Preoperative Hormonal Therapy

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Estrogens Before Surgery for Large Breast Cancers

"The cancers in the treated patients were altered by complete or partial softening. Many of the tumours became mobile, smaller and more difficult or impossible to palpate….".

Kennedy et al Cancer Sept 1957

How Effective Is Preoperative Hormonal Therapy in:

1. Achieving Clinical Tumour Regressions?

2. Downstaging to Avoid Mastectomy?

Randomised Preoperative Hormonal Therapy Trials

B-24	Tamoxifen	v	Letrozole
IMPACT	Tamoxifen	v	Anastrozole v Combination
PROACT	Tamoxifen	v	Anastrozole (±CT)
0223	Anastrozole	v	Anastrozole + Gefitinib
	Tamoxifen	v	Exemestane
	Anastrozole v Exemestane v CT		

First 4 double blind, multicentre, postmenopausal, ER and/or PgR+ve

P24: Preoperative Tamoxifen v Letrozole

- 337 patients Median age 68
- 4 months treatment
- None suitable for conservative surgery
- 14% locally advanced
- Primary endpoint: Clinical Objective Response

Eiermann et al 12:1527 Ann Oncol. 2001

P24: Preoperative Tamoxifen v Letrozole

	Tamoxifen	Letrozole	
n	170	154	
Clinical OR*	**36** (4)%	**56** (10)%	p <0.001
Ultrasound OR*	25%	35%	p 0.04
BCS**	**35%**	**45%**	p 0.02

* Overall Response (CR) **Breast Conserving Surgery

Eiermann et al 12:1527 Ann Oncol. 2001

IMPACT: Preoperative Tamoxifen v Anastrozole v Combination

- 330 patients Median age 73
- Median tumour diameter 3.8 (1-15)cm
- 3 months treatment
- 96 (44%) suitable for conservative surgery
- No locally advanced
- Primary endpoint: Clinical Objective Response

Smith et al JCO 23: 5108 2005

IMPACT: Preoperative Tamoxifen v Anastrozole v Combination

	Tamoxifen	Anastrozole	Combination	
n	108	113	109	
Clinical OR*	**36%**	**37%**	**39%**	nsd
Ultrasound OR*	20%	24%	**28%**	nsd
BCS**	**22%**	**46%**	**26%**	p 0.03

* Overall Response **Breast Conserving Surgery

Smith et al JCO 23: 5108 2005

PROACT: Preoperative Tamoxifen v Anastrozole

- 451 patients ± Chemotherapy
- 330 no CT
- 3 months treatment
- ≥3cm operable or locally advanced
- Primary endpoint: Clinical Objective Response

Cataliotti et al Cancer 106: 2095; 2006

PROACT: Preoperative Tamoxifen v Anastrozole (Endocrine Therapy only)

	Tamoxifen	Anastrozole	
n	151	163	
Clinical OR*	**40%**	**50%**	nsd
Ultrasound OR*	27%	36%	nsd
BCS**	**31%**	**43%**	p0.04

* Overall Response **Breast Conserving Surgery

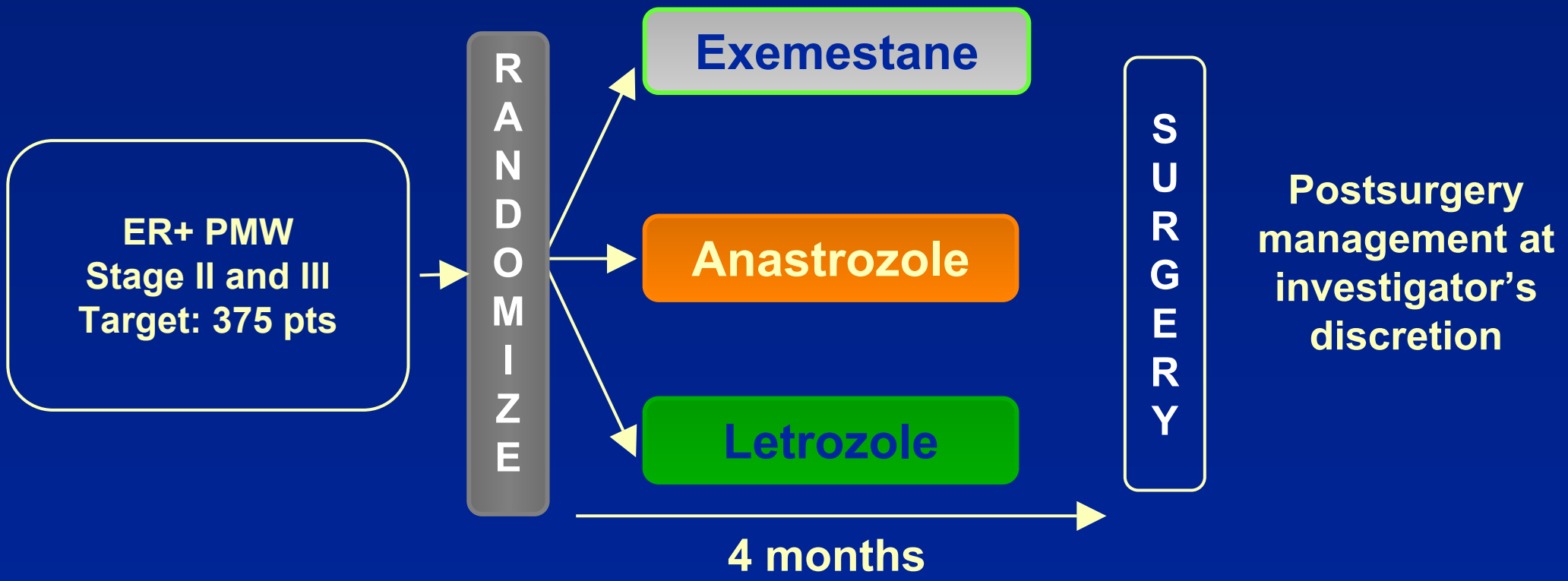
Cataliotti et al Cancer 2006

Preoperative Exemestane vs Tamoxifen
151 patients

	Clinical ORR (%)	Ultrasound ORR (%)	BCS Rate (%)
Exemestane (n=76)	76.3	60.5	36.8
Tamoxifen (n=75)	40.0	37.3	20.0
P Value	<0.05	0.092	<0.05

Update of Semiglazov et al. *J Clin Oncol.* 2005;23(16S):11s. Abstract 530.

