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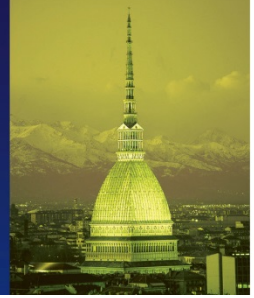


UNIVERSITÁ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

Cardioprotection strategies

Liposomal Anthracyclines

Annalisa Chiappella

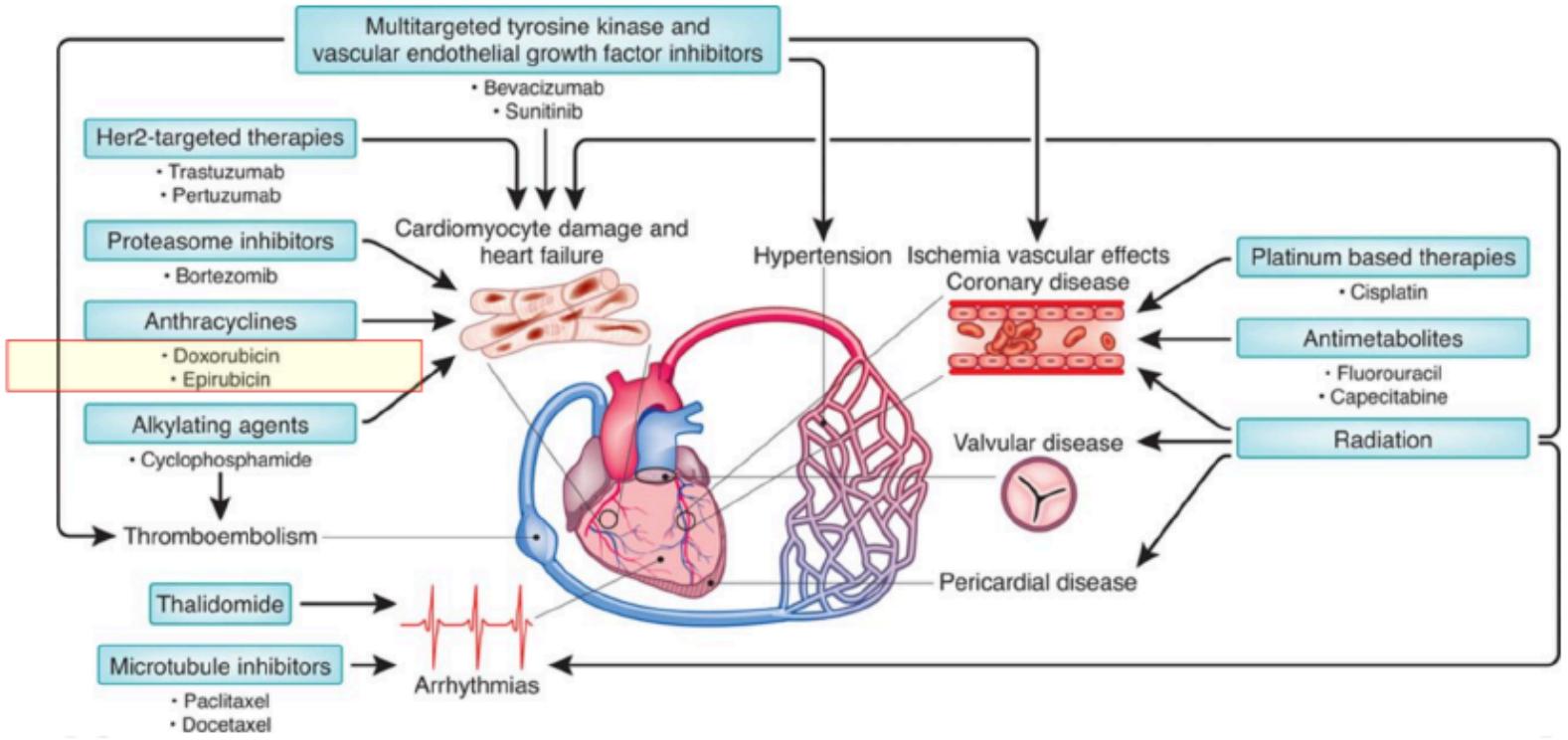
Hematology

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

Disclosures: Annalisa Chiappella

Research Support/P.I.	N/A
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Conferences/Educational Activities	Amgen, Celgene, Janssen, Nanostring, Roche, Teva
Scientific Advisory Board	Celgene, Janssen

CARDIO-ONCOLOGY



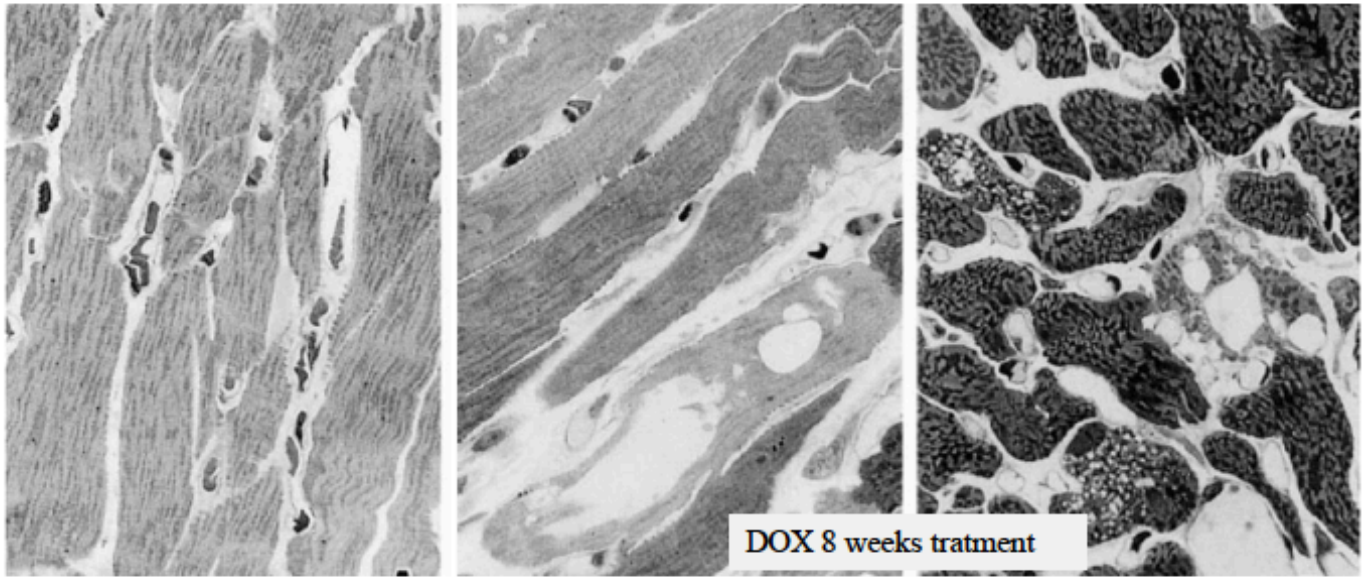
Lenneman, C. G. & Sawyer, D. B. Cardio-Oncology: An Update on Cardiotoxicity of Cancer-Related Treatment. Circ. Res. 118, 1008–20 (2016).

Monitoring for the development of **subclinical cardiotoxicity** is crucial for the prevention of clinical heart failure.
Detecting a decreased LVEF after cancer therapy might be a late finding

Tajiri, K., Aonuma, K. & Sekine, I. Jpn. J. Clin. Oncol. 47, 678–682 (2017).

Molecular mechanism of doxorubicin-induced cardiomyopathy

Cumulative and **Irreversible** Cardiac Mitochondrial Dysfunction Induced by Doxorubicin (1)



