Acute Lymphoblastic Leukemia in Adults

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11th Annual SCCA Comprehensive Heme/Onc Review Course

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Outline & Objectives

- Epidemiology and Classification
- Risk Stratification
- Front-line Treatment and Role of HCT
- Relapsed/Refractory Disease

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Epidemiology and Classification

Leukemia in the U.S., 2020

	New Cases	Deaths
ALL	**6,150**	**1,520**
CLL	21,040	4,060
AML	19,940	11,180
CML	8,450	1,130
Other	4,950	5,210
Total	60,530	23,100

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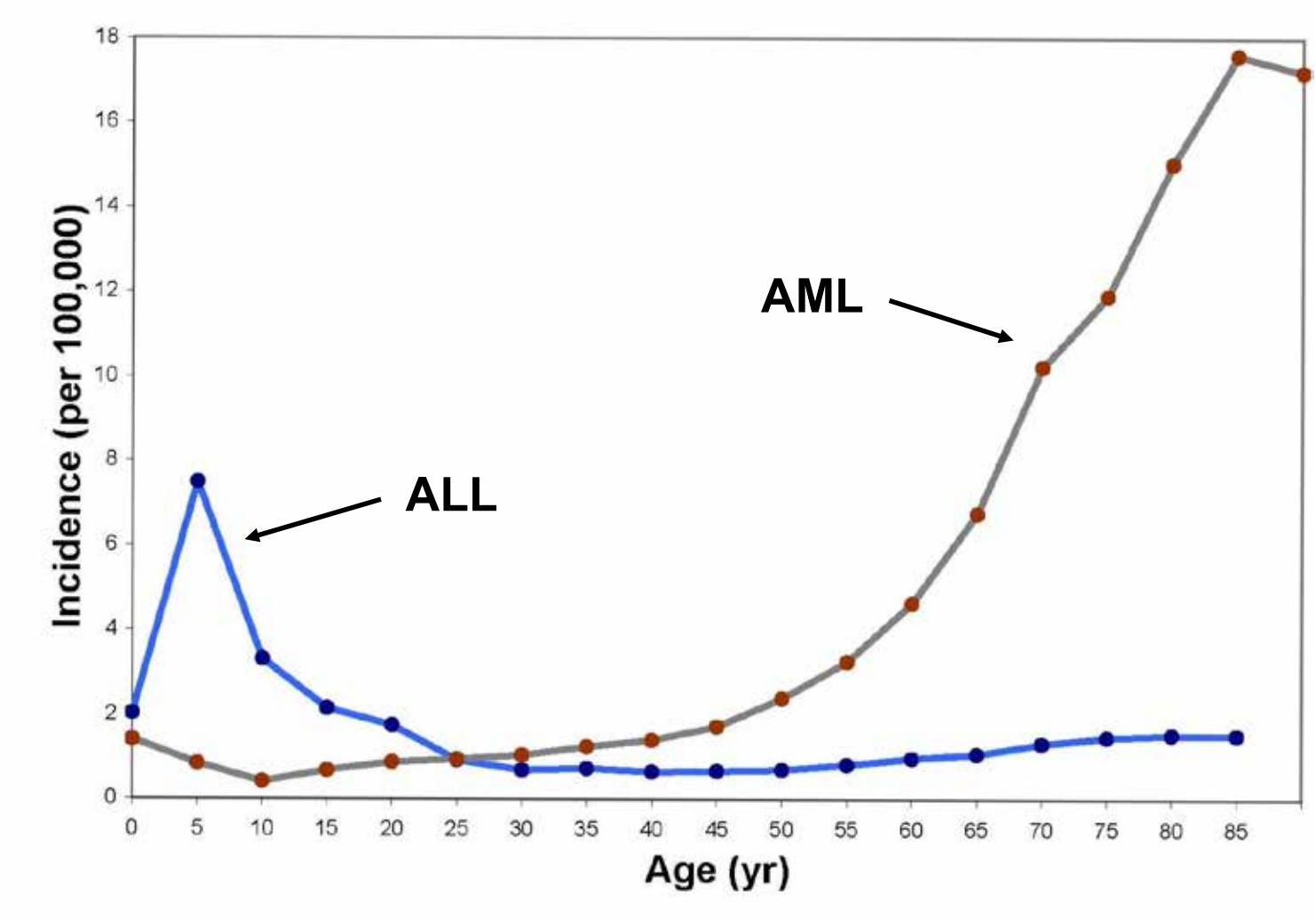
Siegel, *et al*. *CA Cancer J Clin* 2020;70:7-30.

Acute Leukemia Incidence by Age



Adult ALL: Lineage Assignment

- B-lineage:
  - ***Strong*** CD19 with ≥ ***1*** of the following also strong: CD79a, cytoplasmic CD22, or CD10

  OR

  - ***Weak*** CD19 with ≥ ***2*** of the following also strong: CD79a, cytoplasmic CD22, or CD10
- T-lineage:
  - Strong cytoplasmic CD3 (with antibodies to CD3 ε chain)

  OR

  - Strong surface CD3

Arber, et al. *Blood*. 2016;127:2391-2405.

Risk Stratification

Classical Risk Factors at Presentation

- Age > 35

- High WBC
  - B-lineage: >30,000
  - T-lineage: >100,000

Major Cytogenetic Categories in Adult ALL

t(9;22) (Ph+)	19%
Ph-	81%
Favorable	
High hyperdiploidy	10%
Unfavorable	
t(4;11)	7%
-7	6%
+8	10%
Low hypodiploidy/near triploidy	4%
Complex	5%
iAMP21	Rare

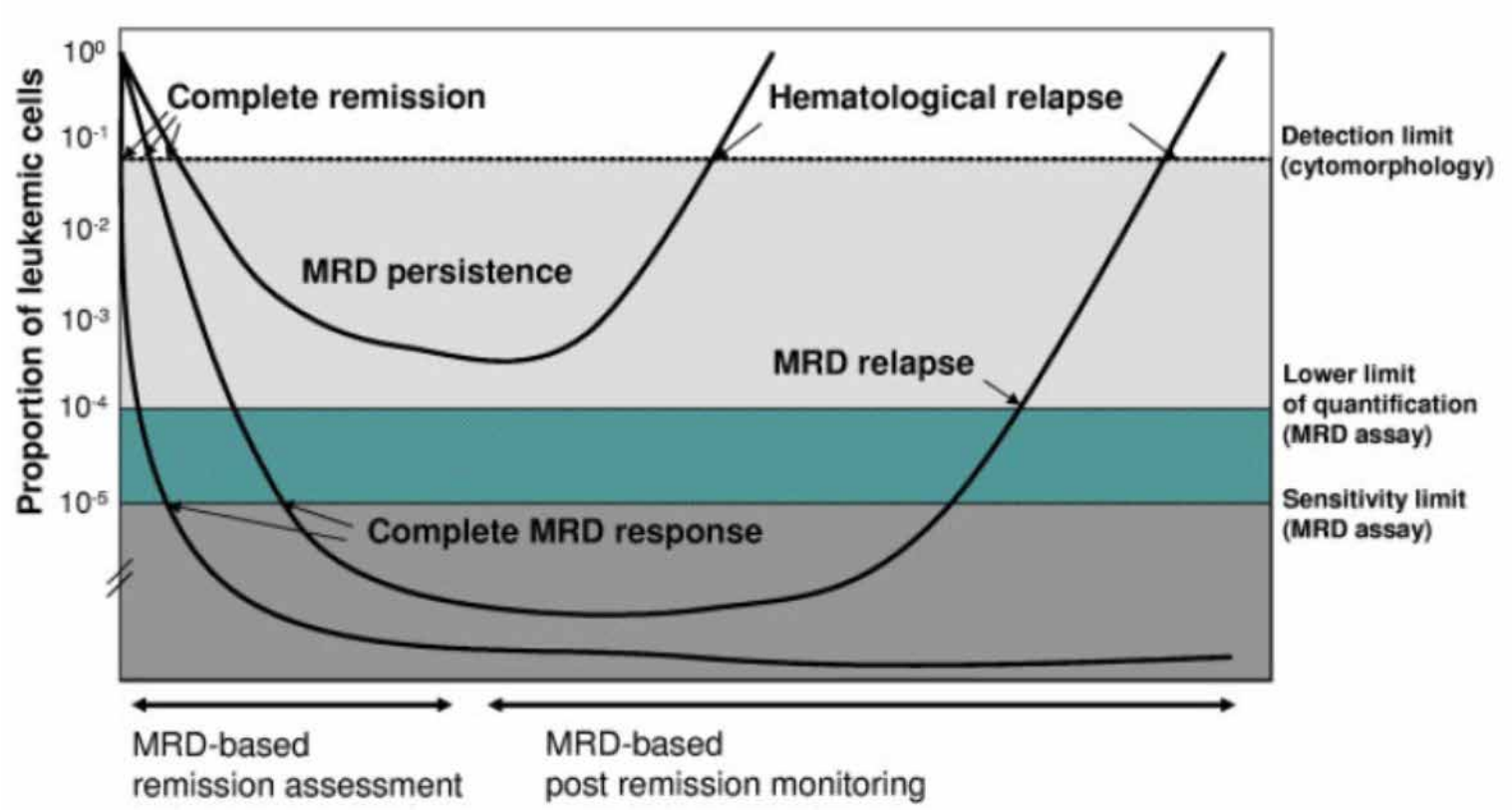
Wetzler, *et al*. *Blood*. 1999;11:3983-39
Moorman, *et al*. *Blood*. 2007;109:3189-97

Early T-Cell Precursor (ETP)-ALL

- Distinct immunophenotype
  - Cytoplasmic CD3
  - Lack CD1a and CD8
  - Weak or absent CD5
  - Often co-express stem cell or myeloid markers → "subset" of biphenotypic leukemia
- Felt to have a relatively poor prognosis

Mullighan. *ASH Educational Program*. 2012:389-96.

Conceptualization of MRD



Bruggemann, *et al. Blood*. 2012;107:4470-81.

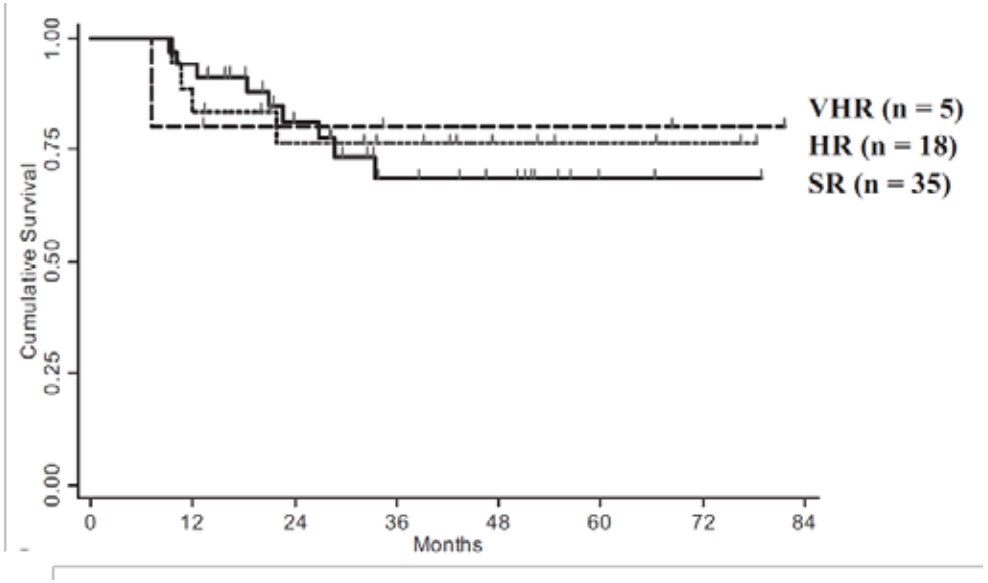
Measurement of MRD in ALL

Target	Method	% Pts.	Sensitivity	Pros	Cons
IG and TCR gene rearrangements	RQ-PCR	~90%	0.01-0.001	Sensitive	Laborious
Fusion transcripts (e.g., BCR-ABL1)	RQ-PCR	~40%	0.01-0.001	Sensitive	Applicability
Leukemia immunophenotype	MFC	~95%	0.01	Rapidly Applicable	User expertise
IG and TCR gene rearrangements	NGS/HTS	Unk	0.00001	Most Sensitive	Role still unclear

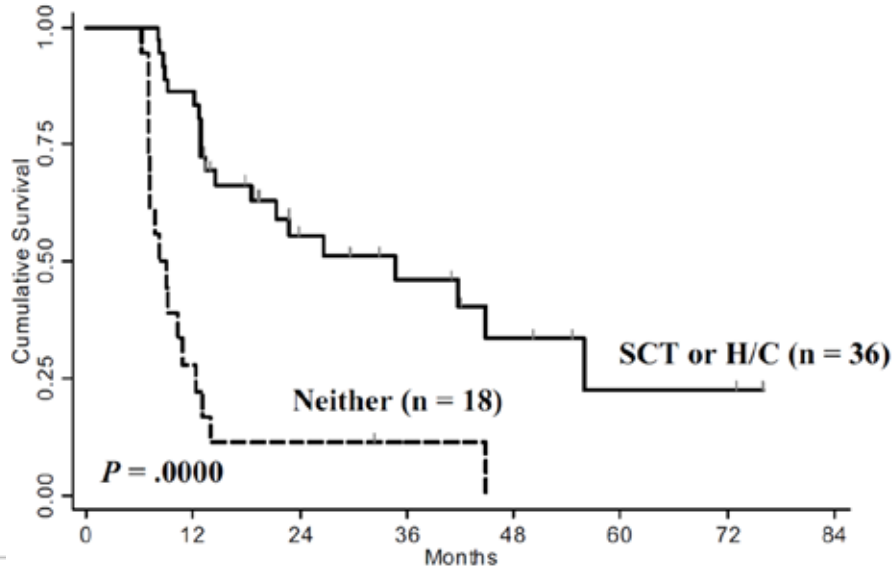
Modified from Bruggemann, *et al. Blood*. 2012;107:4470-81.

