NCCN 10th Annual Congress:
Hematologic Malignancies™

Management of Acute Lymphoblastic Leukemia

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NCCN National Comprehensive Cancer Network®

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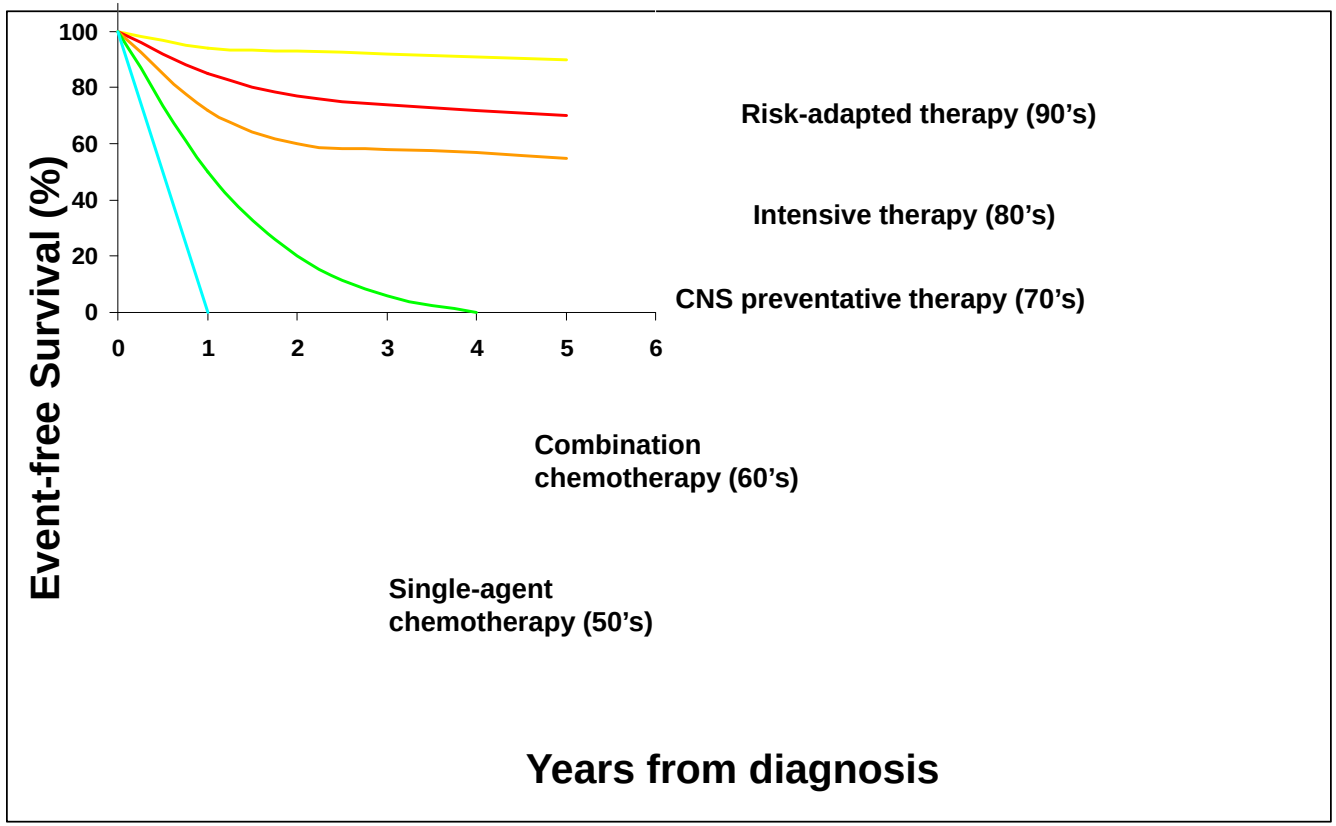
Acute Lymphoblastic Leukemia (ALL)

- Approximately 6,000 patients per year diagnosed with ALL
  - 60% of cases diagnosed at < 20 years of age
  - 11.2% of patients ≥ 65 years of age
- 5-year overall survival between 2005-2011 is 67.5%
- Adult outcomes lag significantly behind those in the pediatric population
- Treatment outcomes in patients ≥ 65 years are very poor
  - 5-year relative survival only 9.1%
  - Account for 35% of patients dying from ALL

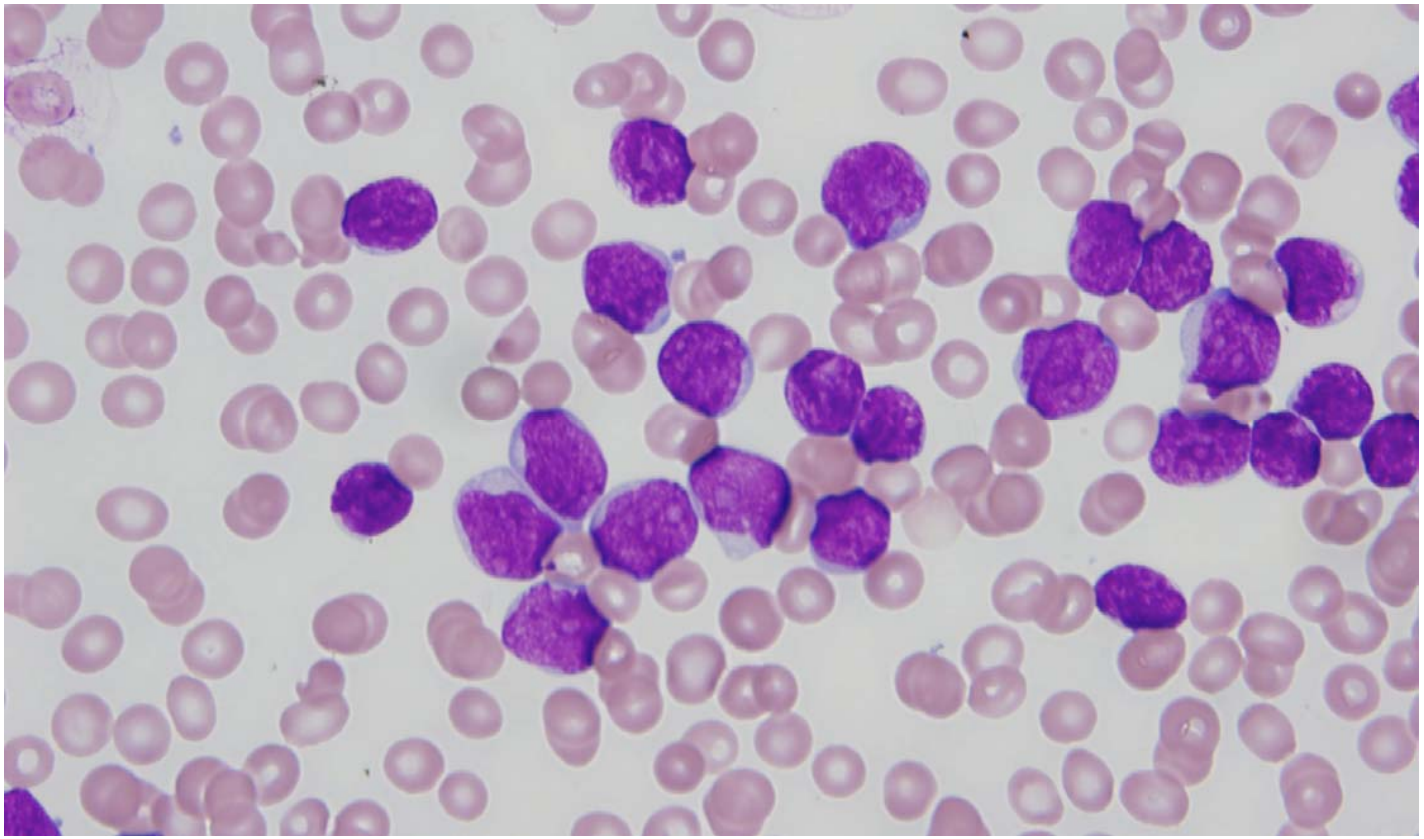
SEER data available at: http://seer.cancer.gov/statfacts/html/alyl.html

What can we learn from the paradigm of pediatric hematology?

