



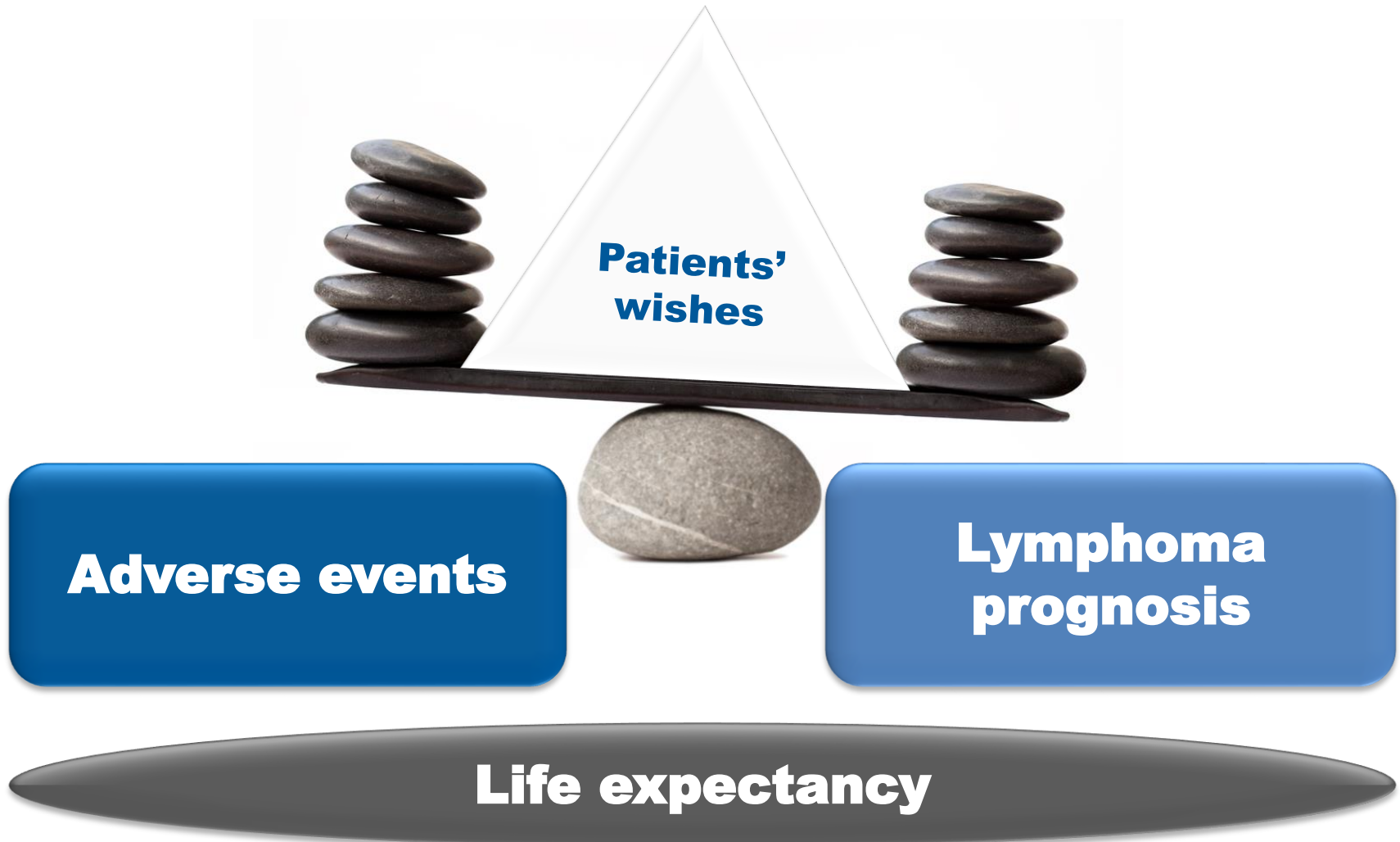
# Geriatric Assessment in Haematological Malignancies

