National Cancer Institute

PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

Some relevant points of the European Experience

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DI MILANO

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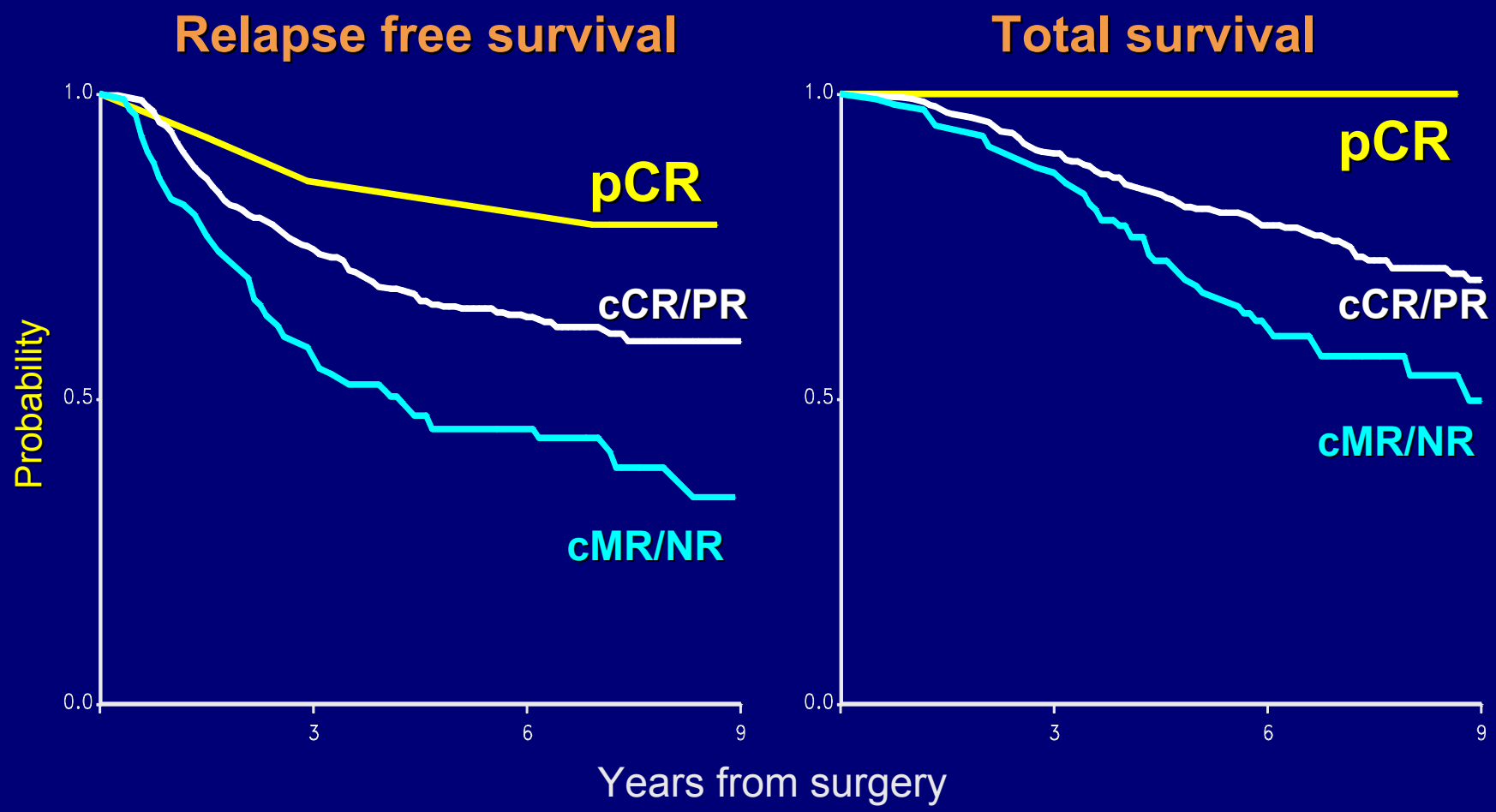
National Institutes of Health

Primary Chemotherapy in Resectable Breast Cancer



Experience at the Istituto Nazionale Tumori of Milan

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	TEST
• How can pCR rate be improved?	⇒ New drugs (taxanes; gemcitabine; trastuzumab) ⇒ New regimens (dose-dense; sequential)
• Does Improved pCR improve efficacy?	⇒ First v. second generation regimens
• Can pCR be predicted?	⇒ Classical variables (hormone receptors; T and N; etc.) ⇒ Pharmacogenomics
• Is pCR prediction useful?	⇒ 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

