Welcome & Introductions

Dr. Lazarus's slides are available for download at
www.LLS.org/programs

Treating Adult Acute Lymphoblastic Leukemia (ALL)

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LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers
someday is today®

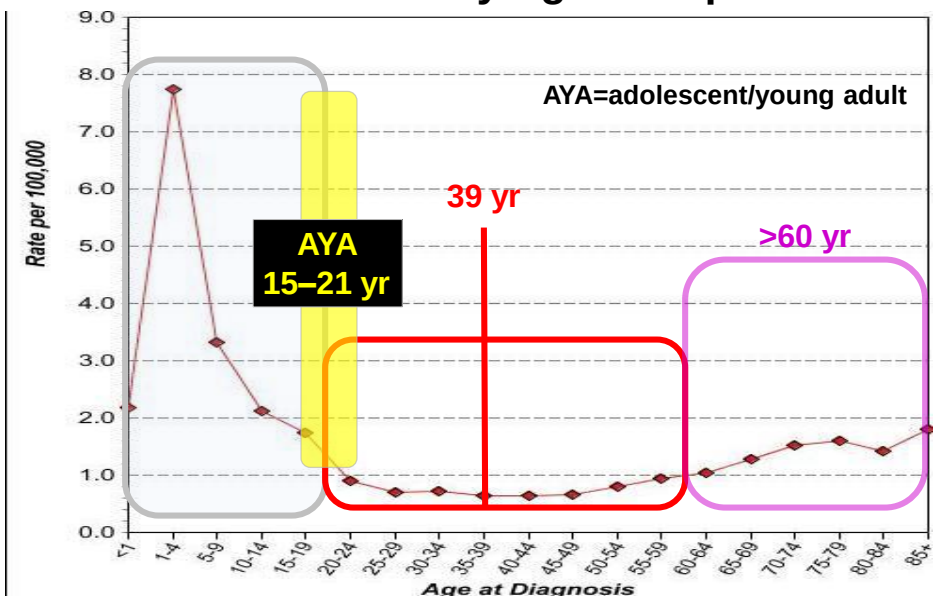
Disclosure

Hillard M. Lazarus, MD, FACP, has affiliations with Amgen, Bristol-Myers Squibb, Jazz Pharmaceuticals (*Speakers' Bureau*); and Jazz Pharmaceuticals (*Consultant*).

PRESENTATION OBJECTIVES
Acute Lymphoblastic Leukemia (ALL)

- **Describe biology and presentation of ALL and sub-types**
- **Review the current treatments and side effects for**
  - **new diagnosis**
  - **relapsed/refractory disease**
- **Discuss new and novel initiatives and side effects**
- **Assess importance of team approach to successful therapy**

ANNUAL INCIDENCE of ALL
SEER Data: By Age Groups



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ACUTE LYMPHOBLASTIC LEUKEMIA
Epidemiology in USA

- 2014: 6,020 new patients and 1,400 deaths
- 60% of ALL are < age 20 yr; childhood peak age 4 yr
- Most common childhood malignancy; 30% all cancers
- Median age onset [adult: ≥20 yr]: 64 yr
- Hispanic > White > Black

Siegel R, et al. CA Cancer J Clin 64: 9-29, 2014

	Complete Remission	Leukemia-Free Survival
Adults	80-90%	35-40%
Children (2-10 yrs)	97%	80%

CH Pui, WE Evans. N Engl J Med 354: 166-78, 2006

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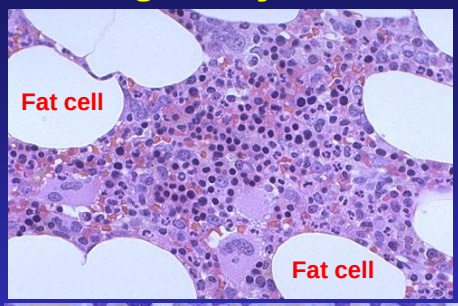
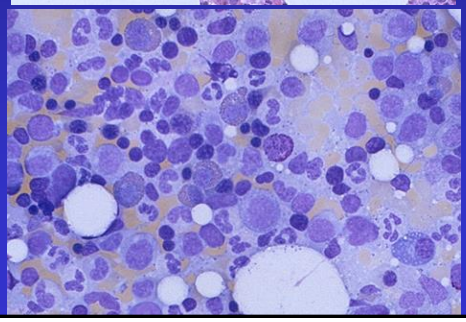
NORMAL HEMATOPOIESIS
Marrow:"Heterogeneity", All Mature Forms





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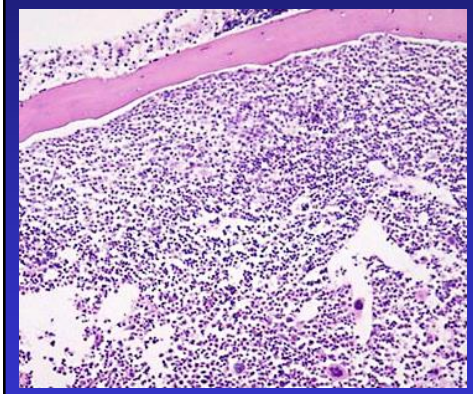
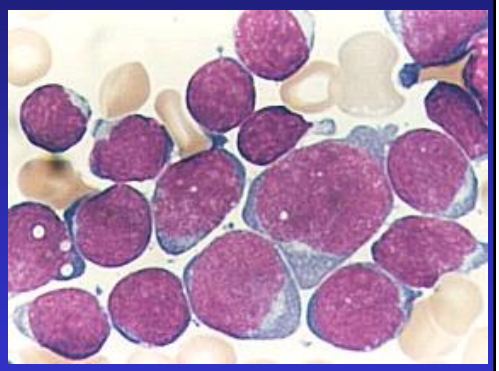
ACUTE LEUKEMIA MARROW
"Monotony", Absence Normal Forms





