Allogeneic HSCT for pediatric malignant diseases

Adriana Seber

Is it worth on taking your patient to transplant?

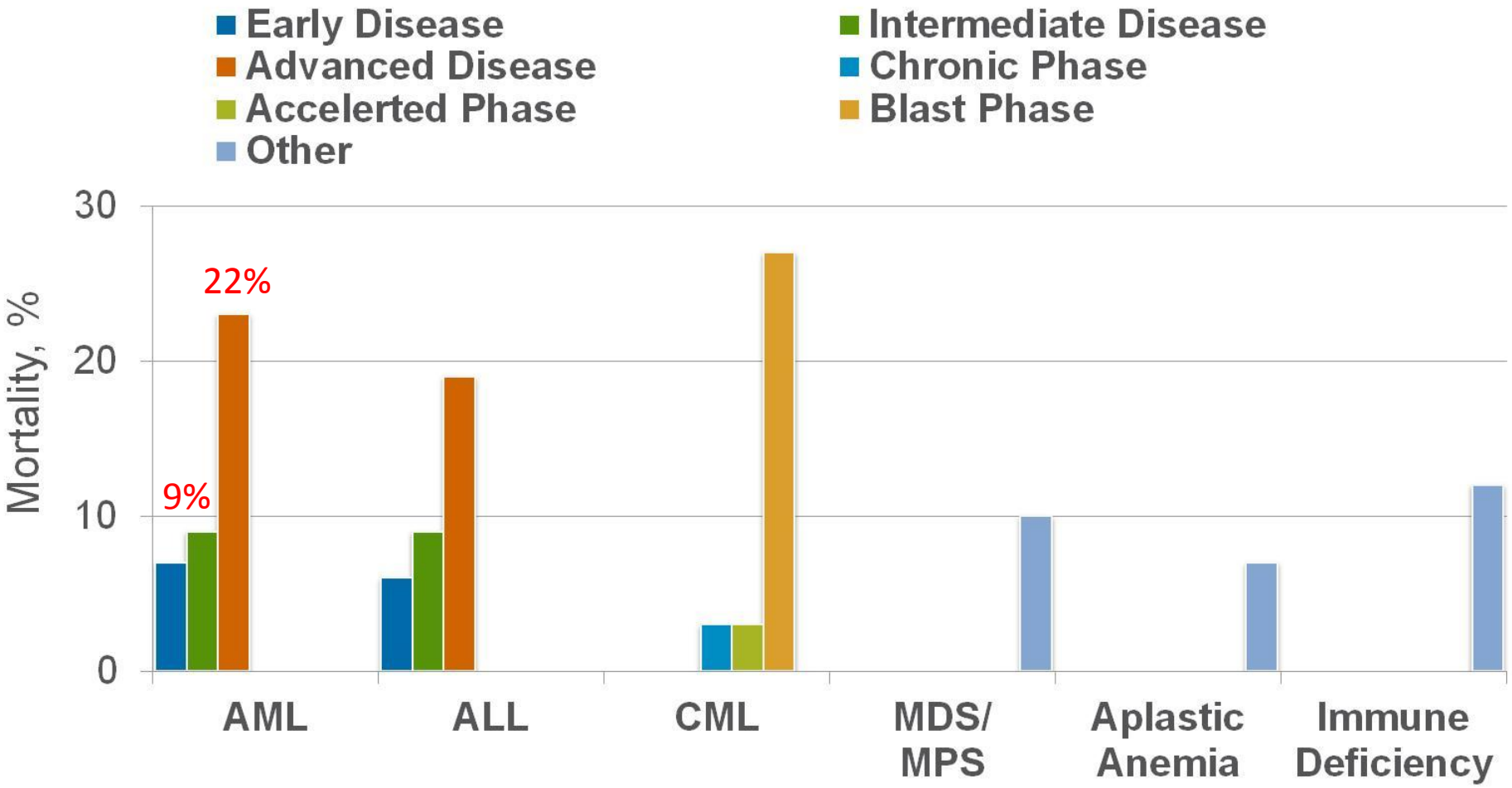
Which are the potential benefits?

What does the patient have to lose?

Transplant-related toxicities

- During the procedure
- Long-term side effects
  - sterility
  - cataract
  - hair changes
  - short stature
  - chronic graft-vs-host disease

100-day Mortality after HLA-identical Sibling Transplants, 2010-2011



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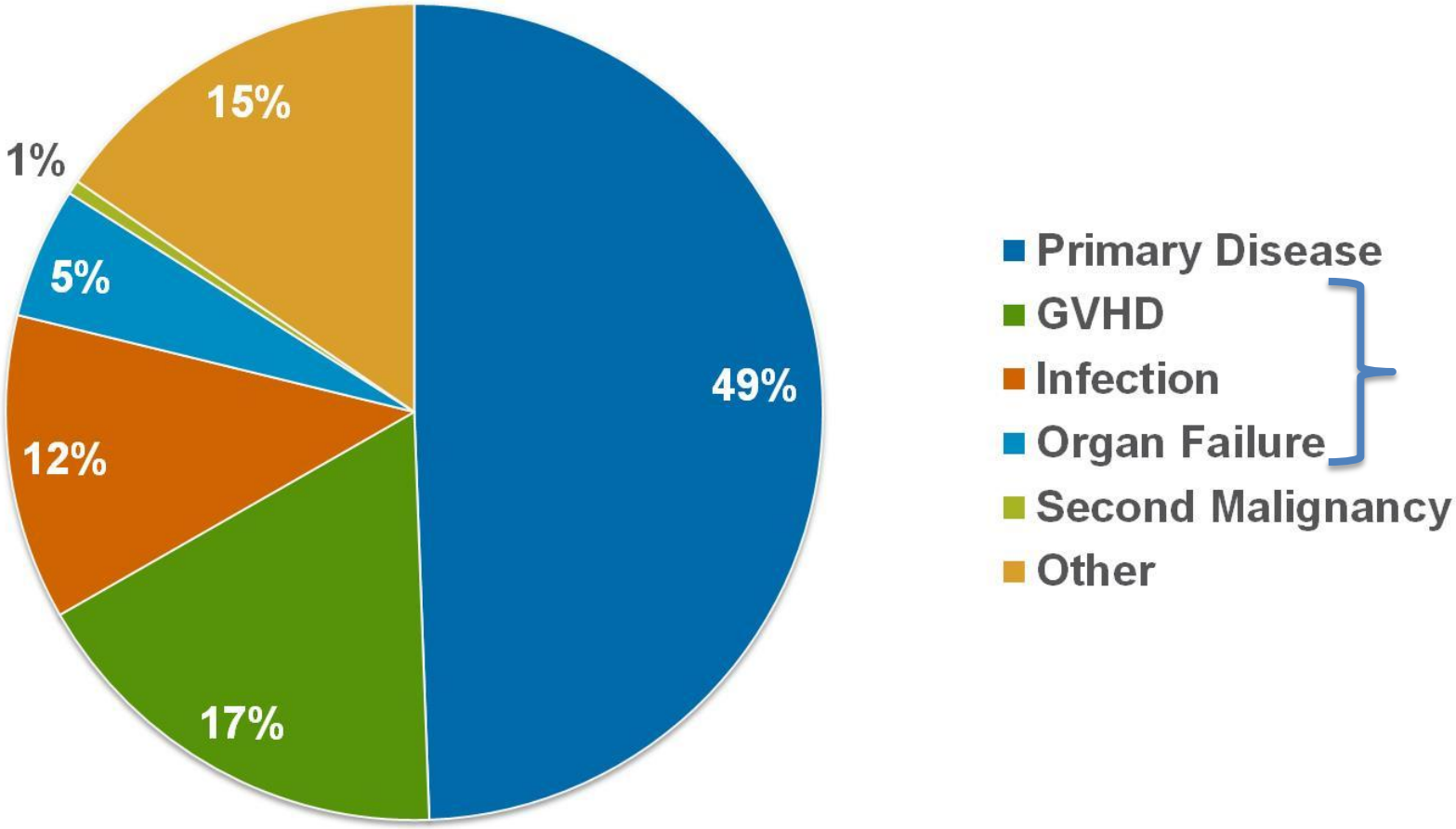
Causes of Death after HLA-identical Sibling Transplants done in 2010-2011



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Transplant-related toxicities

- ✓During the procedure
- Long-term side effects
  - sterility
  - cataract
  - hair changes
  - short stature
  - chronic graft-vs-host disease

Transplant-related toxicities

✓During the procedure

- Long-term side effects
  - sterility
  - cataract
  - hair changes
  - short stature
  - chronic graft-vs-host disease

Relapse of the malignant disease

HSCT in earlier phases of the disease

↓ Toxicity

↓ Long term side effects

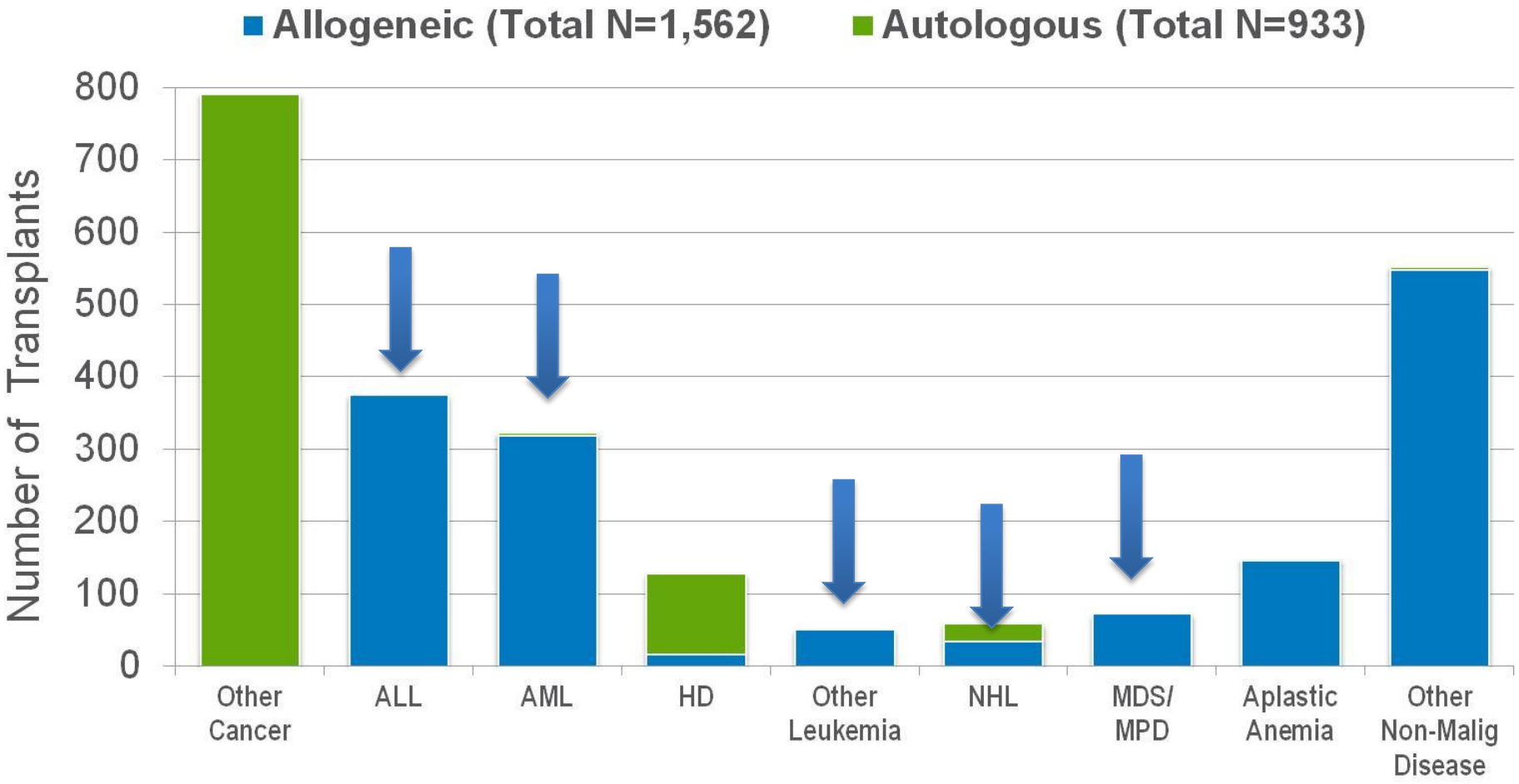
↓ Relapse

↑ Chance of cure

Transplants should be indicated if *overall survival* with transplant is larger than with chemotherapy

TRANSPLANT-RELATED MORTALITY

Indications for Hematopoietic Stem Cell Transplants for Age ≤ 20 years, in the US, 2011



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Which patients to transplant?

- Limited resources
- Limited number of beds
- Set up priorities

Criteria

Urgency

Curability

PORTARIA Nº 2.600, DE 21 DE OUTUBRO DE 2009

Doença	Urgência	Curabilidade	Q Constante(*)
Anemia aplástica grave/síndrome mielodisplásica hipocelular / imunodeficiência combinada severa/osteopetrose	100	80	80
Mielofibrose primária em fase evolutiva	80	40	120
Leucemia aguda falha de indução	100	15	115
Leucemia aguda em 2ª ou remissões posteriores	80	30	110
Síndrome mielodisplásica em transformação	70	40	110
Leucemia mielóide crônica - fase acelerada (de transformação)	90	20	110
Leucemia aguda 1ª remissão completa	50	55	105
Leucemia mielóide crônica - fase crônica < 1 ano diagnóstico e < 20 anos de idade	20	80	100
Talassemia major	10	90	100
Síndromes mielodisplásicas outras /leucemia mielomonocítica crônica	40	50	90
Leucemia mielóide crônica - fase crônica outras	30	50	80

(*) A cada dia somam-se 0,33 (trinta e três centésimos) de pontos igualmente para todos os casos, a partir da data de inclusão do receptor na lista. Receptores menores de 13 anos, independentemente da doença, deverão ter o seu escore final acrescido de 20 pontos.

