La gestione del linfoma non Hodgkin ad alto grado di malignità:

Il punto di vista dell'ematologo del bambino e del giovane adulto

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Per il GdL-LNH AIEOP

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Firenze, 12 Dicembre 2018

LINFOMI NON HODGKIN
IN ETA' PEDIATRICA

Rappresentano dal 10 al 15% di tutti i tumori infantili, collocandosi al terzo posto per frequenza relativa dopo la leucemia acuta e i tumori a carico del SNC.

Hanno un'incidenza che aumenta in modo lineare con l'aumentare dell'età

La frequenza relativa dei diversi sottotipi istologici varia in funzione dell'età del paziente

Nei paesi industrializzati ci sono quattro sottotipi istopatologici principali di LNH pediatrici

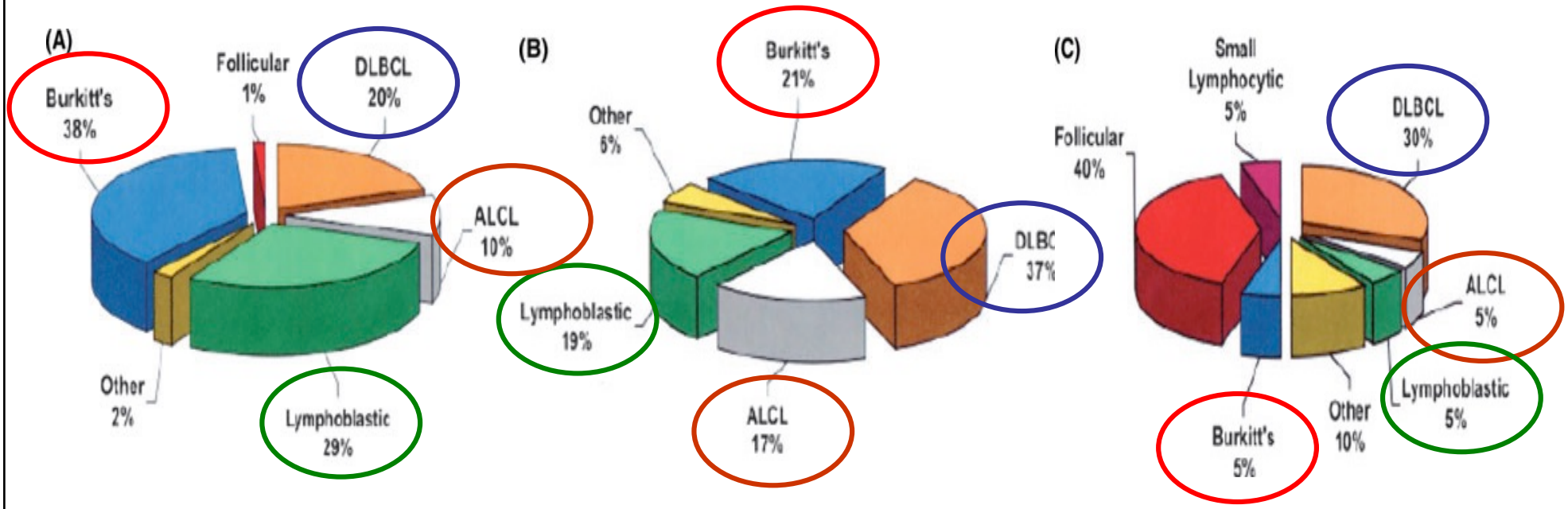
il linfoma di Burkitt

il linfoma diffuso a grandi cellule B

il linfoma linfoblastico

il linfoma anaplastico a grandi cellule

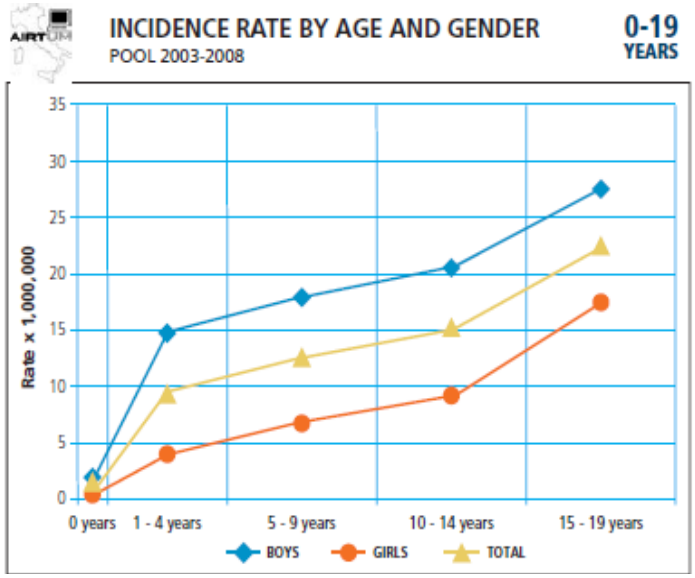
Incidenza dei sottotipi di LNH nei differenti gruppi di età

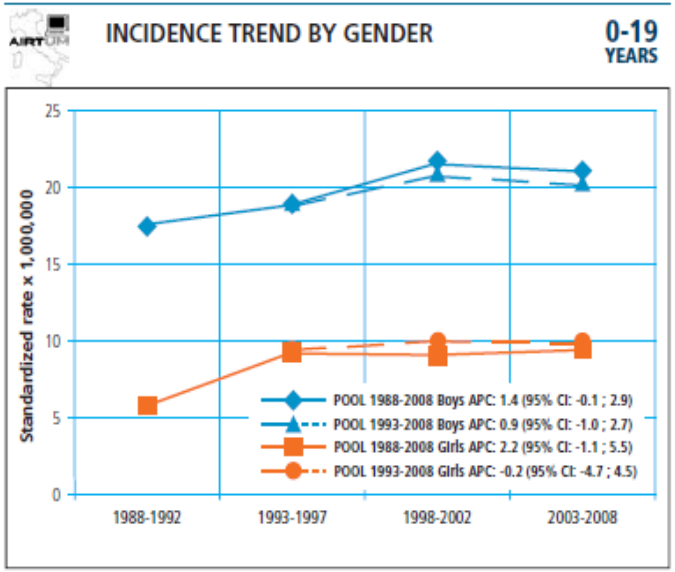


Hochberg J et al, BJH, 2009

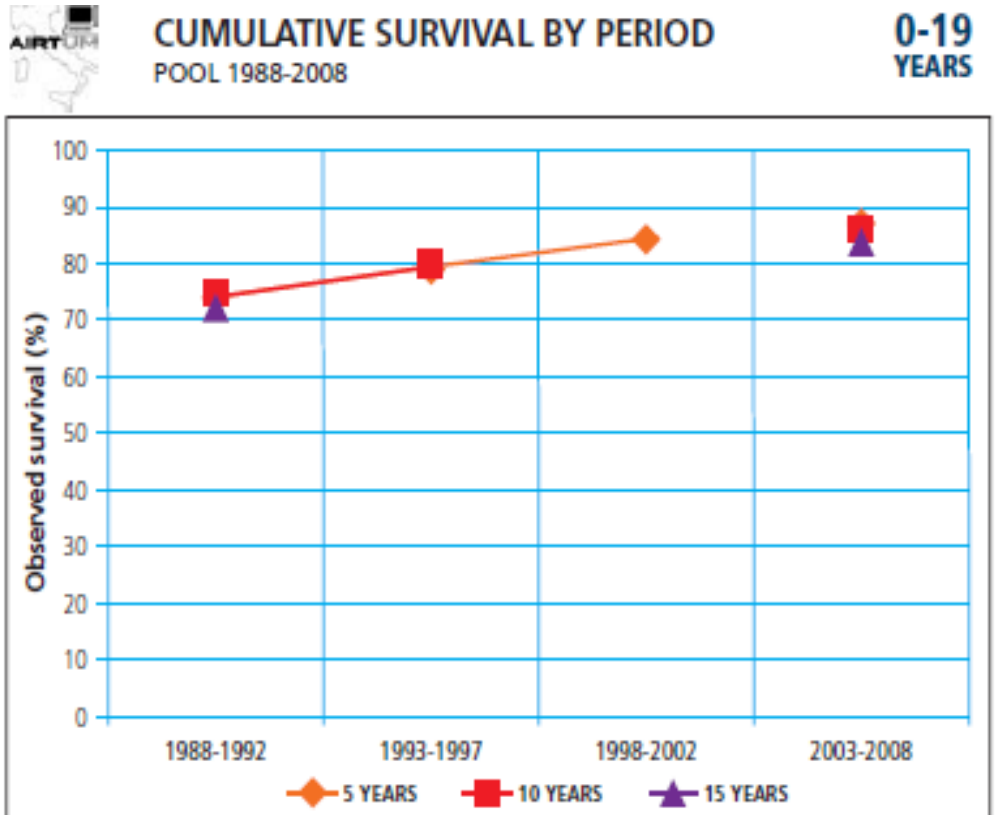
Registro italiano AIRTUM 2003-2008 (31 registri)

Il tasso di indidenza tra 0-19 anni è 13,8 casi per milione (IC95% 12,4-15,4)



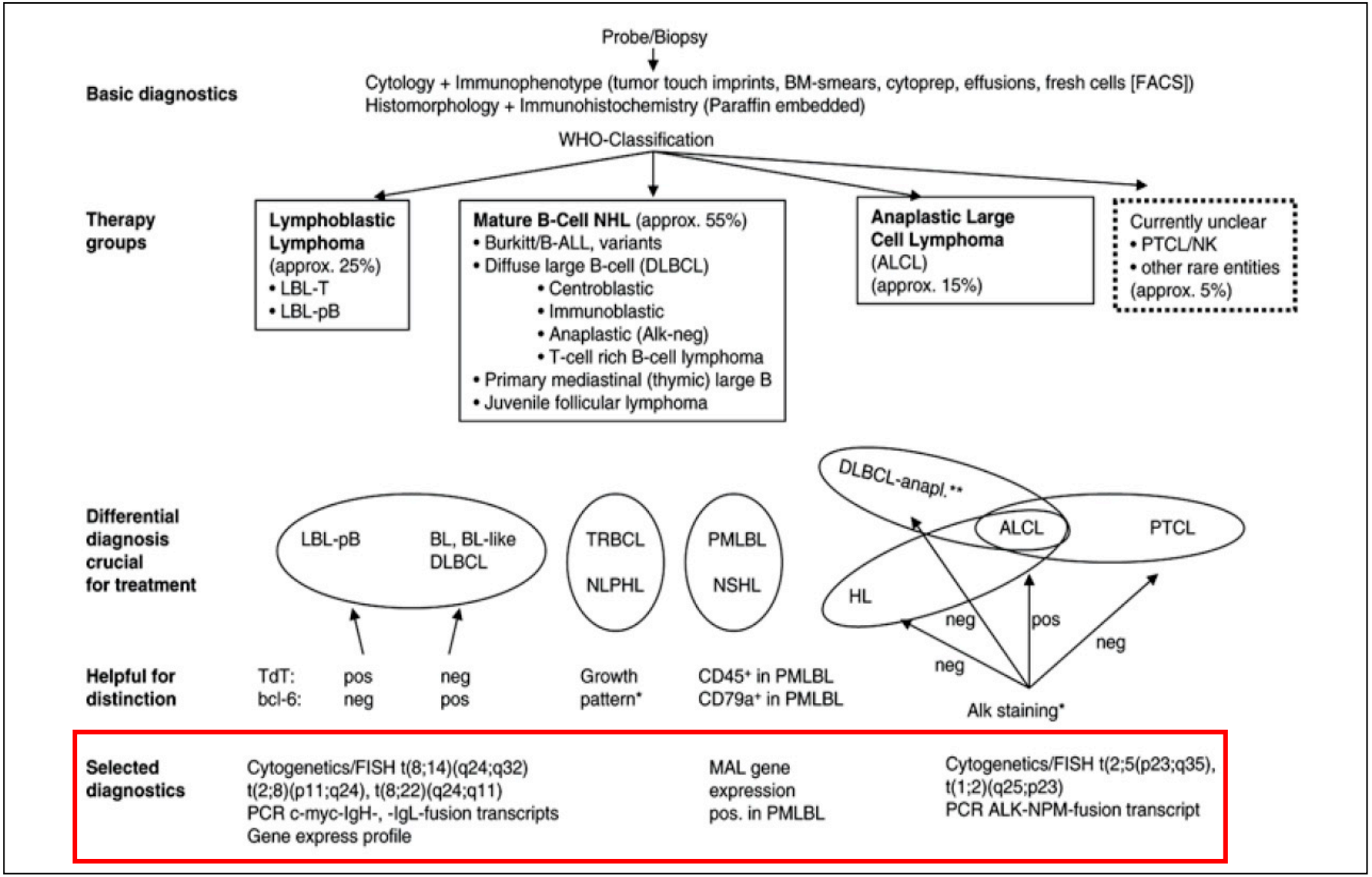


Fonte: **AIRTUM 2012** • Epidemiol Prev 2013; 37(1) Suppl 1



Epidemiol Prev 2013, AIRTUM

Work-up diagnostico, classificazione e stratificazione dei linfomi non Hodgkin pediatrici



Reiter A, Hematology Am Soc Hematol Educ Program. 2007

STADIAZIONE dei LNH

St. Jude

(Murphy, 1980)
Stage 1: A single tumor (extranodal) or a single anatomical site (nodal) with exclusion of the mediastinum or abdomen.

Stage 2: A single tumor (extranodal) with regional involvement
Two or more nodal areas on the same side of the diaphragm
Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm
A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only, grossly completely resected

Stage 3: Two single tumors (extranodal) on opposite sides of the diaphragm
Two or more nodal areas above and below the diaphragm
All primary intrathoracic tumors (mediastinal, pleural, thymic)
All extensive primary intra-abdominal disease, unresectable
All paraspinal or epidural tumors, regardless of other tumor sites

Stage 4: Any of the above with initial CNS and/or bone marrow involvement

Murphy SB, Semin Oncol 1980

STADIAZIONE IPNHLSS

Francoforte 2009

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JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Revised International Pediatric Non-Hodgkin Lymphoma Staging System

Angelo Rosolen, † Sherrie L. Perkins, C. Ross Pinkerton, R. Paul Guillerman, John T. Sandlund, Catherine Patte, Alfred Reiter, and Mitchell S. Cairo

See accompanying article on page 2106

A B S T R A C T

Purpose
Treatment and prognosis of pediatric non-Hodgkin lymphoma (NHL) have improved dramatically in the last 30 years. However, the St Jude NHL staging classification for pediatric NHL was developed more than 35 years ago. The most recent Lugano lymphoma staging classification focused on adult lymphoma. Furthermore, major limitations of the current pediatric NHL staging classification include lack of consideration of new distinct pediatric NHL histologic entities; absence of recognition of frequent skin, bone, kidney, ovarian, and other organ involvement; and lack of newer precise methods to detect bone marrow and CNS involvement, minimal disease quantification, and highly sensitive imaging technologies.

Methods
An international multidisciplinary expert panel convened in Frankfurt, Germany, in 2009 at the Third International Childhood, Adolescent and Young Adult NHL Symposium to develop a revised international pediatric NHL staging system (IPNHLSS), addressing limitations of the current pediatric NHL staging system and creating a revised classification. Evidence-based disease distribution and behavior were reviewed from multiple pediatric cooperative group NHL studies.

Results
A revised IPNHLSS was developed incorporating new histologic entities, extranodal dissemination, improved diagnostic methods, and advanced imaging technology.

Conclusion
This revised IPNHLSS will facilitate more precise staging for children and adolescents with NHL and facilitate comparisons of efficacy across different treatment strategies, various institutions, multicenter trials, and cooperative groups by allowing for reproducible pediatric-based staging at diagnosis and relapse.

J Clin Oncol 33:2112-2118.