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ALL CLASSIFICATION
Immunophenotypic

ALL Philadelphia chromosome (Ph) - negative
ALL Philadelphia chromosome (Ph) - positive
ALL Philadelphia chromosome (Ph) - like

	Children	Adults
B-lineage		
Precursor B	**70%**	**55%**
Pre B	**10%**	**15%**
Mature B	**<5%**	**5%**
T-lineage	**15%**	**25%**

- **20%-30% adult ALL aberrant coexpression myeloid markers**
- **2%-5%: True bi-phenotypic acute leukemia**

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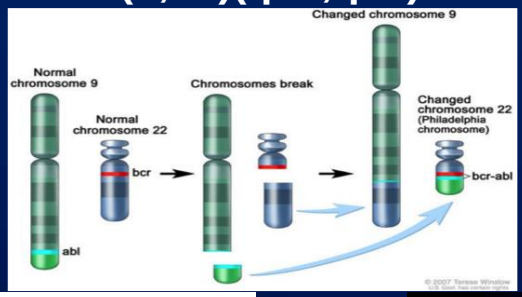
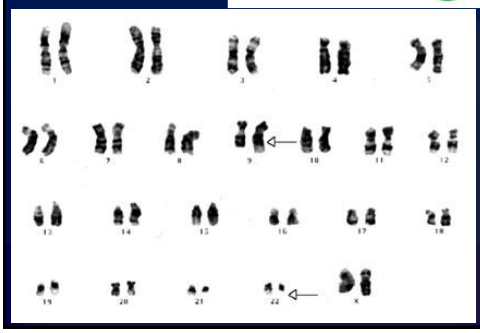
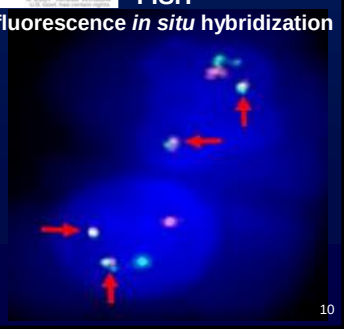
PHILADELPHIA CHROMOSOME
t(9;22)(q34;q11)





FISH
fluorescence *in situ* hybridization



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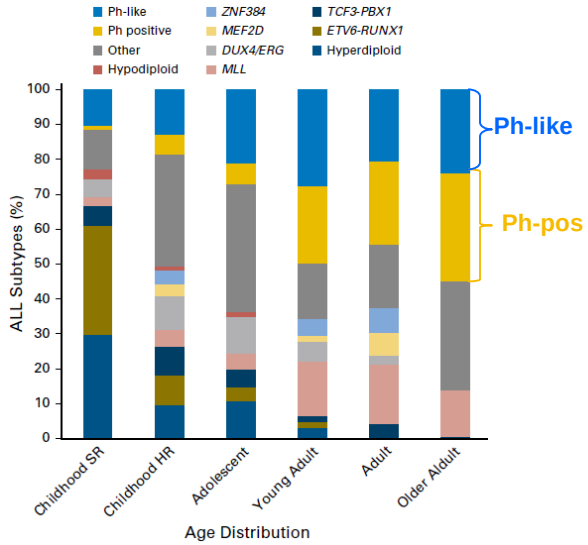
ACUTE LYMPHOBLASTIC LEUKEMIA
Age Distribution Genetic Abnormalities



I Iacobucci, CG Mullighan. J Clin Oncol 35: 2017.

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ALL
Clinical Prognostic Factors: Favorable

Standard risk

- **Decreasing age**
  - **<35 yr**
- **Decreasing WBC**
  - **<30,000/mcL for B-cell lineage**
  - **<100,000/mcL for T-cell lineage**
- **T-cell lineage**
- **Attainment complete remission (CR) within 4 weeks (+/-)**

Myeloid marker co-expression no prognostic impact

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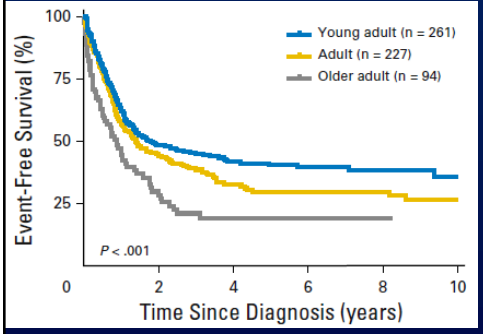
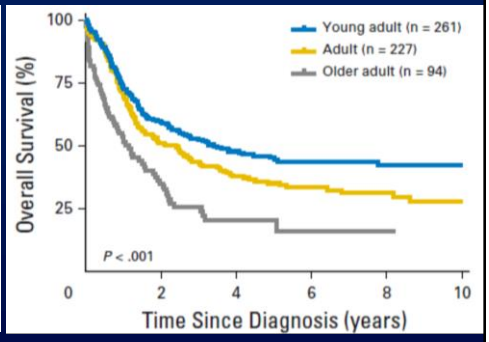
ADULT ACUTE LYMPHOBLASTIC LEUKEMIA
Overall Outcome By Age

Event-Free Survival



Overall Survival



KG Roberts, et al. J Clin Oncol 35: 394-401, 2017.

