Leucemie Acute Linfoblastiche

AULA CHIANTORE
POLICLINICO S. ORSOLA-MALPIGHI
Bologna, 13 maggio 2016

LAL paziente anziano Ph-

F. Fabbiano (Palermo)

III SESSIONE: TERAPIA

Moderatori: *M. Gobbi (Genova), G. Specchia (Bari)*

14.20 **LAL paziente pediatrico**
A. Testi (Roma)

14.40 **LAL paziente giovane adulto**
A. Rambaldi (Bergamo)

15.00 **LAL adulto Ph+**
S. Chiaretti (Roma)

15.20 **LAL adulto Ph-**
F. Ferrara (Napoli)

15.40 **LAL paziente anziano Ph+**
C. Papayannidis (Bologna)

16.00 **LAL paziente anziano Ph-**
F. Fabbiano (Palermo)

How should we define the term "old" in the context of leukemia treatment?

The term "young adults" is frequently used and was extended from age 35 to age 45 years; it is generally used for patients who tolerate and who appear to benefit from treatment with so-called pediatric-based chemotherapy.[3] Does this mean that all patients not meeting the definition of "young" adult are "old" adults? My suggested approach is to define older patients on the basis of their assumed ability to receive intensive chemotherapy, including stem cell transplantation (SCT), which is usually limited to a cut point of 55 to 65 years. In this article, I will refer to patients beyond this age and discuss older patients as defined by biological features and not chronological age only.

How I Treat

How I treat older patients with ALL

Nicola Gökbuget

BLOOD, 22 AUGUST 2013 • VOLUME 122, NUMBER 8

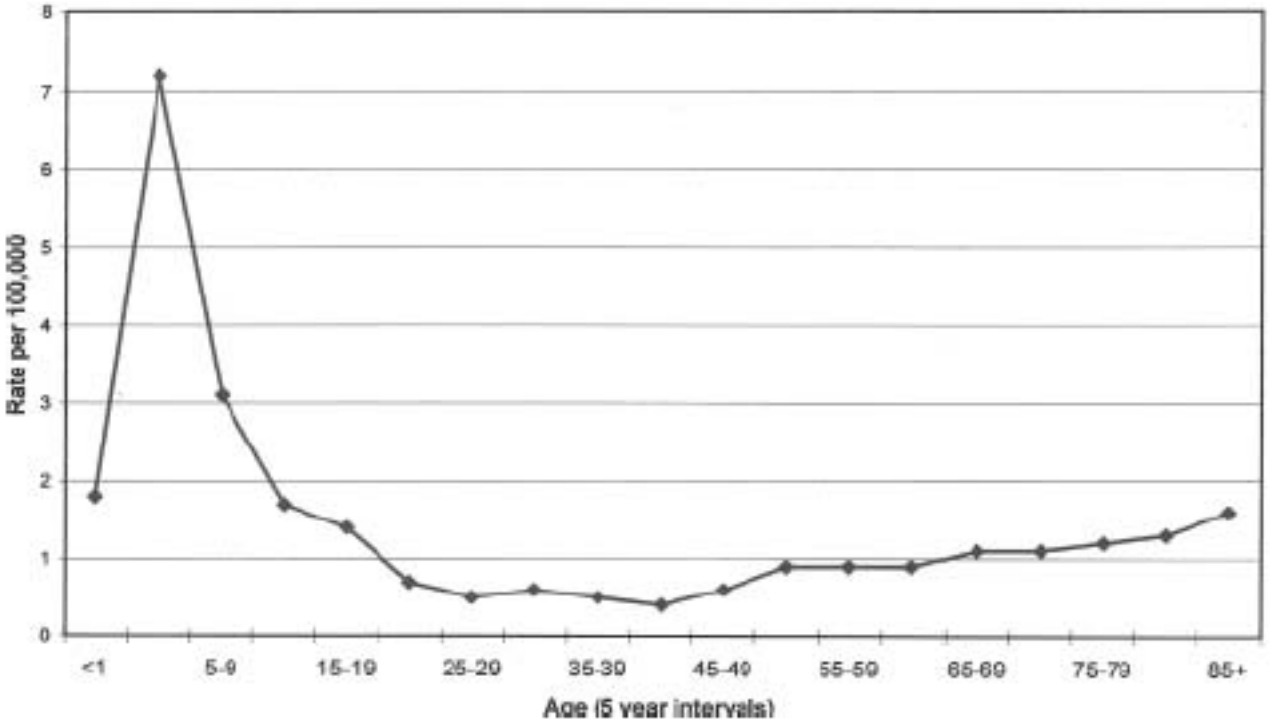
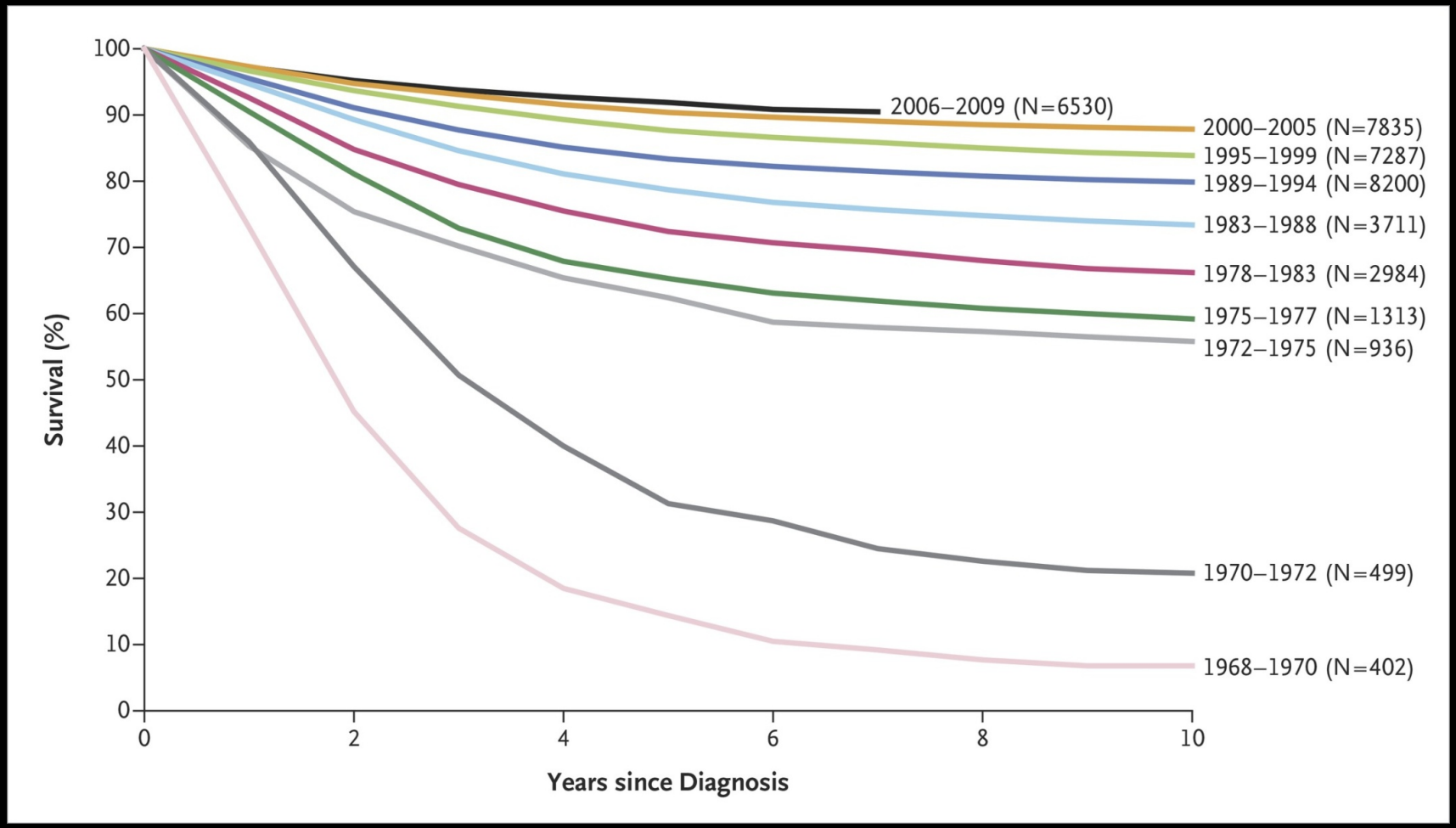


Figure 1. Age-specific annual incidence of acute lymphoblastic leukemia (US-SEER data, 1998–2002).

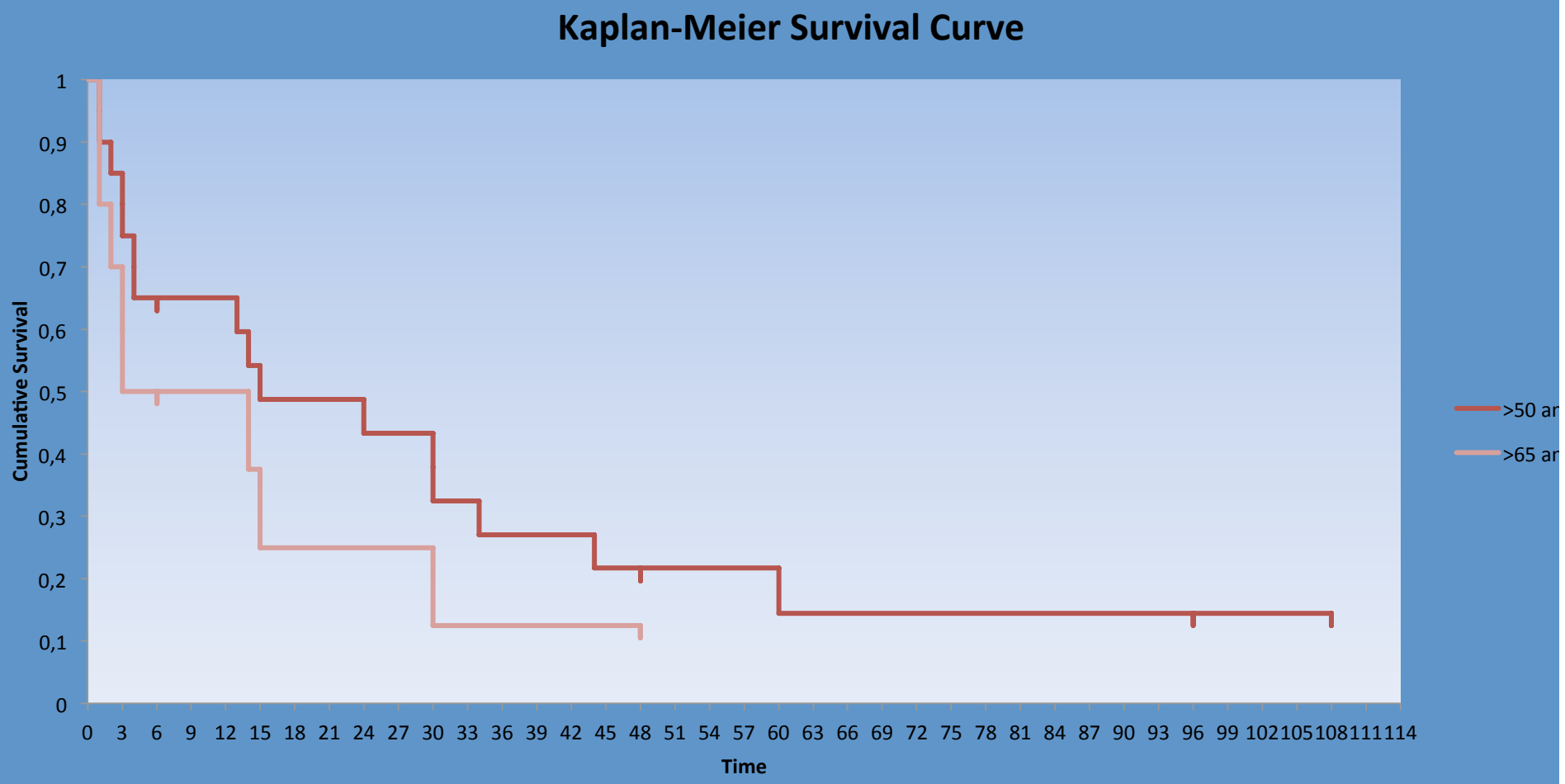
Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968–2009.

