SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

58° Congresso Nazionale SIGG
Torino 27-30 novembre 2013

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

Il linfoma non Hodgkin diffuso a grandi cellule "dell'anziano-anziano"

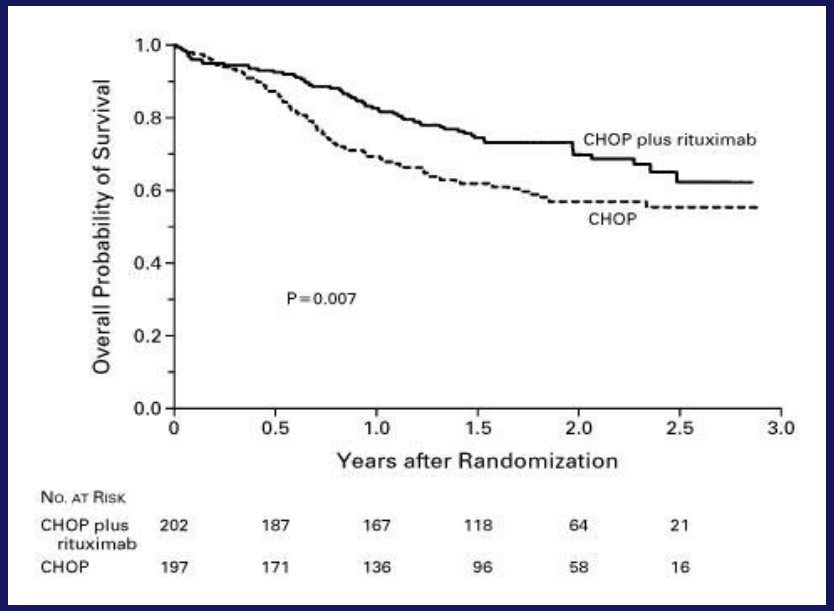
Michele Spina

Oncologia Medica A

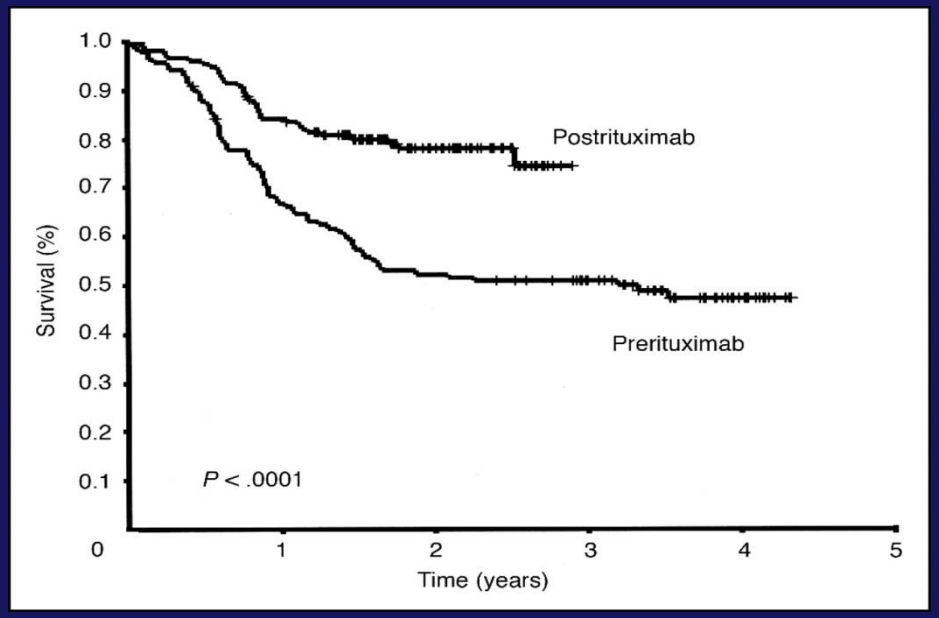
Centro di Riferimento Oncologico - Aviano

NHL in elderly patients

- One third of NHL diagnosed in patients aged 70 years or more
- Age is the most important prognostic factor influencing OS
- A significant increase of NHL in elderly in the next 20-25 years.
- Aggressive NHL more frequent in elderly.



Coiffier B et al. N Engl J Med 2002;346:235-242



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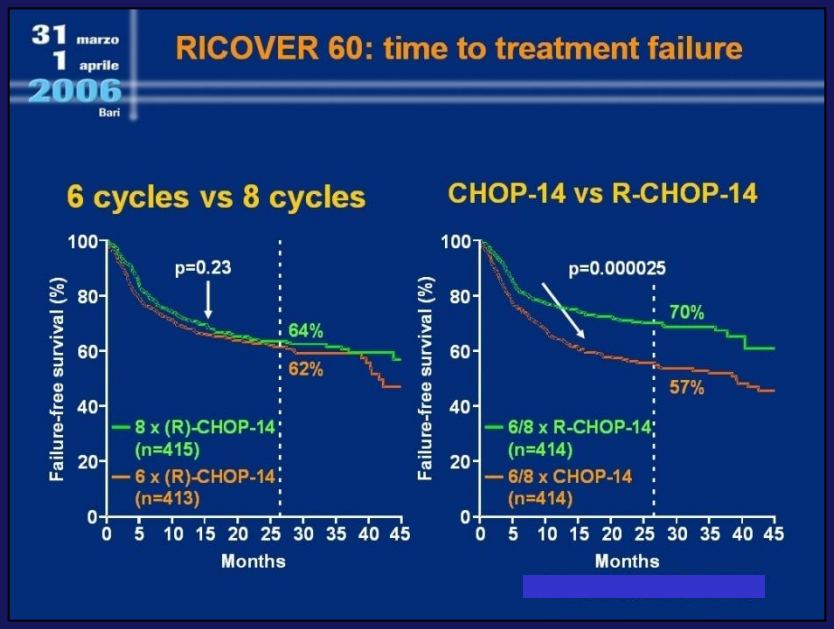

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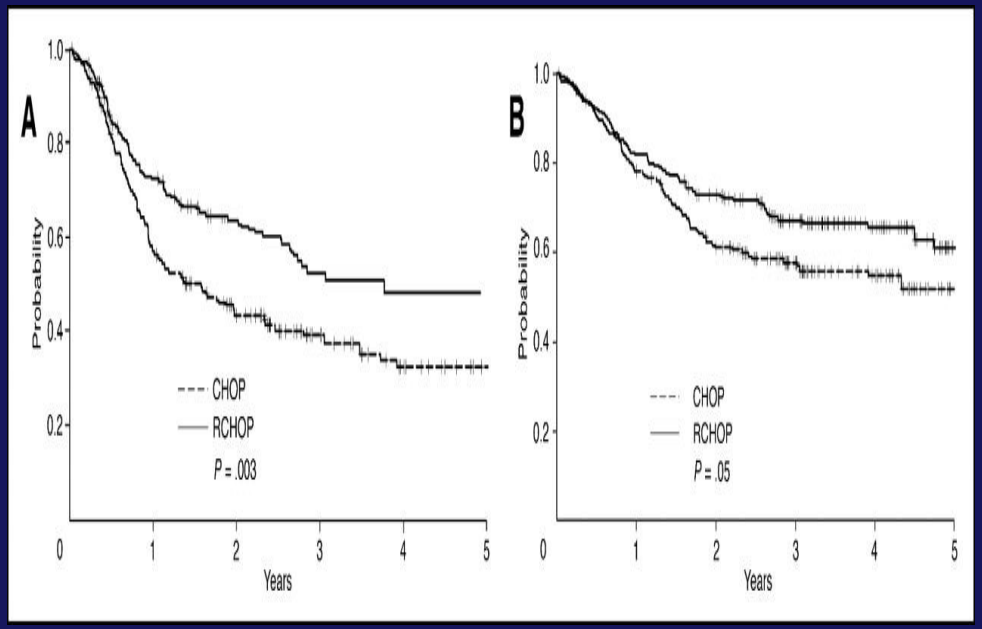


Habermann TM et al. J Clin Oncol; 24:3121-3127 2006

Valutazione geriatrica multidimensionale (VGM)

- Activity of Daily Living (ADL)
- Cumulative Illness Rating Scale Geriatric (CIRS - G)
- Sindromi geriatriche
- Mini Mental State Examination (MMSE)
- Geriatric Depression Scale (GDS)

Instrument	FIT	UNFIT	FRAIL
ADL	6	5*	≤4*
IADL	8	7- 6*	≤5*
CIRS	0 score = 3-4 ≤ 5 score = 2	0 score = 3-4 6-8 score = 2	1 score =3-4 o > 8 score =2
Age		≥ 80 fit	≥80 unfit

* # of residual functions

Prospective collection

Clinical characteristics and outcome of elderly patients (≥ 70 years) with DLBCL stratified according to CGA

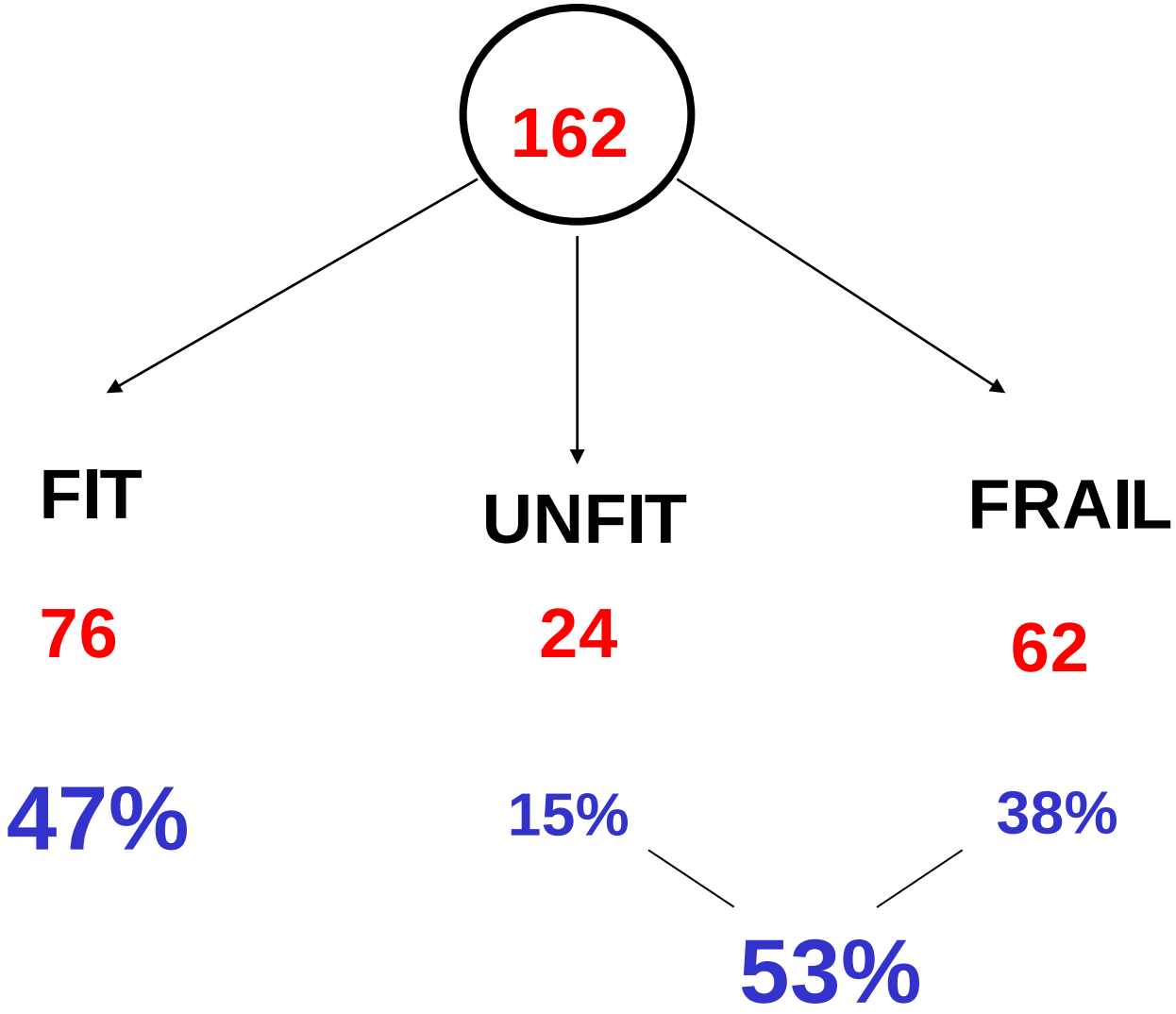
Pazienti consecutivi affetti da LNH aggressivo