*Pierre Soubeyran, Institut Bergonié, Bordeaux*

# Dealing with the elderly



# Dealing with the elderly



# Management of elders



**Lymphoma**



**Treatment**

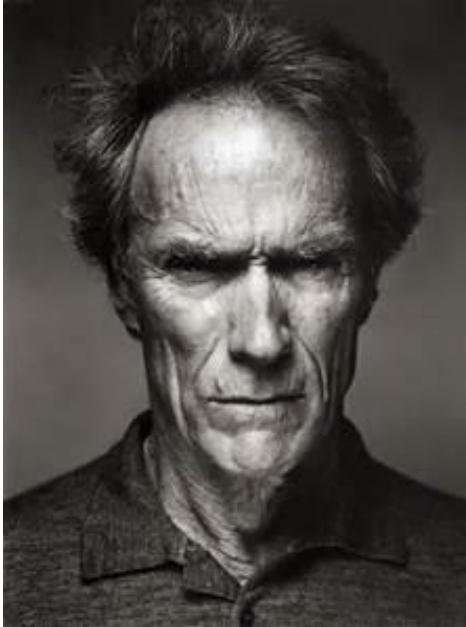


**Disease control**



**Toxicity risk**

# Management of elders



*Comorbidities*  
*Geriatric impairments*

**Lymphoma**



**Treatment**

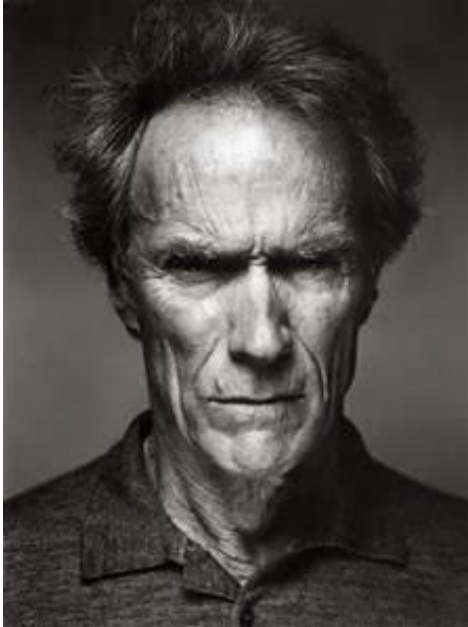


**Disease control**



**Toxicity risk**

# Management of elders



*Comorbidities*

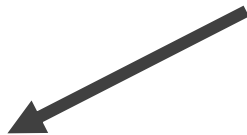
*Geriatric impairments*

*No specific assessment*

**Lymphoma**



**Reduce treatment doses**

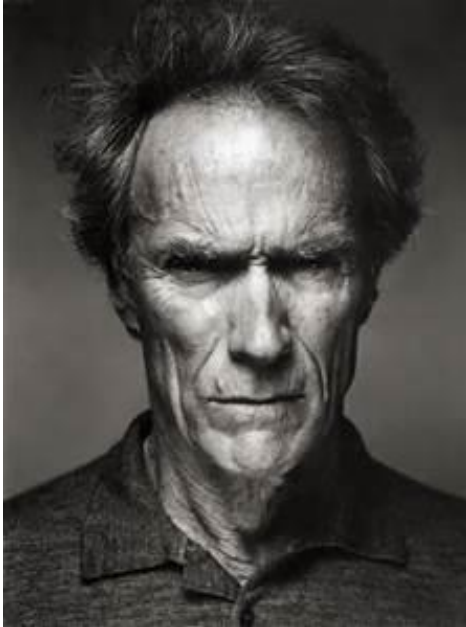


