58° Congresso Nazionale Società Italiana di Gerontologia e Geriatria
Torino 27-30 novembre 2013

Simposio

COSA È CAMBIATO NELL'APPROCCIO TERAPEUTICO DEI LINFOMI NON HODGKIN DEL PAZIENTE ANZIANO?

C'è un ruolo per il trapianto autologo nel linfoma dell'anziano?

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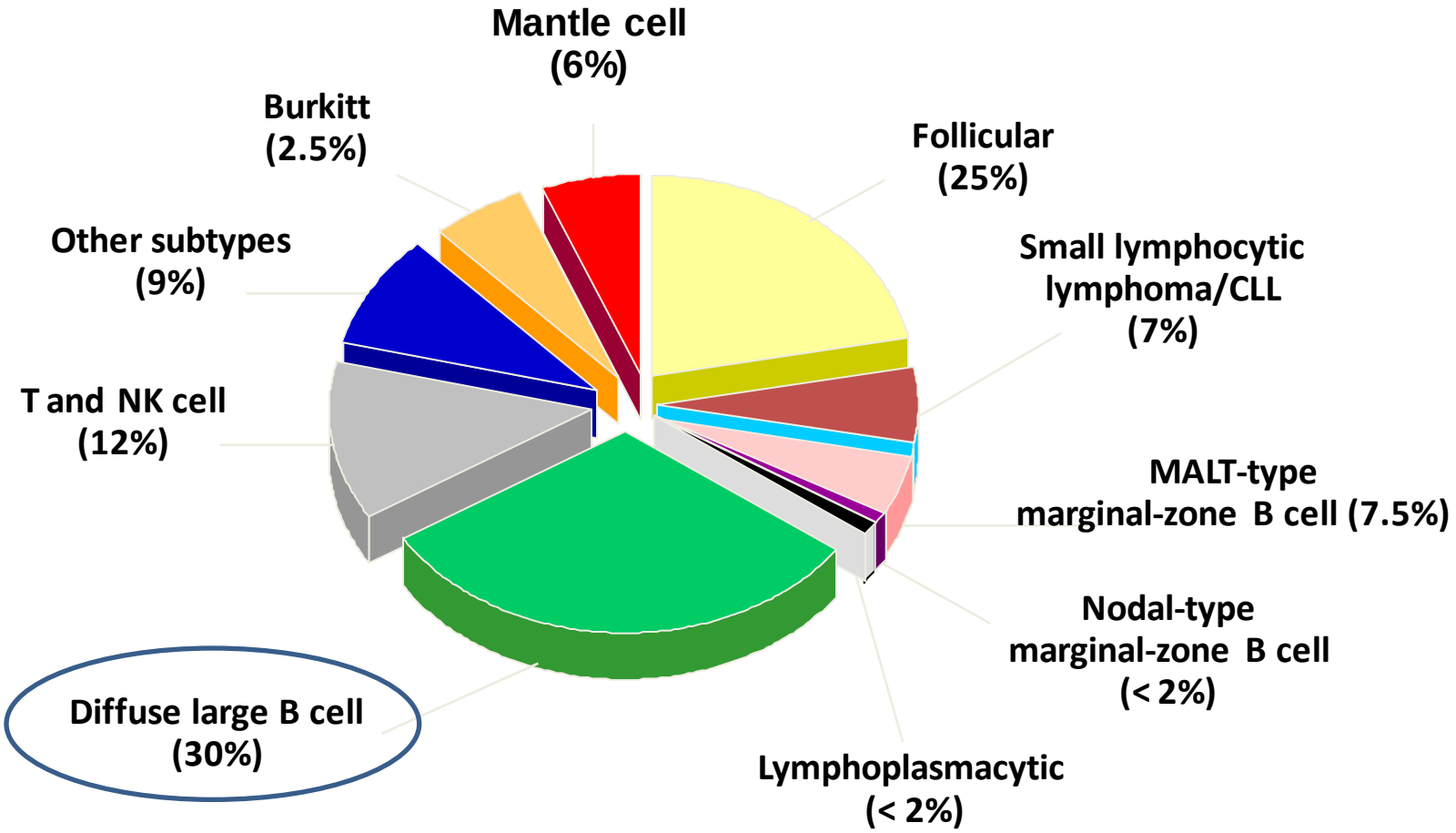
Azienda Ospedaliera Città della Salute e della Scienza
Torino

Subtypes of NHL



Lichtman MA. *Williams Hematology* 2006

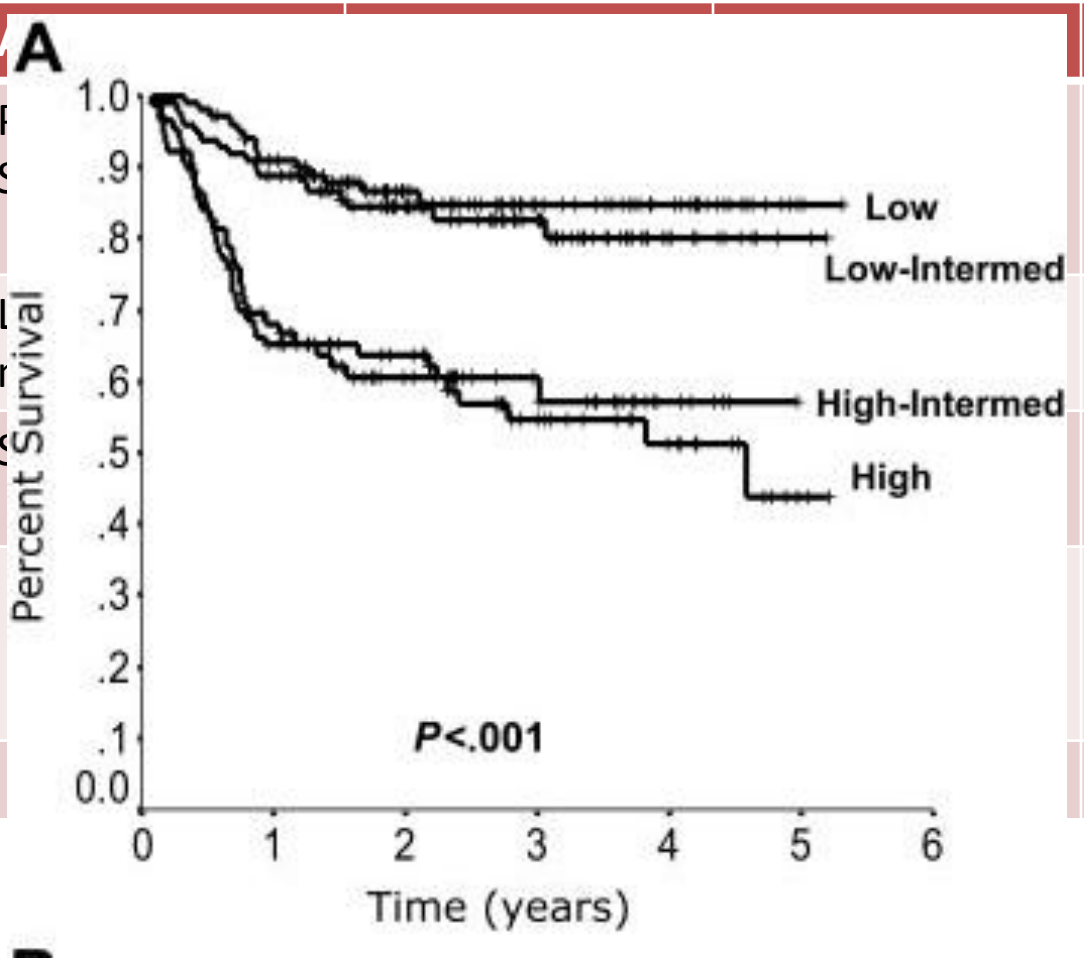
Why elderly?

- Significantly increased life expectancy
- A doubling of NHL cases in >65 yrs-old pts is expected in Western Countries over the next 20-25 yrs

- High frequency of comorbidities
- Greater toxicity during treatment
- Less ability to perform potentially curative treatments or reduced use of curative treatments with adequate dose-intensity
- Few trials specifically designed for elderly pts

Progression-Free Survival Based on IPI

IPI	A	PIT
Age >60 years		Age
Performance Status		Performance Status
LDH above normal		LDH
Two or more extranodal sites		BM Involvement
Stage III or IV		



IPI = International Prognostic Index
AA-IPI = Age Adjusted IPI
FLIPI = Follicular Lymphoma IPI
MIPI = Mantle Cell IPI
PIT = Peripheral T cell NHL IPI

The International Non-Hodgkin's Lymphoma Prognostic Factor Project. *N Engl Med*. 1993;329:987-994.
Solal-Celigny, et al. *Blood*. 2004;104:1258-1265.
Gallamini A, et al. *Blood*. 2004;103:2474-2479.
Geisler C, et al. *Blood*. 2010;115:1530-1533.