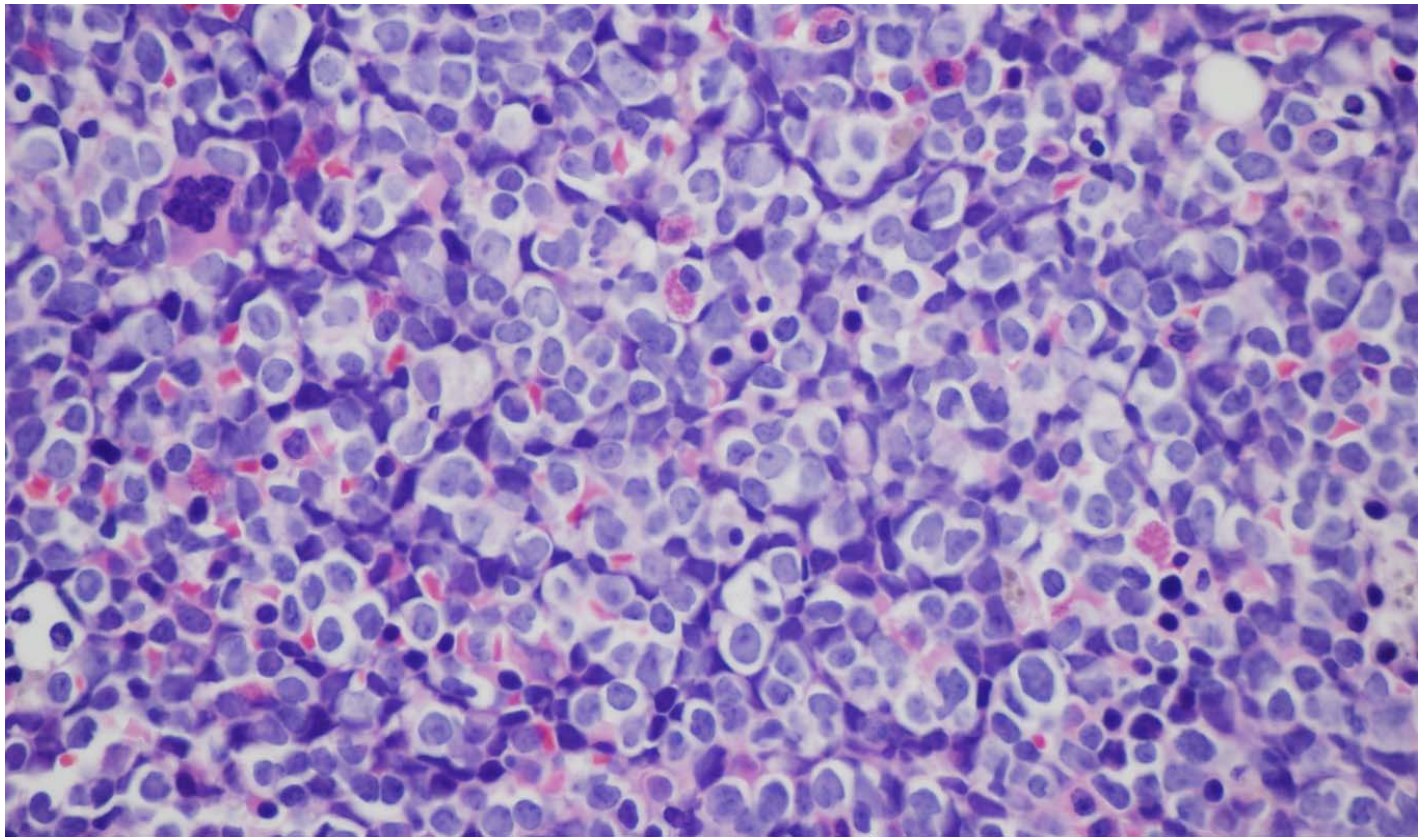


Courtesy Pat Brown, Johns Hopkins

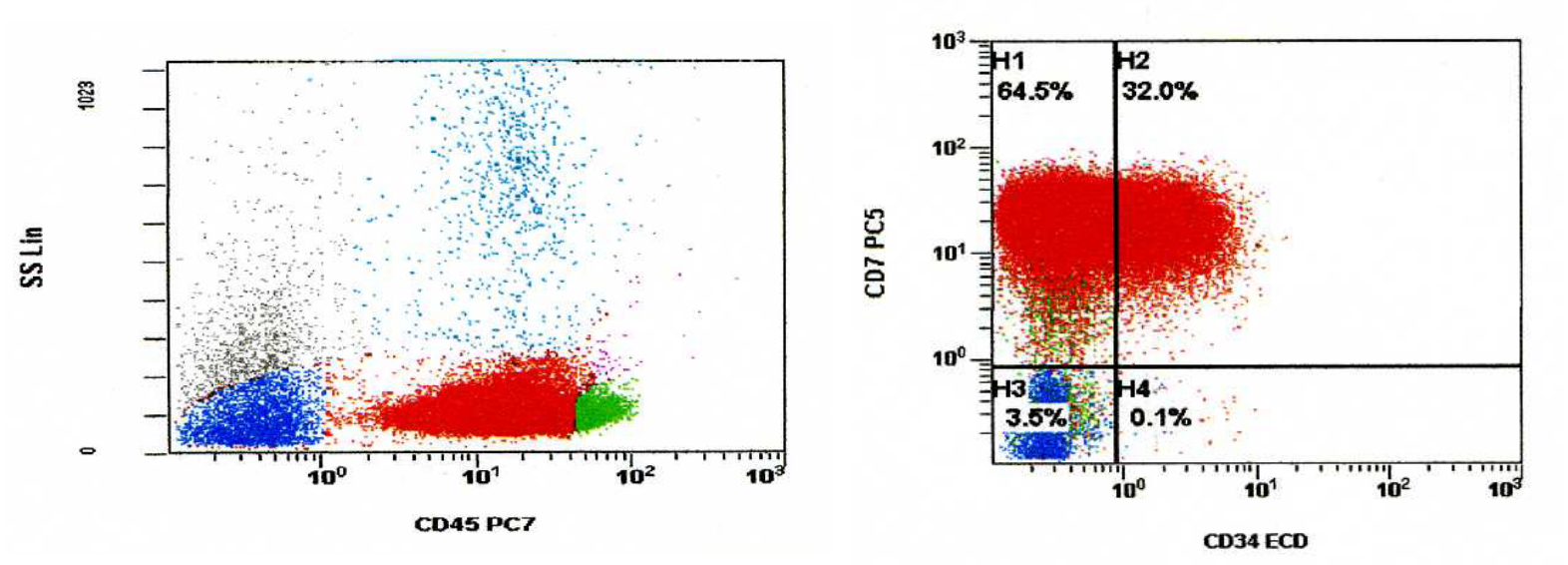
Peripheral Blood Smear in ALL



Bone Marrow Biopsy in ALL



Flow Cytometry in ALL



Advances in the Care of Patients with ALL

- **The best opportunity to improve ALL outcomes is to make the best, evidence-based treatment choices early post-diagnosis/relapse**
- **The inclusion of novel and targeted therapeutic agents in induction and salvage therapy are likely to improve treatment outcomes**

Key Themes – The Need to Think Strategically

- *Other than tyrosine kinase inhibitor (TKI) therapy for Philadelphia chromosome (Ph)+ ALL, many of the improvements in ALL survival outcomes have occurred without the addition of novel therapeutic agents*
- *Pediatric and pediatric-inspired regimens have improved outcomes by effectively maximizing dose-intensity of existing agents*
- *Improving treatment outcomes for adult patients requires that we fully leverage diagnostic, molecular, and demographic data to develop individualized treatment plans*
- *Immunotherapies, particularly monoclonal antibodies, now play an essential role in salvage treatment of ALL*

Key Knowledge Opportunities in Caring for Patients with ALL

- Cytogenetic, molecular, genomic data
  - Ph+ ALL
  - MLL, complex, high-risk karyotypes
  - Ph-like ALL
- Patient demographic data
  - Adolescent/Young Adult Patients
  - ALL in the elderly
- Immunotherapy-based salvage strategies

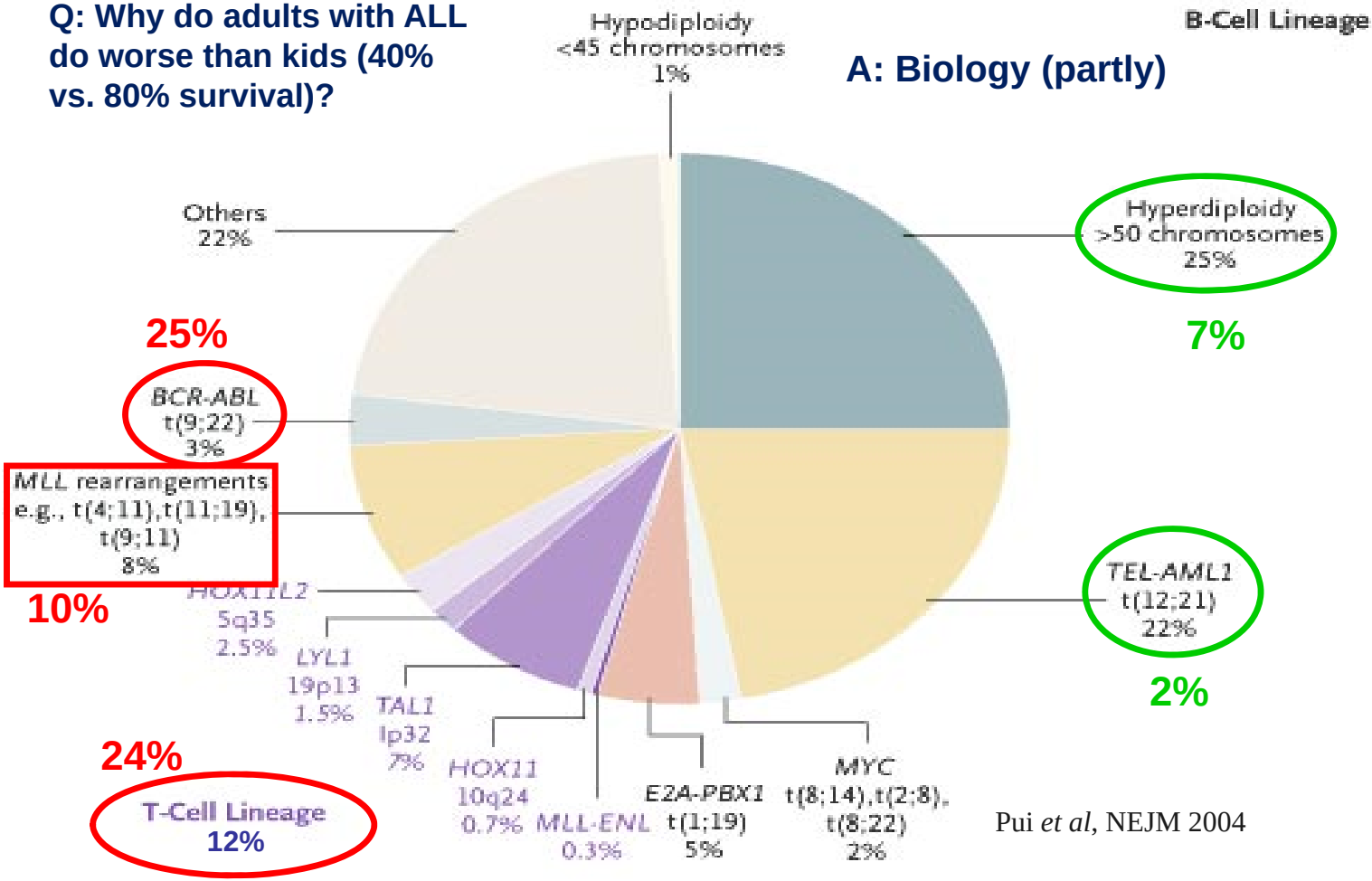
Cytogenetic, Molecular, and Genomic Risk Stratification

Risk-Adapted Treatment in ALL

Prognosis In ALL Is Not Quite That Simple

Q: Why do adults with ALL do worse than kids (40% vs. 80% survival)?

