The role of liposomal doxorubicin in DLBCL lymphomas

Michele Spina
Aviano

Disclosures of *Michele Spina*

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
TEVA					X	X	
Mundipharma					x	x	
Menarini	x		x		x	x	
Roche					x		
Takeda					x		
Janssen-Cilag					x	x	
Gilead					x	x	
CTI					x	x	
Servier					x	x	

Introduction

R-CHOP is the gold standard for patients with DLBCL

Doxorubicin is a key drug for the treatment of aggressive NHL

The presence of cardiac comorbidities contraindicate its use, specially in elderly patients

Comorbidities

Diseases	<60 yrs	60-64 yrs	65-74 yrs	>75 yrs
Hypertension	8.7	34.3	43.5	53.9
Arthrosis/Arthritis	5.5	31.5	42	60
Osteoporosis	2.1	12.3	20.3	35.1
Diabetes	1.6	11.3	14.9	20.3
COPD	1.1	7.8	11.3	20
Heart disease	0.6	4.8	8.8	17
Neurological disease	2.6	6.1	7	13.2
Allergies	12.1	9.2	9.4	9.1

ISTAT 2012

Demographic and Clinical Characteristics of Patients with Advanced DLBCL by Chemotherapy Group

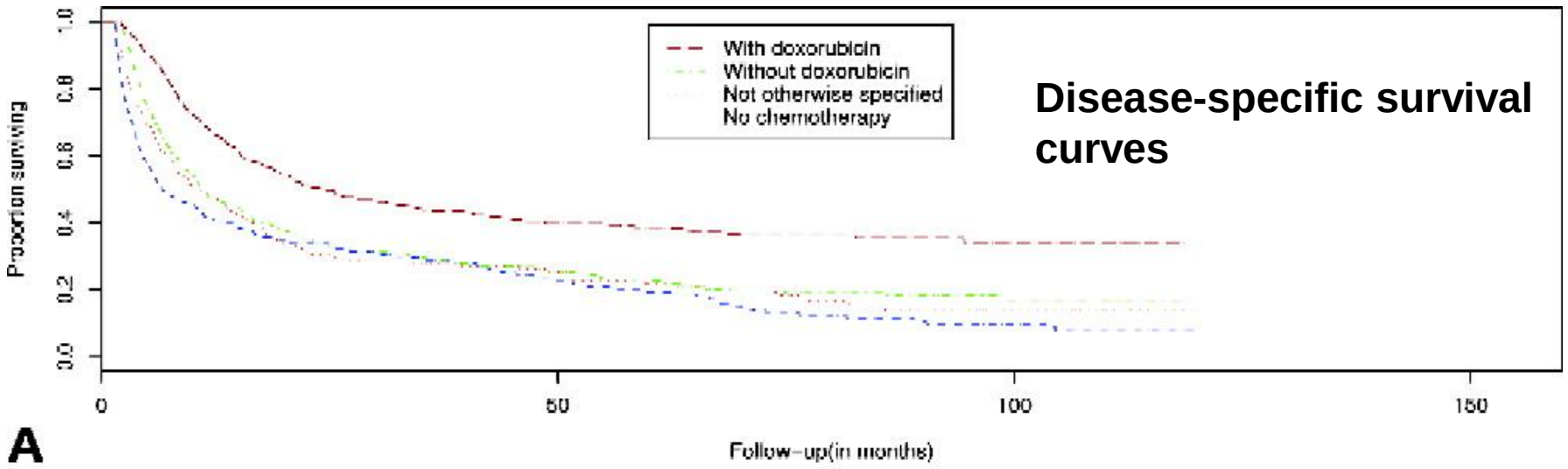
	Treatment received										
	Specified chemotherapy										
	With doxorubicin		Without doxorubicin		CT NOS		No CT		Total		*P*
	No.	%	No.	%	No.	%	No.	%	No.	%	
All pts	768	33	468	20	261	11	829	35	2326	100	<0.001
Age, y											
65-69	174	22	90	19	45	17	77	9	386	16	
70-74	251	32	110	23	60	23	188	22	609	26	
75-79	206	26	138	29	77	29	196	23	617	26	
80-84	105	13	87	18	45	17	171	20	408	17	
>85	32	4	43	9	34	13	197	23	306	13	<0.001

Glenn et al. Cancer 2006

Patients who received doxorubicin survived more than twice as long (24.4 months) as patients who did not receive doxorubicin (11.2 months).

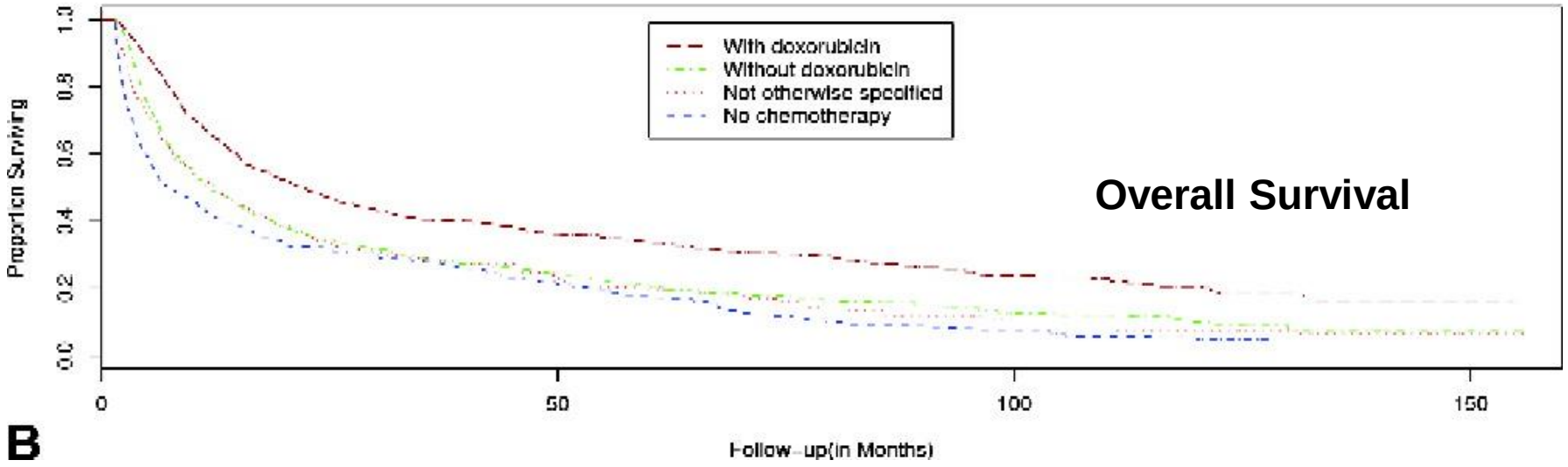
Survival was no better among patients who received chemotherapy without doxorubicin than among patients who received no chemotherapy.

Glenn et al. Cancer 2006



Disease-specific survival curves

A



Overall Survival

B

Glenn et al. Cancer 2006

Leukemia & Lymphoma, March 2015, 56(3): 682–687
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DOI: 10.3109/10428194.2014.921914

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healthcare

ORIGINAL ARTICLE: CLINICAL

The effects of cardiovascular disease on the clinical outcome of elderly patients with diffuse large B-cell lymphoma

Huei-Ting Tsai[1], Ruth M. Pfeiffer[1], Joan Warren[2], Wyndham Wilson[3]* & Ola Landgren[3,4]

[1]Biostatistics Branch, Division of Cancer Epidemiology and Genetics, [2]Division of Cancer Control and Population Sciences, [3]Metabolism Branch, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD, USA and [4]Myeloma Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Table II. Risk of cardiovascular events among patients with DLBCL treated with doxorubicin-based therapy compared to controls, by selected preexisting medical conditions for 6 months and 3 years of follow-up.

	Congestive heart failure/cardiomyopathy		Acute myocardial infarction	
	6 months†: HR (95% CI)	3 years†: HR (95% CI)	6 months†: HR (95% CI)	3 years†: HR (95% CI)
Doxorubicin-based therapy, overall	3.42 (3.02, 3.86)	2.45 (2.26, 2.67)	3.29 (2.53, 4.28)	1.72 (1.44, 2.04)
Doxorubicin-based therapy, history of any cardiovascular disease				
No	6.62 (5.31, 8.26)**	3.61 (3.20, 4.08)**	5.17 (3.57, 7.48)*	2.07 (1.64, 2.62)*
Yes	2.63 (2.26, 3.07)**	1.90 (1.70, 2.12)**	2.33 (1.59, 3.43)*	1.42 (1.09, 1.84)*
Doxorubicin-based therapy, history of diabetes				
No	4.39 (3.74, 5.16)**	2.93 (2.65, 3.25)**	4.11 (2.92, 5.78)	1.93 (1.55, 2.41)
Yes	2.51 (2.06, 3.05)**	1.92 (1.68, 2.19)**	2.51 (1.65, 3.81)	1.43 (1.07, 1.90)
Doxorubicin-based therapy, history of hypertension				
No	6.70 (4.81, 9.33)**	3.69 (3.03, 4.59)**	4.09 (2.06, 8.12)	1.71 (1.10, 2.65)
Yes	3.14 (2.74, 3.59)**	2.29 (2.10, 2.51)**	3.15 (2.37, 4.19)	1.72 (1.43, 2.08)
Doxorubicin-based therapy, history of hyperlipidemia				
No	3.92 (3.14, 4.88)	2.51 (2.17, 2.91)	5.02 (3.10, 8.14)	1.89 (1.38, 2.59)
Yes	3.22 (2.77, 3.74)	2.43 (2.21, 2.68)	2.87 (2.09, 3.92)	1.66 (1.35, 2.04)

DLBCL, diffuse large B-cell lymphoma; CI, confidence interval.

*p-Value from likelihood ratio test for heterogeneity across the strata < 0.05; **p-value from likelihood ratio test for heterogeneity across the strata < 0.001.

†Adjusted hazard ratios (HRs) were estimated from models using age as the time metric, adjusted for sex, history of cardiovascular disease, diabetes, hypertension, hyperlipidemia and SEER registry. The 3 years of follow-up models were additionally adjusted for race, which was not significant in the 6 months models.

