

# **Geriatric cancer management**

**ASCO MULTIDISCIPLINARY CANCER  
MANAGEMENT COURSE**

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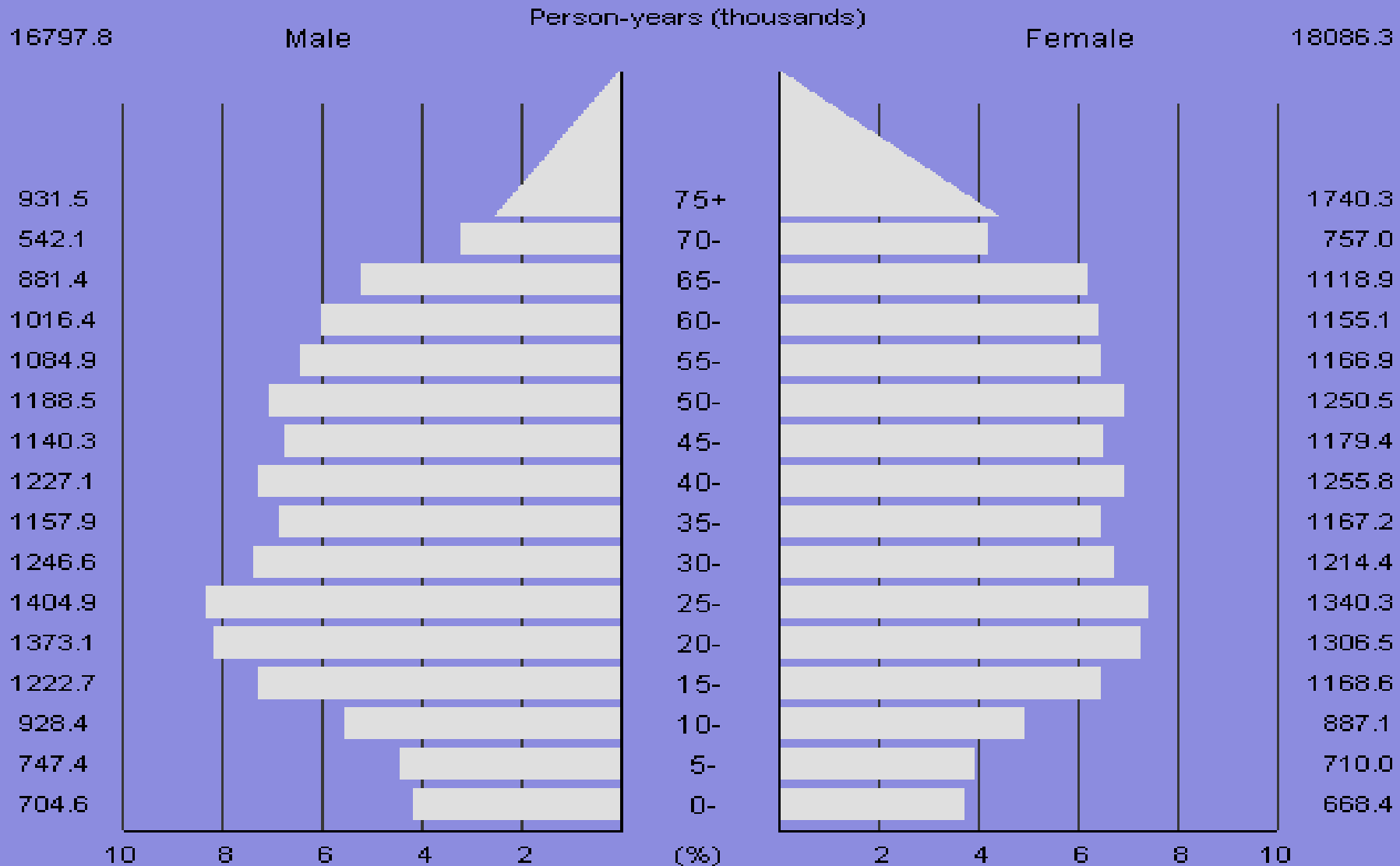
***Centro di Riferimento Oncologico, Aviano, Italy***

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# Age distribution of the Italian population

