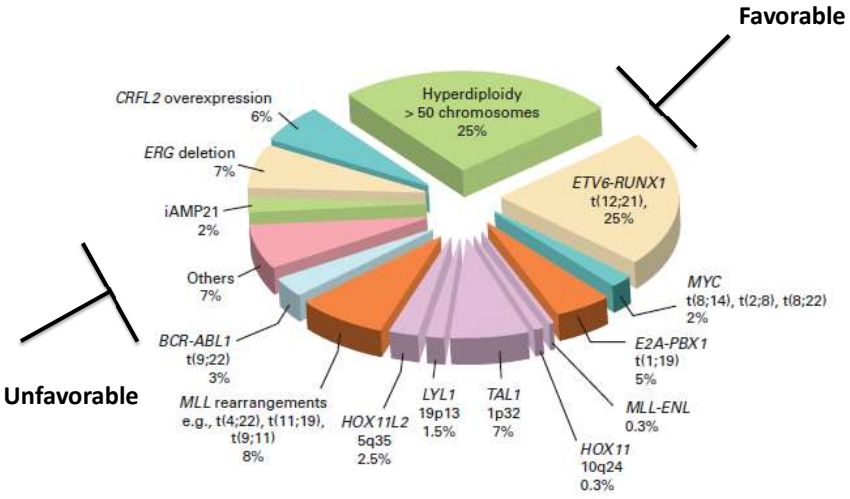
8

Key Clinical Prognostic Factors

Age	• > 1, < 10 years – favorable • ≤ 1 and ≥ 10 years – unfavorable
White Blood Cell Count	• <50,000/µL – favorable • ≥50,000/µL – unfavorable
Immunophenotype	• B-precursor – favorable • T-cell – requires more intensive therapy
Gender	• Female – favorable • Male – historically required longer treatment
Extramedullary Disease	• Absent – favorable • Present – unfavorable

9

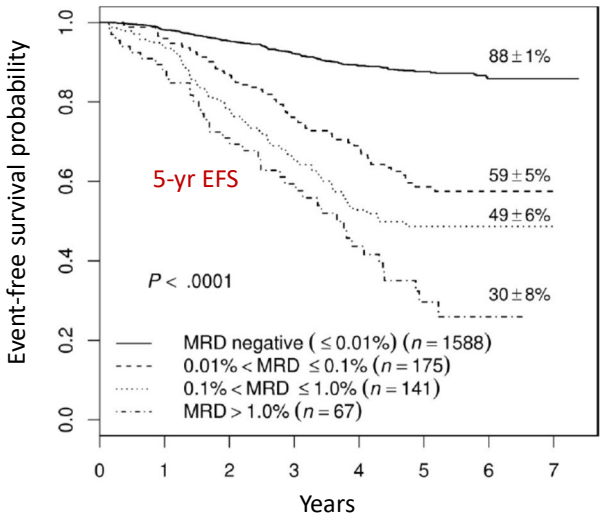
Genetic Subclassification of Childhood ALL



Pui, Carroll, Meshinchi, Arceci. *J Clin Oncol* 2011: 551-565

10

MRD Response is the Most Significant Outcome Predictor



Borowitz et al. *Blood* 2008; 111:5477-5485

11

Approach to Genetic Testing and Classification

- Children's Oncology Group classification studies
  - POG 9900 (12/13/00-2/28/05, n= 3762)
  - AALL03B1 (12/29/03-9/6/11, n=11,206)
  - AALL08B1 (08/09/10-7/23/18, n= 17,372)

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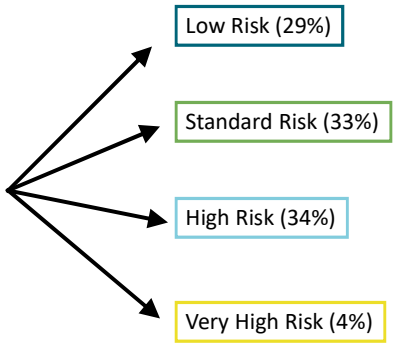
12

Risk Classification in Childhood ALL

- NCI Risk Group & Extramedullary Disease Status
- Sentinel Genetic Lesions
  - Trisomies 4, 10, & 17
  - *ETV6-RUNX1*
  - *BCR-ABL1*
  - *KMT2A*-R
  - iAMP21
  - Chromosomes <44
- Rapidity of Response
  - Morphology day 8/15
  - Day 29 Flow MRD



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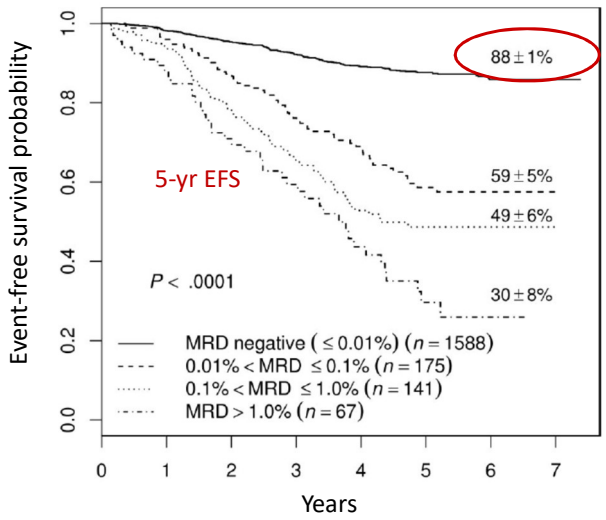
13

Many Relapses Occur Unpredictably



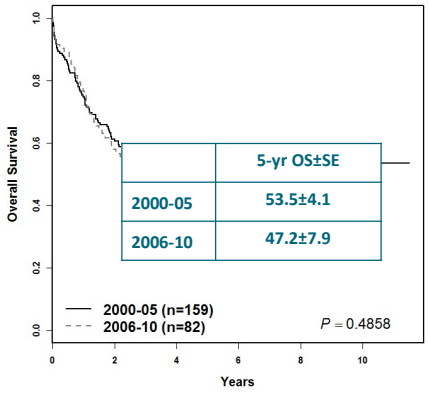
178 of 348 (51%) of treatment failures

Borowitz et al. *Blood* 2008; 111:5477-5485

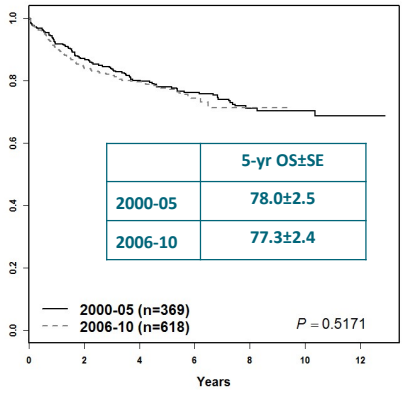
14

ALL Outcomes Across the Age Spectrum

Age ≤ 1 Year



Age 16+ Years



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ASPHO annual meeting, 2018

15

Current Landscape and Future Directions in ALL Therapy

16

Overarching Goals for ALL Therapy

- **Improve cure rates**-Identify patients who will fail current therapies and alter approaches
  - Specific genomic subsets
  - High minimal residual disease (MRD) burdens
  - Adolescents and young adults (AYAs)
  - Infants
- **Decrease acute and late effects**
- **Optimize medication adherence**

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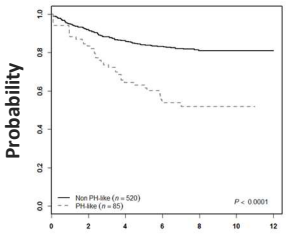
17

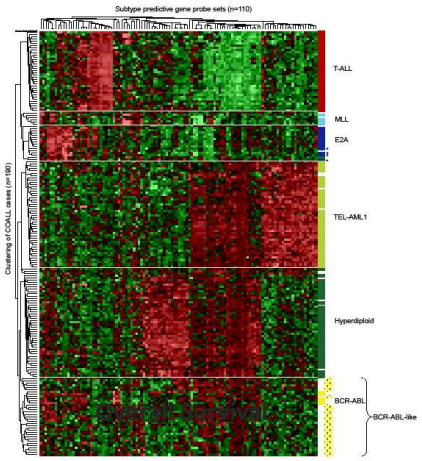
Targeted Therapy for ALL

18

Philadelphia Chromosome-like (Ph-like) ALL

- Ph-like ALL comprises 15-20% of high-risk B-ALL occurring in children and adolescents and 20-40% of B-ALL in adults
  - Driven by genetic alterations that activate kinase signaling
  - High rates of MRD and relapse with conventional chemotherapy