NILG-ALL 09/00: Importance of MRD Status

DFS Among MRD^{neg} Patients



DFS Among MRD^{pos} Patients



In a multivariate analysis of patients with complete data (n = 93), only two factors were predictive of relapse:

- MRD^{pos}
- High WBC

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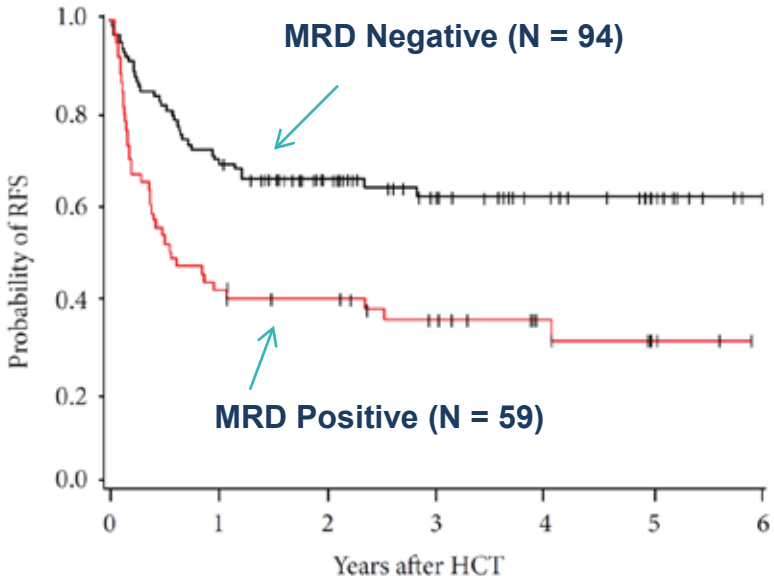
Bassan, *et al*. *Blood*. 2009;113:4153-62.

MRD Predicts Outcome after Allo HCT: The Fred Hutch Experience

Myeloablative HCT



Bar, *et al. Leuk Res Treatment*. Epub 2014 Mar 23.

Non-Myeloablative HCT

Outcomes are anecdotally abysmal if MRD ≥ 0.01%

Ram, et al. Haematologica. 2011;96:1113-20.

Risk Stratification in ALL: Summary

Past

- Age
- WBC at Diagnosis
- Cytogenetics

Present

- MRD
- WBC at Diagnosis
- Cytogenetics
- (Molecular sub-classification)

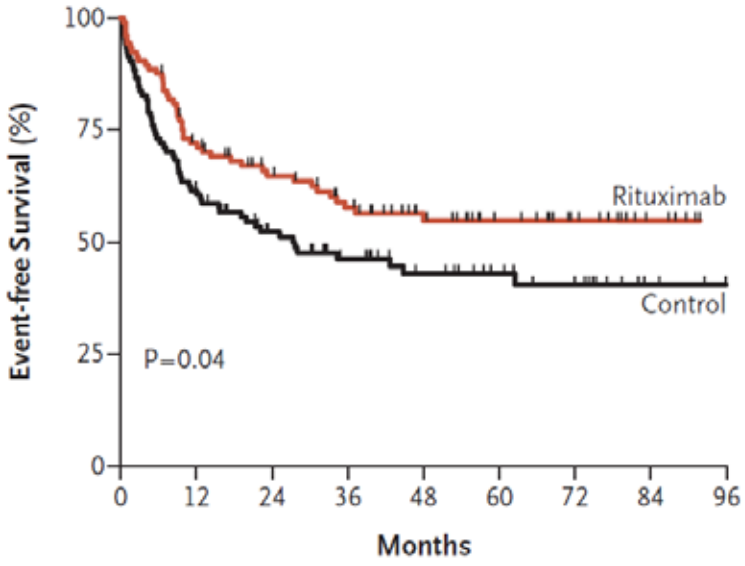
Front-Line Therapy

Contemporary Treatment

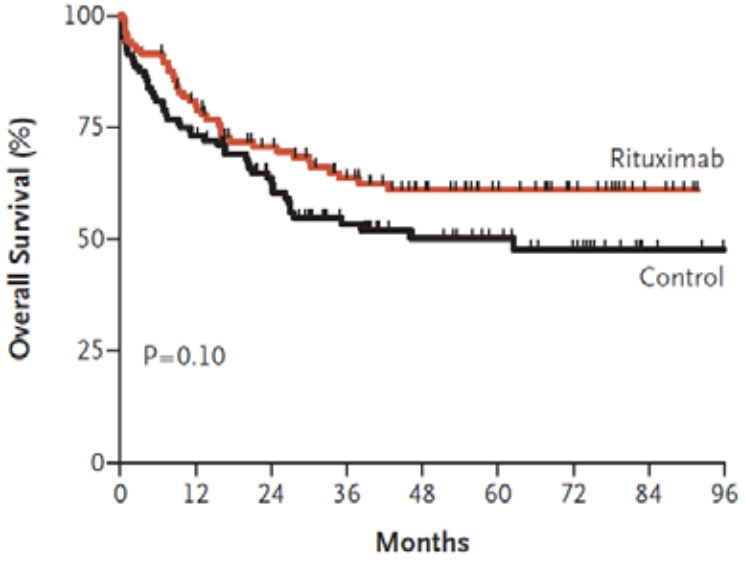
Group	N	Median age (range)	Ph+ (%)	T-cell (%)	CR	DFS at 3-9 yrs (%)
UKALL XII/ ECOG2993	1826	31 (15-65)	19	20	91	38
CALGB 19802	163	41 (16–82)	18	–	78	35
GIMEMA ALL 0288	778	27.5 (12–60)	22	22	82	29
GMALL 05/03	1163	35 (15–65)	24	24	83	35
GOELAMS 02	198	33 (15–59)	22	21	86	41
Hyper-CVAD	288	40 (15–92)	17	13	92	38
JALSG-ALL93	263	31 (15–59)	22	21	78	30
LALA-94	922	33 (15–55)	23	26	84	36

Pui & Evans. *New Engl J Med*. 2006;354:166-78.

Rituximab Improves Outcomes in CD20+ B-ALL: GRAALL-2005/R



No. at Risk									
Control	104	63	45	34	25	19	14	6	3
Rituximab	105	73	58	47	35	26	18	10	5



No. at Risk									
Control	104	75	57	38	28	22	16	6	3
Rituximab	105	82	64	51	39	28	19	10	5

- CD20 positivity = expression on ≥ 20% of blasts
- More patients in R group received HCT (34% vs 20%)
- Adjust for HCT in CR1 → R group had significantly better EFS *and* OS

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Maury, *et al. New Engl J Med.* 2016;375:1044-53.

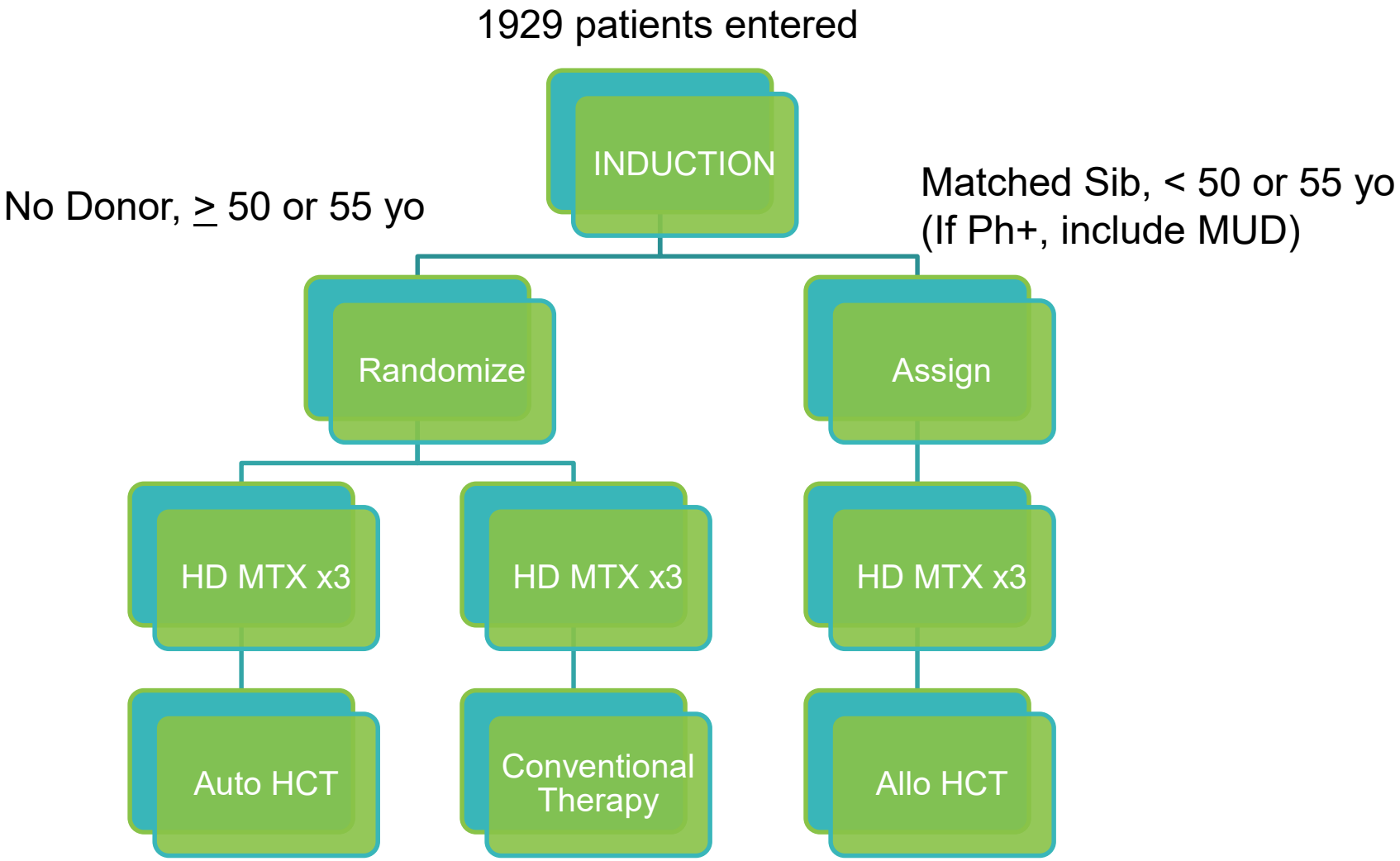
Adult ALL: CNS Prophylaxis

- Without prophylaxis – risk of CNS relapse is 35%
- With prophylaxis – risk is 10%
- Risk factors include
  - ↑ WBC
  - ↑ LDH
  - T-cell or mature B-cell phenotype (i.e., Burkitt)
- ? Need for cranial XRT if IT MTX is used

