

ADULT ACUTE LEUKEMIA

Frederick R. Appelbaum, MD
Northern California Blood Cancer Conference
February 4, 2017

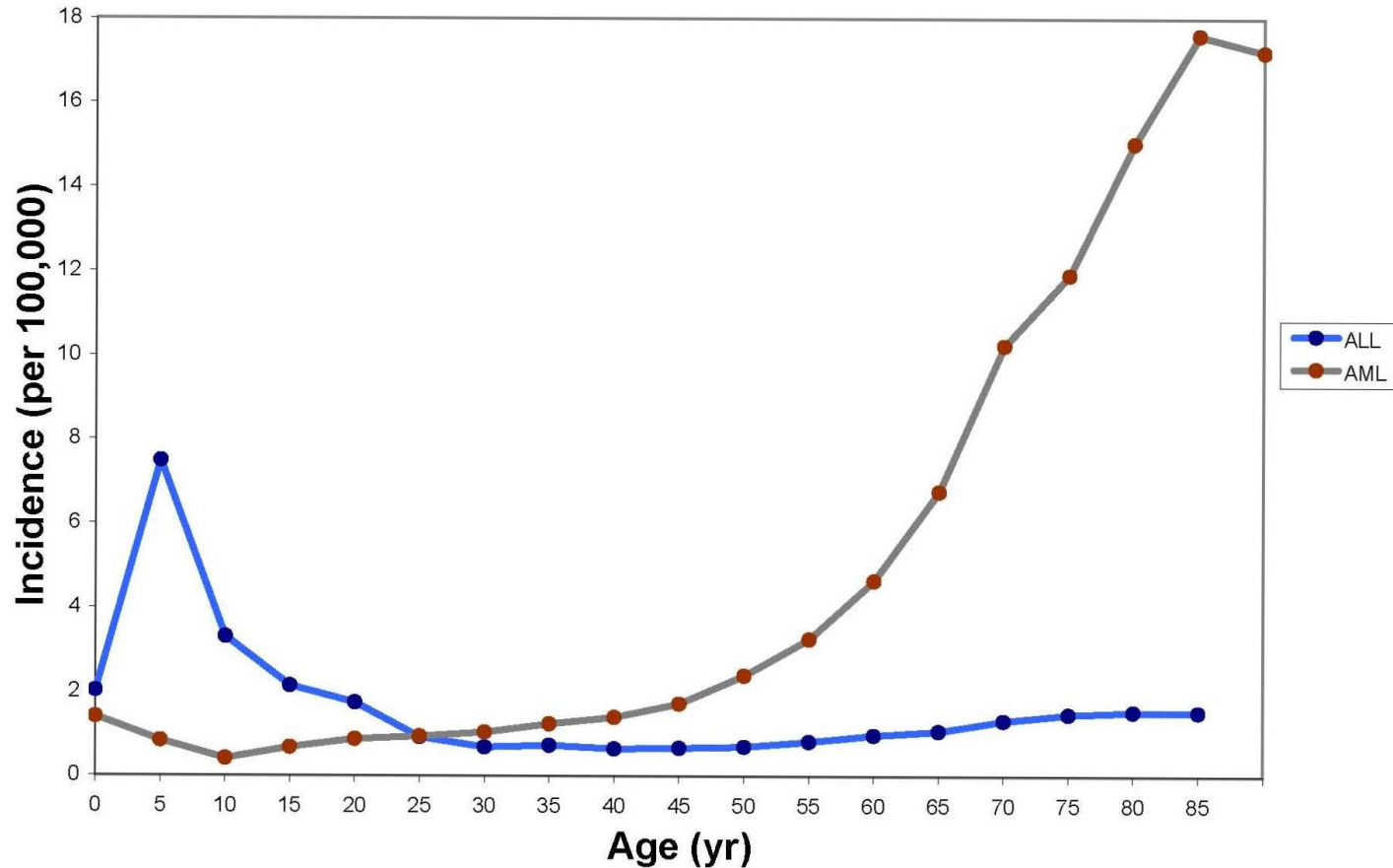


FRED HUTCH[™]
CURES START HERE

Acute Leukemia – 2016 ¹

	<u>New Cases</u>	<u>Deaths</u>	<u>5yr Survival</u>
AML	20,830	10,460	25.9%
ALL	6,250	1,450	67.5%

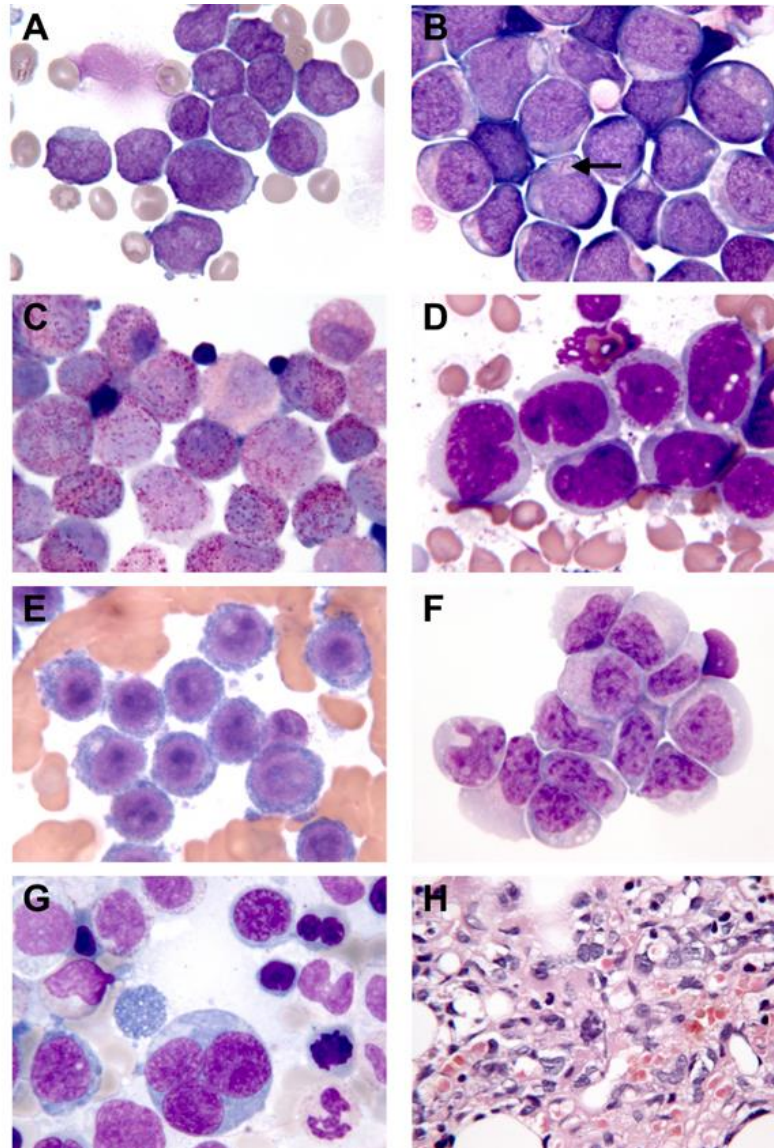
Acute Leukemia Incidence by Age



AML FAB Classification

Classification	Description	Incidence
M0	Undifferentiated	5%
M1	Minimal maturation	15%
M2	With maturation	25%
M3	Promyelocytic	10%
M4	Myelomonocytic	25%
M4eo-		
M5	Monocytic	10%
M5A and M5B		
M6	Erythroid	5%
M7	Megakaryoblastic	10%

AML Morphology



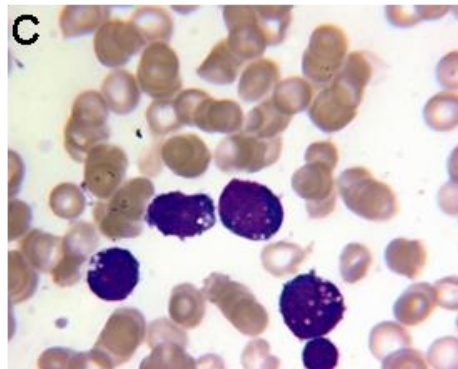
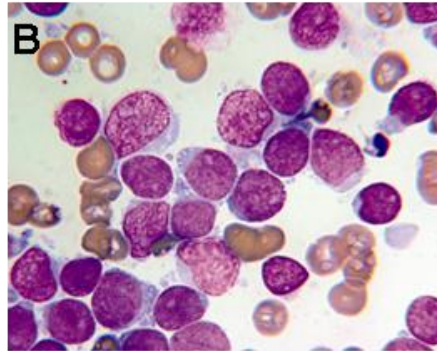
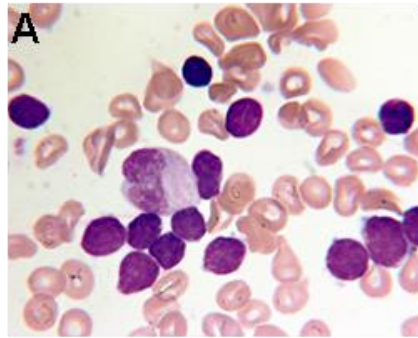
Adult ALL Classification Morphology

