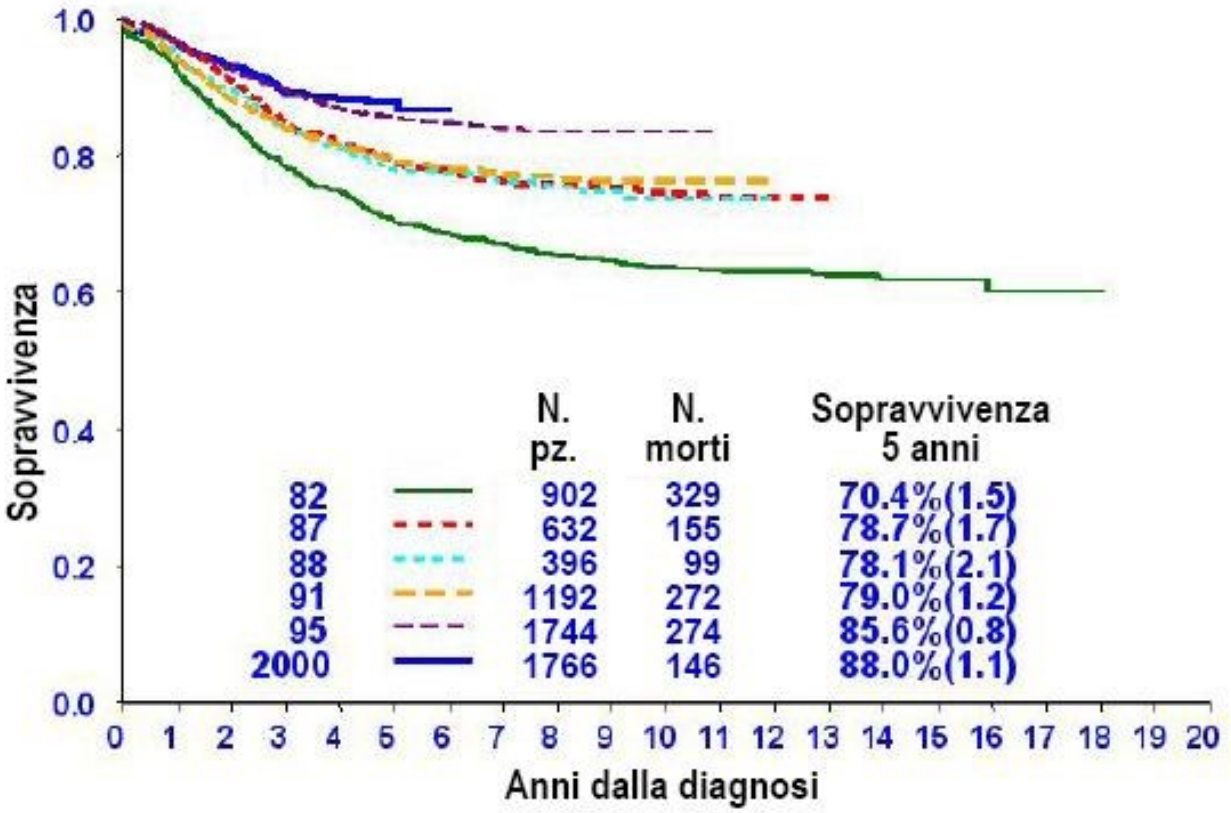
I nuovi farmaci hanno modificato la strategia trapiantologica delle leucemie linfoblastiche acute nel bambino?

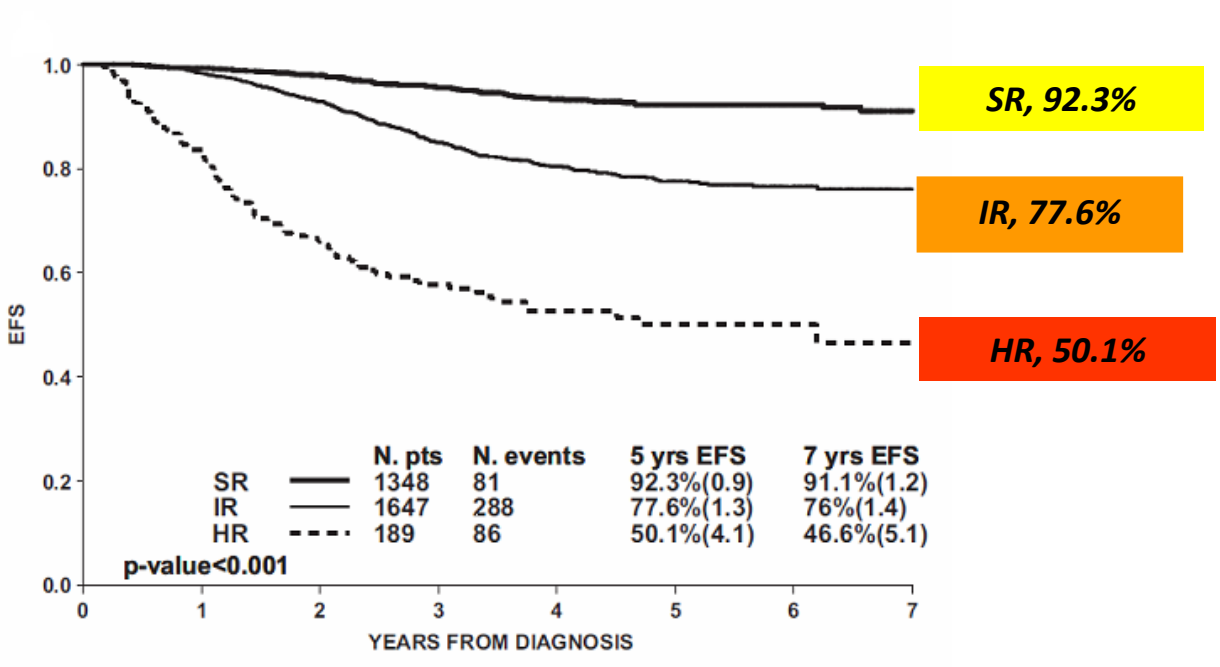
dott. Paola Quarello



INTENSIFICAZIONE DELLA DOSE
TERAPIA DI SUPPORTO
STRATIFICAZIONE DEL RISCHIO

PROTOCOLLO AIEOP LLA 2000

STUDIO COOPERATIVO AIEOP-BFM

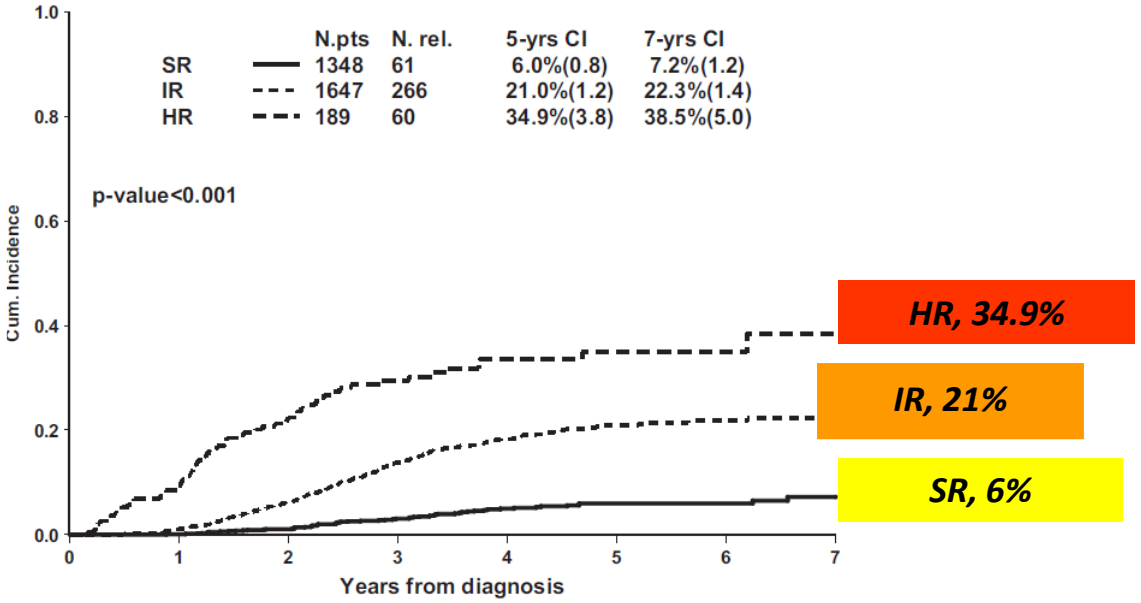


1. PPR
2. no RC gg+33
3. t(9;22) o t(4;11)
4. MRM $\geq 10^{-3}$ alla fine della IB

Conter et al. Blood 2010

PROTOCOLLO AIEOP LLA 2000

STUDIO COOPERATIVO AIEOP-BFM



Conter et al. Blood 2010

Hematopoietic Stem Cell Transplantation For Children With High-Risk Acute Lymphoblastic Leukemia In First Complete Remission: A Report From The AIEOP Registry

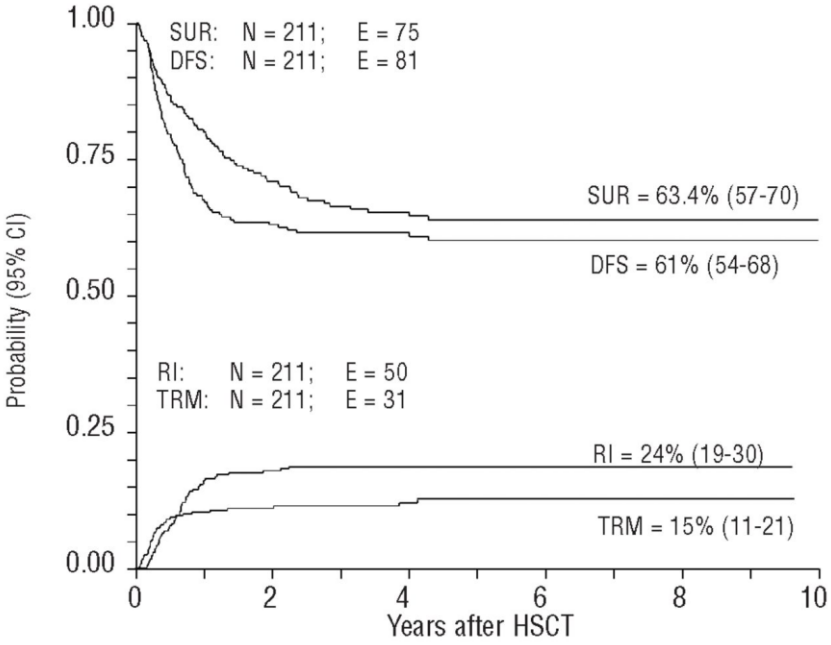
Franca Fagioli, Paola Quarello, Marco Zecca, Edoardo Lanino, Carla Rognoni, Adriana Balduzzi, Chiara Messina, Claudio Favre, Roberto Foà, Mimmo Ripaldi, Sergio Rutella, Giuseppe Basso, Arcangelo Prete, Franco Locatelli

Haematologica August 2013 98: 1273-1281; **Doi:**10.3324/haematol.2012.079707

Table 2. Eligibility criteria for transplantation with a graft from a matched family donor or unrelated donor in high-risk ALL.