Dall' 1/9/2009 al 31/08/2010 in 12 centri

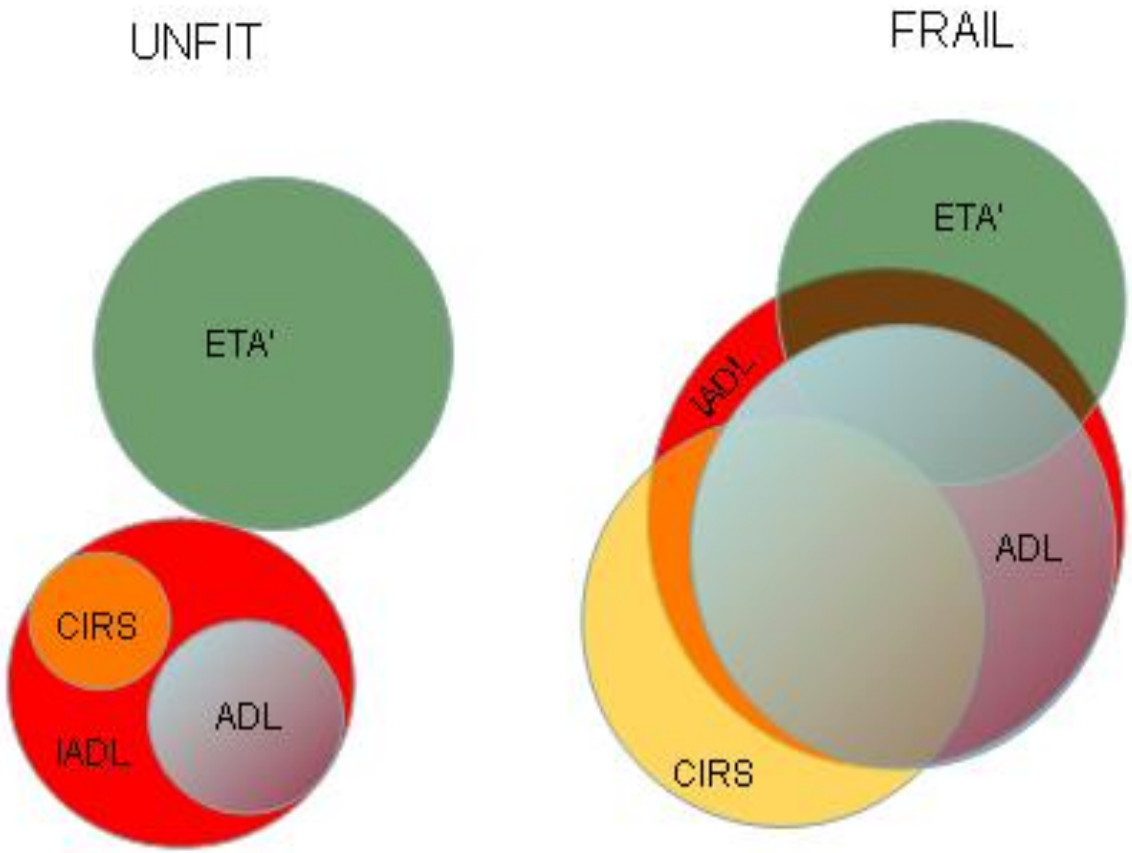
Alessandria	(Salvi)	15
Aviano	(Spina)	10
Brescia	(Tucci)	35
Cagliari	(Cabras)	15
Firenze	(Rigacci)	22
Messina	(Brugiatelli)	4
Padova	(Aversa)	8
Palermo	(Mancuso)	7
Reggio Calabria	(Stelitano)	13
Roma	(Martelli)	29
Siena	(Fabbri)	10
Torino	(Vitolo)	17
Totale		**185**

162 DLBCL

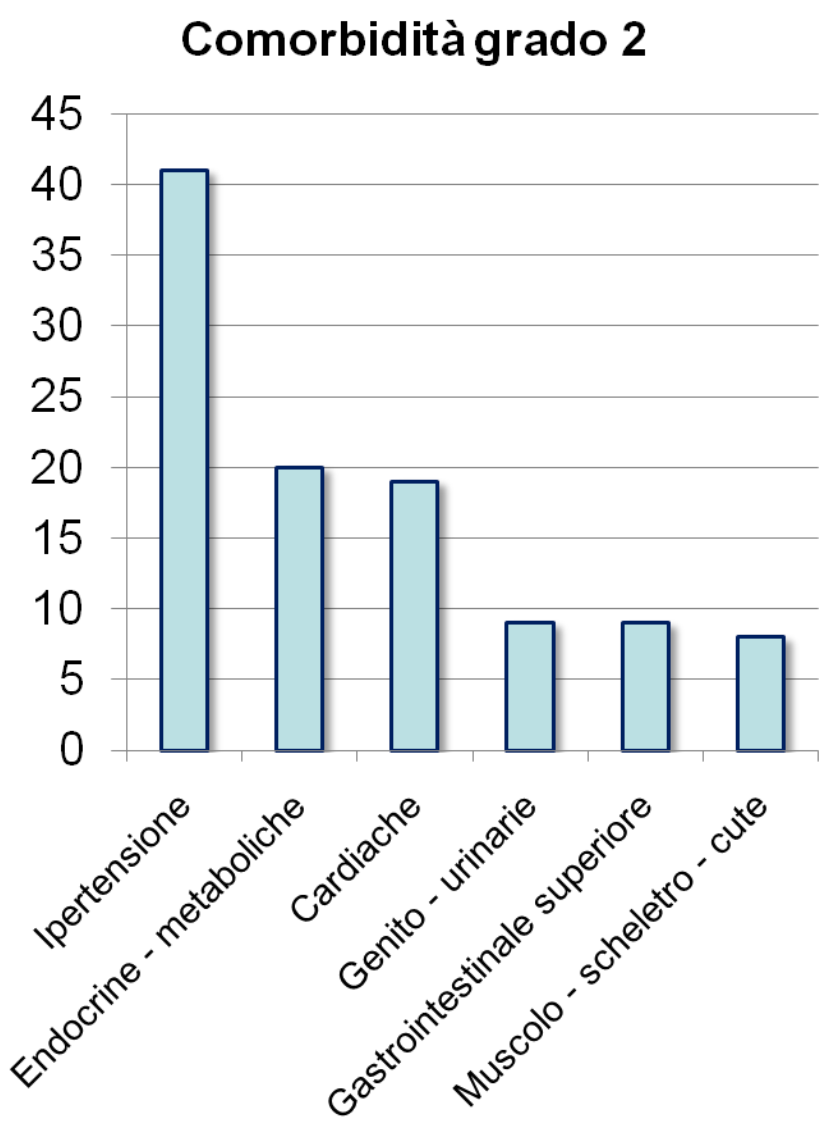
Valutazione Geriatrica Multidimensionale