control myocytes
normal morphology

1week after the treatment

myocyte damage
cytoplasmic vacuolization
in 20% of myocytes

5 weeks after the treatment

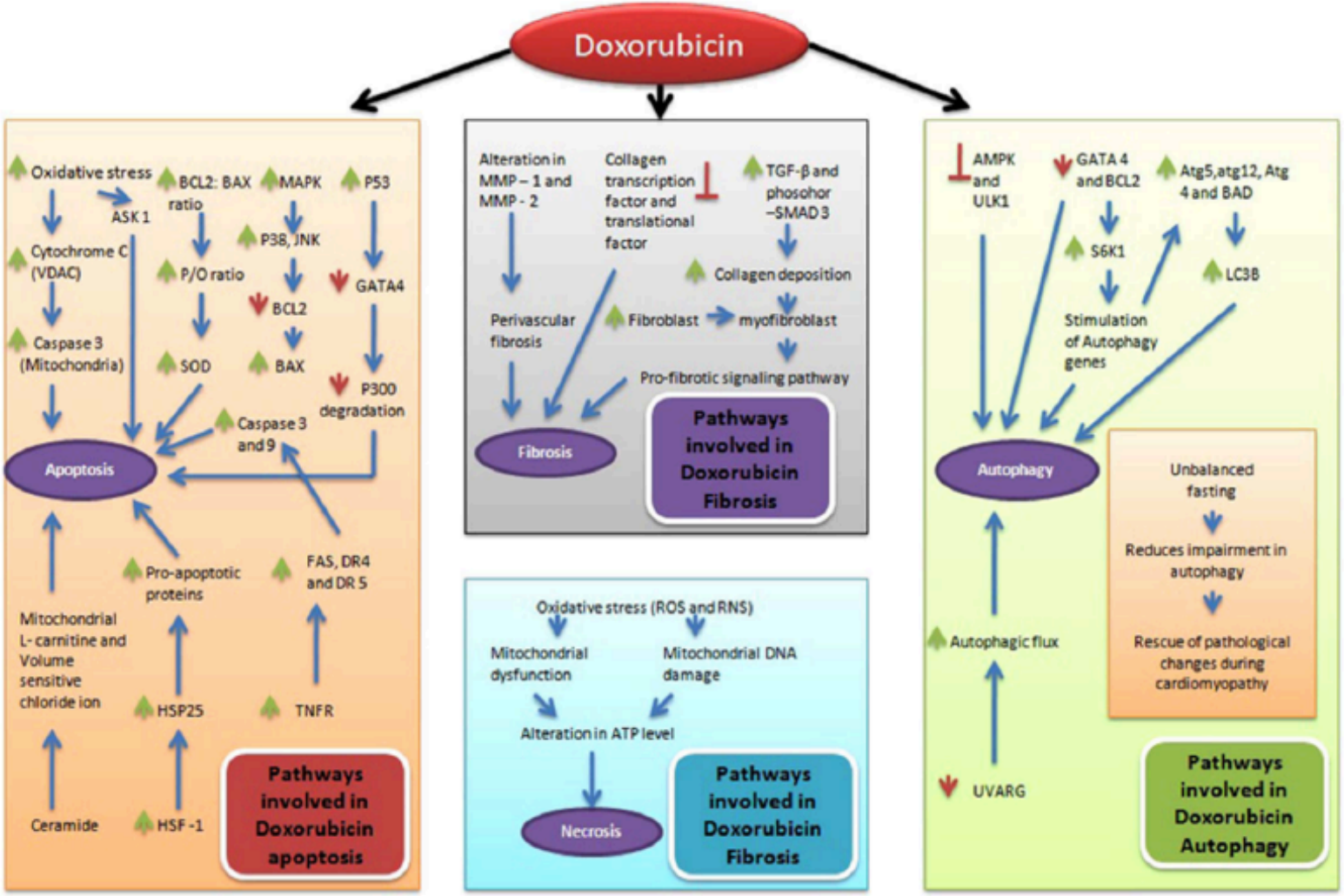
myocyte degeneration
>30% of myocytes

Cell death (2)

- Autophagy
- Apoptosis
- Fibrosis
- Necrosis

1. Zhou, S., Cumulative and irreversible cardiac mitochondrial dysfunction induced by doxorubicin. Cancer Res. 61, 771–7 (2001).
2. Kaviyarasi Renu, Abilash V.G., Tirupathi Pichiah P.B., S. A. Molecular mechanism of doxorubicin-induced cardiomyopathy – An update. *Eur. J. Pharmacol.* **818,** 241–253 (2018).

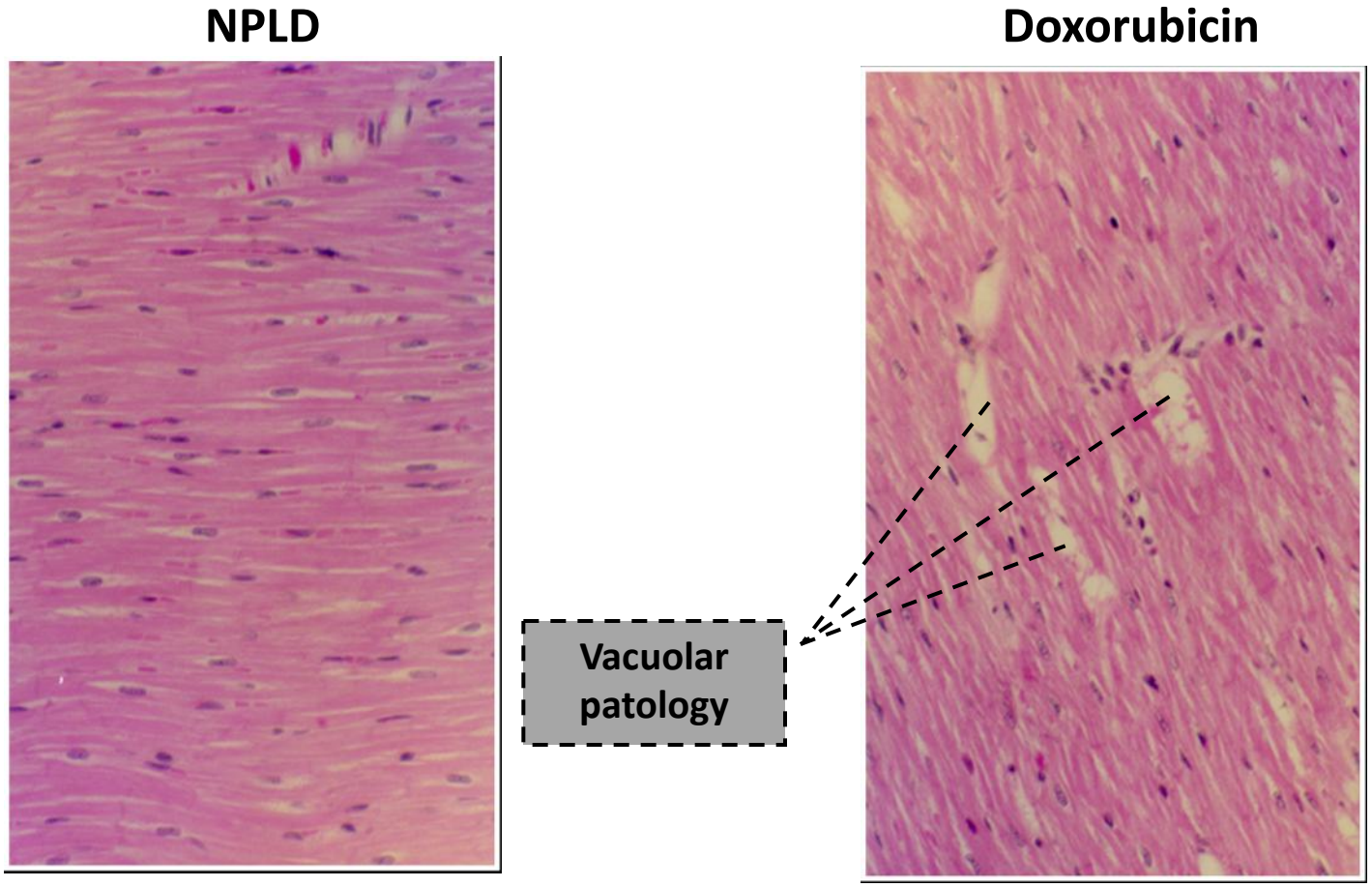
Molecular mechanism of doxorubicin-induced cardiomyopathy



Kaviyarasi Renu, Abilash V.G., Tirupathi Pichiah P.B., S. A. Molecular mechanism of doxorubicin-induced cardiomyopathy – An update. *Eur. J. Pharmacol.* **818,** 241–253 (2018).

NPLD less cardiotoxic than doxorubicin

8 cycles 1.5 mg/sqm every 3 weeks



Comparison of the cardiotoxic effects of liposomal doxorubicin (TLC D-99) versus free doxorubicin in beagle dogs

Kanter PM et al. In Vivo 1993 7(1):17-26 1

Phase III trial
First line MBC

Study 1
Combination treatment
(NPLD-CPA Vs DOX-CPA)
Batist

Study 2
Single agent
(NPLD Vs DOX)
Harris

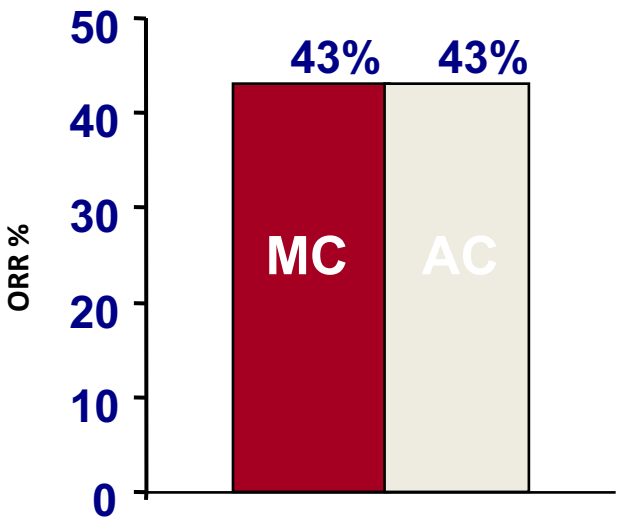
Study 3
Combination treatment
(NPLD-CPA Vs EPI-CPA)
Chan