AIEOP protocol	HSCT eligibility criteria	
	MFD HSCT	UD HSCT
AIEOP ALL 88	Eligibility criteria not specified	Eligibility criteria not specified
AIEOP ALL 91	Eligibility criteria not specified	Eligibility criteria not specified
AIEOP ALL 95	a. NRd33 b. PPR + T lineage c. PPR + pre-pre B lineage d. PPR + WBC > 100x10⁹/L at diagnosis e. t(9;22) f. t(4;11)	a. NRd33 b. PPR + t(9;22) c. PPR + t(4;11)
AIEOP-BFM ALL 2000	a. NRd33 b. PPR + T lineage c. PPR + pre-pre B lineage d. PPR + WBC > 100x10⁹/L at diagnosis e. t(9;22) f. t(4;11) g. MRD day +33≥10⁻³/L e. MRD day +78≥10⁻³/L	a. NRd33 b. PPR + t(9;22) c. PPR + t(4;11) d. MRD day +78≥10⁻³/L

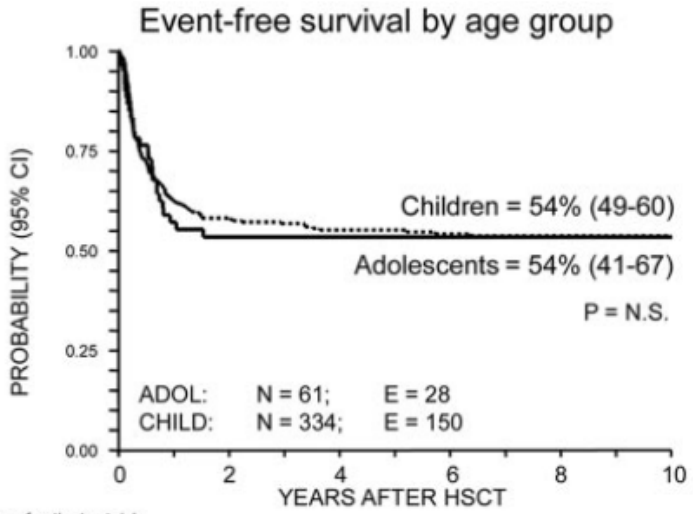
MFD: matched family donor; UD: matched unrelated donor; ALL: acute lymphoblastic leukemia; AIEOP: Associazione Italiana di Ematologia e Oncologia Pediatrica (Italian Association of Pediatric Hematology and Oncology); HSCT: hematopoietic stem cell transplantation; NRd33: non-remission to induction treatment at day +33; PPR: poor prednisone response; WBC: white blood cell count, MRD: minimal residual disease.

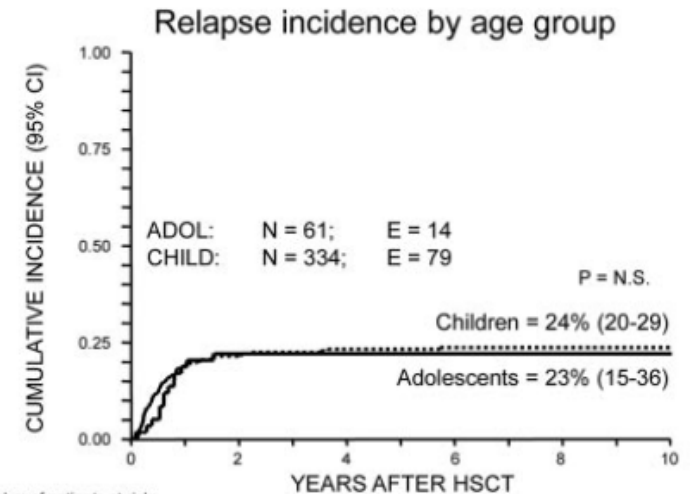


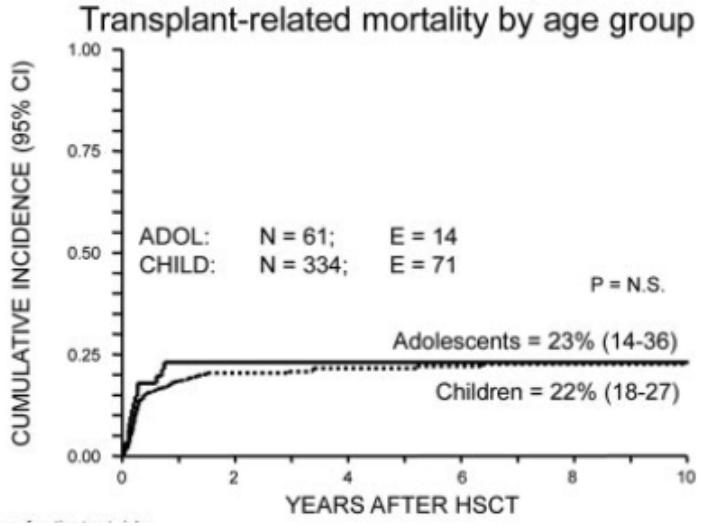
No difference in outcome between children and adolescents transplanted for acute lymphoblastic leukemia in second remission

Giorgio Dini,[1] Marco Zecca,[2] Adriana Balduzzi,[3] Chiara Messina,[4] Riccardo Masetti,[5] Franca Fagioli,[6] Claudio Favre,[7] Marco Rabusin,[8] Fulvio Porta,[9] Erika Biral,[1] Mimmo Ripaldi,[10] Anna Paola Iori,[11] Carla Rognoni,[12] Arcangelo Prete,[5] and Franco Locatelli,[13,14] on behalf of the Associazione Italiana Ematologia ed Oncologia Pediatrica–Hematopoietic Stem Cell Transplantation (AIEOP-HSCT) Group

BLOOD, 15 DECEMBER 2011 • VOLUME 118, NUMBER 25



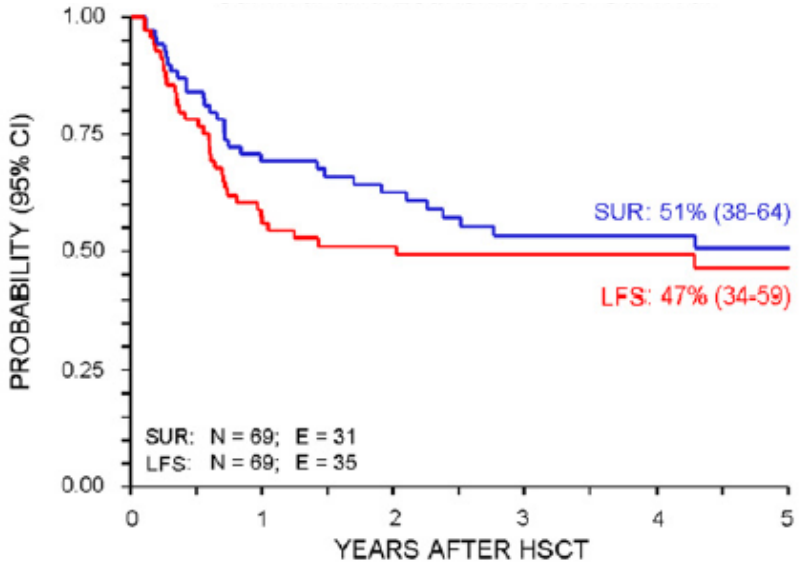


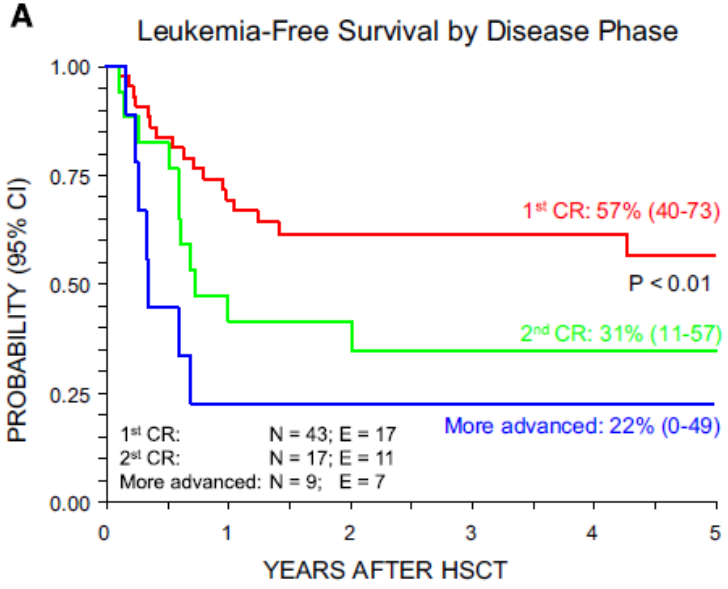


Biol Blood Marrow Transplant 18:852-860, 2012

Allogeneic Hematopoietic Stem Cell Transplantation for Philadelphia-Positive Acute Lymphoblastic Leukemia in Children and Adolescents: A Retrospective Multicenter Study of the Italian Association of Pediatric Hematology and Oncology (AIEOP)