Studies in Rituximab era: FIT elderly patients

	R-CHOP-21 (n=540)	R-CHOP-14 (n=540)
Age (years; median, range)		
Median (years)	61 (19–88)	61 (19–85)
≤60	239 (44%)	237 (44%)
>60	301 (56%)	303 (56%)
Sex		
Male	293 (54%)	289 (54%)
Female	247 (46%)	251 (46%)
WHO performance status		
0	258 (48%)	286 (53%)
1	210 (39%)	182 (34%)
2	72 (13%)	72 (13%)
Stage		
Bulky IA		
IB		
II		
III		
IV		
Bulky disease		
B symptoms	238 (44%)	251 (46%)
Elevated lactate dehydrogenase	350 (65%)	351 (65%)
International prognostic index score		
0	43 (8%)	40 (7%)
1	117 (22%)	116 (21%)
2	143 (26%)	163 (30%)
3	143 (26%)	136 (25%)
4	79 (15%)	75 (14%)
5	15 (3%)	10 (2%)

R-CHOP 21 remains the standard first line treatment
No indication for ASCT

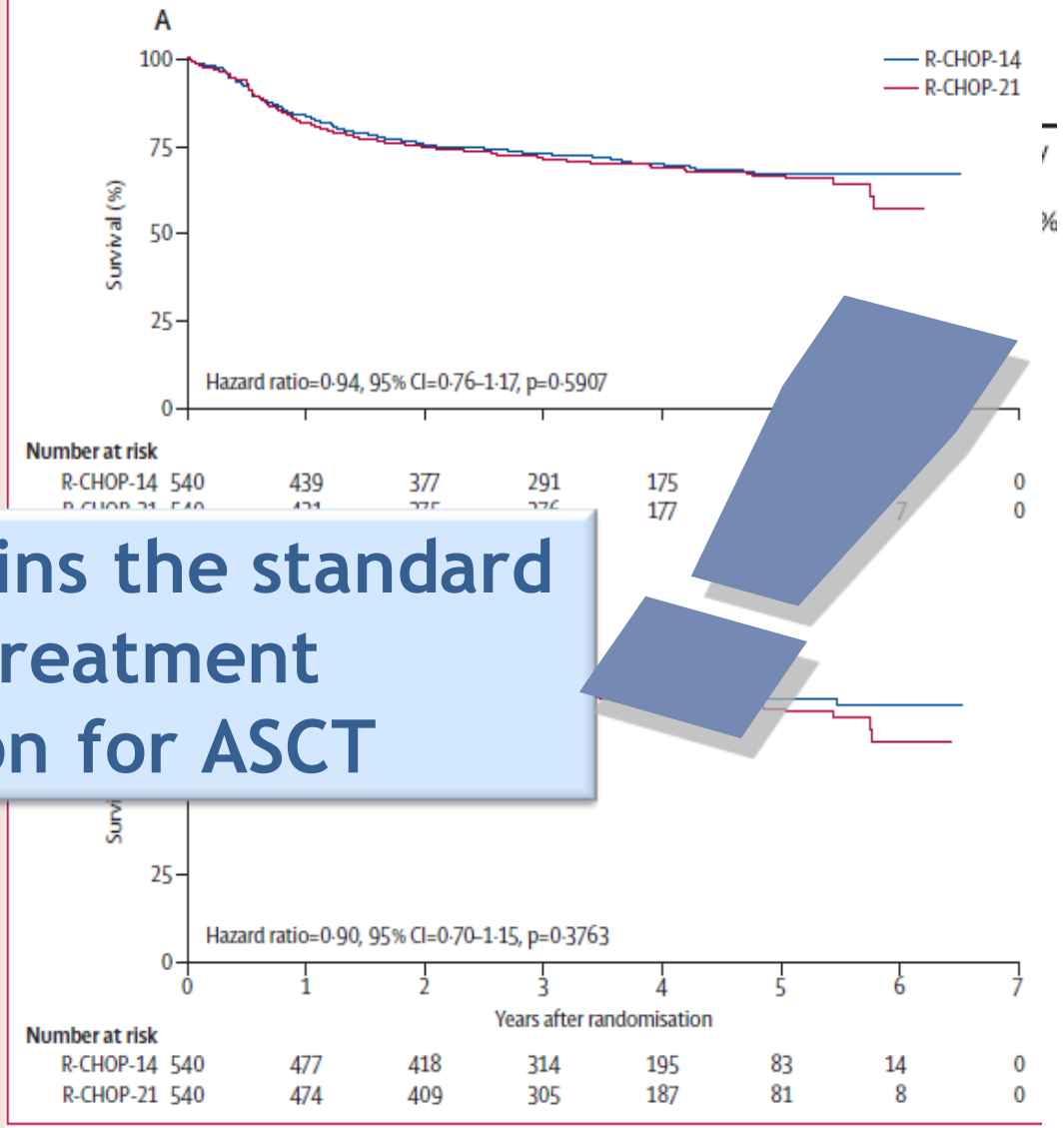
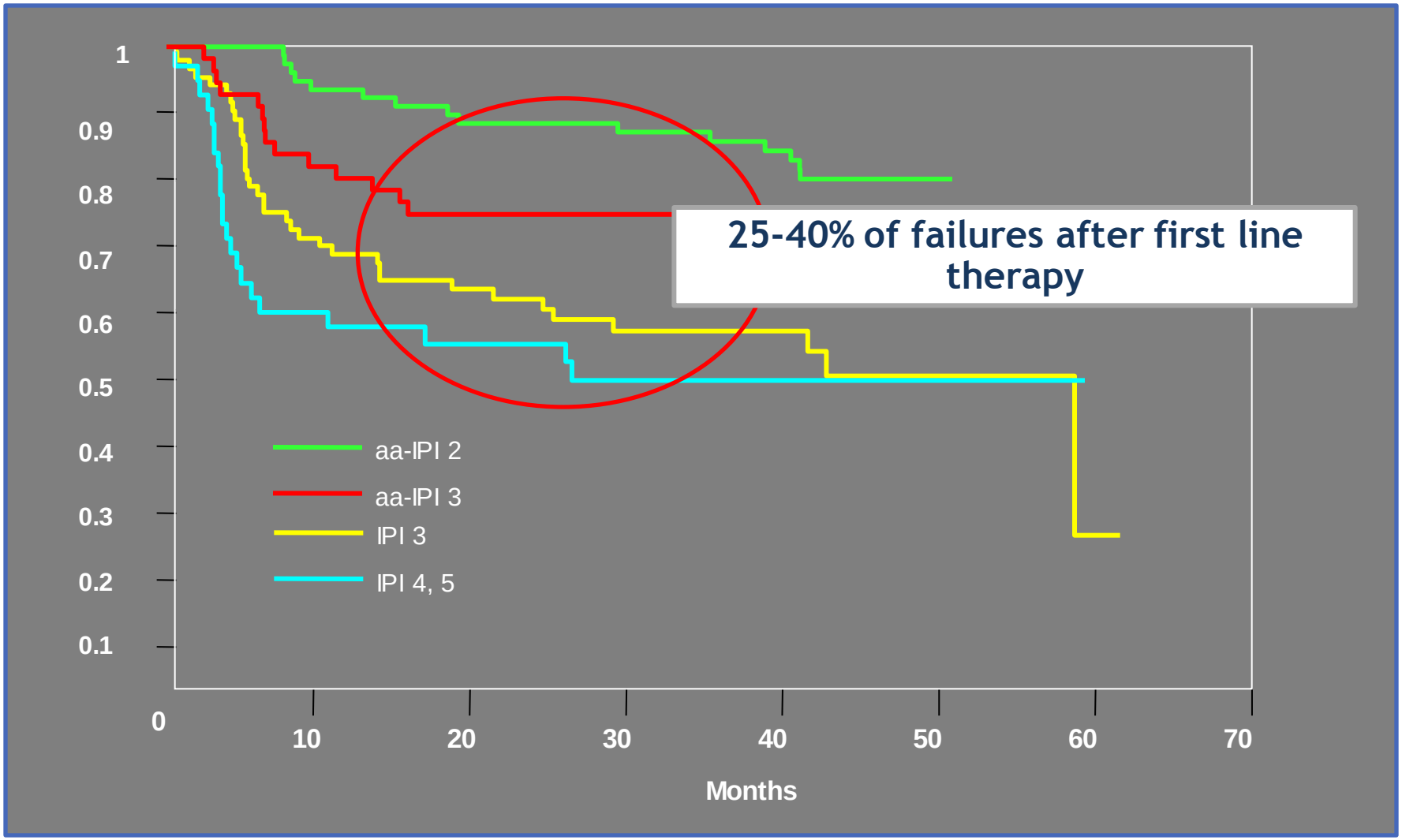