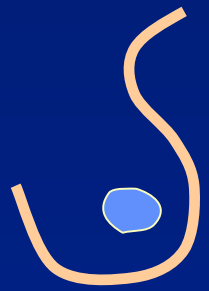
ACOSOG Z1031: Randomized Neoadjuvant AI Protocol



ACOSOG = American College of Surgeons Oncology Group.

Is Preoperative Endocrine Therapy As Effective As Chemotherapy?

Preoperative
Exemestane v Anastrozole v CT



117 older patients ER+ve

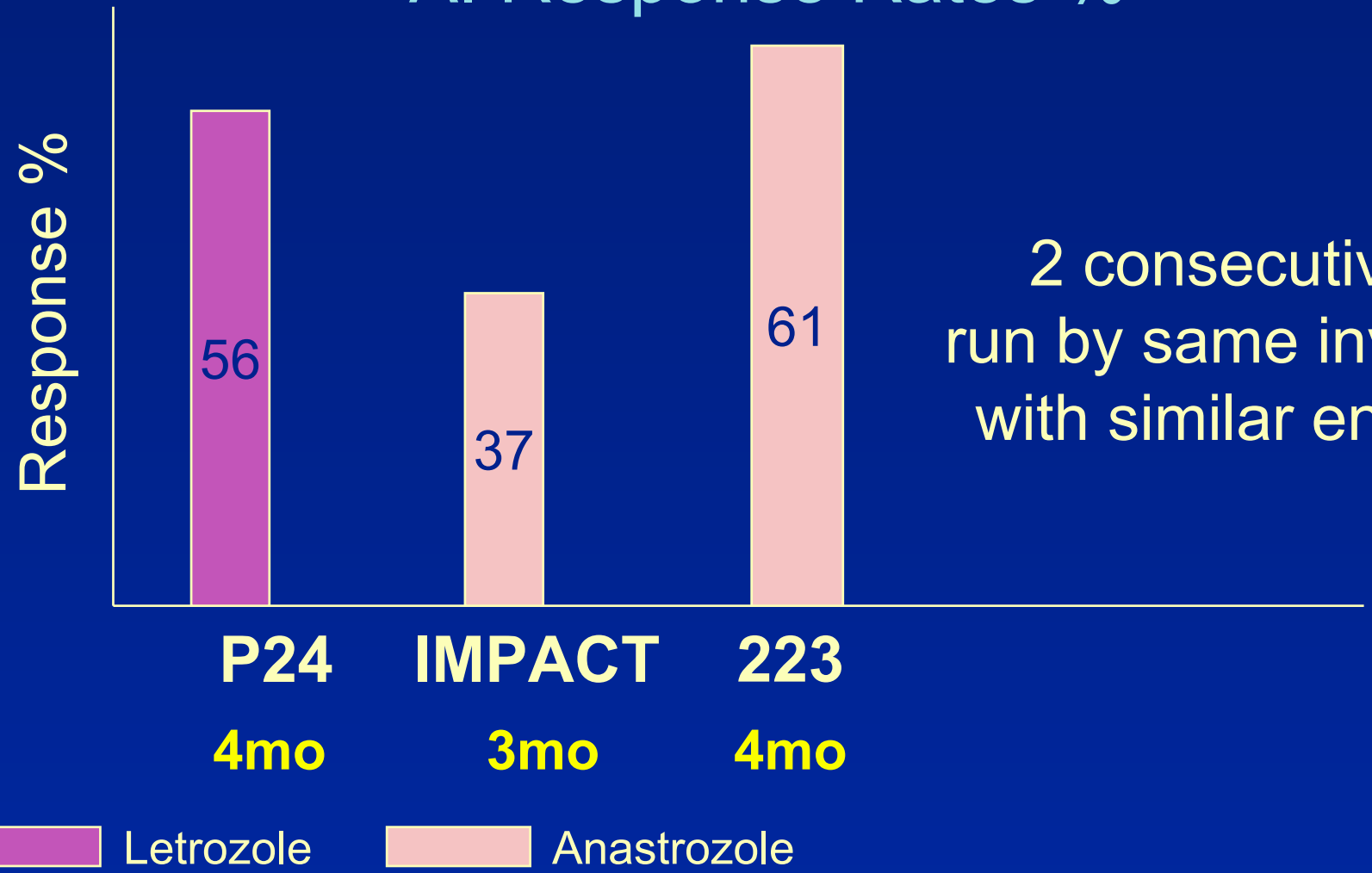
Randomise

	Exemestane	Anastrozole	Adria/ Taxol
OR	**80%**	**91%**	**38%**
BCS	**33%**	**38%**	**21%**

Semiglazov SABCC. 2004

What Is the Optimal Duration of Preoperative Endocrine Therapy?