Primary objectives

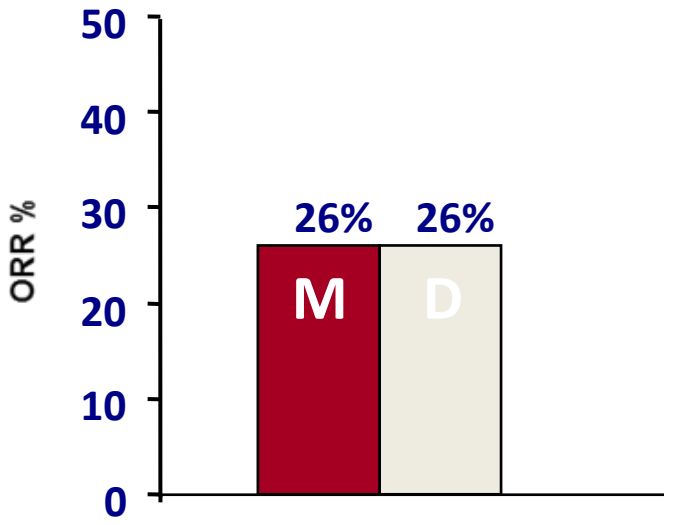
- **ORR, PFS, OS not inferior to conventional doxorubicin**
- **Reduction of cardiotoxicity**

1. Batist G et al. J Clin Oncol. 2001;19:1444-54
2. Harris L et al. Cancer. 2002;94;1:25-36
3. Chan S et al. Annals of Oncology 2004;15: 1527–1534

NPLD vs doxorubicin: ORR



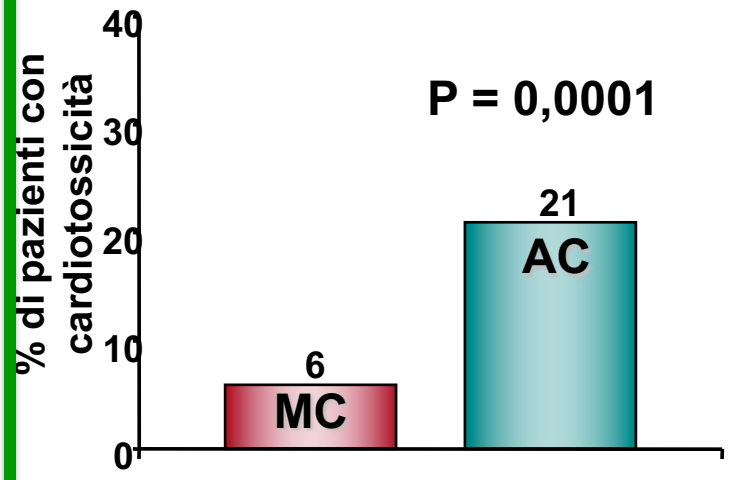
Batist G et al. *J Clin Oncol* 2001; 19: 1444-54



Harris L, et al. *Cancer.* 2002;94:25-36

NPLD vs doxorubicin: cardiotoxicity

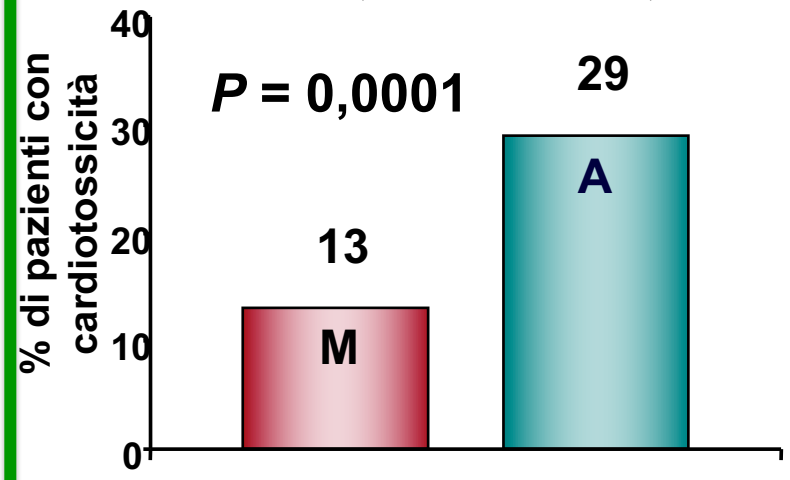
Batist G et al. *J Clin Oncol* 2001; 19: 1444-54



Casi di CHF:

NPLD	0
Doxorubicina	5
	(*P* = 0,02)

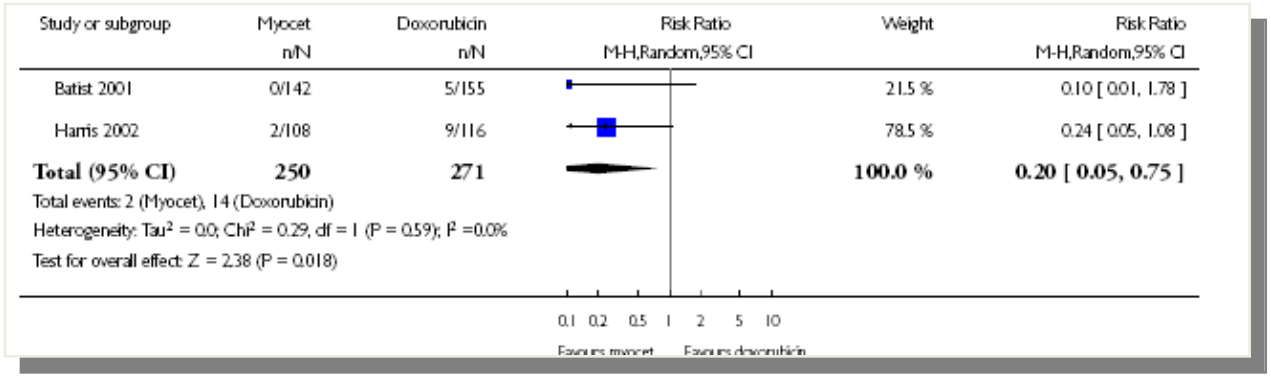
Harris L, et al. *Cancer.* 2002;94:25-36

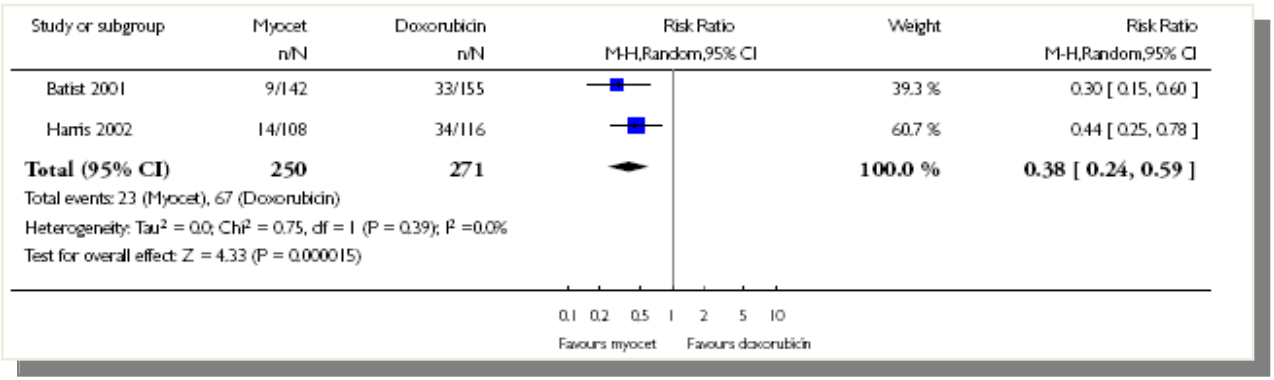


Casi di CHF:

NPLD	2
Doxorubicina	9
	P = 0,049

Risk of CHF





NPLD reduced the risk of CHF compared to conventional doxorubicin *(P=0.02)*

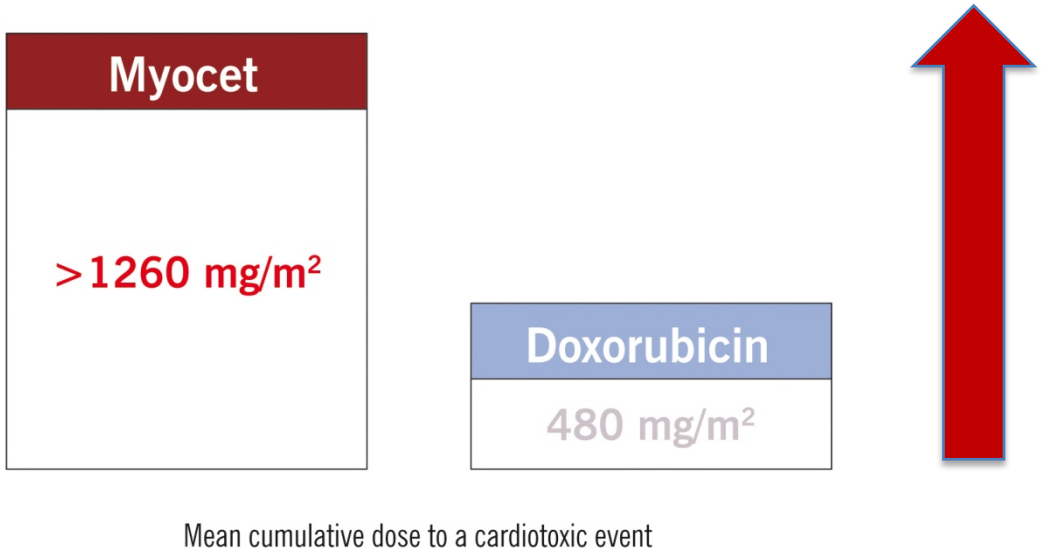
NPLD reduced the risk of clinical and subclinical cardiac failure compared to conventional doxorubicin *(P<0,0001)*