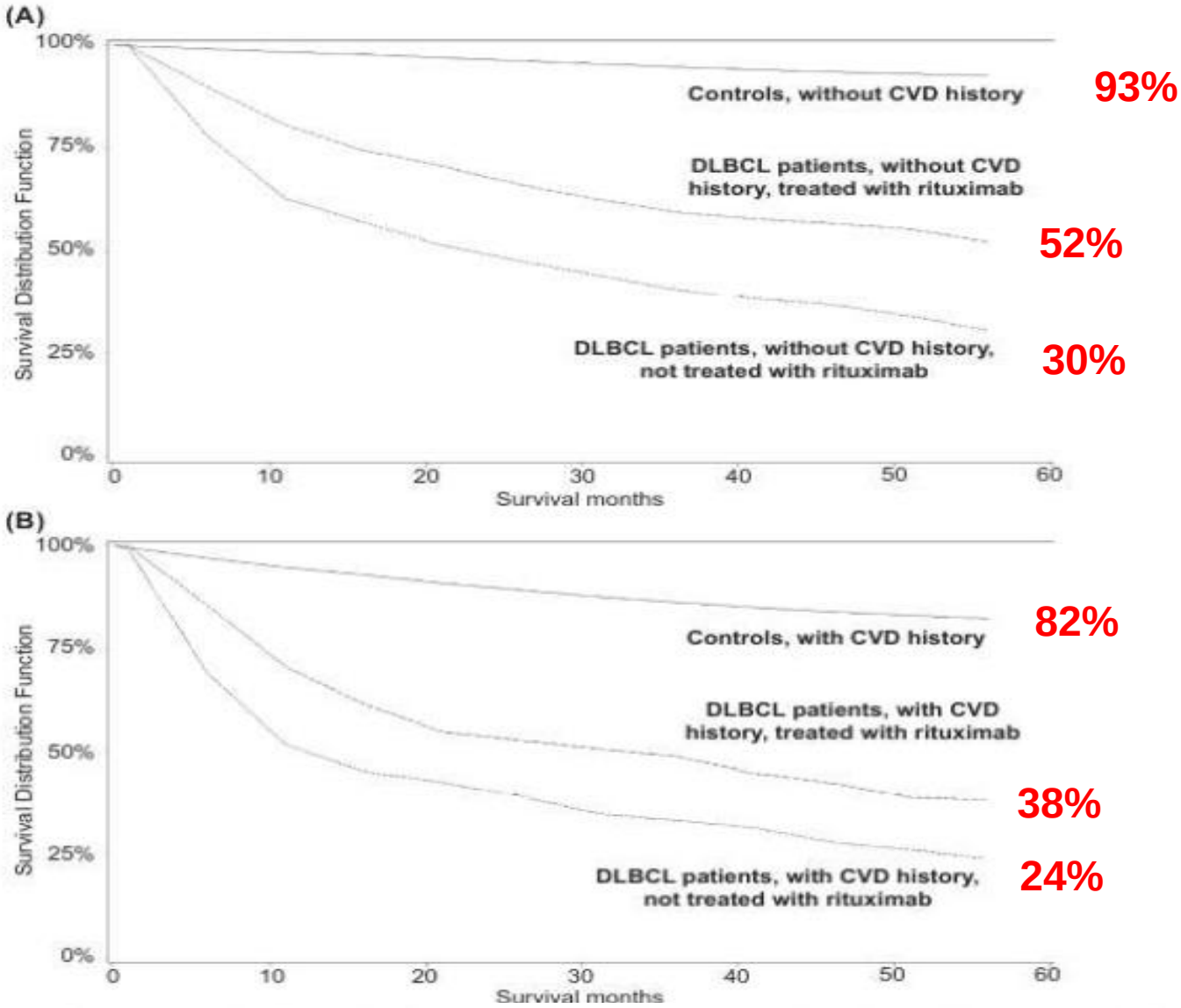


Figure 1. (A) Survival in patients with DLBCL in advanced stage by use of rituximab and controls, all groups without a history of cardiovascular disease (CVD). (B) Survival in patients with DLBCL in advanced stage by use of rituximab and controls, all groups with a history of CVD. For those without a history of any CVD the estimates of 5-year survival were 92.7% for controls, 52.4% for patients with rituximab and 30.4% for patients who did not receive rituximab. Among those with a history of any CVD the estimates of 5-year survival were 82.4% for controls, 38.1% for patients with rituximab and 24.0% for patients who did not receive rituximab.

Late Toxicity of Treatment

Excess mortality

- secondary malignancies
- cardiac disease

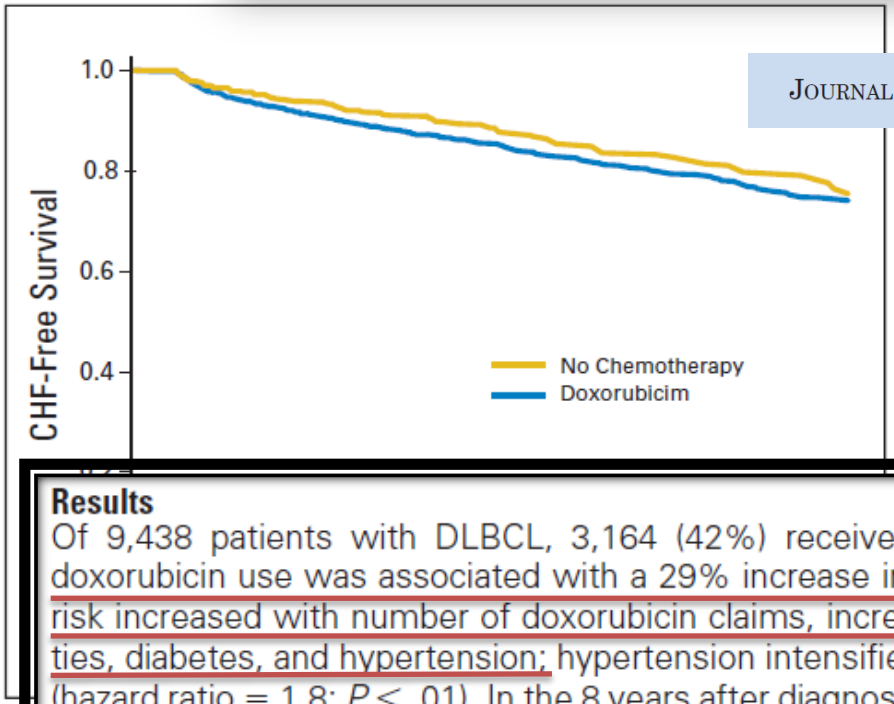
Excess morbidity / decreased Q.O.L

- cardiac disease
- pulmonary disease
- infertility
- fatigue

Doxorubicin, Cardiac Risk Factors, and Cardiac Toxicity in Elderly Patients With Diffuse B-Cell Non-Hodgkin's Lymphoma

Dawn L. Hershman, Russell B. McBride, Andrew Eisenberger, Wei Yann Tsai, Victor R. Grann, and Judith S. Jacobson

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT



Results

Of 9,438 patients with DLBCL, 3,164 (42%) received doxorubicin-based chemotherapy. Any doxorubicin use was associated with a 29% increase in risk of CHF (95% CI, 1.02 to 1.62); CHF risk increased with number of doxorubicin claims, increasing age, prior heart disease, comorbidities, diabetes, and hypertension; hypertension intensified the effect of doxorubicin on risk of CHF (hazard ratio = 1.8; $P < .01$). In the 8 years after diagnosis, the adjusted CHF-free survival rate was 74% in doxorubicin-treated patients versus 79% in patients not treated with doxorubicin.

chemotherapy ($P = .001$).

Hershman D.L. et al – JCO 2008

HNL and cardiotoxicity
The «exit» strategies

1. Design of chemotherapy regimens with reduced drug doses;
2. Addition of cardioprotectors;
3. Use of different dose schedules;
4. Development of doxorubicin analogs with an assumed improvement in the safety profile

Zinzani P.L. et al – Leukemia Lymphoma 2014

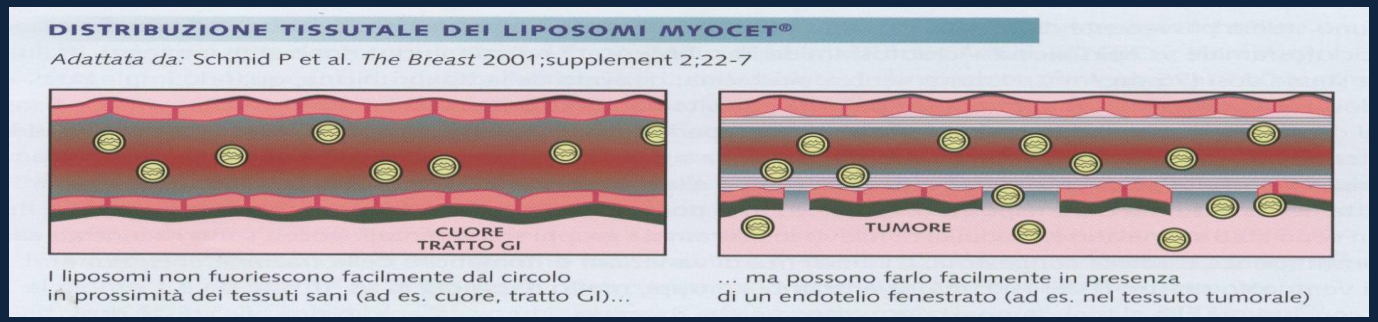
Liposomal doxorubicin in lymphoma

- Liposomes reach elevated concentrations in the reticuloendothelial system
- In respect to conventional doxorubicin:

– ⇑ greater captation in liver, spleen, lymphnodes

– ⇓ smaller captation in miocardium and GI mucosa

– ⇒ no added toxicity



Advantages of NPLD vs. Conventional Anthracyclines

	Doxorubicin	Epirubicin	NPLD
Dose regimen	60-75 mg/m²	60-120 mg/m²	60-75 mg/m²
Max. cardiac cumulative dose (5% CHF risk)	450 mg/m²	900 mg/m²	>1260 mg/m²
Common cumulative used dose in early stage	300-360 mg/m²	450 - 600 mg/m²	-

Kirti et al, JCO:3, 818-826 1985
Chan et al, J Clin Onco 17: 2341-2354, 1999
Gennari et al, Br J Cancer; 90, 962-967, 2004

Batist G et al. *J Clin Oncol* 2001; 19:1444-54
Harris L, et al. *Cancer.* 2002;94:25-36

Clinical studies

- In HIV patients
- In elderly patients
- In cardiopathic patients
- In non cardiopathic patients

Clinical studies

- In HIV patients

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pegylated Liposomal Doxorubicin, Rituximab, Cyclophosphamide, Vincristine, and Prednisone in AIDS-Related Lymphoma: AIDS Malignancy Consortium Study 047

Alexandra M. Levine, Arida Noy, Jeannette Y. Lee, Wayne Tam, Juan Carlos Ramos, David H. Henry, Samir Parekh, Erin G. Reid, Ronald Mitsuyasu, Timothy Cooley, Bruce J. Dezube, Lee Ratner, Ethel Cesarman, and Anil Tulpule

