

CML in elderly patients and children

*Gianantonio Rosti
Institute 'Seràgnoli', Bologna
GIMEMA CML WP*

EUTOS for CML



European Treatment and Outcome Study

GIMEMA CML WP

CML AGE DISTRIBUTION (1973–2007)

AGE	1973–1996 n 2155	2002–2007 n 564
≤ 20	3%	1%
21–30	11%	6%
31–40	15%	19%
41–50	20%	22%
51–60	23%	22%
61–70	19%	19%
≥ 70	8%	11%
Median	51	52

CML – Age and prognosis

	UNIVARIATE	MULTIVARIATE
Sokal, 1984 [#]	0.02	0.001
Euro, 1998*	< 0.0001	< 0.0001

#Conventional CHT: Variable Continuous

***IFN- α : Dichotomous Variable (< 50 / \geq 50 yrs)**

Chronic Myeloid Leukemia (CML): Risk (Sokal) stratification according to age

(GIMEMA CML WP 1986–1997 - 1114 cases)

Age	< 40	41–60	> 61
Number of patients	n = 421	n = 562	n = 131
Low Sokal risk	60%	41%	22%
Int + high Sokal risk	40%	59%	78%



CML: Conventional chemotherapy (CHT) overall survival by Sokal risk (813 cases)

		OVERALL SURVIVAL		
	% of cases	4 years	6 years	8 years
Low	31%	65%	38%	23%
Intermediate	41%	45%	22%	12%
High	28%	30%	13%	< 10%

Rates of MCyR in late CP¹ by baseline characteristics

Age (< 60 / ≥ 60 years)	58% vs 63%
Palpable spleen (no/yes)	63% vs 45%
*Time from diagnosis (< 1 / ≥ 1 to 3 / ≥ 3 year)	79% vs 68% vs 49%
WBC count (< 10 / ≥ 10 to < 20 / ≥ 20 x10⁹/L)	73% vs 57% vs 42%
*Hemoglobin (< 120 / ≥ 120 g/L)	50% vs 66%
Platelet count (< 450 / ≥ 450 x 10⁹/L)	66% vs 46%
*Blast cells in BM (< 5 / ≥ 5%)	64% vs 41%
*Blast cells in PB (0 / ≥ 0 to < 3 / ≥ 3%)	67% vs 42% vs 33%
Ph chromosome + (< 90 / ≥ 90%)	89% vs 56%

***Significant by multivariate analysis**



Imatinib 400 mg in late CP¹ response by age

	< 60 yrs (n 231)	≥ 60 yrs (n 120)	p
CHR	94%	94%	0.05
CCyR	56%	44%	
PCyR	10%	12%	
MCR	66%	57%	
Death rate (median follow-up 24 months)	9%	12%	



Imatinib 400 mg in late CP¹ response by age

	≥ 65 year	< 65 years	p
CHR	31 (53%)	168 (74%)	0.003
MCR	31 (53%)	168 (74%)	0.0037
CCR	21 (36%)	130 (57%)	0.001943



Incidence of hematopoietic toxicity (*)

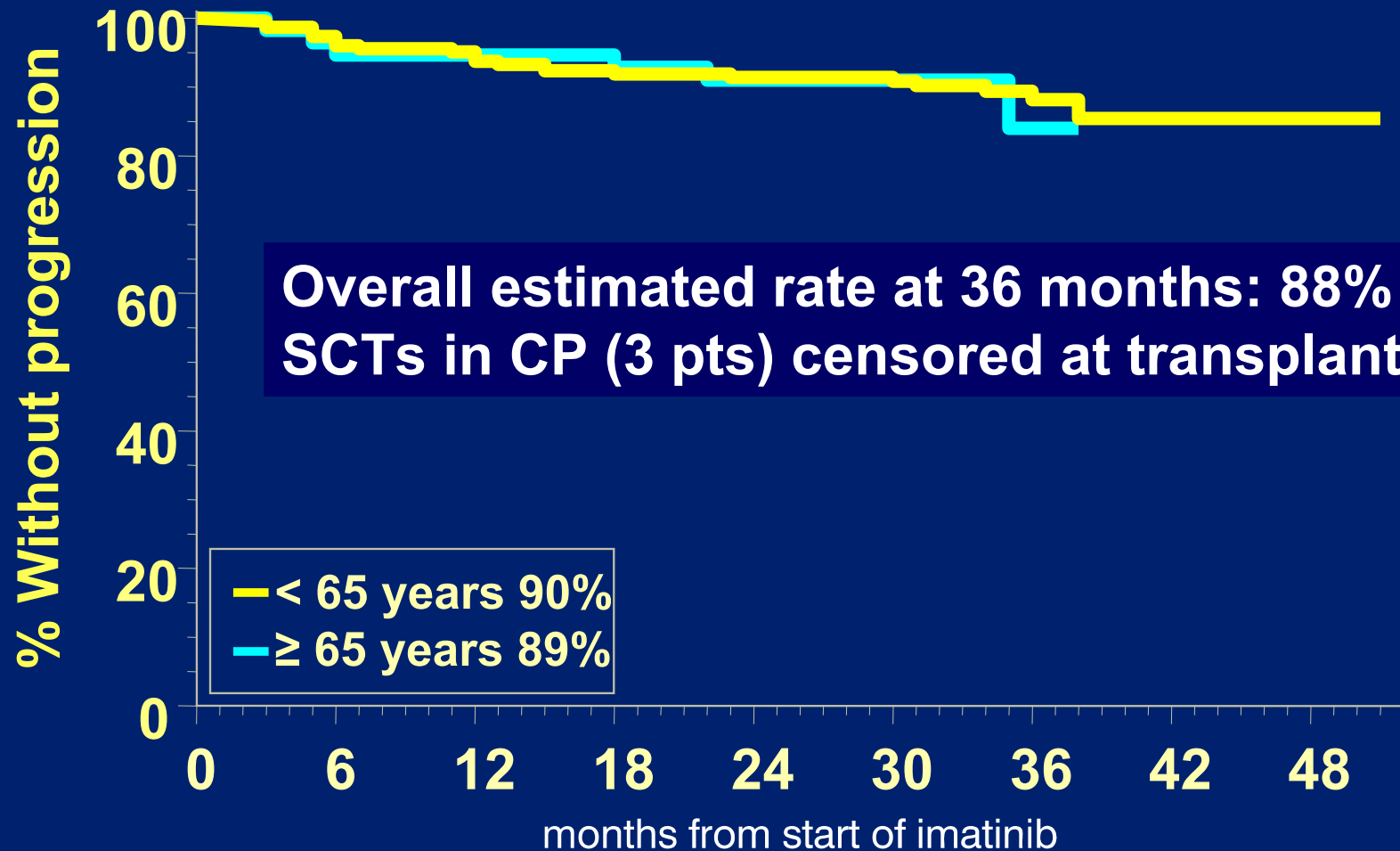
	≥ 65 year	p	< 65 years
Grade III	42 (72%)	0.002	114 (50%)
Grade III + IV	50 (86%)	0.0001	135 (60%)