Figure 2: **Progression-free survival (A) and overall survival (B) according to treatment**

Cunningham D et al, Lancet 2013

Relapse after first line treatment



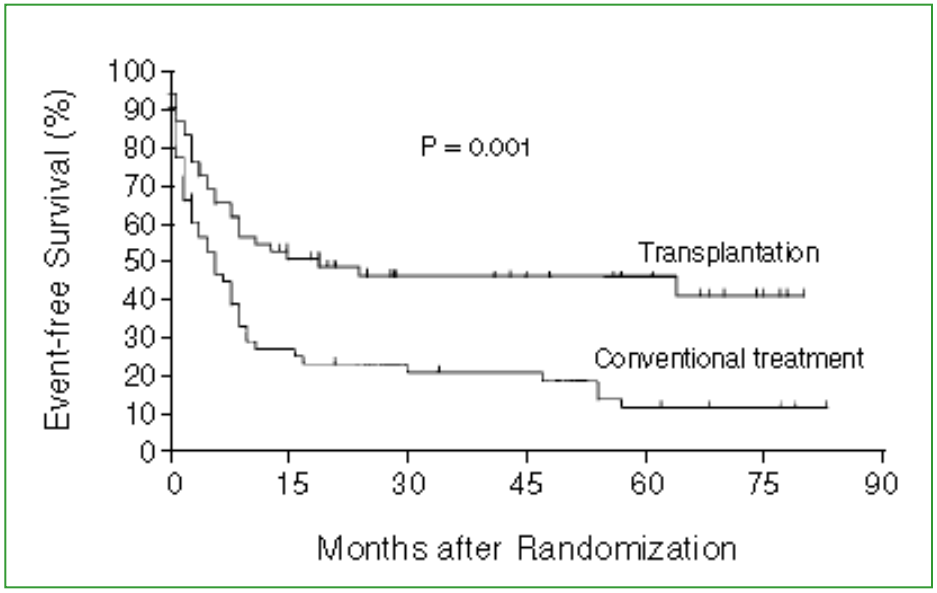
Feugier et al. JCO 2005
Vitolo U et al. Haematologica 2009

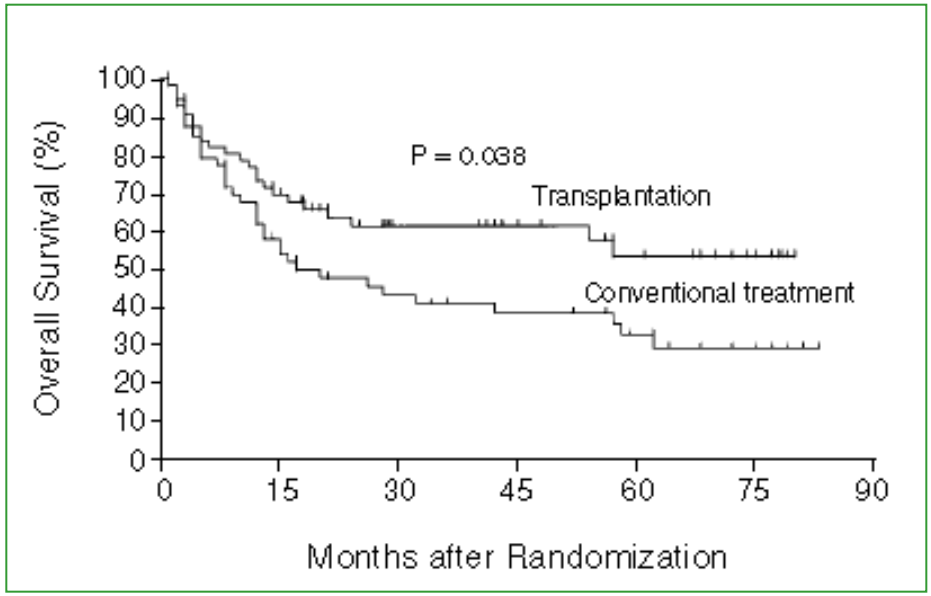
Relapsed DLBCL in FIT elderly
Role of Autologous Tranplant

PARMA TRIAL: 1987-1994: 215 patients, relapsed DLBCL

215 pts
DHAP x 2 ⇒ **CR+PR= 109**
(58%) ⇒ **R**

- **DHAP x 4 +/- IF-RT (54)**
- **BEAC + ASCT +/- IF-RT (55)**





Philip T et al. Blood 1991

Age is the most important factor influencing the choice of aggressive therapy or not?

COMORBIDITY AS AN INDEPENDENT FACTOR

Prognostic Importance of Comorbidity in a Population-Based Analysis of Patients with Advanced-Stage Diffuse Large B-Cell Lymphoma (DLBCL) Treated with R-CHOP

- Perspective study
- Comorbidity as independent factor for OS
- 156 pts (from 2005) DLCL ≥18 age (**range 23-93**)
- Median Follow-up 24 months

- **Evaluation criteria: Charlson Comorbidity Index at diagnosis**
- Low CCI (0-1)
- High CCI (≥2)
  - diabetes (36%)
  - peripheral vasculopaty (32%)
  - BPCO (28%)
  - second neoplasia
  - Myocardial infarction (24%)
  - Heart failure (16%)

Wieringa A, et al; ASH 2011, Abs 3656

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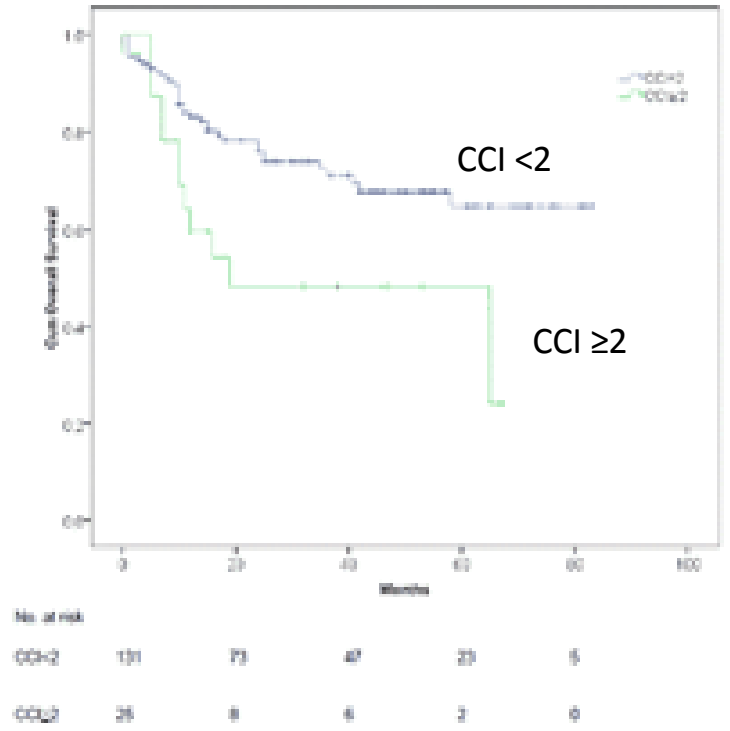
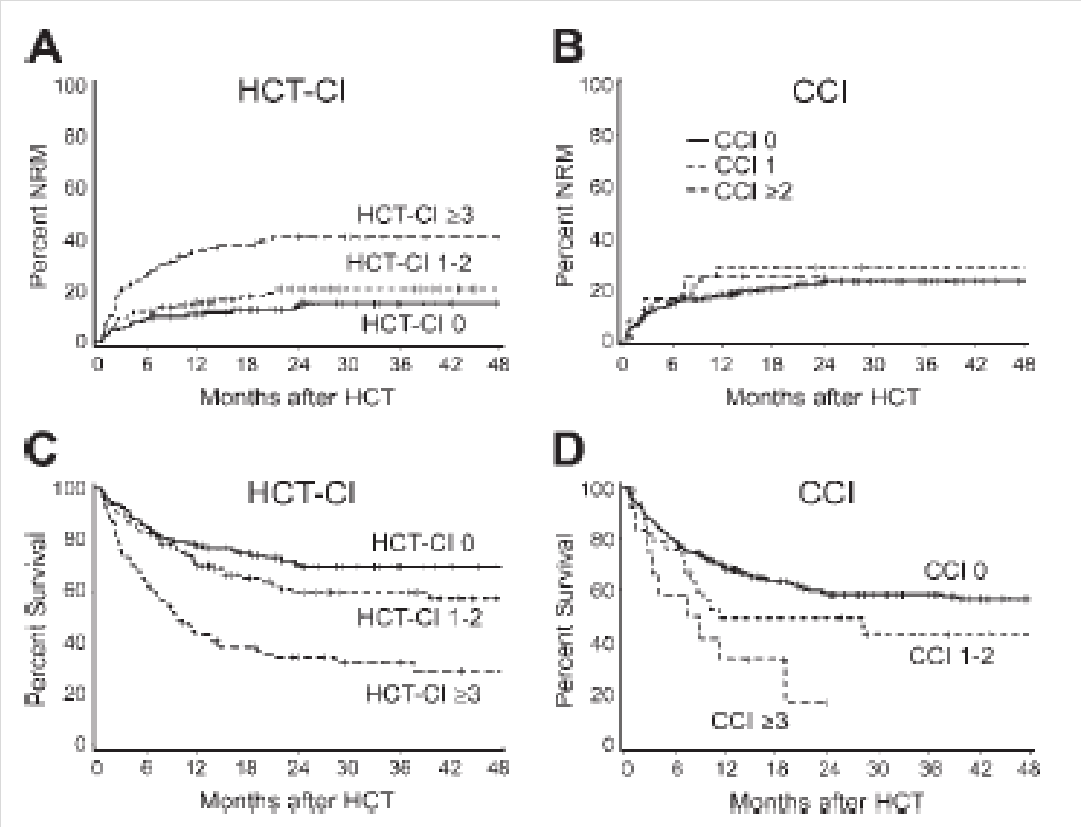


