Acute Lymphoblastic Leukemia in Adults

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Comprehensive Heme/Onc Review Course
2021

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

Outline & Objectives

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

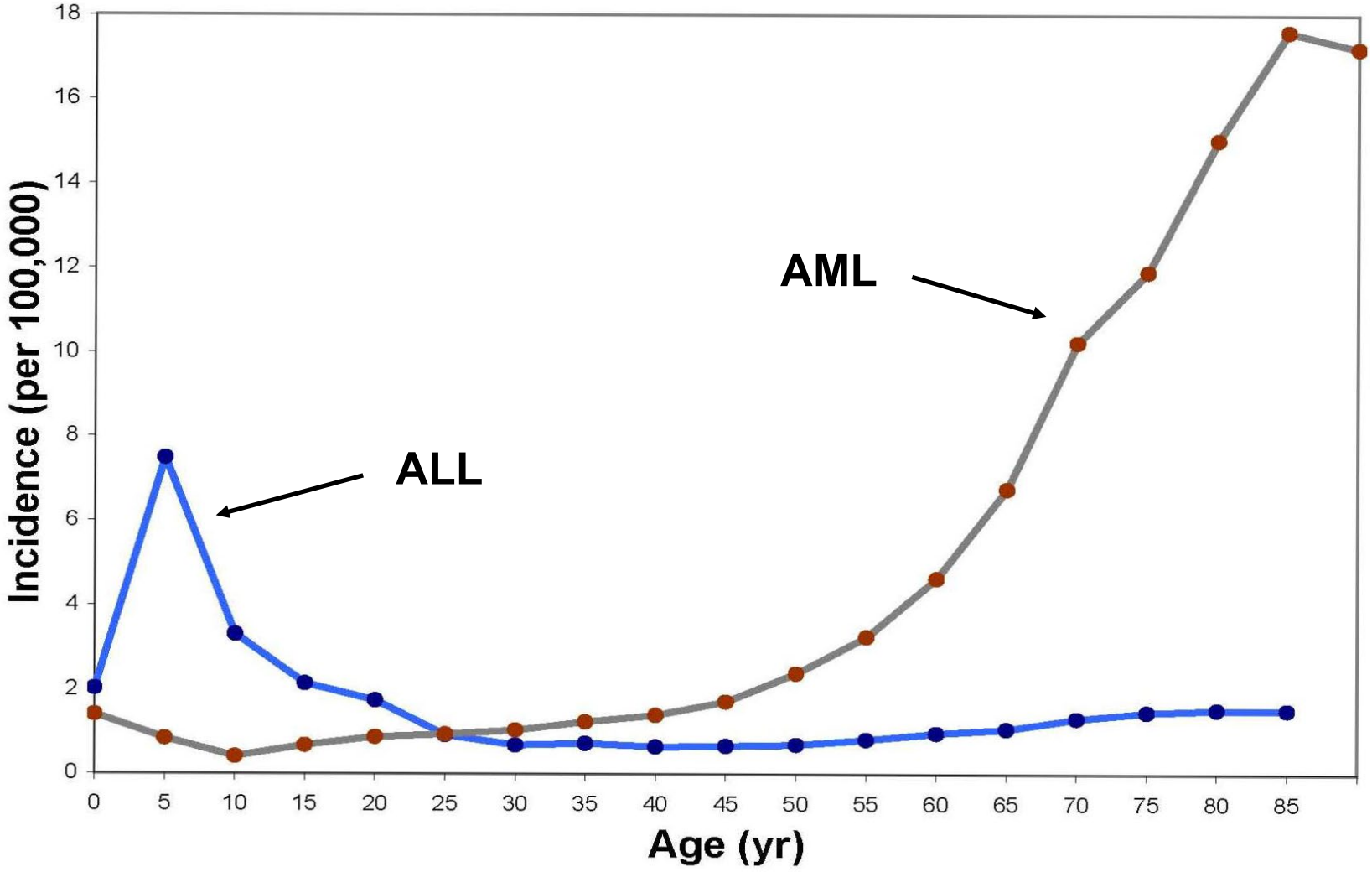
Epidemiology and Classification

Leukemia in the U.S., 2021

	New Cases	Deaths
ALL	5,690	1,580
CLL	21,250	4,320
AML	20,240	11,400
CML	9,110	1,220
Other	4,800	5,140
Total	60,530	23,100

Siegel, *et al*. *CA Cancer J Clin* 2021;71:7-33.

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.

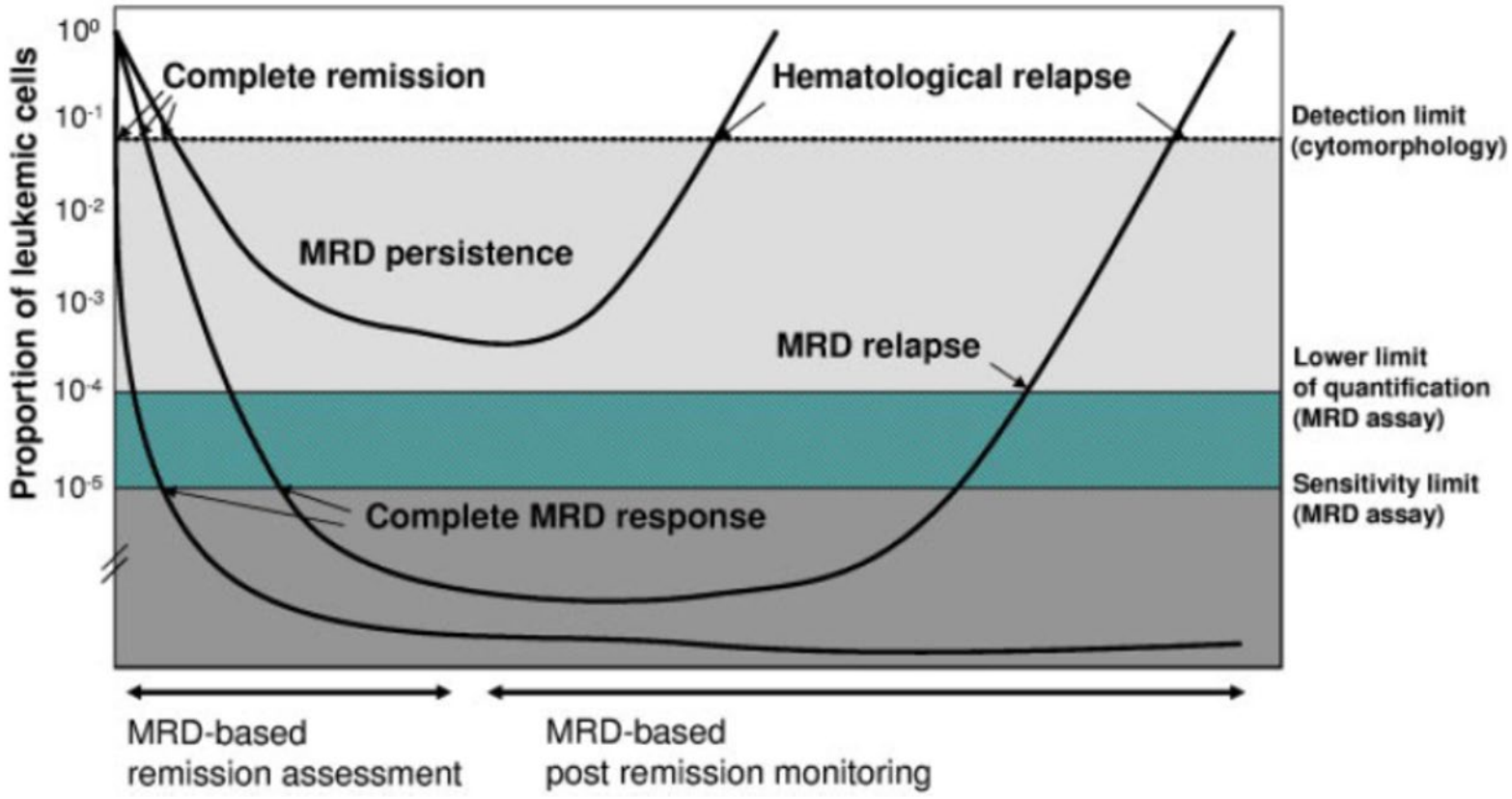
Moorman, *et al*. *Blood*. 2007;109:3189-97.

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 Measurable Residual Disease (MRD)



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

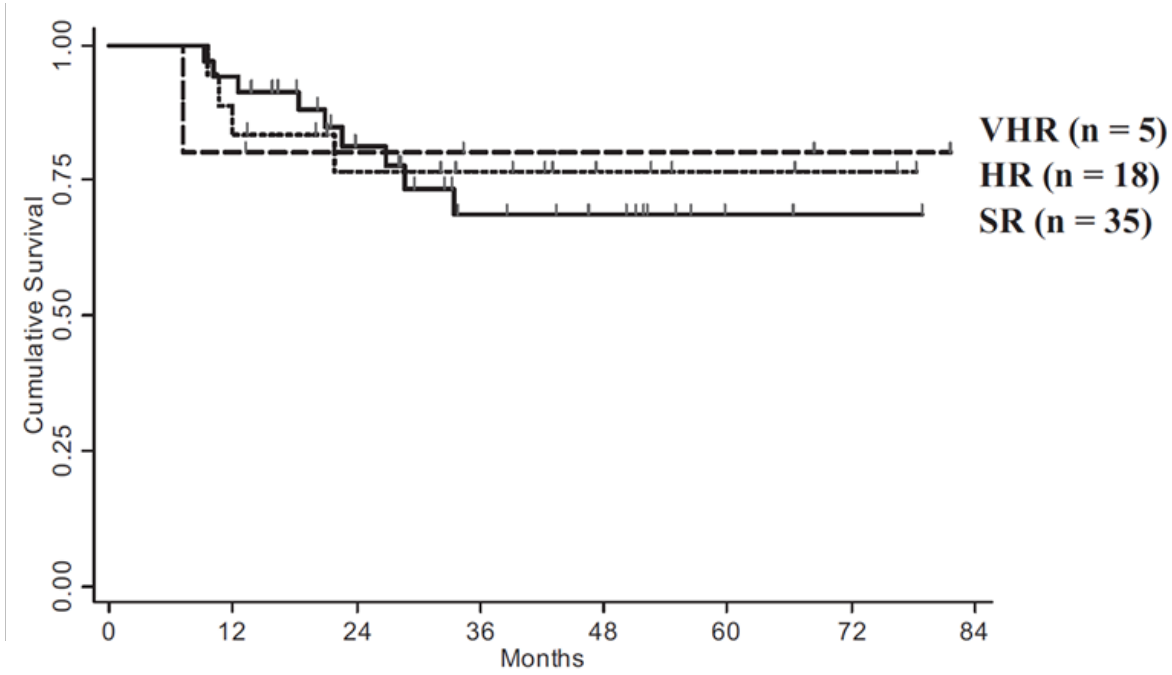
Measurement of MRD in ALL

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

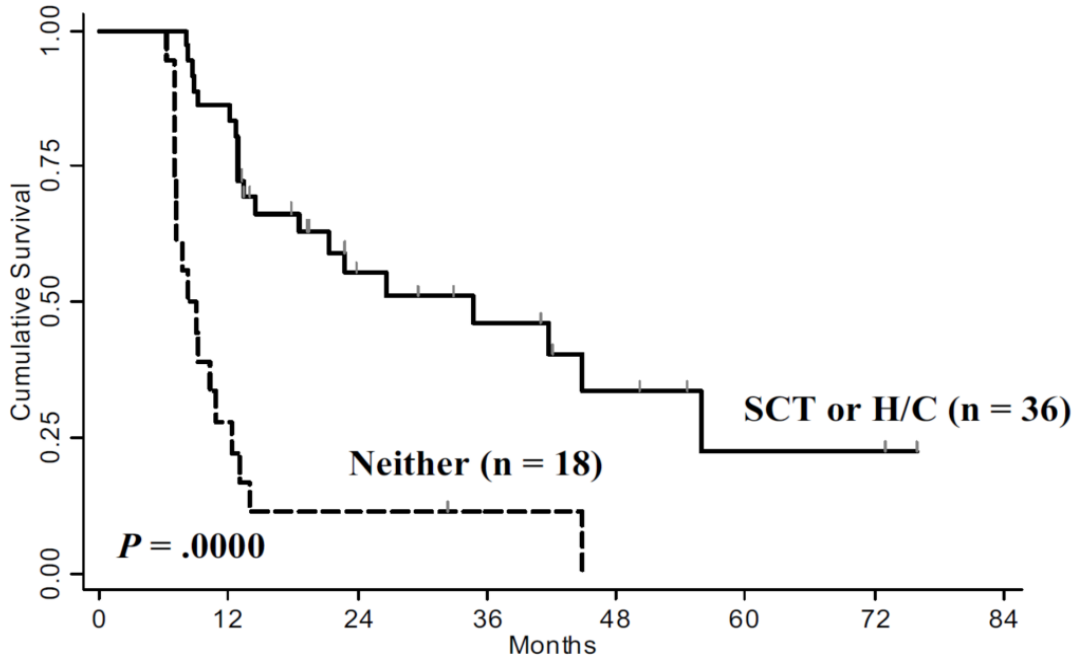
Modified from Bruggemann, *et al. Blood*. 2012;107:4470-81.