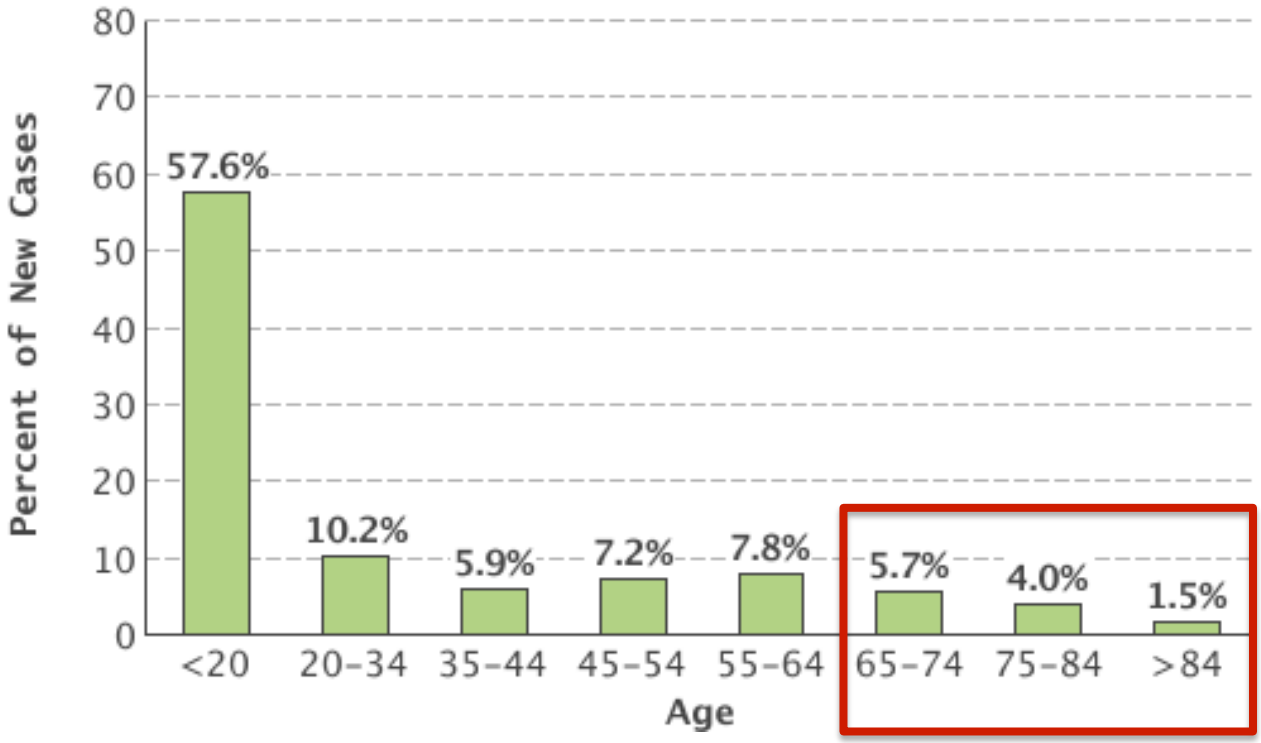


Hunger SP, Mullighan CG. N Engl J Med 2015;373:1541-1552

The NEW ENGLAND JOURNAL of MEDICINE

ALL bcr/abl-. Our data

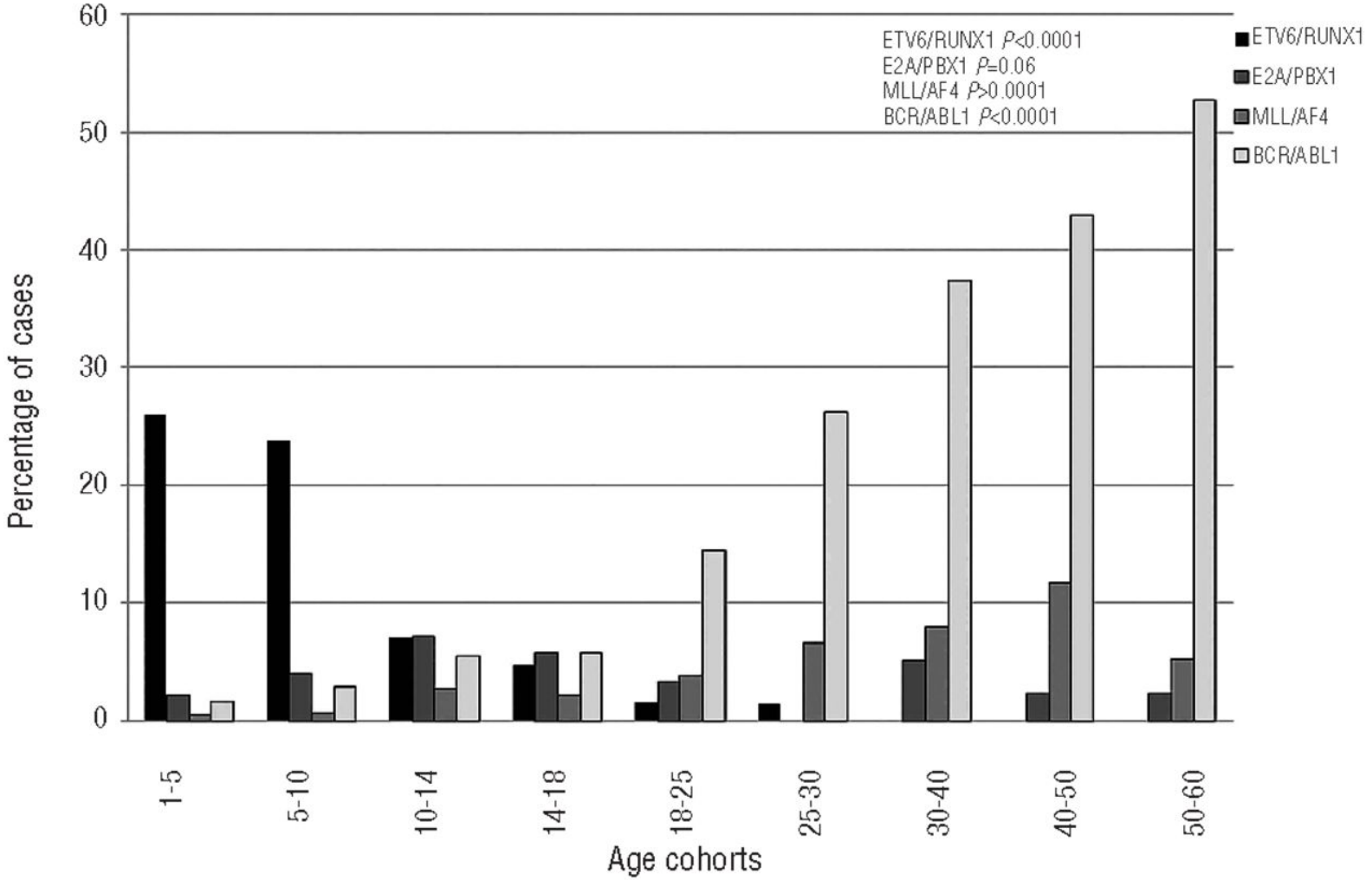




11.12%

SEER 18 2008-2012, All Races, Both Sexes

Incidence of the molecular aberrations in different age cohorts of B-ALL patients.



Sabina Chiaretti et al. Haematologica 2013;98:1702-1710

haematologica
the hematology journal

Ph-like Acute Lymphoblastic Leukemia in Older Adults

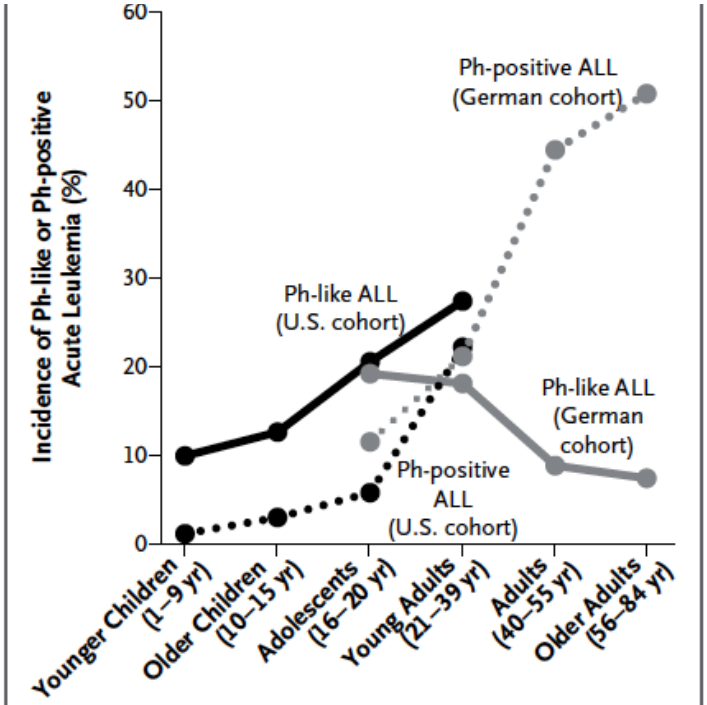
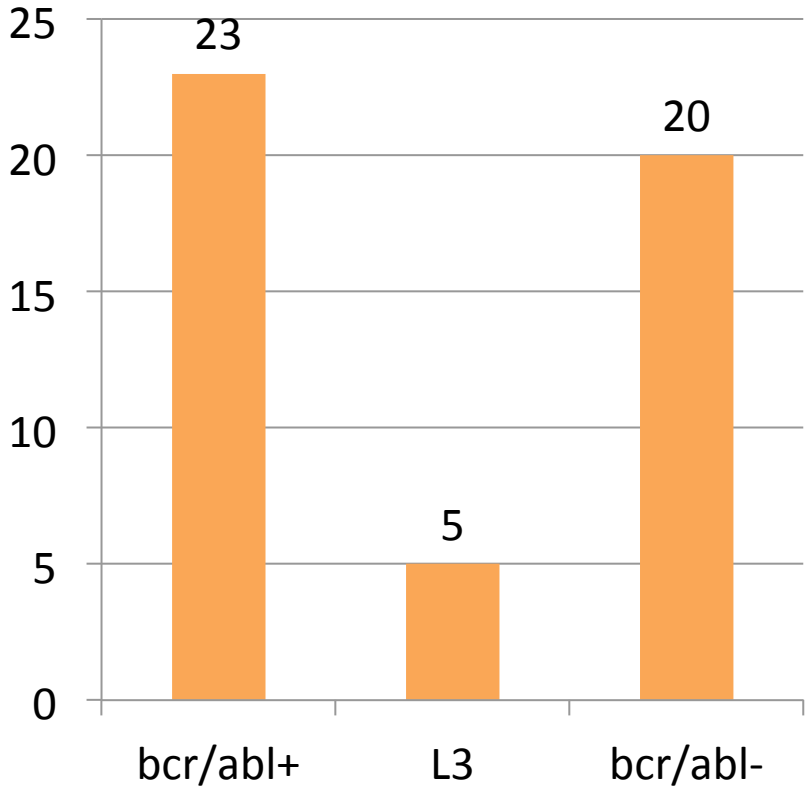