## Multidisciplinary Cancer Management Course



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## Pharmacology and aging

- *Aging brings about a progressive decrease in physiologic reserve that affects each individual at a unique pace.*
- *The physiologic decline begins in the 3rd decade of life*
- *It may not be apparent at rest, but becomes apparent in stress conditions, such as cancer and treatment*
- *A number of age-related changes in drug absorption, distribution, excretion*

## Absorption

- ***Decreased GI motility***
- ***Decreased splanchnic blood flow***
- ***Decreased secretion of digestive enzymes***
- ***Mucosal atrophy***

## Distribution

- ***Increase in body fat, decrease in lean mass and total body water***
- ***Rise in the volume of distribution for lipid soluble drugs, decrease for hydrophilic drugs***
- ***Hypoalbuminemia causes increase of unbound concentration of albumin-bound drugs***

## Excretion (I) - Liver

- *Hepatic mass and blood flow decrease with age*
- *Impact of age upon P450 activity*
- *In 226 pts, the P450 content in the liver decreased by 30% over 70 years of age*

# Excretion (II) - Kidney

- *Over a life span, renal mass decreases by 25-30% and renal blood flow decreases by 1% per year after 50*
- *Decline in GFR about 0.75 mL/min per year after age 40*
- *Often no increase in serum creatinine due to simultaneous loss of muscle mass*
- *Cockcroft and other formulas to be taken with some caution*

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## Preventing toxicity of drugs with predominant renal excretion (I)

- *Hydration status should be optimized and renal function evaluated to establish possible need for dose adjustment.*
- *Serum creatinine alone is insufficient in evaluating renal function.*
- *More accurate tools, including creatinine clearance methods such as Cockcroft-Gault, are available and generally provide accurate indices of a patient's renal function status. However, in older patients, these equations are not as precise as in a younger population.*

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## Preventing toxicity of drugs with predominant renal excretion (II)

- *When dealing with extremes of obesity and cachexia or very high and low creatinine values, no single tool is completely accurate.*
- *Preference should be given to agents that are less likely to be influenced by renal clearance, less toxic to the kidneys or for which there are ways to prevent renal toxicity.*

# Impact of age on PK of some CT drugs

- *Paclitaxel: Increased AUC, decreased clearance*
- *Docetaxel: No difference*
- *Vinorelbine: Increased AUC, decreased clearance*
- *Methotrexate: Decreased clearance*
- *Etoposide: Increased blood concentration*
- *Doxorubicin: lower clearance*
- *Oxaliplatin: no difference*

## Main drug-related toxicities

- **Bone-marrow** (anthracyclines, alkylating agents, taxanes, vinorelbine)
- **Mucosae** (anthracyclines, alkylating agents, fluoropyrimidines, vinorelbine)
- **Heart** (anthracyclines)
- **Peripheral nervous system** (taxanes, vinorelbine)
- **Hand-foot syndrome** (fluoropyrimidine, taxanes)

## One question:

***Is advanced age associated with increased toxicity per se or through PK mechanisms?***

***In other words:***

***If an elderly patient has normal excretory function and hemoglobin and albumin levels, can we proceed without dose adjustment?***

## Answer (tentative):

***Consider that not all toxicities are mediated by PK (e.g. bone marrow, neurotoxicity)***

***Geriatric assessment can capture features that independently predict morbidity and mortality (comorbidities, functional, cognitive, nutritional and psychological status)***

# The case of breast cancer: which adjuvant therapy in the elderly?

- *Life-expectancy.*
- *Risk of cancer recurrence without and with treatment.*
- *Presence and degree of comorbid conditions.*
- *Geriatric assessment.*
- *Treatment related toxicities.*
- *Patient preferences.*

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### Baseline life expectancy for women with various ages and comorbidity levels