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ADULT ALL Ph-NEGATIVE
Initial Treatment: Adopted from Peds

- **Induction (plus CNS prophylaxis) as:**
- **Vincristine, prednisone, anthracycline, L-asparagine vs Hyper CVAD**
- **Consolidation and maintenance + CNS prophylaxis**
- **L-asparaginase: enzyme depletion serum L-asparagine**
  - **Activity related to serum L-asparagine depletion**
  - **No myelosuppression**

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ALL Ph NEGATIVE
How Old Too Old For Peds Regimen?

Patients	N	CR rate	Induction death rate	5-year CIF	5-year CITRM		5-year EFS
					w/o SCT censoring	with SCT censoring	
All patients	787	92%	5.5%	30.5%	17%	12%	52%
Patients aged 18-24y	200	98.5%	0.5%	32.7%	7.6%	1.8%	60%
Patients aged 25-34y	172	95.3%	1.7%	29.4%	12.7%	6.4%	58%
Patients aged 35-44y	171	87.7%	7.6%	31.0%	15.0%	11.3%	54%
Patients aged 45-54y	151	89.4%	6.6%	26.7%	22.4%	16.7%	50%
Patients aged 55y+	93	79.6%	18.3%	33.0%	39.7%	38.4%	26%

Huguet, GRAALL. ASH abstract #762 . Blood 2016

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ADULT ACUTE LYMPHOBLASTIC LEUKEMIA
L-Asparaginase: Unique Toxicities

- Hypersensitivity
  - Neutralizing antibodies
- Liver dysfunction
  - Elevation liver enzymes and bilirubin
  - Low serum albumin
- Hemostasis
  - Bleeding: low clotting factors
  - Clotting: low anti-thrombin III, protein S
- Pancreatitis
- Diabetes mellitus
- Neurological (lethargy, somnolence)

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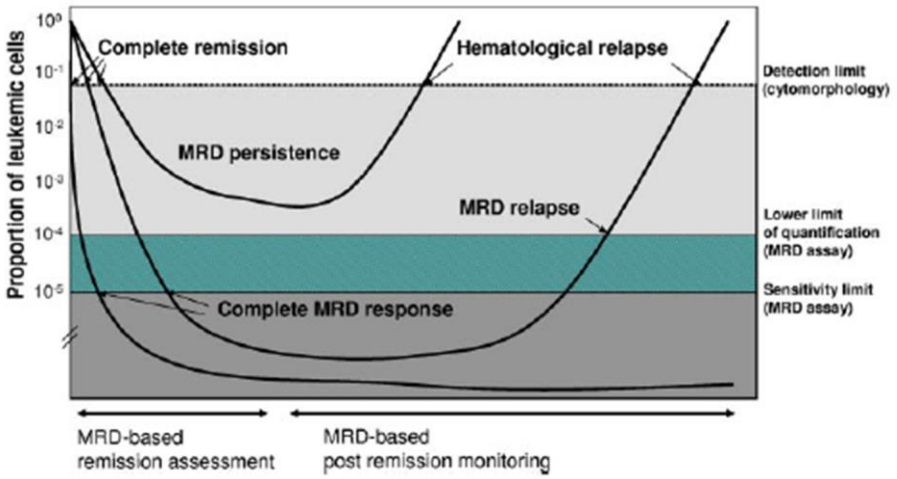
MINIMAL RESIDUAL DISEASE (MRD)
Detection Definitions



M Brüggemann, GMALL: Blood 120:4470-4481, 2012

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MINIMAL RESIDUAL DISEASE (MRD)
Detection Definitions

- Methods
  - Multicolor flow cytometry
  - PCR (polymerase chain reaction)
    - Fusion transcripts
    - Rearranged immunoglobulin & T-cell receptor genes
- Children
  - At CR: MRD <0.01%–excellent outcome
  - After CR: MRD >0.1%–high risk of relapse
- Adults
  - Need to define levels of MRD at different time points that will define prognostic groups

CH Pui, WE Evans. N Engl J Med 354: 166-78, 2006

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MINIMAL RESIDUAL DISEASE (MRD)
Early Detection

196 patients "standard risk"

MRD measurement at multiple time points

Two clear-cut prognostic groups:

Day 11 and 24	Week 16
MRD less than 10^{-4}	MRD ≥10^{-4}
No relapse at 3 yr	94% relapse at 3 yr