AI Response Rates %



2 consecutive trials
run by same investigators
with similar entry criteria

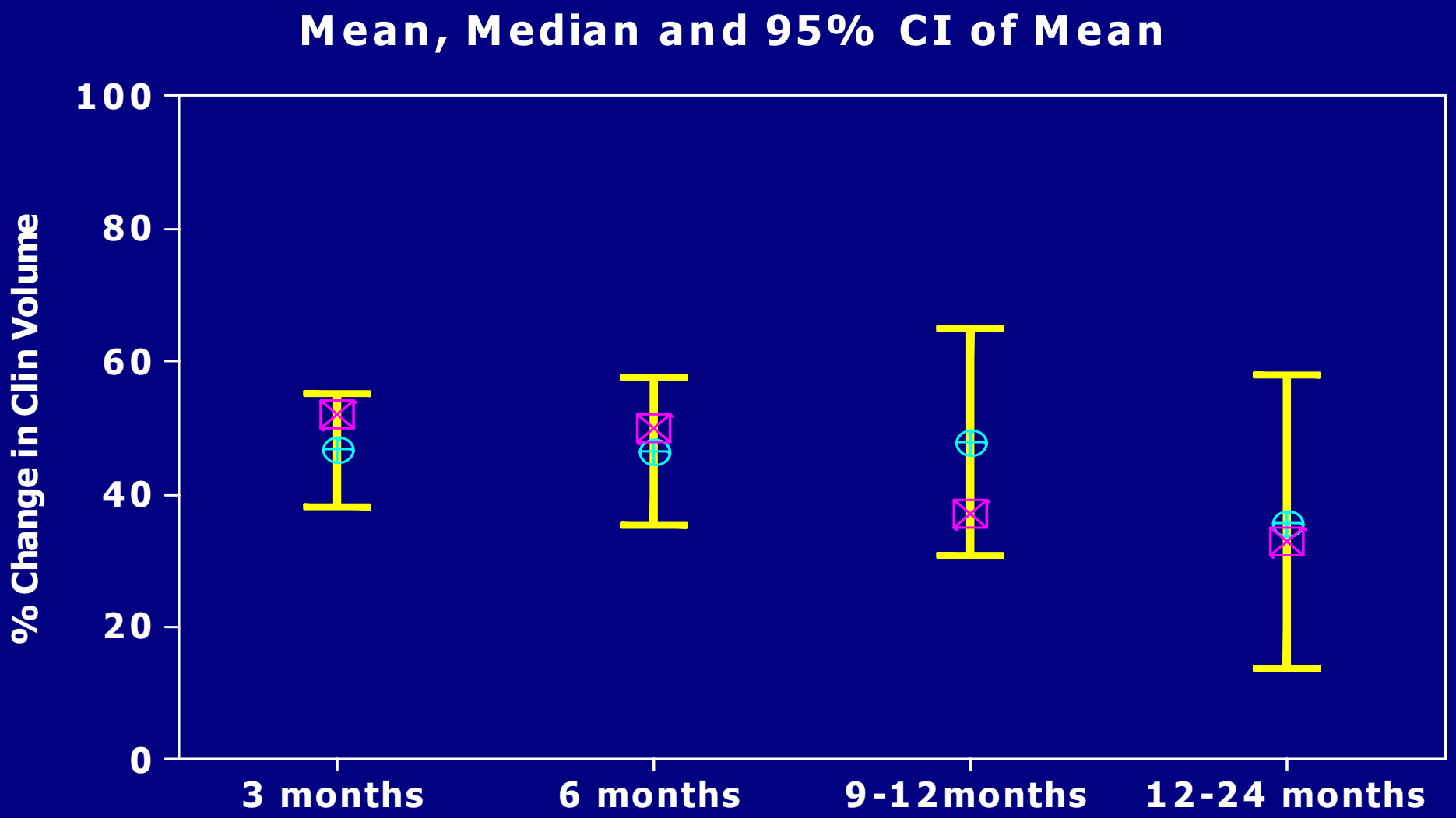
Tamoxifen Alone v Surgery + Tamoxifen: 'Golden Oldies'

- CRC UK trial tamoxifen alone v surgery and tamoxifen
- 451 women 70 years or over
- significantly higher loco-regional relapse rate with tamoxifen alone [23% v 8%]
- Overall and breast cancer mortality worse (HR 1.68) although curves did not diverge for 3 years

