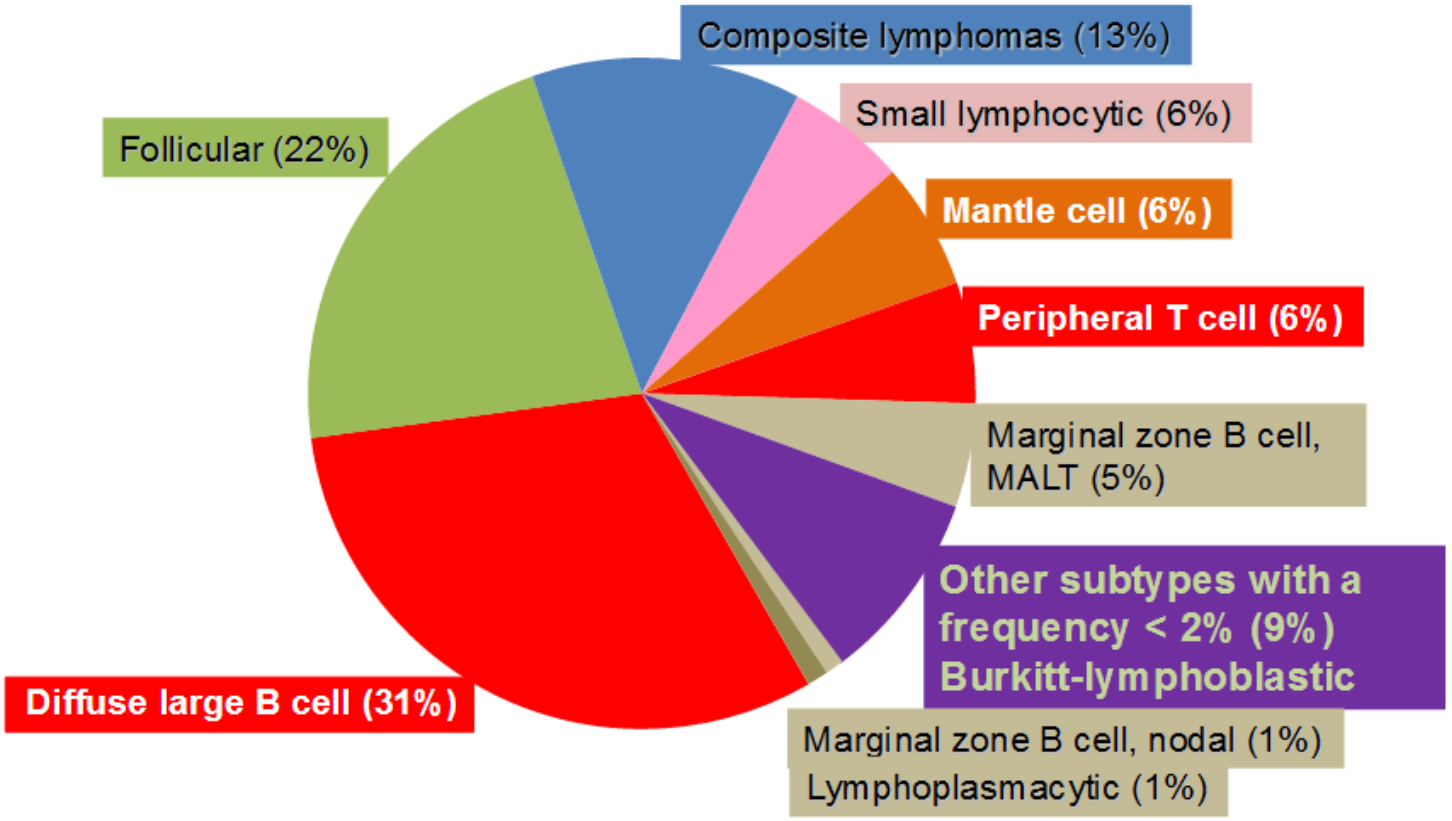
Recidiva precoce nel giovane con DLBCL : autologo o allogenico?

V. Pavone

Bari, 7 Giugno 2017

U.O Ematologia
Az.Osp.Card.G.Panico Tricase

Prevalence of adult NHL

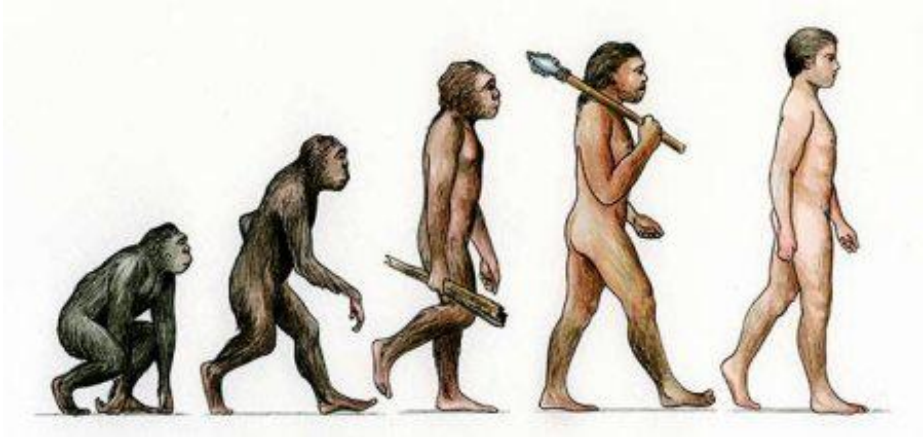


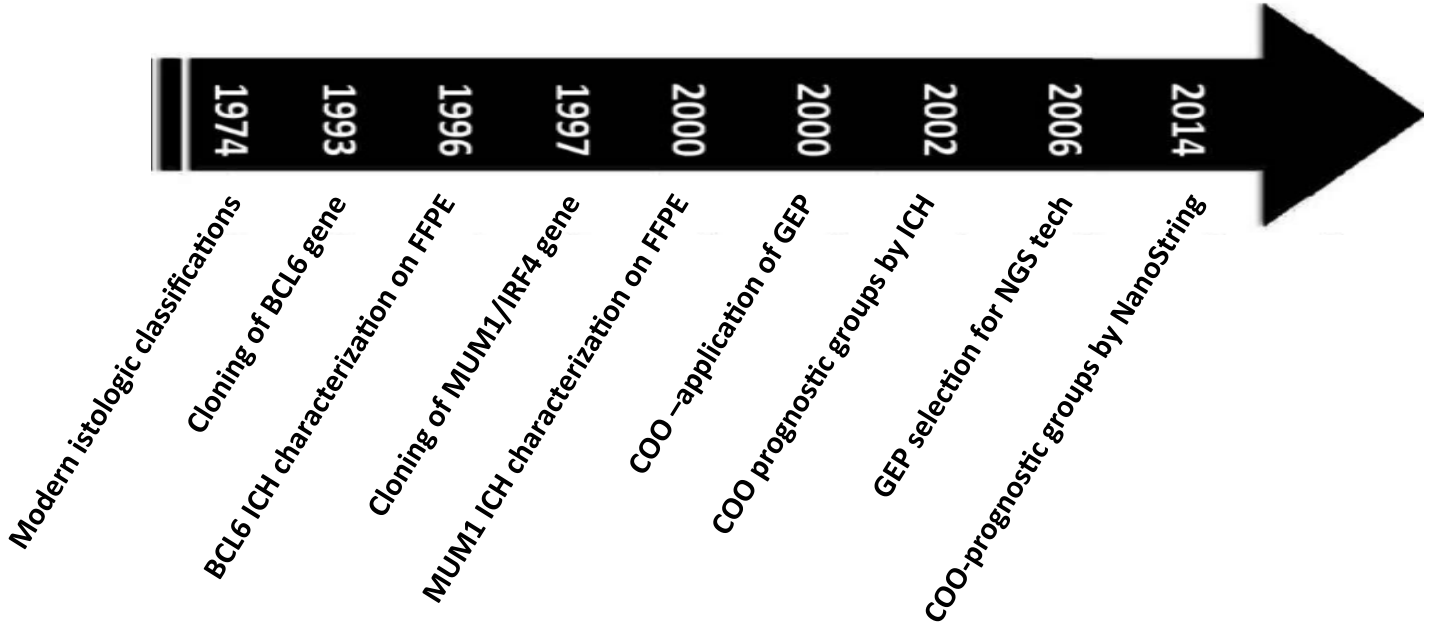
DLBCL is not pathology but multitude of diseases

2 distint COO = GC et ABC

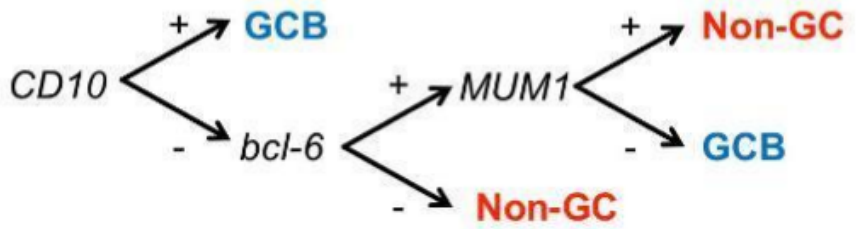
Various molecular pathway dysregulated

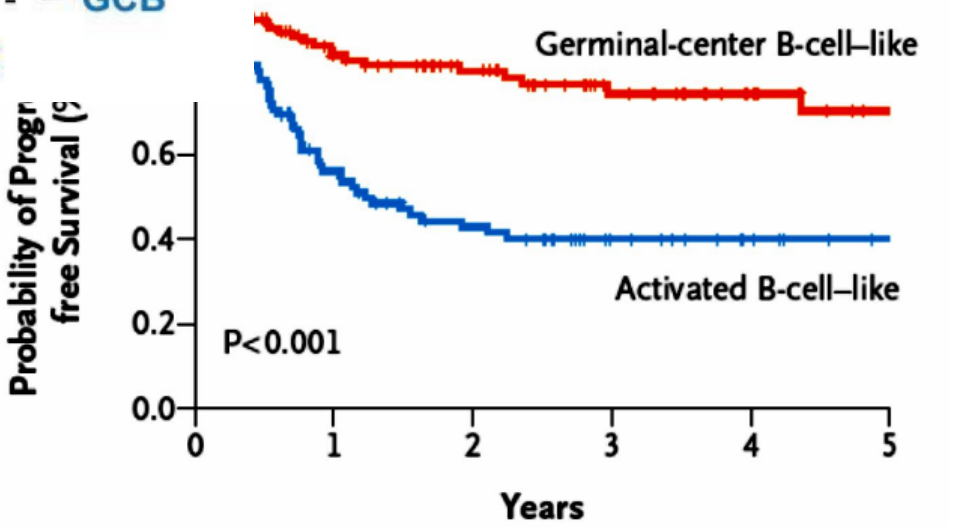
Evolution in Heterogeneity discover in DLBCL

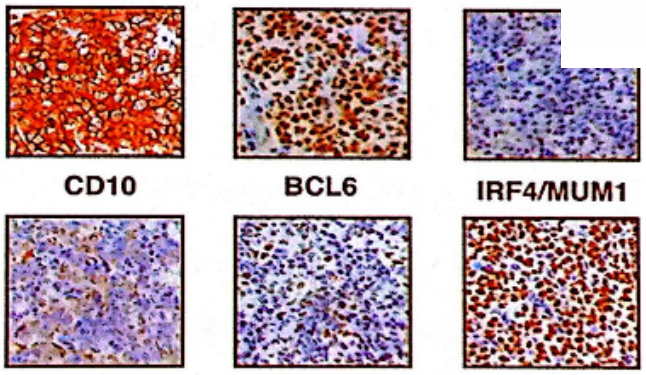




DLBCL: Cell of Origin (COO) by Hans Model







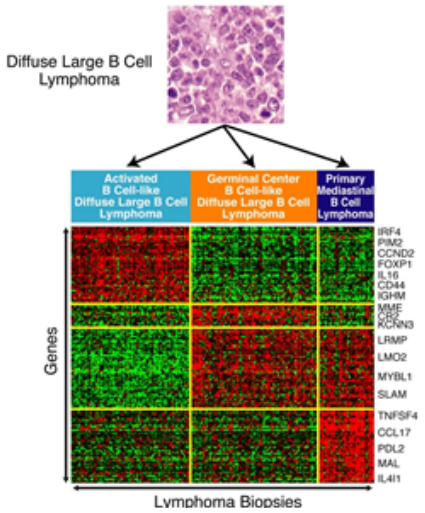
GCB

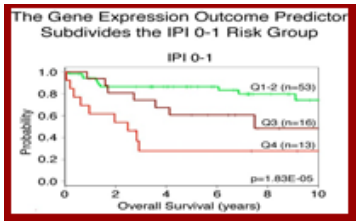
Non-GC (=ABC)

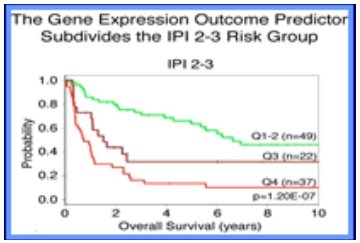
Christine P. Hans et al. Blood 2004

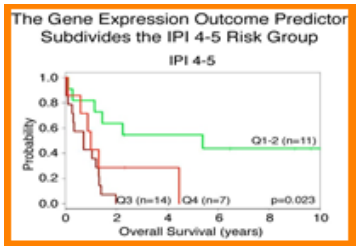
Germinal center vs activated B cell DLBCL

Molecularly and Clinically distinct Subgroups
by Gene Expression Profiling









Rosenwald A et al. NEJM 2002

MYC/BCL2 Doube HIT

- Concurrent translocations of MYC and BCL2
- The most common and well-studied type DHL is characterized by concurrent MYC and BCL2 rearrangements, occurring about 5% of all DLBCL
- Regulators of cell proliferation and apoptosis, respectively
- MYC and BCL2 may act synergistically to drive the pathogenesis, and represent a treatment-refractory subgroup with a mOS of 8 months
- Almost all arise within the GCB cell-like sutype (discordance between clinical behavior and COO subtypes)

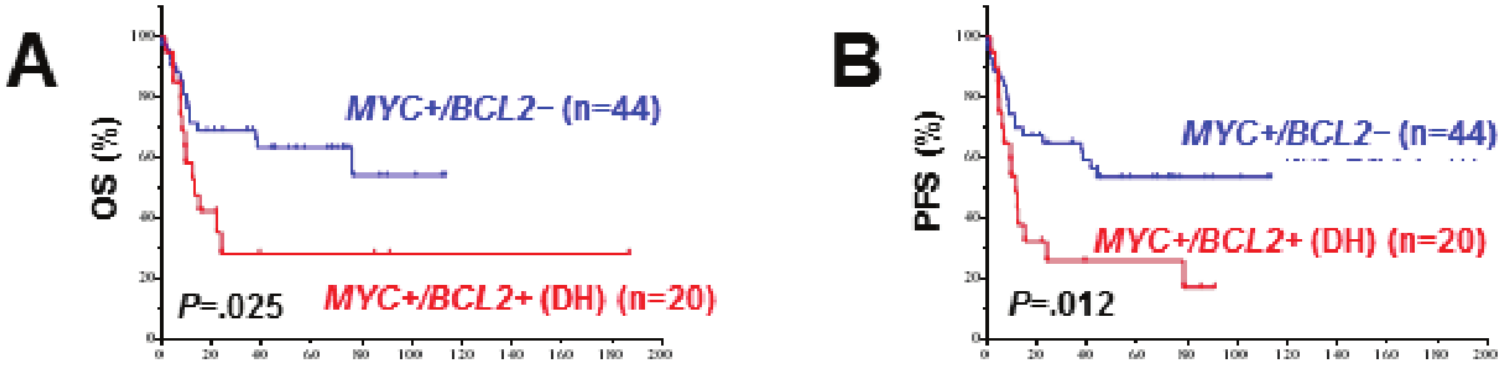
MYC/BCL2 DE

- Significantly poorer outcome than patients who express only one or neither protein
- Accounts for 18-44% of DLBCL cases
- 5 ys PFS of 25% following R-CHOP
- Unlike MYC/BCL2 DHL, DEL is more common in ABC subtype and may largely contribute to inferior survival via NF-kB pathway

Prognostic impact of concurrent *MYC* and *BCL6* rearrangements and expression in *de novo* diffuse large B-cell lymphoma

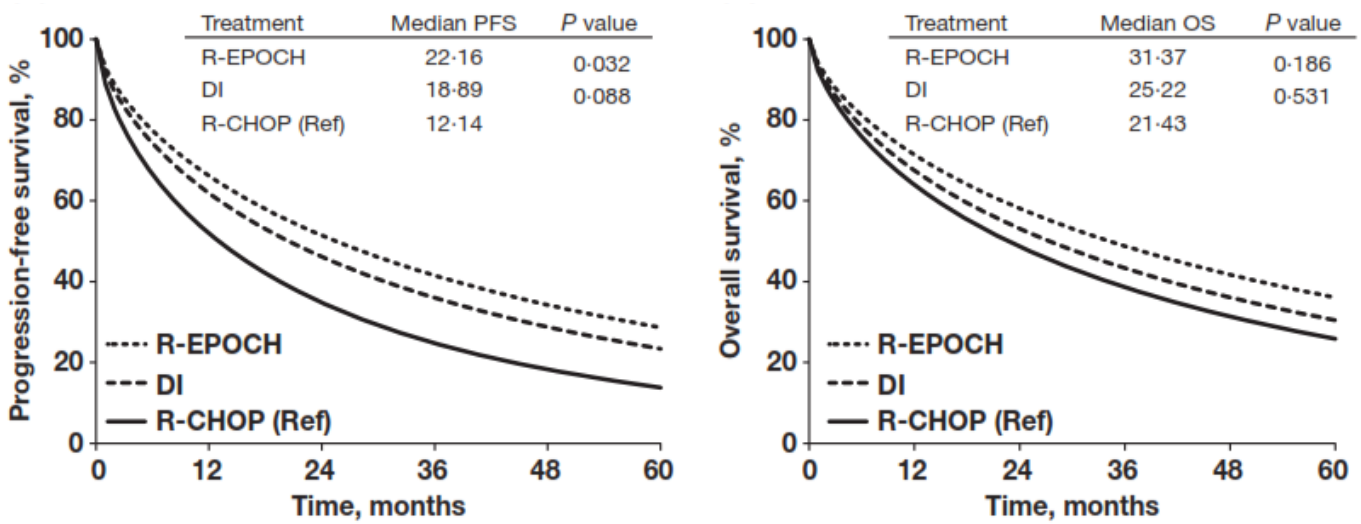
Qing Ye[1,*], Zijun Y. Xu-Monette[1,*], Alexandar Tzankov[2,*], Lijuan Deng[1], Xiaoxiao Wang[1], Ganiraju C. Manyam[3], Carlo Visco[4], Santiago Montes-Moreno[5], Li Zhang[3], Karen Dybkær[6], April Chiu[7], Attilio Orazi[8], Youli Zu[9], Govind Bhagat[10], Kristy L. Richards[11], Eric D. Hsi[12], William W.L. Choi[13], J. Han van Krieken[14], Jooryung Huh[15], Maurilio Ponzoni[16], Andrés J.M. Ferreri[16], Ben M. Parsons[17], Michael B. Møller[18], Miguel A. Piris[5], Jane N. Winter[19], L. Jeffrey Medeiros[1] Shimin Hu[1] and Ken H. Young[1,20]

~900 pz



Front-line dose-escalated immunochemotherapy is associated with a significant PFS advantage in patients with double-hit lymphomas: a systematic review and meta-analysis

Meta-analysis: 11 studies examining 394 pts treated front-line with 1. R-CHOP 2. R-HyperCVAD 3. R-CODOX-M/IVAC 4. R-EPOCH



Treatment	Median OS, months	OS HR (95% CrI)	*P* value	Median PFS, months	PFS HR (95% CrI)	*P* value
R-CHOP	21·4	ref	–	12·1	ref	–
R-EPOCH	31·4	0·77 (0·51–1·13)	0·186	22·2	0·66 (0·44–0·96)	0·032
DI	25·2	0·89 (0·62–1·27)	0·531	18·9	0·74 (0·51–1·05)	0·088

First line treatment with R-EPOCH significantly reduce the risk of progression compared to R-CHOP

Christina Howlett et al BJH 2015

Ongoing clinical trials recruiting patients with double-hit lymphoma

Clinicaltrials.gov identifier (institution/manufacturer)	Patients	Treatment	Phase
NCT01092182 (National Cancer Institute)	Burkitt lymphoma and *MYC*$^{+}$ DLBCL	DA-EPOCH-R	2
NCT02213913 (University of Chicago)	Double-hit B-cell lymphoma*	Lenalidomide plus DA-EPOCH-R	1/2
NCT02272686 (M.D. Anderson Cancer Center)	Double-hit B-cell lymphoma in first remission after chemoimmunotherapy followed by SCT	Ibrutinib	2
NCT01181271 (Massachusetts General Hospital)	High-risk DLBCL, transformed low-grade lymphoma, T-cell lymphoma, mantle cell lymphoma, double-hit lymphoma, Hodgkin lymphoma, CLL/SLL	Non-mycloablative allogeneic transplantation	2
NCT02226965 (Pronai Therapeutics Inc)	Relapsed/refractory DLBCL; patients with double-hit lymphoma were allowed	PNT2258	2
NCT01897012 (National Cancer Institute)	Relapsed/refractory DLBCL; patients with double-hit lymphoma were allowed	Alisertib plus romidepsin	1
NCT01490723 (M.D. Anderson Cancer Center)	CD20^{+} lymphoid malignancies qualifying for SCT; patients with double-hit lymphoma were allowed	Ibritumomab tiuxetan plus low-intensity chemotherapy (rituximab, bendamustine, and fludarabine), followed by SCT	2
NCT01856192 (National Cancer Institute)	Newly-diagnosed DLBCL; *MYC*+ patients were encouraged to seek other trials but were allowed	Lenalidomide plus rituximab	2
NCT02110563 (Dicerna Pharmaceuticals Inc)	Solid tumours, MM, or NHL†	DCR-MYC	1
NCT01949883 (Constellation Pharmaceuticals)	Relapsed/refractory non-Hodgkin or Hodgkin lymphoma for which additional effective standard therapy is not available†	CPI-0610	1

Ibrutinib +R-CHOP as Frontline Therapy for DLBCL
Phase 1b study (Younes et al. 2014)

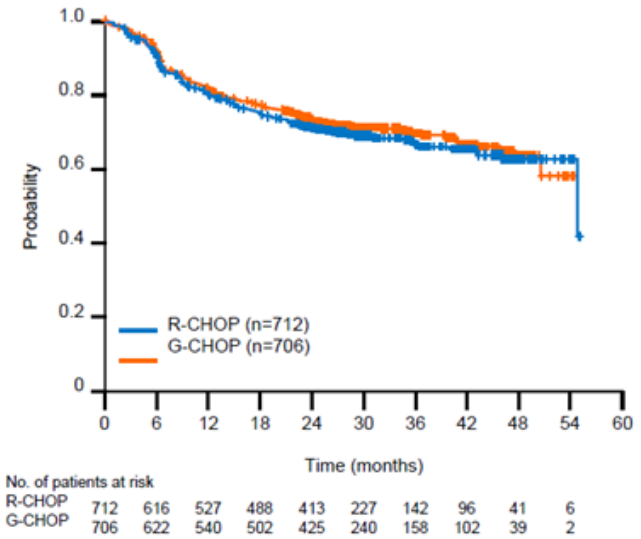
- Treatment plan
  - Ibrutinib 280, 420, or 560 mg daily +R-CHOP q 3 wks
  - Phase 2 dose Ibrutinib 560 mg daily +R-CHOP x 6
- Toxicity
  - neutropenia 73%, thrombocytopenia 21%, febrile neutropenia 18%, anemia 18%
- Results
  - Overall response rate 95%
    - 71% CR for GCB subtype (7 patients)
    - 100% CR for non-GCB (4 patient)
- Conclusion
  - Ibrutinib 560 mg can be given safely with R-CHOP
  - Phase 3 study R-CHOP vs Ibrutinib +R-CHOP in Non-GCB DLBCLis being conducted

Younes et al, 2014

Obinotzumab or Rituximab plus CHOP in previously untreated DLBCL (GOYA)

Umberto Vitolo,[1] Marek Trněný,[2] David Belada,[3] Angelo Michele Carella,[4] Neil Chua,[5] Pau Abrisqueta,[6] Judit Demeter,[7] Ian Flinn,[8] Xiaonan Hong,[9] Won Seog Kim,[10] Antonio Pinto,[11] John M Burke,[12] Yuan Ki Shi,[13] Yoichi Tatsumi,[14] Mikkel Z Oestergaard,[15] Michael Wenger,[16] Günter Fingerle-Rowson,[15] Olivier Catalani,[15] Tina Nielsen,[15] Maurizio Martelli,[17] Laurie H Sehn[18]

KM plot of INV-assessed PFS by treatment arm



*ITT population

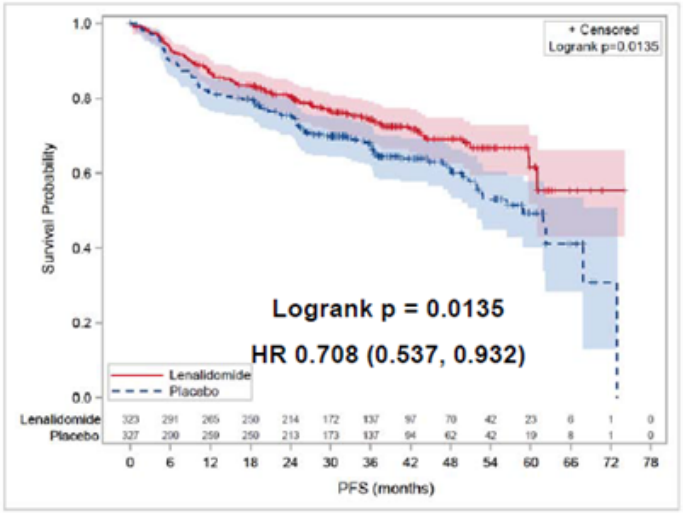
	R-CHOP, n=712	*G-CHOP, n=706*
Pts with event, n (%)	215 (30.2)	201 (28.5)
1-yr PFS, %	79.8	81.6
2-yr PFS, %	71.3	73.4
3-yr PFS, %	66.9	69.6
HR (95% CI), stratified p-value	0.92 (0.76, 1.11), p=0.3868	

Median follow-up: 29 months

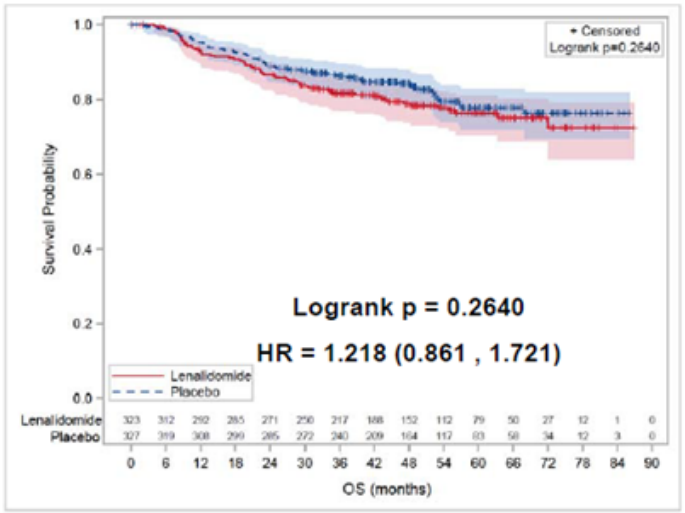
Vitolo UF, et al. ASH 2016. Abstract 470.