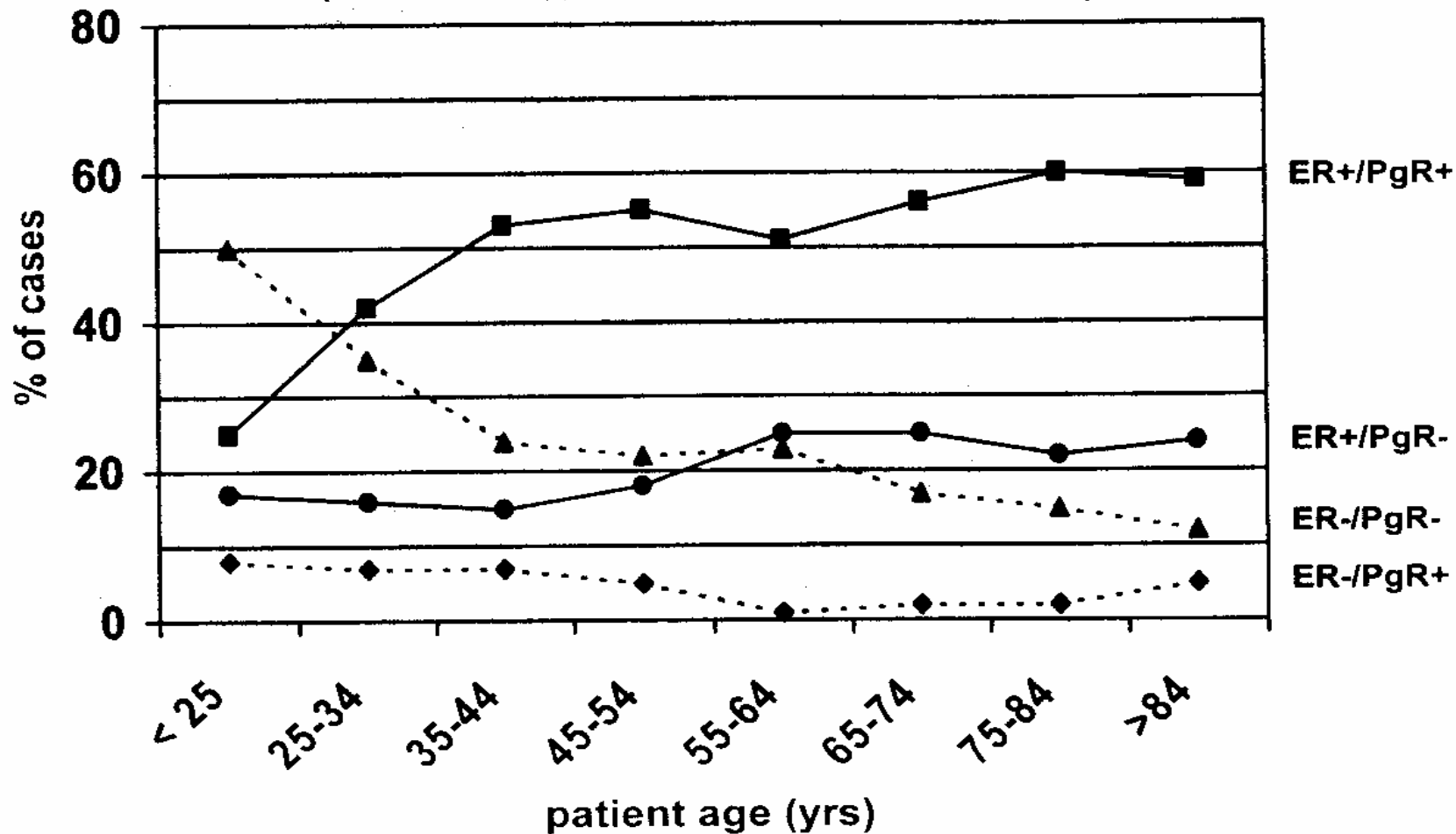
#### Life expectancy (years)

Age (years)	Healthy	Average	Sick
65	20.0	18.5	9.7
70	15.8	14.8	8.6
75	12.1	11.5	7.3
80	8.8	8.4	5.9
85	6.1	5.9	4.5

*Extermann et al, JCO, 2000.*

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ER and PgR status as a function of patient age in 13,517 breast cancer  
(Daidone et al, Crit Rev Oncol Hemato 2003)



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## Adjuvant endocrine therapy outcome EBCTCG, Lancet 1998 and 2005

	10 yrs (1998)		15 yrs (2005)	
Age	DFS	OS	DFS	OS
<50	47	30	44	39
50-59	45	20	34	24
60-69	54	33	45	35
70+	54	34	51	37

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## Adjuvant chemotherapy outcome

EBCTCG, Lancet 1998 and 2005

	10 yrs (1998)		15 yrs (2005)	
Age	DFS	OS	DFS	OS
<50	34	27	36	30
50-59	22	14	23	15
60-69	18	8	13	9
70+	-	-	-	-