Bates et al Br J Surg 78:591-594, 1991

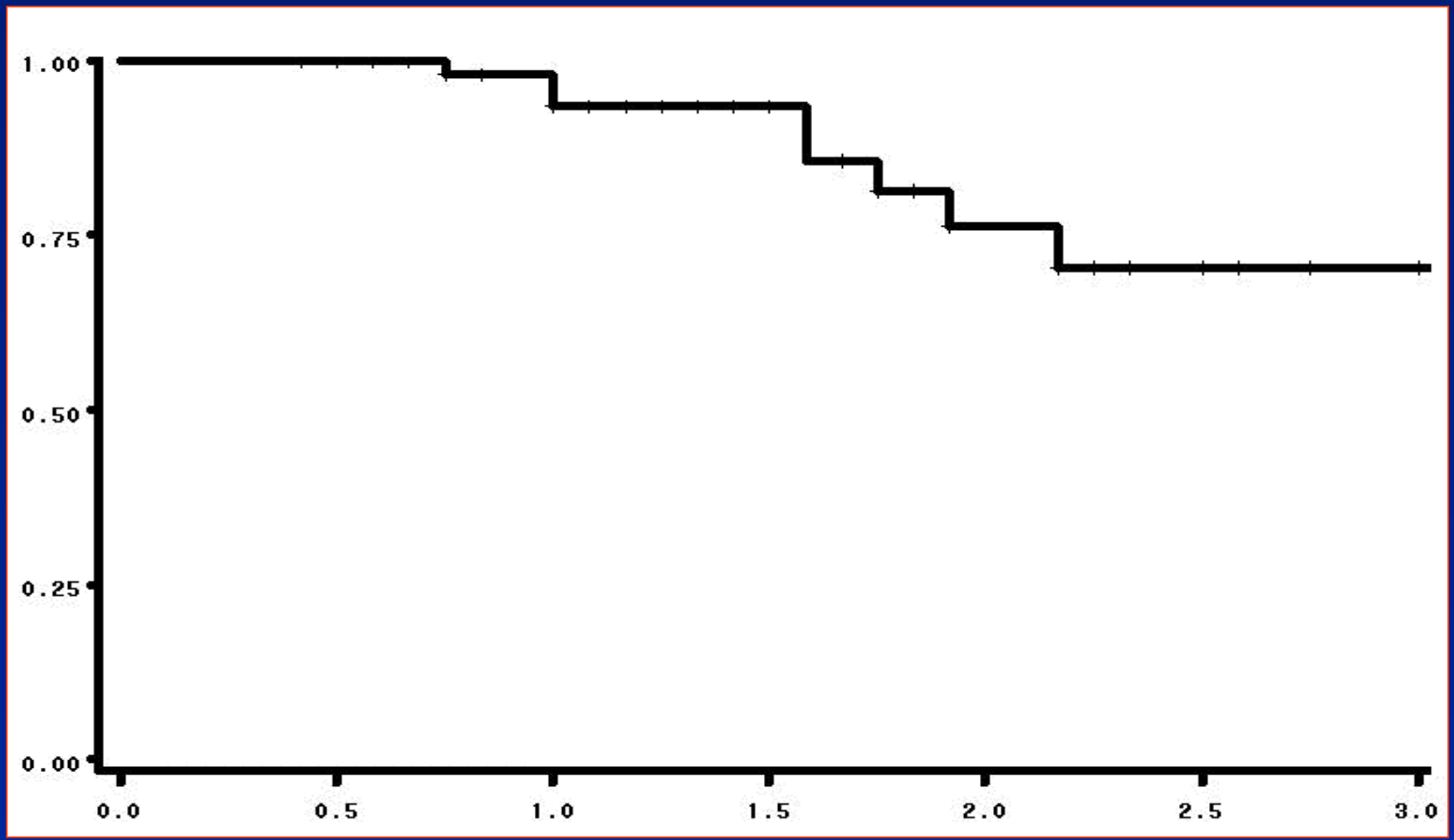
Fennessy et al Br J Surg 91:699 2004

63 patients on Letrozole > 3 months
Changes in Clinical Volume over Time



Dixon et al Edinburgh Breast Unit

63 patients on Letrozole > 3 months : Time to Treatment Failure



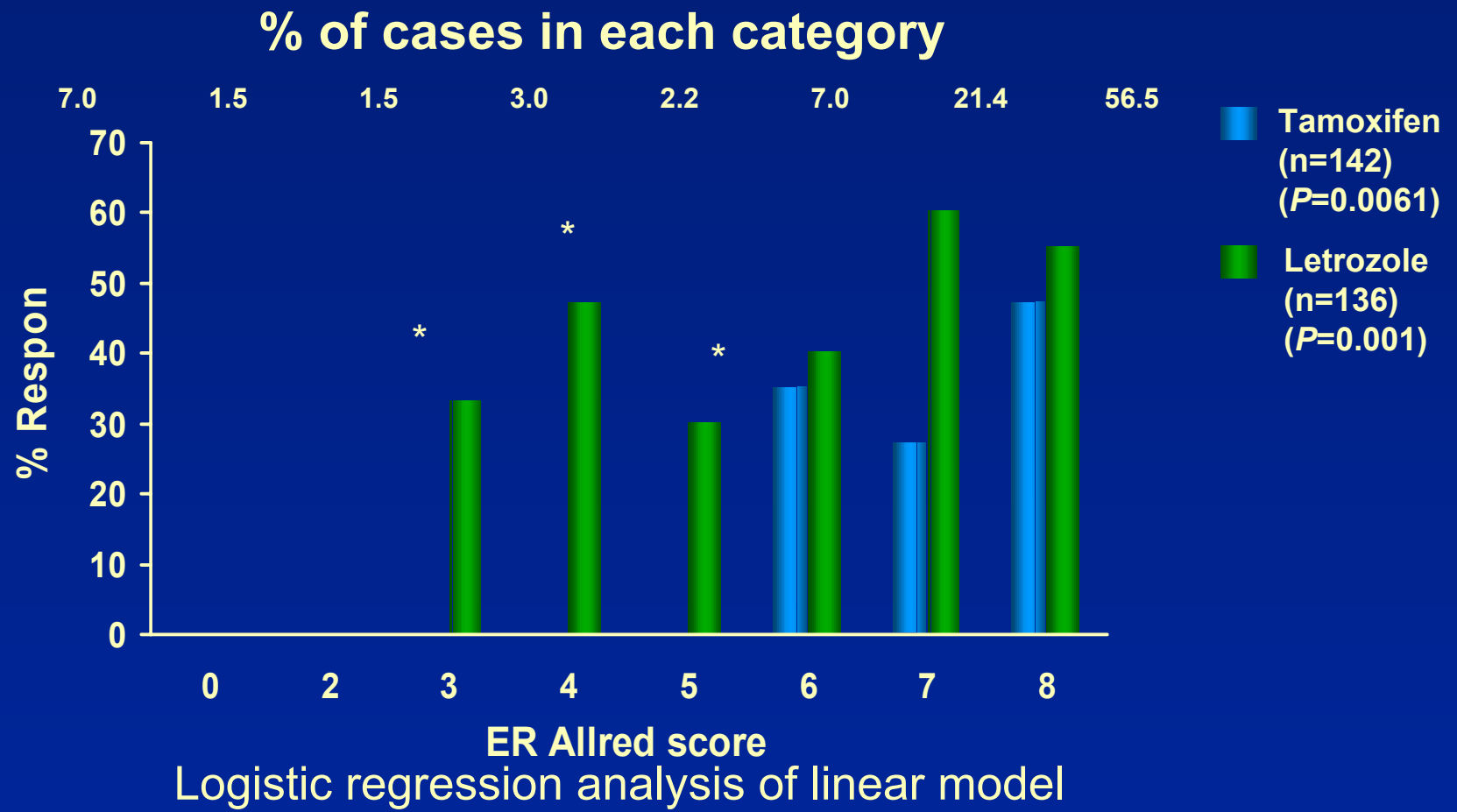
Dixon et al Edinburgh Breast Unit

Duration of Neoadjuvant AI Therapy: Conclusions

- Continuing Response for up to 2 years in some patients
- Longer duration may increase breast conservation
- Optimum duration not yet clear
- In general, not a long term substitute for surgery

Which Patients Are Most Likely to Respond to Preoperative Endocrine Therapy?