NILG-ALL 09/00: Importance of MRD Status

DFS Among MRD^{neg} Patients



DFS Among MRD^{pos} Patients



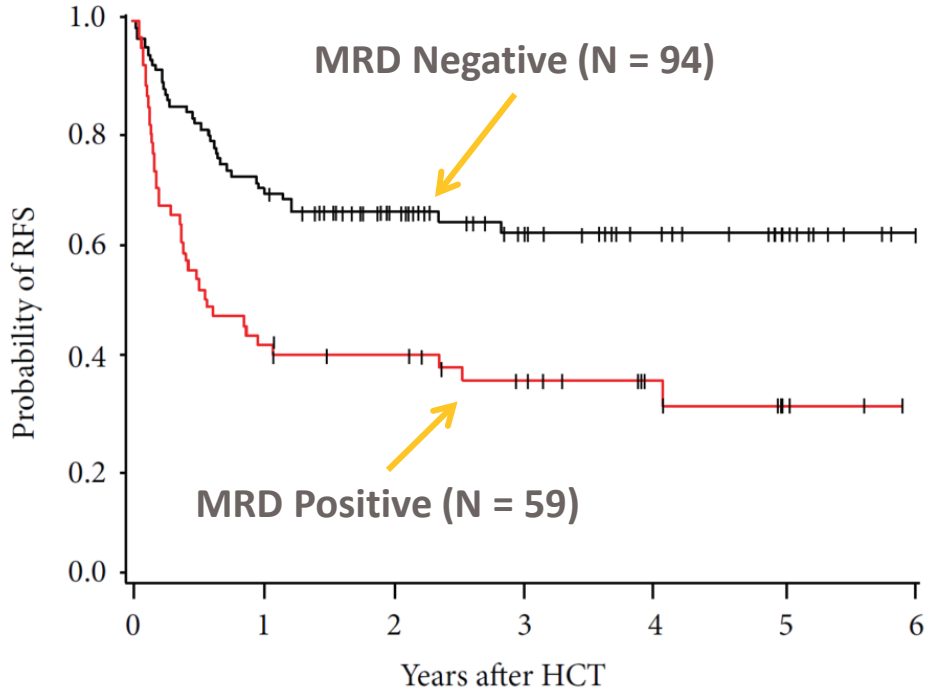
In a multivariate analysis of patients with complete data (n = 93), only two factors were predictive of relapse:

- MRD^{pos}
- High WBC

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 $\geq$ 0.01%

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

Risk Stratification in ALL: Summary

Old School

- Age
- WBC at Diagnosis
- Cytogenetics

New School

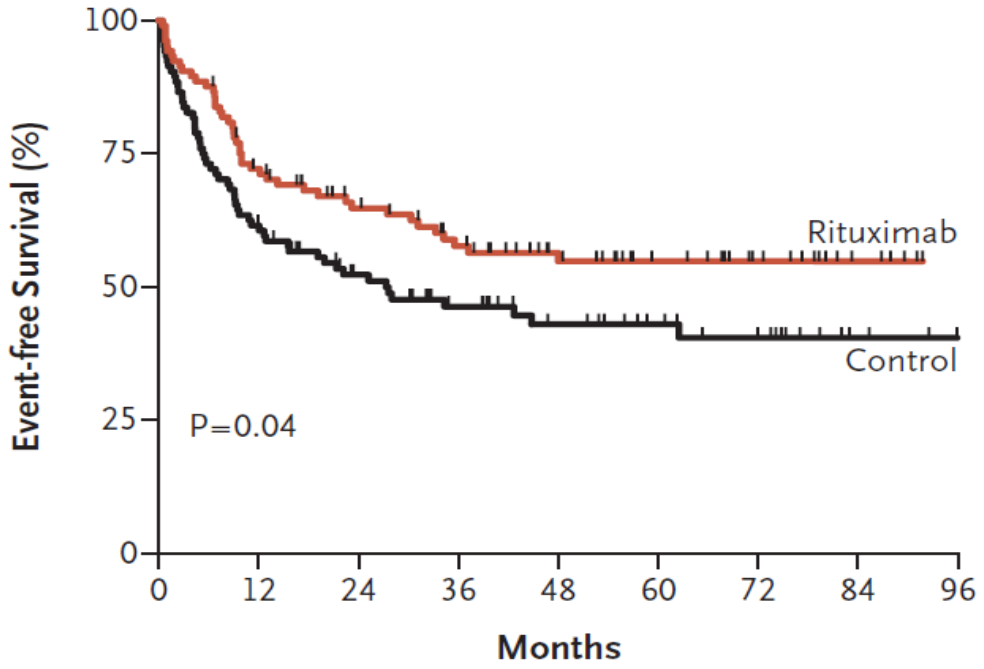
- MRD
- Molecular sub-classification
- WBC at Diagnosis
- Cytogenetics

Front-Line Therapy

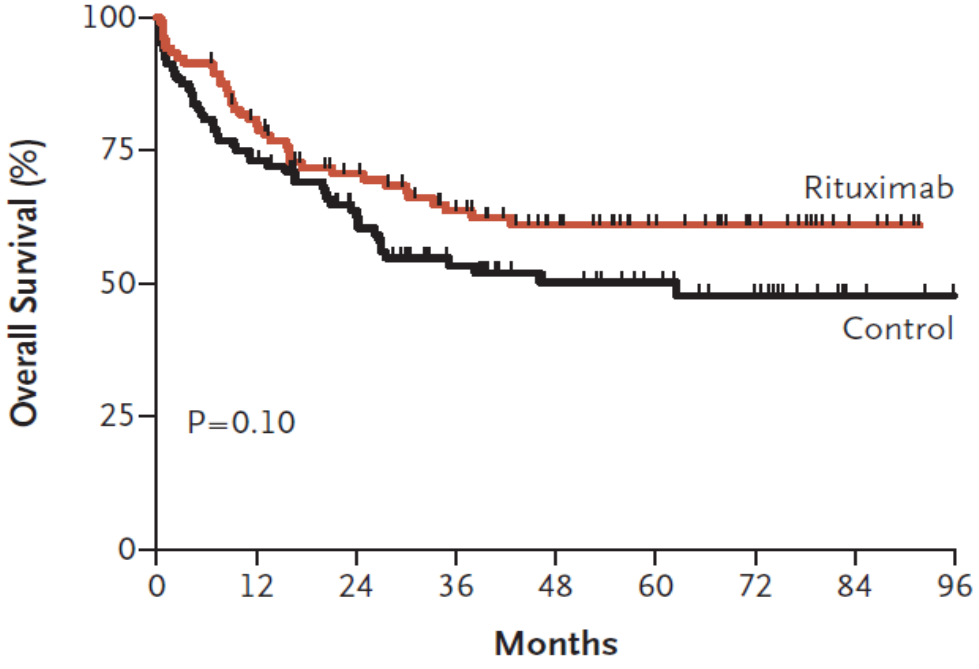
Contemporary Treatment

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

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

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

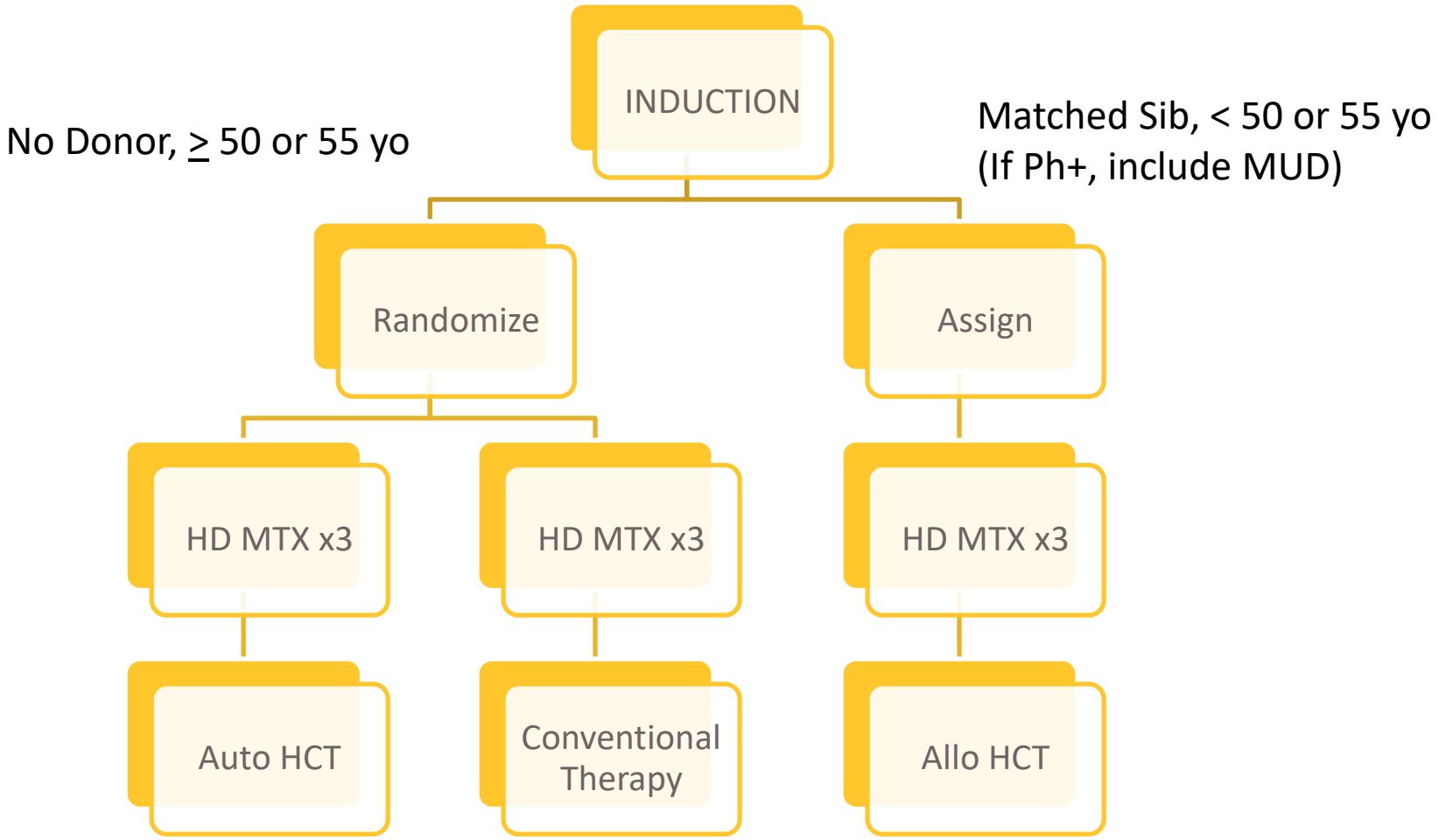
- Intensive multi-drug consolidation followed by maintenance chemotherapy spanning 2+ years