L1 25-30%

L2 65-70%

L3 2-7%

ALL Morphology



Factors Essential for Determining Prognosis in Acute Leukemia

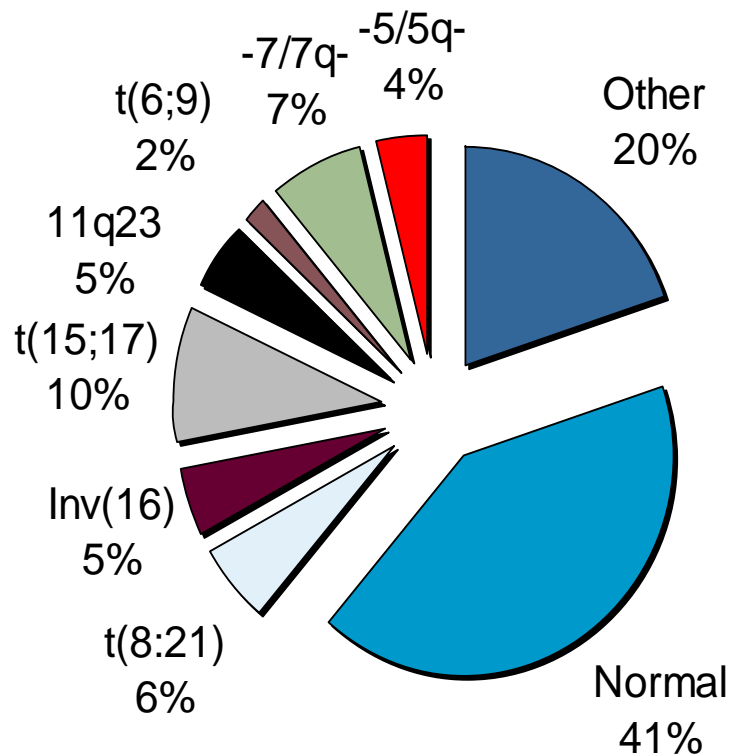
Cytogenetics

Mutational analysis

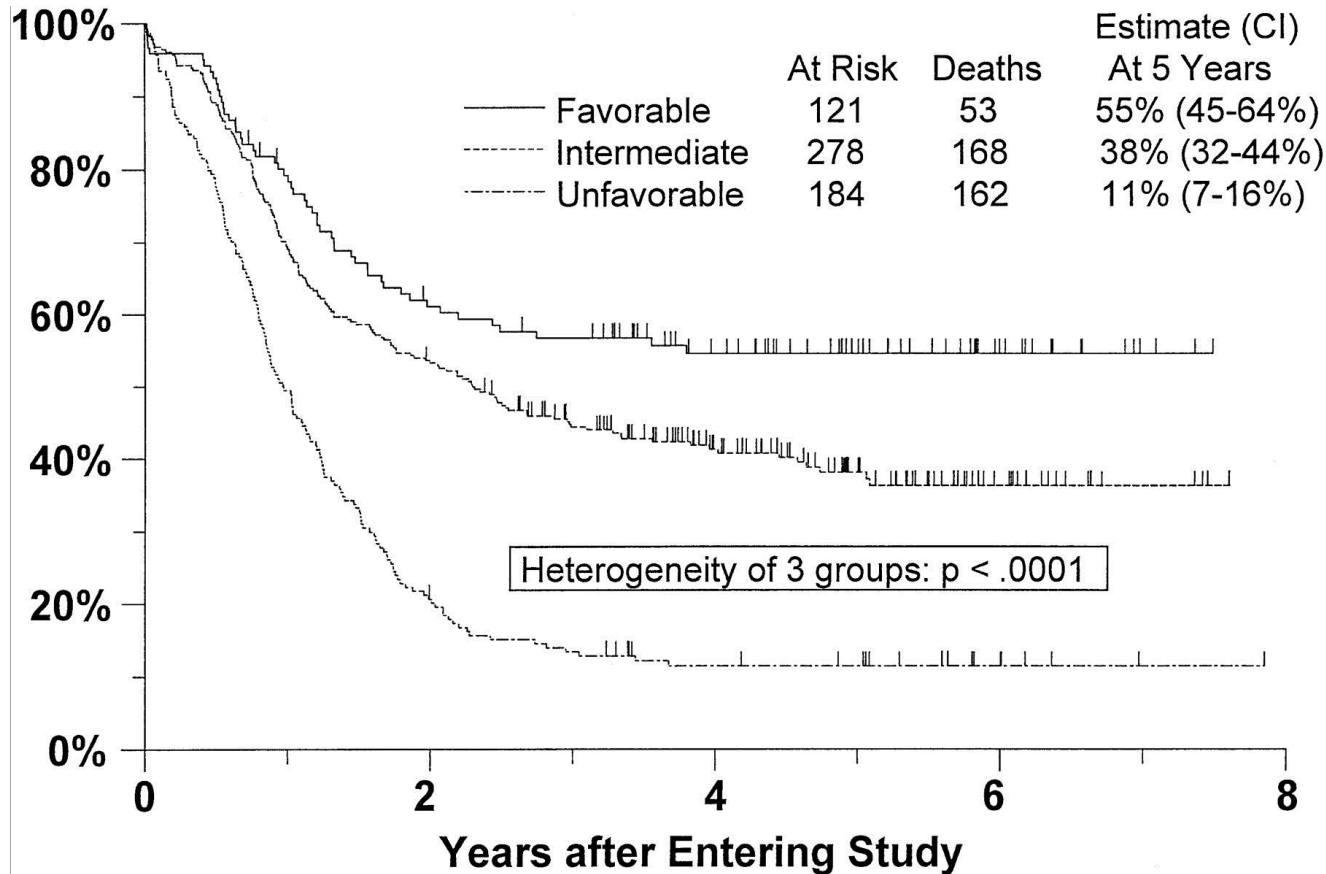
Primary vs secondary

Patient co-morbidities

Clonal Cytogenetic Abnormalities in Adult AML



Survival by Cytogenetic Risk Group in AML¹



Genomic Landscape of AML¹

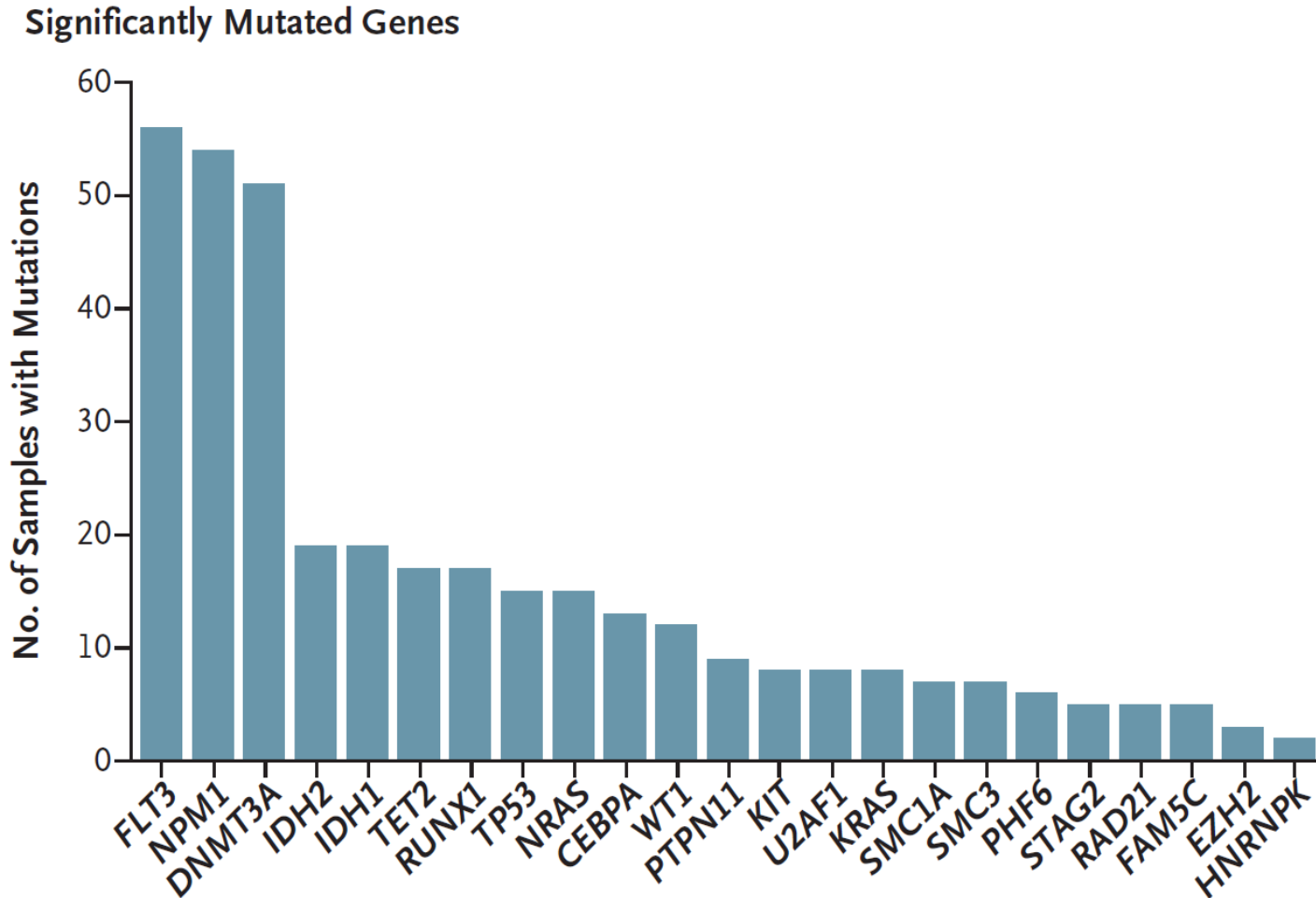
Average # of mutations per case – 13

Average # of “driver” mutations per case – 5

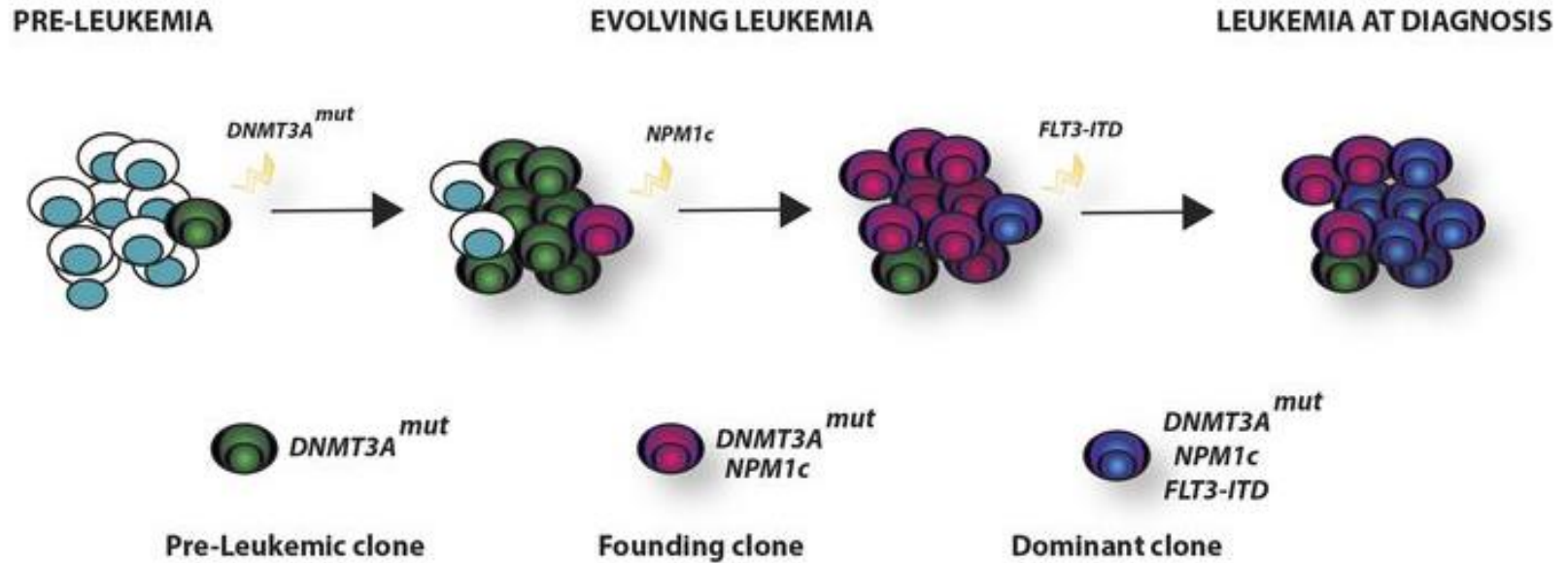
Total # of significantly mutated genes – 23

Total # mutated in two or more samples – 237

Recurrent Mutations in AML¹



Clonal Evolution and Heterogeneity in AML¹



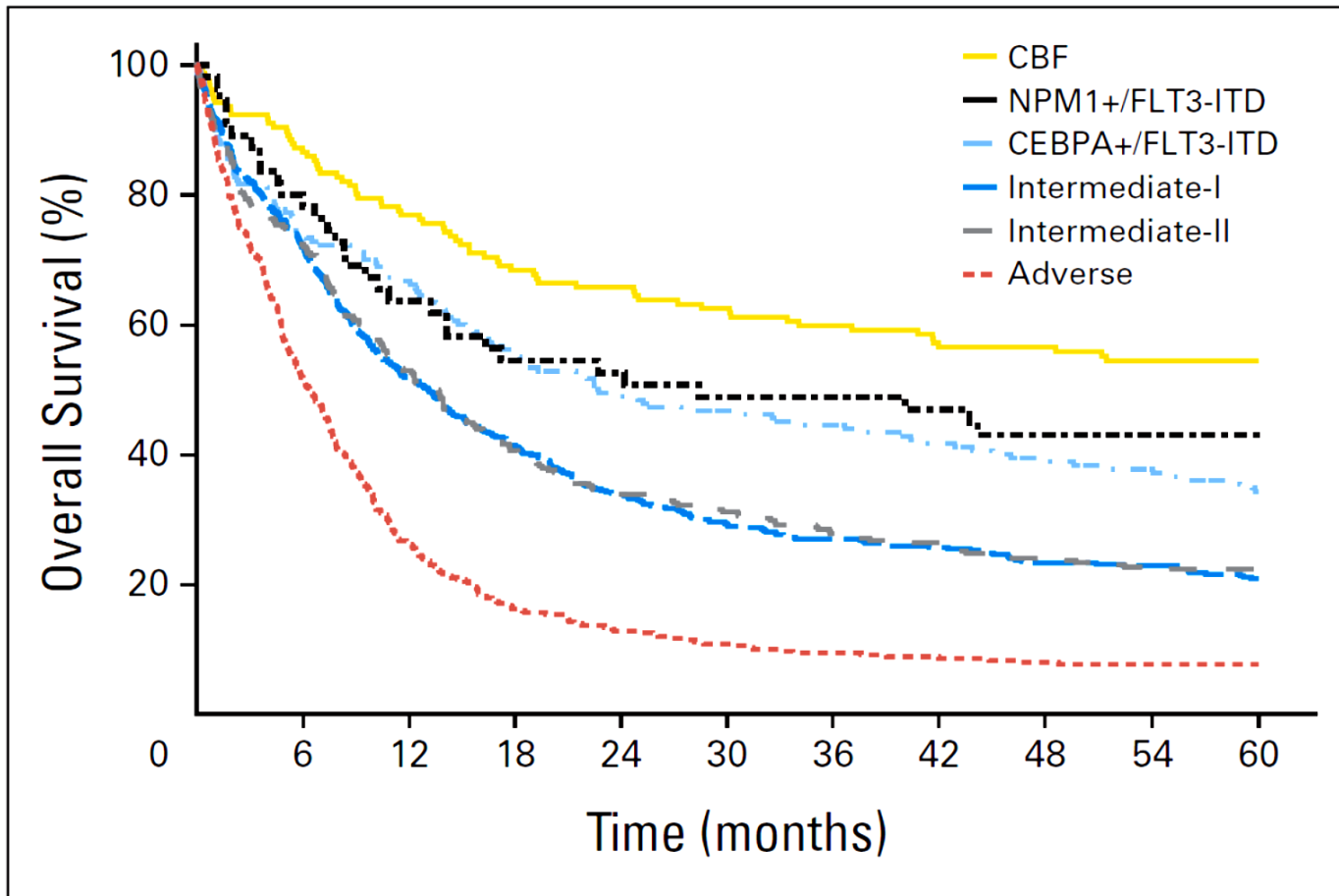
Non-cytogenetic Gene Mutations Relevant to Clinical Practice

<u>Gene</u>	<u>Incidence</u>	<u>Relevance</u>
<i>NPM1</i>	33%	Improved outcome
<i>CEBPA</i>	8%	Improved outcome
<i>FLT3</i>	25%	Inferior outcome
<i>KIT</i>	8%	Inferior outcome

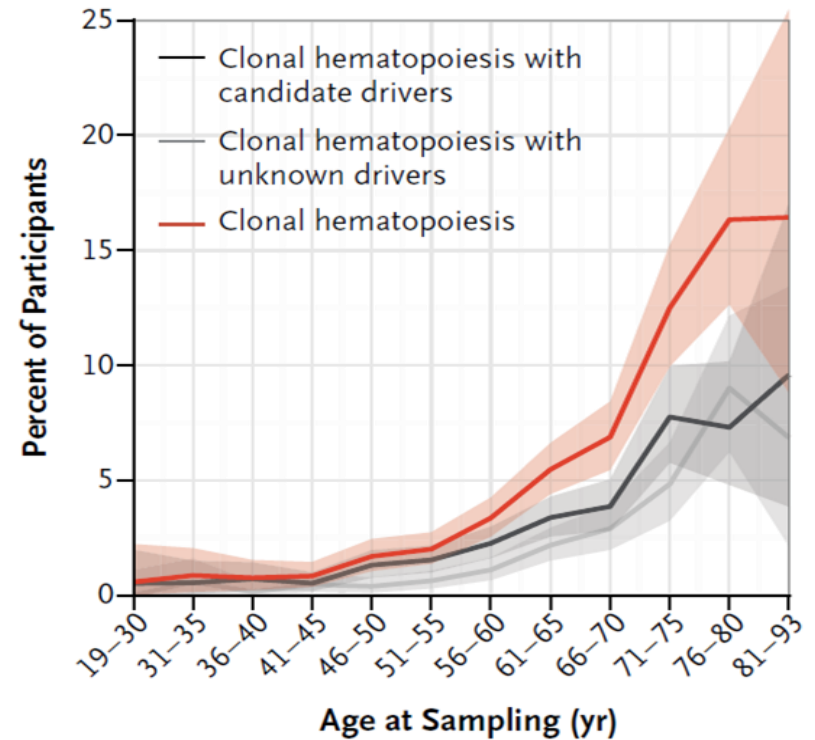
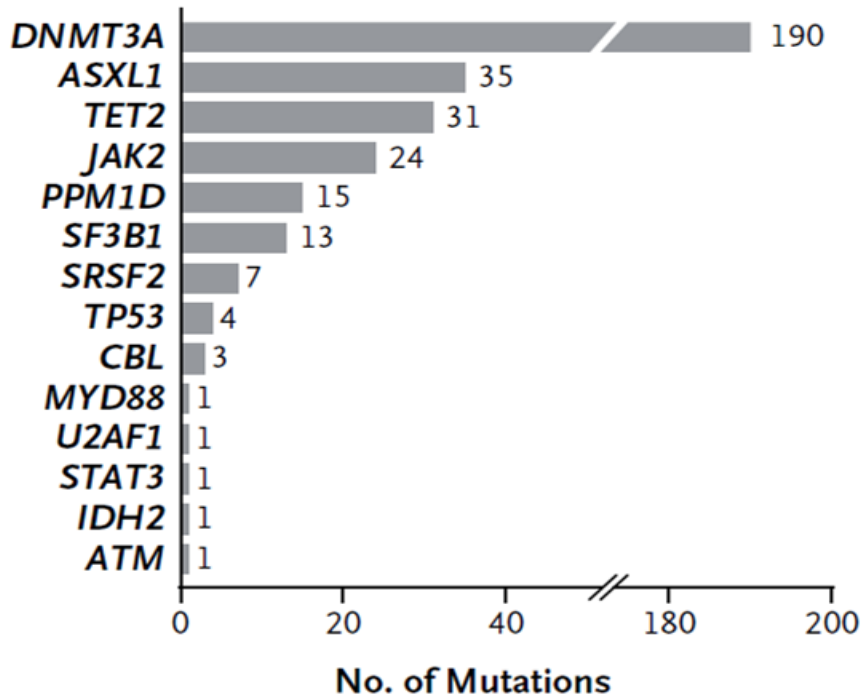
AML – 2016¹

<u>Risk Category</u>	<u>Genetic Abnormality</u>
Favorable	t(8;21) inv(16) <i>NPM1+</i> <i>FLT3-</i> <i>CEBPA+</i> (biallelic)
Intermediate	<i>NPM1+</i> <i>FLT3+</i> <i>NPM1-</i> <i>FLT3-</i> t(9;11) Cyto+, not fav or unfav
Adverse	t(6;9), t(v;11q23) t(9;22), inv(3) -5,-7,-17 Complex, <i>NPM1-</i> <i>FLT3+</i> <i>RUNX1+</i> , <i>ASXL1+</i> , <i>p53+</i>

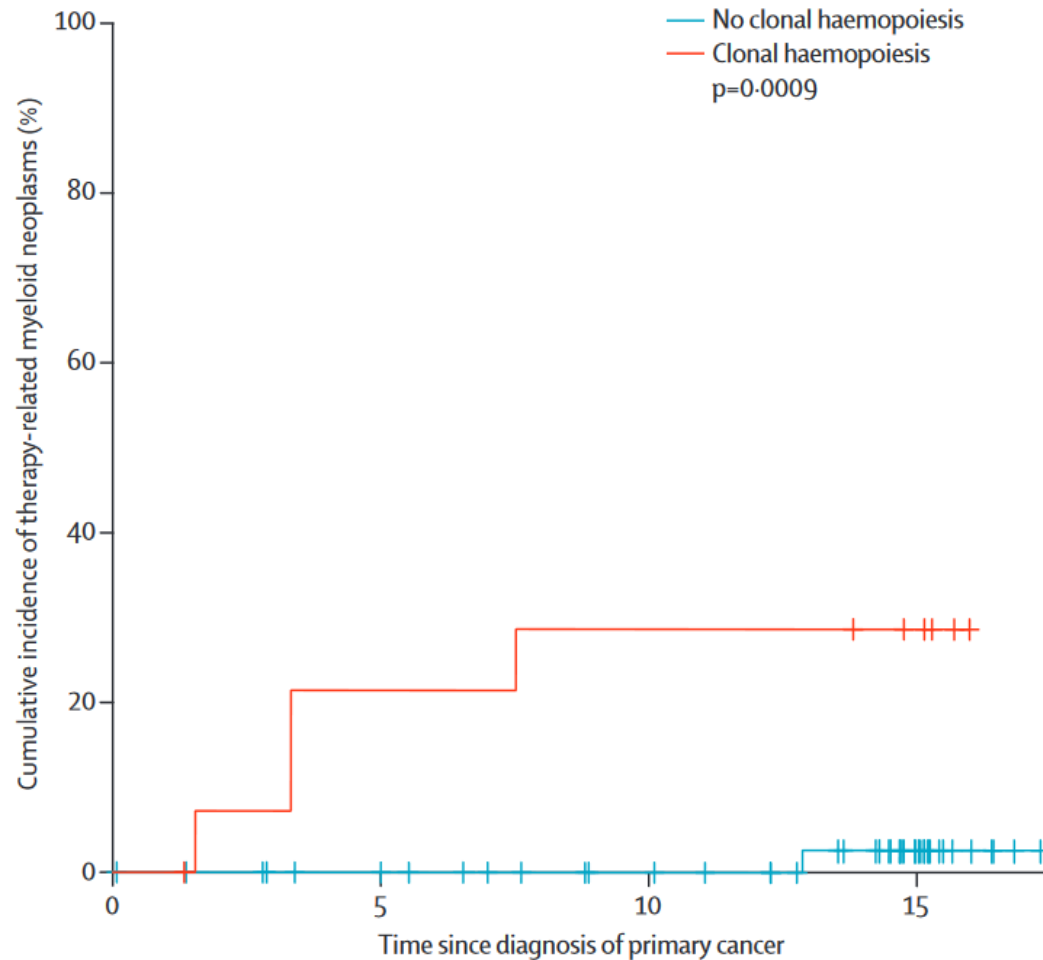
AML Survival by Risk Group¹



Clonal Hematopoiesis in Normal Adults¹



Cumulative Incidence of Therapy-Related AML in Patients with and without CHIP¹



Secondary AML¹

Frequency – 19.8%

Latency

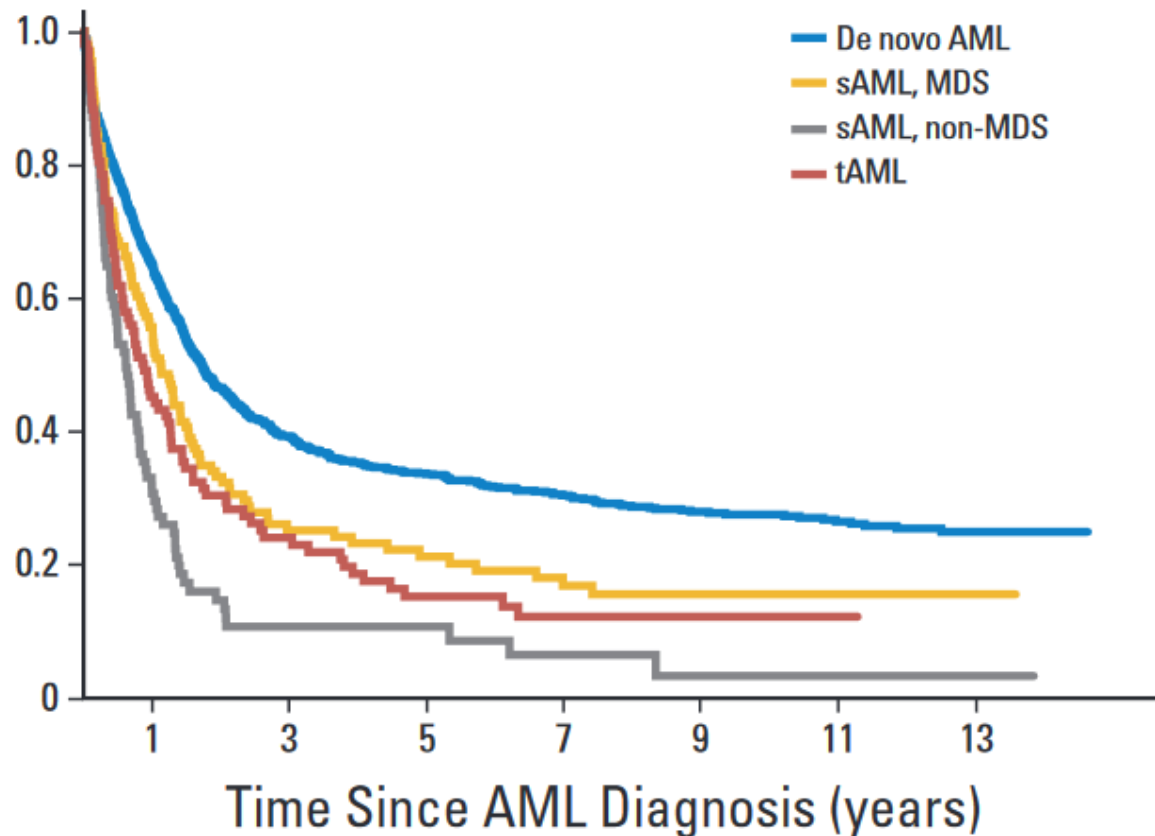
MDS – 17 mo.