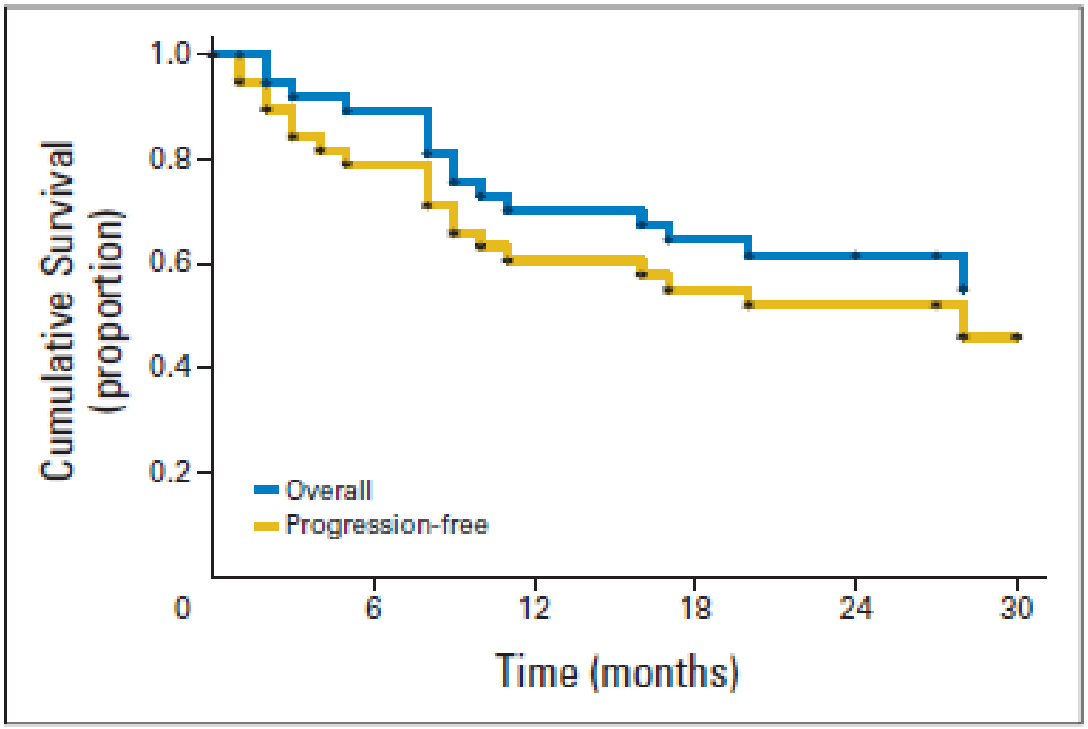


Fig 1. Overall and progression-free survival in 40 evaluable patients.

Clinical studies

- In elderly patients

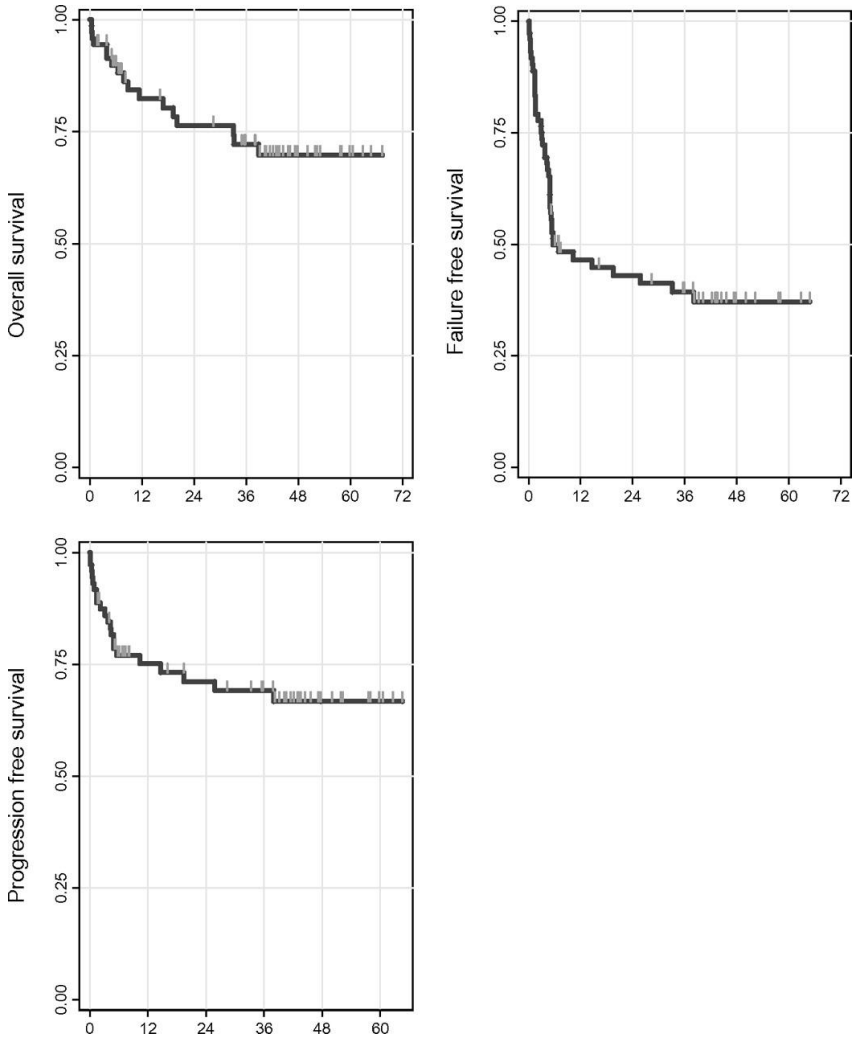
original article

Annals of Oncology
doi:10.1093/annonc/mdp544

Nonpegylated liposomal doxorubicin (Myocet™) combination (R-COMP) chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL): results from the phase II EUR018 trial

S. Luminari[1], A. Montanini[1], D. Caballero[2], S. Bologna[3], M. Notter[4], M. J. S. Dyer[5], A. Chiappella[6], J. Briones[7], M. Petrini[8], A. Barbato[9], L. Kayitalire[9] & M. Federico[1*]

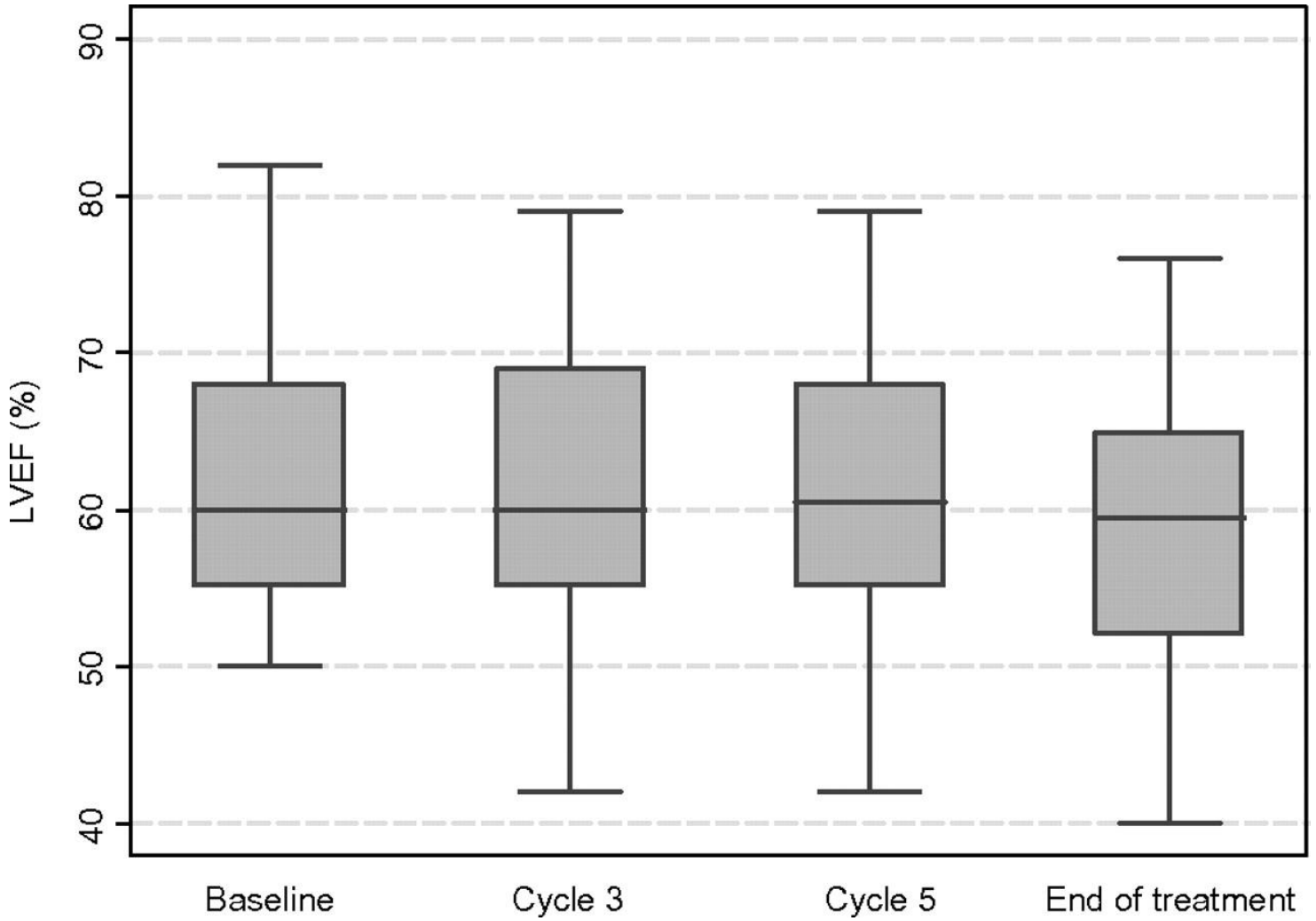
Kaplan–Meier analysis of the probability of survival.



S. Luminari et al. Ann Oncol 2010;21:1492-1499

Annals of Oncology

LVEF (%) from baseline to the end of treatment with R-COMP.

