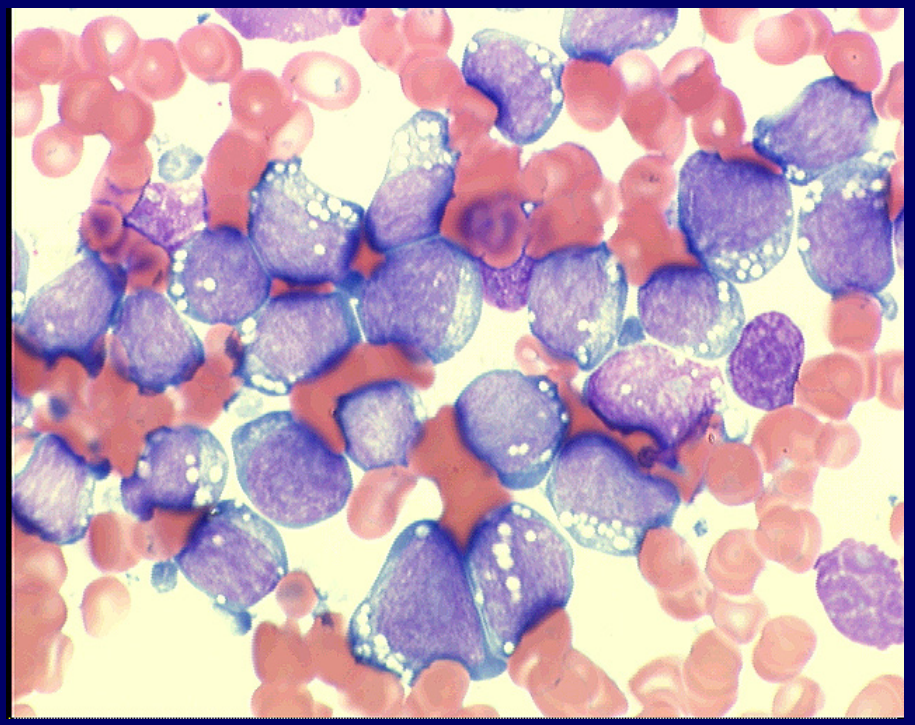
Update on ALL

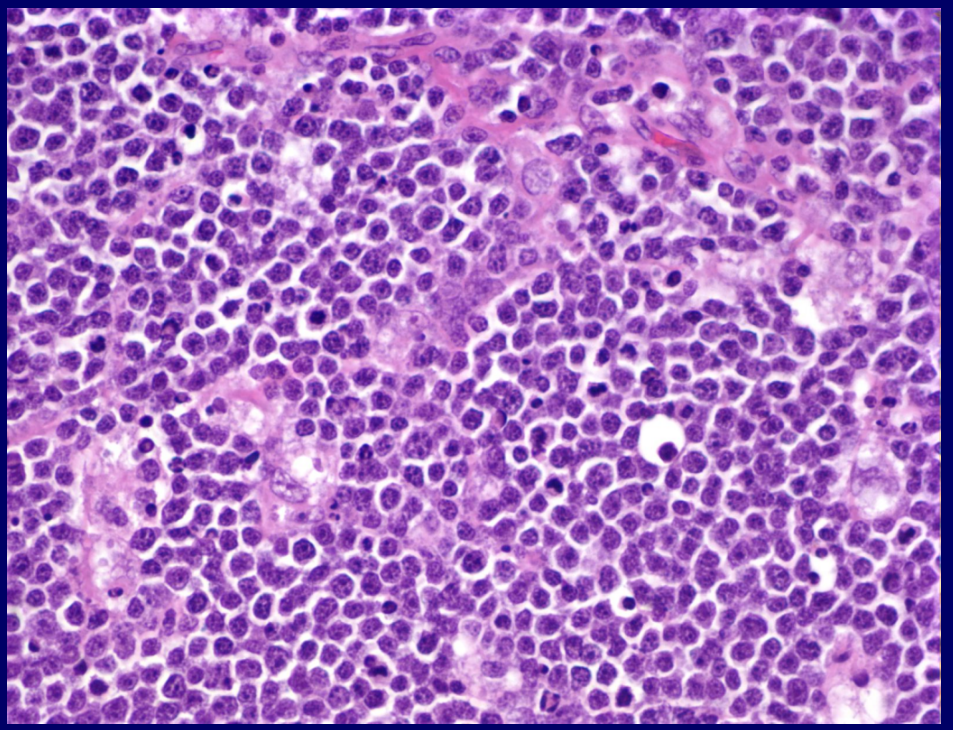
- Subtype-Directed Approaches for Adult ALL

- New Agents

Burkitt-type, Mature B-cell Leukemia/Lymphoma

Burkitt-type leukemia/lymphoma





Thomas et al, Atlas Clin Oncol, Malignant Lymphomas, 2002

Burkitt-type leukemia/lymphoma

- Mature B-cells (TdT negative)
  - CD19, CD20, CD22, CD79a, monotypic sIgM
  - Resemble germinal center cells
    - + Bcl-6, CD10, Tc11, CD38
    - – Bcl-2, Mum-1, CD44, CD138
- Association Epstein Barr Virus (EBV)
  - 20% sporadic cases, 30 – 40% HIV cases
  - *In situ* hydridization for EBV coded RNAs or PCR for DNA
- Activation *MYC* gene at 8q24 loci
  - t(8;14), t(8;2), t(8;22)
  - Transcriptional regulator metabolism, cell growth, apoptosis

Burkitt-type leukemia/lymphoma: Clinical Features

- Median age 25 – 55 years; 59% over 40 yrs
- L3 morphology by FAB
- Rapid doubling time → Emergency Therapy
- Abdominal disease, LAN, HSM, elevated LDH, hyperuricemia, renal failure
- CNS frequently involved; chin numbness 50%
- Dose intensive short-term multi-agent therapy
  - CHOP + rituximab inadequate therapy
  - Tumor lysis prophylaxis mandatory
  - No maintenance therapy

Probability of overall Survival in Adult B-ALL Studies
ALL 01/81, B-NHL 83, B-NHL 86

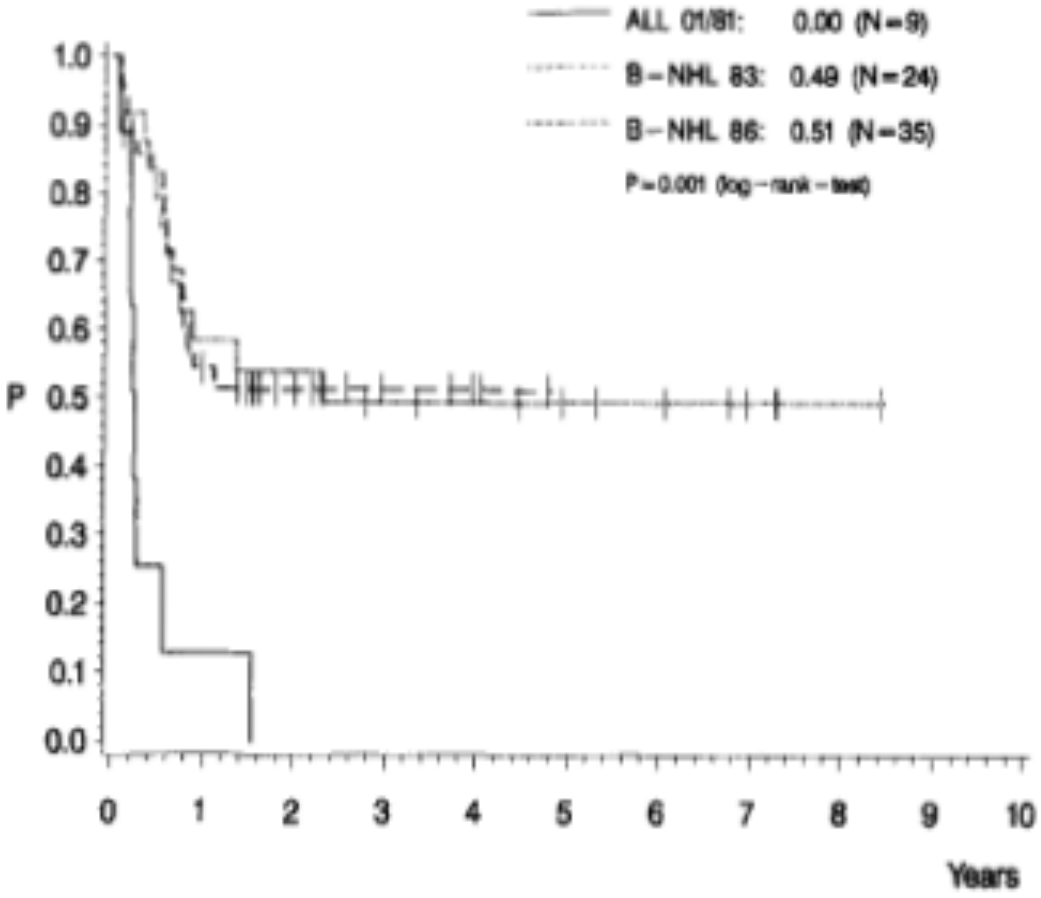
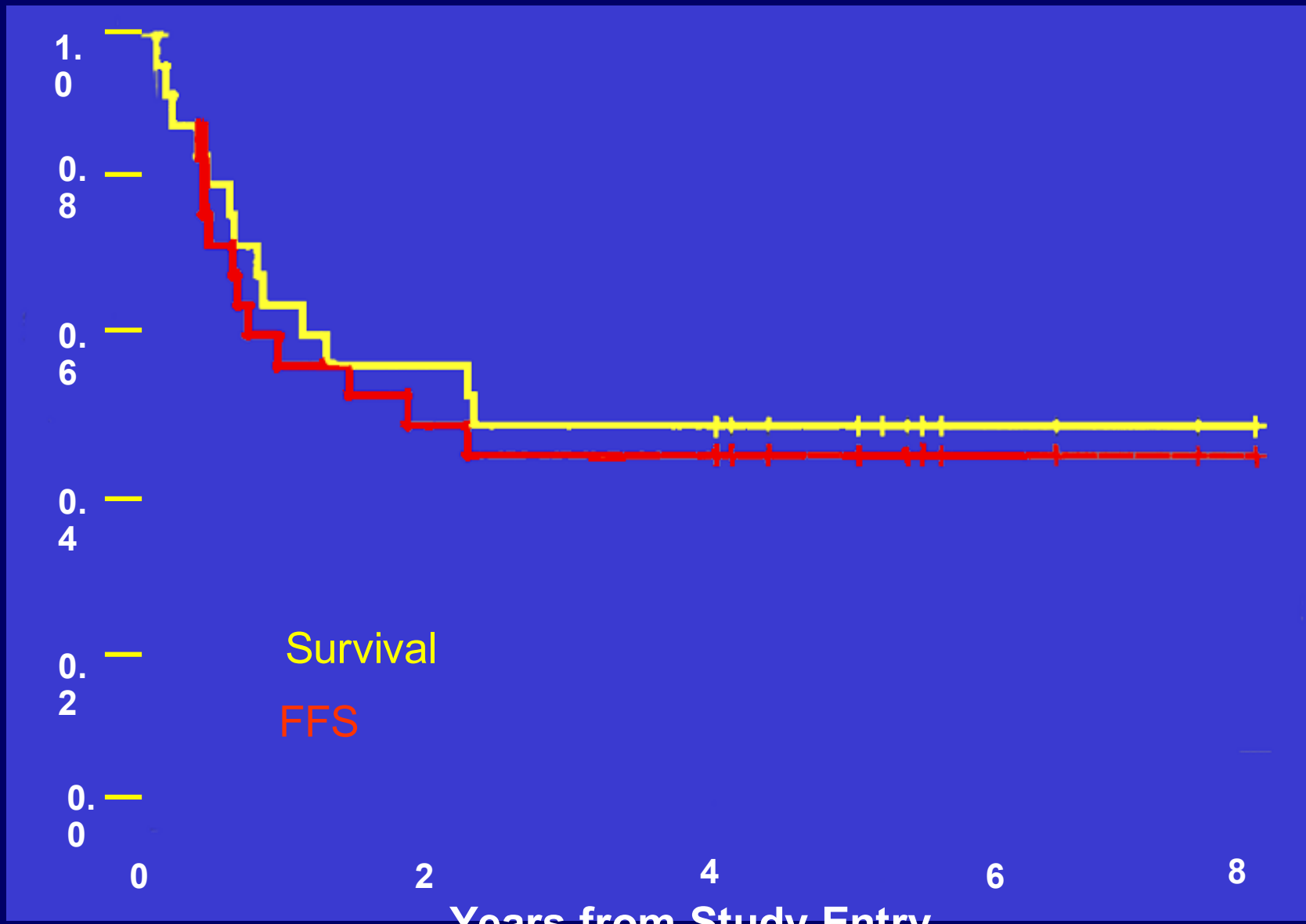