M Brüggemann, GMALL: Blood 120:4470-4481, 2012

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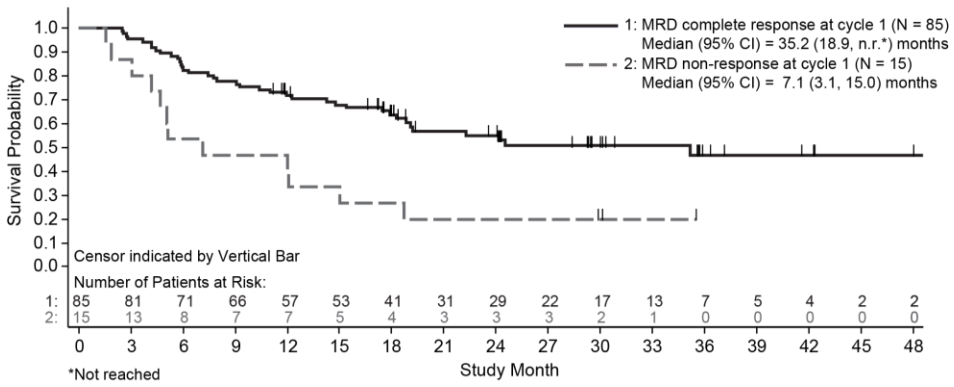
ADULT ALL
Relapse-Free Survival and MRD at Cycle 1



N Gökbuget, et al. ASH abstract #680. Blood 2015

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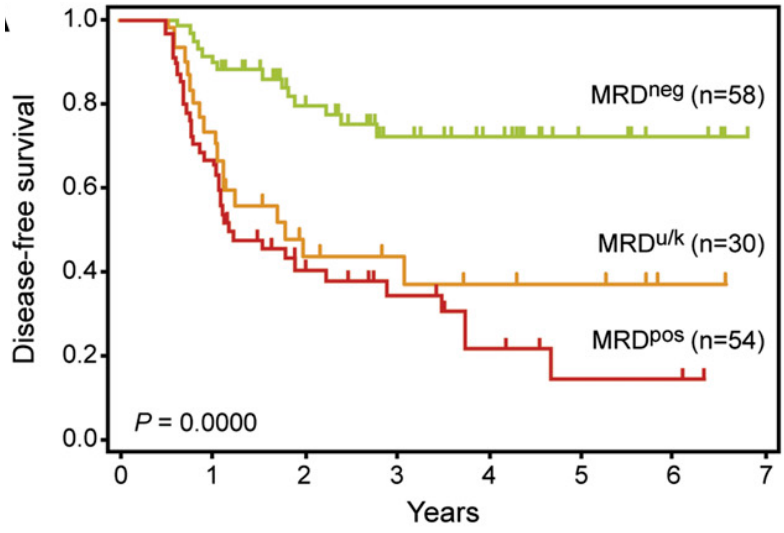
ALL Ph Negative
MRD at 16 & 22 Weeks



JJM van Dongen, et al. Blood 125: 3996-4009, 2015

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ALL Ph NEGATIVE
Recommendations

- **Up to age 35-45 (? 55) yr, enroll on peds intensity regimen**
- **Consider hematopoietic cell transplant (HCT) for high risk**
- **Age 45-55 yr consider HCT ? using reduced-intensity conditioning (RIC)**
- **Age > 55 yr, chemotherapy but consider RIC if fit**

"Could ALL be a setting where more older than younger patients are treated with BMT?"

Tony Goldstone

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Philadelphia Chromosome ALL
Distinguishing Features Ph^+ ALL

- Precursor B cell (PBC) with t(9;22); bcr/abl translocation
- Incidence continuously increases with age
  - rare in children; 50% in ages >55 yr
- Historically very poor outcome
  - No cure with intensive ALL chemotherapy in all ages
  - Cure historically only by HCT but at lower rate than other ALL subtypes
  - Now ? better results with chemotherapy + TKI
- Active clinical investigations:
  - Is chemotherapy still needed?
  - Does allogeneic transplant remain an imperative?

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Philadelphia Chromosome ALL
Tyrosine Kinase Inhibitor (TKI) Use

- For newly diagnosed patients: no clear preference
- Some of best long term data with Imatinib
- Dasatinib often used; better CNS penetrance
- Recent data suggest Nilotinib at least good as Dasatinib
- Ponatinib intriguing but needs to be demonstrate
- Bosutinib retains best toxicity profile, but few data

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Philadelphia Chromosome ALL
Tyrosine Kinase Inhibitor (TKI) Use

- **Until proven otherwise in controlled, prospective trials: TKI-based induction and allogeneic HCT remains standard of care for long-term survival**
- **Some corticosteroid/TKI combinations can give 100% CR rates, but as yet no long-term data to support omitting chemotherapy**
- **National trials soon to be underway**

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ALL Ph-Like
Issues: High-Risk B-Lineage ALL

- **No BCR-ABL1 fusion protein from t(9;22)(q34;q11.2) but gene-expression profile similar**
- **More frequent in males and also Hispanic ethnicity**
- **Difficult diagnosis: need specialized laboratories**
- **Strong association with IKAROS (IKZF1) deletions**
- **Numerous genetic aberrations that share specific activated kinase gene expression pattern: "kinase driven"**
- **Age 21-39 yr - 27.9%**
  40-59 yr - 20.4%
  60-86 yr - 24.0%
- **High expression (~40-50%) of cytokine receptor-like factor 2 (CRLF2) and concomitant JAK1 or JAK2 mutation (>50% among patients with CRLF2 rearrangement)**

Y Ofran, S Izraeli. Blood Reviews 2016
KG Roberts, et al. J Clin Oncol 35: 394-401, 2017

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ALL Ph-Like
Issues: High-Risk B-Lineage ALL (con't)