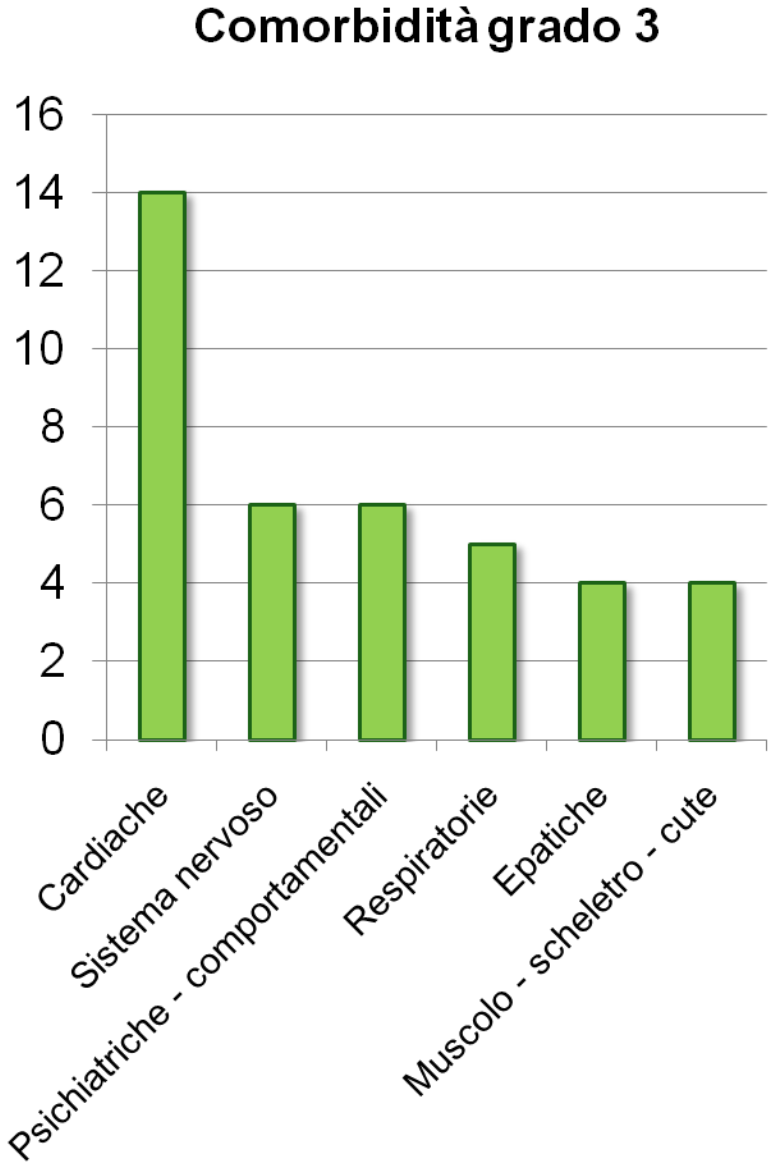


Cause di fragilità

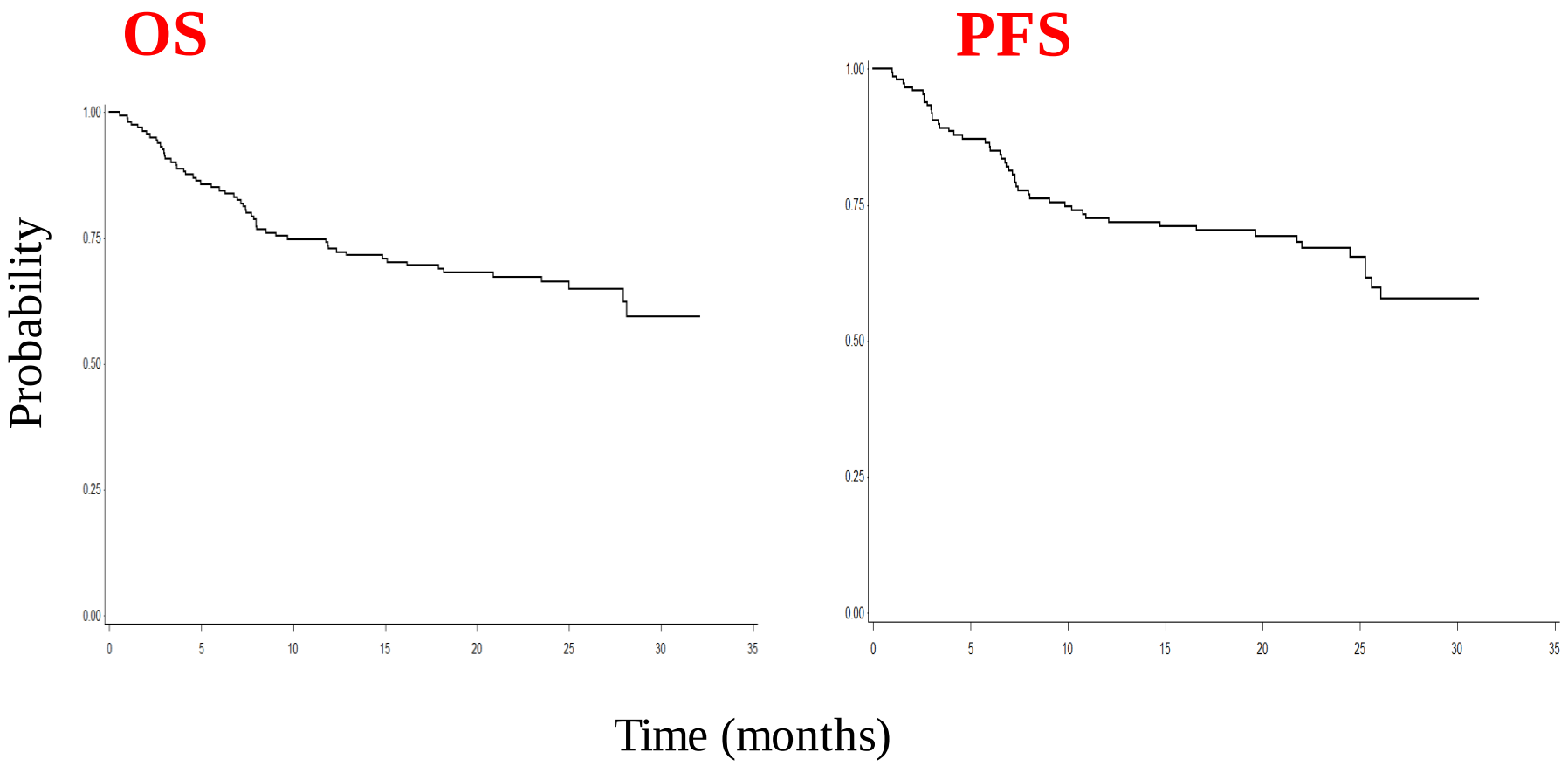


Comorbidità





OS and PFS of 162 elderly patients

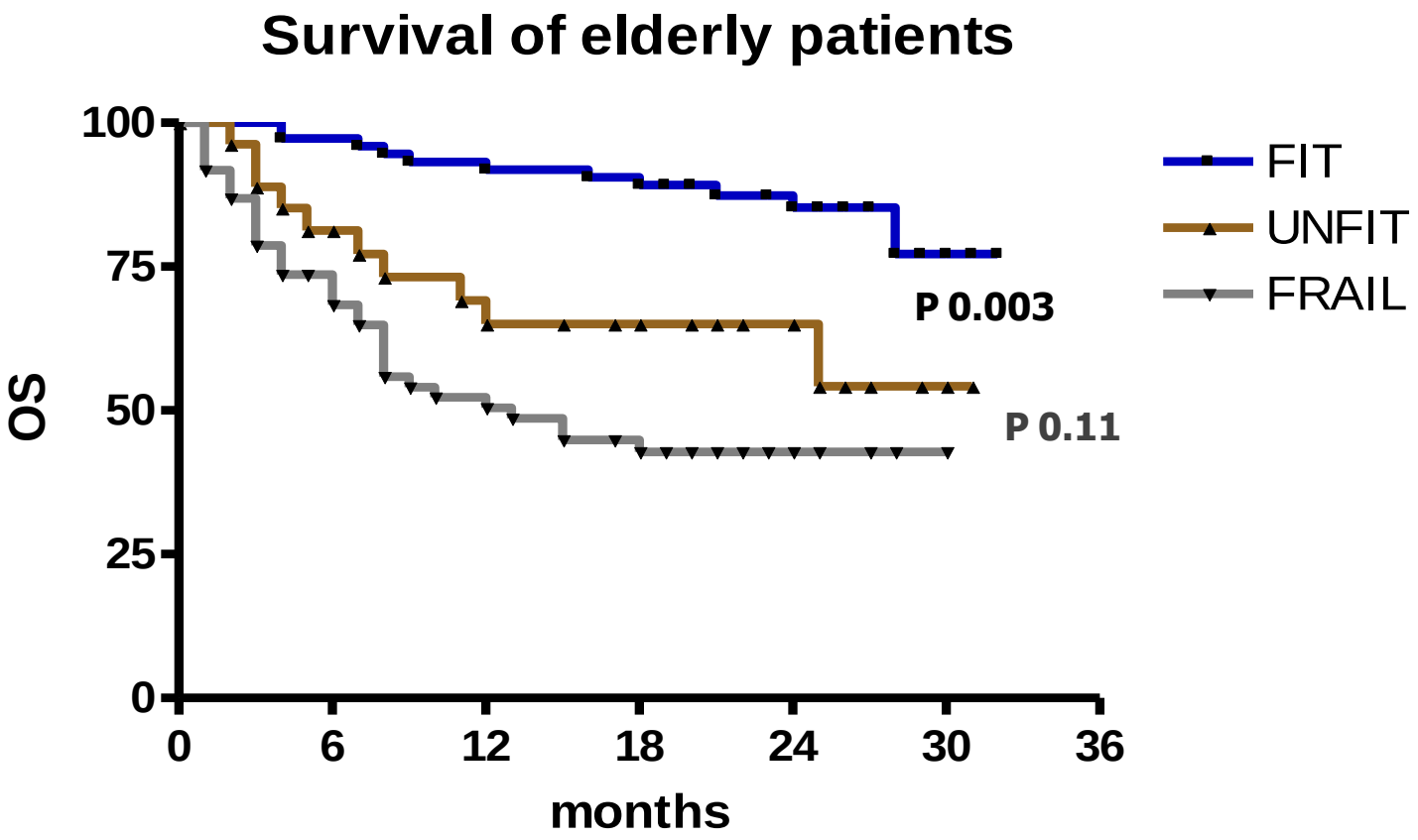


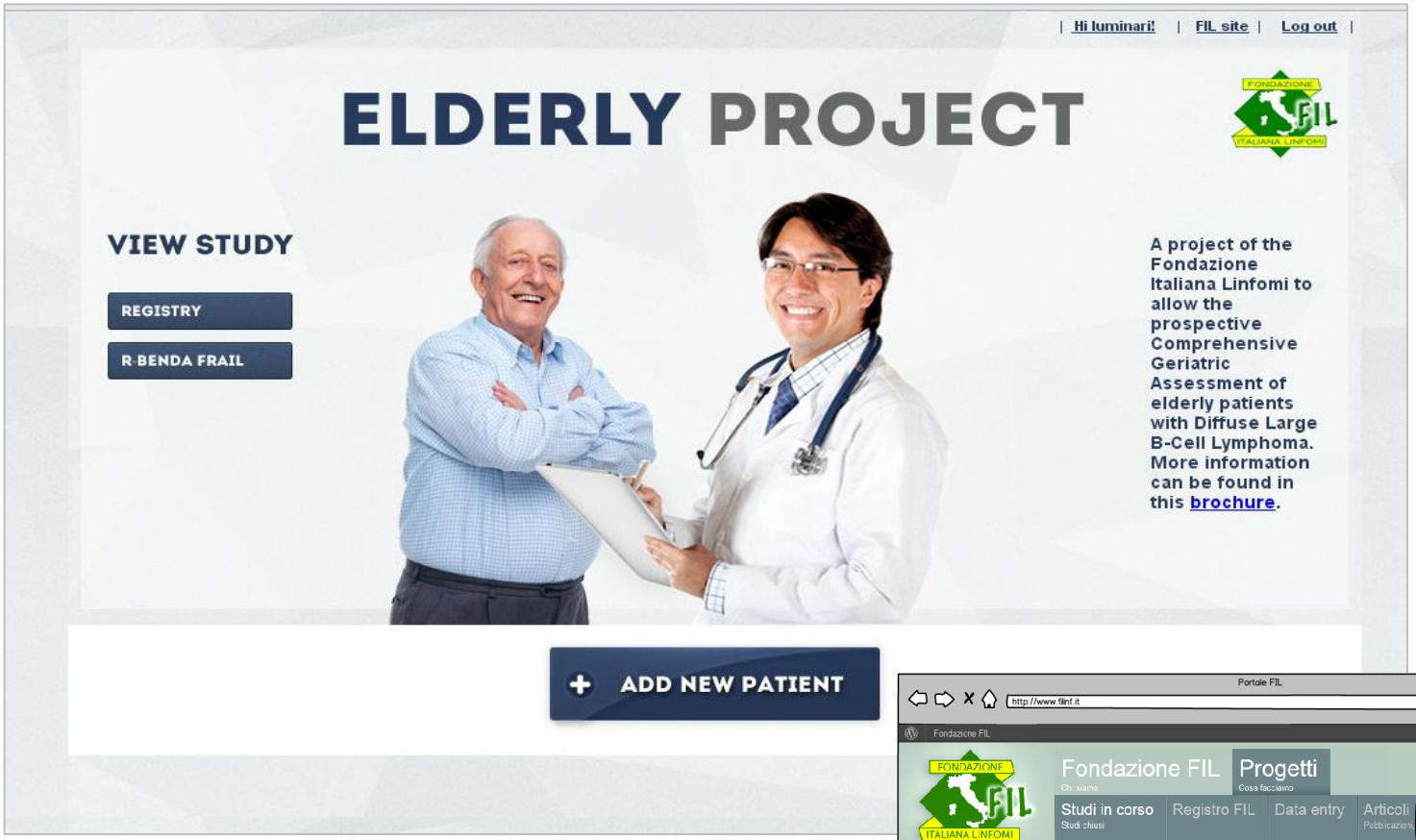
Statistical analysis

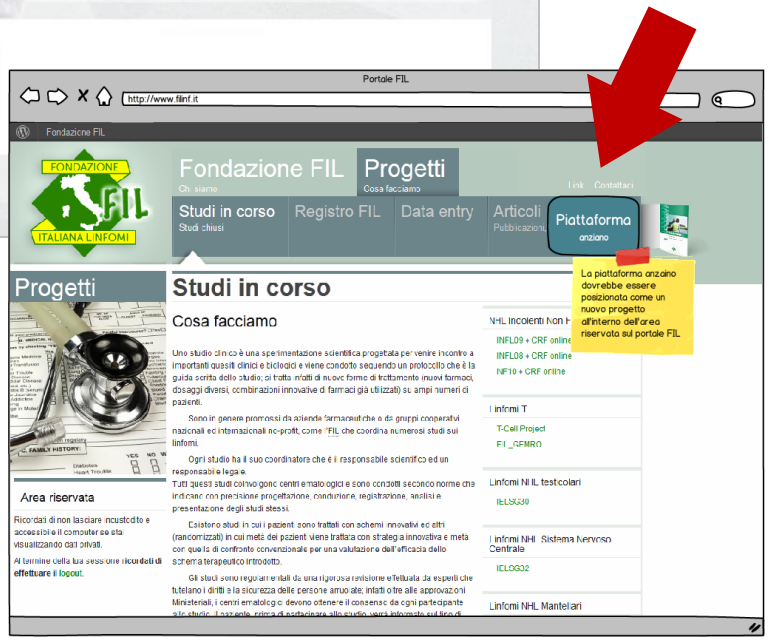
Prognostic factors on overall survival

Patient characteristics	HR (95% CI)	Univariate analysis	Multivariate analysis
Age ≤80 >80	2,6 (1,52-4,45)	P 0.0005	
Stage I-II vs III-IV	1,44 (0,83-3,54)	P 0.2	
IPI	3,53 (1,05-7,55)	p 0.0008	p 0.01
CGA	5,68 (2,90-11,11)	P 0.0001	p 0.04
ADL	0,3 (0,17-0,52)	P 0.0001	
IADL	0,21 (0,12-0,38)	P 0.0001	
Curative vs palliative	0,89 (0,17-0,50)	P 0.0001	
Treatment dose <75% >75%	0,31 (0,14-0,70)	P 0.005	