**Disease control**



**Toxicity risk**

# Management of elders



*Comorbidities*

*Geriatric impairments*

*No specific assessment*

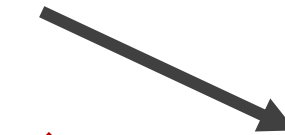
**Lymphoma**



**Maintain treatment doses**

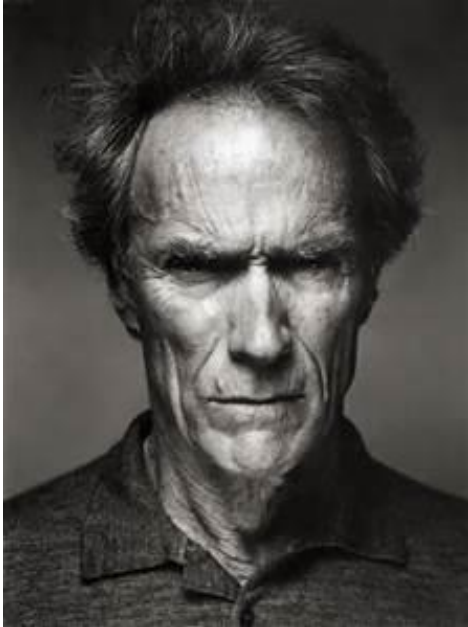


**Disease control**



**Toxicity risk**

# Management of elders



*Comorbidities*

*Geriatric impairments*

*Specific assessment*

**Lymphoma**



**Appropriate treatment**



**Disease control**



**Toxicity risk**

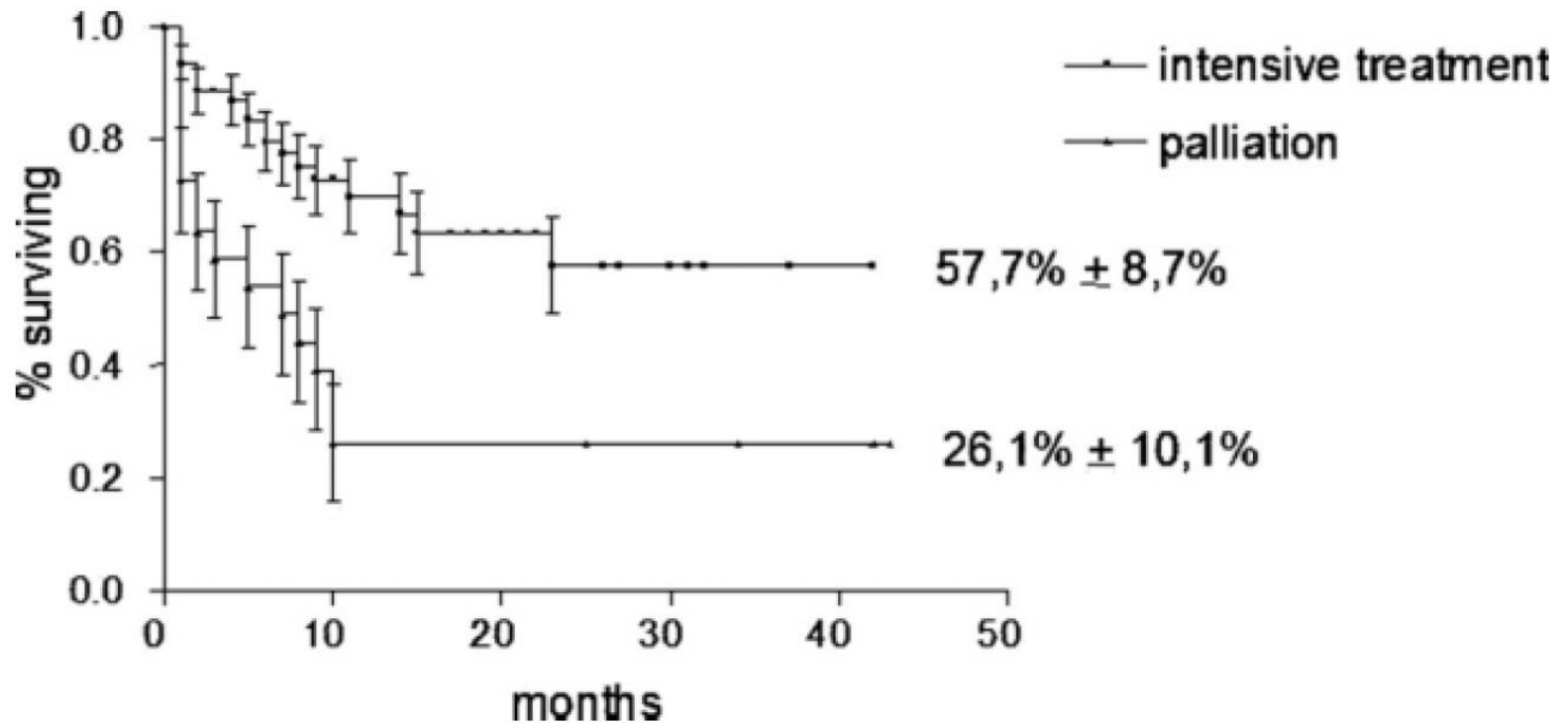


Before treatment decision, identification of risk groups

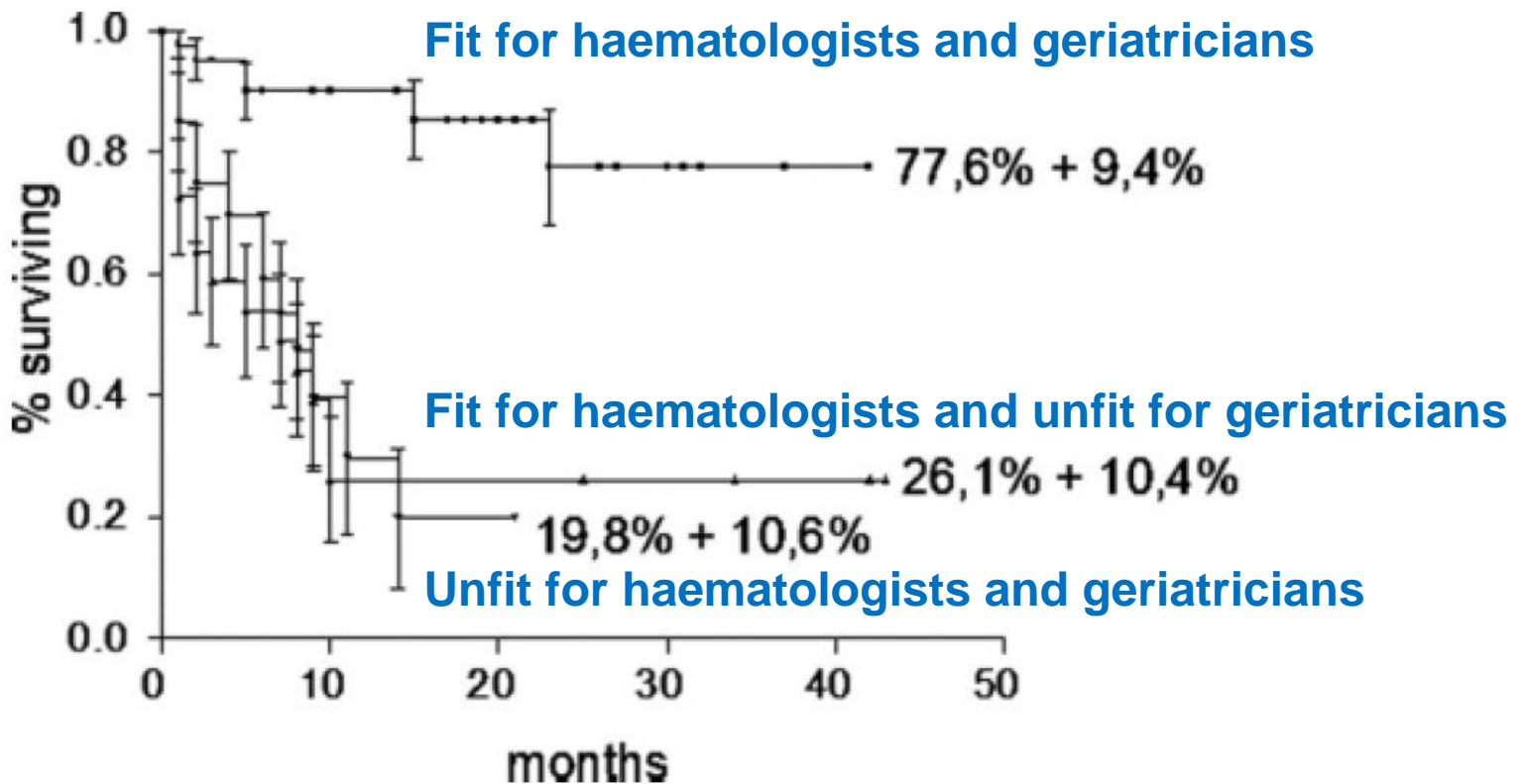
# HOW TO SELECT VULNERABLE AND FRAIL PATIENTS ?