## REASONS FOR PAUCITY OF DATA

- *Exclusion criteria for age in clinical trials*
- *Physician bias : patients will not benefit, will not tolerate, or both*
- *Patients and family members: refuse chemotherapy when it is offered*

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## International Breast Cancer Study Group Trial VII

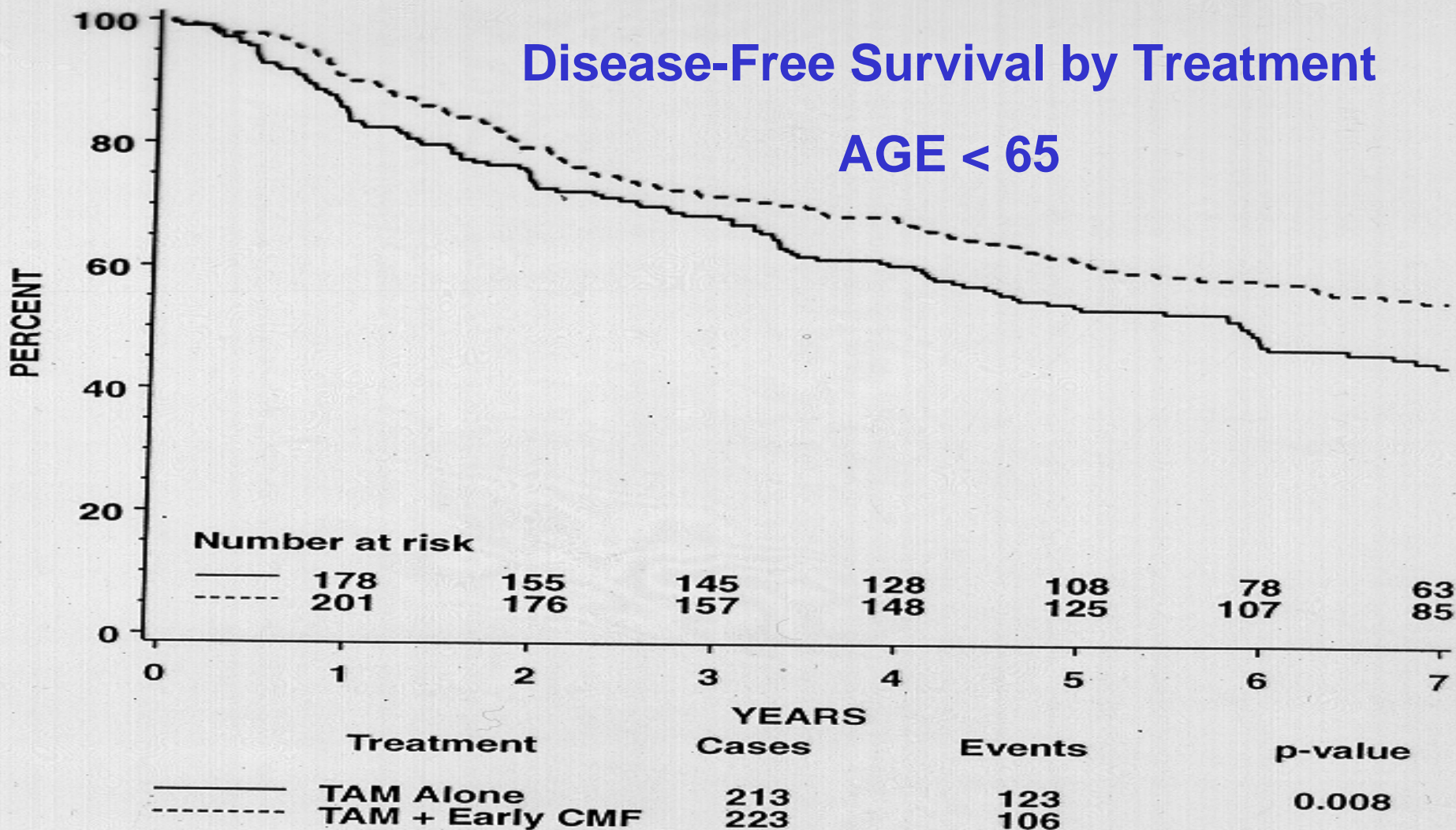
- *Around 600 women with N+ operated breast cancer were randomized to:*
- *TAM alone (213 <65aa; 93 ≥65aa)*  
*or*
- *TAM+CMF(223 <65aa; 79 ≥65aa) for 3 cycles*