A: Biology (partly)



Pui *et al*, NEJM 2004

Patients with High-risk Cytogenetics

- Patients with Ph+ ALL should receive TKIs concomitantly with age-adapted induction and consolidation therapy
  - Mutational analysis should be performed for patients with a poor treatment response
  - Changes among TKIs should be based upon either mutational analysis or issues related to patient tolerance of the agent
  - Adult patients should be considered for early allogeneic hematopoietic cell transplant (HCT) in first complete remission (CR)
- Patients with high-risk cytogenetics – rearranged MLL, complex karyotype – should be considered for early allogeneic HCT in first CR

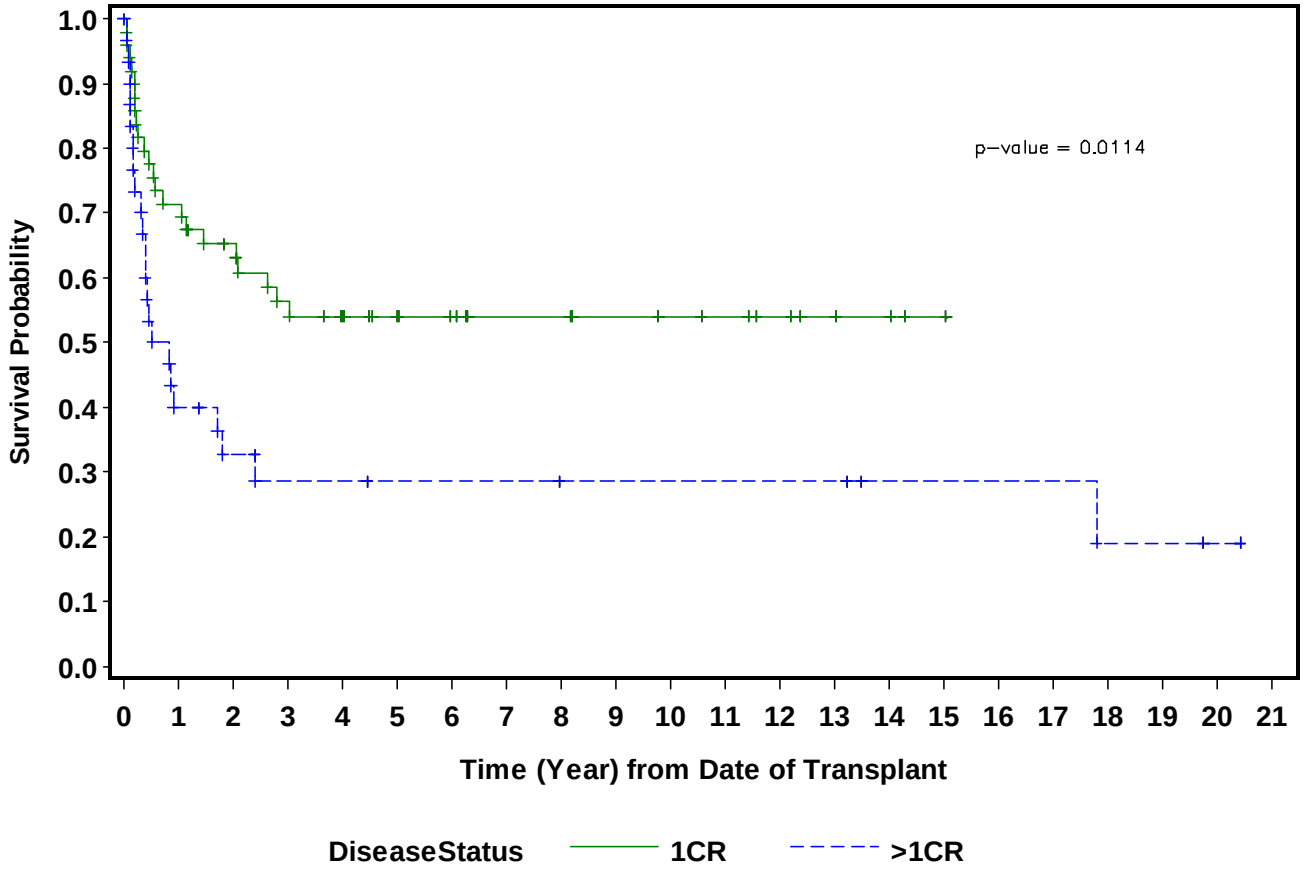
Overall Survival

ALLO SIB: ALL Patients, FTBI/VP-16/CY

Stratified by Disease Status: 1CR (22 events, 27 censored), >1CR (22 events, 8 censored)

Transplant Date Range: 07/09/1985(Inception) - 12/31/2005

Run Date: January 18, 2008



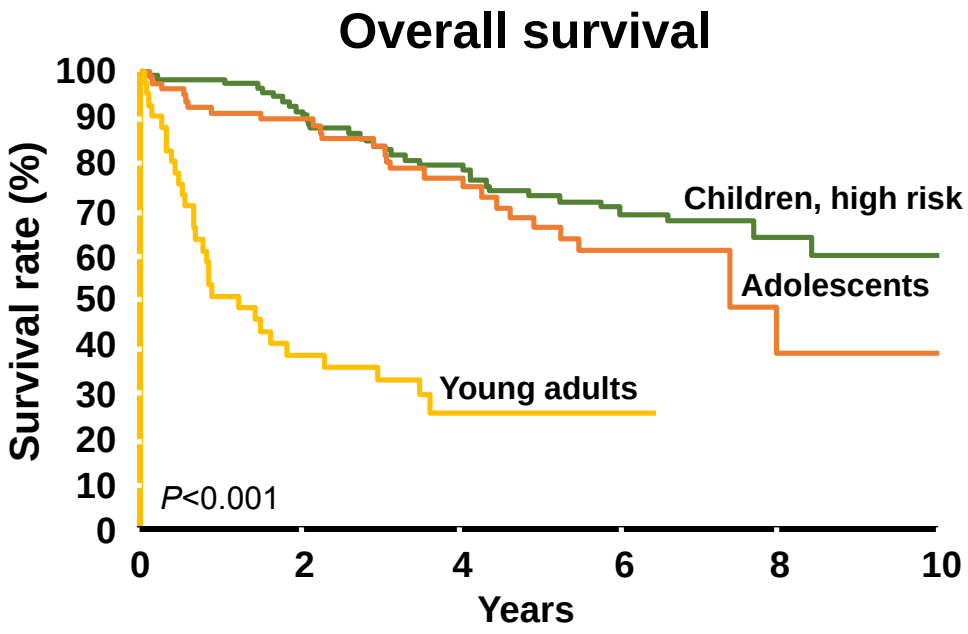
Lapport et al. 2008. Blood, 112 (3):903-909

Novel, High-Risk Genetic Subtypes of ALL: *Philadelphia-Like* ALL

- *Ph-like* ALL
  - Utilizing microarray analysis in 400 children identified subgroup of 43 precursor B-cell ALL patients lacking *bcr-abl* fusion gene with a gene expression profile similar to that of Ph+ ALL
    - Predominantly male
    - Age > 10 years
    - Presenting WBC > 20,000/µL
  - *Ph-like* ALL patients had an inferior prognosis to that of other patients with precursor B-cell ALL
    - 5-year EFS 54.8% vs. 83.1%
    - Relapse incidence 33.9% vs. 14.9%