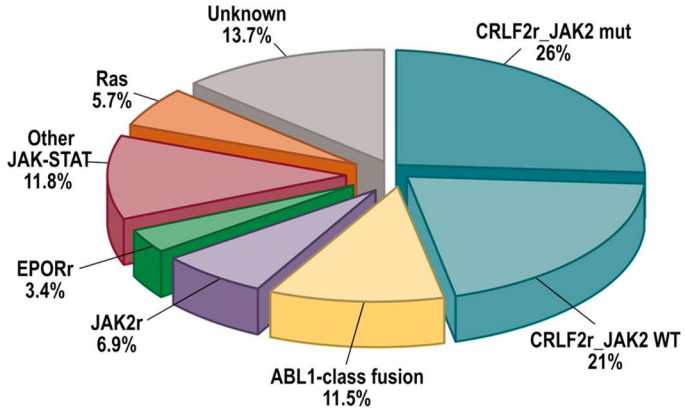




den Boer et al. *Lancet Oncology* 2009; 10:125-134 , Mullighan et al. *NEJM* 2009; 360:470-480

19

Genetic Subtypes of Ph-like ALL



Roberts KG et al. *N Engl J Med* 2014;371:1005-1015

20

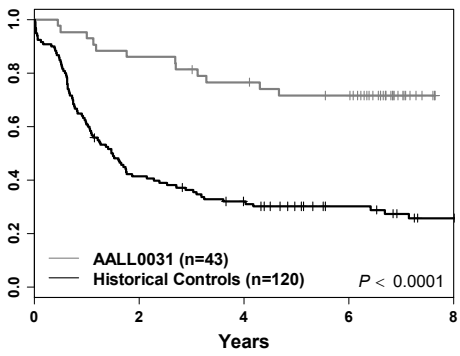
Spectrum of Recurring Genetic Alterations in Ph-like ALL

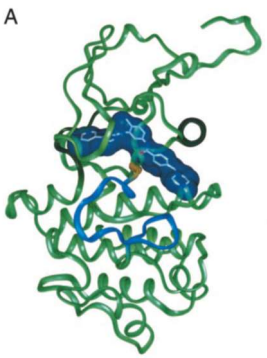
- ABL-class fusions — **ABL-class inhibitors**
- *EPOR* or *JAK2* rearranged
- *CRLF2* rearranged — **JAK inhibitor**
- Other JAK-STAT pathway
- Ras pathway
- Misc or no kinase activation

Roberts KG et al. *N Engl J Med* 2014;371:1005-1015; Graubert TA. *N Engl J Med* 2014;371:1064-1066

21

Can We Build on the Success of TKI + Chemotherapy in Ph+ ALL?





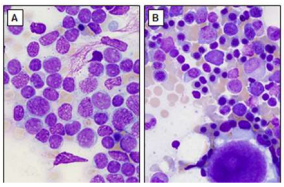
COG AALL0031: 7-yr DFS 71.7% vs. 21.4% for historical controls treated without TKIs

Schultz et al. *J Clin Oncol* 2009: 5175-5181 and *Leukemia* 2014: 1467–1471
Nagar et al. *Cancer Res* 2002: 4236-4243

22

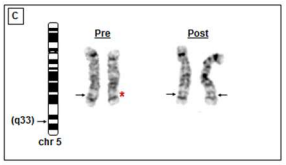
Clinical Response of *EBF1-PDGFRB* ALL to Imatinib

- 10 year old boy with refractory B-ALL – 70% blasts at day 29
- Cytogenetics: 5q33 interstitial deletion at *PDGFRB*
- *EBF1-PDGFRB* positive
- Started imatinib with immediate clinical improvement
- 2 weeks: morphologic remission; MRD 0.059%; normal *PDGFRB* FISH
- Remission sustained

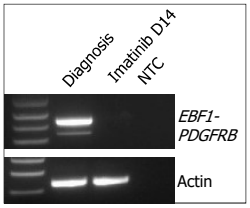


Diagnosis Post imatinib

Bone marrow aspirate



Karyotype



RT-PCR

Weston and Mullighan et al, *J Clin Oncol.* 2013; 31: e413-6

23

Immunotherapy for ALL

24

Promising New Immunotherapies for B-ALL

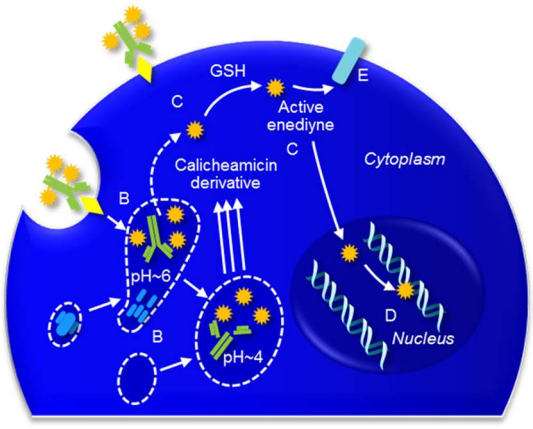
Immune Therapy	Mechanism of Action	Patient Population Studied	Outcome
Inotuzumab	CD22-directed humanized moAB conjugated to calicheamicin	Adults with CD22+ R/R B-ALL	80.7% CR/CRi
Blinatumomab	Bispecific T cell receptor engager (BiTE) that redirects CD3+ T cells to CD19+ blasts	Adults with R/R Ph- B-ALL Children with R/R B-ALL	39% CR 39% CR
CAR T cells	T cells transduced ex-vivo with chimeric anti-CD19 receptor	Children with CD19+ R/R B-ALL	83% CR/CRi

Kantarjian et al. *N Engl J Med*. 2016;375:740-753, Maury S et al. *N Engl J Med*. 2016;375:1044-1053,
Topp M et al. EHA. 2016;149, von Stackelberg A et al. *Blood*. 2016;128:222, Grupp SA et al. *Blood*. 2016;128:221

25

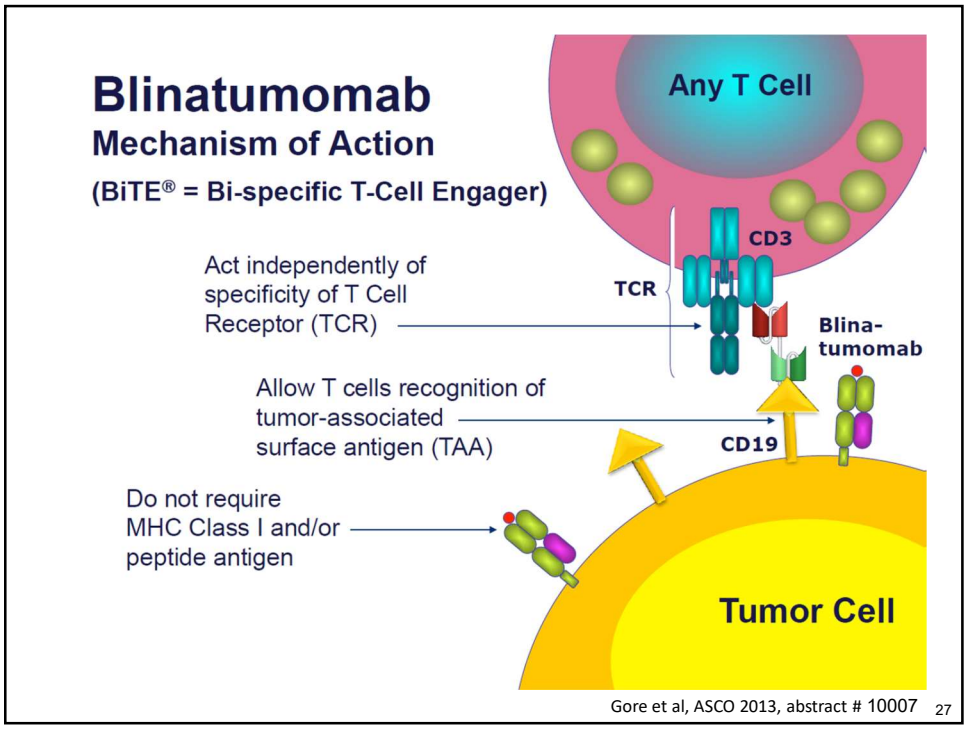
Inotuzumab Ozogamicin (IO)