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Distribution of worst grade of toxicity according to type of toxicity and age category for 299 assessable patients who received CMF chemotherapy. IBCSG Study VII

	Hematologic T.		Mucosal T		Other T.		Worst Grade3/4 Any Toxicity	
	<65	>65	<65	>65	<65	>65	<65	>65
Age at entry	<65	>65	<65	>65	<65	>65	<65	>65
N° of patients	223	76	223	76	223	76	223	76
Percent of patients with:								
Grade 0	12.6	9.2	72.2	55.3	15.3	18.4	3.6	2.6
Grade 1	53.4	30.3	19.3	27.6	45.3	50.0	37.7	23.7
Grade 2	29.6	51.3	7.6	13.2	36.8	25.0	51.6	56.6
Grade 3	4.5	9.2	0.9	4.0	2.7	6.6	7.2	17.1
<i>p-value</i>	0.0002		0.004		0.0335		0.004	

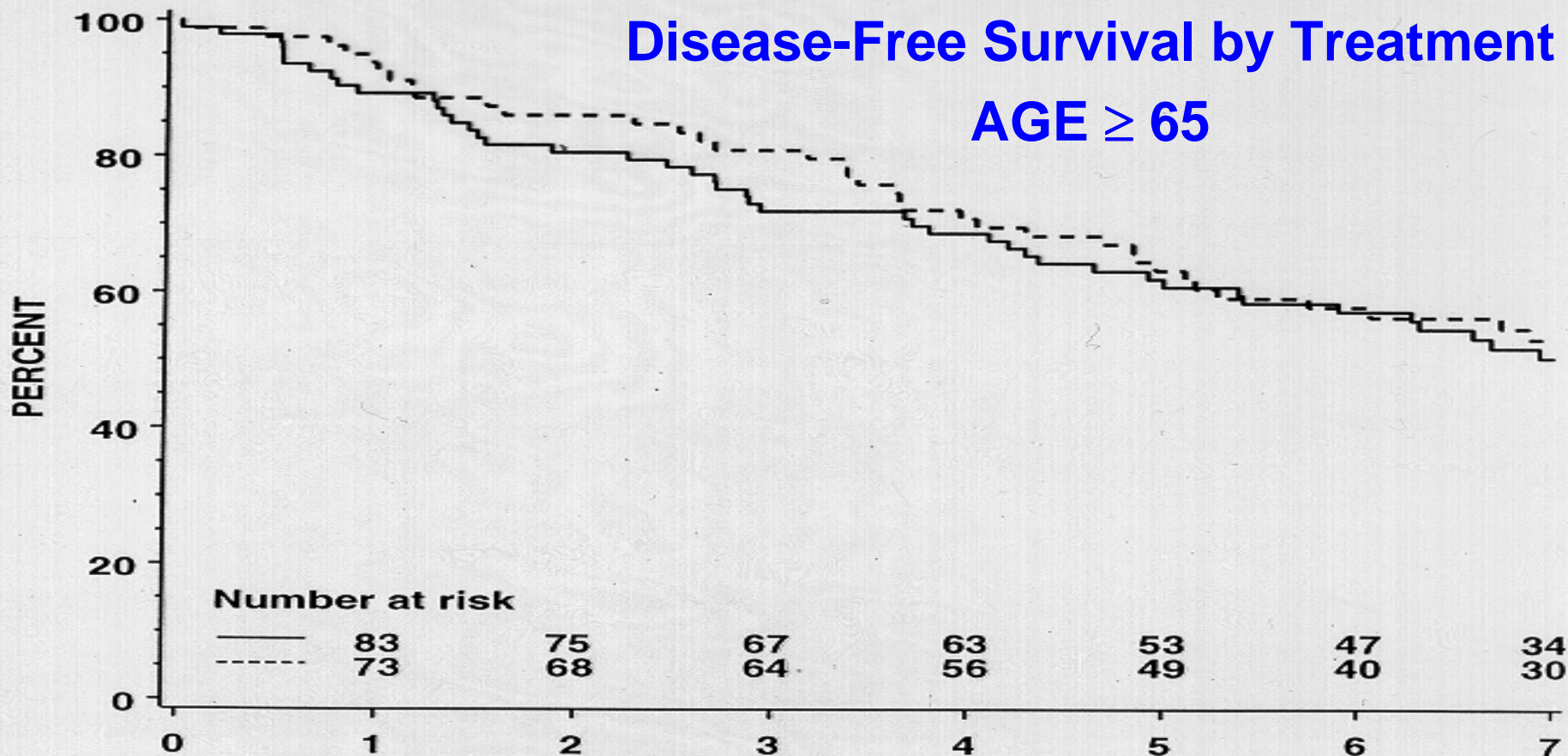
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Crivellari et al, JCO 2000