Neoadjuvant Letrozole vs Tamoxifen (P024): Response by ER Expression

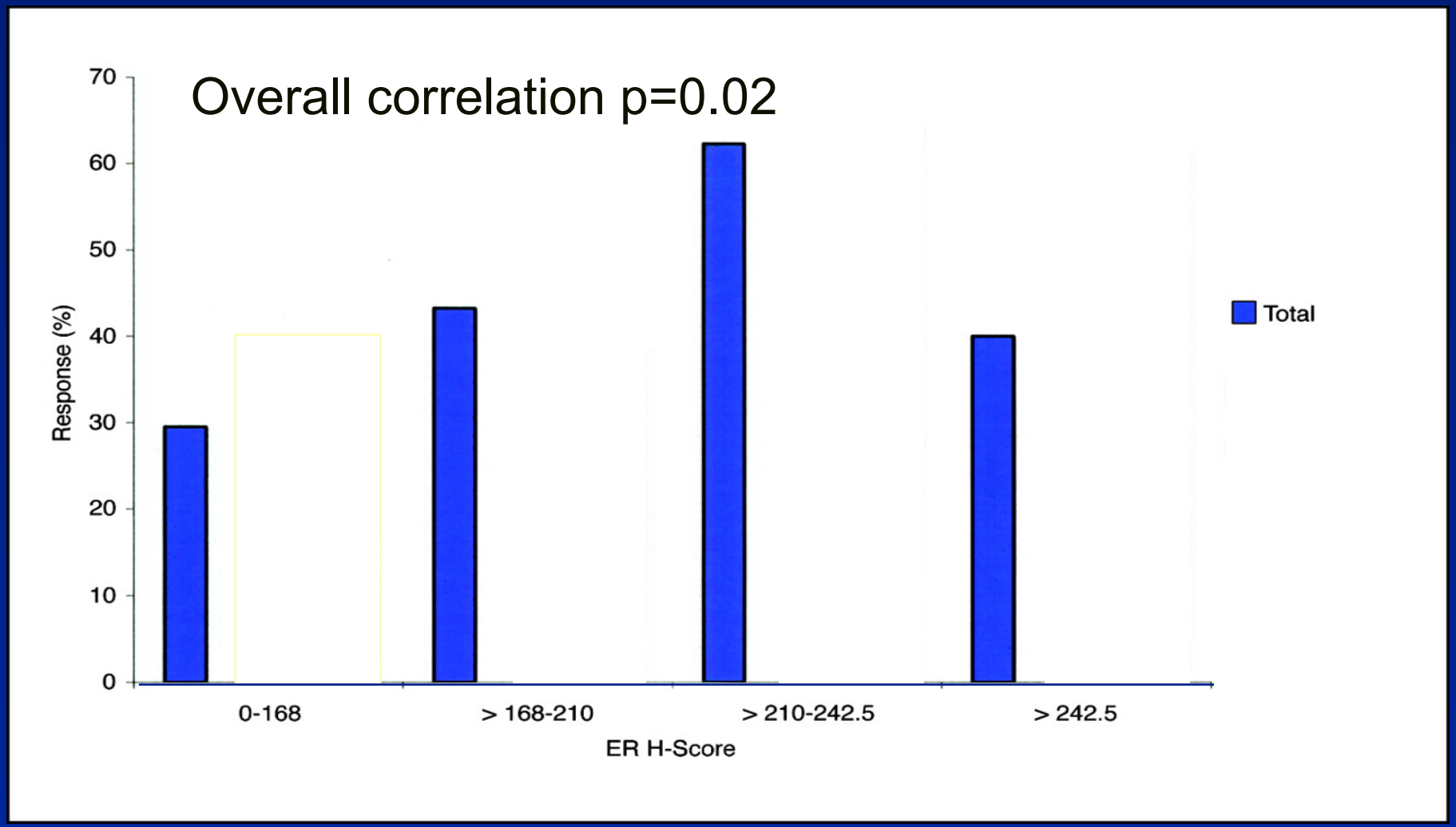


Logistic regression analysis of linear model

*Only 18 patients had ER scores of 3-5.

Ellis et al. *J Clin Oncol*. 2001;19:3808. .

IMPACT (Anastrozole, Tamoxifen and Combination) Clinical Response Rate by ER Quartiles