Rosolen A, JCO 2015

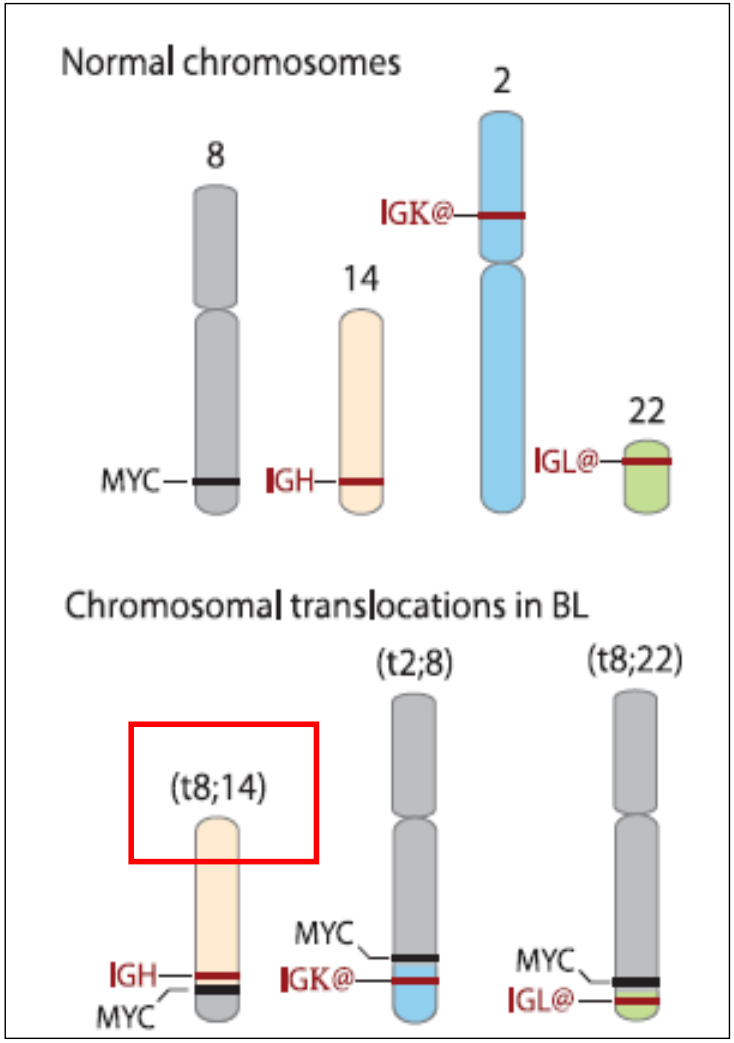
LINFOMA A CELLULE B

LINFOMA DI BURKITT	LINFOMA DIFFUSO A GRANDI CELLULE B (DLBCL)
E' il sottotipo di LNH più frequente nei bambini di età 0-14 anni	E' il più comune sottotipo di LNH negli adolescenti (15-19 anni)
Si presenta con massa addominale associata a sintomi causati dalla compressione delle strutture anatomiche adiacenti	Si presenta con interessamento dei linfonodi periferici e localizzazioni extranodali (es. anello del Waldeyer)

MARKERS	**Linfoma di Burkitt**	Esprime Ig di superficie, positivo per CD19, CD20, CD22, CD79a e spesso CD10. TdT negativo.
	DLBCL	Fenotipo simile al precedente, ma CD10 può essere negativo e circa 1/3 non esprime Ig di superficie.

I linfomi a cellule B sono trattati con cicli di chemioterapia strutturati in base al criterio di alta dose-intensità

Traslocazioni cromosomiche presenti nel linfoma di Burkitt



Nel linfoma di Burkitt la sovraespressione del c-Myc è costantemente associata alla traslocazione cromosomica del protoncogene Myc su altri cromosomi, tra cui 14, 2 e 22, che contengono i geni per la catena pesante μ e catene leggere κ o λ delle immunoglobuline.

Klapproth K, BJH 2010

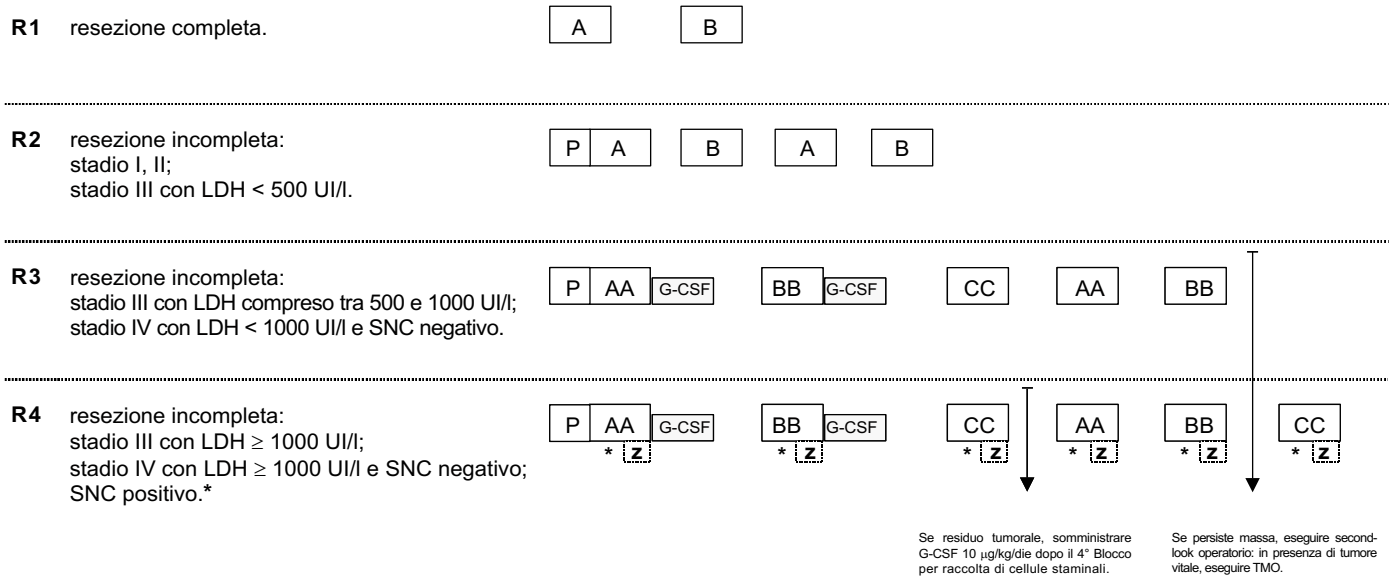
Principali risultati raggiunti a livello internazionale nel trattamento dei LNH-B

Gruppo di studio	Periodo di studio	N.	Regime di trattamento	OS	EFS a 5 aa	Riferimento Bibliografico
POG	1986-1991	59	Terapia a blocchi	na	79% (IV BM-) 65% (LLA B)	Bowman 1996
BFM	1990-1995	413	NHL-BFM90 + LLA B	na	89%	Reiter 1999
UKCCSG	1990-1996	112	Protocollo 9002 + LLA B	87%	84%	Atra 2000
SFOP	1989-1996	561	LMB89 + LLA B	93%	91%	Patte 2001
CCG	1991-1993	42	Orange (CHOP like+ DECAL) St. III, IV + LLA B	80%	77%	Cairo 2002
AIEOP	1992-1997	144	AIEOP LNH-92	89%	82 %	Pillon 2004
BFM	1996-2001	505	BFM 95 + LLA B	na	89%	Woessmann 2005
SFOP UKCCSG CCG	1996-2001	762	FAB/LMB96	93%	90 %	Patte 2007
AIEOP	1997-2010	530	AIEOP LNH-97	93%	90%	Pillon 2016
EICNHL+C	2011-2016	310	Inter B-NHL ritux 2010	na	94,2% R+,	Minard-Colin V, ASCO

PROTOCOLLO AIEOP LNH-97
PER I LNH-B (tutti i sottotipi istologici)

LNH B: PIANO TERAPEUTICO

Gruppi di rischio: definizioni



G-CSF: l'uso del G-CSF è facoltativo; se ne consiglia l'uso dopo il 1° AA(z) e il 1° BB(z).

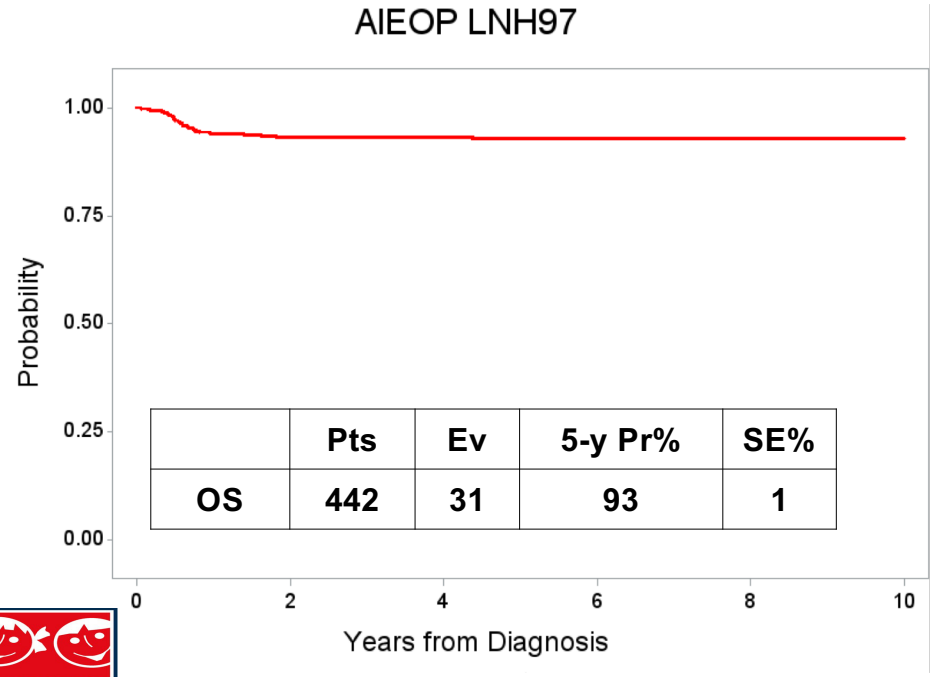
Schema di trattamento BFM-like

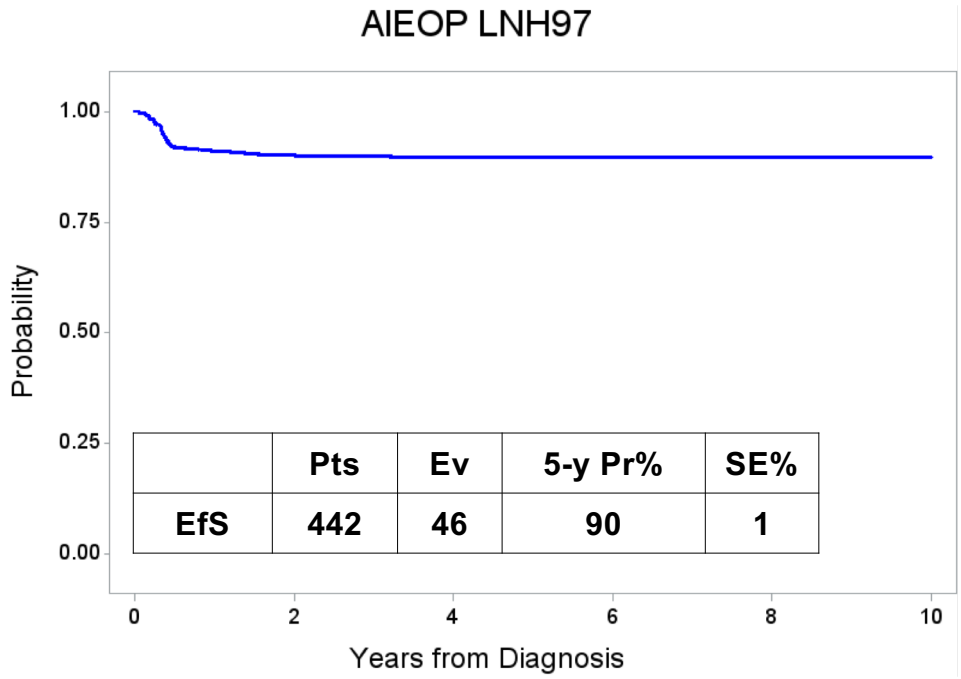
A.I.E.O.P.
Associazione Italiana Ematologia Oncologia Pediatrica

CLINICAL CHARACTERISTICS

Tot. patients 442 (63 DLBCL, 379 BL)	
Median age (years)	8.6 (range, 0.03-17.8)
Median LDH (IU/L)	573 (range, 135-11322)
Median follow-up (years)	5.4 (range, 0.05-15.1)
Period of enrolment	1997-2014

OUTCOME 1/2

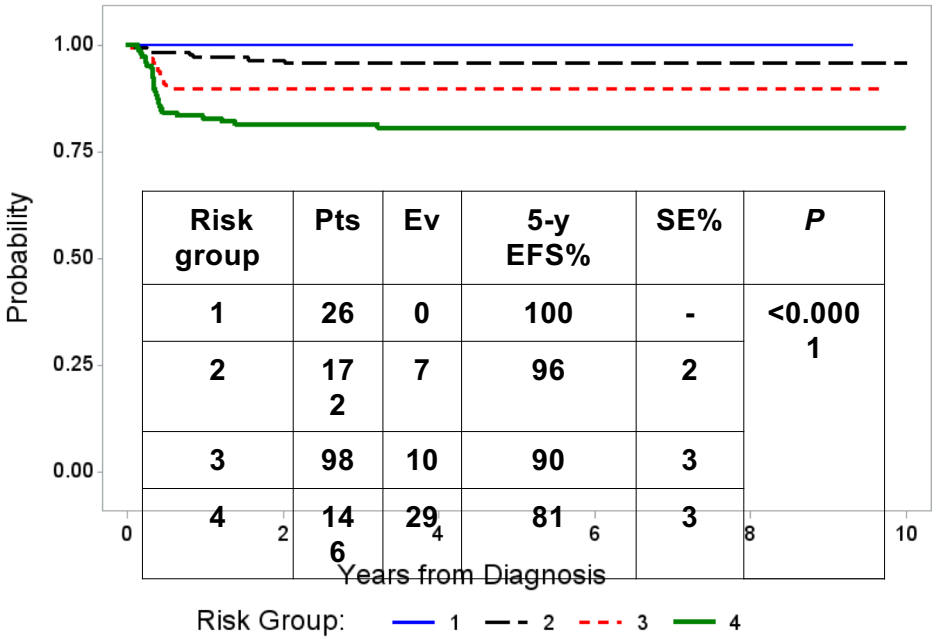




Pillon M, BJH 2016

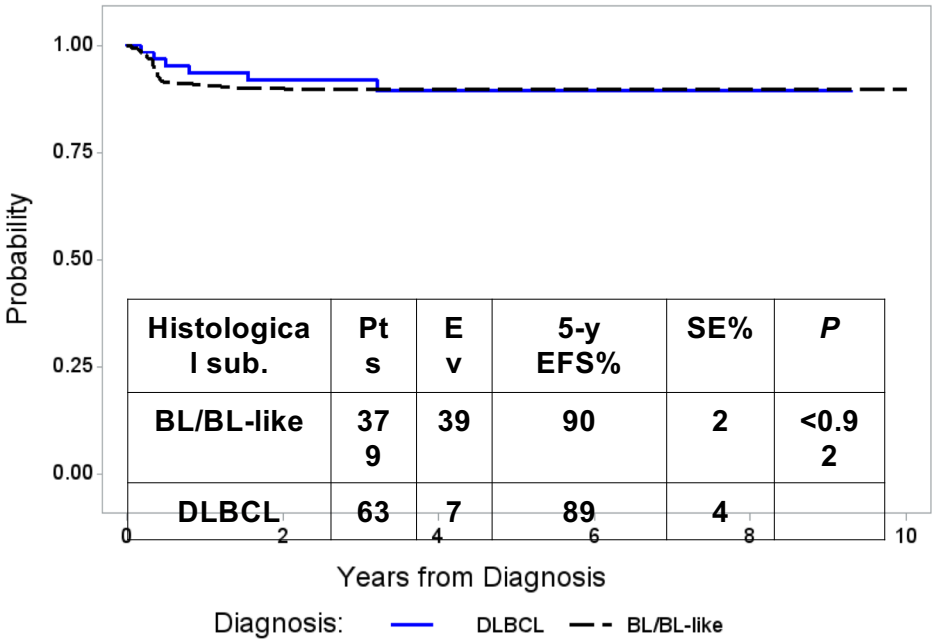
OUTCOME 2/2

AIEOP LNH97



Risk group	Pts	Ev	5-y EFS%	SE%	*P*
1	26	0	100	-	<0.0001
2	172	7	96	2	
3	98	10	90	3	
4	146	29	81	3	

AIEOP LNH97



Histological sub.	Pts	Ev	5-y EFS%	SE%	*P*
BL/BL-like	379	39	90	2	<0.92
DLBCL	63	7	89	4	

		Events by Disease Stage (St. Jude)					
	#	**%**	**I**	**II**	**III**	**IV***	**CNS+**
Patients	442		36	131	218	57	25
Toxic Death	6°	**1.4**	0	0	3	3	2
Non-response	18	**4.1**	0	3	9	6	3
Relapse	20	**4.5**	0	3	13	4	0
Second cancer	2	**0.5**	0	0	0	2	2
° 0.4% early toxic deaths; *including CNS-positive							

Pillon, BJH 2016

Multivariate analysis 1/2

Characteristics	Categories	# Pts	Events	5-y EFS % (SE%)	Univariate p-value	Multivariate p-value	Hazard Ratio (95% CI)
Age	< 8.6 yrs ≥ 8.6 yrs	222 220	19 27	92 (2) 88 (2)	0.17	n.s.	
Gender	Male Female	363 79	33 13	91 (1) 83 (4)	0.04	n.s	
Median LDH	≤ 573 IU/L > 573 IU/L	222 220	7 39	97 (1) 83 (3)	<0.0001	<0.0001	6.1 (2.7-13.6)
Stage	I+II III+IV	167 275	6 40	96 (1) 86 (2)	0.0003	n.s	
Risk group	R1+R2 R3+R4	198 244	7 39	96 (1) 84 (2)	<0.0001	n.s.	
BM Involvement	Yes No	22 420	6 40	77 (9) 90 (1)	0.02	n.s.	
CNS Involvement	Yes No	25 417	7 39	76 (9) 91 (1)	0.009	n.s.	