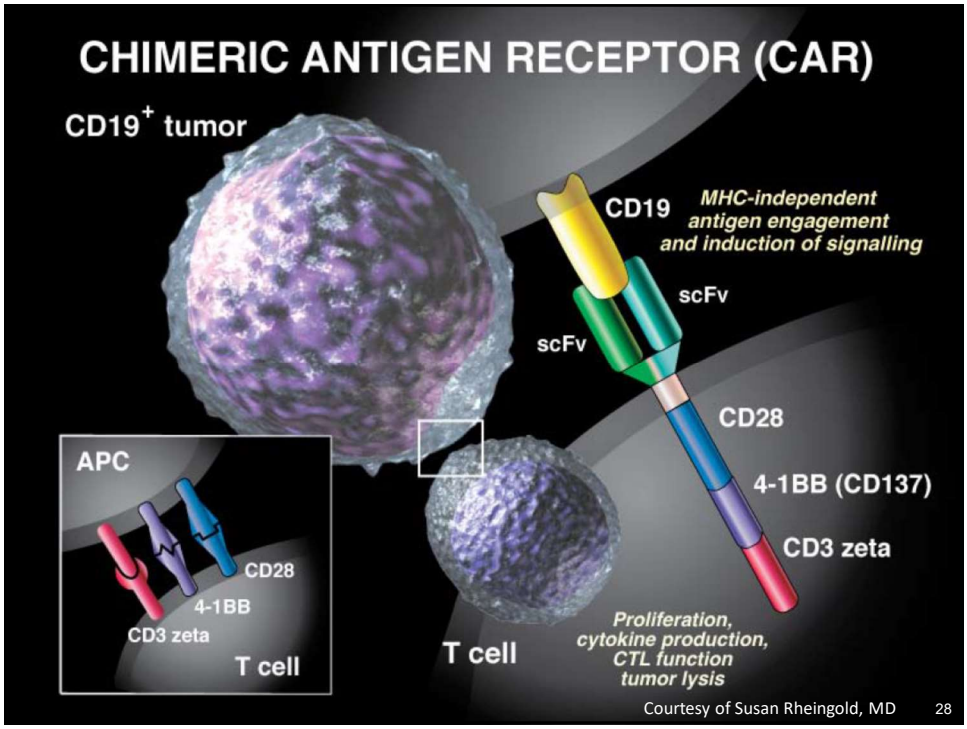
- CD22 is expressed in >90% of pediatric pre-B ALLs
- Humanized IgG4 anti-CD22 antibody conjugated to calicheamicin, a potent cytotoxic antitumor antibiotic
- Rapid internalization upon binding



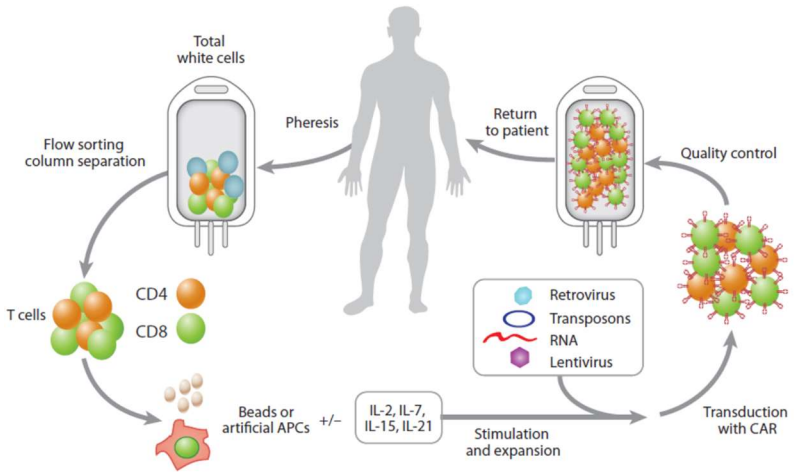
Shah et al. *Pediatr Blood Cancer* 2015; 62: 964-969
Dijoseph JF, et al. *Leukemia* 2007; 21:2240-2245

26


Blinatumomab
Mechanism of Action
(BiTE® = Bi-specific T-Cell Engager)
Act independently of specificity of T Cell Receptor (TCR)
Allow T cells recognition of tumor-associated surface antigen (TAA)
Do not require MHC Class I and/or peptide antigen
Any T Cell
CD3
TCR
Blina-tumomab
CD19
Tumor Cell
Gore et al, ASCO 2013, abstract # 10007
27


CHIMERIC ANTIGEN RECEPTOR (CAR)
CD19+ tumor
CD19
MHC-independent antigen engagement and induction of signalling
scFv
scFv
CD28
4-1BB (CD137)
CD3 zeta
APC
CD28
4-1BB
CD3 zeta
T cell
T cell
Proliferation, cytokine production, CTL function tumor lysis
Courtesy of Susan Rheingold, MD
28

Chimeric Antigen Receptor Therapy



Barrett D et al. *Annu. Rev. Med*. 2014;65:333-47

29

Introduction of Molecularly or Immunologically Targeted Therapy in B-ALL

Risk Group	Projected 5-yr DFS	Therapeutic Question
SR-Favorable	>95%	Standard therapy with 2 year duration
HR-Favorable	>94%	
SR-Avg & High	~89%	Blinatumomab
High Risk	~80%	Inotuzumab
Very High Risk	<50%	CAR T-cell therapy
Ph+, Ph-like	60-85%	Molecularly targeted therapy

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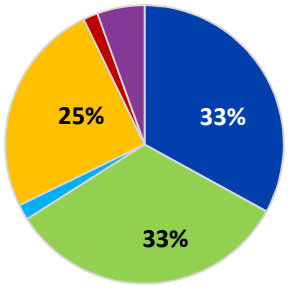
30

B-ALL Frontline Trials 2019

VHR: AALL1721
CTL-019 in CR1 - 1.7%

HR: AALL1732
Randomized to inotuzumab

HR-Fav: AALL1732
No randomized intervention - 1.8%



Precision Medicine - 5.5%
AALL1631: Ph+
AALL1131: ABL class
AALL1521: JAK/STAT

SR-Fav: AALL1731
No randomized intervention

SR-Avg&high: AALL1731
Randomized to blinatumomab

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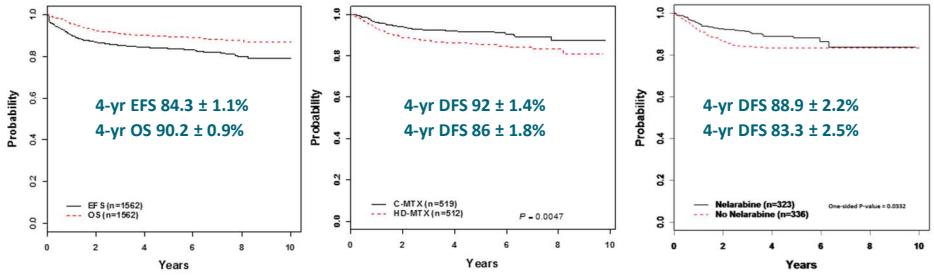
31

T-cell ALL Outcomes: COG AALL0434



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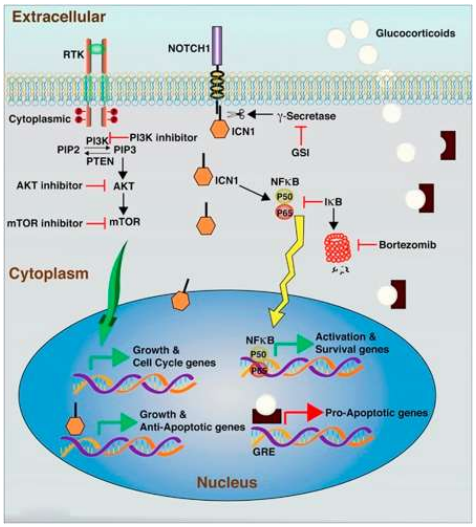
Winter SS et al. *J Clin Oncol* 2018; 36: 2926-2934 and Dunsmore K et al., ASCO 2018

32

Opportunities for Molecularly or Immunologically Targeted Therapy in T-ALL

- Signal transduction pathway inhibitors
  - PI3K/AKT/mTOR
  - JAK/STAT
  - MAPK
- Notch pathway inhibitors (GSIs)
- CDK4/6 inhibitors
- BCL2 family inhibitors
- Epigenetic modulators
- Anti-CD38



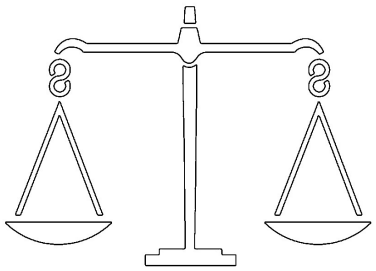
El-Mallawany et al. *Blood Cancer Journal* 2012

33

Decreasing Acute and Late Effects and Optimizing Adherence

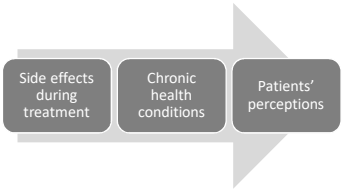
34

Why is it Important Not to Over Treat ALL?