Which patients to transplant first?

- Aplastic anemia
- Osteopetrosis
- Severe combined immunodeficiency
- Acute leukemia in 2nd remission
- Myelodysplastic syndrome
- Chronic myelogenous leukemia

* Children have priority

Which patients to transplant first?

- Aplastic anemia
- Osteopetrosis
- Severe combined immunodeficiency
- Severe sickle cell anemia
- Acute leukemia in 2nd remission
- Myelodysplastic syndrome
- Chronic myelogenous leukemia

* Children have priority

Which donor to use?

The best available donor:

- Matched sibling
- Matched unrelated adult
- Unrelated cord blood

  (≥ 6/8: high resolution A,B,C,DR; no double mismatches, good cellularity)
- Haploidentical related donor

Which allogeneic graft to use?

- **Bone marrow**
- ~~Peripheral blood~~
  - Risk of central lines in children
  - Risk of leukapheresis in small children

Originally published as JCO Early Release 10.1200/JCO.2004.02.189 on November 1 2004

Journal of Clinical Oncology, Vol 22, No 24 (December 15), 2004: pp. 4872-4880

Higher Mortality After Allogeneic Peripheral-Blood Transplantation Compared With Bone Marrow in Children and Adolescents: The Histocompatibility and Alternate Stem Cell Source Working Committee of the International Bone Marrow Transplant Registry

Mary Eapen, Mary M. Horowitz, John P. Klein, Richard E. Champlin, Fausto R. Loberiza, Jr, Olle Ringdén, John E. Wagner

From the International Bone Marrow Transplant Registry, Health Policy

Matched sibling donors

Table 3. Results of Multivariate Analysis Comparing Outcomes in Recipients of Bone Marrow and Peripheral-Blood Stem-Cell Transplants

Outcome	Relative Risk	95% CI	*P*
Treatment-related mortality*	1.89	1.28 to 2.80	.001
Relapse†	1.06	0.77 to 1.46	.7
Treatment failure‡	1.31	1.03 to 1.68	.03
Overall mortality§	1.38	1.07 to 1.79	.01

NOTE. Bone marrow recipients, the reference group, was assigned a relative risk (RR) of 1.00; RR greater than 1.0 indicate a benefit for bone marrow.

*Other significant variables associated with treatment-related mortality in both cohorts were use of growth factor within 7 days of allograft infusion for engraftment (RR, 1.80; 1.27 to 2.55; $P = .001$).

†Other significant variables associated with relapse in both cohorts were disease status; 1st CR (RR, 1.00, baseline), 2nd CR (RR, 1.82;

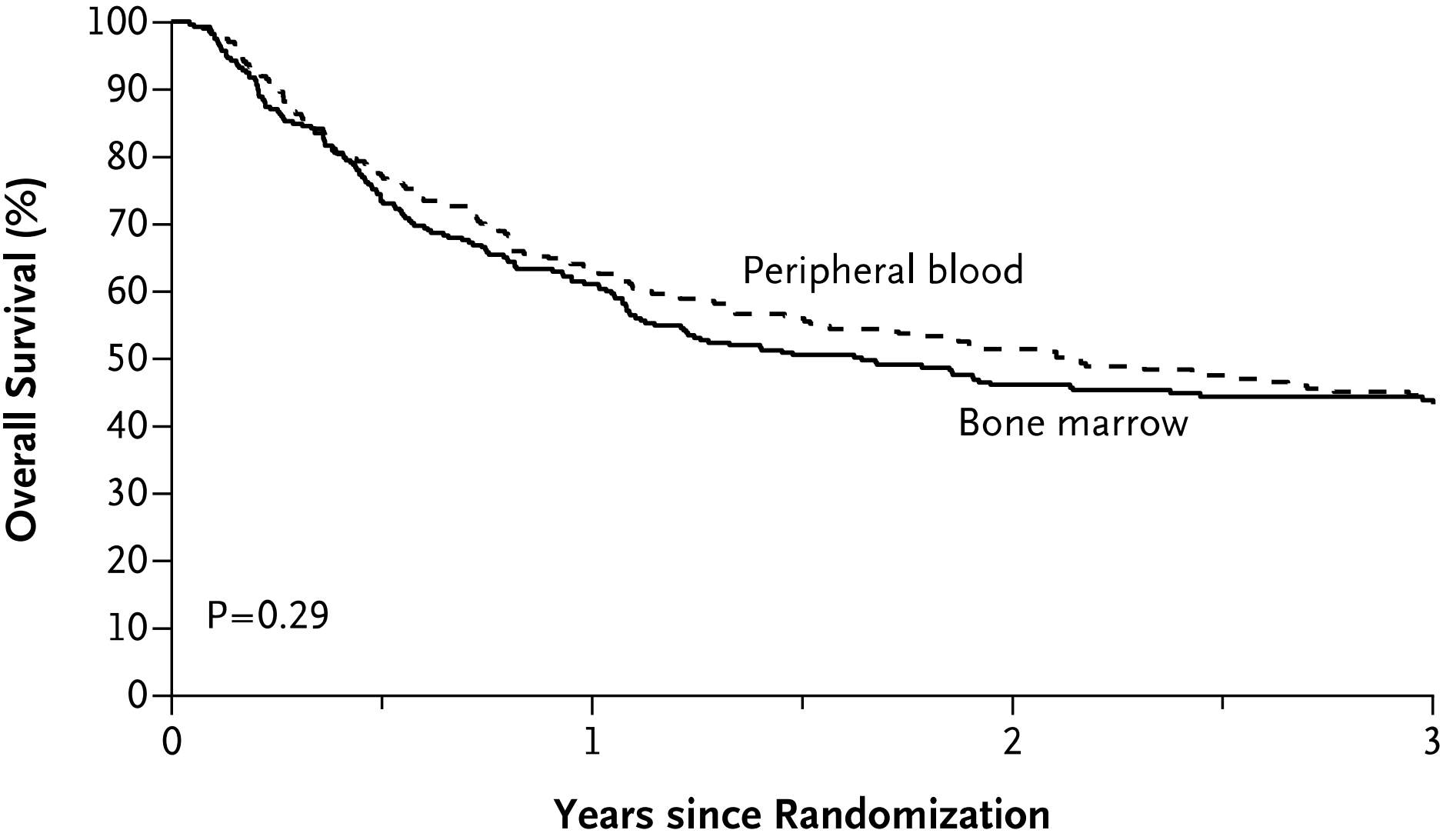
Eapen. JCO 2004; 22(24):1

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 18, 2012 VOL. 367 NO. 16

Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors

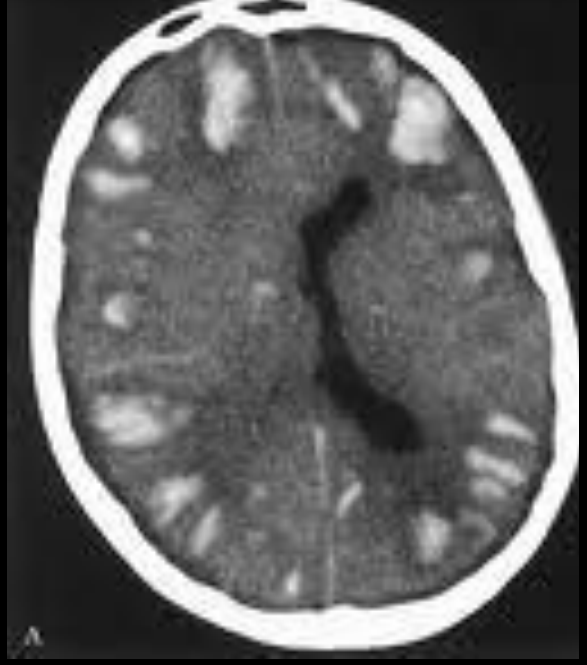
Claudio Anasetti, M.D., Brent R. Logan, Ph.D., Stephanie J. Lee, M.D., M.P.H., Edmund K. Waller, M.D., Ph.D., Daniel J. Weisdorf, M.D., John R. Wingard, M.D., Corey S. Cutler, M.D., M.P.H., Peter Westervelt, M.D., Ph.D., Ann Woolfrey, M.D., Stephen Couban, M.D., Gerhard Ehninger, M.D., Laura Johnston, M.D., Richard T. Maziarz, M.D., Michael A. Pulsipher, M.D., David L. Porter, M.D., Shin Mineishi, M.D., John M. McCarty, M.D., Shakila P. Khan, M.D., Paolo Anderlini, M.D., William I. Bensinger, M.D., Susan F. Leitman, M.D., Scott D. Rowley, M.D., Christopher Bredeson, M.D., Shelly L. Carter, Sc.D., Mary M. Horowitz, M.D., and Dennis L. Confer, M.D., for the Blood and Marrow Transplant Clinical Trials Network*

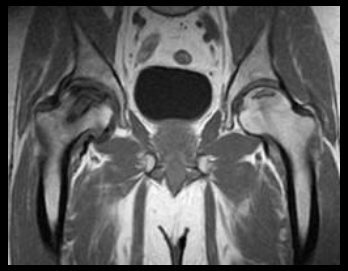

Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Peripheral blood
Bone marrow
P=0.29
0
1
2
3
Years since Randomization

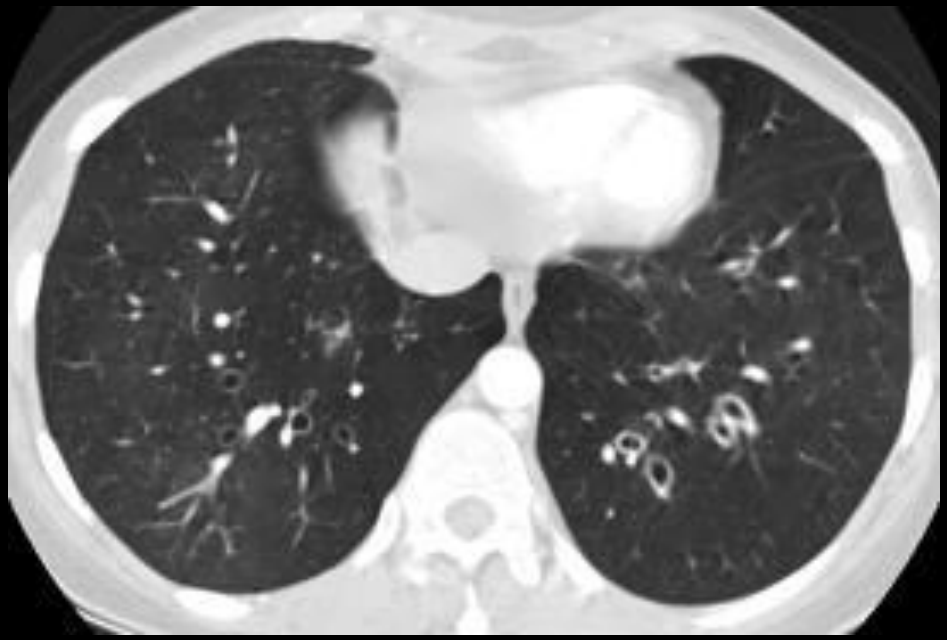
Severe Chronic GVHD

Peripheral blood >> Bone Marrow

(48% vs. 32%, p < 0.001)







Which allogeneic graft to use?

- Bone marrow
- ~~Peripheral blood~~
  - ~~Risk of central lines in children~~
  - ~~Risk of leukapheresis in small children~~

Consensus indications

- European – EBMT

  http://ebmtonline.forumservice.net
- American – ASBMT

  www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm
- British – BSBMT http://bsbmt.org
- Scottish - Royal Hospital for Sick Children
- Brazilian – SBTMO – Pediatric BMT Group

Disease	Disease status	Allogeneic matched related	Allogeneic Unrelated	Haploidentical related
Donor specifics [a,b]		10/10 sibling other 10/10 related other 9/10 related	10/10 adult 9-10/10 adult 4-6/6 cord	<9/10 related
Stem Cell Source		BM/PBPCs/cord	BM/PBPCs/cord	PBPCs/BM
AML	High risk CR1 [c]	S [c]	S [c]	CO
	CR≥2 [d]	S	S	S [e]
	Relapse/refractory	CO	CO	CO [g]
ALL	High risk CR1 [h]	S [h]	S [h]	CO
	CR2 [i]	S [i]	S [i]	S [i]
	CR3	S	S	S
	Relapse/refractory	GNR	GNR	GNR
CML	Chronic phase	S [j]	S [j]	CO [j]
	Accelerated phase	S	S	CO
	Blast crisis	S [k]	S [k]	CO [k]
T-NHL	As per ALL [l]			

UK Paediatric BMT Group HSCT Indications, 23 December 2011

http://bsbmt.org

Disease	Disease status	Allogeneic matched related
Donor specifics [a,b]		10/10 sibling other 10/10 related other 9/10 related
Stem Cell Source		BM/PBPCs/cord
AML	High risk CR1 [c]	S [c]
	CR≥2 [d]	S
	Relapse/refractory	CO
ALL	High risk CR1 [h]	S [h]
	CR2 [i]	S [i]
	CR3	S
	Relapse/refractory	GNR
CML	Chronic phase	S [j]
	Accelerated phase	S
	Blast crisis	S [k]

Pediatric Acute Lymphoblastic Leukemia

- Autologous transplants are not indicated
- Allogeneic transplants:
  - ✓Third remission
  - – Second remission
  - – First remission

Outcome of Myeloablative Conditioning and Unrelated Donor Hematopoietic Cell Transplantation for Childhood Acute Lymphoblastic Leukemia in Third Remission

Eneida R. Nemecek,[1] K
Alexandra Cheerva,[5] Mit
Mary Eapen,[2] Tho
Parinda A
Ann E. Woo