Pillon, BJH 2016

A.I.E.O.P.
Associazione Italiana Emato-Oncologia Pediatrica

Multivariate analysis 2/2

Characteristics	Categories	# Pts	Events	5-y PFS % (SE%)	Univariate p-value	Multivariate p-value	Hazard Ratio (95% CI)
Age	< 7.9 yrs	64	7	89 (4)	0.20	n.s.	
	≥ 7.9 yrs	64	12	81 (5)			
Gender	Male	113	15	87 (3)	0.16	n.s.	
	Female	15	4	73 (11)			
Median LDH	≤ 1009 IU/L	64	6	91 (4)	0.08	n.s.	
	> 1009 IU/L	64	13	79 (5)			
Stage	I+II	26	2	92 (5)	0.27		
	III+IV	102	17	83 (4)			
Risk group	R1+R2	34	2	94 (4)	0.09	n.s.	
	R3+R4	94	17	82 (4)			
BM Involvement	Yes	10	3	70 (14)	0.14	n.s.	
	No	118	16	86 (3)			
CNS Involvement	Yes	7	2	71 (17)	0.22		
	No	121	17	86 (3)			
MDD	Pos	39	10	74 (7)	0.03	0.04	2.6 (1.1-6.5)
	Neg	89	9	90 (3)			

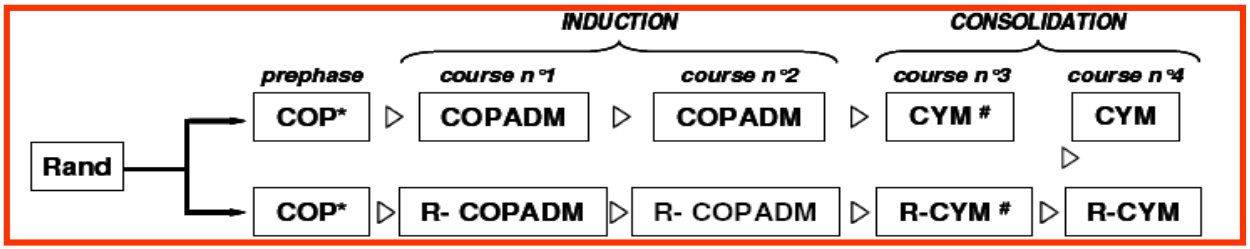
- 169/ 379 patients with BL had available tumor specimens and were assayed for t(8;14)(q24;q32) by LD-PCR

- 128 patients (75%) were positive for t(8;14)(q24;q32) and were assayed for MDD

Pillon, BJH 2016

STUDIO DI FASE III: LNH-B AD ALTO RISCHIO E LLA-B

Group B - high risk: Stage III with high LDH level (> N x 2), Stage IV CNS negative

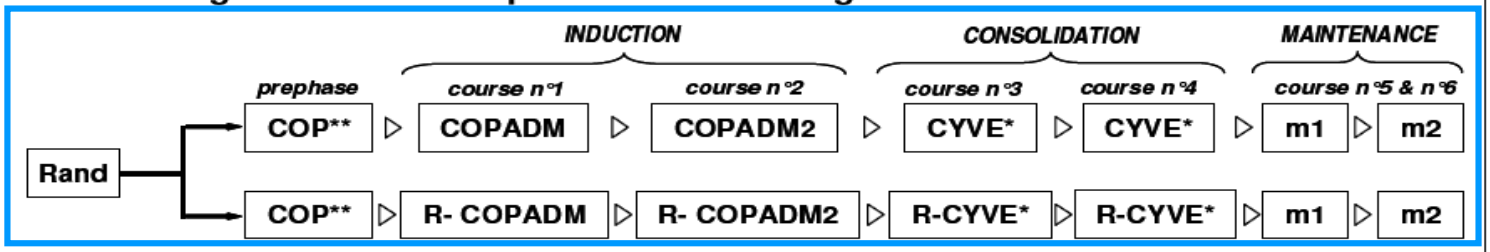


HDMTX 3g/m² infused over 3h

*Non responder at D7: assigned to group C1, rituximab as allocated by randomisation

If residual mass with documented viable cells, « slow responders » assigned to group C1 starting at 1st CYVE, rituximab as allocated by randomisation

Group C1 : B- AL CNS negative, Stage IV & B-AL CNS positive and CSF negative

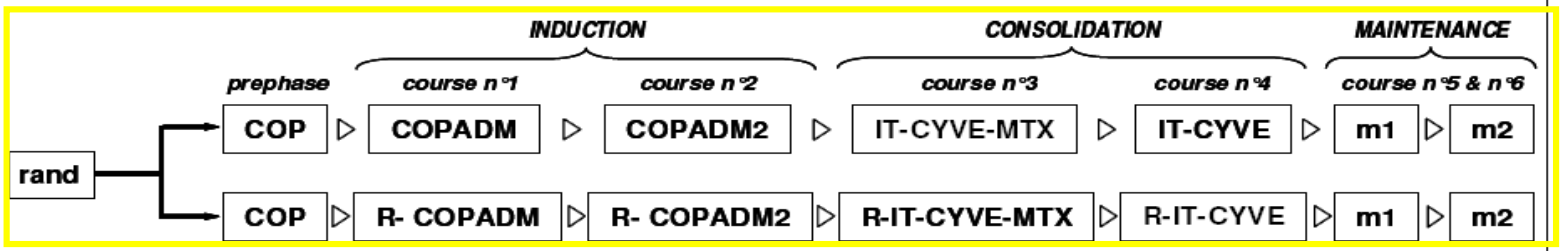


HDMTX 8g/m² infused over 4h

** Pts CNS+: IT before each CYVE and HDMTX between 1st and 2nd CYVE*

**Non responder at D7: assigned to group C3, rituximab as allocated by randomisation

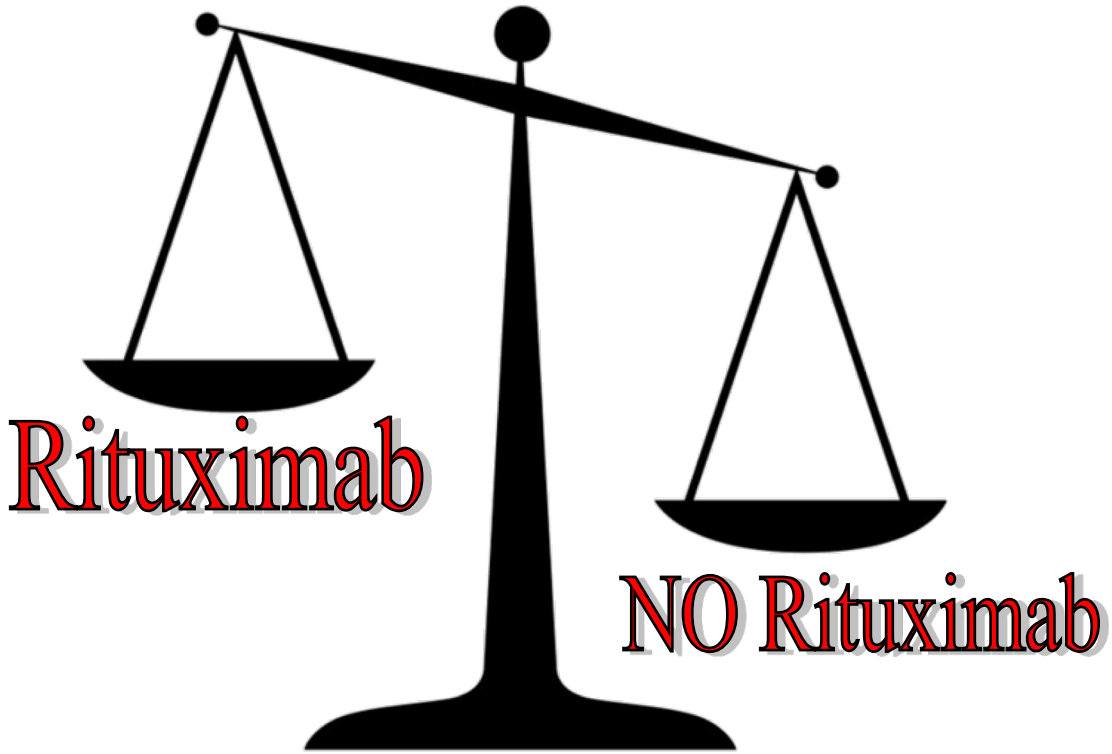
Group C3 : B-AL CSF positive, Stage IV CSF positive



HDMTX 8g/m² infused over 24h except in 1st COPADM

eicnhl

Fase III



2-year EFS: 94%

2-year EFS: 82%

Analisi condotta su 310 pazienti e 27 eventi (20 no ritux, 7 ritux)

STOP RANDOM con RITUXIMAB

STUDIO DI FASE II: Linfoma primitivo a grandi cellule B del mediastino (PMLBL)

6 courses of EPOCH with rituximab, with dose adaptation (DA) at each course based on previous course ANC nadir

R-EPOCH | R-EPOCH | R-EPOCH | R-EPOCH | R-EPOCH | R-EPOCH

Doxorubicin, VCR, VP16 infused over 96h, no IT, no HDMTX

The NEW ENGLAND JOURNAL of MEDICINE

Therapy in Primary Mediastinal B-Cell Lymphoma

TO THE EDITOR: Dunleavy et al. (April 11 issue)[1] had exceptional survival rates when treating adults with primary mediastinal large-B-cell lymphoma with dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab (DA-EPOCH-R), without radiotherapy. The biologic characteristics of the disease in children are similar to those of the disease in adults.[2] Regimens (without rituximab) that have been effective in the treatment of children with other mature B-cell non-Hodgkin's lymphomas have had limited efficacy in the treatment of children with primary mediastinal large-B-cell lymphoma.[3,4] Consequently, the Non-Hodgkin's Lymphoma Berlin–Frankfurt–Münster (NHL-BFM) study committee recommended DA-EPOCH-R[5] for children and adolescents with primary mediastinal large-B-cell lymphoma as the best available clinical practice, and this treatment was adopted for patients in the B-Cell NHL-BFM04 more efficient in terms of both timing and the methods used.

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No potential conflict of interest relevant to this letter was reported.

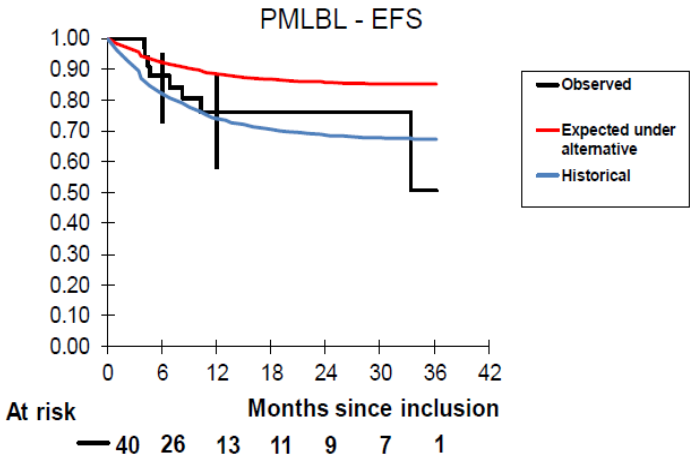
1. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH–rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 2013;368:1408-16.
2. Oschlies I, Burkhardt B, Salaverria I, et al. Clinical, pathological and genetic features of primary mediastinal large B-cell lymphomas and mediastinal gray zone lymphomas in children. Haematologica 2011;96:262-8.
3. Seidemann K, Tiemann M, Lauterbach I, et al. Primary me-

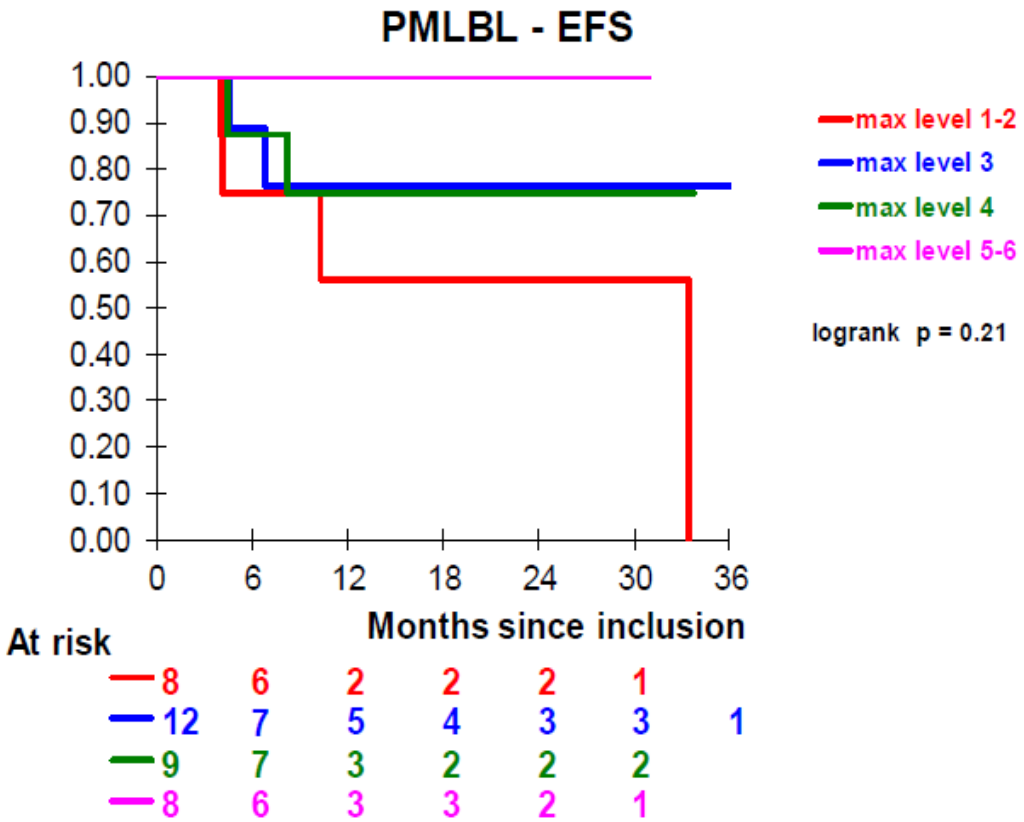
Fase II

Report of the DA-EPOCH-R trial in children/adolescents with Primary Mediastinal Large B cell Lymphoma with futility analysis

EFS rates:

	Observed rate (95%CI)	Expected rate under alternative $[0.67 + 0.33\{\exp(-1.5t)\}]^{0.406}$	Historical rate $0.67 + 0.33\{\exp(-1.5t)\}$
At 6 months	87.8% (72.6%-95.2%)	92.5%	82.6%
At 12 months	76.2% (57.9%-88.1%)	88.7%	74.4%