Smith I.E. et al. J Clin Oncol; 23:5108-5116 2005

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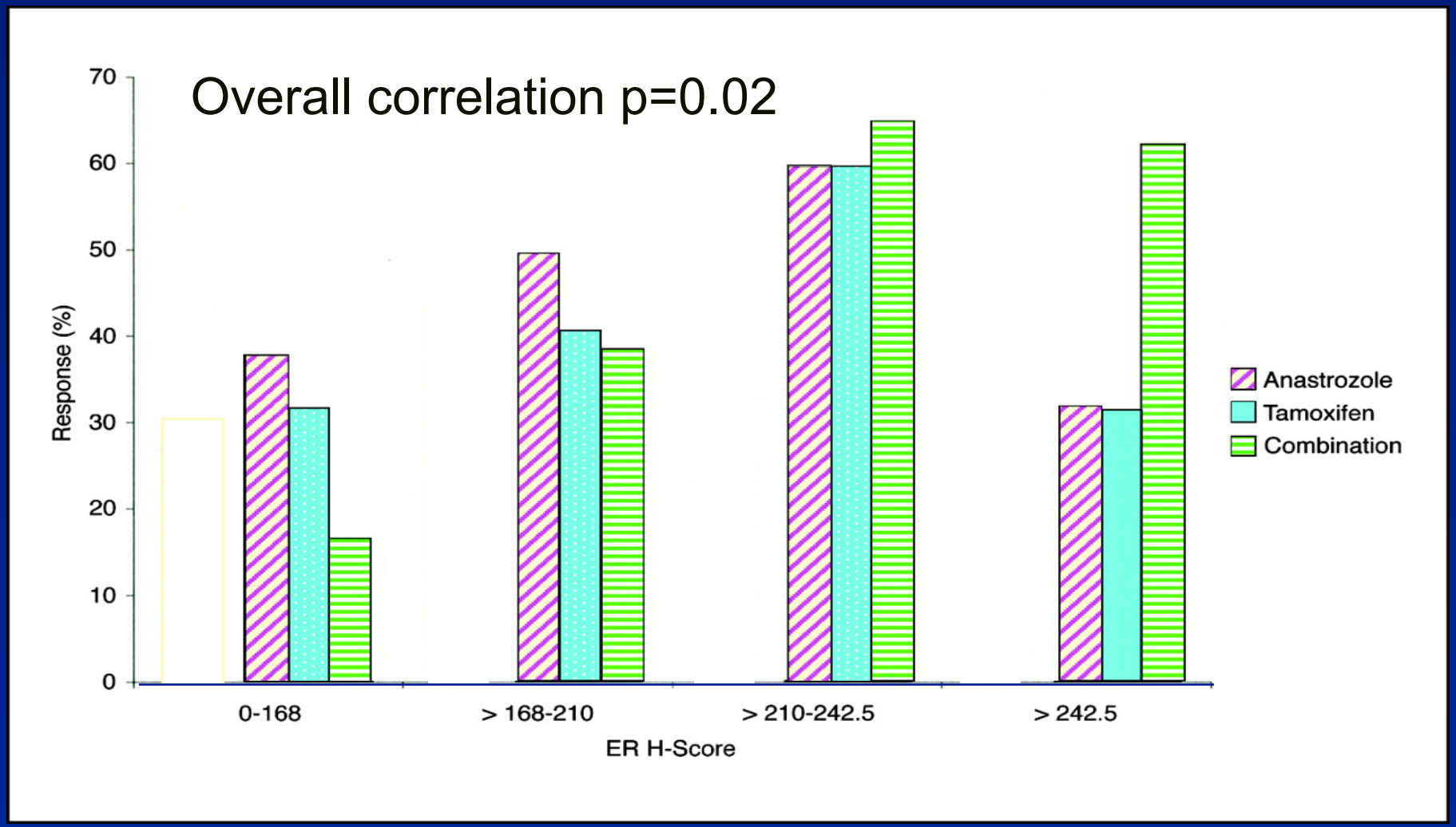
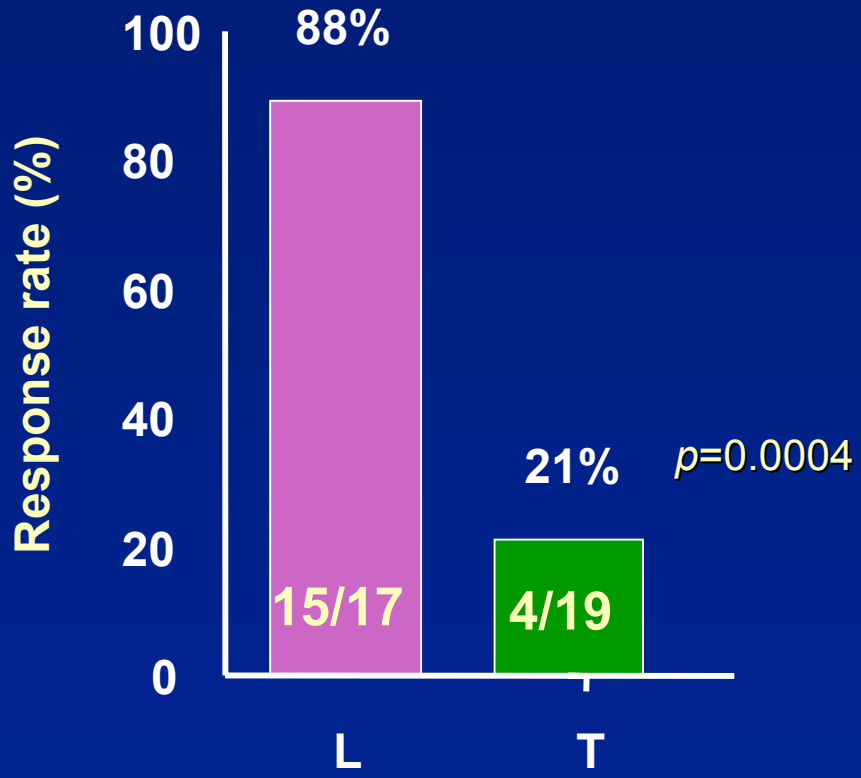
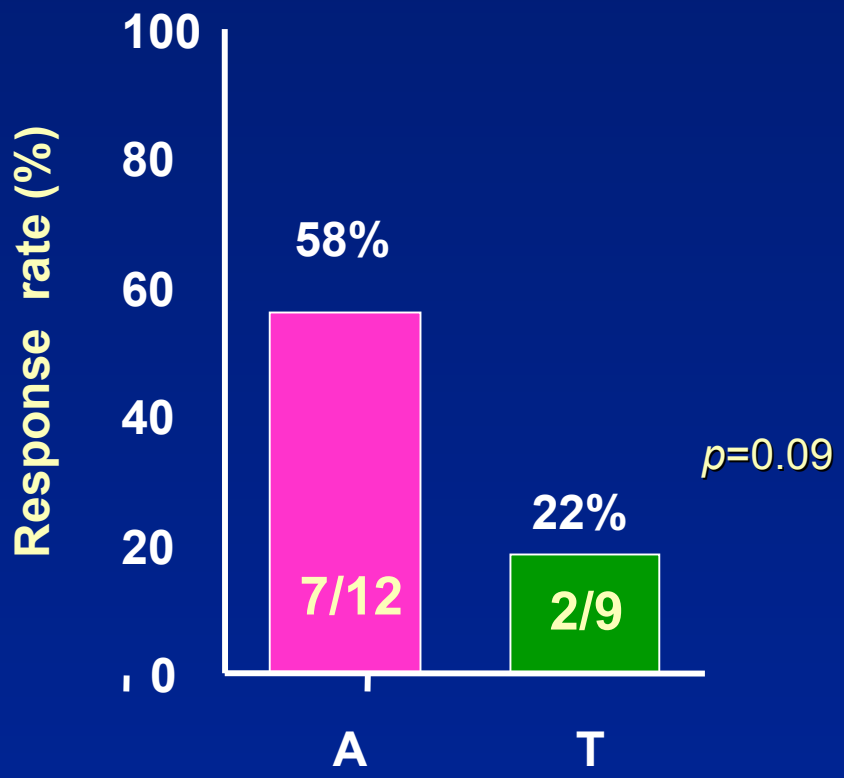