THE COCHRANE COLLABORATION®

Van Dalen EC et al. The Cochrane Library 2010

NPLD in breast cancer

Cumulative dose of NPLD: >1260 mg/sqm

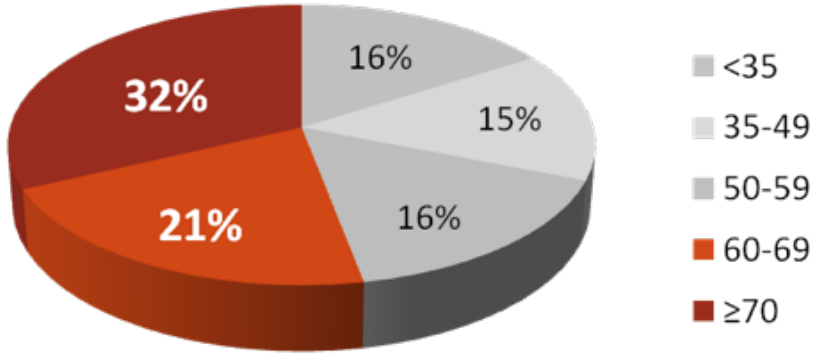


1.Heintel et al. *Ann Hematol.* 2010; 2. Visani et al. *Expert Rev Anticancer Ther.* 2009; 3. Batist et al. *Anticancer Drugs.* 2006; 4. Harris et al. *Cancer.* 2002; 2.5. Chan et al. *Ann Oncol.* 2004; 6. Batist et al. *J Clin Oncol.* 2001; 7. SmPC NPLD; 8. Dando TM et al. *AM J Cancer*. 2005

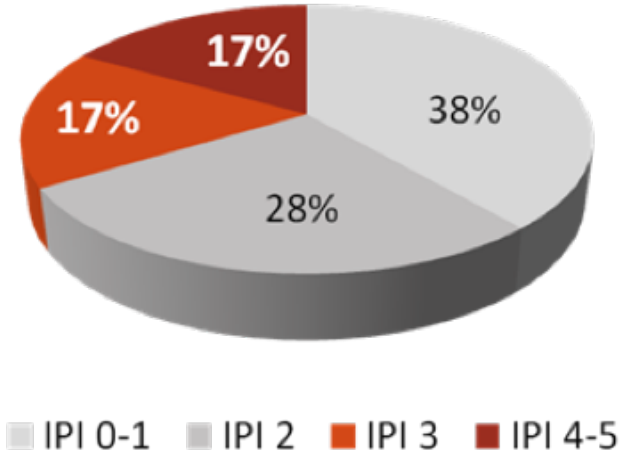
Diffuse Large B-Cell Lymphoma

- **Most common NHL: 31%**
  - **Peak incidence in sixth decade**
  - Incidence increased by 50-90% (depending on race, gender)

Distribution by age: 53% of pts are ≥60



Distribution by IPI score: 34% of patients are IPI 3-5



Prognostic factors for survival

IPI risk factors	Relative risk
Age: ≤60 yrs vs. > 60yrs	**1.96**
Serum LDH: normal vs. above normal	1.85
ECOG PS: 0,1 vs: ≥ 2	1.80
Extranodal involvement: ≤ 1 vs. ≥ 2 sites	1.48
Ann Arbor Stage: I/II vs. III or IV	1.47

Shipp, Blood 1994

COMPREHENSIVE GERIATRIC ASSESSMENT (CGA)

ELDERLY PROJECT

1.General Data 2.Disease Status 3. ADL 4.IADL 5.CIRS-G

Patient age: <80
ADL: 6
IADL 8
Comorbidity grade 2: 0
Comorbidity grade 3-4: 0
Patient profile: FIT

Patient age: ≥80
ADL: 6
IADL 8
Comorbidity grade 2: 0
Comorbidity grade 3-4: 0
Patient profile: UNFIT

TIME SPENT ON DETERMINATE PATIENT STATUS
< 10 MINUTIES

Patient age: >80
ADL: 5
IADL 5
Comorbidity grade 2: 1
Comorbidity grade 3-4: 0
Patient profile: UNFIT

First line treatment

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v116–v125, 2015
doi:10.1093/annonc/mdv304

Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

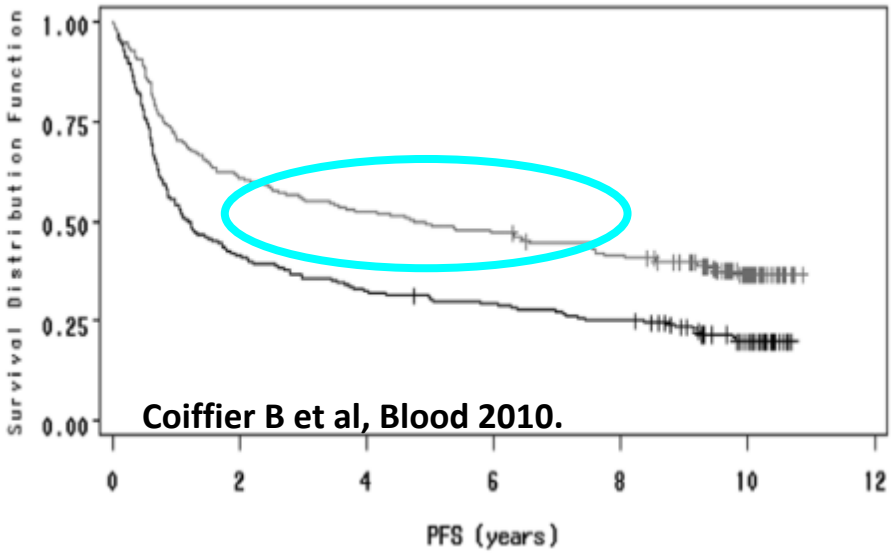
H. Tilly[1], M. Gomes da Silva[2], U. Vitolo[3], A. Jack[4], M. Meignan[5], A. Lopez-Guillermo[6], J. Walewski[7], M. André[8], P. W. Johnson[9], M. Pfreundschuh[10] & M. Ladetto[11], on behalf of the ESMO Guidelines Committee*

Elderly >60 years		
Fit, 60–80 years	>80 years without cardiac dysfunction	Unfit or frail or >60 years with cardiac dysfunction
R-CHOP21 × 6–8 (R-CHOP21 × 6 for IPI low risk) or R-CHOP14 × 6 with 8 R Consider CNS prophylaxis in patients at risk	Attenuated regimens: R-miniCHOP21 × 6	Doxorubicin substitution with gemcitabine, etoposide or liposomal doxorubicin or others: R-C(X)OP21 × 6 or palliative care

First line treatment: FIT patients

RCHOP vs CHOP: 10-yrs PFS 37% vs 20%

CHOP21 vs. R-CHOP21

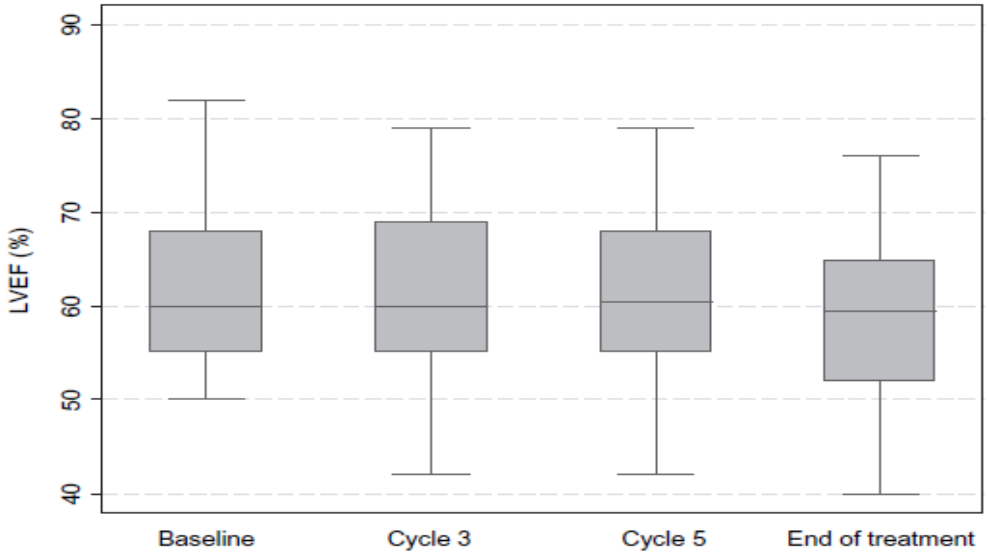


R-CHOP21 is the standard in DLBCL!