# A. Tucci's prospective study

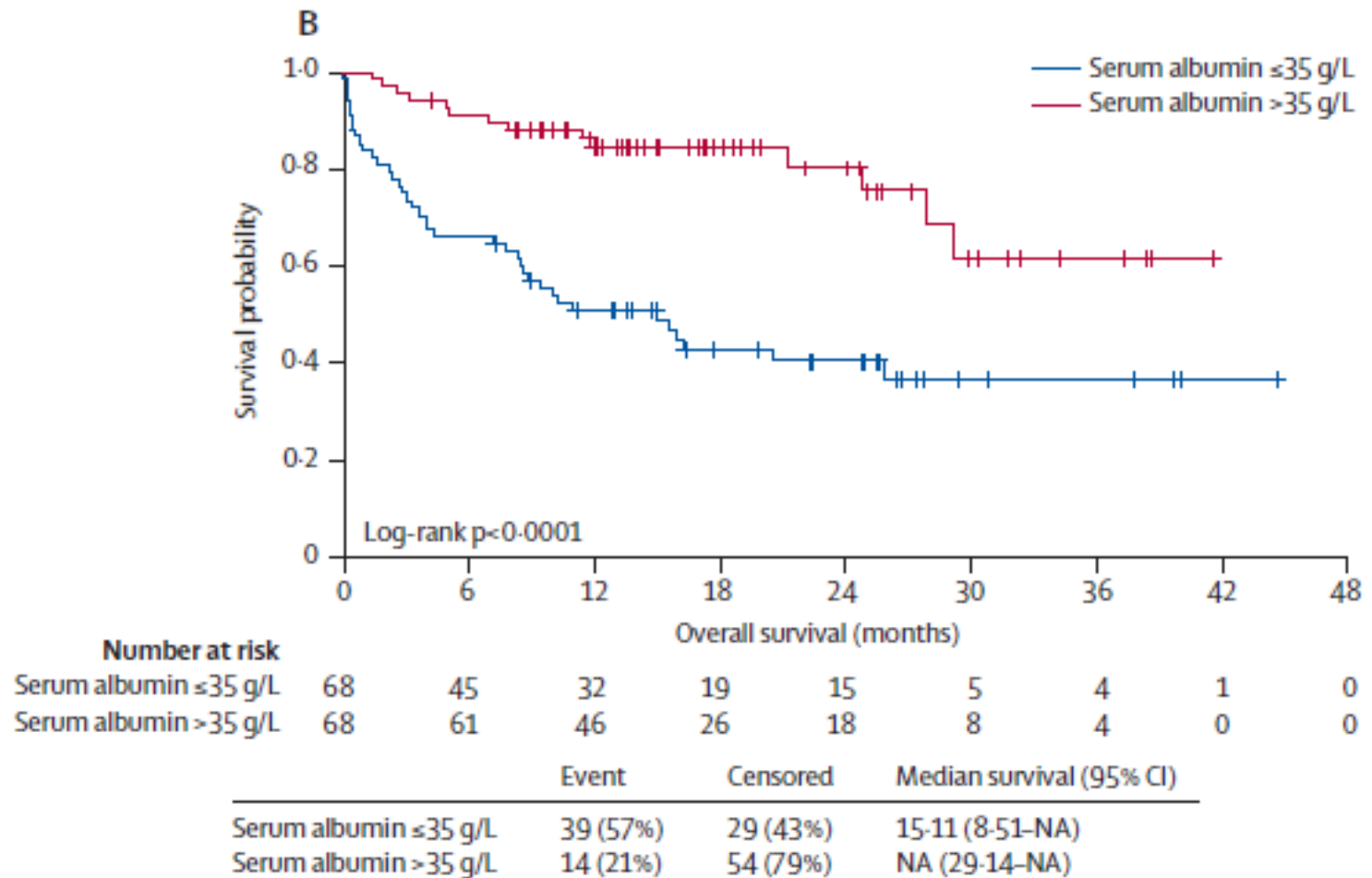
## 84 patients >65 years



# A. Tucci's prospective study

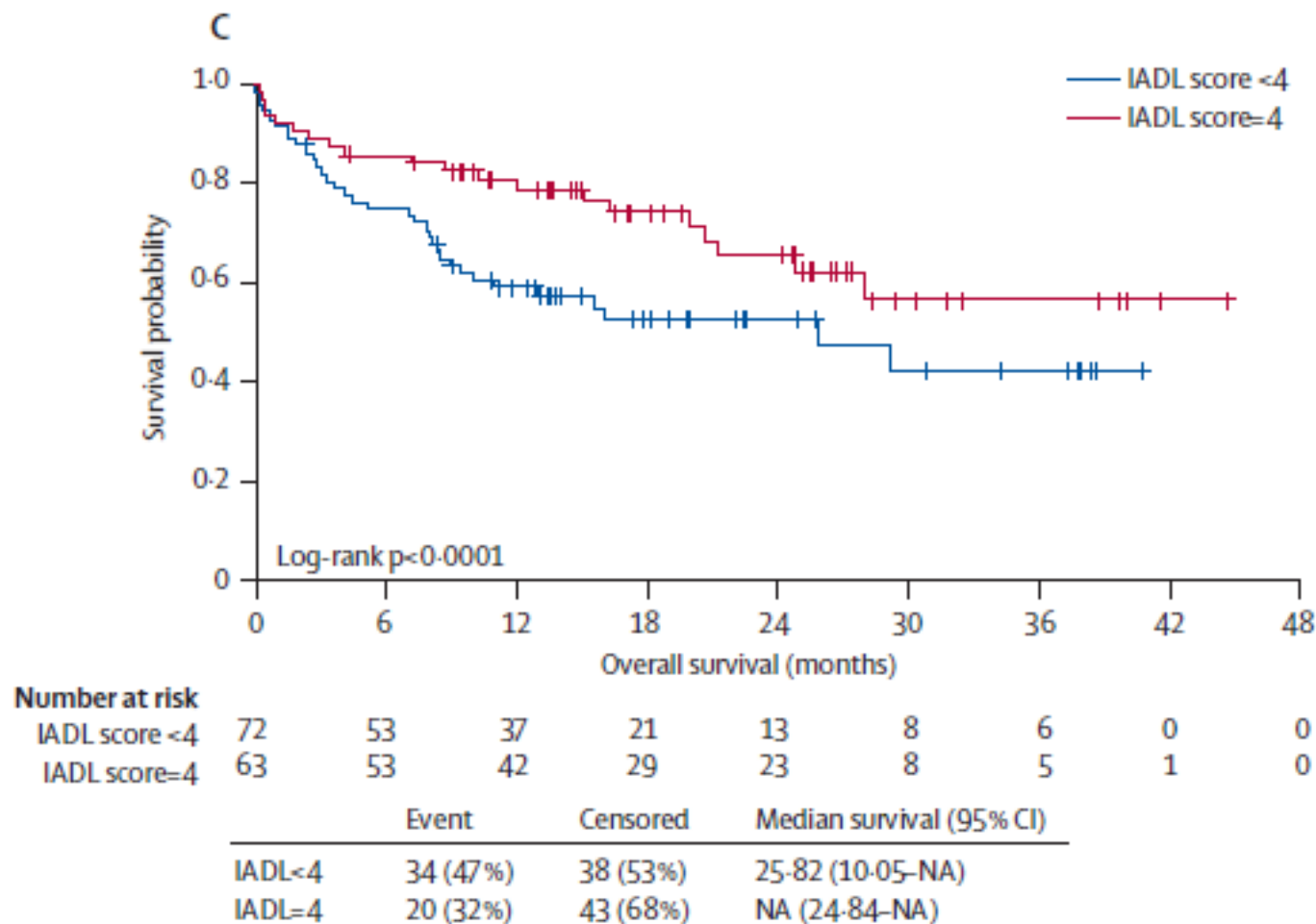


# Fit/Unfit DLBCL > 80 – R-miniCHOP



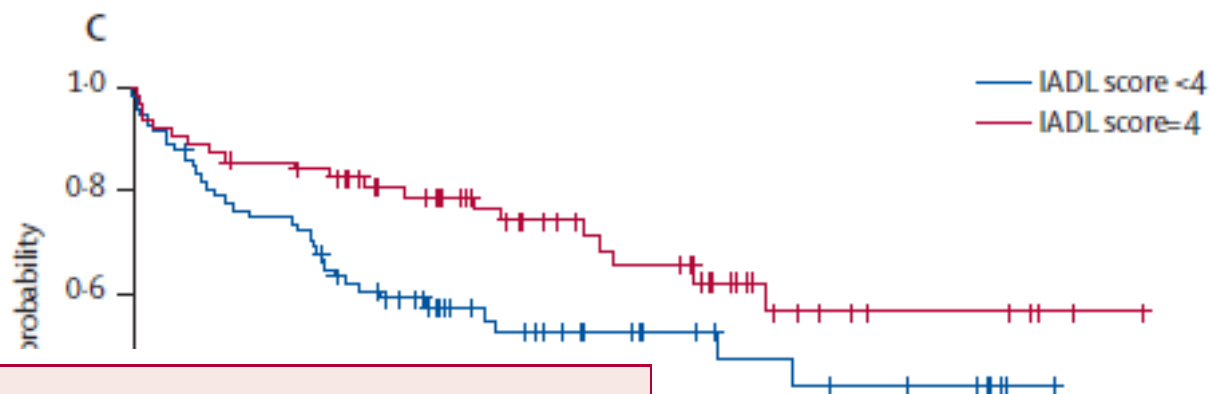
*F Peyrade. Lancet Oncol 2011*

# Fit/Unfit DLBCL > 80 – R-miniCHOP



*F Peyrade. Lancet Oncol 2011*

# Fit/Unfit DLBCL > 80 – R-miniCHOP



	Hazard ratio (95% CI)	p value
Age-adjusted IPI 2-3	1.4 (0.6-3.5)	0.46
Number of extranodal sites >1	1.2 (0.6-2.4)	0.59
Serum albumin ≤35g/L	3.2 (1.4-7.1)	0.0053
β2-microglobulin ≥3mg/L	0.9 (0.4-1.9)	0.75
Tumour mass >10 cm	1.4 (0.6-2.9)	0.43
IADL score <4	1.9 (1.0-3.9)	0.064

IPI=international prognostic index. IADL=instrumental activities of daily living.

