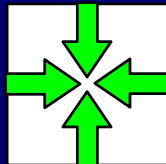


PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

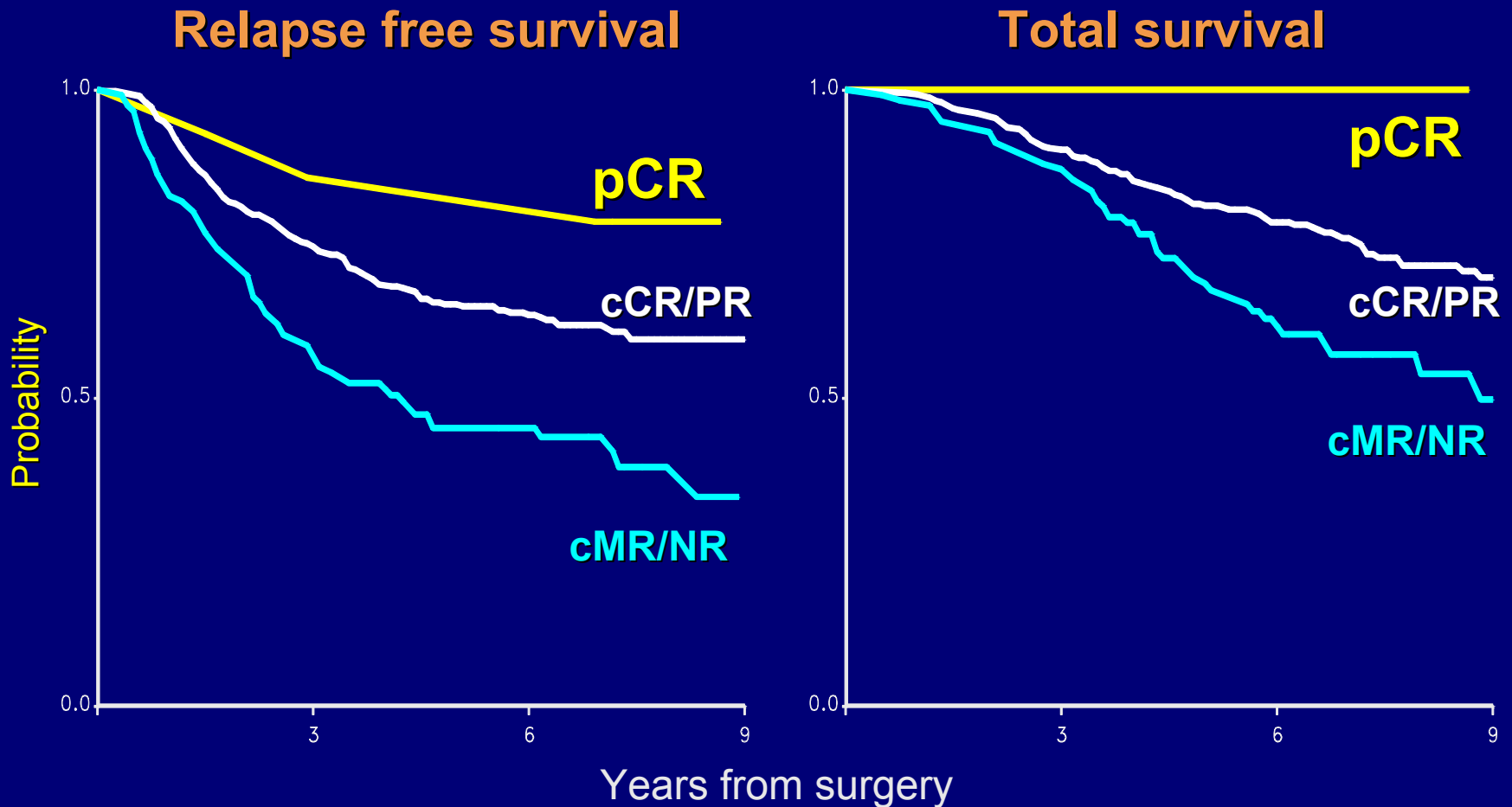
Some relevant points of the European Experience



Fondazione IRCCS
ISTITUTO NAZIONALE
DEI TUMORI
DI MILANO

Luca Gianni

Primary Chemotherapy in Resectable Breast Cancer



First Generation of Randomized Trials 1985 -1999

1st Author	# patients	Median FU (yr)
Mauriac	272	10
Fisher	1,523	9
Scholl	390	9
Jakesz	423	5
Powles	293	~5
Van der Hage	698	~5
Semiglazov	271	~5

Rate of Initial Breast Conservation

1st Author	Adjuvant (%)	PC (%)
Mauriac	0*	63
Fisher	60	68
Scholl	78	82
Jakesz	59	67
Powles	78	90
Van der Hage	22	35
Semiglazov	0*	0*

*BC not planned per protocol

First Generation of Randomized Trials 1985 -1999

Primary chemotherapy

- is at least as effective as classical adjuvant chemotherapy
- downstages tumors and allows for high rate of conservative loco-regional treatment (lumpectomy/quadrantectomy)
- *pathologic complete response (pCR) independently predicts for efficacy outcomes*

Focus on pCR in New Generation Neoadjuvant Chemotherapy Studies

QUESTION

- How can pCR rate be improved?
- Does Improved pCR improve efficacy?
- Can pCR be predicted?
- Is pCR prediction useful?

TEST

- ⇒ New drugs (taxanes; gemcitabine; trastuzumab)
- ⇒ New regimens (dose-dense; sequential)
- ⇒ First v. second generation regimens
- ⇒ Classical variables (hormone receptors; T and N; etc.)
- ⇒ Pharmacogenomics
- ⇒ Prospective validation

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New Drugs/Regimens and pCR

1st Author	N°pts	Regimen	pCR
Evans TR	363	AC x 6	24
		AD x 6	21
Gianni L	451	AT x 4 → CMF x 4	23
Diéras V	200	AT x 4	16
		AC x 4	10
Amat S	88	D x 6	20
Estévez L	56	Dw6/8 x 2	16
Estévez L	63	AC x 4 → Dw6/8 x 2	16
Bellet M	34	XD x 4	20
Schneeweiss A	63	GED x 6	25