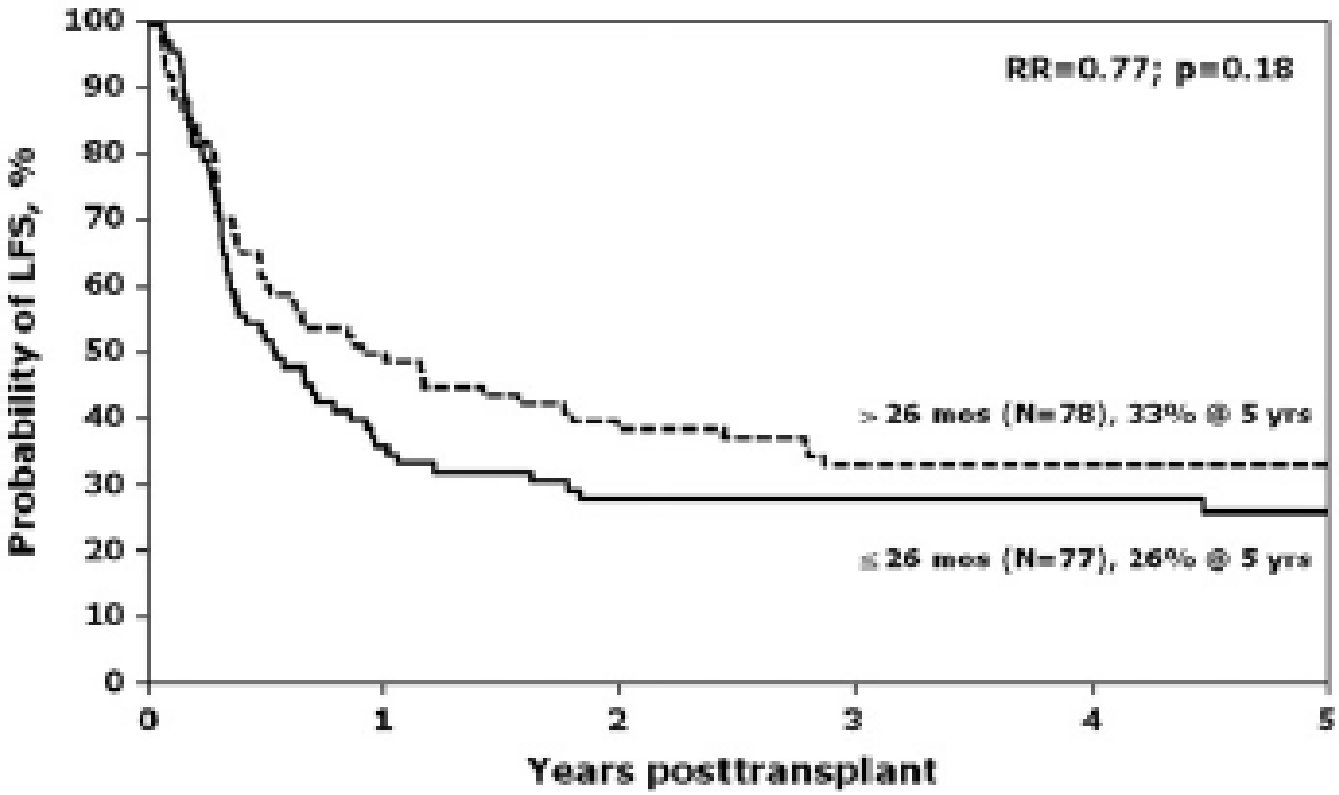


Figure 2. Estimates of leukemia-free survival.

Biol Blood Marrow Transplant 17:1833-1840, 2011

Pediatric Acute Lymphoblastic Leukemia

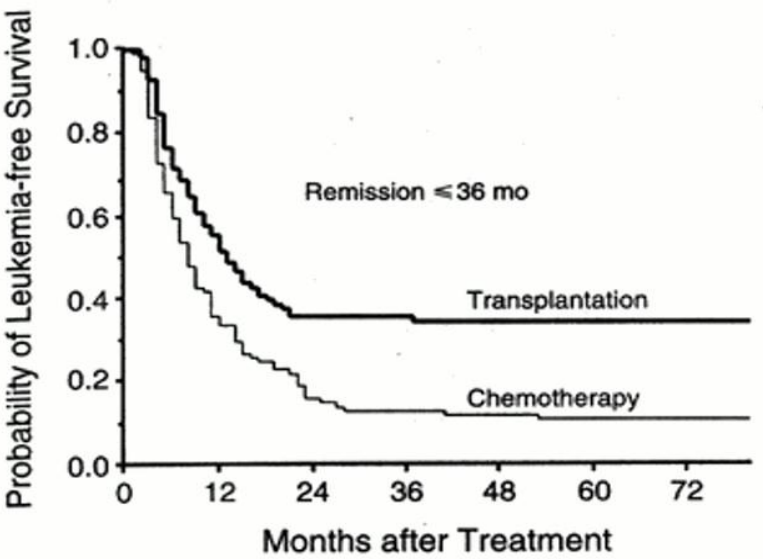
- Autologous transplants are not indicated
- Allogeneic transplants:
  - ✓Third remission
  - – Second remission
  - – First remission

ALL in CR2:

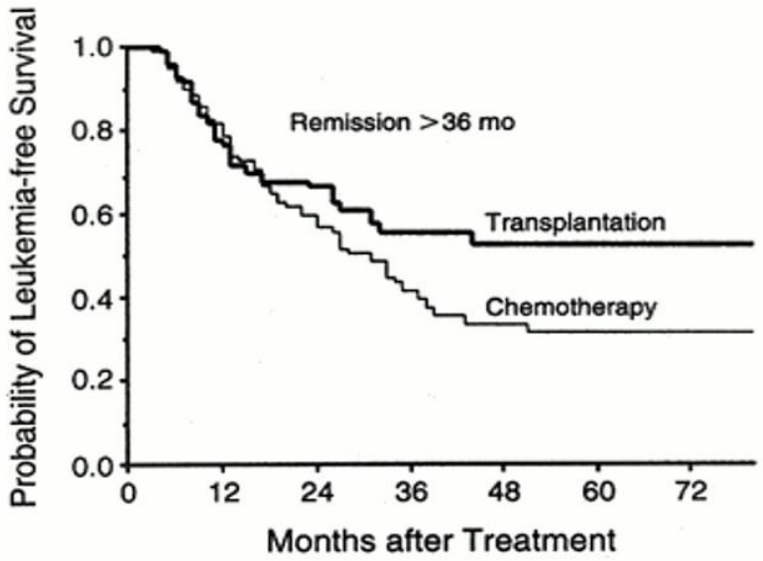
Matched sibling donor BMT

vs.

Chemotherapy



Transplantation	179	85	46	37	32	24	18
Chemotherapy	179	53	22	16	14	10	7



Transplantation	76	48	35	23	15	13	10
Chemotherapy	76	52	36	23	15	9	8

Barrett 1994 NEJM 331:1253-1258

ALL in 2nd remission

Risk	Relapse	EFS	Transplant
High	Early marrow	5-15%	Any BMT
(25%)	CNS/testes	20-25%	
Interm	BM 2-4 years	40-60%	Related
(65%)	Combined	40-60%	
Low	non-T > 4 yr-BM	60-70%	Chemo ± RT
(10%)	non-T > 4 yr-EM	60-80%	

Chessels Hematology 2000

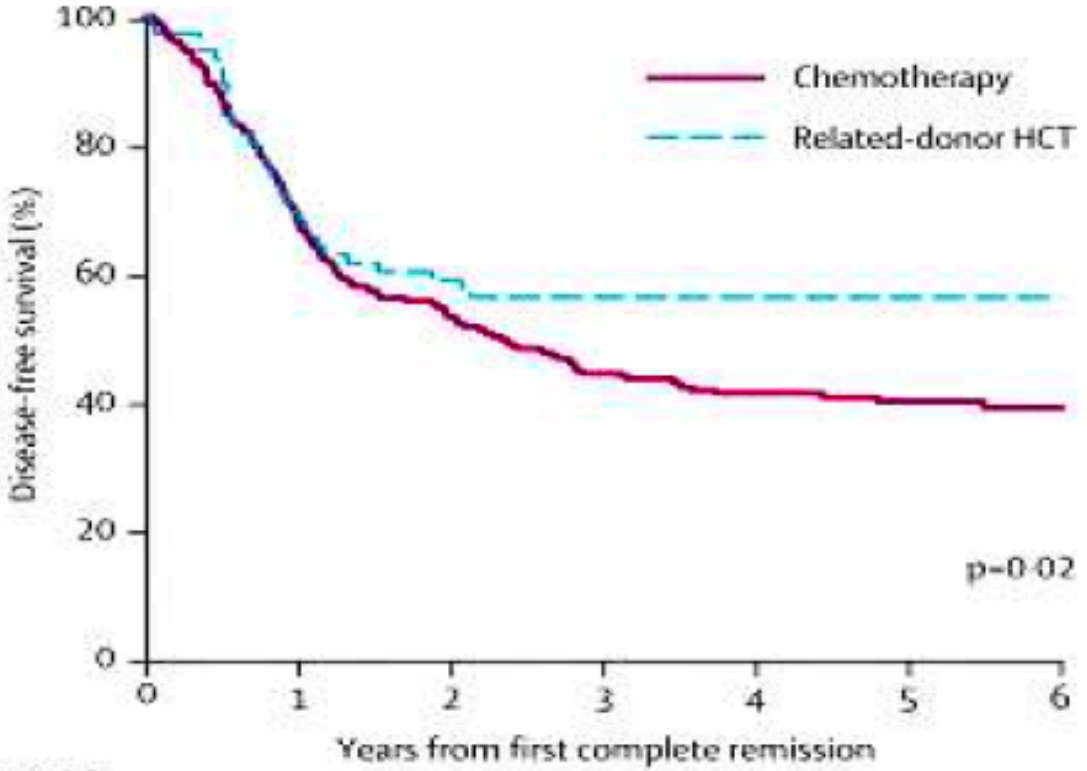
Pediatric Acute Lymphoblastic Leukemia

- Autologous transplants are not indicated
- Allogeneic transplants:
  - ✓Third remission
  - ✓Second remission
  - – First remission

Chemotherapy versus allogeneic transplantation for very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: comparison by genetic randomisation in an international prospective study.

Balduzzi A, Valsecchi MG, Uderzo C, De Lorenzo P, Klingebiel T, Peters C, Stary J, Felice MS, Magyarosy E, Conter V, Reiter A, Messina C, Gadner H, Schrappe M.

Lancet. 2005 Aug 20-26;366(9486):635-42.



Number at risk							
Chemotherapy	280	190	146	112	85	54	31
Related-donor HCT	77	53	45	41	32	21	11

Estimates of disease-free survival, by treatment assigned

Pediatric Acute Lymphoblastic Leukemia

- Autologous transplants are not indicated
- Allogeneic transplants:
  - ✓Third remission
  - ✓Second remission
  - – First remission
    - t(9;22)
    - hypodiploid (<44) chromosome number
    - induction failure (M2/3 marrow on D29)
    - 11q23
    - minimal residual disease

VOLUME 27 · NUMBER 31 · NOVEMBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

From the Children's Oncology Group; Department of Pediatrics, Division of Hematology, Oncology, and Blood and Marrow Transplant, British Columbia's Children's Hospital, University of British Columbia, Vancouver, BC; Cook Children's Medical Center, Hematology and Oncology, Fort Worth; Pediatric Hematology and Oncology, University of Texas Southwestern Medical Center, Dallas, TX; Phyllis and David Komansky Center for Children's Health, Weill Cornell Medical Center, New York; Department of Pediatrics, New York University Medical Center, New York, NY; Department of Pediatrics and University of Florida Shands Cancer Center, University of

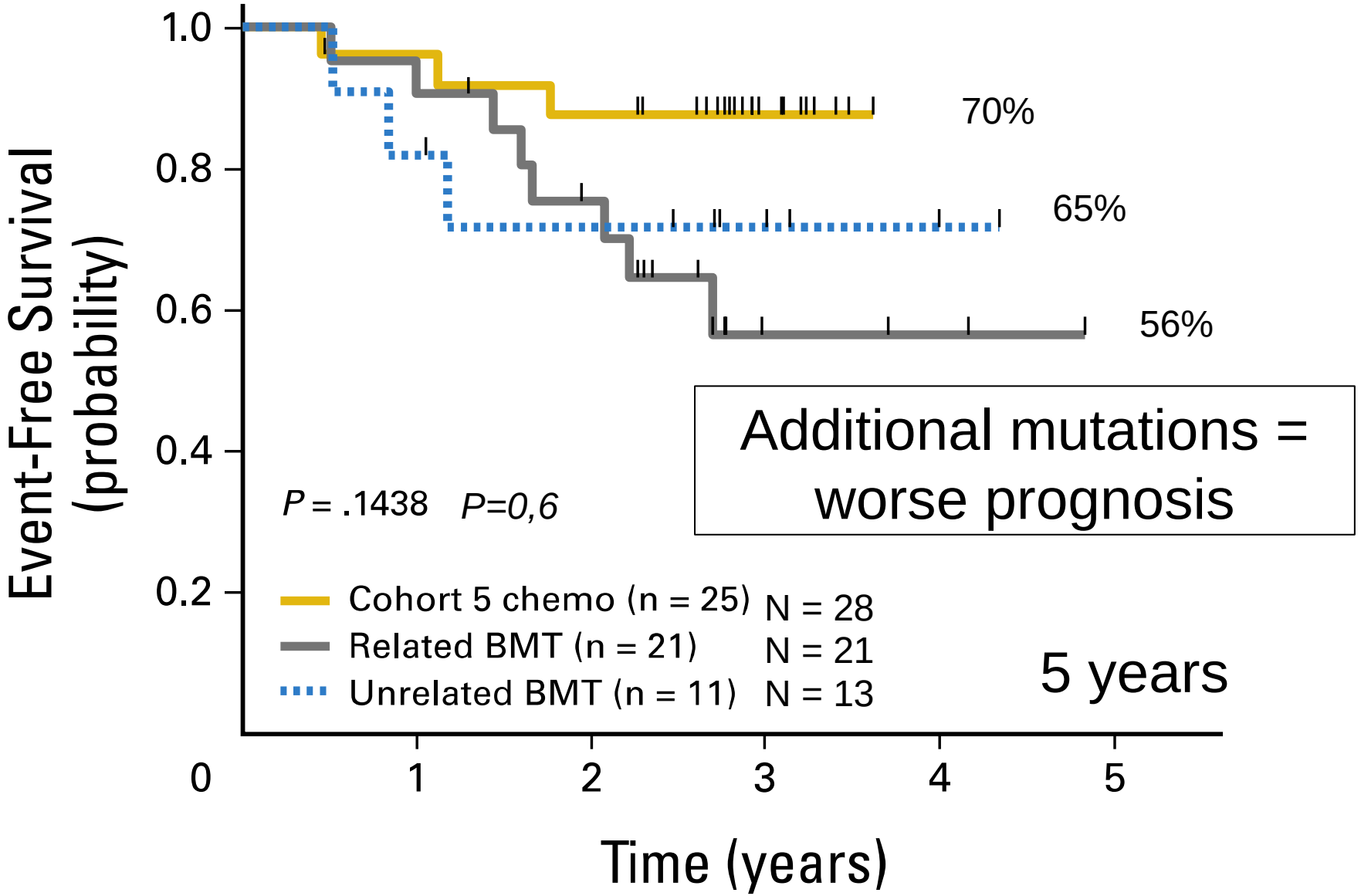
Improved Early Event-Free Survival With Imatinib in Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: A Children's Oncology Group Study