(*) Percentage of patients with event



Imatinib in late CP: Study CML/002

Progression-free by age



Imatinib in elderly patients in early CP

Patients (n = 487)

Younger and older patients differ for a significantly lower proportion of low risk cases among younger patients

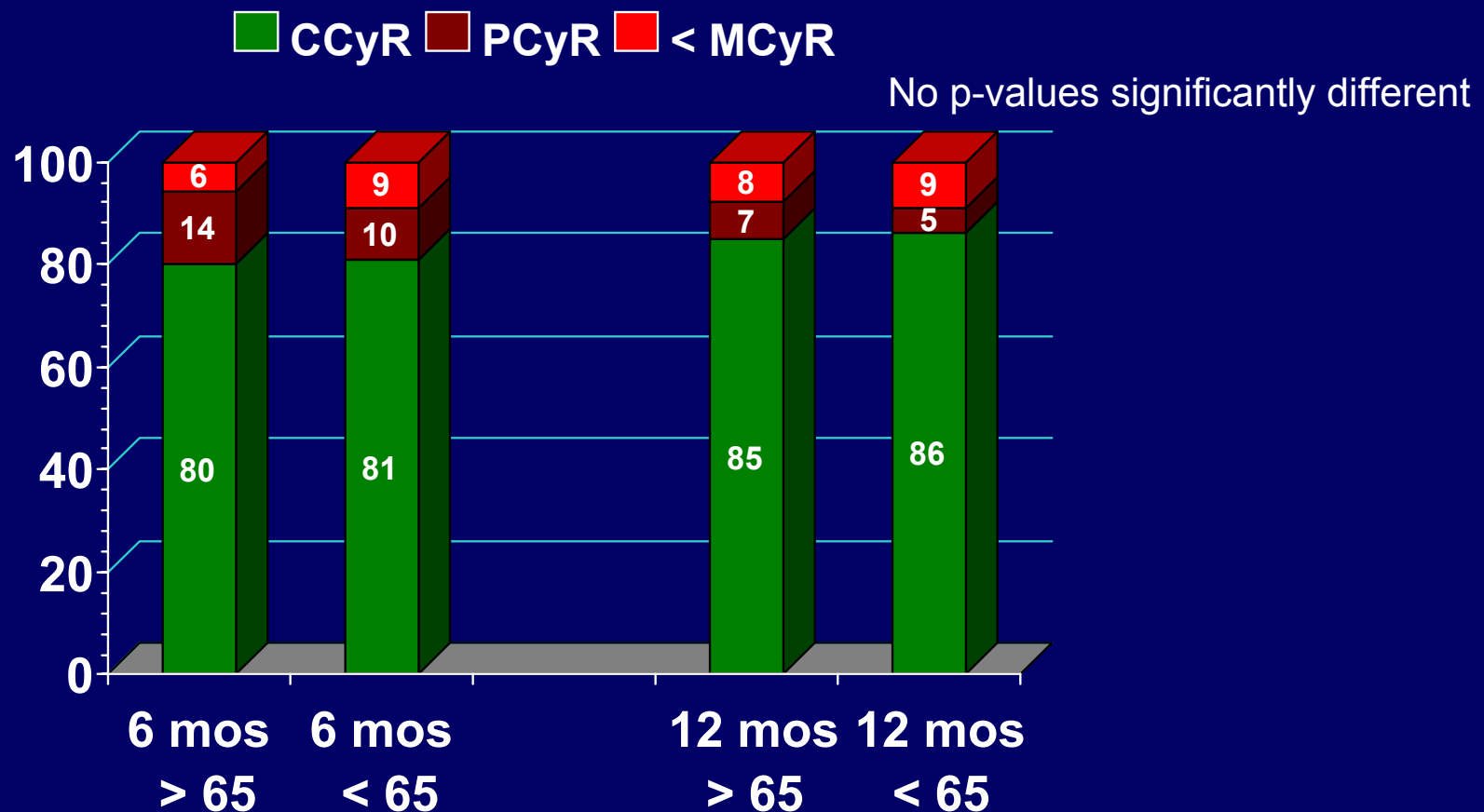
	> 65 years	< 65 years	p
n (%)	105 (22%)	382 (78%)	
Imatinib 800 mg	22 (21%)	84 (22%)	NS
Sokal low	12 (11%)	205 (54%)	< 0.05
Del 9q	5 (5%)	44 (12%)	NS
Median age (Range)	71 (65–84)	56 (18–64)	