Fig 3. Probability of overall survival in the adult B-ALL studies ALL 01/81, B-NHL83, and B-NHL86.

Hoelzer et al Blood 1996; 87:495-508

Survival and Failure-free Survival (FFS) for Adults with Burkitt AL: CALGB 9251



Lee et al: J Clin Oncol 19, 2001

Treatment of Mature B-ALL: High-intensity, short course chemo

Study	Year	Median Age	CR Rate %	DFS (%) 3-5 Yrs	OS (%) 3-5 Yrs
Soussain	1995	29.5	79	57	57
Hoelzer	1996	36	74	71	51
Lee	2001	45	75	61	46
Rizzieri	2004	50	68	67	50
Thomas	1999	58	81	61	49

Improving Treatment of BL: Targeting CD20

Study	Year	Median Age	CR Rate %	DFS (%) 3-5 Yrs	OS (%) 3-5 Yrs
Soussain	1995	29.5	79	57	57
Hoelzer	1996	36	74	71	51
Lee	2001	45	75	61	46
Rizzieri	2004	50	68	67	50
Thomas	1999	58	81	61	49
Thomas	**2007**	**46**	**86**	**80**	**80**

Hyper-CVAD + Rituximab, *Cancer 106:1570, 2006; ASH 2007*

Rituximab + Hyper-CVAD: BL & B-ALL

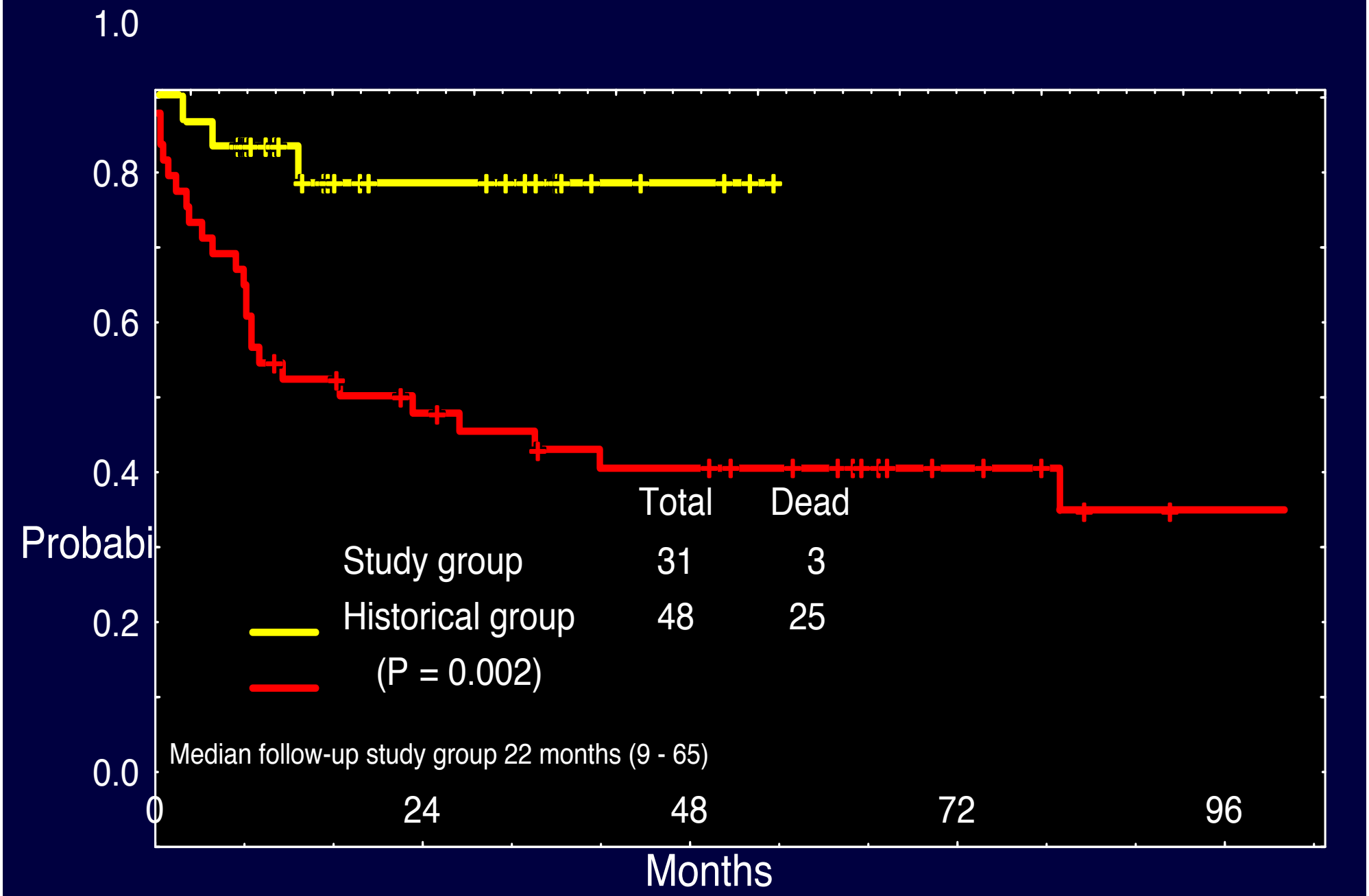
Intensive phase

1 2 3 4 5 6 7 8

- No maintenance phase, No SCT
- Protective Environment for induction if age ≥ 60

Hyper-CVAD	Rituximab
MTX-cytarabine	IT chemotherapy (MTX, ara-C)

Thomas et al, Cancer 106:1659, 2006



Thomas et al, Cancer 2006

Rituximab + BFM Regimens Burkitt-type Lymphoma, B-ALL, Diffuse Large B-cell Lymphoma (DLBCL)