OR

- Allogeneic hematopoietic cell transplantation

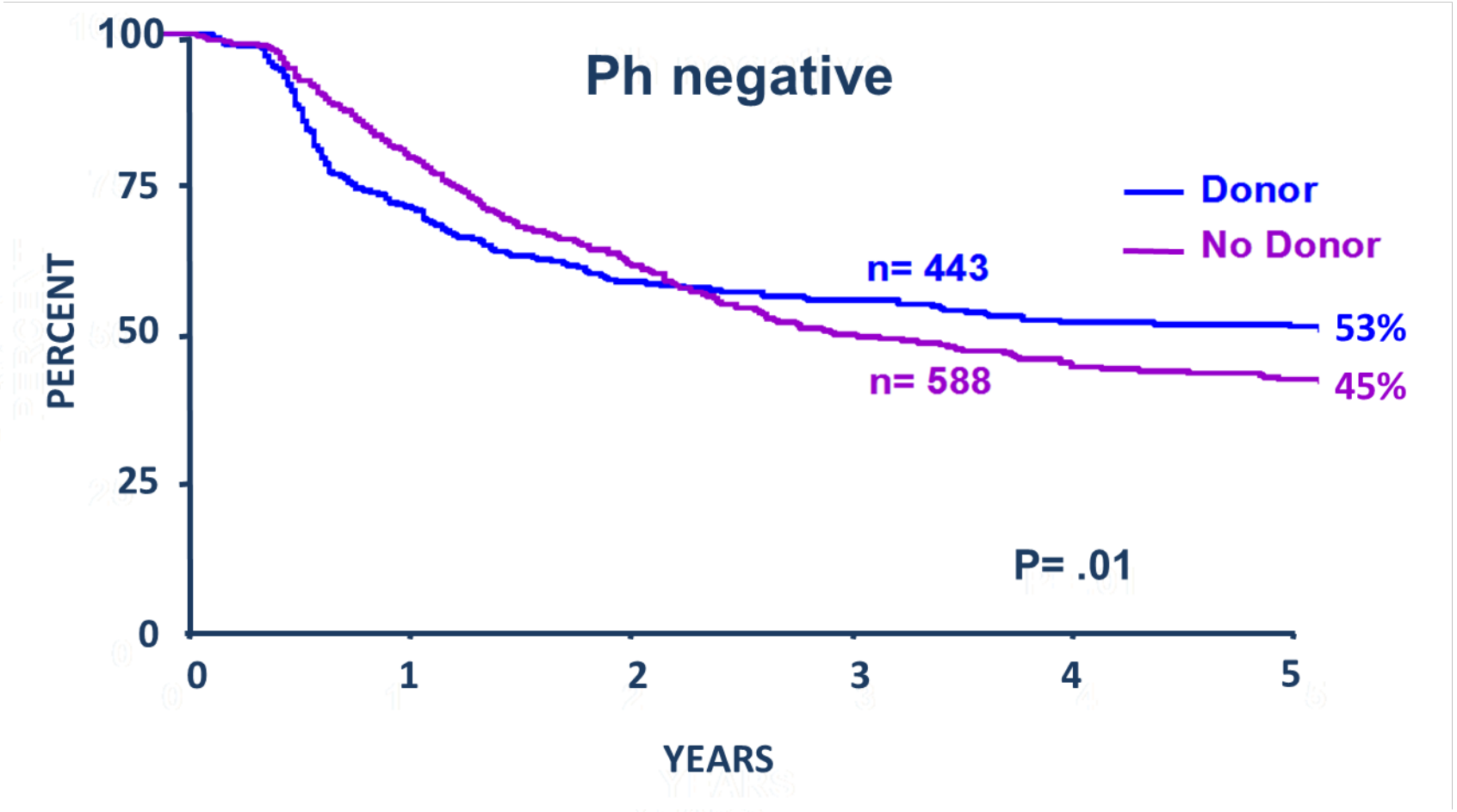
MRC UKALL XII/ECOG2993

1929 patients entered



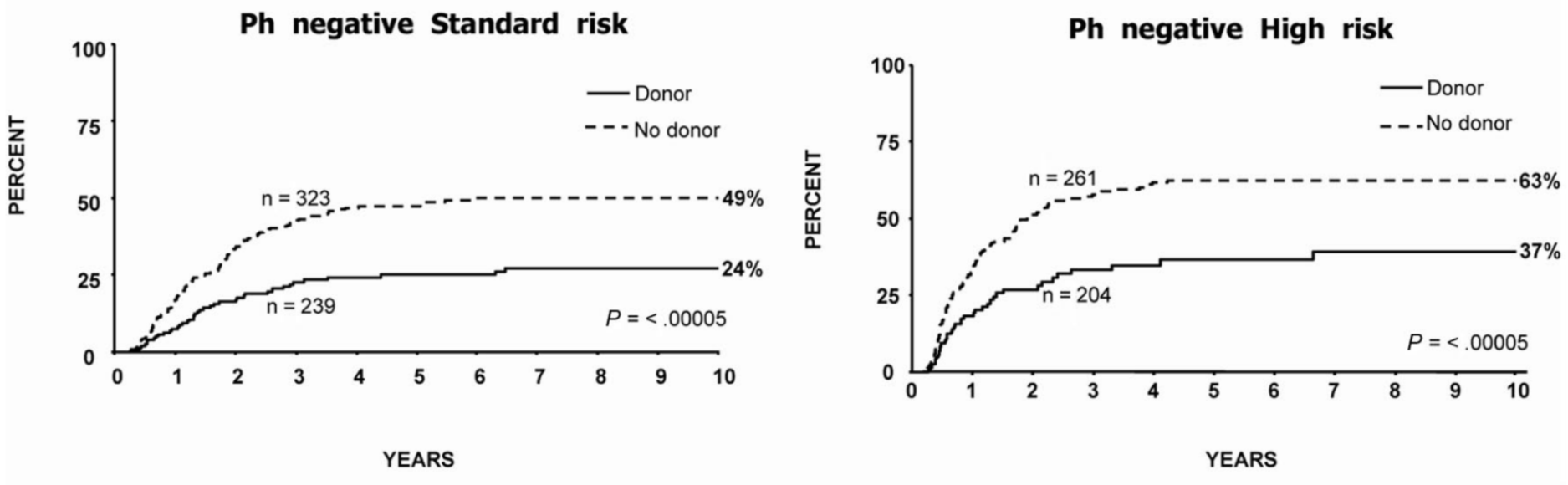
Rowe, *et al*. *Blood*. 2005;106:3760-7.
Goldstone, *et al*. *Blood*. 2008;111:1827-33.

UKALL XII / ECOG2993: Overall Survival



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

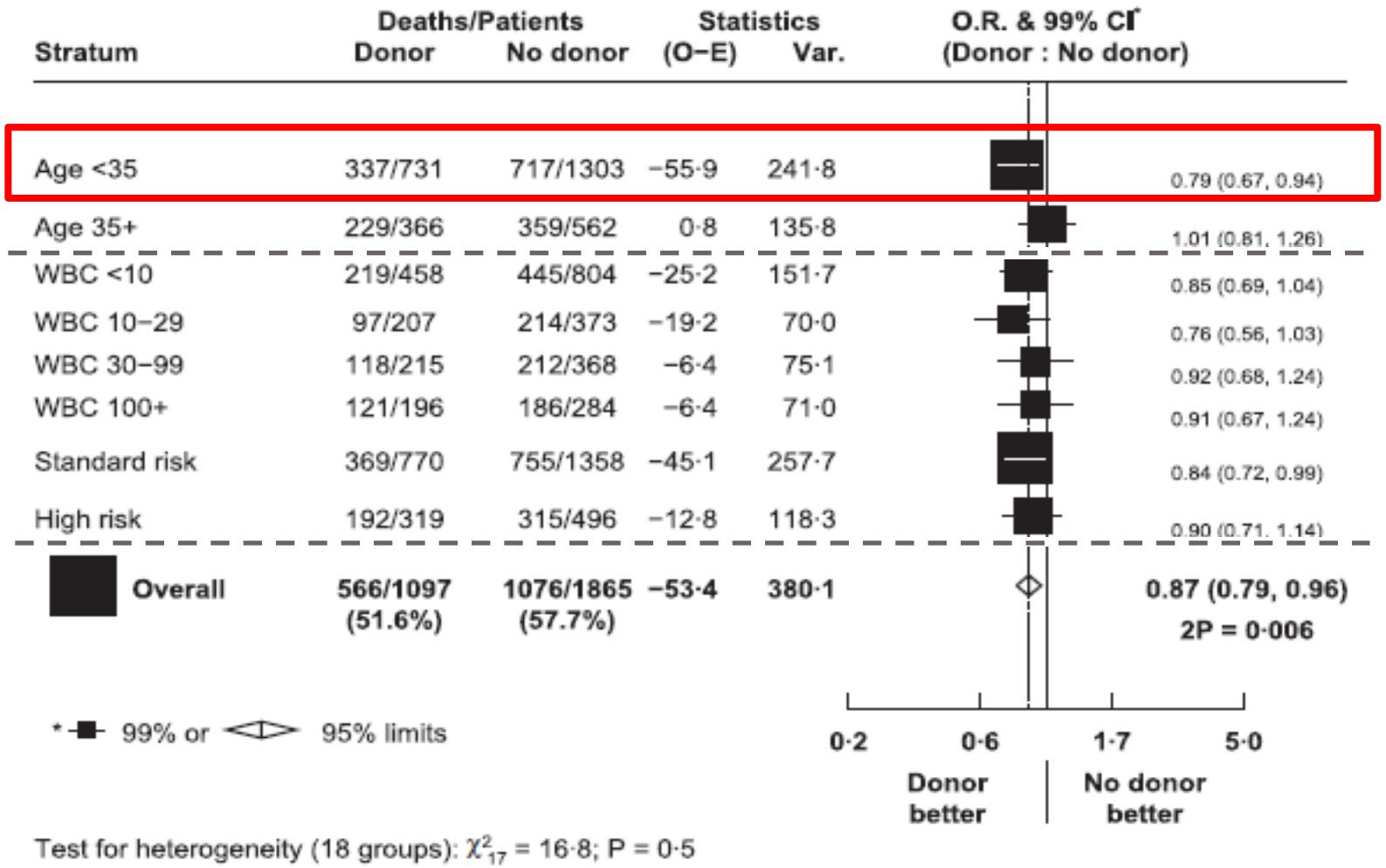
UKALL XII/ECOG2993:
Less Relapse but More NRM with Allo