OS according to CGA

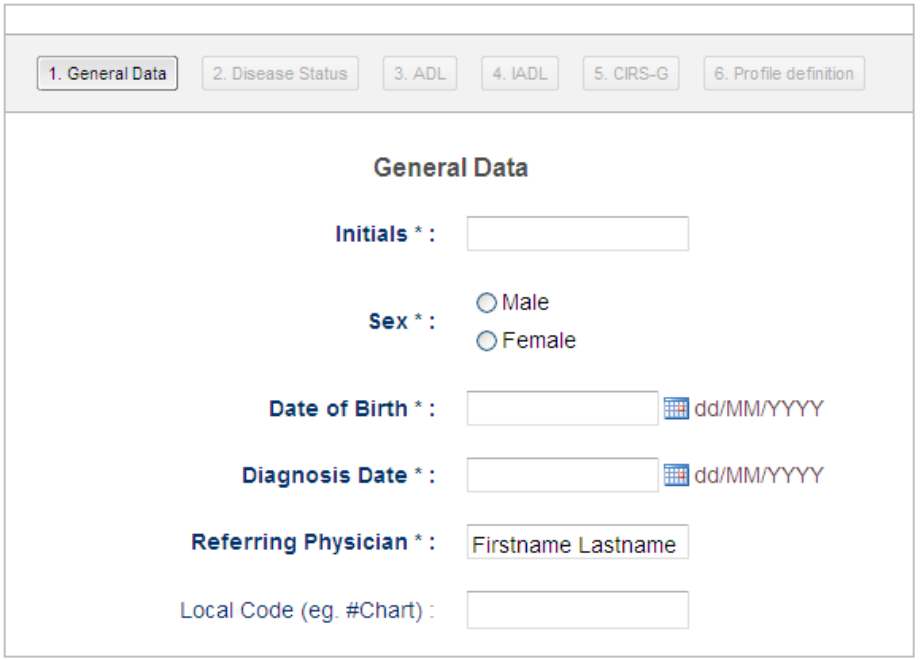




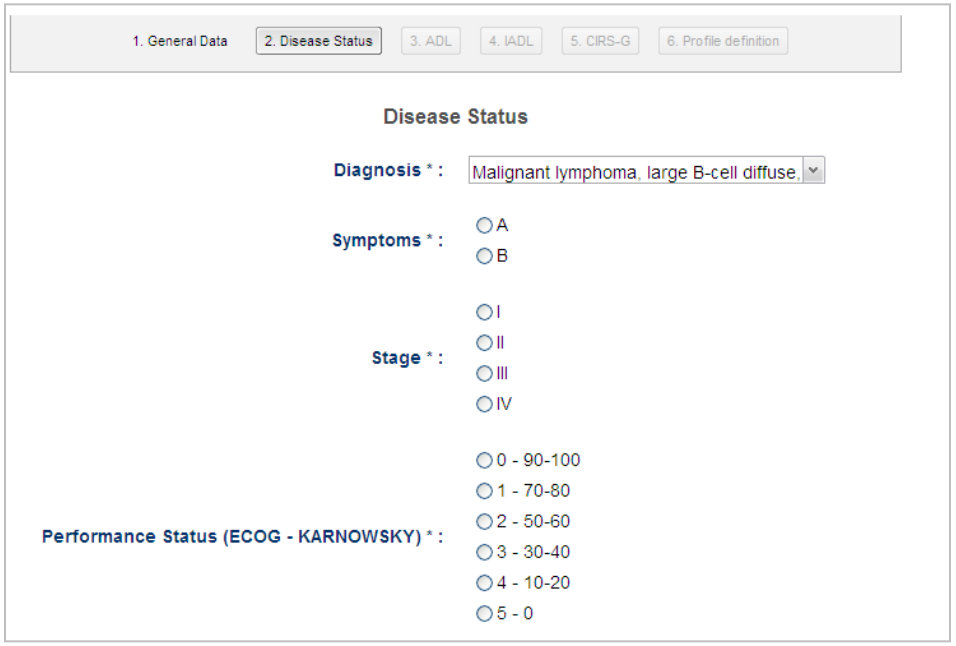


www.filinf.it

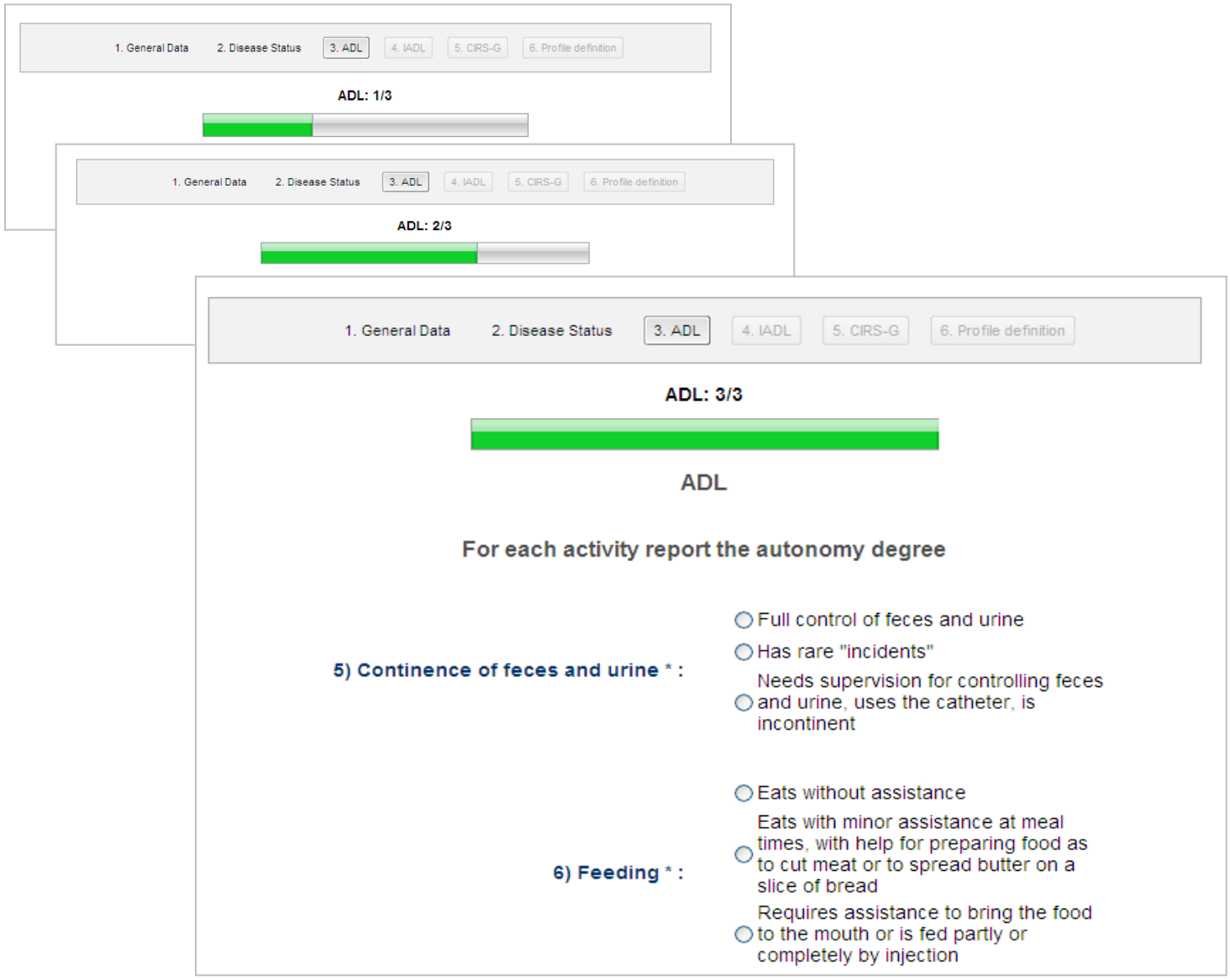
1. General data



2. Disease Status

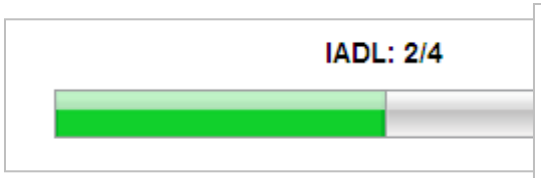


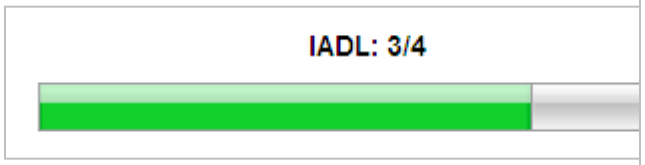
3. ADL

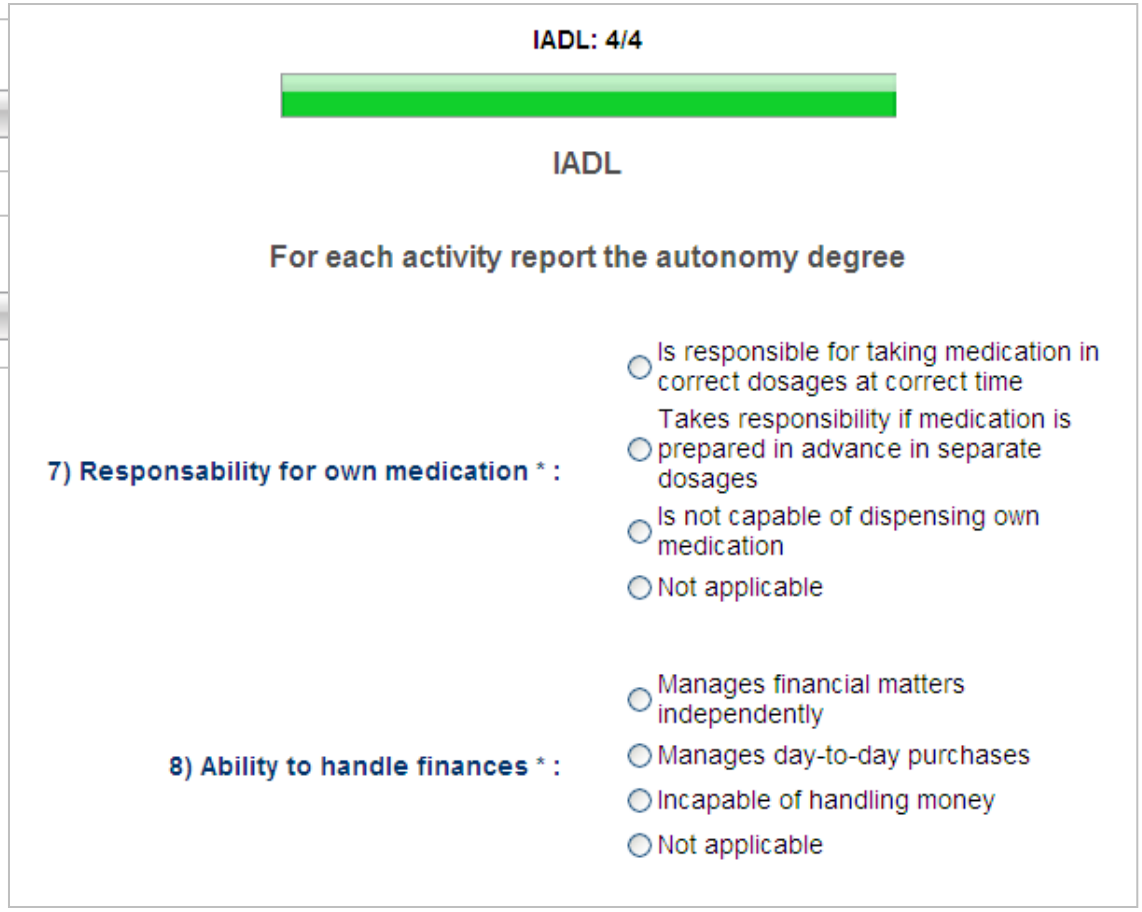

1. General Data
2. Disease Status
3. ADL
4. IADL
5. CIRS-G
6. Profile definition
ADL: 1/3
1. General Data
2. Disease Status
3. ADL
4. IADL
5. CIRS-G
6. Profile definition
ADL: 2/3
1. General Data
2. Disease Status
3. ADL
4. IADL
5. CIRS-G
6. Profile definition
ADL: 3/3
ADL
For each activity report the autonomy degree
5) Continence of feces and urine * :
Full control of feces and urine
Has rare "incidents"
Needs supervision for controlling feces and urine, uses the catheter, is incontinent
6) Feeding * :
Eats without assistance
Eats with minor assistance at meal times, with help for preparing food as to cut meat or to spread butter on a slice of bread
Requires assistance to bring the food to the mouth or is fed partly or completely by injection

4. IADL

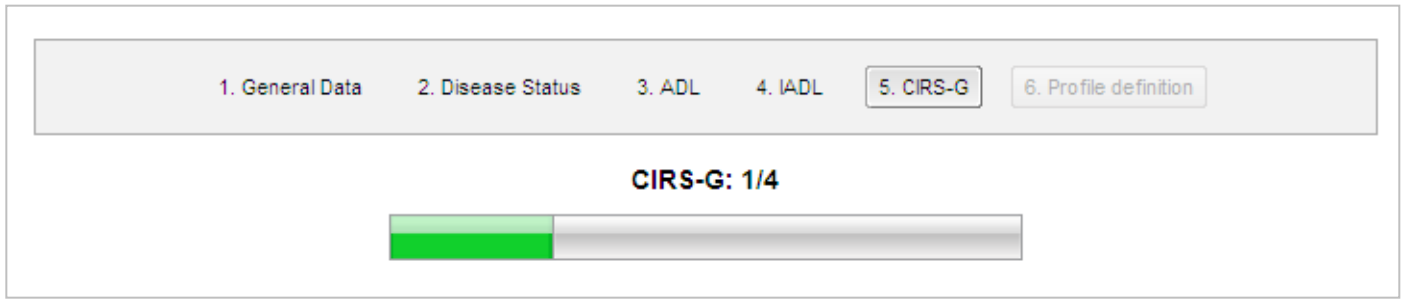
1. General Data
2. Disease Status
3. ADL
4. IADL
5. CIRS-G
6. Profile definition
IADL: 1/4

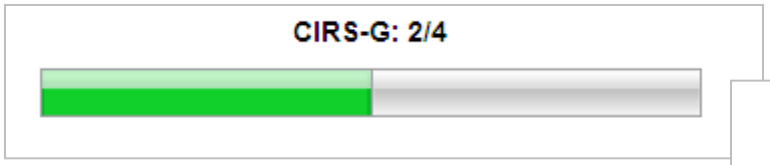

IADL: 2/4

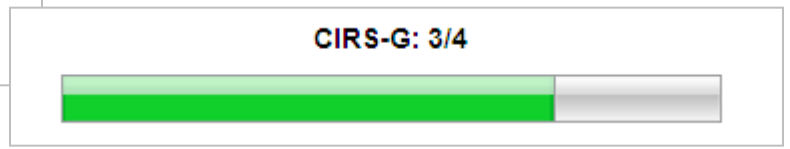

IADL: 3/4

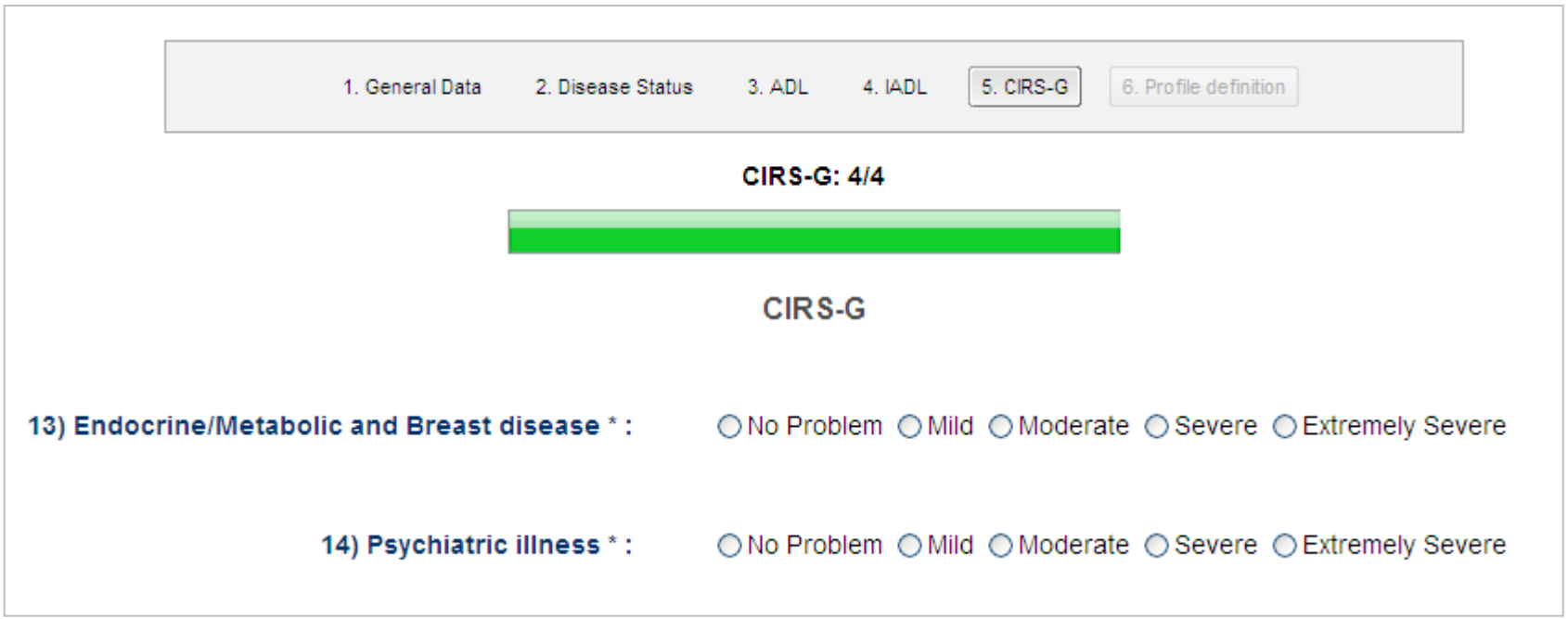

IADL: 4/4
IADL
For each activity report the autonomy degree
7) Responsability for own medication * :
Is responsible for taking medication in correct dosages at correct time
Takes responsibility if medication is prepared in advance in separate dosages
Is not capable of dispensing own medication
Not applicable
8) Ability to handle finances * :
Manages financial matters independently
Manages day-to-day purchases
Incapable of handling money
Not applicable

5. CIRS-G


1. General Data
2. Disease Status
3. ADL
4. IADL
5. CIRS-G
6. Profile definition
CIRS-G: 1/4


CIRS-G: 2/4


CIRS-G: 3/4


1. General Data
2. Disease Status
3. ADL
4. IADL
5. CIRS-G
6. Profile definition
CIRS-G: 4/4
CIRS-G
13) Endocrine/Metabolic and Breast disease * :
No Problem
Mild
Moderate
Severe
Extremely Severe
14) Psychiatric illness * :
No Problem
Mild
Moderate
Severe
Extremely Severe

6. Profile definition

1. General Data | 2. Disease Status | 3. ADL | 4. IADL | 5. CIRS-G | 6. Profile definition

Score and Profile

Patient age: age < 80

ADL: 6

IADL: 8

Comorbidità di grado 2: 0

Comorbidità di grado 3 o 4: 0

Patient profile: FIT

1. General Data | 2. Disease Status | 3. ADL | 4. IADL | 5. CIRS-G | 6. Profile definition

Score and Profile

Patient age: age >= 80

ADL: 6

IADL: 8

Comorbidità di grado 2: 0

Comorbidità di grado 3 o 4: 0

Patient profile: UNFIT

1. General Data | 2. Disease Status | 3. ADL | 4. IADL | 5. CIRS-G | 6. Profile definition

Score and Profile

Patient age: age < 80

ADL: 5

IADL: 5

Comorbidità di grado 2: 1

Comorbidità di grado 3 o 4: 0

Patient profile: FRAIL

1. General Data | 2. Disease Status | 3. ADL | 4. IADL | 5. CIRS-G | 6. Profile definition

Score and Profile

Patient age: age >= 80

ADL: 1

IADL: 5

Comorbidità di grado 2: 1

Comorbidità di grado 3 o 4: 0

Patient profile: SUPERFRAIL

Select study :

Select study : REGISTRY

Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial

Frédéric Peyrade, Fabrice Jardin, Catherine Thieblemont, Antoine Thyss, Jean-François Emile, Sylvie Castaigne, Bertrand Coiffier, Corinne Haioun, Serge Bologna, Olivier Fitoussi, Gérard Lepeu, Christophe Fruchart, Dominique Bordessoule, Michel Blanc, Richard Delarue, Maud Janvier, Bruno Salles, Marc André, Marion Fournier, Philippe Gaulard, Hervé Tilly, for the Groupe d'Etude des Lymphomes de l'Adulte (GELA) investigators*

149 patients

Median age	**83 yrs (80-95)**
Stage III-IV	**75%**
IPI 3-5	**71%**
IADL with limitation	**53%**

Lancet Oncol 2011; 12: 460–68

Of the 149 patients in the intention-to-treat population, 108 completed the six cycles of the treatment regimen. Median interval between cycles was 21 days (range 14–56; one patient had a protocol violation and restarted chemotherapy after 56 days). Relative median dose intensity for the 108 patients who completed all treatment cycles was 97% for both doxorubicin (range 64–106) and cyclophosphamide (66–358).