REMARC Study (A. 471)
R-CHOP -> 24 months Maintenance of Lena.

Progression-Free Survival



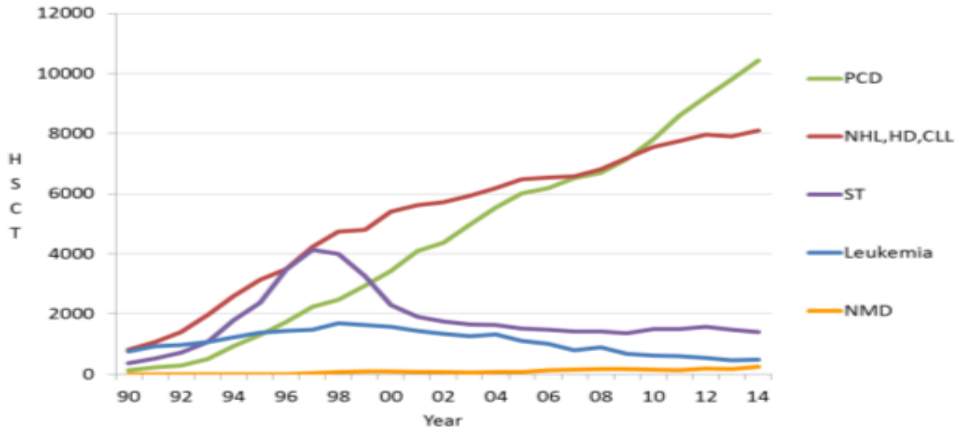
Overall Survival



At a median follow-up of 40 months, median PFS was not reached (NR) for LEN and 58.9 months for PBO

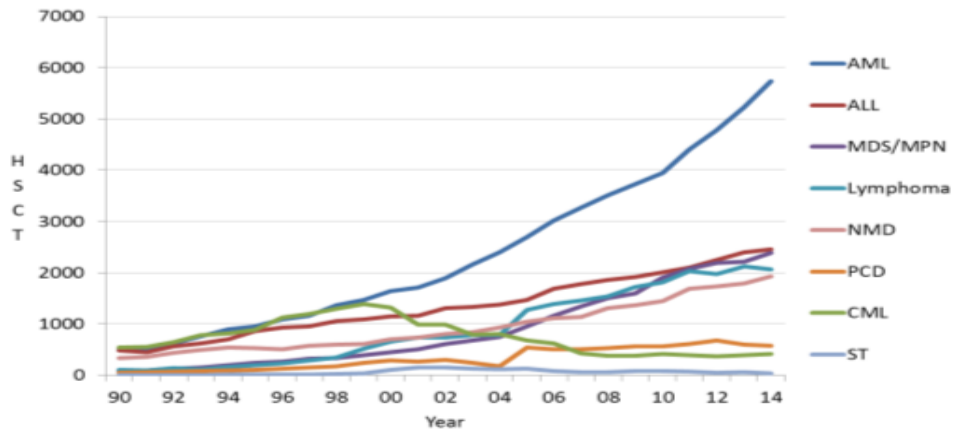
HSCT Activity in Europe 1990-2014:

Main Indications: autologous



HSCT Activity in Europe 1990-2014:

Main Indications: allogeneic




patients
transplant
lymphoma
stem
cell
management
malignancies
lymphoid
role
outcome
LWP
remains
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procedures
advent
promote
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common
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data
availability
treatment
changed
plethora
questioning
authors
number
appropriate
term
thanks
members
significant
years
extraordinarily
education
setting
improvement
available

ASCT:cosa è migliorato ?

- Expertise
- Strategie di mobilizzazione
- Terapia di supporto
- Controllo delle infezioni
- Timing (Pet driven)

- Outcome !?

HSCT results related to:

GOOD INDICATIONS
OPTIMAL TIMING
OPTIMAL MOBILIZATION PROCEDURES
TYPE OF TRANSPLANT
OPTIMAL CD34+ TARGET DOSE

Is there an optimal dose of CD34+ cells to be collected (and reinfused)?

- The current **minimal threshold** CD34+ cell dose to be infused is agreed to be ≥ 2-2.5 million CD34 cells/kg for a single ASCT.
- However, the current optimal dose for ideal platelet recovery is considered to be 4–6 million CD34 cells/kg.
- Reinfusion of high doses of $CD34^+$ cells is associated with:
  - long term stable engraftment
  - fast platelet and neutrophil engraftment
  - reduction in the need for supportive measures, leading to a significant cost sparing

Age= 57.5 ± 12 (17-74)
51.2% Male; 48.8% Female

ITALIAN DATABASE
24 CENTERS

CENTERS	Number of patients	CENTERS	Number of patients
ANCONA	9	PESARO	3
BARI	11	POTENZA	6
BRESCIA	7	RAVENNA	2
CATANIA	13	REGGIO CALABRIA	22
CREMONA	10	RIMINI	5
FERRARA	2	RIONERO IN VULTURE (PZ)	4
FIRENZE (Careggi)	6	ROMA- LAZIO	13
MELDOLA (FC)	4	ROZZANO (MI)	13
MILANO (IEO)	31	SAN GIOVANNI ROTONDO	8
MILANO (S.RAFFAELE)	8	TORINO	5
NOVARA	6	TRICASE (Lecce)	15
PAVIA	10	total patients	213

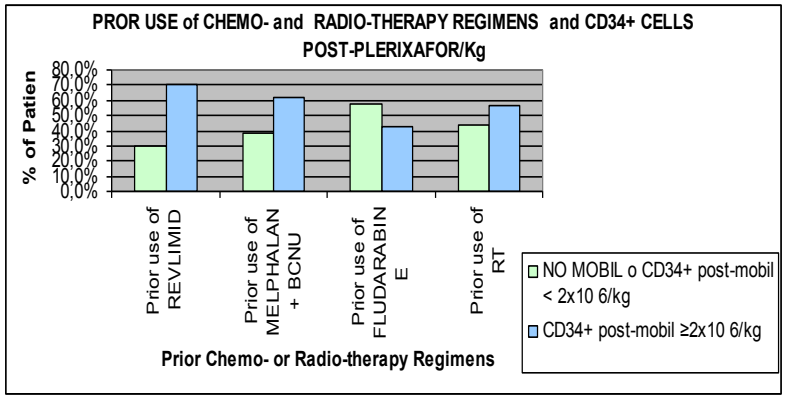
COMPARATIVE EVALUATION OF MOBILIZATION IN STEADY-STATE VS CHEMOMOBILIZATION (CD34+ CELLS POST-PLERIXAFOR/Kg) and DISEASE

N=194 pts	(n.83) MM		n.85 NHL		n.23 HL		OTHER	
	STEADY-STATE	CHEMO THERAPY	STEADY-STATE	CHEMO THERAPY	STEADY-STATE	CHEMO THERAPY	STEADY-STATE	CHEMO THERAPY
NO MOBIL o CD34+ post-mobil **< 2x10 6/ kg**	17.4% (8 pts)	21.6% (8 pts)	**47.1% (24 pts)**	32.4% (11 pts)	23.5% (4 pts)	**33.3% (2 pts)**	100% (2 pts)	0.0%
CD34+ post-mobil **≥2x10 6/ kg**	82.6% (38 pts)	78.4% (29 pts)	**52.9%** (27 pts)	**67.6% (23 pts)**	76.5% (13 pts)	66.7% (4 pts)	0.0%	100% (1 pt)

P< 0.001

PRIOR USE of CHEMO- and RADIO-THERAPY REGIMENS and CD34+ CELLS/Kg POST-PLERIXAFOR

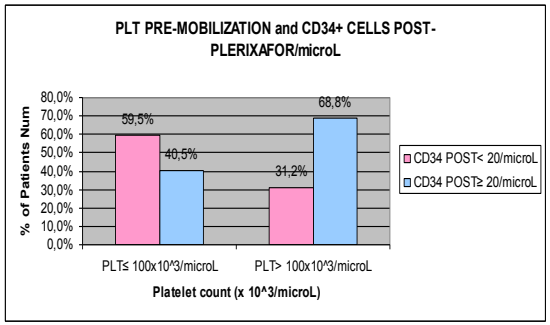
N= 94 pts	Prior use of REVLIMID	Prior use of MELPHALAN or BCNU	Prior use of FLUDARABINE	Prior use of RT
NO MOBIL o CD34+ post-mobil **< 2x10 6/kg**	29.6% (8 pts)	38.1% (8 pts)	57.1% (8 pts)	43.8% (14 pts)
CD34+ post-mobil **≥2x10 6/kg**	70.4% (19 pts)	61.9% (13 pts)	42.9% (6 pts)	56.3% (18 pts)



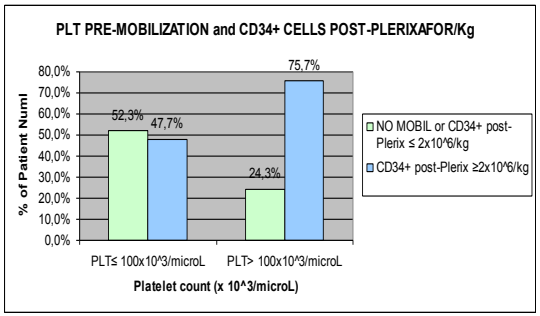
PLATELET COUNT PRE-MOBILIZATION and CD34+ CELLS POST-PLERIXAFOR

Platelet count pre-mob. (median ± st.dv.) = 151.0 ± 88.2 x 10^3/microL

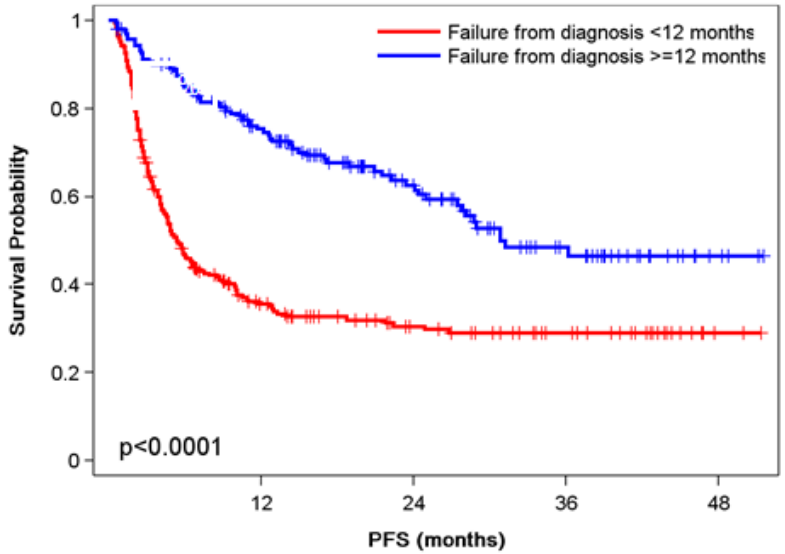
N= 180 pts	PLT pre-Pler ≤ 100x10^3/microL	PLT pre-Pler > 100x10^3/microL
CD34 post-Plerixafor< 20/ microL	59.5% (25 pts)	31.2% (43 pts)
CD34 post-Plerixafor≥ 20/ microL	**40.5% (17 pts)**	**68.8% (95 pts)**



N= 192 pts	PLT pre-Pler ≤ 100x10^3/microL	PLT pre-Pler > 100x10^3/microL
NO MOBIL or CD34+ post-Plerix < 2x10^6/kg	**52.3% (23 pts)**	24.3% (36 pts)
CD34+ post-mobil **≥2x10^ 6/kg**	47.7% (21 pts)	**75.7% (112 pts)**

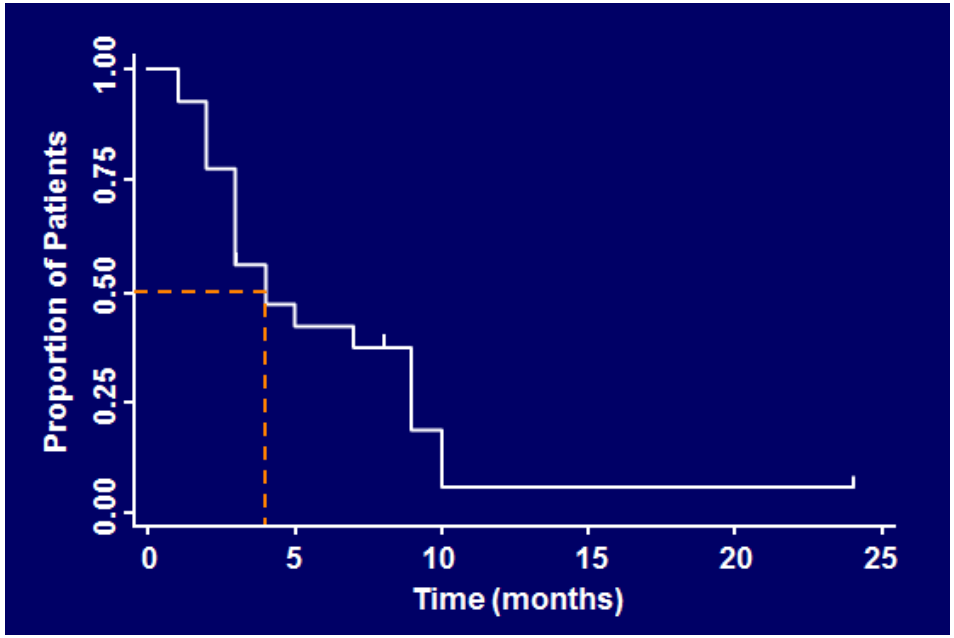


DLBCL patients who recur post R-CHOP 21 do not well



Gisselbrecht C, et al. JCO 2009

Overall survival of patients with DLBCL refractory to second line therapy is very poor



Elstrom, et al. Clin Lymph Myel Leuk 2010

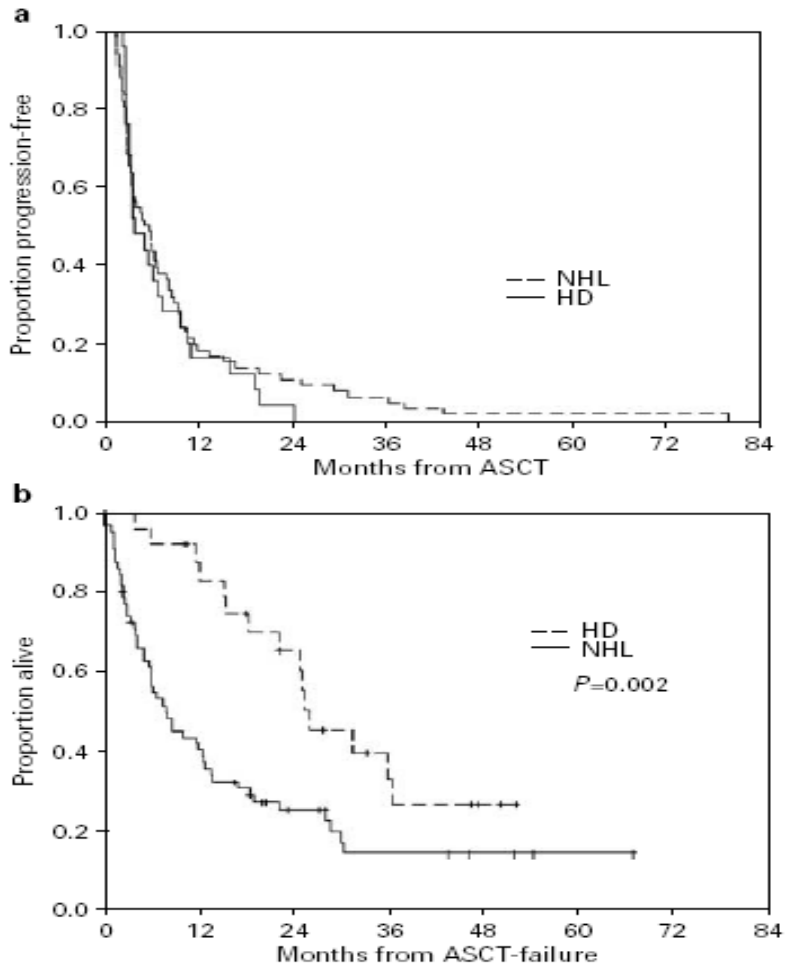


Figure 1 (a) Time to progression following autologous stem cell transplantation (ASCT). HD = Hodgkin's disease; NHL = aggressive non-Hodgkin's lymphoma. (b) Survival following the failure of ASCT.

OUTCOME AFTER ASCT FAILURE IN DLBCL

Kewalramani et al
BMT, 2003

poor P.S.
resistant disease
limited bone marrow reserve
doxorubicin cumulative dose ≥ 300 mg/sm
……are common findings in this setting

ASCT FOR DLBCL IN 1RST RELAPSE

PRE-RITUXIMAB

1540 THE NEW ENGLAND JOURNAL OF MEDICINE Dec. 7, 1995

AUTOLOGOUS BONE MARROW TRANSPLANTATION AS COMPARED WITH SALVAGE CHEMOTHERAPY IN RELAPSES OF CHEMOTHERAPY-SENSITIVE NON-HODGKIN'S LYMPHOMA

THIERRY PHILIP, M.D., CESARE GUGLIELMI, M.D., ANTON HAGENBEEK, M.D., RENIER SOMERS, M.D., HANS VAN DER LELIE, M.D., DOMINIQUE BRON, M.D., PIETER SONNEVELD, M.D., CHRISTIAN GISSELBRECHT, M.D., JEAN-YVES CAHN, M.D., JEAN-LUC HAROUSSEAU, M.D., BERTRAND COIFFIER, M.D., PIERRE BIRON, M.D., FRANCO MANDELLI, M.D., AND FRANCK CHAUVIN, M.D.

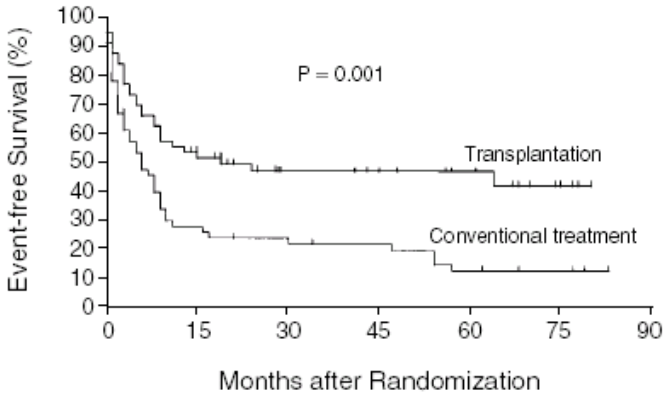
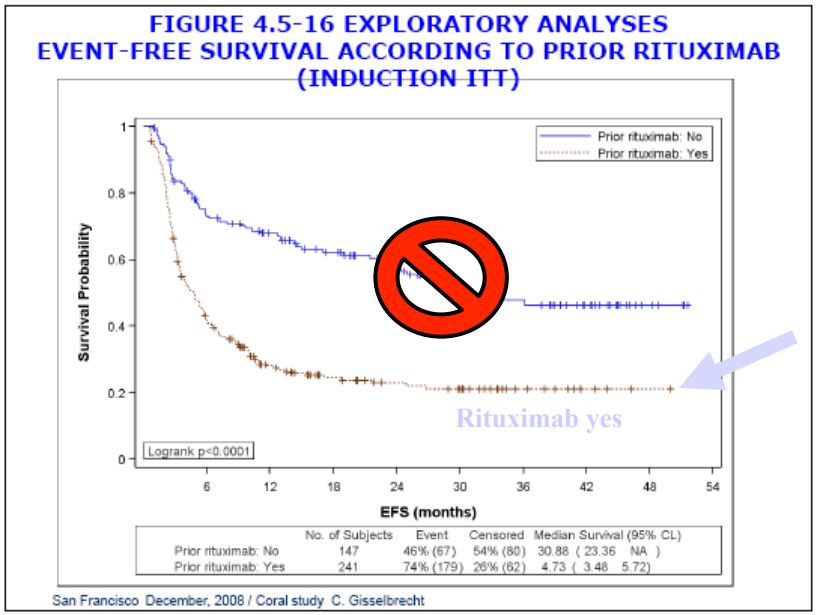


Figure 1. Kaplan–Meier Curves for Event-free Survival of Patients in the Transplantation and Conventional-Treatment Groups. The data are based on an intention-to-treat analysis. Tick marks represent censored data.

POST-RITUXIMAB

CORAL TRIAL

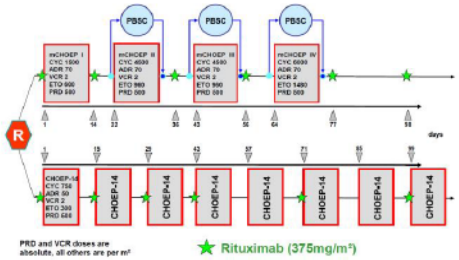


ASCT:OPEN QUESTIONS

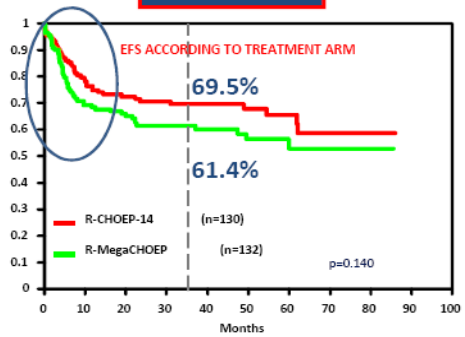
- Mai in Front Line?
- Necessità di piattaforme x very High Risk !
- Come integrare i nuovi farmaci ?
- Esiste un incrementato rischio infettivo Asct +nuovi farmaci ?

How many patients will relapse?