Cure **Toxicity**

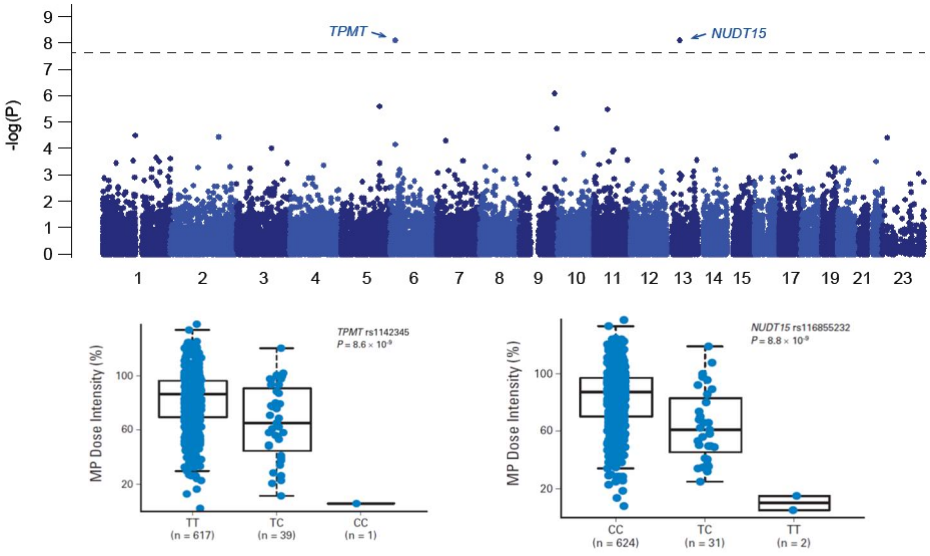
- ~2/3 of childhood ALL survivors have serious chronic health conditions at 30+ years
- Defining quality of survival is essential



Adapted from Kjeld Schmiegelow

35

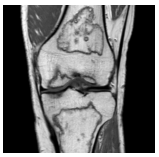
Two Loci Associated with 6MP Tolerance at Genome-wide Significance Level

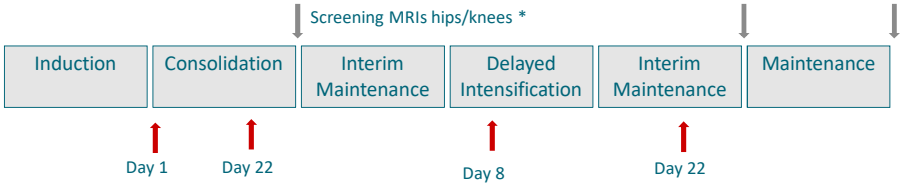


Yang et al., *J Clin Oncol* 2015, 33:1235

36

Natural History of Osteonecrosis





- Biomarkers assays (↑) in subset of 300 patients ≥ 10 years of age at diagnosis to assess the potential role of ASNase and MTX in the development of ON:
- MTX , ASNase and dexamethasone levels, serum albumin (surrogate for ASNase activity) and anti- ASNase antibodies are being measured and will be correlated with the development of ON

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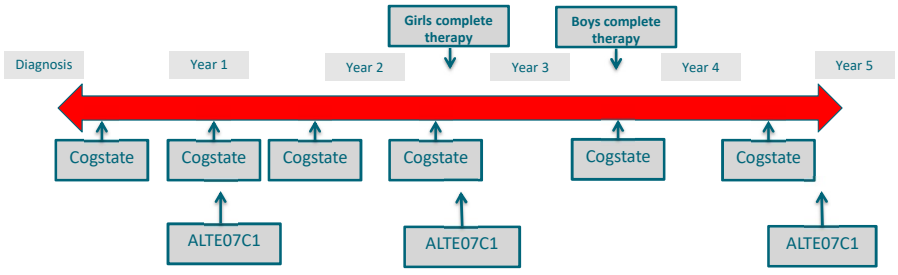
37

Assessing Neuropsychological Outcomes
COG AALL1131 + ALTE07C1



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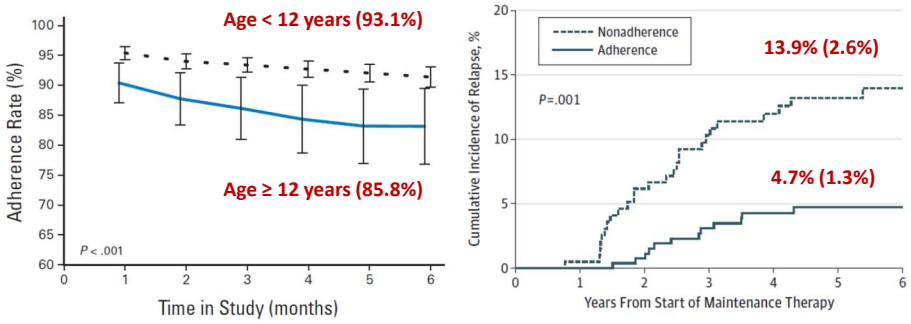
Adapted from Kristi Hardy, PhD

38

Low Adherence to Oral 6MP Significantly Increases Relapse Risk



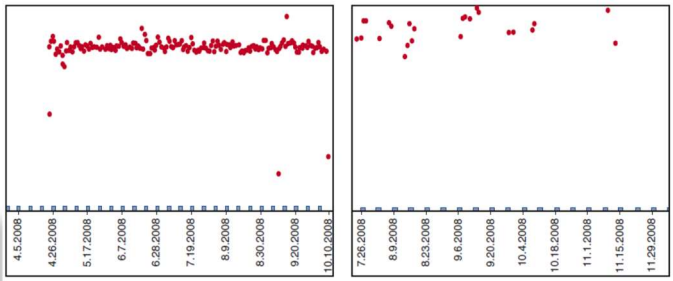
Bhatia et al. *J Clin Oncol* 2012; 30:2094-2102 and *JAMA Oncol*. 2015; 3:287–295

39

Assessing Adherence to Oral 6-Mercaptopurine

Special pill bottles with electronic *TrackCap* to dispense 6MP

Microprocessor chip in cap records date and time of opening of medication bottle



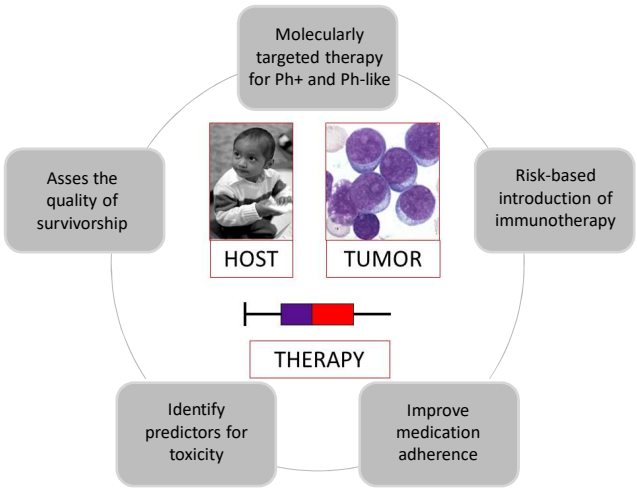
Adherent Non-adherent

$$\text{Adherence Rate} = \frac{\text{\# of days with MEMS cap openings}}{\text{\# of days 6MP was prescribed}} \times 100$$

Bhatia et al. *J Clin Oncol* 2012; 30:2094-2102; Bhatia et al. *JAMA Oncol*. 2015; 3:287–295

40

Summary



41

Acknowledgements

A special thank you to all of the incredible children and families!

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Susan Rheingold
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Jennifer McNeer
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Sumit Gupta
Rachel Rau
Shannon Maude
John Kairalla

42

ALL in Adults: Promising Times for Our Patients

Wendy Stock, MD
Anjuli Seth Nayak Professor of Leukemia Research
University of Chicago Medicine

43

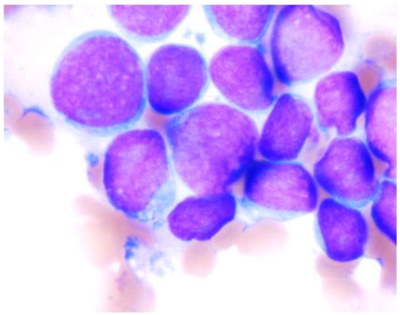
Objectives

1) Highlight treatment challenges and recent progress in treatment of adults with ALL

2) Review novel therapies for patients with relapsed ALL, focusing on recently approved agents

3) Overview of strategies to introduce new agents into the frontline setting to optimize outcomes

44



Intro:

FRAMING THE PROBLEM: SURVIVAL OVER THE PAST DECADES

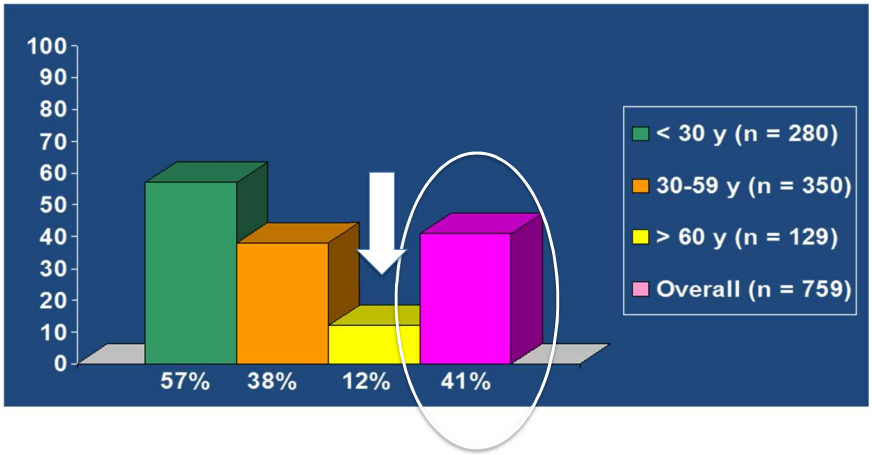
45

ALL in Adults: The "Old" State of Affairs (circa 2005)