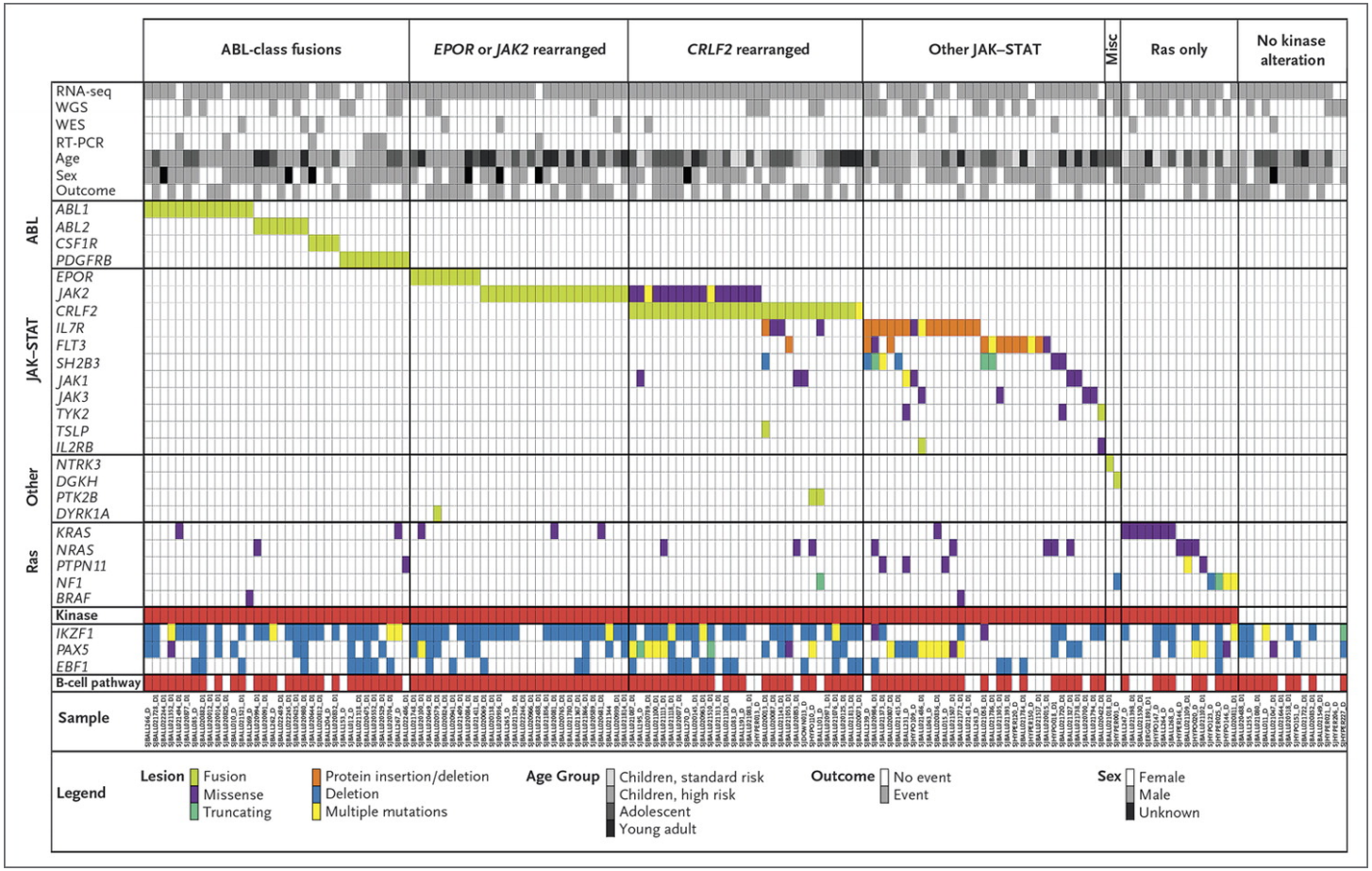
Kronnie et al. 2013. Blood, 122(21):353

Overall Survival Among Patients With Ph-like ALL



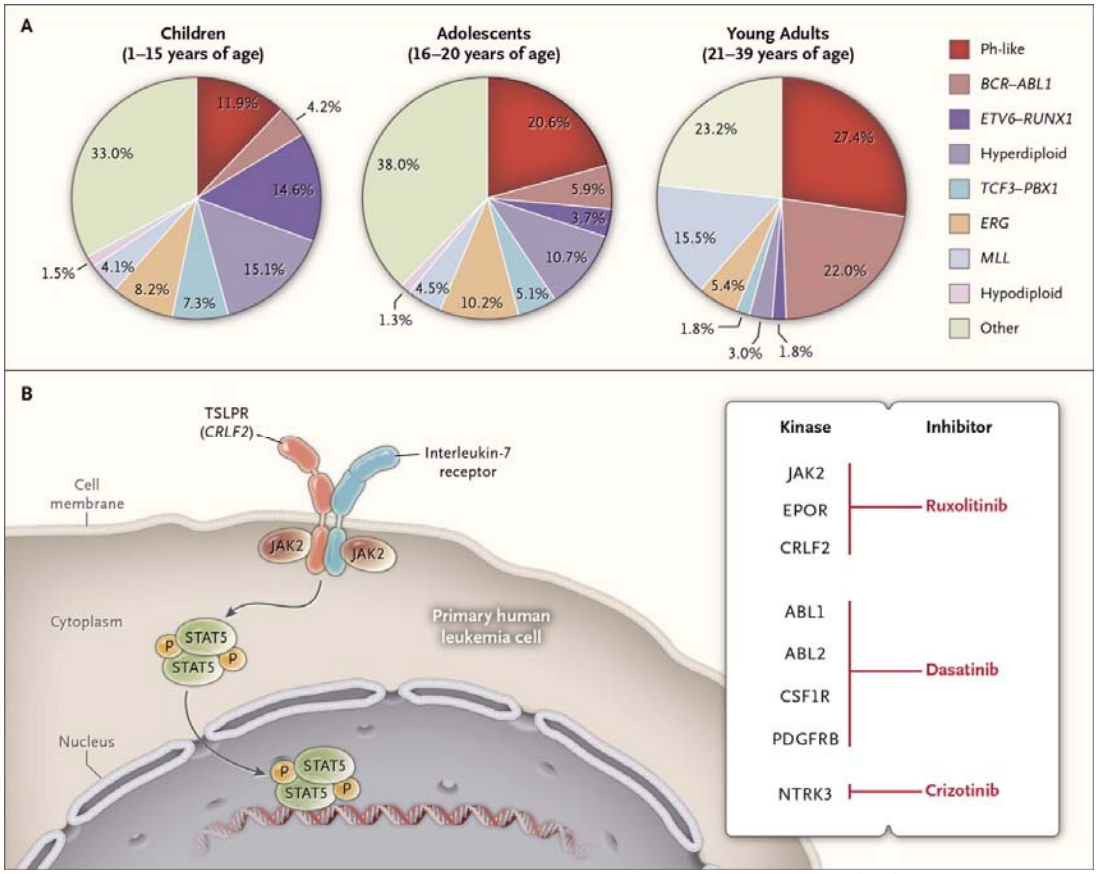
No. at Risk						
Children, high risk	105	101	85	61	37	13
Adolescents	76	63	53	28	11	4
Young adults	41	20	12	4	0	0

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



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

Actionable Genetic Lesions in Ph-like Precursor B-Cell ALL



Graubert TA. N Engl J Med 2014;371:1064-1066.

Treating Patients with Ph-like ALL

- Genomic alterations potentially responsive to inhibition with approved tyrosine kinase inhibitors (TKIs) (Ph+ and “Ph-like” ALL)
- Agents such as crizotinib, imatinib, ruxolitinib are being investigated
- Patients with Ph-like ALL should be considered for participation on a clinical trial

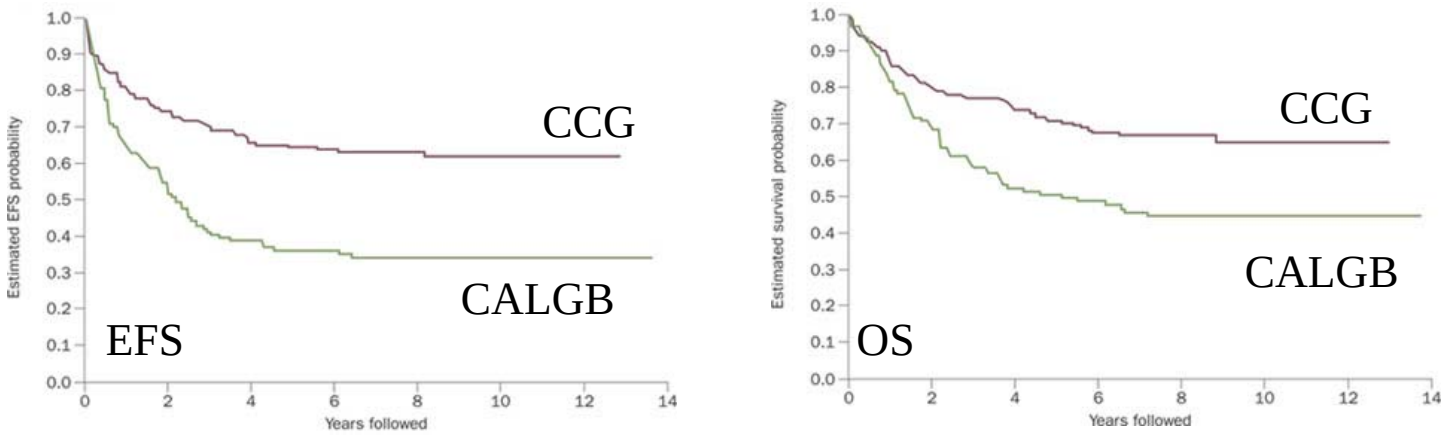
Patient Demographic Data

Risk-Adapted Treatment in ALL

AYA Patient Population

- AYA patients defined as those between the ages of 15-39 years
- This patient group is fitter and less likely to have significant comorbid conditions
- Patients in this age group can benefit significantly from treatment with pediatric or pediatric-inspired regimens
  - These regimens make use of greater chemo-therapeutic dose-density
  - They include intensive dosing schemes for L-asparaginase
- Patients need to be screened carefully for their candidacy for use of pediatric/pediatric-inspired regimens
- Practitioners need to be prepared to treat potential complications associated with the use of these regimens

AYA: Superior Outcomes With Pediatric Protocols



Stock W, et al. *Blood* 2008;112

- Prospective studies of "pediatric-inspired" regimens in "young adults" (variably defined) have demonstrated feasibility and better outcomes compared to historical controls – intergroup C-10403 trial is ongoing for patients up to 40*

*"Chronological age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis."

Pediatric and Pediatric-Inspired Regimens

GRAALL-2003 regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide (patients aged <60 years)

COG AALL-0434 regimen with nelarabine (for T-ALL): daunorubicin, vincristine, prednisone, and pegaspargase; nelarabine added to consolidation regimen (ongoing study)

CCG-1961 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (patients aged ≤21 years)

PETHEMA ALL-96 regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide (patients aged <30 years)

CALGB 10403 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (ongoing study in patients aged <40 years)

DFCI ALL regimen (based on DFCI Protocol 00-01): doxorubicin, vincristine, prednisone, high-dose methotrexate, and pegaspargase (ongoing study in patients aged <50 years)

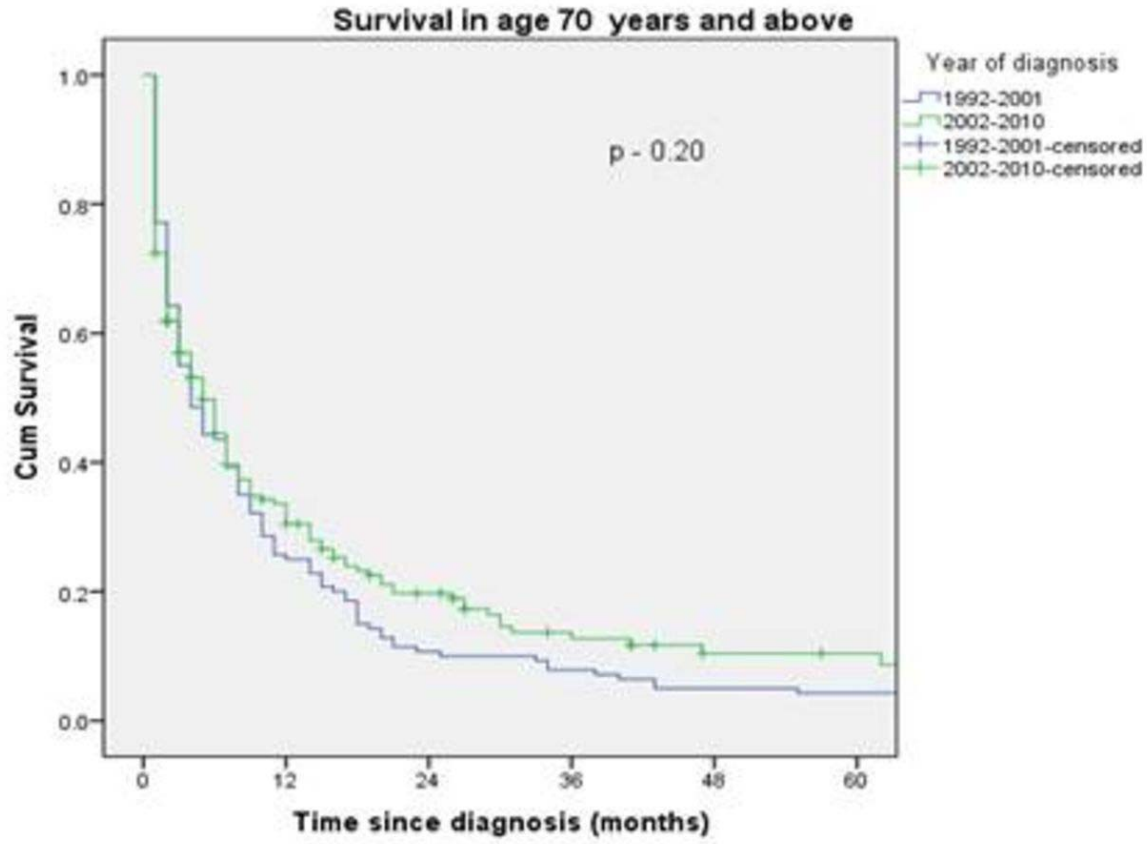
USC ALL regimen (based on CCG-1882 regimen): daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase (patients aged 18–57 years)