185 young untreated DLBCL aa-IPI 2-3
R-CHOEP vs R-MegaCHOEP



Relapse rate 30-40%

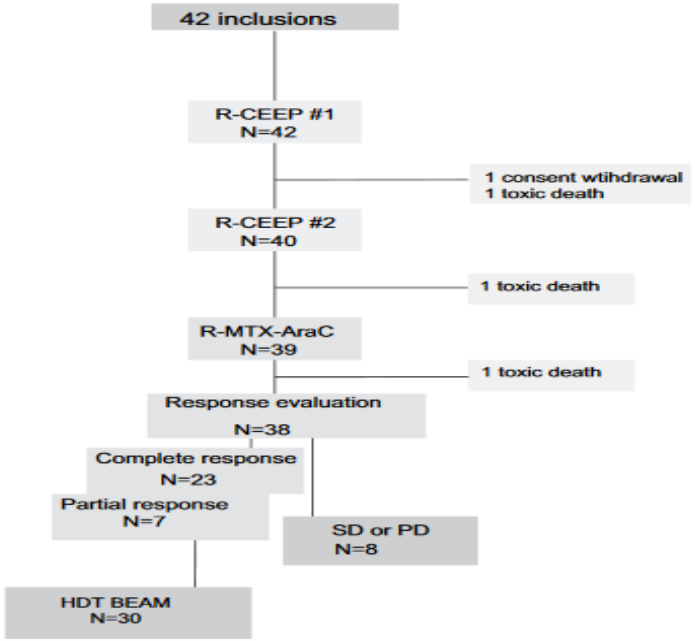


Randomized Phase III studies with rituximab: no benefit for HDC+ASCT

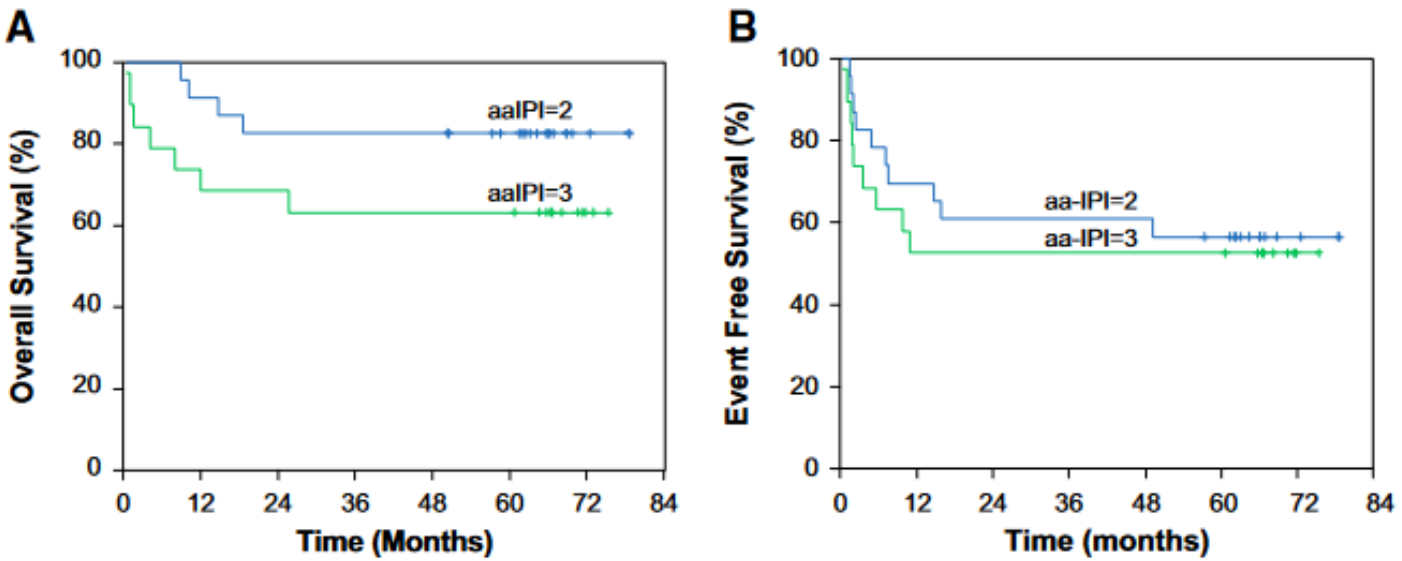
Schmitz et al. Annal oncol 2011; 22(4): Abstract 73

Front-line High-Dose Chemotherapy with Rituximab Showed Excellent Long-Term Survival in Adults with Aggressive Large B-Cell Lymphoma: Final Results of a Phase II GOELAMS Study

Marie-Sarah Dilhuydy,[1] Thierry Lamy,[2] Charles Foussard,[3] Remy Gressin,[4] Philippe Casassus,[5] Eric Deconninck,[6] Christine Le Maignan,[7] Diane Damotte,[8] Noel Milpied[1] for the Groupe Ouest-Est des Leucémies et Autres Maladies du Sang (GOELAMS)



Biol Blood Marrow Transplant 16:672-677, 2010



Biol Blood Marrow Transplant 16:672-677, 2010

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 31, 2013 VOL. 369 NO. 18

Autologous Transplantation as Consolidation for Aggressive Non-Hodgkin's Lymphoma

Patrick J. Stiff, M.D., Joseph M. Unger, Ph.D., James R. Cook, M.D., Ph.D., Louis S. Constine, M.D., Stephen Couban, M.D., Douglas A. Stewart, M.D., Thomas C. Shea, M.D., Pierluigi Porcu, M.D., Jane N. Winter, M.D., Brad S. Kahl, M.D., Thomas P. Miller, M.D., Raymond R. Tubbs, D.O., Deborah Marcellus, M.D., Jonathan W. Friedberg, M.D., Kevin P. Barton, M.D., Glenn M. Mills, M.D., Michael LeBlanc, Ph.D., Lisa M. Rimsza, M.D., Stephen J. Forman, M.D., and Richard I. Fisher, M.D.

BACKGROUND

The efficacy of autologous stem-cell transplantation during the first remission in patients with diffuse, aggressive non-Hodgkin's lymphoma classified as high-intermediate risk or high risk on the International Prognostic Index remains controversial and is untested in the rituximab era.

METHODS

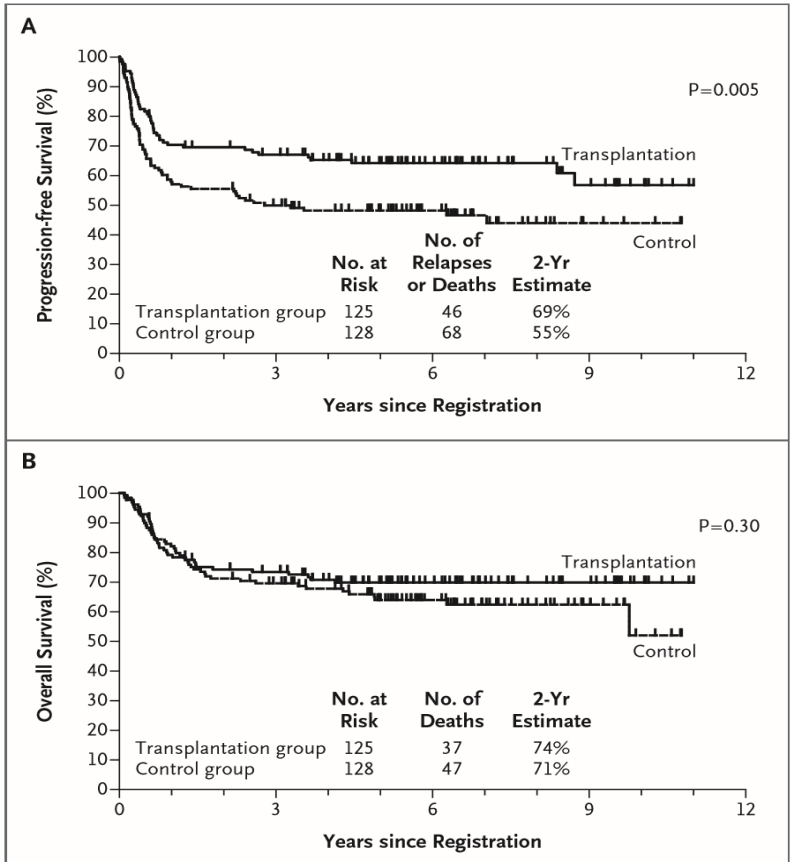
We treated 397 patients who had disease with an age-adjusted classification of high risk or high-intermediate risk with five cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP plus rituximab. Patients with a response were randomly assigned to receive three additional cycles of induction chemotherapy (control group) or one additional cycle of induction chemotherapy followed by autologous stem-cell transplantation (transplantation group). The primary efficacy end points were 2-year progression-free survival and overall survival.

RESULTS

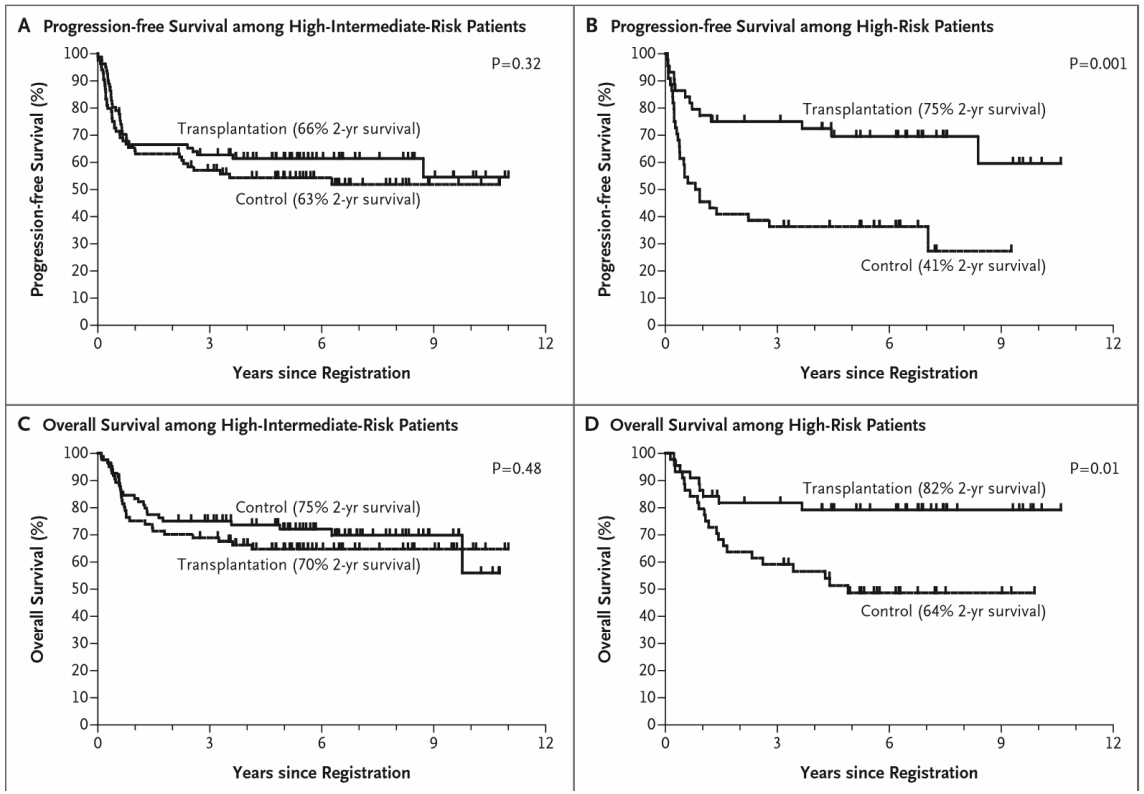
Of 370 induction-eligible patients, 253 were randomly assigned to the transplantation group (125) or the control group (128). Forty-six patients in the transplantation group and 68 in the control group had disease progression or died, with 2-year progression-free survival rates of 69 and 55%, respectively (hazard ratio in the control group vs. the transplantation group, 1.72; 95% confidence interval [CI], 1.18 to 2.51; P=0.005). Thirty-seven patients in the transplantation group and 47 in the control group died, with 2-year overall survival rates of 74 and 71%, respectively (hazard ratio, 1.26; 95% CI, 0.82 to 1.94; P=0.30). Exploratory analyses showed a differential treatment effect according to risk level for both progression-free survival (P=0.04 for interaction) and overall survival (P=0.01 for interaction). Among high-risk patients, the 2-year overall survival rate was 82% in the transplantation group and 64% in the control group.

CONCLUSIONS

Early autologous stem-cell transplantation improved progression-free survival among patients with high-intermediate-risk or high-risk disease who had a response to induction therapy. Overall survival after transplantation was not improved, probably because of the effectiveness of salvage transplantation. (Funded by the National Cancer Institute, Department of Health and Human Services, and others; SWOG-9704 ClinicalTrials.gov number, NCT00004031.)



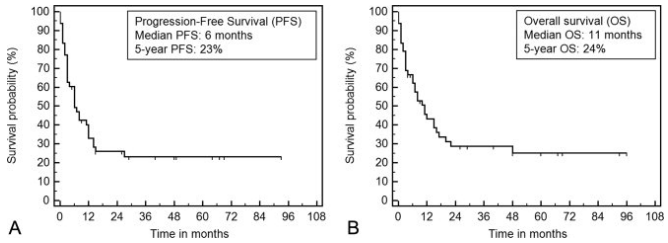
New England Journal of Medicine 2013

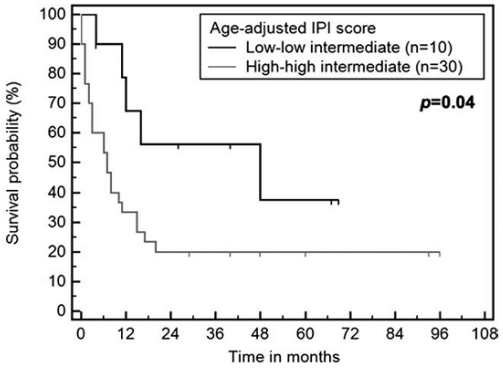


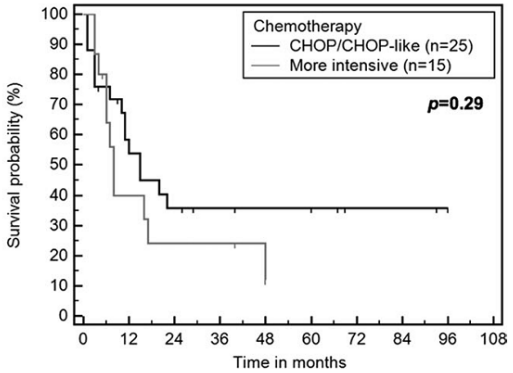
New England Journal of Medicine 2013

LINFOMA PLASMABLASTICO:PROGNOSI

MULTI-ISTITUTIONAL
RETROSPECTIVE
STUDY
50 HIV+PLB pts
(2000-2013)

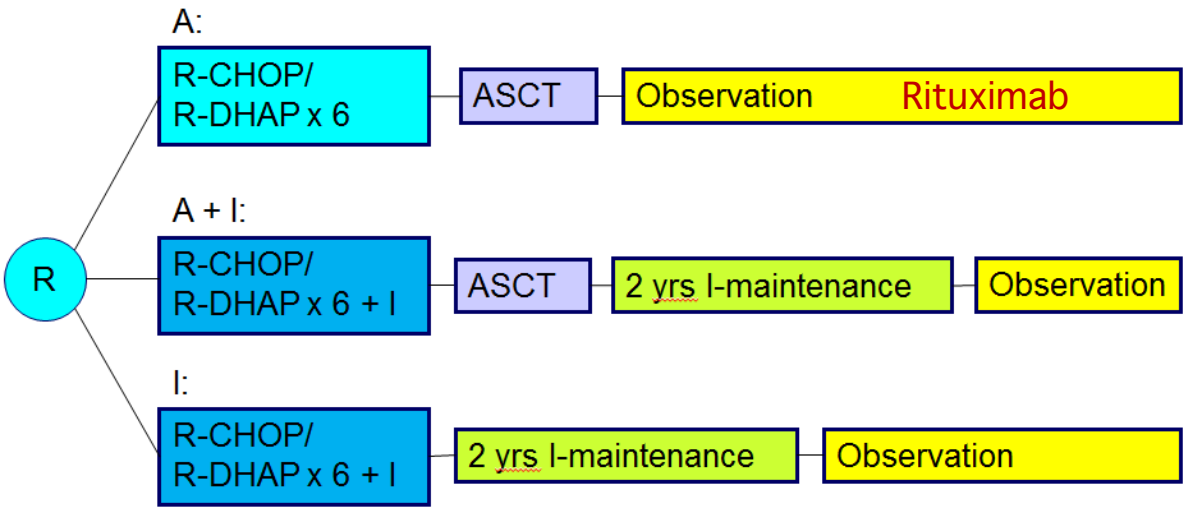






HIV-Positive Plasmablastic Lymphoma/Castillo et al
Cancer 2012;118:5270-7.

TRIANGLE trial design

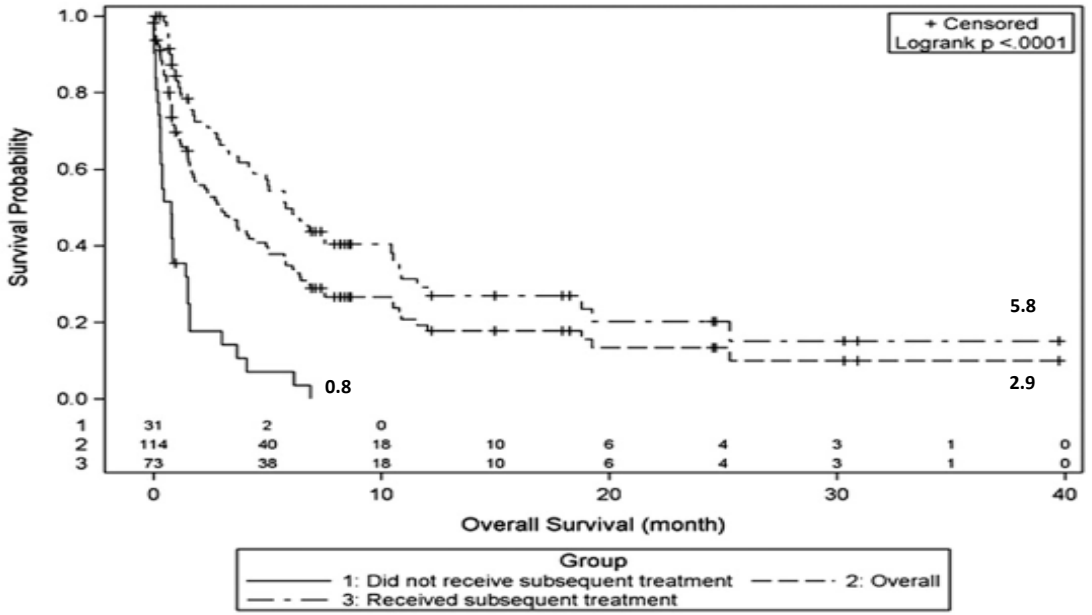


MA **CON I NUOVI FARMACI**
TRAPIANTIAMO IL **PAZIENTE**
MIGLIORE O PEGGIORE?

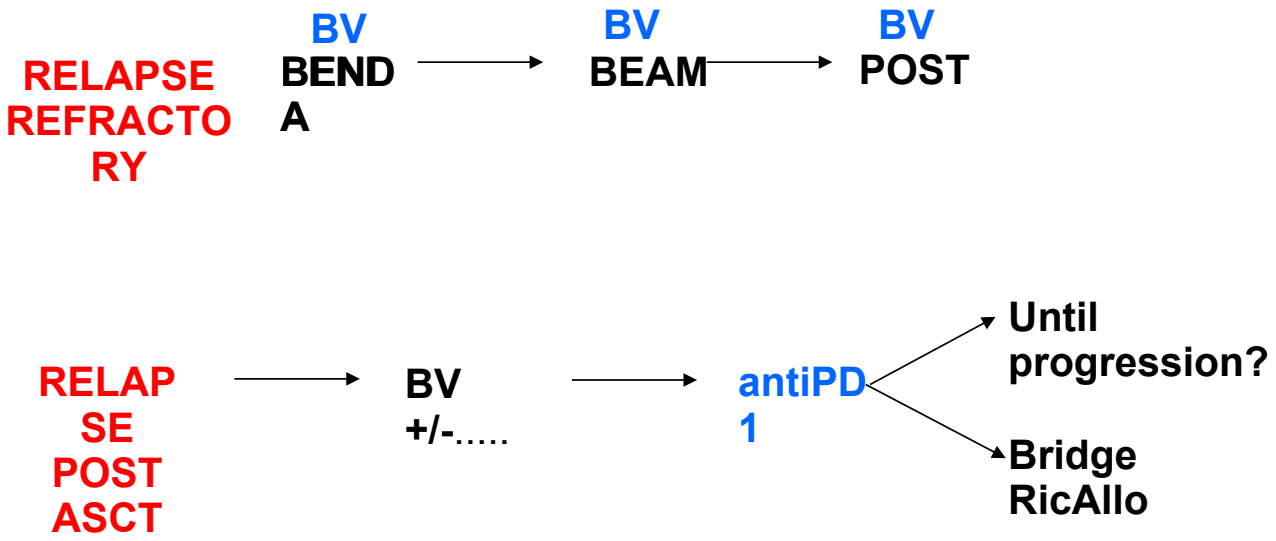
O RISCHIAMO DI NON TRAPIANTARE?

Postibrutinib outcomes in patients with mantle cell lymphoma

Peter Martin,[1] Kami Maddocks,[2] John P. Leonard,[1] Jia Ruan,[1] Andre Goy,[3] Nina Wagner-Johnston,[4] Simon Rule,[5] Ranjana Advani,[6] David Iberri,[6] Tycel Phillips,[7] Stephen Spurgeon,[8] Eliana Kozin,[8] Katherine Noto,[1] Zhengming Chen,[9] Wojciech Jurczak,[10] Rebecca Auer,[11] Ewa Chmielowska,[12] Stephan Stilgenbauer,[13] Johannes Bloehdorn,[13] Craig Portell,[14] Michael E. Williams,[14] Martin Dreyling,[15] Paul M. Barr,[16] Selina Chen-Kiang,[17] Maurizio DiLiberto,[17] Richard R. Furman,[1] and Kristie A. Blum[2]



Blood 2016


RELAPSE REFRACTORY
BV BENDA
BV BEAM
BV POST
RELAPSE POST ASCT
BV +/-.....
antiPD1
Until progression?
Bridge RicAllo

Identificazione popolazioni High Risk

- Refractory 1st line e Pet+ post salvataggio
- Refractory 1°st line e Pet+ post ASCT
- Relapse< 6 mesi
- Refractory 1st line ma sensibili (Pet-) post salvataggio
- IPI MIPI Bulky Ki67
- Istologia (Double HIT , Non germinal center,blastoid for MCL.
- Molecular pattern P53 , Notch 11.