Dose Dense Schedules and pCR

1st Author	N°pts	Regimen	pCR
von Minckwitz G	912	ddAD x 4	11
		AC x 4 → D x 4	22
Untch M	631	ddE x 3 → ddT x 3	18
		ET x 4	10
Romieu G	43	ddD x 4 → FEC100 x 3	50
García-Mata J	54	ddD x 4 → ddAC x 4	12
Cramer EM	81	ddEC x 4 → ddD x 4	25
Schneeweiss A	37	ddGE x 5 → ddD x 4	24
Levy E	62	[ddGDx2 → ddEVx2] x 2	27

Sequential regimens and pCR

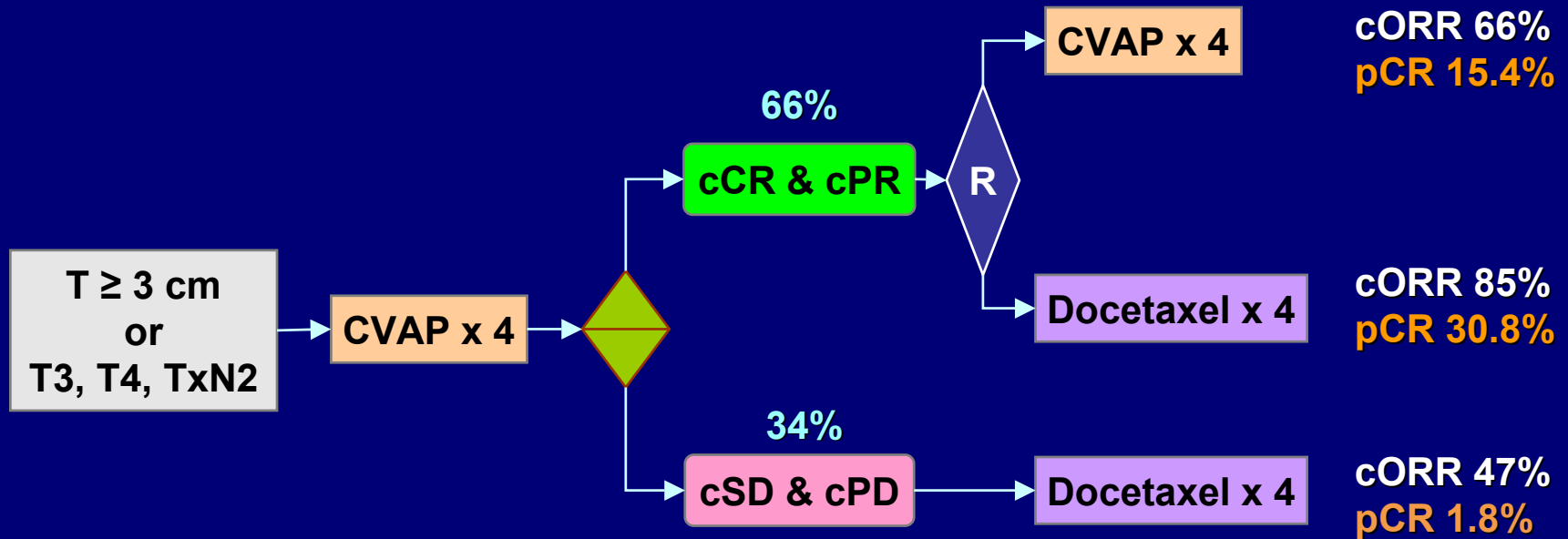
1st Author	N°pts	Regimen	pCR
Smith I	162	CVAP x 4 [R] → CVAP x 4	15
		CVAP x 4 [R] → D x 4	31
		CVAP x 4 [NR] → D x 4	2
von Minckwitz G	2106	TAC x 2 [R] → TAC x 4	21
		TAC x 2 [R] → TAC x 6	24
		TAC x 2 [NR] → TAC x 4	5
		TAC x 2 [NR] → NX x 4	6

[R] clinically responsive after CT

[NR] clinically not responsive after CT

Sequence or duration ?

The Aberdeen study



Sequence, not duration

DFS and OS at 3-years of follow-up

CVAP x 8

DFS = 71%

OS = 84%

P=0.03

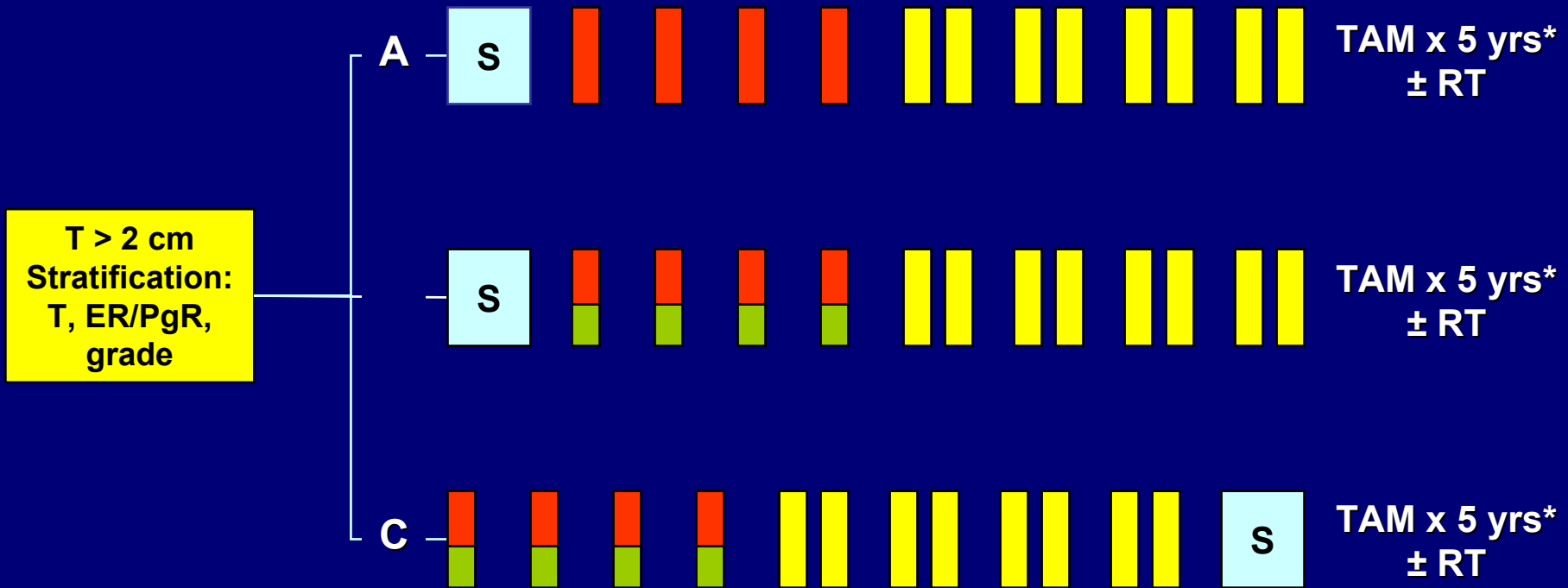
P=0.05

CVAP x 4 →
Docetaxel x 4

DFS = 90%

OS = 97%

ECTO Study Design




A vs B; B vs C. End-points: disease free & overall survival
 * since December 2000 in ER+ve and/or Pg+ve R only