Imatinib in elderly patients in early CP

Cytogenetic response¹

No difference in the rates of CCyR at 6 and 12 months according to age



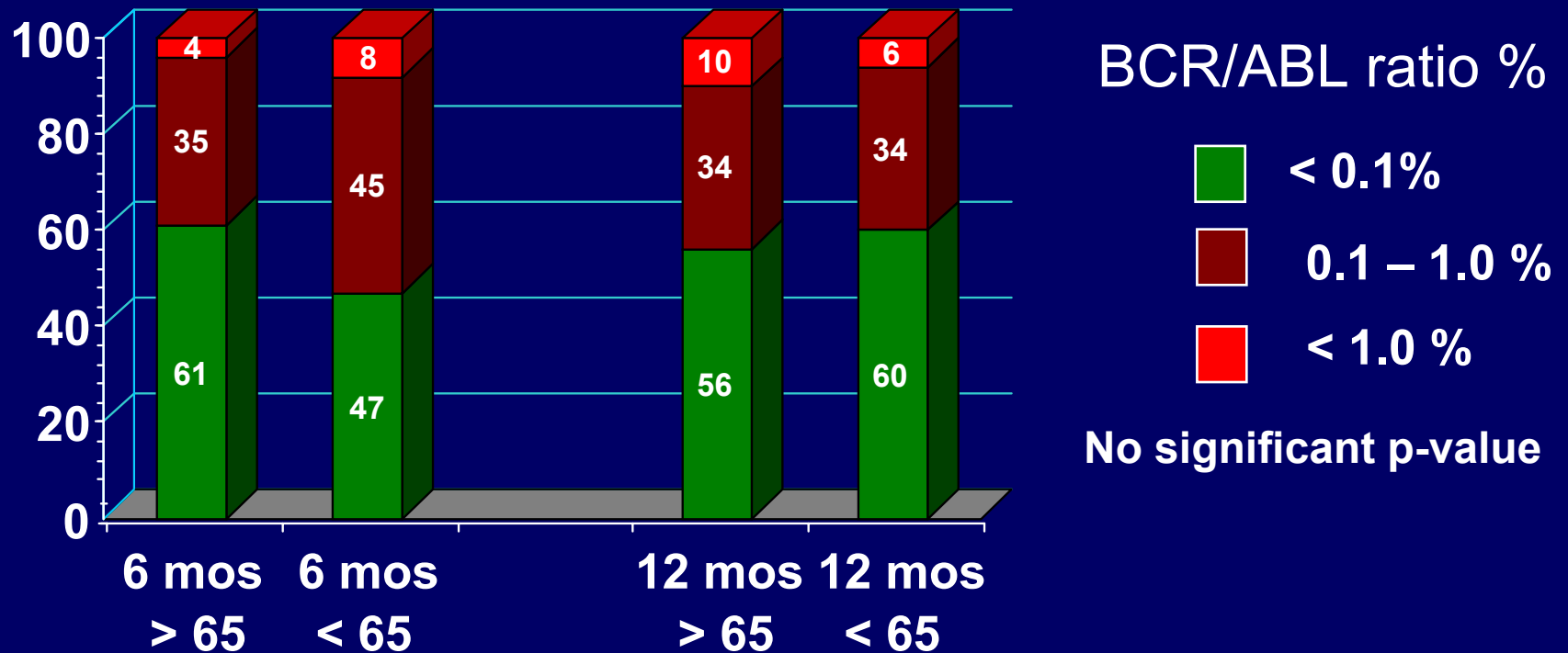
1. GIMEMA CML WP, data on file



Imatinib in elderly patients in early CP

Molecular response (in CCyR, PB only)

No difference in the rates of major molecular response at 6 and 12 months according to age