Treatment of Older Patients with ALL

- Patients with ALL > 65 years of age have poorer survival outcomes
  - These patients are more likely to suffer treatment-related complications/toxicities
  - Many of these patients may have poor outcomes when treated with standard therapeutic regimens
- Patients need to be screened carefully for comorbidities that might impact treatment
  - Physiological fitness and performance status need to guide therapeutic choices
- Perform Comprehensive Geriatric Assessment (CGA)
- Where possible, patients should be considered for participation in clinical trials
- Selected patients may be considered for more intensive therapeutic approaches, including allogeneic HCT

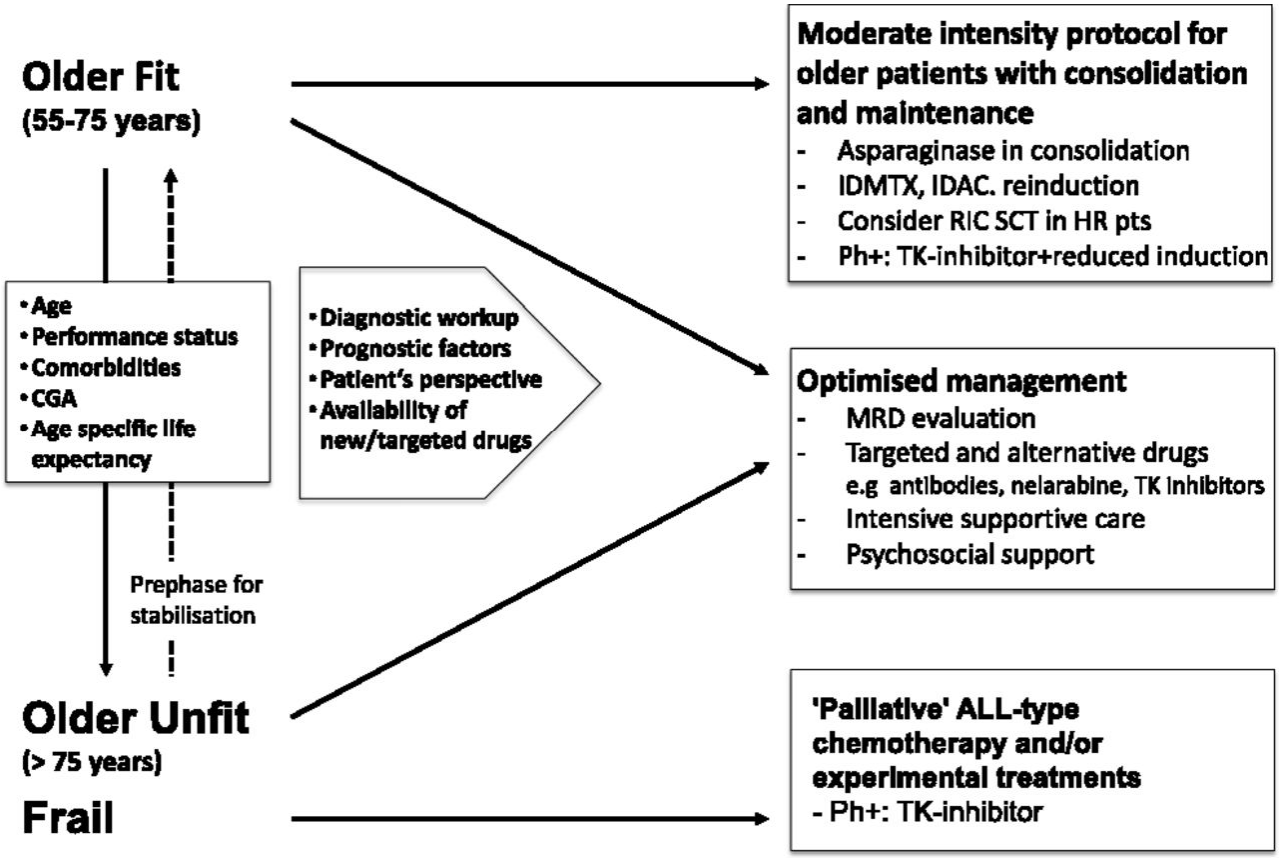
Trends in Survival of Elderly Patients with B-Lineage Acute Lymphoblastic Leukemia: Analysis of SEER

13 SEER Registry Sites (70+ years)



Mehta P, Venkitachalam R. Blood 2013;122:1404

Comprehensive Approach to Managing Older Patients with ALL



HR - high risk
Pts - patients
TK - tyrosine kinase
IDMTX - intermediate dose methotrexate
IDAC - intermediate dose cytarabine

Nicola Gökbuget Blood 2013;122:1366-1375

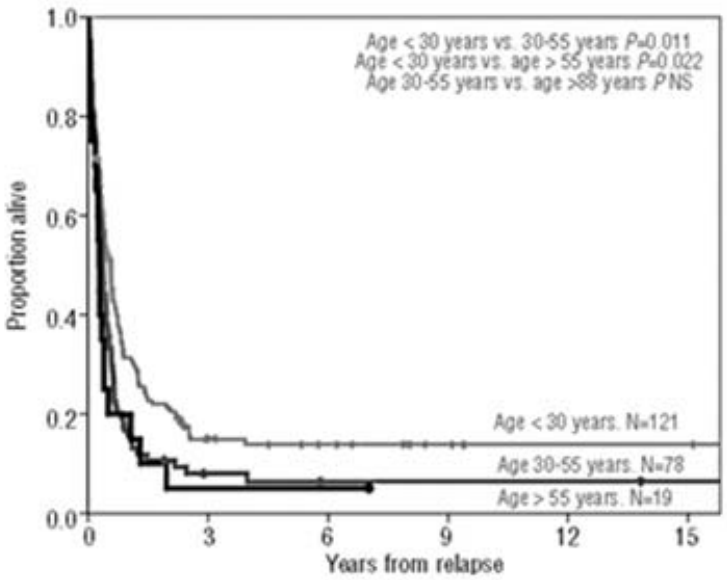
Treatment of Less Fit Older Patients or Patients with Significant Comorbidities with ALL

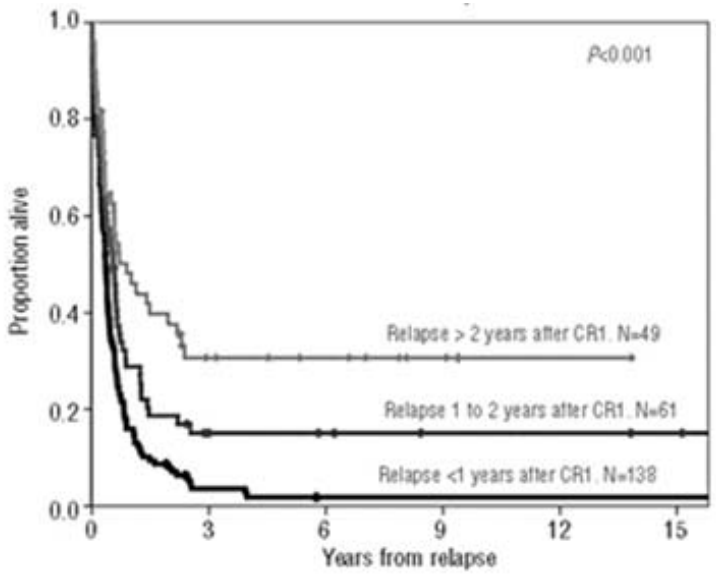
- It is essential to have frank conversations with patients and their families regarding the goals of care
  - Patient goals should inform the treatment plan
  - Patients should be carefully informed of the risks and potential benefits of treatment
- Patients should receive early Supportive Care evaluation and management
- Patients with significant comorbidities, poor performance status should be considered for Palliative Care
- Please refer to the NCCN Guidelines for the Treatment of Older Adult Oncology Patients