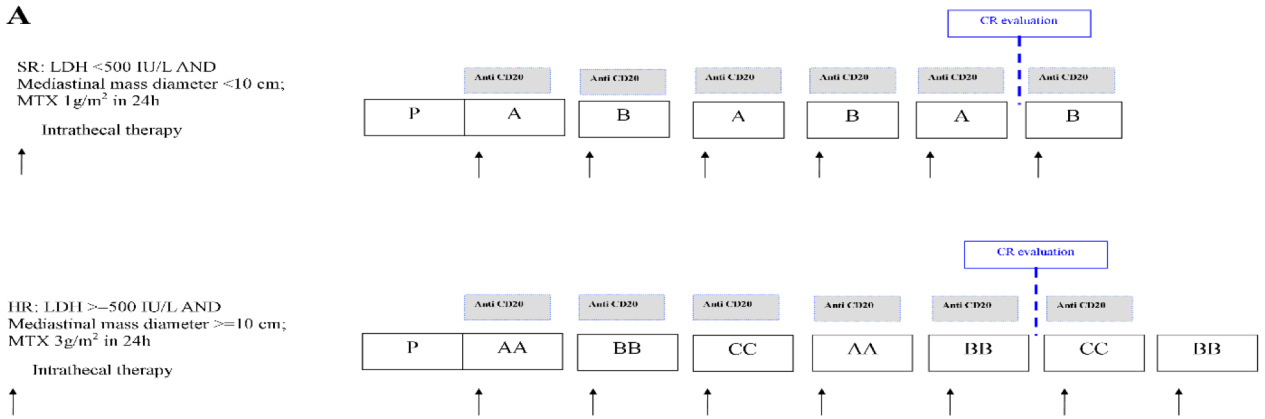


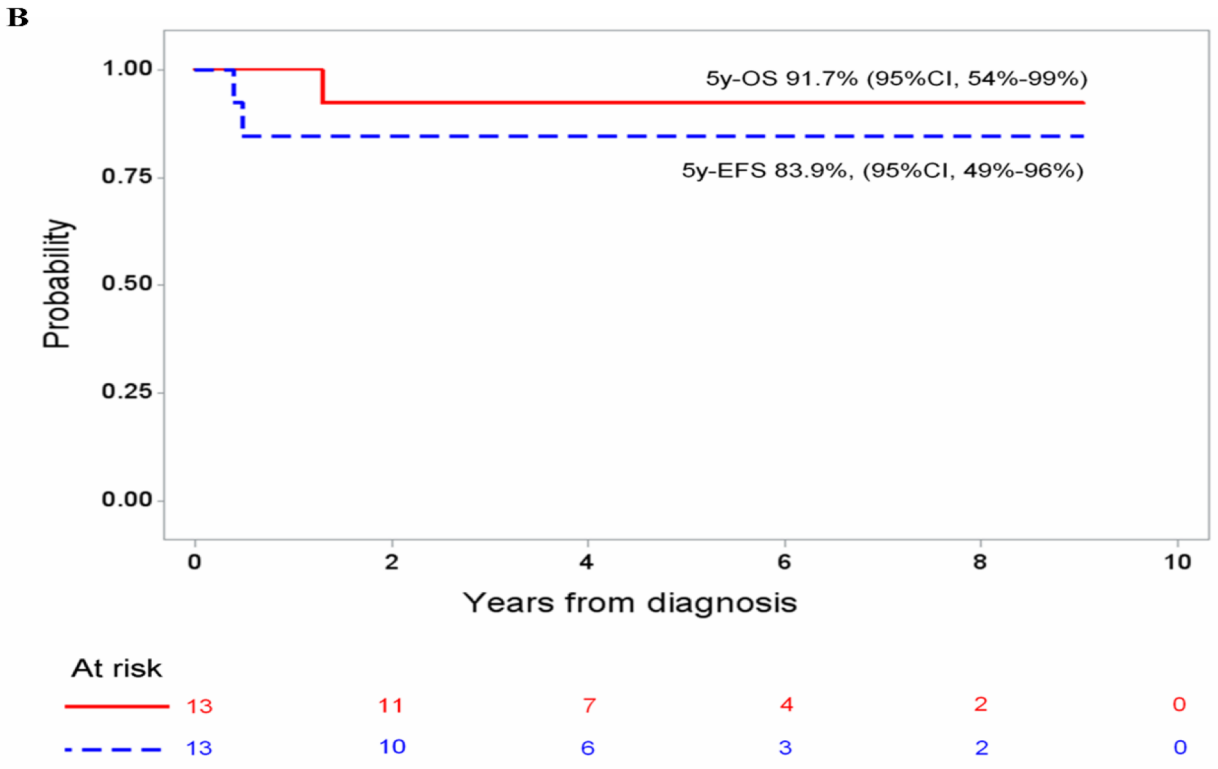


18 Aprile 2016: STOP FASE 2 (raggiungimento totale pts)

Burke A et al, ASH 2017
Paper in progress..

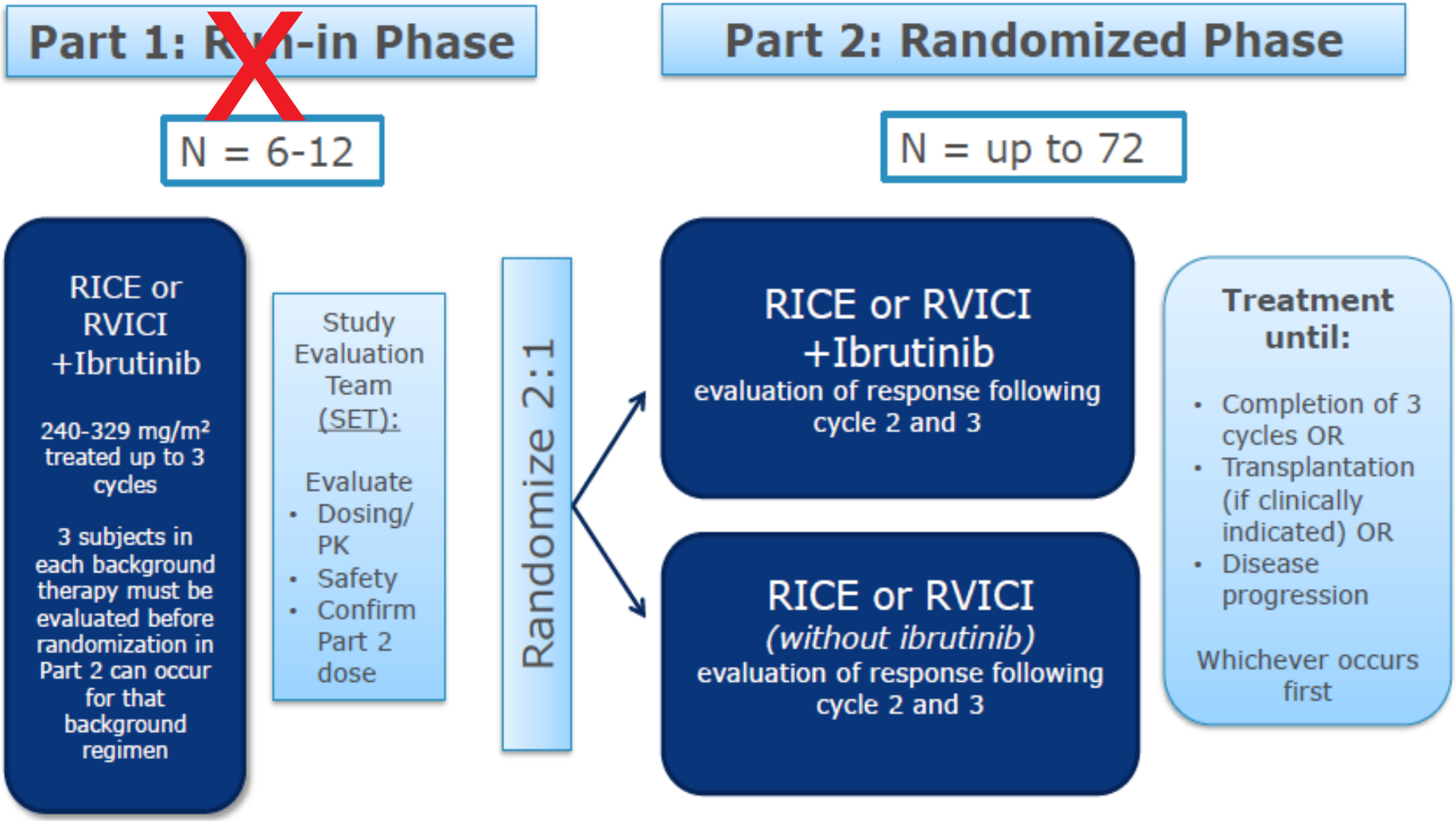
LINEE GUIDA INTERINALI PER PMLBCL





Pillon et al, PBC 2018

LYM3003: Study Schematic



LINFOMA LINFOBLASTICO (LBL)

- **E' trattato con regimi di chemioterapia simili a quelli usati per la LLA**
- **Per gli stadi localizzati possono essere utili regimi terapeutici più brevi**
- **L'aspetto più rilevante per la diagnosi è l'espressione di TdT**

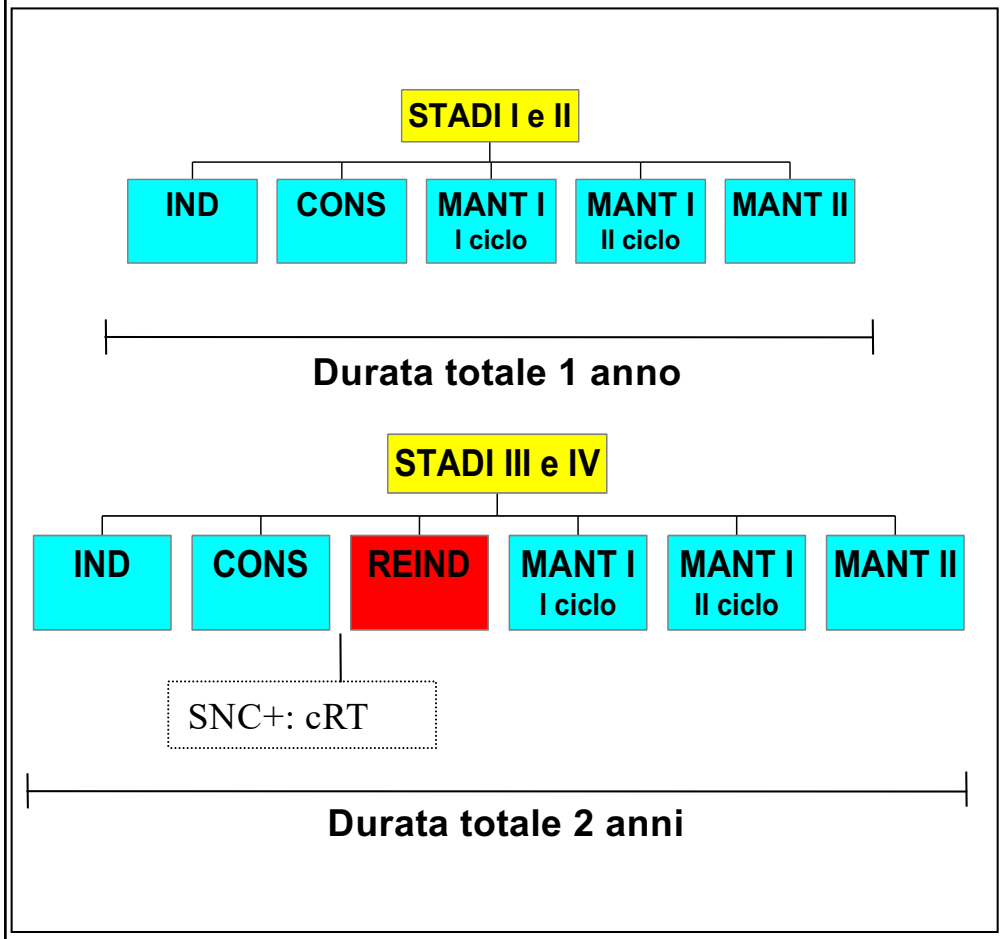
IMMUNOFENOTIPO	PRESENTAZIONE CLINICA
T (80%)	Massa mediastinica che può causare tosse, dispnea, disfagia, edema a mantellina
pre-B (20%)	Coinvolgimento dei linfonodi periferici, della cute o sottocute o dell'osso

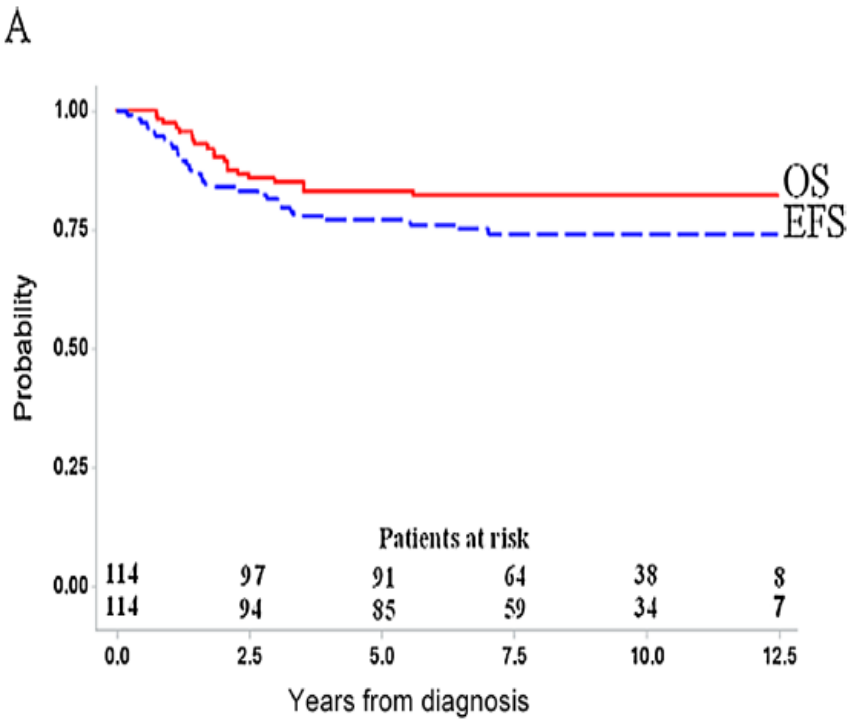
MARKERS	LNH-T	CD3 positivo citoplasmatico o di membrana, HLA-DR negativo e CD34 negativo.
	LNH pre-B	Esprime CD19 e/o CD79a e/o CD22, HLA-DR positivo, ma non Ig di superficie.

LBL: RISULTATI TERAPEUTICI

Gruppo	Periodo di studio	N.	Regime di trattamento	RT locale	RT-SNC profilassi	Durata (mesi)	OS	EFS 5 aa	Riferimento Bibliografico
SFOP	1981-1989	84	LMT-81 (mod LSA2L2)	no	no	24	76%	75%	Patte 1992
UKCCSG	1985-1990	95	Prot 8503 st III-IV T-LL	no	si	24	na	65%	Eden 1992
CCG	1983-1990	281	Random LSA2L2/ADCOMP	si si	no no	18 18	77% 60%	74% 64%	Tubergen 1995
POG	1987-1992	195	LSA2L2 random HD-Asp si/no	no	si GB>50000	24	na	78% 64%	Amylon 1999
BFM	1986-1995	27	NHL86 e 90 PBLL	no	si	24	na	73%	Neth 2000
BFM	1990-1995	105	BFM- 90 T-LL	no	si	24	na	90%	Reiter 2000
BFM	1995-2001	156	BFM-95 (III-IV st. SNC neg)	no	no	24	na	82%	Burkhardt 2006 Abs
SFOP	1997-2003	83	LMT-96	no	si	24	na	87%	Bergeron 2006 Abs
CCG	1994-1997	107	CCG-5941 Pilota III-IV st.	no	no	12	85%	78%	Abromowitch 2008
EORTC	1989-1998	121	58881 (BFM-like)	no	no	24	86%	78%	Uyttebroeck 2008
St. JUDE	1992-2002	41	NHL-13 III-IV st.	no	no	24	90%	83%	Sandlund 2009
AIEOP	1997-2003	114	AIEOP LNH-97	no	no	11-24	82%	74%	Pillon 2015
EORTC/SFOP	1989-2008	53	58881-58951/LMT96 PBLL	no	no/si	24/12-18	85%	82%	Ducassou 2011
EURO-LB02	2002-2007	319	BFM random	no	no	11-24	87%	82%	Landmann 2017

LBL: PROTOCOLLO AIEOP LNH-97





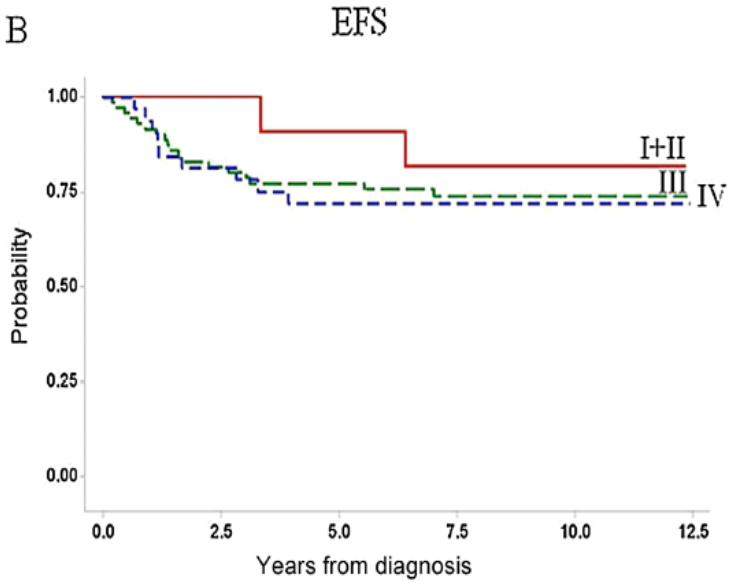
Schema di trattamento:
LSA2-L2 modificato

Pillon M, PBC 2015

AIEOP LNH-97: RISULTATI

TABLE III. Univariate Analysis of Risk Factors

	Patients No.	7-year EFS % (SE)	Events	P value
Gender				
Male	84	73 (5)	22	0.69
Female	30	76 (8)	7	
Median age at diagnosis				
< 9 years	57	71 (6)	16	0.49
≥ 9 years	57	77 (6)	13	
Immunophenotype				
T	88	71 (5)	25	0.17
Pre-B	26	83 (8)	4	
LDH				
<500 IU/L	43	69 (7)	13	0.56
≥500 IU/L	71	77 (5)	16	
Bone marrow involvement				
Yes	31	71 (8)	9	0.61
No	83	75 (5)	20	
Mediastinal mass				
Yes	76	75 (5)	19	0.91
No	38	72 (8)	10	
Stage				
I + II	11	82 (12)	2	0.48
III + IV	103	73 (4)	27	
Early response				
CR on day +15	19	83 (9)	3	0.36
CR after day +15	93	74 (5)	24	