**Table 3: Multivariate analyses of prognostic factors for overall survival**

	4	30	36	42	48
(months)					
3	8	6	0	0	0
3	8	5	1	0	0
Median survival (95% CI)					
≥82 (10.05-NA)					
A (24.84-NA)					

*F Peyrade. Lancet Oncol 2011*

# Determinants of the outcome may change with age

# Frailty criteria

## ■ Geriatricians' point of view

- *Patients with appropriate **reserves***
- *From Patients who will not deal with stress*

## ■ Hematologists' point of view

- *Patients who will **tolerate** standard treatment such as R-CHOP*
- *From Patients who cannot receive standard R-CHOP*



# Frailty criteria

- Geriatricians' point of view
  - *Should be **precise** to anticipate adverse events*
  
- Hematologists' point of view
  - *Should be **rapid** to save time*

# Search for predictors of unacceptable events

- **Early events which should not happen**
  - *Early death*
  - *Functional decline*
  - *Severe toxicity*

# Unacceptable clinical events

<b>364 patients</b>	<b>Death &lt; 6 m.</b> <i>Odd ratio (95% CI)</i>	<b>Functional decline</b> <i>Odd ratio (95% CI)</i>	<b>Unplanned hospitalization</b> <i>Odd ratio (95% CI)</i>
<b>Events</b>	<b>59/339</b>	<b>50/299</b>	<b>47/354</b>
<b>Advanced disease</b>	<b>4.1 (1.65-10.1)</b>		
<b>Sex</b>	<b>2.62 (1.31-5.28)</b>		
<b>Platelets &lt; 150 G/l</b>			<b>3.8 (1,3-10,8)</b>
<b>Clinian's opinion</b>		<b>ns</b>	<b>0.51 (0,26-0,99)</b>
<b>PS</b>	<b>ns</b>	<b>ns</b>	
<b>MNA ≤ 23.5</b>	<b>2.91 (1.31-56.48)</b>	<b>ns</b>	<b>4.19 (1,7-10,3)</b>
<b>Get up and go &gt; 20 s</b>	<b>2.51 (1,31-4,82)</b>	<b>ns</b>	
<b>IADL ≤ 7</b>	<b>ns</b>	<b>3 (1,13-8,09)</b>	
<b>GDS15 ≥ 6</b>		<b>2.4 (1,23-4,66)</b>	
<b>MMS</b>	<b>ns</b>	<b>ns</b>	
<b>ADL</b>	<b>ns</b>		
<b>CIRS-G</b>			

*Soubeyran JCO 2012*

*Hoppe JCO 2013*

*Warkus SIOG2011*

**Determinants of the outcome  
may change with age**

**Geriatric assessment data may  
add major information to better  
tailor treatment**

# CGA is time-consuming

In a prospective series of 1435 patients

- *Duration of CGA* **67.7 mn**  $\pm$  24.6



***Screening tools***

*Soubeyran P, Plos One 2014*

# G8 Screening Questionnaire

	Items	Possible answers (score)
<b>A</b>	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 : severe decrease in food intake
		1 : moderate decrease in food intake
		2 : no decrease in food intake
<b>B</b>	Weight loss during the last 3 months	0 : weight loss > 3 kg
		1 : does not know
		2 : weight loss between 1 and 3 kgs
		3 : no weight loss
<b>C</b>	Mobility	0 : bed or chair bound
		1 : able to get out of bed/chair but does not go out
		2 : goes out
<b>E</b>	Neuropsychological problems	0 : severe dementia or depression
		1 : mild dementia or depression
		2 : no psychological problems
<b>F</b>	Body Mass Index (BMI (weight in kg) / (height in m <sup>2</sup> ))	0 : BMI < 19
		1 : BMI = 19 to BMI < 21
		2 : BMI = 21 to BMI < 23
		3 : BMI = 23 and > 23
<b>H</b>	Takes more than 3 medications per day	0 : yes
		1 : no
<b>P</b>	In comparison with other people of the same age, how does the patient consider his/her health status?	0 : not as good
		0.5 : does not know
		1 : as good
		2 : better
	Age	0 : >85
		1 : 80-85
		2 : <80
	<b>TOTAL SCORE</b>	<b>0 – 17</b>

# G8 questionnaire

**Eight questions**

**Performed by a nurse**

**5 to 10 min**

**Appetite, weight loss, BMI  
Mobility**

**Mood and cognition**

**Number of medications**

**Self-related health**

**Age**

**Abnormal if  $\leq 14$**

**Preliminary analysis**

**Se: 89.6% ; Sp: 60.4%**

	Items	Possible answers (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 : severe decrease in food intake
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		0.5 : does not know
		1 : as good
		2 : better
	Age	0 : >85
	1 : 80-85	
	2 : <80	
TOTAL SCORE		0 – 17

## Gold standard: Impaired Multidimensional Geriatric Assessment (MGA)

	Items	Possible answers (score)
<b>A</b>	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 : severe decrease in food intake
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		2 : no decrease in food intake
<b>B</b>	Weight loss during the last 3 months	0 : weight loss > 3 kg
		1 : does not know
		2 : weight loss between 1 and 3 kgs
<b>C</b>	Mobility	0 : no weight loss
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		1 : severe dementia or depression
		2 : mild dementia or depression
<b>F</b>	Body Mass Index (BMI (weight in kg) / (height in m <sup>2</sup> ))	0 : no psychological problems
		0 : BMI < 19
		1 : BMI = 19 to BMI < 21
<b>H</b>	Takes more than 3 medications per day	2 : BMI = 21 to BMI < 23
		3 : BMI = 23 and > 23
		0 : yes
<b>P</b>	In comparison with other people of the same age, how does the patient consider his/her health status?	1 : no
		0 : not as good
		0.5 : does not know
	Age	1 : as good
		2 : better
		0 : >85
	TOTAL SCORE	1 : 80-85
		2 : <80
		0 - 17

### Impaired MGA if

#### ≥ one abnormal questionnaire

- **CIRS-G :** **at least one grade ≥ 3**
- **ADL :** **score ≤ 5**
- **IADL :** **score ≤ 7**
- **Timed Get up and Go :** **> 20 s**
- **MNA :** **score ≤ 23,5**
- **MMSE :** **score ≤ 23**
- **GDS-15 :** **score ≥ 6**