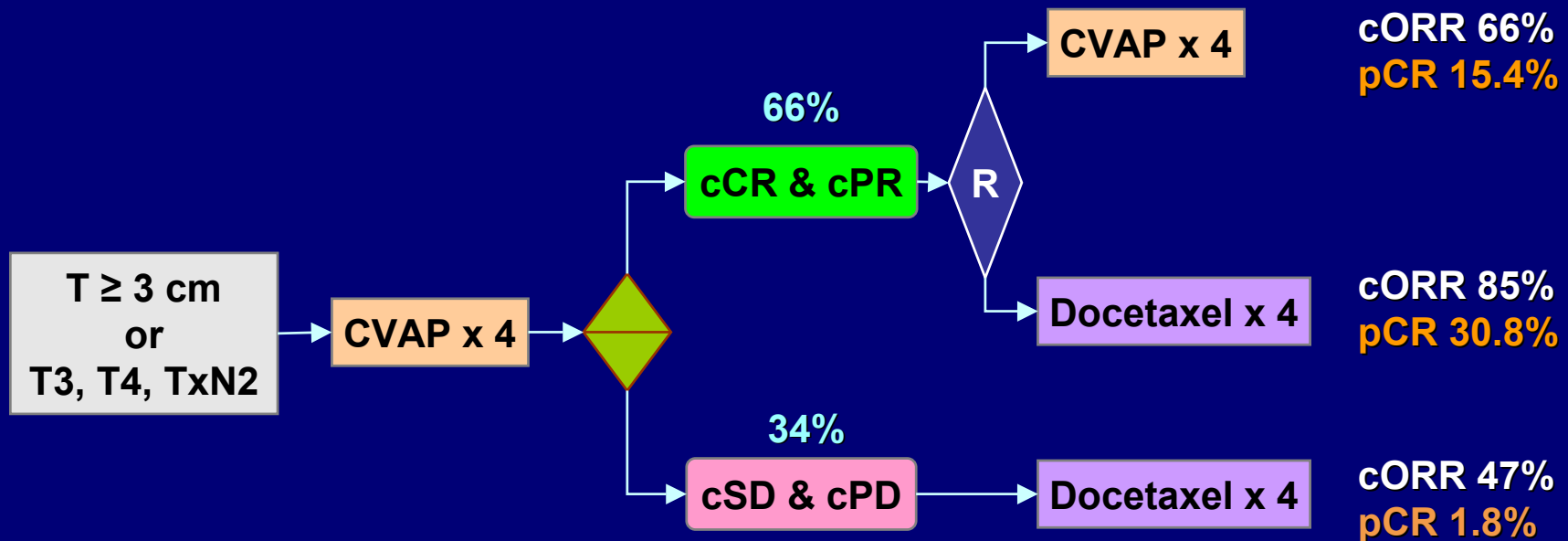
1st Author	N°pts	Regimen	pCR
von Minckwitz G	912	ddAD x 4	11
		AC x 4 → D x 4	22
Untch M	631	ddE x 3 → ddT x 3	18
		ET x 4	10
Romieu G	43	ddD x 4 → FEC100 x 3	50
García-Mata J	54	ddD x 4 → ddAC x 4	12
Cramer EM	81	ddEC x 4 → ddD x 4	25
Schneeweiss A	37	ddGE x 5 → ddD x 4	24
Levy E	62	[ddGDx2 → ddEVx2]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



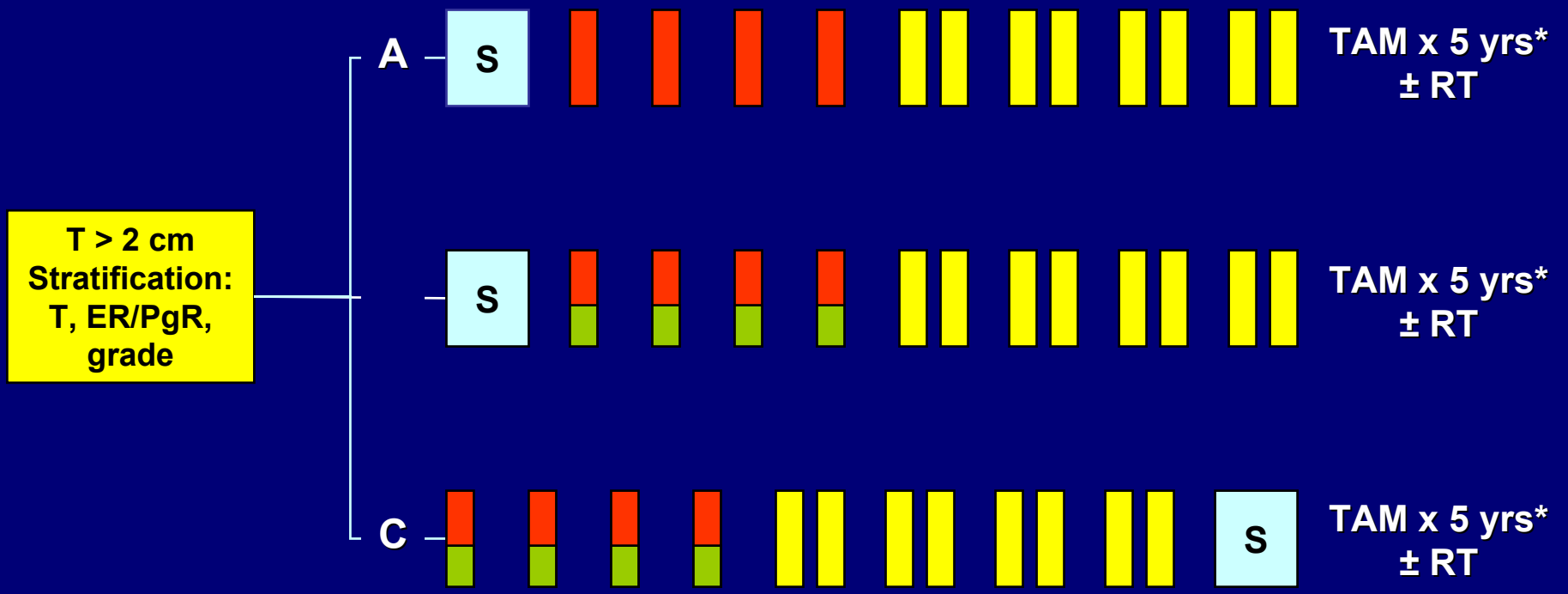
Smith IC et al., *J Clin Oncol* 2002

Sequence, not duration
DFS and OS at 3-years of follow-up

CVAP x 8		CVAP x 4 → Docetaxel x 4
DFS = 71%	***P=0.03***	**DFS = 90%**
OS = 84%	***P=0.05***	**OS = 97%**