CMML – 18 mo.

MPN – 43 mo.

Survival Following Intensive Therapy for AML¹

Primary vs. Secondary vs. Treatment related



Major Cytogenetic Categories in Adult ALL

Favorable

High hyperdiploidy
del 9p

Incidence

10%
9%

Unfavorable

t(4;11)
Low hypodiploidy/near triploidy
Complex

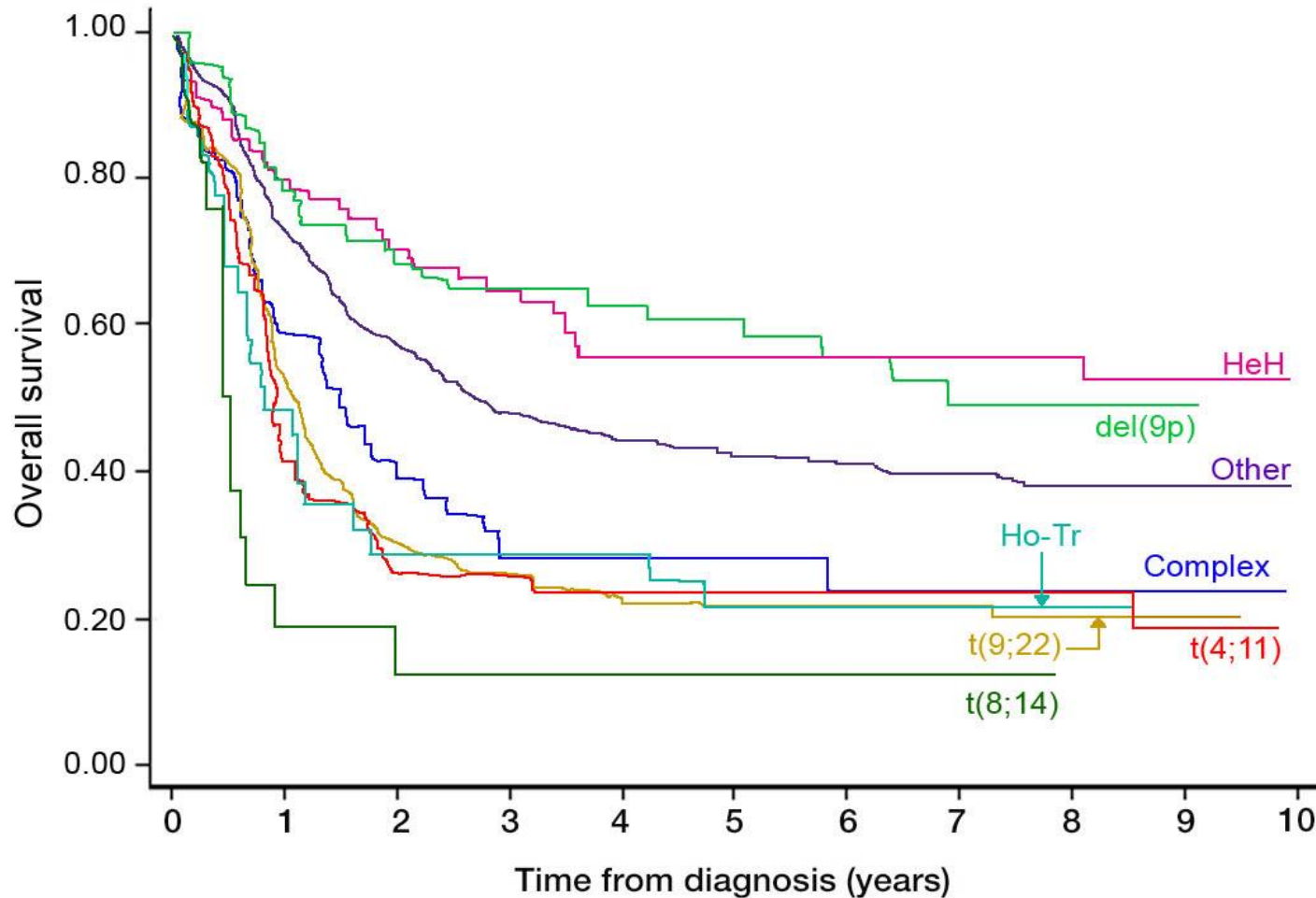
7%
4%
5%

Other

t(9;22)
t(8;14)

19%
2%

Overall Survival by Cytogenetic Subgroup: MRC UKALL XII / ECOG 2993¹



Genome-wide Analysis of Genetic Alterations in ALL¹

B-cell mutations: *ETV6, TCF3, MLL, CRLF2, RUNX1, PBX1, PAX5, IK2F1*

T-cell mutations: *NOTCH1*

Ph-like ALL¹

1. Approximately 15% of B-cell ALL
2. Increase with age, males and high WBC
3. Molecular Abnormalities:
 - Abl-class fusions
 - JAK2 rearrangements
 - CRLF2 rearrangements
 - Other JAK-STAT abnormalities
 - RAS mutations
4. Poorer prognosis
5. May respond to TKIs

¹ Roberts, NEJM 371:1005,2014

Adult ALL

Risk Factors

1. Age > 30
2. WBC
 - > 30,000/ μ L (B lineage)
 - > 100,000/ μ L (T lineage)
3. Cytogenetics
 - t(9;22)
 - t(4;11)
 - t(8;14)
 - Complex
 - LoHypo/Near Trip

AML Induction Dosing (Age <65)

Anthracycline/Anthracenedione

Daunorubicin 60 to 90 x 3

Idarubicin 10 to 12 x 3

Mitoxantrone 12 to 15 x 3

Cytarabine 100 to 200 x 7

Third drugs?

60 vs 90 mg/m² of Daunorubicin for AML¹

N – 1206

Design – 10 + 3 DNR 60 vs 90

Outcome

	<u>DNR 60</u>	<u>DNR 90</u>
CR	84%	81%
ED	4%	6%
RFS (2 yr)	50%	52%
Relapse	41%	37%

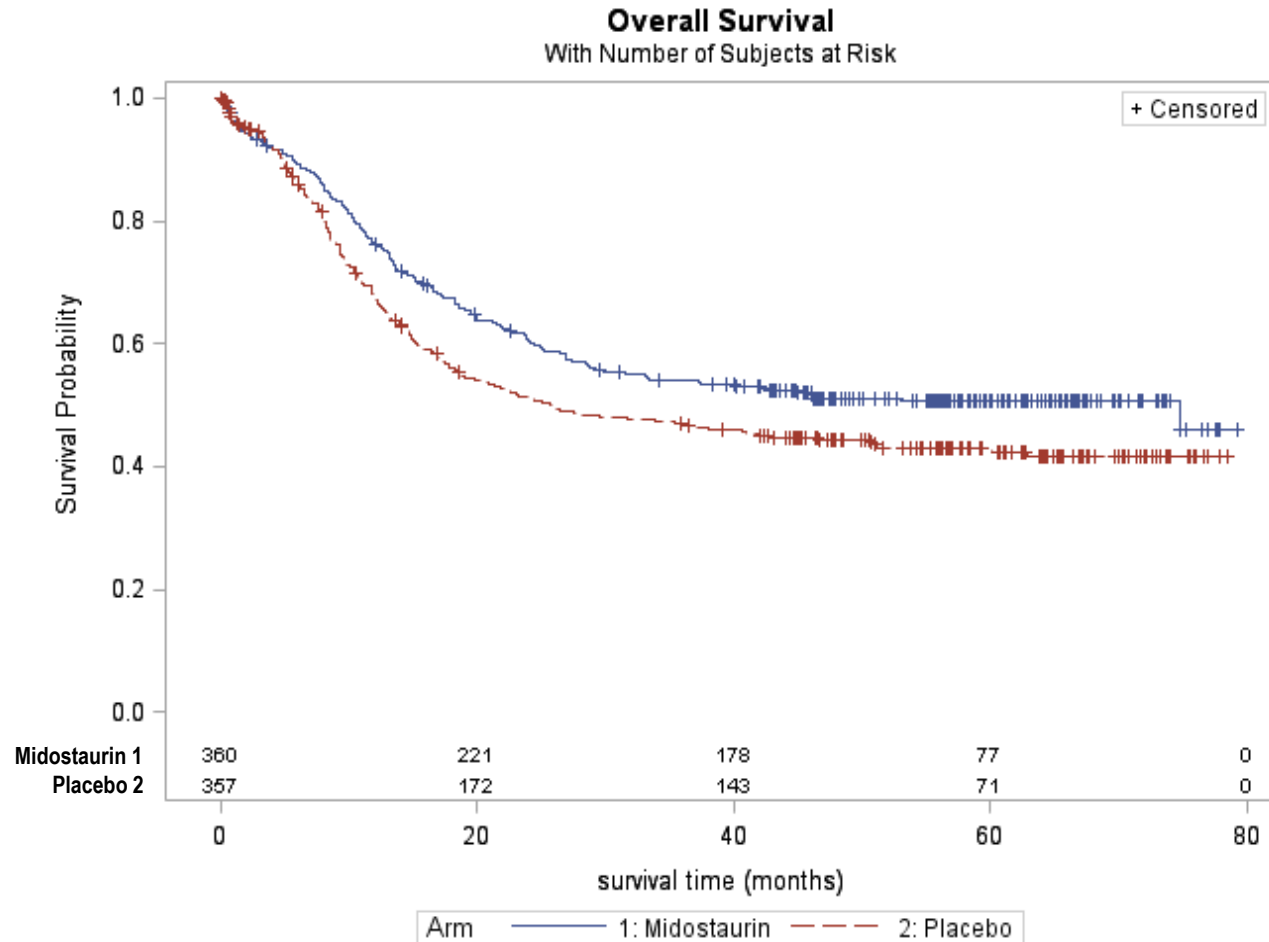
CPX 351 for Secondary AML¹

N – 309

Age – 60-75

	<u>CPX 100m/m² d1,3,5</u>	<u>DNR 60x3, AraC 100x7</u>
CR+CRi	47%	33%
CR	37%	26%
OS 12 mo.	41%	27%
OS 24 mo.	31%	12%

Standard Induction +/- Midostaurin in *FLT3* +AML¹



Alternative *FLT3* Inhibitors

1st generation

Sorafenib

Sunitinib

Lesaurtinib

Midostaurin

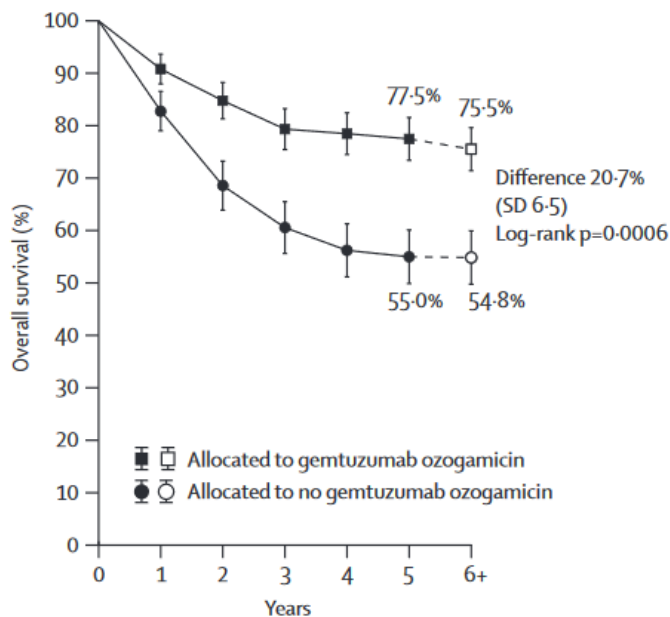
2nd generation

Quizartinib

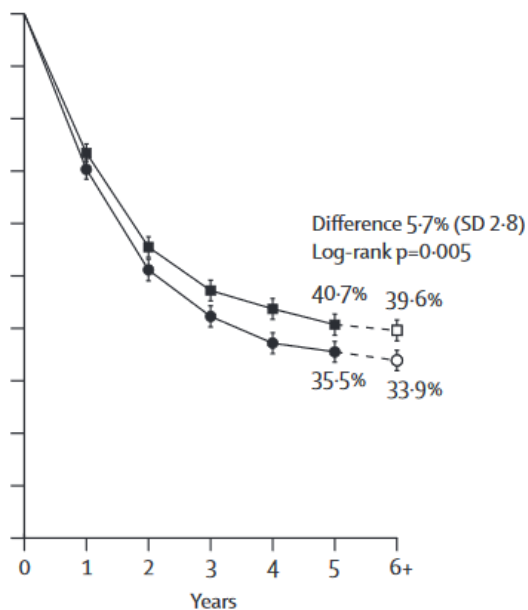
Crenolanib

Gilteritinib

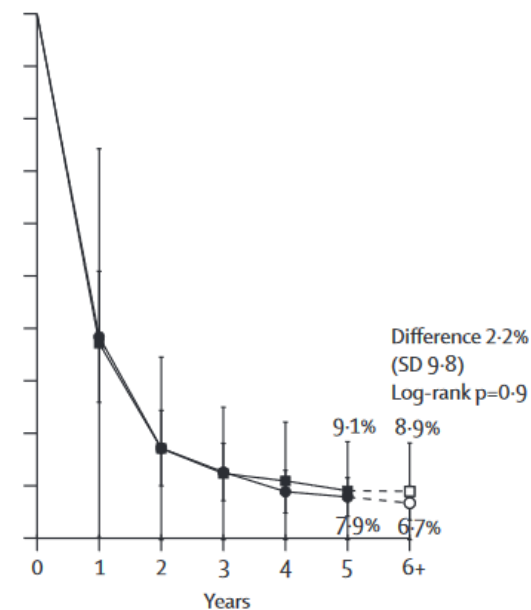
Meta-Analysis of Chemo Therapy +/- GO¹



Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	5.8% SD 1.1	2.3% SD 1.3
No gemtuzumab ozogamicin	14.1% SD 1.9	0.0% SD 0.0