- Multi-drug regimens "similar" in design to pediatric trials
  - But traditional adult regimens have lower intensity dosing of steroids, vincristine, asparaginase; less CNS prophylaxis compared to pediatric regimens
  - "one size fits all"
- High rates of remission in adults (80-90%)
- Post-remission therapy dictated largely by age/ cytogenetics
  - Limited options for targeted therapy except for Ph+ ALL
  - High risk patients receive allogeneic transplant if donor available
    - Lower relapse rates but….Survival benefit questionable due to transplant related mortality
- Long term survival : 30-40% overall

46

Survival of 759 adults with ALL treated on CALGB studies from 1988-2006

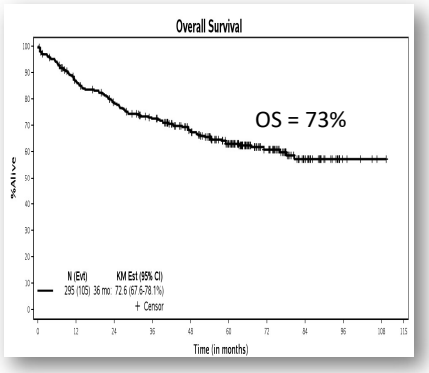


47

ALL in Young Adults: Adoption of Pediatric Regimens Has Become the New Standard

CALGB 10403

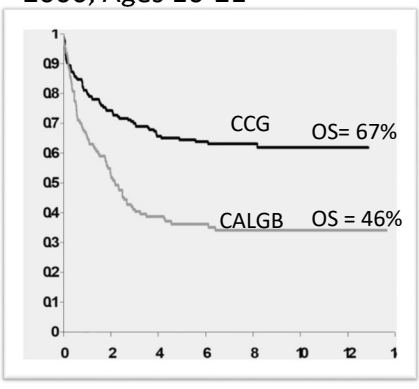
- 2019, Ages 16-39



Blood, 2019: 133, 1548-1559

Historical CALGB vs CCG

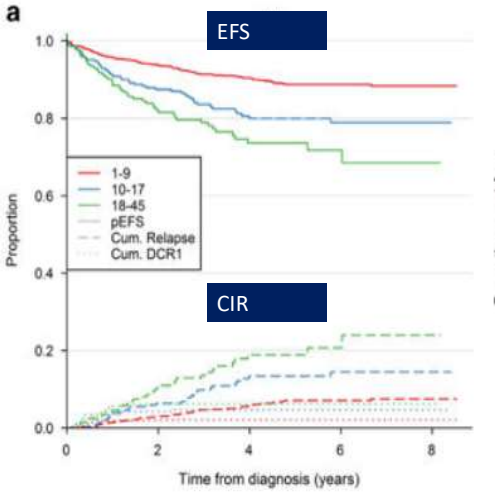
- 2000, Ages 16-21



Blood, 2008: 112, 1646-54

48

Risk-adapted approach for patients 1-45 yrs: A single protocol for all in NOPHO ALL2008



1-9 yrs EFS: 89%

10-17 yrs EFS: 80%

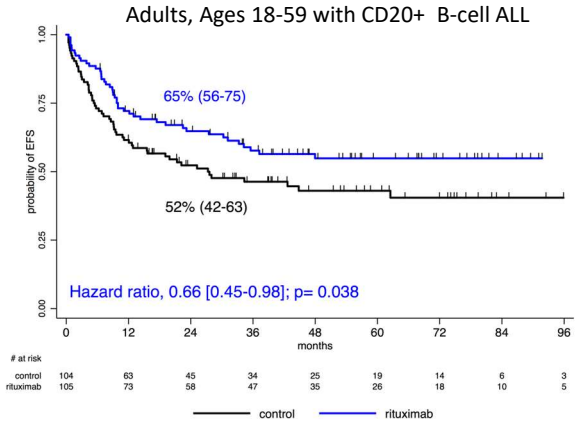
18-45 yrs EFS: 74%

Median f/u = 4.6 years; Includes B and T precursor ALL

Toft et al, *Leukemia* doi:10.1038/leu.2017

49

Progress: Addition of Rituximab Improves Outcomes



Rituximab in CD20+ ALL Improves EFS in Phase III Trial

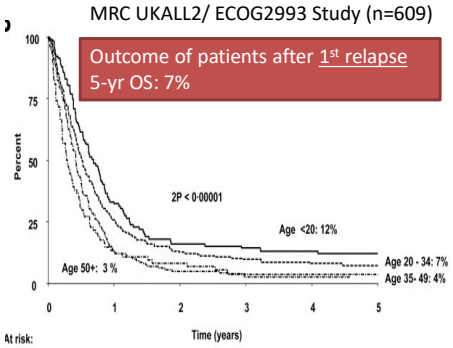
EFS = 66% vs 52% , p = 0.038

Maury S et al, NEJM 2016 ; Sep 15;375(11):1044-53

50

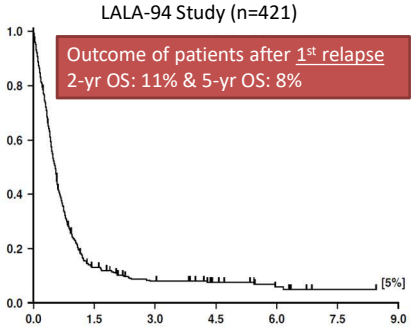
Historical Survival Rates after Relapse

MRC UKALL2/ ECOG2993 Study (n=609)



Fielding A, et al. *Blood* 2007;109(3):944-95.

LALA-94 Study (n=421)



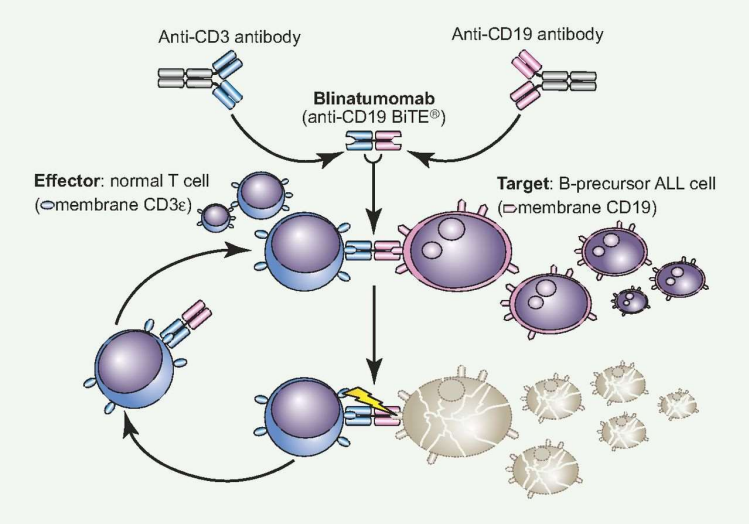
Tavernier E, et al. *Leukemia* 2007;21:1907-1914

Setting the Stage for the Frontline:

PROGRESS IN THE RELAPSE SETTING

51

Blinatumomab



Bassan Blood 2012

52

Blinatumomab: Relapsed/Refractory ALL

- 189 pts Rx with blina x 4 wks Q 6 wks

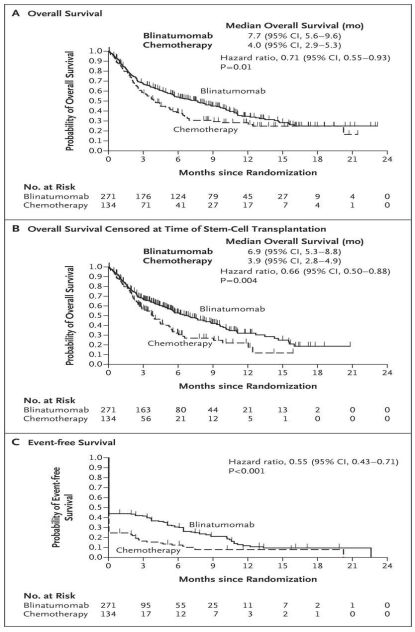
Response	No. (%)
-CR	63(33)
-CRh	18(10)
-CR+CRh	81(43)
-No marrow blasts	17(9)

- Median OS 5.9 mo; Median RFS 6.1 mo
- Toxicities: CNS
- 64/81 (79%) responders achieved CR or CRh in cycle one

Topp. Lancet Oncology 2015; 1:57

53

Blinatumomab Phase III (Tower): Higher CR, EFS and OS



Randomized 2:1 Phase III Trial of 405 patients; multinational trial

Patients with primary refractory, relapsed disease, including post-transplant relapses

Blina was superior to SOC in primary endpoint of survival:
7.7 mos vs 4.0 months

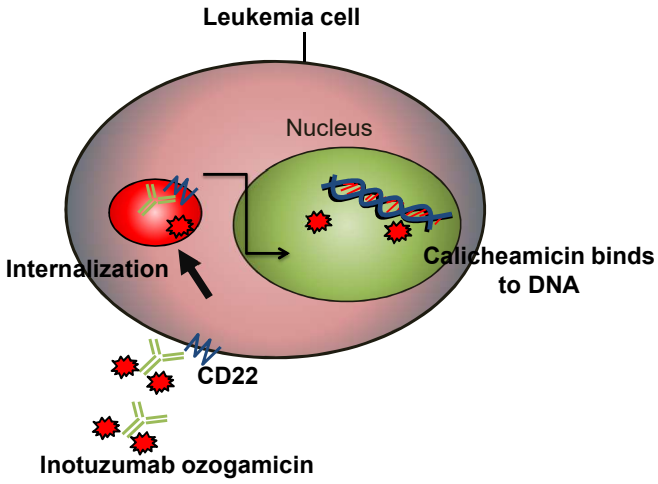
Blina had superior CR rates:
34% vs 16%

Blina had superior EFS:
7.3 mos. vs 4.6 mos.