Smith I.E. et al. J Clin Oncol; 23:5108-5116 2005

Clinical Response (%) in HER2+ Tumours



Letrozole:P024
227 pts

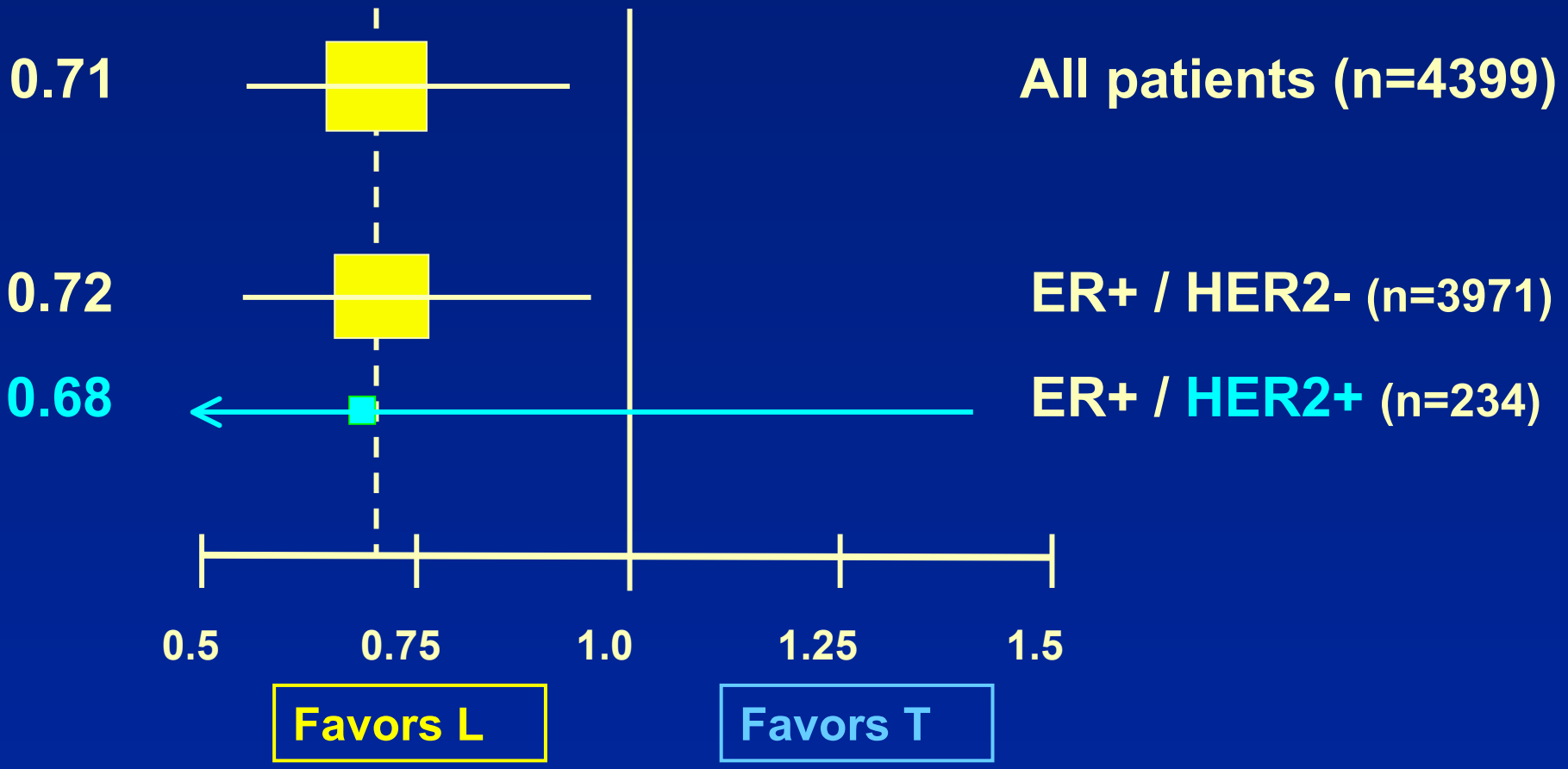


IMPACT
239 pts

Ellis et al. *J C.O.* 2001;19:3808. .