Prognostic Factors Predicting Outcome Of Autologous Stem Cell Transplantation

150 patients with chemosensitive DLBCL

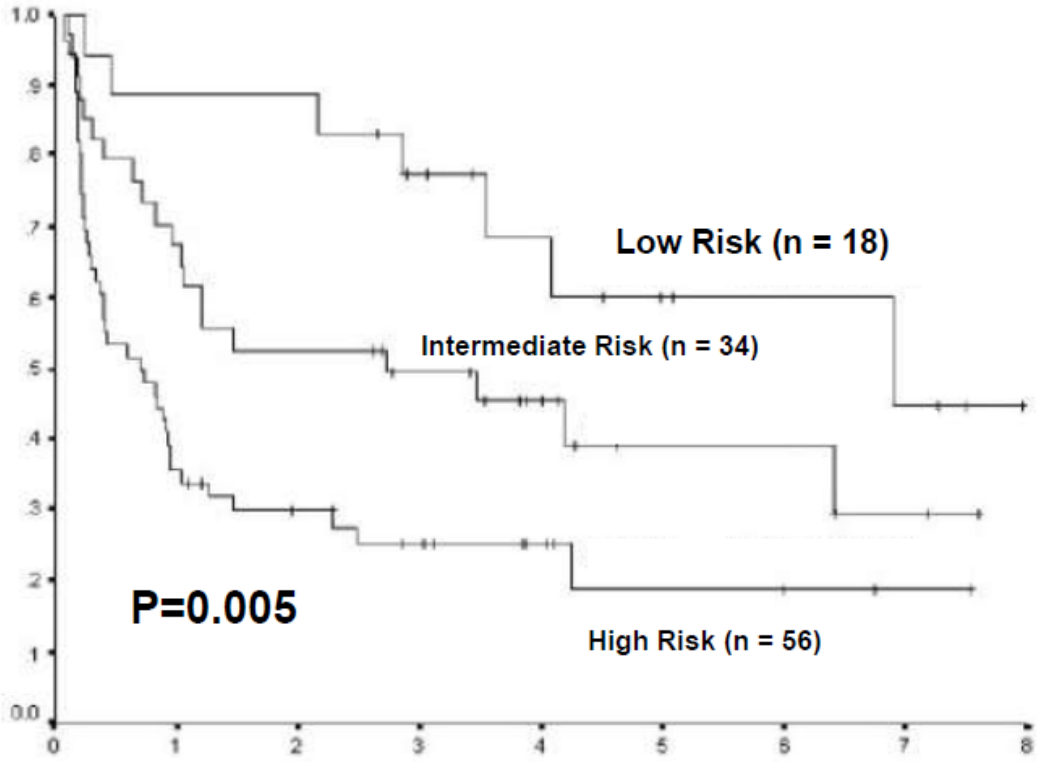
Second line age adjusted IPI (sAAIPI)

Factors: High LDH, Stage 3 or 4, Poor performance status

Low risk: 0 factors
Int. risk: 1 factor
High risk: 2 or 3 factors

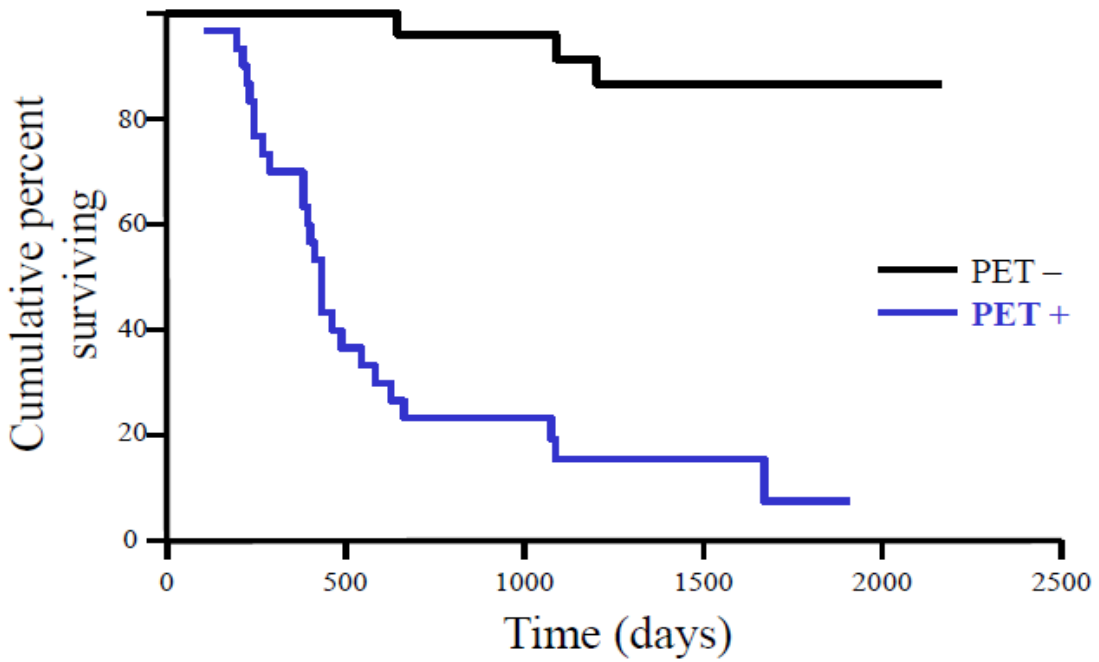
Hamlin el al. Blood 102:1989, 2003

Prognostic Factors Predicting Outcome Of Autologous Stem Cell Transplantation



Hamlin el al. Blood 102:1989, 2003

Prognostic value of PET status pre-auto transplant for aggressive lymphoma: PFS



Spaepen et al. Blood 2003;102:53–59

PIA FONDAZIONE DI CULTO E RELIGIONE CARD. G. PANICO
A z i e n d a O s p e d a l i e r a
U. O. DI EMATOLOGIA E TRAPIANTO DI CELLULE STAMINALI EMOPOIETICHE
Direttore Dottor VINCENZO PAVONE

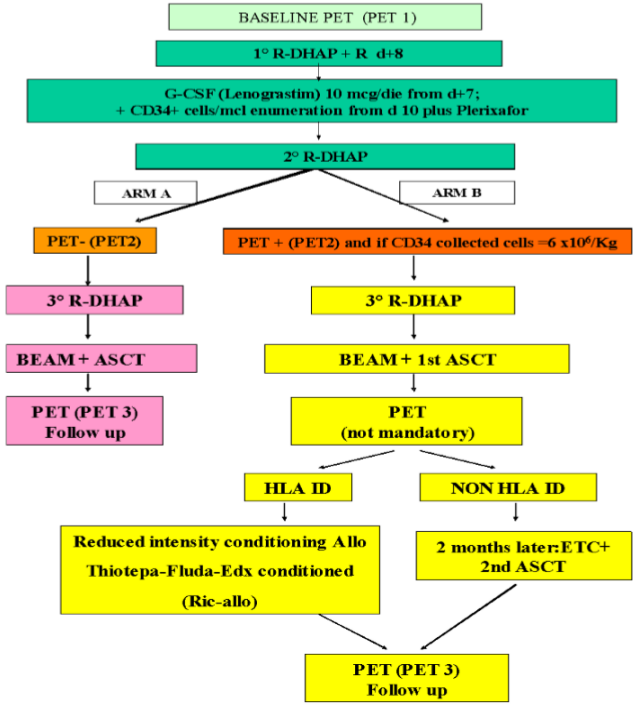
Centri di Ematologia e Trapianto dell'Italia Meridionale (CETIM)

A PHASE II STUDY OF CHEMOTHERAPY, MOZOBIL AND G-CSF AS MOBILIZING THERAPY FOR DOUBLE AUTOLOGOUS TRANSPLANTATION (ASCT) IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B CELL NON HODGKIN LYMPHOMA (DLBCL), PET POSITIVE AFTER TWO R-DHAP

CETIM PROTOCOL 00109
VERSION2
Dr. V. Pavone

Trani, Hotel San Paolo al Convento –24 gennaio 2014

IL PROTOCOLLO: Flow Chart



Importance of blood graft characteristics in auto-SCT: implications for optimizing mobilization regimens

E Jantunen[1] and S Fruehauf[2]

Bone Marrow Transplantation (2011) 46, 627–635

Effect of mobilization regimen on autologous graft content

Parameter	G-CSF alone	CT+G-CSF	G-CSF+plerixafor
Clonogenic	More LTC-IC than G-CSF	More LTC-IC than G-CSF	
CD34+	More than G-CSF	More than G-CSF	More that G-CSF
CD34+CD33-	More than CT+G-CSF	More than G-CSF	More than CT+G-CSF
CD34+CD38-	More than with CT+G-CSF		More than G-CSF
Lymphocytes alone			
CD3+	More than G-CSF alone		
CD4+	More than G-CSF alone		
CD8+			

…the number of CD34+ cells collected remains the most important parameter for efficient blood stem-cell mobilization and collection in clinical practice and for engraftment (neutrophils and platelet recovery)

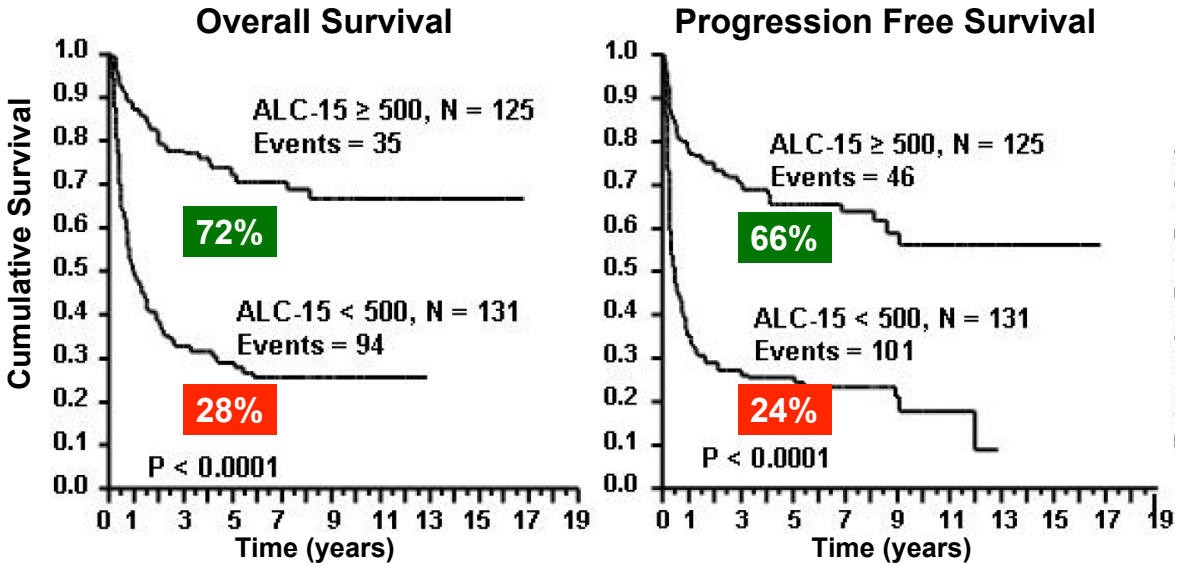
Table 1 Graft characteristics of potential importance in the autologous setting

Parameter	*Potential impact*
LTC-IC	Engraftment
$CD34^+$ cell dose	Engraftment, patient outcome
Other $CD34^+$ subsets (for example, $CD34^+CD33^-$, $CD34^+CD38^-$ and $CD34^+CD110^+$)	Engraftment
Lymphocyte subsets	Immune recovery, patient outcome
NK cells	Immune recovery, patient outcome
DCs	Immune recovery, patient outcome
Tumour cells	Patient outcome
Other progenitor cell types	May be important in non-malignant setting (e.g. cardiac and neurological repair)

Abbreviations: LTC-IC = long-term culture initiating cells; NK = natural killer.

The ALC-15 will be a major predictive factor even in DLCBL

The median follow-up for the whole cohort **(256 pts)** was 2.8 years and **5.6 years** for the living patients.

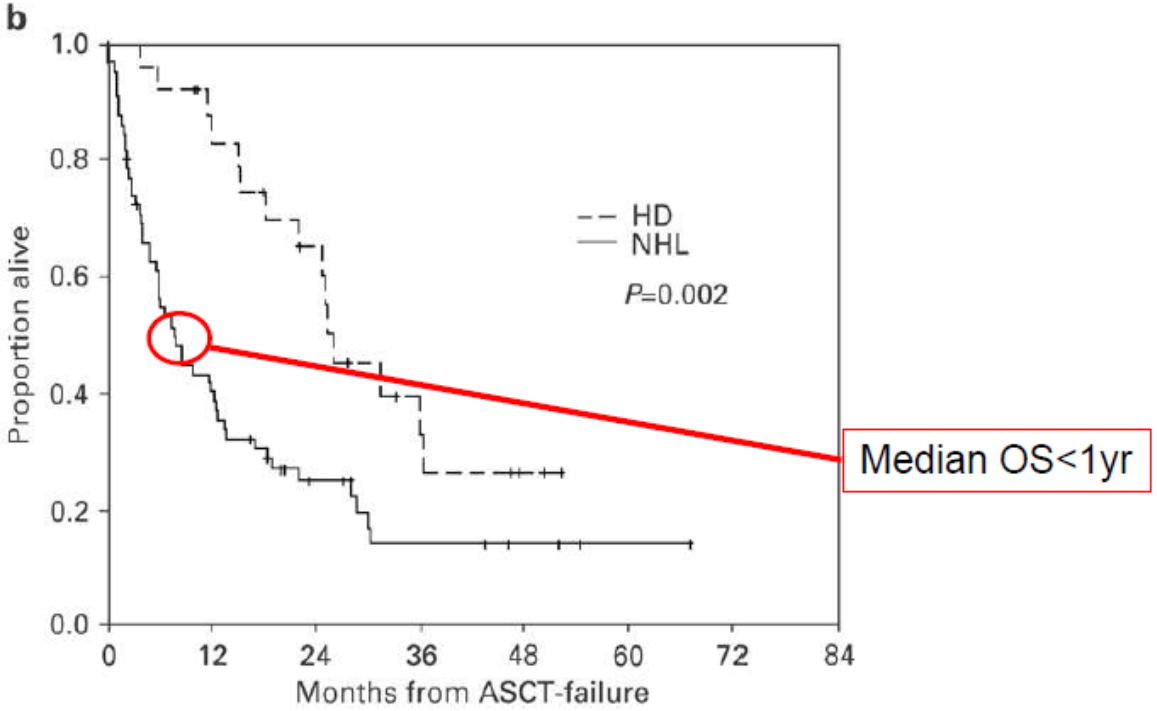


Porrata et al. (2011) J Stem Cell Res Ther 2:103.

Table 2 . Mobilization and collection data	Mean (range)
Total number of patients	30
Time to collection*	13 (12-17)
Plerixafor administration number#	2,4 (1-4)
Apheresis days	1,2 (1-2)
CD34/uL pre-apheresis$	74,4 (19,1-176,2)
WBCx10e6/mL pre-apheresis$	2,9 (1,1-6,4)
PLTx10e6/mL pre-apheresis$	23,7 (15,0-35,3)
CD34x10e6/kg yield	11,5 (3,6-24,7)

* Data available for N = 17 patients
# Data available for N = 18 patients
$ Data available for N = 10 patients

Survival Post Relapse After Autologous Stem Cell Transplantation



(Kewalramani et al BMT 2003)

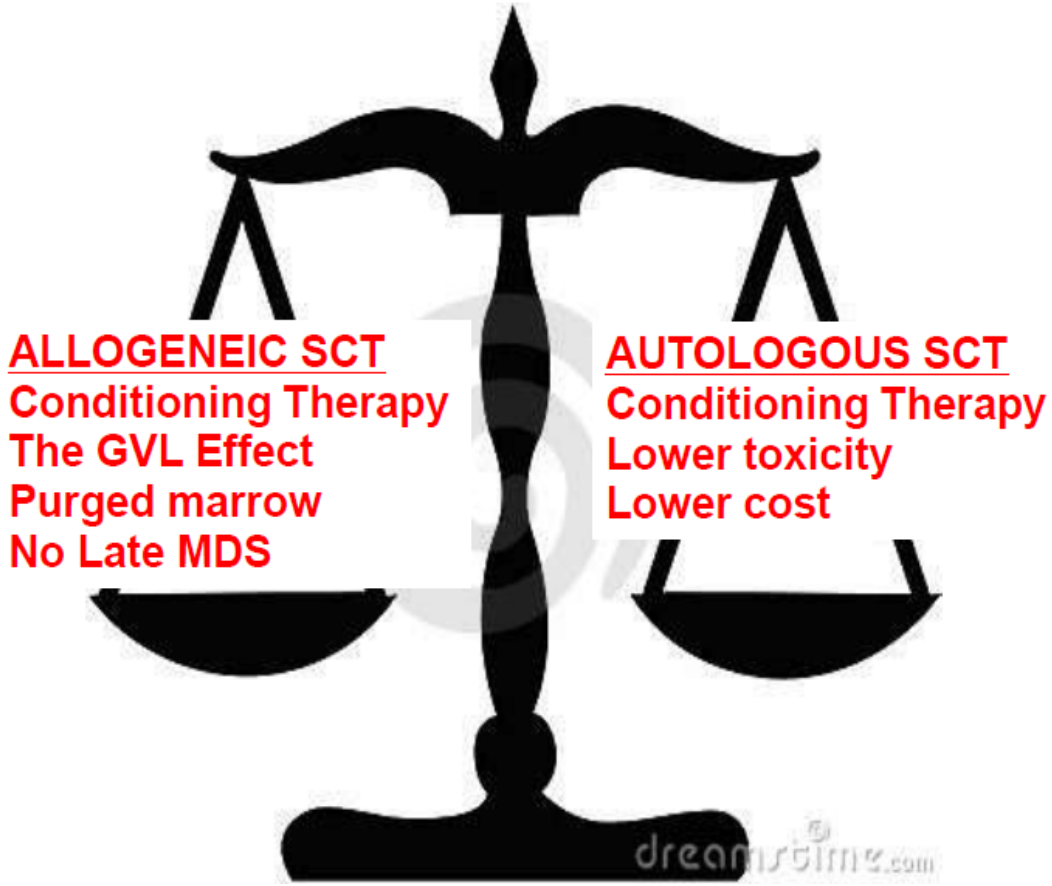
What is the role of alloSCT in DLBCL in the current era?

- Relapse post autoSCT?
- As an alternative to autoSCT in patients failing first line therapy?

Allogenic Transplantation for recurrent or refractory: alternative to ASCT ?

- Limits of ASCT
- Limits of indications for Allo
  - Very Refractory
  - CR >2

Allogeneic Stem Cell Transplant As An Alternative To Autologous Stem Cell Transplant?



ASCT vs ALLO in nHL

↓ Relapse Incidence

= OS

↑ TRM

Different Population

Age

Chemiosensitive

BM involvement

Treatment

Role of Allo in Nhl: to be redefined

- Advance in Lymphoma classification
- Diagnostic methods
- PET scan
- New prognostic features
- Advance in technology
- HLA typing
- Advance in expertice
- Advance in supportive setting
- New conditioning(rituximab-RIT-Beam)

Outcome of Allo in nHL : depends

- Patients characteristics
- Risk factors (lymphoma and patient related)
- Time to transplant
- IPI at transplant
- Chemiosensitivity
- Hystologic subtypes (T cell-NK)

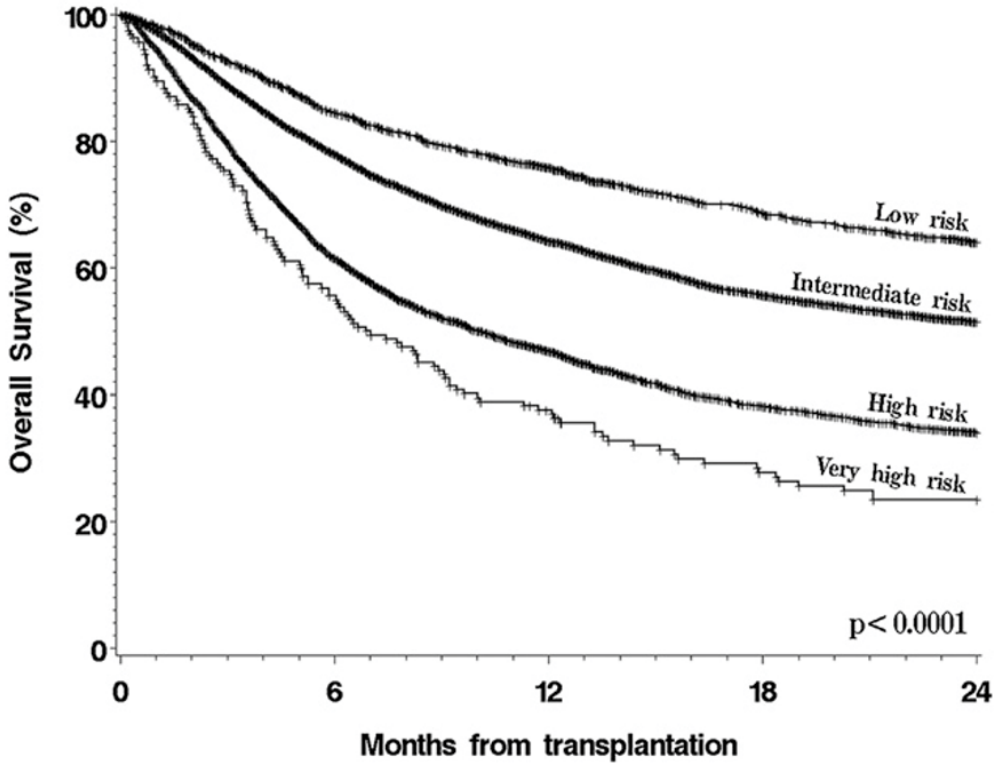
Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation

Philippe Armand,[1] Haesook T. Kim,[2] Brent R. Logan,[3,4] Zhiwei Wang,[3] Edwin P. Alyea,[1] Matt E. Kalaycio,[5] Richard T. Maziarz,[6] Joseph H. Antin,[1] Robert J. Soiffer,[1] Daniel J. Weisdorf,[7] J. Douglas Rizzo,[3] Mary M. Horowitz,[3] and Wael Saber[3]

Key Points

- The DRI successfully stratified patients in a very large allogeneic transplantation registry cohort.
- The DRI was refined by using this cohort to build a more inclusive and conditioning intensity–independent index.

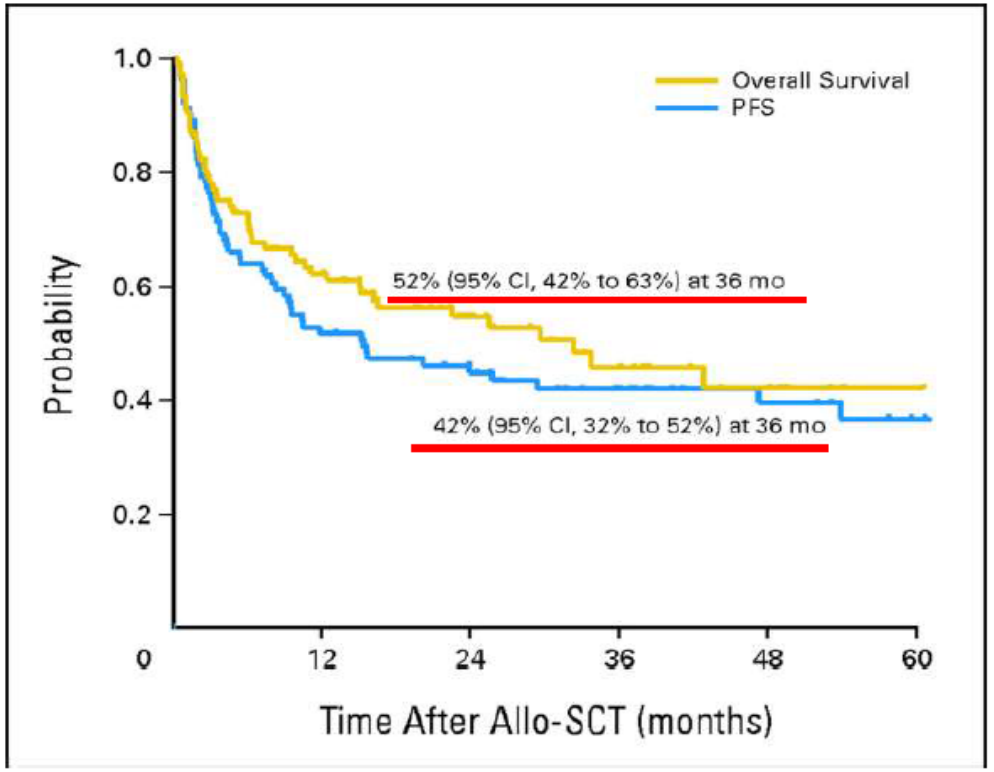
Because the outcome of allogeneic hematopoietic cell transplantation (HCT) is predominantly influenced by disease type and status, it is essential to be able to stratify patients undergoing HCT by disease risk. The Disease Risk Index (DRI) was developed for this purpose. In this study, we analyzed 13 131 patients reported to the Center for International Blood and Marrow Transplant Research who underwent HCT between 2008 and 2010. The DRI stratified patients into 4 groups with 2-year overall survival (OS) ranging from 64% to 24% and was the strongest prognostic factor, regardless of age, conditioning intensity, graft source, or donor type. A randomly selected training subgroup of 9849 patients was used to refine the DRI, using a multivariable regression model for OS. This refined DRI had improved prediction ability for the remaining 3282 patients compared with the original DRI or other existing schemes. This validated and refined DRI can be used as a 4- or 3-group index, depending on the size of the cohort under study, for prognostication; to facilitate the interpretation of single-center, multicenter, or registry studies; to adjust center outcome data; and to stratify patients entering clinical trials that enroll patients across disease categories. (*Blood*. 2014;123(23):3664-3671)


100
80
60
40
20
0
Overall Survival (%)
Low risk
Intermediate risk
High risk
Very high risk
p< 0.0001
0
6
12
18
24
Months from transplantation