- Most attain morphologic CR; but only 35% MRD neg
- Most important: eradication of MRD as early as possible
- Approach with targeted therapies:
- Add TKI (dasatinib) to Ph-like ALL with abnl ABL activation
- Add JAK inhibitors (ruxolitinib) to JAK-STAT derived ALL
- JAK inhibition alone (momelotinib & ruxolitinib) not good strategy:
  - Preclinical mouse data demonstrated clonal heterogeneity, outgrowth of resistant clones
- Mostly small studies; definitive studies awaited
- Frontline trials combining targeted kinase inhibitor + chemotherapy have been initiated

EMP Steeghs, et al. ASH 2016 Abstract #583. Blood 2016

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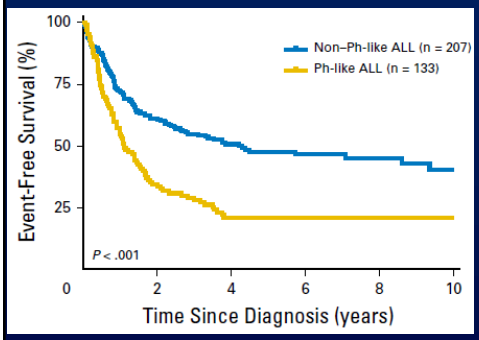
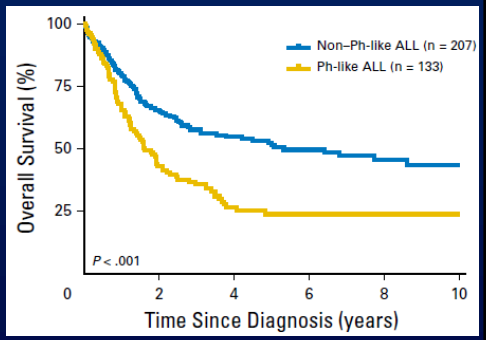
ADULT ACUTE LYMPHOBLASTIC LEUKEMIA
Overall Outcome By Ph-Like Status

Event-Free Survival



Overall Survival



KG Roberts, et al. J Clin Oncol 35: 394-401, 2017

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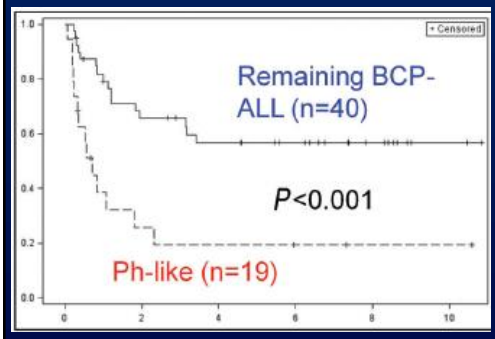
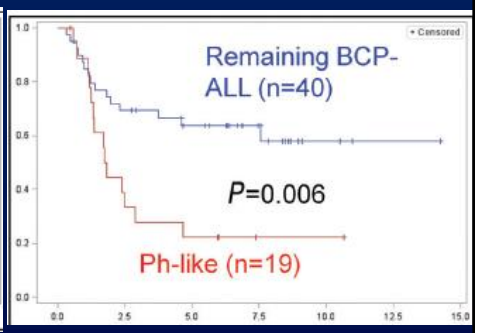
ADULT ALL
Ph-like ALL vs B-Cell Precursor (BCP)

Disease-Free Survival %



Overall Survival %



T Herold, et al. Haematologica 102: 130-138 ,2017

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RECURRENT/REFRACTORY ALL
New Agents: Monoclonal Antibodies

Surface antigen	ALL subtype	Antigen Expression for Targeted Therapy	Monoclonal Antibody
CD20	B-precursor	40%	Rituximab
CD22	B-precursor	95%	Epratuzumab Moxetumomab Pasudotox (HA22) Inotuzumab Ozogamicin
CD52	B-precursor T-precursor	80% 80%	Alemtuzumab
CD19	B-precursor	95-100% high density	Blinatumomab Bispecific (BiTE)

D Hoelzer. Curr Opin Oncol 25: 701-6, 2013

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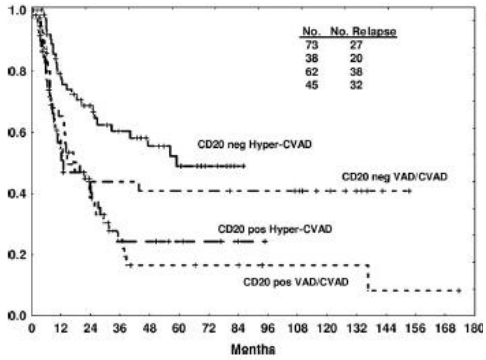
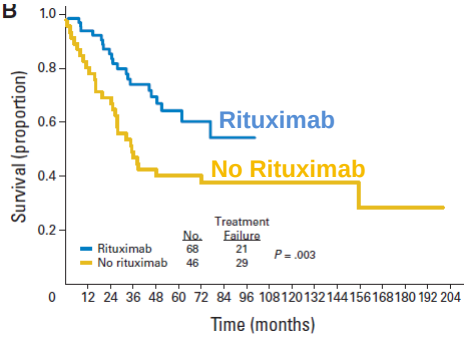
De Novo ALL Treatment with Hyper-CVAD CD20+ ALL With/Without Rituximab