Post-Remission Therapy of Adult ALL

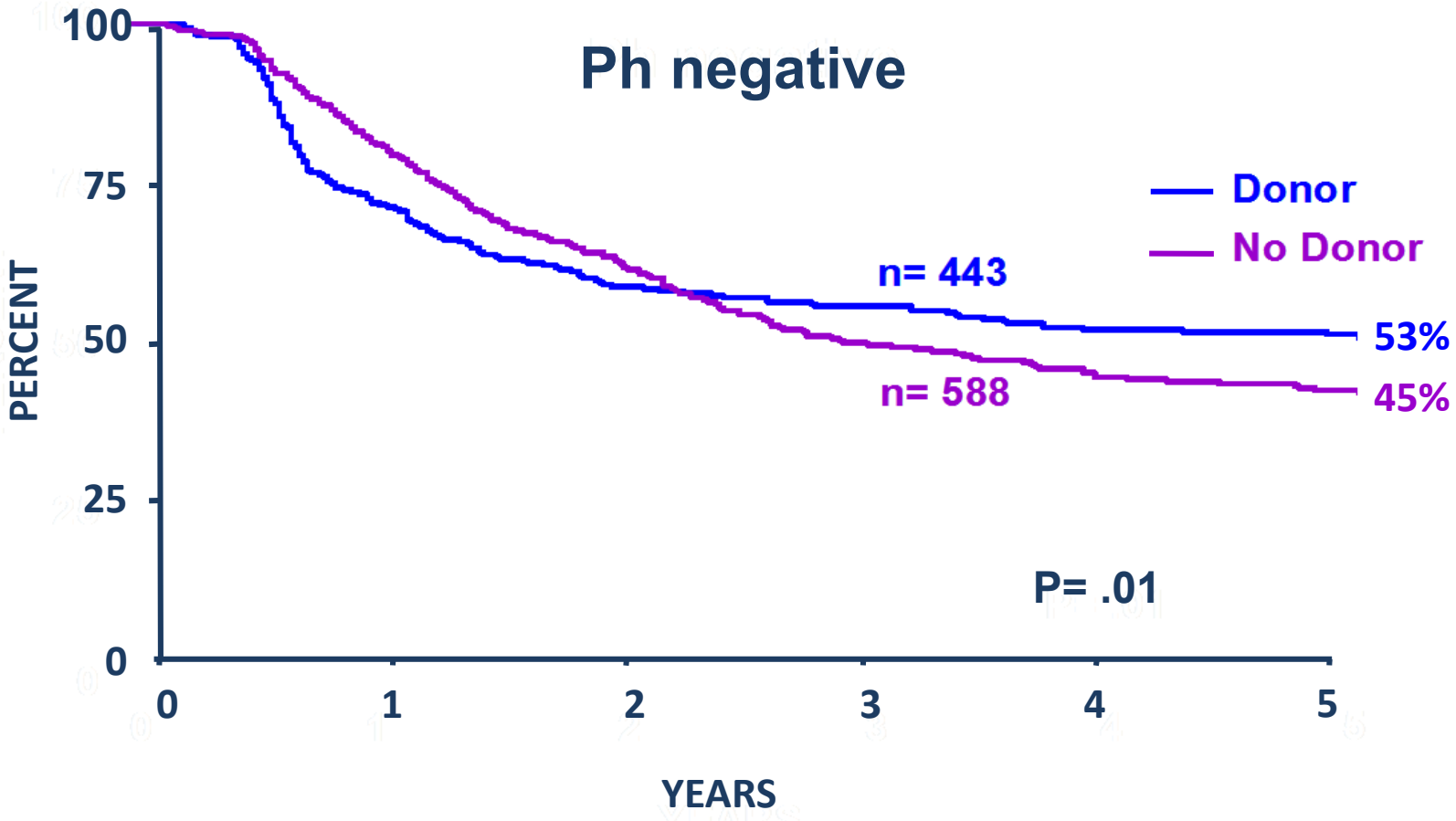
- Intensive multi-drug consolidation followed by maintenance chemotherapy
- Allogeneic transplantation

MRC UKALL XII/ECOG2993



Rowe, *et al. Blood*. 2005;106:3760-7.
Goldstone, *et al. Blood*. 2008;111:1827-33.

UKALL XII / ECOG2993: Overall Survival



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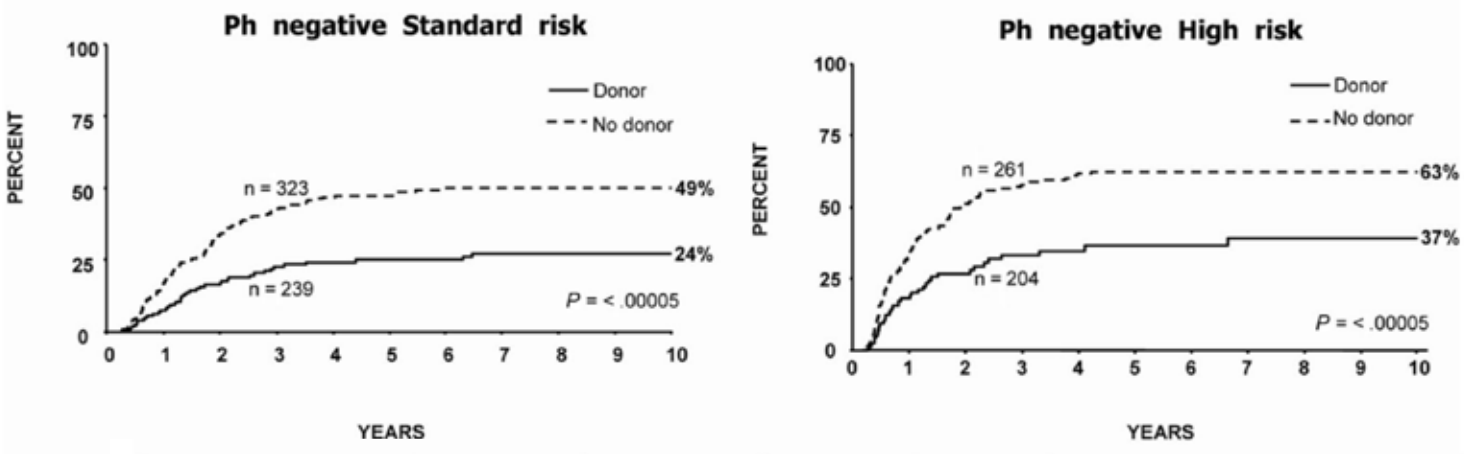
Goldstone, *et al*. *Blood*. 2008;111:1827-33.

UKALL XII/ECOG2993: Less Relapse but More NRM with Allo

Less Relapse



More NRM

	3 months	6 months	1 year	2 years
High Risk				
Donor	1.5	7.3	26.0	35.8
No Donor	1.2	2.0	10.3	13.6
Standard Risk				
Donor	0.4	3.4	17.6	19.5
No Donor	0.3	1.2	5.3	6.9

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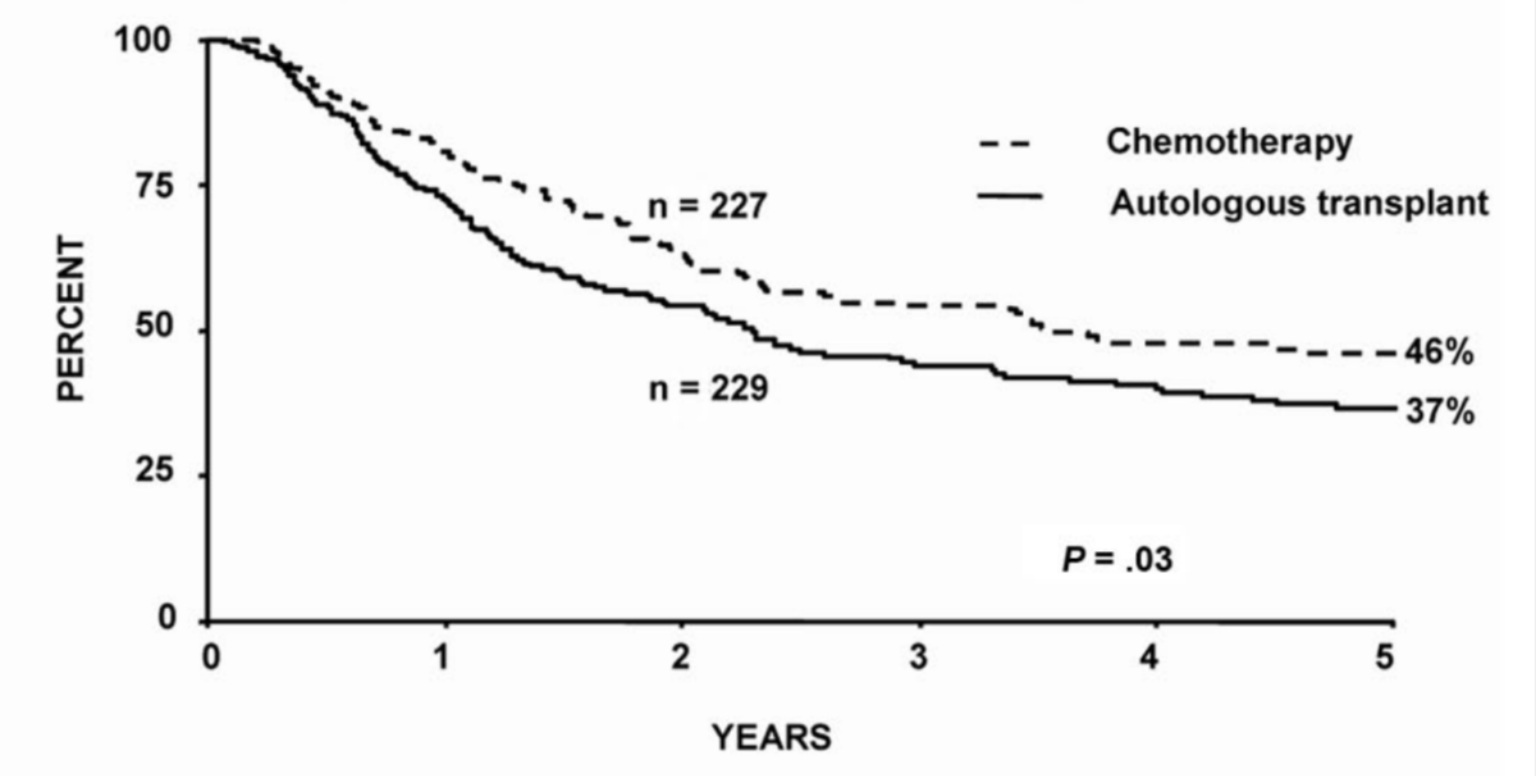
Goldstone, *et al*. *Blood*. 2008;111:1827-33.

UKALL XII/ECOG2993: Auto x 1 vs POMP x 2 years



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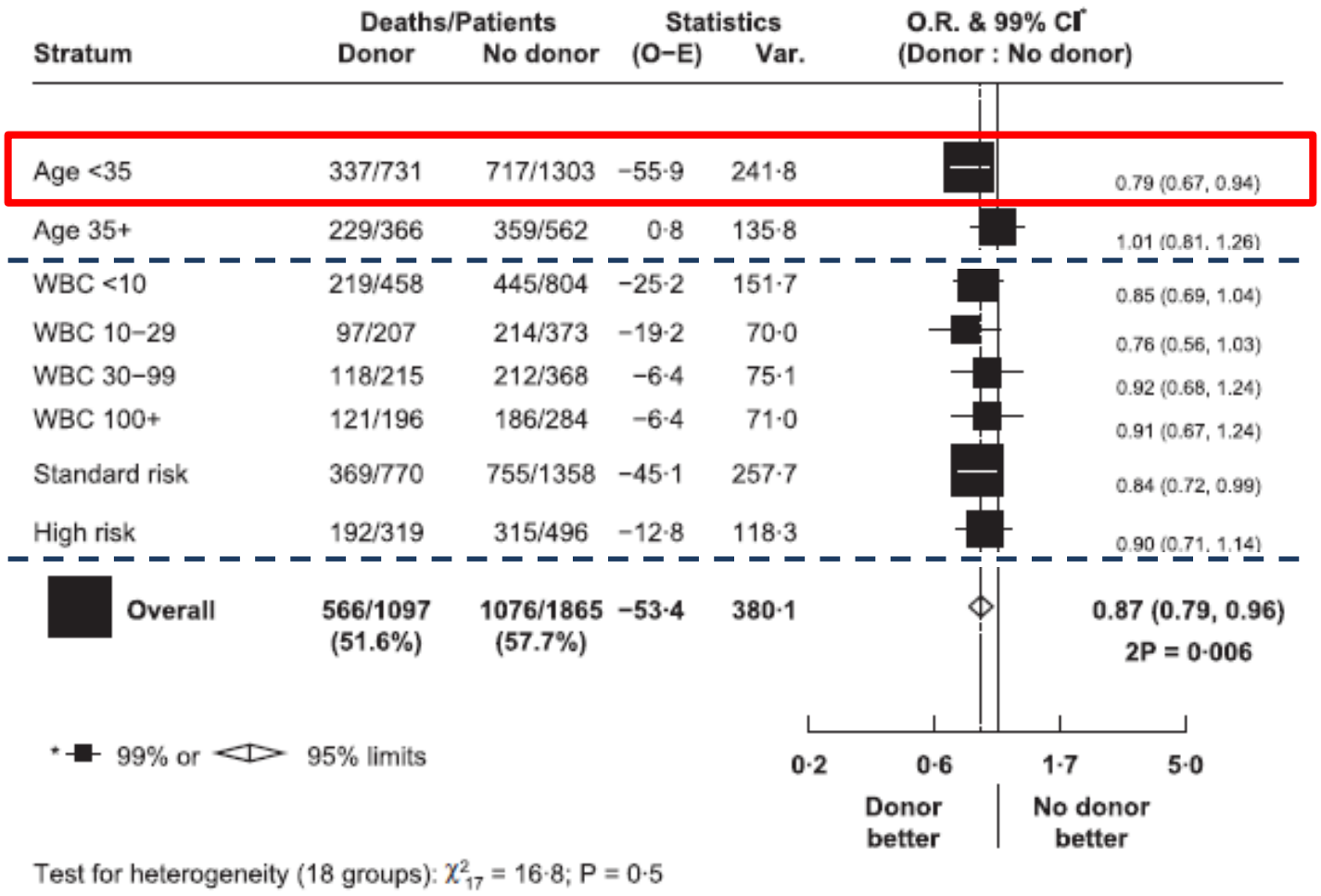
Goldstone, *et al*. *Blood*. 2008;111:1827-33.