Franca Fagioli,[1] Marco Zecca,[2] Carla Rognoni,[3] Edoardo Lanino,[4] Adriana Balduzzi,[5] Massimo Berger,[1] Chiara Messina,[6] Claudio Favre,[7] Marco Rabusin,[8] Luca Lo Nigro,[9] Riccardo Masetti,[10] Arcangelo Prete,[10] Franco Locatelli,[11] on behalf of the AIEOP-HSCT Group





INDICAZIONI TRAPIANTO CELLULE STAMINALI EMOPOIETICHE

PROTOCOLLO DI DIAGNOSI E TERAPIA DELLA

LEUCEMIA LINFOBLASTICA ACUTA

IN ETA' PEDIATRICA

SPONSOR:

University Hospital Schleswig-Holstein, Campus Kiel,
Brunswiker Str. 10, 24105 Kiel, Germany

AIEOP-BFM ALL 2009

Studio cooperativo internazionale AIEOP-BFM per il trattamento

di bambini ed adolescenti affetti da Leucemia Linfoblastica Acuta

EudraCT Number AIEOP-BFM ALL 2009: 2007-004270-43

Responsabile del Protocollo: Valentino Conter

Coordinatore Comitato Scientifico AIEOP LLA: Giuseppe Masera

Apertura al reclutamento: 01.06.2010

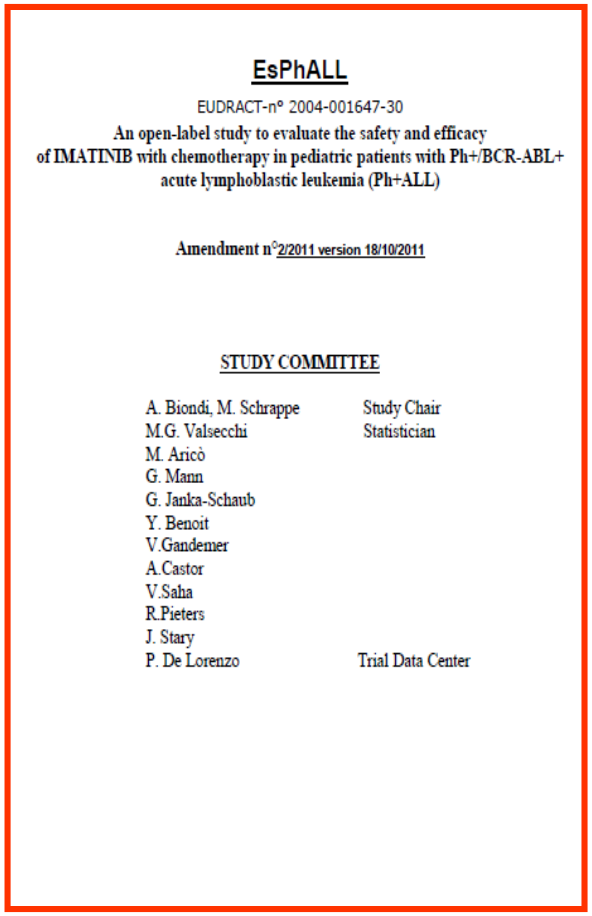
Co- Sponsor:
Associazione Italiana Ematologia Oncologia Pediatrica,
Centro Operativo c/o Policlinico Sant'Orsola Malpighi
Oncologia ed Ematologia Pediatrica "Lalla Seràgnoli",
Clinica Pediatrica Via Massarenti 11, 40138 Bologna, Italy

Coordinatore nazionale dello Studio (in rappresentanza dello sponsor):
Dr. Valentino Conter,
Clinica Pediatrica dell'Università degli Studi di Milano-Bicocca,
Ospedale S. Gerardo, via Pergolesi 33
20052, Monza (MI), Italia
Tel: +39 039 2333513, Fax: +39 039 2301646, Email: v.conter@hsgerardo.org

indicazioni ad alloHSCT		Risultati PCR-MRD [a]				
		MRD-SR	MRD-MR[b]	MRD-HR		no risultati MRD
				MRD TP2 $\geq 10^{-3}$ - $<10^{-2}$	MRD TP2 $\geq 10^{-2}$	
criteri (ordine gerarchico)	No CR g+33	no[f]	MMD	MMD	MMD	MMD
	t(4;11)[c]	no	MD	MD	MMD	MD
	ipodiploidia < 44 cromosomi[d]	no	MD	MD	MMD	MD
	PPR + T-LLA	no	no	MD	MMD	MD
	nessuna delle caratteristiche di cui sopra[e]	no	no	MD	MMD	no

no alloHSCT non indicato
MD donatore consentito: HLA-compatibile familiare o non-familiare
MMD donatore consentito: HLA-compatibile o HLA-mismatched
[a] i risultati di FCM-MRD non hanno impatto sulle indicazioni ad alloHSCT
[b] inclusi MRD-MR SER (MRD TP1 $\geq 10^{-3}$ and TP2 $10^{-4/-5}$)
[c] indipendente dalla risposta al prednisone
[d] il riscontro esattamente di 44 cromosomi qualifica per il trattamento HR ma non è indicazione ad alloHSCT
[e] inclusi pazienti con 44 cromosomi
[f] la non-remissione nei pazienti con questa rara combinazione dovrebbe essere dovuta alla presenza di malattia extramidollare. In questi casi, l' indicazione a trapianto dovrebbe essere discussa con il coordinatore nazionale.

INDICAZIONI TRAPIANTO CELLULE STAMINALI EMOPOIETICHE



EsPhALL

EUDRACT-n° 2004-001647-30

An open-label study to evaluate the safety and efficacy of IMATINIB with chemotherapy in pediatric patients with Ph+/BCR-ABL+ acute lymphoblastic leukemia (Ph+ALL)

Amendment n°2/2011 version 18/10/2011

STUDY COMMITTEE

A. Biondi, M. Schrappe	Study Chair
M.G. Valsecchi	Statistician
M. Aricò	
G. Mann	
G. Janka-Schaub	
Y. Benoit	
V.Gandemer	
A.Castor	
V.Saha	
R.Pieters	
J. Stary	
P. De Lorenzo	Trial Data Center

GOOD RISK

1. GPR
2. M1/M2 gg + 15
3. RC post induzione

Donatore HLA identico (9/10 o 10/10)

POOR RISK

1. PPR
2. M3 gg + 15
3. No RC post induzione

Donatore familiare/non familiare Matched/Mismatched/Aplo

AIEOP LLA REC 2003

PROTOCOLLO PER IL TRATTAMENTO DELLA PRIMA RECIDIVA DI LEUCEMIA LINFOBLASTICA ACUTA Ph neg

Coordinatori: V. Conter, F. Locatelli

Gruppo di Lavoro: M. Aricò, C. De Fusco, F. Fagioli C. Favre, M. Luciani, C. Messina A. Pession, P. Pierani, A.M. Testi, M. Zecca, R. Chiesa

Consulenti: A. Biondi, G. Basso, M. D'Incalci C. Rizzari, P. Indolfi, E. Castagnola, M. Jankovic, G. Cazzaniga, S. Songia G. Germano, L. Del Giudice