	Patients (n=149)
Complete response	59 (40%)
Unconfirmed complete response	34 (23%)
Partial response	16 (11%)
Stable disease	2 (1%)
Progression during treatment	8 (5%)
Death	27 (18%)
Not assessed	3 (2%)

Table 5: Response at end of treatment

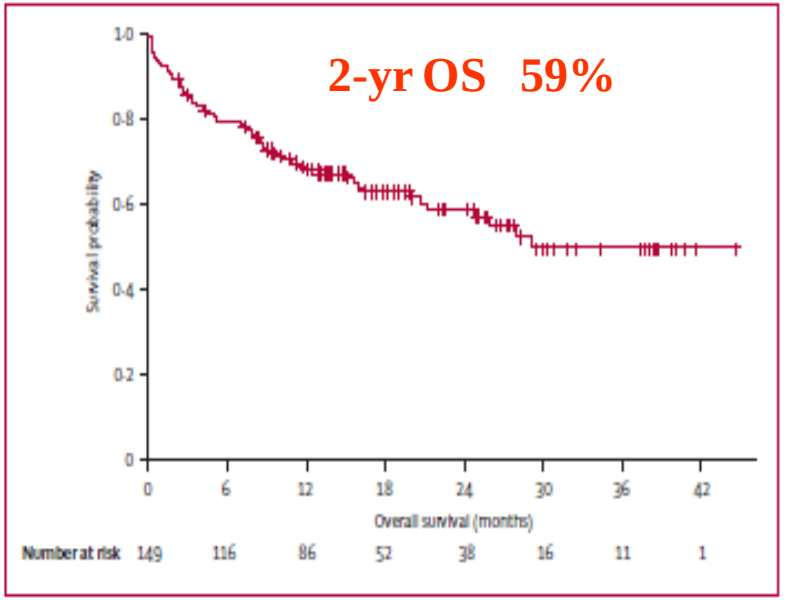


Figure 2: Overall survival

Lancet Oncol 2011; 12: 460–68

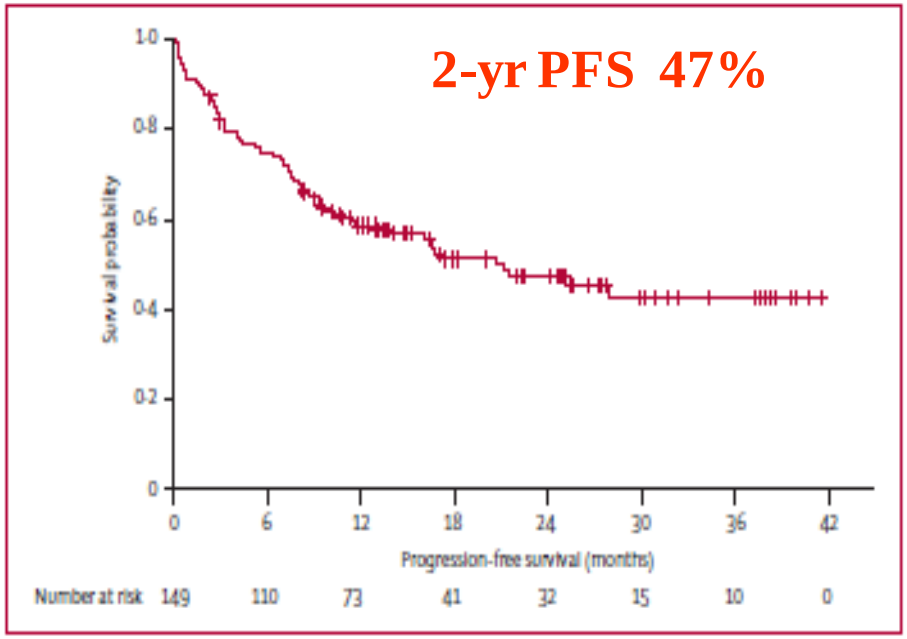


Figure 4: Progression-free survival

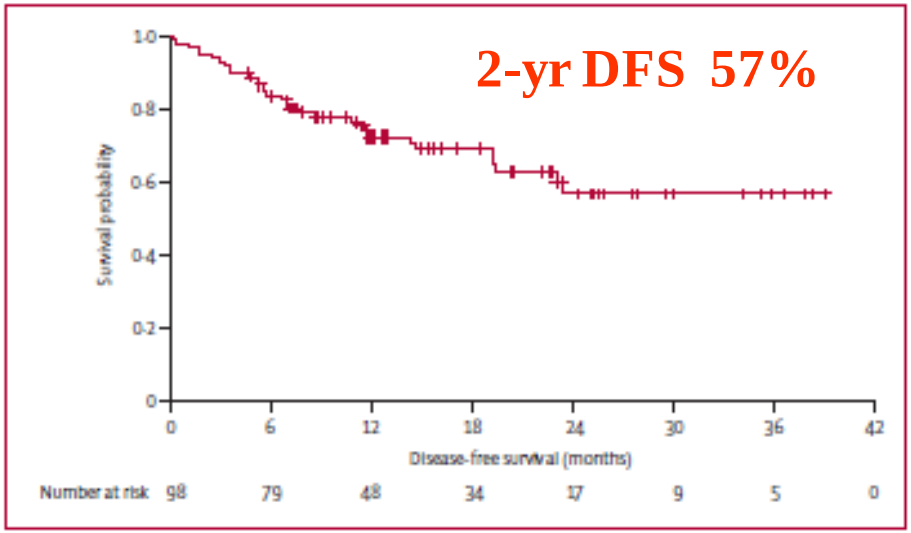
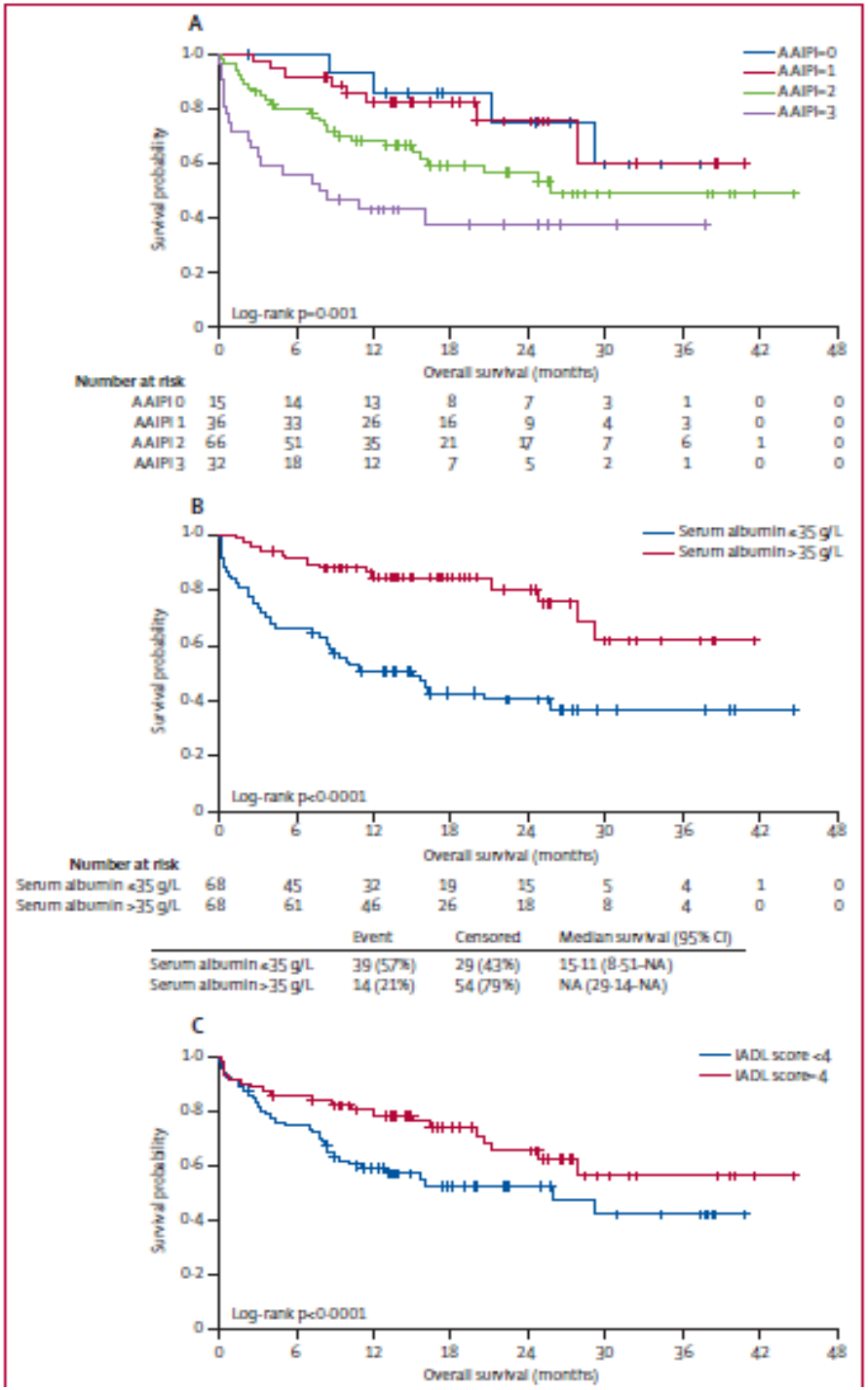


Figure 5: Disease-free survival
Only patients who attained a complete response or an unconfirmed complete response during treatment are included.

Lancet Oncol 2011; 12: 460–68



Lancet Oncol 2011; 12: 460–68

	No toxicity	Grade 1–2	Grade 3	Grade 4	Grade 5
Infection without neutropenia	113 (76%)	22 (15%)	12 (8%)	0 (0%)	2 (1%)
Febrile neutropenia	138 (93%)	1 (1%)	7 (5%)	0 (0%)	3 (2%)
Constitutional symptoms	69 (46%)	68 (46%)	7 (5%)	2 (1%)	3 (2%)
Neurological toxicity	109 (73%)	30 (20%)	7 (5%)	3 (2%)	0 (0%)
Pulmonary toxicity	118 (79%)	25 (17%)	4 (3%)	1 (0%)	1 (1%)
Renal toxicity	137 (92%)	8 (5%)	2 (1%)	1 (0%)	1 (1%)
Cardiac arrhythmia	134 (90%)	11 (7%)	2 (1%)	2 (1%)	0 (0%)
Cardiac (other)	133 (89%)	13 (9%)	2 (1%)	0 (0%)	1 (1%)
Vascular toxicity	137 (92%)	8 (5%)	3 (2%)	1 (1%)	0 (0%)
Mucositis	138 (93%)	11 (7%)	0 (0%)	0 (0%)	0 (0%)
Creatinine	117 (79%)	31 (21%)	0 (0%)	1 (1%)	0 (0%)
Transaminases	128 (86%)	20 (13%)	0 (0%)	1 (1%)	0 (0%)

Data are number (%). Percentages do not add up to 100% in some cases because of rounding.

Table 6: Incidence of non-haematological toxicity by grade

	Serious adverse event (n=70)
Infections and infestations	19 (27%)
General disorders	12 (17%)
Respiratory and mediastinal disorders	10 (14%)
Gastrointestinal disorders	7 (10%)
Nervous system disorders	7 (10%)
Renal and urinary disorders	4 (6%)
Cardiac and vascular disorders	4 (6%)
Injury and procedural complications	3 (4%)
Hepatobiliary disorders	2 (3%)
Skin disorders	1 (1%)
Musculoskeletal tissue disorders	1 (1%)

Data are number (%). Percentages do not add up to 100% because of rounding.