Wieringa A, et al; ASH 2011, Abs 3656

COMORBIDITY AS AN INDEPENDENT FACTOR IN TRANSPLANT

- To establish comorbidity scores that were suited for Hematopoietic Cell Transplantation (HCT)
- To improve Charlon Comorbidity Index (CCI)
- To better define previously identified comorbidities using pretransplant data



NRM: non relapse mortality

OS: overall survival

Sorror ML, et al; Blood 2005

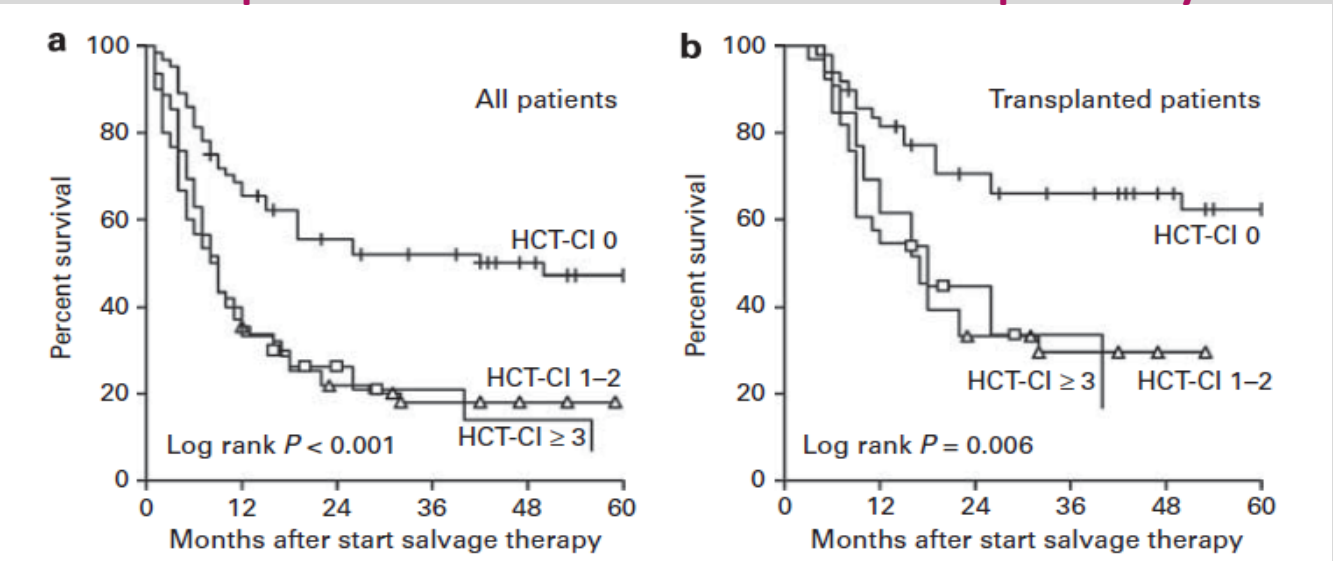
COMORBIDITY AS AN INDEPENDENT FACTOR IN TRANSPLANT

Both relapse-CI and sIPI remained significant in predicting receipt of transplant

Table 4 Univariate and multivariate odds ratios (ORs) for relapse HCT-CI scores and sAAIPI scores for not receiving auto-SCT

	n	*Univariate*			*Multivariate*		
		OR	*95% CI*	P	*OR*	*95% CI*	P
Relapse HCT-CI scores				0.003			0.02
0	64	1			1		
1–2	62	2.9	1.3–6.2	0.007	2.5	1.1–5.6	0.02
⩾3	30	4.3	1.7–10.8	0.002	3.3	1.3–8.6	0.02
sAAIPI scores							
Low risk (0–1)	58	1			1		
High risk (2–3)	97	4.4	2.0–9.4	<0.001	3.8	1.7–8.3	0.001

Relapse HCT-CI can predict for survival after auto-SCT indipendently from sIPI scores



Raimondi R, et al; Blood 2012

Comorbidities, Not Age, Impact Outcomes in Autologous Stem Cell Transplant for Relapsed Non-Hodgkin Lymphoma

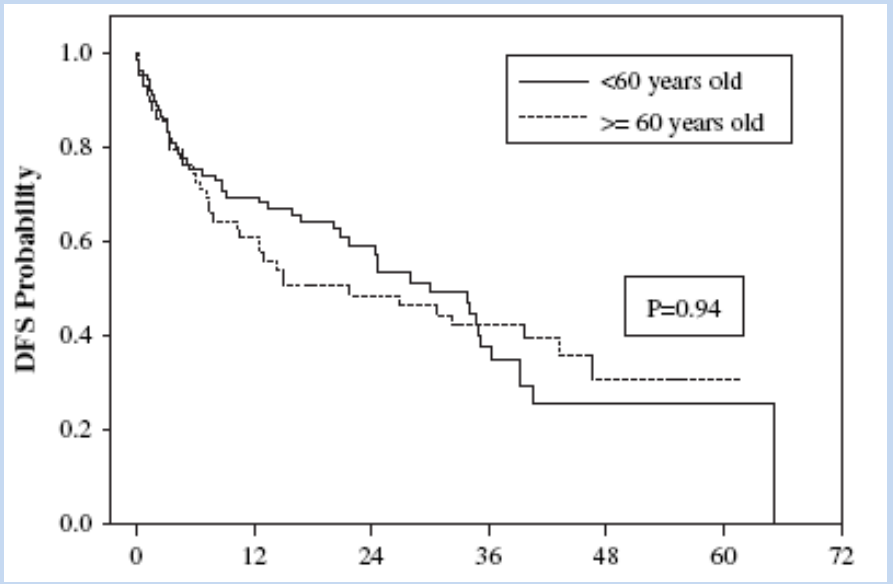
152 consecutive patients from a single institution treated with ASCT
59 were age >60 or older
Charlson Comorbidity Index Score done in all patients
Frequency of comorbidities similar between the two groups