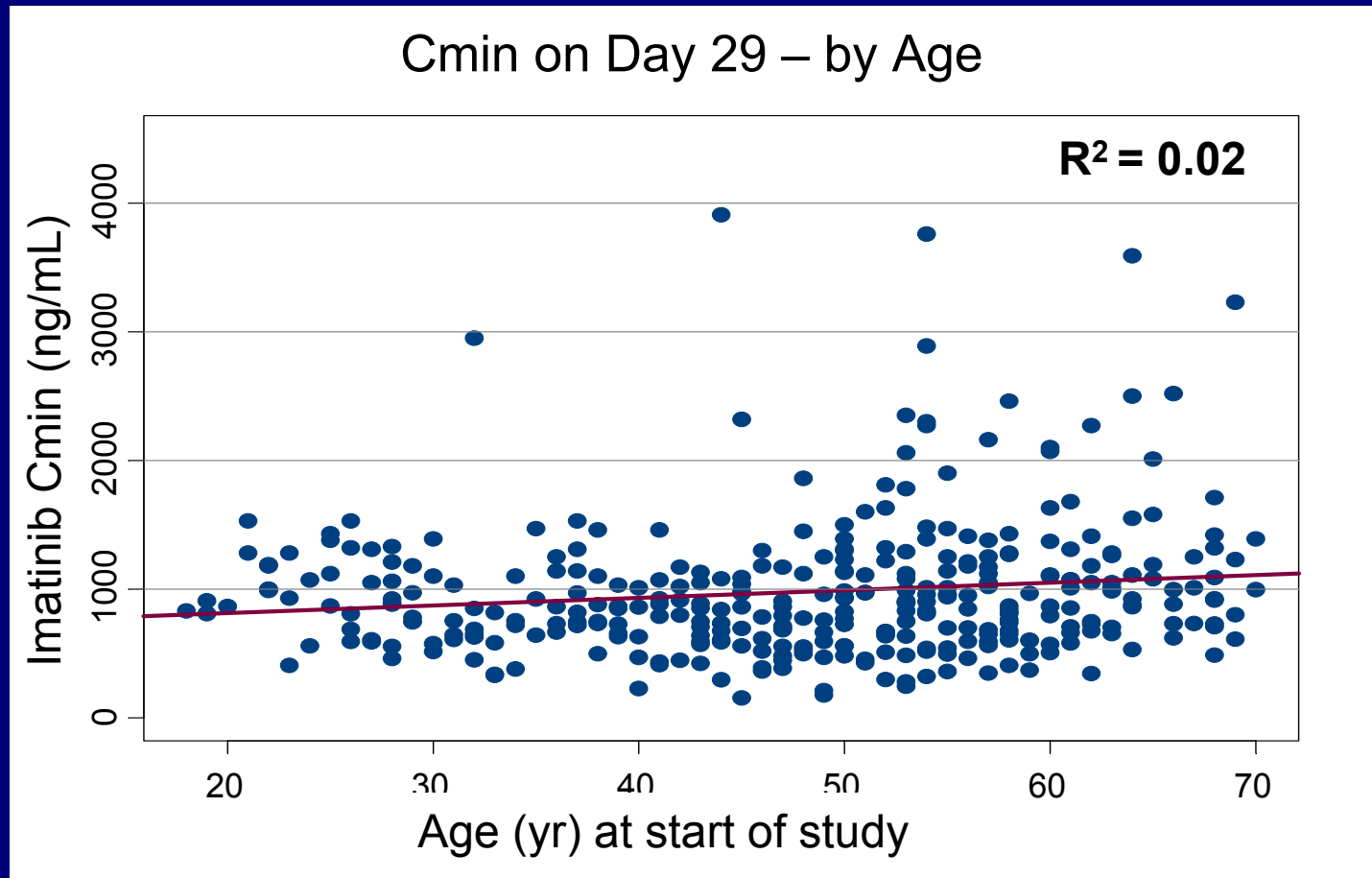
Patients taking drugs on a daily basis by age

Italy, Year 2005¹

AGE	%
45–54	27
55–64	48
65–69	63
70–74	71
75–79	81

1. www.istat.it – accessed August 25, 2008

PK exposure by age



No trend was observed between imatinib PK trough level on day 29 with age

Imatinib in elderly persons concomitant treatment(s)

- **Drug–drug interactions**
- **Additional adverse events**
- **Blood level testing**

Nilotinib in elderly patients with CML-CP

Analysis of efficacy and tolerability
of nilotinib in elderly (≥ 65 years)
patients with CML-CP with a
minimum follow-up of 19 months

Nilotinib in elderly patients with CML-CP

Baseline characteristics and prior therapy		
	< 65 years (n = 223)	≥ 65 years (n = 98)
Median duration of CML, months (range)	52 (5–266)	75 (5–275)
Median duration of imatinib treatment, months (range)	33 (< 1–95)	32 (< 1–69)
Prior highest imatinib dose, n (%)[*]		
< 600 mg/day	57 (26)	31 (32)
≥ 600 to <800 mg/day	70 (31)	39 (40)
≥ 800 mg/day [†]	96 (43)	27 (28)
Other prior therapy, n (%)		
Hydroxyurea, n (%)	180 (81)	86 (88)
Interferon, n (%) [‡]	122 (55)	65 (66)
Cytarabine, n (%) [‡]	63 (28)	15 (15)

* Missing data from 1 patient.

† A significantly lower percentage of elderly patients given 800 mg/day imatinib before study entry ($P = 0.0365$).