7-year EFS by stage:

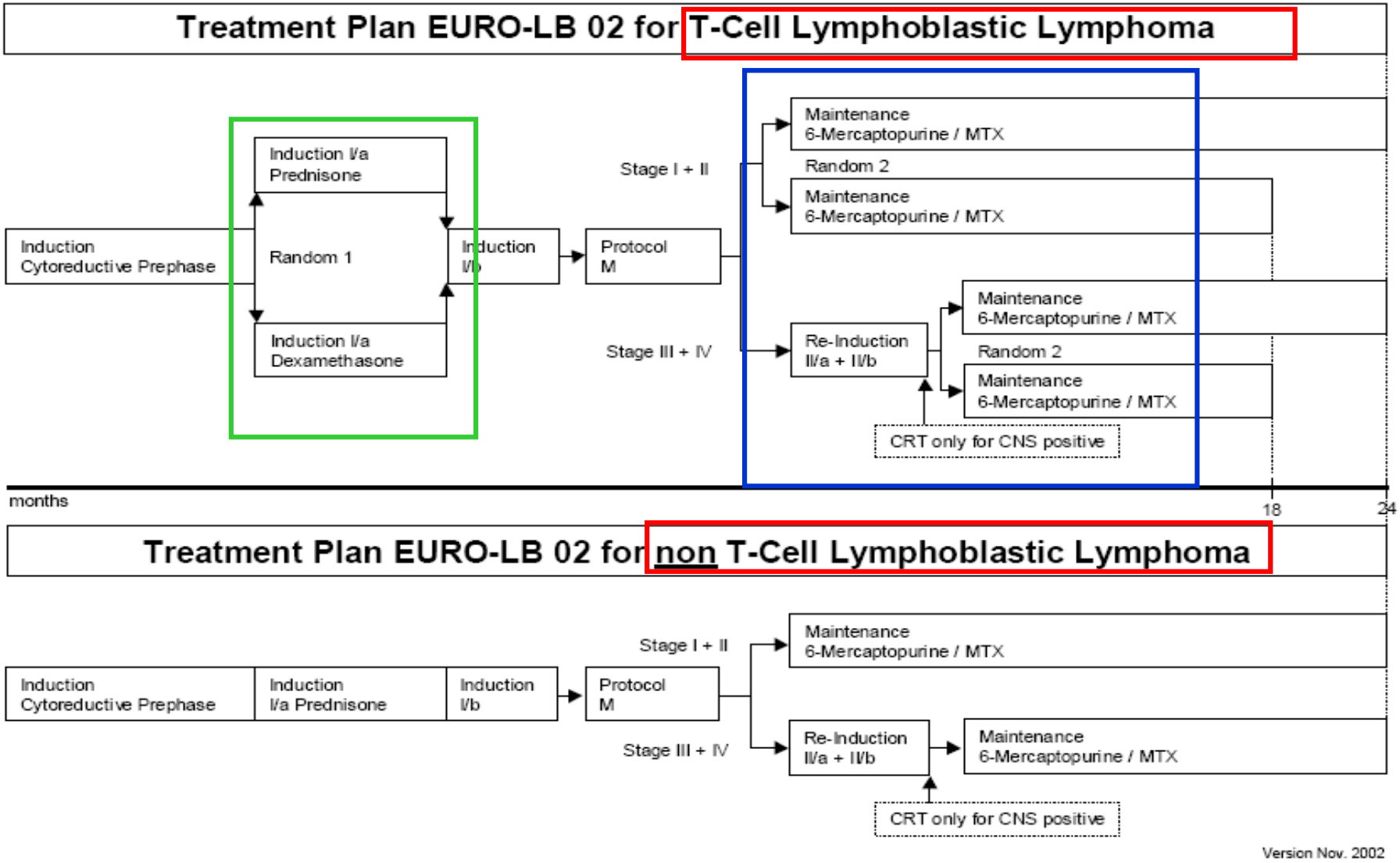
stage I–II, 82+/-12%;

stage III, 74+/-5%;

stage IV, 72+/-8%; p=0.76

Pillon M, PBC 2015

EURO-LB 02: STUDIO RANDOMIZZATO



Landmann E, Haematologica 2017

EURO-LB02: risultati

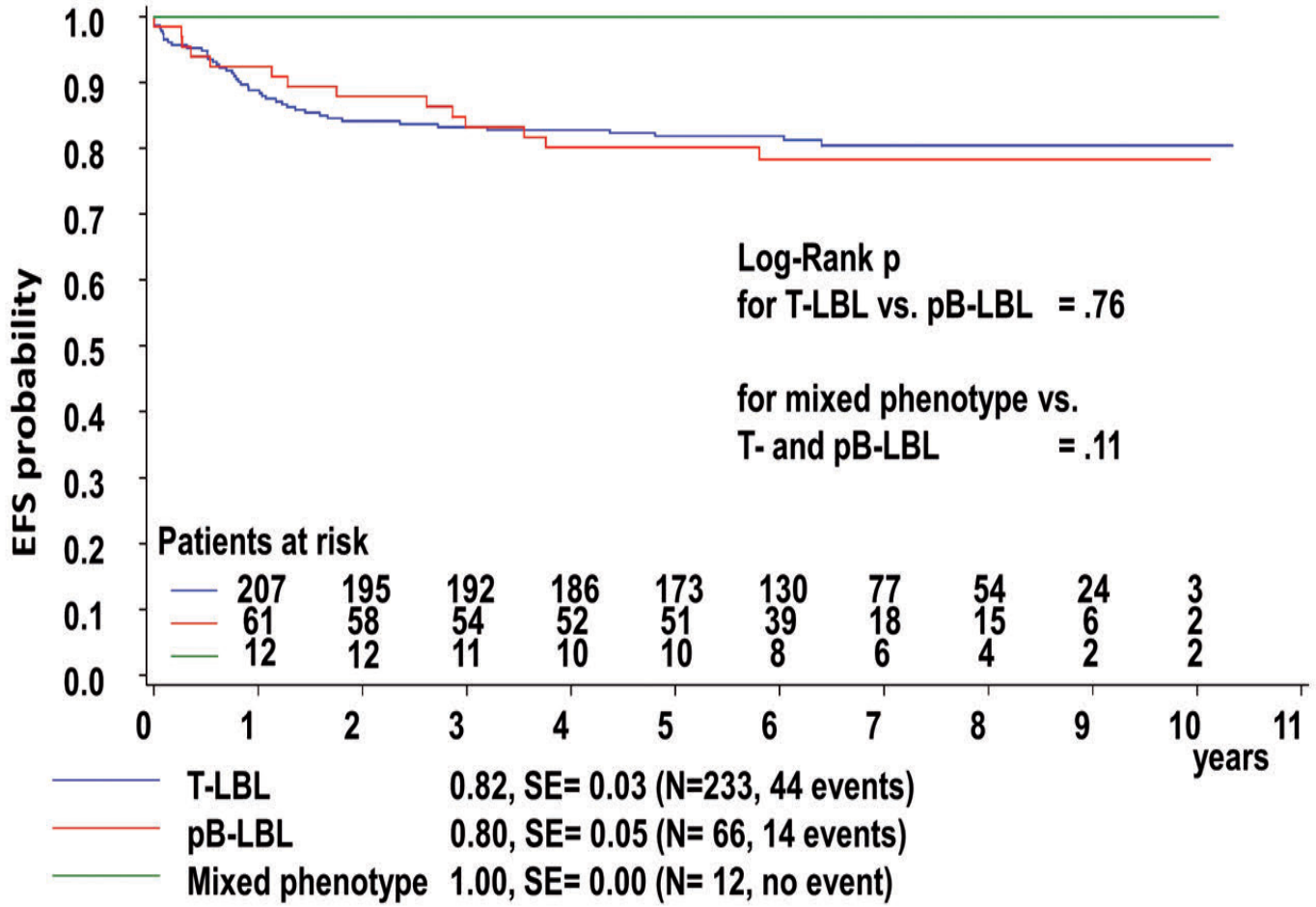
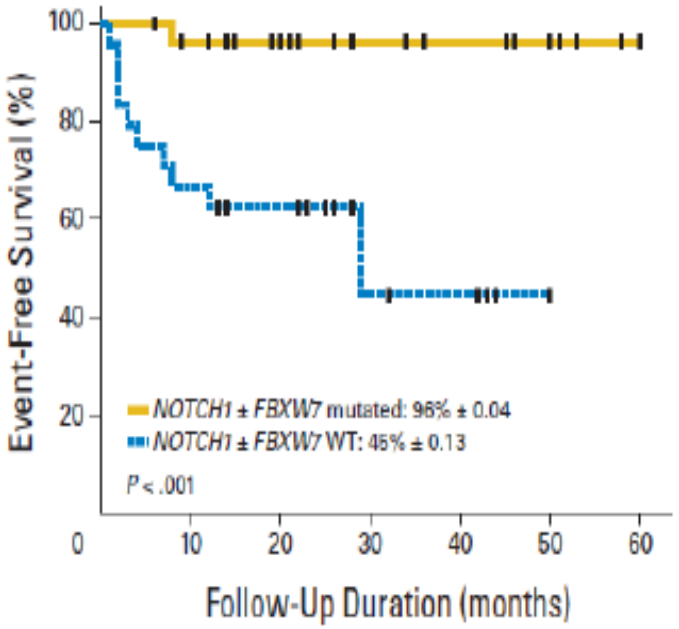


Figure 2. The 5-year event-free survival (EFS, from diagnosis) of protocol patients with T-cell, precursor B-cell and biphenotypic lymphoblastic lymphoma. EFS: event-free survival; SE: standard error. The median time to an event was 0.9 and 2.3 years (P=0.21) in patients suffering from T-LBL and pB-LBL, respectively.

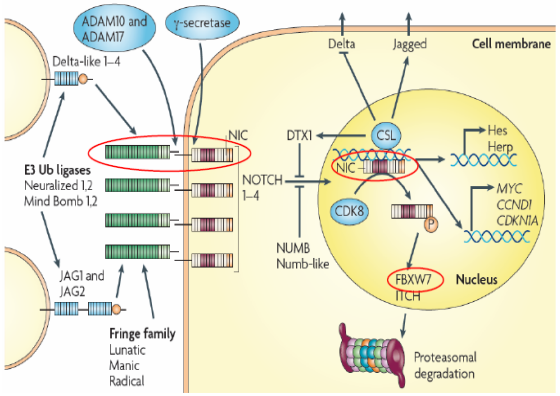
Landmann E, Haematologica 2017

Analisi ad interim: NOTCH1 e FBXW7



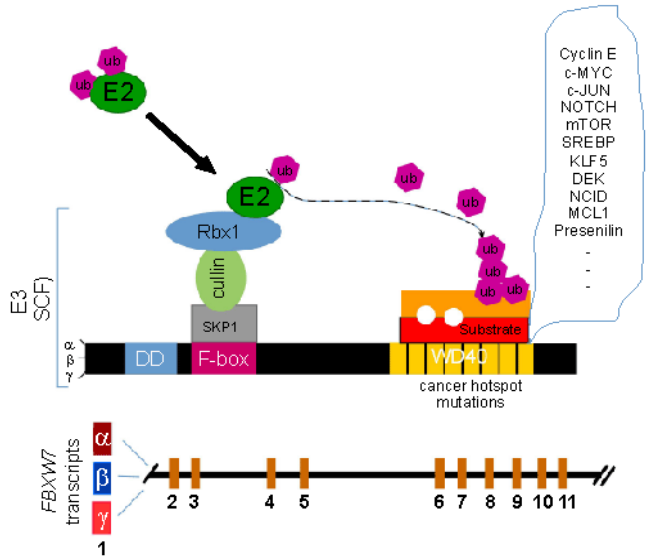
from: Kox et al., Leukemia. 2010;24(12):2005-13
and Callens et al., J Clin Oncol. 2012

NOTCH1: function

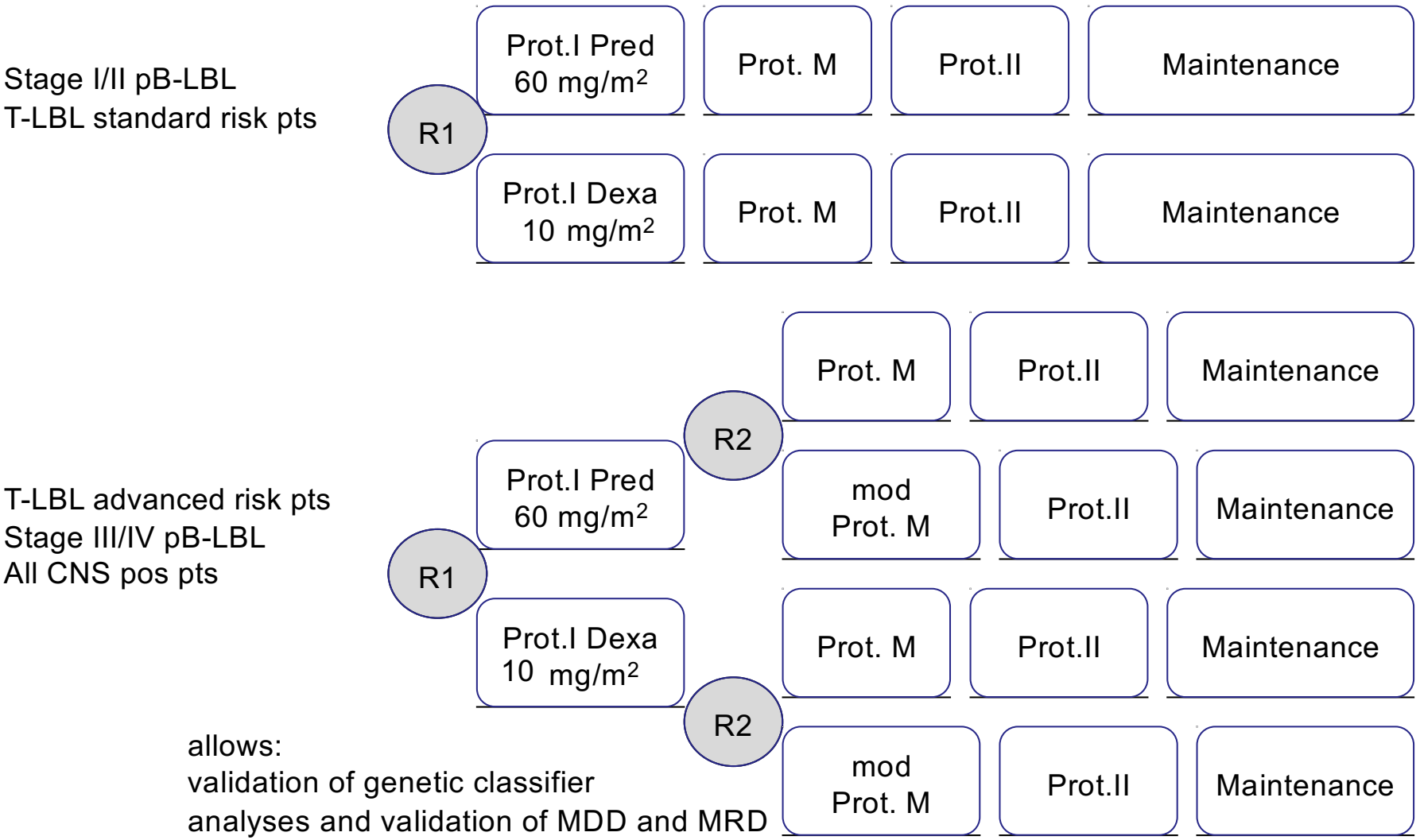


- involved in regulation of many cellular processes, e. g. early T-cell development
- important for its degradation: tumor suppressor FBXW7

from: Dotto GP. Nat Rev Cancer. 2009 Aug;9(8):587-95



Nuovo Protocollo: LBL 2018



allows:
validation of genetic classifier
analyses and validation of MDD and MRD

LBL: ricadute

Daratumomab (anti-CD38)

CD38

- transmembrane glycoprotein
- overexpressed on a variety of hematological maligancies

Daratumomab

- human IgG1kappa monoclonal antibody
- high affinity to a unique epitope on CD38
- induces lysis of CD38 positive cells via
- complement-dependent cytotocicity (CDC)
- antibody-dependent cell mediated cytotoxicity (ADCC)
- antibody-dependent cell mediated phagocytosis

De Weers M., et al., J Immunol., 2011
Overdijk MB et al., ASH abstract 51257, 2012

LINFOMA ANAPLASTICO A GRANDI CELLULE (ALCL)

E' il sottotipo di LNH pediatrico meno frequente (10-15%)

Si presenta spesso con sintomi sistemici (B) quali febbre, calo ponderale, sudorazione notturna e con coinvolgimento dei linfonodi periferici