Figure 1. Incidence of Ph-like and Ph-Positive Acute Lymphoblastic Leukemia (ALL), According to Age.

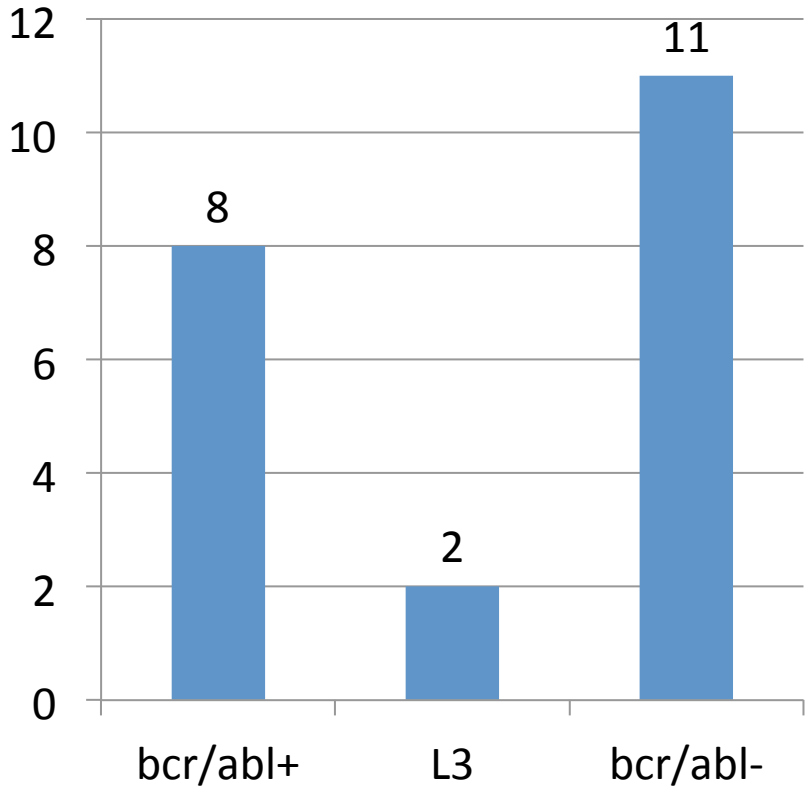
The proportions of patients with the molecular subgroups of B-cell precursor ALL are shown. The German cohort was composed of patients who received treatment in the German Multicenter Study Group for Adult ALL trials, and the U.S. cohort was composed of the patients in the study reported by Roberts et al.

Ematologia Villa Sofia - Cervello

48 pazienti >50 aa 2005-2016



21 pazienti >65 aa



Popolazione italiana 60.656.000

Incidenza SEER - 2012	**1.5/100.000**	**900 casi/anno in Italia**
ALL (SEER)> 65 aa	**11%**	**99 casi/anno in Italia**
bcr/abl -	**50 -60%**	**40-60 casi/ anno in Italia**

- Gli studi clinici sono pochi, includono nella categoria “older patients” > 50, >55, >60, >65 aa.
- Frequentemente mettono insieme ALL bcr/abl + e -
- Spesso hanno problemi di reclutamento

Terapia "Geriatric assessment adapted" per il trattamento della Leucemia acuta linfoblastica Ph negativa dell'anziano. GIMEMA LAL 1104

PREVISIONE ARRUOLAMENTO

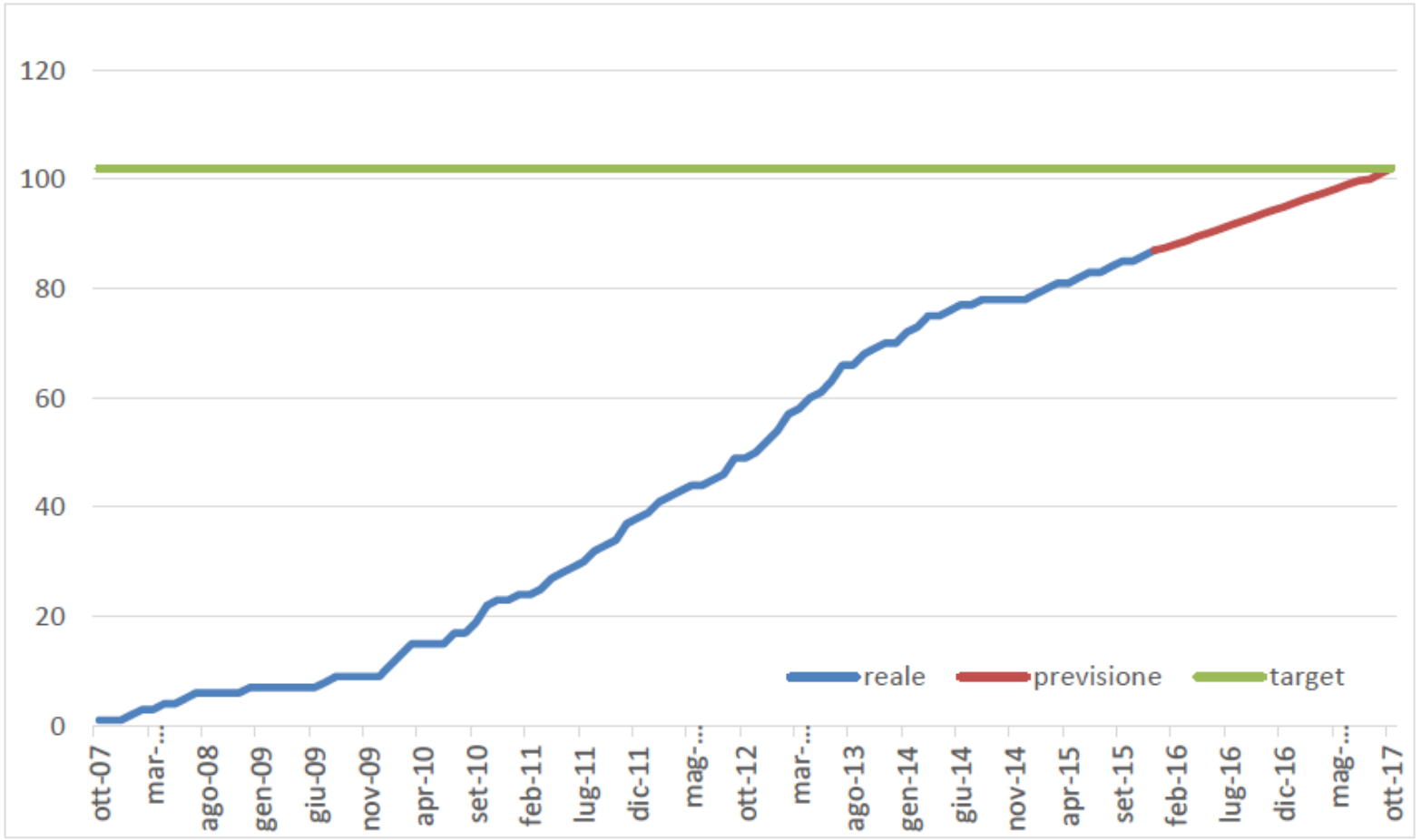


Table 2. Outcome from prospective trials designed for older ALL patients

Reference	Year	Age (range) (y)	Ph+	No. of patients	CR rate (%)	Early death (%)	Failure (%)	CCR*		DFS*	OS†	
								%	Years		%	Years
Bassan et al[51]	1996	64 (60-73)	Yes	22	59	18	14	12		9	20	2
Delannoy et al[52]	1997	67 (55-86)	Yes	40	85	N/R	N/R	N/R		14	16	2
Delannoy et al[64]	2002	65 (55-81)	Yes	58	43	10	47	5		10	N/R	
Offidani et al[14]	2004	69 (61-79)	Yes	17	76	17	6	20		21	38	2
Sancho et al[53]	2007	65 (56-77)	No	33	58	36	6	46	2	7	39	1
Kao et al[54]	2008	66 (60-78)	Yes	17	71	29	0	82	1	N/R	71	1
Gökbuget et al[55]	2008	66 (56-73)	No	54	85	0	15	9		N/R	61	1
Hunault-Berger et al[56]	2010											
Arm 1		68 (55-77)	No	31	90	7	3	32	2	N/R	35	2
Arm 2		66 (60-80)		29	72	10	17	52	2		24	2
Gökbuget et al[28]	2012	57 (55-85)	No	268	76	14	10	32	5	N/R	23	5

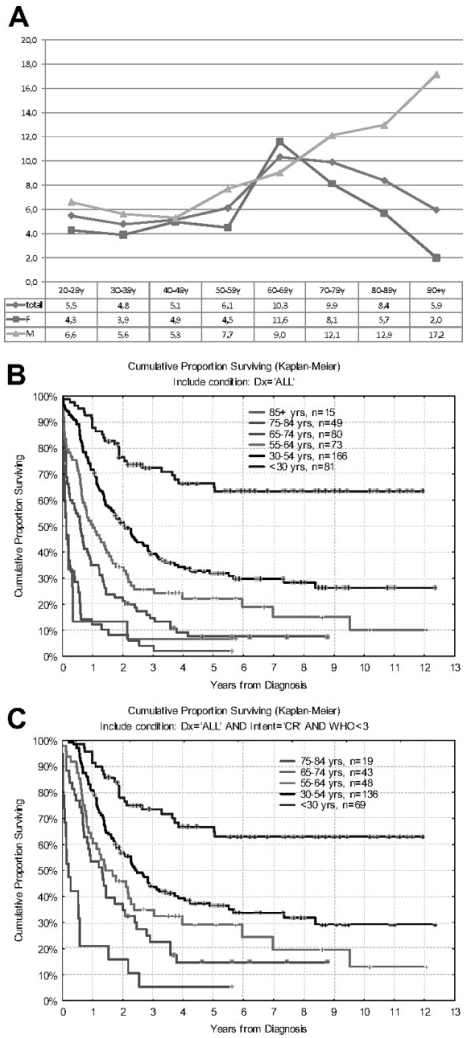
Ph+, Ph/BCR-ABL–positive ALL included; Arm 1, continuous infusion doxorubicine; Arm 2, pegylated doxorubicine.
CCR, continuous complete remission; DFS, disease-free survival; OS, overall survival.
*Median months or probability.
†Probability.