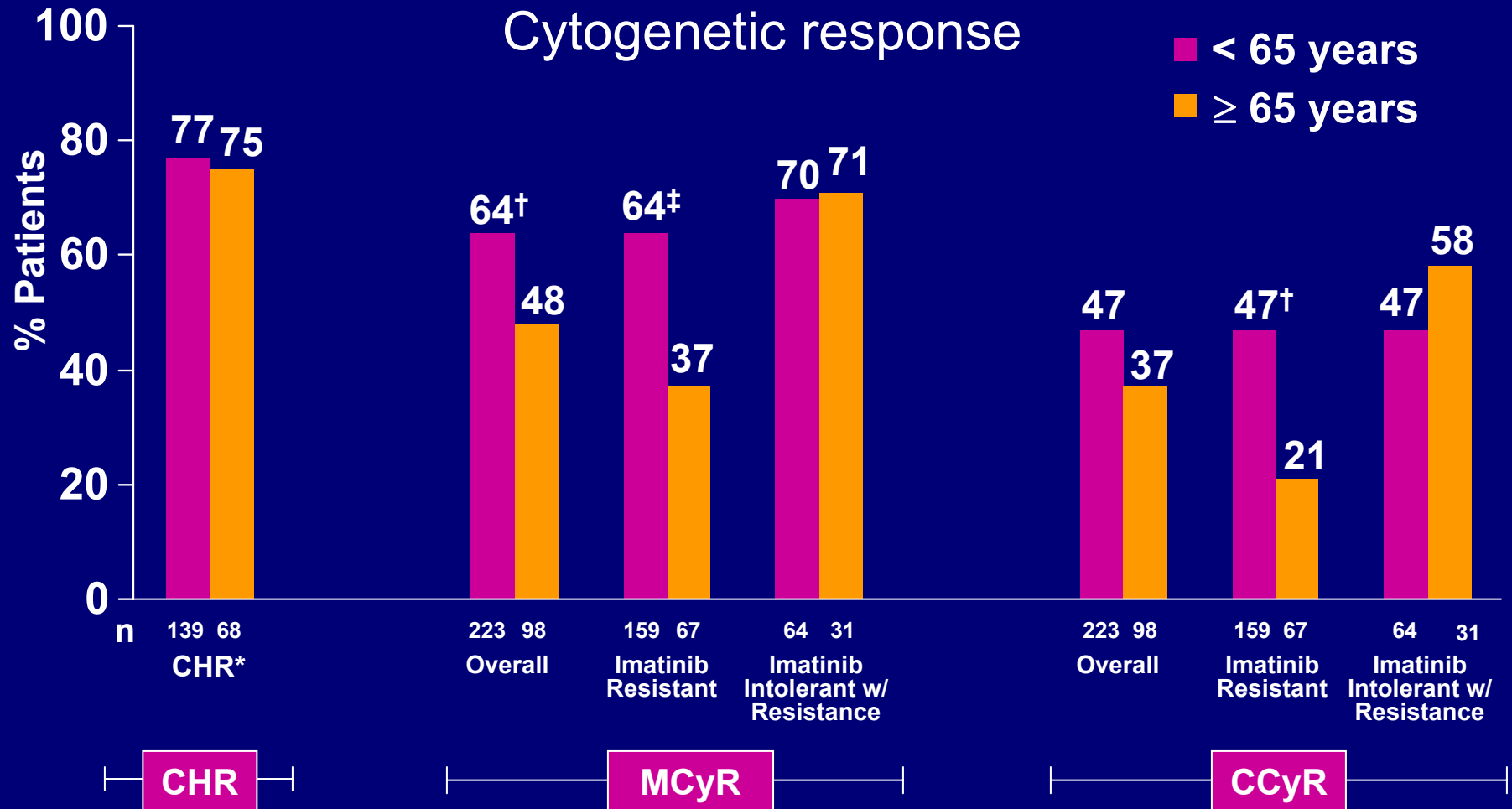
‡ Significantly more elderly patients received prior interferon ($P = 0.05$) and significantly fewer elderly patients received prior cytarabine ($P = 0.013$).

Nilotinib in elderly patients with CML-CP

Prior best response to imatinib			
	< 65 years (n = 223)	≥ 65 years (n = 98)	P Value
Never achieved CHR, n (%)	20 (9)	7 (7)	---
CHR but no CyR, n (%)	65 (29)	40 (41)	NS
Cytogenetic response, n (%)	136 (61)	50 (51)	---
Major	142 (64)	47 (48)	< 0.05
<i>Complete</i>	104 (47)	36 (37)	NS

NS, not significant.