	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

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

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

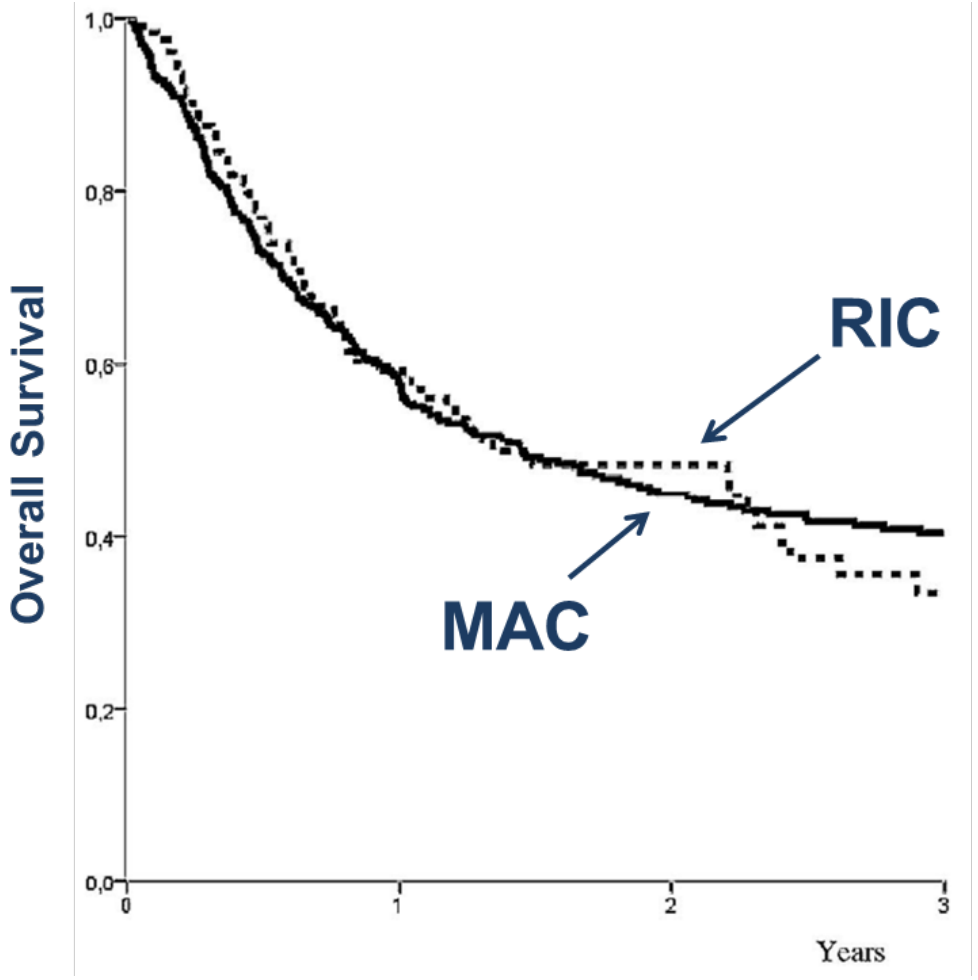


Only sub-group with improved mortality with allogeneic HCT = Age < 35

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

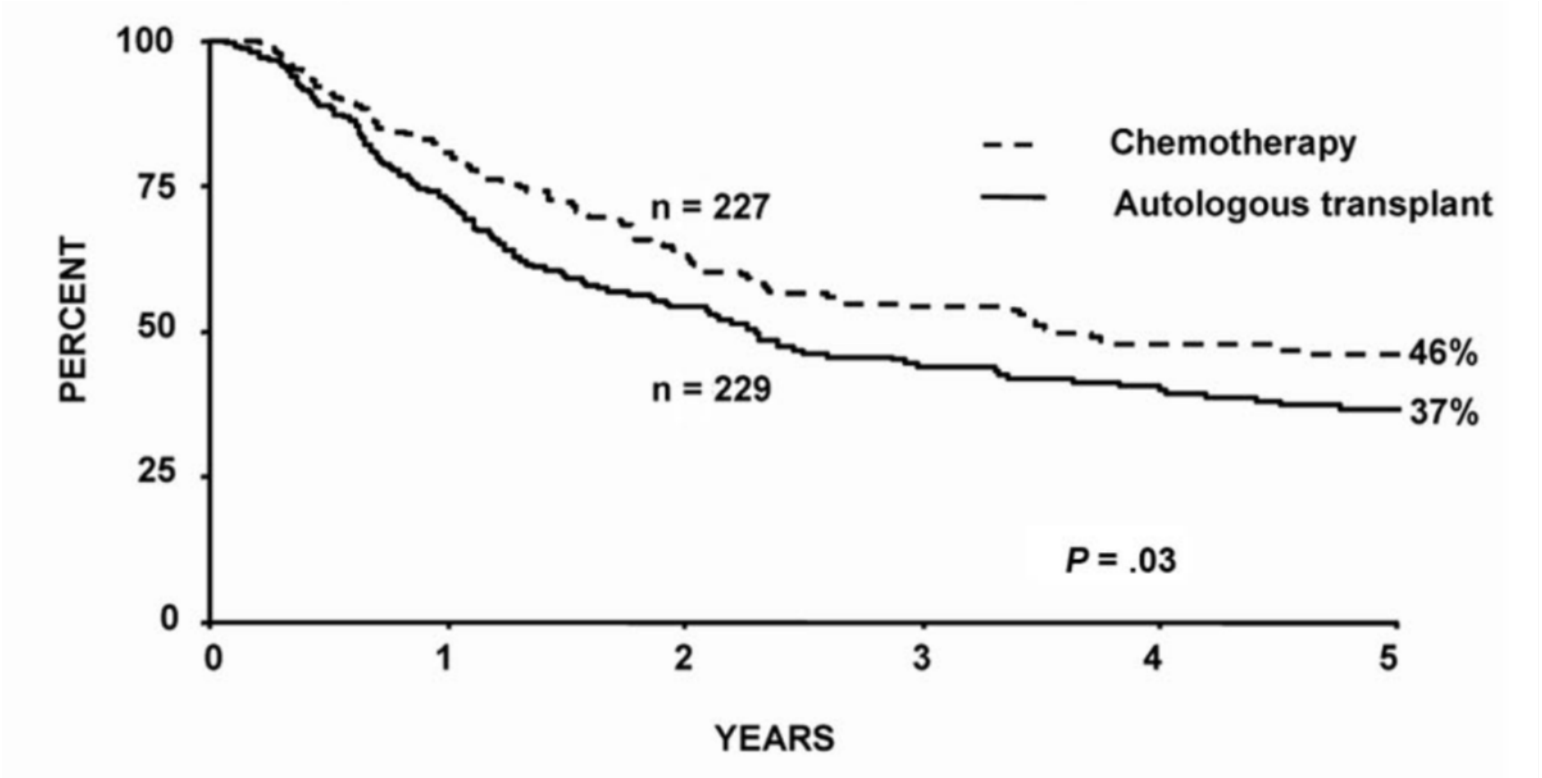
Comparison of RIC vs MAC: EBMT

- 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.

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



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

Summary: Role of HCT in CR1 for ALL

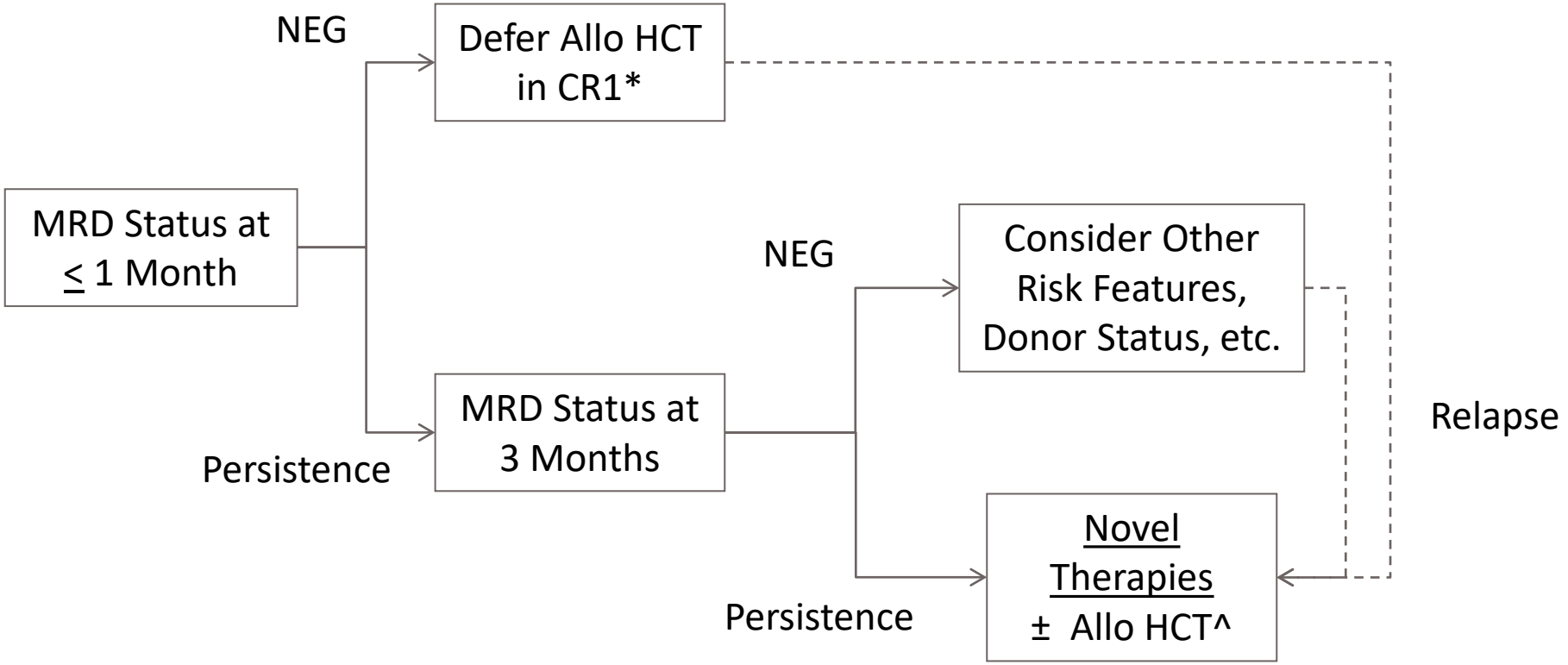
Level I evidence supporting matched related-donor myeloablative allogeneic HCT in CR1 for adults with ALL (UKALL XII/ECOG 2993), though overall benefit is modest

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



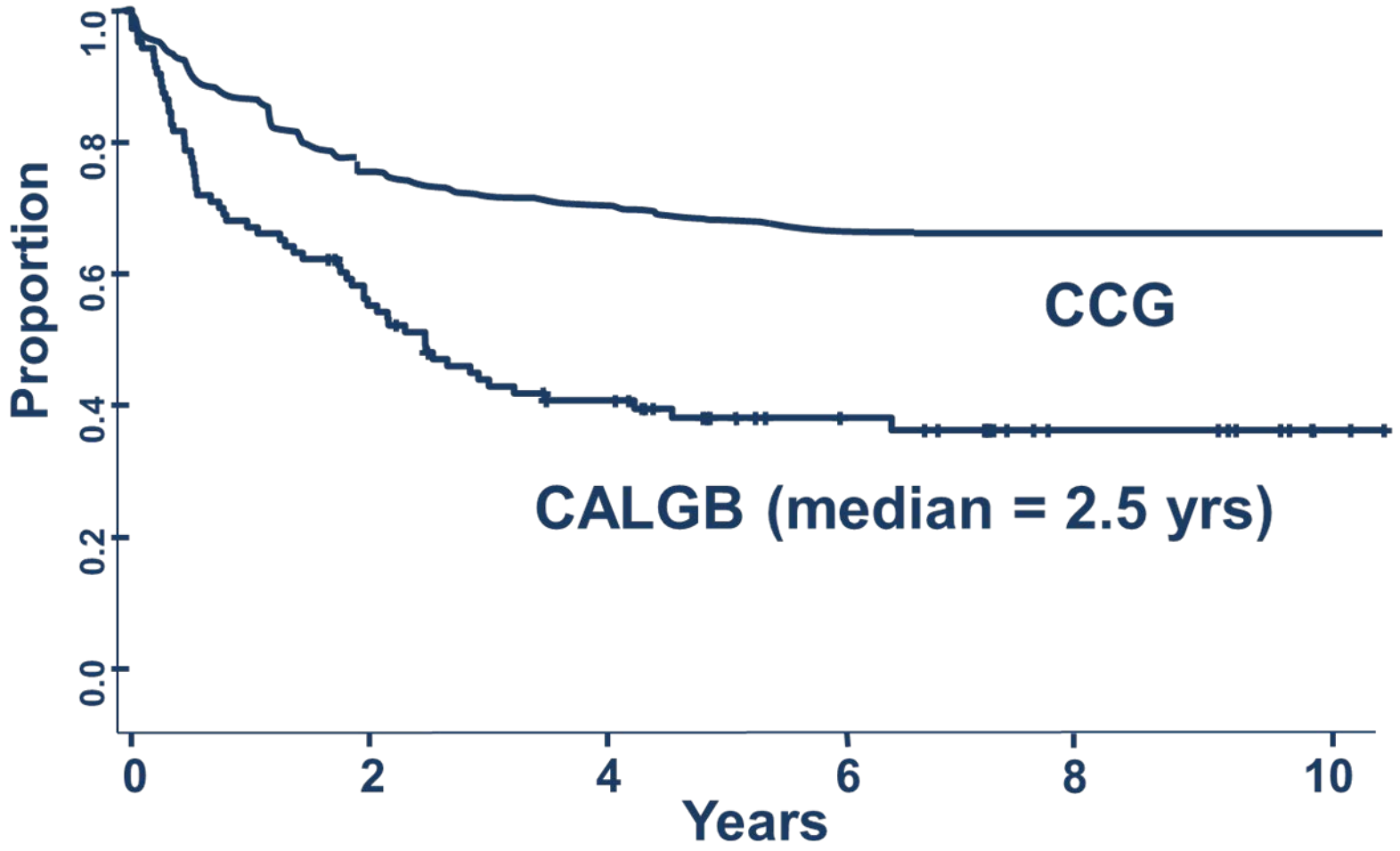
* Assuming (1) reliable MRD testing and (2) patients can complete a *relatively* full course of treatment and (3) remain MRD negative

^ Assuming patients are eligible for and interested in HCT

Specific Scenarios:

Adolescents and Young Adults (AYA)