Immunotherapeutic Therapies in Relapsed/Refractory ALL

Risk-Adapted Treatment in ALL

Outcome for Relapsed ALL



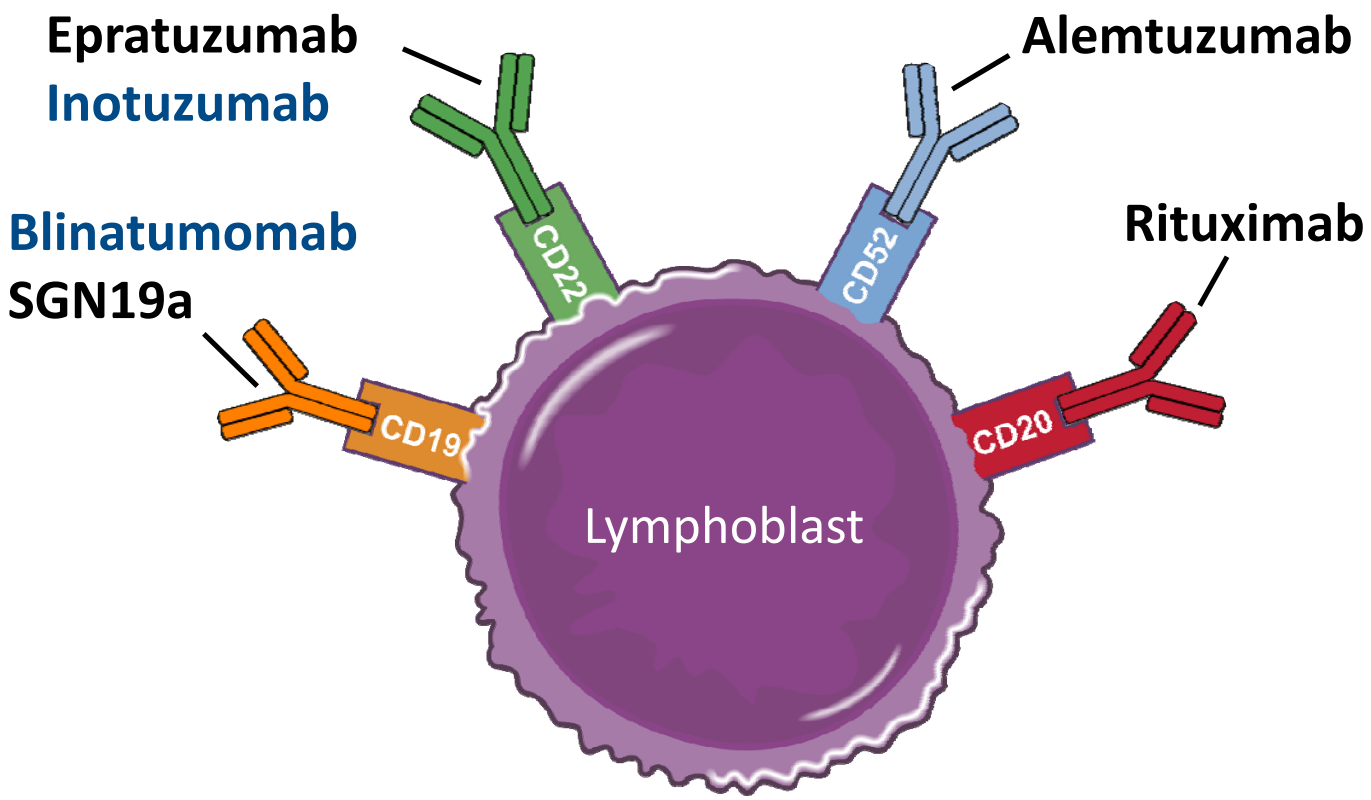


Targeted Therapies for ALL

Therapy	Description
CD20	
Rituximab	When added to conventional chemotherapy has been shown to improve survival in younger adults
Ofatumumab	Binds to a different epitope than rituximab, which may allow it to overcome rituximab-resistant disease
Obinutuzumab	Novel glycoengineered type II CD20 monoclonal antibody superior to rituximab and ofatumumab in the induction of direct cell death.
CD19	
SAR3419	Conjugated to a synthetic maytansinoid that is release intracellularly after antigen internalization
SGN-CD19A	Humanized anti-CD19 monoclonal antibody conjugated to the microtubule-disrupting agent. On internalization, it binds to tubulin and induces G2/M arrest and apoptosis
Blinatumomab	Bispecific antibody that redirects cytotoxic T cells to cells that express CD19
CD22	
Epratuzumab	Studied as part of combination therapy in adults and children with modest activity
Epratuzumab-SN38	Antibody conjugated to a topoisomerase I inhibitor to enhance cell killing potential
Inotuzumab ozogamicin	Antibody conjugated to the cytotoxin calicheamicin
Moxetumomab	Antibody conjugated to bacterial or plant toxin
CD52	
Alemtuzumab	Antibody that has only displayed little activity in B- and T-cell disease

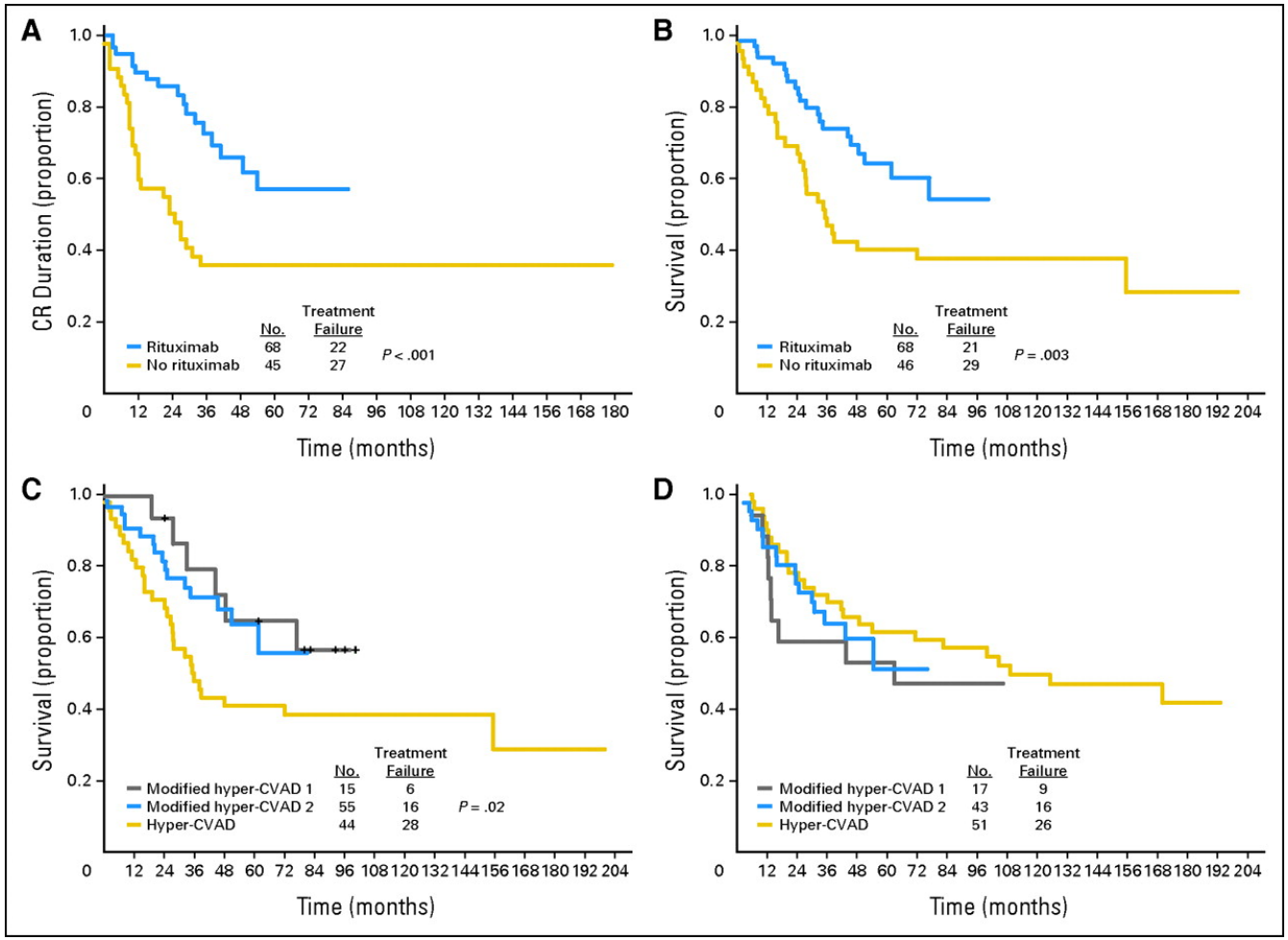
Jabbour et al. 2015. Blood. 125(26): 4010-6

Pre B ALL - Monoclonal Antibodies



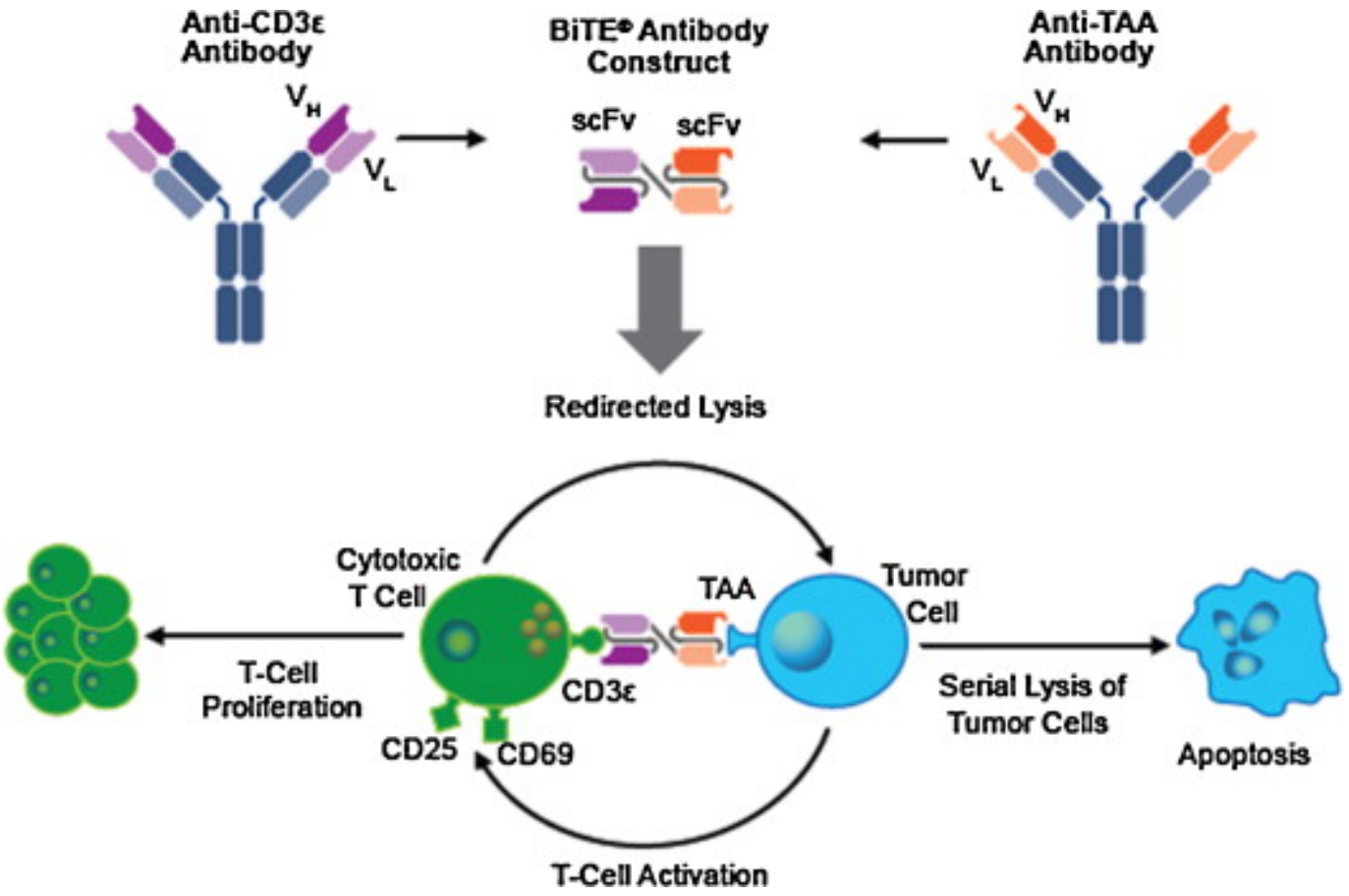
Adapted from Advani A. Presented at: Spanning Our Life Cycle: Novel Therapies, Targets, and Transplant Strategies in ALL. December 2014. San Francisco, CA.