Kantarjian et al, N Engl J Med. 2017 Mar 2;376(9):836-847

54

Inotuzumab Ozogamycin: Antibody Conjugate Targeting CD22 Delivers Calicheamycin Toxin



Leonard, Blood, in press, 2017

55

International Phase III: Ino vs Standard of Care

Phase 3 study: 326 patients randomized at 117 sites in 19 countries (INO-VATE ALL; NCT01564784)

- Relapsed/refractory CD22+ ALL
- Due for salvage 1 or 2 therapy
- Ph– or Ph+

1:1 Randomization (N=326)

Stratifications:
- Duration of 1st remission ≥12 vs <12 mo
- Salvage 2 vs 1
- Aged ≥55 y vs <55 y

Inotuzumab ozogamicin (InO)
- Starting dose 1.8 mg/m^2/cycle
- 0.8 mg/m^2 on day 1; 0.5 mg/m^2 on days 8 and 15 of a 21–28 day cycle (≤6 cycles)

Standard of Care (SOC)
- FLAG or
- Ara-C plus mitoxantrone or
- HIDAC
- ≤4 cycles

- InO dose was reduced to 1.5 mg/m^2/cycle once the patient achieved CR/CRi

Ara-C=cytarabine; FLAG=fludarabine/ara-C/granulocyte colony-stimulating factor; HIDAC=high-dose ara-C; Ph=Philadelphia chromosome

Kantarjian HM et al. N Engl J Med 2016;375:740-753

56

Inotuzumab superior to standard of care

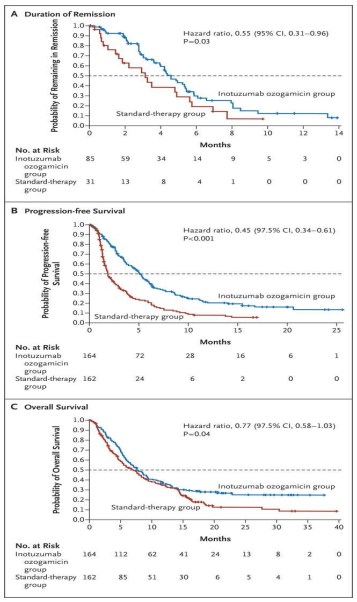
	InO	SOC	1-Sided *P* Value
N[a]	109	96	
CR/CRi,% (95% CI)	80.7 (72−88)	33.3 (24−44)	<0.0001
CR	35.8 (27−46)	19.8 (12−29)	0.0056
CRi	45.0 (35−55)	13.5 (7−22)	<0.0001
MRD-negativity among responders, n (%) [95% CI]			
CR/CRi	69/88 (78.4) [68−87]	9/32 (28.1) [14−47]	<0.0001
CR	35/39 (89.7) [76−97]	6/19 (31.6) [13−57]	<0.0001
CRi	34/49 (69.4) [55−82]	3/13 (23.1) [5−54]	0.0034

- In both arms, most patients achieved CR/CRi in Cycle 1 (InO, 73%; SOC, 91%)

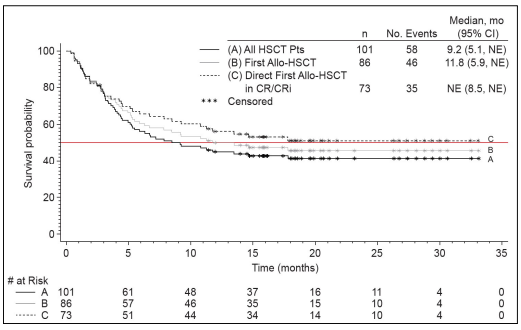
Kantarjian HM et al. N Engl J Med 2016;375:740-753

57

Duration of Remission, Progression-Free and Overall Survival : Favors Inotuzumab



Outcomes of allogeneic SCT following Ino



Kantarjian HM et al. N Engl J Med 2016;375:740-753
Kebriaei, Marks, BBMT 2019

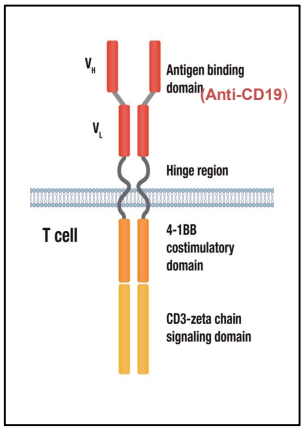
58

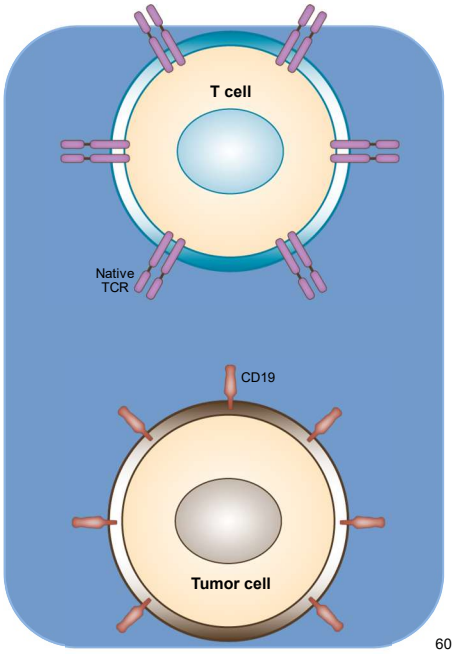
In Relapse, How do we choose?

	Blinatumomab	Inotuzumab
Unique treatment related toxicities	Neurologic toxicity: 6% blinatumomab vs none in control group CRS: 5% of blinatumomab vs none in control group	Veno-occlusive disease: 11% inotuzumab vs 1% control (SOC)
Disease status	Lower disease burden, T cell function?	High or Low disease burden
Treatment options	CAR-T? Loss of CD19 with Bina?	CAR-T? CD22 (early studies ongoing)
Administration	Continuous IV infusion X 4 weeks	Short IV infusion weekly X 3
Cost (drug cost only at UChicago)	$88,984/cycle	$89,760/cycle

59

Anti-CD19 Directed CAR T cells

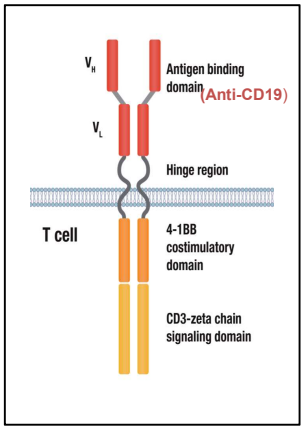




- Infused at singular point in time
- Capable of in vivo proliferation and persistence

60

Anti-CD19 Directed CAR T cells



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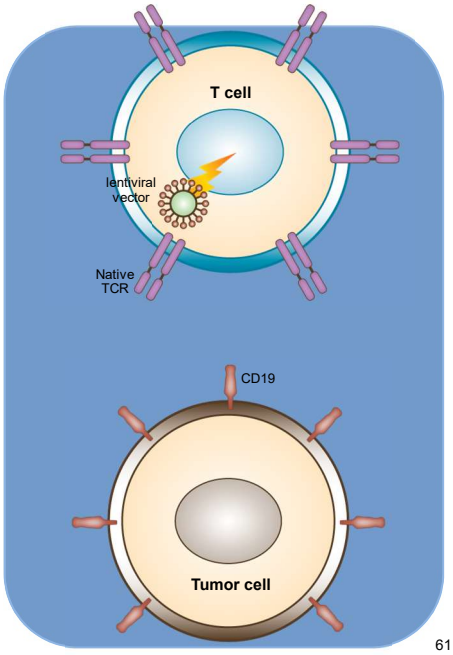
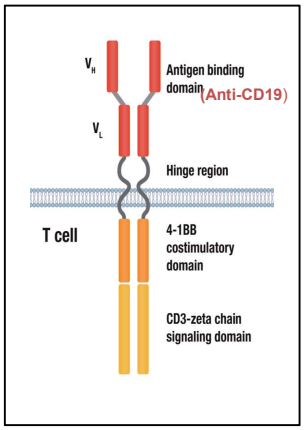