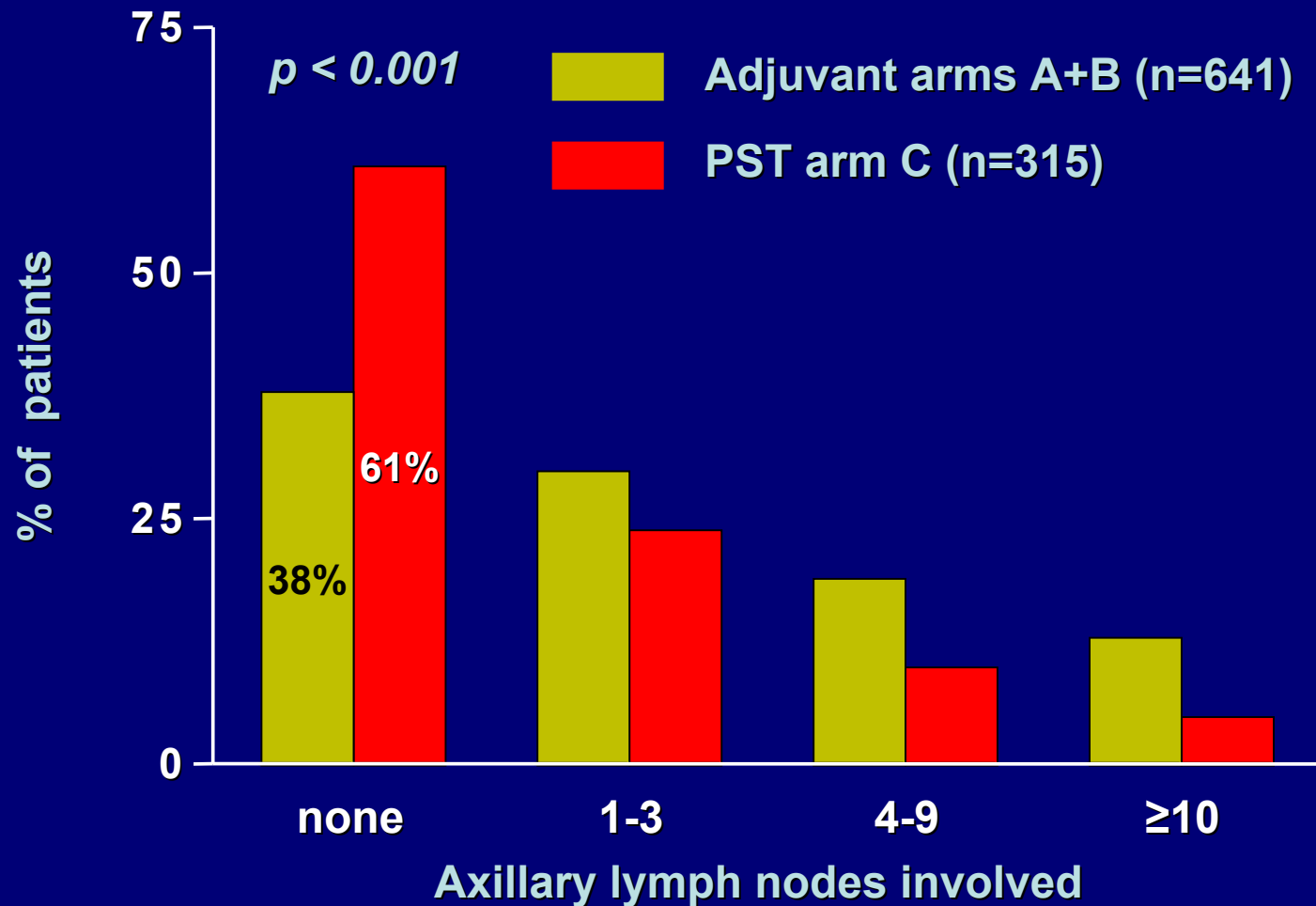
N = 1350

█ Doxorubicin
 █ AT
 █ █ CMF
 S surgery

ECTO: Clinical response after AT and after CMF

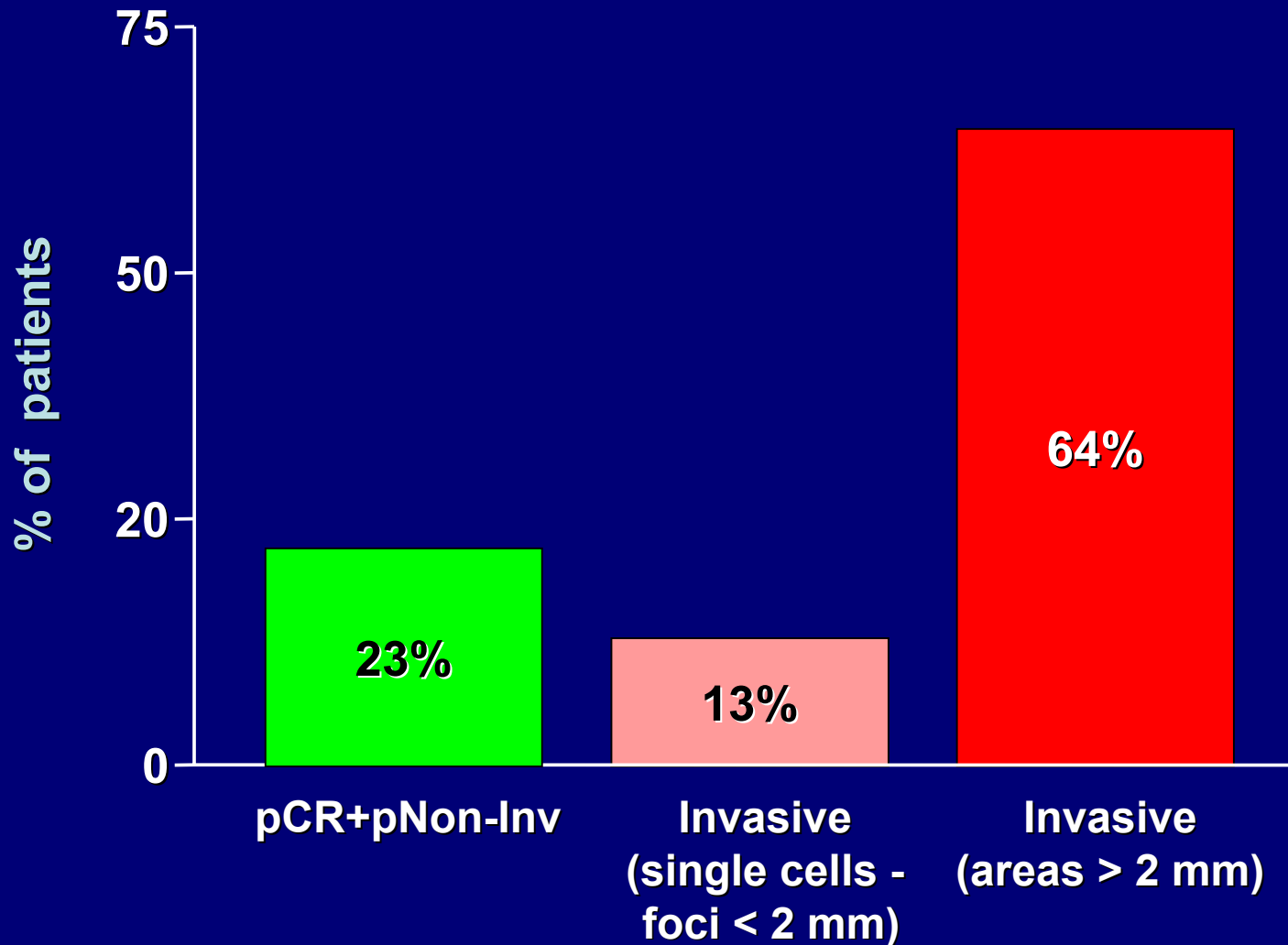
Response after AT	Response after CMF				
	CR	PR	Minor	NR	PRO
CR	72	72			-
PR	85	43	41		1