**Setting: Patients >70 with cancer**



## Gold standard: Impaired Multidimensional Geriatric Assessment (MGA)

	Items	Possible answers (score)
<b>A</b>	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 : severe decrease in food intake 1 : moderate decrease in food intake 2 : no decrease in food intake
<b>B</b>	Weight loss	
<b>C</b>	Mobility	
<b>E</b>	Neuropsych	
<b>F</b>	Body Mass (height in m)	
<b>H</b>	Takes more	
<b>P</b>	In comparis same age, h his/her heal	
		2 : better
	Age	0 : >85 1 : 80-85 2 : <80
	TOTAL SCORE	0 - 17

**Impaired MGA if**  
**≥ one abnormal questionnaire**

		Se	Sp	PPV	NPV	K	Time (mn)
<b>G8</b>		<b>76.6%</b> (74-79)	<b>64.4%</b> (58.6-70)	<b>89.6%</b> (87.6-91.5)	<b>40.7%</b> (36.1-45.4)	<b>0.65</b>	<b>4.4 +/- 2.9</b>
<b>VES13</b>		<b>68.7%</b> (65.9-71.4)	<b>74.3%</b> (68.8-79.3)	<b>91.5%</b> (89.4-93.3)	<b>37.1%</b> (33.2-41.3)	<b>0.64</b>	<b>4.3 +/- 4.6</b>

– **GDS-15 :** **score ≥ 6**

**Setting: Patients >70 with cancer**

# Prediction of geriatric domain impairments

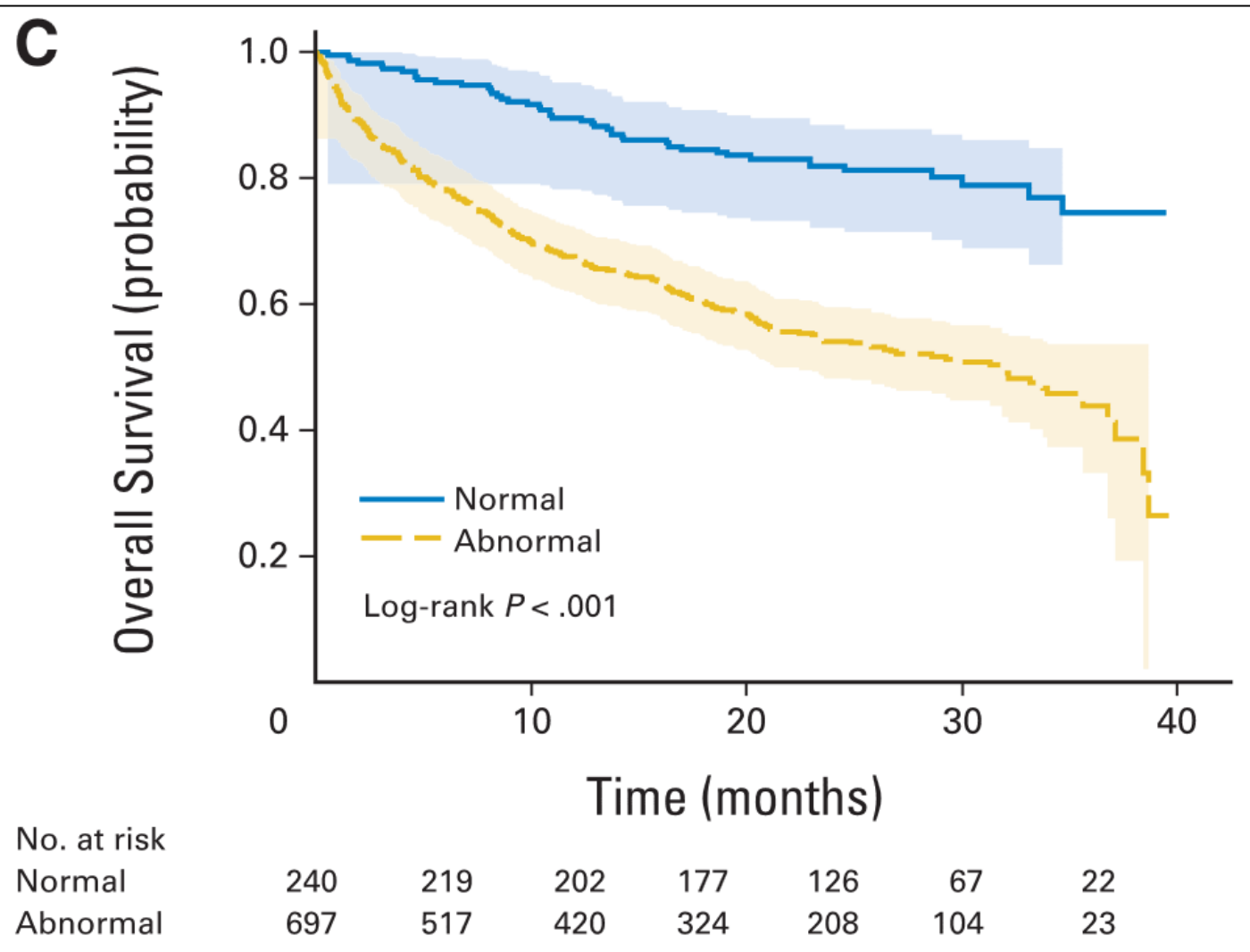
## ■ Detection of

- *Abnormal MNA* 94,4%
- *Abnormal ADL* 93,6%
- *Abnormal TGUG* 91,3%
- *Abnormal GDS15* 84,8%
- *Abnormal IADL* 84,5%
- *Abnormal MMS* 80,5%
- *CLRS-G grade 3 – 4* 77,4%

# G8 has survival prognostic value

	Univariate analysis (1365 patients)		Multivariate analysis (1167 patients)	
	Hazard ratio (95% CI*)	P value	Hazard ratio (95% CI*)	P value
Age				
70 – 74	Reference	0.0024	Reference	0.5582
75 - 79	1.12 (0.78 to 1.59)		0.85 (0.57 to 1.25)	
80 - 84	1.49 (1.04 to 2.12)		0.88 (0.60 to 1.30)	
85 and over	1.95 (1.33 to 2.88)		0.72 (0.45 to 1.14)	
Sex				
Female	Reference	<0.0001	Reference	<0.0001
Male	3.09 (2.40 to 3.99)		2.69 (2.02 to 3.58)	
ECOG PS*				
0-1	Reference	<0.0001	Reference	<0.0001
2-4	5.30 (4.07 to 6.90)		3.28 (2.41 to 4.46)	
Stage				
Non-metastatic	Reference	<0.0001	Reference	<0.0001
Mx**	1.09 (0.69 to 1.69)		1.14 (0.72 to 1.79)	
Metastatic	5.67 (4.23 to 7.60)		3.30 (2.42 to 4.50)	
G8				
Normal	Reference	<0.0001	Reference	<0.0001
Abnormal	4.72 (3.07 to 7.26)		2.72 (1.66 to 4.47)	