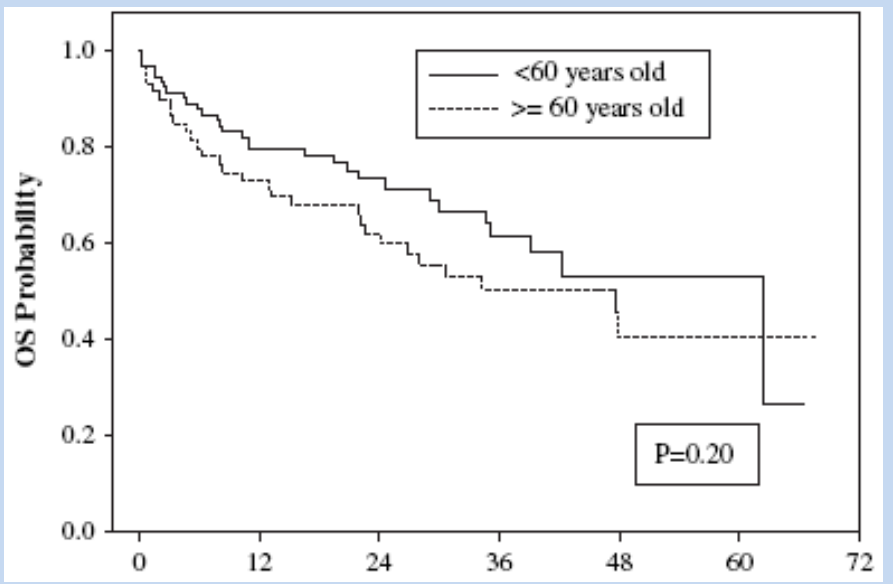
	Age ≥60 Years	Age <60 Years	*P* Value
Number of patients	59	93	
Mean age in years: mean ± standard deviation (range)	64.1 ± 3.4 (60-73)	48.6 ± 9.0 (21-59)	
Gender: frequency (percent)			>.1
Female	25 (42%)	44 (47%)	
Male	34 (58%)	49 (53%)	
Histology: frequency (percent)			>.1
Diffuse large B cell	36/59 (61%)	44/93(47%)	
Follicular lymphoma	15/59 (25%)	26/93 (28%)	
Mantle cell lymphoma	6/59 (10.2%)	6/93 (6.5%)	
Anaplastic large cell lymphoma	1/59 (1.7%)	5/93 (5.4%)	
Peripheral T cell lymphomas	1/59 (1.7%)	7/93 (7.5%)	
Other high grade	0/59 (0%)	5/93 (5.4%)	
Mean Charlson Comorbidity Index Score	2.6 ± 0.8	2.4 ± 0.7	.10
Number of pretranspant chemotherapy regimens: mean (range)	2.2 (1-4)	1.9 (1-3)	.005

TRM was similar between older and younger patients (8.5% versus 5.4%)
The score on the **CCI significantly correlated with TRM**

Wildes MT, Biol BMT 2008

Comorbidities, Not Age, Impact Outcomes in Autologous Stem Cell Transplant for Relapsed Non-Hodgkin Lymphoma





DFS similar between older and younger (21.8 vs 29.9 months)
Median OS was 47.7 vs 62.5 months without difference
Age not significant influence on DFS and OS
Comorbidities independent influential factor

Wildes MT, Biol BMT 2008

Autologous stem cell transplantation in elderly patients (≥60 years) with diffuse large B-cell lymphoma: an analysis based on data in the European Blood and Marrow Transplantation registry

	<60 years (n= 2149)	*≥60 years (n=463)*	*p*
Age, median (range), years	47 (18-59)	63 (60-74)	—
Male sex	58.5%	59%	n.s.
Stage III-IV	72%	71.5%	n.s.
B-symptoms	49%	43%	0.04
Elevated LDH	49%	48%	n.s.
Bulky disease	30%	19%	<0.001
Time from dx to tx, (median), months	7.5	14	<0.001
Two or more previous treatment lines	57%	76%	<0.001
Prior rituximab therapy	26%	33%	0.009
Disease status/tx			
CR1	30%	23%	0.005
CR ≥2/PR/sens rel	63%	71%	
untested/refractory	7%	6%	
Poor performance status at tx#	2.3%	3.7%	n.s.

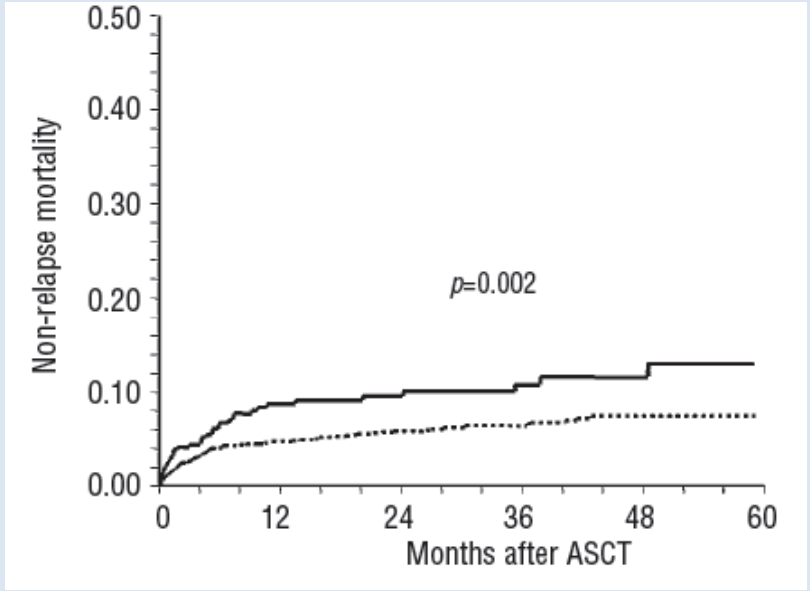
EBMT database was used to identify DLBCL aged 18-75 years treated with ASCT between 2000 and 2005.

6758 patients in the registry

1327 (20 %) 60 years old at the time of transplantation.

Jantunen Hematologica 2008

Autologous stem cell transplantation in elderly patients (≥60 years) with diffuse large B-cell lymphoma: an analysis based on data in the European Blood and Marrow Transplantation registry

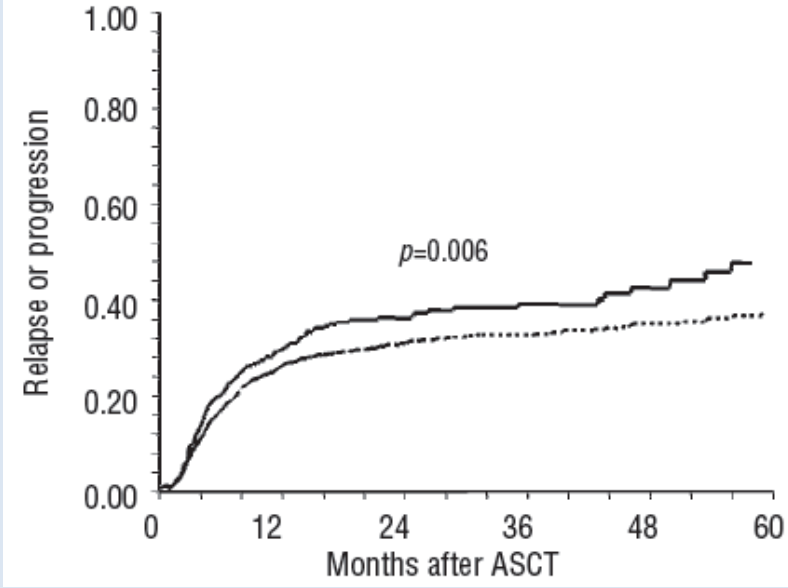


3 yrs Risk of Relapse
38% elderly vs 32% younger

In a multivariate analysis influenced by:
No prior rituximab
two or more lines of prior therapy
poor performance status
refractory disease at ASCT

3 yrs Non Relapse Mortality
10.8% elderly vs. 6.5% younger

In multivariate analysis NRM influenced by:
Age 60 years
two or more lines of therapy
poor performance status
refractory disease at ASCT



Jantunen Hematologica 2008

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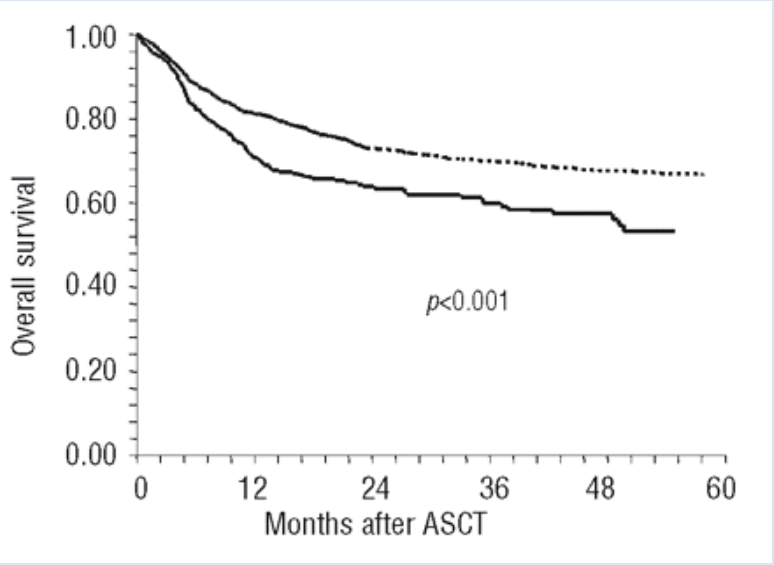
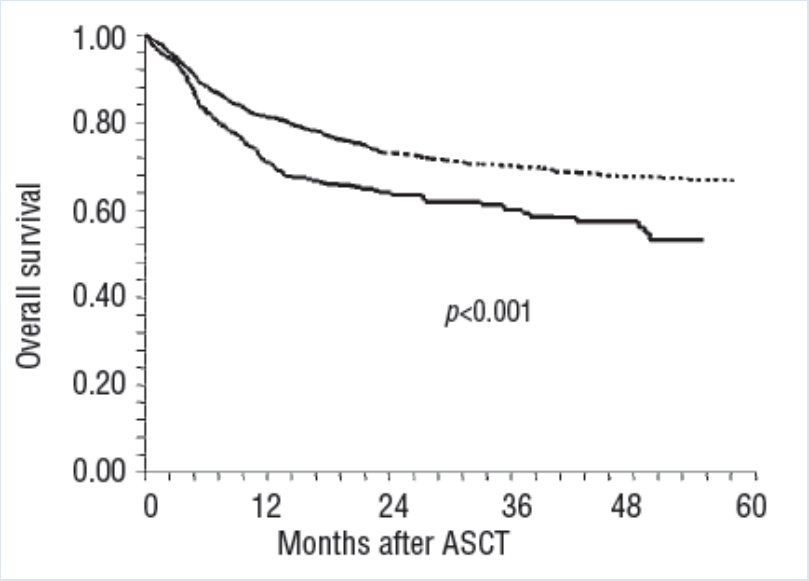