R-COMP in elderly DLBCL

Characteristic	Population ($N = 72$)	
	n	%
Age, years		
Median	72	
Range	61–83	
≥70 years	43	60
Male gender	32	44
Clinical stage		
I–II	22	31
III–IV	50	69
Extranodal involvement	46	64
Bone marrow involvement	16	22
ECOG performance status		
0–1	59	82
>1	13	18
Elevated LDH	49	72
International Prognostic Index		
1	14	21
2	16	23
3–5	38	56
LVEF		
Median	61	
Range	50–89	

	ITT population ($n = 72$)			Efficacy population ($n = 62$)		
	n	%	95% CI	*n*	%	95% CI
Response to chemotherapy						
CR	41	57	43–67	41	66	53–78
PR	10	14	7–24	10	16	8–28
Less than PR	21	29	19–41	11	18	9–30
Alive, NED	55	76	65–86	50	81	69–90
Relapsed NHL*	5	12	4–26	5	12	4–26
Deaths	17	24	14–35	12	20	11–32
3-year survival						
OS		72	58–82		77	62–87
FFS		39	28–51		46	32–58
PFS		69	56–79		74	60–83

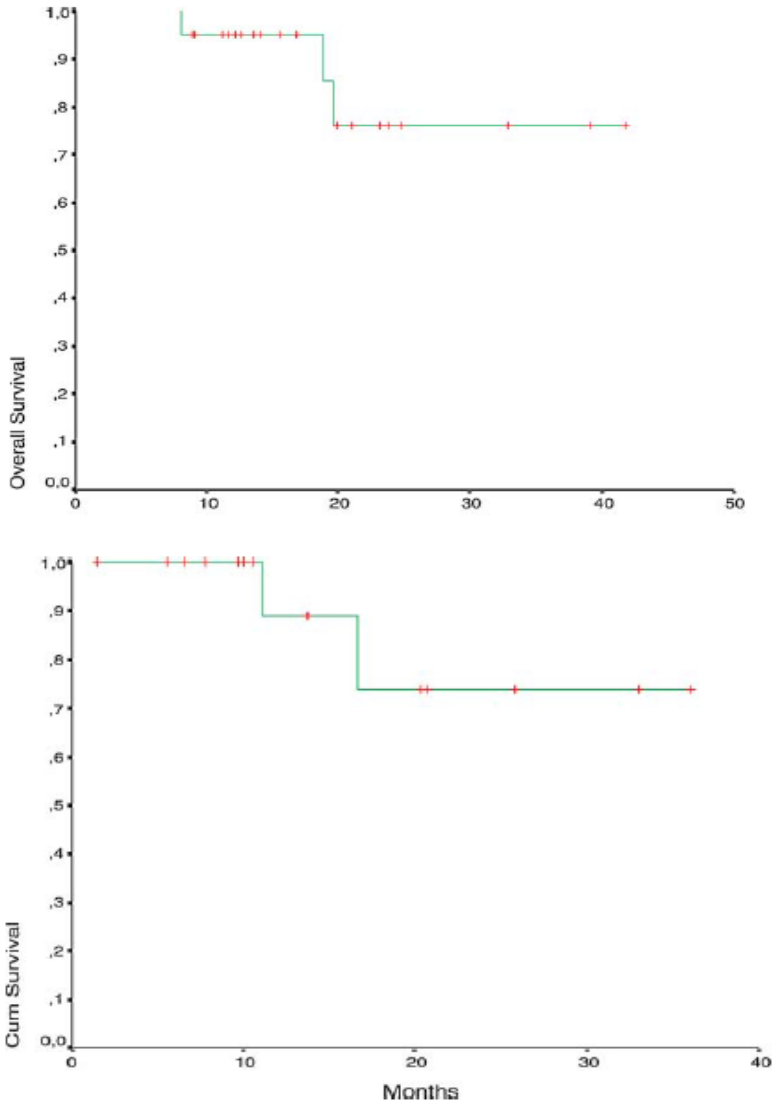


Luminari S et al, Ann Oncol 2010

R-COMP in elderly aggressive NHL with concurrent cardiac disease or pretreated with anthracyclines

Table 1. Patients' characteristics at baseline

Patients characteristics	*N* (%)
Sex (male/female)	13 (62)/8 (38)
Age (median)	70 (range 54–76)
Histology (B-cell diffuse large/B-cell mantle)	18 (86)/3 (14)
Stage (I/II/III/IV)	2 (9)/5 (24)/5 (24)/9 (43)
Symptoms (A/B)	16 (76)/5 (24)
IPI (low, low/intermediate, intermediate/high, high)	7 (33)/8 (38)/5 (24)/1 (5)
Extranodal involvement	11 (52)
Bulky disease	5 (24)
Previous antracycline chemotherapy	8 (38)



Rigacci L et al, Hematol Oncol 2007

R-COMP in elderly aggressive NHL with concurrent cardiac disease or pretreated with anthracyclines

Table 2. Characteristics of patients with cardiac comorbidity or pre-treated patients

Patients	Cardiac disease	LVEF (%)			p
		Baseline	3rd cycle	End of study	
1	Hypertensive cardiomyopathy	54	60	57	n.s.
2	CAD	58	65	60	n.s.
3	Hypokinesia	50	20*	n.e.	n.e.
4	CAD	45	59	60	n.s
5	Hypokinesia	45	42	47	n.s
6	Hypertensive cardiomyopathy	60	58	63	n.s
7	Hypertensive cardiomyopathy	60	61	60	n.s
8	CAD	69	64	69	n.s
9	Hypertensive cardiomyopathy	50	58	53	n.s
10	CAD	44	55	60	n.s
11	Hypertensive cardiomyopathy	57	60	58	n.s
12	Hypertensive cardiomyopathy	65	60	60	n.s
13	CAD	40	38	40	n.s.
14	Pre-treated	63	60	60	n.s.
15	Pre-treated	61	70	60	n.s.
16	Pre-treated	66	61	63	n.s.
17	Pre-treated	60	65	60	n.s.
18	Pre-treated	70	60	60	n.s.
19	Pre-treated	60	58	58	n.s.
20	Pre-treated	60	60	65	n.s.
21	Pre-treated	59	70	65	n.s.

LVEF, Left Ventricular Ejection Fraction; CAD, Coronary Artery Disease; n.e., not evaluated; n.s., not significant.
*Congestive heart failure after 1st cycle.

One case of CHF* resolved with farmacologic approach

- ✓ **Median LVEF after 3 courses: 60% (range, 38–74%)**
- ✓ **Median LVEF at the end of treatment: 60% (range, 40–69%)**

Rigacci L et al, Hematol Oncol 2007

Nonpegylated Liposomal Doxorubicin as a Component of R-CHOP Is an Effective and Safe Alternative to Conventional Doxorubicin in the Treatment of Patients With Diffuse Large B-Cell Lymphoma and Preexisting Cardiac Diseases

Sarah Rohlfing,[1] Matthias Aurich,[2] Tilman Schöning,[3] Anthony D. Ho,[1] Mathias Witzens-Harig[1]

25 DLBCL patients

Table 2 Preexisting Cardiac Diseases

Variable	n
Heart Failure	14
Coronary Heart Disease/Ischemic Cardiopathy	10
Cardiac Arrhythmia	10
History of Anthracyclines and Breast Radiation	2
Dilated Cardiomyopathy	2
Cerebral Stroke/Transient Ischemic Attack	2
Pulmonary Hypertension With Reduced RVEF	1
Aortic Valve Replacement	1
Distinct LV Hypertrophy With Aortic Stenosis	1

Table 1 Demographic Data

Variable	n
Age, Years	
<60	5
60-75	9
>75	11
Sex	
Male	20
Female	5
Ann Arbor Stage	
I/II	12
III/IV	13
International Prognostic Index	
Low/low-intermediate risk	12
High/high-intermediate risk	13
Therapeutic Situation	
First-line	23
Second-line	2

Rohlfing et al. Clinical Lymphoma, Myeloma and Leukemia 2015

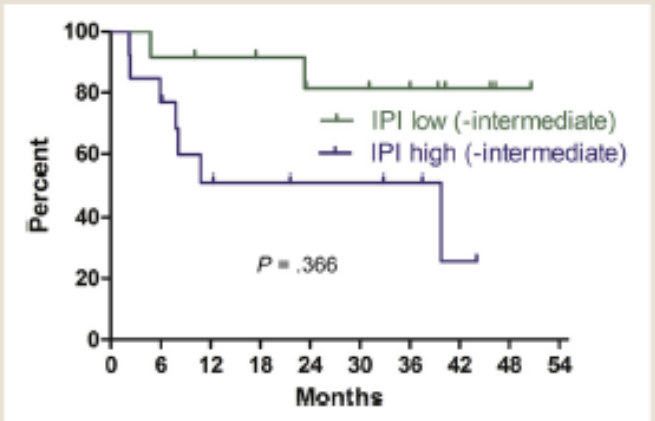
Nonpegylated Liposomal Doxorubicin as a Component of R-CHOP Is an Effective and Safe Alternative to Conventional Doxorubicin in the Treatment of Patients With Diffuse Large B-Cell Lymphoma and Preexisting Cardiac Diseases