Donor vs No-Donor Meta-Analysis: Ph- ALL in CR1



Only sub-group with improved mortality with allogeneic HCT = Age < 35

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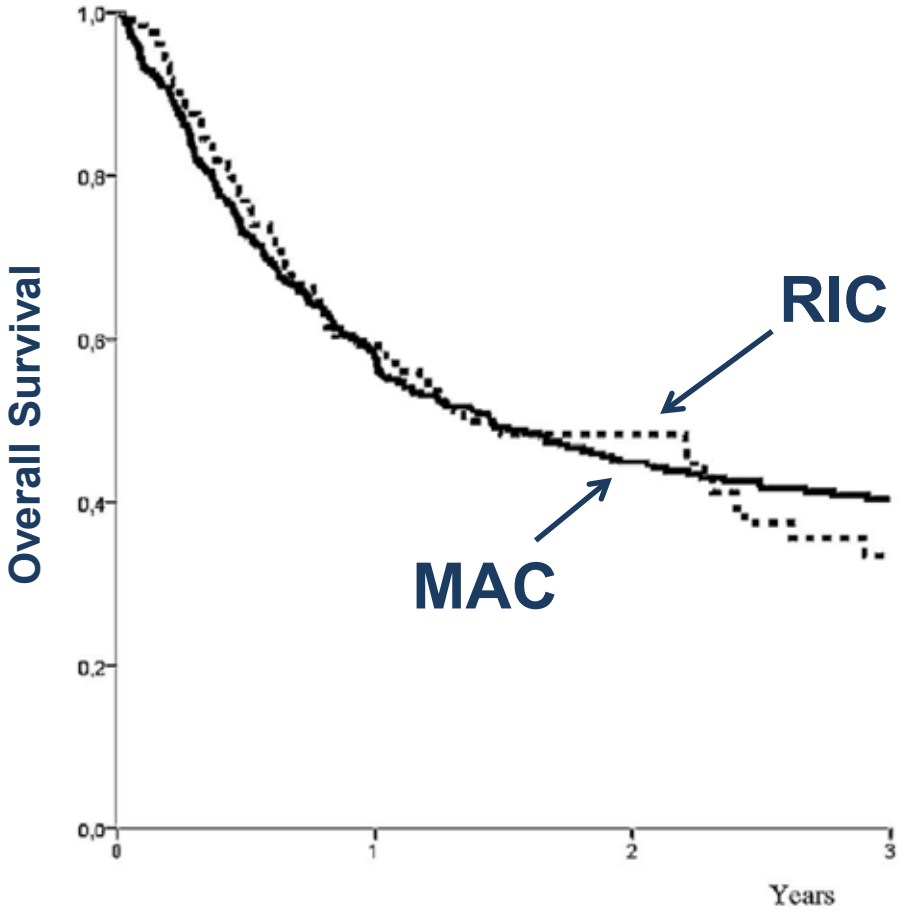
Modified from Gupta, *et al. Blood.* 2013;121:339-50.

Comparison of RIC vs MAC: EBMT

Characteristics:

- Any ALL in CR1 or CR2
- 45 years or older
- MSD PBSCT or BMT from 1997-2007

127 RIC's vs 449 MAC's

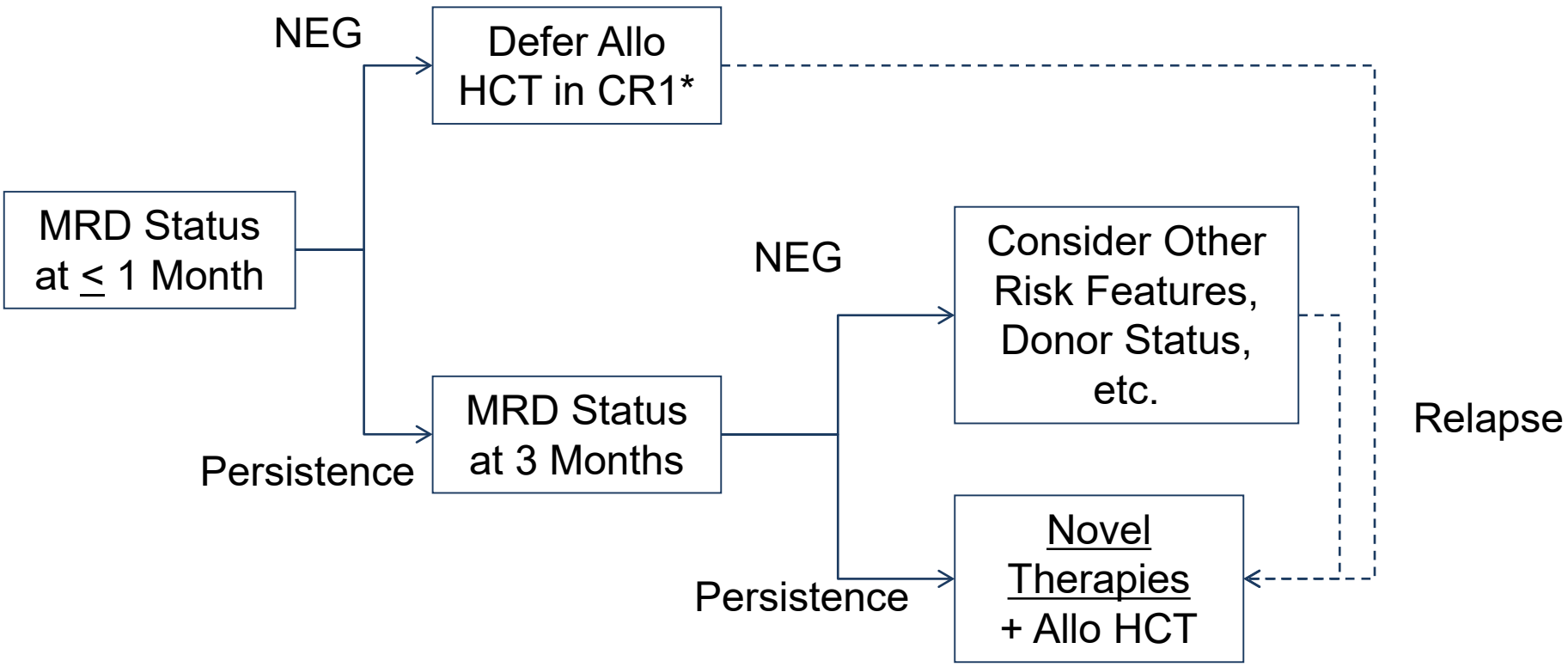


Mohty, *et al*. *Blood*. 2010;116:4439-43.

Summary: Role of HCT in CR1 for ALL

- Level I evidence supporting matched related-donor myeloablative allogeneic HCT in CR1 for adults with ALL, though overall benefit is modest
- Autologous HCT is not superior (and is likely inferior) to prolonged maintenance therapy
- Reduced-intensity/non-myeloablative allogeneic HCT may be reasonable in pts ineligible for high-intensity conditioning, based on retrospective/registry data
- Improved risk-stratification methods can help determine which patients are most likely to benefit from allogeneic HCT in CR1 (particularly MRD)

MRD and Transplant for Ph-, *KMT2A*- ALL: The Cassaday Approach

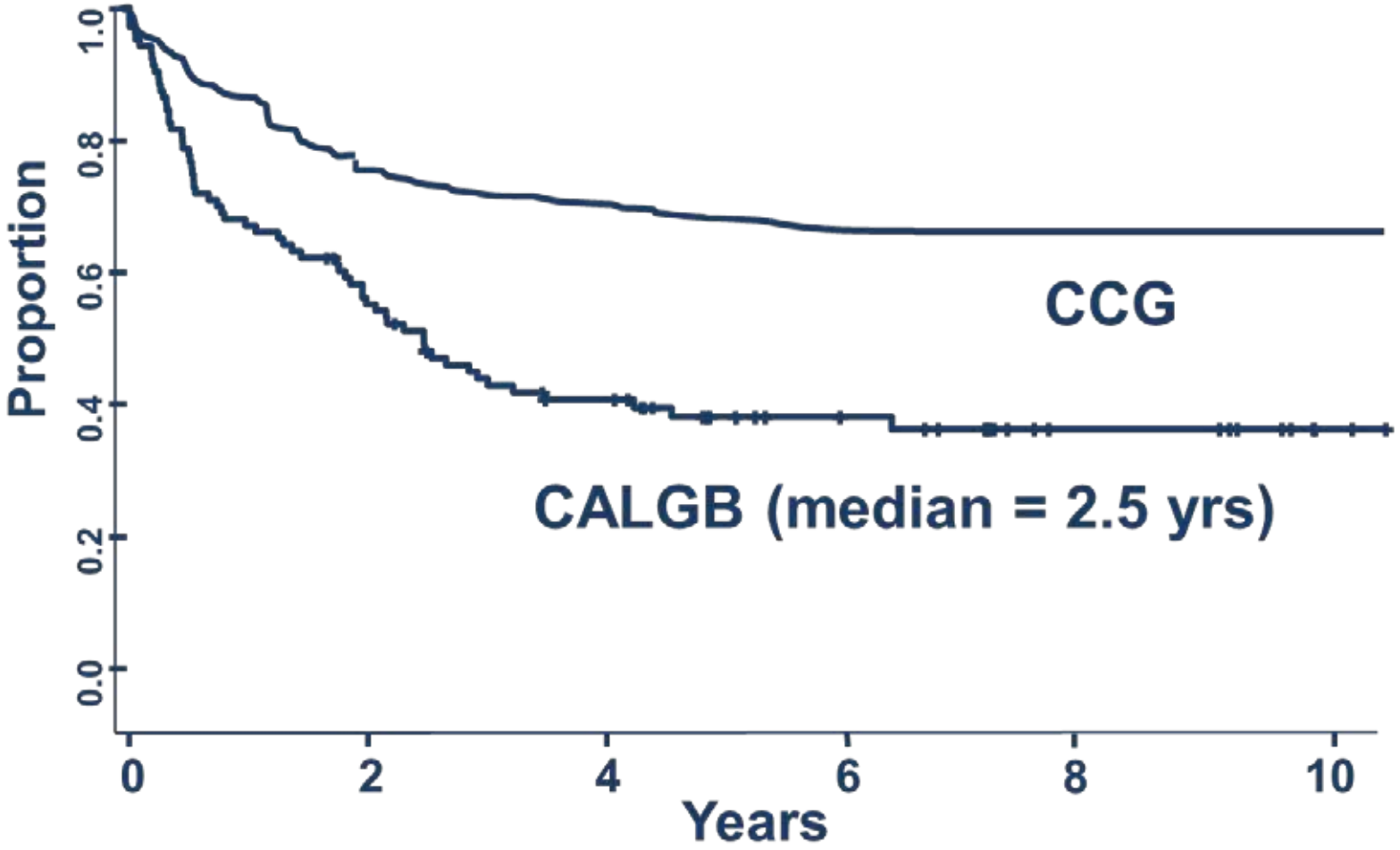


* Assuming patients can complete a full course of treatment and remain MRD negative