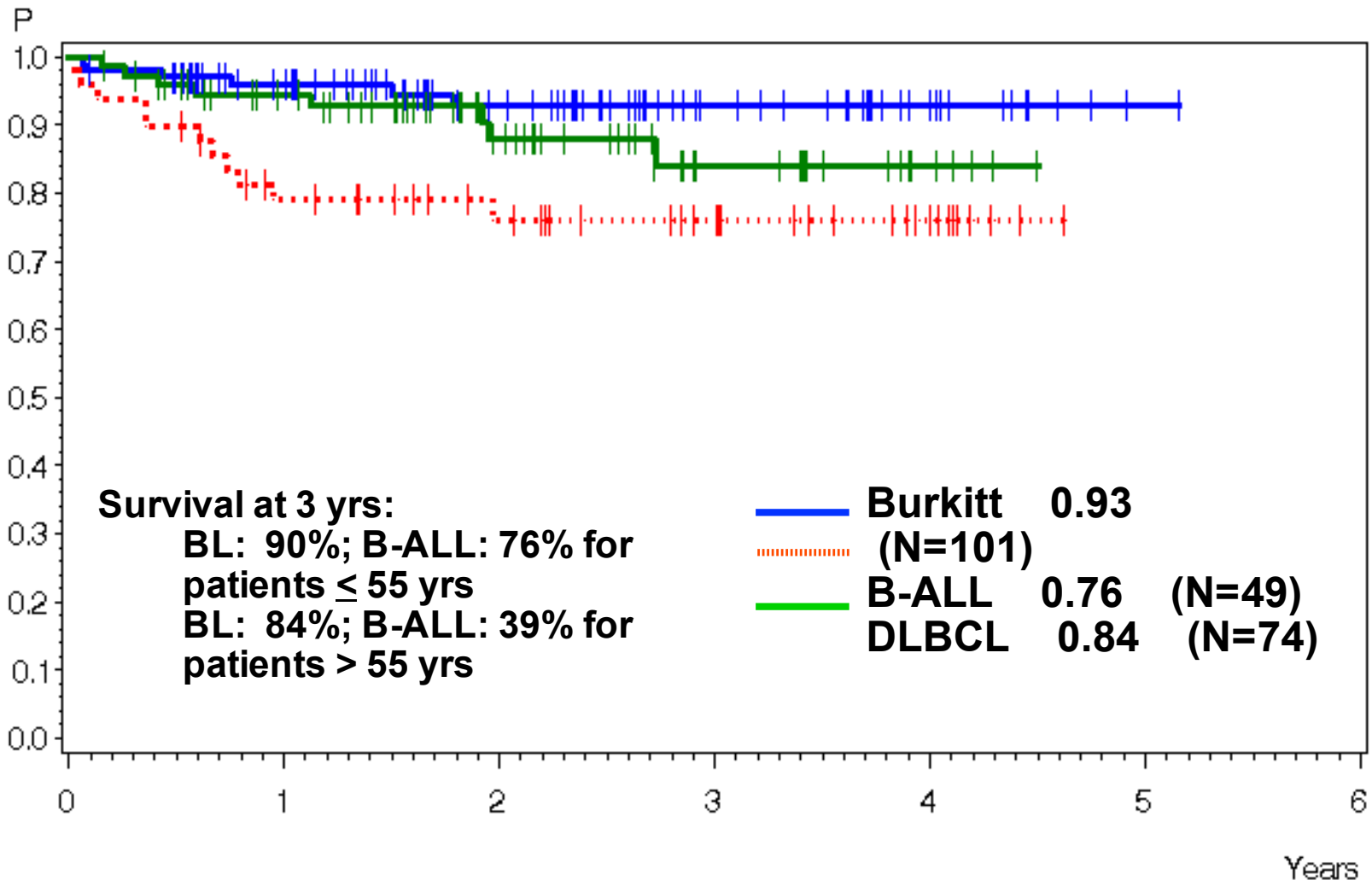
- Chemotherapy blocks ABC x 2
- Standard dose rituximab x 8

	No.	Age	%CR	% 3-yr OS
		< 55 yrs	≥ 55 yrs	
BL	115	36	90	91	84
B-ALL	70	46	83	79	39*
DLBCL	42	35	69	90	67

*CNS relapses

Hoelzer et al, ASH 2007, abstract 518

Overall Survival (<55 yrs)
GMALL B-ALL/NHL 2002



Hoelzer et al, ASH 2007

Hyper-CVAD + Rituximab
BL (non-HIV) & Mature B-ALL

- 56 non-HIV BL (n=28), B-ALL (n=27)
  - Median age 45 yrs (range 17-77), 25% ≥ 60 yrs
  - CR rate 95% (1 induction death)
  - Median follow-up 54 mos (1 – 124+)
    - 3 relapses; 9 deaths in CR (3 infections, 3 secondary malignancies, 3 other)
    - Poor risk AML 7 yrs, 1 t(8;21) AML 3 yrs, 3 MDS 3-1/2 yrs

% Estimated 5-yr OS	H-CVAD + R (n=56)
Overall	75
Age < 60 yrs	74
Age ≥ 60 yrs	73

Thomas et al, 2010

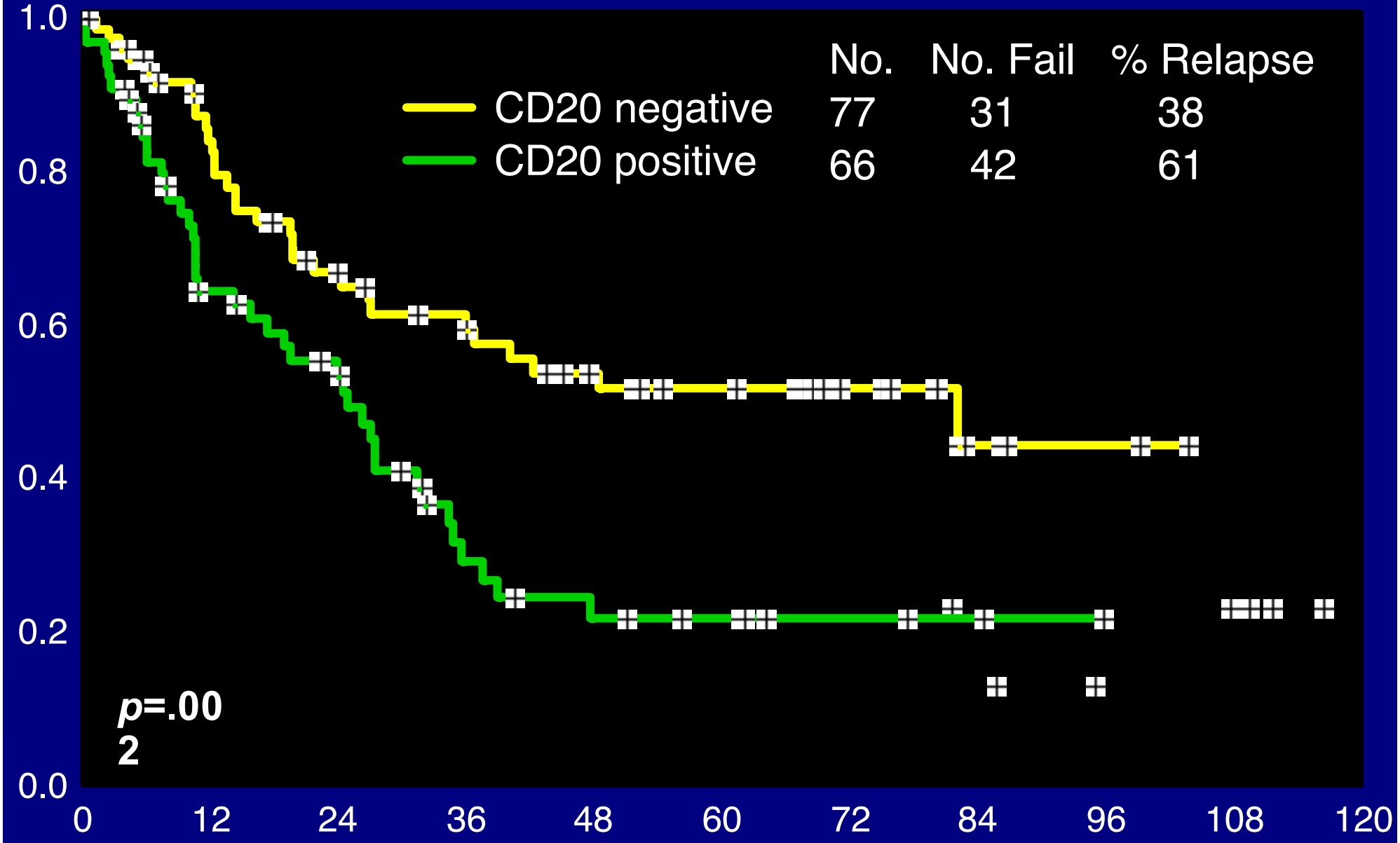
Precursor B-cell ALL

Prognostic Significance of CD20 Expression in Precursor B-cell ALL

Parameter	CD20 neg (n=133)	CD20 pos (n=120)	P-value
% CR			
VAD/CVAD	68	83	.06
Hyper-CVAD	95	94	NS
% Relapse			
VAD/CVAD	53	71	.08
Hyper-CVAD	37	61	.005
% 3-yr CRD			
VAD/CVAD	42	18	NS
Hyper-CVAD	58	22	< .001
% 3-yr OS			
VAD/CVAD	28	26	NS
Hyper-CVAD	60	27	.003

Hyper-CVAD +/- Rituximab in B-lymphoblastic leukemia

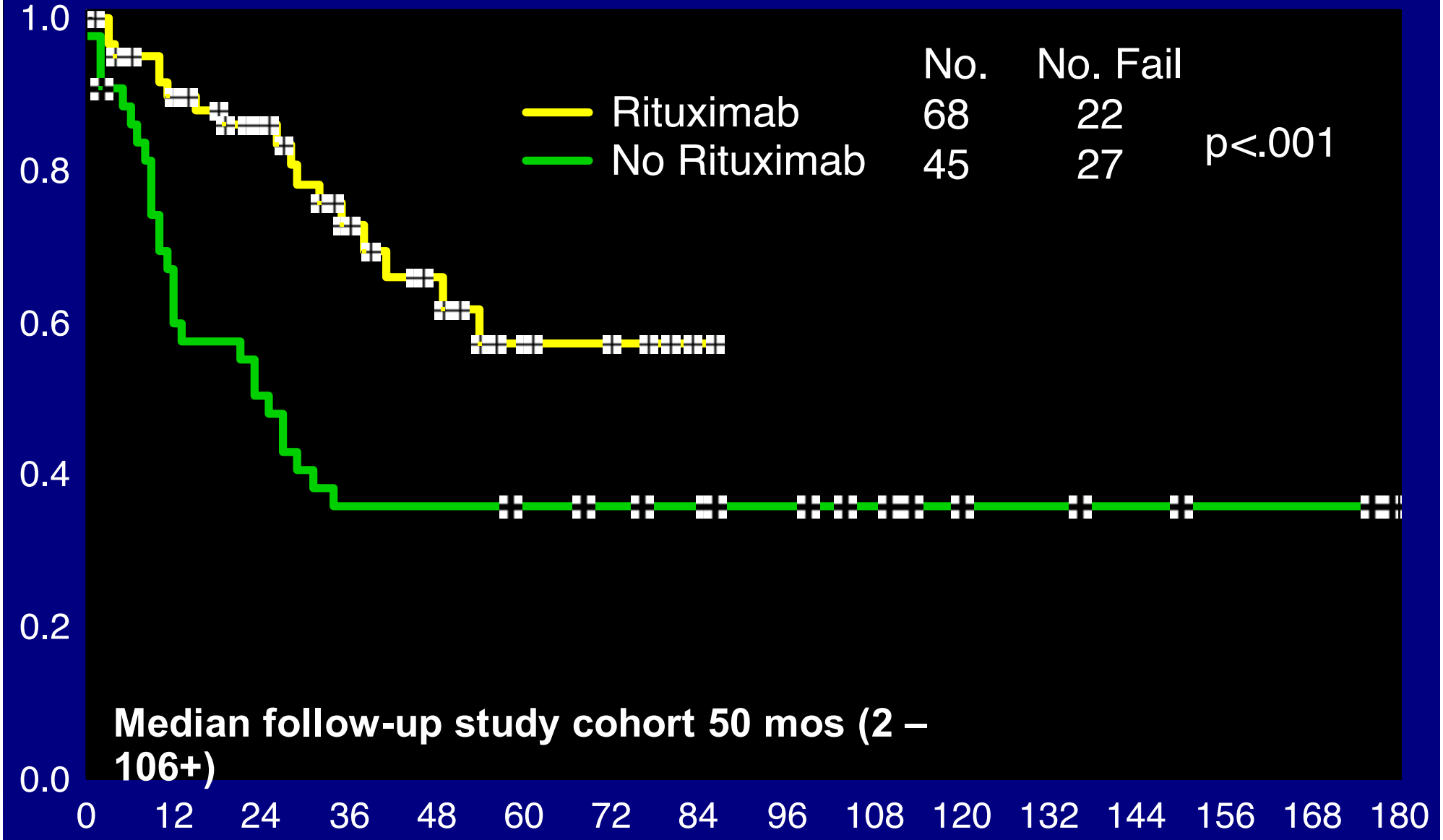
Survival by CD20 Expression with Standard Hyper-CVAD without Rituximab