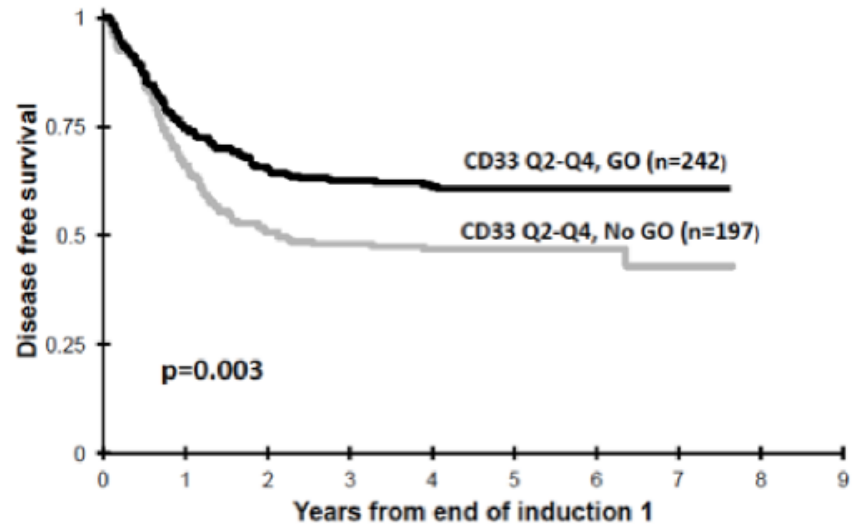
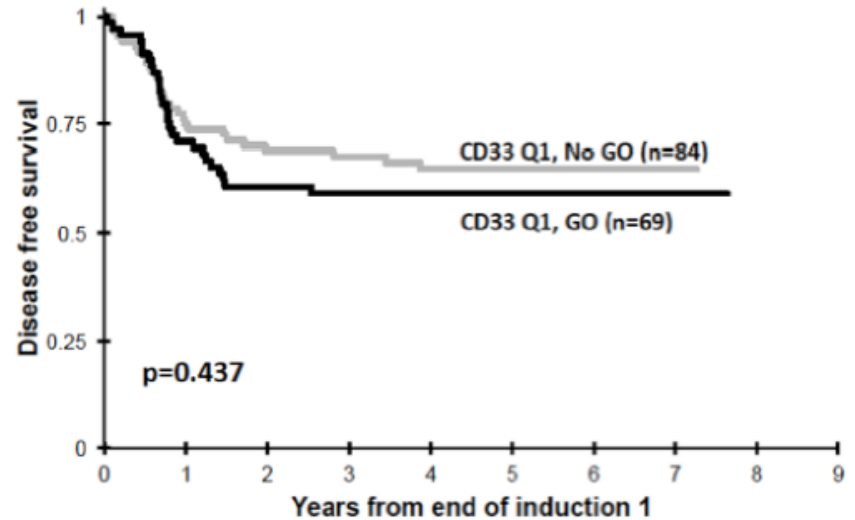
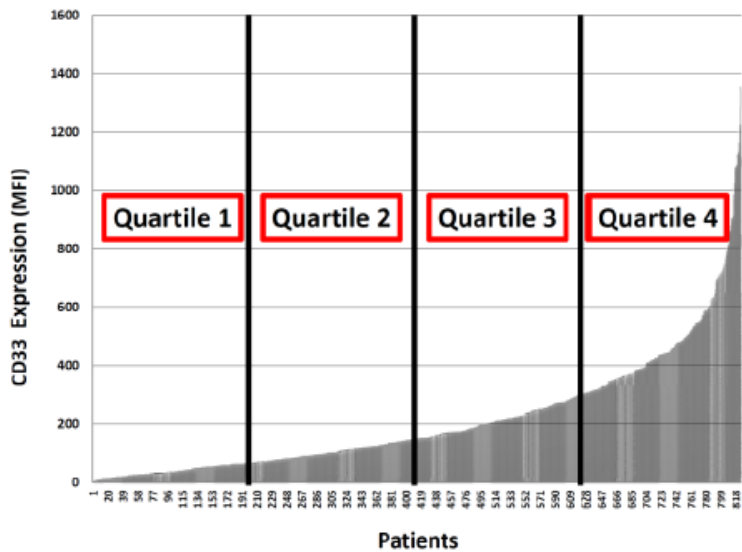


Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	22.4% SD 1.0	2.7% SD 0.9
No gemtuzumab ozogamicin	26.2% SD 1.1	4.9% SD 1.3



Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	73.8% SD 4.6	2.4% SD 2.4
No gemtuzumab ozogamicin	76.7% SD 4.8	21.1% SD 10.5