Specific Scenarios:

Adolescents and Young Adults (AYA)

EFS of Young Adults (16-21 yo) on CCG and CALGB Trials for ALL (1988-1995)



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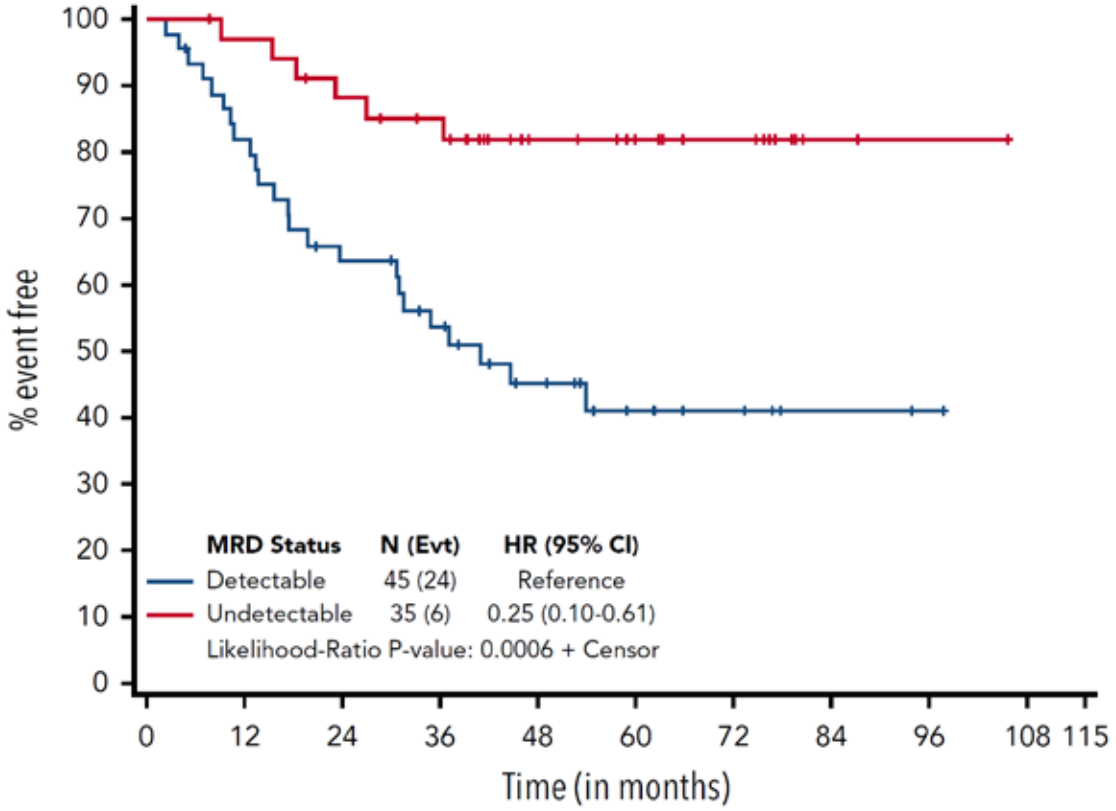
Stock, *et al*. *Blood*. 2008;112:1646-54.

Pediatric vs. Adult Therapy for ALL: Reasons for Different Outcomes

- Therapies are different
- Doctors are different
- Patients are different

EFS by MRD Status: C10403



- **Of 263 patient who achieved remission, only 20 (8%) underwent HCT in CR1 → reserve HCT for MRD+?**
- **Increased BMI associated with worse outcome**

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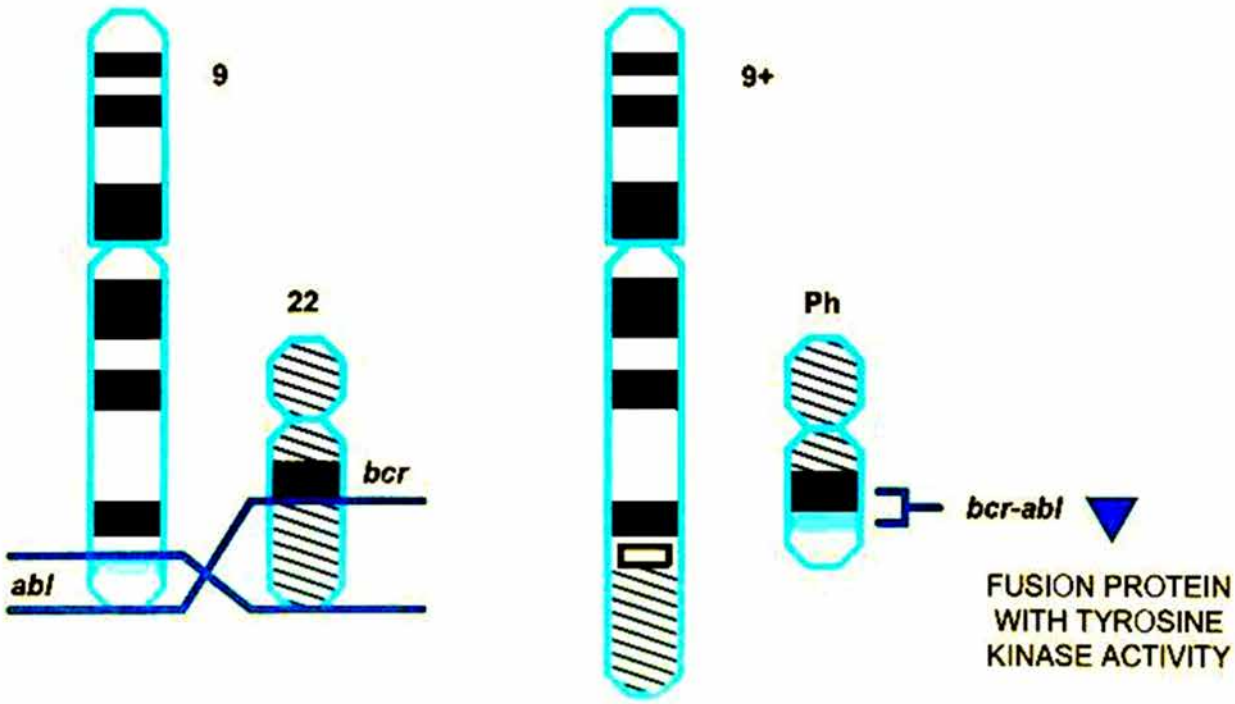
Stock, *et al. Blood.* 2019;133:1548-59.

Specific Scenarios:

Ph+ ALL

The Philadelphia Chromosome: t(9;22) Translocation



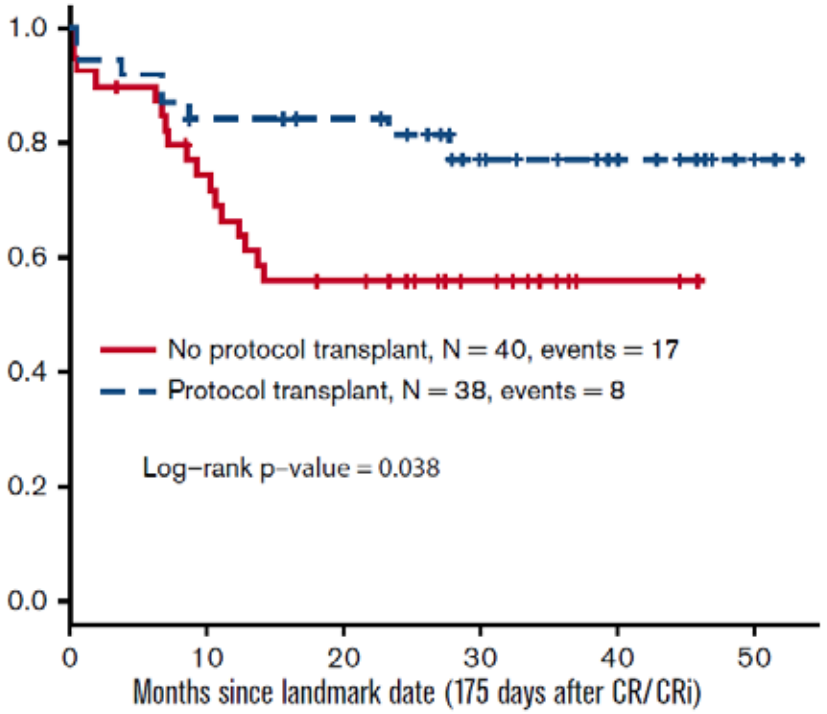
Management of Ph+ ALL: Summary

- The basics:
  - Include TKI with chemotherapy

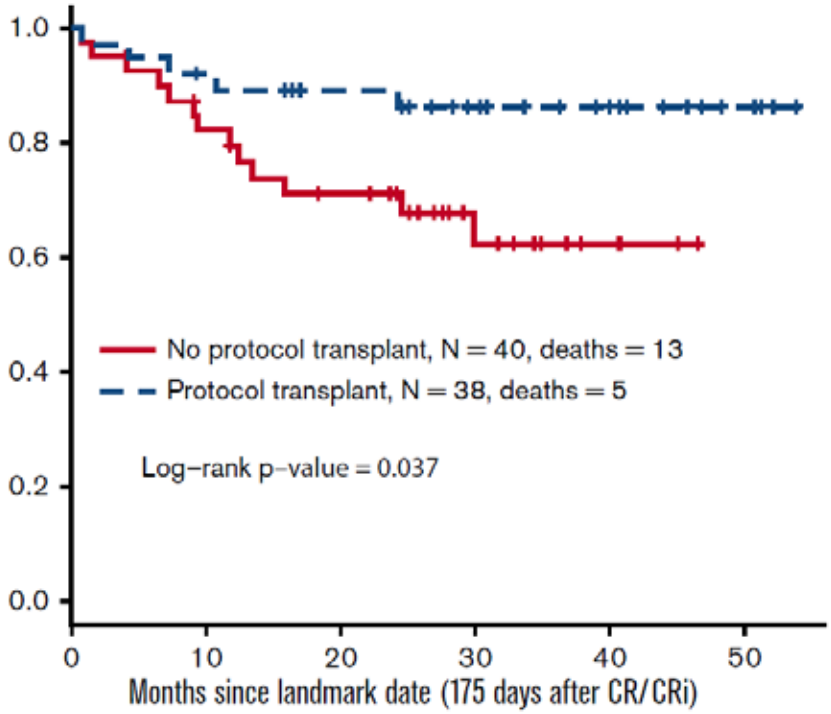
- Controversial topics:
  - Is one particular TKI superior?
  - How much chemo is necessary?
  - HCT in CR1 for all patients?

SWOG 0805: HyperCVAD + Dasatinib

Relapse-Free Survival



Overall Survival



- All patients with matched donor were “encouraged” to undergo allogeneic HCT followed by dasatinib maintenance
- If no HCT, dasatinib-based maintenance therapy

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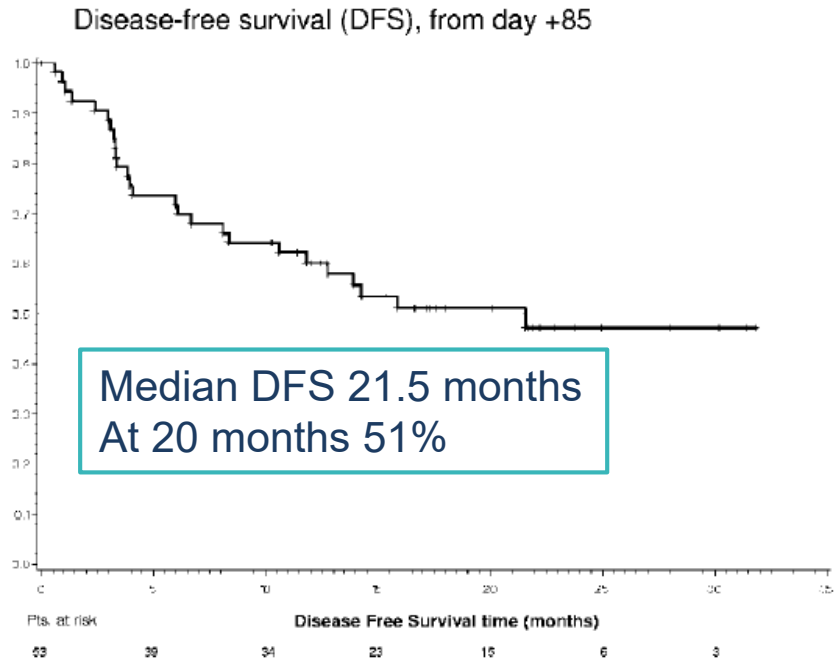
Ravandi, *et al*. *Blood Advances*. 2016;1:250-9.