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



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

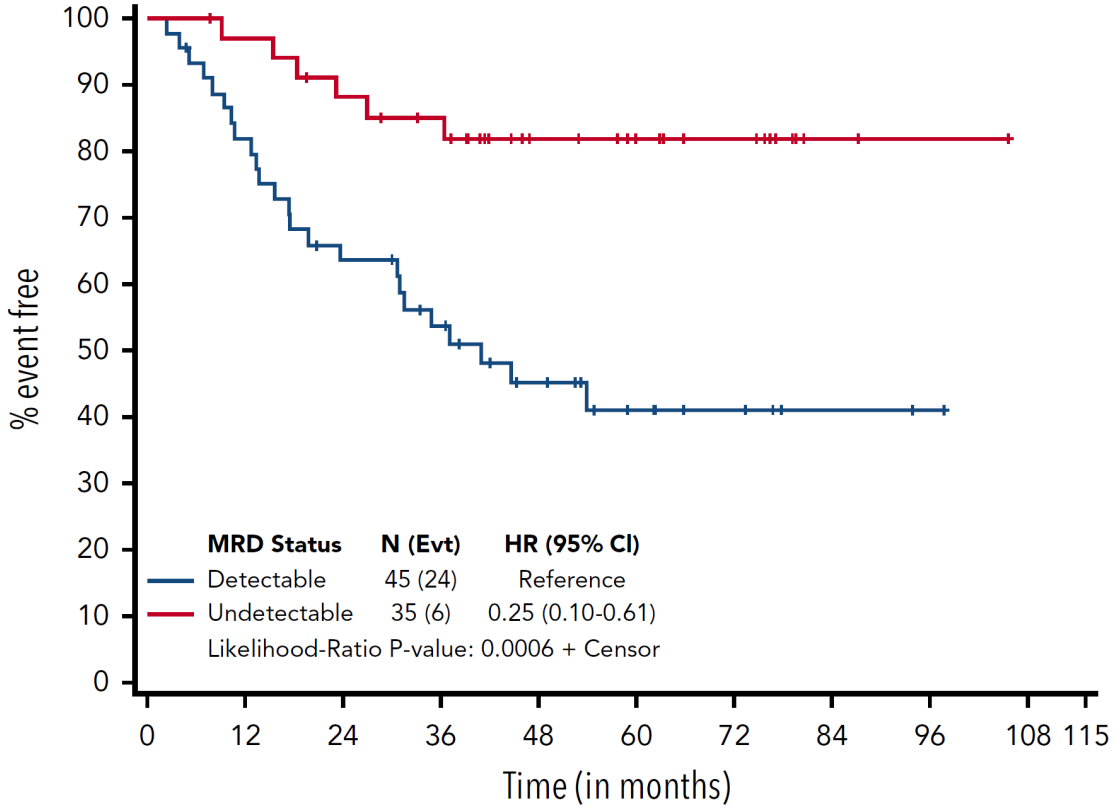
Pediatric vs. Adult Therapy for ALL: Reasons for Different Outcomes

Therapies are different

Doctors are different

Patients are different

EFS by MRD Status: C10403



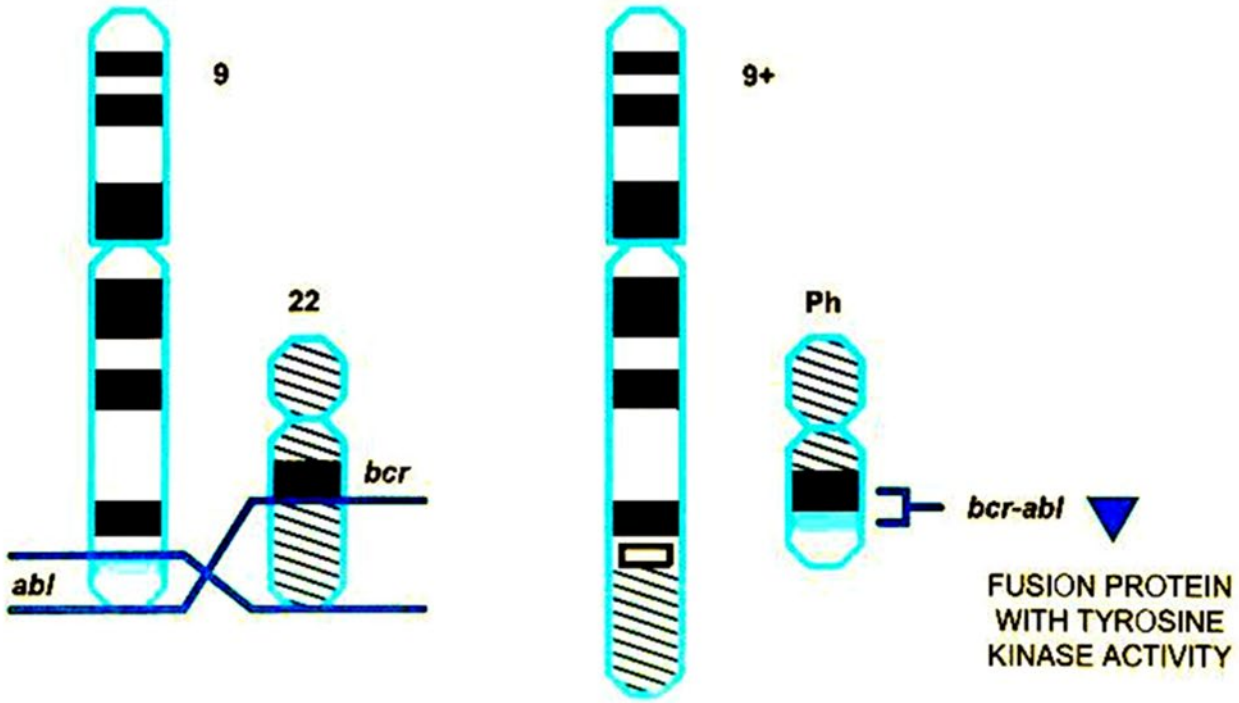
- Of 263 patient who achieved remission, only 20 (8%) underwent HCT in CR1 → reserve HCT for MRD+?
- Increased BMI and Ph-like associated with worse outcome

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:

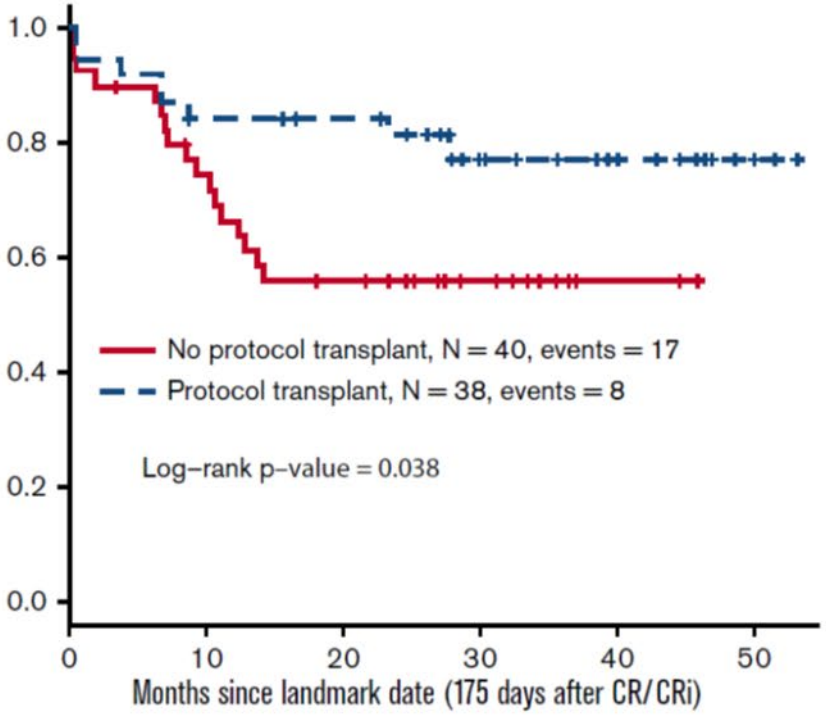
- Include TKI with chemotherapy

Controversial topics:

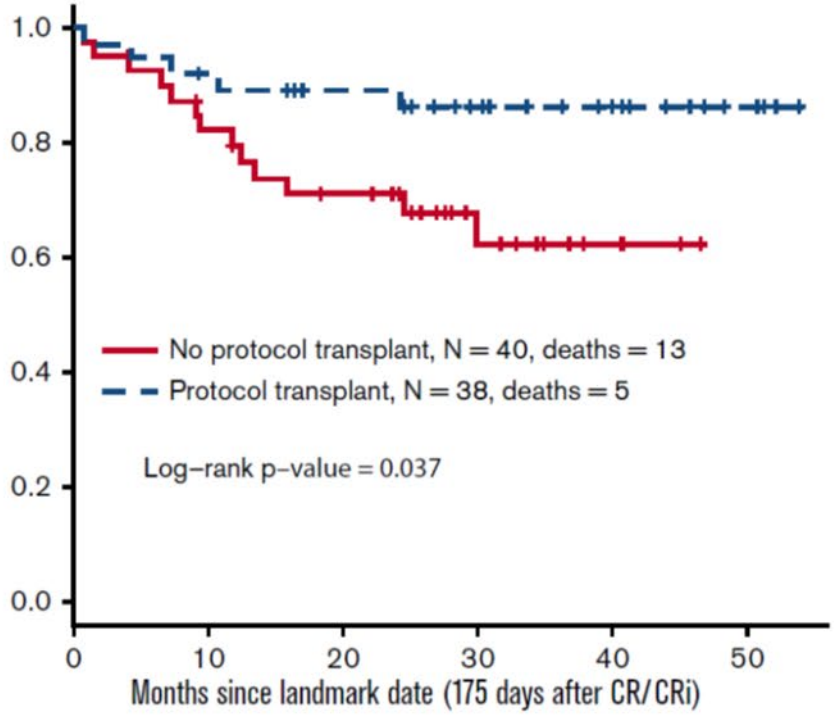
- Is one particular TKI superior?
- How much chemo is necessary?
- HCT in CR1 for all patients?

SWOG 0805: HyperCVAD + Dasatinib

Relapse-Free Survival



Overall Survival

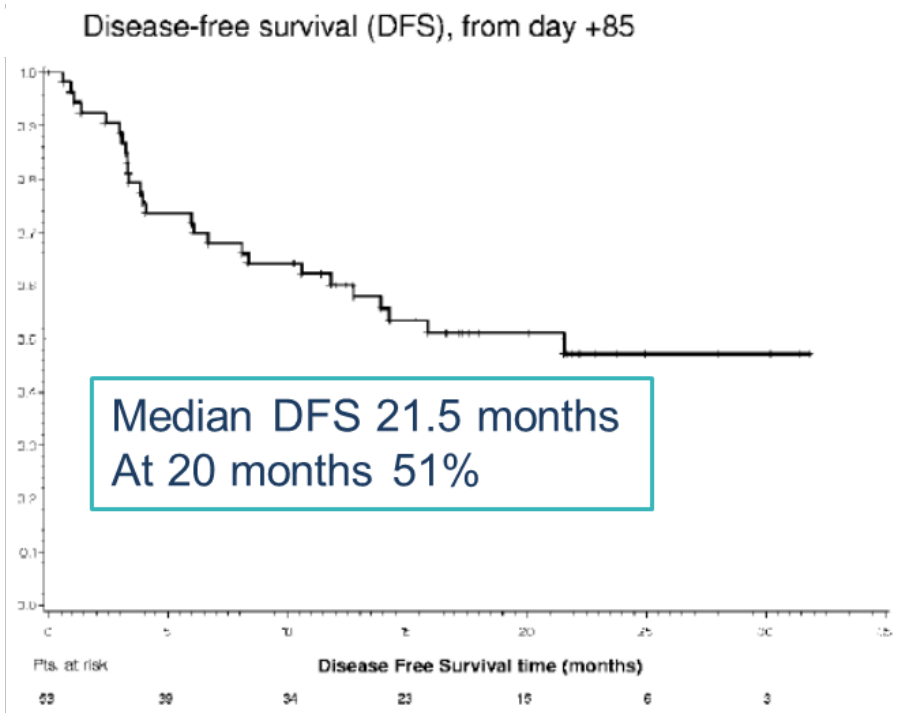


- All patients with matched donor were “encouraged” to undergo allogeneic HCT followed by dasatinib maintenance
- If no HCT, dasatinib-based maintenance therapy