CD33 Expression and Impact of Gemtuzumab Ozogamicin



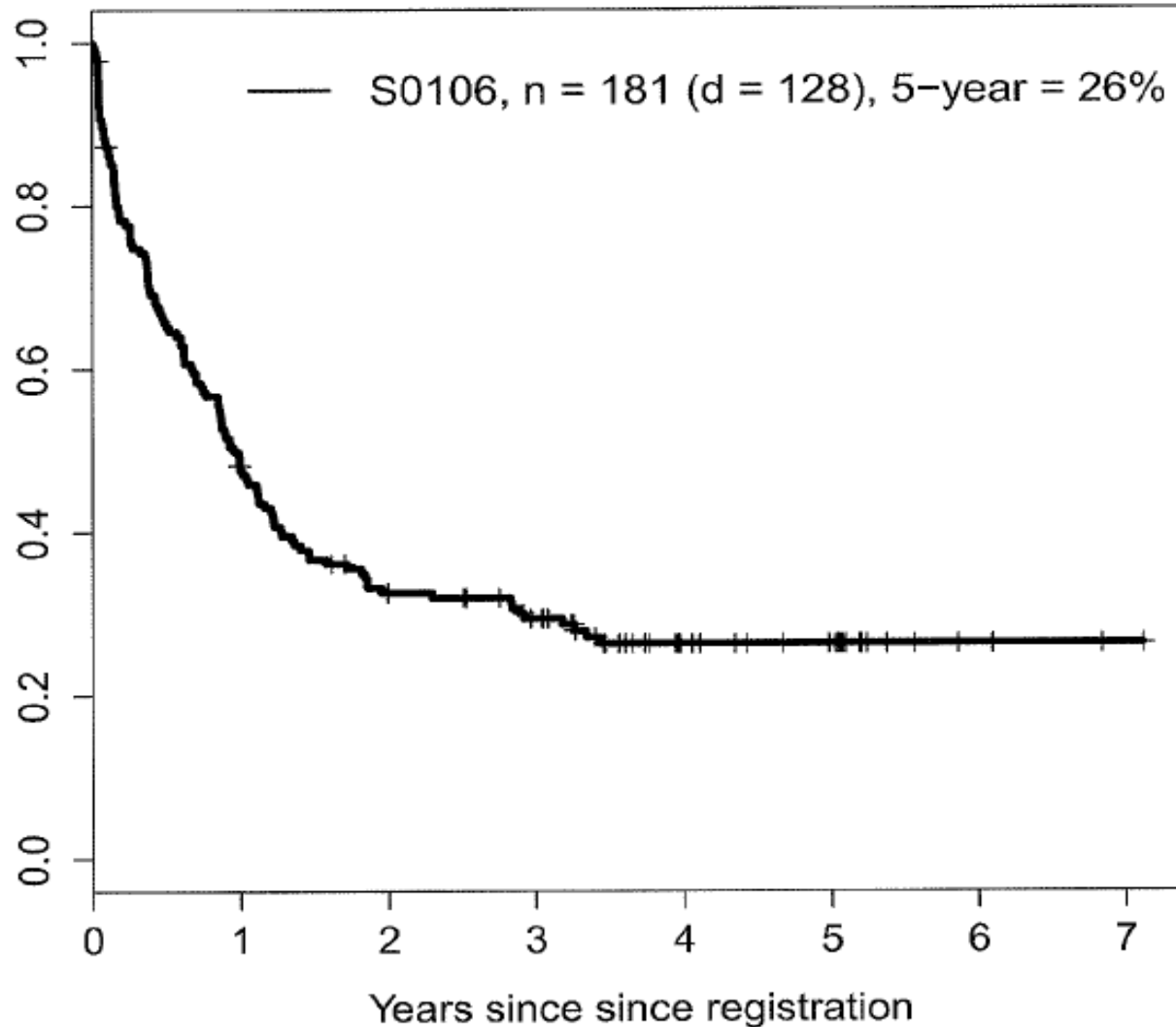
Novel Anti-CD33 Targeted Therapies

SGN-CD33A
-pyrrolobenzodiazepine

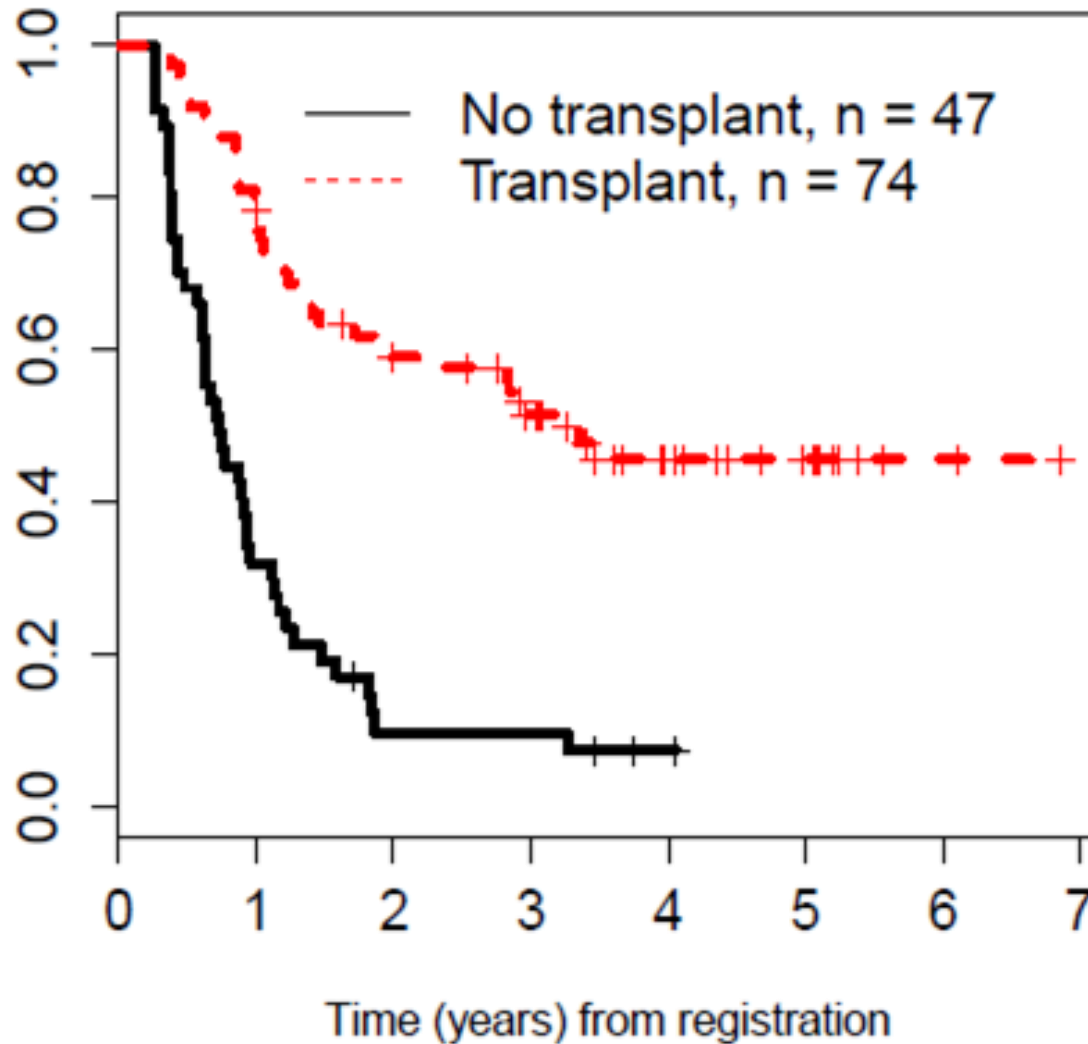
AMG 330
-CD33/CD3 BITE

CD33 CARTs

Survival in S0106 Induction Failures¹

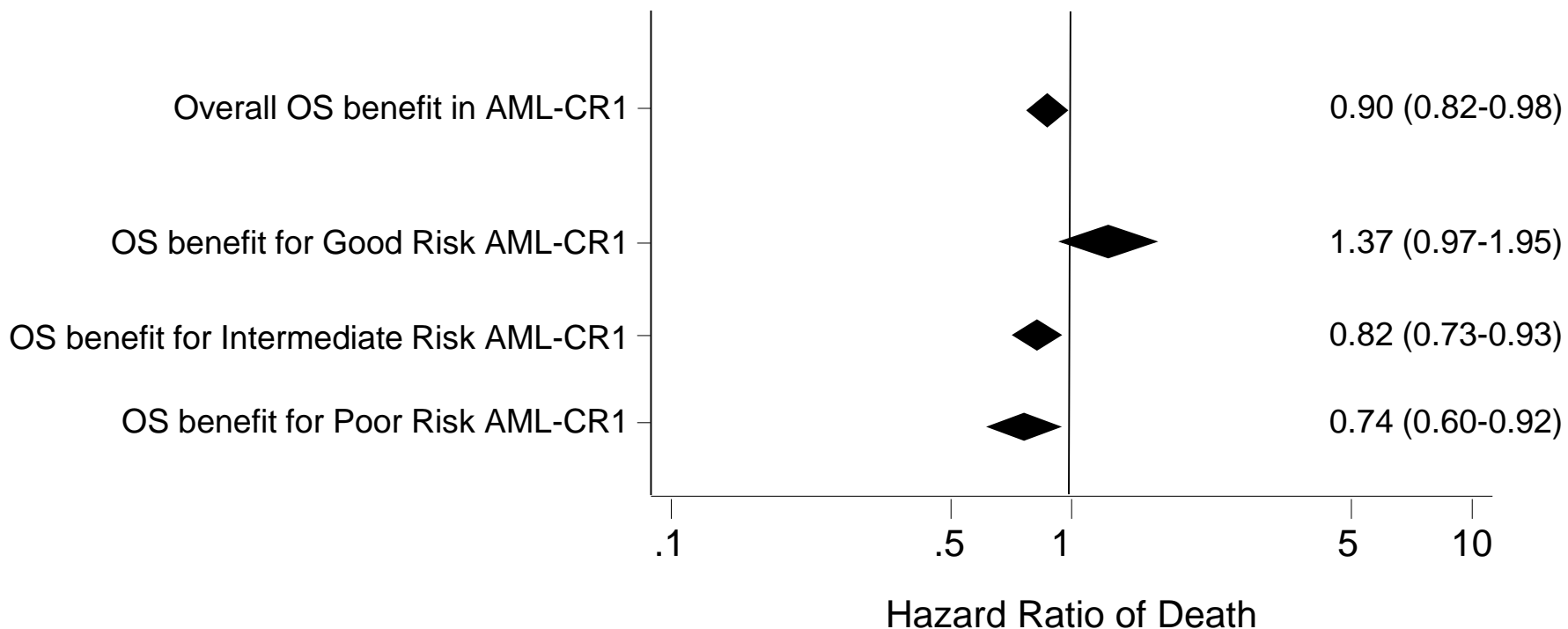


S0106 PIF – OS After Day 90¹



Meta-Analysis of RCTs of HCT for AML CR1 ¹

Trials = 23
Patients = 5,839



Measurement of MRD after Induction

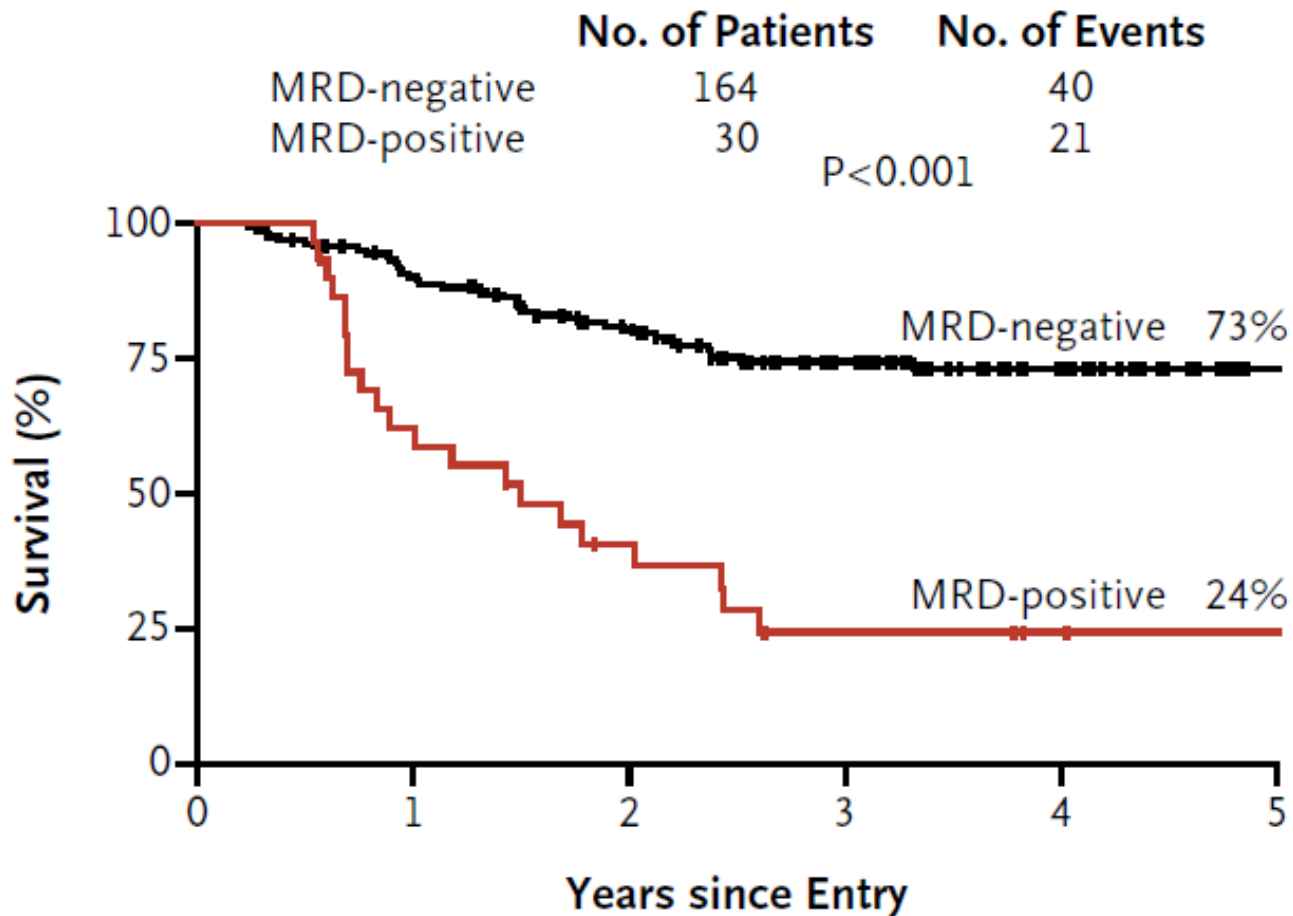
Polymerase-chain reaction

Multiparameter flow cytometry

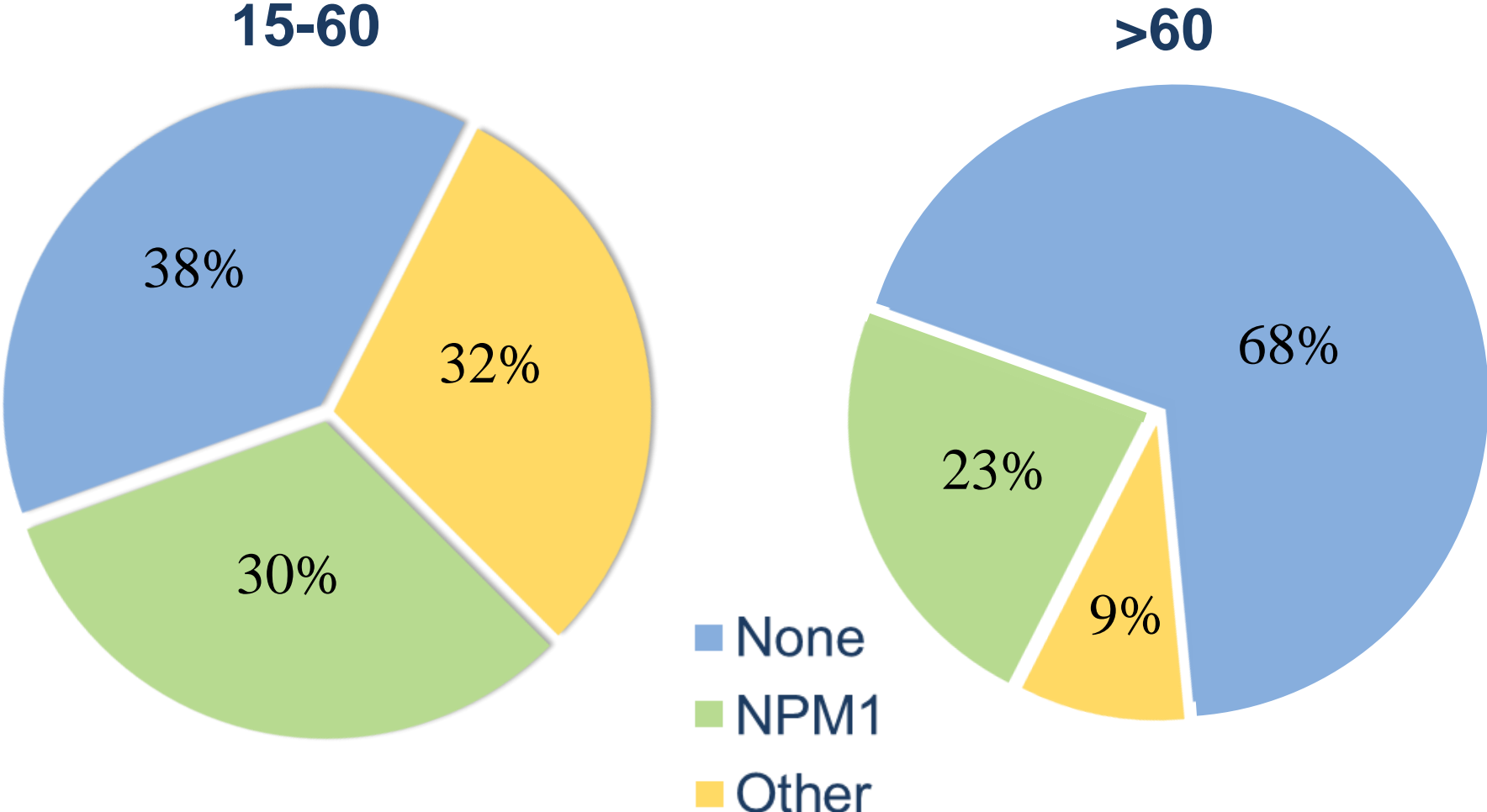
Next generation sequencing

MRD in NPM-1 Mutated AML by PCR¹

Overall Survival



Targets for PCR Detection of AML in Adults¹

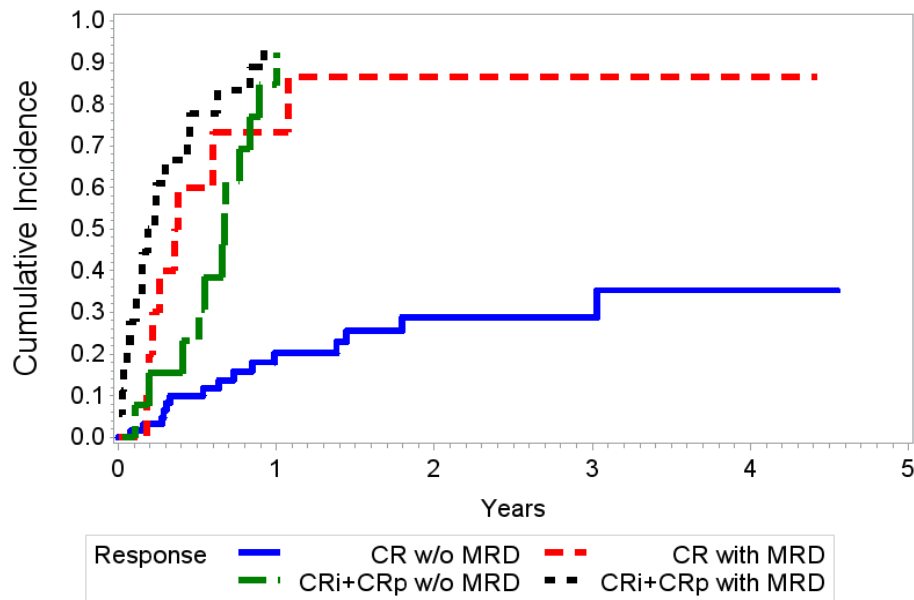


¹Grimwade et al. Blood 124:3345, 2014

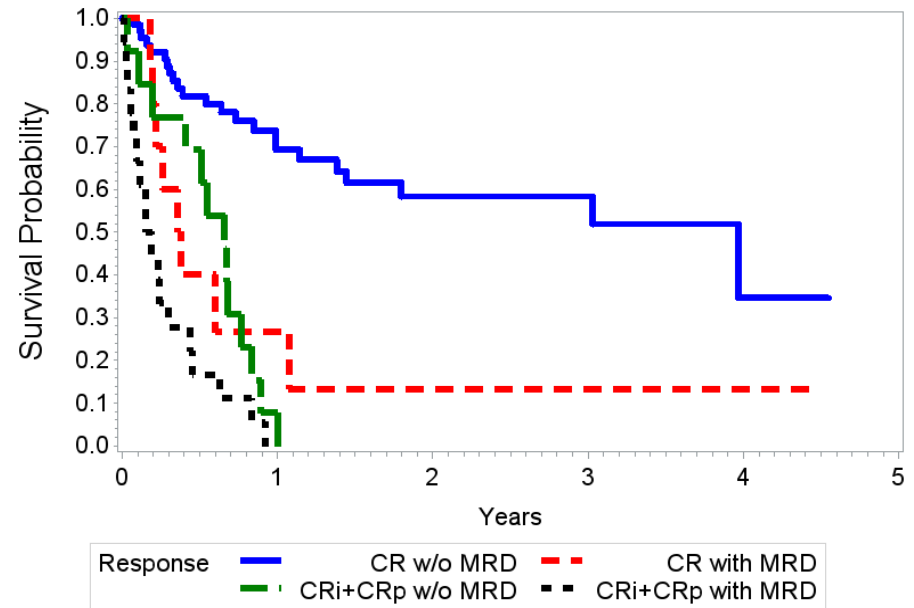
FHCRC Study of Quality of CR¹

Non-Transplant Cohort

Cumulative Incidence of Relapse



Kaplan-Meier Curve of Relapse-Free Survival



Favorable Risk AML

Post-remission therapy

Multiple cycles of HDAC containing chemotherapy

Reserve HCT until 1st relapse

Consider HCT in CR1 if <3 log reduction in MRD or reappearance

Intermediate Risk AML

Post-remission therapy

Allogeneic HCT in CR1 if appropriate donor available

Consider withholding HCT if MRD negative and HCT CI > 2

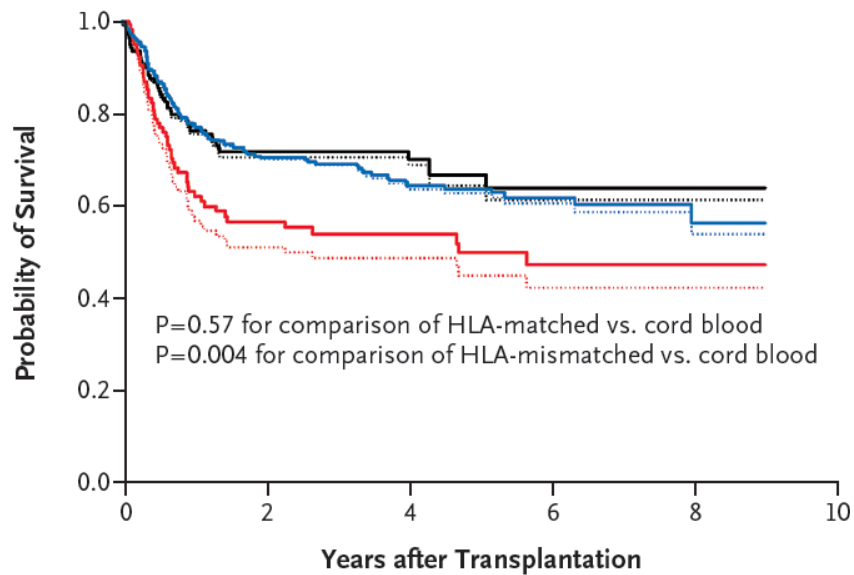
Advance Risk AML

Post-remission therapy

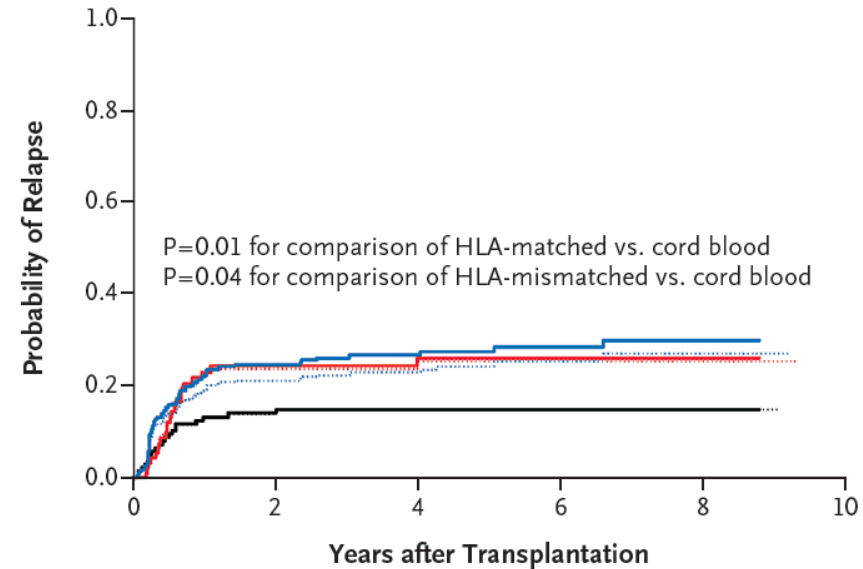
Allogeneic HCT if possible

Survival and Relapse Following CB vs MUD vs MMUD¹

Survival



Relapse

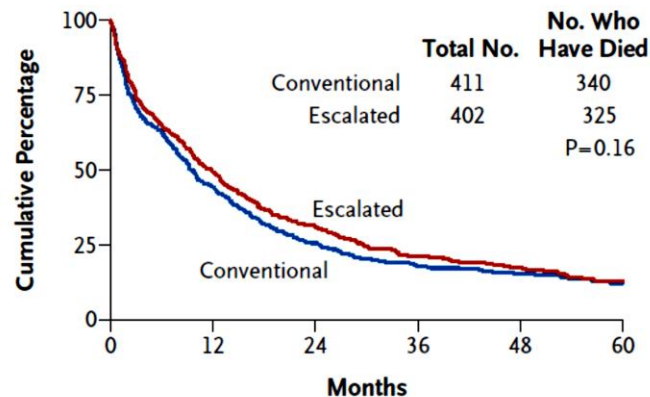


AML in Older Patients¹

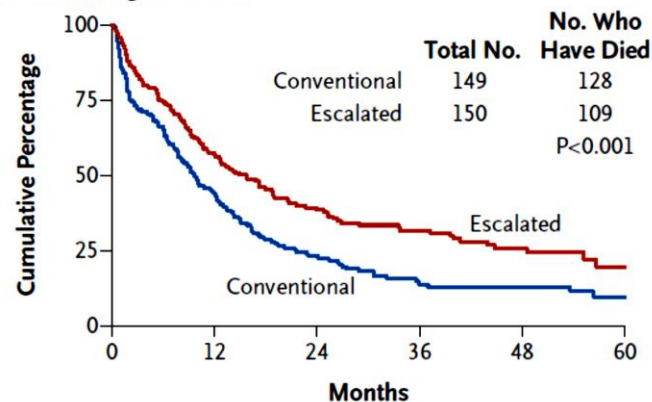
1. Increased incidence of MDR¹ expression
2. Higher probability of unfavorable cytogenetics
3. More frequently associated with MDS
4. Comorbidities more common