Minor	56	15	26	14	1
NR	49	7	9	14	19
PRO	1				1
Overall response to AT→CMF	137 (52%)	76 (29%)	28 (11%)	19 (7%)	3 (1%)
	 81%				

Axillary nodes in Adjuvant arms vs. Preoperative arm*



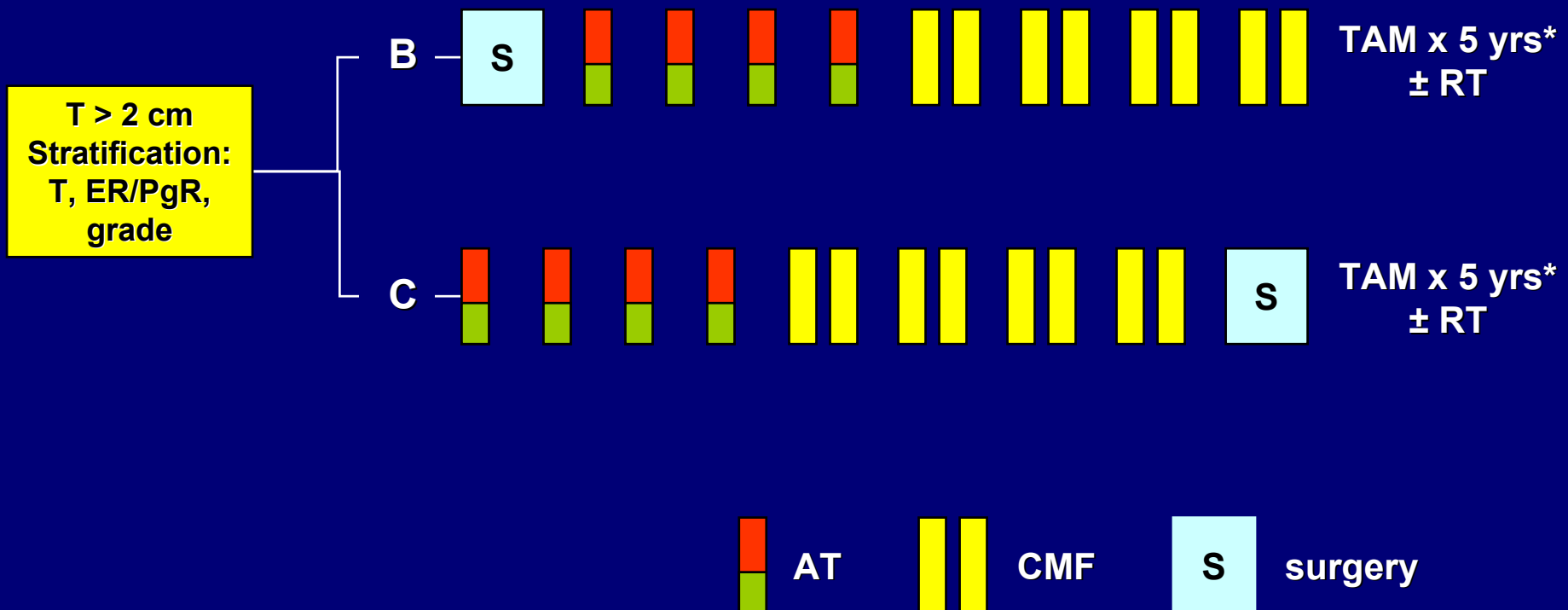
*full axillary dissection in > 80% of all patients