Thomas, Blood 113:6330, 2009

Hyper-CVAD + Rituximab in B-lymphoblastic leukemia

CR Duration by Therapy for CD20 Positive Age < 60 years



Thomas et al, JCO 28:3880, 2010

Philadelphia Positive ALL Tyrosine Kinase Inhibitor-based Chemotherapy

Philadelphia Positive (Ph+) ALL

- t(9;22) or bcr-abl in 20-30% adults with ALL
  - p190bcr-abl in 70%, p210bcr-abl in remainder
- CD10+ B-lineage (CALLA, pre-B)
  - Frequent co-expression CD13 & CD33
  - Distinguish from bilineage leukemia
    - Myeloperoxidase negative
    - C-kit negative
- Increased incidence with older age

Outcome with Chemotherapy for Adult Ph+ ALL in Pre-Imatinib Era

Study	Year	No.	% CR	% Survival (X yrs)
Bloomfield	1989	29	46	11*
Gotz	1992	25	76	8*
Larson	1995	25	70	16 (3)
Secker-Walker	1997	40	83	13 (3)
Wetzler	1999	67	82	11 (5)
Faderl**	2000	67	90	16*
Dombret	2002	154	67	19 (3)
Gleissner	2003	175	68	13 (3)
Cimino	2006	101	67	16 (7)

*Median survival in mos, **hyper-CVAD

Single Agent Imatinib in Relapsed/Refractory Ph+ ALL & CML-LBP

% Response	ALL (n=48)		CML-LBP (n=8)	
	All	Sustained	All	Sustained
Overall	60	27	50	25
CR	19	6	50	12.5
Marrow CR	10	0	0	0
Marrow PR	31	21	0	12.5
%CG CR	17		12.5	
TTP (mo)	2.2		NA	
Survival (mo)	4.9		6.6	

Ottmann et al, Blood 100:1965, 2002

Imatinib + Chemotherapy for de *novo* Adult Ph+ ALL: Regimens

- Concurrent induction & consolidation
  - Hyper-CVAD + imatinib (Thomas et al)
  - PETHEMA (Ribera et al)
- Concurrent induction, alternating consolidation
  - JALSG ALL202 (Yanada et al)
- After induction, alternating consolidation
  - Hyper-CVID (Lee et al)
  - GRAALL AFR09 (Delannoy et al)
  - GMALL 06/99 (Wassmann et al)
- After induction, concurrent consolidation
  - AFR03 HAM + imatinib (Dombret et al)
  - GMALL 07/03 (Wassmann et al)
  - GMALL (Ottmann et al)