HOVON Study¹

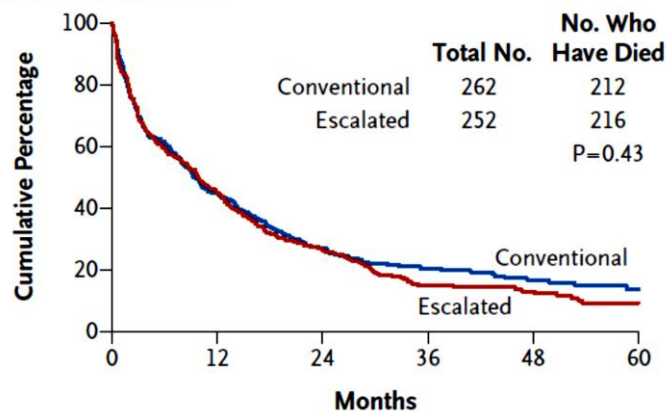
Overall Survival



Overall Survival, Age 60–65 Yr

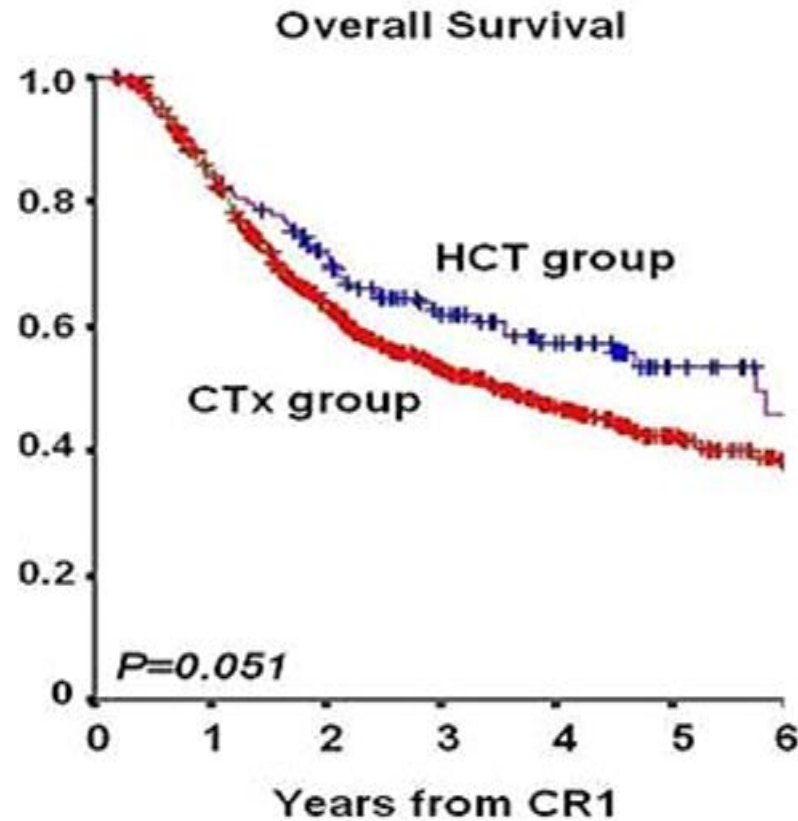


Overall Survival, Age >65 Yr



Allogeneic HCT versus Chemotherapy for AML CR1 age 50-70 ¹

National Cancer Center Hospital, Tokyo



Alternatives to LD ARA-C in Older AML Patients Unfit for Intensive Chemotherapy

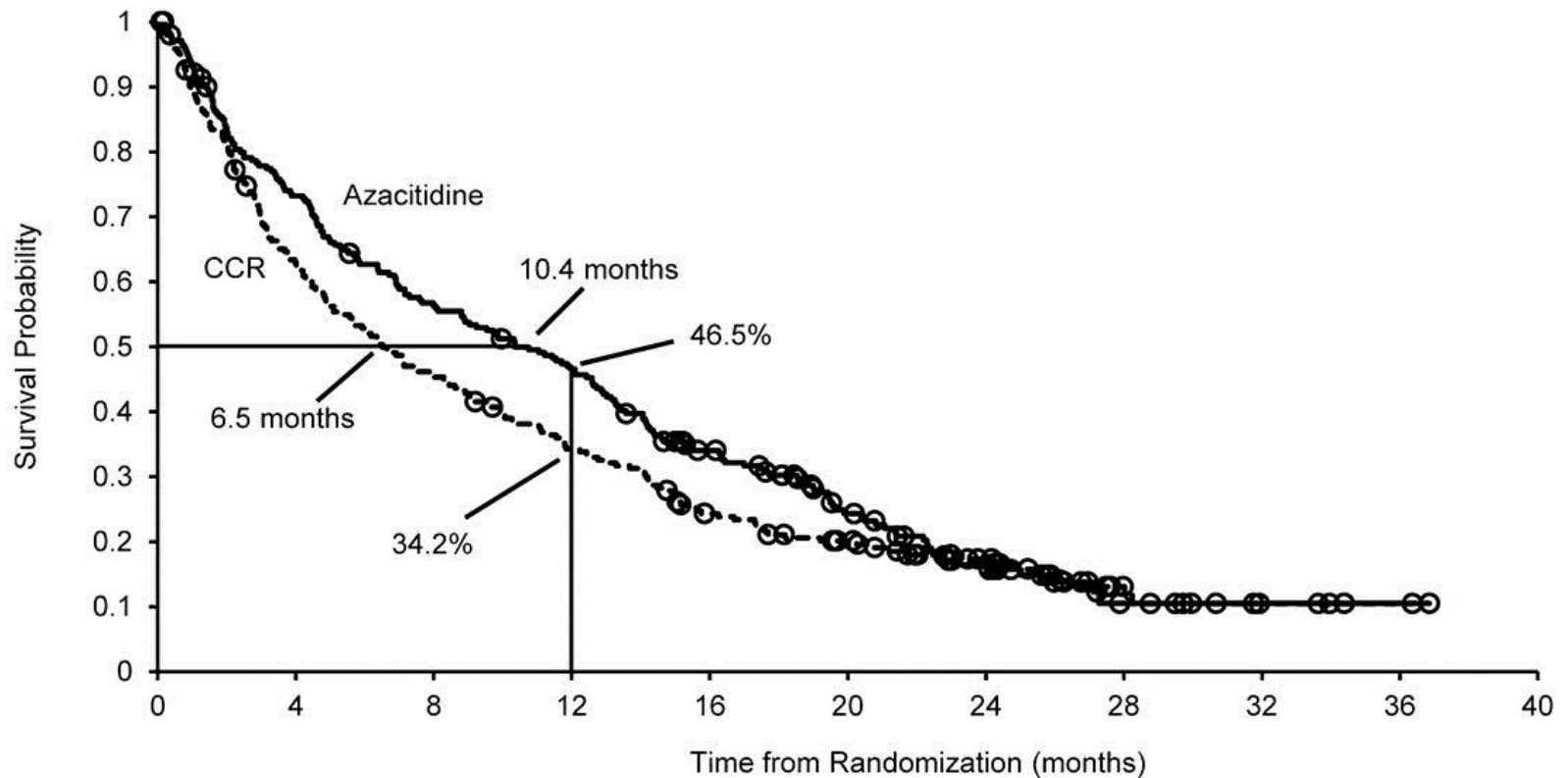
5-azacytadine

decitabine

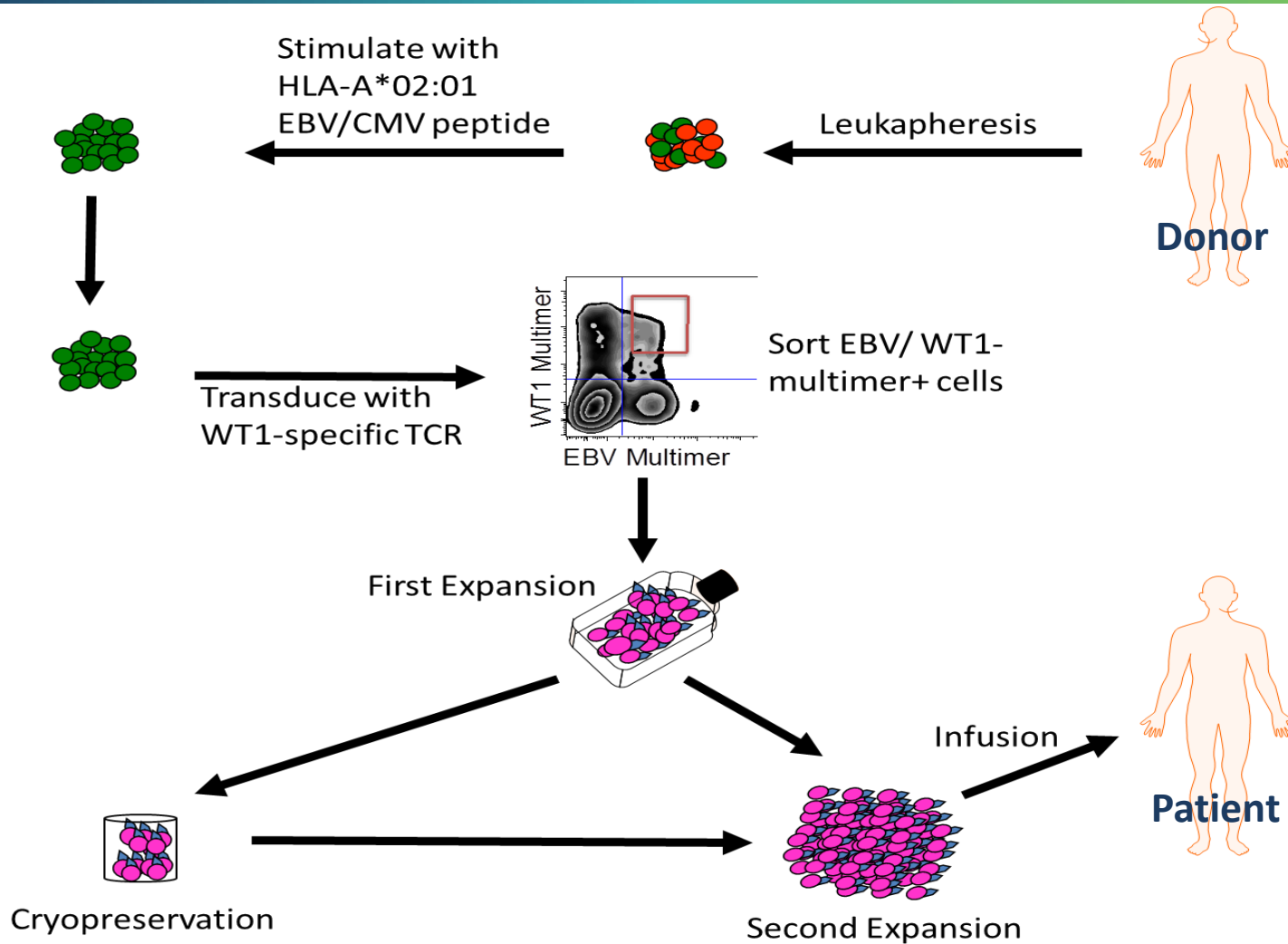
clofarabine

lenolidomide (5q-)

International Azacitidine Trial¹



Generation of WT1-specific CTL

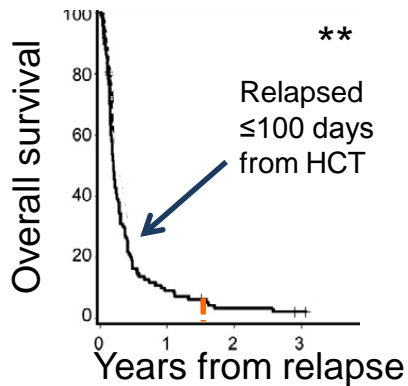


Total production time: ~ 6 weeks

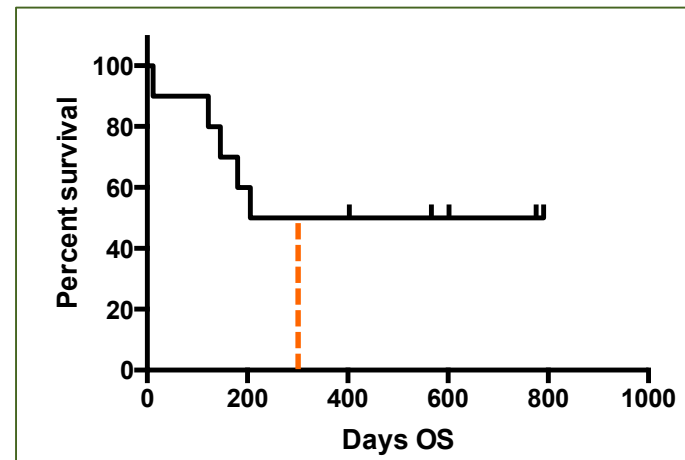
Preliminary Clinical Outcomes: Treatment Arm

Patients on ARM 2 had many risk factors entering transplant

Arm	Pt#	>CR1	cyto	refractory (>1cycle to achieve CR)	Dz at HCT	MDS->AML or secondary AML	2ND TX	chloroma
2	1	X	X	X		X		
2	2	X	X	X	16% blasts		X	
2	4	X	X	X	0.02% blasts		X	X
2	5	X	X	X	42% blasts	X		
2	6	X	X	X			X	
2	7	X	X	X	3.8% by cyto			
2	8	X	X	X	0.01% blasts	X		
2	9	X	X		no counts			
2	14	X	X	X	0.02% blasts	X	X	
2	15	X	X	X		X		
2	17		X					X



OS since 1st CTL infusion



**Mielcarek M. et al., Biol Blood and Marrow Trans, 2007

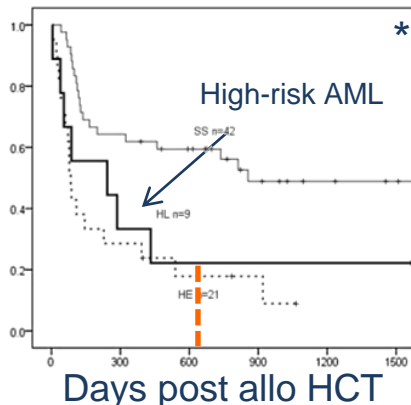
Median days between HCT and 1st CTL infusion: 104

Preliminary Clinical Outcomes: Prophylactic Arm

Cumulation of risk factors on the prophylactic Arm

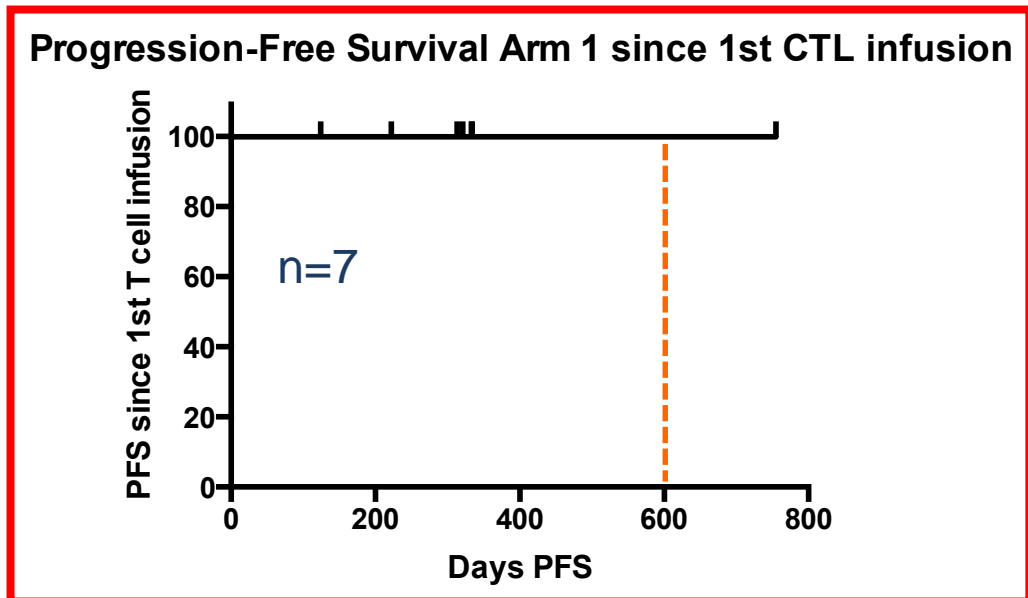
Pt#	>CR1	Cyto	refractory (>1cycle to achieve CR)	Dz at HCT	MDS->AML or secondary AML	Chloroma
3	X	X				
10		X	X			
11		X	X			
12		X (FLT3+)		MRD (cyto)		
13		X	X			
16				5.5% blasts	X	
17		X (MLL)				X

Historical PFS



*Chen GL et al., Biol Blood Marrow Trans. 2014.