Pathological findings after AT→CMF

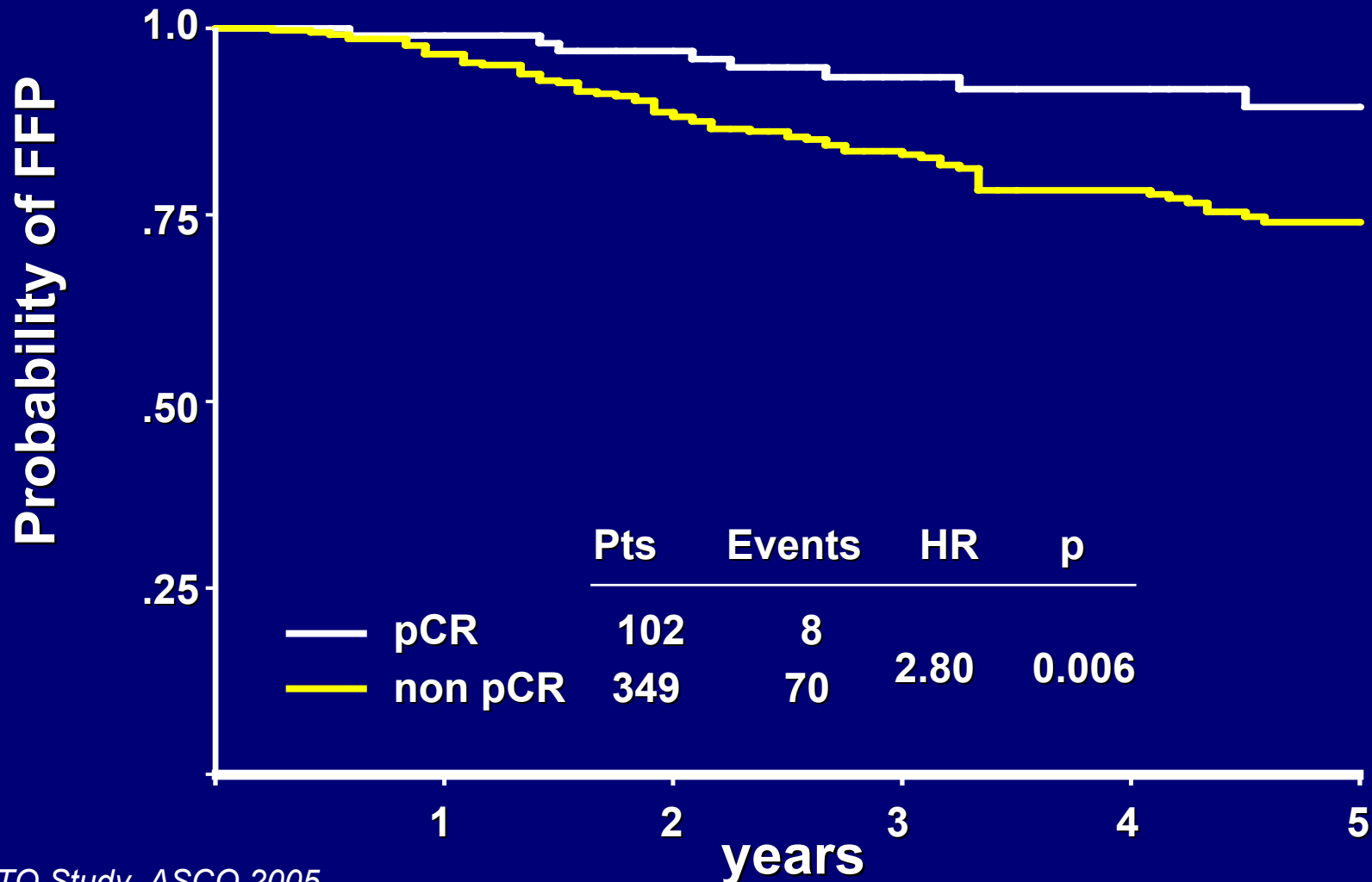


ECTO: Main planned analysis

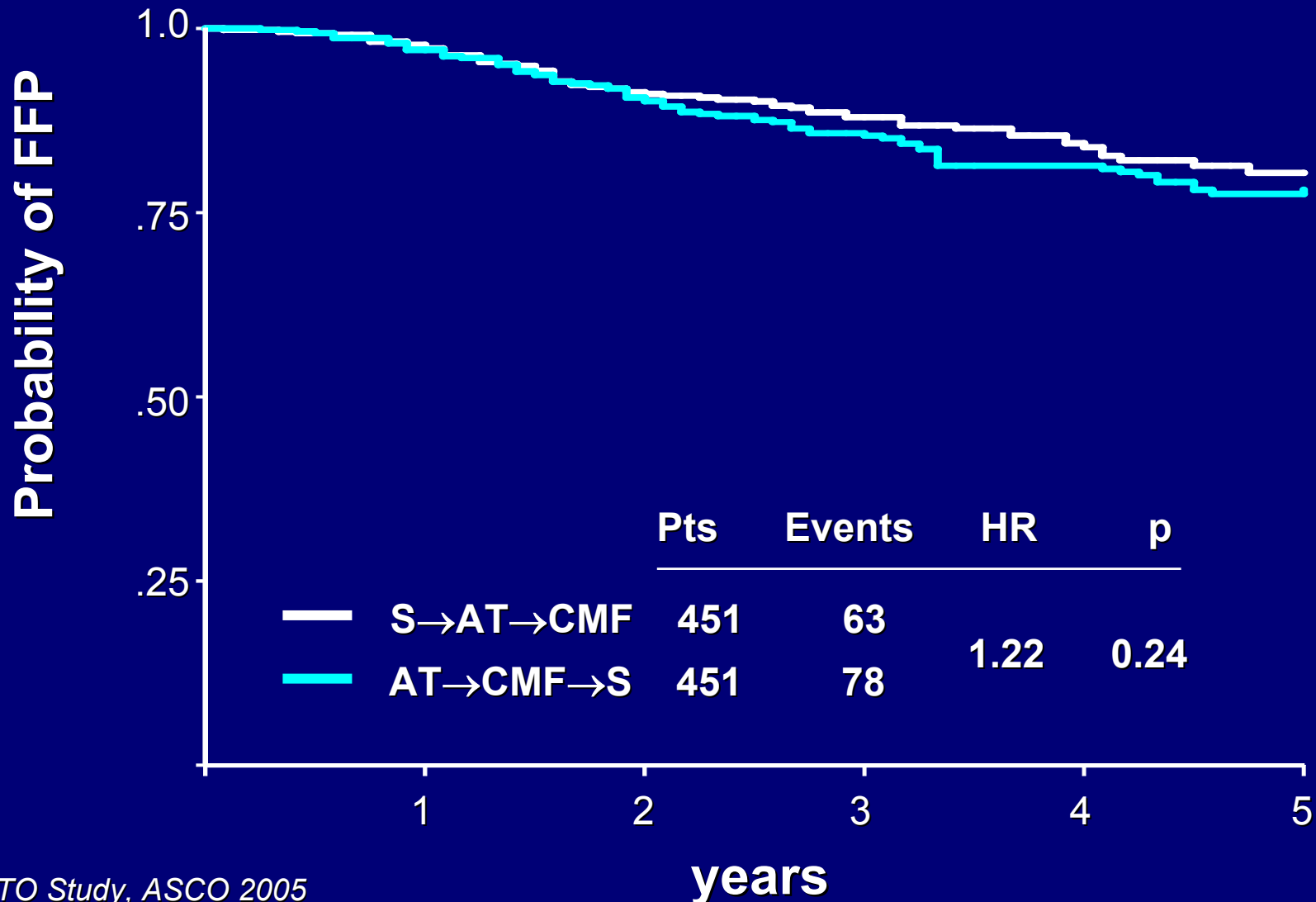
Is AT → CMF before surgery better than adjuvant ?