Table 7: Serious adverse events

Annals of Oncology 24: 2612–2618, 2013
doi:10.1093/annonc/mdt282
Published online 22 August 2013

Lymphoma occurring in patients over 90 years of age: characteristics, outcomes, and prognostic factors. A retrospective analysis of 234 cases from the LYSA

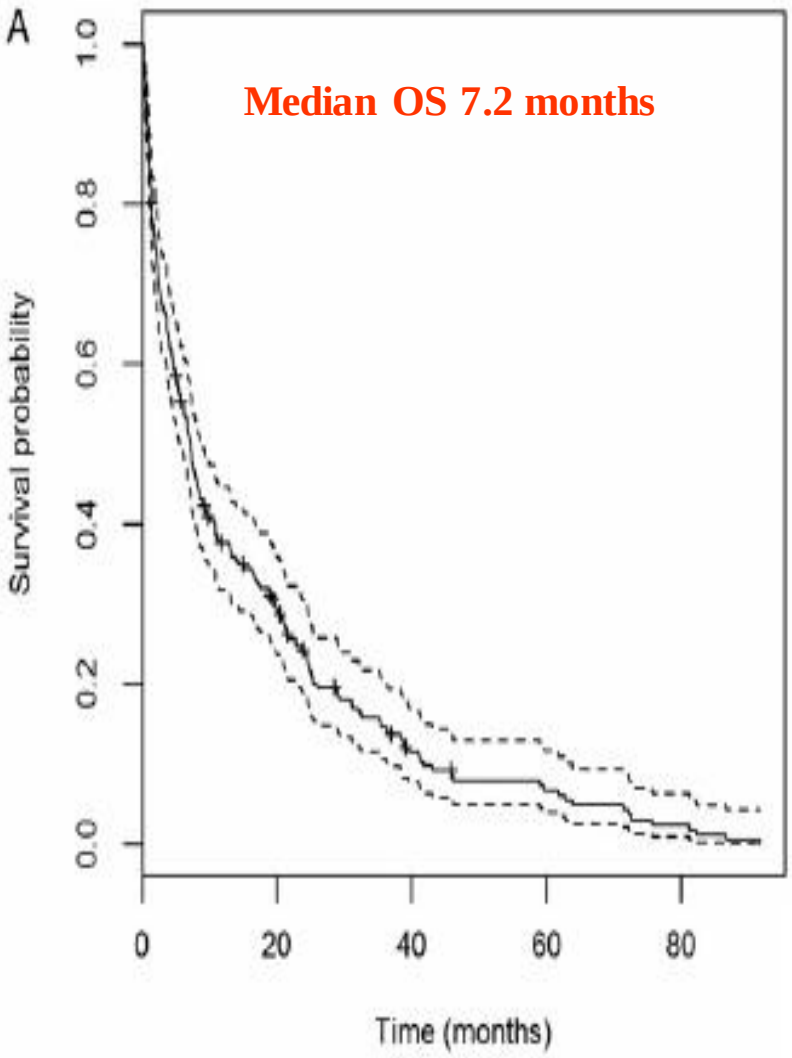
A. Trebouet[1], T. Marchand[1], R. Lemal[2], E. Gyan[3], F. Broussais-Guillaumot[4], Y. Guillermin[5], H. Monjanel[6], G. Salles[7], S. Le Gouill[8], P. Godmer[9], C. Fruchart[10], G. Damaj[11], P. Feugier[12], C. Thieblemont[6], M. Maynadié[13], A. Monnereau[14], X. Troussard[15], D. Rossille[16], T. Lamy[1] & R. Houot[1*]

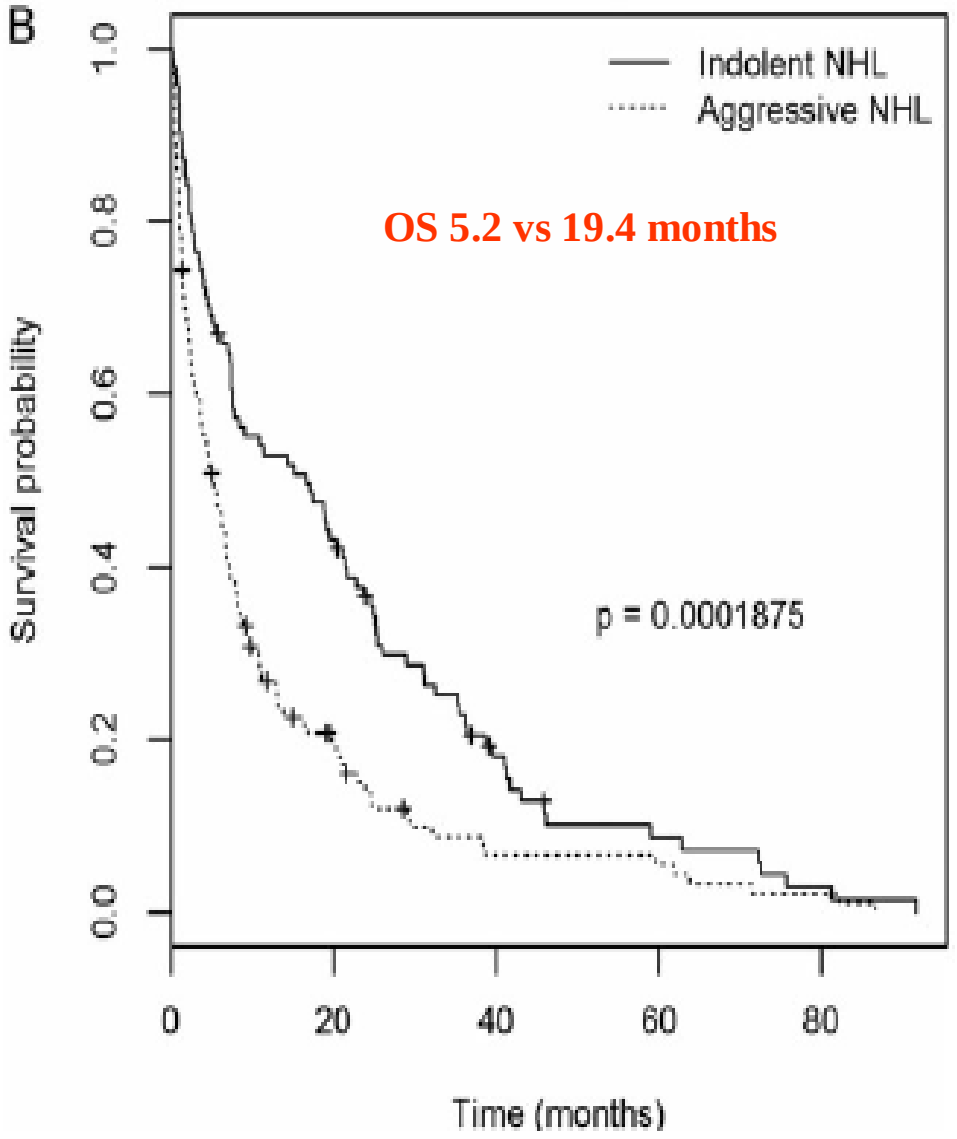
[1]Department of Hematology, Centre Hospitalier Universitaire de Rennes, INSERM U917, Rennes; [2]Department of Hematology, Centre Hospitalier Universitaire de Clermont-Ferrand Hôpital Estaing, Université d'Auvergne CREaT - EA 7283, Inserm CIC-501, Clermont-Ferrand; [3]Department of Hematology, Centre Hospitalier Universitaire de Tours, CIC INSERM U202, Tours; [4]Department of Hematology, Institut Paoli Calmettes, Marseille; [5]Department of Hematology, Centre Léon Bérard, Université Lyon 1, Lyon; [6]Department of Hematology, AP-HP, Hôpital Saint Louis, Université Paris 7, INSERM U728, Paris; [7]Department of Hematology, Hospices Civils de Lyon, Université Lyon-1, Pierre-Bénite; [8]Department of Hematology, Centre Hospitalier Universitaire de Nantes, Nantes; [9]Department of Hematology, Centre Hospitalier de Bretagne Atlantique, Vannes; [10]Department of Hematology, Centre de lutte contre le Cancer François Baclesse, Caen; [11]Department of Hematology, Centre Hospitalier Universitaire d'Amiens, Amiens; [12]Department of Hematology, Centre Hospitalier Universitaire de Nancy, Nancy; [13]Hematological Cancer Registry of Côte d'Or, UCOG de Bourgogne, EA4184, Université de Bourgogne, Dijon; [14]Hematological Cancer Registry of Gironde, Institut Bergonié, Bordeaux; [15]Hematological Cancer Registry of Basse Normandie, Centre Hospitalier Universitaire de Caen, Caen; [16]Department of Biology, Centre Hospitalier Universitaire de Rennes, Rennes, France

Received 8 May 2013; revised 24 June 2013; accepted 25 June 2013

Table 3. Distribution of treatment according to the aggressiveness of NHL

Treatment, *n* (%)	Overall	Aggressive NHL	Indolent NHL
No treatment or corticosteroids	58 (36.5)	35 (33.6)	23 (41.8)
Radiotherapy or surgery alone	12 (7.5)	10 (9.65)	2 (3.65)
Single agent therapy	38 (23.9)	14 (13.5)	24 (43.65)
Polychemotherapy without anthracycline	41 (25.8)	35 (33.65)	6 (10.9)
Polychemotherapy with anthracycline	10 (6.3)	10 (9.6)	0 (0)


A
Median OS 7.2 months
Survival probability
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
Time (months)

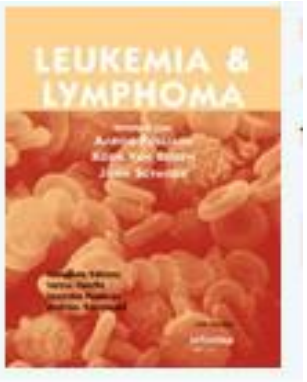

B
Indolent NHL
Aggressive NHL
OS 5.2 vs 19.4 months
p = 0.0001875
Survival probability
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
Time (months)

Prognostic Factors on Overall Survival

Indolent NHL			
Factor	HR	95%CI	P value
> 4 medications	2.43	1.04-5.71	0.04
Anemia	4.23	1.62-11.05	0.003

Aggressive NHL			
Factor	HR	95%CI	P value
Hypoalbuminemia	2.95	1.43-6.08	0.003
No treatment	2.50	1.24-5.14	0.01

Leukemia & Lymphoma, 2013; Early Online: 1–6
© 2013 Informa UK, Ltd.
ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2013.788176



ORIGINAL ARTICLE: CLINICAL

Outcome of frail elderly patients with diffuse large B-cell lymphoma prospectively identified by Comprehensive Geriatric Assessment: results from a study of the Fondazione Italiana Linfomi

Francesco Merli, Stefano Luminari, Giuseppe Rossi, Caterina Mammi, Luigi Marcheselli, Angela Ferrari, Michele Spina, Alessandra Tucci, Caterina Stelitano, Isabella Capodanno, Alberto Fragasso, Luca Baldini, Chiara Bottelli, Elisa Montechiarello, Stefano Fogazzi, Cinzia Lamorgese, Lara Cavalli and Massimo Federico
Fondazione Italiana Linfomi

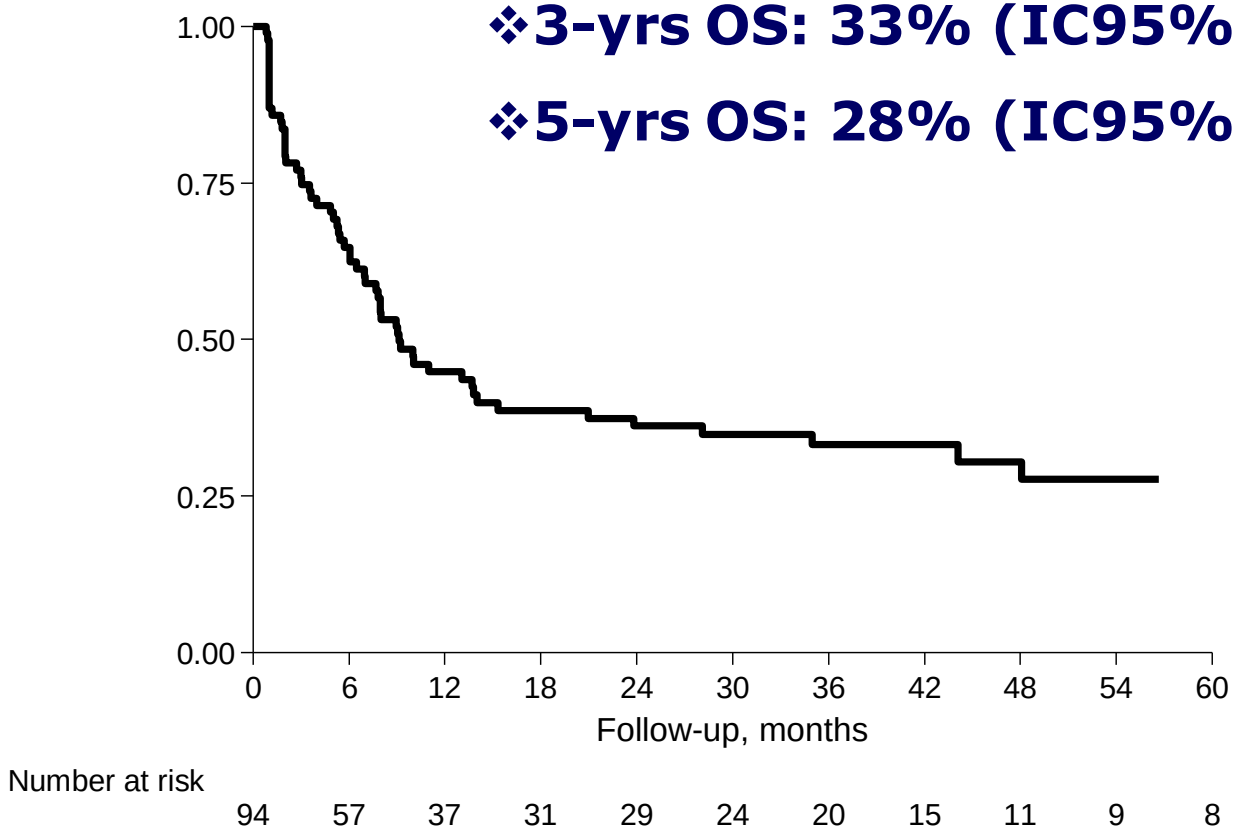
Merli F. et al, Leuk Lymph, 2013

Reasons for considering patients as frail

FRAIL	99 patients
Age >80 yrs	34 %
Comorbidity	54 %
Impaired ADL	32 %
Geriatric syndrome	25 %