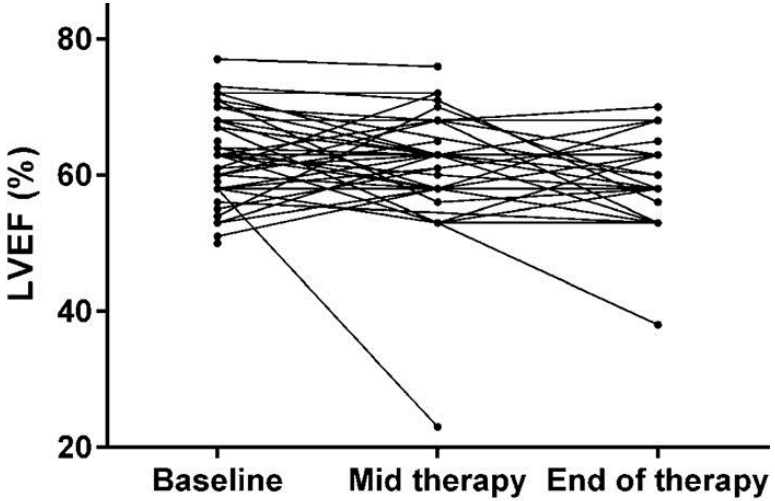


S. Luminari et al. Ann Oncol 2010;21:1492-1499

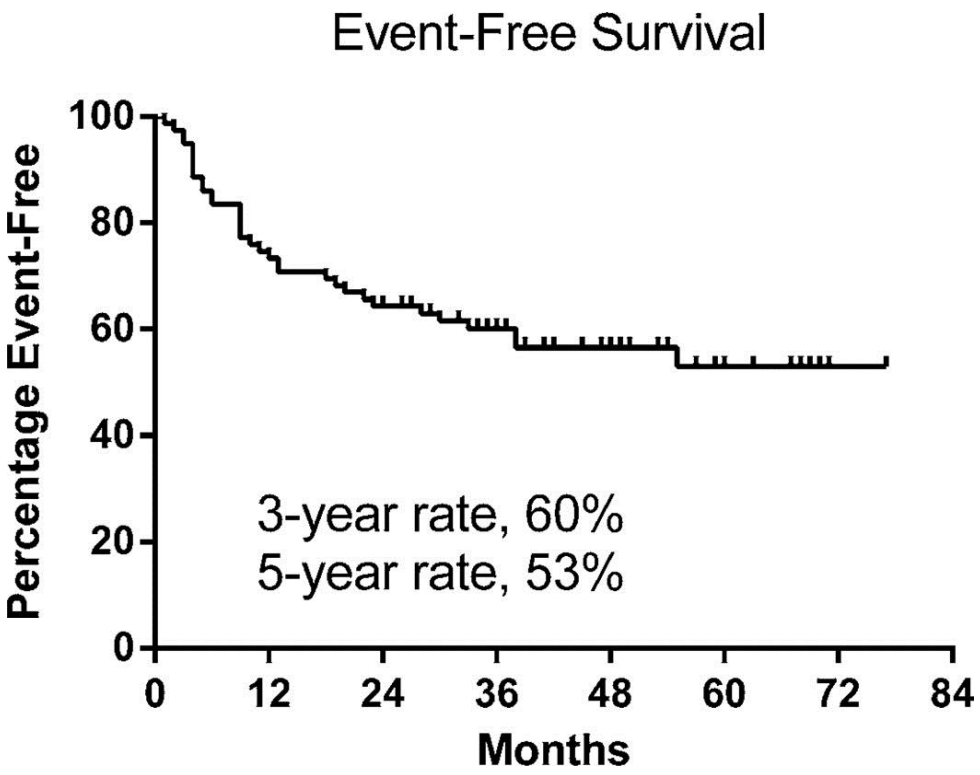
Annals of Oncology

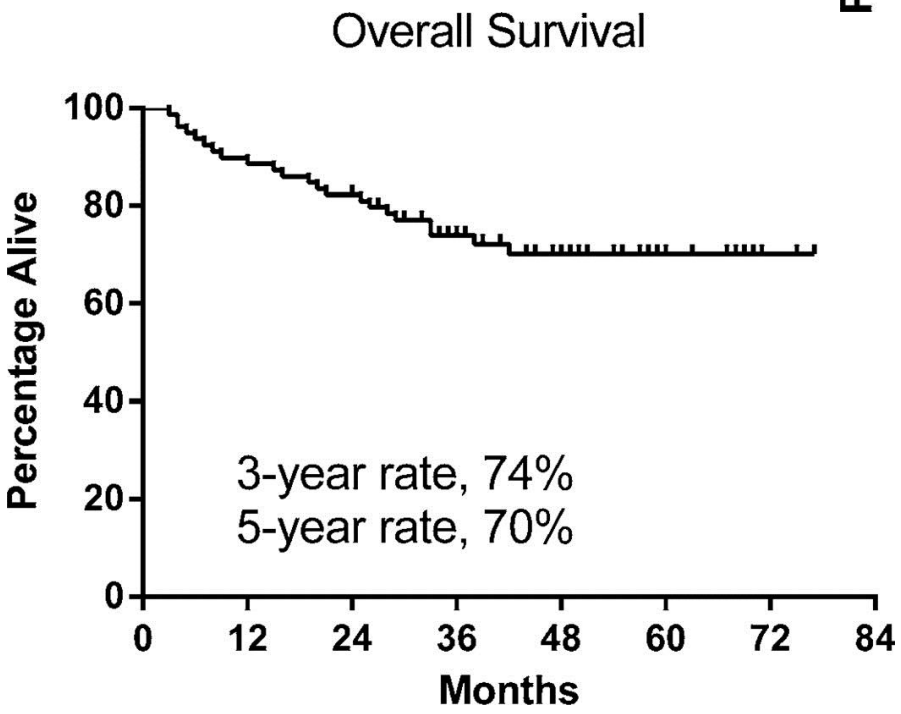
Pegylated Liposomal Doxorubicin Replacing Conventional Doxorubicin in Standard R-CHOP Chemotherapy for Elderly Patients With Diffuse Large B-Cell Lymphoma: An Open Label, Single Arm, Phase II Trial

Yasuhiro Oki,[1] Michael S. Ewer,[2] Daniel J. Lenihan,[3] Michael J. Fisch,[4] Fredrick B. Hagemeister,[1] Michelle Fanale,[1] Jorge Romaguera,[1] Barbara Pro,[1] Nathan Fowler,[1] Anas Younes,[1] Alan B. Astrow,[5] Xuelin Huang,[6] Larry W. Kwak,[1] Felipe Samaniego,[1] Peter McLaughlin,[1] Sattva S. Neelapu,[1] Michael Wang,[1] Luis E. Fayad,[1] Jean-Bernard Durand,[2] M. Alma Rodriguez[1]



	Baseline	Mid therapy	End of therapy
	n=80	n=65	n=38
Median	63%	63%	63%
Mean	63%	61%	60%
p-value (from baseline)		P=0.03	P=0.02
Grade 2 (LVEF decrease 10-19%)		6 (9%)	4 (11%)
Grade 3 (LVEF decrease 20-29%)		2 (3%)	1 (3%)
Grade 4 (LVEF <20%)		0	0
Measured by Echo	69 (86%)	61 (94%)	37 (97%)


Event-Free Survival
Percentage Event-Free
100
80
60
40
20
0
0
12
24
36
48
60
72
84
Months
3-year rate, 60%
5-year rate, 53%


Overall Survival
Percentage Alive
100
80
60
40
20
0
0
12
24
36
48
60
72
84
Months
3-year rate, 74%
5-year rate, 70%

Clinical studies

- In cardiopathic patients

Hematological Oncology
Hematol Oncol 2007; **25**: 198–203
Published online 25 July 2007 in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/hon.827

Research Article

Liposome-encapsulated doxorubicin in combination with cyclophosphamide, vincristine, prednisone and rituximab in patients with lymphoma and concurrent cardiac diseases or pre-treated with anthracyclines

Luigi Rigacci*, Silvia Mappa, Luca Nassi, Renato Alterini, Valentina Carrai, Franco Bernardi and Alberto Bosi
Department of Hematology, Careggi Hospital and University of Florence, Italy

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.

Leukemia & Lymphoma, June 2008; 49(6): 1081 – 1086

informa
healthcare

ORIGINAL ARTICLE: CLINICAL

R-COMP 21 for frail elderly patients with aggressive B-cell non-Hodgkin lymphoma: A pilot study

GIUSEPPE VISANI[1], FELICETTO FERRARA[2], FRANCESCO ALESIANI[3], SONIA RONCONI[4], MASSIMO CATARINI[5], FRANCESCA D'ADAMO[1], BARBARA GUIDUCCI[1], DANIELE BERNARDI[6], SARA BARULLI[1], PIERPAOLO PICCALUGA[7], MARCO ROCCHI[8], & ALESSANDRO ISIDORI[1]

[1]*Hematology and Hematopoietic Stem Cell Transplant Center, San Salvatore Hospital, Pesaro, Italy,* [2]*Division of Hematology and Stem Cell Transplantation Unit, Cardarelli Hospital, Naples, Italy,* [3]*Onco-Hematology Unit, Bartolomeo Eustacchio Hospital, San Severino Marche, Italy,* [4]*Division of Oncology and Diagnostics, Ospedale G.B. Morgagni, Forli, Italy,* [5]*Department of Internal Medicine, General Hospital of Macerata, Italy,* [6]*Division of Medical Oncology, Civil Hospital, Vittorio Veneto, Italy,* [7]*Institute of Hematology and Medical Oncology, "L. & A. Seràgnoli", University of Bologna, Bologna, Italy, and* [8]*Institute of Biomathematics, Urbino University, Urbino, Italy*

(Received 21 November 2007; accepted 7 March 2008)

Table II. List of comorbidities.

Diabetes mellitus	7
Hypertension controlled by medication	10
Chronic obstructive bronchopneumonia	4
Myocardiopathy	1
Coronary heart disease	3
Atrial fibrillation or other cardiac arrhythmias	3
Congestive heart failure	2
Peptic ulcer	3
Myasthenia gravis	1
Rheumatic polymyalgia	1
Antiphospholipid syndrome	1

Of the remaining 19 patients, two presented a congestive heart failure (NYHA 3) after 1 and 3 cycles of R-COMP, respectively, with a decrease of 20% of the left ventricular ejection fraction (LVEF). They partially recovered after medical therapy and were shifted to receive an anthracycline-free regimen while in CR after R-COMP. There was no significant difference between LVEF at baseline, after the third cycle, and at the end of study in the residual 17 patients.