Table 1. Outcome with different treatment approaches in older patients with ALL

Approach	Age range (y)	No. of studies	No. of patients	CR (range) (%)*	Early death (range) (%)*	Survival (range) †	
						%	Months
Population-based studies[1,11,40,42]	>65	4	N/R	40[49]	N/R	6-30	
Palliative treatment[4,5,41,43]	60-91	4	94	43 (34-53)	24 (18-42)		7 (3-10)
Intensive chemotherapy designed for adult ALL without focus on older patients[6,14,15,38,39,44-50]	60-92	12	519	56 (40-81)	23 (6-42)	14 (3-29)	
Prospective studies for older ALL patients‡[13,14,51-56]	55-81	9	447	71 (43-90)	15 (0-36)	33 (16-71)	

N/R, not reported.
*Weighted means and range from cited studies for CR rates, early death rates, and survival.
†Weighted means and ranges for survival probability at 2 or more years, as reported in the cited studies, or median survival time and ranges, respectively.
‡Details are given in Table 2.

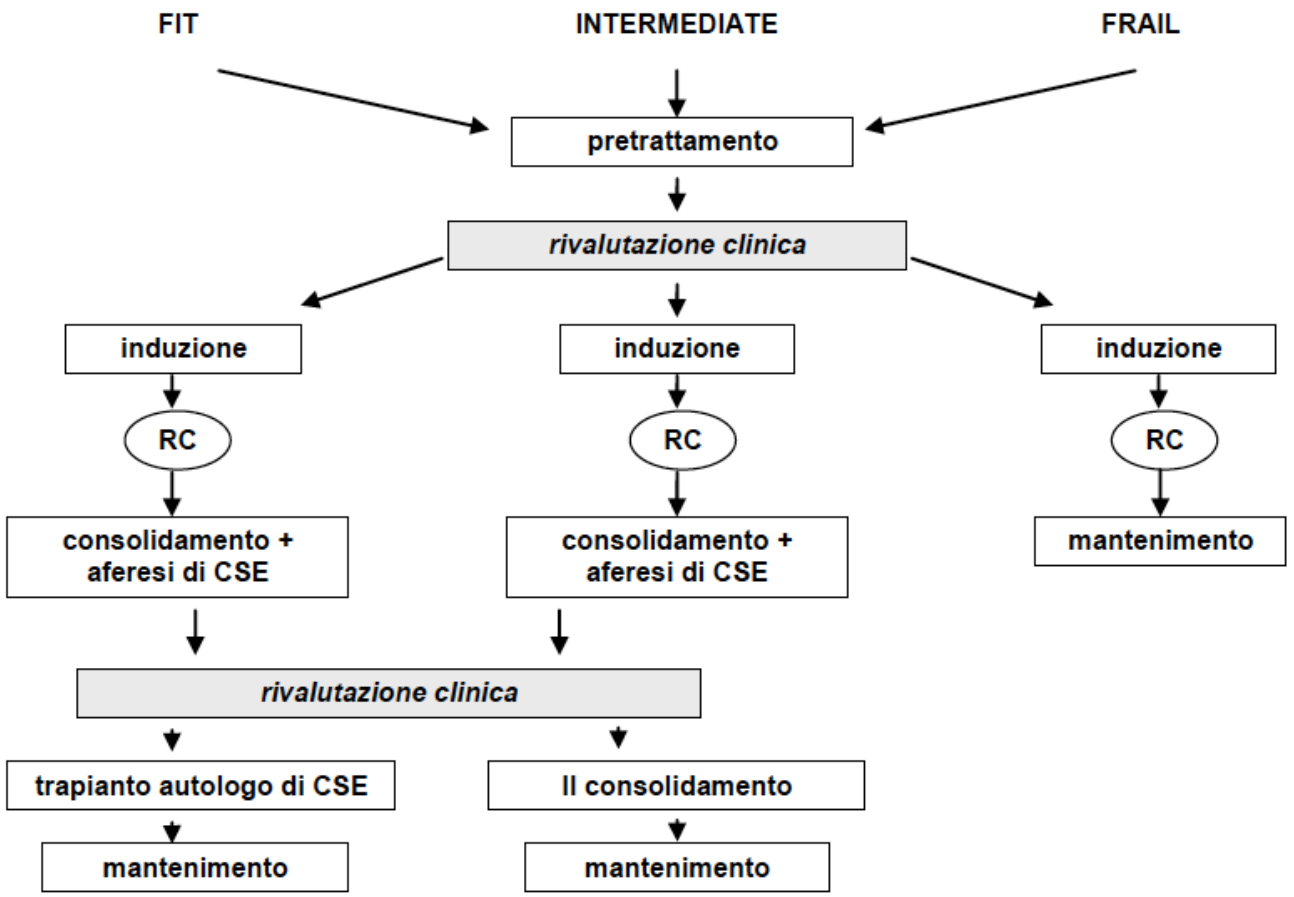
ALL incidence and survival among adults in Sweden.



Gunnar Juliusson et al. Blood 2010;116:1011

Gimema LAL 1104

Titolo: ***Terapia "geriatric assessment adapted" per il trattamento della Leucemia acuta linfoblastica Ph negativa dell'anziano***

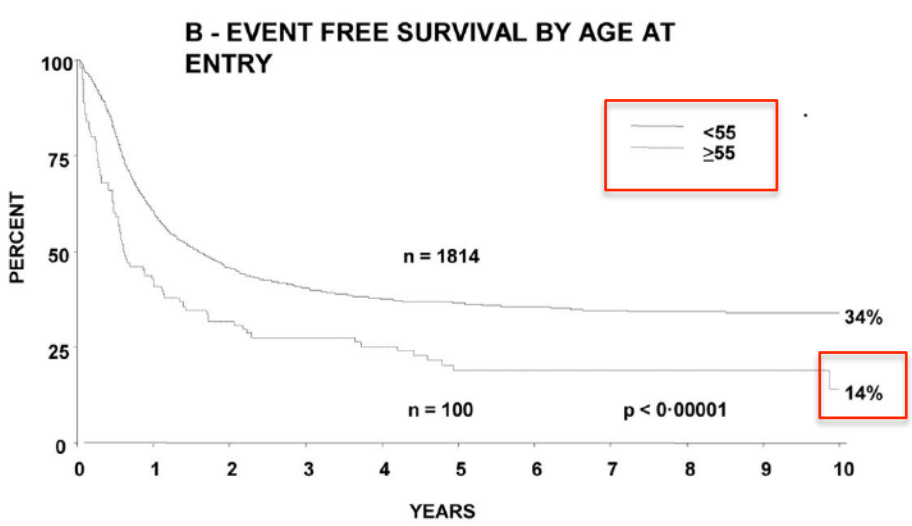


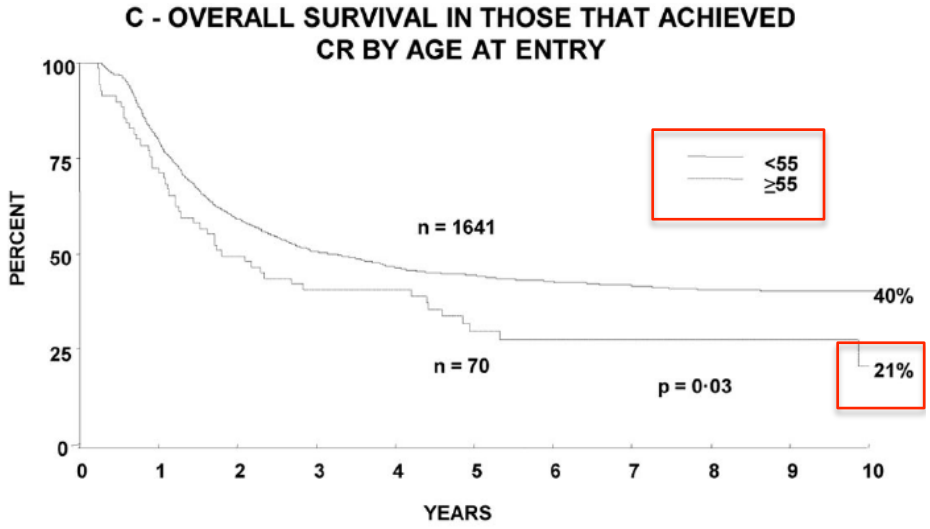
Br J Haematol. 2012 May ; 157(4): 463–471. doi:10.1111/j.1365-2141.2012.09095.x.

Outcomes In Older Adults with Acute Lymphoblastic Leukemia (ALL): Results From the International MRC UKALL XII/ECOG2993 Trial

Jonathan I. Sive[1], **Georgina Buck**[2], **Adele Fielding**[3], **Hillard M. Lazarus**[4], **Mark R. Litzow**[5], **Selina Luger**[6], **David I. Marks**[7], **Andrew McMillan**[8], **Anthony V. Moorman**[9], **Susan M. Richards**[2], **Jacob M. Rowe**[10], **Martin S. Tallman**[11], and **Anthony H. Goldstone**[1]

1914 pts of whom 100 were aged 55 years or more (median 56, range 55–65)