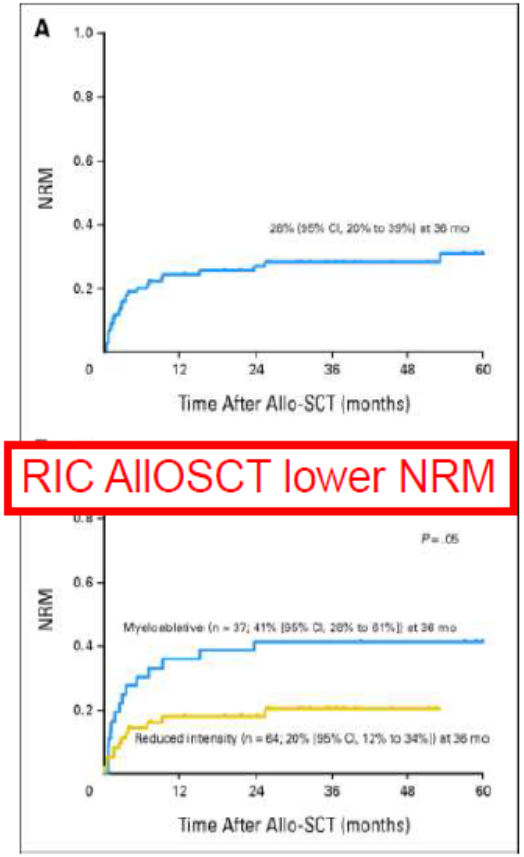
AlloSCT For Relapsed DLBCL After AutoSCT (van Kampen 2010)

- EBMT retrospective analysis
- 101 patients
- 37 Myeloablative 64 Reduced Intensity
- 1997-2006
- 19 Prior Rituximab
- 72 sibling/29 MUD

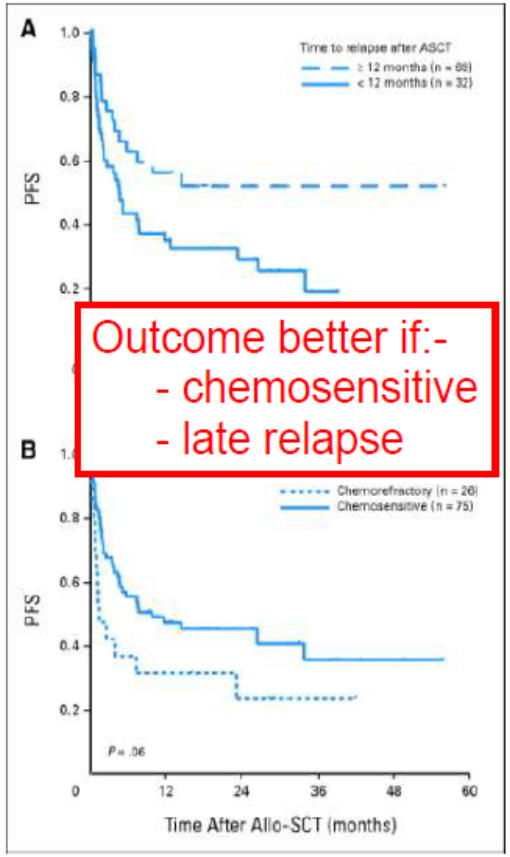
AlloSCT For Relapse After AutoSCT (van Kampen 2010)



AlloSCT For Relapse After AutoSCT (van Kampen 2010)



RIC AllOSCT lower NRM



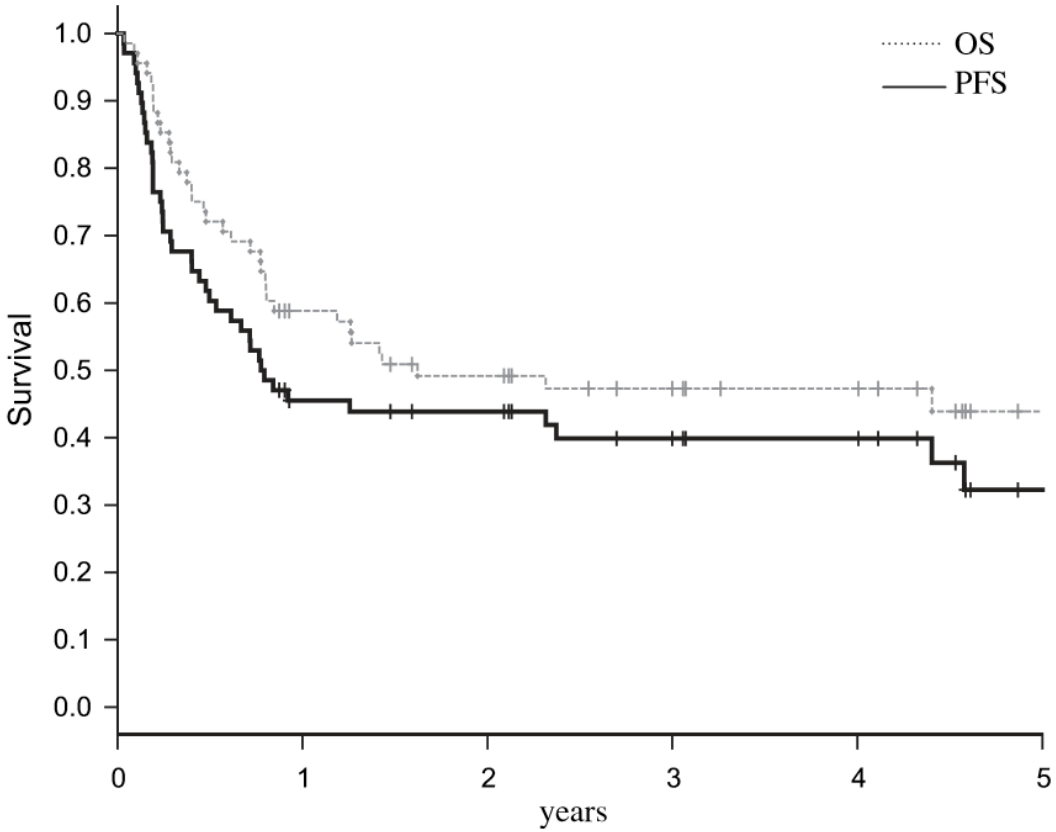
Outcome better if:-
- chemosensitive
- late relapse

Low Nonrelapse Mortality and Prolonged Long-Term Survival after Reduced-Intensity Allogeneic Stem Cell Transplantation for Relapsed or Refractory Diffuse Large B Cell Lymphoma: Report of the Société Française de Greffe de Moelle et de Thérapie Cellulaire

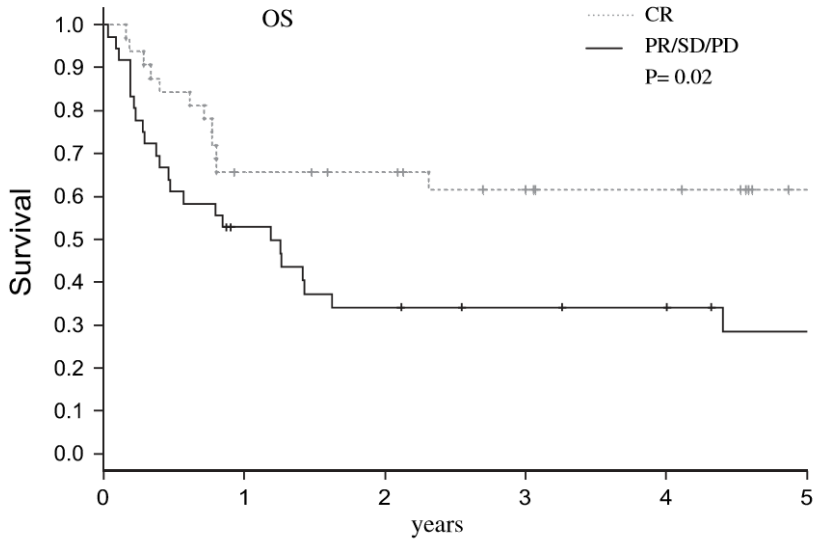
Anne Sirvent,[1] Nathalie Dhedin,[2] Mauricette Michallet,[3] Nicolas Mounier,[1] Catherine Faucher,[4] Ibrahim Yakoub-Agha,[5] Mohamad Mohty,[6] Marie Robin,[7] Reza Tabrizi,[8] Laurence Clement,[9] Karin Bilger,[10] Fabrice Larosa,[11] Nathalie Contentin,[12] Anne Huyn,[13] Sylvie François,[14] Claude-Eric Bulabois,[15] Patrice Ceballos,[16] Jean-Henri Bourrhis,[17] Agnès Buzyn,[18] Jérôme Cornillon,[19] Gaelle Guillerm,[20] Thierry de Revel,[21] Jacques-Olivier Bay,[22] François Guilhot,[23] Noël Milpied[7,8]

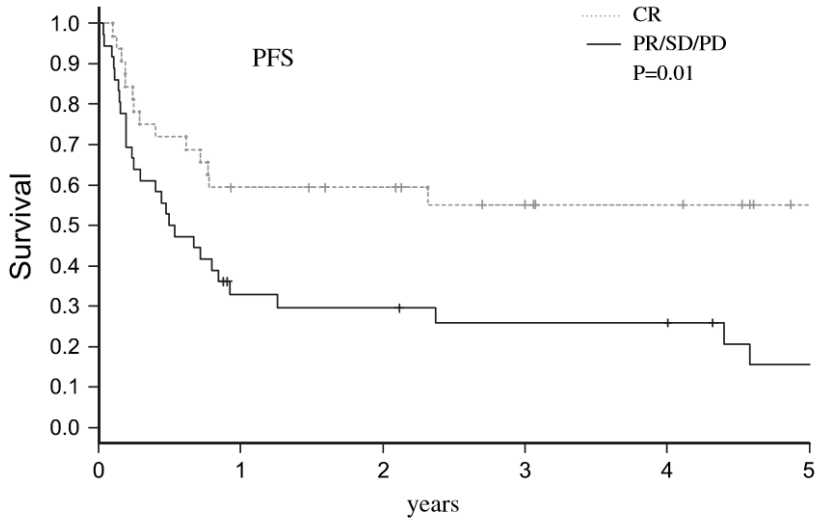
Patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) have a very poor prognosis. However, they may achieve long-term survival by undergoing allogeneic stem cell transplantation (SCT). The purpose of this study was to assess the outcome of all adult patients with DLBCL whose treatment included a reduced-intensity conditioning (RIC) regimen for allogeneic SCT and whose data were reported in the French Society of Marrow Transplantation and Cellular Therapy registry. Sixty-eight patients (median age: 48 years) were transplanted from October 1998 to January 2007. They had received a median of 2 regimens of therapy prior to allogeneic SCT, and 54 (79%) had already undergone SCT. Prior to transplantation, 32 patients (47%) were in complete remission (CR). For all patients but 1, conditioning regimens were based on fludarabine (Flu), which was combined with other chemotherapy drugs in 50 cases (74%) and with total body irradiation (TBI) in 17 (25%). For 56 patients (82%), the donor was an HLA-matched sibling, and peripheral blood was the most widely used source of stem cells (57 patients, 84%). With a median follow-up of 49 months, estimated 2-year overall survival (OS), progression-free survival (PFS), and the cumulative incidence of relapse were 49%, 44%, and 41%, respectively. The 1-year cumulative incidence of nonrelapse mortality (NRM) was 23%. According to multivariate analysis, the patients in CR before transplantation had a significantly longer PFS and a lower CI of relapse than patients transplanted during partial remission or stable or progressive disease. These results suggest that reduced-intensity allergenic transplantation is an attractive therapeutic option for patients with high-risk DLBCL.

Biol Blood Marrow Transplant 16:78-85, 2010

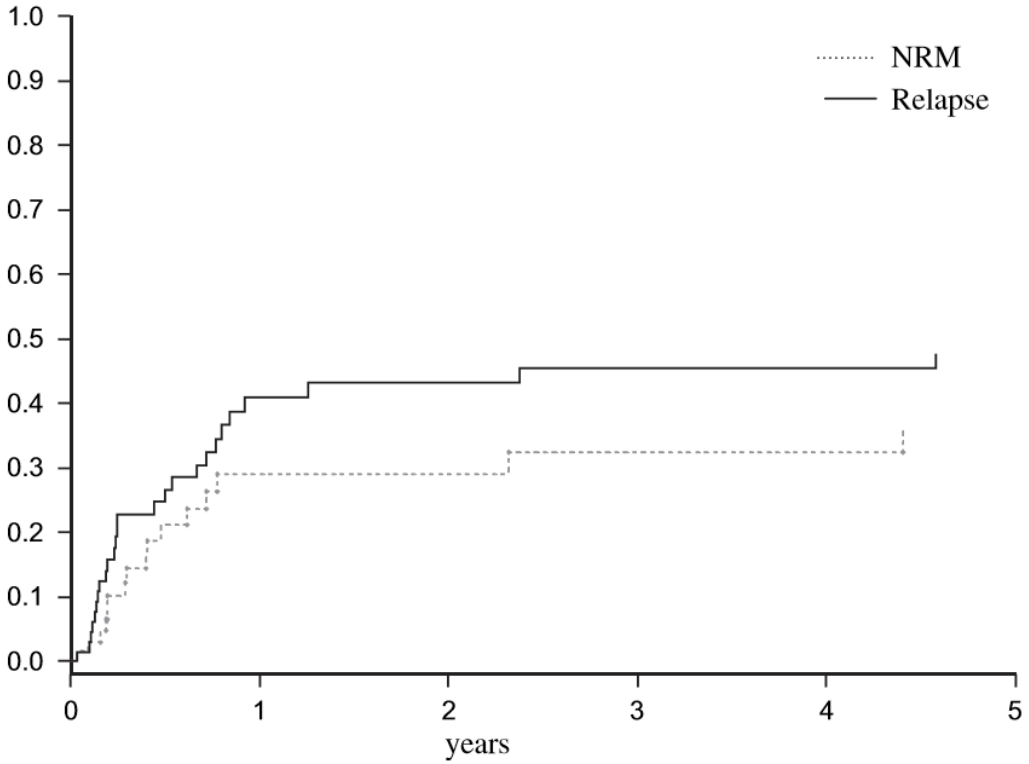


Biol Blood Marrow Transplant 16:78-85, 2010



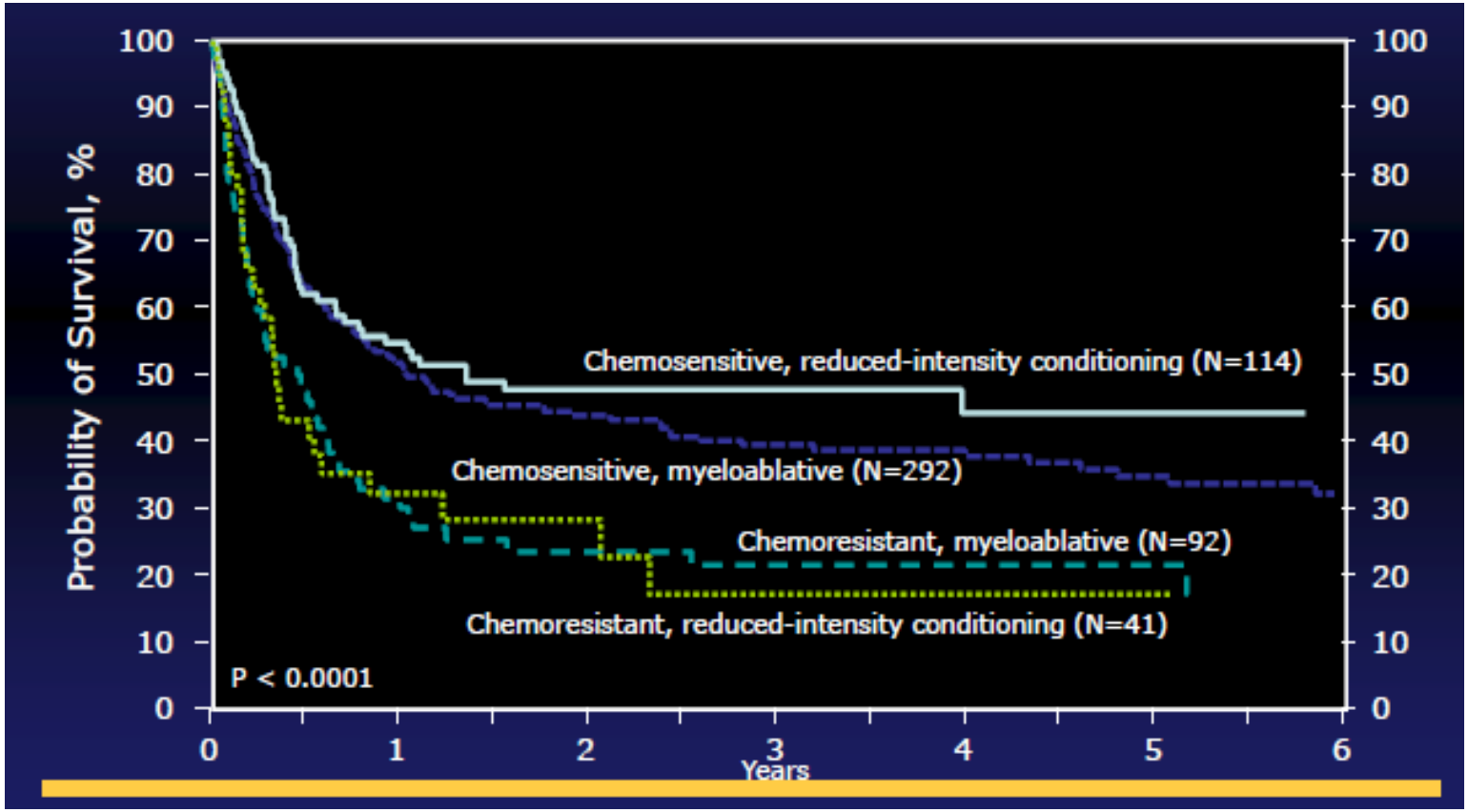


Biol Blood Marrow Transplant 16:78-85, 2010



Biol Blood Marrow Transplant 16:78-85, 2010

Survival after HLA-matched Sibling
Allotransplants for DLCL
by Disease Status and Conditioning Regimen



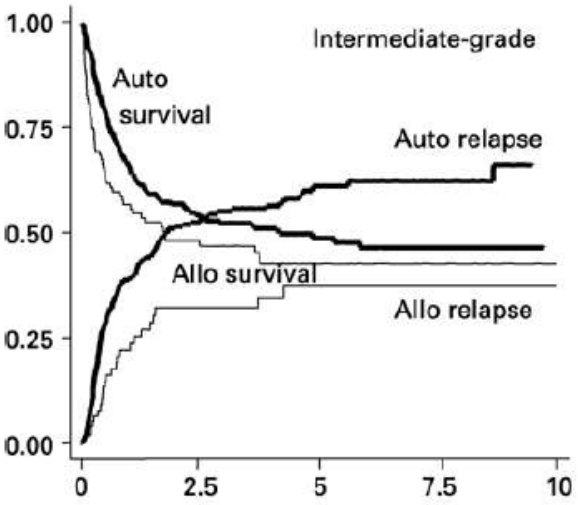
1998-2007 (CIBMTR) ASH 2010 Ed. Session

Results Of RIC AlloSCT In DLBCL

	n	Prior SCT	NRM % (years)	RR	PFS
EBMT Registry 2010	64	64/64	20 1yr	3yr	42 3yr
Thiotepa/Cyclo/ Fludara 2005	61	34/61	15 3yr	15 3yr	54 3yr
2Gy TBI+/-Flu 2008	33	24/33	25 3yr	25 3yr	35 3yr
Flu/Mel/CPATH 2010	48	34/48	32 4yr	32 4yr	48 4yr
French Registry 2010	68	54/68	23 1yr	23 1yr	44 2yr

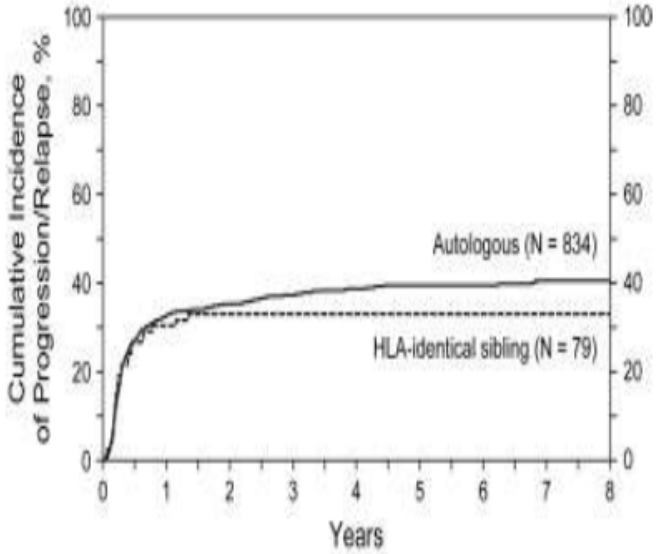
Is The Relapse Rate Following AlloSCT Lower Relative To AutoSCT?

Yes



(Peniket BMT 2003)

No



(Lazarus BBMT 2010)

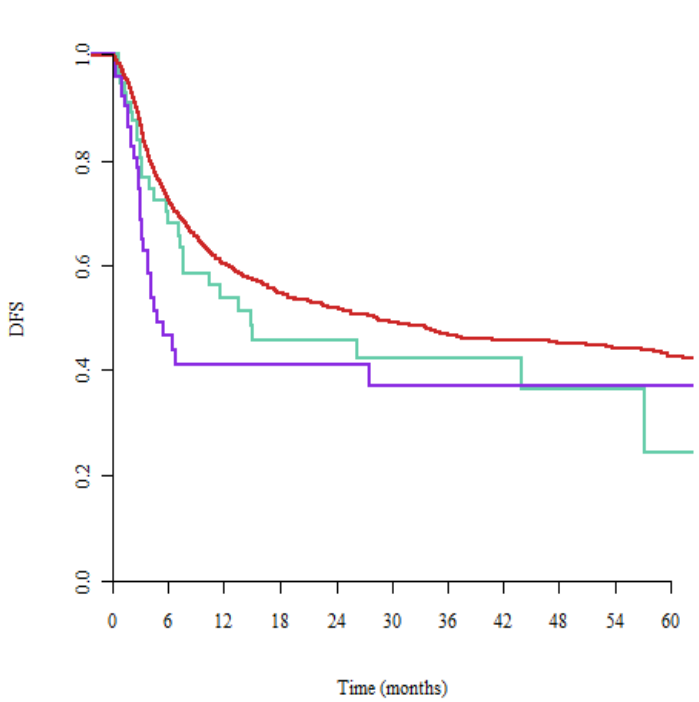
Jones et al Blood 1991, 77, 649
Ratanatharathorn et al Blood 1994, 84, 1050
Schimmer et al BMT 2000, 26, 859

Stem Cell Transplantation For Diffuse Large B Cell Lymphoma In The Rituximab Era.