Analisi Statistica: R. Rondelli, M. Zecca

Approvato dal CSS LLA – Responsabile: G. Masera

S1 EM >= 6 m da OT

S2 EM < 18 m da dgn o 18m da dgn o < 6 m da OT, BM >= 6 m da OT, BM + EM non T

S3 BM >= 18 m da dgn o < 6 m da OT non T

S4 BM < 18 m da dgn o BM + EM < 18 m da dgn, BM-T

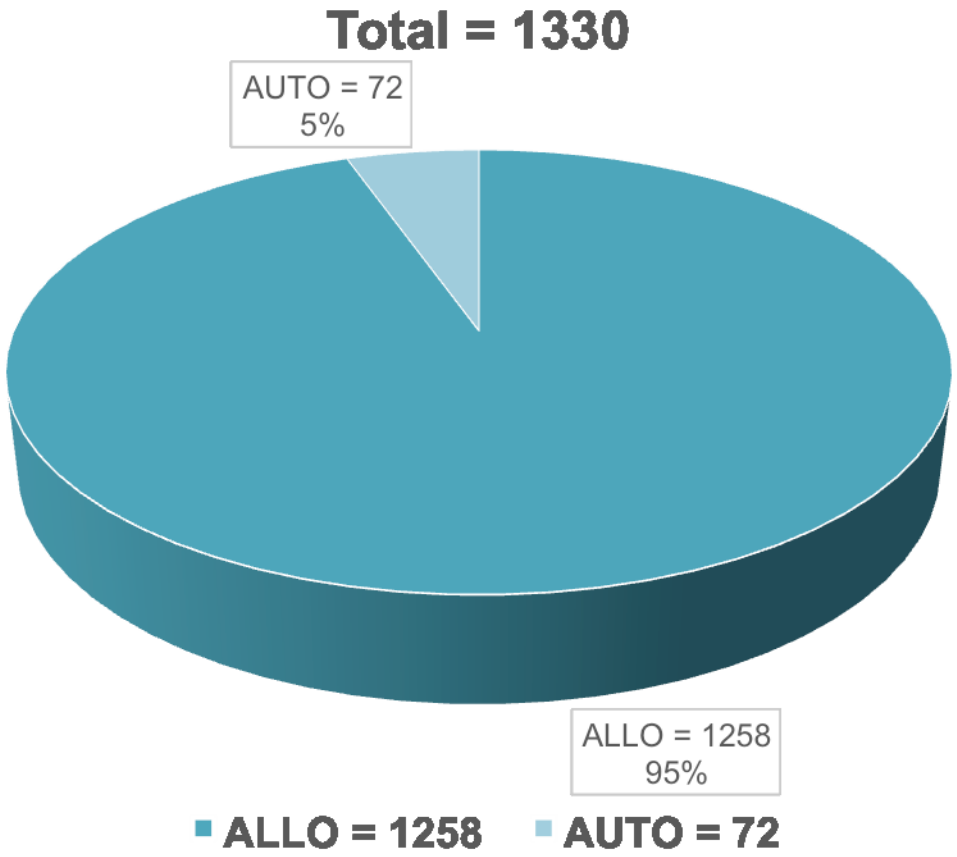
S2

1. Donatore familiare -> tutti
2. Donatore non familiare HLA identico -> tutti tranne ricaduta > 48 m con MRD bassa

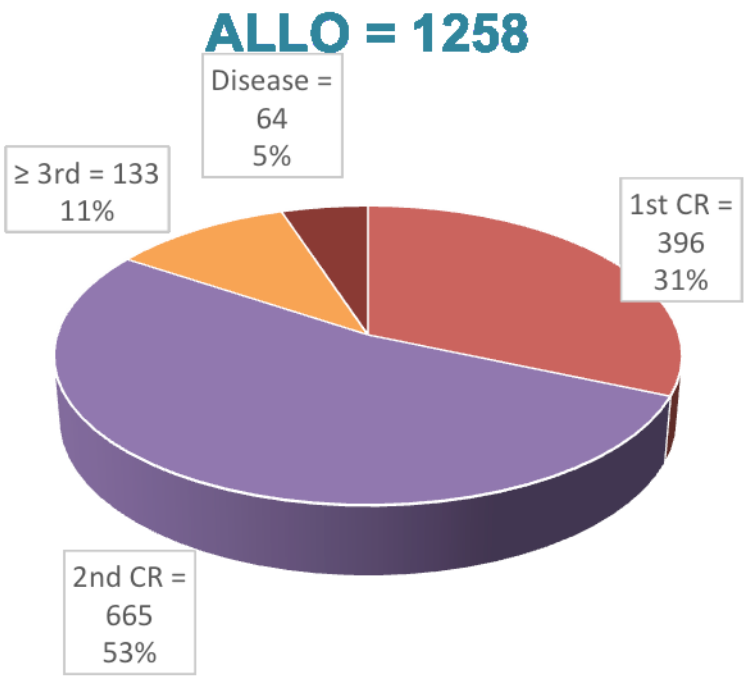
S3-S4

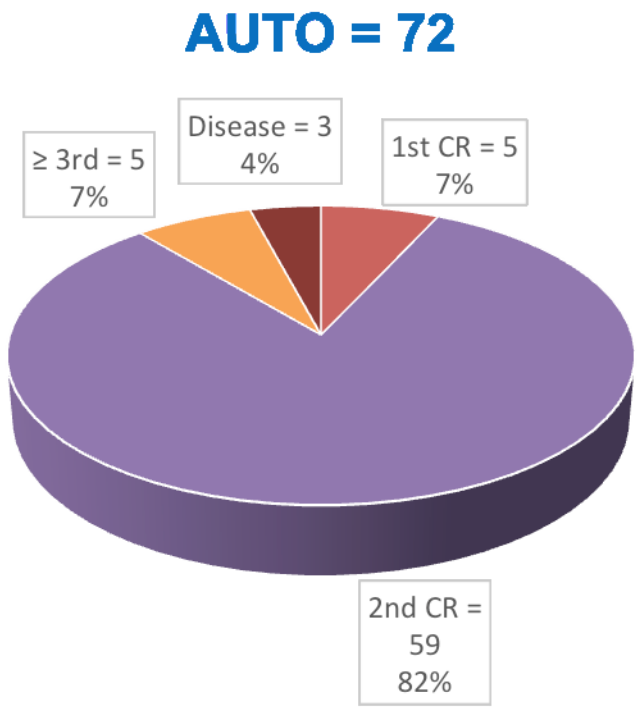
1. Qualsiasi tipo di donatore

Acute Lymphoblastic Leukemia
Age 1 – 18 years
Number of patients transplanted 2000 - 2014



Acute Lymphoblastic Leukemia
Age 1 – 18 years
Number of patients transplanted 2000 - 2014

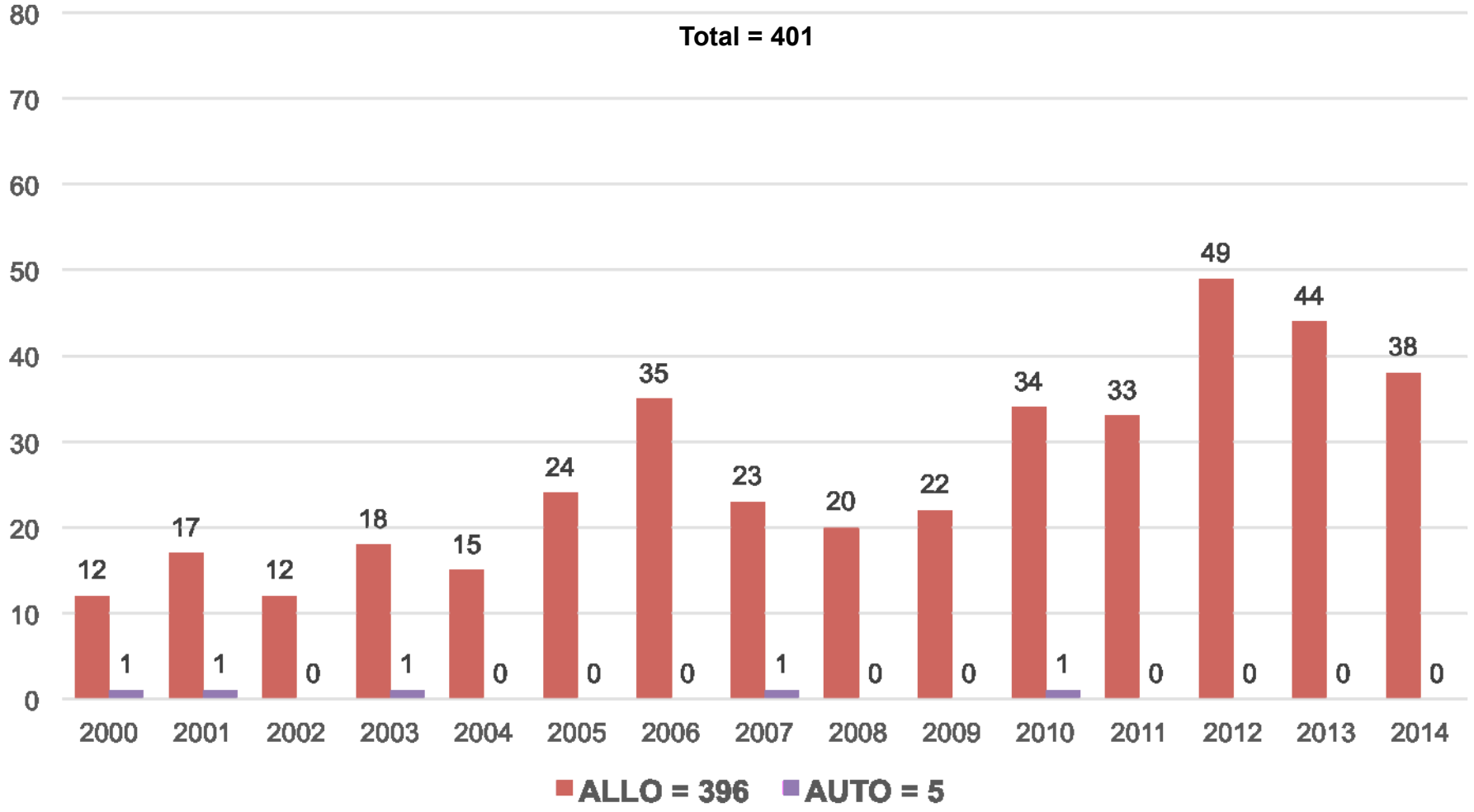




Acute Lymphoblastic Leukemia

Age 1 – 18 years

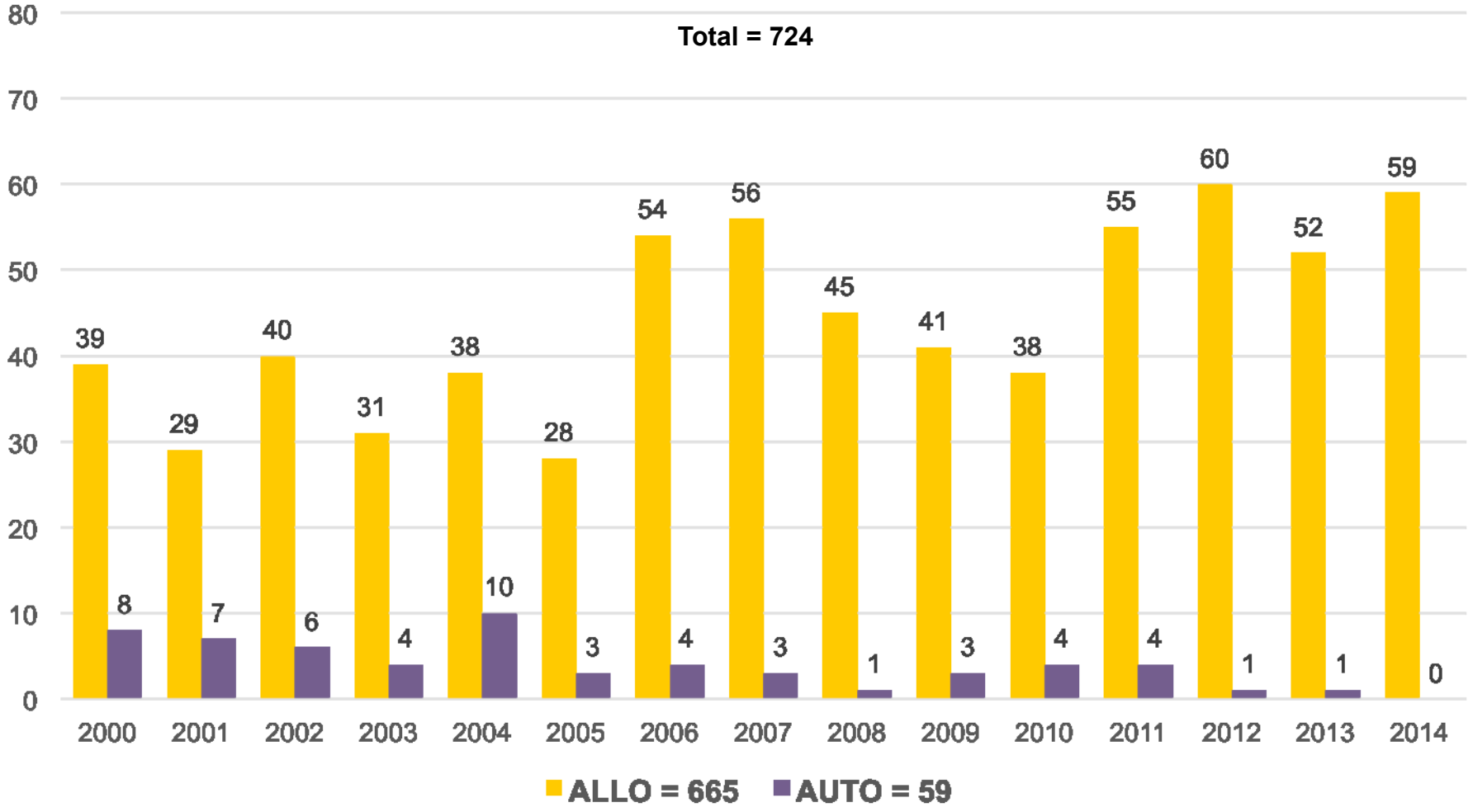
Number of patients transplanted in 1st CR per year