Nilotinib in elderly patients with CML-CP

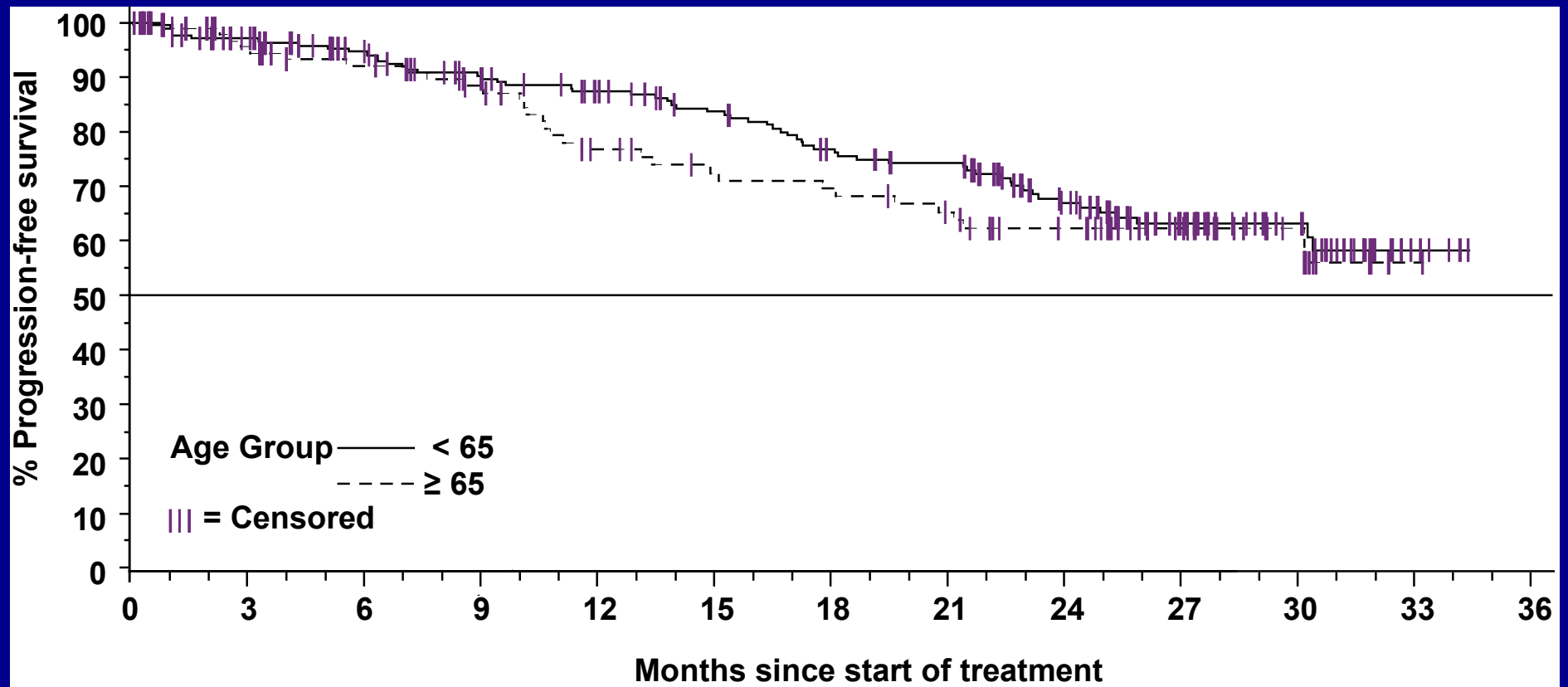


*Patients without CHR at baseline † P value < 0.05 ‡ P value < 0.005 All other P values were not significant

Lipton et al. Blood. 2008;112(11):Abstract 3233. Poster presentation at ASH 2008

Nilotinib in Elderly with CML-CP

Progression Free Survival*



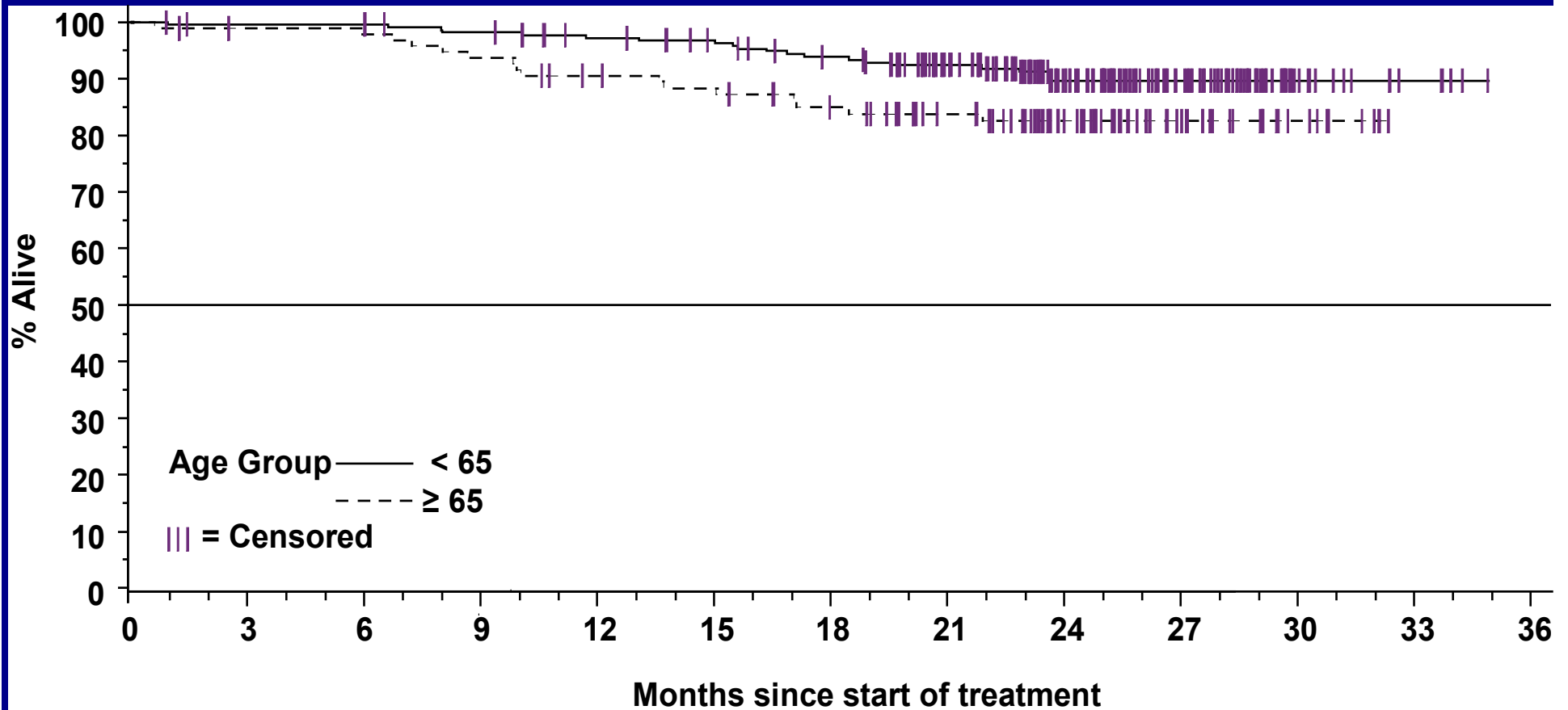
* Patients who did not progress to AP or BC and patients who did not discontinue due to death or progression.