- Objectives:-
  - To assess the outcome of SCT for DLBCL failing first line therapy in the last decade

- Methods
  - Retrospective study, SCT 2002-2010
  - Relapsed/refractory DLBCL
  - First transplant
    - AutoSCT or alloSCT (RIC and MA)

Chemosensitive Relapse: Disease Free Survival

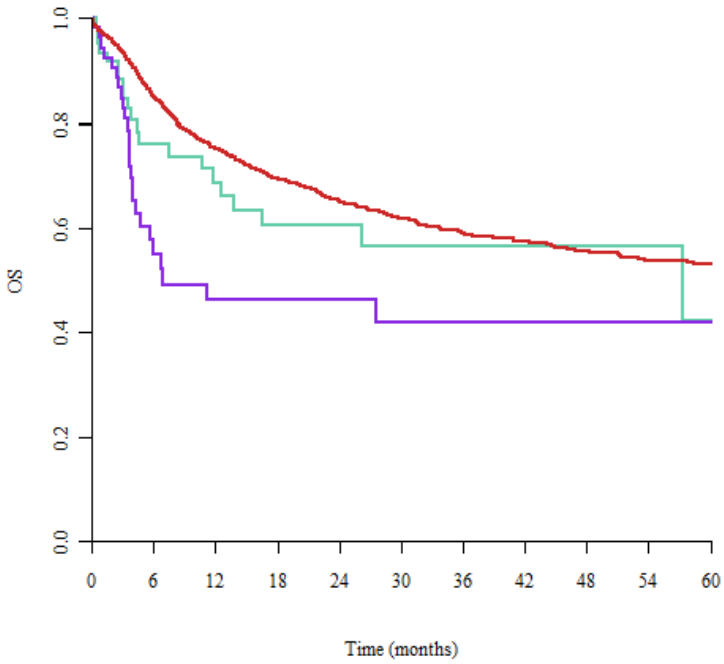


DFS Auto 46% 4yrs
DFS MACallo 37% 4yrs
DFS RICallo 37% 4yrs

Adverse Risk Factors For DFS:
- Male Sex
- Diag-SCT<1yr
- MACallo SCT

(Robinson ASH 2012)

Chemosensitive Relapse: Overall Survival



OS Auto 55% 4yrs
OS MACallo 42% 4yrs
OS RICallo 57% 4yrs

Adverse Risk Factors For OS:
- Age>50
- Diag-SCT<1yr
- MACallo SCT

(Robinson ASH 2012)

Stem Cell Transplantation In DLBCL

BSBMT Current Guidelines 2013

	Autograft	Sibling transplant	MUD transplant
CR1	GNR[1]	GNR	GNR
PR1 (sensitive to salvage)	S[2]	S[2]	S[2]
CR/PR>1	S[3]	CO[4]	CO[4]
Chemorefractory	GNR	D	D
Relapse post autograft	GNR	S[5]	S[5]

Leukemia (2007) 21, 2316–2323

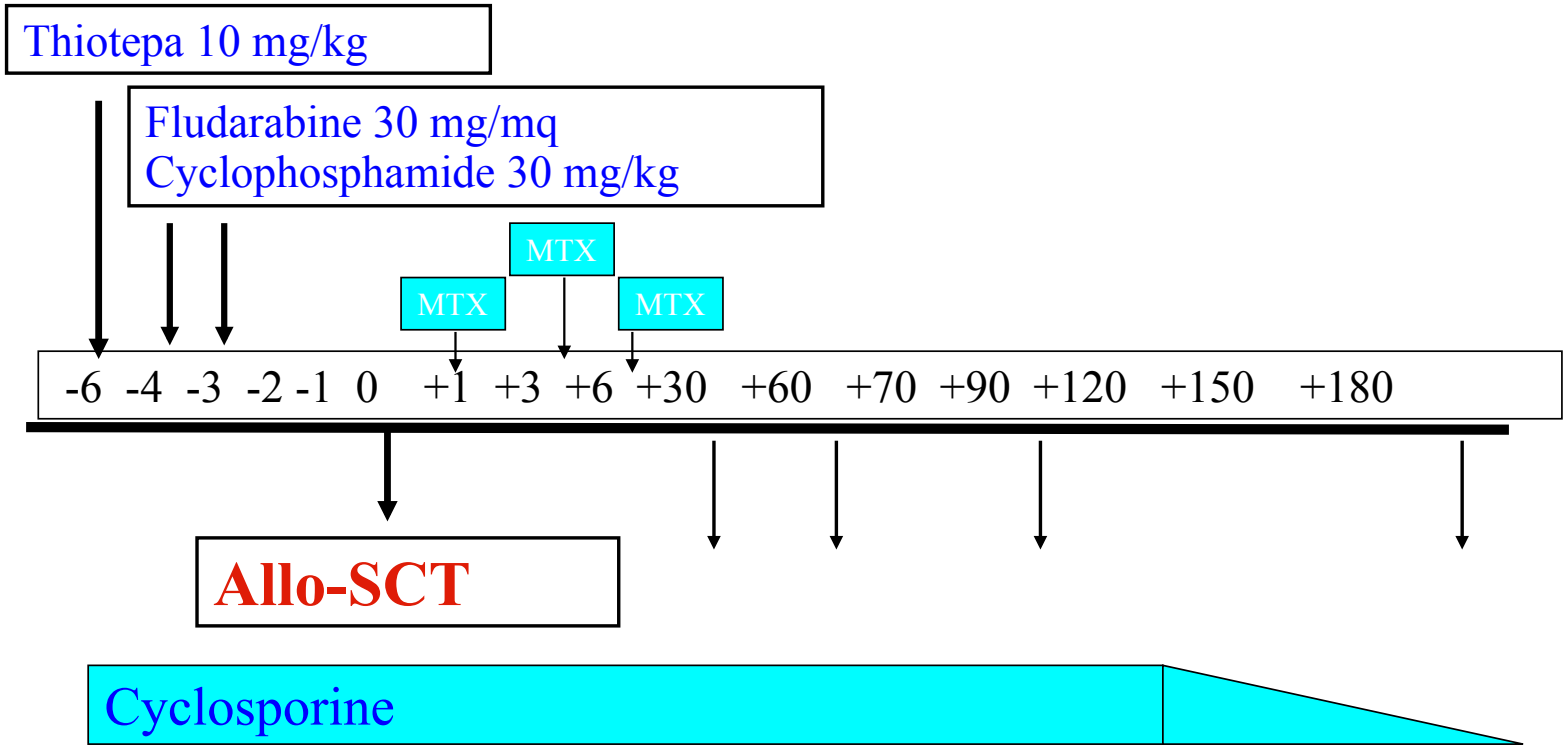
www.nature.com/leu

ORIGINAL ARTICLE

GITMO
GRUPPO ITALIANO TRAPIANTO MIDOLLO OSSEO

Allogeneic stem cell transplantation following reduced-intensity conditioning can induce durable clinical and molecular remissions in relapsed lymphomas: pre-transplant disease status and histotype heavily influence outcome

P Corradini[1], A Dodero[1], L Farina[1], R Fanin[2], F Patriarca[2], R Miceli[3], P Matteucci[4], M Bregni[5], R Scimè[6], F Narni[7], E Pogliani[8], A Locasciulli[9], R Milani[1], C Camiti[1], A Bacigalupo[10], A Rambaldi[11], F Bonifazi[12], A Olivieri[13], AM Gianni[4] and C Tarella[14]
on behalf of Gruppo Italiano Trapianto di Midollo Osseo (GITMO)



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Disease status at transplantation		
CR	43	25%
Indolent	15	
Aggressive	20	
MCL	1	
HD	7	
PR	76	45%
Indolent	29	
Aggressive	27	
MCL	7	
HD	13	
Refractory	49	29%
Indolent	19	
Aggressive	14	
MCL	6	
HD	10	

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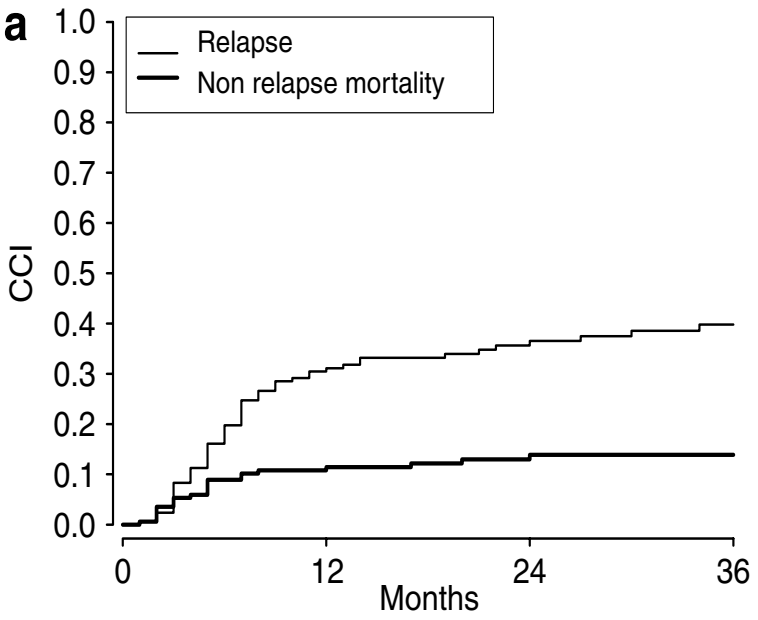

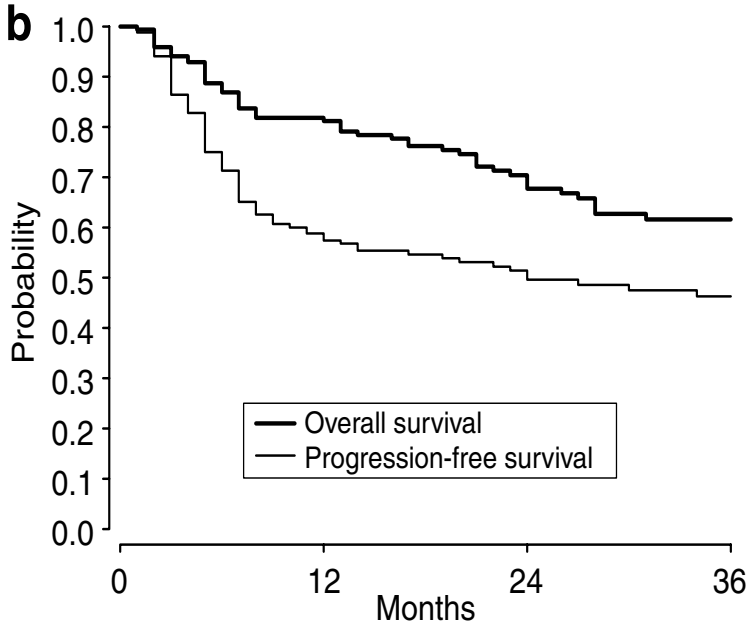

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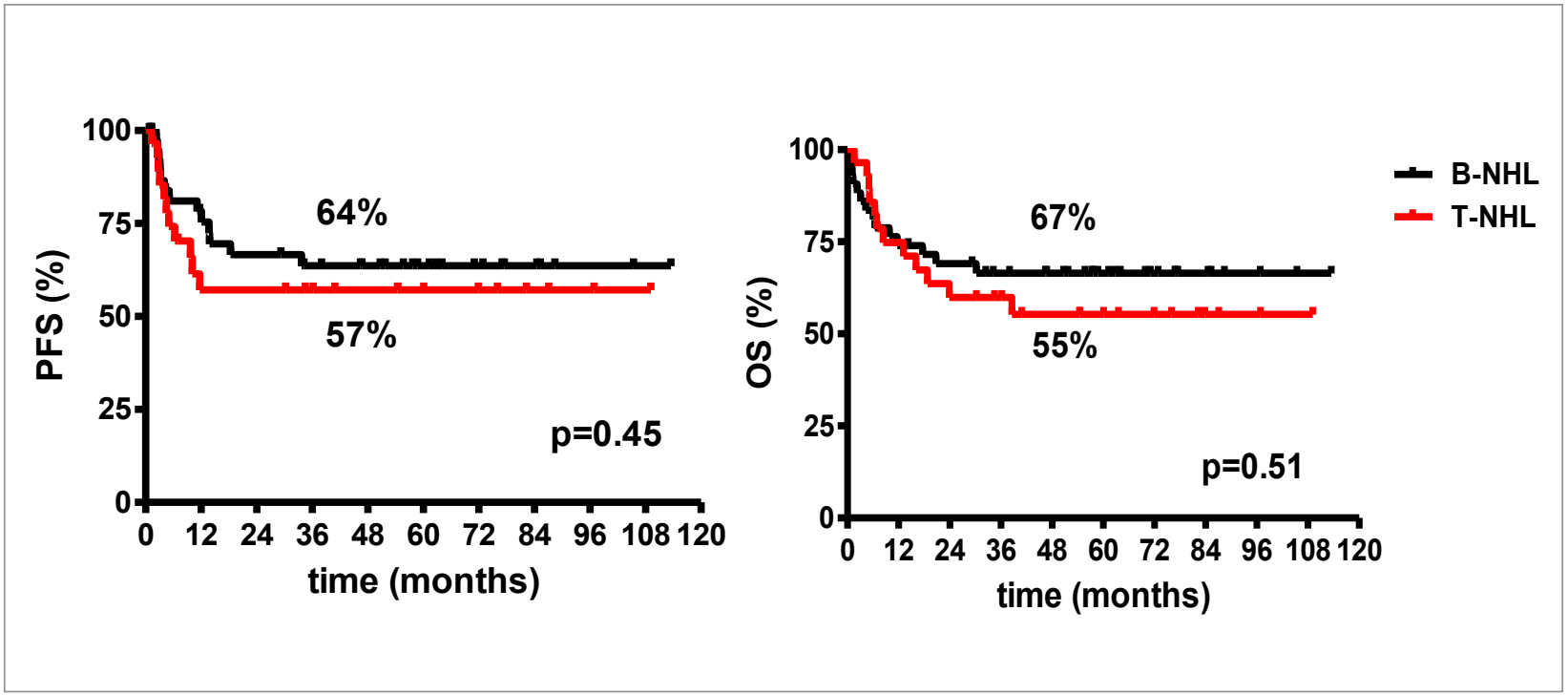
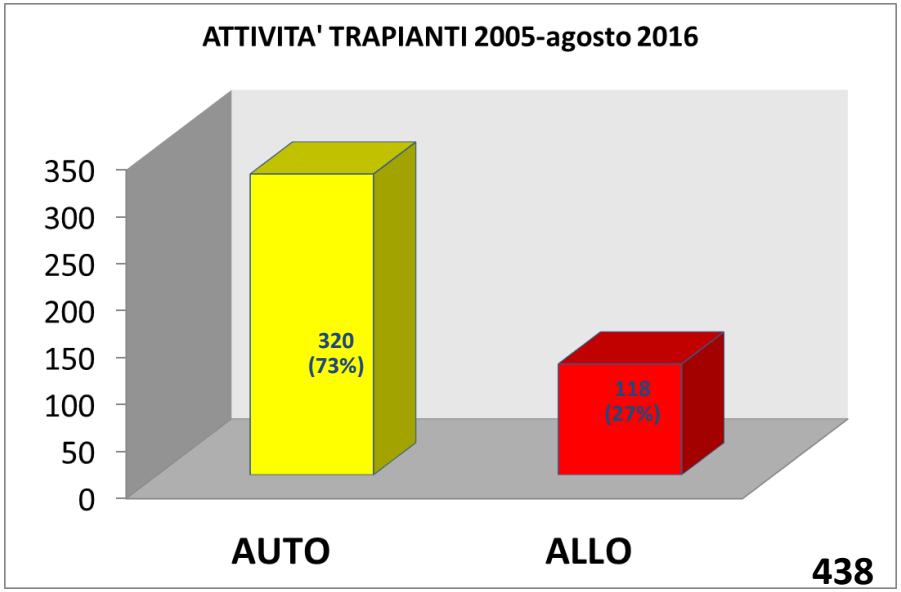
Update of RIC allo in relapsed lymphomas

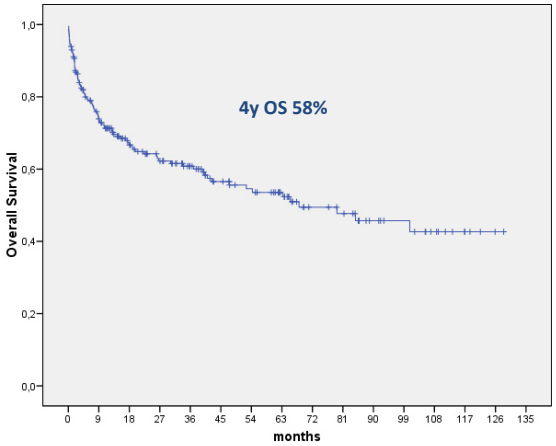
High grade B- and T-NHL median F/U 5 yrs

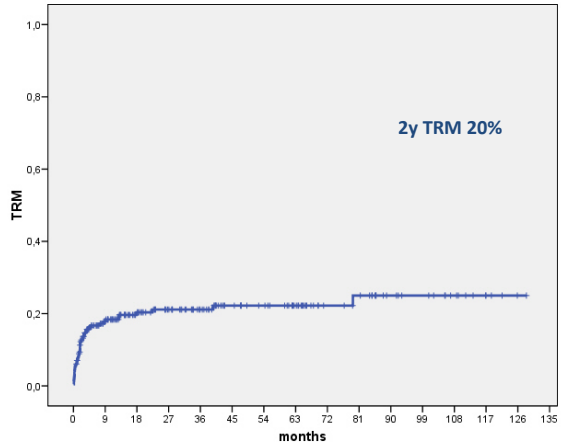




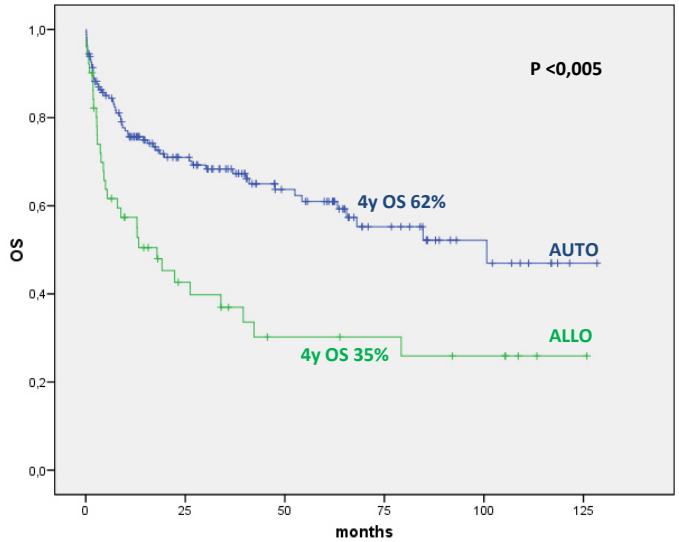
Linfomi	166 (52%)		52 (44%)
nHL	127 (76%)		33 (63%)
HL	39 (24%)		19 (37%)

Lymphomas

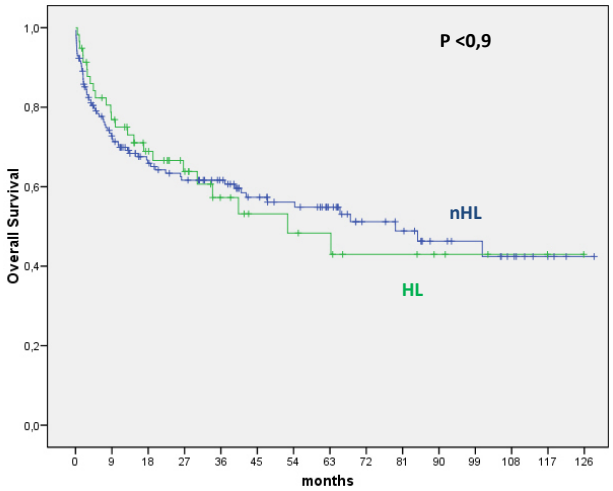

4y OS 58%
Overall Survival
1,0
0,8
0,6
0,4
0,2
0,0
0 9 18 27 36 45 54 63 72 81 90 99 108 117 126 135
months

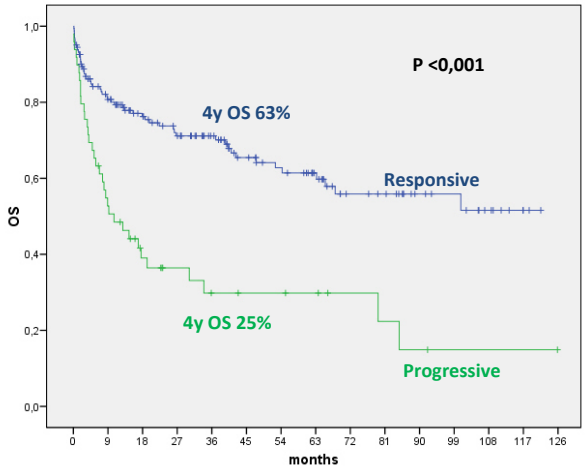

2y TRM 20%
TRM
1,0
0,8
0,6
0,4
0,2
0,0
0 9 18 27 36 45 54 63 72 81 90 99 108 117 126 135
months

Lymphomas


P <0,005
4y OS 62%
AUTO
ALLO
4y OS 35%
OS
1,0
0,8
0,6
0,4
0,2
0,0
0
25
50
75
100
125
months

Lymphomas


P <0,9
nHL
HL
Overall Survival
1,0
0,8
0,6
0,4
0,2
0,0
0 9 18 27 36 45 54 63 72 81 90 99 108 117 126
months


P <0,001
4y OS 63%
Responsive
4y OS 25%
Progressive
OS
1,0
0,8
0,6
0,4
0,2
0,0
0 9 18 27 36 45 54 63 72 81 90 99 108 117 126
months

Improved Survival in Lymphoma Patients Receiving Sirolimus for Graft-Versus-Host Disease Prophylaxis After Allogeneic Hematopoietic Stem-Cell Transplantation With Reduced-Intensity Conditioning

Philippe Armand, Supriya Gannamaneni, Haesook T. Kim, Corey S. Cutler, Vincent T. Ho, John Koreth, Edwin P. Alyea, Ann S. LaCasce, Eric D. Jacobsen, David C. Fisher, Jennifer R. Brown, George P. Canellos, Arnold S. Freedman, Robert J. Soiffer, and Joseph H. Antin

Purpose

Inhibitors of the mammalian target of rapamycin (mTOR) kinase have shown clinical activity in several lymphoma subtypes. Sirolimus, an mTOR inhibitor, also has activity in the treatment and prophylaxis of graft-versus-host disease (GVHD) after allogeneic hematopoietic stem-cell transplantation (HSCT). We hypothesized that the use of sirolimus for GVHD prophylaxis in patients with lymphoma might lead to improved survival after transplantation through a decreased incidence of disease progression.

Patients and Methods

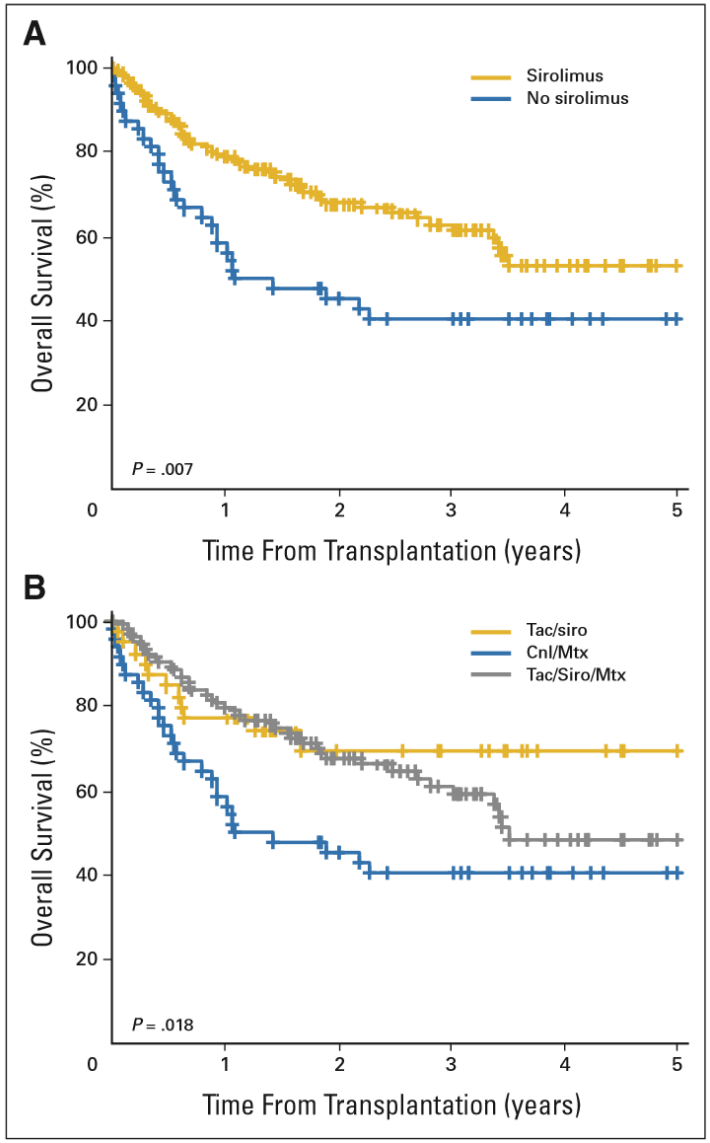
We retrospectively analyzed 190 patients who underwent transplantation for lymphoma. We compared the outcomes of patients who received sirolimus for GVHD prophylaxis with those of patients who received transplantation with a combination of a calcineurin inhibitor and methotrexate without sirolimus.

Results

Overall survival (OS) after transplantation was significantly superior in the sirolimus group, which was confirmed in multivariable analysis. The benefit was restricted to patients undergoing reduced-intensity conditioning (RIC) HSCT (3-year OS, 66% for sirolimus group *v* 38% for no-sirolimus group; $P = .007$; hazard ratio [HR] for mortality in multivariable analysis = 0.5, $P = .042$). Patients who received sirolimus had a similar incidence of nonrelapse mortality but a decreased incidence of disease progression compared with patients who did not receive sirolimus (3-year cumulative incidence of progression, 42% *v* 74%, respectively; $P < .001$; HR for progression in multivariable analysis = 0.4, $P = .01$). The effect of sirolimus persisted after adjusting for the occurrence of GVHD. No such survival advantage was apparent in a similar comparison of patients who underwent transplantation for diseases other than lymphoma.

Conclusion

This study suggests that sirolimus can independently decrease the risk of lymphoma progression after RIC HSCT, paving the way for prospective clinical trials.



J Clin Oncol 26:5767-5774. © 2008

Is there any role for allogeneic SCT in place of autoSCT?

- Failure to collect autologous stem cells
- In patients predicted to be at high risk of failing an autoSCT?

Who Should Be Considered For An AlloSCT Rather Than An Auto Transplant?