Freedom From Progression: pCR v. non pCR in the ECTO study



Freedom From Progression: Adjuvant v. Primary Chemotherapy



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ECTO: AT→CMF and likelihood of pCR+pNon-Inv: Univariate analysis

Variable		N	pCR + pNon-Inv	Other	p
<i>Age</i>	< 50 yr	139	23%	77%	NS
	≥ 50 yr	176	22%	78%	
<i>T size</i>	≤ 4 cm	226	23%	77%	NS
	> 4 cm	89	21%	79%	
<i>Clinical</i>	N0	179	25%	75%	NS
	N1-2	130	19%	81%	
<i>Tumor grade</i>	Low-Int.	199	19%	81%	0.10
	High	106	27%	73%	
<i>ER status</i>	ER+ve	114	10%	90%	0.001
	ER-ve	197	45%	55%	
<i>PgR status</i>	PgR+ve	134	13%	87%	0.001
	PgR-ve	176	36%	64%	

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	PgR-ve	176	36%	64%	

AT→CMF and likelihood of pCR + pNon-Inv

Multivariate Analysis

Category	Odds ratio (95%CI)	p
ER status		
neg vs pos	5.8 (3.5-9.5)	0.0001

Hormone Receptor Status and pCR

Study	N	Regimen	% HR neg	% pCR in HR-neg	% pCR in HR-pos
MD Anderson pooled	1018	Pooled	NA	21	5.6
Geparduo	913	dd AC/AD→T	26.3	23	6.2
ECTO	438	AT →CMF	38.2	45	10
NSABP-B27	2411	AC v. AC →TXT	32	17	8.3
Gepartrio	286	DAC/DAC →NX	31.9	37	10
EIO pooled	117	Pooled	18	23	7

Multivariate Analysis of Freedom From Progression (FFP): Primary Chemotherapy Arm

	HR	95% CI	P
Response			
<i>non pCR v. pCR</i>	3.03	1.39-6.54	0.005
Axillary Lymph nodes			
<i>positive v. negative</i>	2.79	1.71-4.57	< 0.001
Hormone Receptors			
<i>Negative v. positive</i>	2.97	1.81-4.88	0.01

Multivariate Analysis of Freedom From Progression (FFP): Primary Chemotherapy Arm

	HR	95% CI	P
Response			
<i>non pCR v. pCR</i>	3.03	1.39-6.54	0.005
Axillary Lymph nodes			
<i>positive v. negative</i>	2.79	1.71-4.57	< 0.001
Hormone Receptors			
<i>Negative v. positive</i>	2.97	1.81-4.88	0.01

Is there any reliable factor predicting for the likelihood of response to PC ?

ER-poor tumors

Increased pCR (4-6 fold)