# G8 has survival prognostic value



value

.5582

0.0001

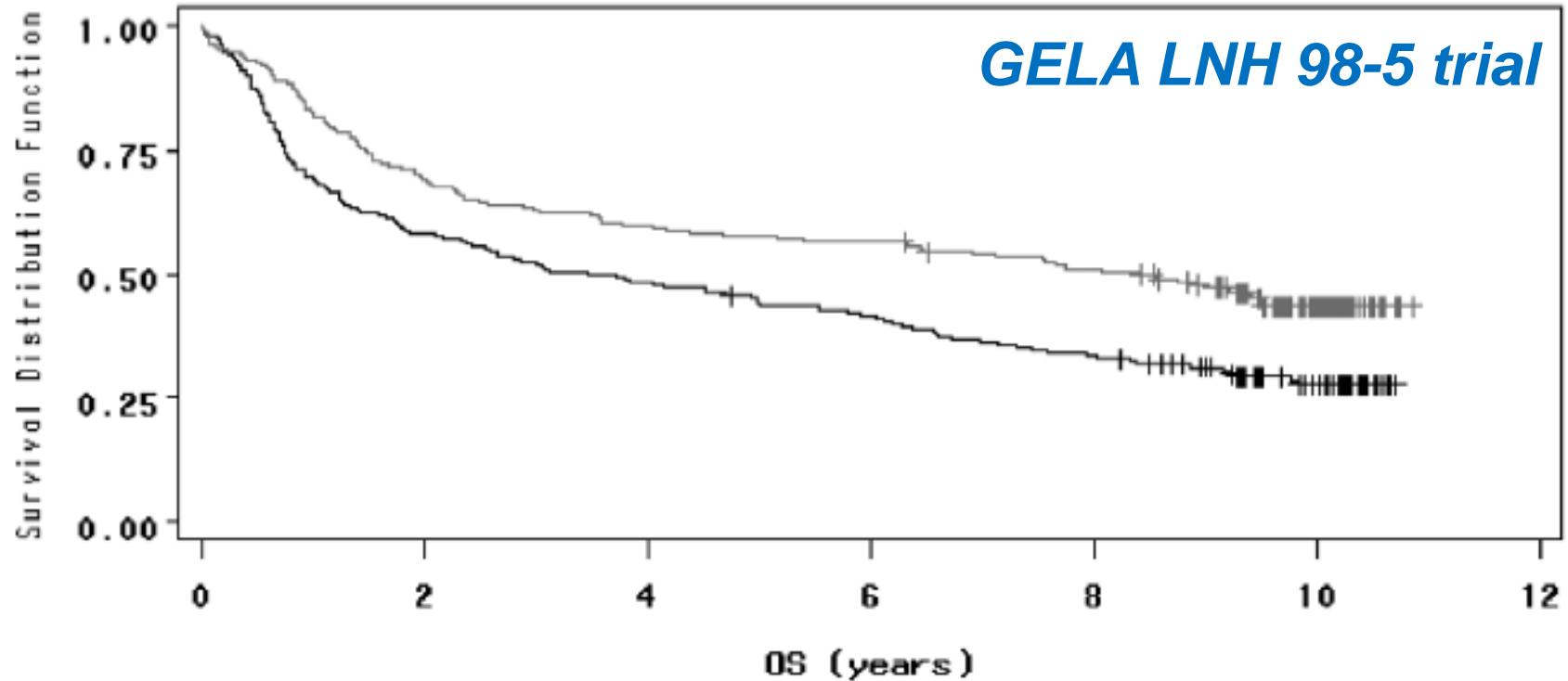
0.0001

0.0001

0.0001

# HOW TO TREAT VULNERABLE AND FRAIL PATIENTS ?

# Fit DLBCL – R-CHOP

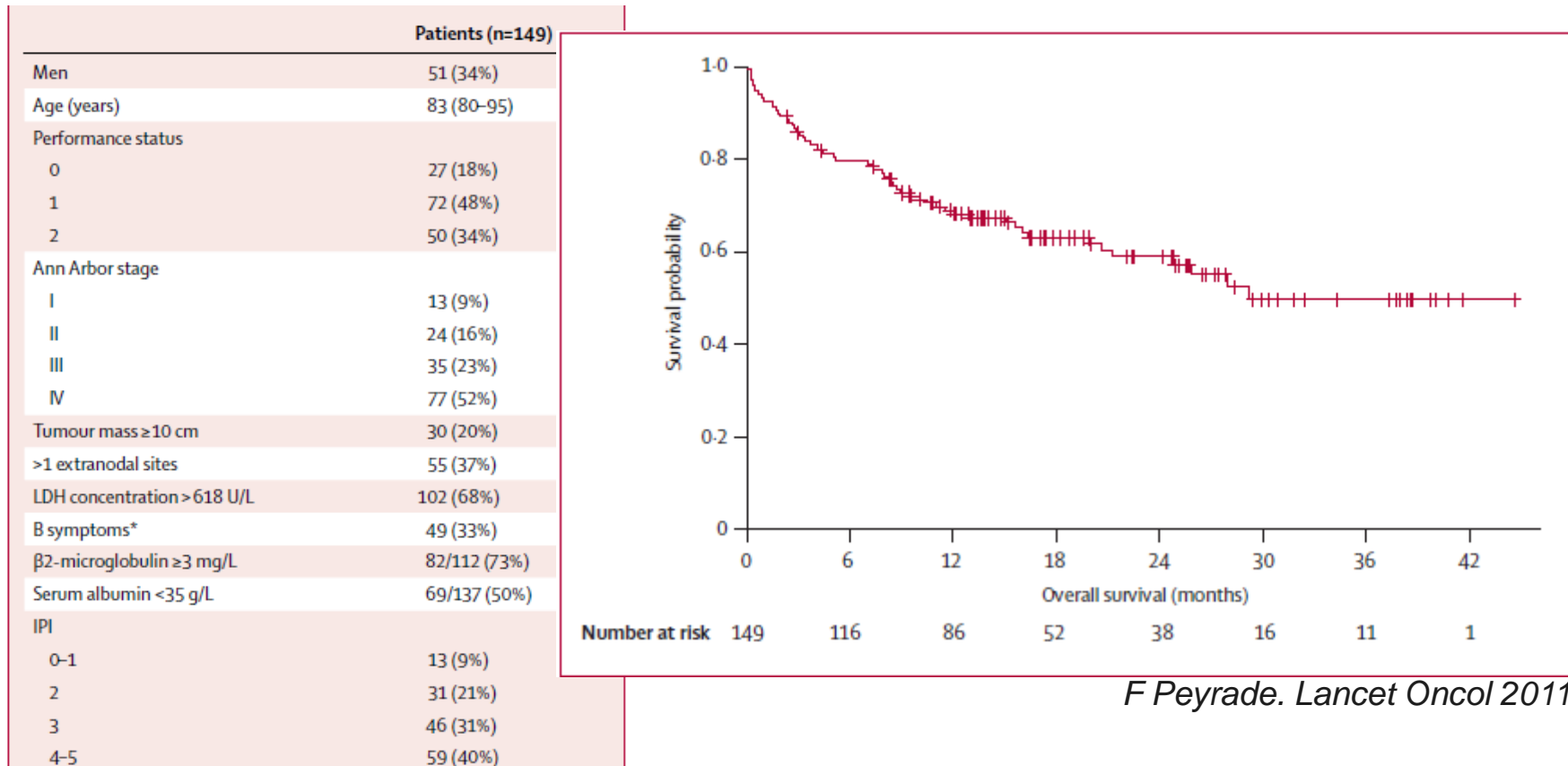


**202 R-CHOP patients**

**13% deaths from treatment-related toxicity**

# Fit/Unfit DLBCL > 80

**149 patients treated by R-MiniCHOP- 62% CR-CRu**  
**12 deaths from treatment toxicity (8%)**  
**13 deaths unrelated to lymphoma or treatment (8.7%)**



F Peyrade. Lancet Oncol 2011

**DLBCL > 70**

**R-CHOP not feasible**

**Pretreatment work-up**

**Lymphoma**

**CGA**

**Ⓡ**

**R-COP**

**R-COPY**

**Liposomal doxorubicin reduced dose**

**Geriatric assessment and management  
allowed**



# Bryant and Day design

## *First step*

	20 pts per arm	Target	R-COP	R-COPY
CR-CRu		$\geq 4$	6	12
Severe toxicity	Febrile neutropenia		0	7
	Toxic death		2	1
	All events	$\leq 3$	2	8

**Design suggest to stop R-COPY arm**

*IDMC confirmed the decision*

**Pursue R-COP arm alone up to 47 pts**

# Patients' characteristics

## *Poor physiological status*

67 patients	n	%
Creatinine clearance <50 ml/mn	35	52
PS 3	32	48
LVEF <50%	8	12
Comorbidities	8	12
Serum bilirubin >30 $\mu$ mol/l	2	3

**Patients entered the trial mainly because of low creatinine clearance or poor PS**

# Patients' characteristics

## *Geriatric assessment*

Abnormal	%	ONCODAGE
ADL	39%	15,2%
IADL	66%	47,9%
GDS15	42%	32,1%
MNA	64%	43,7%
MMS	45%	20,3%
CIRS-G grade 3-4	42%	41,8%

**Patients with geriatric adverse features**

# Bryant and Day design

## *Second step*

	47 pts	Target	R-COP	%
CR-CRu		$\geq 10$	<b>19</b>	40,4
Severe toxicity	Febrile neutropenia		7	14,9
	Toxic death		4	8,5
	All events	$\leq 5$	<b>10</b>	21,3

# Response at the end of treatment

		R-COP	%	R-COPY	%
<b>Withdrawal from treatment</b>	Total	23	<b>48,9</b>	6	<b>30</b>
	Progression	12	<b>25,5</b>	1	<b>5</b>
	Death, toxicity or general deterioration	11	<b>23,4</b>	5	<b>25</b>
<b>CR + CRu</b>		19	<b>40,4</b>	12	<b>60</b>

# Results at the end of treatment

	R-COP (47 pts)	R-COPY (20 pts)
aalPI 2-3	85%	80%
<b>RC + RCu</b>	<b>19 (40%)</b>	12 (60%)
<b>Progression</b>	<b>8 (17%)</b>	1 (5%)
<b>Response duration for CR/CRu</b>	<b>15,5 mois</b>	38,5 mois
<b>Febrile Neutropenia</b>	7 (15%)	<b>7 (35%)</b>
<b>Mucositis</b>	4 (9%)	<b>3 (16%)</b>