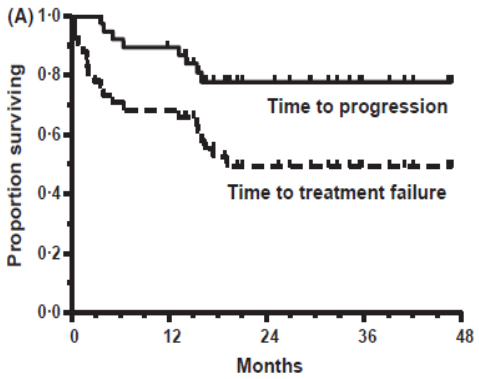
bjh research paper

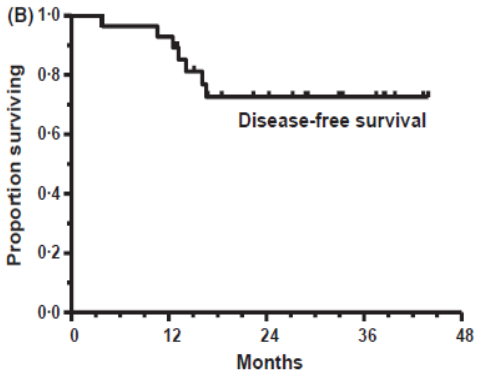
Biweekly rituximab, cyclophosphamide, vincristine, non-pegylated liposome-encapsulated doxorubicin and prednisone (R-COMP-14) in elderly patients with poor-risk diffuse large B-cell lymphoma and moderate to high 'life threat' impact cardiopathy

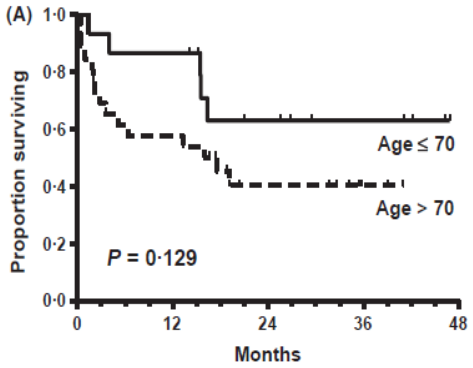
Gaetano Corazzelli,[1] Ferdinando Frigeri,[1] Manuela Arcamone,[1] Anna Lucania,[2] Maria RosariaVilla,[2] Emanuela Morelli,[1] Alfonso Amore,[3] Gaetana Capobianco,[1] Antonietta Caronna,[4] Cristina Becchimanzi,[1] Francesco Volzone,[1] Gianpaolo Marcacci,[1] Filippo Russo,[1] Rosaria De Filippi,[1,5] Lucia Mastrullo[2] and Antonio Pinto[1]

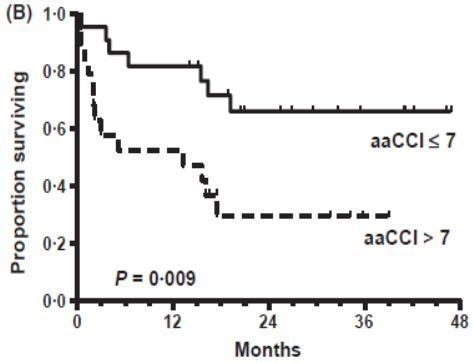
 British Journal of Haematology, **154,** 579–589

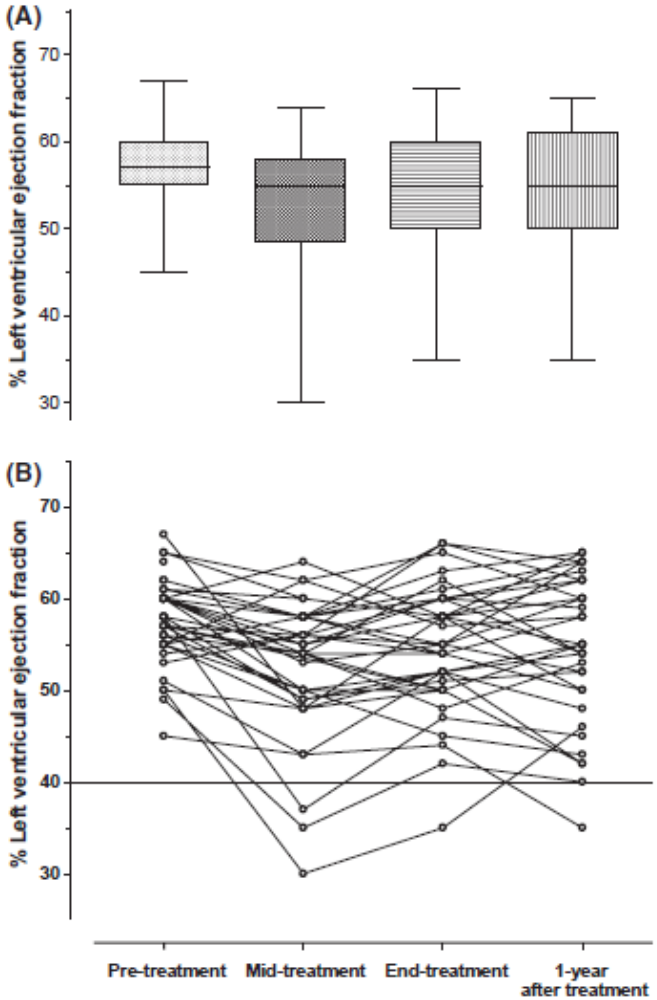
First published online 28 June 2011
doi:10.1111/j.1365-2141.2011.08786.x


(A)
Proportion surviving
Time to progression
Time to treatment failure
Months


(B)
Proportion surviving
Disease-free survival
Months


(A)
Proportion surviving
Age ≤ 70
Age > 70
P = 0·129
Months


(B)
Proportion surviving
aaCCI ≤ 7
aaCCI > 7
P = 0·009
Months


(A)
% Left ventricular ejection fraction
(B)
% Left ventricular ejection fraction
Pre-treatment
Mid-treatment
End-treatment
1-year after treatment

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 2 Preexisting Cardiac Diseases

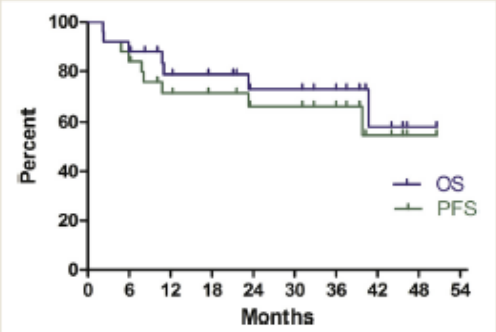
Variable	n
Heart Failure	14
Coronary Heart Disease/Ischemic Cardiopathy	10
Cardiac Arrhythmia	10
History of Anthracyclines and Breast Radiation	2
Dilated Cardiomyopathy	2
Cerebral Stroke/Transient Ischemic Attack	2
Pulmonary Hypertension With Reduced RVEF	1
Aortic Valve Replacement	1
Distinct LV Hypertrophy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

Abbreviations: LV = left ventricular; RVEF = right ventricular ejection fraction.

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 1 Progression-Free (PFS) and Overall Survival (OS)



HEART01

MULTICENTRE PHASE II STUDY WITH RITUXIMAB, CYCLOPHOSPHAMIDE, NPL-DOXORUBICIN, VINCRISTINE, PREDNISONE (R-COMP) IN CARDIOPATHIC PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

EUDRACT NUMBER 2009-012143-42

PI: Michele Spina (Aviano)

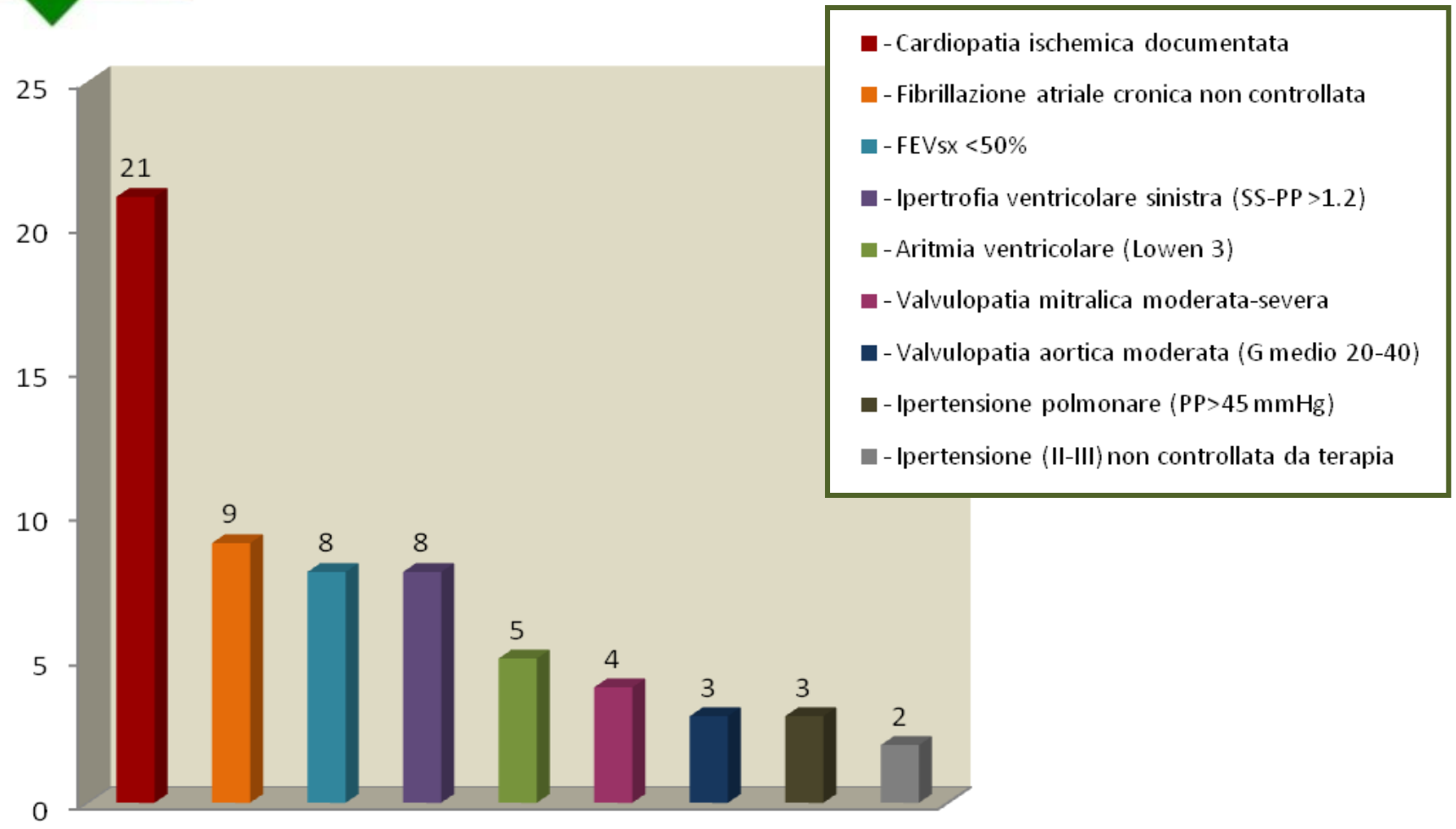
A phase II multicentre study with R-COMP in cardiopathic pts with DLBCL

- **Histologically proven CD20 + DLBCL**
- **Clinical stages I – IV**
- **Age ≥ 18 years**
- **Previously untreated patients**
- **“Cardiopathy”(doxorubicin not allowed)**

DEFINITION OF CARDIOPATHY

LVEF < 50%
Left Ventricular Hypertrophy (PP-SS>1.2)
Moderate/severe uncontrolled hypertension
Ischemic cardiopathy
Ventricular arrhythmias (Lown 3)
Chronic atrial fibrillation
Pulmonary Hypertension (PP > 45 mmHg)
Moderate/severe mitral valvulopathy
Moderate aortic valvulopathy (G 20-40)