Acute Lymphoblastic Leukemia

Age 1 – 18 years

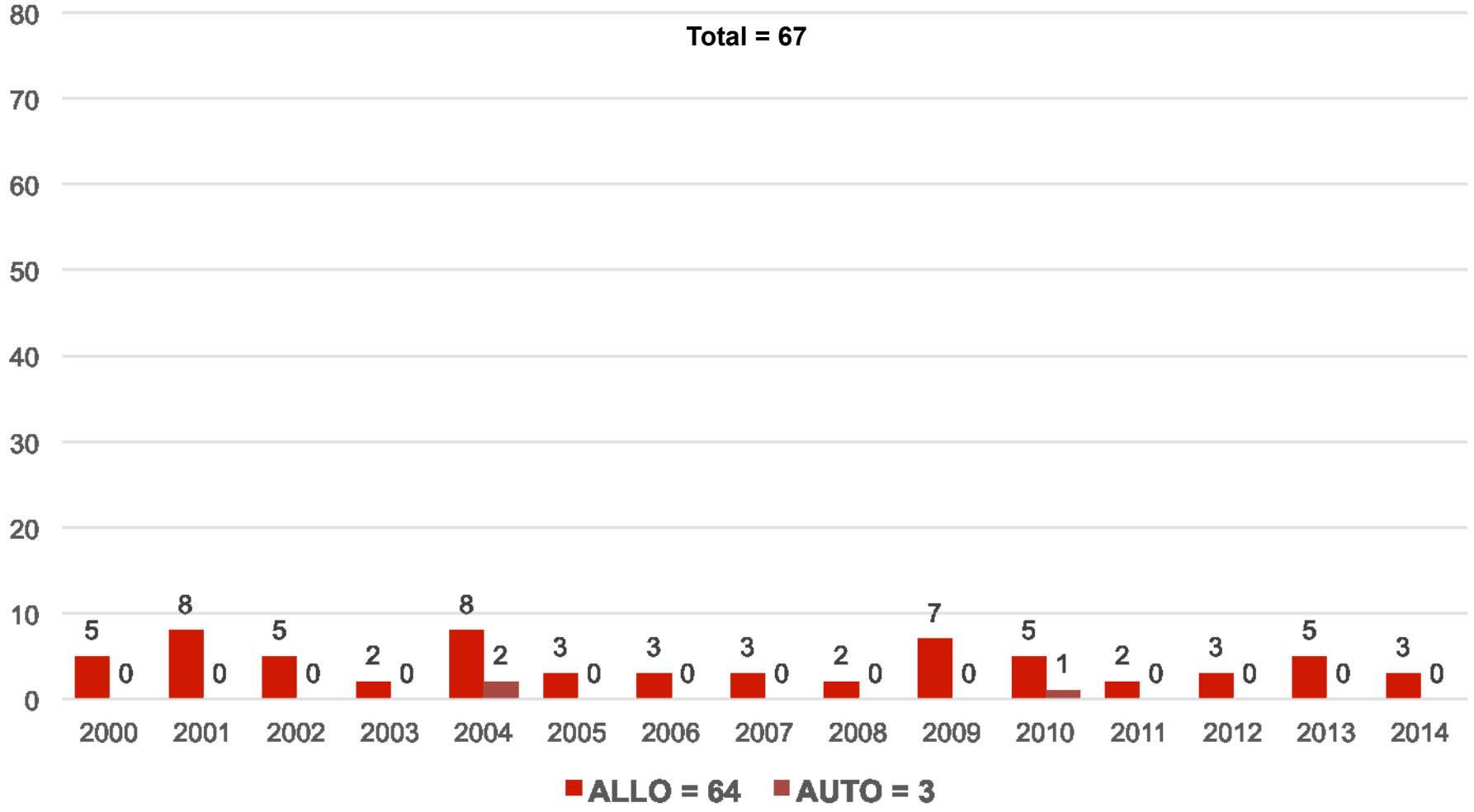
Number of patients transplanted in 2nd CR per year



Acute Lymphoblastic Leukemia

Age 1 – 18 years

Number of patients transplanted with disease per year

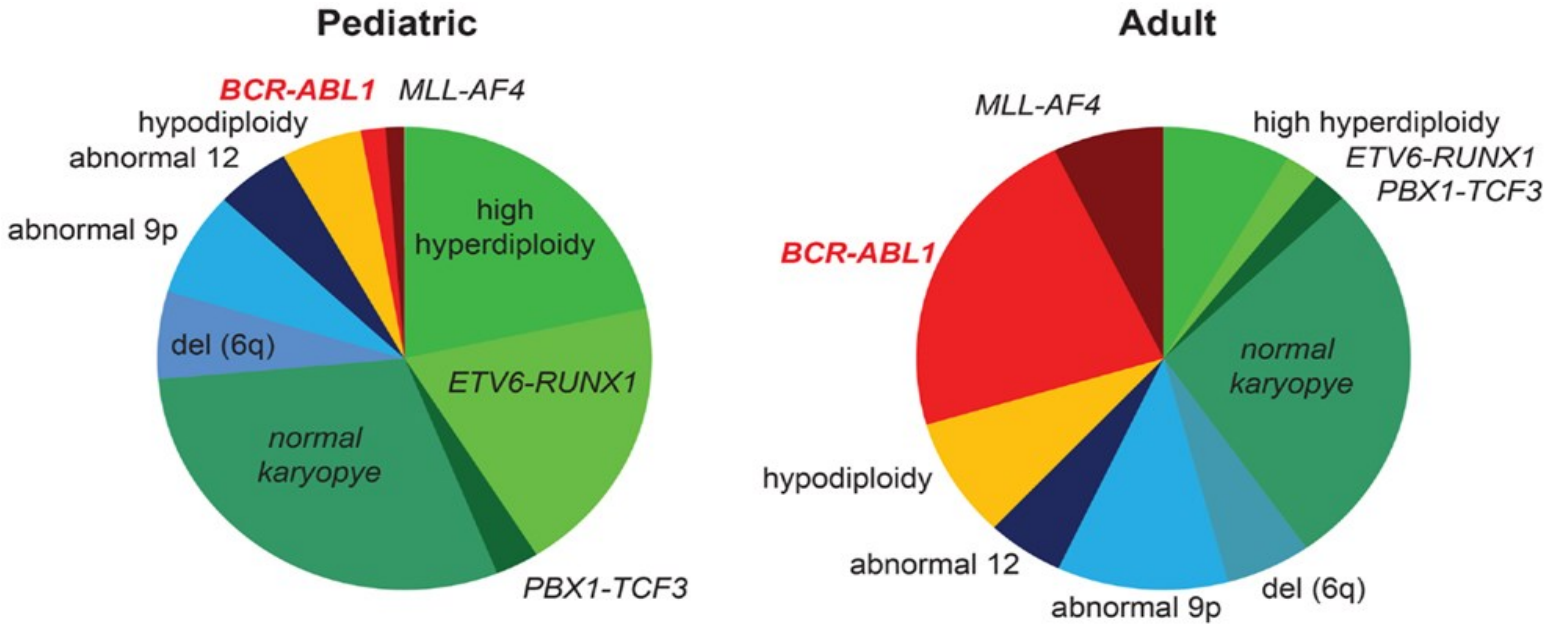


I nuovi farmaci hanno modificato la strategia trapiantologica delle leucemie linfoblastiche acute nel bambino?

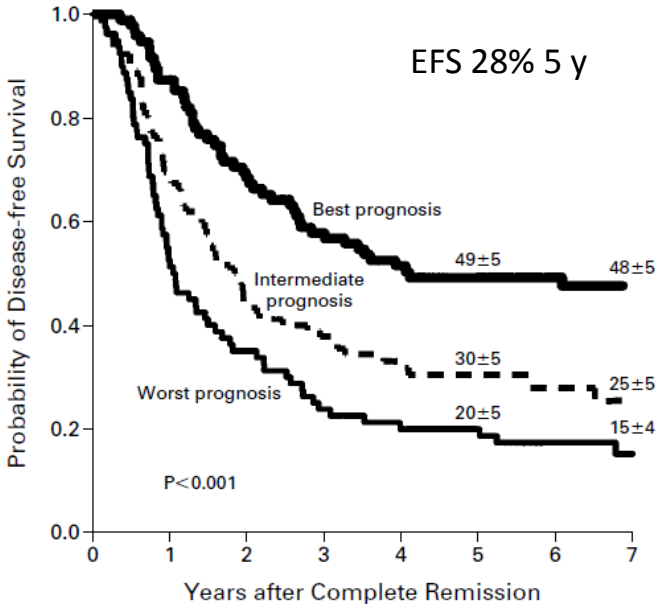
Ridurre l'utilizzo della procedura trapiantologica