Imatinib + Hyper-CVAD in Ph+ ALL

Intensive phase

1 2 3 4 5 6 7 8

Maintenance phase

Hyper-CVAD

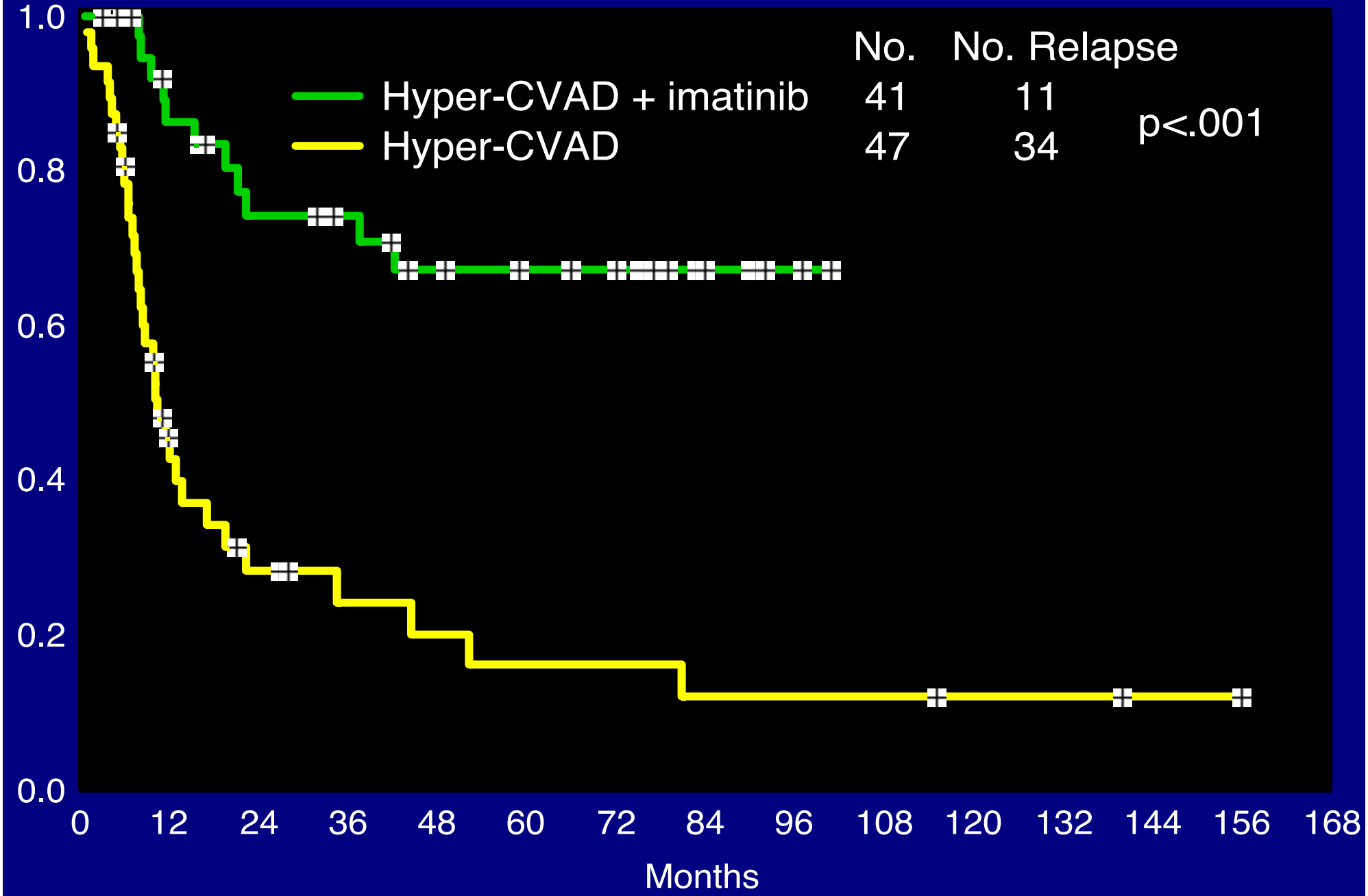
MTX-cytarabine

Imatinib

Vincristine + prednisone

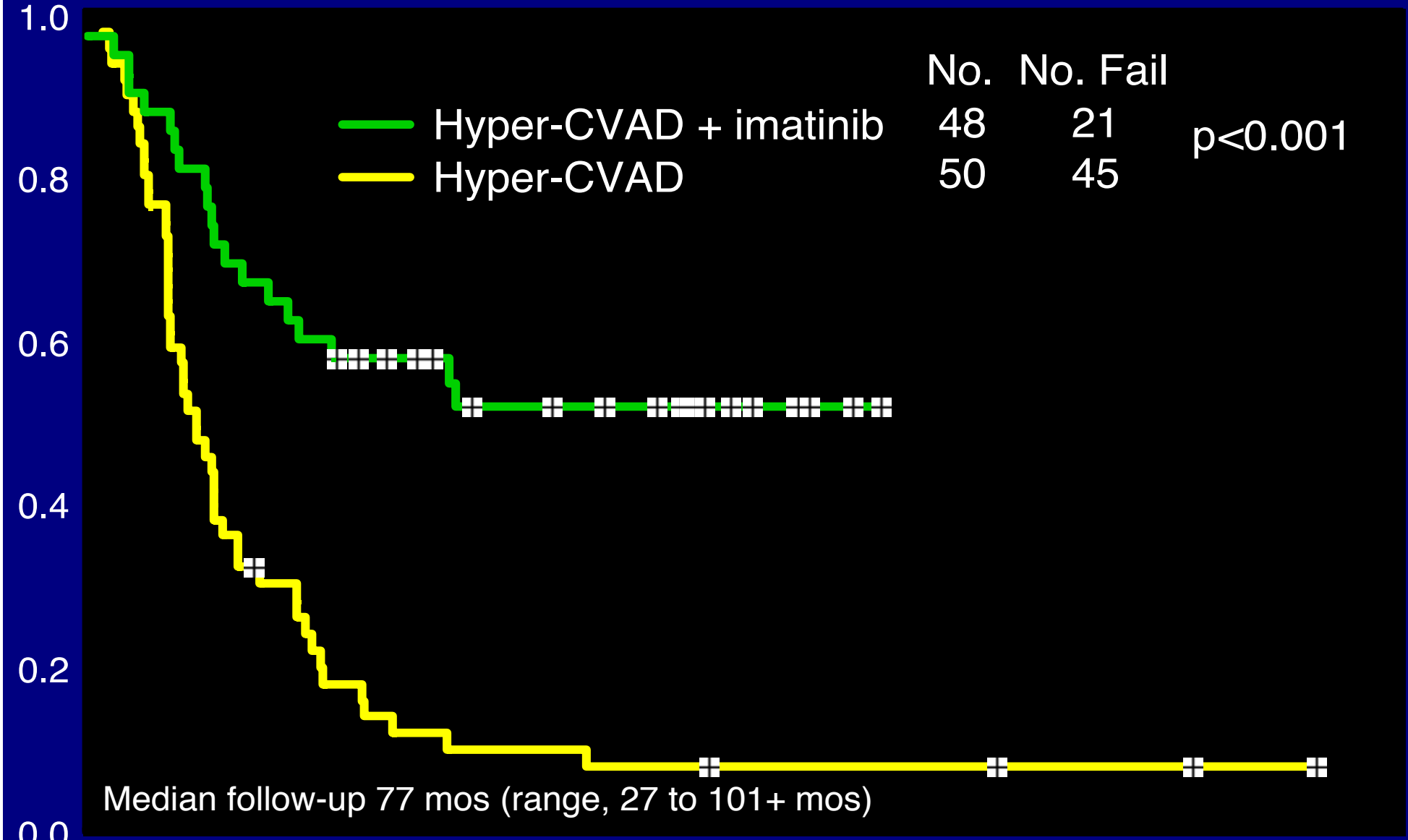
Thomas et al, Blood 103:4396, 2004

CR Duration in Ph-ALL by Regimen (Excluding Primary Refractory)



Thomas et al, ASCO 2010, abstract 6506

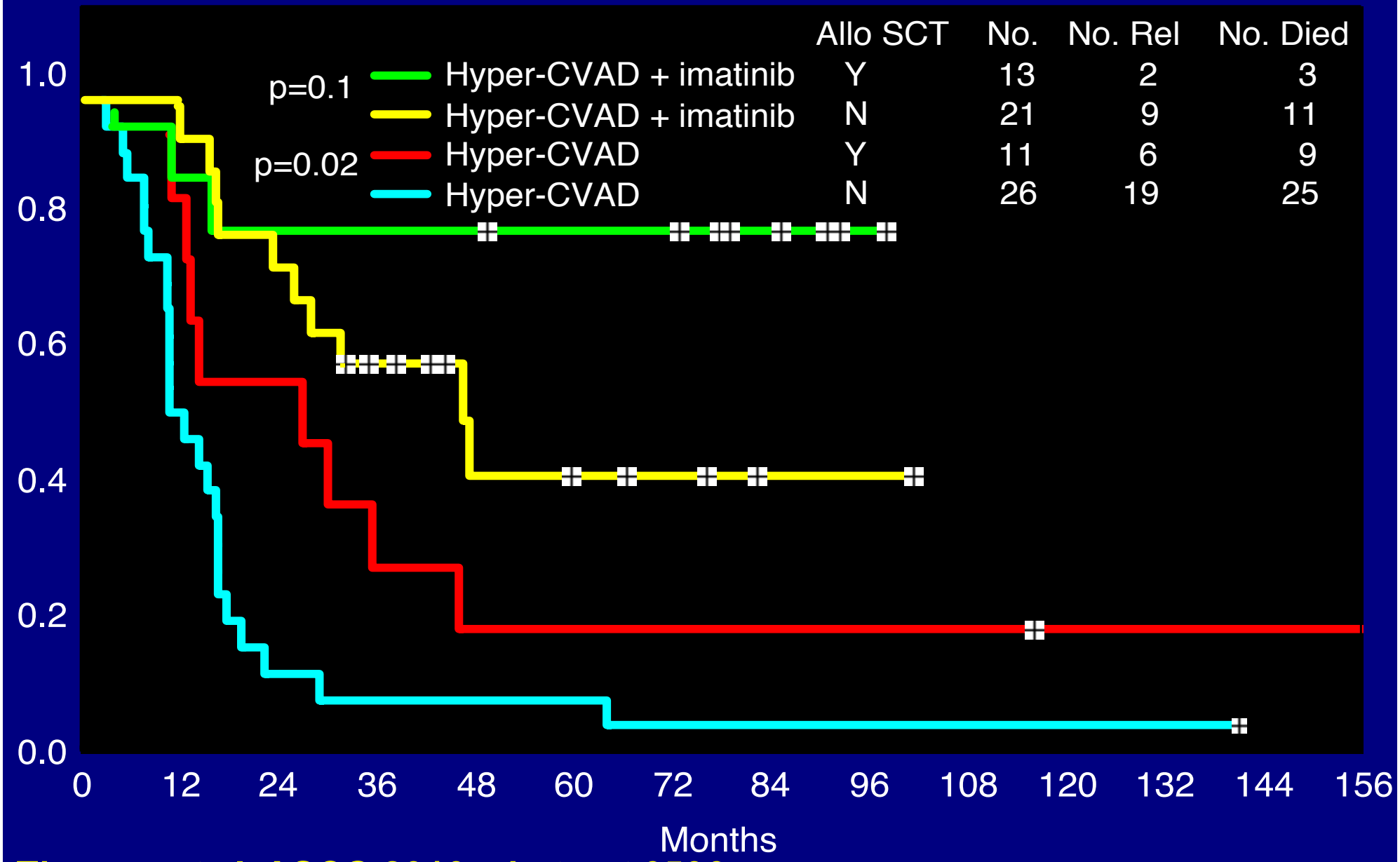
Survival in Ph-ALL by Regimen (Excluding Primary Refractory)



Thomas et al, ASCO 2010, abstract 6506

Survival in Ph-ALL: Hyper-CVAD +/- Imatinib +/- aSCT (1st CR)

(Age < 60 years)



Thomas et al, ASCO 2010, abstract 6506

Imatinib-based Chemotherapy Regimens for *de novo* Adult Ph+ ALL

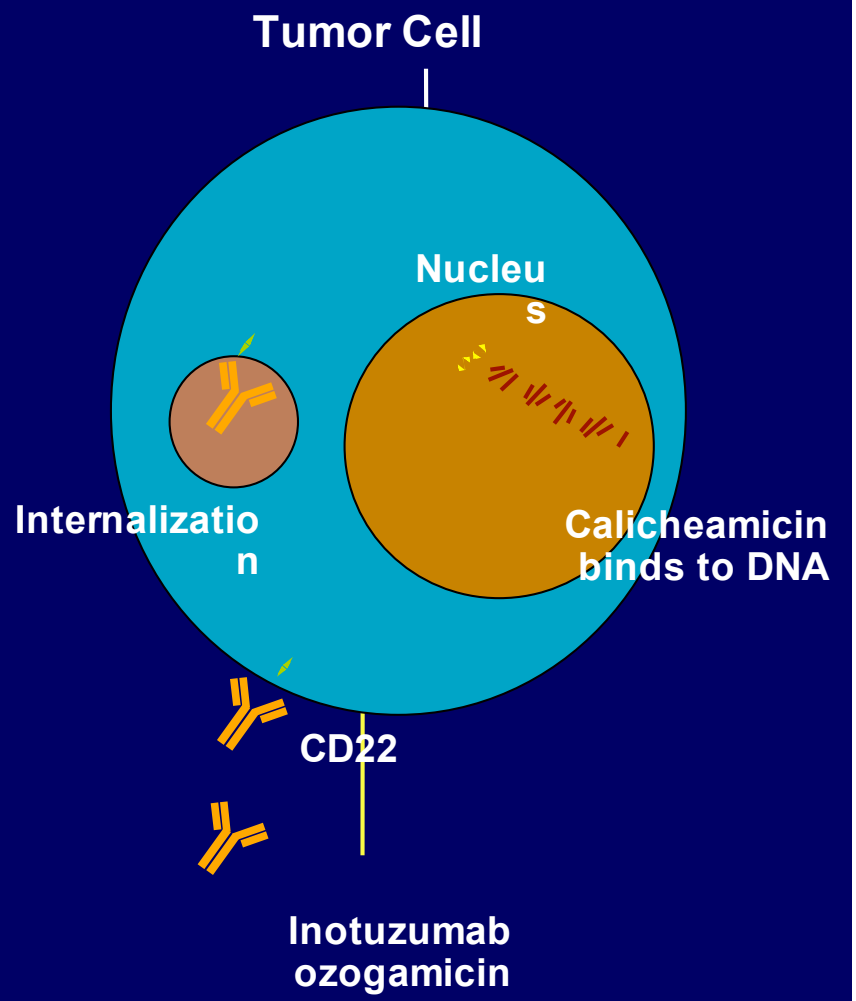
Regimen	No.	%CR	%Rel	%DFS (X yrs)	%OS (X yrs)
Age > 15 yrs					
Hyper-CVAD	39	92	22	66 (4)	55 (4)
Adults age < 65 years					
JASALG ALL202	80	96	26	60 (1)	76 (1)
GMALL					
Alternating	47	NA	NR	52 (2)	36 (2)
Concurrent	45	NA	NR	61 (2)	43 (2)
GRAAPH-2003	45	96	19	55 (1.5)	65 (1.5)

Thomas et al ASH 2007; Yanada et al J Clin Oncol 24:460, 2006; Wassmann et al Blood 108:1469, 2006; de Labarthe et al Blood 109: 1408, 2007