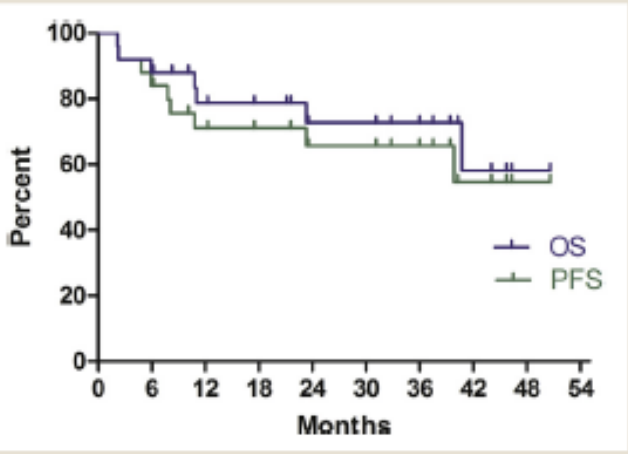
Sarah Rohlfing,[1] Matthias Aurich,[2] Tilman Schöning,[3] Anthony D. Ho,[1] Mathias Witzens-Harig[1]

Table 3 Median LVEF Before and After Therapy With NPLD

	LVEF Before	LVEF After
All Patients	51%	50%
Patients With Normal LVEF (≥55%)	60% (55%-65%)	57% (40%-61%)
Patients With Reduced LVEF (<55%)	45.5% (35%-53%)	46.5% (15%-56%)

Figure 2 Progression-Free Survival Depending on International Prognostic Index (IPI)





Rohlfing et al. Clinical Lymphoma, Myeloma and Leukemia 2015

Nonpegylated liposomal doxorubicin combination regimen in patients with diffuse large B-cell lymphoma and cardiac comorbidity. Results of the HEART01 phase II trial conducted by the Fondazione Italiana Linfomi

Stefano Luminari[1,2] | Elda Viel[3] | Andrés José Maria Ferreri[4] | Francesco Zaja[5] | Emanuela Chimienti[6] | Gerardo Musuraca[7] | Alessandra Tucci[8] | Monica Balzarotti[9] | Monica Tani[10] | Francesca Salvi[11] | Emanuela A. Pesce[12] | Angela Ferrari[1] | Anna M. Liberati[13] | Antonio Spadea[14] | Dario Marino[15] | Maria Bruno-Ventre[4] | Stefano Volpetti[5] | Chiara Bottelli[8] | Elena Ravaioli[6] | Francesco Merli[1] | Michele Spina[6]

Hematological Oncology. 2018;**36**:68–75.

Variable	N	%	Missing N (%)
Age			
Median	76		
Range	53-90		-
>60	47	94	
Sex, M	35	70	-
Stage			
I-II	19	38	-
III-IV	31	62	
PS > 1	7	14	-
LDH > UNL	23	51	5 (10)
ENS > 1	5	10	-
Bulky[a]	5	10	1 (2)
IPI			
0-1	11	24	
2	16	26	5 (10)
3-5	18	40	

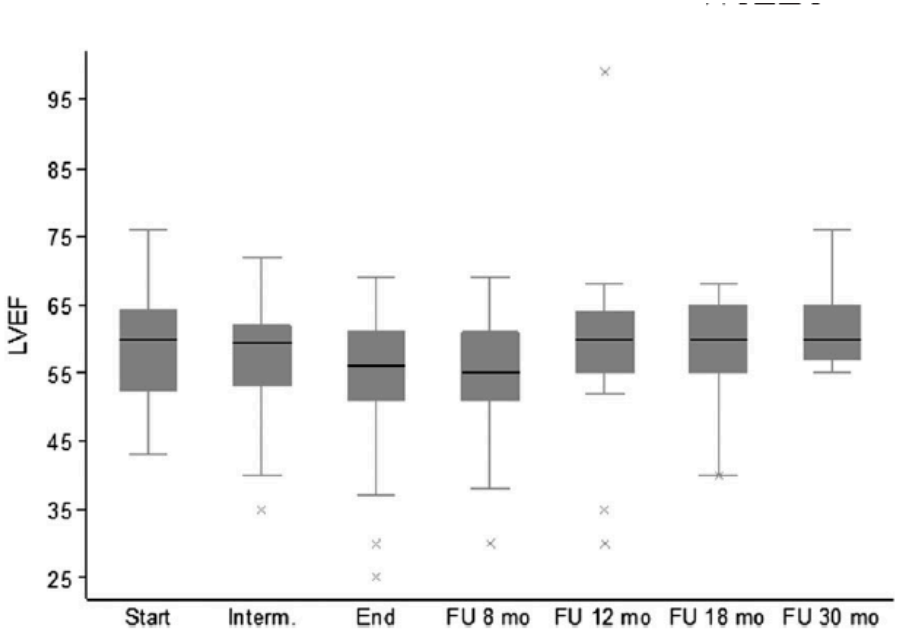
Variable	N	%	Missing N (%)
Cardiac disorders			
Ischemic cardiopathy	21	35	
Atrial fibrillation	9	15	
Left ventricular hypertrophy	8	13	
LVEF <50%	7	12	
Ventricular arrhythmia	5	8	-
Moderate/severe mitral valve disease	3	5	
Moderate aortic valve disease	3	5	
Pulmonary hypertension	2	3	
Uncontrolled hypertension	2	3	
Altered ECG	27	59	4 (8)
LVEF			
Median	60	-	3 (6)
IQR	12		

Nonpegylated liposomal doxorubicin combination regimen in patients with diffuse large B-cell lymphoma and cardiac comorbidity. Results of the HEART01 phase II trial conducted by the Fondazione Italiana Linfomi

Response	N	% (95CI)
CR	28	56 (41-70)
PR	8	16 (4-29)
ORR	36	72 (58-84)
SD/PD	10	20 (10-34)
NA/EW	4	8 (2-19)
3-yr survival	# events	% (95CI
OS	22	50 (34-65)
PFS	30	38 (24-51)
FFS	36	27 (15-40)

TABLE 4 Summary of cardiac events during treatment

	Population (N = 50)	
Cardiac disorder	Grades 1-2, n (%)	Grades 3-4, n (%)
Heart failure	1(2)	1(2)
LVEF drop ≥20%	2(4)[a]	3(6)
Increased troponin	2(4)	-
Angina	-	1(2)
Atrial fibrillation	-	1(2)
Tot	5(10)	6(12)



No significant modifications from baseline values of LVEF were observed during treatment and follow-up.

Luminari S et al, Hematol Oncol 2018

R-CHOP versus R-COMP: Are They Really Equally Effective?

M. Mian *, I. Wasle *, G. Gamerith *, P. Mondello †, T. Melchardt ‡, T. Jäger §, W. Linkesch ¶, M. Fiegl *

Clinical Oncol 2014

Retrospective analysis

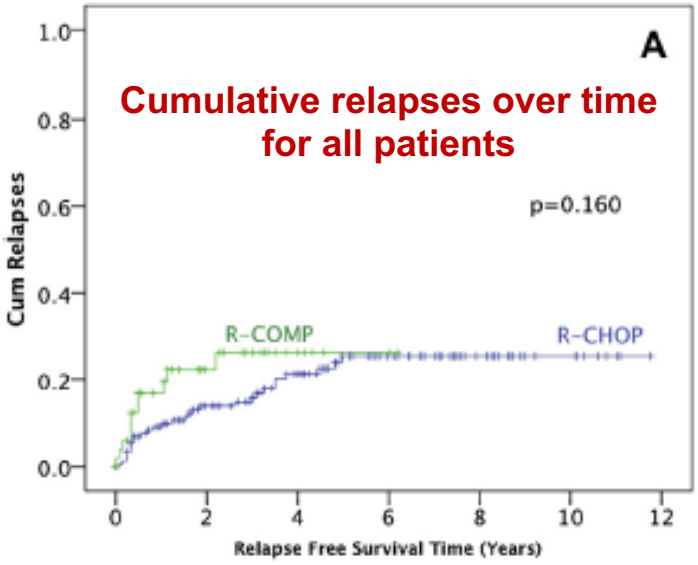
364 untreated DLBCL patients: 218 (60%) R-CHOP, 146 (40%) R-COMP.