Impact of Rituximab on Patients with Ph–Negative Precursor B-lineage ALL



Deborah A. Thomas et al. JCO 2010;28:3880-3889

Construct of Bispecific Agent Blinatumomab and Mechanism of Activity

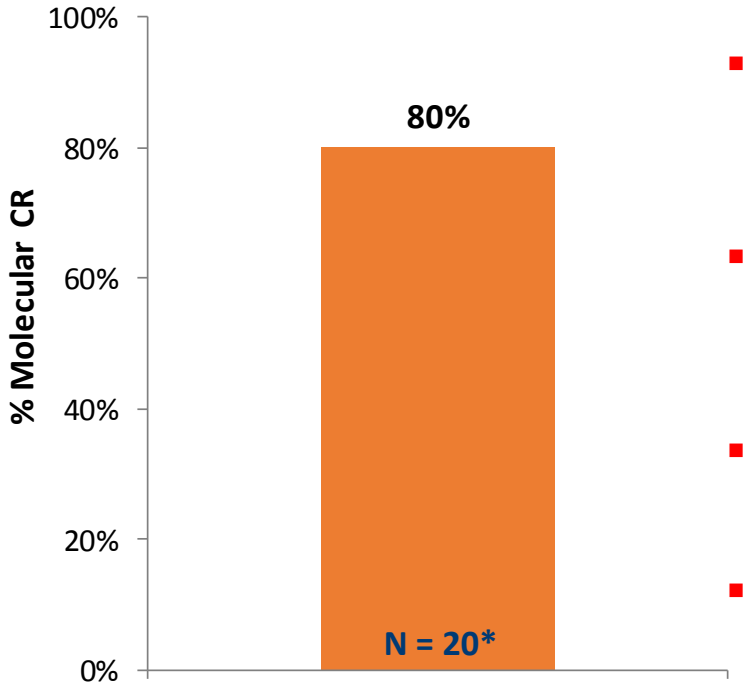


Molecular Immunology, 2015, Available online 13 April 2015

Blinatumomab

- Approximately 75% of patients with ALL have B-cell lineage disease
- CD19 expressed in > 90% patients with B-lineage ALL
- Apposition of CD19-expressing tumor cells with T-cells causes granzyme/perforin-related tumor lysis
- Key risk of agent is cytokine release syndrome
  - Patients with high leukemic burden at high risk
- Neurological toxicity seen in a significant number of patients
- Drug has a short half-life; must be administered as a continuous infusion
- Tumor cell escape based upon loss of CD19 expression
- This agent represents a “bridge toward cure”; it increases likelihood that patient can undergo allogeneic HCT

Blinatumomab Molecular Complete Response

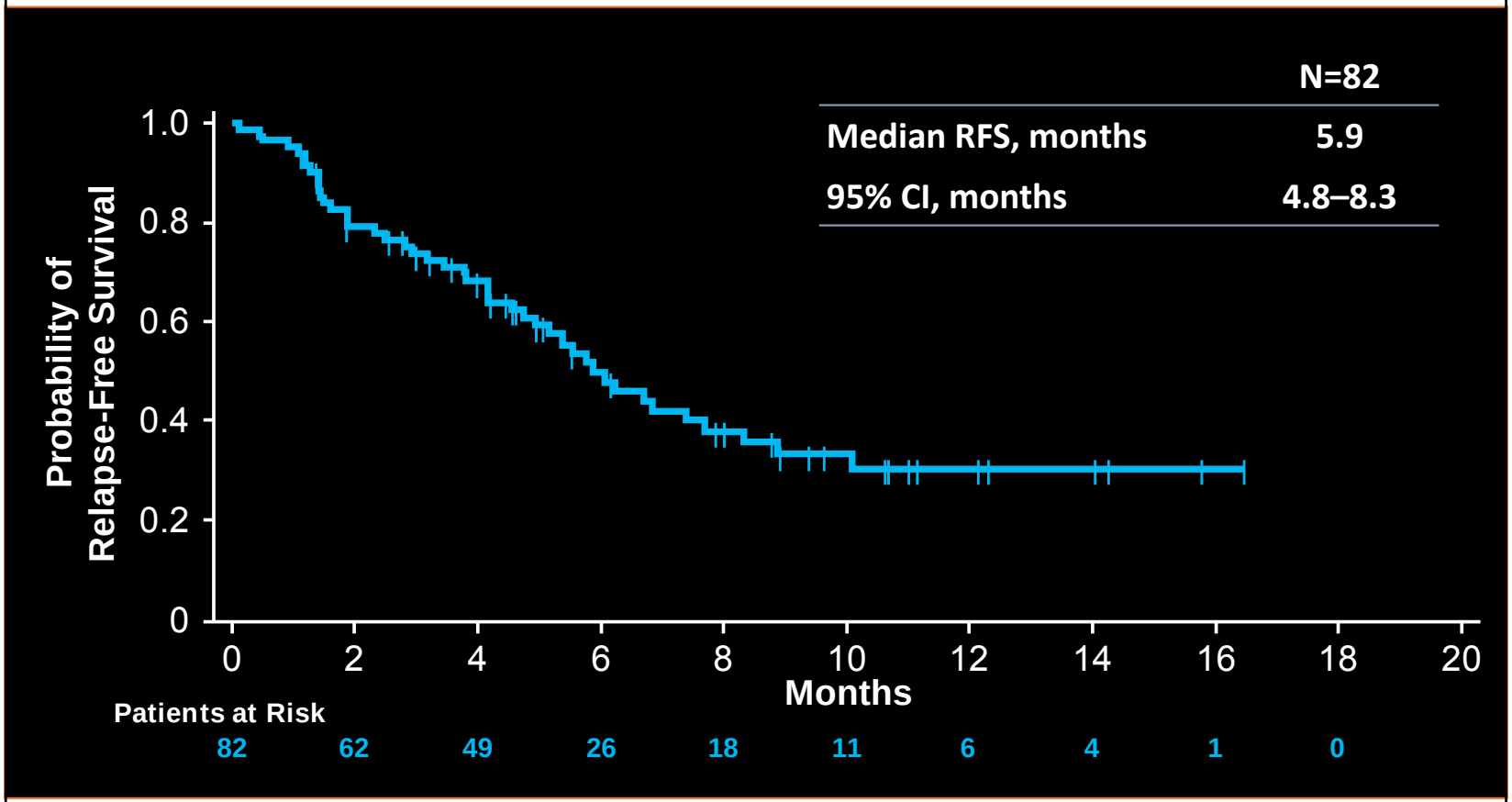


- 80% of patients achieved molecular complete response (CR) on blinatumomab
- Responses were rapid, all responses occurred after the first cycle of treatment
- 4 patients had stable MRD levels as best response
- Responders include
  - 3/5 patients were *BCR-ABL*(+)
  - 13/15 patients were *BCR-ABL* (-)
  - 1/2 patients were *MLL-AF4* (+)

*One patient not evaluable

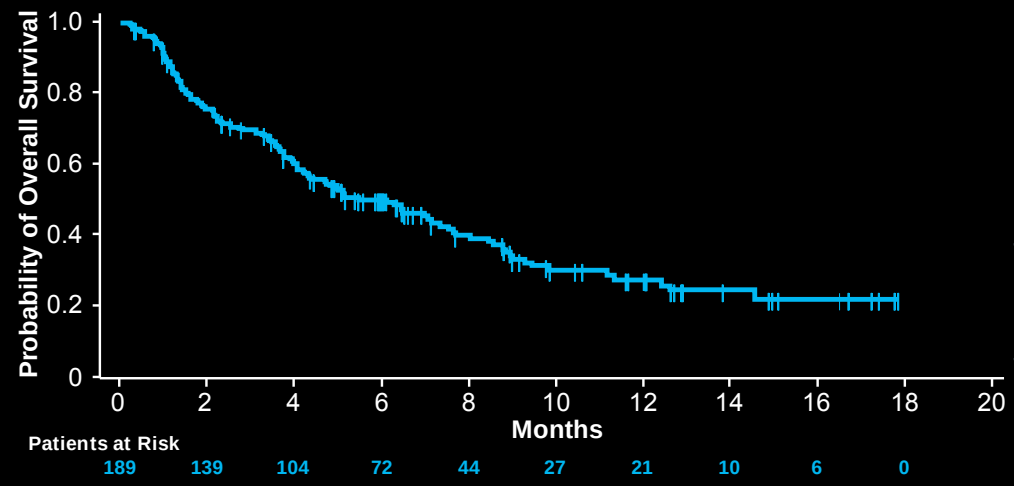
Topp MS, et al. J Clin Oncol. 2011;29(18):2493-2498.