Hutcheon AW et al., *Breast Cancer Res Treat* 2002

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**

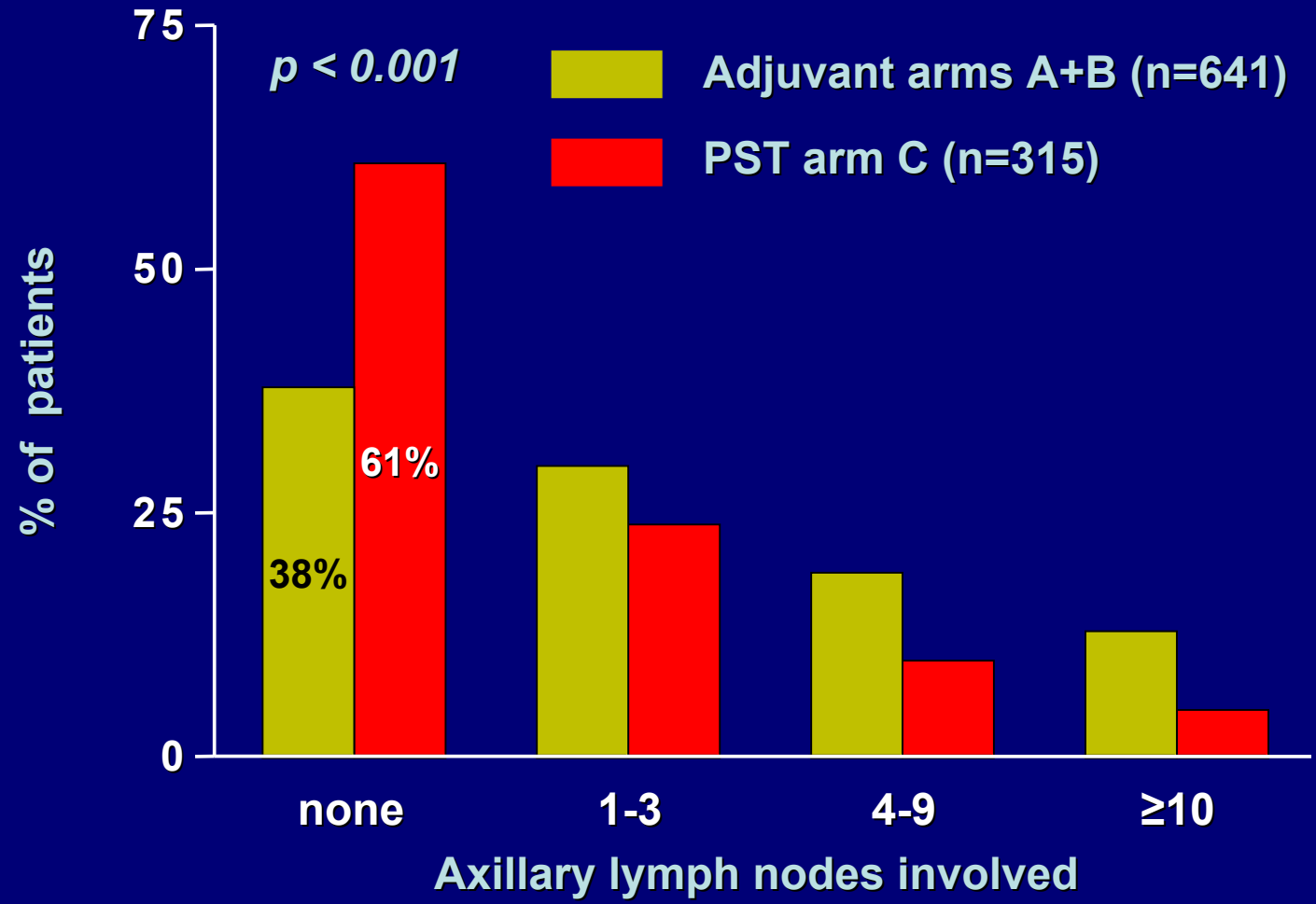
N = 1350 Doxorubicin AT CMF S surgery

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%)