Merli F. et al, Leuk Lymph, 2013

FRAIL: Overall Survival



- **3-yrs OS: 33% (IC95% 23-43%)**
- **5-yrs OS: 28% (IC95% 17-39%)**

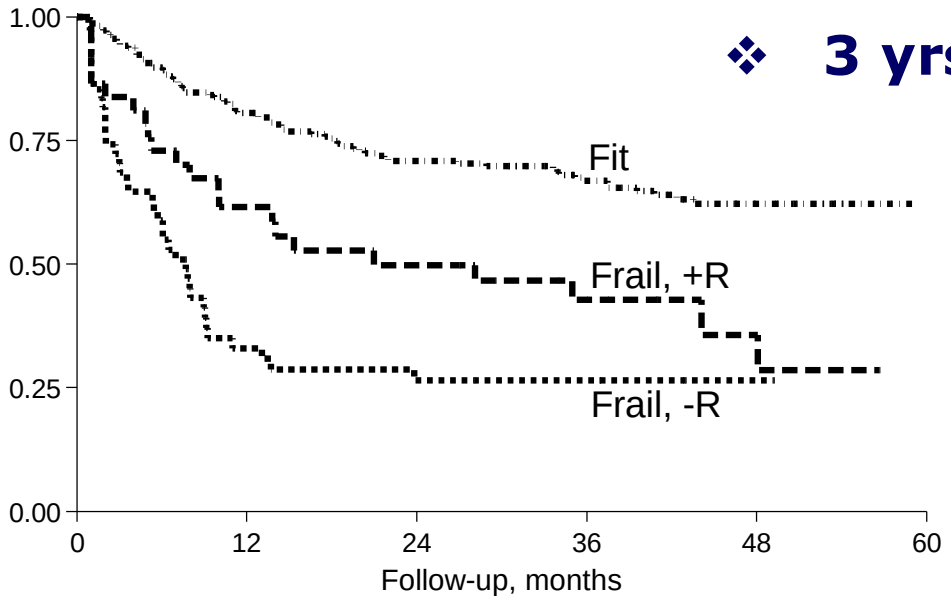
Median follow up: 36 months for living pts (1-70)

Merli F. et al, Leuk Lymph, 2013

Frail vs FIT: Overall Survival

- **3-yrs OS frail + R: 43%**
- **3 yrs OS frail - R: 26%**

P=0.152



Number at risk

Fit	224	173	141	106	55	25
Frail, +R	37	21	17	11	5	3
Frail, -R	57	16	12	9	6	5

Frail pts:

- **poorer outcome than FIT** (**P<0.001**)
- **even treated with rituximab** (**P<0.001**)

Merli F. et al, Leuk Lymph, 2013

FRAIL: Univariate and Multivariate analysis for OS

		Univariate			Multivariate		
Variable	**Status**	**HR**	**IC95%**	**P**	**HR**	**IC95%**	**P**
Age	>80	1.08	0.65-1.70	0.782			
aaIPI	2-3	2.49	1.46-4.25	**0.001**	2.24	1.28-3.91	**0.005**
Stage	III-IV	1.96	1.13-3.41	**0.017**			
Rituximab	+	0.68	0.40-1.16	0.152			
ADL	<6	1.59	0.91-2.77	0.103			
Geriatric syndrome	Yes	1.04	0.53-2.00	0.914			
Comorbidity	$\geq$ 3 gr.3	1.31	0.69-2.49	0.412			
	$\geq$ 1 gr.4	1.56	0.69-3.50	0.282			

Merli F. et al, Leuk Lymph, 2013

FRAIL: Univariate and Multivariate analysis for OS

		Univariate			Multivariate		
Single CGA items	**Status**	**HR**	**IC95%**	**P**	**HR**	**IC95%**	**P**
CIRS-G (Resp. sys.)	grade $\geq$ 3	2.31	1.19-4.49	**0.013**	2.00	1.02-3.93	**0.044**
ADL (Ambulation)	unable	2.04	1.04-4.01	**0.038**			
ADL (Functional Transfers)	unable	2.24	1.13-4.43	**0.020**			

Univariate Analysis:
ambulation, functional transfers, respiratory comorbidities: worse survival

Merli F. et al, Leuk Lymph, 2013

HEART-01

Phase II Multicentre Study with Rituximab, Cyclophosphamide, Non pegylated Liposomal doxorubicin (Myocet®), Vincristine and Prednisone (R-COMP) in Cardiopathic Patients with diffuse large B cell Non-Hodgkin's Lymphoma : study HEART-01 of the Fondazione Italiana Linfomi (F.I.L)

Study coordinator : Michele Spina (Aviano)

Writing commitee :
Savina Aversa (Padova)
Lucia Fratino (Aviano)
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Alessandro Levis (Alessandria)
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Luigi Rigacci (Firenze)
Flavia Salvi (Alessandria)
Sergio Storti (Campobasso)
Alessandra Tucci (Brescia)
Elda Viel (Aviano)

Analysis and data management:
Monica Bellei (Modena)
Stefano Luminari (Modena)
Luigi Marcheselli (Modena)

CRITERI DI CARDIOPATIA

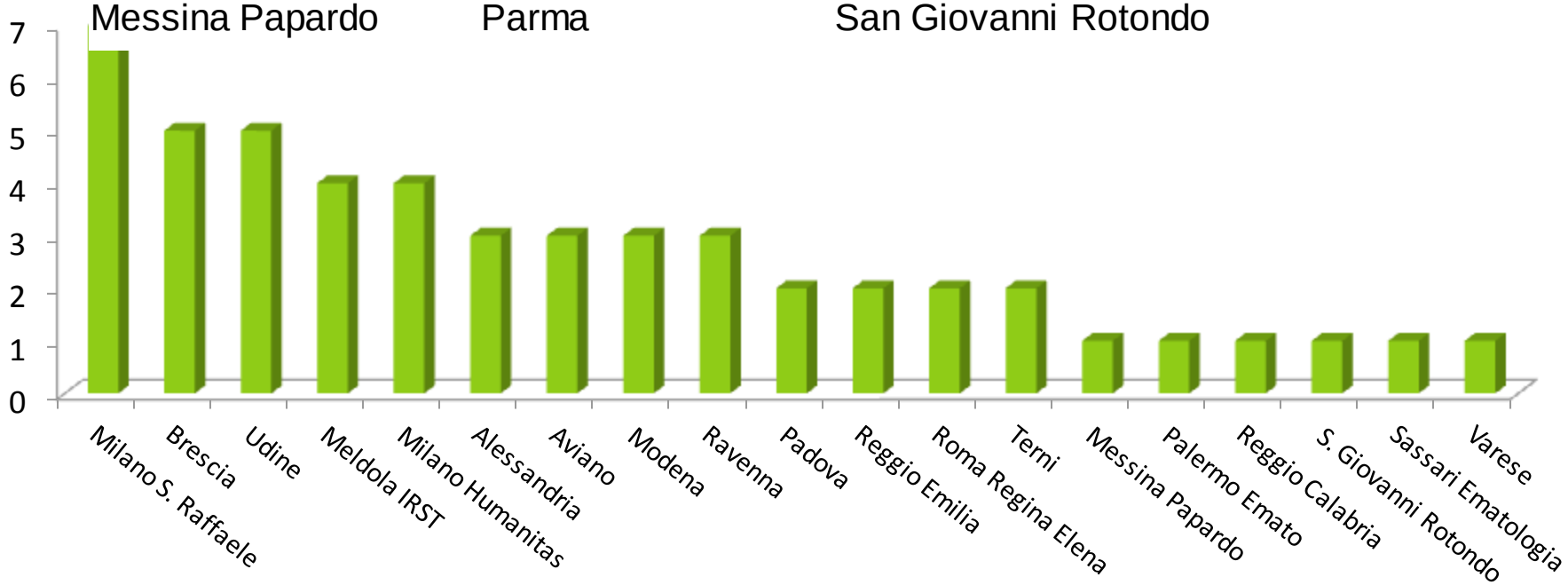
- ✓ **FEVS < 50%**
- ✓ **Ipertrofia ventricolare sinistra (SS-PP>1.2)**
- ✓ **Ipertensione arteriosa moderata-severa non controllata dalla terapia**
- ✓ **Cardiopatia ischemica documentata**
- ✓ **Aritmie ventricolari significative note (Lown 3)**
- ✓ **Fibrillazione atriale cronica non controllata**
- ✓ **Ipertensione polmonare (PP > 45 mmHg)**
- ✓ **Valvulopatia mitralica moderata-severa**
- ✓ **Valvulopatia aortica moderata (G medio 20-40)**

DIMENSIONE CAMPIONARIA

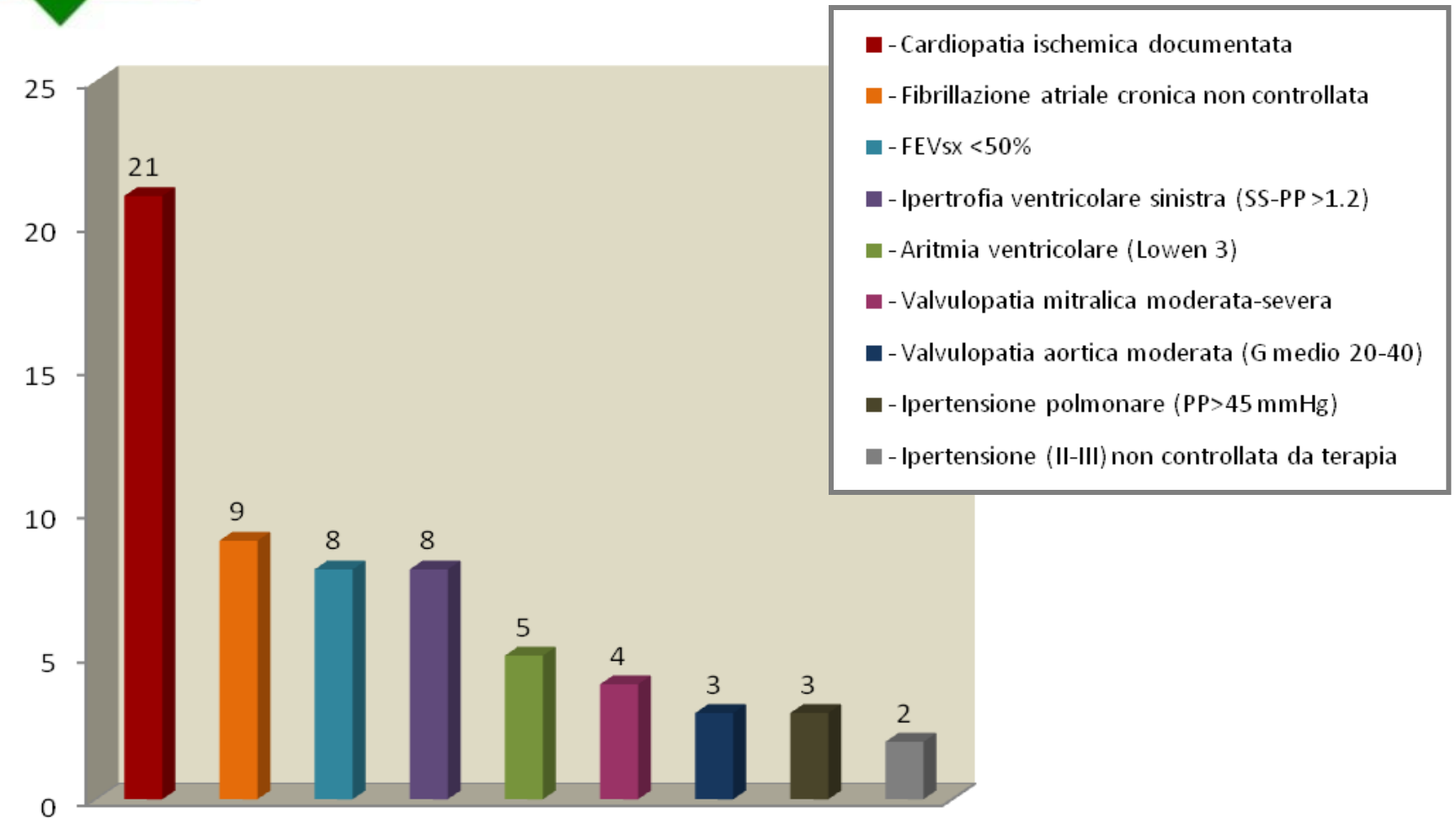
50 pts in 3 anni

27 Centri Autorizzati – 19 Centri Attivi

Alessandria
Aviano
Brescia
Firenze
Genova S. Martino
Meldola IRST
Messina Papardo
Milano HSR
Milano Humanitas
Milano Niguarda
Modena
Padova
Palermo Giaccone
Parma
Perugia Ematologia
Ravenna
Reggio Calabria
Reggio Emilia
Roma La Sapienza
Roma Regina Elena
San Giovanni Rotondo
Sassari Ematologia
Siena
Terni
Torino Molinette
Udine
Varese