Relapse-Free Survival



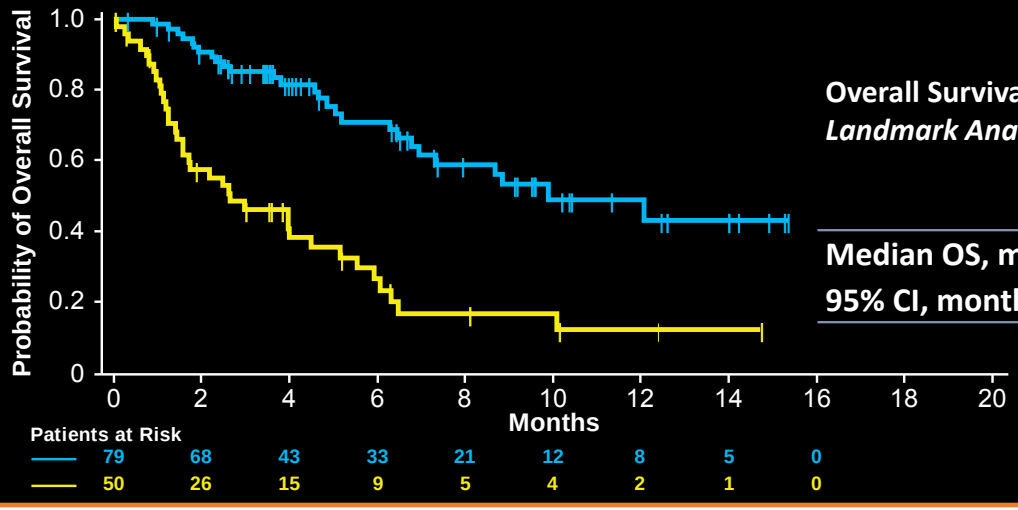
Topp. Lancet Oncology. 2015;16:57.

Overall Survival



Overall Survival

	N=189
Median OS, months	6.1
95% CI, months	4.2–7.5



Overall Survival
Landmark Analysis Day 77*

	CR/CRh N=79	No CR/CRh N=50
Median OS, months	9.9	2.7
95% CI, months	6.8–NE	1.6–4.5

*After two treatment cycles
NE, not estimable

Topp. Lancet Oncology. 2015;16:57.

Adverse Events (Regardless of Causality)*

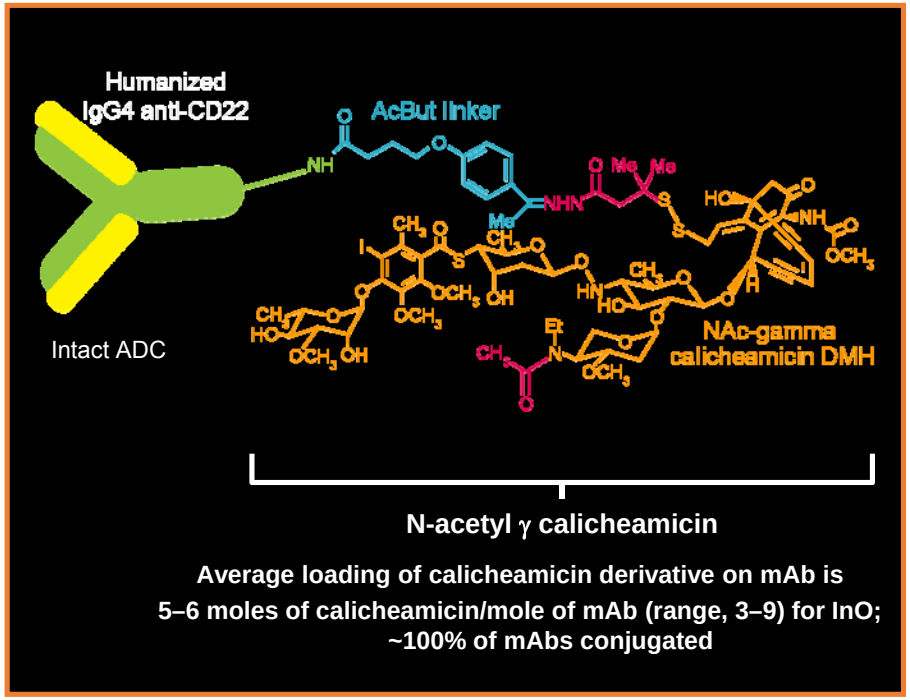
Adverse events, n (%)†	All Patients (N=189)
Worst grade 1 or 2	33 (17)
Worst grade 3 or 4	127 (67)
Worst grade 5 (death)	28 (15)
Grade ≥ 3 occurring in ≥ 5% of patients†	
Febrile neutropenia	48 (25)
Neutropenia	30 (16)
Anemia	27 (14)
Pneumonia	17 (9)
Thrombocytopenia	16 (8)
Hyperglycemia	15 (8)
Leukopenia	15 (8)
Alanine aminotransferase increased	13 (7)
Hypokalemia	13 (7)
Pyrexia	13 (7)
Sepsis	11 (6)
Hypophosphatemia	10 (5)

*During treatment until 30 days post treatment; †CTCAE v4.0

Topp, et al. 2015. Lancet Oncol. 16(1) 57-66.

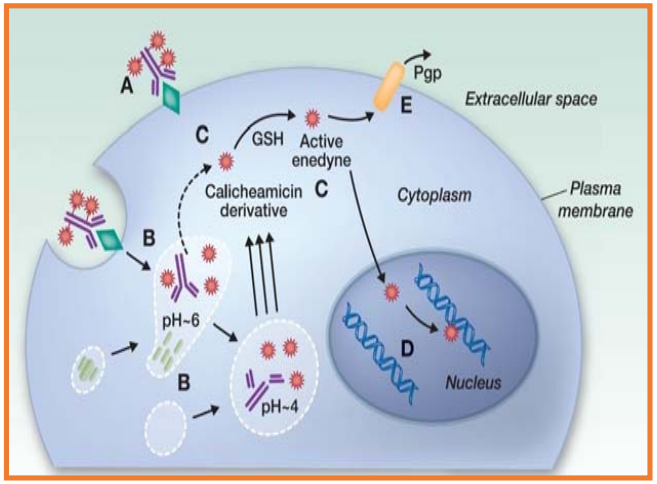
Inotuzumab Ozogamicin (InO)

AcBut linker:
4-(4'-acetylphenoxy) butanoic acid dimethyl hydrazide



Average loading of calicheamicin derivative on mAb is 5–6 moles of calicheamicin/mole of mAb (range, 3–9) for InO; ~100% of mAbs conjugated

MOA retains activity against tumor cells with slow cycling times



MOA = mechanism of action.

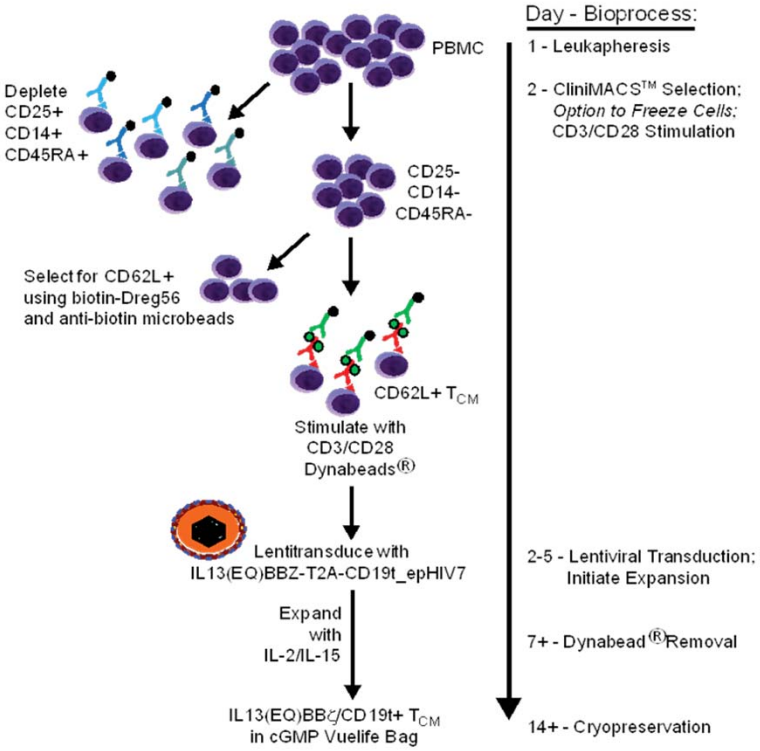
1. Jabbour E et al. *Blood.* 2014;124(21): abstract 794.

Inotuzumab Ozogamicin

- CD22 expression in > 80% patients with B-lineage ALL
- Inotuzumab ozogamicin is an antibody drug conjugate
- Initial monthly treatment showed efficacy and tolerability
  - 90 patients treated
    - CR 19%
    - CRp 30%
    - 9% marrow CR without recovery of blood counts
  - 36 of 90 patients underwent subsequent allogeneic HCT
    - VOD in 17% of BMT patients
    - VOD seen less often in patients treated with weekly schedule
- Similar response rates between single-dose scheme vs. weekly dosing (57% vs. 59%)
  - Weekly dosing associated with less toxicity
- Putative registration trial completed
- Agent has not yet received FDA approval

Kantarjian, et al. 2013. Cancer. 119(15) 2728-36.

Chimeric Antigen Receptor (CAR) T-cell Therapeutics for ALL



- Form of adoptive immunotherapy
- Autologous T-cells engineered to express T-cell receptor (TCR) with CD19 specificity
- Target cells killed by T-cell specific tumor killing
- Important toxicities
  - Tumor lysis syndrome
  - Cytokine release syndrome
  - Macrophage activation syndrome
  - Neurological toxicities
  - B-cell aplasia
- *In vivo* persistence of CAR T-cells

Wang et al. *Journal of immunotherapy* 2012;35(9):689-701.

CAR T-cell Therapeutics

- Phase I trials from multiple centers
  - University of Washington/Seattle Childrens/Fred Hutch
  - MD Anderson Cancer Center
  - Baylor
  - Memorial Sloan Kettering
  - University of Pennsylvania
- CR rates from 67-90% in high-risk, refractory patients
- On-going phase II trials
- Likely to become an important component in management of patients with relapsed/refractory ALL

Take Home Messages

- Early care decisions in newly diagnosed ALL have an irrevocable impact on patient outcomes
- Prognosis of newly diagnosed ALL can be improved significantly through rigorous risk stratification and use of risk-adapted therapies
- AYA patients should be screened for treatment with pediatric/pediatric-inspired regimens
- Older patients with ALL should have a thorough evaluation of their comorbidities and functional status prior to initiation of aggressive chemotherapeutic treatments
- Immunotherapeutic agents can play a life-saving role in patients with relapsed and refractory ALL
- Immunotherapeutic agents likely to play an increasing role in the care of patients with ALL

Questions?

NCCN Member Institutions