Duration CR: CD20+ adverse prognosis



DA Thomas, et al. Blood 113: 6330, 2009

Eligible if CD20 > 20%



DA Thomas, et al. JCO: 28: 3880-9, 2010

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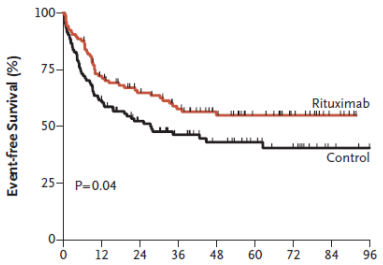
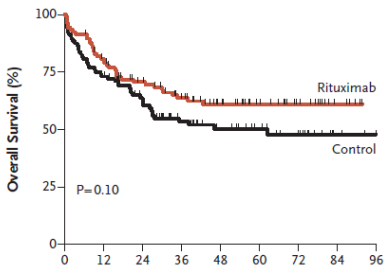
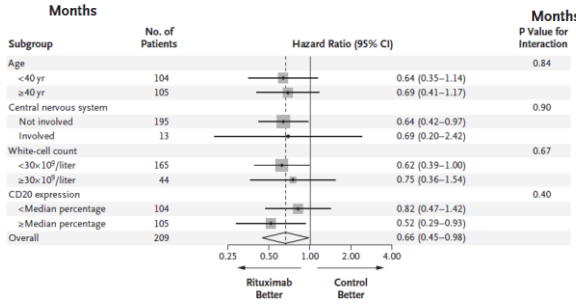
De Novo ALL Treatment with Hyper-CVAD CD20+ ALL With/Without Rituximab







S Maury, GRAALL. N Engl J Med: 375: 1044-1053, 2016

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RELAPSED/REFRACTORY ALL
Inotuzumab Anti-CD22 Monoclonal Antibody

CD22 expressed on >90% B cell lymphoid malignant cells

CD22 internalized upon antibody binding; not shed into the extracellular environment: conjugated to calicheamicin

Phase 3 inotuzumab vs standard intensive therapy (N=326)

CR: Inotuzumab ozogamicin (Ino) 81% vs chemotherapy 30%

MRD <0.01% marrow blasts: Ino 78% vs chemo 28%

CR median duration: Ino 4.6 mo vs chemo 3.1 mo

PFS: Ino 5 mo vs chemo 1.8 mo; OS Ino 7.7 mo vs chemo 6.7

Hepatic veno-occlusive disease: Ino 11% vs chemo 1%

HM Kantarjian, et al. N Engl J Med 375: 740-53, 2016.

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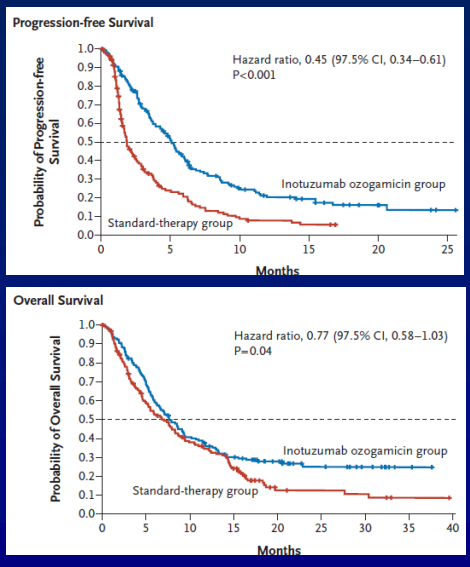
RELAPSED/REFRACTORY ALL
Inotuzumab Anti-CD22 Monoclonal Antibody

2C



HM Kantarjian, et al. N Engl J Med 375: 740-53, 2016.

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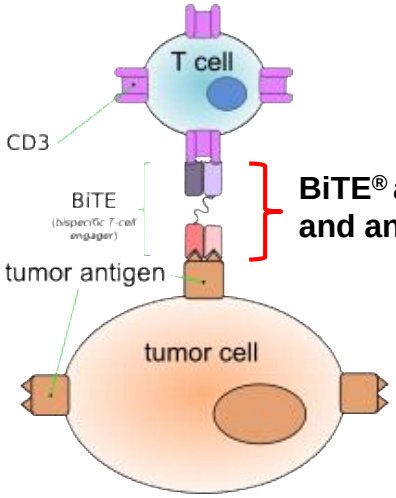
Mode of Action of Blinatumomab Bispecific T-Cell Engager (BiTE®) Antibody



Directs cytotoxic T-cells to CD19 expressing cancer cells

R Bargou, et al. Science 321 (5891): 974-7, 2008

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ADULT ALL B-CELL PRECURSOR Blinatumumab for MRD Positive Disease

- **Adults ≥18 years in morphologic CR (<5% blasts in bone marrow) after ≥3 chemotherapy but MRD ≥10^{-3} were eligible**
- **Blinatumomab 15 µg/m²/d cont IV x 4 wk: 4 cycles or HCT**
- **N=116; median age 45 (18-76) yr; 1/3 >CR2**
- **80% complete MRD response after 1-2 cycles**
- **Monitor for potential toxicities:**
- **Cytokine release syndrome: flu-like, with fever and myalgia**
- **More severe: vascular leak, hypotension, pulmonary edema, coagulopathy, multi-organ system failure**
- **Neutropenia, lymphopenia, hypogammaglobulinemia**
- **CNS dysfunction**