3 yrs PFS 51% elderly *vs. 62% younger* (*p<0.001*).

In a multivariate analysis poorer PFS:
Age >60 years
No rituximab therapy prior to ASCT
Two or more lines of therapy before ASCT
Poor performance status
Refractory disease

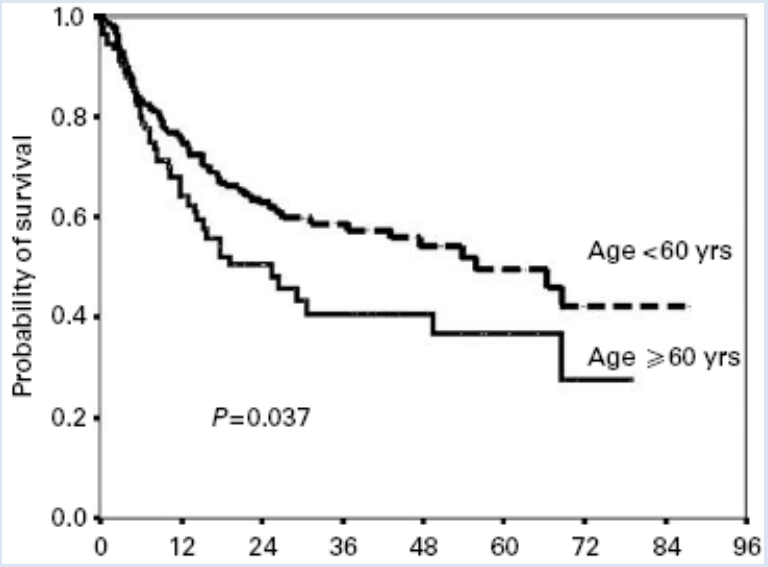
3 yrs OS 60% elderly *vs. 70% younger* (*p<0.001*)

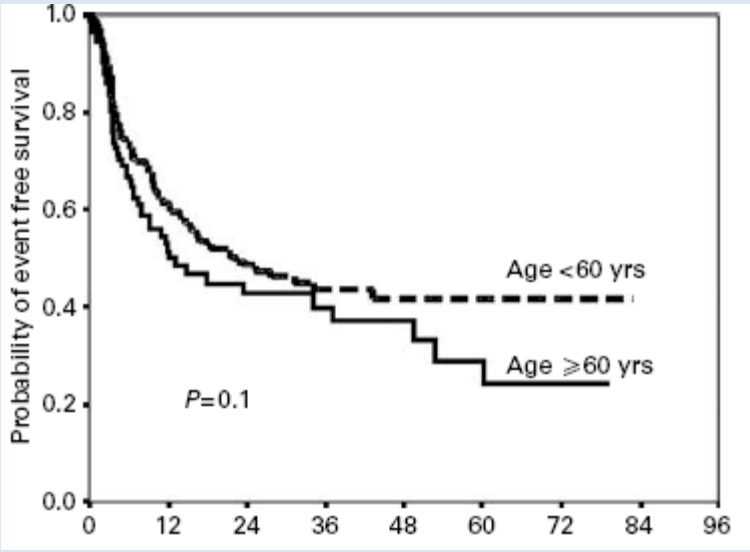
In multivariate analysis lower OS:
Male gender
Age 60 years
No rituximab therapy prior to ASCT
Elevated LDH level
Two or more lines of therapy prior to ASCT
Poor performance status at ASCT
Refractory disease at ASCT

Jantunen Hematologica 2008

Autologous hematopoietic stem cell transplantation for older patients with relapsed non-Hodgkin's lymphoma

93 patients with aggressive NHL age 60 or older treated with ASCT at relapse 24/93 over 70 years



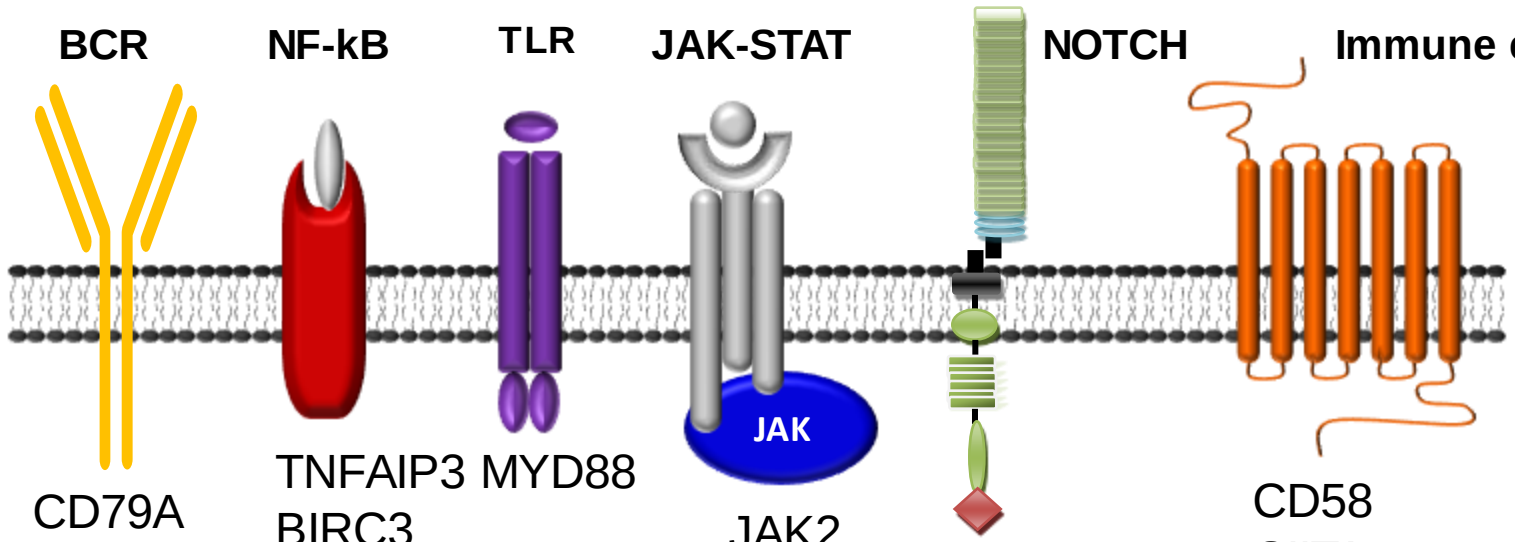


TRM was not different 5.4% older vs 2.2% young
Median follow up14 months
OS different (25 months older vs 56 months younger)
Lower IPI at relapse better
4 yrs EFS not different (38% older vs 42% young)

Buadi FK BMT 2006

Other options different from ASCT in elderly relapsed DLBCL? New drugs?