New Monoclonal Antibodies

Inotuzumab in ALL. Mechanisms of Action

- The antibody-antigen complex is rapidly internalized upon binding to CD22
- Calicheamicin is released inside the tumor cell
  - Calicheamicin is more potent than other cytotoxic chemotherapeutic agents
- Calicheamicin binds to DNA, inducing double-stranded DNA breaks



Inotuzumab in ALL. Study Group (N=49)

Characteristic	Category	No. (%)
Age (yrs)	≥ 60	12 (24)
PS (ECOG)	≥ 2	5 (10)
Salvage status	S1, CRD1 < 12 mos	3 (6)
	S1, CRD1 ≥ 12 mos	7 (14)
	S2	24 (49)
	≥ S3	12 (24)
Prior allo SCT	Yes	7 (14)
Karyotype	Ph-positive	7 (14)
	T (4;11)	5 (10)
	Diploid	12 (24)
	Other	25 (51)
% CD22 – positive	> 90	28 (57)
	70-89	14 (29)
	50-69	7 (14)

Inotuzumab in ALL. Response (N=49)

Response	No (%)
CR	9 (18)
CRp	14 (29)
CRi (marrow CR)	5 (10)
PR	0
Resistant	19 (39)
Death < 4 wks	2 (4)
OR: 9 CR + 14 CRp + 5 CRi	28 (57)

O'Brien. Blood 118: abst 875; 2011

Inotuzumab in ALL. CG Response (N=18)

Parameter	CG Response
CR	CR 5/6
	PR 1/6
CRp	CR 6/7
CRi (marrow CR)	CR 5/5
CGCR: 5 CR + 6 CRp + 5 CRi	16/18 (89%)

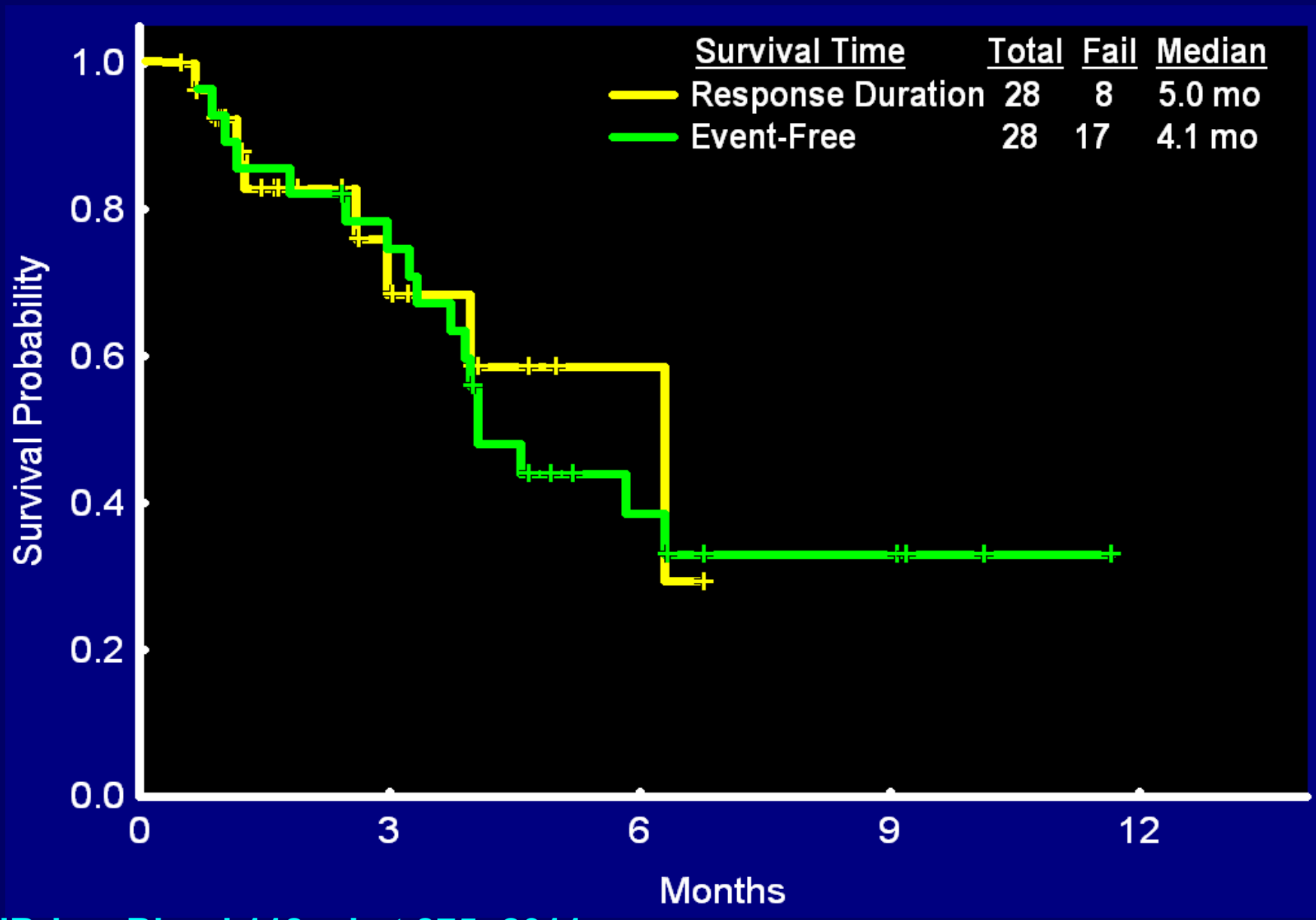
O'Brien. Blood 118: abst 875; 2011

Inotuzumab in ALL. MRD (N=27)

Parameter	MRD Negative N (%)
CR	8/9 (89)
CRp	9/14 (64)
CRi (marrow CR)	0/4 (0)
MRD negative: 8 CR + 9 CRp + 0 CRi	**17/27 (63)**