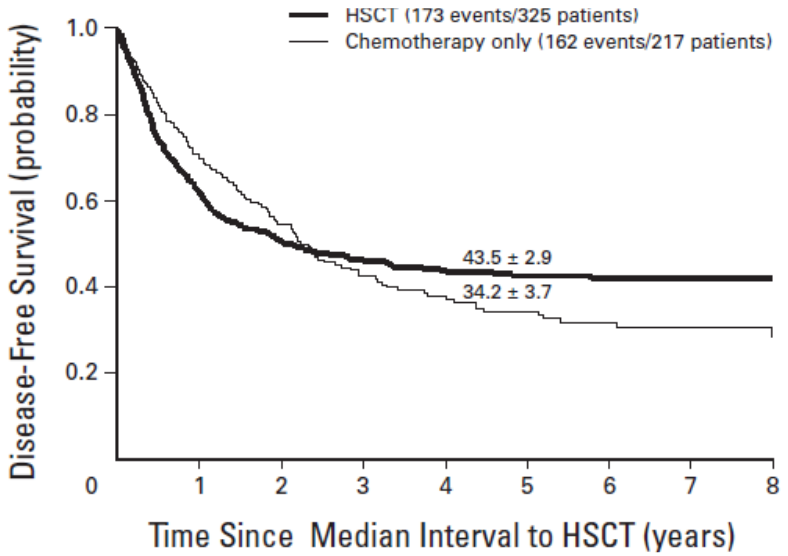
Rendere accessibile la procedura trapiantologica

LLA Ph+


Pediatric
BCR-ABL1
MLL-AF4
hypodiploidy
abnormal 12
abnormal 9p
high hyperdiploidy
del (6q)
ETV6-RUNX1
normal karyopye
PBX1-TCF3
Adult
MLL-AF4
high hyperdiploidy
ETV6-RUNX1
PBX1-TCF3
BCR-ABL1
normal karyopye
hypodiploidy
abnormal 12
abnormal 9p
del (6q)