Kirk R. Schultz, W. Paul Bowman, Alexander Aledo, William B. Slayton, Harland Sather, Meenakshi Devidas, Chenguang Wang, Stella M. Davies, Paul S. Gaynon, Michael Trig… Dean Jorstad, Andrew Carroll, Nyla A. Heerema, Naomi Winick, … William L. Carroll, and Bruce Camitta

340 mg/m²/dia

Therapy	Cons 1 (3 wk)	Cons 2 (3 wk)	Reind 1 (3 wk)	Intens 1 (9 wk)	Reind 2 (3 wk)	Intens 2 (9 wk)	Maint 1-4 (8-wk cycles)	Maint 5-12 (8-wk cycles)
Cohort 1				Imatinib × 3 wk		Imatinib × 3 wk	Imatinib × 3 wk	Imatinib × 2 wk every 4 wk
Cohort 2		Imatinib × 3 wk	Imatinib × 3 wk		Imatinib × 3 wk		Imatinib × 3 wk	Imatinib × 2 wk every 4 wk
Cohort 3	Imatinib × 3 wk →	→	→		Imatinib × 3 wk		Imatinib × 3 wk	Imatinib × 2 wk every 4 wk
Cohort 4	Imatinib × 3 wk →	→	→	→	→	→	→	Imatinib × 2 wk every 4 wk
Cohort 5	Continuous dosing of imatinib							Imatinib × 2 wk every 4 wk

Long-term follow-up of imatinib in pediatric Ph+ ALL: Children's Oncology Group AALL0031



Pediatric Acute Lymphoblastic Leukemia

- Autologous transplants are not indicated
- Allogeneic transplants:
  - ✓Third remission
  - ✓Second remission
  - – First remission
    - ~~t(9;22)~~ : chemotherapy + TKI
    - hypodiploid (<44 chromosomes)
    - induction failure (M2/3 marrow on D29)
    - 11q23
    - minimal residual disease

Philadelphia chromosome-negative very high-risk acute lymphoblastic leukemia in children and adolescents: results from Children's Oncology Group Study AALL0031

Leukemia (2014) **28,** 964–967; doi:10.1038/leu.2014.29

The Children's Oncology Group (COG) AALL0031 study included very high-risk (VHR) pediatric acute lymphoblastic leukemia (ALL) patients who had an expected 5-year event-free survival $\leqslant$45%. The chemotherapy regimen was based on previous strategies; eligible patients received 4 weeks of standard induction chemotherapy and then were enrolled on AALL0031, which included an intensive consolidation followed by a continuation regimen (Supplementary Figure 1).[1] COG AALL0031 enrolled patients aged 1–21 years with VHR ALL from 14 October 2002 to 20 October 2006. Induction therapy was limited to a combination of vincristine, prednisone or dexamethasone, and asparaginase with or without daunomycin. VHR features included the following: (a) Philadelphia chromosome [t(9;22)(q34;q11.2)]; (b) hypodiploidy: defined as $\leqslant$44 chromosomes or DNA index $<$0.81; (c) any rearrangement of the *MLL* gene in conjunction with a slow early response $\geqslant$5% marrow blasts at day 15 and/or $\geqslant$0.1% minimal residual disease (MRD) at the end of induction as detected by multiparameter flow cytometry;[2,3] and (d) induction failure (IF) defined as either $>$25% blasts (M3 marrow status) by histology at the end of 4 weeks of induction therapy or an M2 marrow (5–25% blasts) or MRD $\geqslant$1% by flow cytometry at the end of induction followed by an M2 (or M3) marrow or MRD$\geqslant$1% after receiving two additional weeks of induction therapy (M2/M2 IFs). The therapy was identical to that presented in a previous publication on outcomes for Ph^+ ALL patients,[1] except that the Ph^- patients received no imatinib (see Supplementary Figure 1).

Prior approval was obtained from the National Cancer Institute and the Institutional Review Boards of the COG member institutions. Informed consent was obtained in accordance with the Federal guidelines. Sixty-three hypodiploid (41) and IF (22) patients were enrolled in AALL0031 after 4 weeks of a three- or four-drug induction regimen for National Cancer Institute standard and high-risk ALL, respectively. Data on adverse events and clinically significant abnormal laboratory findings were collected using National Cancer Institute Common Terminology Criteria version 2.0. MRD was assessed by multiparameter flow cytometry.[2] Samples were available from 46 of 63 (73%) patients at study entry. MRD high was defined as $>$0.01% and low as $\leqslant$0.01%.

The primary outcome in this report is disease-free survival (DFS). Overall survival (OS), DFS and event-free survival were all defined as the time from the end of consolidation to the first event or last contact. An event was defined as relapse at any site, secondary malignancy or death in remission. A historical control data set of hypodiploid patients included patients enrolled on the Pediatric Oncology Group 8602, 9005, 9006, 9201, 9405, 9406 and 9605 protocols for B-ALL (January 1986–November 1999).[3] The percentage of patients undergoing bone marrow transplant (BMT) in these comparator studies is unknown. IF patients were excluded from post-induction therapy in the historical control trial. Estimates of DFS, event-free survival and OS were computed using the Kaplan–Meier method[4] and s.e. of the estimates according to Peto and Peto.[5] The log-rank test was used for comparison of survival curves

Accepted article preview online 17 January 2014; advance online publication, 11 February 2014

Hypodiploid + MRD

- MRD after consolidation cycle 2

4-year DFS rates:

- MRD < 0.01% = 83% with BMT
  47% with chemotherapy
- MRD > 0.01% = 56% with BMT
  29% with chemotherapy

Leukemia (2014) 935 – 979

Pediatric Acute Lymphoblastic Leukemia

- Autologous transplants are not indicated
- Allogeneic transplants:
  - ✓Third remission
  - ✓Second remission
  - – First remission
    - ~~t(9;22)~~ : chemotherapy + TKI
    - ✓hypodiploid (<44 chromosomes)
    - induction failure (M2/3 marrow on D29)
    - 11q23
    - minimal residual disease

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 12, 2012 VOL. 366 NO. 15

Outcomes after Induction Failure in Childhood Acute Lymphoblastic Leukemia

Martin Schrappe, M.D., Stephen P. Hunger, M.D., Ching-Hon Pui, M.D., Vaskar Saha, F.R.C.P.C.H., Paul S. Gaynon, M.D., André Baruchel, M.D., Valentino Conter, M.D., Jacques Otten, M.D., Akira Ohara, M.D., Ph.D., Anne Birgitta Versluys, M.D., Gabriele Escherich, M.D., Mats Heyman, M.D., Ph.D., Lewis B. Silverman, M.D., Keizo Horibe, M.D., Ph.D., Georg Mann, M.D., Bruce M. Camitta, M.D., Jochen Harbott, Ph.D., Hansjörg Riehm, M.D., Sue Richards, D.Phil., Meenakshi Devidas, Ph.D., and Martin Zimmermann, Ph.D.

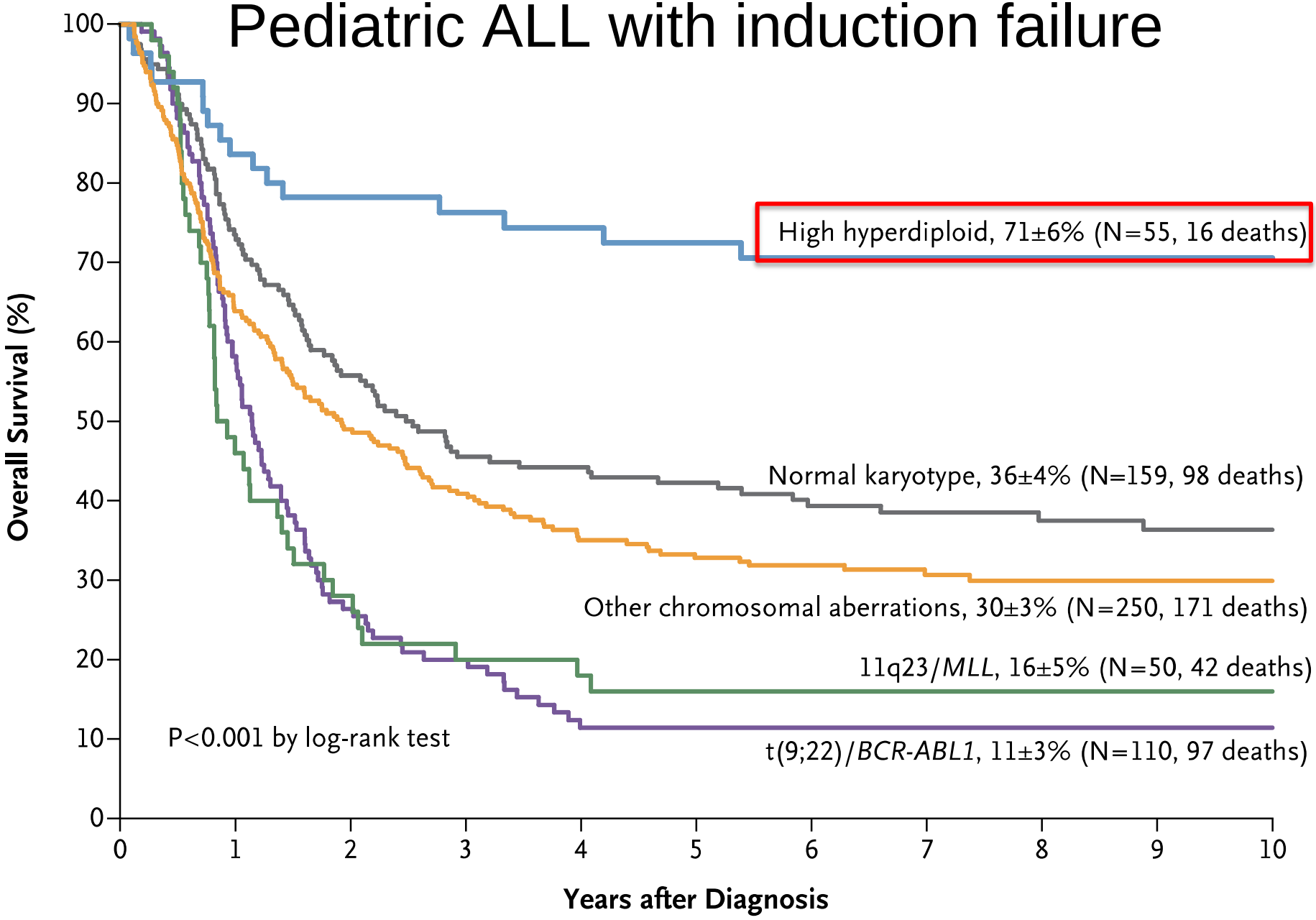
N Engl J Med 2012;366:1371

Study group	Patients treated	Induction failures N (%)
Associazione Italiana Ematologia ed Oncologia Pediatrica (AIEOP; Italy)	2938	88 (3.0)
Berlin-Frankfurt-Münster Group (BFM; Austria, Germany, Switzerland)	5828	137 (2.3)
Children's Cancer Group (CCG; U.S.A., Canada, Australia, New Zealand)	5122	120 (2.3)
Cooperative ALL Group (COALL; Germany)	1686	49 (2.9)
Dutch Childhood Oncology Group (DCOG; The Netherlands)	1729	30 (1.7)
Dana-Farber Cancer Institute ALL Consortium (DFCI; U.S.A., Canada)	1457	31 (2.1)
Children's Leukemia Group of the European Organisation for Research and Treatment of Cancer, (CLG-EORTC; Belgium, France, Portugal)	2316	69 (3.0)
French Acute Lymphoblastic Leukaemia Study Group (FRALLE; France)	3455	81 (2.3)
Japanese Association of Childhood Leukemia Study (JACLS, Japan)	1263	62 (4.9)
Childrens Cancer and Leukaemia Group (CCLG; United Kingdom)	5100	139 (2.5)
Nordic Society for Pediatric Hematology and Oncology (NOPHO; Sweden, Denmark, Norway, Finland, Iceland)	1546	53 (3.4)
Pediatric Oncology Group (POG; U.S.A., Canada)	8511	119 (1.4)
St. Jude Children's Research Hospital (SJCRH; Memphis, U.S.A.)	929	14 (1.5)
Tokyo Children Cancer Study Group (TCCSG; Tokyo, Japan)	2137	49 (2.3)
Total	**44017**	**1041 (2.4)**

14 cooperative groups
1985 – 2000
44.017 children
1.041 induction failures
(2,4%)