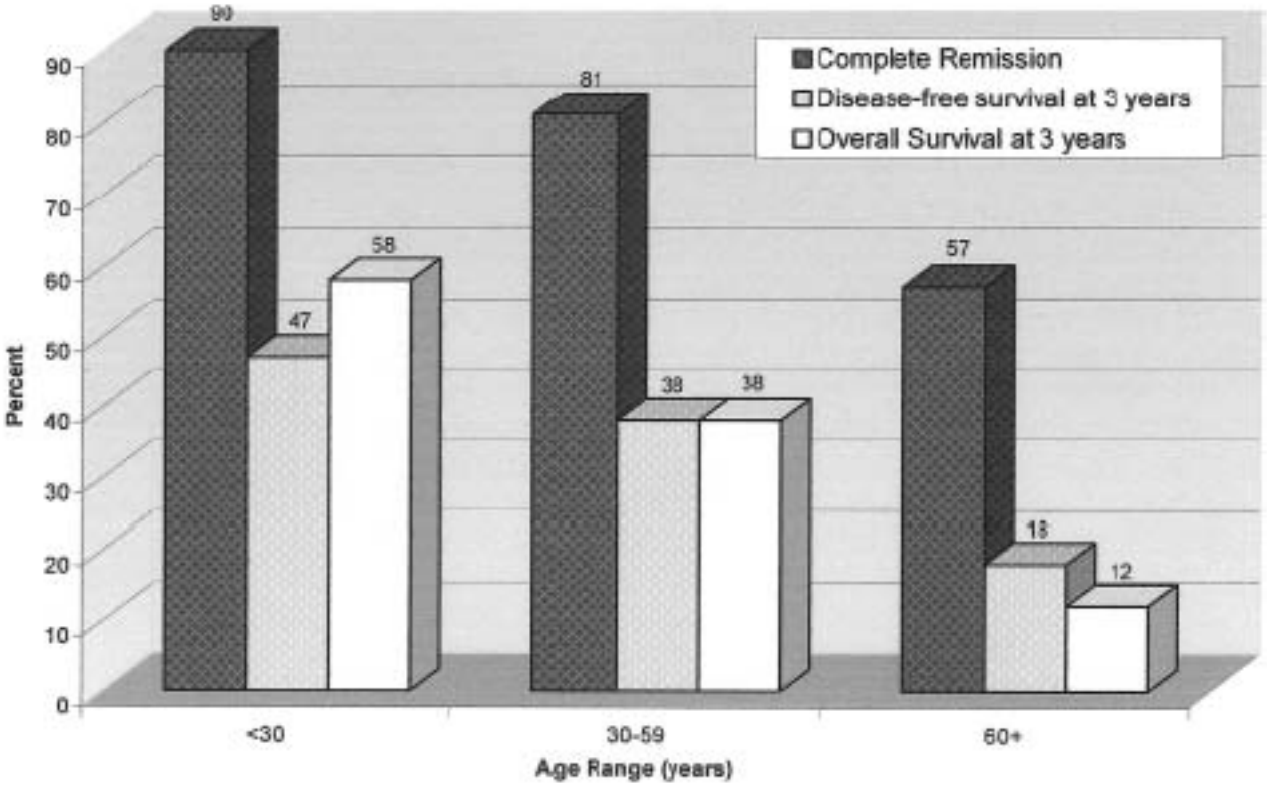
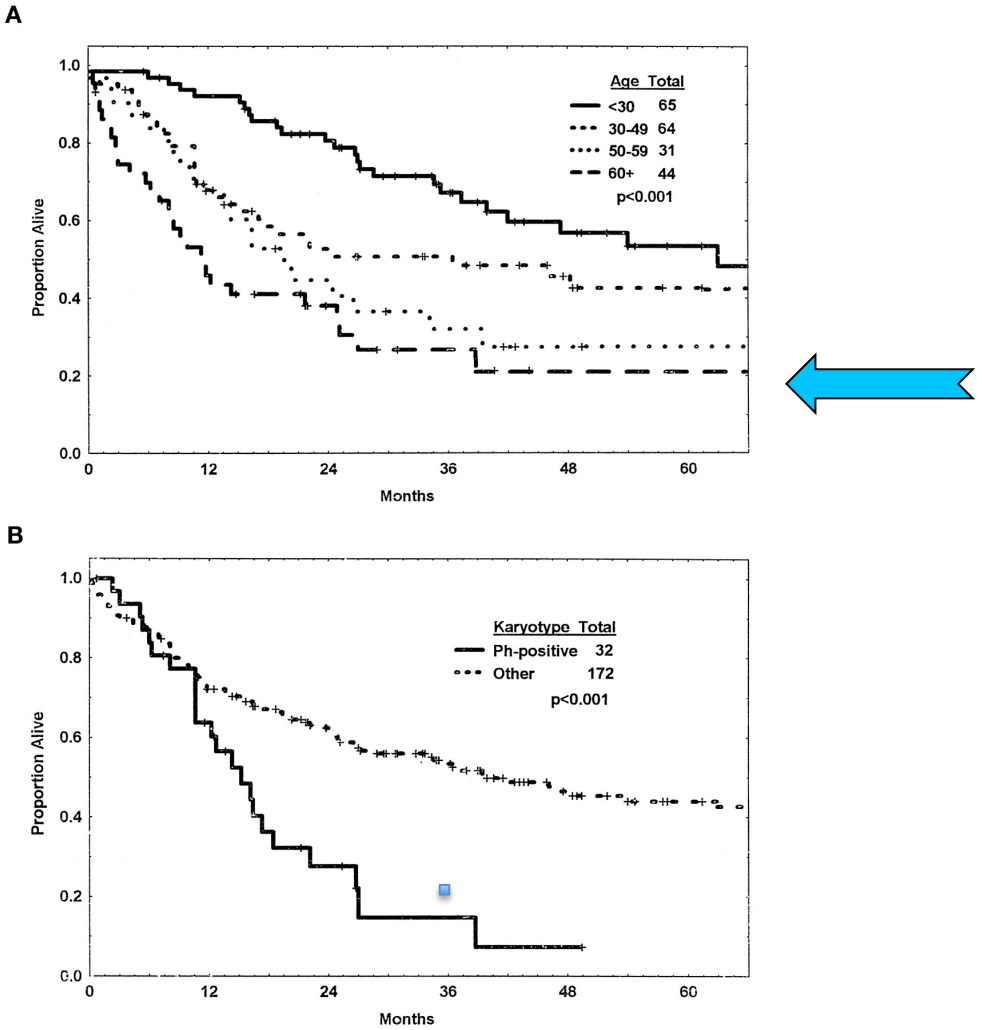


Figure 2. Treatment outcome by age cohort (CALGB studies with 759 acute lymphoblastic leukemia (ALL) patients, 1988–2002).

Fig 2.



Hagop M. Kantarjian et al. JCO 2000;18:547

Event-free survival according to randomization arm.

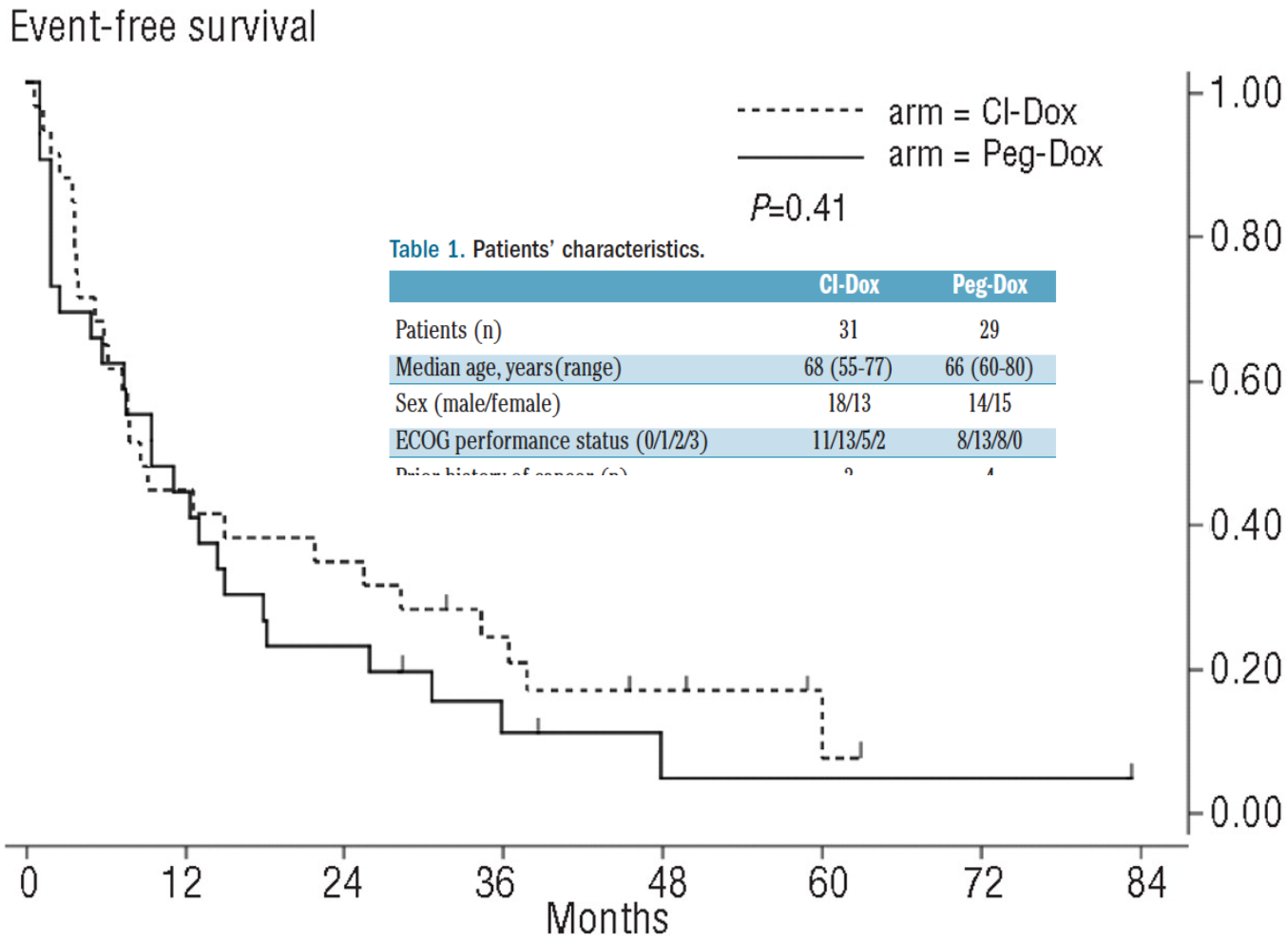


Table 1. Patients' characteristics.