Progression-Free Survival Arm 1 since 1st CTL infusion



Median days between HCT and 1st CTL infusion: 104

Adult ALL – Remission Induction

V + P 46%

V + P + LASP 47%

V + P + DNR 68%

V + P + DNR + LASP 83%

Adult ALL- CNS Prophylaxis

Without prophylaxis – risk is 35%

risk factors include ↑ WBC, ↑ LDH, T-cell or mature B-cell phenotype

With prophylaxis – risk is 10%

? need for CXRT if IT-MTX is used

Post-Remission Therapy of Adult ALL

Intensive multi-drug consolidation

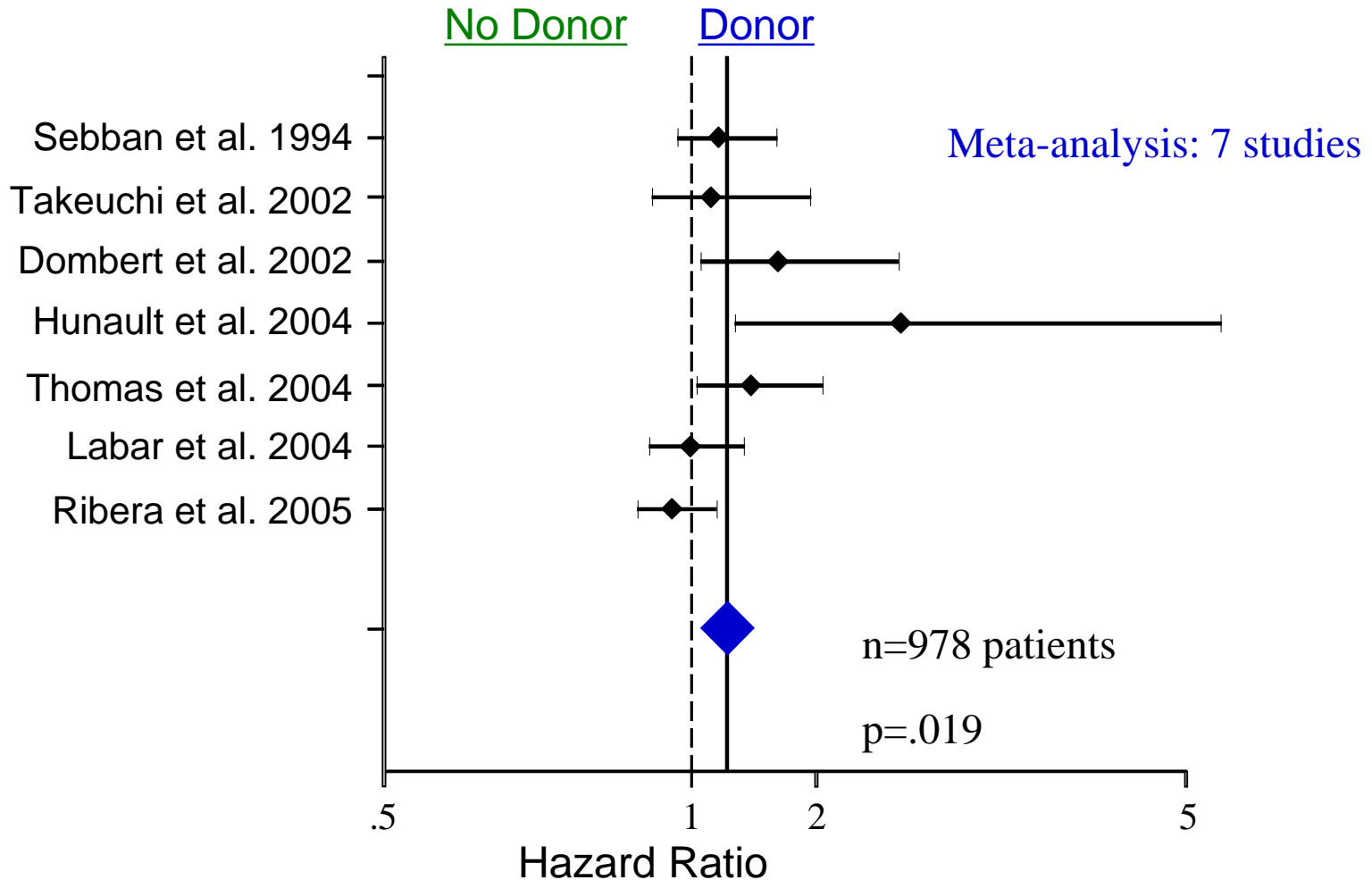
Autologous transplantation

Allogeneic transplantation

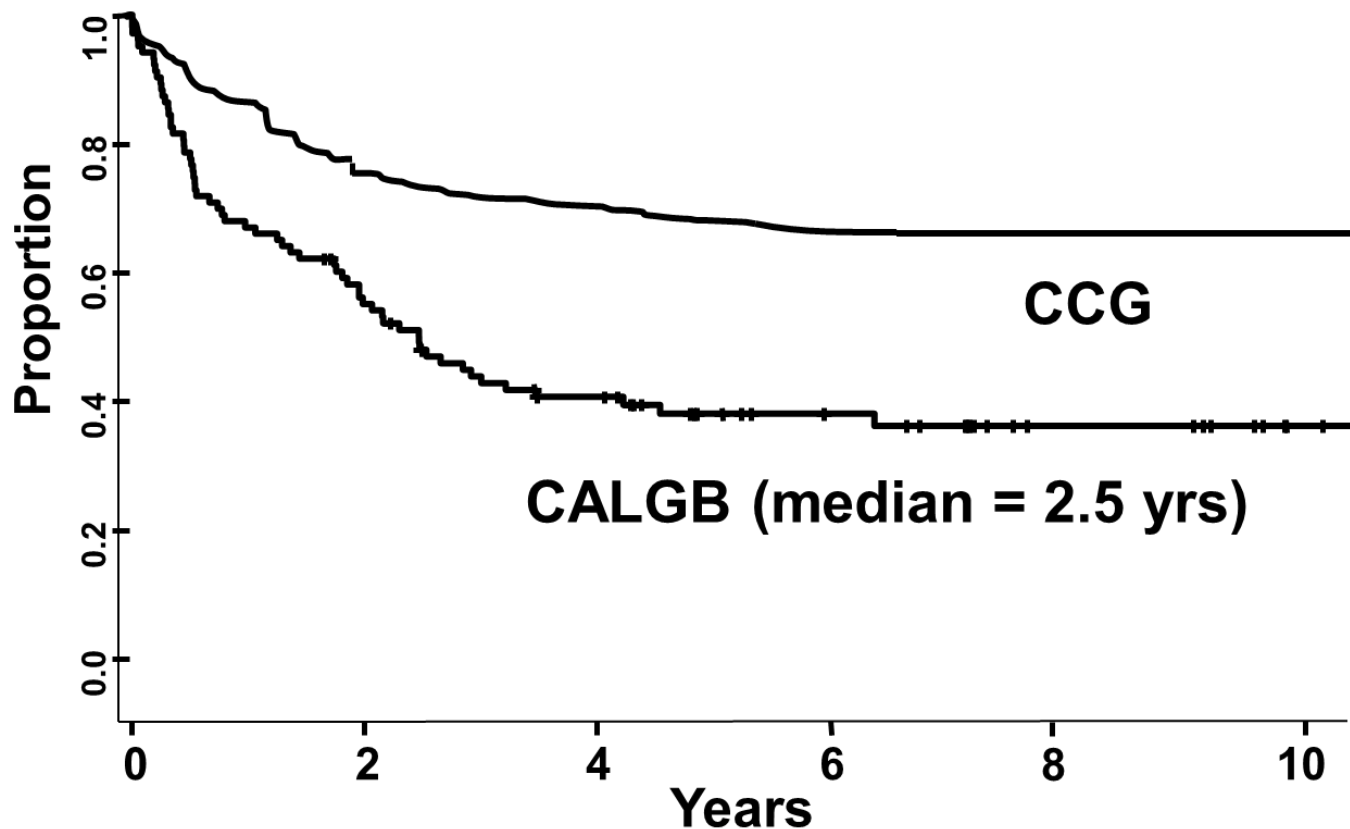
Contemporary Treatment

Group	N	Median age (range)	Ph+ (%)	T-cell (%)	CR	DFS at 3-9 yrs (%)
MRC/ECOG E2993	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

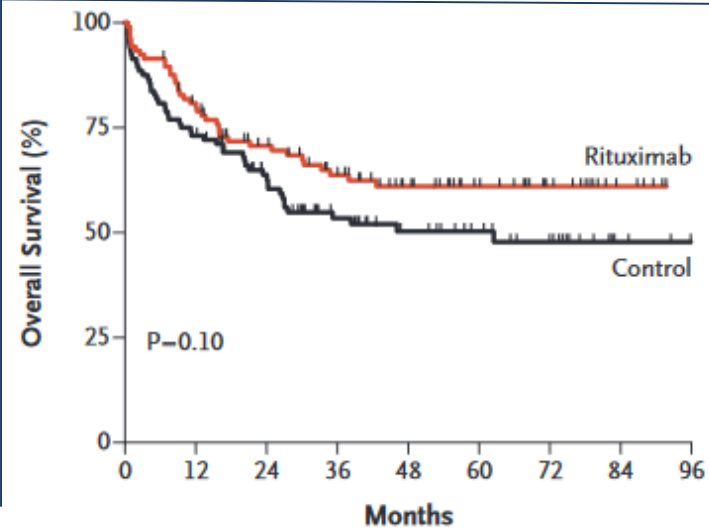
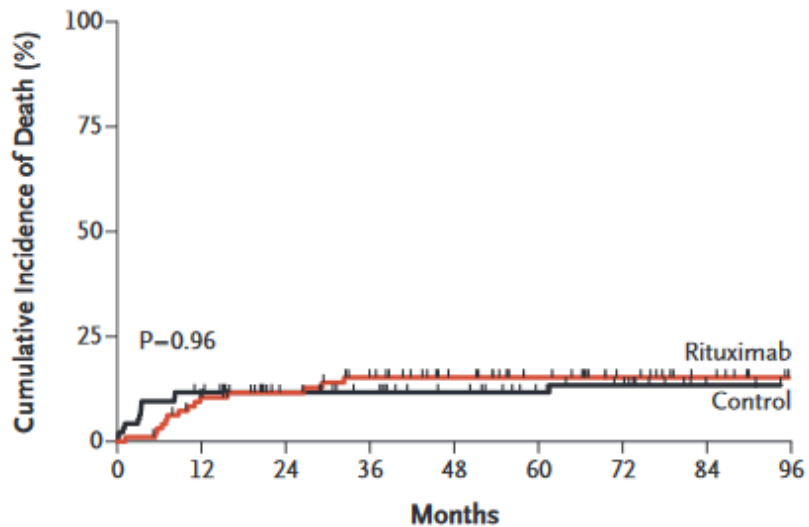
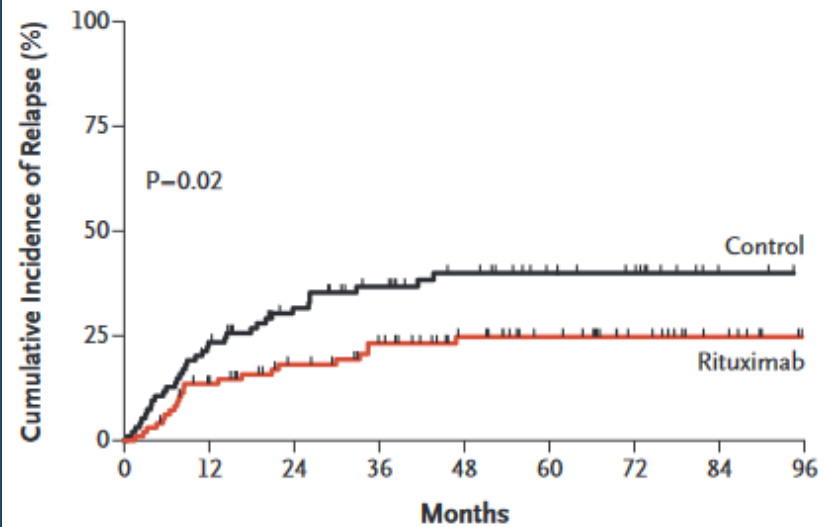
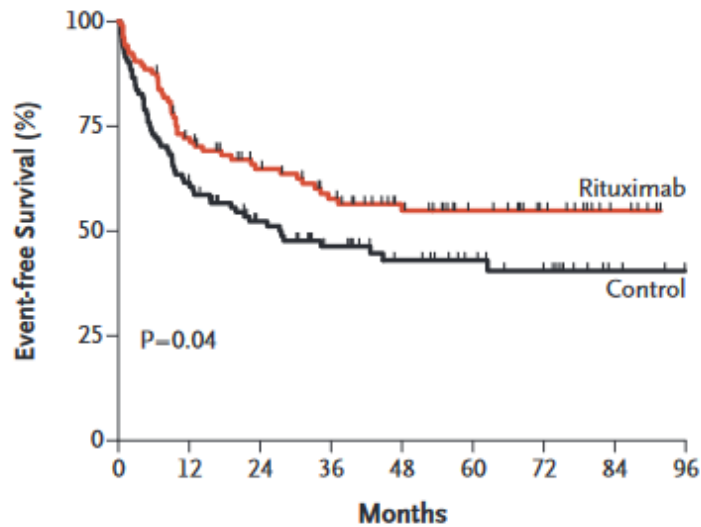
High Risk ALL in CR1



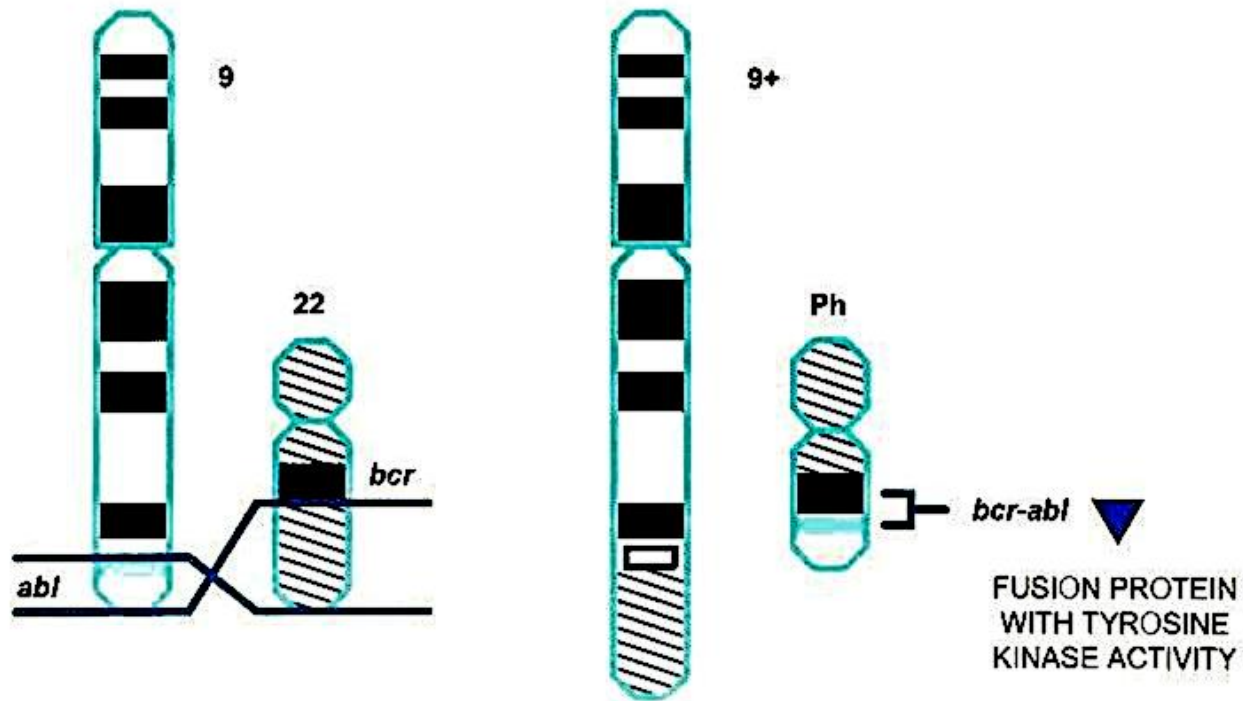
EFS of Young Adults 16-21 years old on CCG and CALGB Trials for ALL (1988-1995)



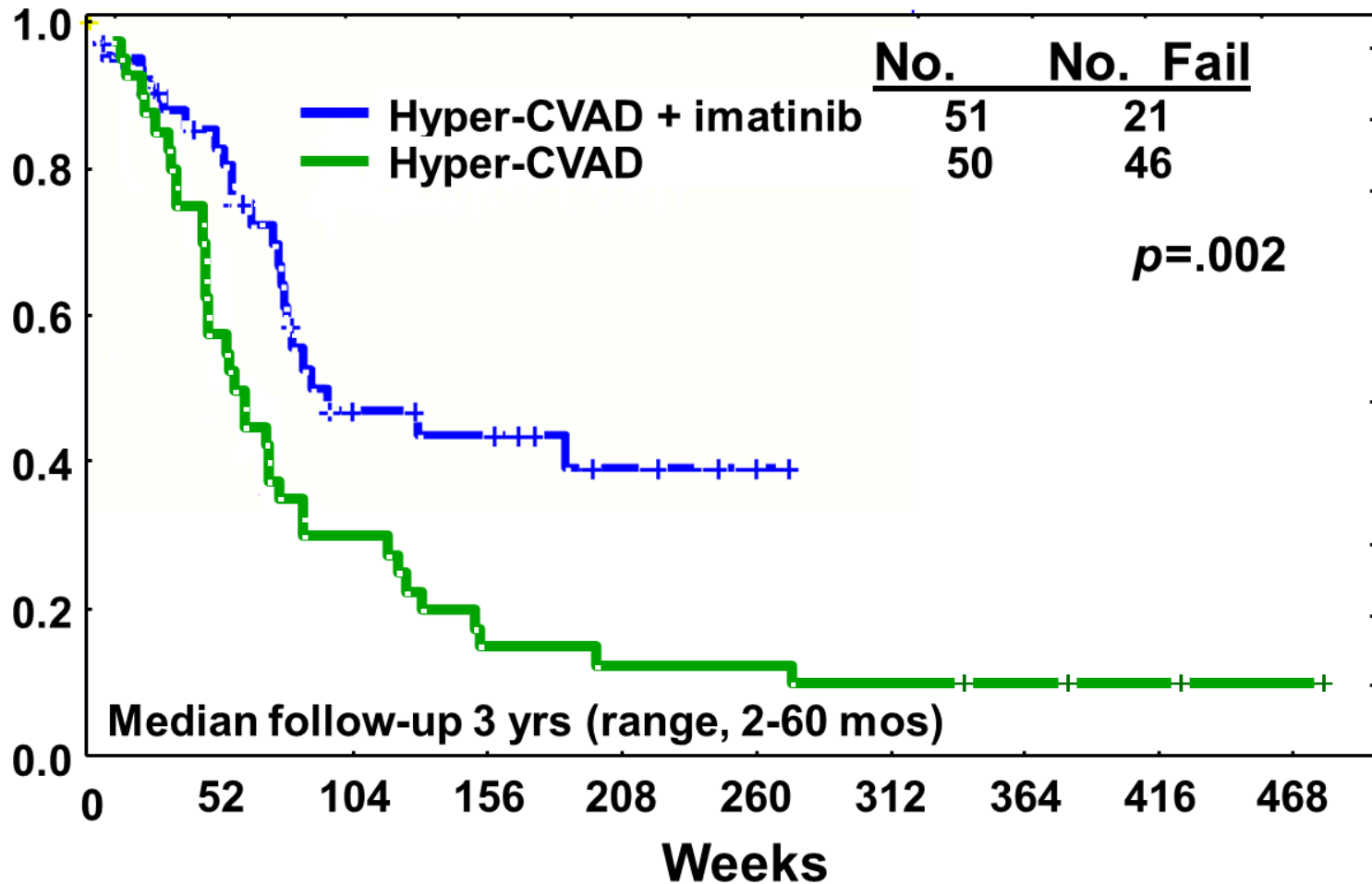
Rituximab in B-Lineage Adult ALL¹



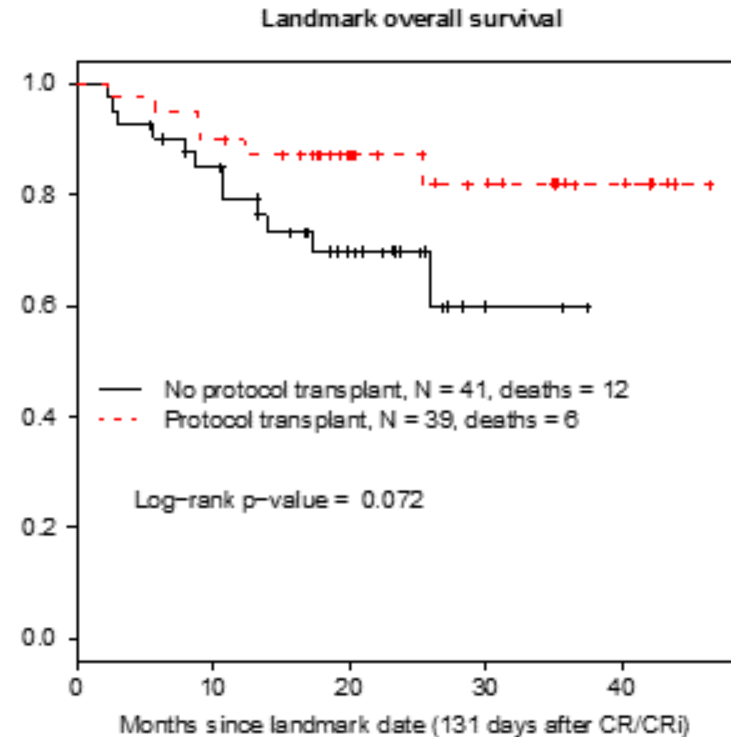
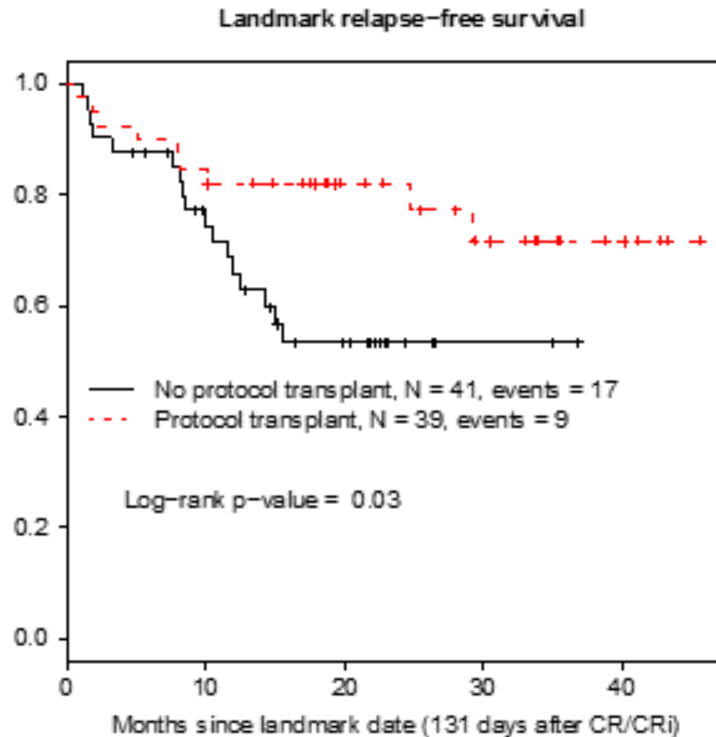
The Philadelphia Chromosome: t(9;22) Translocation