Pre-TKI





326 pt, dgn 1986-1996

Best prognosis ≤ 10 y, WBC dgn ≤ 50000/mmc

Worst prognosis WBC dgn > 100000/mmc

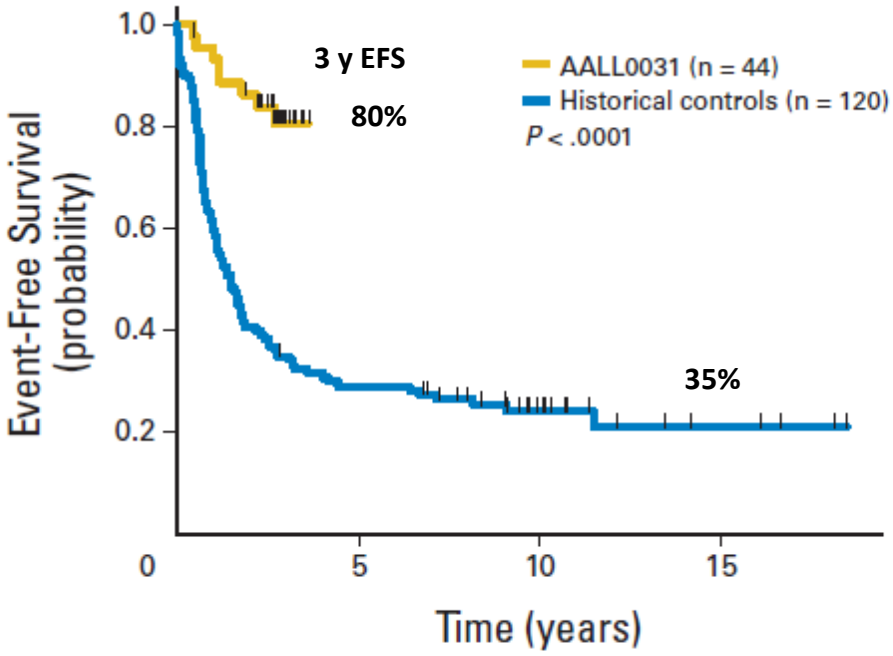
Aricò et al. NEJM 2000

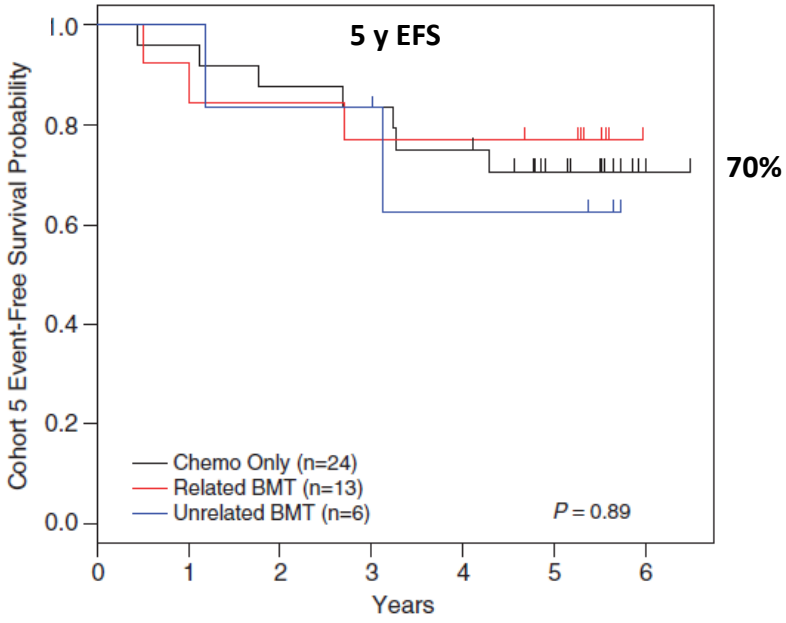
610 pt, dgn 1995-2005

Aricò et al. JCO 2010

CHILDREN'S ONCOLOGY GROUP

AALL0031





44 pt

25 CT + Imatinib 280 days

13 CT + Imatinib 280 days + HSCT SIB

6 CT + Imatinib 280 days + HSCT NON SIB

dgn 2002-2006

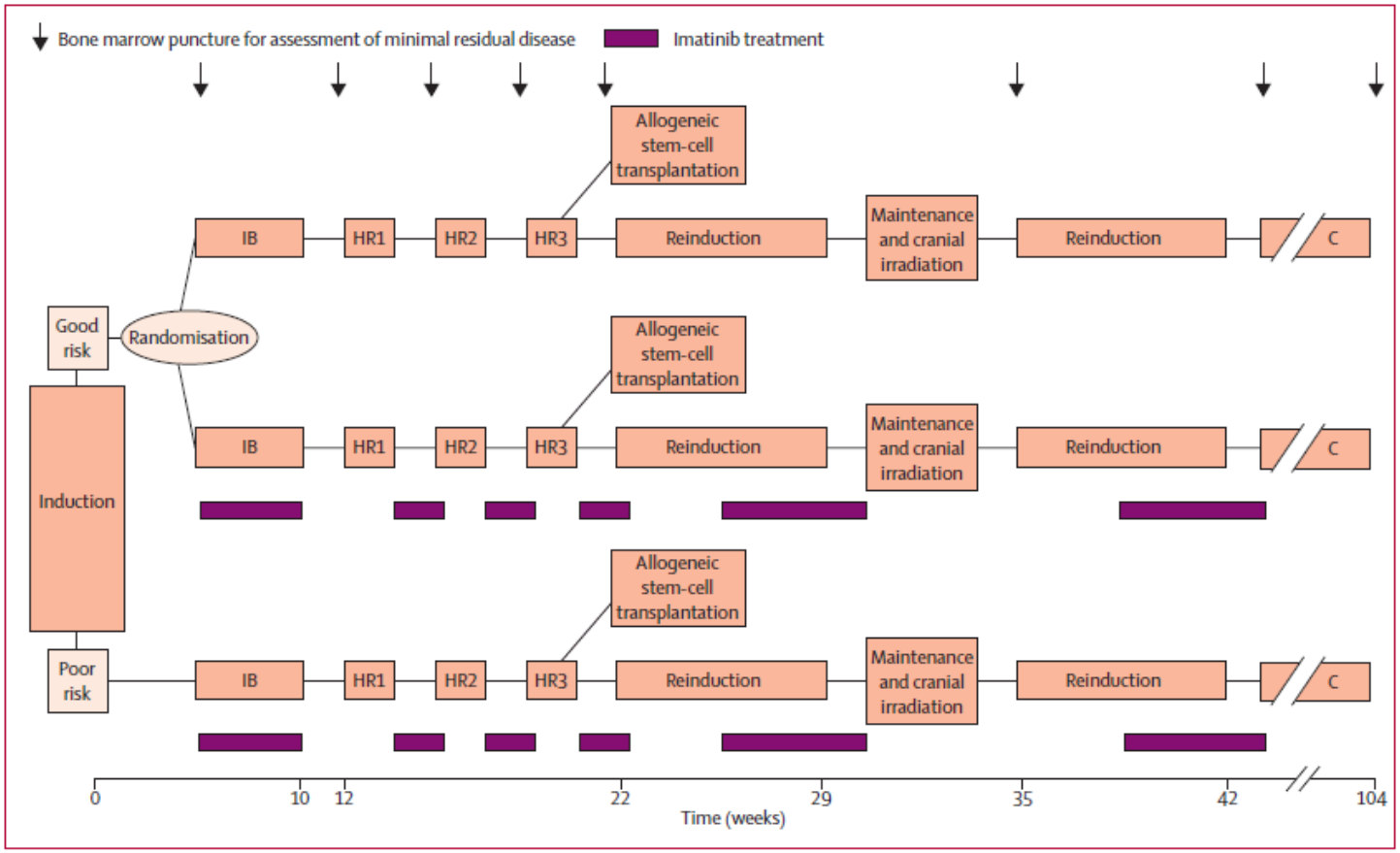
Esclusione di pts con induction failure

MRD no ruolo su outcome

Schultz et al. JCO 2009

Schultz et al. Leukemia 2014

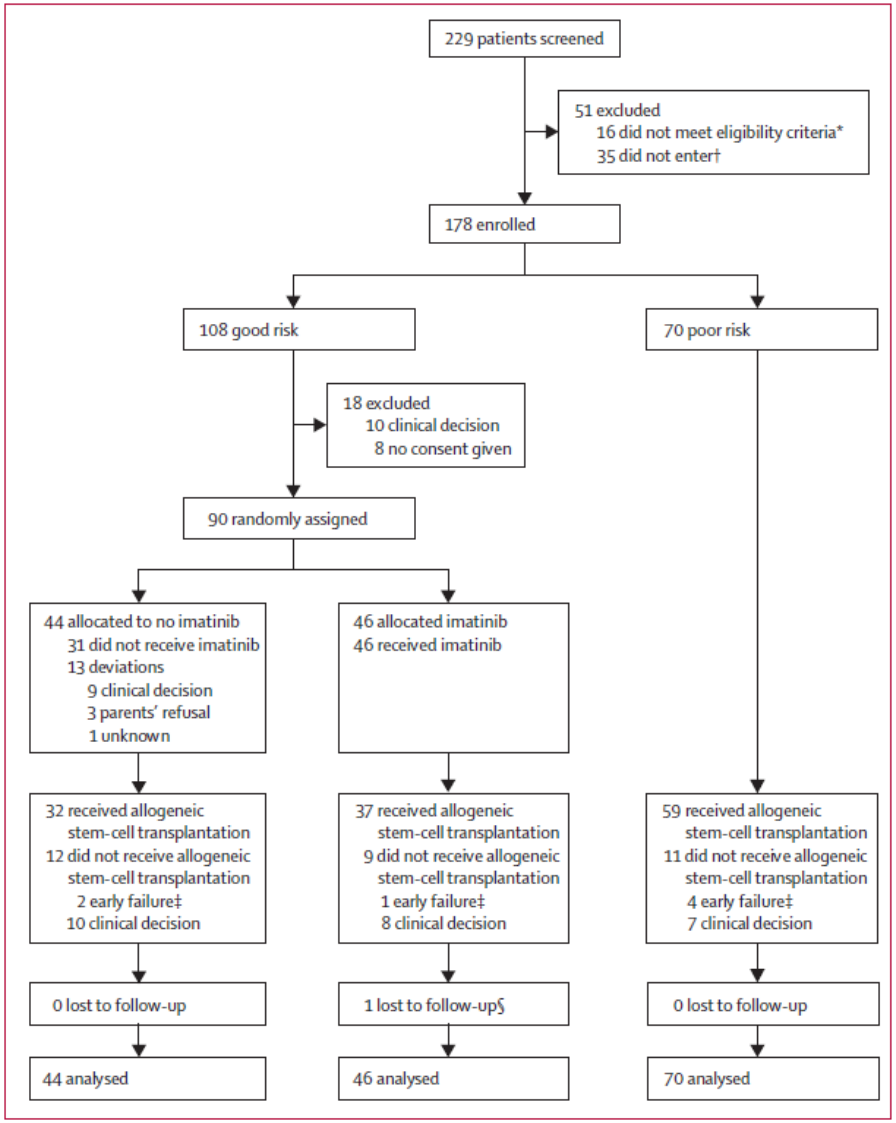
EsPhALL



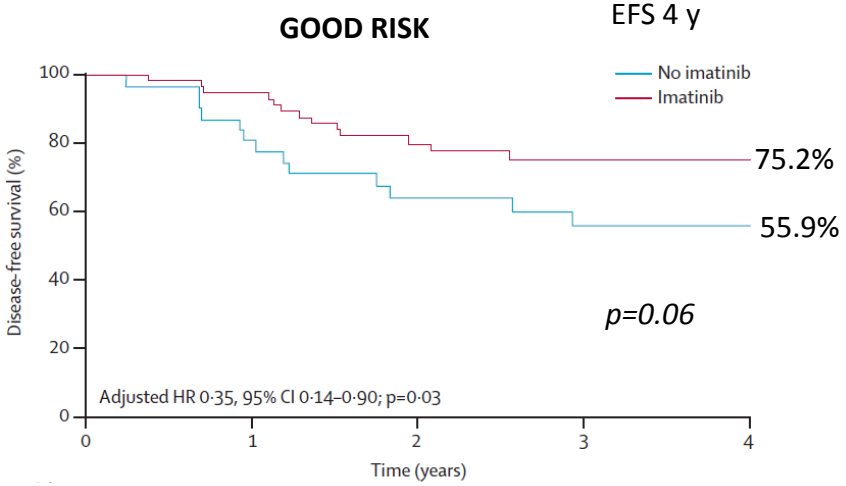
Analisi pazienti arruolati tra 2004 e 2009 (stop randomization nel 2009)

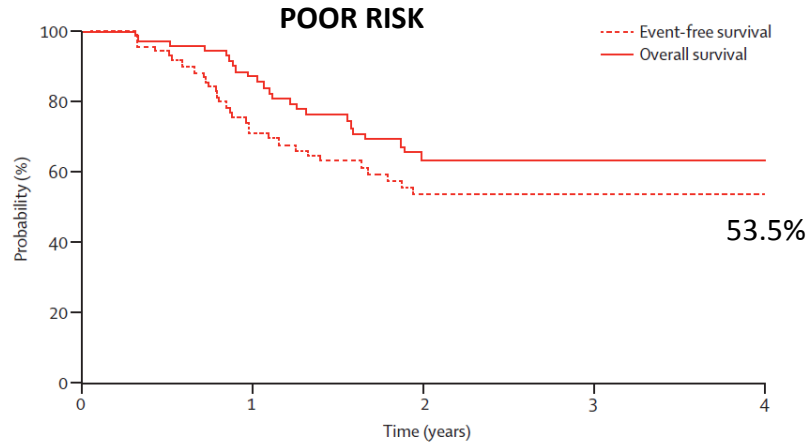
Biondi et al. Lancet Oncol 2012

EsPhALL



EFS 4 y

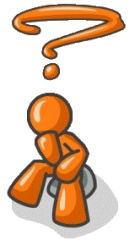




80% pts (GR e PR) HSCT

16 pts imatinib senza HSCT, poor outcome

Biondi et al. Lancet Oncol 2012



OPEN QUESTIONS

1. Riduzione di intensità della backbone therapy
2. Durata ottimale TKI (tossicità tardiva!)
3. Ruolo HSCT in 1 RC
4. Utilizzo e durata TKI post HSCT
5. Quale TKI utilizzare

SECOND GENERATION TKI - DASATINIB -

Studi fase I/II monoterapia con dasatinib -> sicuro e tollerato

(Zwaan et al. JCO 2013, Aplenc et al. JCO 2011)

Trial AALL0622 COG -> confermata sicurezza ed evidenziato miglioramento di early response (no induction failures)

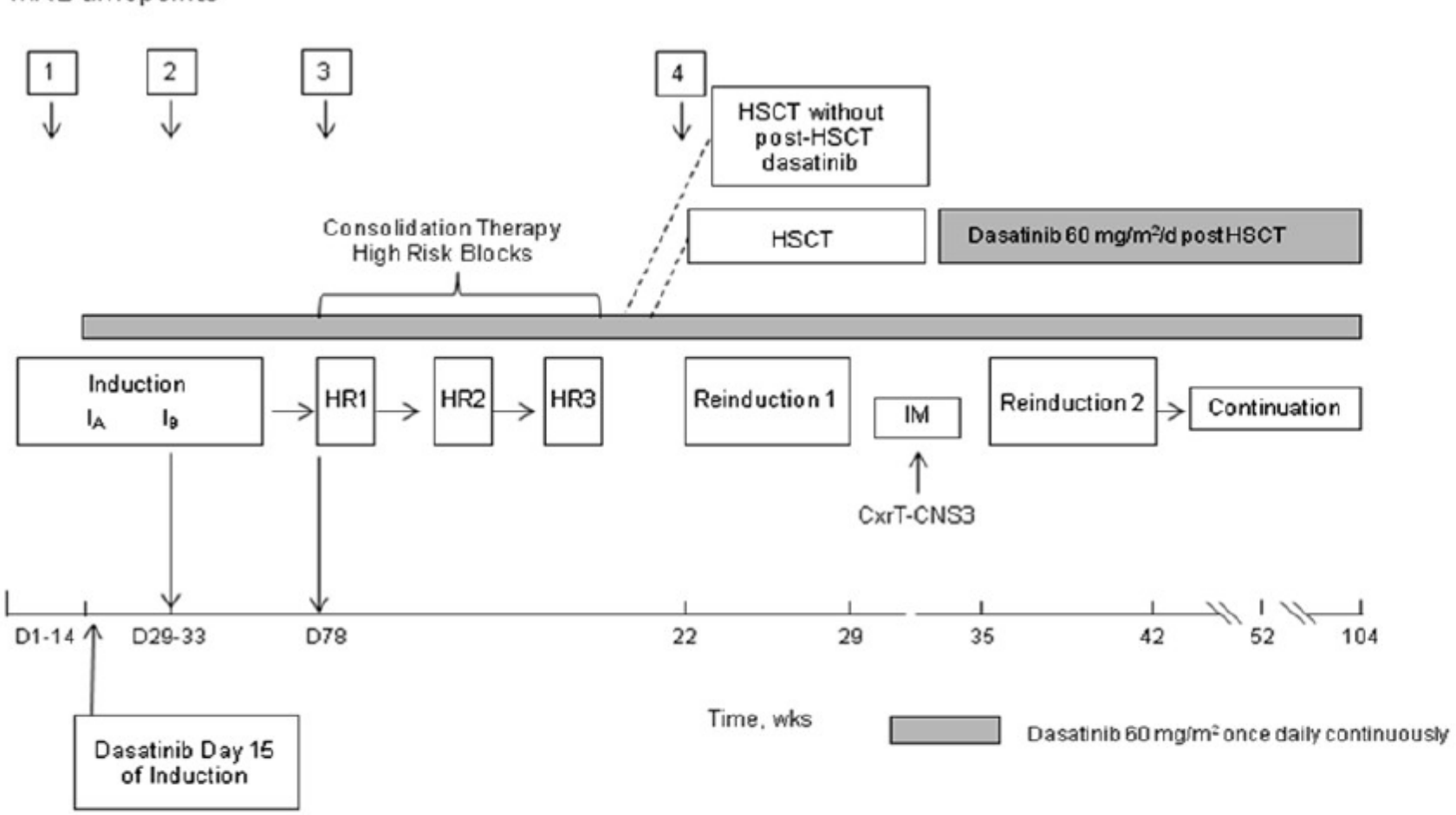
[Slayton et al. Blood 2012 (abs), Slayton et al. PBC 2012 (abs)]

A Phase 2 Multi-Center, Historically Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients With Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia
NCT01460160, CA180-372, AALL1122

Collaborators: COG, EsPhALL
Start date: January 2012
Active, not recruiting

CA180-372

Figure 1: Schematic Study Design



SECOND GENERATION TKI

NILOTINIB

NCT01077544, fase I, completed

A Multi-center, Open-label, Pharmacokinetic Study of Oral Nilotinib in Pediatric Patients With Newly Diagnosed Chronic Phase (CP) Ph+ CML, With CP or Accelerated Phase (AP) Ph+ CML Resistant/Intolerant to Imatinib and/or Dasatinib, or With Refractory/Relapsed Ph+ ALL

No studi fase II

PONATINIB - RUXOLITINIB

Nessuno studio in ambito pediatrico

I nuovi farmaci hanno modificato la strategia trapiantologica delle leucemie linfoblastiche acute nel bambino?