	Cl-Dox	Peg-Dox
Patients (n)	31	29
Median age, years (range)	68 (55-77)	66 (60-80)
Sex (male/female)	18/13	14/15
ECOG performance status (0/1/2/3)	11/13/5/2	8/13/8/0
Prior history of cancer (n)	3	4

Mathilde Hunault-Berger et al. Haematologica 2011;96:245-252

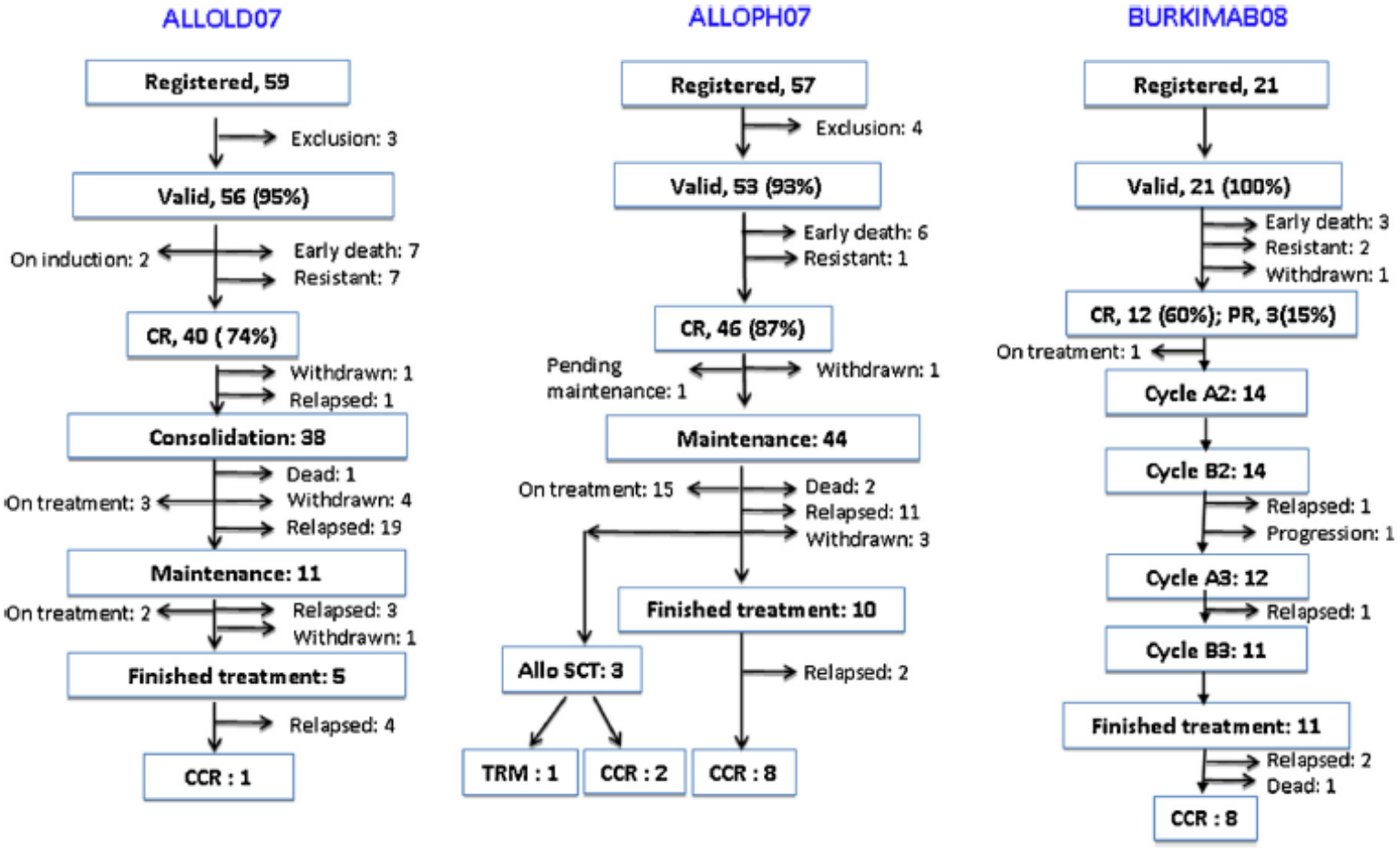
haematologica
the hematology journal

Feasibility and results of subtype-oriented protocols in older adults and fit elderly patients with acute lymphoblastic leukemia: Results of three prospective parallel trials from the PETHEMA group

Leukemia Research 41 (2016) 12–20

Table 1
Main clinical and hematological characteristics of the 130 evaluable patients included in the in the ALLOLD07, ALLOPH07 a

	ALLOLD07 ($n=56$)	ALLOPH07 ($n=53$)	BURKIMAB08 ($n=21$)	P
Gender, male,	26/56 (46)	22/53 (42)	17/21 (81)	0.007
Age, years, median (range)	66 (56-79)	66 (56-86)	64 (58–75)	0.412
Age >70 years,	14/56 (25)	21/53 (40)	5/21 (24)	0.220
ECOG score ≥2,	8/55 (15)	11/51 (22)	11/21 (52)	0.002



	ALLOLD07 ($n=56$)	ALLOPH07 ($n=53$)	BURKIMAB08 ($n=21$)
Early death	7/54[a] (13%)	6/53 (11%)	3/20[b] (15%)
Failure	7/54[a] (13%)	1/53 (2%)	3/20[b] (15%)
CR	40/54[a] (74%)	46/53 (87%)	14/20[b] (70%)
Death in remission	1/40 (3%)	3/46 (7%)	1/14 (7%)
Withdrawn	6/56 (11%)	4/53 (8%)	1/21 (5%)
Relapsed	27/40 (70%)	13/46 (28%)	4/14 (29%)
Median DFS, months (95% CI)	8 (4–12.1)	38 (15.5–60.4)	NR
Alive	18/56 (32%)	31/53 (59%)	11/21 (52%)
Median OS, months (95% CI)	12.4 (6.9–17.9)	37.3 (16.6–57.9)	25.3 (0.6–49.9)
Median follow-up (alive patients), months (range)	11.4 (0.3–75.4)	17.9 (1.5–63.1)	19.9 (1.6–68.9)

Note: BM: bone marrow; CR: complete remission; DFS: disease-free survival; CI: confidence interval; OS: overall survival; NE: not evaluated; NR: not reached.

[a] ALLOLD07: 2 patients in induction.

[b] BURKIMAB08: 1 withdrawal before reevaluation.

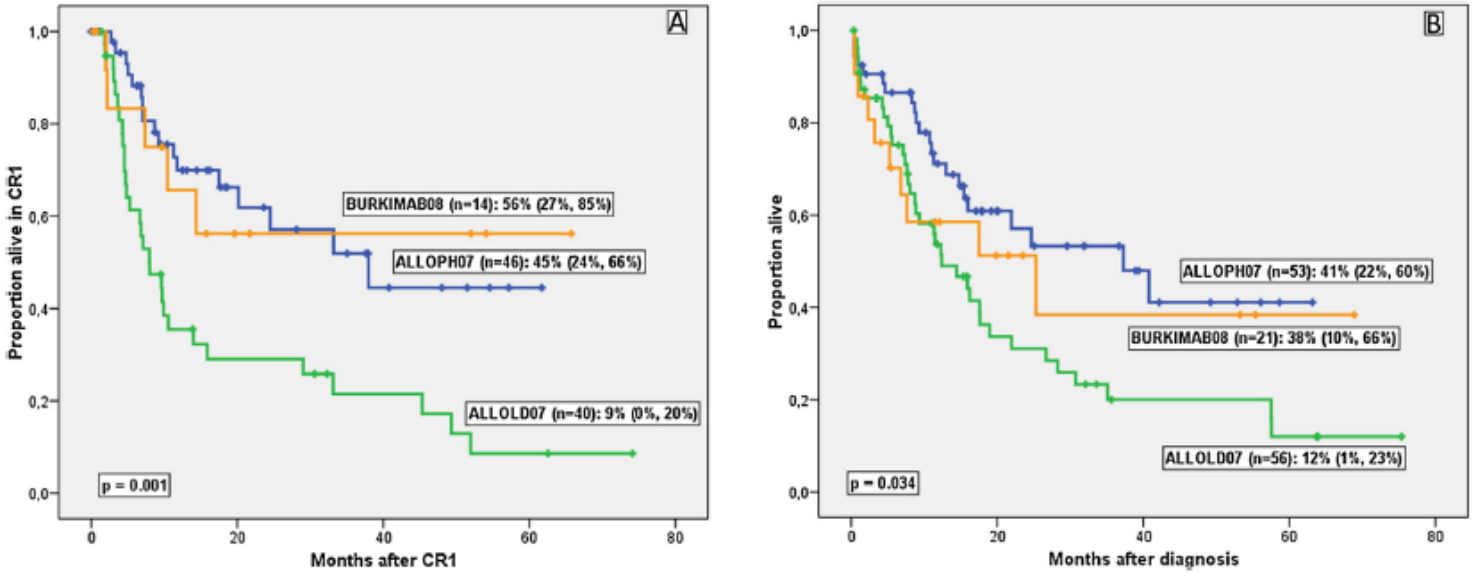
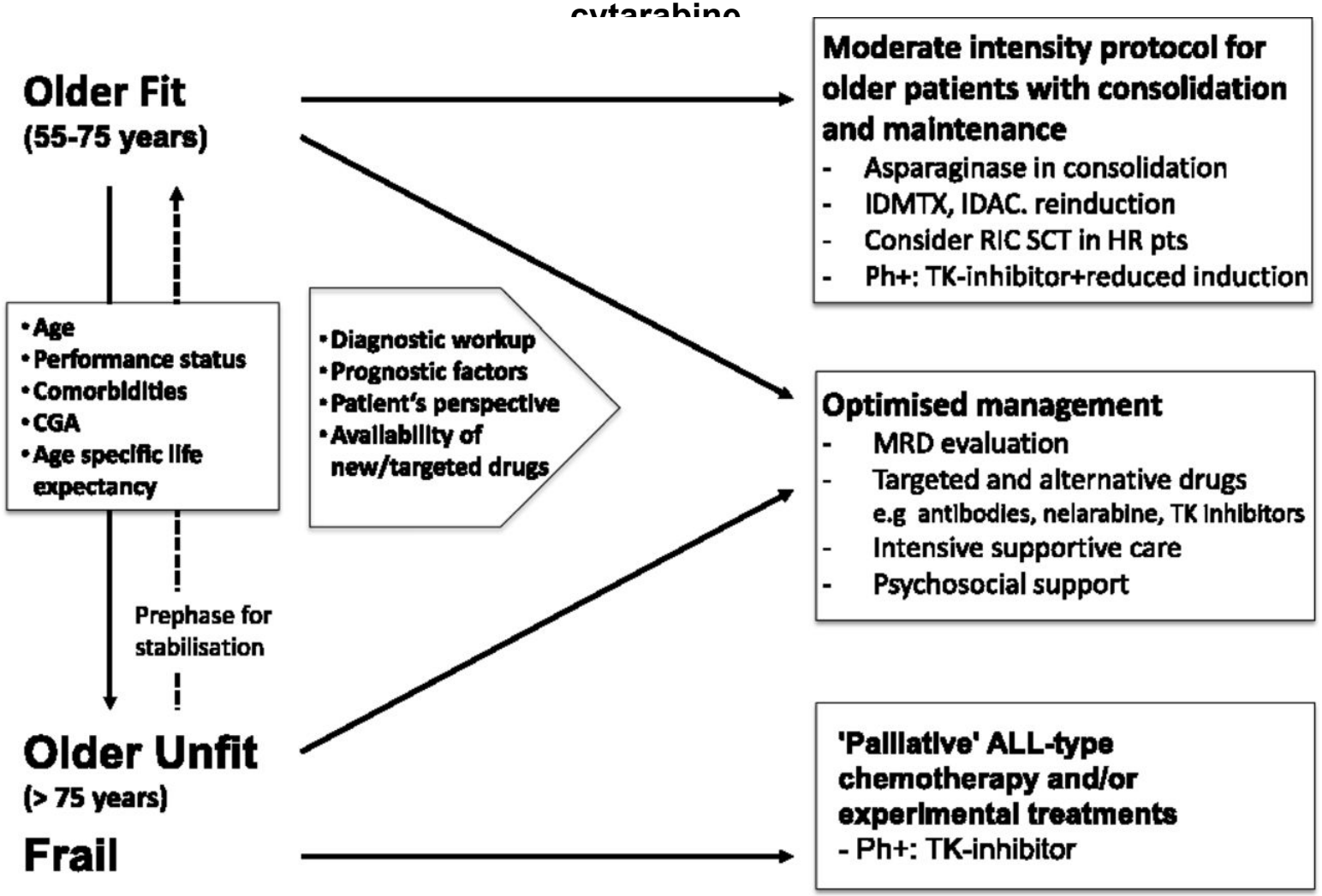