Survival in Ph-ALL by Treatment



Impact of Dasatinib plus Allogeneic HCT in Ph+ ALL¹



Chemotherapy for Recurrent ALL¹

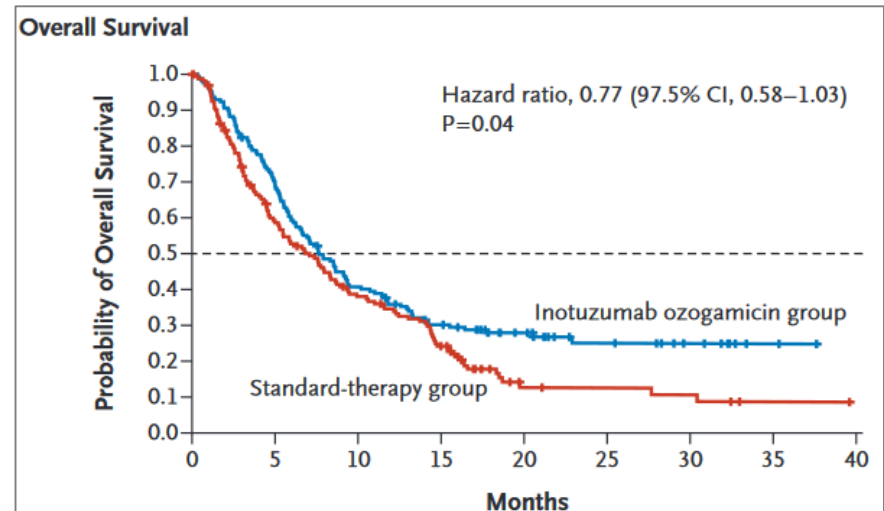
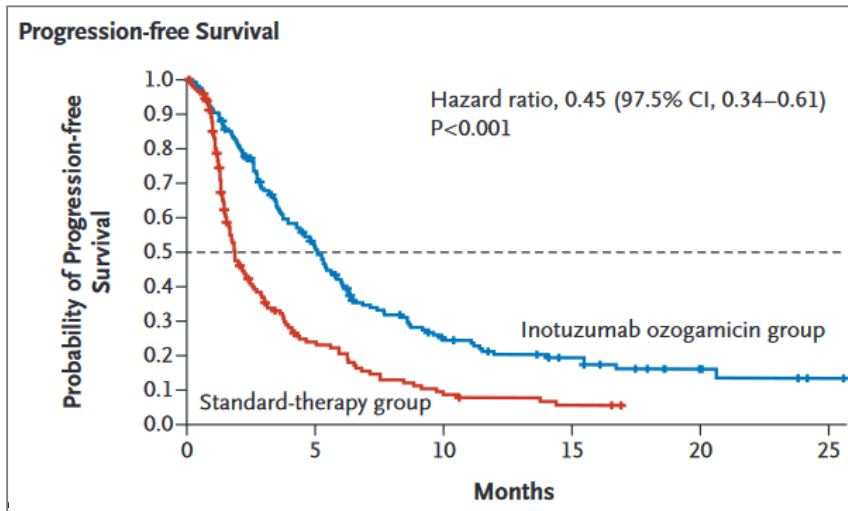
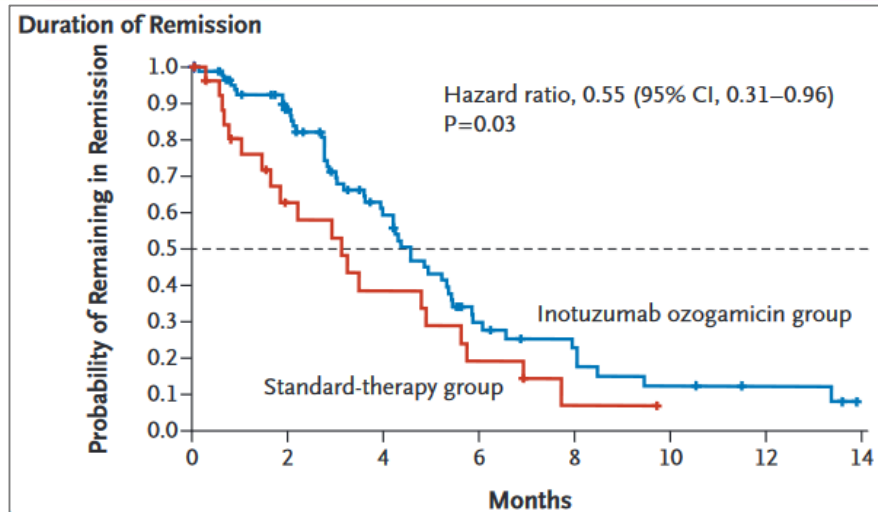
Salvage CR rate - 34%

CR duration - 6 months

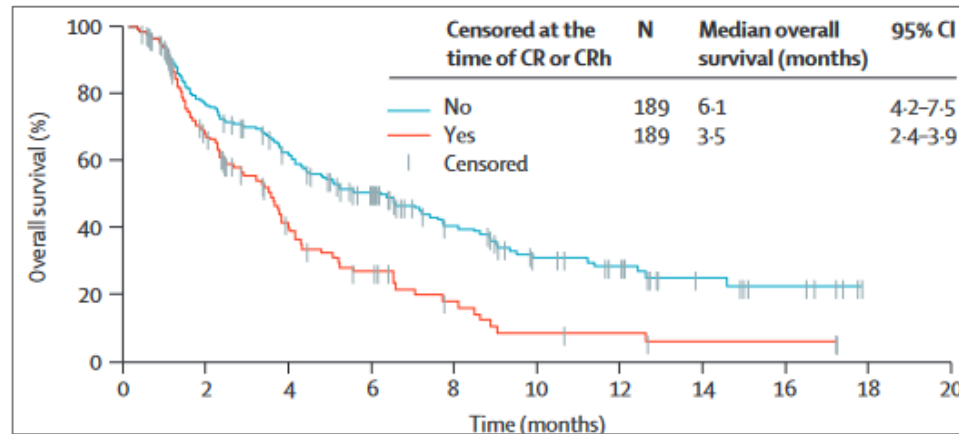
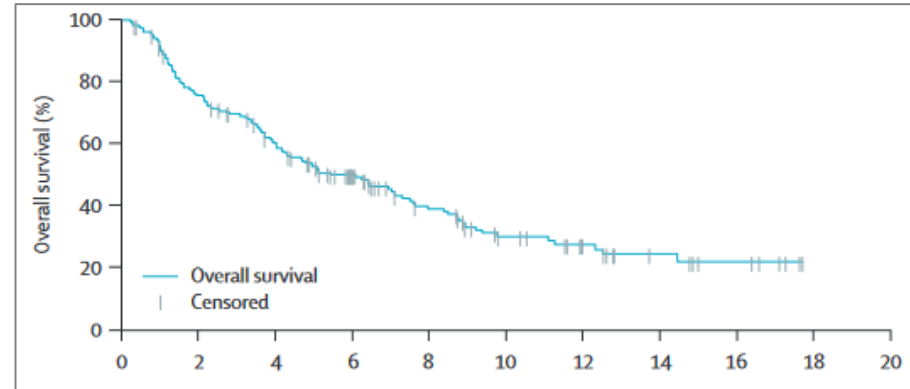
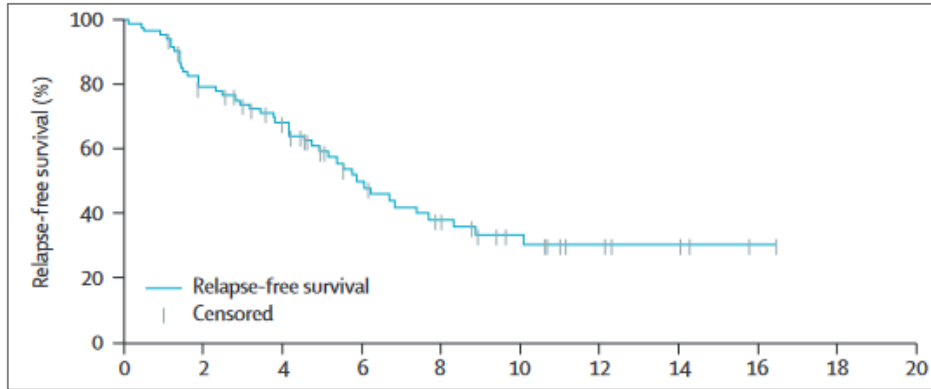
1 yr survival - 24%

5 yr survival - 3%

Inotuzumab Ozogamicin for Recurrent Adult ALL¹

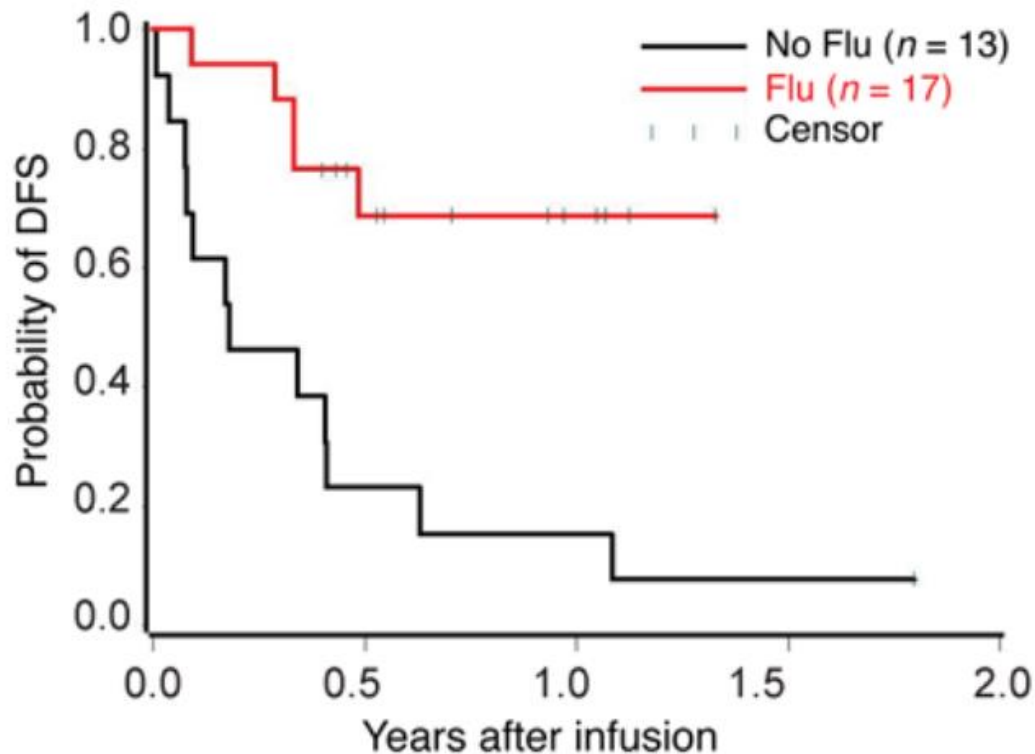


Blinatumomab for Recurrent Adult ALL¹



CD19 CAR T Cells for Recurrent Adult ALL¹

N = 29
CR = 27 (93%)



Acknowledgements

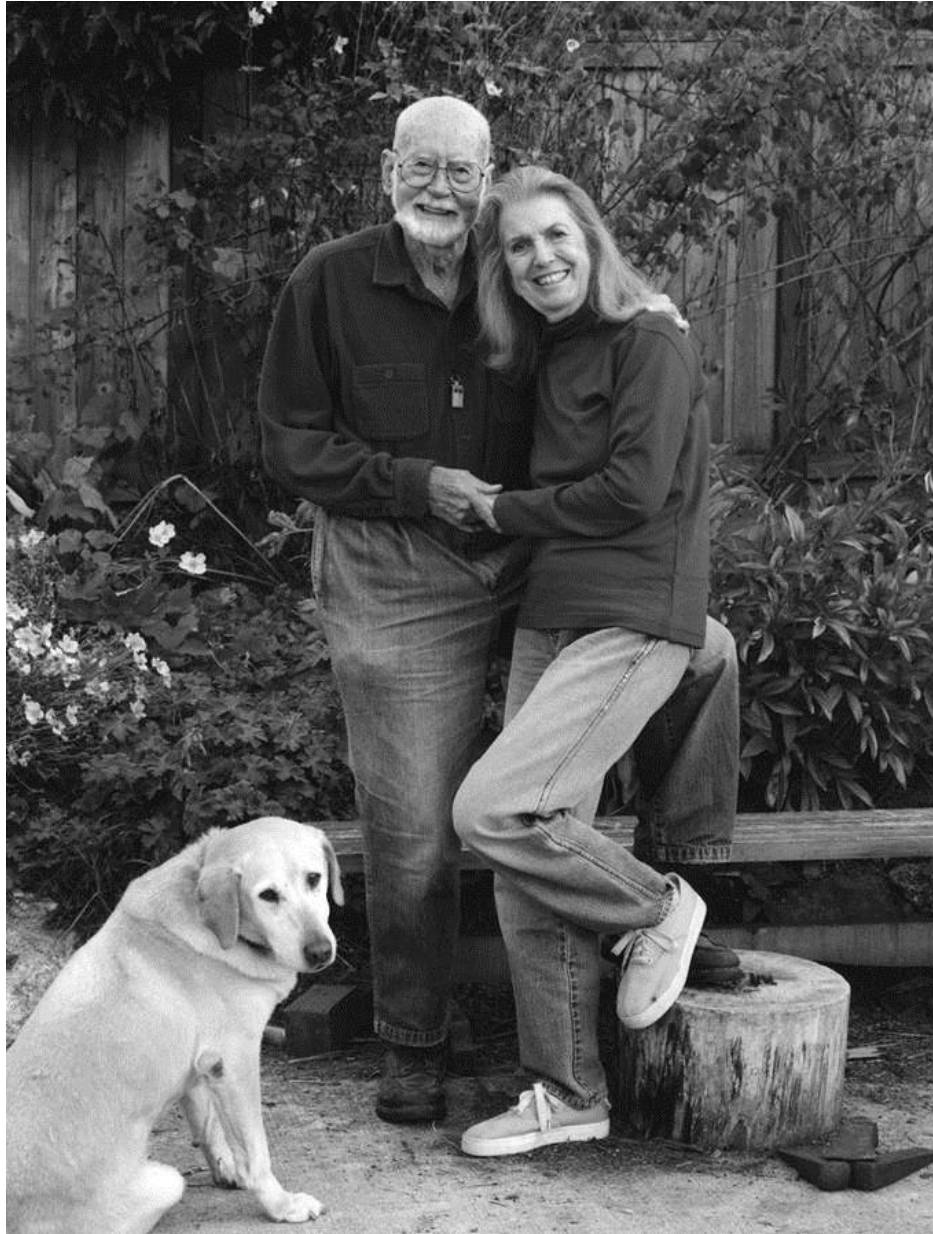
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THANK YOU



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