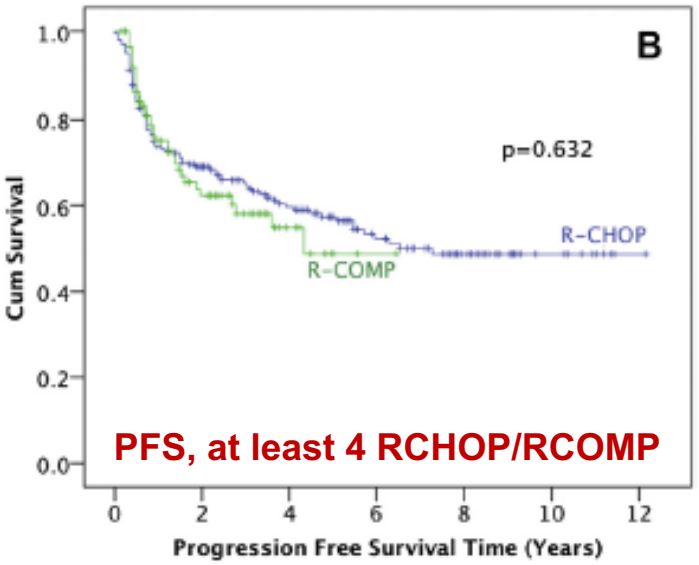
Parameter	R-CHOP ($n = 218$)			R-COMP ($n = 146$)			*P* value
	No.	Valid	%	No.	Valid	%	
Male:female	118:100	218	54:46	75:71	146	51:49	0.605
B symptoms	77	187	41	58	146	40	0.789
Age categories (years)							
<60	93	216	43	13	146	9	<0.001
60–69	50		23	30		20	
70–79	61		28	62		43	
>80	12		6	41		28	
Stage							
I	37	218	17	22	146	15	0.461
II	60		27	34		23	
III	45		21	27		19	
IV	76		35	63		43	
Stage III/IV	121	218	55	88	146	60	0.367
≥2 extranodal sites	64	208	31	44	146	30	0.899
Performance status ≥2	48	188	25	37	145	25	0.998
LDH > UNL	108	190	57	80	146	55	0.708
International prognostic index ≥2	140	197	71	112	146	77	0.242
Lymphadenopathy >5 cm and/or maximum spleen diameter ≥20 cm	93	202	46	30	123	24	<0.001
Pre-existing comorbidities							
Cardiovascular disease	83	206	40	103	146	71	<0.001
Diabetes mellitus	18	206	9	21	146	14	0.096
COPD and/or asthma	11	205	5	21	146	14	0.004
Gastrointestinal disorders	17	206	8	22	146	15	0.045
Other neoplasias	25	205	12	30	146	20	0.033
Creatinine >2 mg/dl	18	205	9	21	146	14	0.100
Neurological disorders	16	205	8	23	146	16	0.020
Rheumatological diseases	18	205	9	17	146	12	0.378
Psychiatric disorders	15	205	7	5	146	3	0.121
Sum of comorbidities							
None	79	204	39	18	146	12	<0.001
1–2	98		48	85		58	
3–4	26		13	40		27	
>4	1		0.5	3		2	

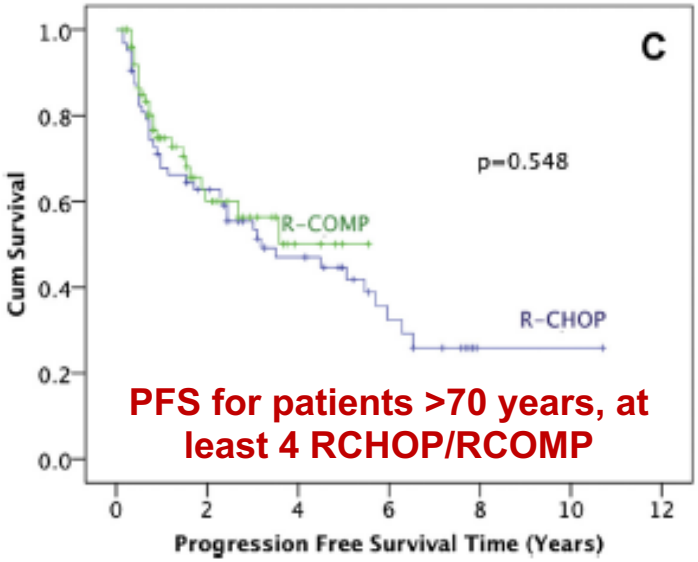
R-CHOP versus R-COMP: Are They Really Equally Effective?

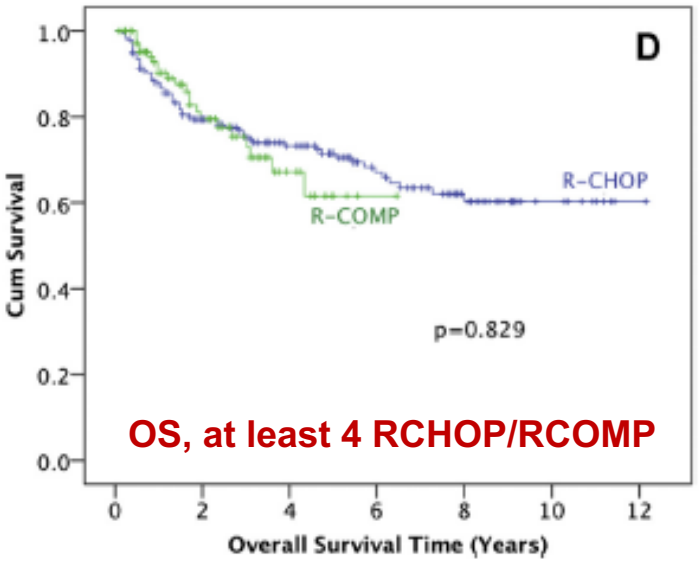
M. Mian *, I. Wasle *, G. Gamerith *, P. Mondello †, T. Melchardt ‡, T. Jäger §, W. Linkesch ¶, M. Fiegl *

Clinical Oncol 2014





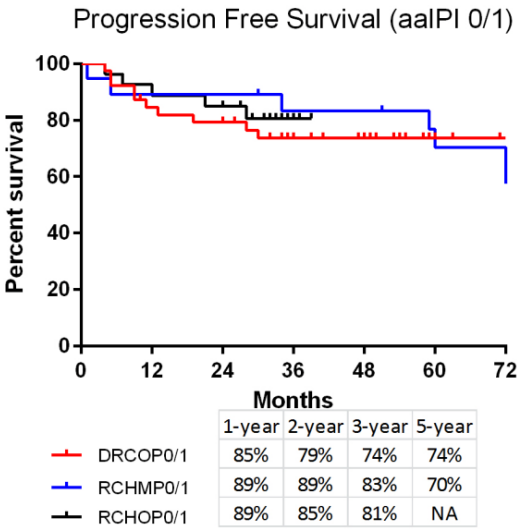




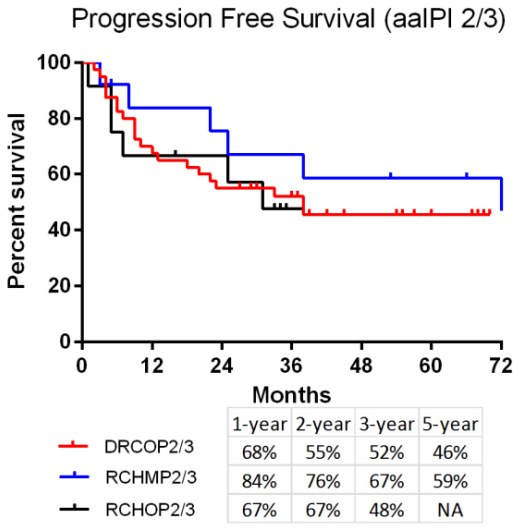
The Clinical Outcome of Newly Diagnosed Patients >60 Years of Age with DLBCL Treated with Standard or Liposomal Chemotherapies

Retrospective analysis; DLBCL patients, age > 60

- ✓ 39 patients: RCHOP
- ✓ 79 patients: DRCOP, with pegylated liposomal doxorubicin in place of conventional doxorubicin
- ✓ 32 patients: RCHMP, with liposomal vincristine in place of conventional vincristine



	1-year	2-year	3-year	5-year
DRCOP0/1	85%	79%	74%	74%
RCHMP0/1	89%	89%	83%	70%
RCHOP0/1	89%	85%	81%	NA



	1-year	2-year	3-year	5-year
DRCOP2/3	68%	55%	52%	46%
RCHMP2/3	84%	76%	67%	59%
RCHOP2/3	67%	67%	48%	NA

Ahmed MA et al, Poster 3965, ASH 2015

Liposomal doxorubicin vs. conventional formulation

PS1038

LIPOSOMAL DOXORUBICIN IN AGGRESSIVE B CELL LYMPHOMA SHOWS SIMILAR EFFICACY TO THE CONVENTIONAL FORMULATION: LONG TERM RESULTS FROM A RETROSPECTIVE COHORT STUDY

A. García-Noblejas[1,*], J. Cannata-Ortiz[1], E. Acuña[1], J. Loscertales[1], A. Alegre[1], R. Arranz[1]

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EUROPEAN HEMATOLOGY ASSOCIATION

Retrospective analysis.