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

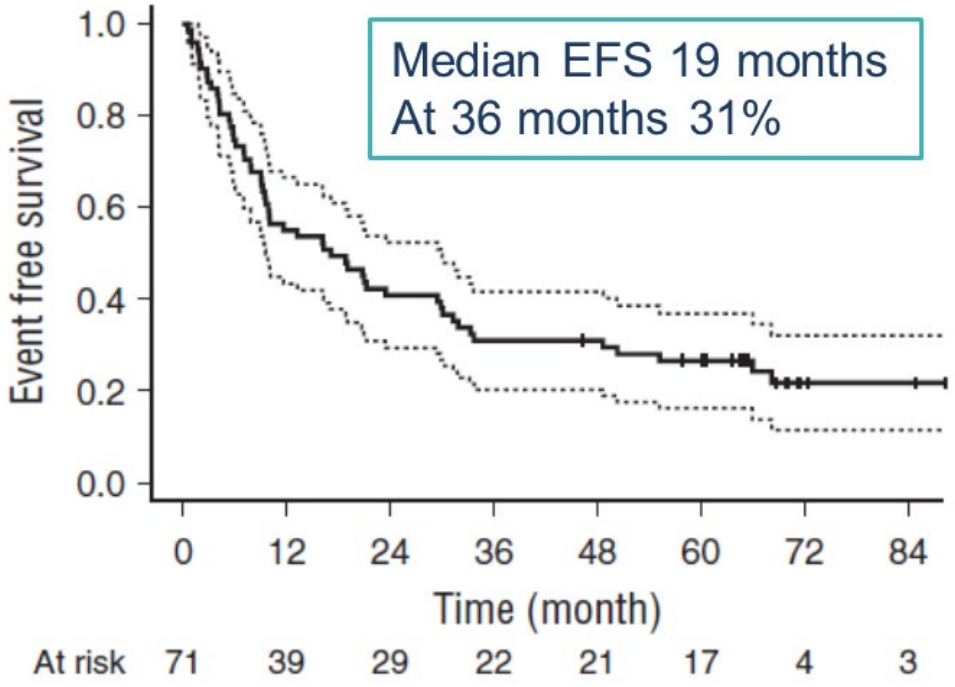
Lower-Intensity Options: Likely Safer, but Less Effective?

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

Specific Scenarios:

ALL In The Elderly

Outcomes with Different Approaches for Older Patients with ALL

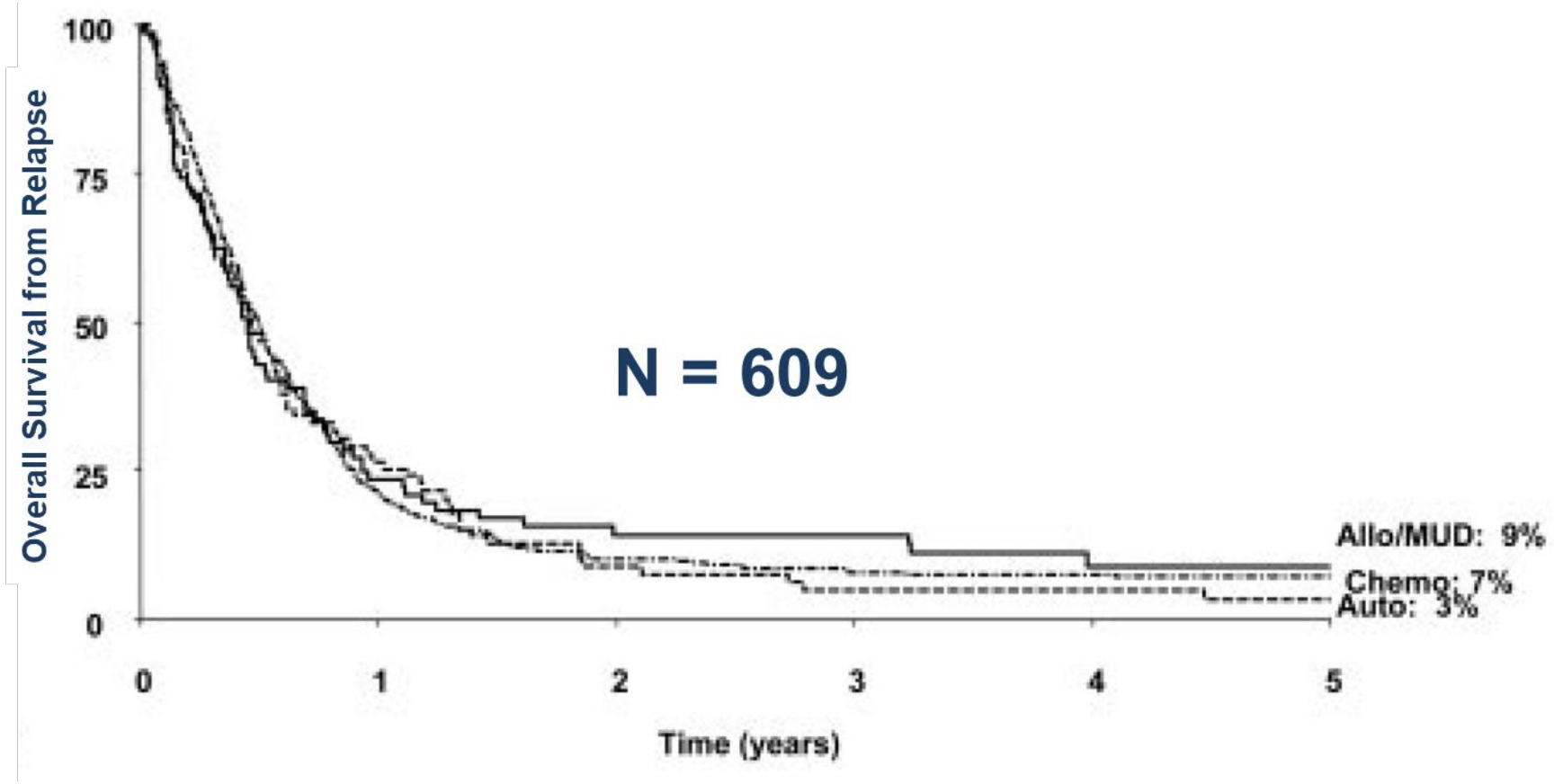
Approach	N	CR Rate	Early Death Rate	Survival (Median/2-yr)
Population-Based Studies	N/R	40%	N/R	6-30%
Palliative Treatment	94	43%	24%	7 mo
Intense chemotherapy designed for younger adults	519	56%	23%	14%
Prospective studies specifically for older adults	447	71%	15%	33%

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 Gökbuget. *Blood*. 2013;122:1366-75.

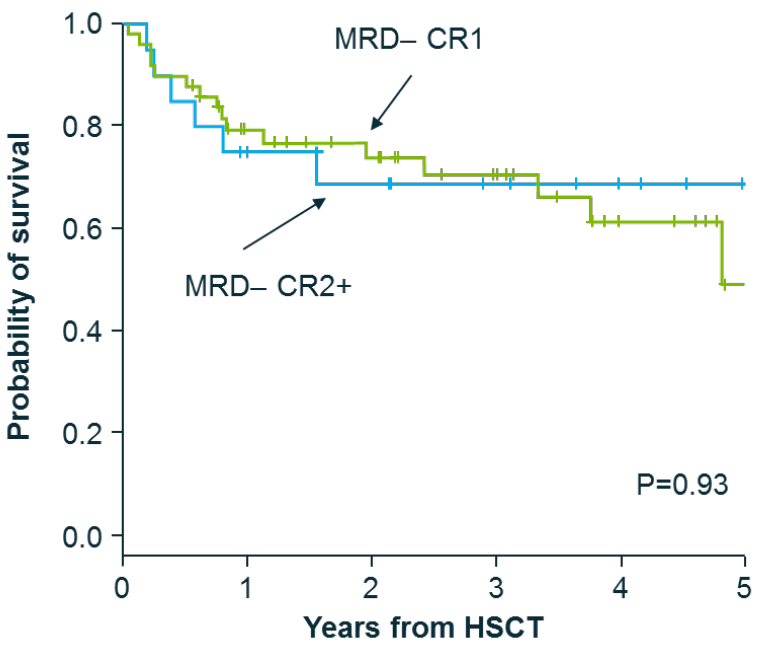
Relapsed/Refractory ALL

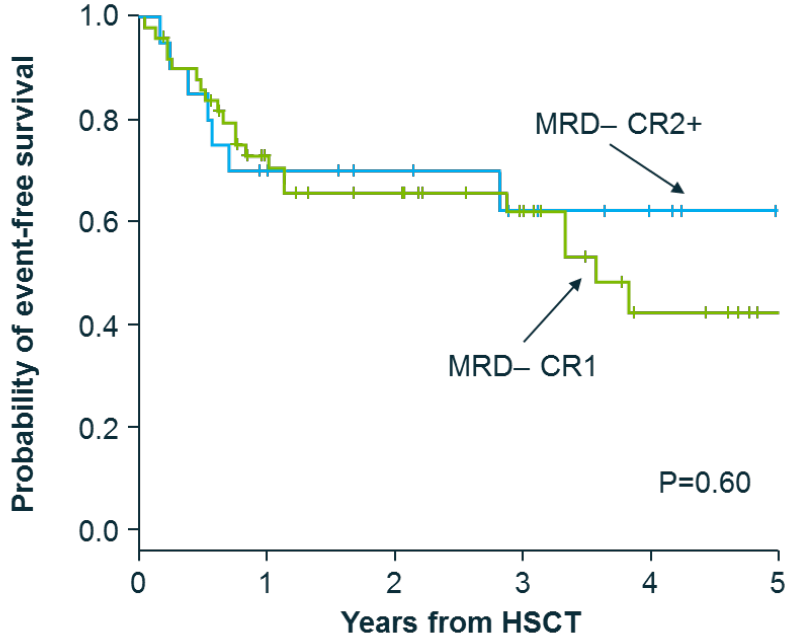
Outcome of Relapsed ALL: UKALL XII/ECOG2993



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

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





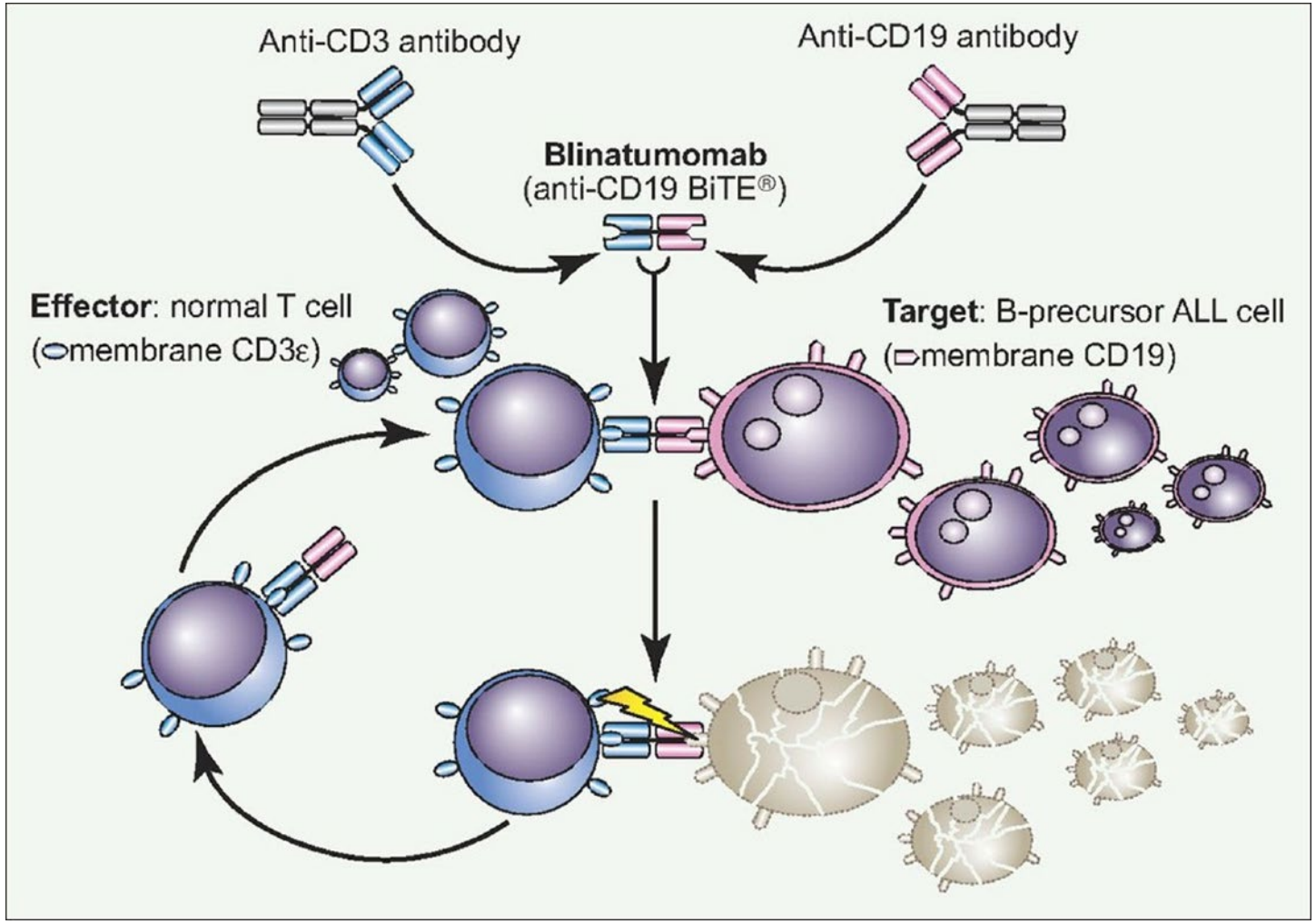
Patients who achieve MRD^{Neg} CR1 are significantly more likely to achieve MRD^{Neg} CR2+ if they relapse.