<b>Number of days hosp. for toxicity</b>	2,5 days	<b>4,8 days</b>
Toxic deaths	4 (8,5%)	1 (5%)
Median follow-up	22,95 m	51,08 m
Median survival	20,1 mois	25,4 mois
<b>2-year survival</b>	<b>39,4%</b>	50%

# Conclusions



- **None of the two regimens appear appropriate in this population of frail elderly**
  - *R-COPY is more efficacious but more toxic*
  - *R-COP is less toxic but less efficient*
  - *Both reached the toxicity stopping rules which are however debatable*
- **When appropriately managed, febrile neutropenia is not life-threatening**

# First Conclusions

- **None of the two regimens is perfect for vulnerable and frail patients BUT**
- **Possible solutions**
  - ***Firstly, exclusion of patients based on CGA***
    - Identification of patients who should be treated palliatively
  - ***For the remaining patients:***
    - **Proposal 1: R-COPY/R-CHOP-like as a standard**
      - But geriatricians should keep close to hematologists
    - **Proposal 2: R-COP plus targeted treatment**
      - R-COP as a basis for addition of targeted therapies
      - With better efficacy/toxicity ratio
      - Previous exclusion may be avoided



# Search for predictive factors of treatment success

## ■ Definition of Success

- *Treatment completed*
- *Responder*
- *Alive at 6 months*

## ■ Success = 34 pts (45% R-COP / 65% R-COPY)

## ■ Factors

- *IPI, sex, PS, geriatric assessment, treatment arm*

## ■ Results

- *5 factors retained at the univariate level (treatment arm, IPI, MMS, ADL, MNA) adjusted for sex*
- *Only one is predictive after multivariate analysis: MNA  
OR=4,5 (95CI: 1,2-17,2)*

# Search for predictive factors of treatment success

MNA	Failure	%	Success	%
<b>Normal</b> (reference)	5	29,5	12	<b>70,5</b>
<b>Abnormal</b>	26	60,5	17	<b>39,5</b>
Missing	7			

# Conclusions

- Geriatric assessment data has potential utility in treatment decision making
- It's time-consuming so that screening tools should be proposed first
- Screening tools may help but are not sufficient to take a decision

# Conclusions

- **The frontier between fit and unfit may vary according to treatment and disease**
- **Anthracyclines remain major drugs** but some patients should probably be treated palliatively
- Some toxicities and complications can be managed with the **help of geriatricians**



**Thank you**