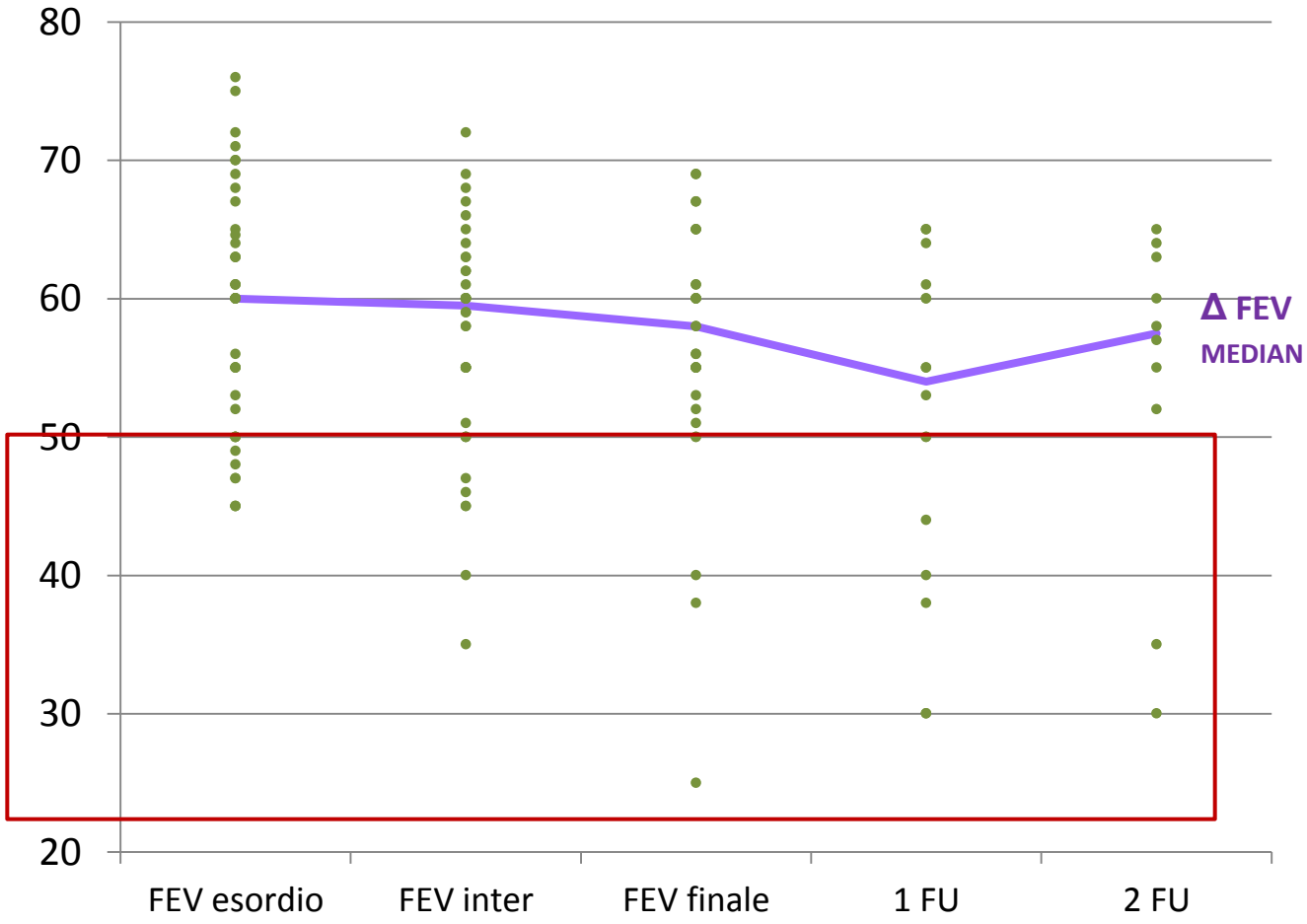
CARDIAC DISEASES (N=63*)



* Patients with two or more cardiopathies = 8 cases

LVEF

Baseline	Intermediate	Final	1FU	2FU
49	38	34	21	13



LVEF ≤ 50%

CARDIAC EVENTS

	N (%)
LVEF reduction	2 (33%)
Troponine increase	2 (33%)
Hearth failure	1 (17%)
Cardiac arrest	1 (17%)

OUTCOME (N=51)

	N	%
Alive	**32**	**63**
Dead	**19**	**37**

Causes of death	N
Tossicity	**6**
Sepsis	2
Haemorrhage	1
Cardiac arrest	1
Heart failure	1
Renal failure	1
NHL	**9**
Secondary tumor	**1**
COPD	**1**
Unknown	**2**
Total	**19**

3-yr OS: 54% (CI95% 34-70%)
3-yr PFS: 40% (CI95% 25-54%)

Conclusions

The substitution of conventional doxorubicin with non pegilated liposomal doxorubicin in the R-CHOP regimen is a safe and active option for patients with DLBCL presenting with concomitant moderate/severe cardiac disorders.

Clinical studies

- In non cardiopathic patients

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journal homepage: www.ejcancer.com

Clinical Trial

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]

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[b] *Medical University Vienna, Department of Medicine I, Hematology and Hemostaseology, Austria*
[c] *Barmherzige Schwestern Hospital Linz, Department of Medical Oncology, Hematology and Gastroenterology, Austria*
[d] *University of Innsbruck, Internal Medicine V: Hematology–Oncology, Austria*
[e] *Hanusch Hospital Vienna, Department of Medicine III: Hematology Oncology, Austria*
[f] *LKH Feldkirch, Department of Internal Medicine, Austria*
[g] *LKH Steyr, Department of Internal Medicine II, Austria*
[h] *Klinikum Wels-Grieskirchen, Department of Internal Medicine IV, Austria*
[i] *Elisabethinen Hospital Linz, Department of Internal Medicine I, Austria*
[j] *TILAK, Clinical Epidemiology, Austria*
[k] *AKH Linz, Department of Internal Medicine I, Austria*
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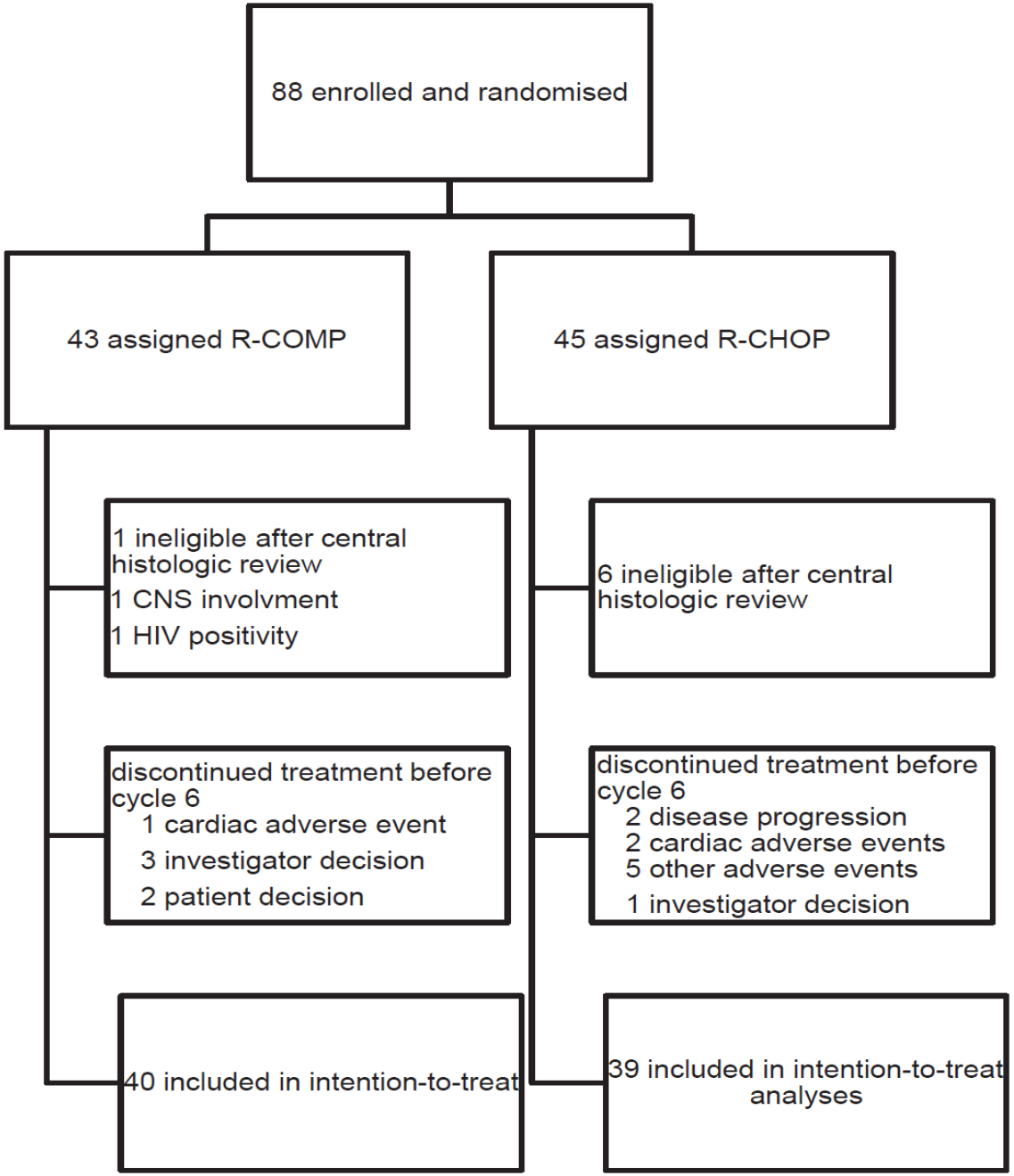
88 enrolled and randomised
43 assigned R-COMP
45 assigned R-CHOP
1 ineligible after central histologic review
1 CNS involvment
1 HIV positivity
6 ineligible after central histologic review
discontinued treatment before cycle 6
1 cardiac adverse event
3 investigator decision
2 patient decision
discontinued treatment before cycle 6
2 disease progression
2 cardiac adverse events
5 other adverse events
1 investigator decision
40 included in intention-to-treat
39 included in intention-to-treat analyses

Cardiotoxicity

LVEF values at the beginning of treatment cycles and 4–8 weeks after the last cycle.