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

Approvals for Relapsed/Refractory ALL

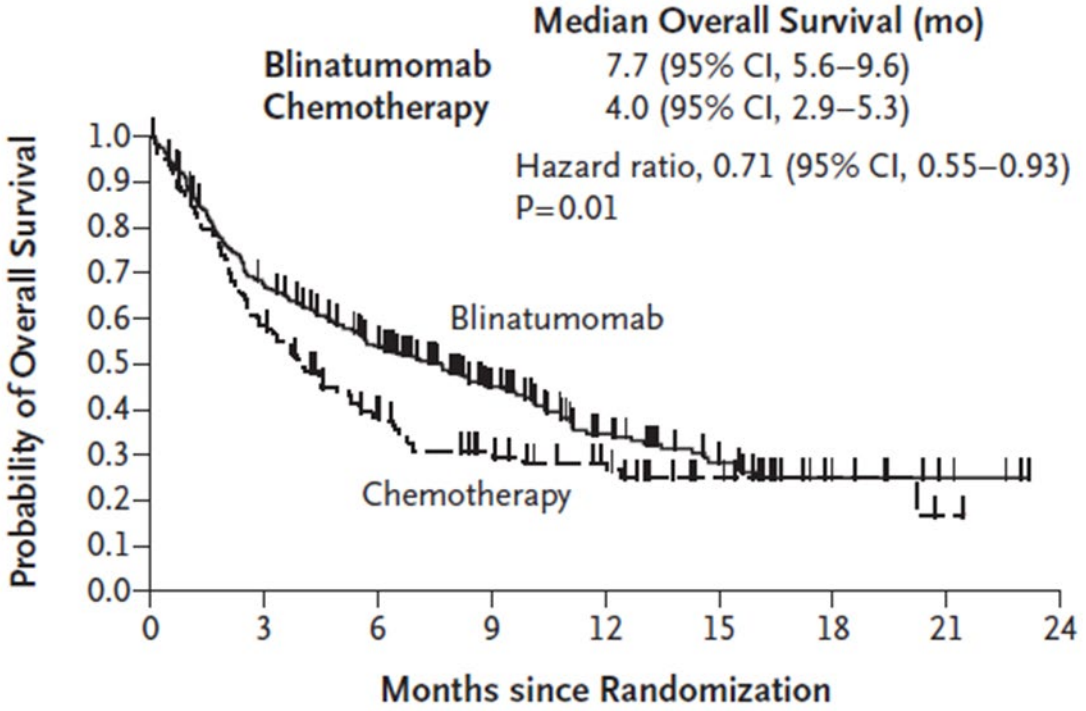
- Purine analogues
  - Nelarabine (T-ALL)
  - Clofarabine (age ≤ 21; ≥ 2 prior therapies)
- Liposomal vincristine (≥ 2 prior therapies; Ph- only)
- *ABL* kinase inhibitors: ponatinib (Ph+ with T315I or no other option)
- CD3-CD19 BiTE: blinatumomab
- CD22 antibody-drug conjugate: inotuzumab ozogamicin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

Blinatumomab = Bispecific T-Cell Engager



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

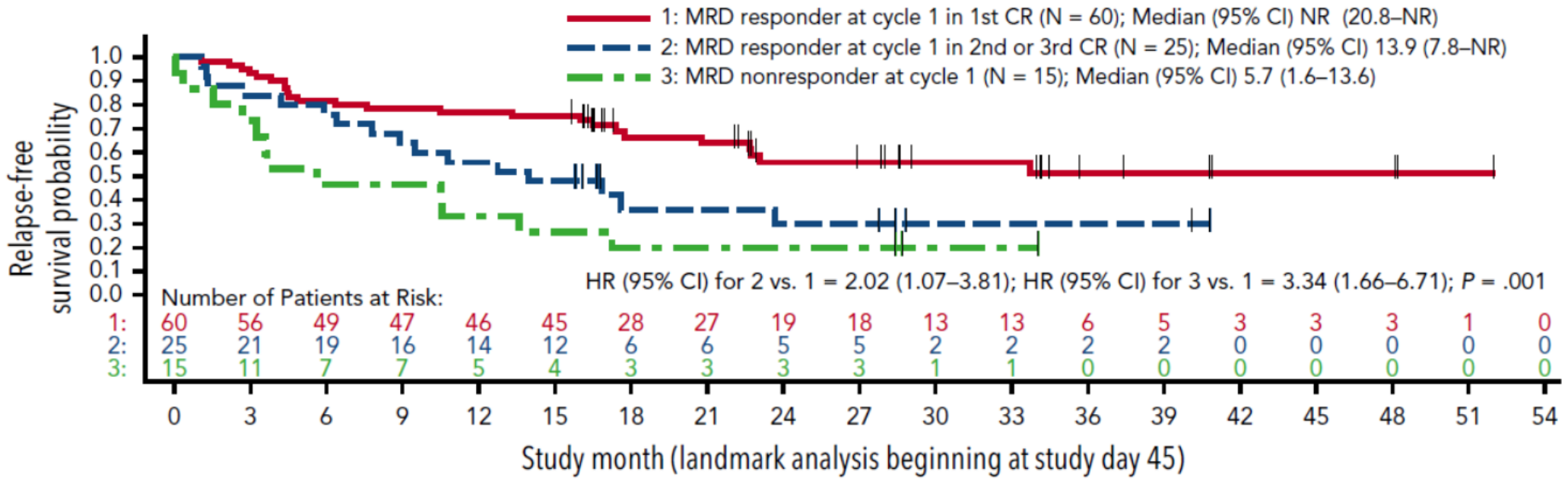
Blinatumomab for Rel/Ref B-ALL



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

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

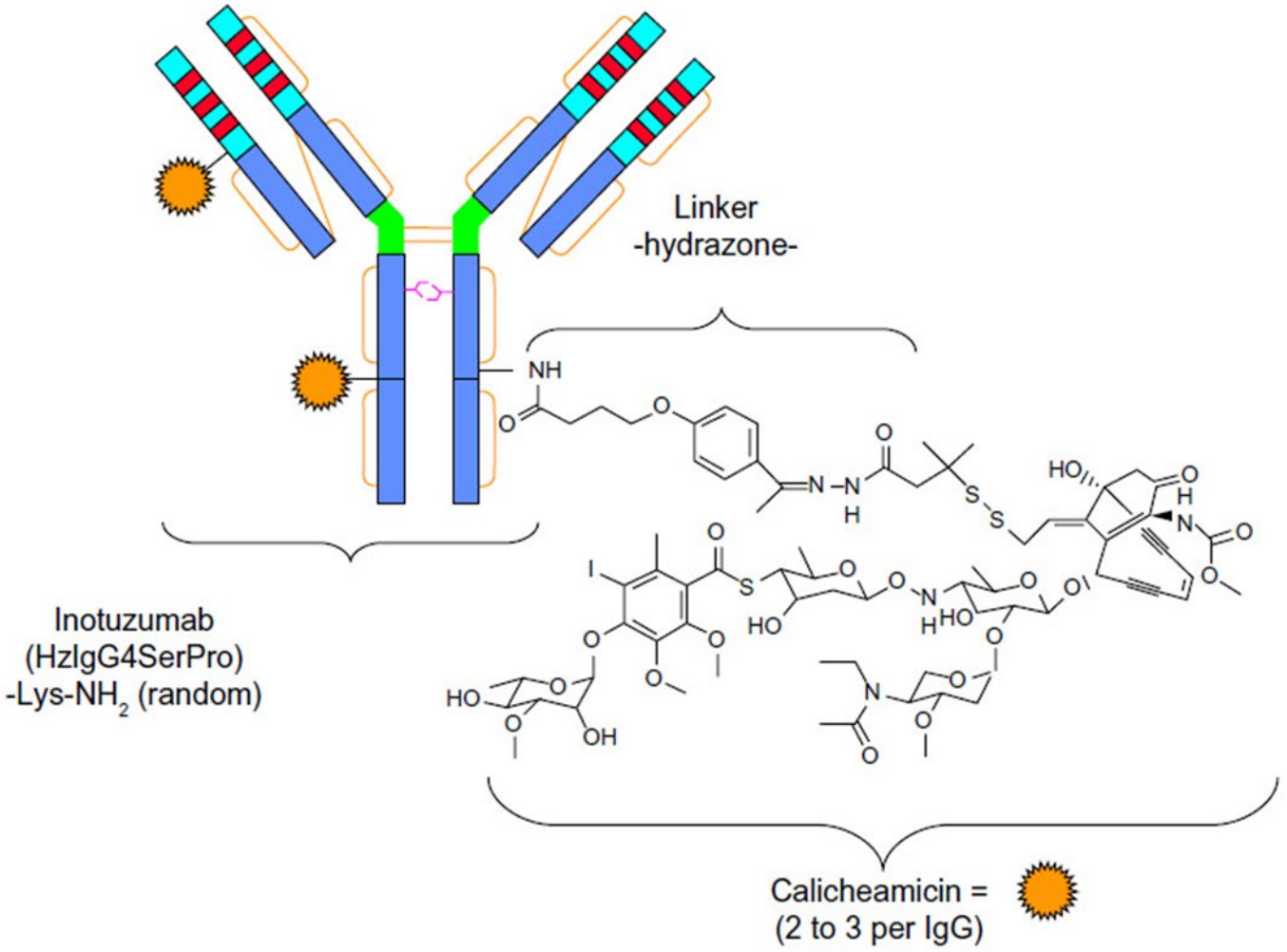
Blinatumomab for MRD



- 78% achieve complete MRD response
- CRS and severe neurotoxicity are uncommon (~10%)
- If no HCT after complete MRD response to blin, 30% alive and in remission (median f/u 5 years)