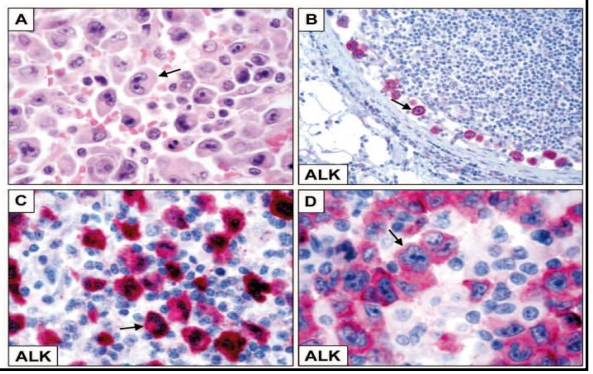
L'interessamento dell'SNC alla diagnosi è raro

Tipicamente le cellule esprimono il CD30

Il 90-95% dei casi di ALCL pediatrico presentano la traslocazione t(2;5)(p23;q35), che coinvolge il gene NPM e ALK

Costituisce un modello ideale di malattia per lo studio della risposta immunitaria tumore-specifica

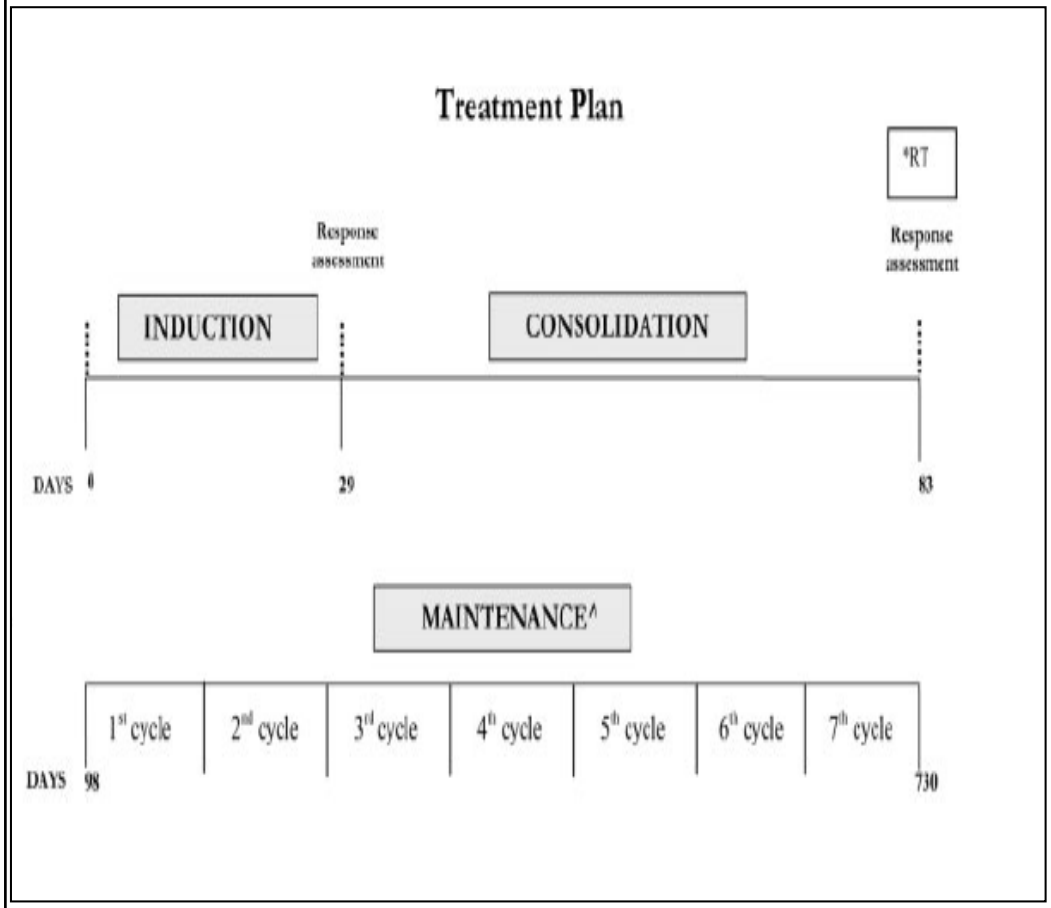
Il regime terapeutico ottimale è ancora da definire

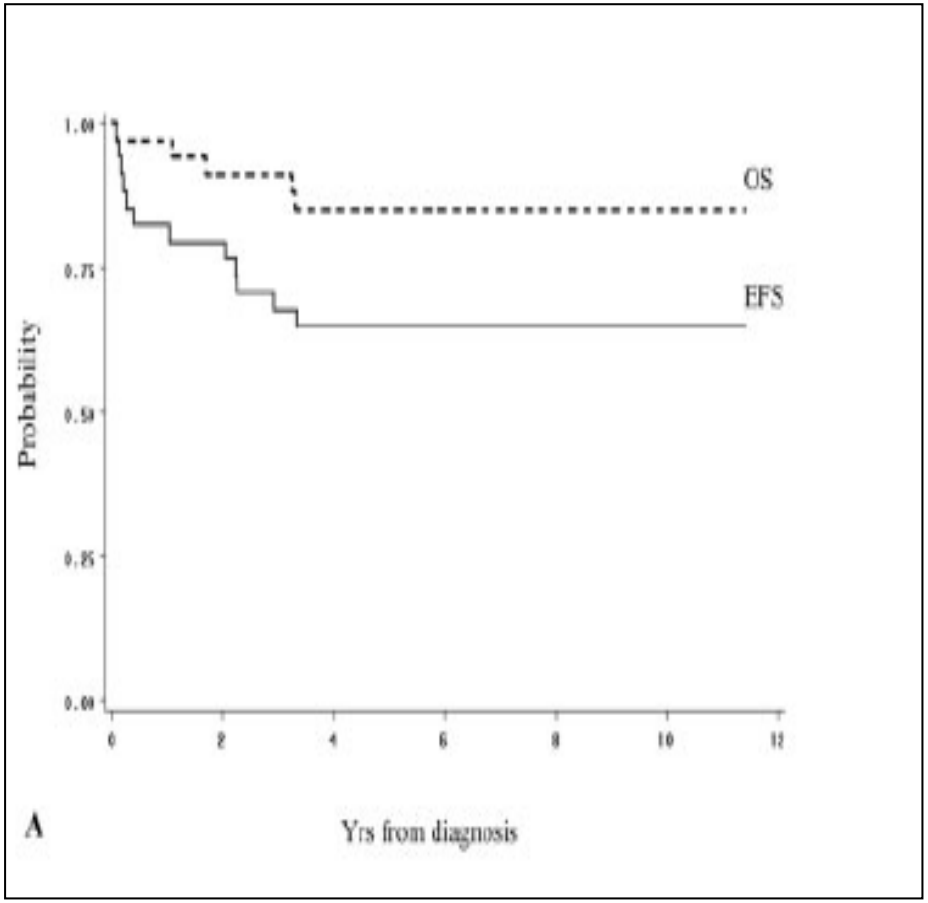


ALCL:risultati terapeutici

Gruppo	Periodo di studio	N.	Regime di trattamento	RT locale	SNC profilassi	Durata (mesi)	OS	EFS	Bibliografia
Studio spont. Bologna	1983-1989	13	mod LSA_2-L_2	si	si	24	100%	63% (4aa)	Vecchi 1993
BFM	1983-1992	62	BFM 83,86,90	no	si	2-5	83%	81% (9aa)	Reiter 1994
St Jude	1975-1993	18	CHOP or MACOP-B +/- mantenimento	si	na	na	84%	57% (5aa)	Sandlund 1994
ITM	1976-1993	27	Protocollo Locale per T-LLA	si	no	8-24	84%	72% (8aa)	Massimino 1995
SFOP	1988-1997	82	HM-89; HM-91 COP-COPADM	no	no	7-8	83%	66% (3aa)	Brugières 1998
MSKCC	1972-1997	19	LSA_2-L_2	si	si	24	84%	56% (5aa)	Mora 2000
BFM	1990-1995	89	NHL-BFM-90	no	si	2-5	na	76% (5aa)	Seidemann 2001
UKCCSG	1990-1998	72	NHL-9000;NHL-9602 COP-COPADM	no	si	5	65%	59% (5aa)	Williams 2002
TCCSG	1986-2001	34	BFM like	si	si	2-5	71%	67% (5aa)	Mori 2003
AIEOP	1993-1997	34	AIEOP LNH-92 (mod LSA_2-L_2)	si	si	24	85%	65% (10aa)	Rosolen 2005
POG	1994-2000	86	APO + mantenimento	si	si	12	88%	72% (4aa)	Laver 2005
CCG	1996-2001	152	CCG-5941 (mod LNH-T)	si	si	11	80%	68% (5aa)	Lowe 2009
EICNHL	1999-2006	217	ALCL99 Random	no	si/no	4-6/12	93%	74% (2aa)	Le Deley 2010

ALCL: Risultati del Protocollo AIEOP LNH-92





OS a 10 anni **85**% ± 6%,
EFS a 10 anni **65**% **±** 8%

Rosolen A, Cancer 2005

AIEOP LNH-97 per ALCL

R1 Stage I+II, completely resected

P A B A

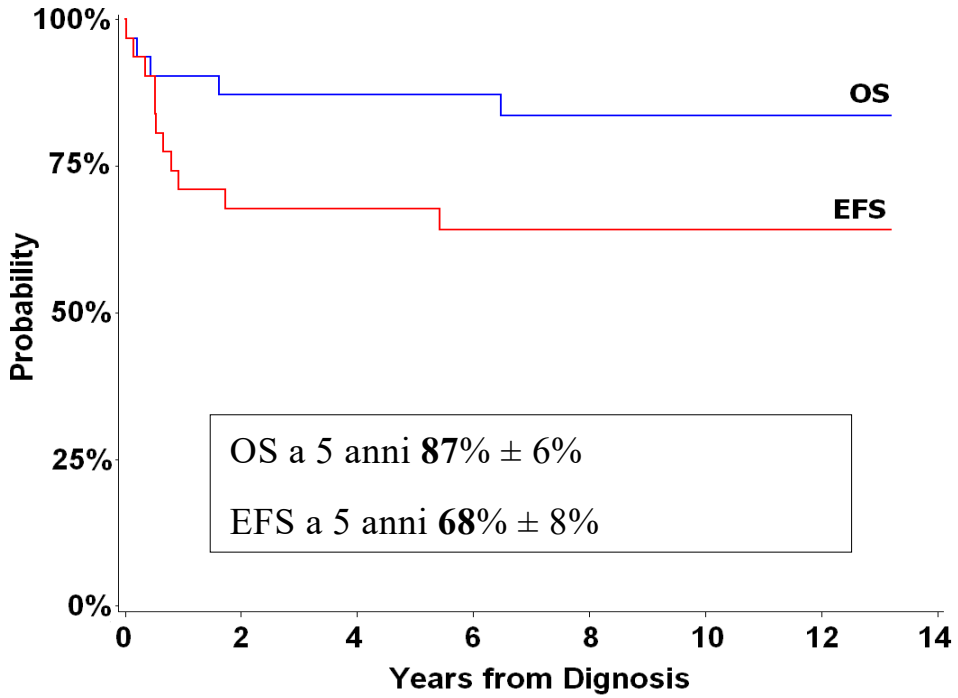
R2 Stage I+II, not resected
Stage III

P A B A B A B

R3 Stage IV (BM/CNS positive*)
Independently from stage, all the patients with:
-multifocal bone lesions
-skin
-lung
-lymphohistiocytic lymphoma

P AA BB CC AA BB CC

* Z * Z * Z * Z * Z * Z



Pillon M, PBC 2012

Characteristics	Patients: No. of patients	Patients: %	Outcome: No. of events	Outcome: pEFS % (SE)	*P* univariate
All eligible patients	34				
Median age	11.6 yrs				
Range in yrs	4.2–14.9				
Median follow-up	8.4 yrs				
Range in yrs	0.1–11.4				
Gender					
Male	18	53	8	55 (11)	0.21
Female	16	47	4	75 (10)	
Age					
< 10 yrs	11	32	4	63 (14)	0.84
≥ 10 yrs	23	68	8	65 (9)	
Stage					
II	10	29	4	60 (15)	
III	17	50	6	65 (12)	0.96
IV (CNS-)	7	21	2	71 (17)	
Immunology					
T	23	68	6	74 (9)	
Null	3	9	2		
Not available	8	23	4		
Tumor sites					
Lymph-nodes	27	79	11	59 (9)	0.19
Mediastinal mass	16	47	4	56 (11)	0.26
Skin/subc. nodules	4	12	2		
Bone	8	24	2	75 (15)	0.59
Lung	2	6	1		
Splenomegaly	4	12	2		
Hepatomegaly	3	9	1		
Bone marrow	2	6	2		
Abdomen	3	9	2		
Other	3	9	0		
LDH					
< 500 IU/L	25	74	4	68 (19)	0.54
≥ 500 IU/L	9	26	8	55 (16)	

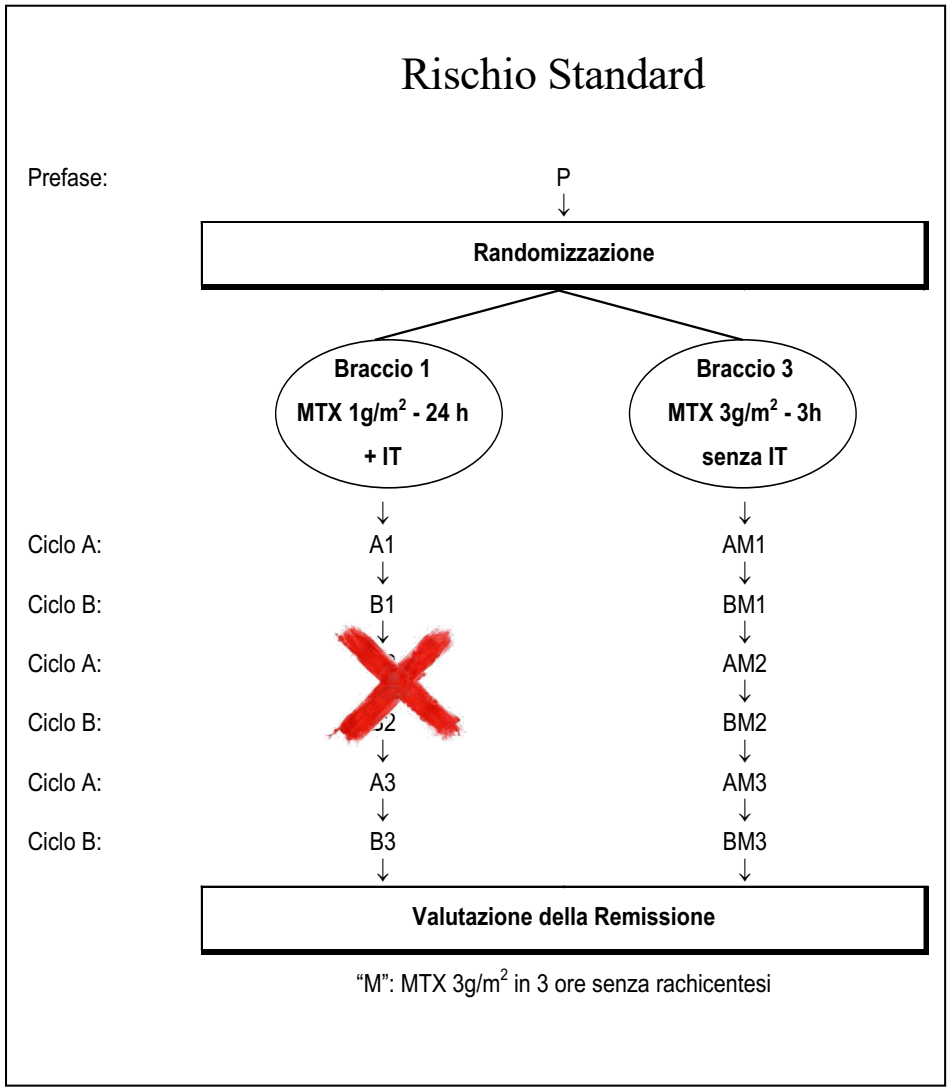
pEFS: probability of event-free survival; SE: standard error: CNS: central nervous system; LDH: lactate dehydrogenase.