N Gökbuget, et al. ASH abstract #680. Blood 2015

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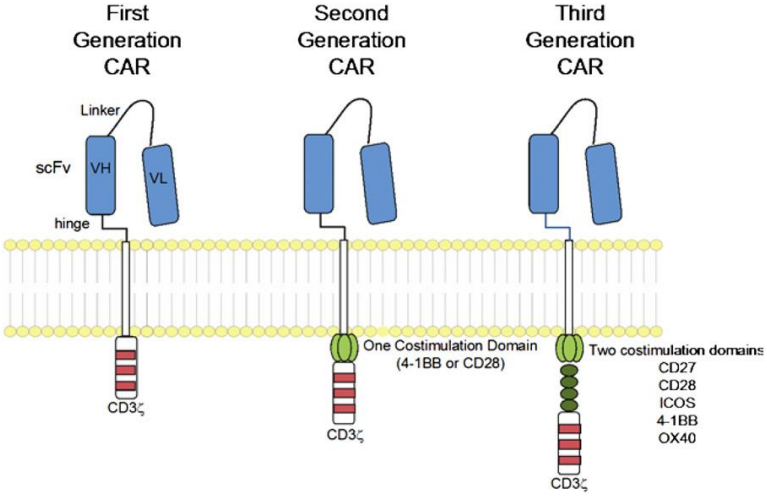
CAR-T CELLS: ANATOMY
"Living Drug" Cellular Therapy



Antigen recognition: extracellular heavy or light chain (scFv)
Intracellular signaling: CD3z of T-cell receptor + co-stimulatory domains
MV Maus, et al. Blood 123: 2625-35, 2014.

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Why CAR-T Cells?

- **Best of both worlds of the immune system**
  - **Modify T cell to have anti-B cell specificity**
  - **T cell cytotoxicity without presentation**
- **Form of Adoptive T Cell Therapy**
- **Synthetically engineered receptors designed to overcome immune tolerance / tumor evasion**
- **Targets surface molecules in native confirmation**
- **Engage target independent of antigen presenting cell (APC) and MHC complex**

- **Trials conducted in relapsed/refractory patients**

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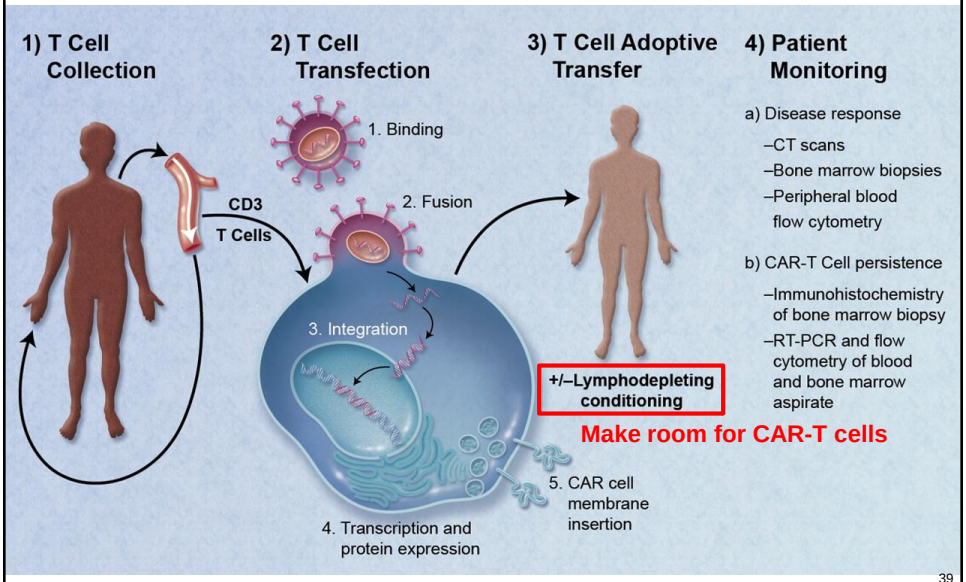
CHIMERIC ANTIGEN T-CELL THERAPY
Production, Infusion, Monitoring



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CAR-T CELL THERAPY
Complications

Cytokine Release Syndrome (CRS)

- **Typically within 5 days of infusion and CRP best predictor**
- **Due to exponential T cell proliferation**
- **Leads to out-pouring IL-2, IL-6, IFN**
- **Get macrophage activation syndrome, shock, organ failure**
- **Stress cardiomyopathy: Takotsubo cardiomyopathy**
- **Treat with anti-IL-6 monoclonal antibodies (Tocilizumab) and dexamethasone**
- **Recent data: Efficacy, engraftment & persistence CAR-T not impacted by when given early after onset of CRS**

SL Maude, et al. Blood 125: 4017-23, 2015.
DW Lee, et al. Blood 124: 188–195, 2014.
R Gardner, et al. ASH abstract #587. Blood 2016

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CAR T CELL THERAPY
Complications (con't)

- Allergy/anaphylaxis
  - Immune response to mouse- or recombinant- proteins
- B Cell aplasia
  - No circulating B cells by flow cytometry; persists to 1 yr
  - Immunoglobulin replacement: keep serum Ig > 500
- Neurologic deficits: delirium, aphasia, seizures, encephalopathy
  - Unclear pathogenesis and self-limited
  - No long term complications
  - CAR-T cells in CSF in all patients

SL Maude, et al. Blood 125: 4017-23, 2015 and N Engl J Med 371: 1507-17, 2014
DW Lee, et al. Blood 124: 188–195, 2014.