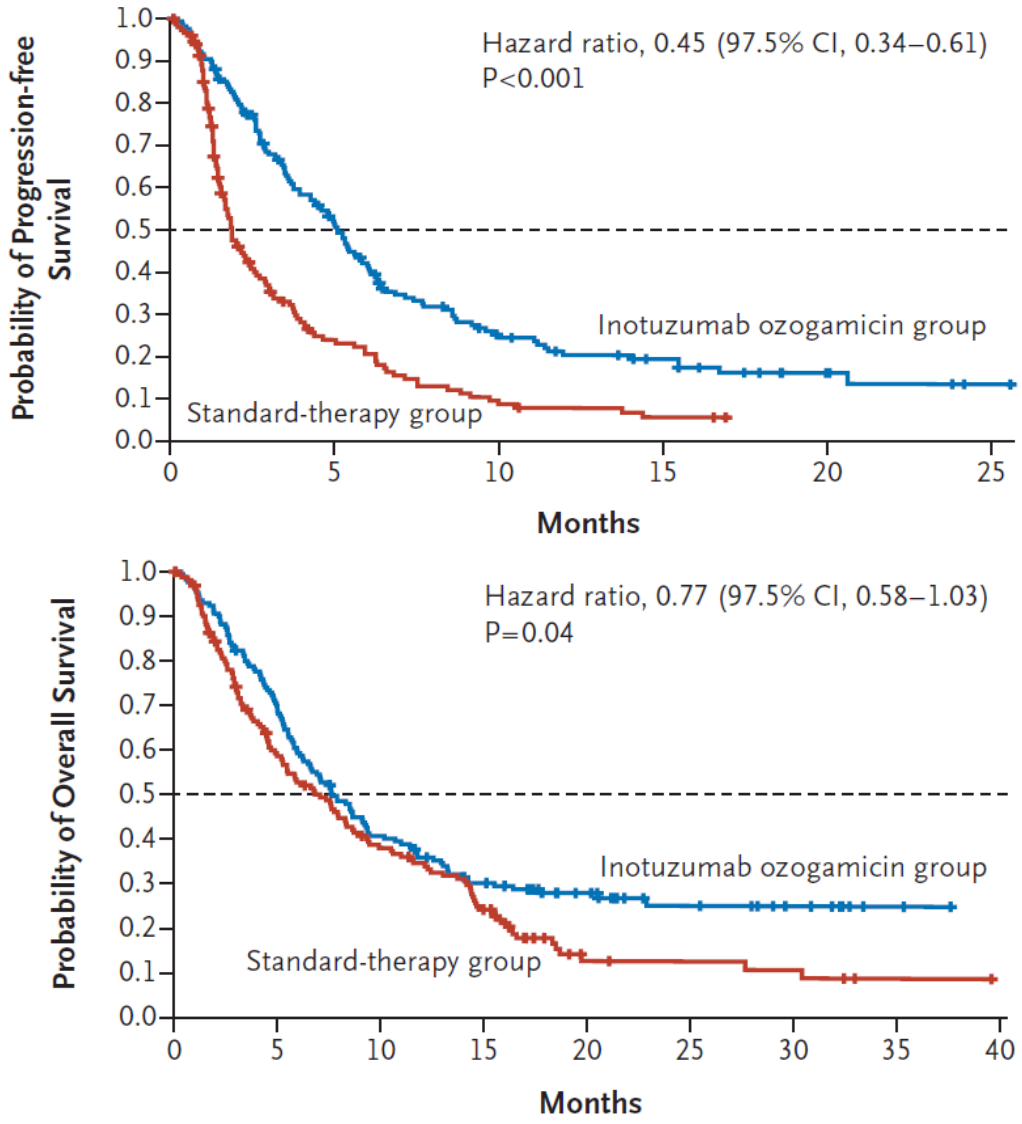
Gökbuget, *et al*. *Blood*. 2018;131:1522-31.
Gökbuget, *et al*. *Leuk Lymphoma*. 2020;61:2665-73.

Inotuzumab Ozogamicin = Anti-CD22 ADC



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

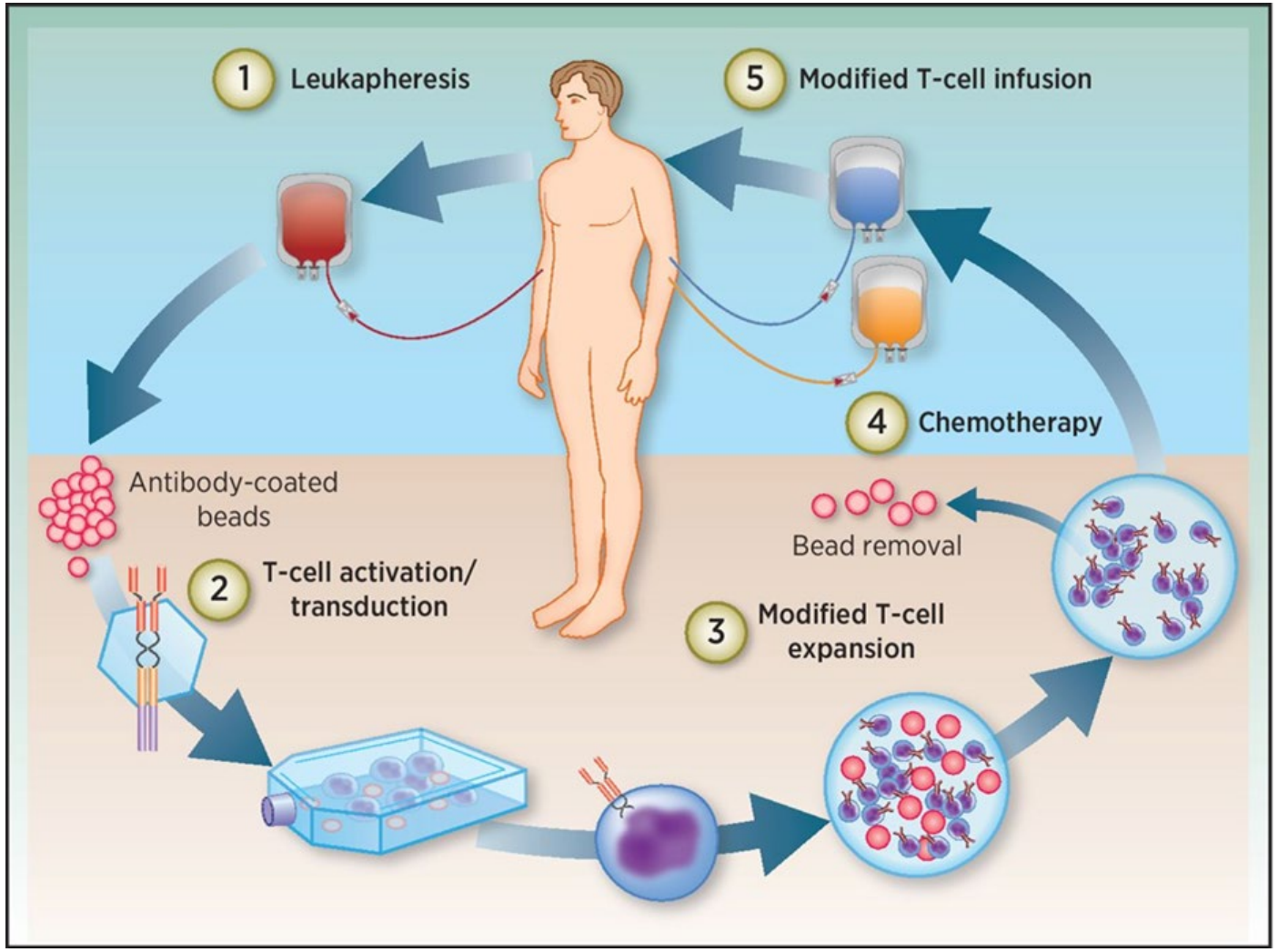
Inotuzumab Ozogamicin for Rel/Ref B-ALL



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

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

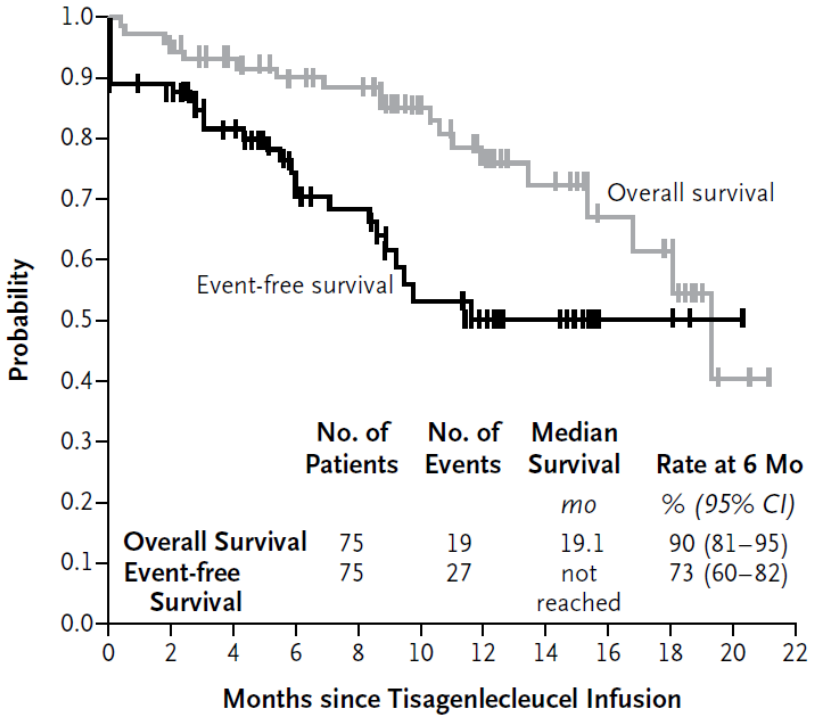
Tisagenlecleucel = CD19 CAR-T Cells



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



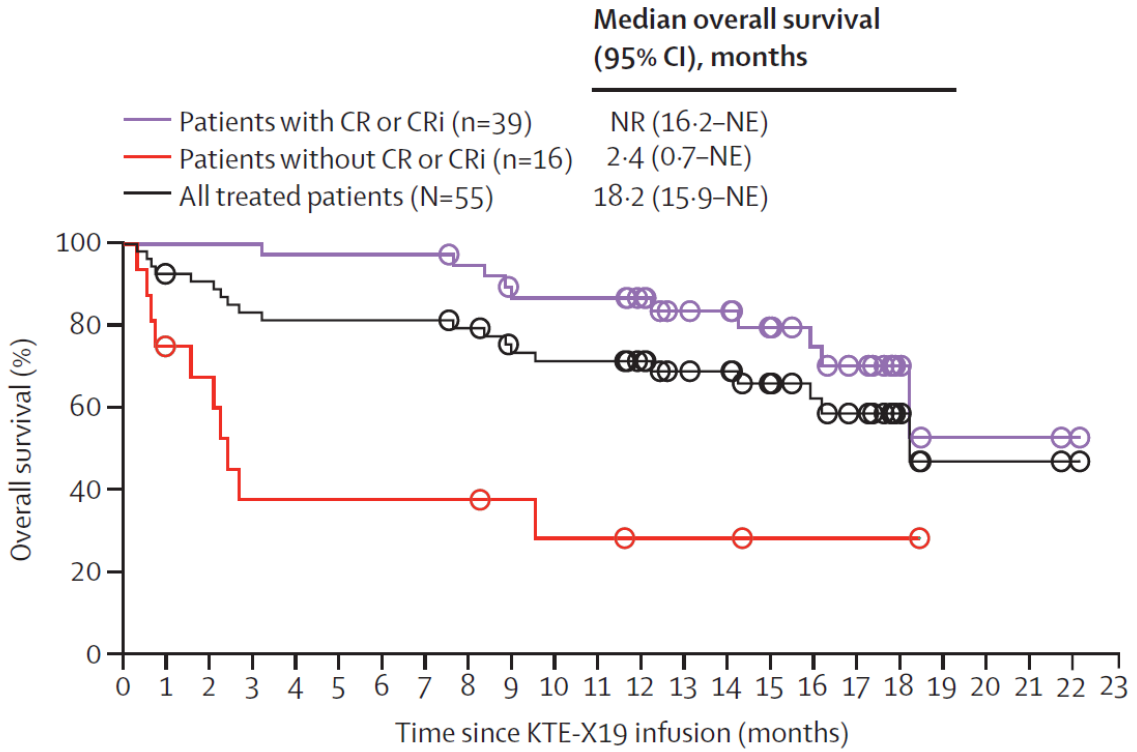
	No. of Patients	No. of Events	Median Survival (mo)	Rate at 6 Mo % (95% CI)
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

No. at Risk

Overall survival	75	72	64	58	55	40	30	20	12	8	2	0
Event-free survival	75	64	51	37	33	19	13	8	3	3	1	0

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

KTE-X19: An Approved CAR-T for Adult B-ALL?



- 71 enrolled, 65 had manufactured product, 55 treated (attrition rate = 23%)
- 39 treated patients (71%; 95% CI = 57-82%) achieved remission, 38 (97%) were MRD-
- Median duration of remission = 12.8 mo (95% CI = 8.7-NR)
- 10 (18%) underwent allogeneic HCT after KTE-X19 infusion
- Grade 3+ CRS = 24%; Grade 3+ neurologic events = 25%; treatment-related death = 4%

Shah, *et al*. *Lancet*. E-pub online: 4 June 2021.

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

Seattle Cancer Care Alliance

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