- DLBCL Failing R-Chemo AutoSCT REMAINS the standard therapy

- However high risk of failure in some patients:-
  - High sAAIPI Score
  - Time to relapse <12 Months
  - PET+ve post salvage
  - Myc+?
  - ABC subtype?
  - "Double Hit" lymphomas

- Clinical studies required to assess efficacy of alloSCT in this setting

Current Status of Allogeneic transplantation for Aggressive Non-Hodgkin lymphoma

Koen van Besien, M.D.
Stem Cell Transplant Program, University of Chicago

Abstract

Purpose—To provide a succinct update on the role of allogeneic stem cell transplantation in the management of patients with aggressive lymphomas. To clarify the indications for allogeneic transplantation vis-à-vis autologous transplant and to discuss the rational and potential benefits of reduced intensity conditioning(RIC), non-myeloablative (NMA) transplant, T-cell depletion and variations in GVHD prophylaxis.

Recent findings—Considerable effort has been spent in developing transplant regimens with reduced toxicity and reduced GVHD. The role of allogeneic transplantation has also been redefined in light of advances in lymphoma classification, diagnostic methods, particularly PET scan and advances in transplant technology. Haplo and UCB SCT allow identification of a donor for nearly all patients.

Summary—RIC and NMA conditioning have reduced early toxicity but are associated with increased risk for disease recurrence. Promising data have been reported from a novel conditioning regimen combining NMAwith ibritumomab tiuxetan. T-cell depletion reduces cGVHD but has some increase in rate of recurrence. Rapamycin may be associated with reduction in risk for disease recurrence. In diffuse large B cell lymphoma, the outcome of allo SCT depends on patient characteristics and chemosensitivity. It is seful after failure of autoSCT and in partial responses to salvage therapy. Allo SCT may be the treatment of choice for advanced T-cell and NK cell lymphoma and for ATLL. Prophylactic or preemptive DLI may be useful, but requires controlled studies.

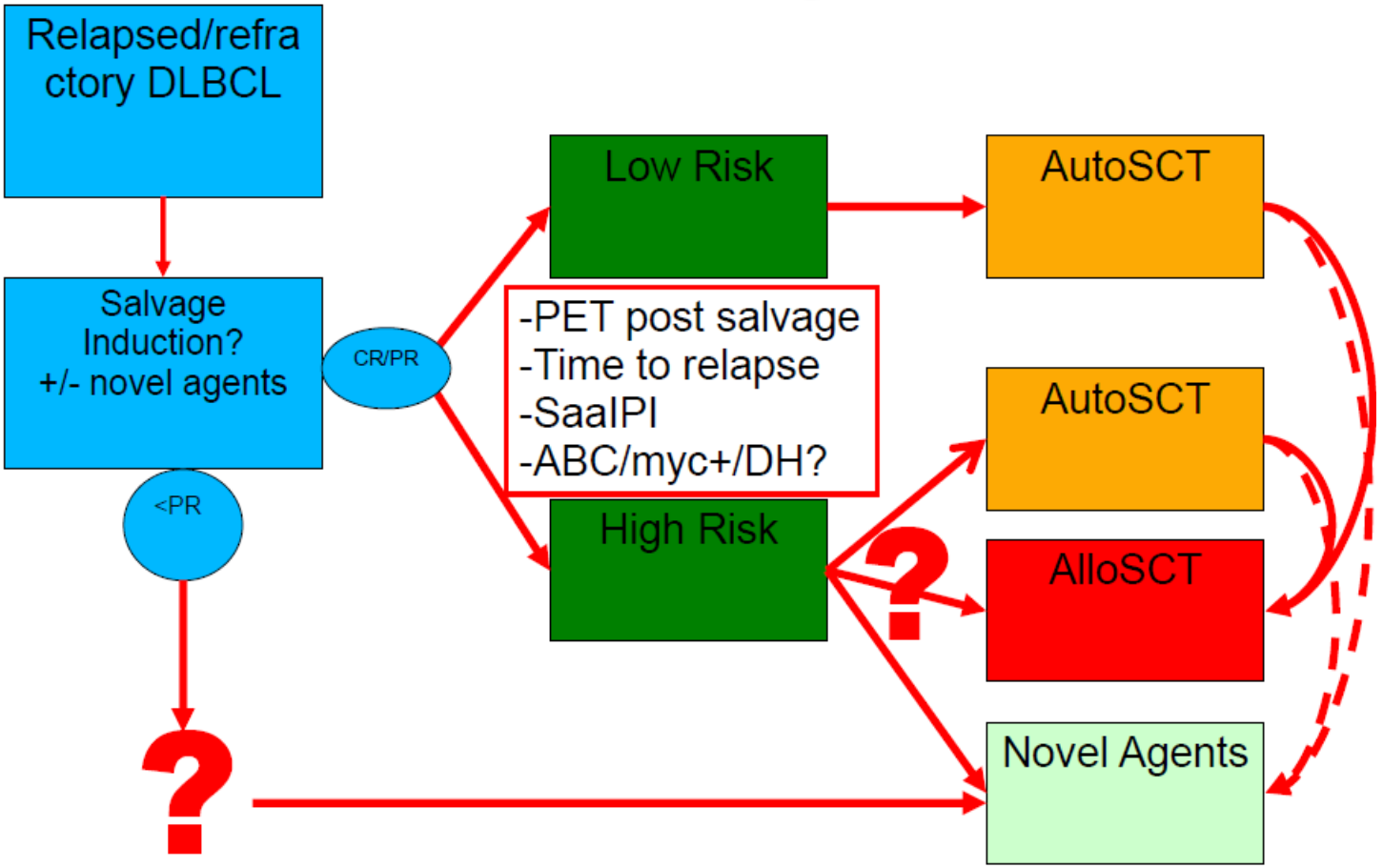
Curr Opin Oncol. 2011 November

Bullet Points

- AlloSCT is the treatment of choice for DLBCL relapsing after auto SCT of with PR to salvage.
- Outcome of AlloSCT is dependent more on patient characteristics and chemosensitivity than on conditioning regimens.
- AlloSCT is the treatment of choice for advanced PTCL and NK cell lymphoma.
- RIC and NMA conditioning have reduced early toxicity at the expense of more cGVHD and recurrence rate.
- In some studies, outcomes are better with mismatched or unrelated donors. One should therefore be able to identify suitable donors for all patients.

Curr Opin Oncol. 2011 November

Summary


Relapsed/refra
ctory DLBCL
Salvage
Induction?
+/- novel agents
CR/PR
<PR
?
Low Risk
-PET post salvage
-Time to relapse
-SaaIPI
-ABC/myc+/DH?
High Risk
?
AutoSCT
AutoSCT
AlloSCT
Novel Agents

Pet -
dopo 1°/2°
Salvataggio

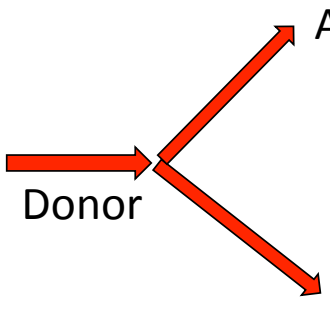
ASCT

Mantenimento

Rituximab
Lenalidimide
Ibrutinib

Pet +
dopo 1°/2°
Salvataggio

New drug



ASCT

Mantenimento

RIC Allo

Today CHT+/-ASCT can cure <50% of patients with aggressive lymphoma (B-cell or T-cell) with unfavourable IPI or adverse histology/genotype

NEW DRUGS ARE PROMISING,

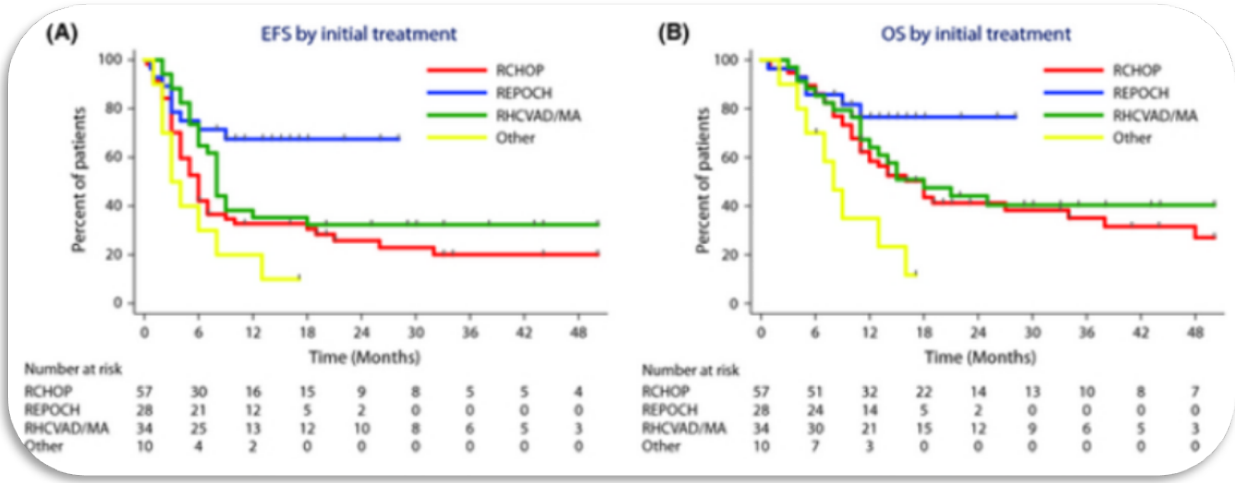
BUT ALLOGENEIC SCT IS THE ONLY CHANCE TU CURE THE REMAINING 50%

Double hit lymphoma:
the MD Anderson Cancer Center clinical experience

129 patients
Median (range) age 62 (17-84)
Male 65%
IPI score
- 0-1: 13%
- 2-3: 61%
- 4-5: 26%

DLBCL or BCLU in 92%
Translocations
- MYC: 81%
- BCL2: 84%
- BCL6: 12%
- MYC and BCL2: 72%
- Triple hit: 11%

GCB by IHC in >90%



Two-year EFS was better in R-EPOCH group (67%)

Oki et al, BJH 2014

Eur J Haematol. 2006 Aug;77(2):114-9.

Late non-relapse mortality among adult autologous stem cell transplant recipients: a nation-wide analysis of 1,482 patients transplanted in 1990-2003.

Jantunen E[1], Itälä M, Siitonen T, Koivunen E, Leppä S, Juvonen E, Kuittinen O, Lehtinen T, Koistinen P, Nyman H, Nousiainen T, Volin L, Remes K.

Author information

Abstract

Data on the incidence and causes of late (>100 d) non-relapse mortality (NRM) in autologous stem cell transplant (ASCT) recipients is limited. We have analysed NRM in a cohort of 1,482 adult patients who received ASCT in 1990-2003 in six Finnish transplant centres. The most common diagnoses included non-Hodgkin's lymphoma (NHL) (n = 542), multiple myeloma (MM) (n = 528), breast cancer (n = 132); Hodgkin's lymphoma (HL) (n = 86) and chronic lymphocytic leukaemia (CLL) (n = 63). Until September 2005, 646 patients (44%) have died. Late NRM was observed in 68 patients (4.6% of ASCT recipients; 11% of all deaths). There were 38 males and 30 females with a median age of 58 yr (20-69) at the time of ASCT. The median time to NRM was 27 months from ASCT (3-112). The risk of NRM was highest in patients with CLL (9.5%) and those with HL (8.1%) followed by MM and NHL (4.9% and 4.8%, respectively). The risk of late NRM was comparable in patients who received total body irradiation (TBI) and those who received chemotherapy-only regimens (6.7% vs. 4.3%). Another malignancy was the most common cause of late NRM (24 patients, 35% of late NRM). Twelve patients (0.8% of ASCT recipients) have died due to secondary haematological malignancy. Altogether 22 patients (32% of late NRM) died from infectious causes. Malignancies and late infections are important causes of NRM after ASCT. These facts point out the importance of prolonged follow-up in ASCT recipients.

Leuk Lymphoma. 2006 Aug;47(8):1488-94.

Morbidity and transplant-related mortality of CBV and BEAM preparative regimens for patients with lymphoid malignancies undergoing autologous stem-cell transplantation.

Puig N[1], de la Rubia J, Remigia MJ, Jarque I, Martín G, Cupelli L, Sanz GF, Lorenzo I, Sanz J, Martínez JA, Jiménez C, Sanz MA.

Author information

Abstract

CBV and BEAM are the two most frequently used regimens for patients with lymphoma undergoing autologous hematopoietic stem-cell transplantation (ASCT). This study compared their morbidity and transplant-related mortality (TRM) in 113 patients with non-Hodgkin's lymphoma (69) and Hodgkin's disease (44) undergoing ASCT between 1990 - 2004. CBV (cyclophosphamide, 6000 mg m(-2); VP-16, 750 mg m(-2); and high-dose BCNU, 800 mg m(-2)) was administered to 75 patients and 38 received BEAM (BCNU, 300 mg m(-2); VP-16, 800 mg m(-2); cytarabine, 800 mg m(-2); melphalan, 140 mg m (-2)). Patients in the BEAM group had a significantly higher median age (p = 0.002) and were more heavily treated before ASCT (p = 0.003). More patients showed active disease at transplant in the BEAM group (p = 0.04). Sinusoidal obstruction syndrome (SOS) was more frequent in the CBV group (11% vs 0%, p = 0.048). There were 20 (18%) transplant-related deaths, 18 in the CBV and two in the BEAM group. Infectious complications (12 patients, seven with pneumonia) and SOS (four) were the most frequent causes of death. The cumulative incidences of TRM were 25% in the CBV and 7% in the BEAM group (p = 0.02). CBV thus produced a higher incidence of SOS and TRM than BEAM in this series.

Characteristics of patients

	AUTOLOGOUS 166	ALLOGENEIC 52	p
Age, median (range) >60 yrs, n (%)	49 (16-71) 48 (29)	46 (18-67) 12 (23)	0,41
III-IV stage, n (%)	118 (71)	40 (77)	0,34
B symptoms, n (%)	28 (36)	20 (43)	0,30
Bulky, n (%)	33 (42)	13 (30)	0,16
High risk, n (%)	79 (99)	41 (95)	0,244
Responsive disease, n (%)	132 (81)	34 (65)	0,02
Prior Therapies, median (range) > 2, n (%)	2 (1-5) 35 (27)	3 (1-6) 39 (75)	0,001
Months to TMO, median (range) > 12 yrs n (%)	13 (2-261) 88 (59)	20 (5-154) 40 (82)	0,002

Transplant Toxicity

	AUTOLOGOUS 166	ALLOGENEIC 52	p
Mucosites, n (%) III-IV grade	136 (89) 61 (44)	45 (88) 12 (27)	0,1 0,03
Diarrhea, n (%) III-IV grade	138 (90) 41 (30)	37 (73) 6 (16)	0,02 0.09
II grade Neurotoxicity, n (%)	11 (7)	12 (24)	0,013
Renal toxicity, n (%) III-IV grade	6 (4) 3	5 (90) 2	0,1
I-II liver toxicity, n (%)	7 (5)	15 (29)	0,01
Febrile Neutropenia, n (%) IFI	143 (88) 21 (13)	38 (73) 14 (27)	0,01 0,01
Chronic GvHD, n (%) Limited		14 (29) 6 (43)	////
Acute GvHD, n (%) I-!! Glucksberg		16 (31) 8	/////

Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis

Adam M. Petrich,[1] Mitul Gandhi,[1] Borko Jovanovic,[1] Jorge J. Castillo,[2] Saurabh Rajguru,[3] David T. Yang,[4]

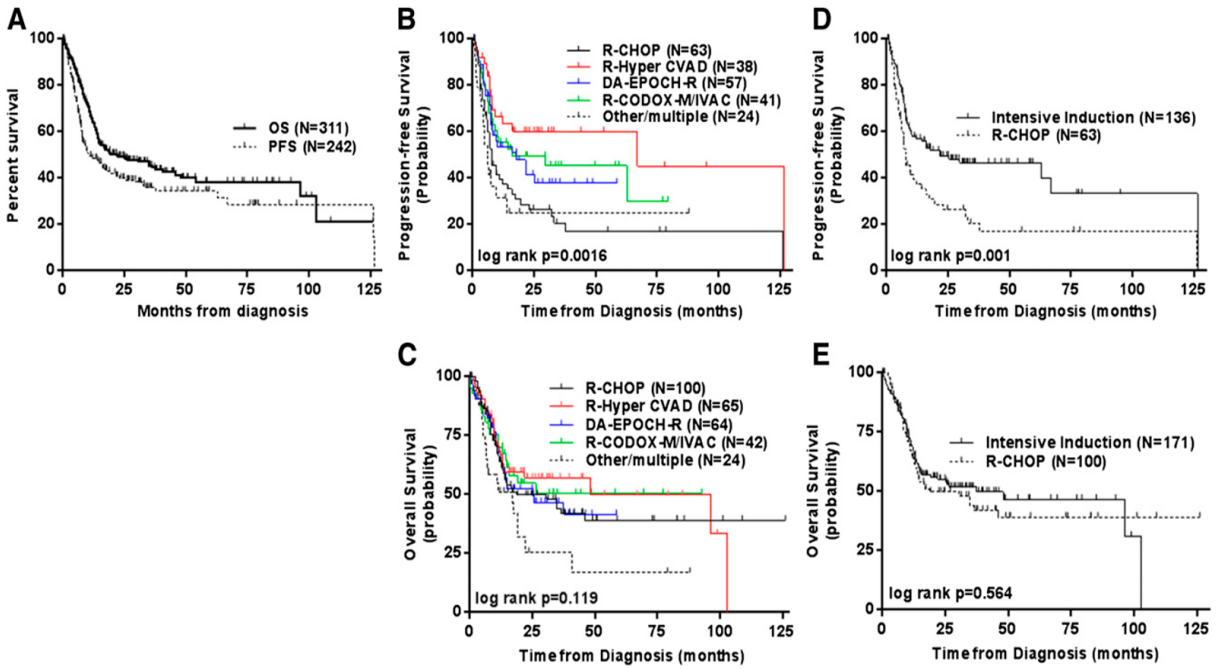
Key Points

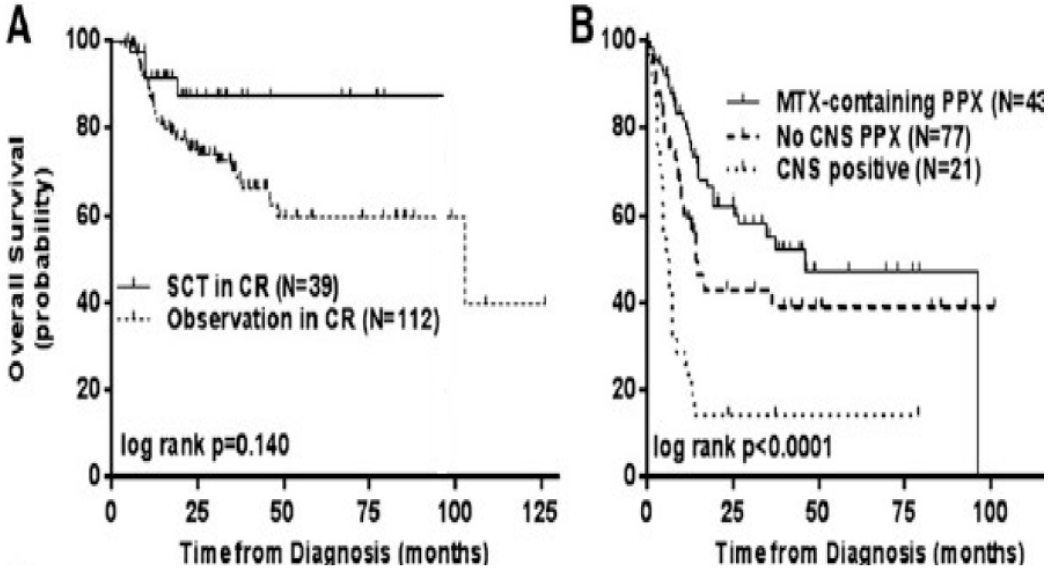
- A subset of DHL patients may be cured, and some patients may benefit from intensive induction.
- Further investigations into the roles of SCT and novel agents are needed.

Patients with double-hit lymphoma (DHL), which is characterized by rearrangements of MYC and either BCL2 or BCL6, face poor prognoses. We conducted a retrospective multicenter study of the impact of baseline clinical factors, induction therapy, and stem cell transplant (SCT) on the outcomes of 311 patients with previously untreated DHL. At median follow-up of 23 months, the median progression-free survival (PFS) and overall survival (OS) rates among all patients were 10.9 and 21.9 months, respectively. Forty percent of patients remain disease-free and 49% remain alive at 2 years. Intensive induction was associated with improved PFS, but not OS, and SCT was not associated with improved OS among patients achieving first complete remission ($P = .14$). By multivariate analysis, advanced stage, central nervous system involvement, leukocytosis, and LDH >3 times the upper limit of normal were associated with higher risk of death. Correcting for these, intensive induction was associated with improved OS. We developed a novel risk score for DHL, which divides patients into high-, intermediate-, and low-risk groups. In conclusion, a subset of DHL patients may be cured, and some patients may benefit from intensive induction. Further investigations into the roles of SCT and novel agents are needed. (*Blood*. 2014;124(15):2354-2361)

Allogeneic Transplantation for Aggressive Lymphoma

Advantages	**Limitations**
Tumor free graft	Treatment-related mortality
GVL	Long-term morbidity from GVHD
Replaces damaged host hematopoiesis	Need for donor
(less risk of MDS)	Limited early disease control
DLI to augment anti-tumor activity	(non-ablative regimens)
Can be used after post ASCT relapse	
(non-ablative regimens)	

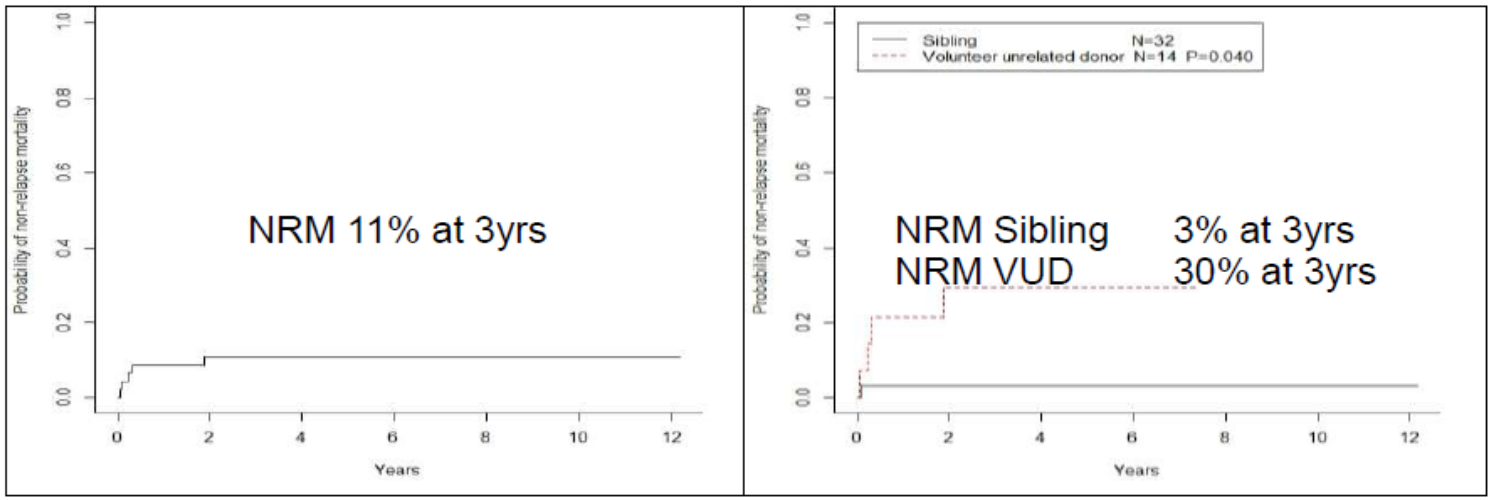

A
Percent survival
Months from diagnosis
OS (N=311)
PFS (N=242)
B
Progression-free Survival (Probability)
Time from Diagnosis (months)
R-CHOP (N=63)
R-Hyper CVAD (N=38)
DA-EPOCH-R (N=57)
R-CODOX-M/IVAC (N=41)
Other/multiple (N=24)
log rank p=0.0016
C
Overall Survival (probability)
Time from Diagnosis (months)
R-CHOP (N=100)
R-Hyper CVAD (N=65)
DA-EPOCH-R (N=64)
R-CODOX-M/IVAC (N=42)
Other/multiple (N=24)
log rank p=0.119
D
Progression-free Survival (Probability)
Time from Diagnosis (months)
Intensive Induction (N=136)
R-CHOP (N=63)
log rank p=0.001
E
Overall Survival (probability)
Time from Diagnosis (months)
Intensive Induction (N=171)
R-CHOP (N=100)
log rank p=0.564