61

Anti-CD19 Directed CAR T cells



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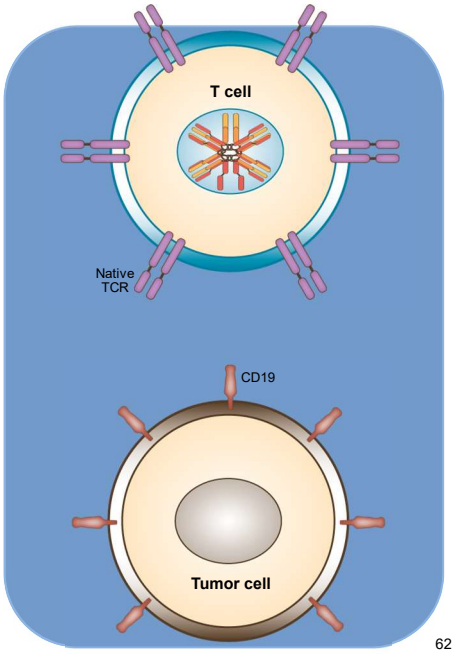
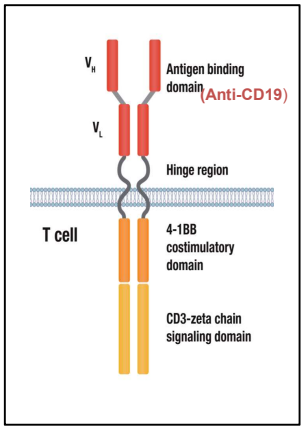


62

Anti-CD19 Directed CAR T cells



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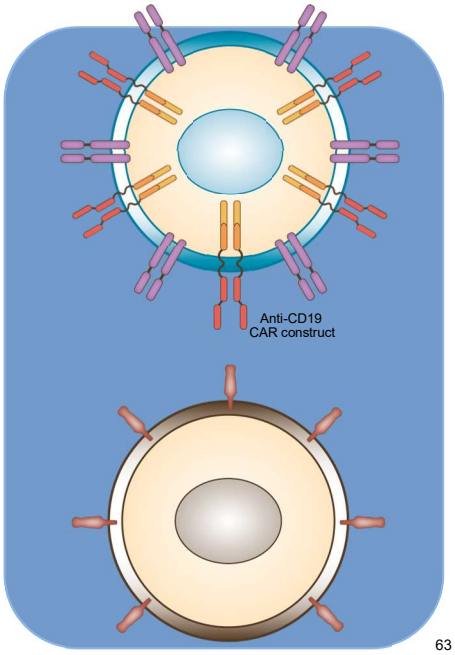
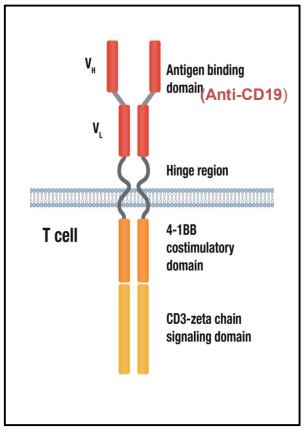
- Capable of in vivo proliferation and persistence

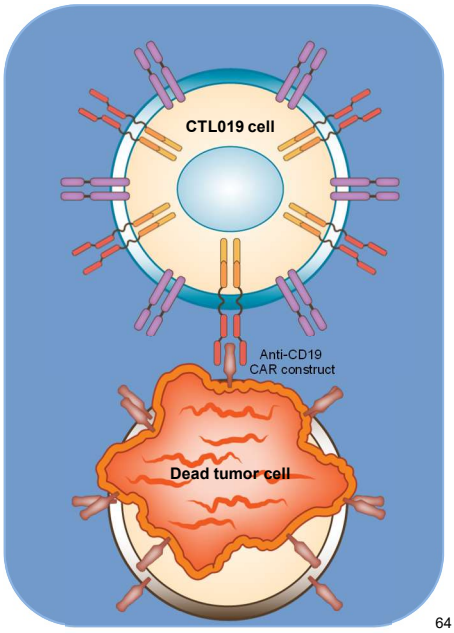


63

Anti-CD19 Directed CAR T cells



- Infused at singular point in time
- Capable of in vivo proliferation and persistence



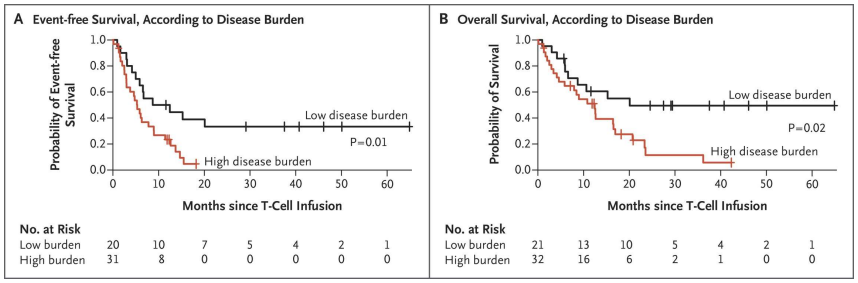
64

CD-19 CAR-T cells:High Response Rates, Durability of Response Varies

Ref	T cell Engager	Population	Response	CRS
Maude et al. NEJM 2014	Anti-CD19 CART 4-1BB	N=30 Peds&Adults	CR=90%	100% CRS 27% Severe
Davila et al. SciTrMed 2014	Anti-CD19 CART CD28	N=44 Adults	CR=82%	43% Severe
Lee et al. Lancet 2015	Anti-CD19 CART CD28	N=21 Peds&AYA	CR=67%	76% CRS 28% Severe
Turtle et al. JCI 2016	Anti-CD19 CART 4-1BB	N=30 Adults	CR=93%	83%CRS
Shah et al, ASH, 2017, Abstract 888	Anti-CD19	N=22 Adults	CR/CRi=82%	25%≥Grade 3 65% neurotox ≥ Grade 3

65

Long-term Follow-up MSKCC CAR-T based on Disease Burden at Time of Treatment



Durable responses with low disease burden: <5% blasts

Park et al, NEJM, Feb 1, 2018

66

Considerations for CAR-T in the Frontline

- Can very significant toxicities resulting from T-cell activation that occur in majority of patients (CRS, neurologic) be minimized?
  - Likely to be less frequent in setting of MRD
- Sequencing of CAR-T cells: May need to administered as final "consolidative therapy"
  - Concerns about CAR-T loss/depletion if additional immunosuppressive chemotherapy is used
- Durability of CAR-T cells? Resistance mechanisms
- Cost! - estimated at $475,000 for a single administration

67

Blintumomab Inotuzumab

Incorporate into B-cell ALL

Nelarabine

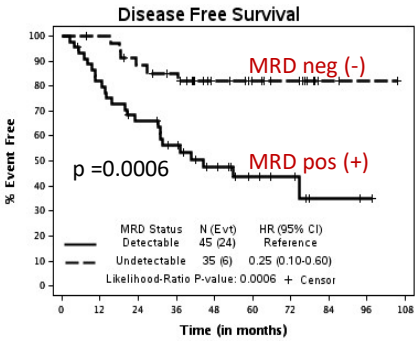
Incorporate into T-cell ALL

Strategies for Improving Outcomes in Adults:

MOVING NEW AGENTS INTO FRONTLINE THERAPY

68

Strategy: Incorporate new antibodies into multi-agent platform to eradicate MRD: Will it help?



C 10403

69

Testing Blinatumomab in Frontline: 2 studies in the US Intergroup

C1910: Phase III randomized trial testing addition of Blinatumomab to Frontline Therapy for adult ALL ages 30-65:

Will blinatumomab eradicate MRD and improve DFS with/without alloSCT in CR1?

- S1318: A Phase II Study of Blinatumomab and POMP for Patients ≥ 65 Years of Age with Newly Diagnosed Ph- ALL and of Dasatinib (NSC-732517), Prednisone and Blinatumomab for Patients ≥ 65 Years of Age with Newly Diagnosed Ph+ ALL

Can blinatumomab (chemotherapy-free induction) induce high remission rates with low toxicity and improve EFS in older adults?