Ridurre il ricorso alla procedura trapiantologica

Rendere accessibile la procedura trapiantologica

NUOVI FARMACI

SMALL MOLECULES INHIBITORS

(EPZ 5675)

TARGETED THERAPY

IMMUNOTHERAPIES

(monoclonal antibodies, CAR T-cells)

SMALL INTERFERING RNA (siRNA)

NUOVI FARMACI

SMALL
MOL
INHI
(EP2

IMMUNOTHERAPIES
odies,

CD19	**Blinatumomab, SGN19a, SAR3419, Combotox**
CD20	**Rituximab, Ofatumumab**
CD22	**Epratuxumab, Inotuzumab, Combotox, BL22, HA22**
CD52	**Alemtuzumab**

SMALL
INTERFERING RNA
(siRNA)

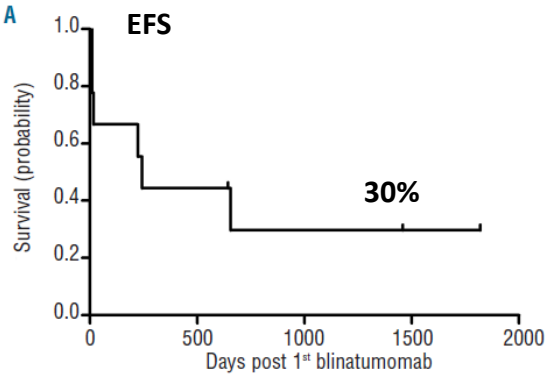
BLINATUMOMAB - uso compassionevole -

3 pt ricaduta post TCSE -> RC con MRD negativa

(Handgretinger et al. Leukemia 2011)

N.	Number of cycles and dosages (μg/m²/day)	Prior leukemic load	Primary response	Secondary response	Best response, post treatment MRD level	Detection method	Further treatment	Outcome
1	2 (5)	97%	yes	no	MRD negative	PCR, FC	haplo SCT	molecular remission (d675)
2	1 (15)	3.10%	yes	no	MRD negative	PCR	haplo SCT	molecular remission (d1851)
3	4 (15)	0.40%	yes	no	MRD negative	PCR, FC	nilotinib	molecular remission (d1490)
4	1 (15)	70%	yes	no	<1%	microscope	none	died from gram-negative sepsis (d17)
5	4 (5, 15, 15, 15)	70%, 30%	no	yes	MRD negative	PCR	haplo SCT	died from gram-negative sepsis (d655)
6	2 (5, 15)	80%, 11%	no	yes	MRD negative	PCR, FC	haplo SCT	died from relapse (d398)
7	1 (5)	7%	no	no	>90%	FC	palliative care	died from progression (d58)
8	2 (15, 15, 30)	11%	no	no	6.70%	FC	palliative care	died from progression (d166)
9	1 (5, 15)	51%	no	no	>90% blast load	FC	haplo SCT	died from relapse (d265)

Outcome (days) is calculated from the first day of blinatumomab administration to the last day of follow up or date of death. Minimal residual disease (MRD) negative defined as (<0.01% or <10E-4). PCR: polymerase chain reaction; FC: flow cytometry; d: days.



(Schlegel et al. Haematologica 2014)

BLINATUMOMAB

"A Single-Arm Multicenter Phase II Study Preceded by Dose Evaluation to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab (MT103) in Pediatric and Adolescent Patients With Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL)"

Start date October 2011

This study is ongoing, but not recruiting participants

Studio fase I/II, NCT01471782

41 pts, LLA refrattaria/recidivate

63% recidiva post TCSE

Dose escalation 5-15 ug/m^2/die (MTD 15 ug/m^2/die)

32% pt remissione completa morfologica -> 69% HSCT

"Phase 3 Trial of Blinatumomab vs Standard Chemotherapy in Pediatric Subjects With HR First Relapse B-precursor ALL"

This study is currently recruiting participants

Studio fase III, NCT02393859

Start date March 2015

EPRATUZUMAB

CHILDREN'S ONCOLOGY GROUP

Fase I-II ADVL04P2, NCT00098839

"A Feasibility Pilot and Phase II Study Of Chemoimmunotherapy With Epratuzumab (IND #12034) for Children With Relapsed CD22-Positive Acute Lymphoblastic Leukemia (ALL)"

This study is ongoing, but not recruiting participants

Raetz et al. JCO 2008

Epratuzumab in combinazione con CT di re-induzione -> ben tollerato

	Stratum	AALL01P2 (chemotherapy only)	B1 Cohort (weekly x 4)	B2 Cohort (twice weekly x 8)
Response-evaluable patients		58	48	50
CR2 after Block 1	Overall	74% (43/58)	65% (31/48) ($P=0.1964$)	66% (33/50) ($P=0.2380$)
	Very early relapse (<18 months)	56% (9/16)	50% (10/20) ($P=0.4854$)	35% (6/17) ($P=0.1956$)
	Early relapse (18–36 months)	81% (34/42)	75% (21/28) ($P=0.3795$)	82% (27/33) ($P=0.5602$)
MRD <0.01%	Overall	25% (9/36)	31% (8/26) ($P=0.4128$)	39% (12/31) ($P=0.1731$)
	Very early relapse (<18 months)	25% (2/8)	30% (3/10) ($P=0.6176$)	17% (1/6) ($P=0.8462$)
	Early relapse (18–36 months)	25% (7/28)	31% (5/16) ($P=0.4560$)	44% (11/25) ($P=0.1215$)

P-values are provided for comparisons of CR2 rates and MRD response in the B1 and B2 cohorts to AALL01P2. *P*-values for MRD responses were based on the one-sided Fisher's exact test.

Raetz et al. PBC 2015

EPRATUZUMAB

Fase III IntReALL SR 2010, NCT01802814

"International Study for Treatment of Standard Risk Chilhood Relapsed ALL 2010"

This study is currently recruiting partecipants

Start date February 2013

IntReALL SR 2010

IntReALL SR 2010

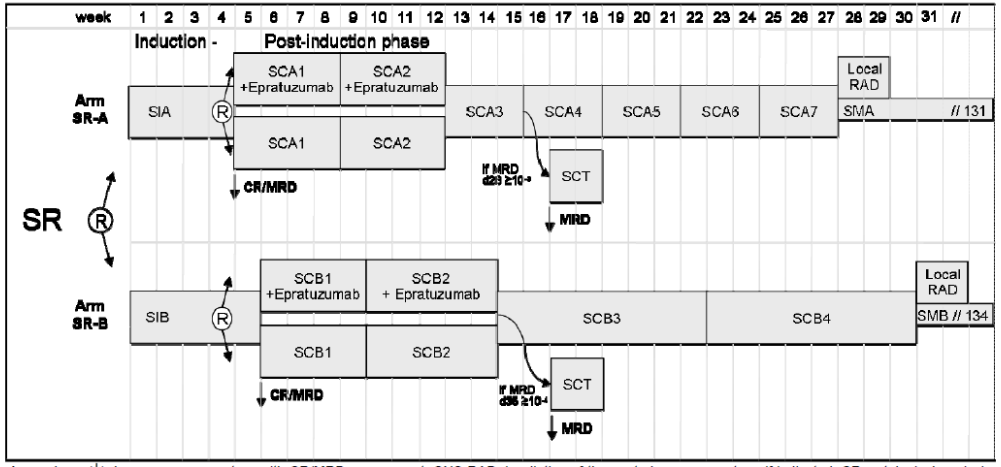
International Study for Treatment of
Standard Risk Childhood Relapsed ALL 2010

A randomized Phase III Study Conducted by the
Resistant Disease Committee of the International BFM Study Group

Protocol Version 1.7, Date 01.07.2012, Sta

Eudra-CT Number: 2012-000793-30

2 TREATMENT SCHEDULE INTREALL SR 2010

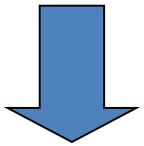


.Arrow down (↓), bone marrow puncture with CR/MRD assessment; CNS-RAD, irradiation of the central nervous system, if indicated; CR, cytological remission; MRD, minimal residual disease; SIA ALL-REZ BFM induction course; SCA 1-7 ALL-REZ BFM consolidation courses; ®, randomization; SIB, UK-R3 induction courses; SCB 1-4 UK-R3 consolidation / intensification courses; SCT, stem-cell transplantation; SR, standard risk group.

Difficoltà a svolgere studi clinici per le peculiarità del mondo pediatrico

FROM BENCH TO BEDSIDE AND FROM BEDSIDE TO BENCH

1. NUMERI PICCOLI
2. FARMACI EFFICACI NELL'ADULTO NON SEMPRE SONO FRUIBILI NEL BAMBINO
3. MODELLI DI TUMORI PEDIATRICI DIFFERENTI DA QUELLI DELL'ADULTO



1. DISEGNI STATISTICI DEDICATI
   (*arruolare il maggior numero di pazienti in breve tempo e in modo sicuro)*
2. VALUTAZIONE DELLA DOSE E TOSSICITA'
3. NECESSITA' DI STRATEGIE "DISEASE CENTRIC" E NON "DRUG CENTRIC"

CHILDREN'S ONCOLOGY GROUP

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

SIOP
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

BFM
Berlin-Frankfurt
-Münster

Innovative Therapies for Children with Cancer
ITCC
European Consortium

Italian Sarcoma Group

SIE

AIOM
Associazione Italiana di Oncologia Medica