Lipton et al. Blood. 2008;112(11):Abstract 3233. Poster presentation at ASH 2008

Lipton et al. Blood. 2008;112(11):Abstract 3233. Poster presentation at ASH 2008

Nilotinib in Elderly with CML-CP

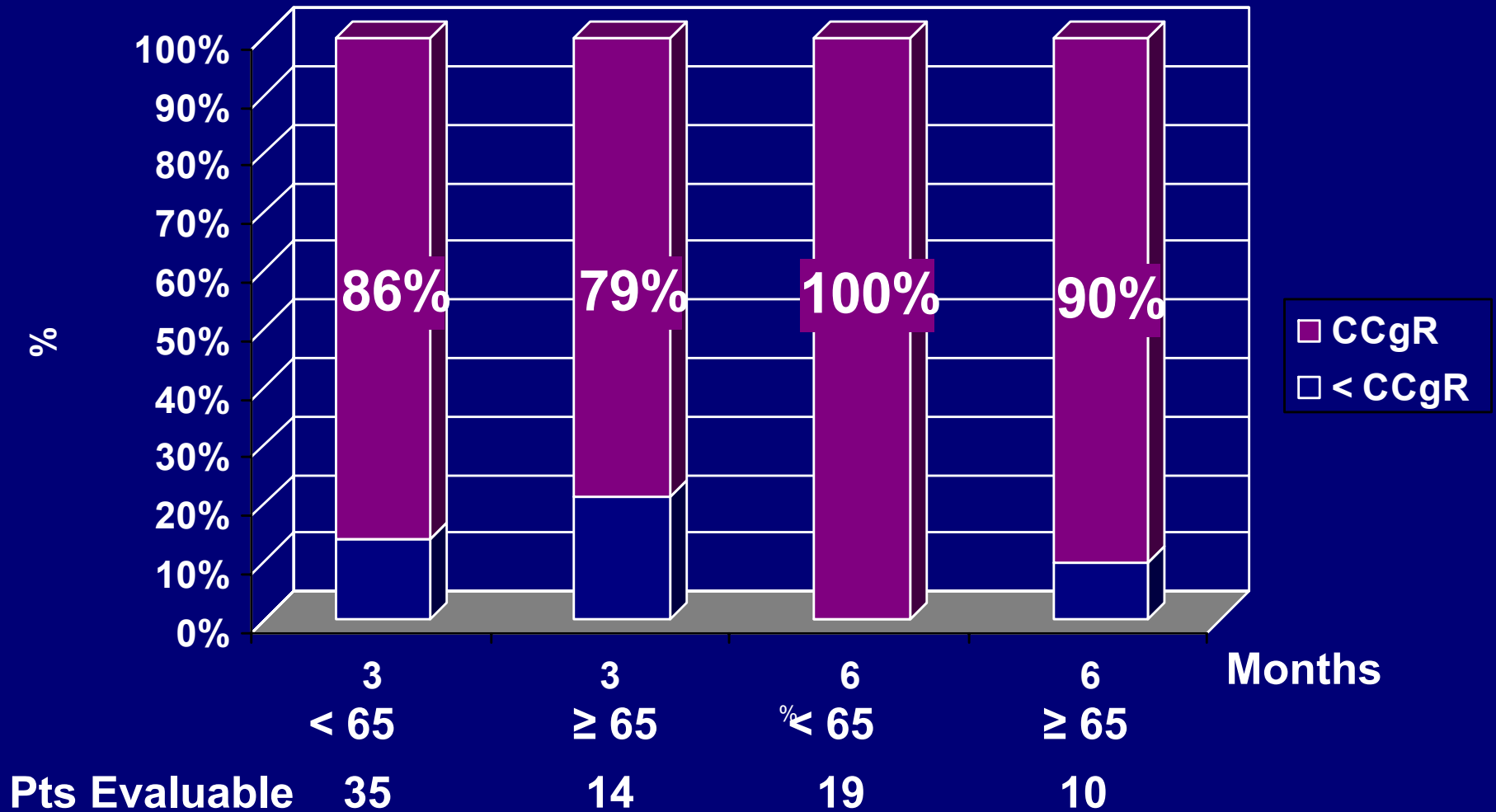
Overall Survival



Lipton et al. Blood. 2008;112(11):Abstract 3233. Poster presentation at ASH 2008

Lipton et al. Blood. 2008;112(11):Abstract 3233. Poster presentation at ASH 2008

Cytogenetic response by age



All P-values > 0.1



OLD WHO, FOLKS??

Issues in children in the imatinib era

- Rarity of the disease
- Different disease from adult CML?
 - in utero origin?
 - no comparative biology
- No validated prognostic index
- Allo-SCT versus TKI
 - Curative vs non curative
 - Immediate risk and long term sequelae vs delayed risk (disease, long-term safety)

Epidemiology: a very rare disease in childhood

- United States SEER program:
 - **age < 15 yrs:** 2% of all leukemias
1 case / million / yr
 - **age 15-19 yrs:** 9% of all leukemias
2.2 cases / million / yr

Ries et al. SEER 1975-2004, 2007

BMT in children and adolescents

- EBMT (1985-2001)
- 314 children < 18y (MSD:182 / VUD: 132)

	MSD CP1 (n=156)	VUD CP1 (n=97)	ALL (n=314)
3y OS (%)	75	65	66
3y LFS (%)	63	56	55