Fig. 2. Disease-free survival (panel A) and overall survival (panel B) of the patients included in the ALLOLD07, ALLOPH07 and BURKIMAB08 trials.
CR1: first complete remission

Comprehensive approach to managing older patients with ALL. HR, high risk; pts, patients; TK, tyrosine kinase; IDMTX, intermediate dose methotrexate; IDAC, intermediate dose cytarabine



Nicola Gökbuget Blood 2013;122:1366-1375

Complete Remission

Early Mortality

Relapse Rate

Survival

? Incidence of poor prognostic factor

Comorbidity and high PS score

Intensive chemioterapy

BMT

MRD

NUOVE PROSPETTIVE

Monoclonal antibodies in acute lymphoblastic leukemia

Elias Jabbour, Susan O'Brien, Farhad Ravandi, and Hagop Kantarjian

Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX

BLOOD, 25 JUNE 2015 • VOLUME 125, NUMBER 26

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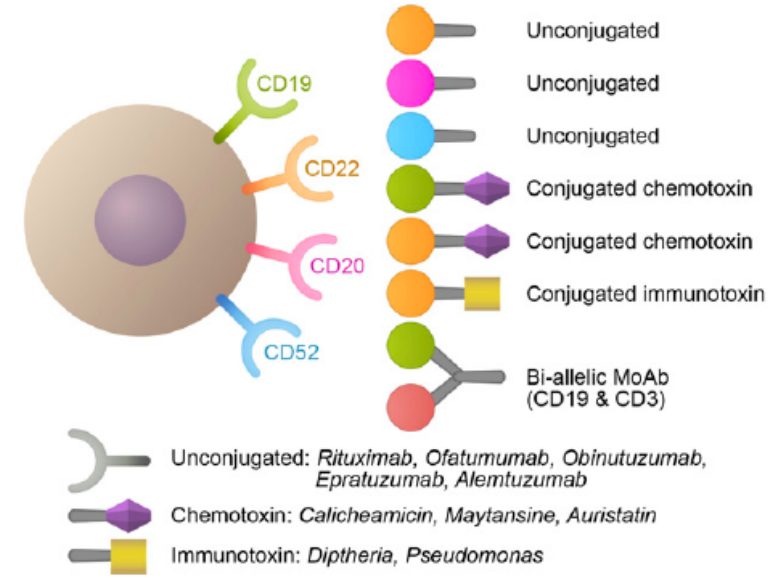


Figure 1. Schema of different monoclonal antibodies.

Table 1. Targeted therapies for ALL

Therapy	Description
CD20	
Rituximab	When added to conventional chemotherapy has been shown to improve survival in younger adults
Ofatumumab	Binds to a different epitope than rituximab, which may allow it to overcome rituximab-resistant disease
Obinutuzumab	Novel glycoengineered type II CD20 monoclonal antibody superior to rituximab and ofatumumab in the induction of direct cell death.
CD19	
SAR3419	Conjugated to a synthetic maytansinoid that is release intracellularly after antigen internalization
SGN-CD19A	Humanized anti-CD19 monoclonal antibody conjugated to the microtubule-disrupting agent. On internalization, it binds to tubulin and induces G2/M arrest and apoptosis
Blinatumomab	Bispecific antibody that redirects cytotoxic T cells to cells that express CD19
CD22	
Epratuzumab	Studied as part of combination therapy in adults and children with modest activity
Epratuzumab-SN38	Antibody conjugated to a topoisomerase I inhibitor to enhance cell killing potential
Inotuzumab ozogamicin	Antibody conjugated to the cytotoxin calicheamicin
Moxetumomab	Antibody conjugated to bacterial or plant toxin
CD52	
Alemtuzumab	Antibody that has only displayed little activity in B- and T-cell disease

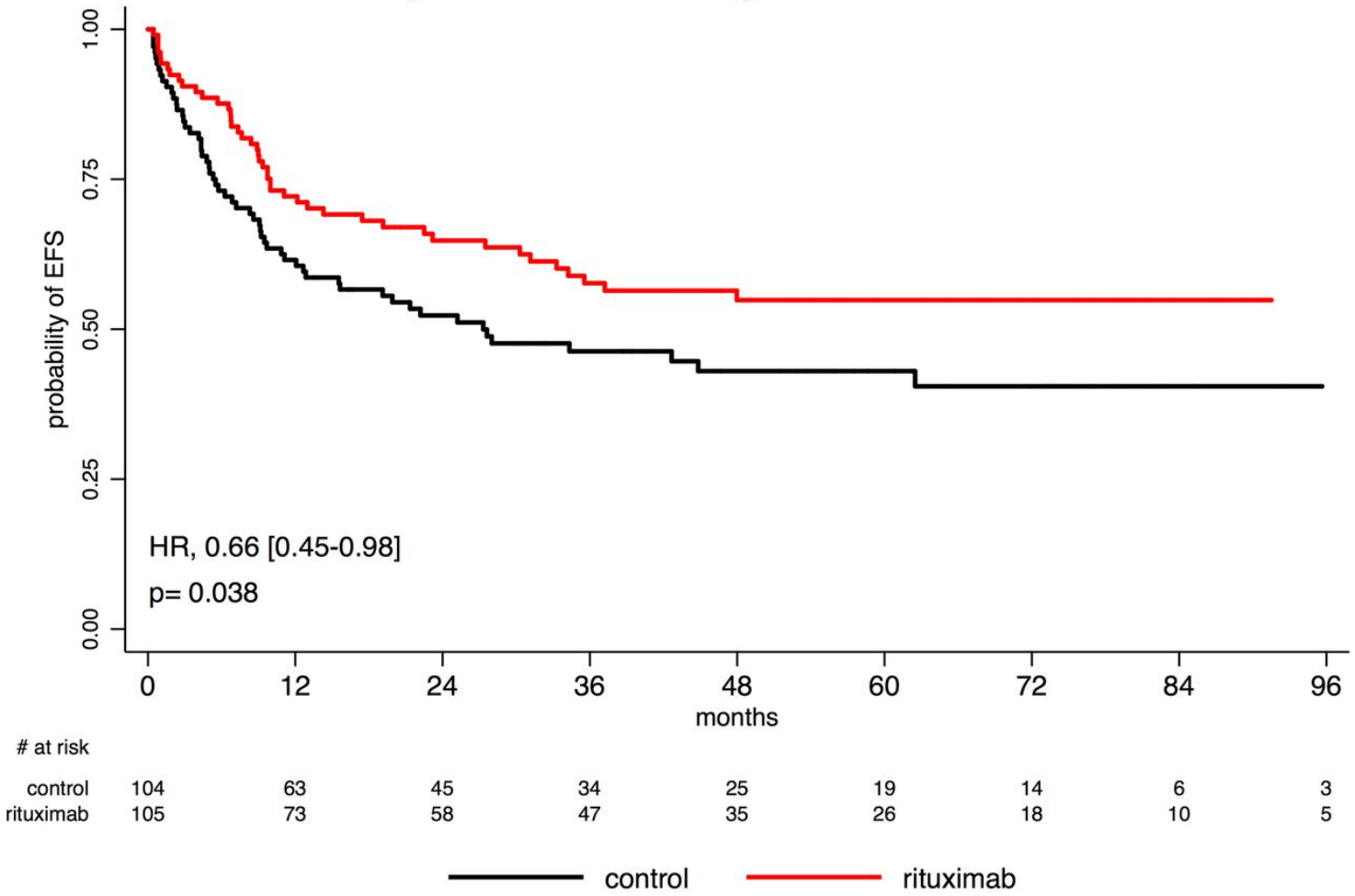
CD20+ : 30-50% of precursor B-ALL

Table 2. Activity of rituximab in patients with Burkitt leukemia

	Percent survival		
	MDACC[9]	Germany[19]	CALGB[20]
Therapy	4 years	3 years	4 years
Chemotherapy	50	50	52
Chemotherapy + rituximab	77	79	78

the Randomized Graall-R 2005 Study

Figure 1. EFS according to randomization arm



SébastienMaury et al. Blood 2015;126:1

Inotuzumab ozogamicin (IO) in combination with low-intensity chemotherapy as front-line therapy for older patients (pts) and as salvage therapy for adult with R/R acute lymphoblastic leukemia (ALL).

Parameter	Frontline (N=20)
Follow-up (mos)	13 [2-26]
Age (yrs)	69 [60-79]
CR	15 (75)
CRp	4 (20)
Cri	0
Neg MRD	
at D21	12/16 (75)
overall	19/20 (95)
Early death	0
ORR	19 (95)
PFS %	at 1-yr, 83
OS %	at 1-yr, 84

- JClinOncol 32:5s, 2014 (suppl; abstr 7019)
- Author(s): EliasJabbour

Asco 2015

Safety and Activity of Blinatumomab for Older Patients With Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia in Two Phase 2 Studies

HagopM. Kantarjian,[1] Anthony S. Stein,[2] Ralf C. Bargou,[3] Carlos Grande Garcia,[4] Richard A. Larson,[5] Matthias Stelljes,[6] Jonathan Benjamin,[7] Catherine Jia,[8]Max S. Topp[9]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]City of Hope, Duarte, CA, USA; [3]Comprehensive Cancer Center Mainfranken, UniversitätsklinikumWürzburg, Würzburg, Germany; [4]Hospital Universitario 12 de Octubre, Madrid, Spain; [5]University of Chicago, Chicago, Illinois, USA; [6]University Hospital of Münster, Münster, Germany; [7]Amgen Inc., Thousand Oaks, CA, USA; [8]Amgen Inc., South San Francisco, CA, USA; [9]Medizinische Klinik und Poliklinik II, UniversitätsklinikumWürzburg, Würzburg, Germany

Results

Table 4. Patient/Disease Characteristics

Characteristic	Age ≥ 65 Years (n = 36)	Age < 65 Years (n = 225)
Male, n (%)	18 (50.0)	143 (63.6)
Age, years, median (range)	70 (65–79)	34 (18–64)
ECOG performance status, n (%)		
0	11 (30.6)	81 (36.0)
1	20 (55.6)	109 (48.4)
≥ 2	5 (13.9)	33 (14.7)
No. of prior relapses, n (%)		
0 (primary refractory)	5 (13.9)	20 (8.9)
1	24 (66.7)	124 (55.1)
2	5 (13.9)	59 (26.2)
≥ 3	2 (5.6)	22 (9.8)
Risk stratification, n (%)		
Prior HSCT	4 (11.1)	84 (37.3)
No prior HSCT, no prior relapse	5 (13.9)	20 (8.9)
No prior HSCT, 1 prior relapse	22 (61.1)	93 (41.3)
No prior HSCT, ≥ 2 prior relapses	5 (13.9)	28 (12.4)
Blinatumomab cycles started		
Median (range)	2 (1–6)	2 (1–7)
1st, 3rd quartiles	1, 3	1, 2