78 patients:

- ✓ **61 control arm (A): conventional doxo**
- ✓ **17 study arm (B): lyposomal doxo**

Characteristics	Group A N= 61	Group B N= 17	p
Age (range)	70 (41-88)	78 (59-89)	0.001
Male / female	21/40	9/8	0.165
ECOG >2	4 (7%)	2 (11%)	0.617
Ann Arbor III-IV	43 (70%)	10 (56%)	0.389
B symptoms	38 (63%)	8 (44%)	0.179
Comorbidities			
HBP	24 (39%)	13 (76%)	0.007
DM	3 (5%)	2 (12%)	0.308
Dyslipemia	11 (18%)	5 (29%)	0.304
Smoking	15 (25%)	2 (12%)	0.257
Cardiopathy			0.001
Atrial fibrillation	6 (10%)	3 (18%)	
Ischemic	-	3 (18%)	
cardiopathy	-	1 (6%)	
Other			
LVEF <50%	2 (4%)	5 (31%)	0.001

Summary/Conclusion: In this study, the association use of LD to inmunochemotherapy in fragile patients showed similar efficacy as conventional doxorubicin, without increased toxicity.

Cardiotoxicity with rituximab, cyclophosphamide, non-pegylated liposomal doxorubicin, vincristine and prednisolone compared to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone in frontline treatment of patients with diffuse large B-cell lymphoma A randomised phase-III study from the Austrian Cancer Drug Therapy Working Group *[Arbeitsgemeinschaft Medikamentöse Tumortherapie AGMT]* (NHL-14)

Michael A. Fridrik [a,*], Ulrich Jaeger [b], Andreas Petzer [c], Wolfgang Willenbacher [d], Felix Keil [e], Alois Lang [f], Johannes Andel [g], Sonja Burgstaller [h], Otto Krieger [i], Willi Oberaigner [j], Kurt Sihorsch [k], Richard Greil [l]

European Journal of Cancer 58 (2016) 112–121

Baseline characteristics.

	R-COMP	R-CHOP
Randomised	43	45
Excluded (n)	3	6
Eligible (n)	40	39
Age median years (range)	65 (18–81)	65 (22–84)
Age >60 years	24 (60.0%)	25 (64.1%)
Male/female	23/17	22/17
WHO >1	1 (2.5%)	3 (7.7%)
IPI very good (0 P)	3 (7.5%)	1 (2.6%)
IPI good (1–2 P)	27 (67.5%)	28 (71.8%)
IPI poor (>2 P)	10 (25.0%)	10 (25.7%)
St III, IV	19 (47.5%)	18 (46.2%)
Non-smoker	20 (50.0%)	21 (53.8%)
Cardiac function WHO° 0	40 (100%)	39 (100%)
Hypertension	5 (12.5%)	6 (15.4%)
NT-proBNP (pg/ml)	108 (19–2072)	134·5 (10–920)
NT-proBNP <400 pg/ml	34 (89.0%)	35 (89.7%)
LVEF median (range)	64 (52–83)	63·5 (45–75)
LVEF <50%	0 (0.0%)	1 (2.6%)
Cumulative doxorubicin dose (mg/sqm)	295 mg/m^2	294.5 mg/m^2

R-COMP vs. R-CHOP

mean LVEF: 63.31% vs. 62.25%, (P 0.167).

LVEF < 50% during treatment: 4.6% vs. 15.8% (P<0.001).

NT-proBNP levels < 400 pg/ml during and at the end of treatment: 90% patients vs. 66.7% (P 0.013).

SAE: 26 vs. 40 (Infections: 15 vs. 28) (P 0.029).

Cardiotoxicity with rituximab, cyclophosphamide, non-pegylated liposomal doxorubicin, vincristine and prednisolone compared to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone in frontline treatment of patients with diffuse large B-cell lymphoma A randomised phase-III study from the Austrian Cancer Drug Therapy Working Group *[Arbeitsgemeinschaft Medikamentöse Tumortherapie AGMT]* (NHL-14)

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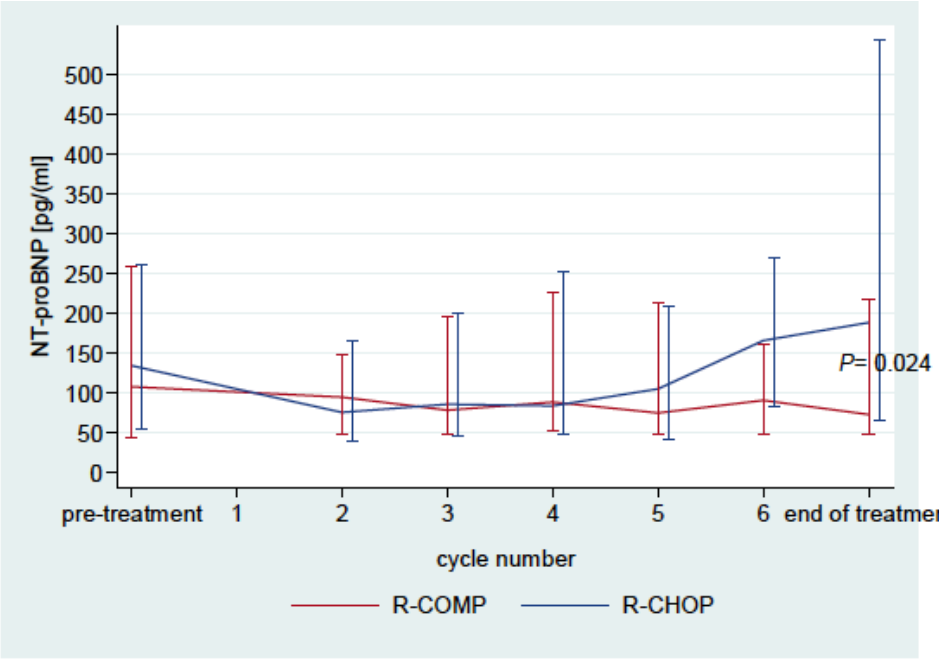

In patients with normal cardiac function, 6 cycles of R-CHOP resulted in a low rate of early cardiotoxicity. NPL-doxorubicin did not reduce cardiotoxicity, although cardiac safety signals were elevated in R-CHOP compared to R-COMP.

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Armenian, S. H. et al. J. Clin. Oncol. 35, 893–911 (2017).

1. **Which patients with cancer are at increased risk for developing cardiac dysfunction?**

2. **Which preventive strategies are effective in minimizing risk during the administration of potentially cardiotoxic cancer therapy?**

3. **What are the preferred surveillance and monitoring approaches in patients at risk for cardiac dysfunction?**

Recommendation 1.1. It is recommended that patients with cancer who meet any of the following criteria should be considered at increased risk for developing cardiac dysfunction.

➢ **Treatment that includes any of the following:**

- **High-dose anthracycline**
  - doxorubicin ≥ 250 mg/m2
  - epirubicin ≥ 600 mg/m2
- **Lower-dose anthracycline + lower-dose RT**
  (where the heart is in the treatment field)
  - doxorubicin < 250 mg/m2
  - epirubicin < 600 mg/m2
  - RT < 30 Gy
- **High-dose radiotherapy**
  (where the heart is in the treatment field)
  - RT ≥ 30 Gy

ASCO guidelines

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers:
American Society of Clinical Oncology Clinical Practice Guideline

Armenian, S. H. et al. J. Clin. Oncol. 35, 893–911 (2017).

3 **Which preventive strategies** are effective **in minimizing risk** during the administration of potentially cardiotoxic cancer therapy?

Recommendation 3.1.
Clinicians should screen for and actively manage modifiable cardiovascular risk factors in all patients receiving potentially cardiotoxic treatments.

- Smoking
- Hypertension
- Diabetes
- Dyslipidemia
- Obesity

Recommendation 3.2.
Clinicians may incorporate a number of strategies

- **liposomal formulation** of doxorubicin
- continuous infusion of doxorubicin
- cardioprotectant dexrazoxane

Recommendation 4.2.
In individuals with clinical signs or symptoms concerning for cardiac dysfunction during routine clinical assessment, the following strategy is recommended:

- Echocardiogram for diagnostic workup
- Cardiac magnetic resonance imaging (MRI) or multigated acquisition (MUGA)
- Serum cardiac biomarkers

TAKE HOME MESSAGES

- ✓ A better definition of elderly patients with the CGA is mandatory.
- ✓ Consider clinical and biological markers of early cardiac dysfunction.
- ✓ For patients at high-risk of developing cardiac dysfunctions, alternative measures aimed at reducing cardiotoxicity without limiting the antitumor efficacy of treatment must be used.
- ✓ One randomized study and retrospective analyses reported similar effect between conventional and lyposomal doxorubicin.
- ✓ Clinicians may incorporate lyposomal anthracyclines in the treatment of UNFIT/FRAIL patients or patients at increased risk of developing cardiac dysfunctions.

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