Lower-Intensity Options: Likely Safer, but Less Effective?

GIMEMA LAL1205:

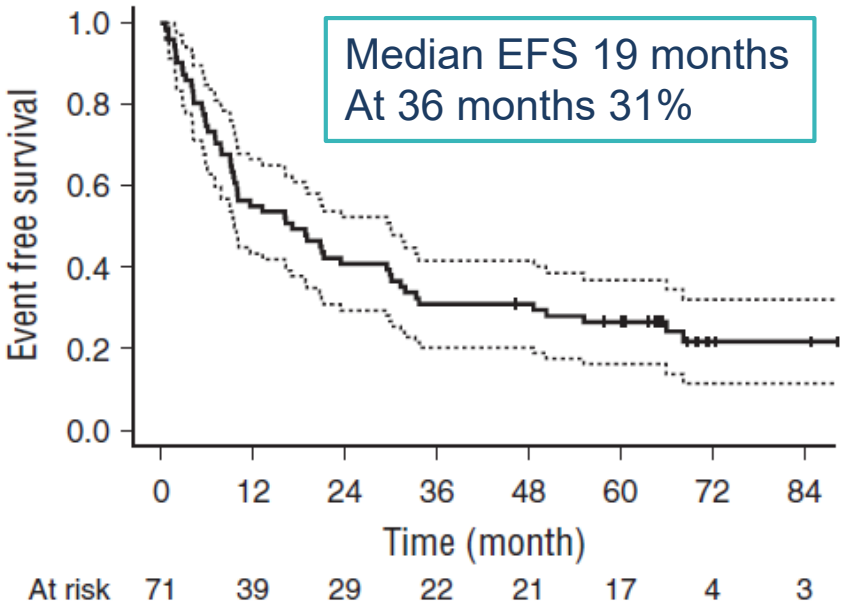
Dasatinib + Prednisone



Foa, *et al*. *Blood*. 2011;118:6521-8.

EWALL-PH-01:

Dasatinib + Low-Intensity Chemo



Rousselot, *et al*. *Blood*. 2016;128:774-82.

T315I mutations at relapse are COMMON

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Specific Scenarios:

ALL In The Elderly

Outcomes with Different Approaches for Older Patients with ALL

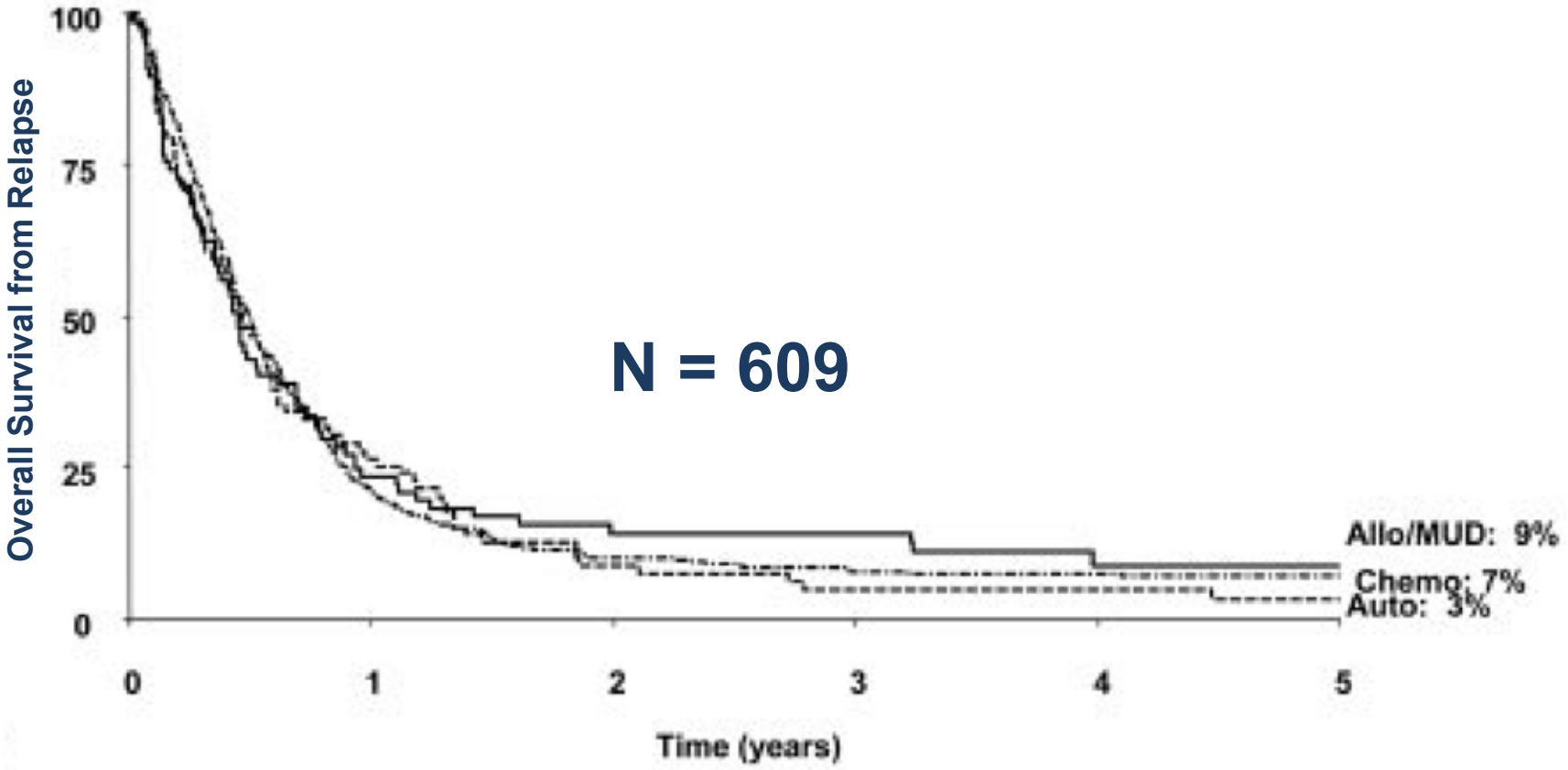
Approach	N	CR Rate	Early Death Rate	Survival (Median/2-yr)
Population-Based Studies	N/R	40%	N/R	6-30%
Palliative Treatment	94	43%	24%	7 mo
Intense chemotherapy designed for younger adults	519	56%	23%	14%
Prospective studies specifically for older adults	447	71%	15%	33%

Author's Conclusion: "Palliative, supportive treatment in acute leukemia does not, in general, reduce the risk of early death and does not improve quality of life compared to moderate intensive chemotherapy."

Reviewed by Gokbuget. *Blood*. 2013;122:1366-75.

Relapsed/Refractory ALL

Outcome of Relapsed ALL: UKALL XII/ECOG2993



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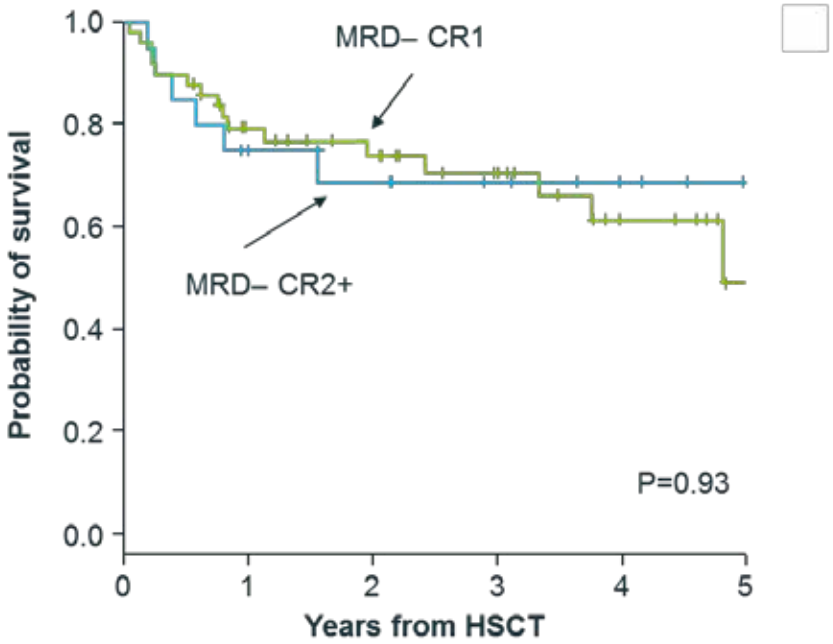
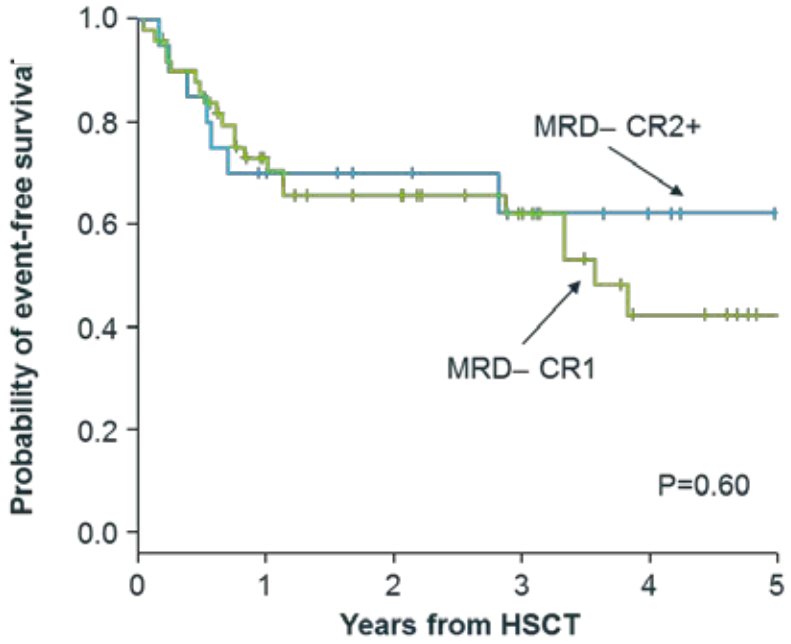
Fielding, *et al*. *Blood*. 2007;109:944-50.

HCT in MRD^{Neg} CR2+ Comparable to MRD^{Neg} CR1





Patients who achieve MRD^{Neg} CR1 are significantly more likely to achieve MRD^{Neg} CR2+ if they relapse.

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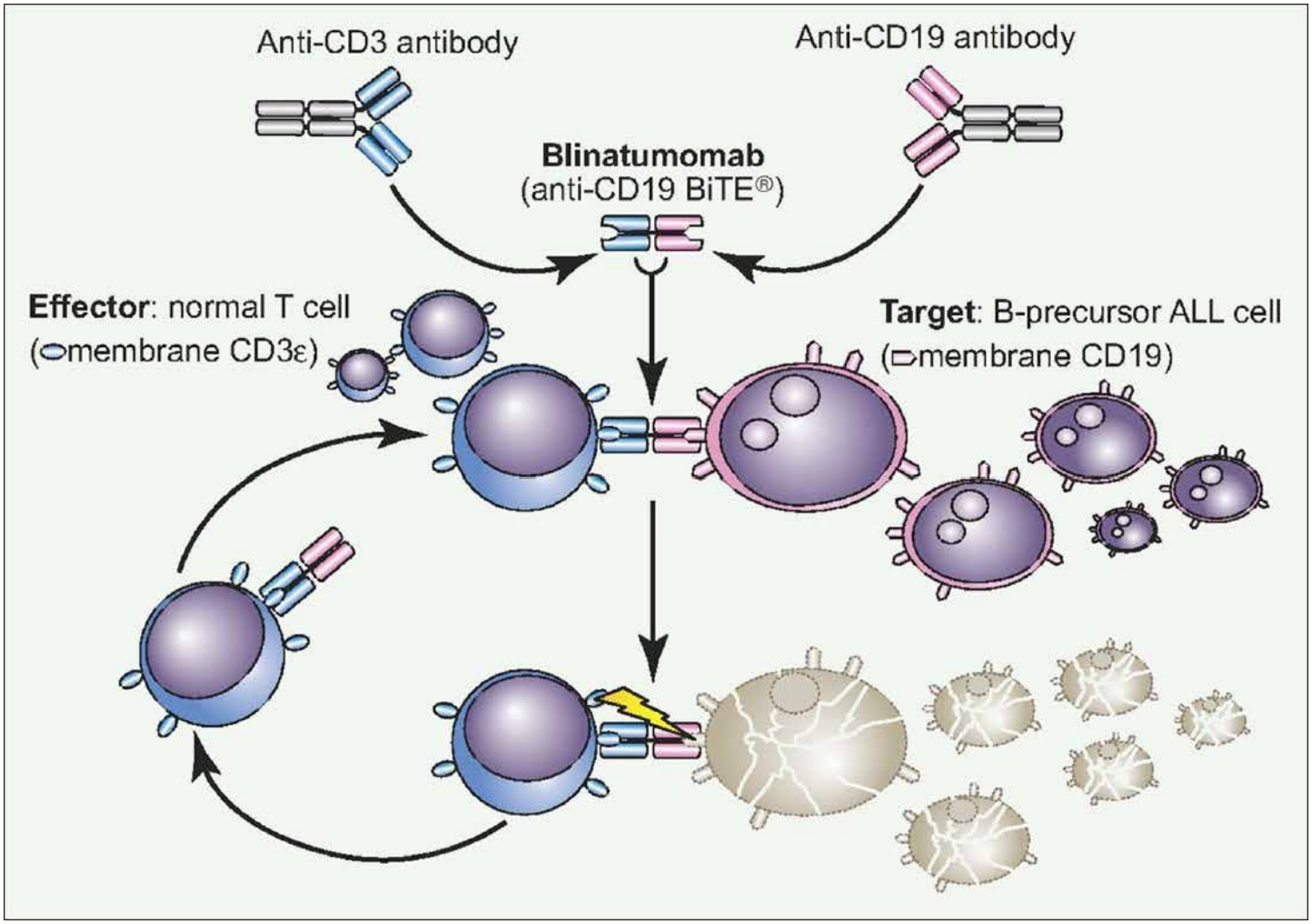
Revised from Cassaday, *et al*. *Leuk Lymphoma*. 2016;57:2109-118.