N Engl J Med 2012;366:1371

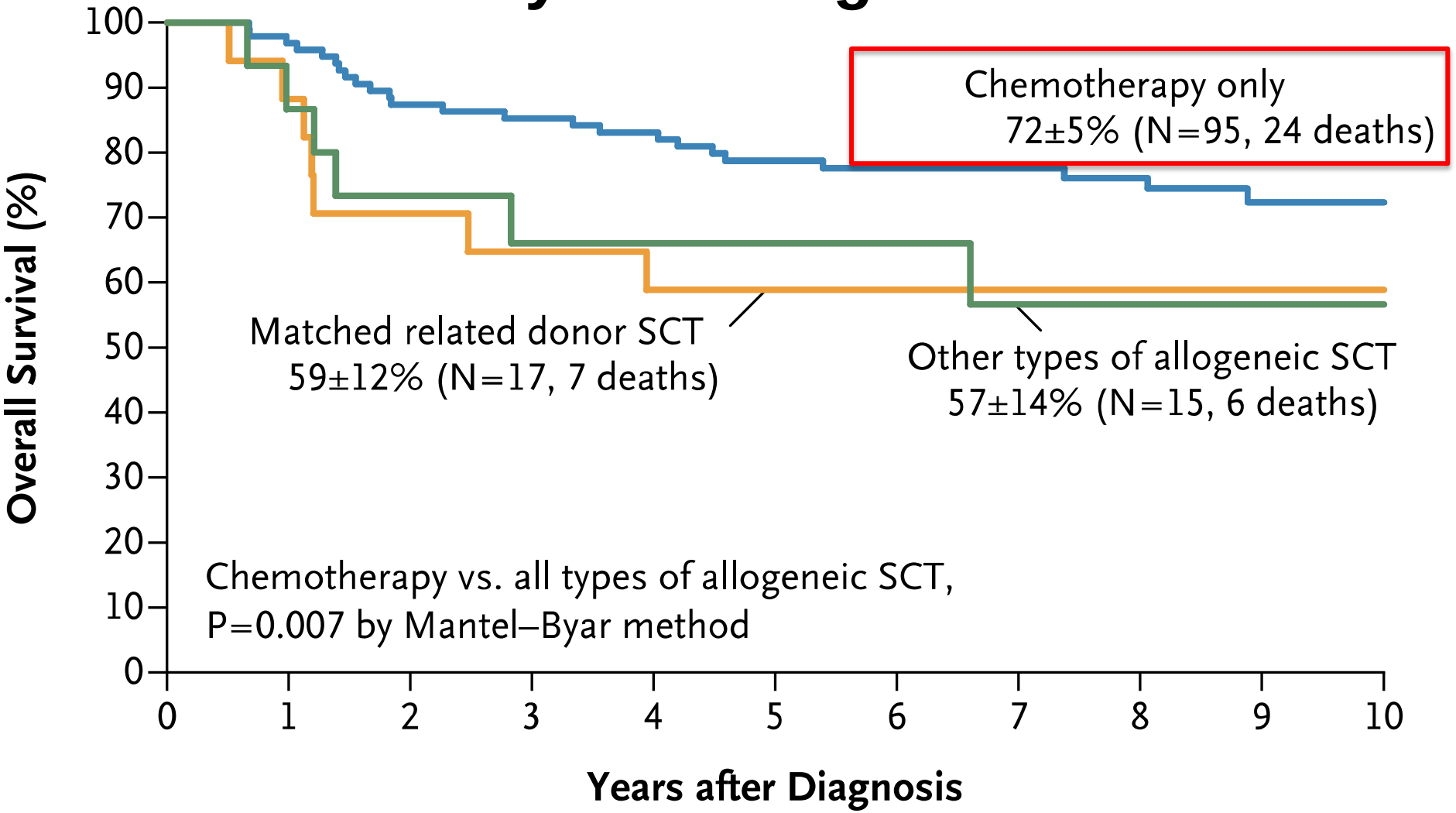
Pediatric ALL with induction failure



N Engl J Med 2012;366:1371

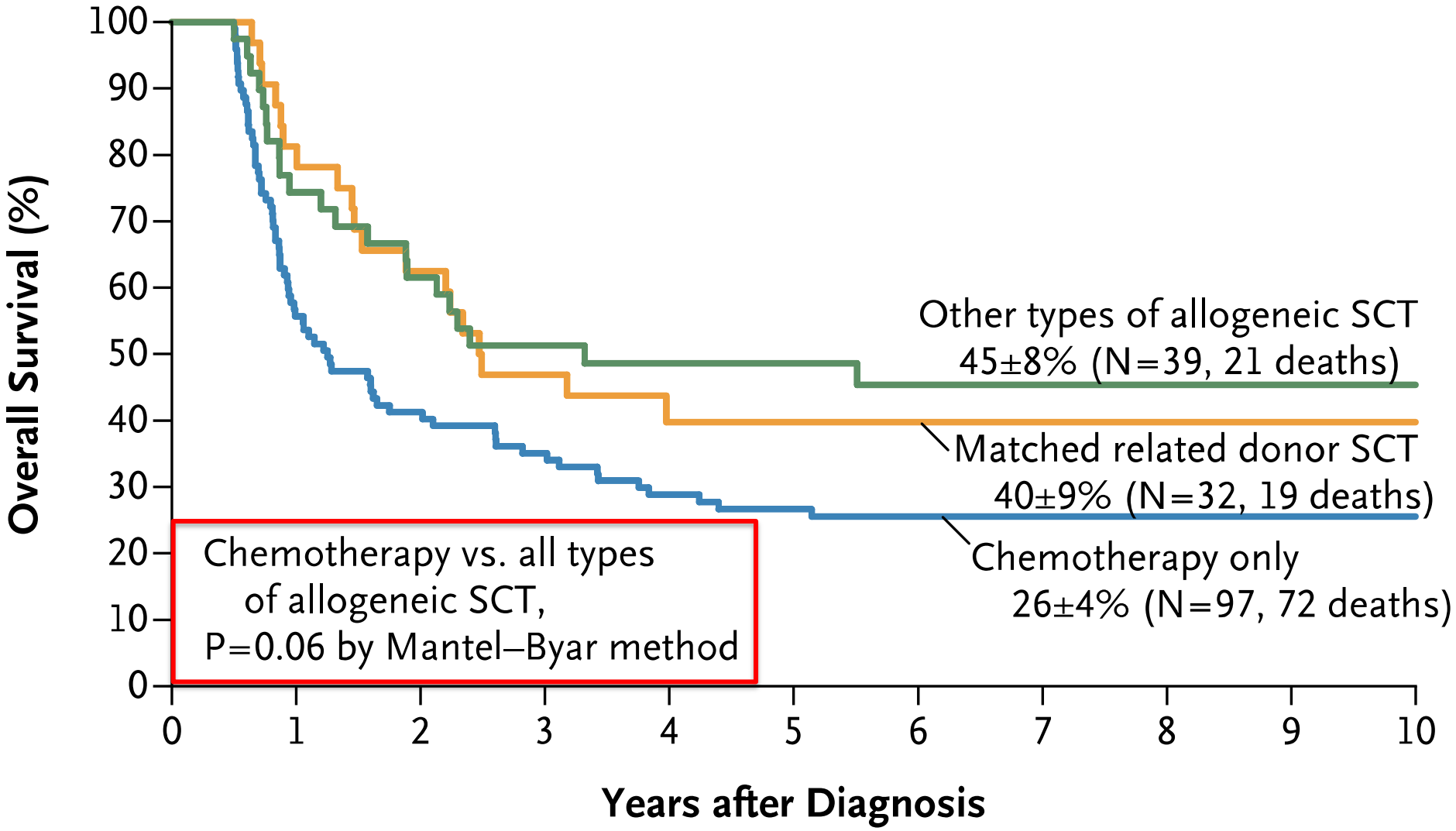
B-lineage ALL (non-MLL)

< 6 years of age



N Engl J Med 2012;366:1371

ALL – T lineage



N Engl J Med 2012;366:1371

Pediatric Acute Lymphoblastic Leukemia

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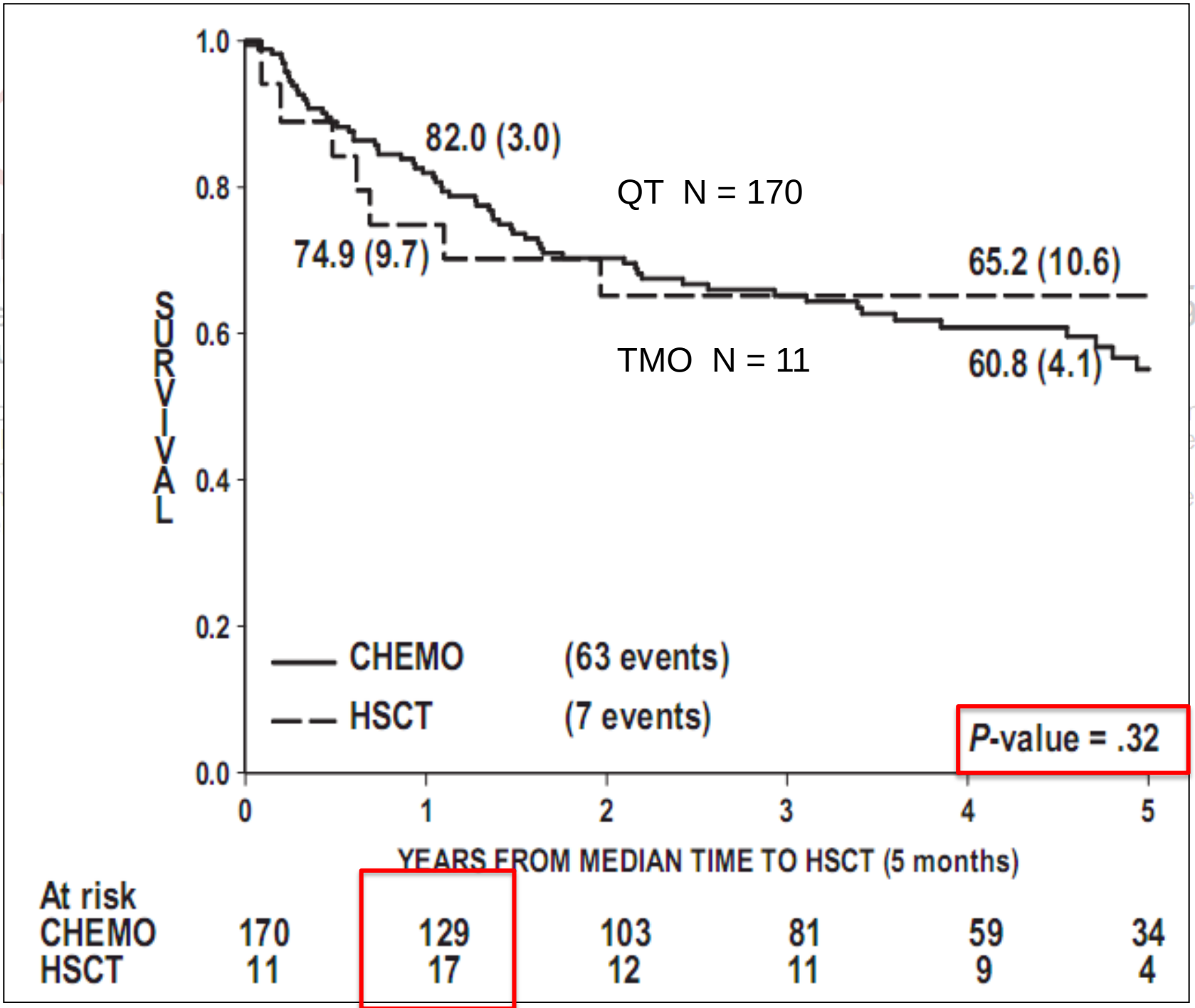
  - – First remission
    - ~~t(9;22)~~
    - ? hypodiploid (<44) chromosome number
    - ✓Induction failure (M2/3 marrow on D29)
    - 11q23
    - MRD D29 >0,1%

blood

2010 116: 2644-2650
Prepublished online June 30, 2010;
doi:10.1182/blood-2010-03-273532

Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with *mixed-lineage-leukemia* (*MLL*) –rearranged acute lymphoblastic leukemia: results from the Interfant-99 Study