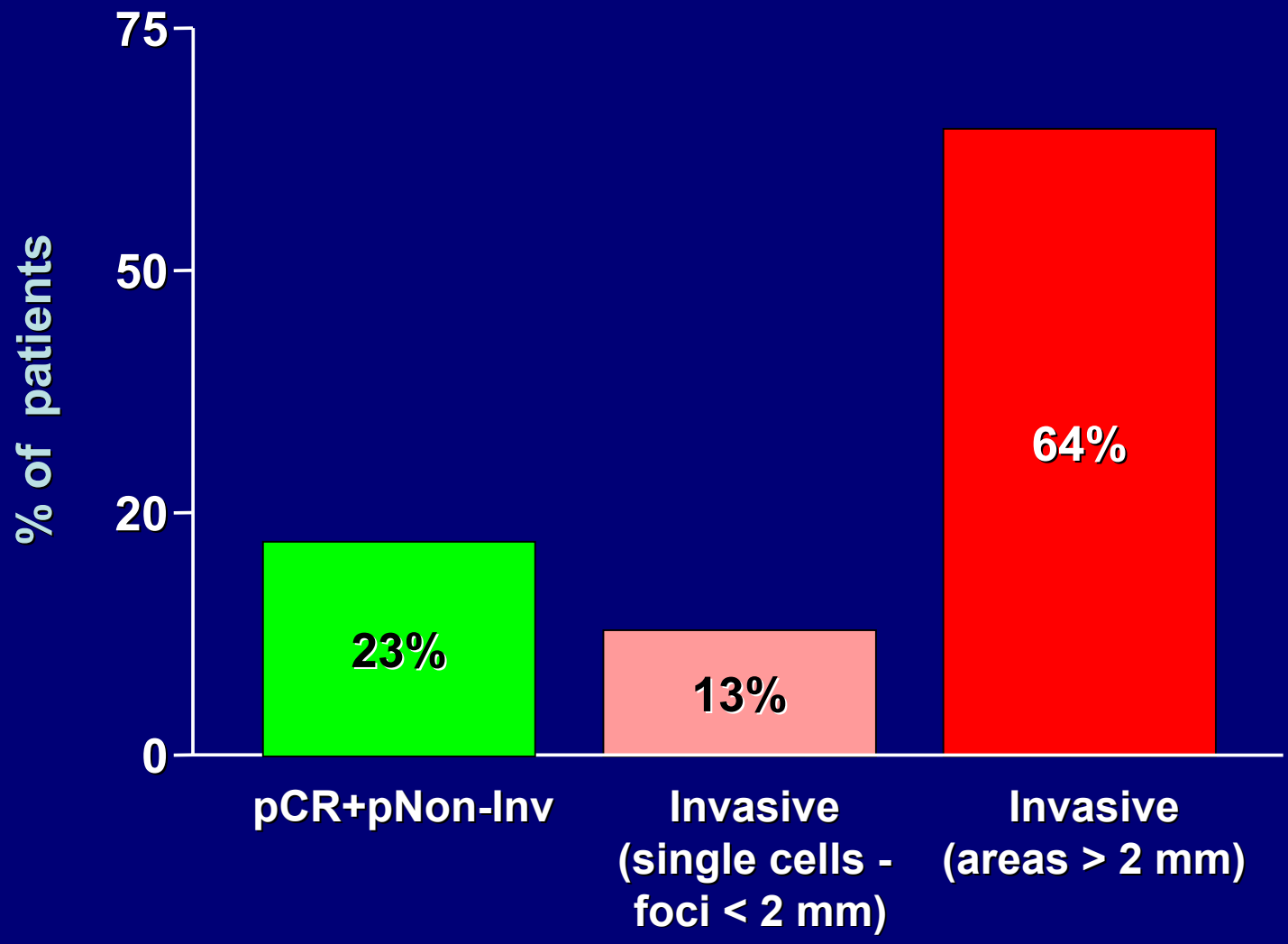
81%

Axillary nodes in Adjuvant arms vs. Preoperative arm*



*full axillary dissection in > 80% of all patients

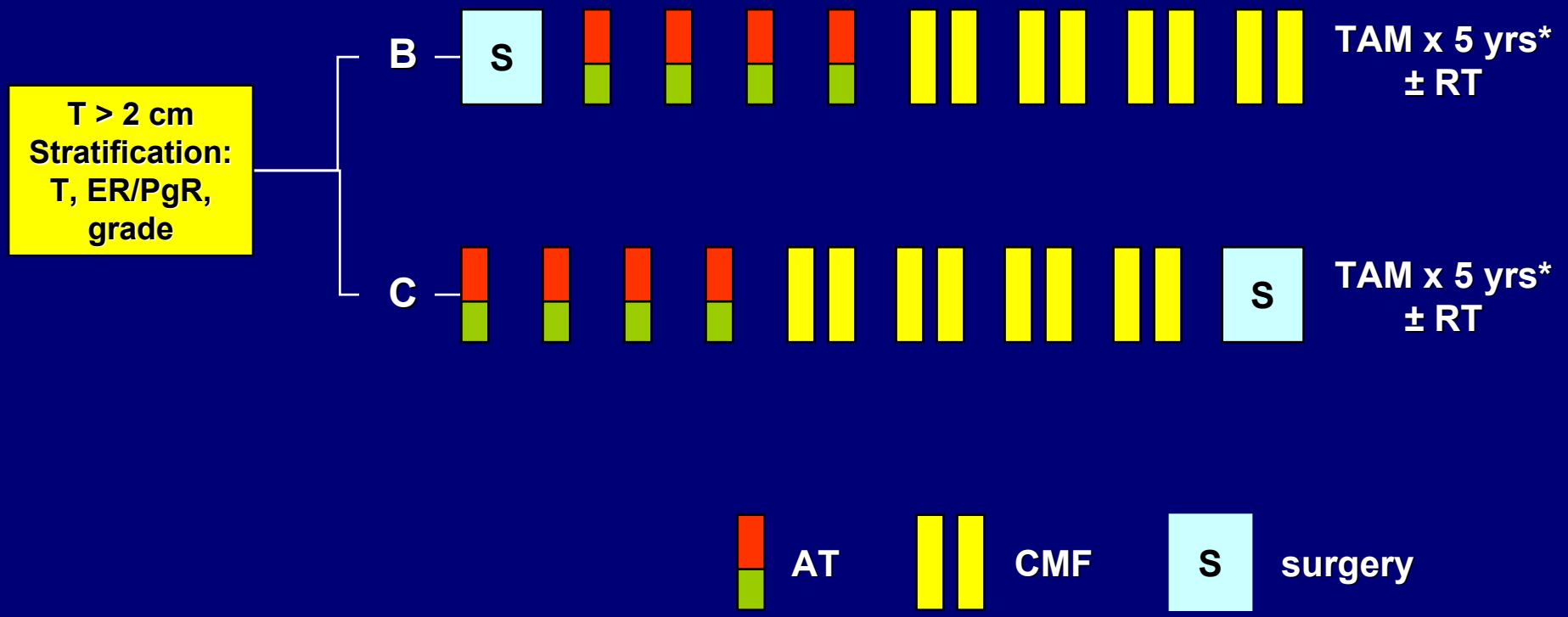