A
Overall Survival (probability)
100
80
60
40
20
0
SCT in CR (N=39)
Observation in CR (N=112)
log rank p=0.140
0
25
50
75
100
125
Time from Diagnosis (months)
B
MTX-containing PPX (N=43
No CNS PPX (N=77)
CNS positive (N=21)
log rank p<0.0001
Time from Diagnosis (months)

BEAM-CAMPATH AlloSCT For DLBCL and PTCL

n	46
Median age	43 (17-59)
DLBCL	31
TCL	15
Prior auto	5

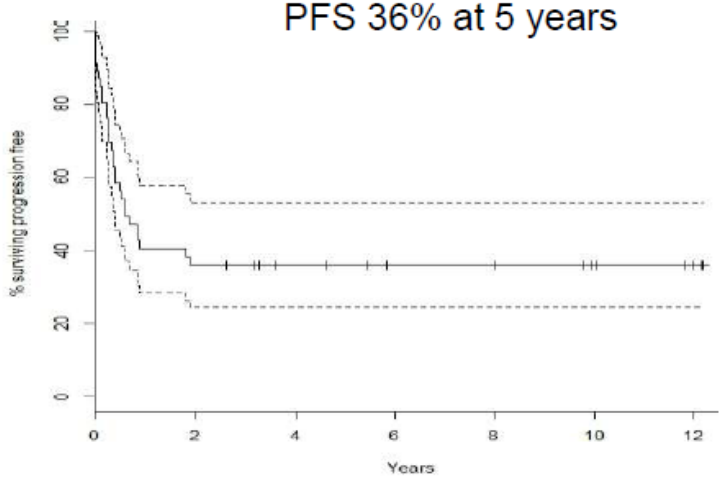
Median Prior Lines	2.5 (1-5)
Chemosensitive	34
Chemrefractory	11
Sib/UD	32/14



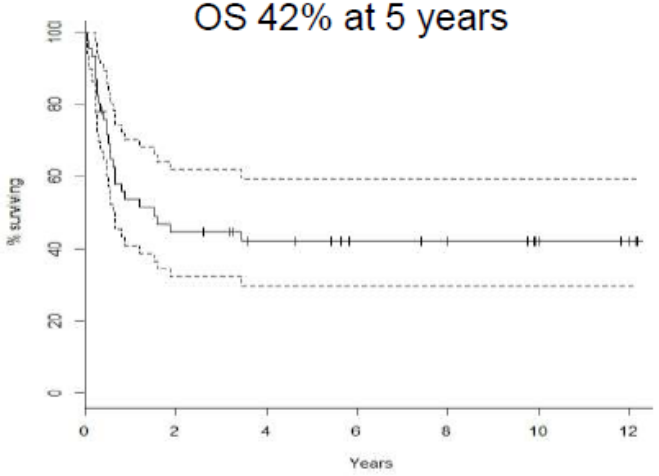
(Robinson ASH 2012)

BEAM-CAMPATH AlloSCT For DLBCL and PTCL

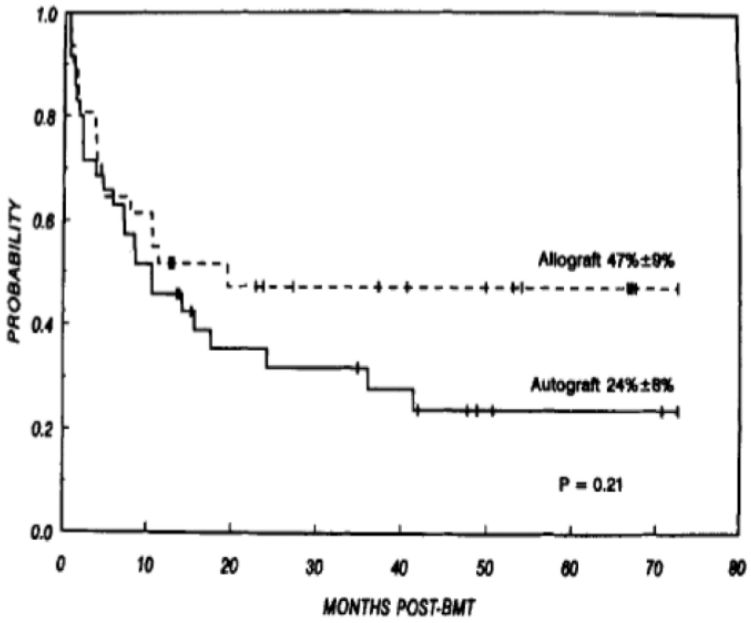
PFS 36% at 5 years

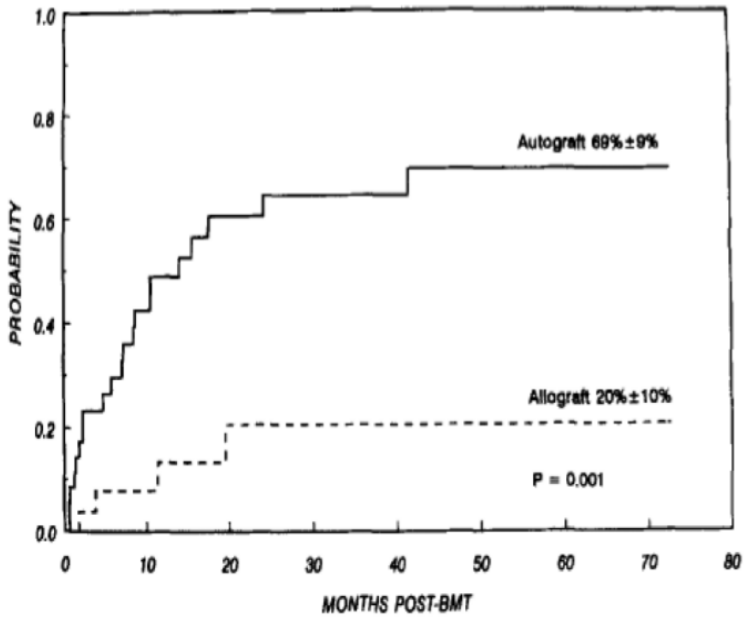


OS 42% at 5 years

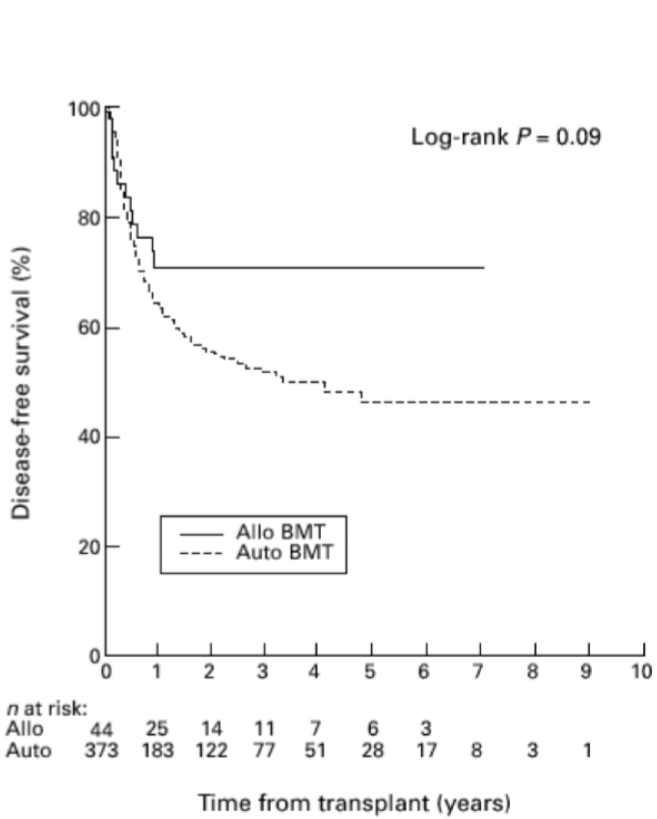


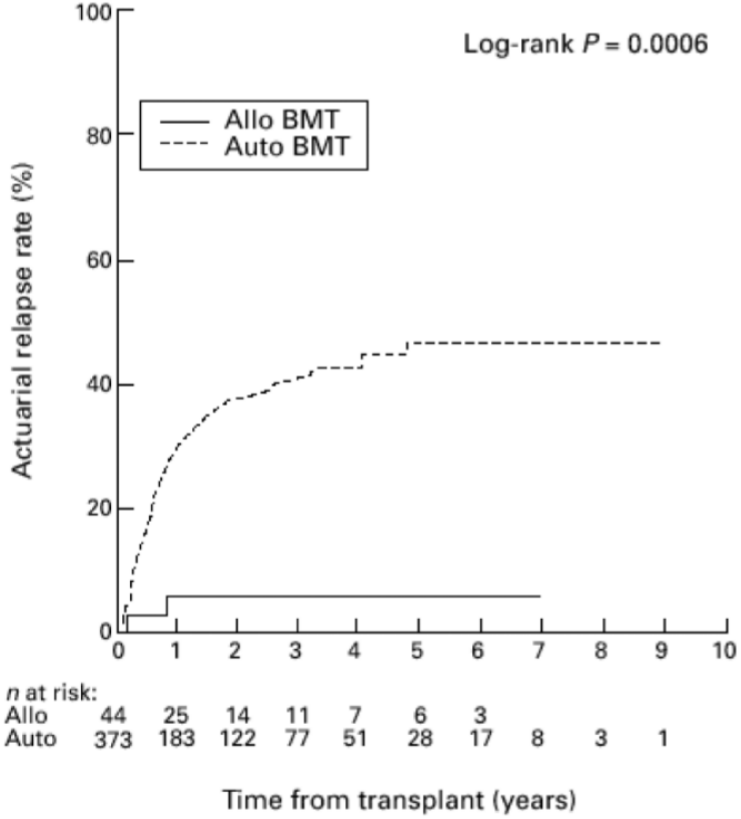
(Robinson ASH 2012)



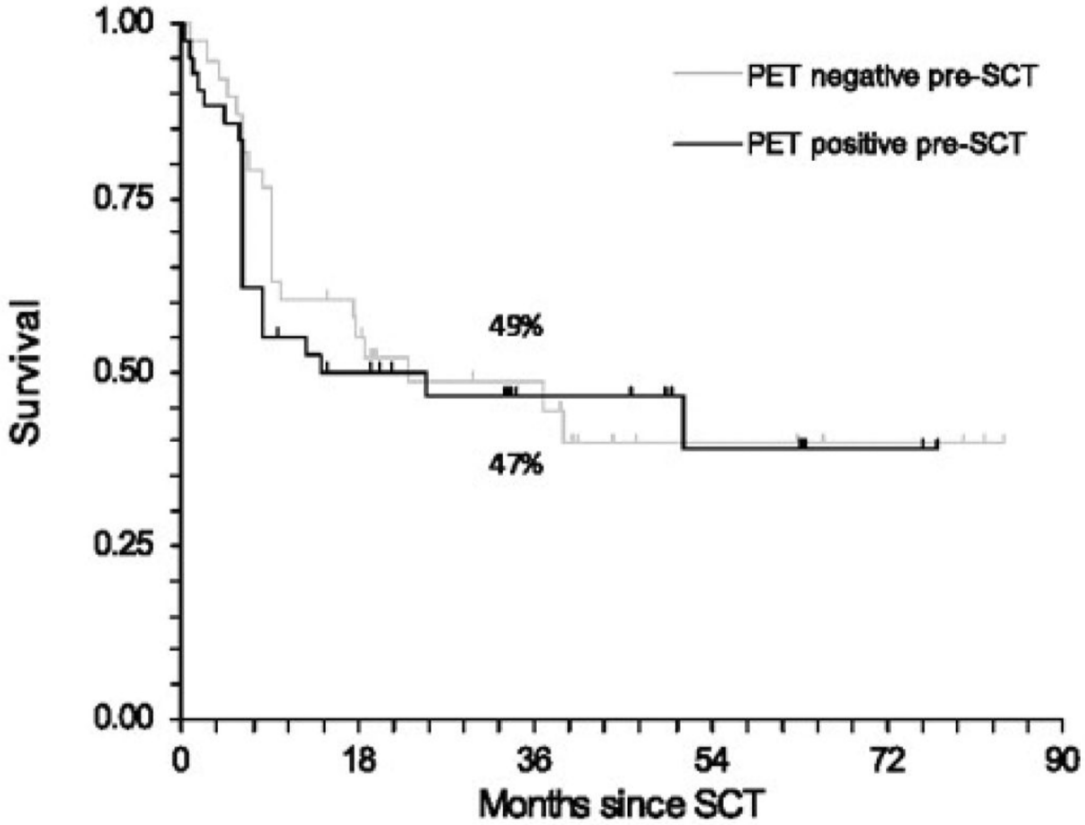


Curr Opin Oncol. 2011 November





Curr Opin Oncol. 2011 November



Curr Opin Oncol. 2011 November

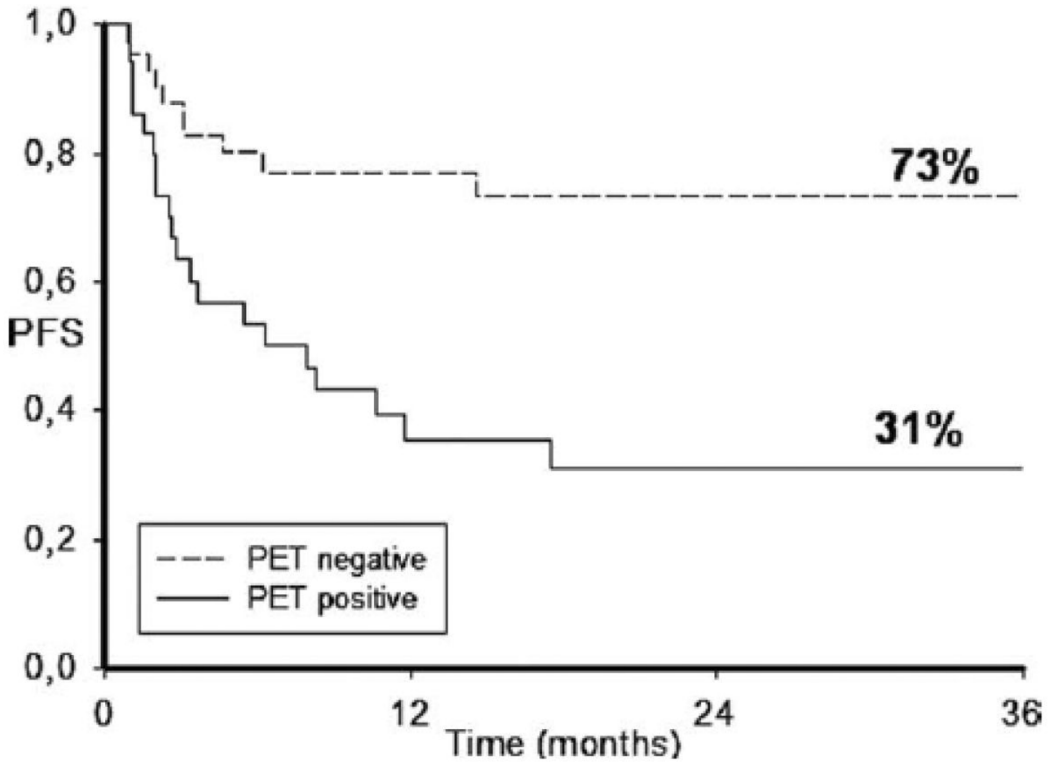


Figure 3.
Progression Free Survival after Allo SCT depending on PET scan results

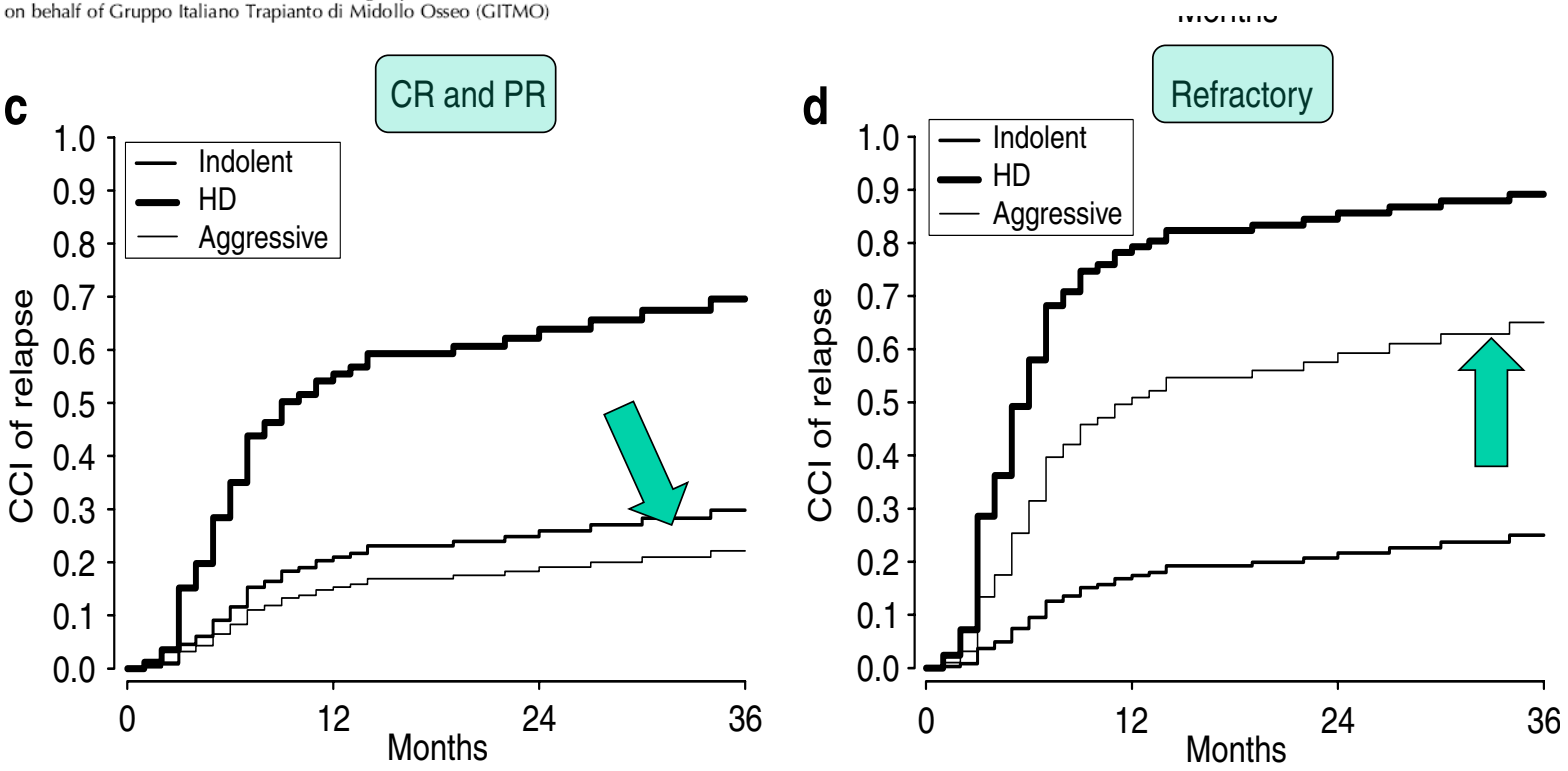
Leukemia (2007) 21, 2316–2323

www.nature.com/leu

ORIGINAL ARTICLE

Allogeneic stem cell transplantation following reduced-intensity conditioning can induce durable clinical and molecular remissions in relapsed lymphomas: pre-transplant disease status and histotype heavily influence outcome

P Corradini[1], A Dodero[1], L Farina[1], R Fanin[2], F Patriarca[2], R Miceli[3], P Matteucci[4], M Bregni[5], R Scimè[6], F Narni[7], E Pogliani[8], A Locasciulli[9], R Milani[1], C Camiti[1], A Bacigalupo[10], A Rambaldi[11], F Bonifazi[12], A Olivieri[13], AM Gianni[4] and C Tarella[14] on behalf of Gruppo Italiano Trapianto di Midollo Osseo (GITMO)

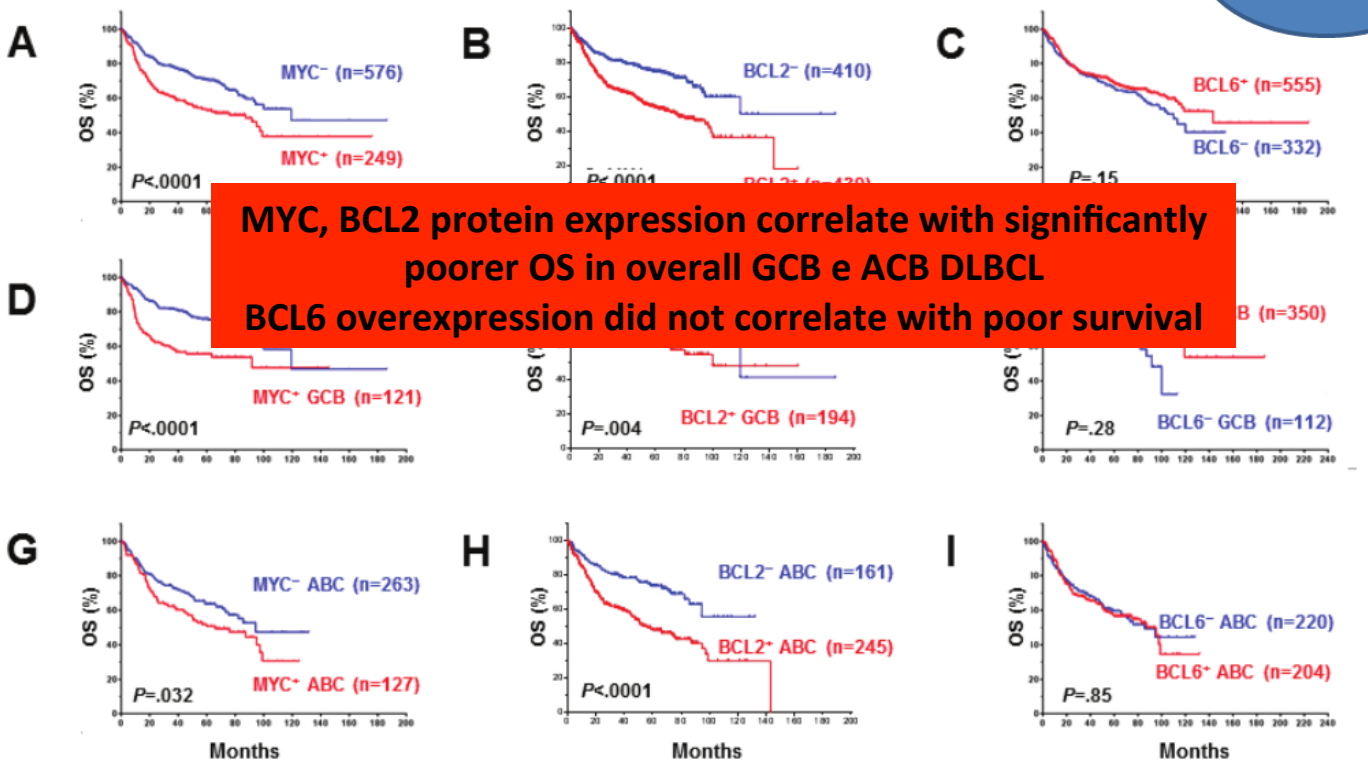


GITMO
GRUPPO ITALIANO TRAPIANTO MIDOLLO OSSEO

Prognostic impact of concurrent *MYC* and *BCL6* rearrangements and expression in *de novo* diffuse large B-cell lymphoma

Qing Ye[1,*], Zijun Y. Xu-Monette[1,*], Alexandar Tzankov[2,*], Lijuan Deng[1], Xiaoxiao Wang[1], Ganiraju C. Manyam[3], Carlo Visco[4], Santiago Montes-Moreno[5], Li Zhang[3], Karen Dybkær[6], April Chiu[7], Attilio Orazi[8], Youli Zu[9], Govind Bhagat[10], Kristy L. Richards[11], Eric D. Hsi[12], William W.L. Choi[13], J. Han van Krieken[14], Jooryung Huh[15], Maurilio Ponzoni[16], Andrés J.M. Ferreri[16], Ben M. Parsons[17], Michael B. Møller[18], Miguel A. Piris[5], Jane N. Winter[19], L. Jeffrey Medeiros[1] Shimin Hu[1] and Ken H. Young[1,20]

~900 pz



MYC, BCL2 protein expression correlate with significantly poorer OS in overall GCB e ACB DLBCL

BCL6 overexpression did not correlate with poor survival