High tumor/
nuclear grade

Increased pCR

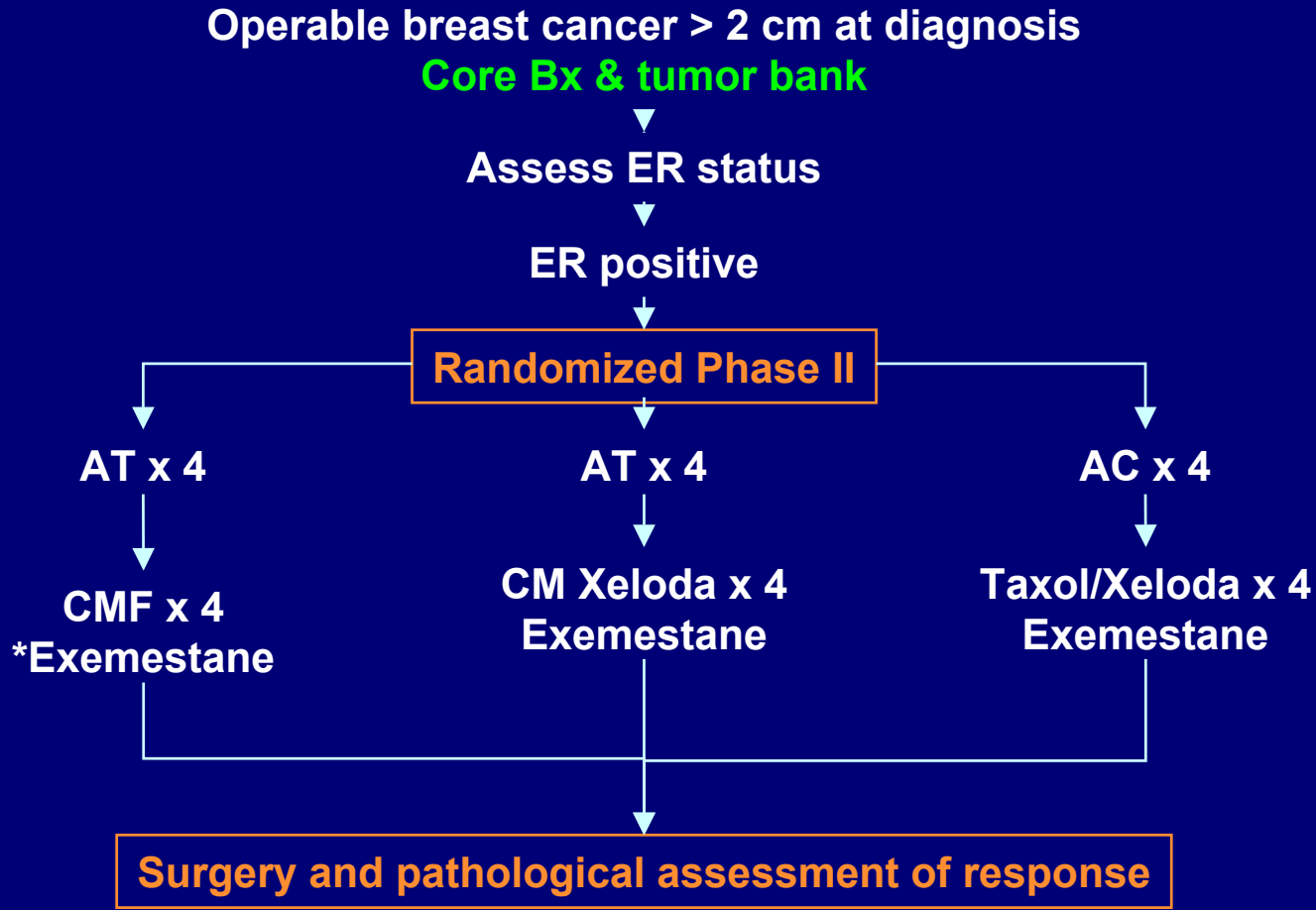
High proliferation
index

Increased clinical response

pCR and Efficacy - the key difference and its implications

- pCR is strongly directly associated with likelihood of improved DFS
- Likelihood of pCR (↑ in ER-) and likelihood of DFS (↑ in ER+) are differently associated with hormone receptor status in multivariate analyses
- Enriching for ER- cases and sorting out ER+ based on probability of pCR would negate a valid therapeutic option to many patients
- Are there ways to improve pCR rate in HR+ tumors?

ECTO-II: Design for ER+



* Exemestane to be started with the first cycle of chemotherapy

AT = doxorubicin plus taxol; AC = doxorubicin + cyclophosphamide;
CM = cyclophosphamide, methotrexate; F = fluorouracil

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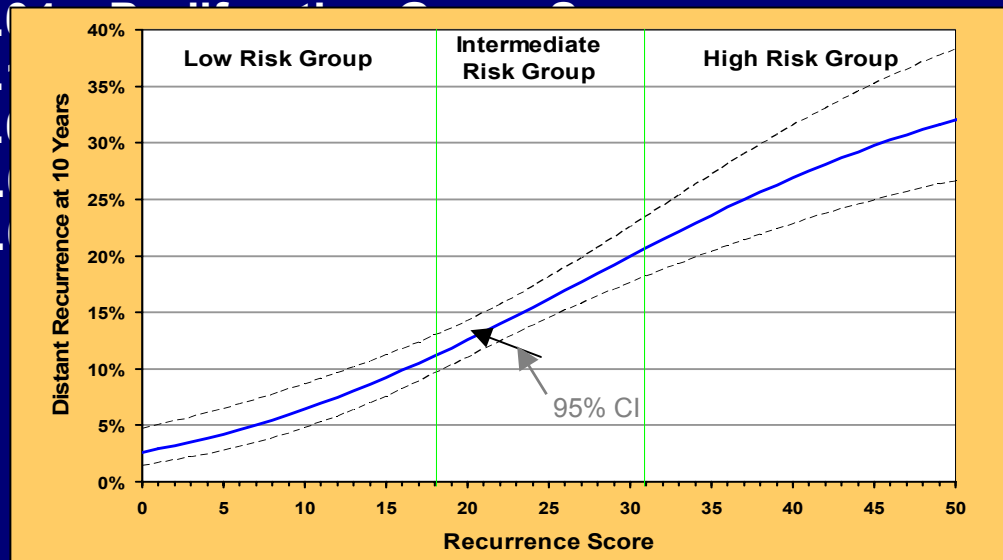
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What relationship between Recurrence Score Assay and pCR?

- Recurrence Score assay (based on expression of 21 genes) predicts the likelihood of distant recurrence (Paik S et al, N Engl J Med. 2004;351:2817-26)

$$\text{RS} = 0.47 \times \text{GRB7 Group Score} - 0.34 \times \text{ER Group Score} + 1.0$$



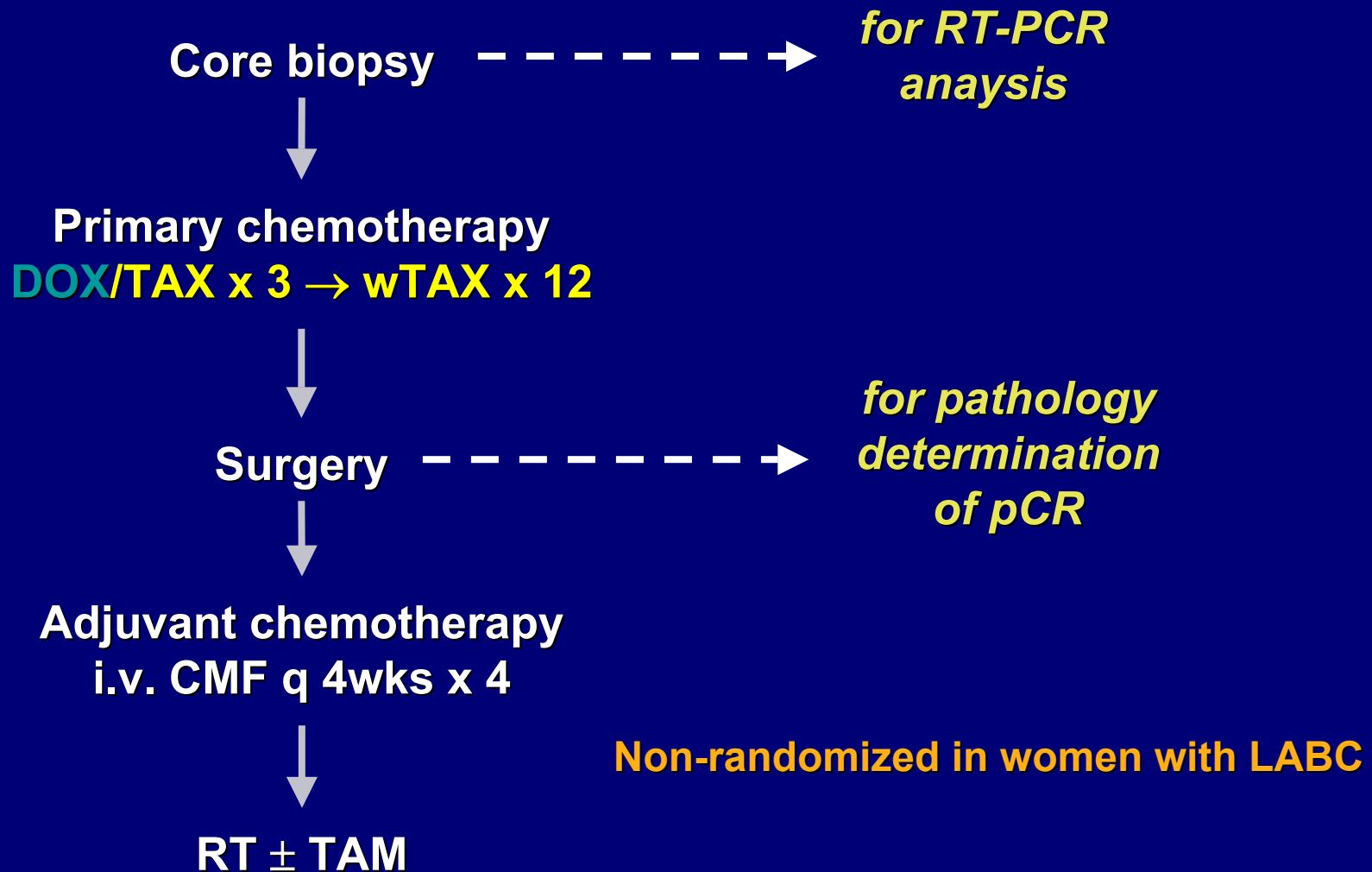
High proliferation and low ER
→ Higher RS