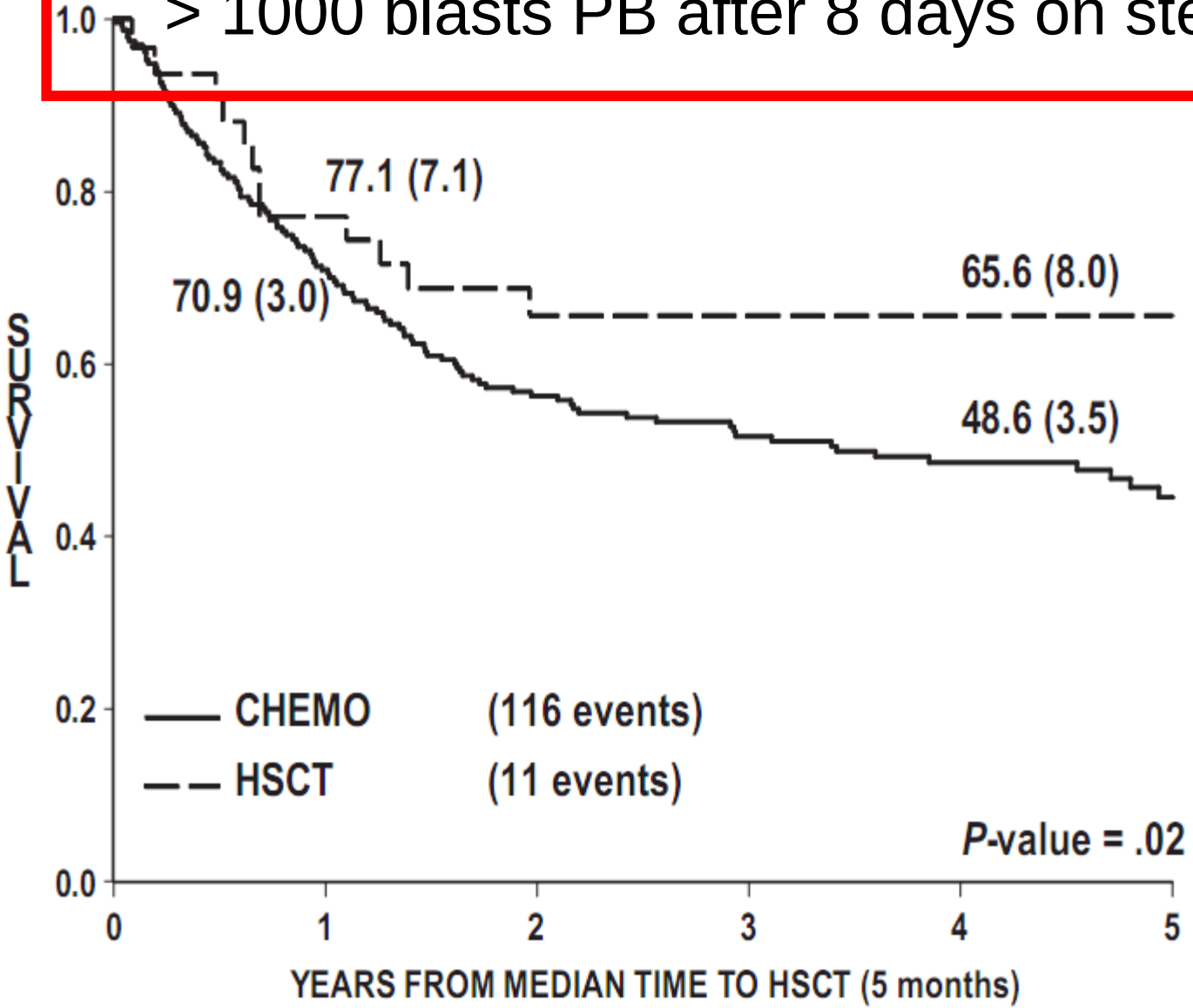
Georg Mann, Andishe Attarbaschi, Martin Schrappe, Paola De Lorenzo, Christina Peters, Ian Hann, Giulio De Rossi, Maria Felice, Birgitte Lausen, Thierry LeBlanc, Tomasz Szczepanski, Alina Ferster, Gritta Janka-Schaub, Jeffrey Rubnitz, Lewis B. Silverman, Jan Stary, Myriam Campbell, Chi Kong Li, Ram Suppiah, Andrea Biondi, Ajay Vora, Maria Grazia Valsecchi, Rob Pieters and on behalf of the Interfant-99 Study Group


1.0
0.8
0.6
0.4
0.2
0.0
SURVIVAL
82.0 (3.0)
74.9 (9.7)
QT N = 170
65.2 (10.6)
TMO N = 11
60.8 (4.1)
CHEMO (63 events)
HSCT (7 events)
P-value = .32
0
1
2
3
4
5
YEARS FROM MEDIAN TIME TO HSCT (5 months)
At risk
CHEMO 170 129 103 81 59 34
HSCT 11 17 12 11 9 4

MLL+ and age < 6 months and :

> 300.000 leukocytes at diagnosis or

> 1000 blasts PB after 8 days on steroids



Pediatric Acute Lymphoblastic Leukemia

- Autologous transplants are not indicated
- Allogeneic transplants:
  - ✓Third remission
  - ✓Second remission
  - – First remission
    - ~~t(9;22)~~
    - ? hypodiploid (<44) chromosome number
    - ✓Induction failure (M2/3 marrow on D29)
    - 11q23
    - Minimal Residual Disease D29 >0,1%

D+78

blood

2010 115: 3206-3214
Prepublished online February 12, 2010;
doi:10.1182/blood-2009-10-248146

Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study

Valentino Conter, Claus R. Bartram, Maria Grazia Valsecchi, André Schrauder, Renate Panzer-Grümayer, Anja Möricke, Maurizio Aricò, Martin Zimmermann, Georg Mann, Giulio De Rossi, Martin Stanulla, Franco Locatelli, Giuseppe Basso, Felix Niggli, Elena Barisone, Günter Henze, Wolf-Dieter Ludwig, Oskar A. Haas, Giovanni Cazzaniga, Rolf Koehler, Daniela Silvestri, Jutta Bradtke, Rosanna Parasole, Rita Beier, Jacques J. M. van Dongen, Andrea Biondi and Martin Schrappe

blood

2011 118: 2077-2084
Prepublished online June 30, 2011;
doi:10.1182/blood-2011-03-338707

Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study

Martin Schrappe, Maria Grazia Valsecchi, Claus R. Bartram, André Schrauder, Renate Panzer-Grümayer, Anja Möricke, Rosanna Parasole, Martin Zimmermann, Michael Dworzak, Barbara Buldini, Alfred Reiter, Giuseppe Basso, Thomas Klingebiel, Chiara Messina, Richard Ratei, Giovanni Cazzaniga, Rolf Koehler, Franco Locatelli, Beat W. Schäfer, Maurizio Aricò, Karl Welte, Jacques J.M. van Dongen, Helmut Gadner, Andrea Biondi and Valentino Conter

B

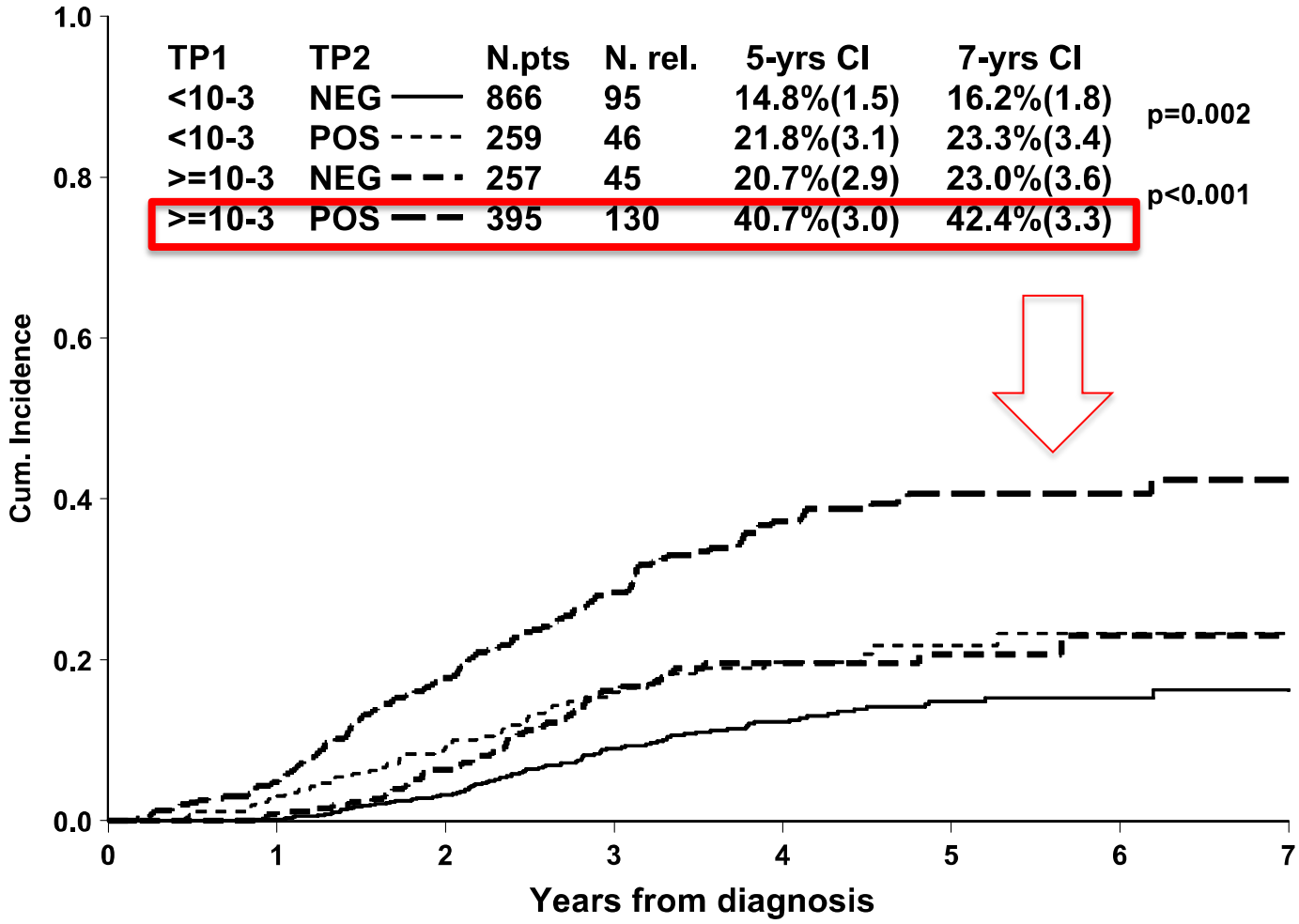


Figure 4. Prognostic value of TP1 and TP2 in 1777 non–MRD-HR patients (ie, patients with MRD < 10^{-3} at TP2) who are MRD positive at TP1.

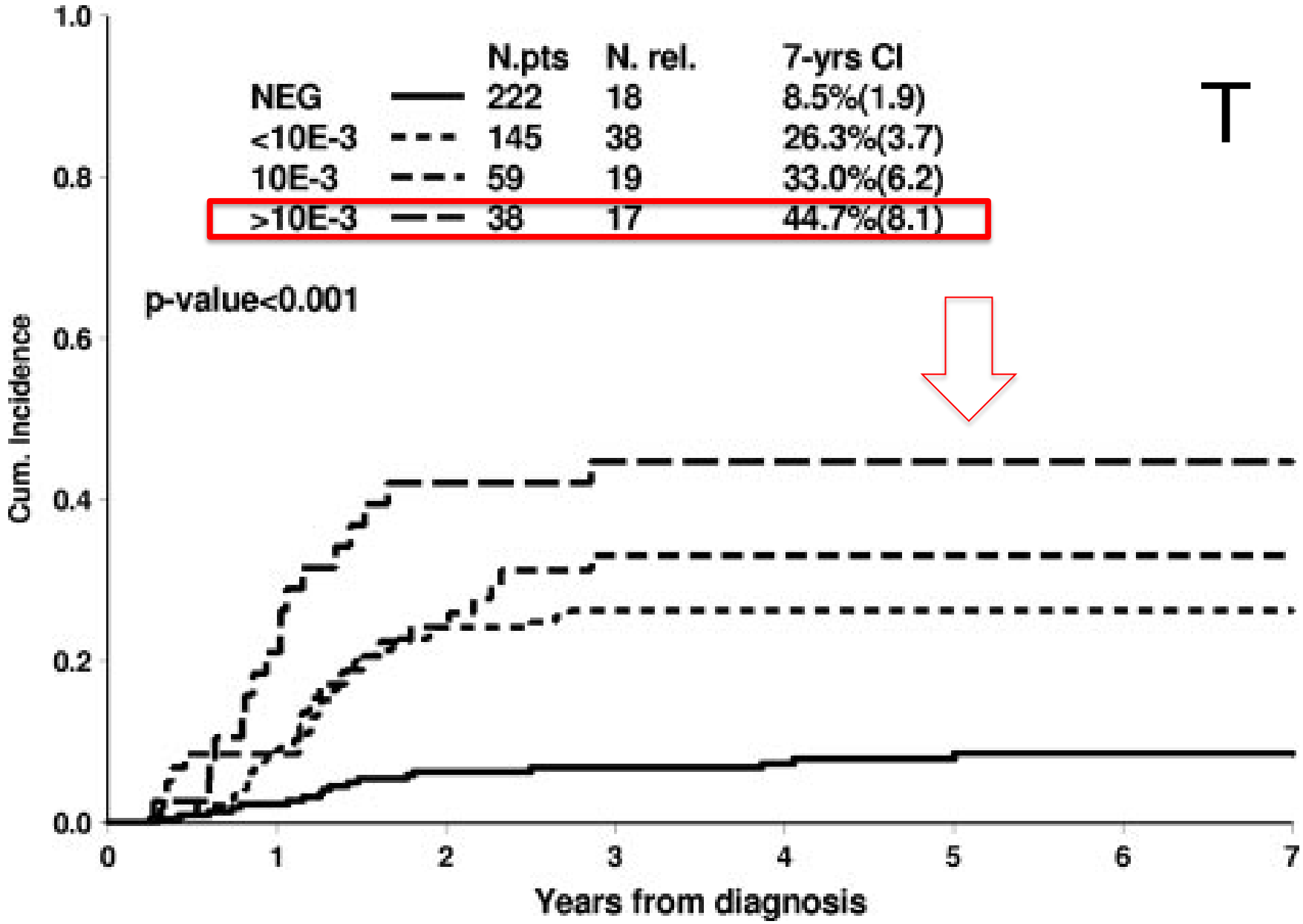
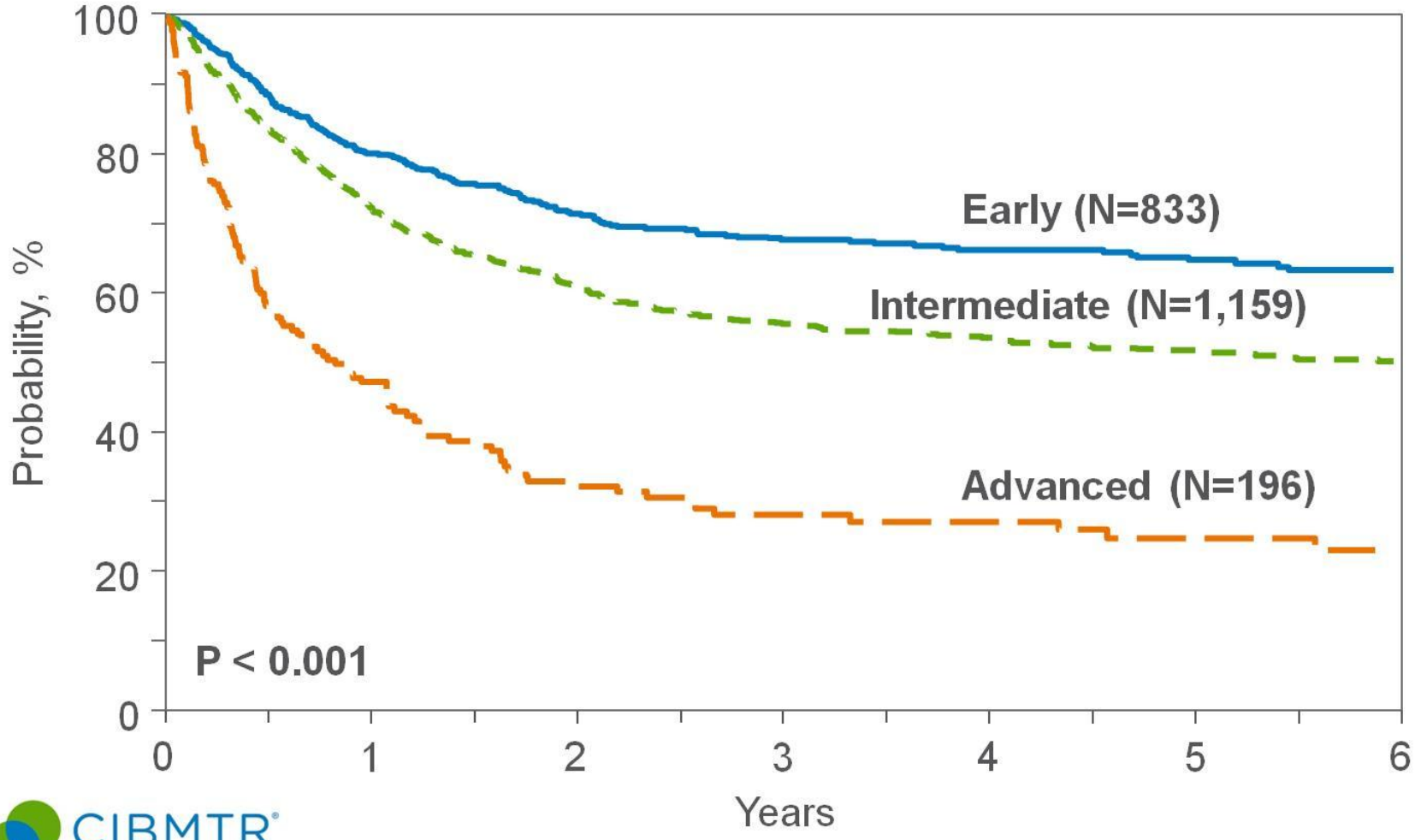