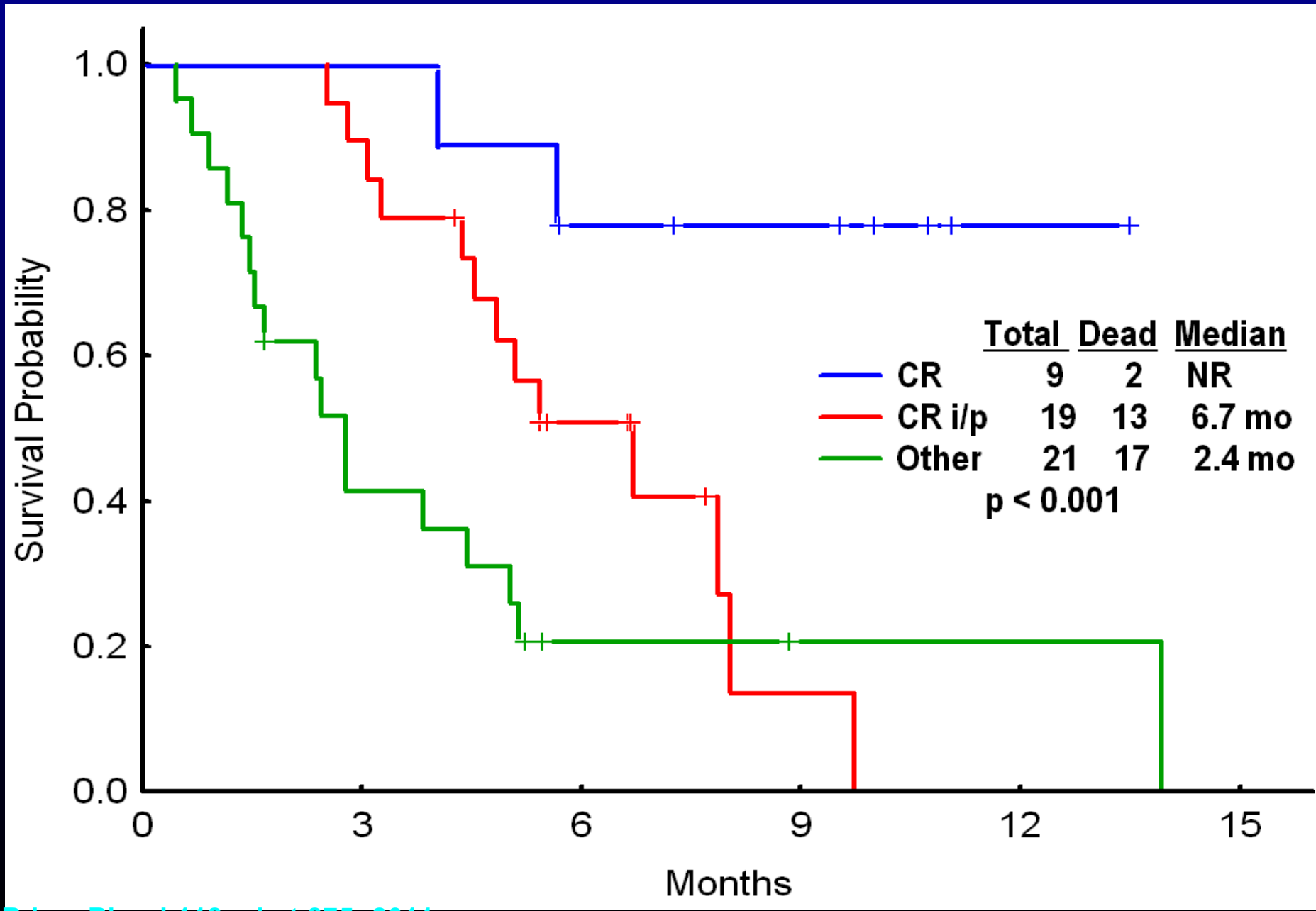
O'Brien. Blood 118: abst 875; 2011

Inotuzumab in ALL.
Progression-free Survival + Response Duration



O'Brien. Blood 118: abst 875; 2011

Inotuzumab in ALL. OS by Treatment Responses

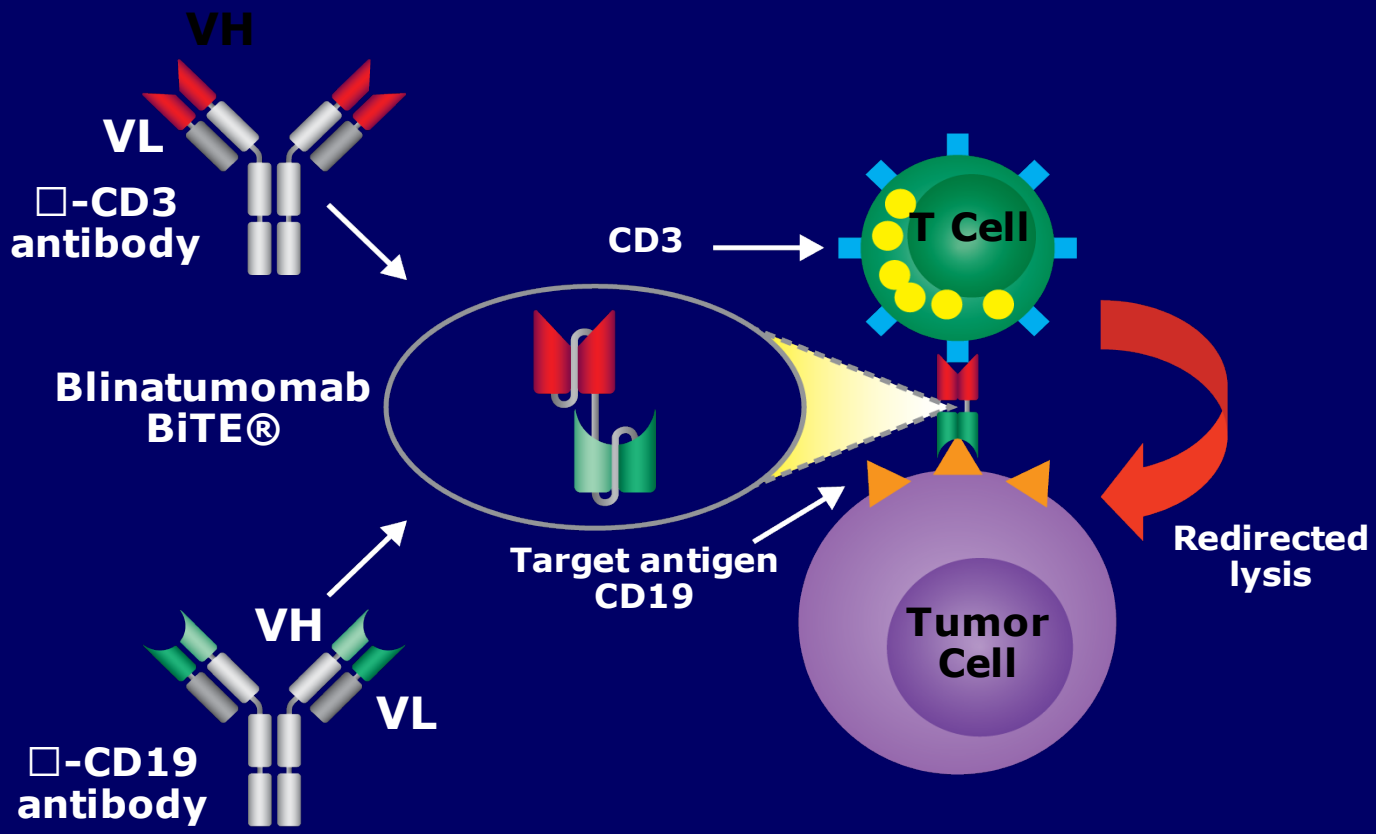


O'Brien. Blood 118: abst 875; 2011

Inotuzumab in ALL. Efficacy

Parameter	% ORR		P-value
	Inotuzumab N=49	Chemotherapy N=459	
Overall	**57**	**32**	**<0.001**
S1	69	38	0.004
S2	46	23	0.032
≥ S3	67	13	<0.001

Mode of Action of BiTE® Antibody Blinatumomab



- Blinatumomab (MT103) is a bispecific T-cell engager (BiTE) antibody designed to direct cytotoxic T cells to CD19 expressing cancer cells

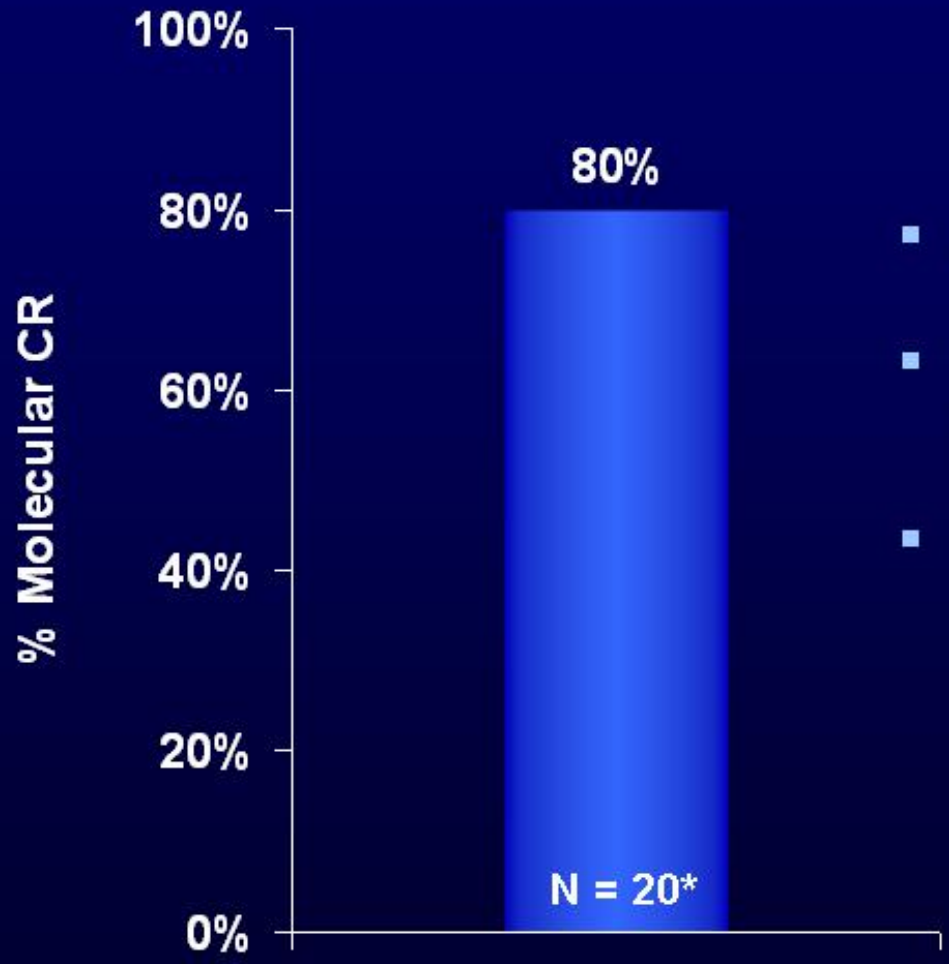
Bargou R., et al. *Science* 2008;321(5891):974-977.

Cellular Therapy- Blinatumomab

- Bi-specific antibody ; redirects T cells toward lysis of cells expressing CD19 antigen
- Used as single agent in precursor B-ALL with persistent MRD
- 21 pt Rx; 20 evaluable for response: 16 achieved molecular CR after 1 cycle of Rx. 3-yr RFS 78%.
- Adverse events: lymphopenia, fever,

Topp. JCO 29:2493, 2011

Blinatumomab Molecular Complete Response

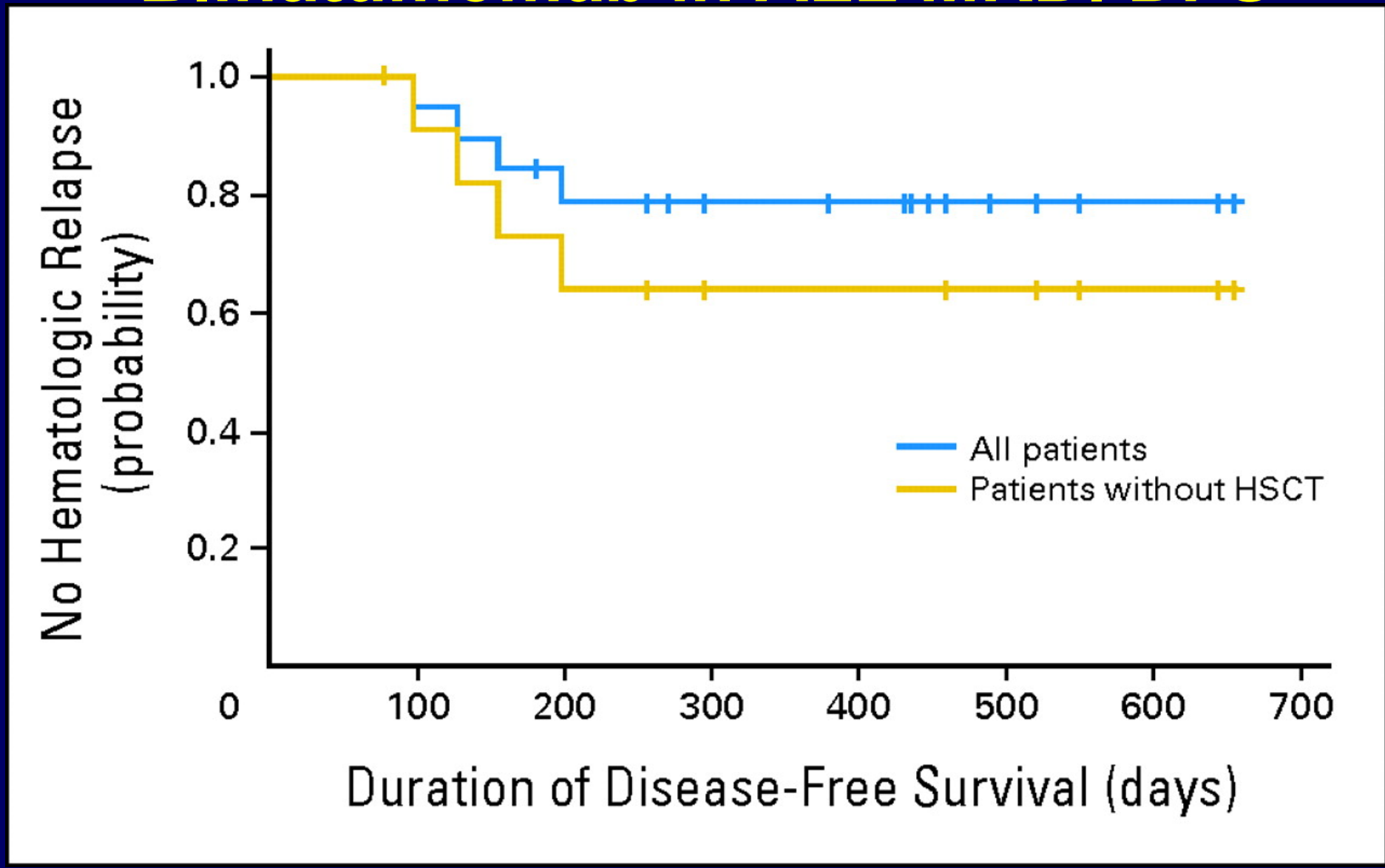


- 80% of patients achieved molecular CR on blinatumomab
- Responses were rapid, all occurring within the first cycle of treatment
- Responders include
  - 3/5 patients with Ph+ ALL (one T315I mutation)
  - 1/2 patients with t(4;11)