Pathological findings after AT→CMF



Clin cancer Res 2005

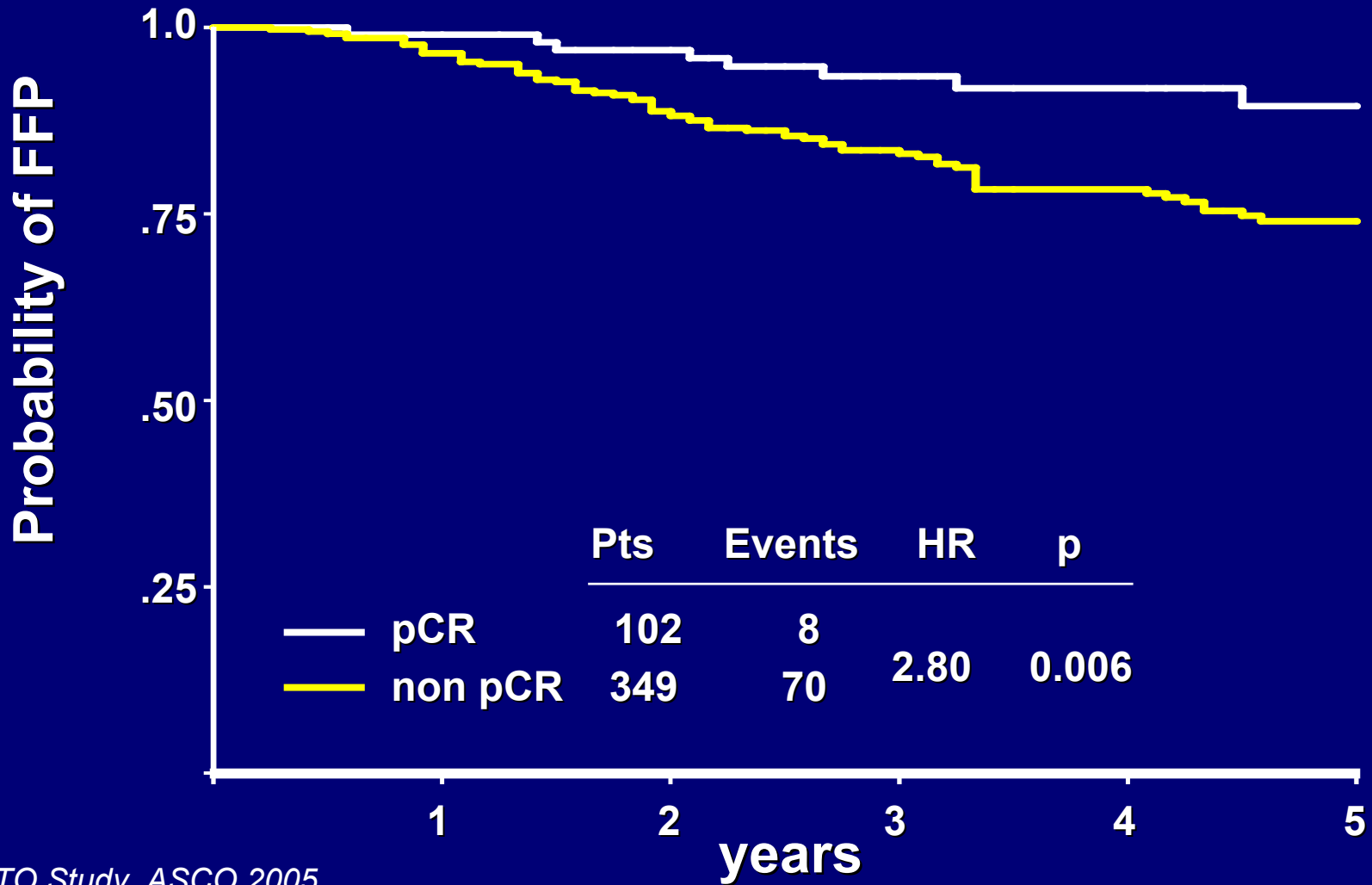
ECTO: Main planned analysis

Is AT→CMF before surgery better than adjuvant ?