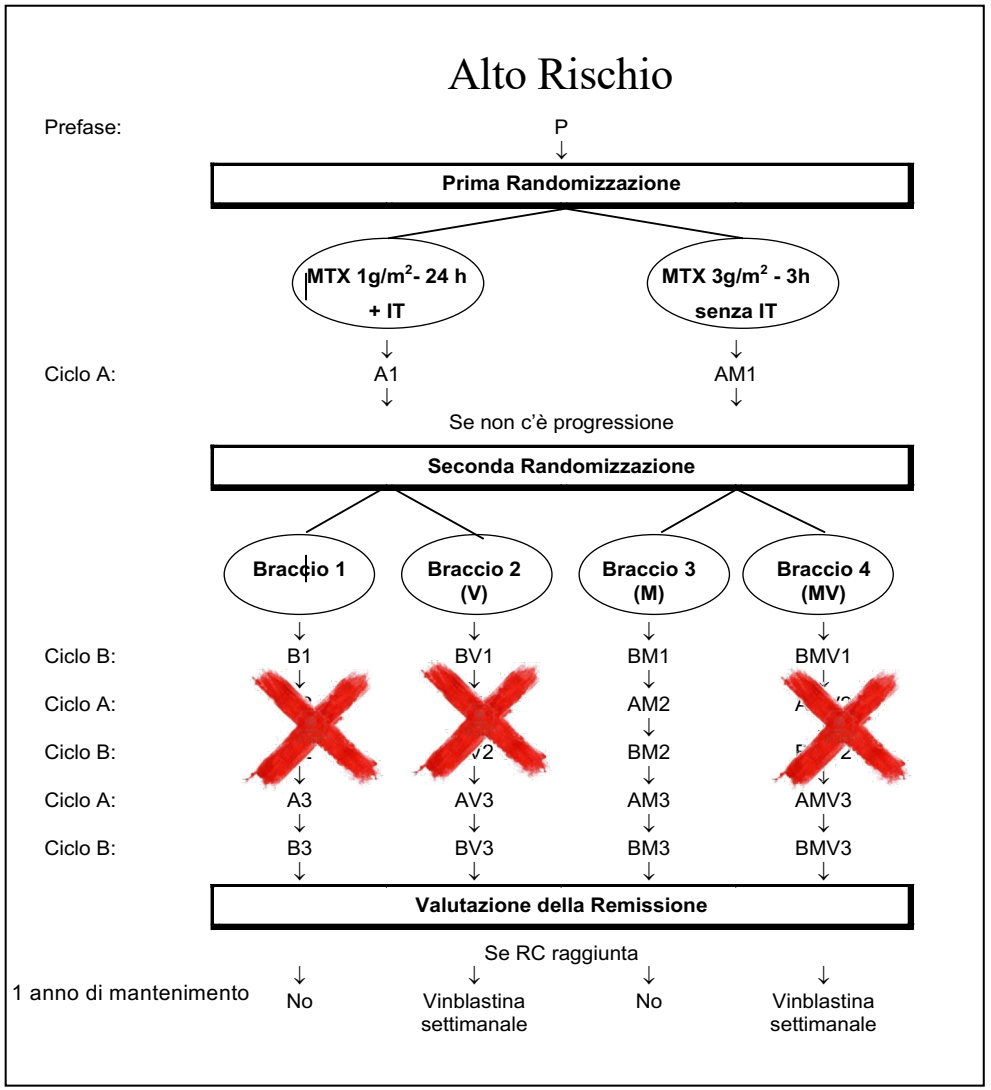
Nessun fattore prognostico!

Pillon M, PBC 2012

A.I.E.O.P. Associazione Italiana Ematologia Oncologia Pediatrica

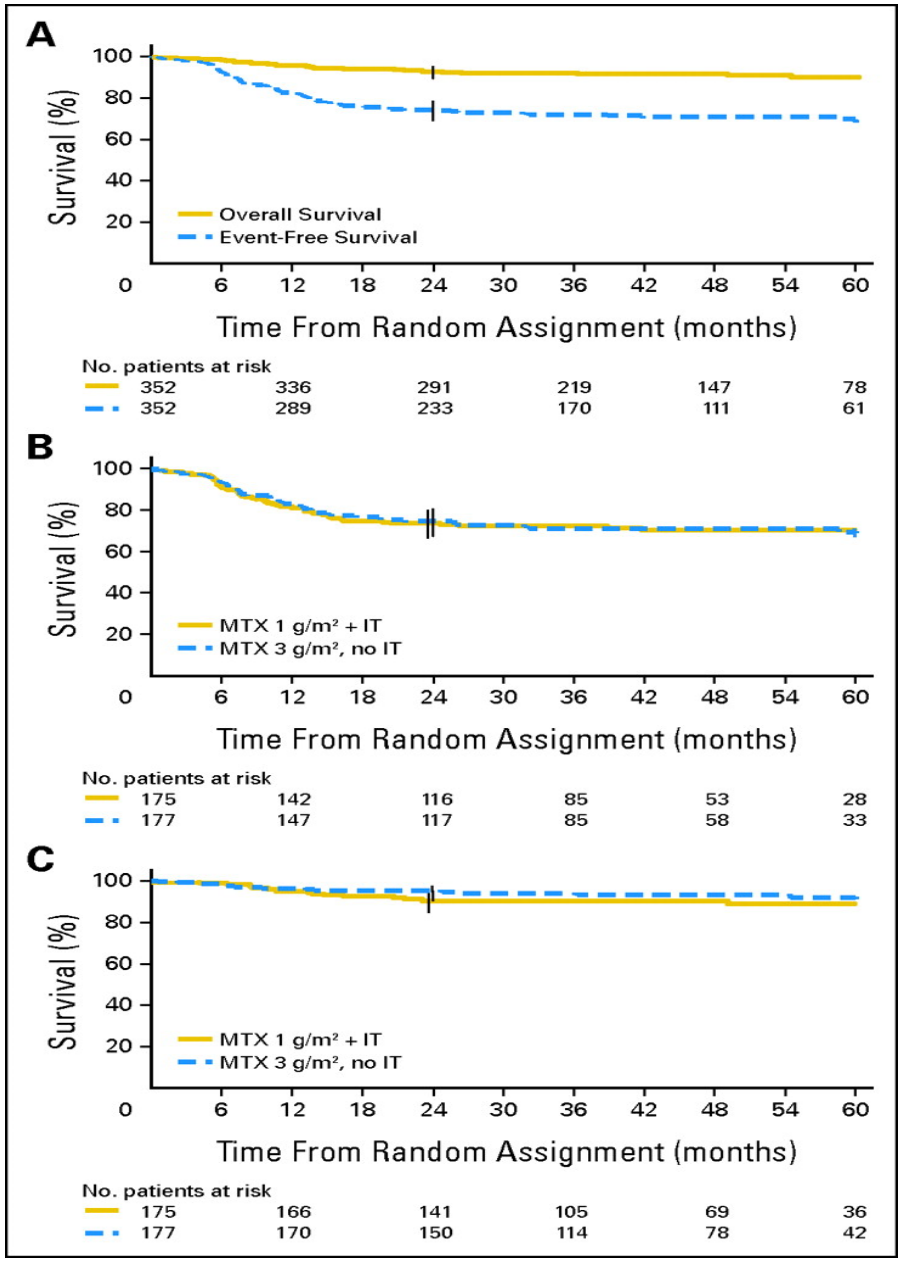
"INTERNATIONAL TRIAL ALCL 99"
PER IL TRATTAMENTO DEGLI ALCL - STUDIO RANDOMIZZATO





1° random per SR e HR: MTX 1 gr/mq in 24 ore+ IT vs. MTX 3 gr/mq in 3 ore senza IT
2° random per HR: mantenimento con Vinblastina vs. mantenimento senza Vinblastina

RISULTATI DELLA PRIMA RANDOMIZZAZIONE



(A) **OS** a 2 anni per intera popolazione-352 pazienti: **92.5%** (95% I.C., 89.3%-94.8%)

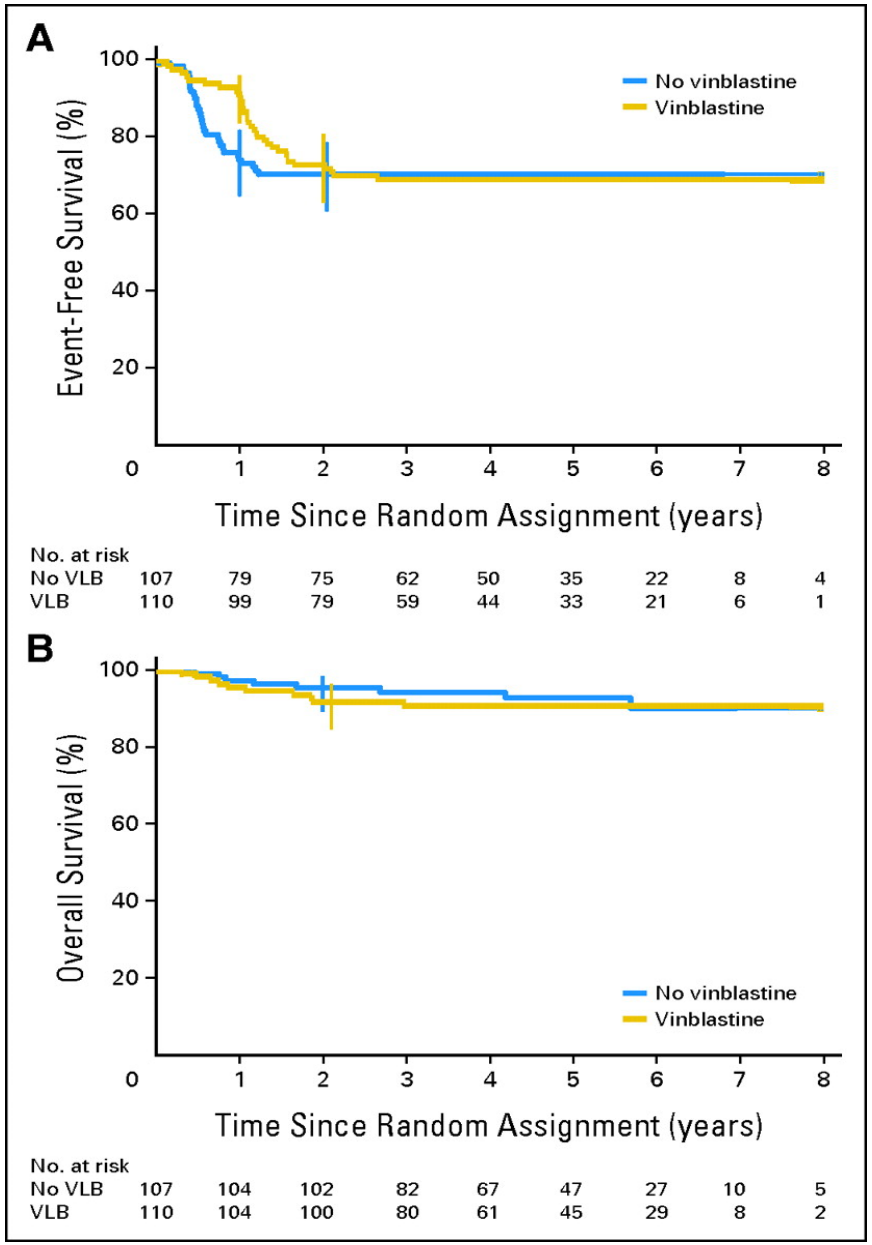
EFS a 2 anni per intera popolazione-352 pazienti: **74.1%** (95% I.C., 69.2%-78.4%)

(B) EFS a 2 anni per gruppo di trattamento:
MTX 3 gr/mq senza IT, 74.5%
MTX 1 gr/mq con IT, 73.7%, P=n.s.

(C) OS a 2 anni per gruppo di trattamento:
MTX 3 gr/mq senza IT, 94.9%
MTX 1 gr/mq con IT, 90.1%, P=n.s.

Brugières L et al, JCO, 2009

RISULTATI DELLA SECONDA RANDOMIZZAZIONE



EFS a 2 anni per gruppo di trattamento:
si VBL : **72.5%**
no VBL: **70.1%**, P=n.s.
EFS a 2 anni per intera popolazione-217 pazienti: 71% (95% I.C., 75%-77%)

OS a 2 anni per gruppo di trattamento:
si VBL vs. no VBL: HR=1.28; 95%I.C., 0.49 to 3.38; P=n.s.
OS a 2 anni per intero gruppo-217 pazienti:
94% (95% I.C., 89%-96%)

Le Deley MC et al, JCO, 2010

FATTORI PROGNOSTICI		Univariate Analysis				Multivariate Analysis (p-value <0.25)			
Parameter		**P-value**	**HR**	**95% CI**		**P-value**	**HR**	**95% CI**	
Sex	**M**		1*						
	F	*0.5312*	1.210	0.666	2.197				
Median age	**<10 yrs**		1*						
	>=10 yrs	*0.5849*	0.850	0.474	1.525				
Risk group	**LR+SR**		1*						
	HR	*0.2051*	1.504	0.800	2.828	0.1986	0.461	0.141	1.502
B symptom	**no**		1*						
	yes	*0.6757*	1.138	0.620	2.088				
mediastinum	**no**		1*						
	yes	*0.0958*	1.654	0.915	2.989	0.4146	1.524	0.554	4.192
lung	**no**		1*						
	yes	*0.4037*	1.349	0.668	2.725				
liver	**no**		1*						
	yes	*0.9403*	1.036	0.409	2.625				
spleen	**no**		1*						
	yes	*0.9051*	0.952	0.425	2.132				

		Univariate Analysis				Multivariate Analysis (p-value <0.25)			
Parameter		**P-value**	**HR**	**95% CI**		**P-value**	**HR**	**95% CI**	
Abdominal LN	**no**		1*						
	yes	*0.9000*	1.038	0.577	1.870				
Peripheral LN	**no**		1*						
	yes	*0.0743*	3.637	0.881	15.017	0.1880	2.661	0.620	11.428
Median LDH	**no**		1*						
	yes	*0.6598*	0.877	0.488	1.575				
visceral	**no**		1*						
	yes	*0.4427*	1.275	0.686	2.370				
Visceral bis	**no**		1*						
	yes	*0.6948*	0.753	0.182	3.107				
BM	**no**		1*						
	yes	*0.1589*	1.951	0.770	4.945	0.8312	1.123	0.387	3.257
Alkc	**neg**		1*						
	pos		-						
Subtype_SCLH	**no**		1*						
	yes	***0.0008***	2.771	1.524	5.037	**0.0069**	2.428	1.276	4.619

ALCL

Leukemia (2013) 27, 416–422

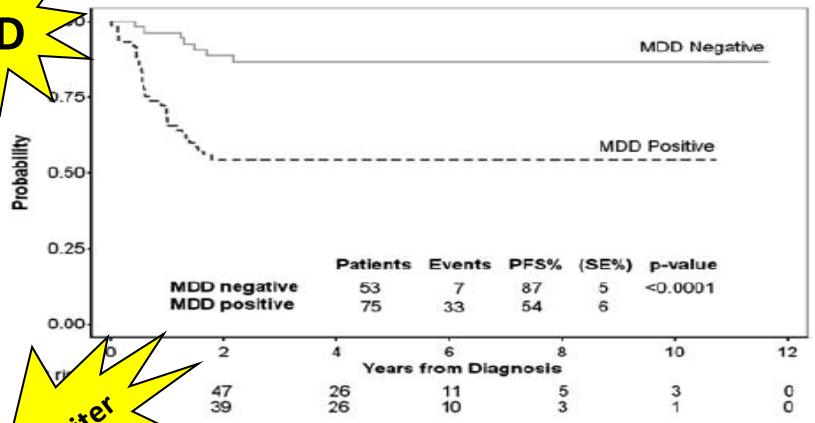
www.nature.com/leu

ORIGINAL ARTICLE

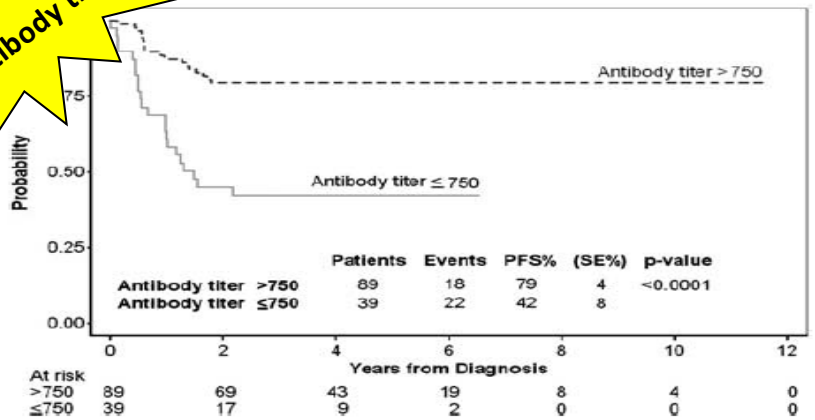
Use of minimal disseminated disease and immunity to NPM-ALK antigen to stratify ALK-positive ALCL patients with different prognosis

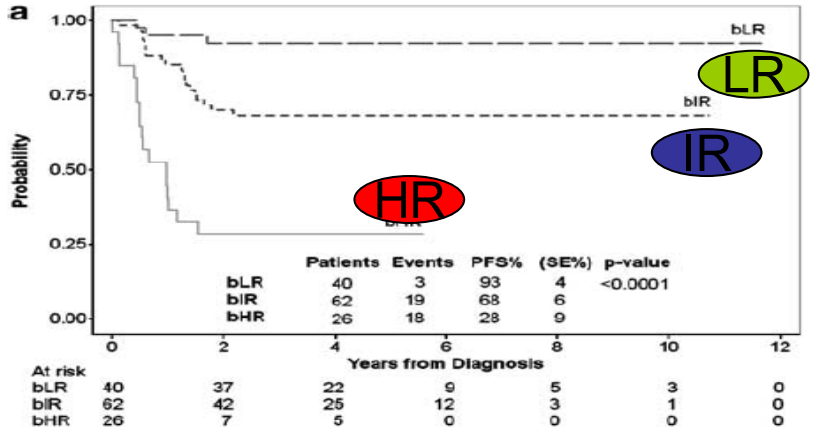
L Mussolin[1,4], C Damm-Welk[2,4], M Pillon[1], M Zimmermann[2], G Franceschetto[1], K Pulford[3], A Reiter[2], A Rosolen[1,5] and W Woessmann[2,5]