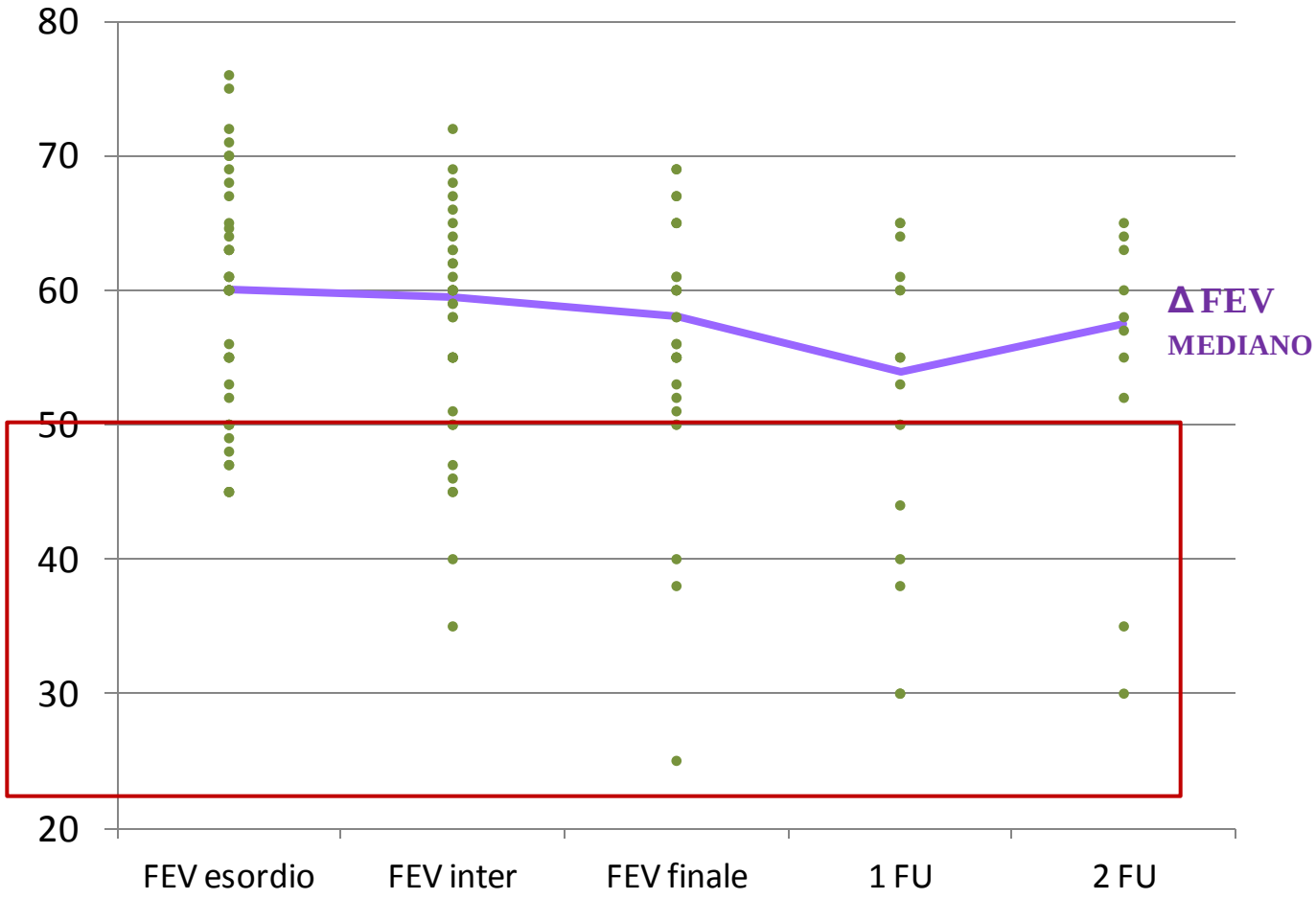
PATOLOGIA CARDIACA (N=63*)



*Concomitanza di due diversi tipi di cardiopatie = 4 casi
Concomitanza di tre diversi tipi di cardiopatie = 4 casi

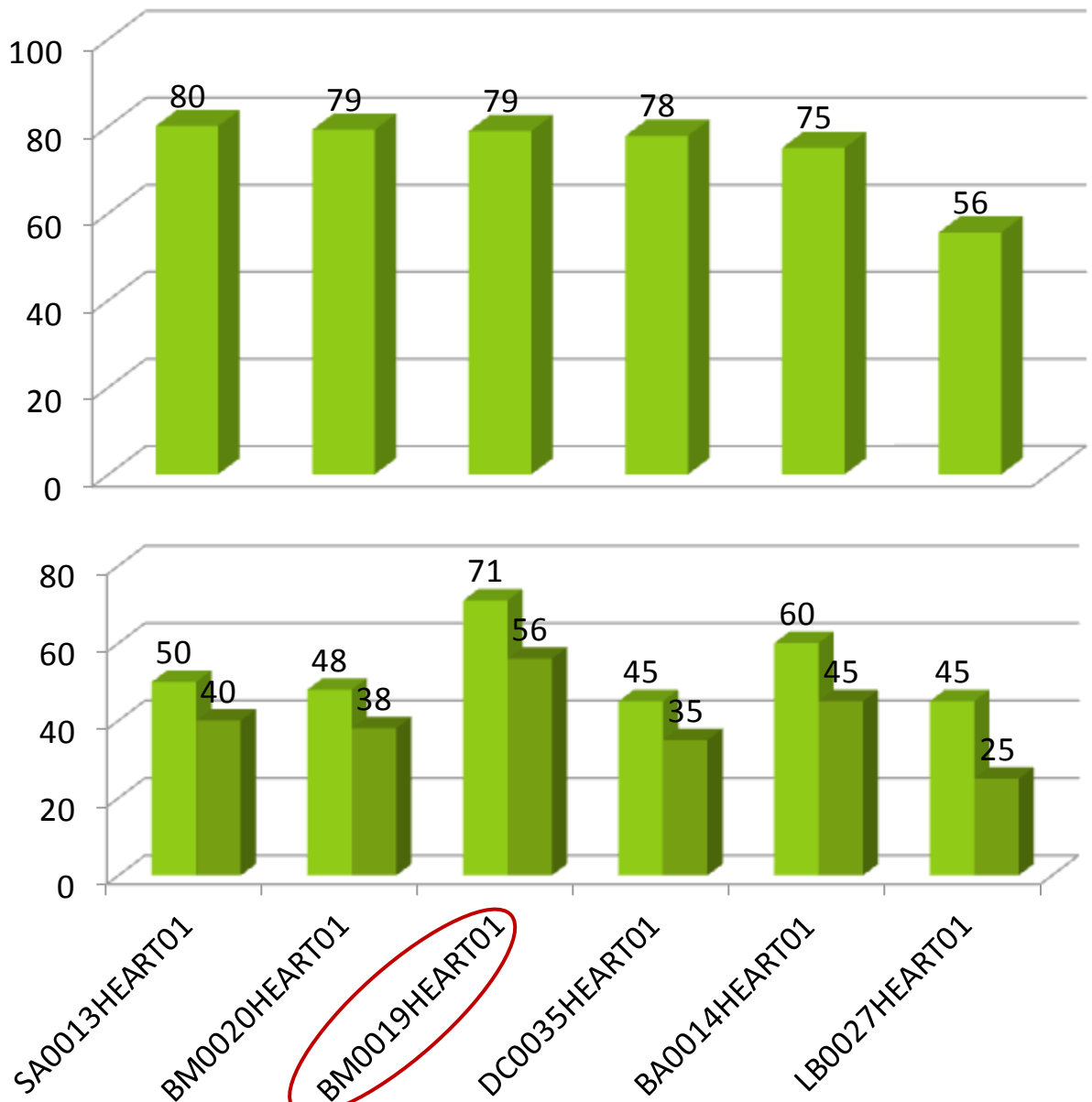
VARIAZIONE FEV

Dati FEV Disponibili				
Esordio	**Intermedio**	**Finale**	**1FU**	**2FU**
45 pts	38 pts	31 pts	16 pts	10 pts



Valori ≤ 50%

RIDUZIONE ≥20% RISPETTO ALLA FEV D'ESORDIO



Riduzione > del 20% rispetto alla FEV basale, ma che resta comunque > 50%

RISPOSTA AL TRATTAMENTO

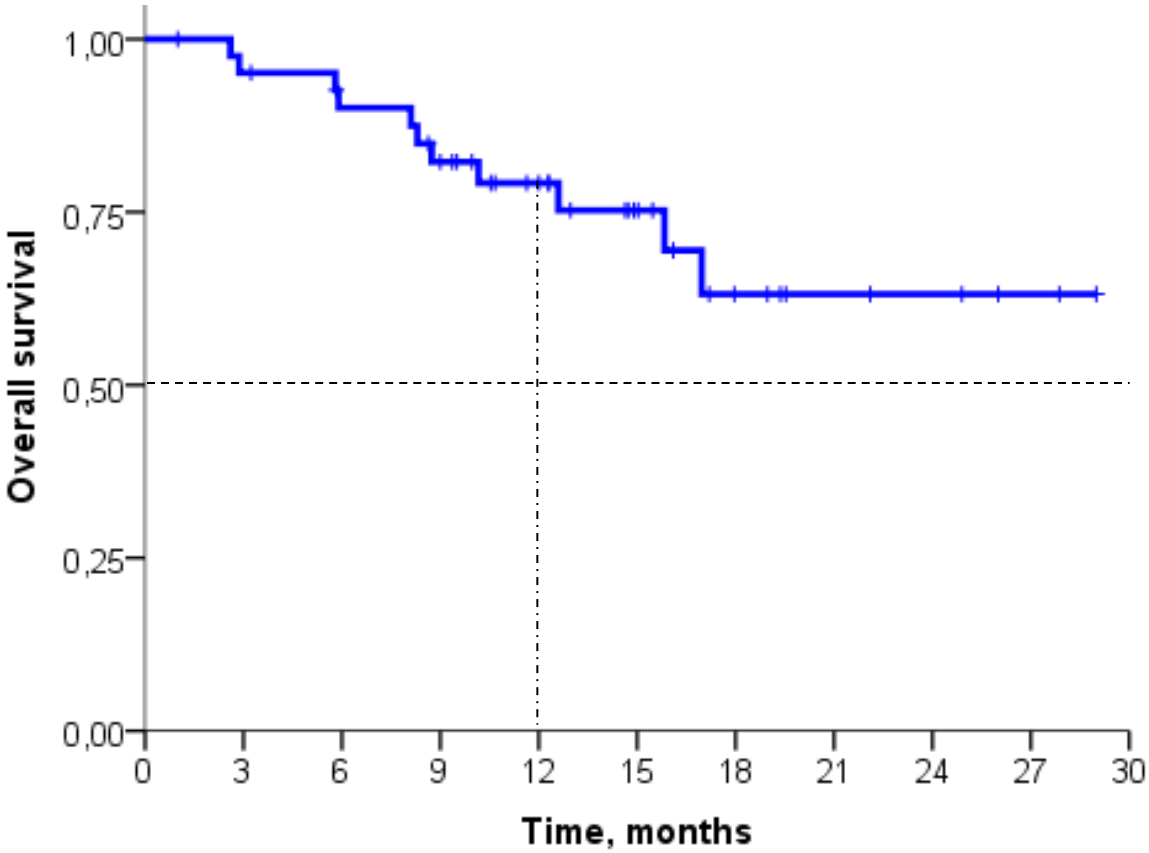
	N	$\%_{val}$
RC	26	52
Rcu	2	4
RP	9	18
NR	1	2
PG	9	18
NV	3	6
Tot	50	
Missing	1	

Casi NV	Cicli eseguiti	Causa interruzione trattamento
RF0048HEART01	3	Decesso per emorragia
BC0009HEART01	3	Decesso per arresto cardiaco
OO0033HEART01	1	Perso di vista

OVERALL SURVIVAL (N=51)

	N	%
Vivi	38	74
Deceduti	11	22
Persi di vista	2	4

Causa di morte	N
Tossicità	5
Sepsi	2
Emorragia	1
Arresto cardiaco	1
Insufficienza renale	1
Progressione	2
Secondo tumore	1
Insufficienza respiratoria	1
Non nota	2
Tot	**11**



OS a 12 mesi: 79% (IC95% 63-89%)

R-Benda Frail

Rituximab plus Bendamustine as front line treatment in frail elderly (>70 years) patients with DLBCL: a phase II multicenter study of the Fondazione Italiana Linfomi (FIL)

Eudract Number: **2011-001421-24**

(Study Coordinators: M.Spina-S.Storti)

Main Inclusion Criteria

- Histologically proven CD20 positive DLBCL
- Age > 70 years
- No previous treatment
- FRAIL patients:
  - **Age > 80 years with UNFIT profile**
  - Age < 80 years with
    - ADL < 4 residual functions, or
    - IADL < 5 residual functions, or
    - CIRS : 1 co-morbidity of grade 3-4, or > 8 co-morb. of grade 2

R-Benda Frail

R-BENDA administration schema *(cycles Q28dd)*

	dose	route	day(s)	# of courses	
				Pts with IPI=0 and stage I-II non bulky	All other Pts
Rituximab	375 mg/m2	IV	1 ***(day 8 on cycle 1)***	6	8
Bendamustine	90 mg/m2	IV	1-2 or 2-3 ***(days 2-3 on cycle 1)***	4	6

- SAMPLE SIZE
  - **Stage 1**: 19 patients; if at least 4 patients will achieve CR the study will continue
  - **Stage 2**: additional 25 patients
  - Considering a drop-out of 10%, the enrolment will continue until 49 patients are accrued in order to have at least 44 valuable patients.

R-BENDA FRAIL

Enrolled	**23 pts**
Protocol violation	**2 pts**
Evaluable	**21(91%)**
Median age	**81 yrs (range 76-89)**
Males	**62%**
Stage III-IV	**70%**
ECOG-PS>1	**45%**
LDH>NL	**40%**

R-BENDA FRAIL

Stopping rules

Less than 4 CR

CR	5/14 (36%)
PR	1/14
Pro	8/14

Less than 12 G3-G4 non hema tox

Cardiovascular	3	1
Neurological	1	0
Hemorrhage	1	0
Fatigue	1	0

Angrilli Francesco	Ematologia Pescara
Arcari Annalisa	Ematologia Piacenza
Balzarotti Monica	Ematologia Rozzano (MI)
Brugiatelli Maura	Ematologia Messina
Cabras Giuseppina	Ematologia Cagliari
Cox Maria Christina	Ematologia Roma
Fabbri Alberto	Ematologia Siena
Fratino Lucia	CRO Aviano
Gini Guido	Ematologia Ancona
Isidori Alessandro	Ematologia Pesaro
Mancuso Salvatrice	Ematologia Policlinico Palermo
Martelli Maurizio	Ematologia La Sapienza Roma
Merli Francesco	Ematologia Reggio Emilia
Rattotti Sara	Ematologia Pavia
Rigacci Luigi	Ematologia Firenze
Rossini Fausto	Ematologia Monza
Rusconi Chiara	Ematologia Niguarda Milano
Salvi Flavia	Ematologia Alessandria
Spina Michele	CRO Aviano
Storti Sergio	Ematologia Campobasso
Tucci Alessandra	Ematologia Brescia
Zilioli Vitotrio	Ematologia Niguarda Milano