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## Disease-Free Survival by Treatment AGE ≥ 65



Treatment	Cases	Events	p-value
TAM Alone	93	48	0.99
TAM + Early CMF	79	41	

Crivellari et al, JCO 2000

# Trials Evaluating Additive Value of Anthracycline-Based regimens to Tamoxifen in Postmenopausal Patients with Node-Positive Breast Cancer

<b>GROUP</b>	<b>NUMBER OF PATIENTS</b>	<b>REGIMEN</b>	<b>MEDIAN FOLLOW-UP</b>	<b>DFS</b>	<b>OS</b>
<b>FARGEOT</b>	<b>338</b>	<b>Tamoxifen vs.Epirubicin/Tamoxifen</b>	<b>6 years</b>	<b>Benefit</b>	<b>No benefit</b>
<b>WILS</b>	<b>604</b>	<b>Tamoxifen vs.Tamoxifen/Epirubicin</b>	<b>5.7 years</b>	<b>Benefit</b>	<b>No Benefit</b>
<b>FISHER</b>	<b>1124</b>	<b>Tamoxifen vs. AC/Tam vs.PAF/Tam</b>	<b>3 years</b>	<b>Benefit</b>	<b>Benefit with Doxorubicin/Cyclophosphamide</b>
<b>ALBAIN</b>	<b>1477</b>	<b>Tamoxifen vs.CAF/Tam vs. CAF followed by Tam</b>	<b>8.5 years</b>	<b>Benefit only for N &gt;3</b>	<b>Benefit</b>
<b>FARGEOT</b>	<b>335</b>	<b>Tamoxifen vs.FEC/Tam</b>	<b>4 years</b>	<b>Benefit</b>	<b>NA</b>

## FASG 08 Trial

**N+, ≥ 65 years**

**R  
A  
+  
N  
D  
O  
M**



**Epirubicin 30 mg d 1,8,15 q 4 wk x 6**



**Tamoxifen 30 mg p.o. qd x 3 y**

**Tamoxifen 30 mg p.o. qd x 3 y**

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## FASG 08 Trial

Table 5. Six-Year DFS Stratified on Hormone Receptor Status

Hormone Receptors	TAM	EPI-TAM	P
Positive			
No. of patients	127	132	
Relapse, %	25.2	20.5	
6-year DFS, %	74.3	76.2	.29
Negative			
No. of patients	16	20	
Relapse, %	75.0	45.0	
6-year DFS, %	20.8	51.2	.01
Stratified log-rank			.03

Abbreviations: TAM, tamoxifen; EPI-TAM, epirubicin plus TAM; DFS, disease-free survival.

# Chemotherapy Adjuvant Study for Women at Advanced Age (CASA)

- Phase III Trial Evaluating the Role of Adjuvant Pegylated Liposomal Doxorubicin (PLD, Caelyx®, Doxil®) for Women (age 66 years or older) with Endocrine **Non-Responsive** Breast Cancer Who Are **NOT Suitable** for Being Offered a “Standard Chemotherapy Regimen”
- **Two Individual Complementary Randomization Options:**
- **Option 1:** CASA-nil (PLD versus nil)
- **Option 2:** CASA-CM (PLD versus CM)
- **Coordinating Group: IBCSG**

## Summing up:

- *Few trials in the elderly*
- *In elderly trials, selection bias*
- *In selected patients, treatment as effective but more toxic*
- *Population studies suggest that a minor group (30%-40%) is treated and that age (and comorbidities) represent a strong deterrent to adjuvant treatment*
- *A standard treatment in high-risk cases impacts upon survival*