Deregulated pathways in B-NHL



CD79A
CD79B
CARD11

TNFAIP3
BIRC3
TRAF3

MYD88

JAK2

NOTCH1
NOTCH2
SPEN

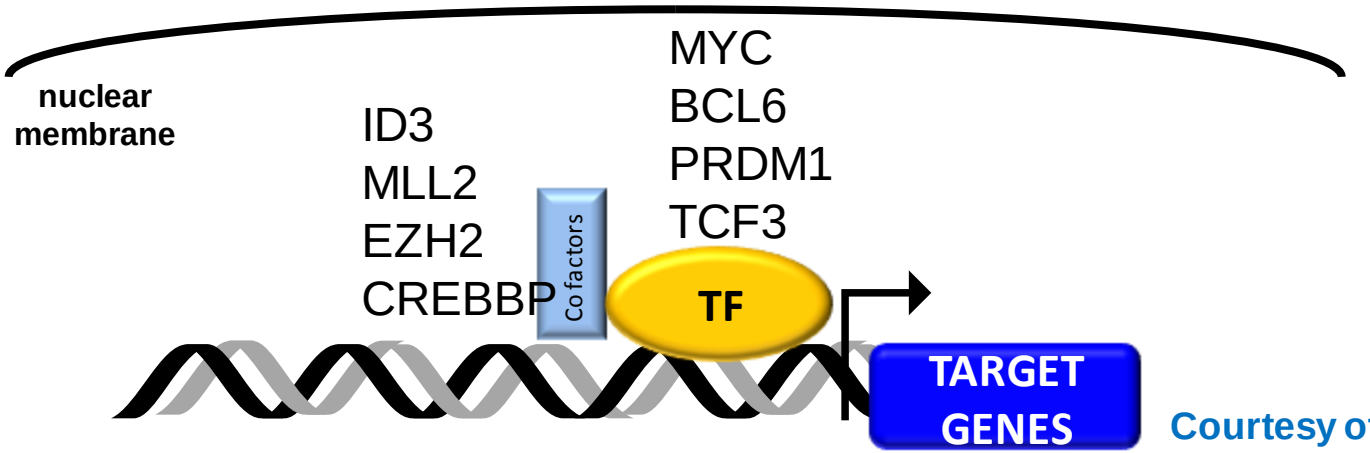
CD58
CIITA
PDL1
B2M
HLAII

Apoptosis

BCL2

Cell cycle

CCND1
CCND3
CDKN2A
ATM
TP53



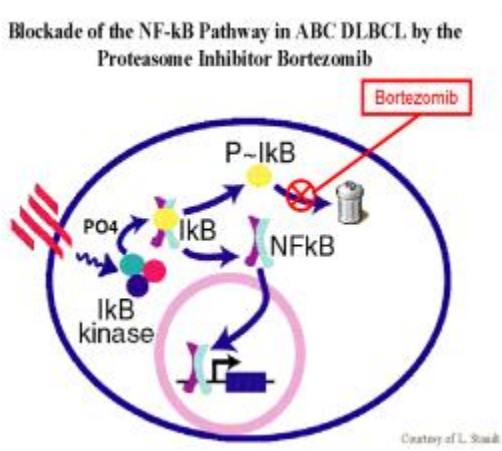
Courtesy of G. Gaidano

DLBCL and MCL

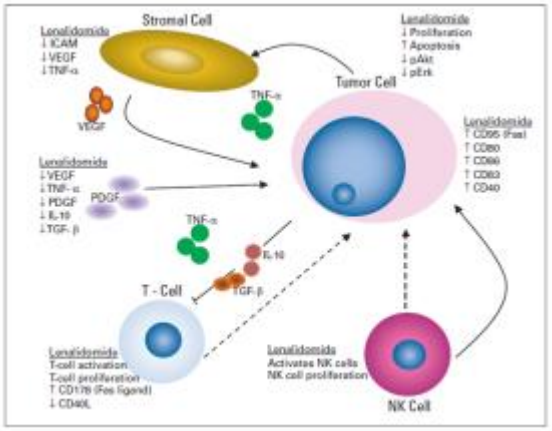
Signaling pathway inhibition

- Immunomodulators: lenalidomide
- Proteasome inhibitors: bortezomib
- mTOR inhibitors: everolimus
- HDACs inhibitors
- BCR inhibitors (BTKI: PCI-32765)
- Inhibitors of Syk in B-cell signaling pathway: tamatinib
- PKCβ-selective inhibitors: enzastaurin
- Pro-apoptotic ABT-263 Bcl-2 family; AT-101 Bcl-2 family

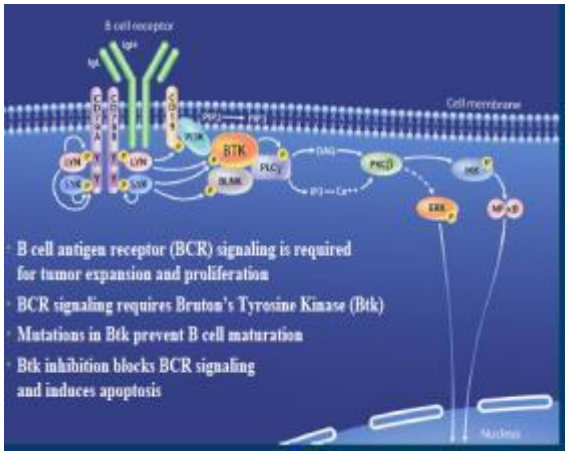
Bortezomib



Lenalidomide



BTKI PCI-32765



Lenalidomide plus Rituximab in Elderly R/R DLBCL Patients
Efficacy data

Efficacy data	N = 23
Response, N (%)	
Overall response	8 (35)
Complete response	7 (30)
Partial response	1 (5)
Stable disease	2 (9)
Progressive disease	13 (56)
1-year DFS*, % (CI)	34.8 (14.4-56.2)
18-month OS, % (CI)	55.1 (32.3-72.9)

*: median follow–up of 16 months
CI: confidence interval; DFS: disease-free survival; DLBCL: diffuse large B-cell lymphoma; OS: overall survival; rel/ref: relapsed / refractory

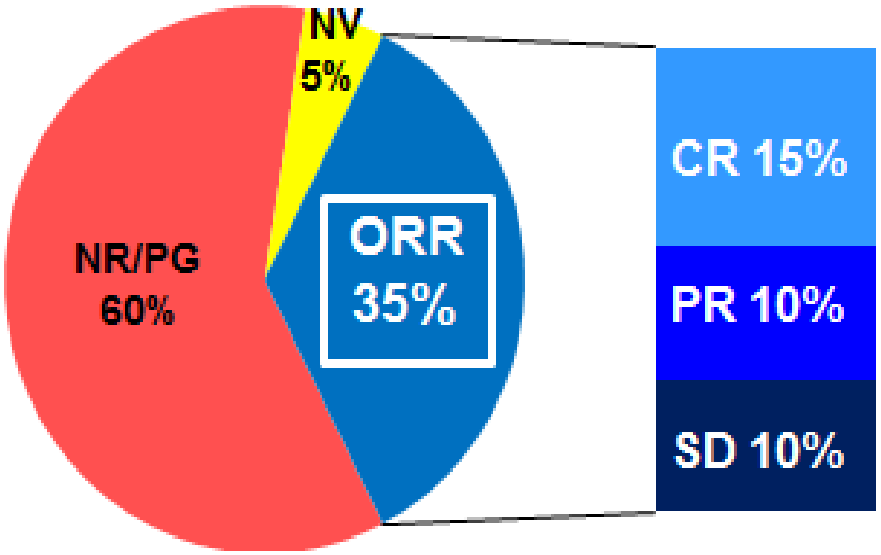
Zinzani et al. Clin Lymph Myel Leuk 2011

Lenalidomide in R/R DLBCL patients: Torino's experience

CLINICAL CHARACTERISTICS:

53 patients treated from 2007 to 2012; Median age: 68 years (20-92)

FINAL RESPONSE ON 53 PATIENTS

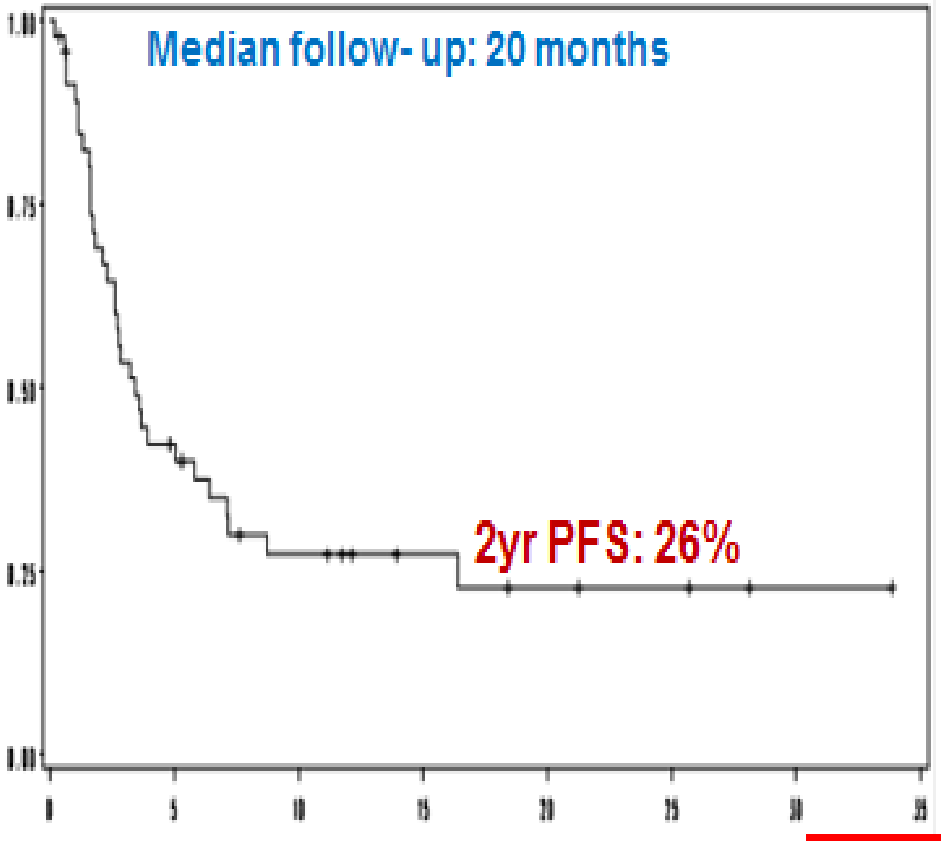


Median DOR: 12 months (0,2- 24)