Low proliferation and high ER
→ Lower RS

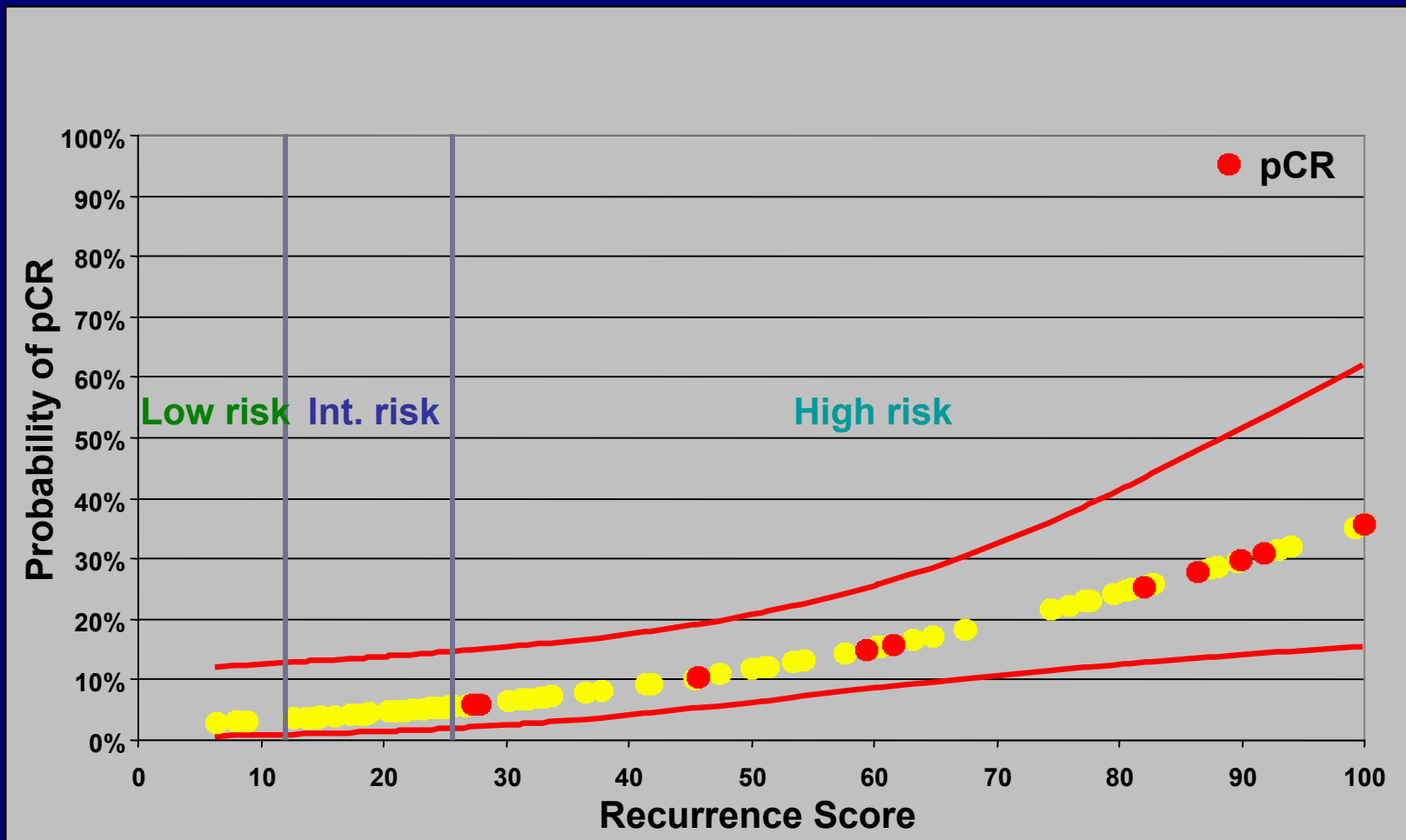
Recurrence Score and pCR - Study design

Istituto Nazionale Tumori - Milan

Start on August 1998



Higher Recurrence Score as in TailorRX Associated with Higher Likelihood of pCR



Is prediction of pCR useful?

- pCR is more frequent in patients classified as “High Risk” according to classical variables (no expression of Hormone Receptors) as well as newer gene-expression classifiers (Oncotype DX)
- Any classifier of pCR should be tested for its ability to *predict efficacy* with high sensitivity and high specificity in adjuvant setting rather than simply antitumor activity in the neoadjuvant one.