	R-COMP			R-CHOP			
	n	mean %	SD %	n	mean %	SD %	*P*-value
Pre-treatment	40	64.7	6.8	38	62.5	7.3	0.17
Cycle 2	33	63.9	7.2	29	61.9	7.8	0.30
Cycle 3	28	63.1	6.9	27	64.4	7.6	0.52
Cycle 4	31	64.1	6.1	24	61.9	6.3	0.20
Cycle 5	28	63.6	5.4	24	63	6.2	0.79
Cycle 6	24	63.8	5.9	24	62.8	6.9	0.58
End of treatment	34	61.6	6.2	30	59.9	10.2	0.42
All values	178	63.3	6.3	158	62.2	7.8	0.167
LVEF <50%	10				31		<0.001

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Non-cardiac toxicities

Toxicity	R-CHOP	R-COMP	P value
SAEs	40%	26%	0.029
Infections	28%	15%	0.012
Stomatitis	46%	15%	0.022
Serum creatinine level >N	30%	8%	0.021

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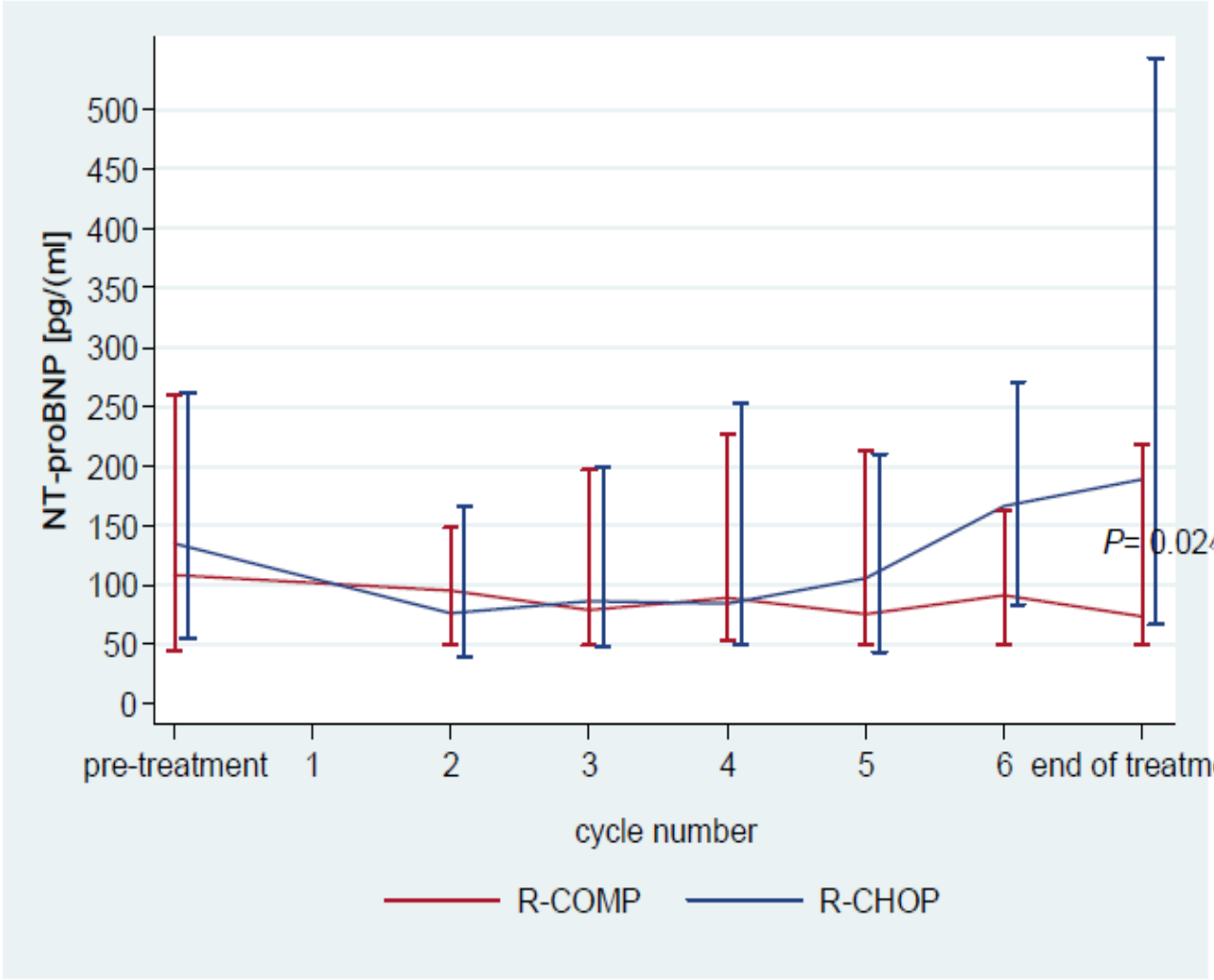
Median NT-proBNP levels during therapy



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The overall response in the R-COMP arm was 39/40 (97.5%), with complete remissions in 30 patients (75%). The overall response in the R-CHOP arm was 32/39 (82%), with complete remissions in 27 patients (69.2%) ($P = 0.062$). The three patients who experienced disease progression during treatment were in the R-CHOP arm. Five patients were not evaluable in regard of response.

Median follow-up: 52 months (range 4-62 months)

No difference in OS, EFS, PFS

Fridrik et al. EJC 2016

CONCLUSIONS

Primary end-point – a difference in the mean LVEF of all measurement after each cycle between the arms – NOT ACHIEVED

However, cardiac safety warnings more frequent in R-CHOP arm

LVEF every 3 weeks doesn't improve the detection of anthracycline cardiotoxicity

NT-proBNP more convenient (large prospective trials are needed)

Long term cardiotoxicity and the efficacy of NPL-doxorubicin should be studied further in order to clarify its role in patients without risk factors

Fridrik et al. EJC 2016

EFFICACY

Clinical Oncology 26 (2014) 648–652

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Short Report

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 *

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† Department of Medical Oncology, University of Messina, Messina, Italy
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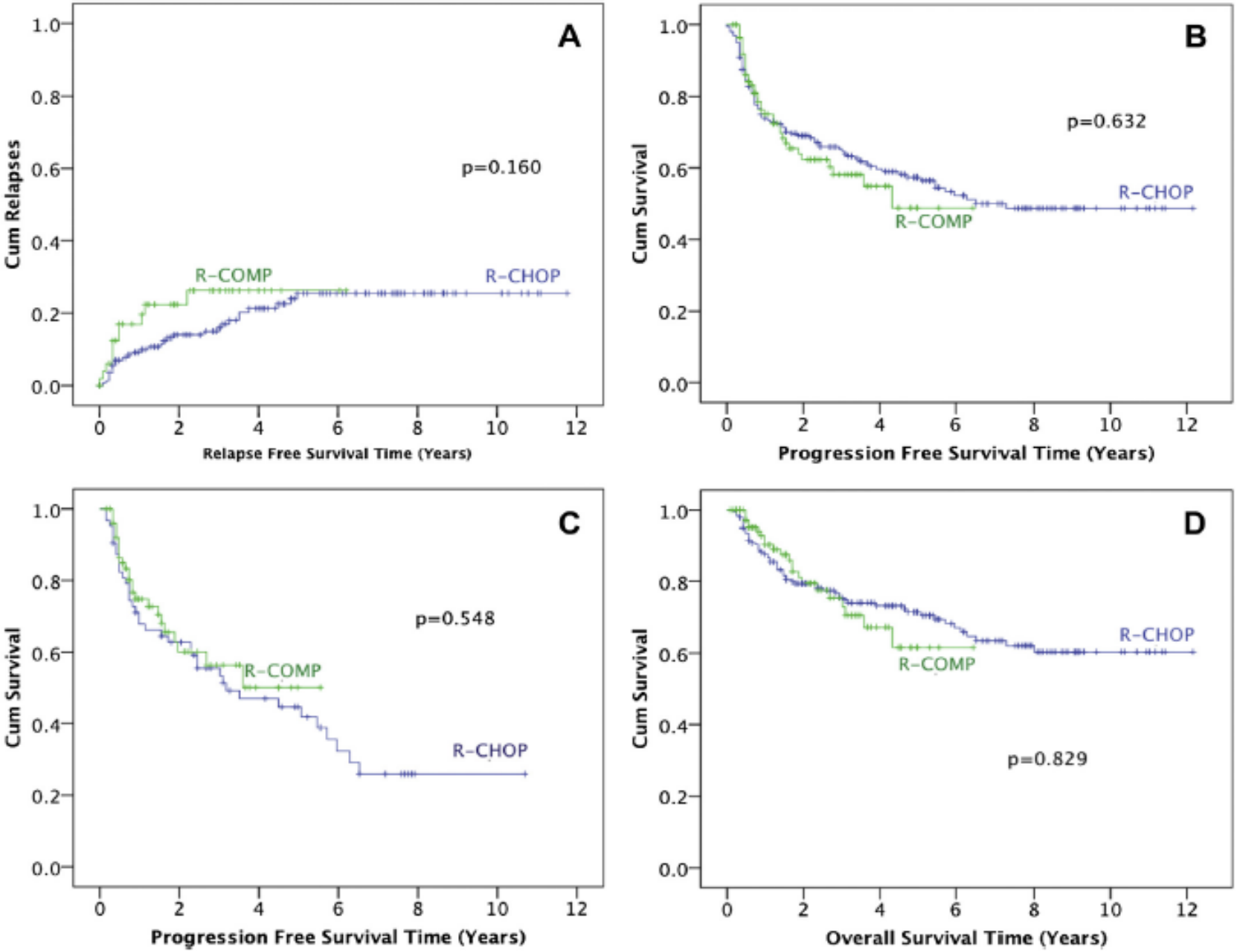
Received 26 February 2014; received in revised form 28 April 2014; accepted 29 April 2014

We retrospectively assessed 364 consecutive DLBCL patients who underwent either R-CHOP (218; 60%) or R-COMP (146; 40%) with or without radiotherapy as first-line


A
Cum Relapses
p=0.160
R-COMP
R-CHOP
Relapse Free Survival Time (Years)
B
Cum Survival
p=0.632
R-CHOP
R-COMP
Progression Free Survival Time (Years)
C
Cum Survival
p=0.548
R-COMP
R-CHOP
Progression Free Survival Time (Years)
D
Cum Survival
R-CHOP
R-COMP
p=0.829
Overall Survival Time (Years)

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In conclusion, R-COMP is a valid treatment alternative for DLBCL patients, who are at high risk of suffering from treatment-related toxicity. For the first time, we proved that both regimens induce a high and comparable number of complete remissions and both are able to cure patients with aggressive lymphoma. However, prospective trials are needed to confirm our data.

Meta-analysis of clinical and preclinical studies comparing the anticancer efficacy of liposomal versus conventional non-liposomal doxorubicin

Grant H. Petersen, Saeed K. Alzghari, Wayne Chee, Sana S. Sankari, Ninh M. La-Beck

PII: S0168-3659(16)30241-3
DOI: doi: 10.1016/j.jconrel.2016.04.028
Reference: COREL 8231

To appear in: *Journal of Controlled Release*

Received date: 11 February 2016
Revised date: 12 April 2016
Accepted date: 18 April 2016

Figure 3. Objective response in patients treated with liposomal versus conventional chemotherapy formulations.