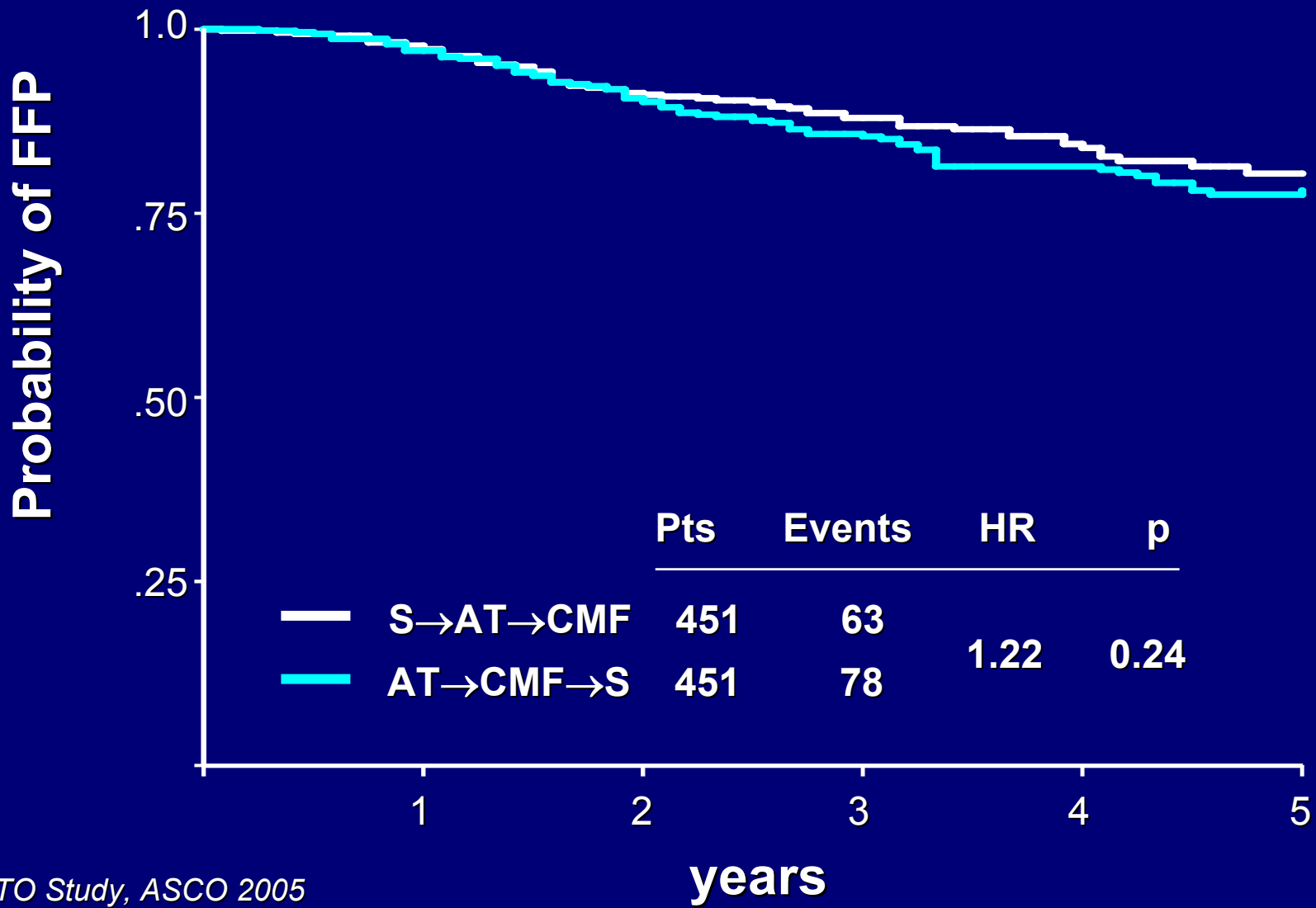
ECTO Study, ASCO 2005

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



ECTO Study, ASCO 2005

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

Clin cancer Res 2005

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	ER-ve	**197**	**45%**	**55%**	
PgR status	PgR+ve	134	13%	87%	0.001
	PgR-ve	176	36%	64%	

Clin cancer Res 2005

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

Clin cancer Res 2005

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 XT	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

Modified from Kaufmann M et al., JCO 2006, 24:1940-49

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

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

ECTO Study, ASCO 2005

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Hormone Receptors			
Negative v. positive	2.97	1.81-4.88	0.01

ECTO Study, ASCO 2005

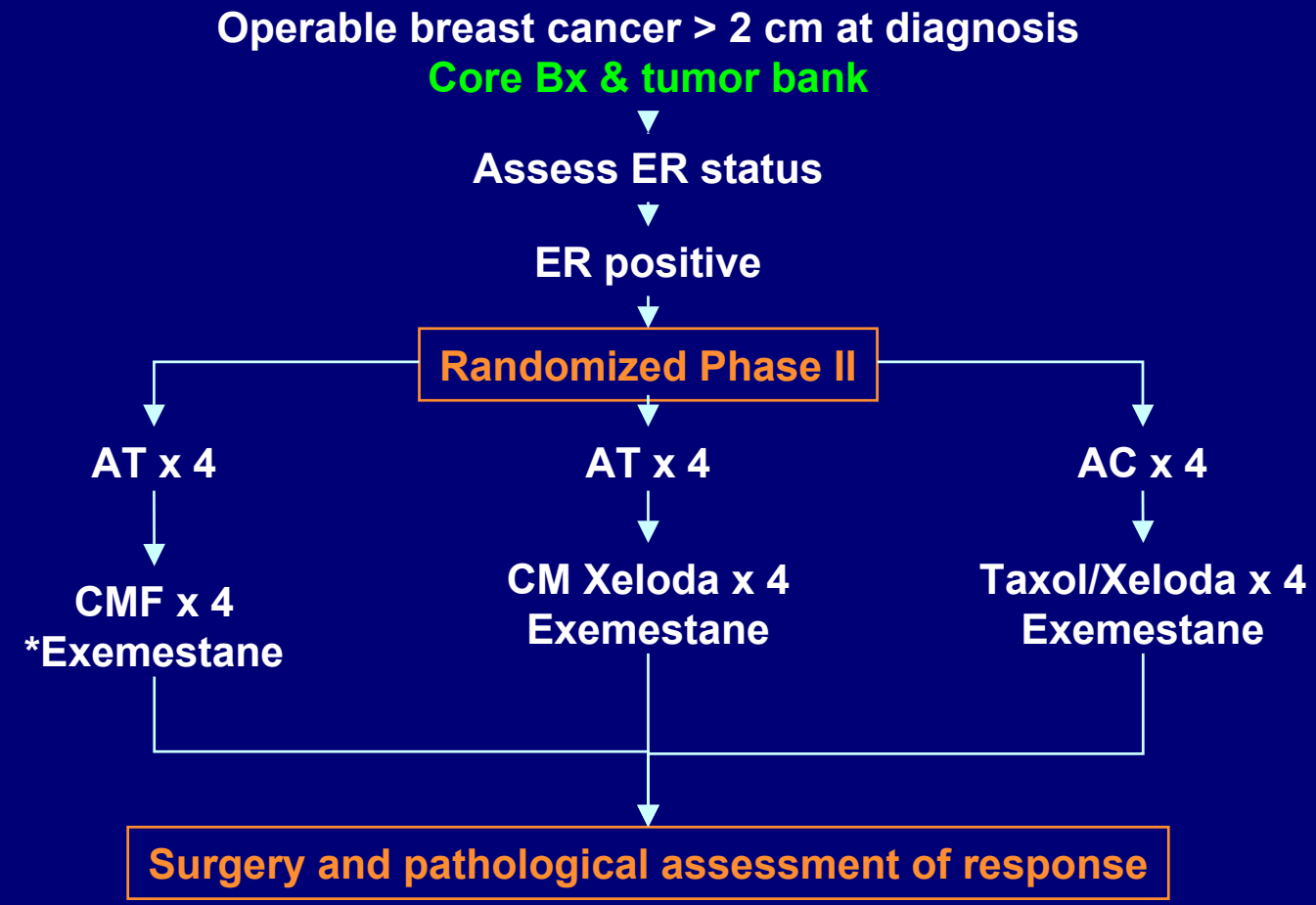
Is there any reliable factor predicting for the likelihood of response to PC ?