FINAL RESPONSE:

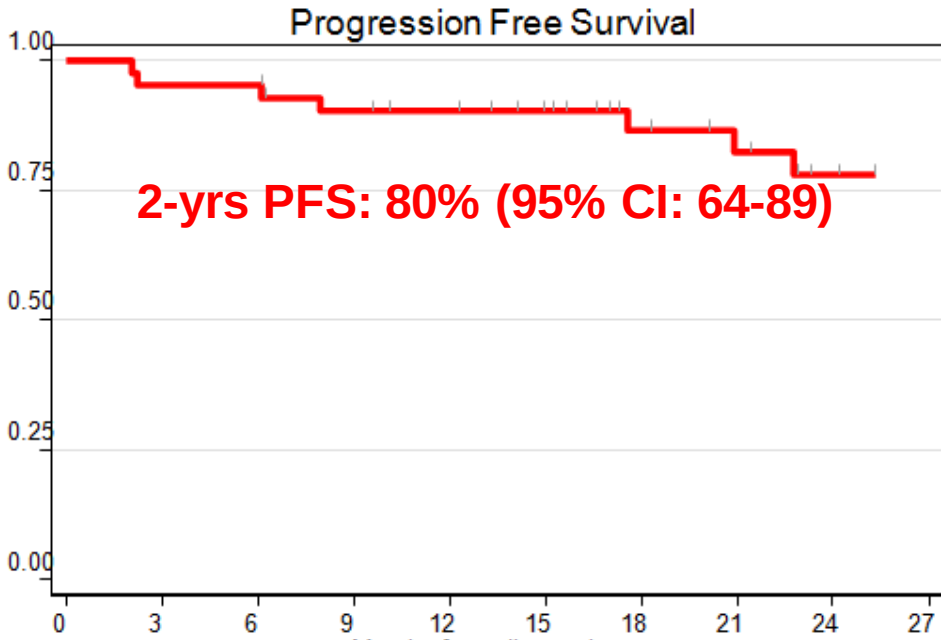
- 34 DLBCL ORR 41% (CR 15%)
- 11 MCL ORR 27% (CR 18%)

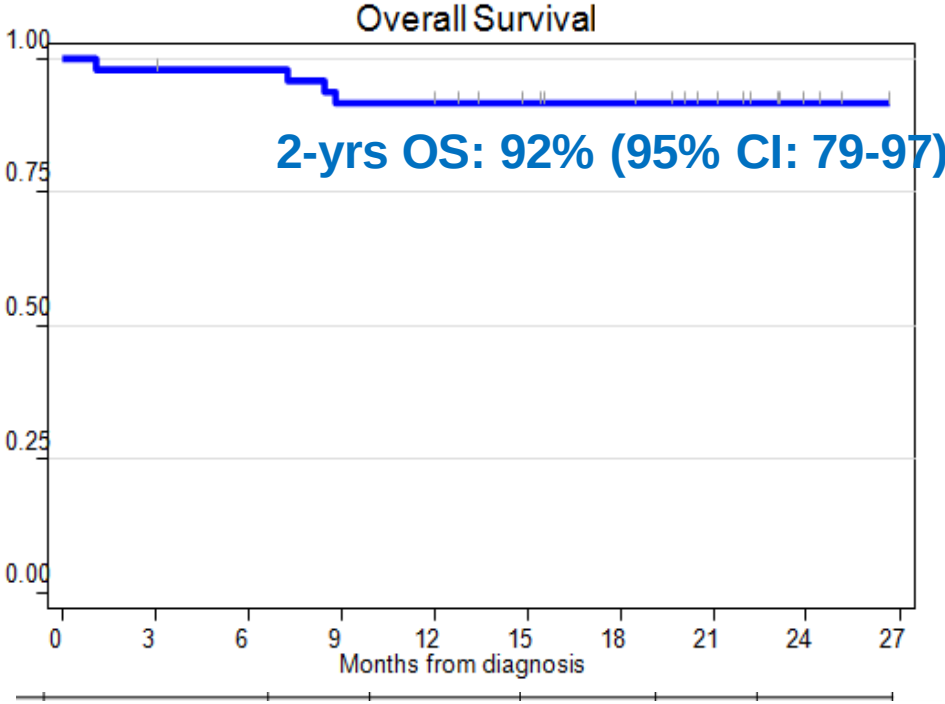
SURVIVAL ANALYSIS

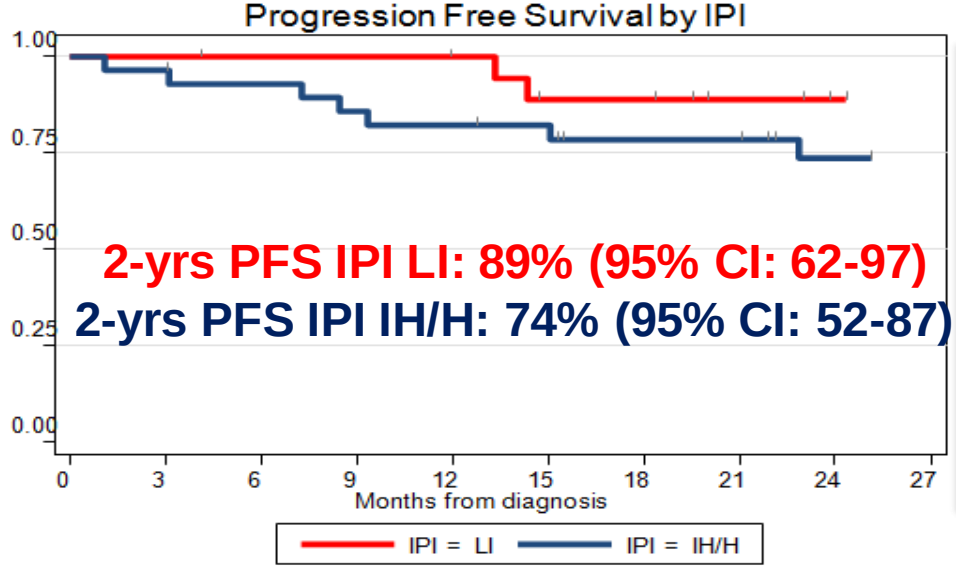


Castellino A, SIE 2013

CR 86%. PFS, OS, median FU 27.7 months (Cheson 2007 criteria)







Chiappella et al, Haematol 2013

Management of nodal diffuse large B-cell lymphomas: practice guidelines from the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation

At first relapse, patients need to receive non-cross-resistant chemotherapy regimens (i.e. ICE, DHAP, MIME, HDS), with or without rituximab followed, in eligible patients, by high-dose chemotherapy and HDT/SCT.

Patients **eligible for HDT/SCT** include those aged < 65 years, with chemosensitive disease and a **good performance status, without comorbidities** and with good availability of autologous stem cells .

Patients who are **not eligible for HDT/SCT should be enrolled into approved study protocols of investigational therapies** or receive supportive therapy

Barosi, Hematologica 2006

TAKE HOME MESSAGES

✓ Conventional first line chemoimmunotherapy can cure only 60% of all newly diagnosed DLBCL

✓ A large number of patients will relapse and require further therapy

✓ ASCT in chemosensitive relapsed aggressive NHL produces superior PFS and OS

✓ **Benefits of ASCT are less certain in older patients**. Few studies with small number of patients, lack of randomized trials.

✓ **Elderly patients need to be accurately stratified** (not only by age,but also by comorbiditites and GCA) in order to select the best salvage therapy.

✓ Clinical trials with novel drug is a promising alternative treatment