MDD



Antibody titer





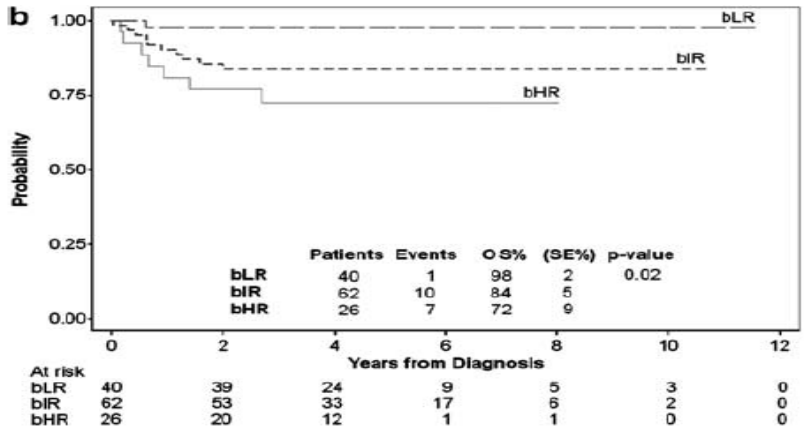
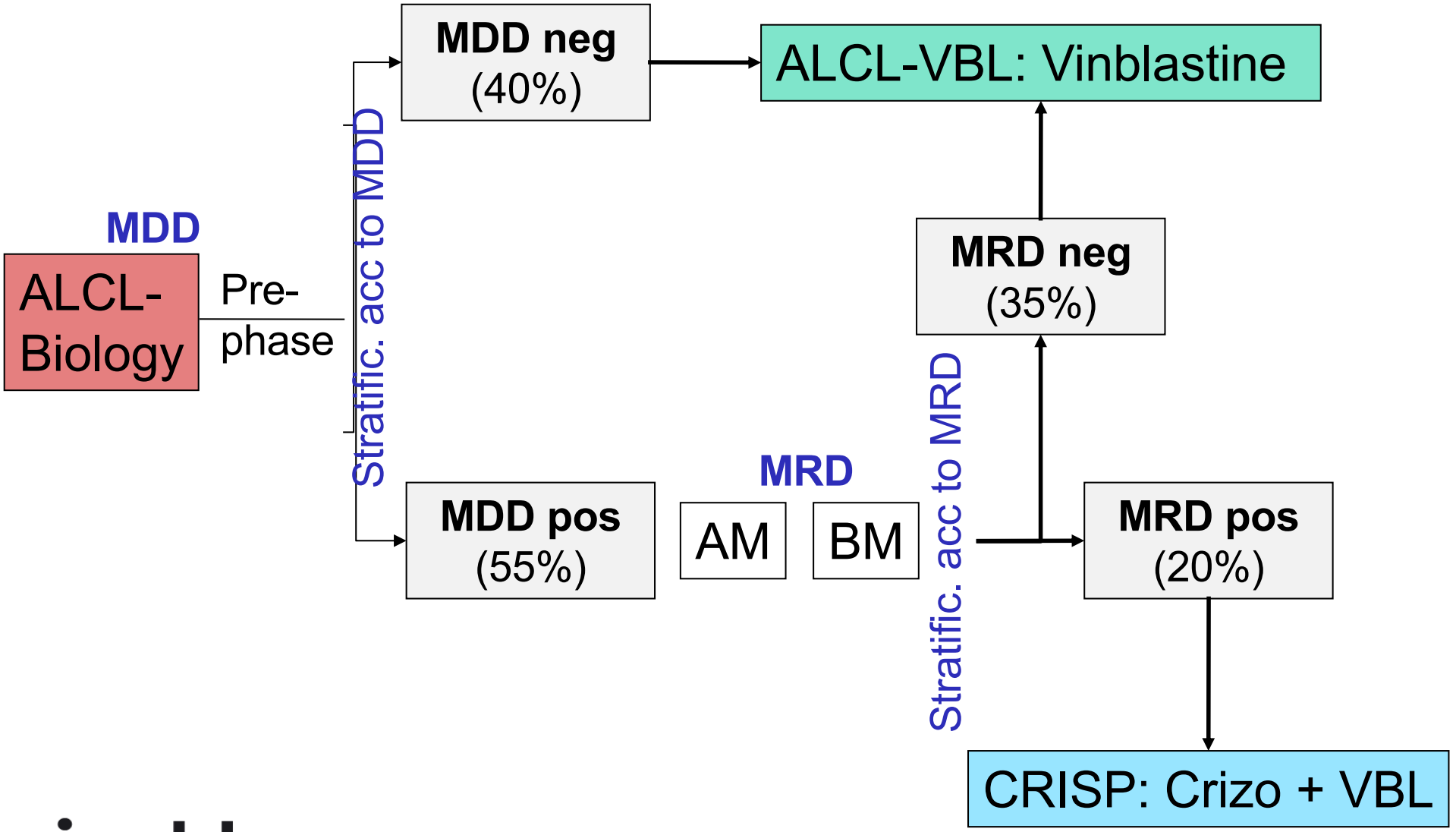


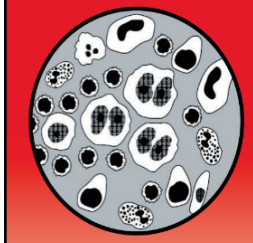
Figure 1. Five-year PFS of patients with NPM-ALK-positive anaplastic

ALCL: NUOVA PROPOSTA DI STUDIO



eicnhl
European Inter-Group for Childhood Non-Hodgkin Lymphoma

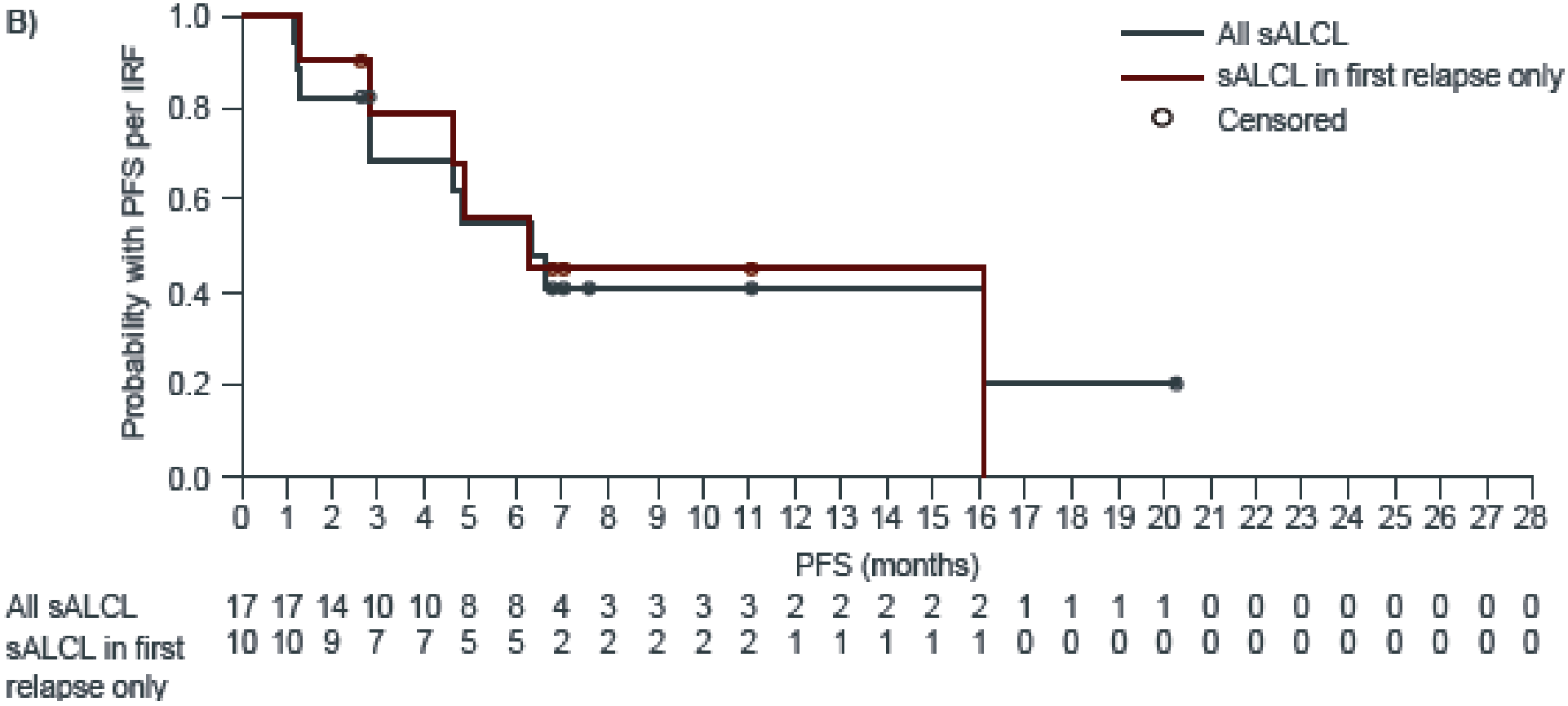
251



Phase 1/2 study of brentuximab vedotin in pediatric patients with relapsed/refractory systemic anaplastic large-cell lymphoma or relapsed/refractory Hodgkin lymphoma

Franco Locatelli,[1] Christine Mauz-Koerholz,[2] Kathleen Neville,[3] Anna Llort,[4] Auke Beishuizen,[5] Stephen Daw,[6] Marta Pillon,[7] Nathalie Aladjidi,[8] Thomas Klingebiel,[9] Judith Landman-Parker,[10] Aurora Medina-Sanson,[11] Keith August,[12] Dirk Huebner,[13] Jessica Sachs,[13] Kristen Hoffman,[13] Judith Kinley,[13] Sam Song,[13] Gregory Song,[13] Steven Zhang,[13] Lia Gore[14]

[1]Department of Pediatric Haematology-Oncology, Istituto di Ricovero e Cura a Carattere Scientifico, Ospedale Bambino Gesù, Rome; University of Pavia, Pavia, Italy; [2]University Hospital Giessen, Pediatric Hematology and Oncology; Justus-Liebig University, Giessen; Medical Faculty, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany; [3]Division of Hematology and Oncology, Arkansas Children's Hospital, Little Rock, AR, USA; [4]Laboratory of Translational Research in Pediatric Cancer, Vall d'Hebron Research Institute, Barcelona, Spain; [5]Department of Pediatric Oncology/Hematology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; [6]Department Paediatric & Adolescent Oncology, University College London Hospital NHS Foundation Trust, London, UK; [7]Clinic of Paediatric Haemato-Oncology, Department of Women's and Children's Health, University of Padova, Padova, Italy; [8]Pediatric Hematology Unit, Centre de Référence National des Cytopénies Auto-immunes de l'Enfant (CEREVANCE) Hôpital des Enfants, Hôpital Pellegrin, CHU Bordeaux, France; [9]Clinic for Pediatric and Adolescent Medicine, University Hospital, Frankfurt, Germany; [10]Service d'hématologie et d'oncologie pédiatrique, Hopital A, Trousseau, Univ Paris, Paris, France; [11]Departamento de Hemato-Oncología, Hospital Infantil de México Federico Gómez, Secretaria de Salud (SS), Ciudad de México, México; [12]Children's Mercy Hospital, Kansas City, MO, USA; [13]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [14]Department of Pediatrics, University of Colorado School of Medicine and Center for Cancer and Blood Disorders, Childrens Hospital Colorado, Aurora, CO, USA



TTR (totale ALCL e ALCL 1° ricaduta): 1.5 mesi

Tempo mediano di PFS: 4.8 mesi

9/17 (totali) e 6/10 (1° ricaduta) sottoposti a TMO

Terapia di seconda linea per i LNH ricaduti/refrattari

Pochi studi pubblicati.

I pazienti resistenti/ricaduti hanno una OS a lungo termine che dipende dal sottotipo istologico, dal trattamento di prima linea e dal tempo di ricaduta:

EFS a lungo termine per Burkitt, DLBCL e LBL: 10-40%

EFS a lungo termine per ALCL: 40%-60%

Regimi di salvataggio usati più frequentemente:

ICE (ifosfamide, carboplatino, etoposide)

DECAL (dexametasone, etoposide, cisplatino,HD citarabina, L-Asparaginasi)

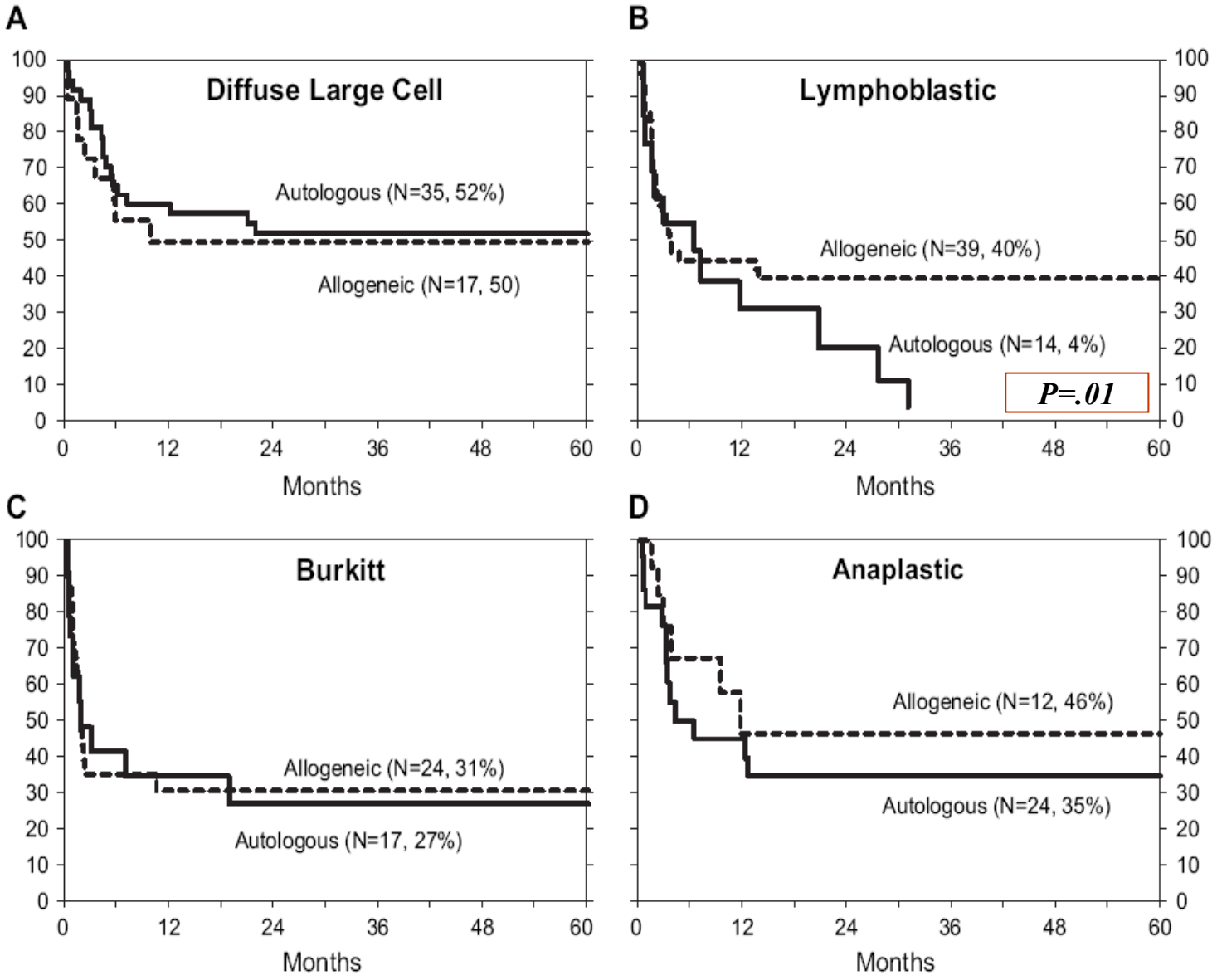
Protocolli per le Ricadute LLA

Vinblastina

Protocollo ALCL Relapse

Chemioterapia ad alte dosi seguita da TMO (autologo o allogenico)

LNH ricaduti/refrattari:
pEFS dopo auto o allo-HSCT



Gross TG et al, Biol BMT, 2010

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per il
Centro Leucemie Infantili
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