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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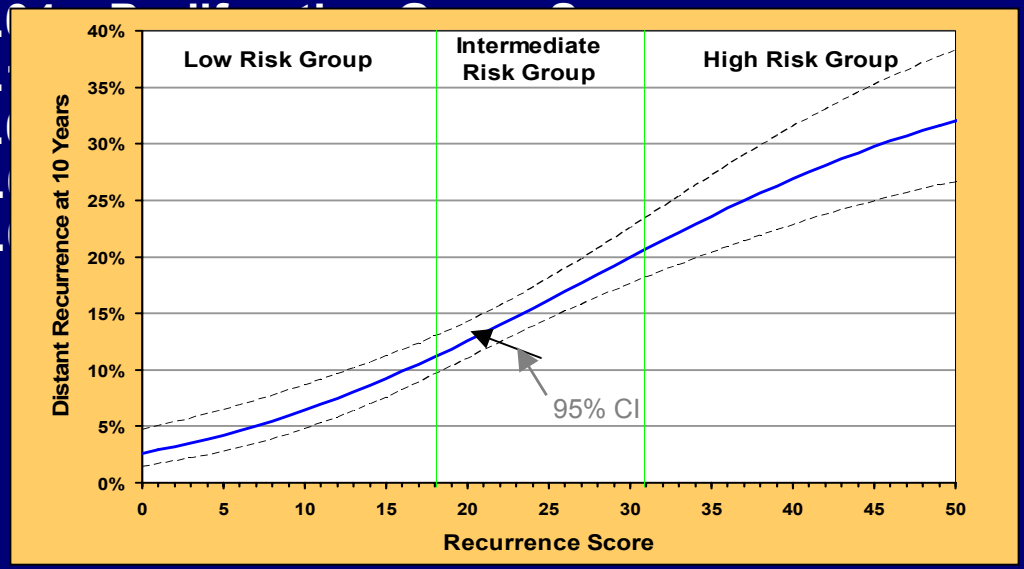
What relationship between Recurrence Score Assay and pCR?

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

RS = 0.47 x GRB7 Group Score
- 0.34 x ER Group Score
+ 1.
+ 0.
+ 0.
- 0.
- 0.