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RELAPSED B-ALL
Anti-CD19 CAR T Cell Therapy

Reference	T cell Engager	Population	Response
Maude, et al. NEJM 2014	Anti-CD19 CART 4-1BB	N=30 Peds & Adults	CR=90%
Davila, et al. Sci Tr Med 2014	Anti-CD19 CART CD28	N=16 Adults	CR=88%
Lee, et al. Lancet 2015	Anti-CD19 CART CD28	N=21 Peds & AYA	CR=67%
Turtle, et al. J Clin Invest 2016	Anti-CD19 CART 4-1BB	N=30 Adults	CR=93%

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ALL CTL019 CAR-T THERAPY
Broader Access: ELIANA Study

First global multi-center CAR-T cell (registration) trial

Industrial cell processing of CTL019 therapy: US mtg and global supply

Adolescent-young adult relapsed/refractory ALL: BM ≥5% lymphoblasts

Exclusions: Isolated extra-medullary disease relapse; prior anti-CD19 or anti-CD3 therapy; prior gene therapy

CR/CRi in 82%; durable CRs; all CRs were MRD-negative

Most eligible pts got CTL019 ~ 94% success central mfg

Manageable toxicities; no deaths due to cytokine release syndrome (CRS)

SA Grupp, et al. ASH abstract #221. Blood 2016

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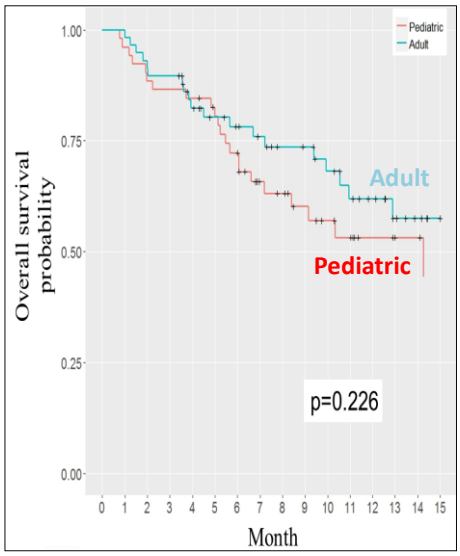
ALL LV-4SCAR19 CAR-T THERAPY
Broader Access: Chinese Study

LV-4SCAR19: 4th generation CAR

Chinese multisite study; 30 centers

110 pts (58 kids; 52 adults)

CR 87%; median survival 222d



L-J Chang, et al. ASH abstract #587. Blood 2016

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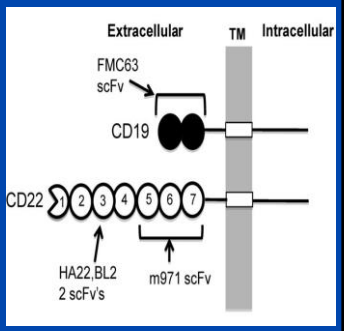
ACUTE LYMPHOBLASTIC LEUKEMIA
Anti-CD22 CAR T cells

- Rationale: anti-CD19 CAR highly effective but CD19- relapses occur
- CD22: B-lineage restricted antigen; promising target for mmunotherapy
  - Example: Inotuzumab ozogamicin
- Anti-CD22 CAR-T
  - Utilizes m971 anti-CD22 scFv
  - 4-1BB/CD3-zeta signaling



W Haso, et al. Blood 121: 1165-1174, 2013.

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ACUTE LYMPHOBLASTIC LEUKEMIA
Healthcare Team Issues

- Open discussions throughout
- Immediate, short-term
  - Side effect prevention and management
  - Vigorous supportive care: medical and emotional
  - Anti-emetics, antibiotics, transfusions, electrolytes
  - Physical therapy, exercise
- Intermediate- and long-term
  - Transplantation
  - Second malignancy, osteoporosis, endocrine & sexual dysfunction, fertility, cognitive dysfunction, cardiovascular disease

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ACUTE LYMPHOBLASTIC LEUKEMIA
The Future

- MRD evaluation standard of care for all ALL
- Fewer allografts in younger adults, more in older
- Blinatumomab incorporation into 1st line therapy for both Ph-negative and Ph-positive
- Blinatumomab use in relapse as bridge to HCT
- Using TKI and blinatumomab, less Ph^+ pts referred for allogeneic HCT
- Increased use CAR-T, in tandem with reduced procedural-morbidity – confined mostly to relapsed disease or very high risk

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Treating Adult Acute Lymphoblastic Leukemia (ALL)

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

someday is today®

Q&A Session

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’ve asked your question, the operator will transfer you back into the audience line.

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Treating Adult Acute Lymphoblastic Leukemia (ALL)

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers
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SUPPORT RESOURCES

- **Online chats:** Online moderated chat forums: **www.LLS.org/chat**
- **What to ask:** Questions to ask your treatment team: **www.LLS.org/whattoask**
- **Free education materials: www.LLS.org/booklets**
- **Past ALL education programs: www.LLS.org/programs**
- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - **EMAIL: infocenter@LLS.org**
  - **TOLL-FREE PHONE: (800) 955- 4572**

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