Study (Year)	Odds Ratio (CI)	P value	Drug
Judson, et al. (2001)	1.11 (0.28; 4.4)	0.8819	Anthracycline
Dimopoulos, et al. (2003)	1.1 (0.74; 1.63)	0.6361	Anthracycline
O'Brien, et al. (2004)	0.79 (0.36; 1.72)	0.5517	Anthracycline
Rifkin, et al. (2006)	1.14 (0.68; 1.92)	0.6207	Anthracycline
Hunault-Berger, et al. (2011)	0.28 (0.13; 0.6)	0.0011	Anthracycline
Batist, et al. (2001)	1.02 (0.67; 1.55)	0.9257	Anthracycline
Harris, et al. (2002)	1 (0.56; 1.79)	1	Anthracycline
Latagliata, et al. (2008)	0.94 (0.64; 1.39)	0.7571	Anthracycline
Jehn, et al. (2008)	0.41 (0.12; 1.42)	0.1584	Cisplatin
Kosmas, et al. (2009)	2.01 (0.94; 4.31)	0.0732	Cisplatin
Mylonakis, et al. (2010)	1.19 (0.47; 3)	0.7125	Cisplatin
Stathopoulos, et al. (2010)	1.67 (1.07; 2.6)	0.0236	Cisplatin
Yang, et al. (2012)	1.11 (0.46; 2.67)	0.8161	Paclitaxel
Roy, et al. (2013)	2.16 (0.51; 9.16)	0.2963	Irinotecan
Overall	**1.03 (0.82; 1.3)**	**0.7732**	

$I^2 = 42.8\%$, $Q = 22.7$, $P = 0.0451$

Subgroups:

Anthracyclines	0.94 (0.78; 1.14)
Cisplatin	1.49 (1.06; 2.09)

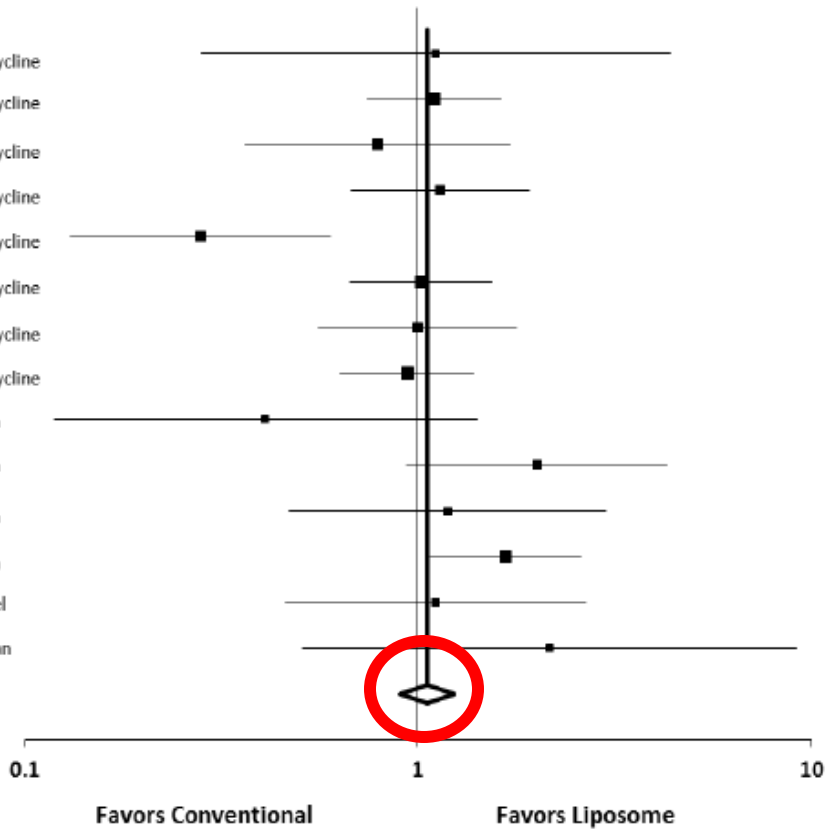


Figure 4. Overall survival in patients treated with liposomal versus conventional chemotherapy formulations.

Study (Year)	Hazard Ratio (CI)	P value	Drug
Judson, et al. (2001)	0.64 (0.38; 1.1)	0.1062	Anthracycline
Dimopoulos, et al. (2003)	1.36 (0.85; 2.17)	0.1952	Anthracycline
O'Brien, et al. (2004)	0.94 (0.74; 1.19)	0.6097	Anthracycline
Rifkin, et al. (2006)	0.69 (0.31; 1.52)	0.3612	Anthracycline
Hunault-Berger, et al. (2011)	0.97 (0.54; 1.77)	0.9298	Anthracycline
Batist, et al. (2001)	1.04 (0.77; 1.41)	0.8017	Anthracycline
Harris, et al. (2002)	1.32 (0.97; 1.8)	0.0807	Anthracycline
Latagliata, et al. (2008)	0.95 (0.72; 1.26)	0.7459	Anthracycline
Mylonakis, et al. (2010)	0.92 (0.54; 1.56)	0.7462	Cisplatin
Stathopoulos, et al. (2010)	1.21 (0.87; 1.68)	0.2669	Cisplatin
Yang, et al. (2012)	1.27 (0.81; 1.97)	0.2949	Paclitaxel
Roy, et al. (2013)	1.32 (0.79; 2.21)	0.2816	Irinotecan
Overall	**1.05 (0.95; 1.17)**	**0.3408**	
$I^2 = 2.6\%$, $Q = 11.3$, $P = 0.4187$			
Subgroup:			
Anthracyclines	1.01 (0.89; 1.15)		

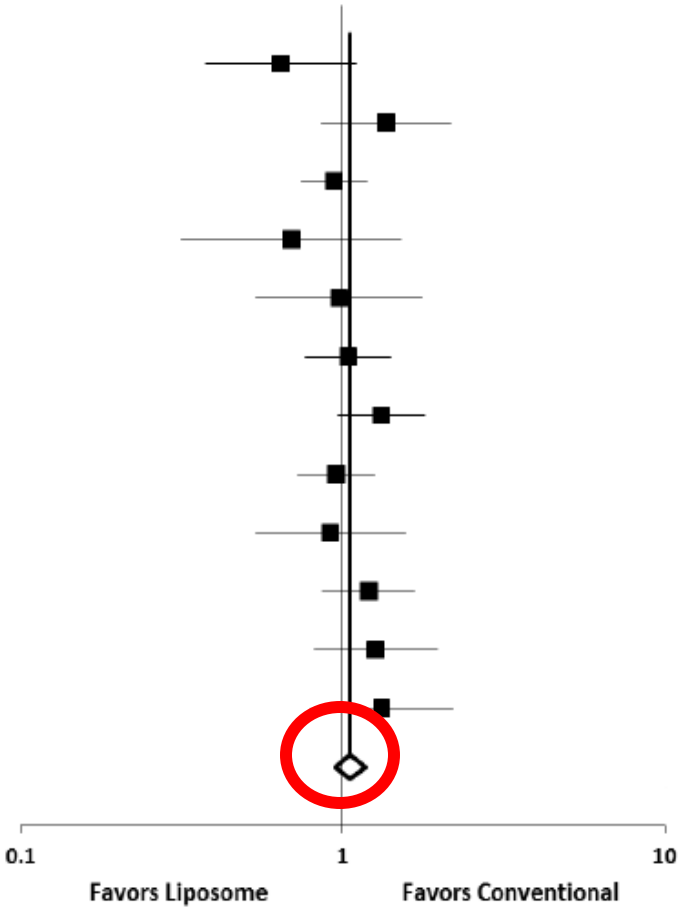
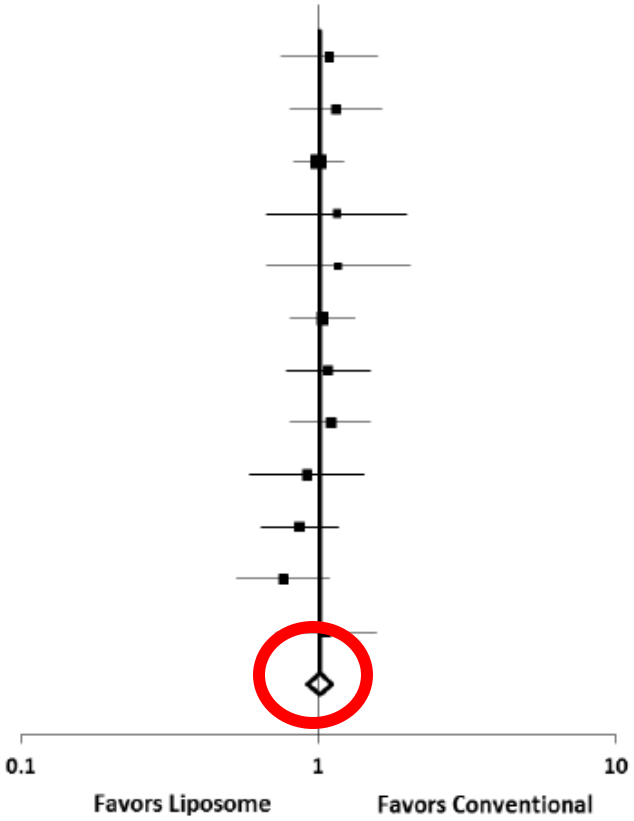


Figure 5. Progression free survival in patients treated with liposomal versus conventional chemotherapy formulations.

Study (Year)	Hazard Ratio (CI)	P value	Drug
Judson, et al. (2001)	1.09 (0.75; 1.58)	0.6578	Anthracycline
Dimopoulos, et al. (2003)	1.15 (0.8; 1.64)	0.4523	Anthracycline
O'Brien, et al. (2004)	1 (0.82; 1.22)	1	Anthracycline
Rifkin, et al. (2006)	1.15 (0.67; 1.98)	0.6070	Anthracycline
Hunault-Berger, et al. (2011)	1.16 (0.67; 2.03)	0.5948	Anthracycline
Batist, et al. (2001)	1.03 (0.8; 1.33)	0.8197	Anthracycline
Harris, et al. (2002)	1.08 (0.78; 1.5)	0.6448	Anthracycline
Latagliata, et al. (2008)	1.1 (0.8; 1.5)	0.5518	Anthracycline
Mylonakis, et al. (2010)	0.91 (0.59; 1.42)	0.6817	Cisplatin
Stathopoulos, et al. (2010)	0.86 (0.64; 1.16)	0.3339	Cisplatin
Yang, et al. (2012)	0.76 (0.53; 1.09)	0.1355	Paclitaxel
Roy, et al. (2013)	1.06 (0.71; 1.57)	0.7794	Irinotecan
Overall	**1.01 (0.92; 1.11)**	**0.8646**	
$I^2 = 0\%$, $Q = 5.3$, $P = 0.9154$			
Subgroup:			
Anthracyclines	1.06 (0.95; 1.18)		



CONCLUSIONS

- **No RCT**
- **Safe in cardiopathic or at risk patients**
- **No prospective trials evaluating the efficacy**
- **Not useful in non cardiopathic patients**
- **No data on survivors**
- **Use of biomarkers vs LVEF**