High proliferation and low ER → Higher RS

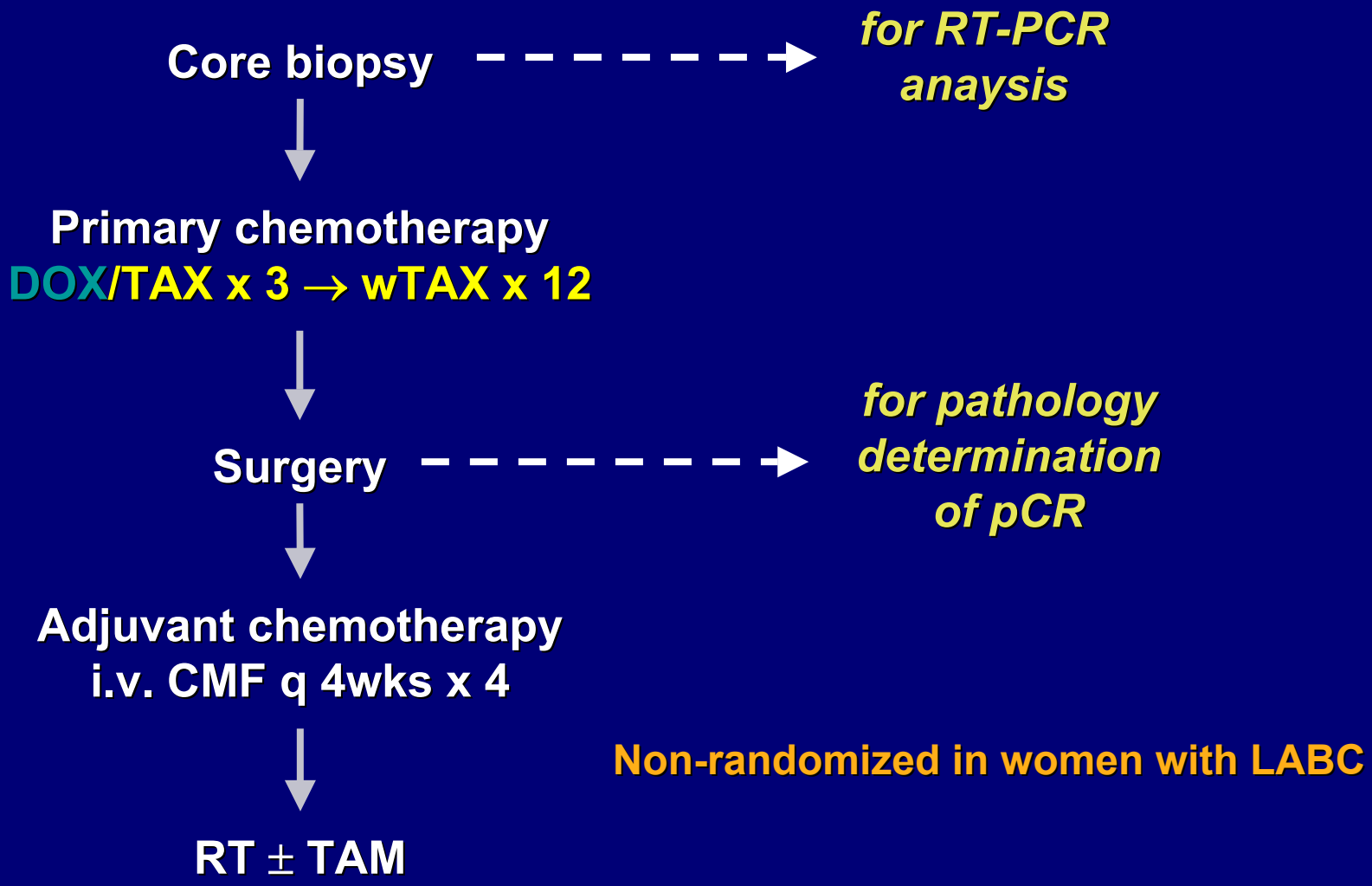


Low proliferation and high ER → Lower RS

Recurrence Score and pCR - Study design

Istituto Nazionale Tumori - Milan

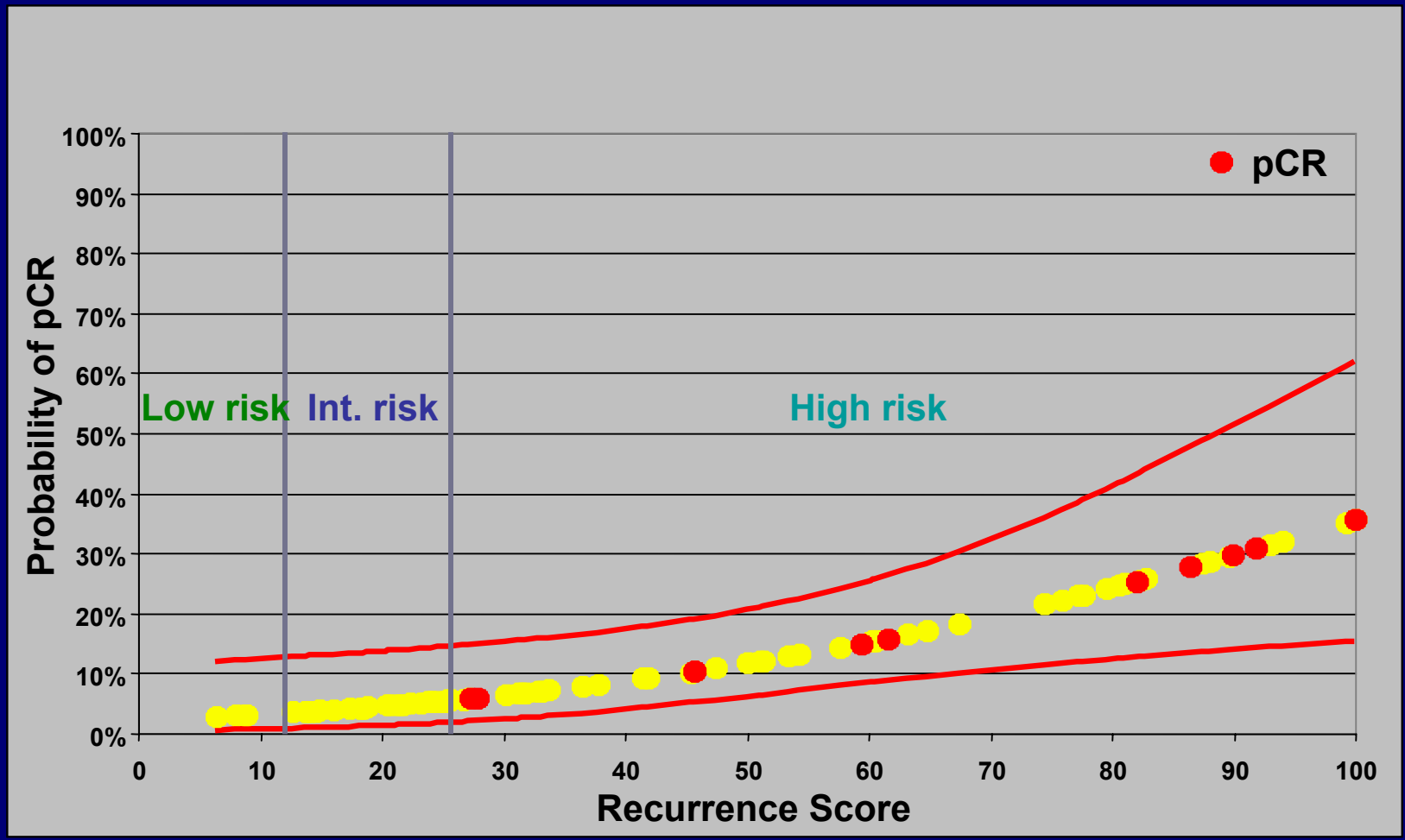
Start on August 1998



Non-randomized in women with LABC

Gianni L et al., *J Clin Oncol* 2005; 23:7265-77

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



Gianni L et al., *J Clin Oncol* 2005; 23:7265-77

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.