Figure 5. Cumulative incidence of relapse in 464 T-ALL patients by MRD levels at TP2.

Survival after HLA-identical Sibling Donor Transplants for ALL, Age < 20 years, 2001-2011



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By Disease Status

Pediatric Malignant Diseases Treated with Allogeneic Transplantation

- ✓Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Myelodysplastic syndrome
- Chronic myelogenous leukemia
- Lymphomas

Disease	Disease status	Allogeneic matched related
Donor specifics [a,b]		10/10 sibling other 10/10 related other 9/10 related
Stem Cell Source		BM/PBPCs/cord
AML	High risk CR1 [c]	S [c]
	CR≥2 [d]	S
	Relapse/refractory	CO
ALL	High risk CR1 [h]	S [h]
	CR2 [i]	S [i]
	CR3	S
	Relapse/refractory	GNR
CML	Chronic phase	S [j]
	Accelerated phase	S
	Blast crisis	S [k]

Pediatric Acute Lymphoblastic Leukemia

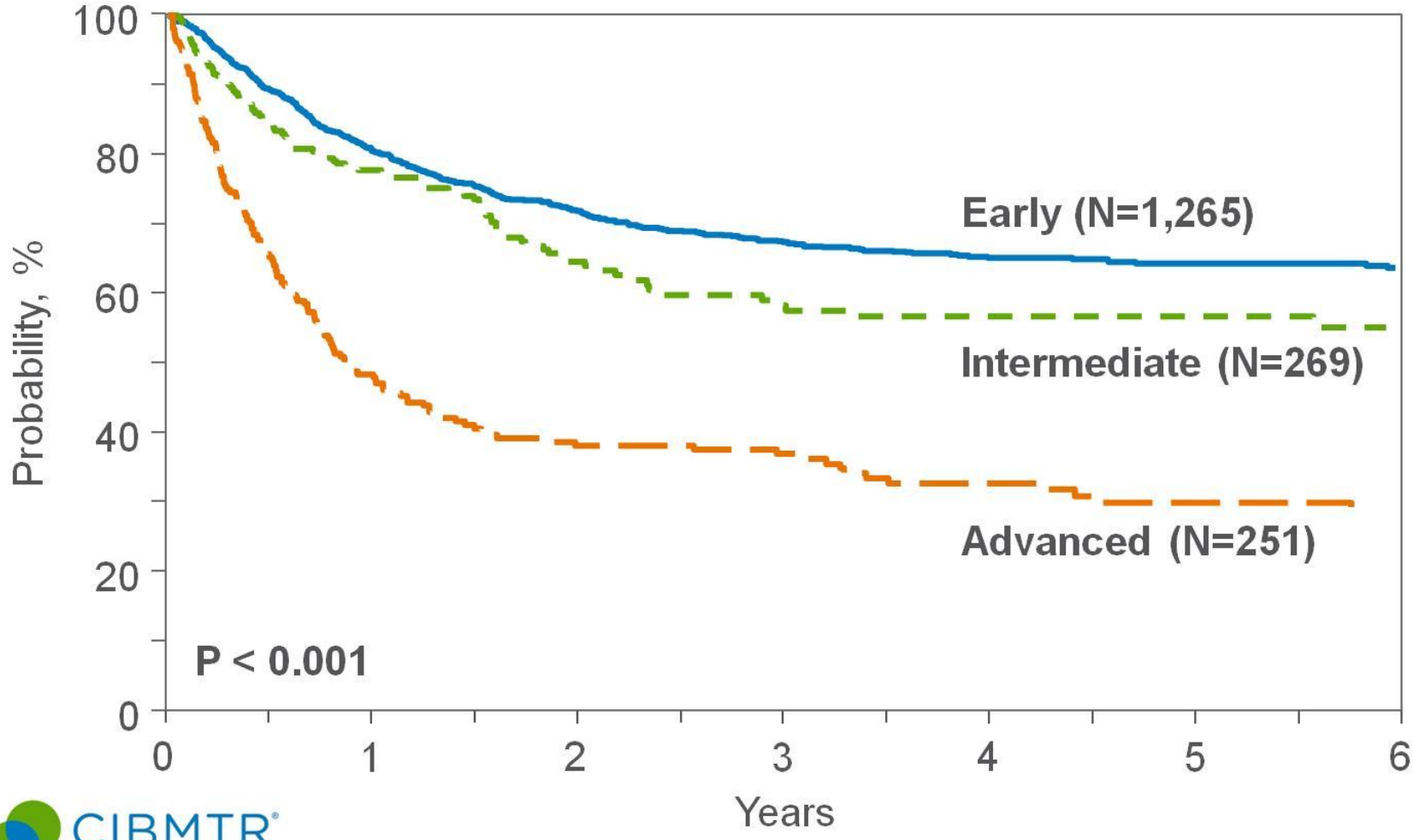
Pediatric leukemia:
Cytogenetics and/or
Molecular markers
Measure response

? hypodiploid (<44) chromosome number

✓Induction failure (M2/3 marrow on D29)

- 11q23
- Minimal Residual Disease D29 >0,1%

Survival after HLA-identical Sibling Donor Transplants for AML, Age < 20 years, 2001-2011



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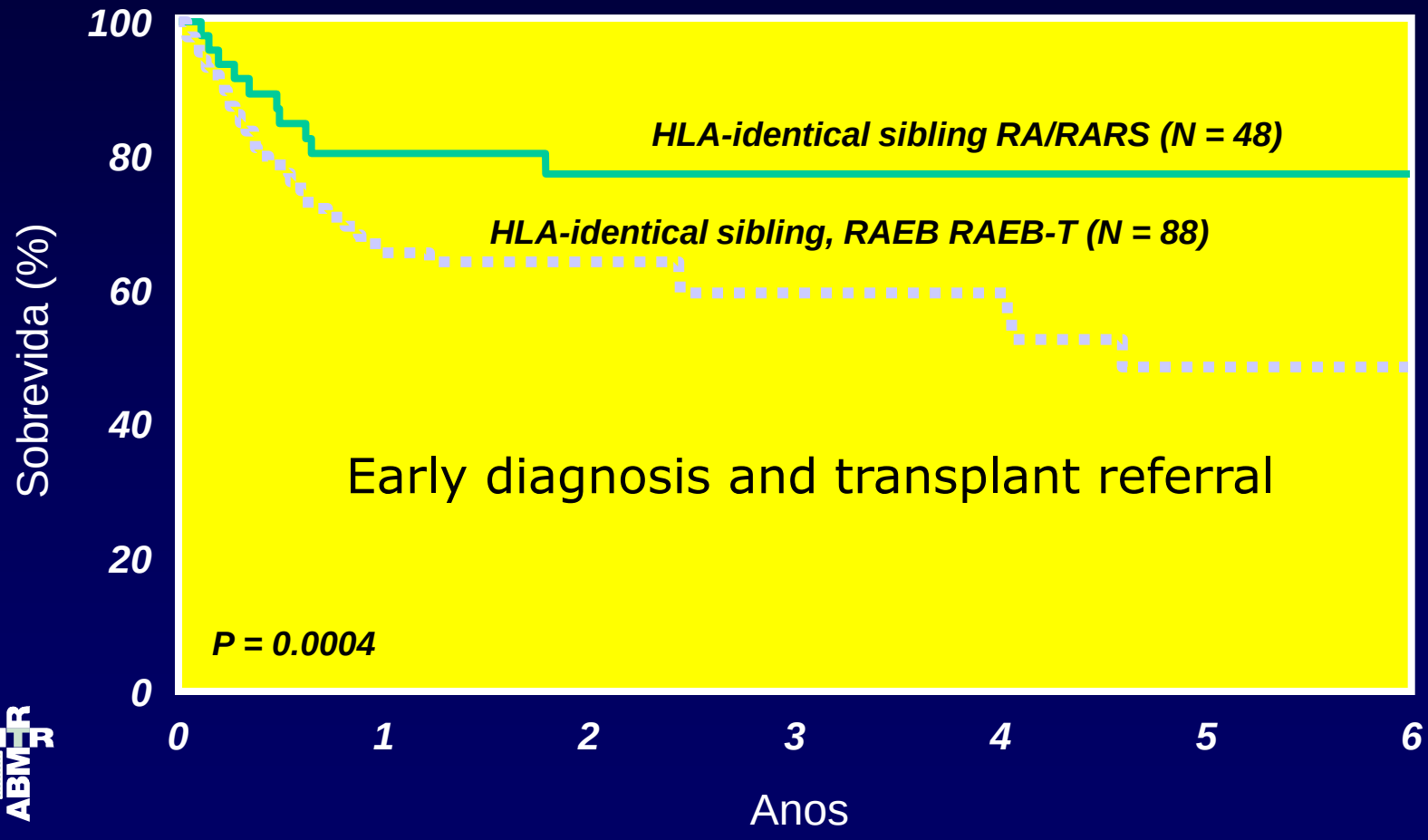
By Disease Status

Pediatric Malignant Diseases Treated with Allogeneic Transplantation

- ✓Acute lymphoblastic leukemia
- ✓Acute myeloid leukemia
- Myelodysplastic syndrome
- Chronic myelogenous leukemia
- Lymphomas

Overall survival after myeloablative transplants for Myelodysplastic Syndrome 1996-2001



http://instruct.mcw.edu/IBMTR/BWebServer/summarysldset/summset2_files/frame.htm IBMTR 2003