Options for Relapsed/Refractory ALL

- Purine analogues
  - Nelarabine (T-ALL)
  - Clofarabine (age ≤ 21; ≥ 2 prior therapies)
- Liposomal vincristine (≥ 2 prior therapies; Ph- only)
- *ABL* kinase inhibitors: ponatinib (Ph+ with T315I or no other option)
- CD3-CD19 BiTE: blinatumomab
- CD22 antibody-drug conjugate: inotuzumab ozogamicin
- CD19 CAR-T cells: tisagenlecleucel (age ≤ 25; refractory or ≥ 2nd relapse)

Blinatumomab = Bispecific T-Cell Engager



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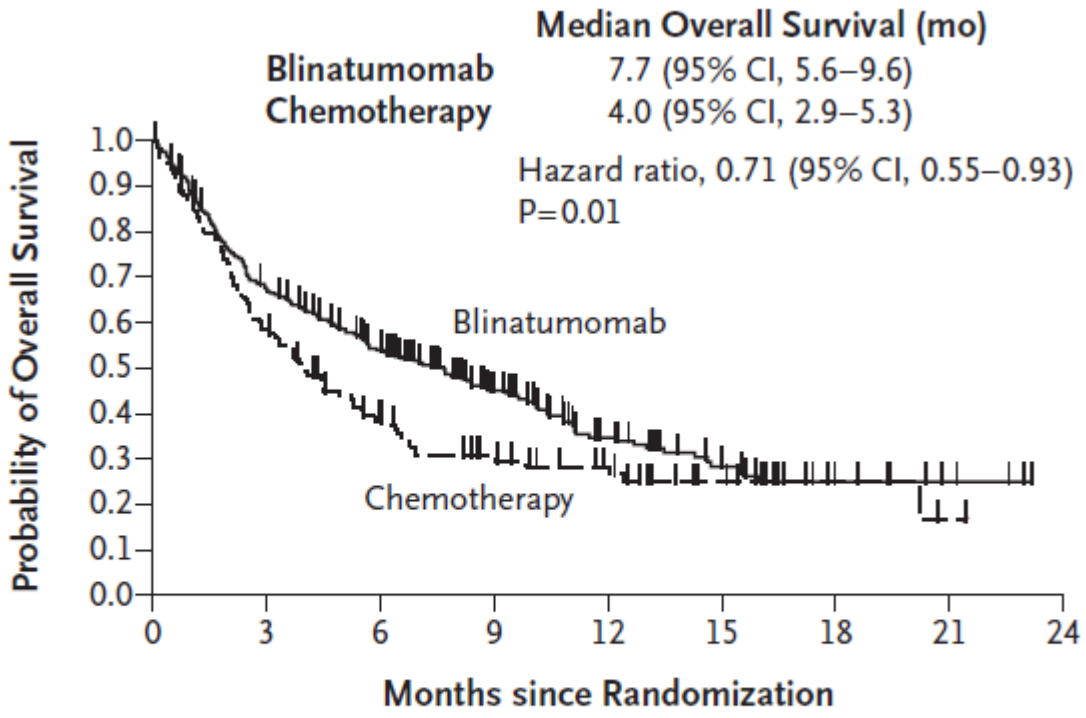
Kapoor, *et al. Clin Cancer Invest J.* 2014;3(6):577-8.

Blinatumomab for Rel/Ref B-ALL



No. at Risk									
Blinatumomab	271	176	124	79	45	27	9	4	0
Chemotherapy	134	71	41	27	17	7	4	1	0

- Given as 24-hr continuous infusion: 4 weeks on, 2 weeks off
- Side-Effects: neurologic toxicity, cytokine release syndrome

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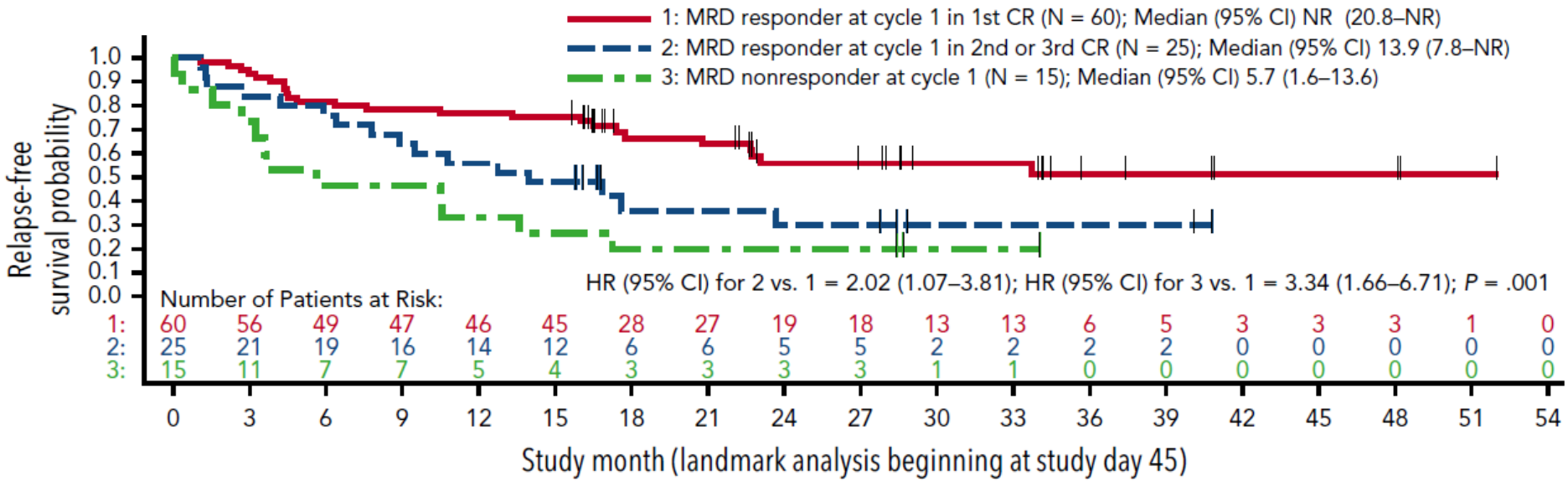
Kantarjian, *et al. New Engl J Med.* 2017;376:836-47.

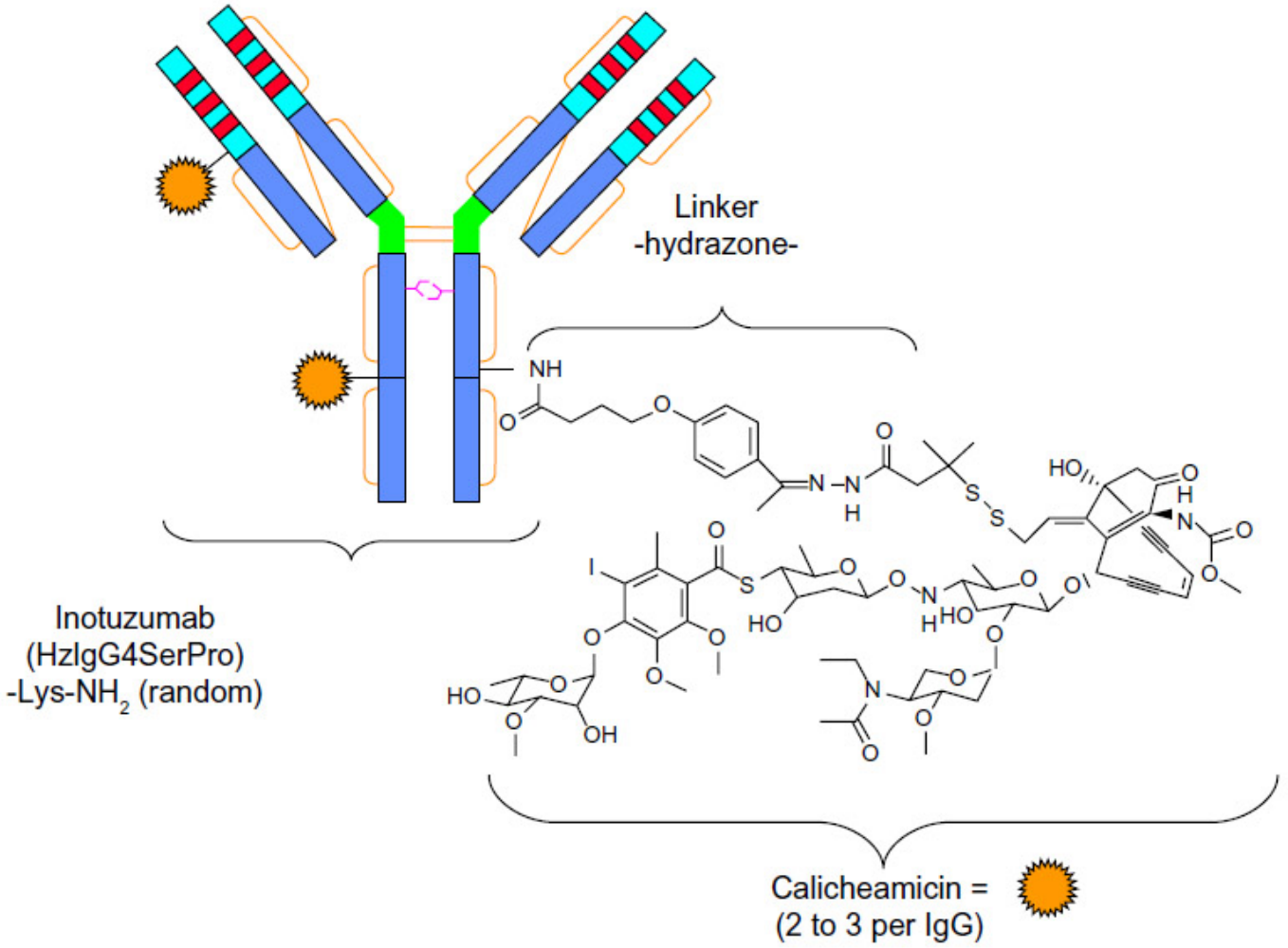
Blinatumomab for MRD



- 78% achieve complete MRD response
- CRS and severe neurotoxicity are uncommon (~10%)
- If no HCT or chemo after response to blin, 25% in continuous CR (median f/u = 24 mo)

Gokbuget, *et al. Blood*. 2018;131:1522-31.