- Presented at ASH 2018 with exciting preliminary results
- Suggests BiTE induction and low dose chemotherapy "maintenance" may be effective approach

70

Inotuzumab in the "Frontline"

- Older adults – MDACC
  - Ino + "mini-hyperCVD" in 48 patients
    - Median age = 68
    - CR rate = 84%
    - With median f/u of 24%, estimated 3 year OS = 54%
      - » Sasaki et al, ASH 2016, Abstract 588
- US intergroup A041501 for AYA (ages 18-39)
  - Frontline phase III trial with/without Ino consolidation
    - Uses C10403 backbone; AYA regimen
  - Goal: Improved 3 year EFS from 55% to 75%

71

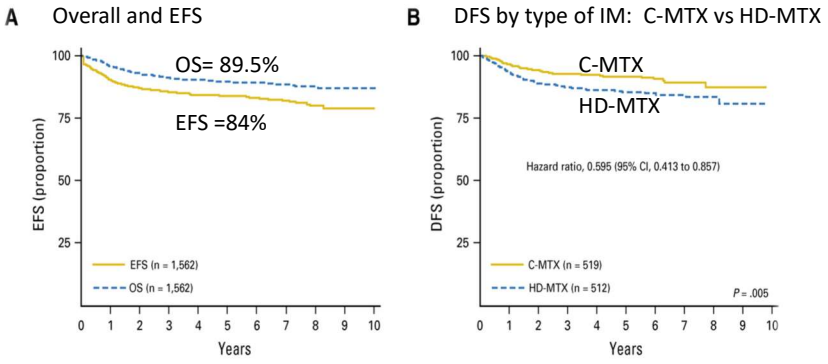
Can We Add Inotuzumab and Improve EFS to 80%? US Intergroup study for AYA: A041501

I		C	IM	DI	M
DNR	*Inotuzumab*	Cyclo	MTX	DOX	DEX
VCR		VCR	VCR	Cyclo	VCR
Dex		Dex	Peg-ASP	Dex	6MP
Peg-Asp		Peg-Asp	IT-MTX	Peg-Asp	MTX
IT-MTX		Ara-C		Ara-C	IT-MTX
IT-AraC		6MP		6-TG	
		IT-MTX		IT-MTX	

CD20+ Patients will Receive Rituximab with I, C, IM, DI
Maintenance therapy continues for 2 (F) – 3 (M) years

72

T-ALL: Capizzi Methotrexate + Nelarabine Improves Survival in COG AALL0434



- **Nelarabine incorporated into ABFM; six 5-day courses**
- **4yr DFS was 88.9% with nelarabine vs 83% DFS without nelarabine**

Winter SS et al, J Clin Oncol 2018: 36, 2926
Dunsmore et al, Proc ASCO, 2018

73

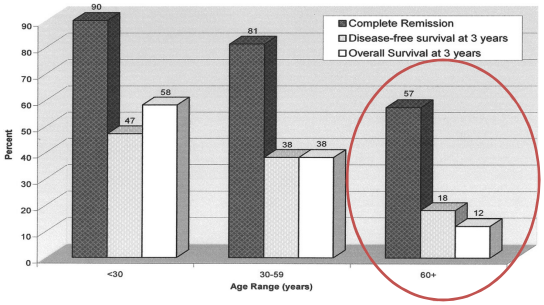
Moving Forward with T-ALL

- Based on COG data, can/should we be incorporating nelarabine into frontline therapy for all AYAs?
  - Dose/schedule – should "adult" schedule be used?
- Other considerations: targeting survival pathways: Venetoclax/Navitoclax
  - Ongoing phase I has promising results in heavily pretreated patients (B and T with overall response rate of 50%)
- Immune targeting: CD 5 CAR-T trial initiated; others coming (gene edited CD7 CAR-T)
  - Daratumomab: Anti-CD38 Nice preclinical data in PDX precursor T and ETP ALL

Bride et al. Blood 2018;131:995-999
Hantel et al, SOHO abstract, 2018

74

Older Adults with ALL: Historical Data: 10-20% 3 yr Survival



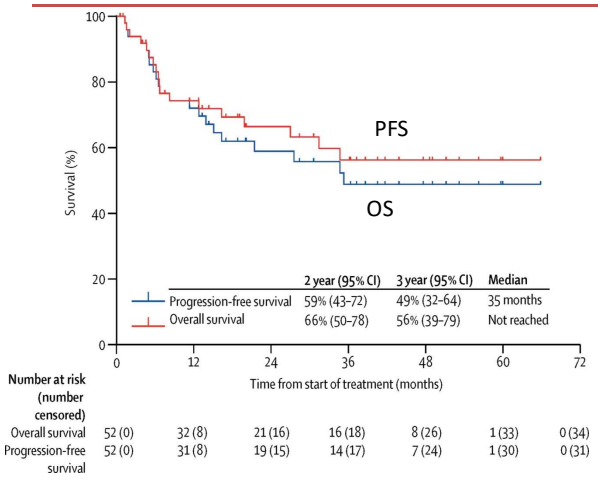
Survival: 759 adults treated on CALGB regimens from 1988-2008
Courtesy, Ben Sanford, Richard Larson

HYPER-CVAD in older adults treated at MDACC: 122 adults ≥ 60 years
- CR rate of 84%, induction mortality 10%
- Death in CR = 34%
- Median Survival of 15 months
- 3 year OS = 20%

O'Brien S et al, Cancer 2008; 113: 2097-101

75

Ino with low-intensity chemo for age ≥ 60



Kantarjian, Lancet Onc, 2018

N= 52
Median age = 68
CR rate = 85%;
Overall response = 98%

MRD negative (assessed by flow):
- --76% at time of "CR"
- -- 96% overall

Toxicities: prolonged thrombocytopenia, abnormal LFTs, VOD in 6 pts (1 fatal)

PFS at 3 years: 49% (32-64)
OS at 3 yrs: 56% (39-79)

Ino + mini-CVD (no anthracycline) : Ino given day 3 of first four cycles

76

Now enrolling: A041701, A regimen without traditional chemotherapy for Adults > 60 years

INOTUZUMAB Ozogamycin induction

BLINATUMOMAB consolidation

77

Summary/Conclusions

- Survival Rates for both younger and older adults with ALL are improving
- Incorporation of new agents into frontline treatment is an exciting new approach
- Clinical trial participation is crucial for ongoing progress
- Thanks to all of you, patients, family and friends, for your courage, strength and grace!

78

The Leukemia and AYA Programs: UC Medicine

Faculty/Fellows
Andy Artz, MD
Jane Churpek, MD
Emily Curran, MD
Michael Drazer, MD
Lucy A. Godley, MD, PhD
Andrew Hantel, MD
Tara Henderson, MD
Richard A. Larson, MD
Hongtao Liu, MD, PhD
Satya Kosuri, MD
Jen McNeer, MD
Toyosi Odenike,MD
Wendy Stock, MD
Nicole Sunseri, MD, PhD
Michael J. Thirman, MD
Joe Wynne, MD, PhD
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Sandeep Gurbuxani, MD, PhD
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Girish Venkataraman, MD
James W. Vardiman, MD
Dan Arber, MD

Nurse Specialists
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Tracy Paruszkiewicz, RN
Peggy Green, RN
Kelly Kramer, APN
Rebecca Pape, APN
Lauren Ziskind, APN

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Noreen Fulton, BS
Bart Eisfelder, PhD

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Megan McNerney, MD,PhD
Angela Lager, PhD
Jeremy P. Segal, MD, PhD

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Belen Aguado, BS
Calvin Pullins, BA
Tyler Crump, BA
Haley Hamann, BS
Judith Murray, BA
Luke Moma, BS

Alliance Leukemia
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Clara Bloomfield, MD

ECOG: Selina Luger MD

SWOG: Anjali Advani MD

COG/St. Jude
Charles Mullighan, MD
Mary Relling, PharmD
Bill Evans, PharmD
Cheryl Willman, MD
Richard Harvey, PhD
I-Ming Chen, DVM, MS

79

Thanks to our patients – they are our inspiration!

80

Q&A SESSION

Acute Lymphoblastic Leukemia (ALL) in Children and Adults

- **Ask a question by phone:**
  - Press star (*) then the number 1 on your keypad.
- **Ask a question by web:**
  - Click “Ask a question”
  - Type your question
  - Click “Submit”

Due to time constraints, we can only take one question per person. Once you have asked your question, the operator will transfer you back into the audience line.

LLS EDUCATION & SUPPORT RESOURCES

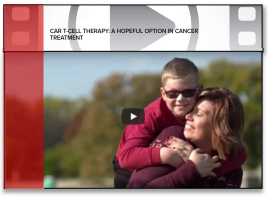
- **Information Specialists**

  Master’s level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials, and survivorship.
  - **E-MAIL:** infocenter@LLS.org
  - **TOLL-FREE PHONE:** 1-800-955-4572
- **Free Education Booklets:**
  - www.LLS.org/booklets
- **Free Telephone/Web Programs:**
  - www.LLS.org/programs
- **Live, Weekly Online Chats:**
  - www.LLS.org/chat
- **Additional Information About Leukemia:**
  - www.LLS.org/leukemia

LLS EDUCATION & SUPPORT RESOURCES

- **LLS Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.thebloodline.org



- **Education Videos**

  Free education videos about survivorship, treatment, disease updates, and other topics: www.LLS.org/educationvideos

- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection

83

LLS EDUCATION & SUPPORT RESOURCES

- **Free Nutrition Consults**

  Telephone and e-mail consultations with a registered dietitian: www.LLS.org/nutrition

- **What to Ask**

  Questions to ask your treatment team: www.LLS.org/whattoask

- **Other Support Resources**

  LLS community, discussion boards, blogs, support groups, financial assistance, and more: www.LLS.org/support

84


THANK YOU
We have one goal: A world without blood cancers
LEUKEMIA & LYMPHOMA SOCIETY
85