Pediatric Malignant Diseases Treated with Allogeneic Transplantation

- ✓Acute lymphoblastic leukemia
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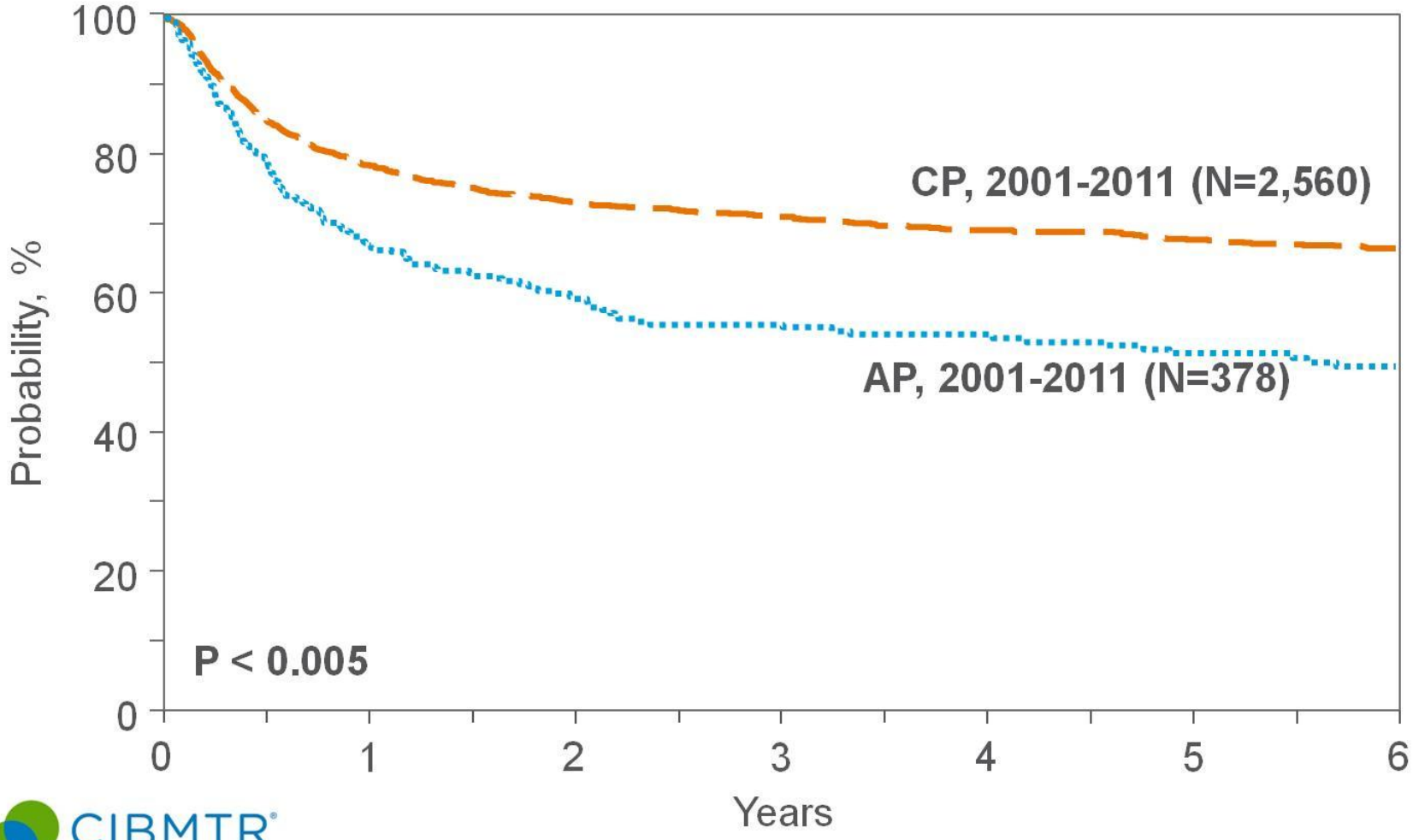
	CR≥2 [d]	S
	Relapse/refractory	CO
ALL	High risk CR1 [h]	S [h]
	CR2 [i]	S [i]
	CR3	S
	Relapse/refractory	GNR
CML	Chronic phase	S [j]
	Accelerated phase	S
	Blast crisis	S [k]

Survival after HLA-identical Sibling Donor Transplants for CML, 2001-2011



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By Disease Status

Stem cell transplantation for chronic myeloid leukemia in children

Kate Cwynarski, Irene A. G. Roberts, Simona Iacobelli, Anja van Biezen, Ronald Brand, Agnes Devergie, Jaak M. Vo
William Arcese, Franco Locatelli, Giorgio Dini, Dietrich Niethammer, Dietger Niederwieser, and Jane F. Apperley, for t
Chronic Leukaemia Working Parties of the European Group for Blood and Marrow Transplantation

- EBMT
- BMT Jan, 1985 - Dec, 2001
- N = 314 children
- Median 14 years
  - 182 MSD; 132 MUD
- Bone Marrow

Cwynarski - Paediatric and Chronic Leukaemia Working Parties of the European Group for Blood and Marrow Transplantation. Blood, 2003; 102 (4):1224

Stem cell transplantation for chronic myeloid leukemia in children

Kate Cwynarski, Irene A. G. Roberts, Simona Iacobelli, Anja van Biezen, Ronald Brand, Agnes Devergie, Jaak M. Vossen, Mahmoud Aljurf, William Arcese, Franco Locatelli, Giorgio Dini, Dietrich Niethammer, Dietger Niederwieser, and Jane F. Apperley, for the Paediatric and

Table 2. HLA-identical sibling recipients

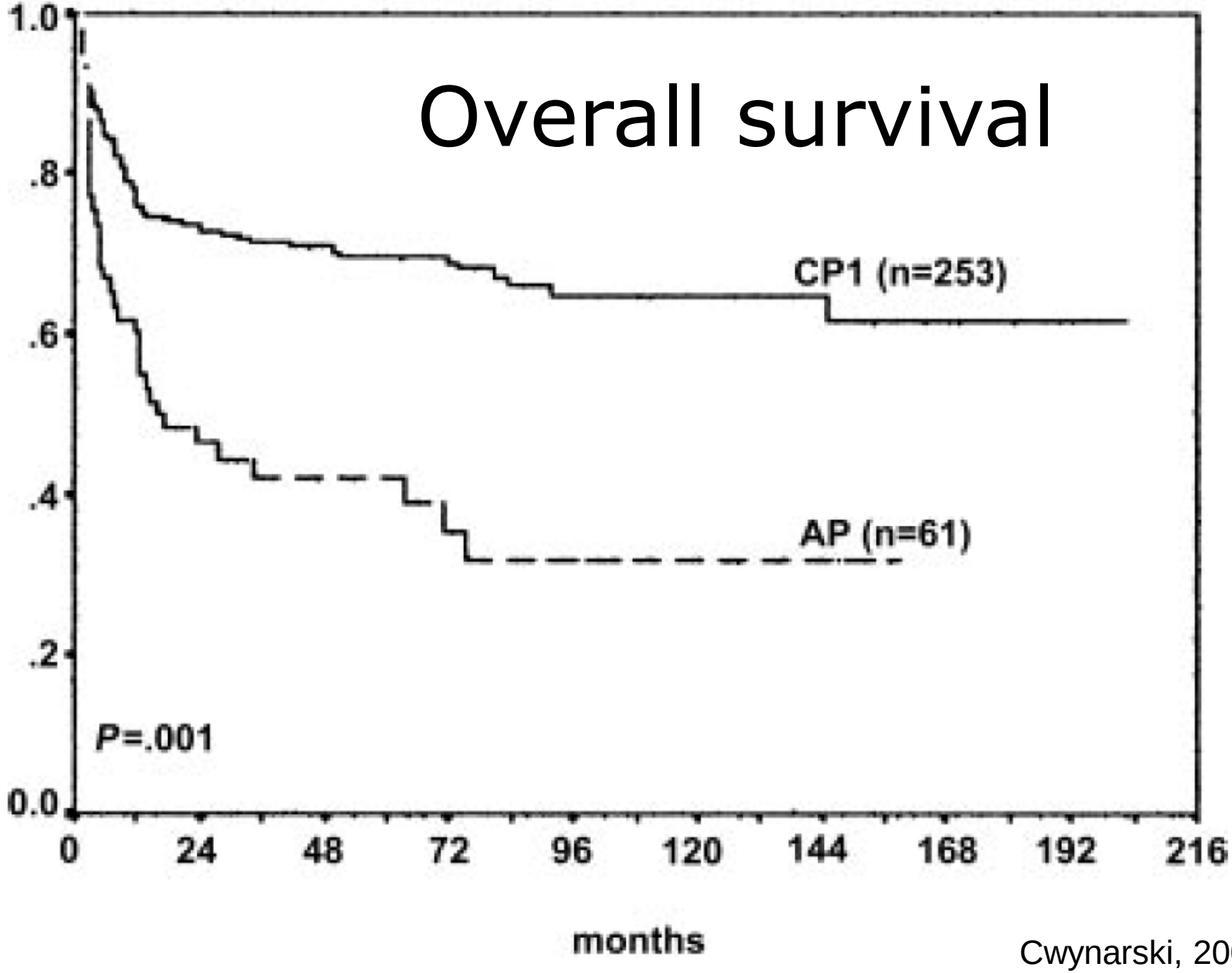
	N, 3y	Survival, %	LFS, %	Relapse, %	TRM, %
Total	100	71	59	21	20
Stage					
CP1	93	75	63	17	20
No CP1	7	46	35	49	16

Table 3. VUD recipients

	N, 3 y	Survival, %	LFS, %	Relapse, %	TRM, %
Total	58	57	50	15	35
Stage					
CP1	47	65	56	13	31
No CP1	11	39	34	20	46

Cwynarski - Paediatric and Chronic Leukaemia Working Parties of the European Group for Blood and Marrow Transplantation. Blood, 2003; 102 (4):1224

Overall survival



Cwynarski, 2003

Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: transplant activity, long-term data and current results. An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT)

Alois Gratwohl

Haematologica 2006; 91:513-521

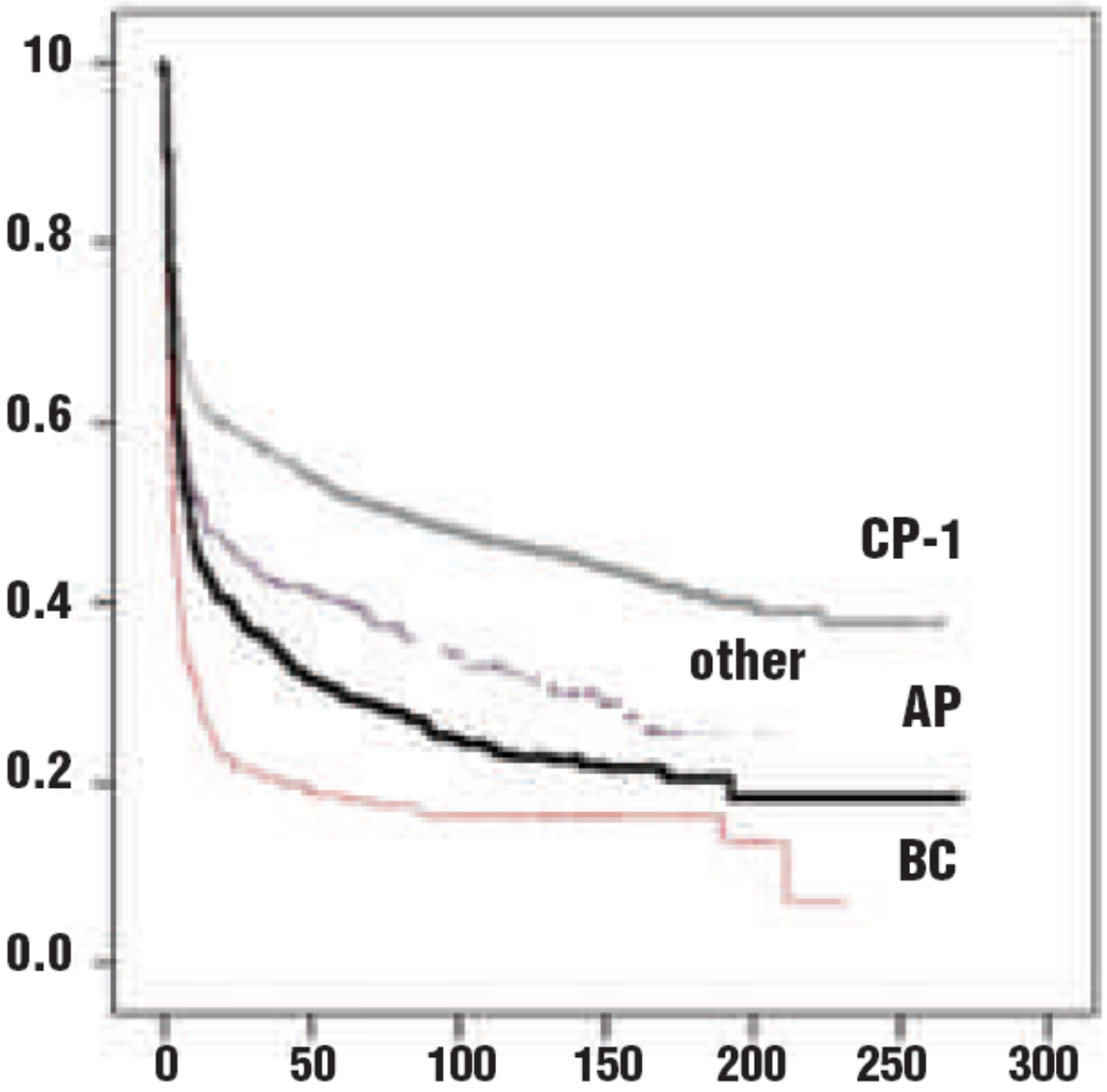


Figure 3. Survival probability of 2,628 patients transplanted between 1980 and 1990

Gratwohl. Haematologica 2006; 91:513

Table 2. Probability of survival and cur
undergoing allogeneic HSCT for CML b

	At Tx N	At 2 years N	SURV	TRM
All patients	2628	1365	50%	–
Donor type				
HLA-id sibling	2238	1228	53%	38%
Twin	40	28	69%	10%
Other	164	56	32%	50%
Unrelated	186	53	27%	58%
Disease stage				
1st chronic phase	1828	1069	57%	–
Accelerated phase	444	175	35%	–
Other				
Blast c				
First cl				
phase				
HLA-id				

	At 15 years N	SURV	TRM	RI
All pt	255	34%	–	–
MSD	241	36%	44%	26%

Gratwohl. Haematologica 2006; 91:513

IBFM-Protocol on Allogeneic Stem Cell Transplantation in Paediatric CML

Study Title:
Allogeneic stem cell transplantation for children and adolescents with CML: Conditioning regimen, donor selection, supportive care and diagnostic procedures.

Short title: CML-SCT

Study coordinator
Univ.Doz. Dr. Susanne Matthes-Martin
Department for Stem Cell Transplantation
St Anna Children's Hospital

Conditioning regimen:

Fludarabine 40 mg/m²/d on 4 days, Melphalan 140 mg/m²/d on 1 day and Thiotepa 2 x 5 mg/kg/d on 1 day + ATG

T-NHL	As per ALL [l]	
Lymphoblastic (non-Burkitt) B-NHL	As per ALL [l]	
ALCL Anaplastic Large Cell Lymphoma	CR2	S [m]
	CR≥3	S
	Refractory	S
Burkitt NHL	CR2	CO
	Refractory	CO

R-ICE: Rituximab + Ifosfamide – Carboplatin – Etoposide

Autologous BMT

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St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder

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How Cure4Kids can Help

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adrianaseber@gmail.com

Grupo de Trabalho de TMO em Pediatria