OS after BMT according to disease stage

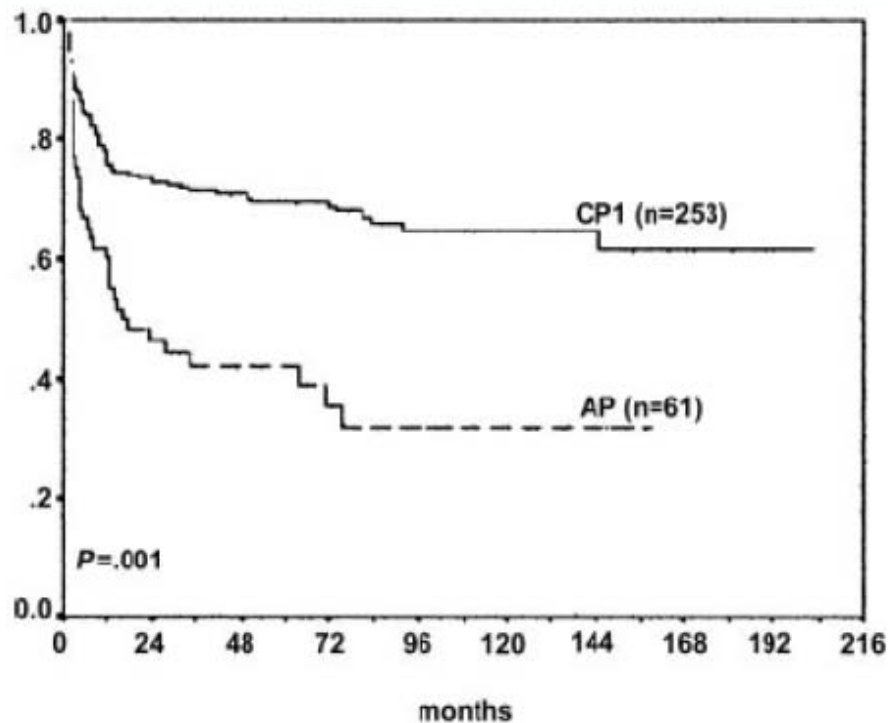
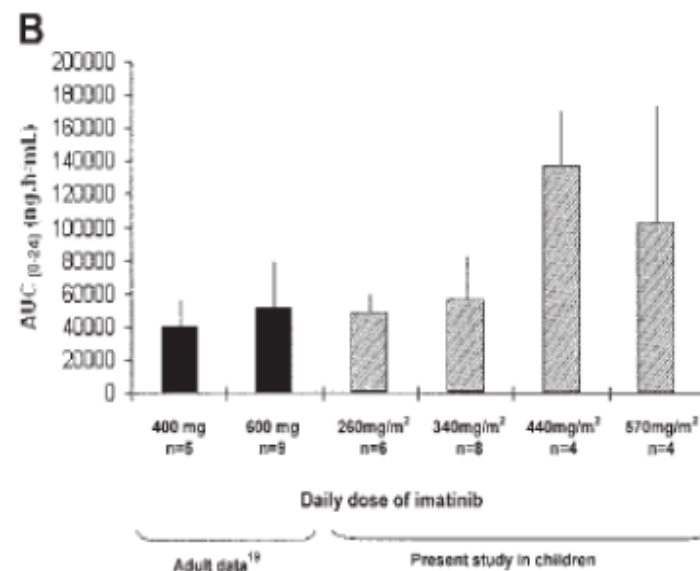


Figure 3. Overall survival (stage of disease at SCT). OS was significantly higher for children who underwent transplantation in CP1 (n = 253) than for children who underwent transplantation in AP (n = 61) (adjusted HR, AP:CP1, 2.0; 95% CI, 1.3-3.0; $P = .001$).

Phase I study of imatinib in children with Ph1+ leukemias (CML/ALL)

- 22 children with PK
 - Substantial interpatient variability
 - Plasma concentration at steady state comparable to adults

AUC adults vs children



Champagne et al. Blood. 2004;104(9):2655-60

Phase II trial (STI571-CML-Ped) of imatinib in children with CML: a European Pediatric Intergroup Study

- 2001 - 2003
- 30 pts (17M/13F) from 8 countries (23 centres)
- median age: 13 years (2-17.5)
- interval from diagnosis to imatinib therapy:
 - < 12 months: 8 pts
 - 12-36 months: 15 pts
 - > 36 months: 7 pts
- once daily oral administration
- median dose: 290 mg/m²/d (240-330)
 - median duration: 53 weeks (5-106)
 - median follow up: 12 months (2-27)

Imatinib-CML-Ped-Trial: inclusion features

- **Advanced phase de novo :** 4 pts
- **Pretreatment with IFN :** 13 pts
 - hematologic resistance (7 pts) or relapse (1pt)
 - cytogenetic resistance (2 pts) or relapse (1pt)
 - intolerance: 2 pts
- **Relapse after allo-SCT:** 13 pts (8 MUD, 5 MSD, 1 mMFD)
 - hematologic: 4 pts
 - cytogenetic: 7 pts
 - molecular: 2 pts

Response to imatinib according to stage of disease

Table 2 Response to imatinib mesylate therapy according to the stage of the disease at inclusion

	<i>Complete hematologic response</i>	<i>Complete cytogenetic response or FISH negativity</i>	<i>Molecular response bcr-abl/abl < 10⁻⁴ or undetectable transcript</i>
<i>Status at inclusion (no. of patients)</i>			
Chronic phase (22)	8/10 ^a (80%)	12/20 ^b (60%)	11/22 (50%)
Accelerated phase (5)	4/5 (80%)	2/5 (40%)	0/5
Blastic crisis (3)	2/3 (67%)	0/3	0/3

^aIn all, 12 patients were still in complete hematologic response at inclusion.

^bTwo patients were still in complete cytogenetic response at inclusion.

For pts in CP: 80% CHR, 60% CCR, 50% MMoIR

Potential Scheme in children and adolescents < 18 y

- At diagnosis: HU / imatinib
- If HLA-id sibling: BMT after BU-Cy
- If no HLA-id: continue imatinib 300 mg/m²
- If less than CCR or even less than major molecular reponse at 12 m, discuss after mutational screening
 - other TKIs
 - MUD transplant