Inotuzumab Ozogamicin = Anti-CD22 ADC



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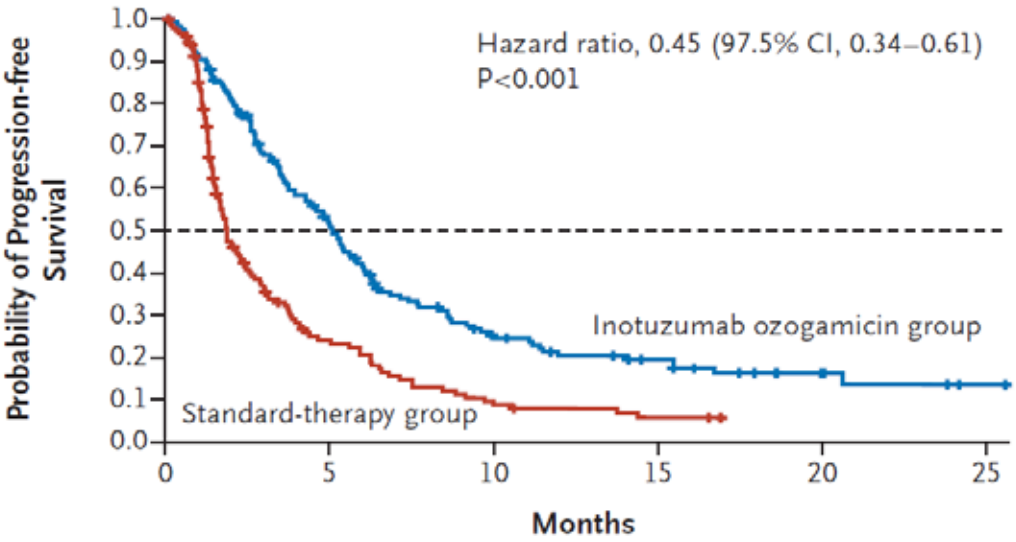
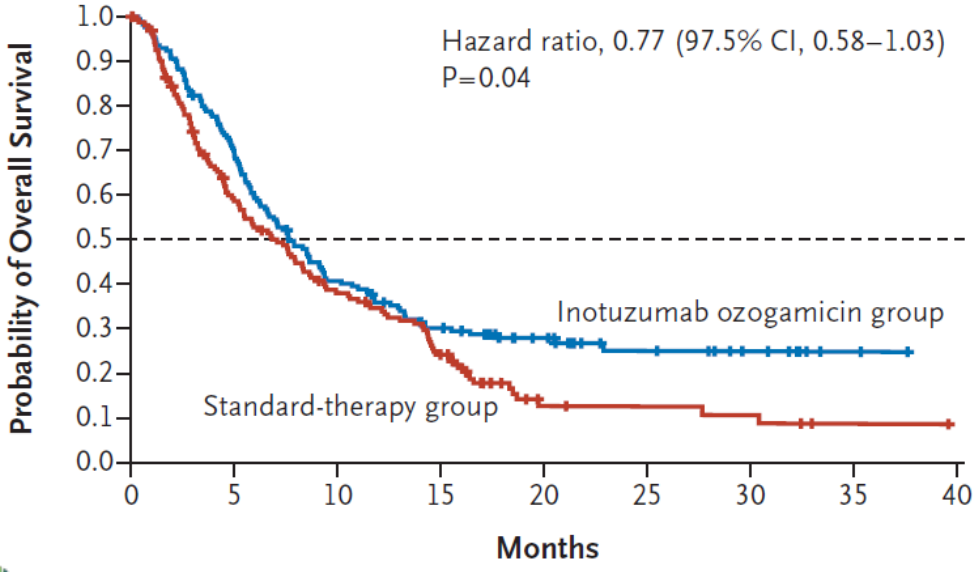
Thomas. *Blood Lymph Cancer: Targets and Therapy*. 2014;4:1-8.

Inotuzumab Ozogamicin for Rel/Ref B-ALL





- Dosing:
  - 1-hr IV infusion
  - Days 1, 8, &15
  - Every 21 (C1) to 28 (C2+) days
- Side effects:
  - SOS/VOD
  - Elevated ALT/AST
  - Cytopenias

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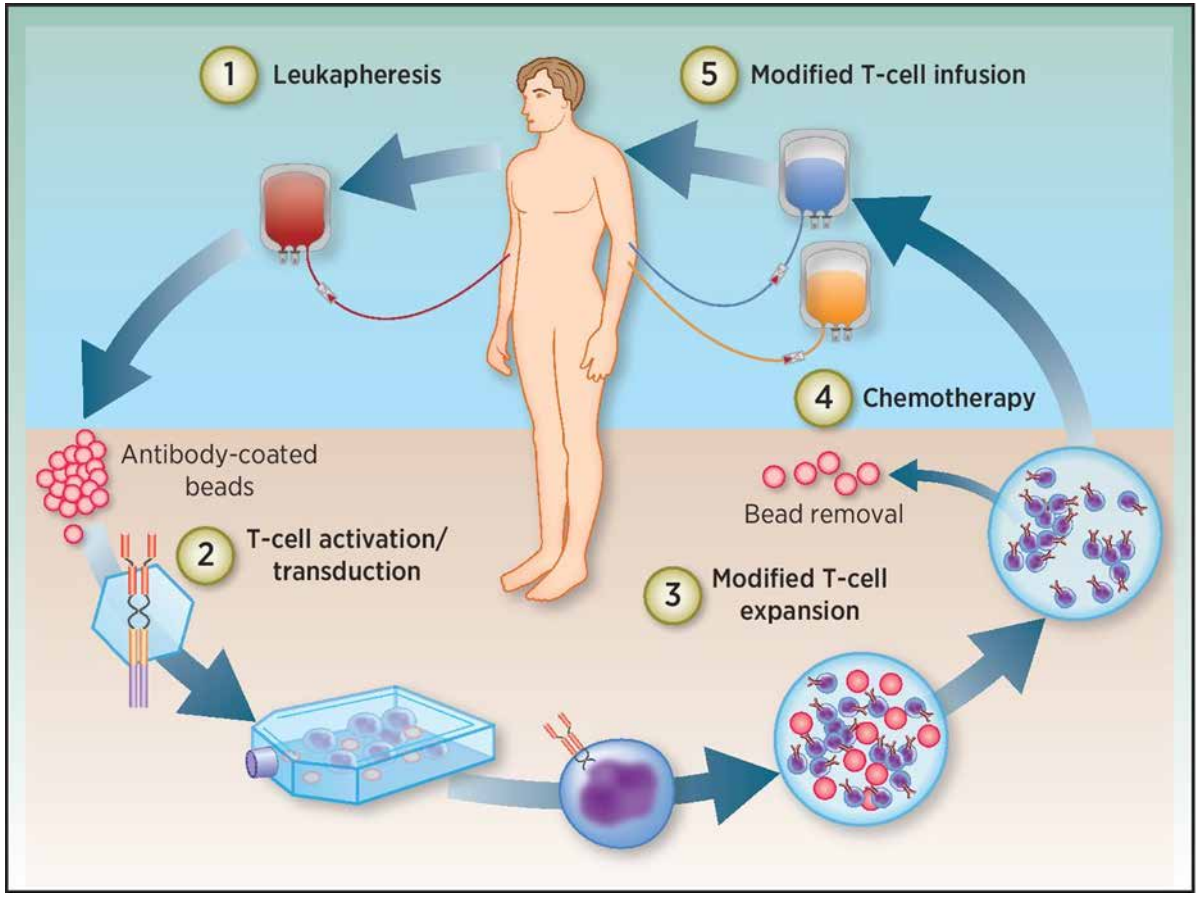
Kantarjian, *et al. New Engl J Med.* 2016;375:740-53.

Tisagenlecleucel = CD19 CAR-T Cells



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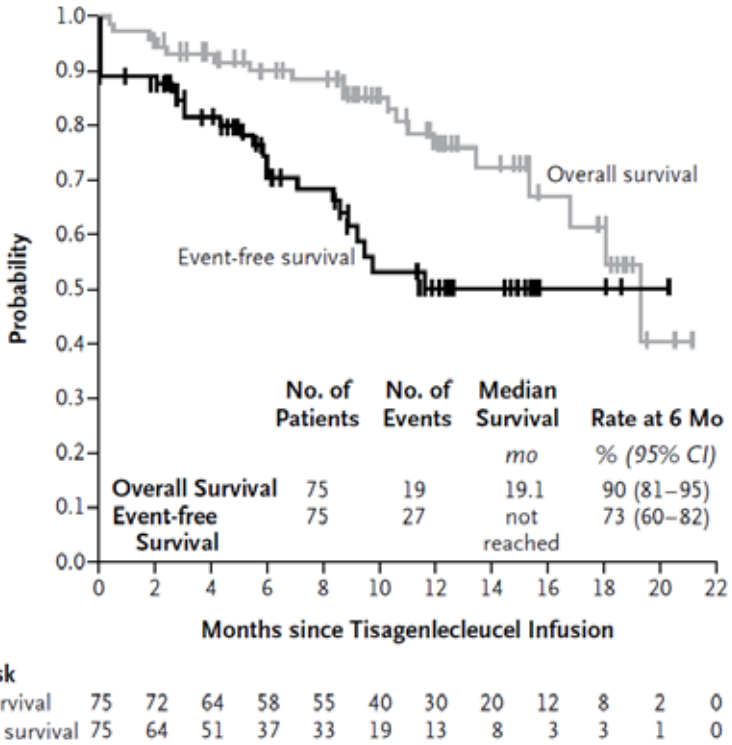
Maus & June. *Clin Cancer Res*. 2016;22(8):1875-84.

Tisagenlecleucel in Children and Young Adults with Rel/Ref B-ALL

- Multicenter, single-arm phase II trial (ELIANA)
- 107 pts screened → 92 enrolled → 75 treated
  - Median age = 11 yr
  - Median prior therapies = 3 (range: 1-8)
- CR/CRi rate within 3 mo:
  - Treated: 81% (all MRD^{Neg})
  - ITT: 66% (all MRD^{Neg})
- Toxicity:
  - 77% developed CRS
  - 47% admitted to ICU
  - 13% had Grade 3 neuro events
  - 19 deaths, 4 not due to relapse



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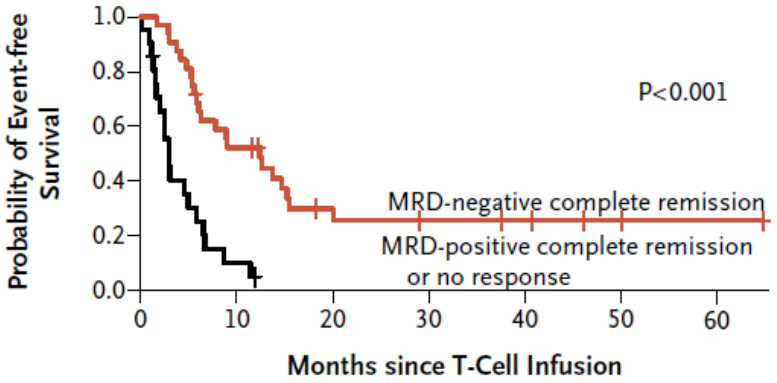
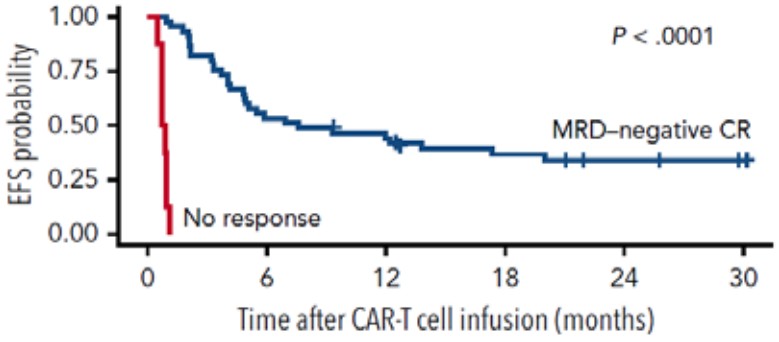
Maude, *et al. New Engl J Med.* 2018;378:439-48.

Long-Term Outcomes with CAR-T Cells in Adults with Rel/Ref B-ALL



Park, *et al. New Engl J Med.* 2018;378:449-59.



Hay, *et al. Blood.* 2019;133:1652-63

- Factors associated with better EFS:
  - Lower disease burden
  - Lower LDH
  - Higher platelet count
  - Use of fludarabine
- Role of HCT after CAR-T is controversial

ALL in Adults: Summary

- Disease risk primarily defined by WBC, cytogenetics, and response to therapy (MRD)
- Several standard options for front-line therapy
- Allogeneic HCT in CR1 reserved for high-risk patients—MRD may be best tool to determine this
- Single-agent options for relapsed/refractory disease:
  - B-ALL: inotuzumab ozogamicin, blinatumomab (including MRD), tisagenlecleucel
  - T-ALL: nelarabine
  - Ph+: ponatinib
  - Ph-: liposomal vincristine

THANK YOU

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