*One patient not evaluable: < 1 treatment cycle and lack of response assessment

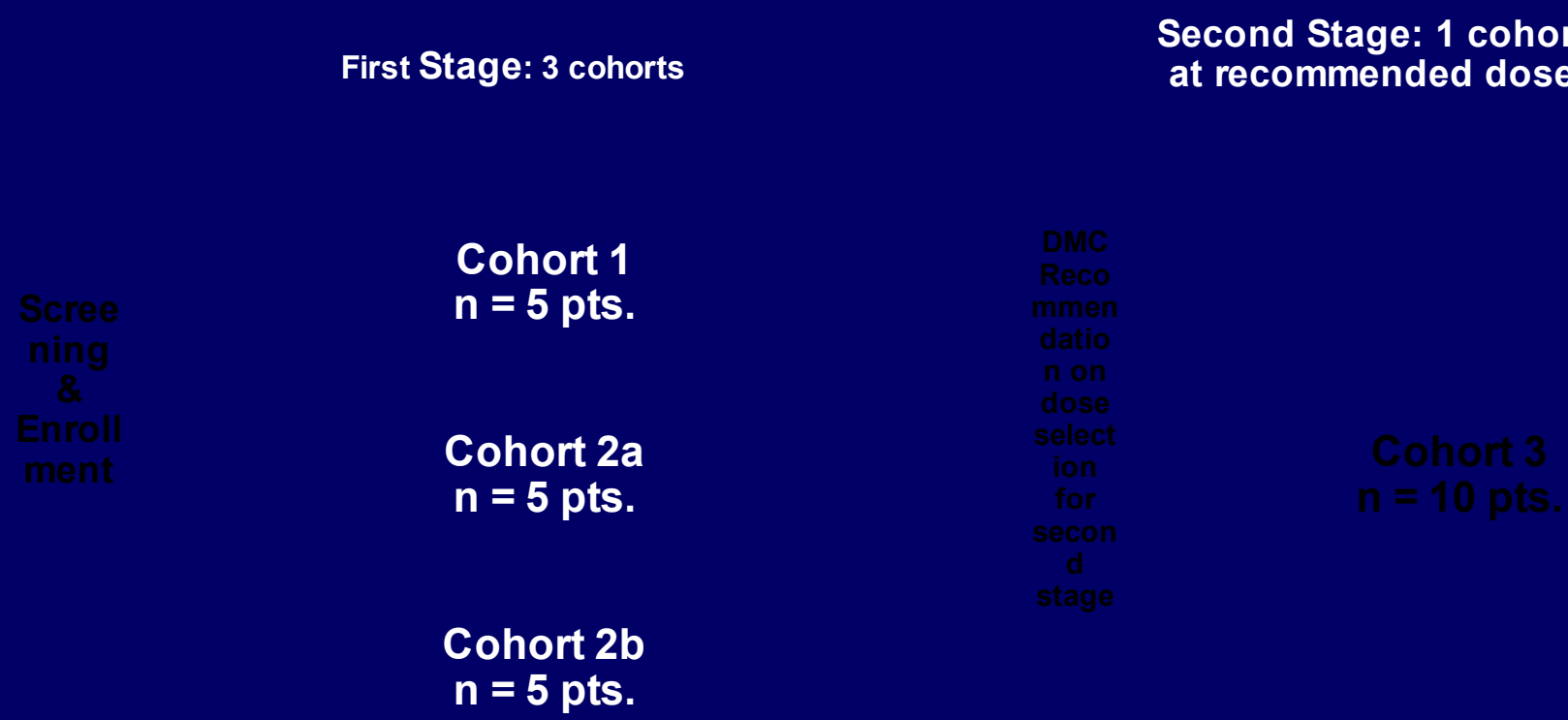
Topp, JCO 29:2493, 2011

Blinatumomab in ALL MRD. DFS



Topp. JCO 29: 2493; 2011

MT103-206 Trial Design



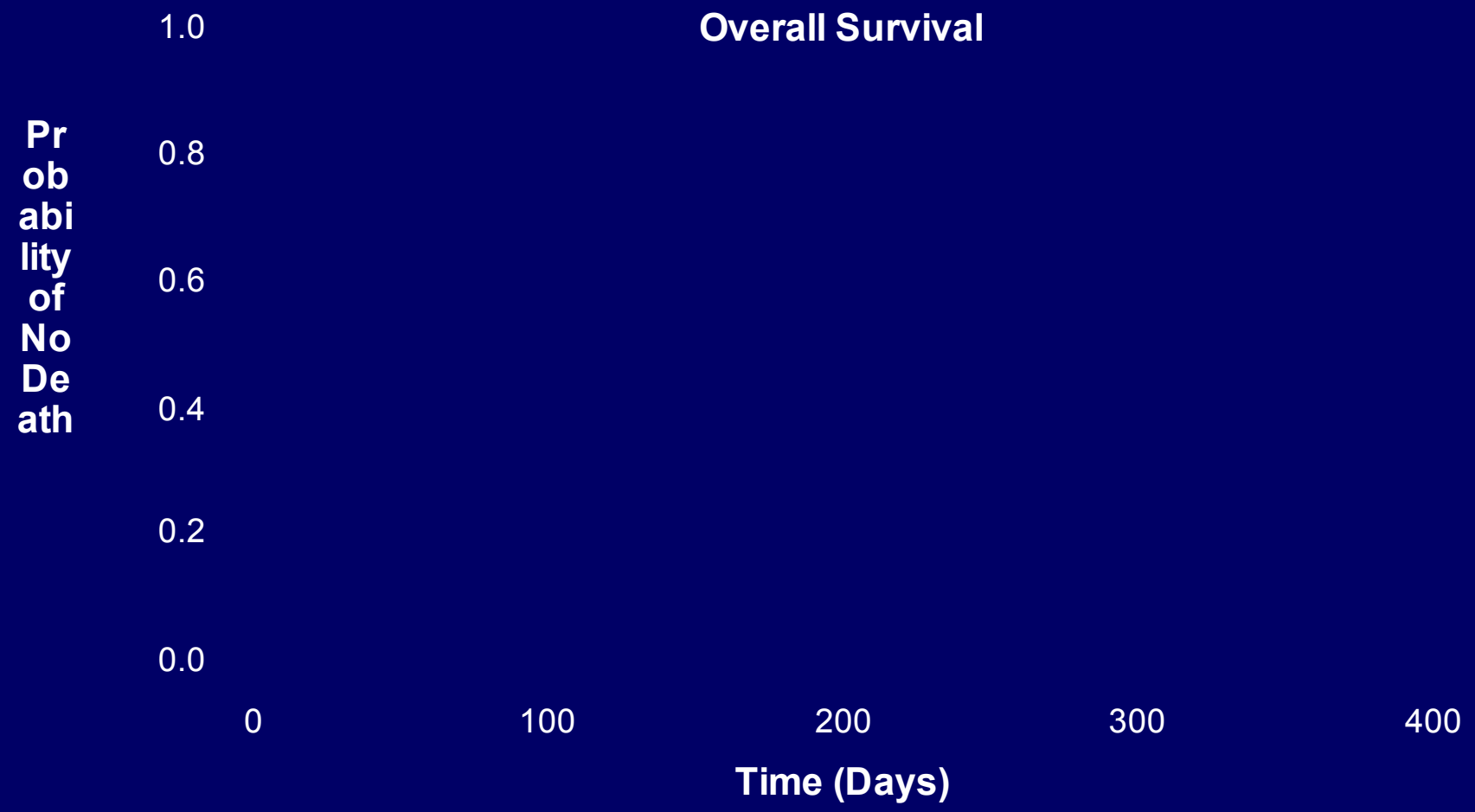
- Open label, multicenter, exploratory phase 2 trial
- Simon 2-stage design – the dose in Stage 2 (cohort 3) will depend on the outcome of cohorts 1, 2a, and 2b

Blinatumomab in ALL. Response

	15 µg/m²/d Cohort 1 (n = 7), n (%)	5-15-30 µg/m²/d Cohort 2b (n = 6), n (%)	5-15 µg/m²/d Cohorts 2a + 3 (n = 12), n (%)
CR/CRh*	5 (71)	3 (50)	9 (75)
CR	2 (29)	3 (50)	7 (58)
CRh*	3 (43)	0	2 (17)
Nonresponder	1 (14)	3 (50)	3 (25)
Not evaluable	1 (14)	0	0

- All patients with CR/CRh* achieved MRD-response (MRD <10-4)

Blinatumomab in ALL. Survival for Cohorts 1 + 2a + 2b (n=18)



Median survival not reached (median follow-up of 9.7 months, n=18)
Median duration of complete hematologic remission of 7.1 months