ECOG, Eastern Cooperative Oncology Group; HSCT, hematologic stem cell transplantation

Results

Table 5. Best Response in the First Two Cycles

	Age ≥ 65 Years (n = 36)		Age < 65 Years (n = 225)	
Response	**n (%)**	**(95% CI)**	**n (%)**	**(95% CI)**
CR/CRh	20 (55.6)	(38.1–72.1)	104 (46.2)	(39.6–53.0)
CR	14 (38.9)	(23.1–56.5)	78 (34.7)	(28.5–41.3)
CRh	6 (16.7)	(6.4–32.8)	26 (11.6)	(7.7–16.5)
BFM	3 (8.3)	(1.8–22.5)	17 (7.6)	(4.5–11.8)
Partial remission	1 (2.8)	(0.1–14.5)	5 (2.2)	(0.7–5.1)
Non-responder	12 (33.3)		97 (43.1)	

CR, complete remission; CRh, CR with partial hematologic recovery; BFM, blast free hypoplastic or aplastic bone marrow

Results

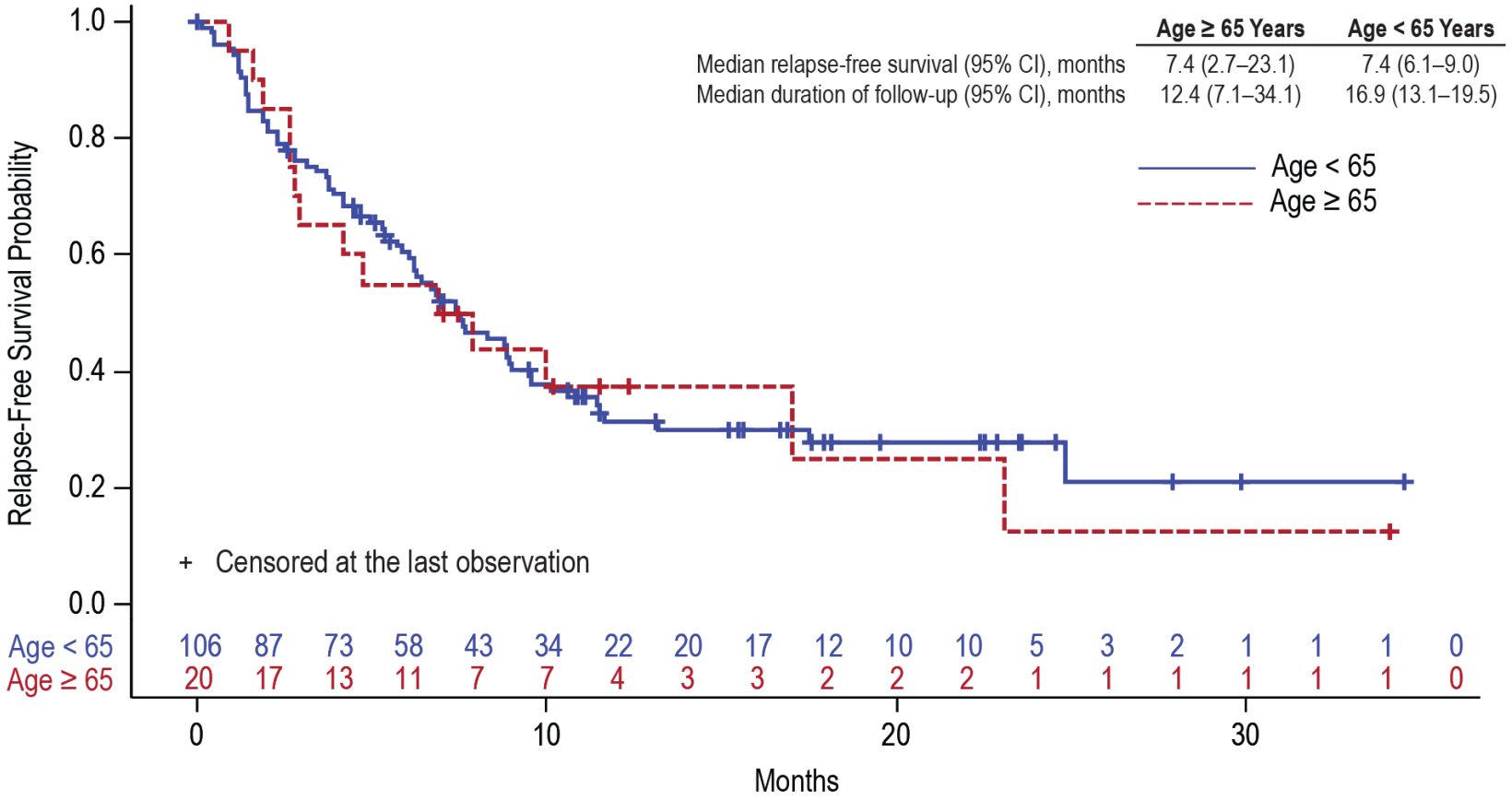
Table 6. MRD and HSCT After Response

	Responders Age ≥ 65 Years (n = 20)		Responders Age < 65 Years (n = 104)	
	n (%)	(95% CI)	n (%)	(95% CI)
MRD				
MRD response	12 (60.0)	(36.1–80.9)	73 (70.2)	(60.4–78.8)
No MRD response/no MRD data	8 (40.0)	(19.1–63.9)	31 (29.8)	(21.2–39.6)
HSCT after blinatumomab				
Any HSCT after CR/CRh	3 (15.0)	(3.2–37.9)	61 (58.7)	(48.6–68.2)
HSCT while in remission with no antileukemic medications	2 (10.0)	(1.2–31.7)	50 (48.1)	(38.2–58.1)
HSCT while in remission with antileukemic medications	0 (0.0)	(0.0–16.8)	3 (2.9)	(0.6–8.2)
HSCT after CR/CRh and relapse	1 (5.0)	(0.1–24.9)	8 (7.7)	(3.4–14.6)

CR, complete remission; CRh, CR with partial hematologic recovery; HSCT, hematologic stem cell transplantation; MRD, minimal residual disease

Results

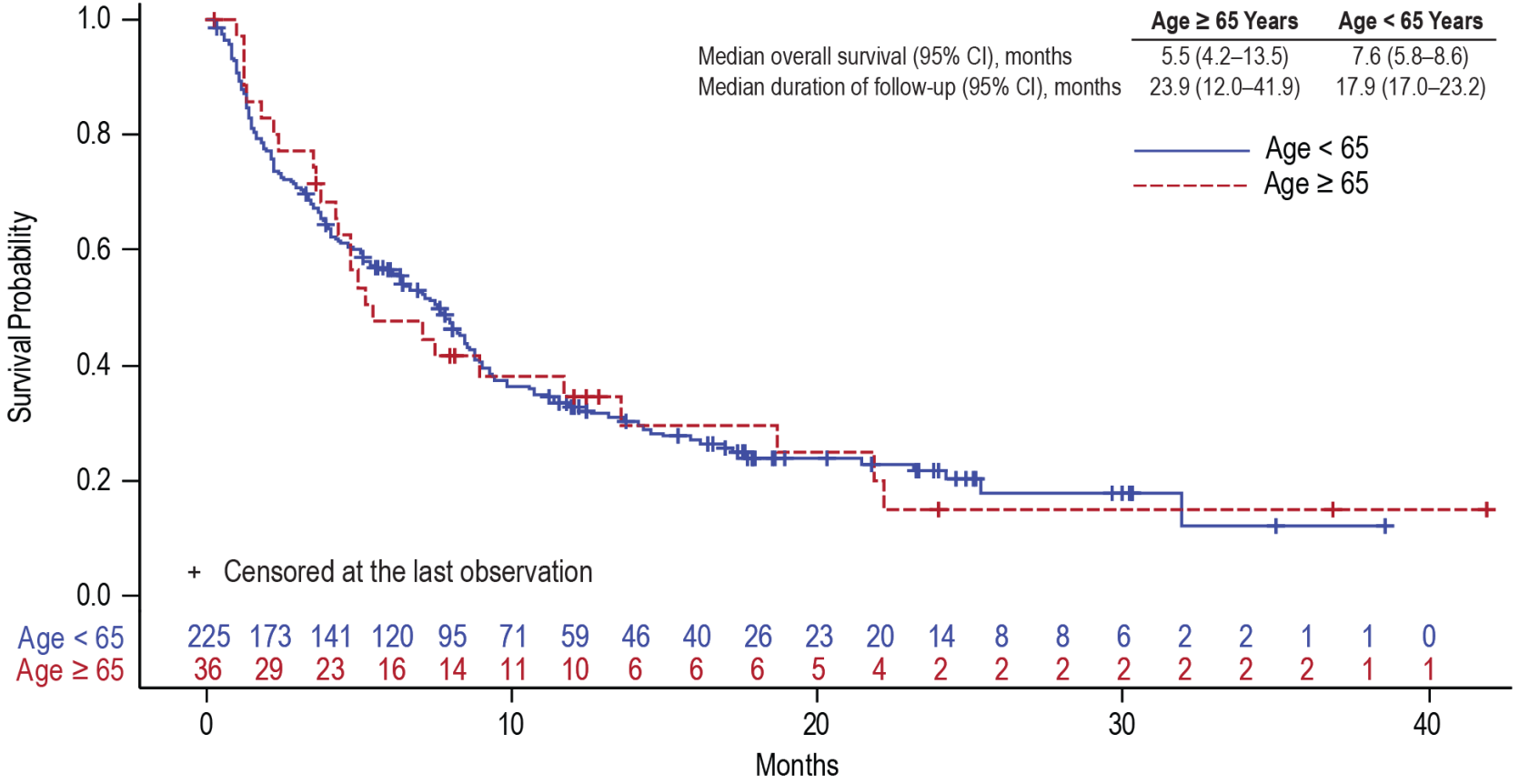
Figure 1. Relapse-free Survival



- Of 20 older responders, 14 (70.0%) relapsed and 6 (30.0%) were censored at their last observation; of 106 younger responders, 70 (66.0%) relapsed and 36 (34.0%) were censored at their last observation

Results

Figure 2. Overall Survival



- Ten (28%) older patients and 63 (28%) younger patients were alive at their last follow-up

Conclusioni

- La ALL dell'anziano (>65 yrs) bcr/abl– è attualmente una malattia incurabile
- Nessun significativo miglioramento negli ultimi 20 anni
- Nuovi approcci terapeutici sono assolutamente necessari
- E' probabilmente necessario andare oltre la chemioterapia.