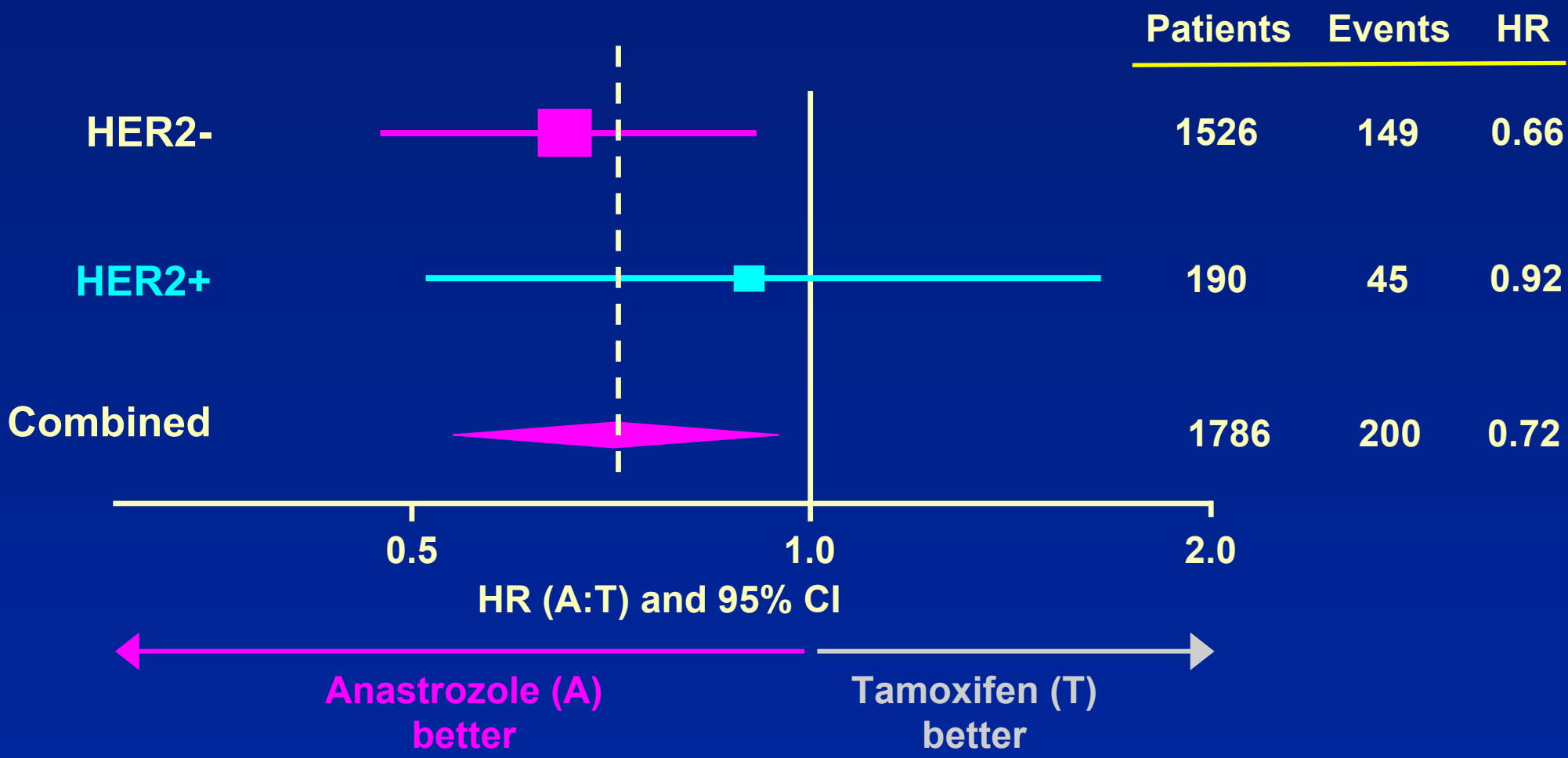
Smith et al JCO 23: 5108 2005

Letrozole v tamoxifen by HER2 status
DFS (BIG 1-98 Central Analysis)



Viale et al SABCC.2005

Anastrozole vs tamoxifen by HER2 status: DFS
(TransATAC central analysis)



Dowsett et al SABCC.2006

Can Neoadjuvant Endocrine Therapy Provide Short Term Surrogate Endpoints for Long Term Outcome?

Can Neoadjuvant Endocrine Therapy Provide Short Term Surrogate Endpoints for Long Term Outcome?

- Clinical Objective Response?

Neoadjuvant		Adjuvant	
P24 Letrozole v Tam	►	BIG 1-98	Yes
IMPACT A v T v C	►	ATAC	No
PROACT A v Tam	►	ATAC	No
HER2+ve P24/ IMPACT	►	ATAC/B 1-98	No

Can Neoadjuvant Endocrine Therapy Provide Short Term Surrogate Endpoints for Long Term Outcome?

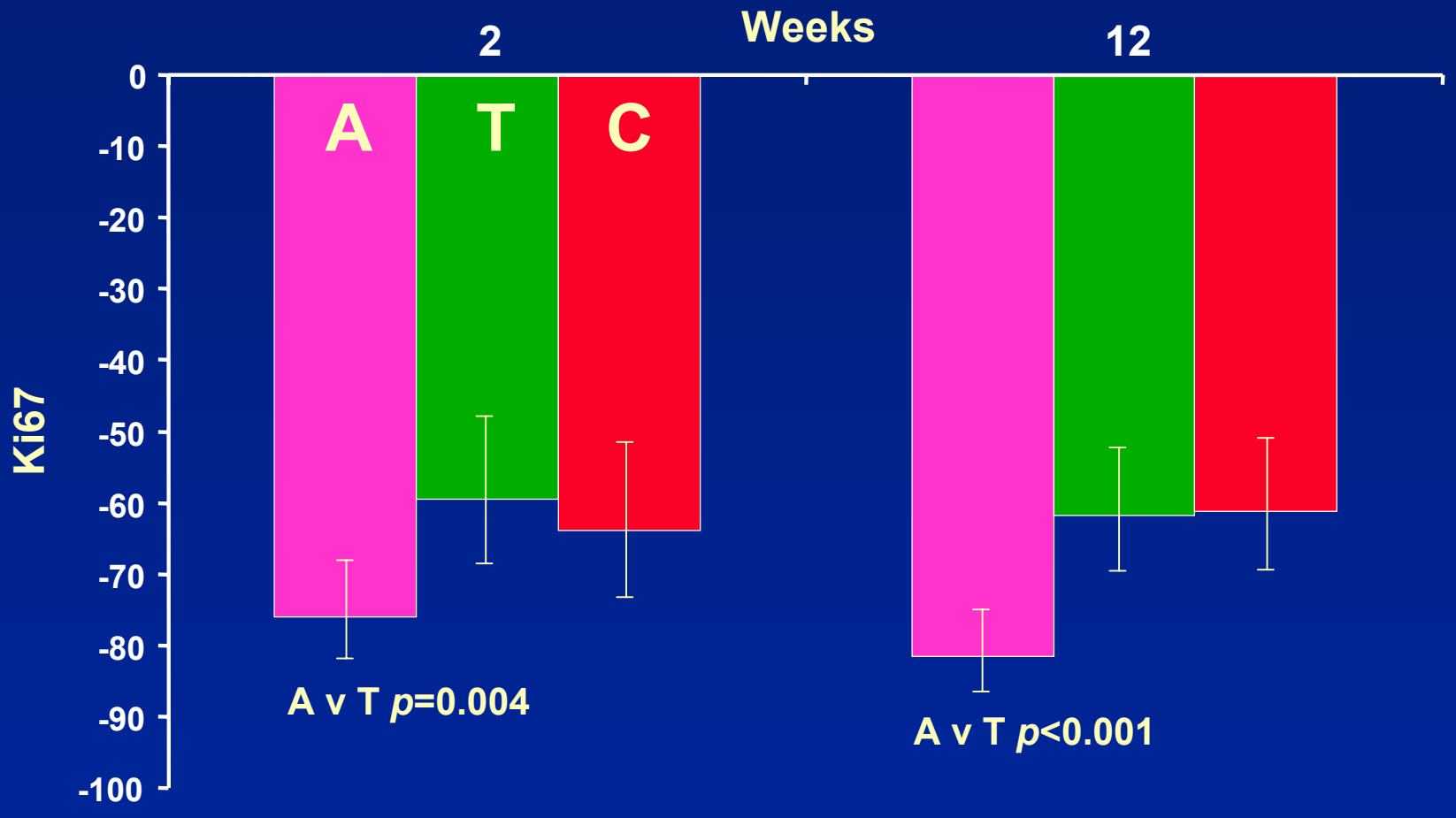
- Path Complete Remission?

		pCR
IMPACT	A v T v C	0.5%
223	A v A +G	0%
P24	L v T	1.5%

Can Neoadjuvant Endocrine Therapy Provide Short Term Surrogate Endpoints for Long Term Outcome?

- Molecular Endpoints?

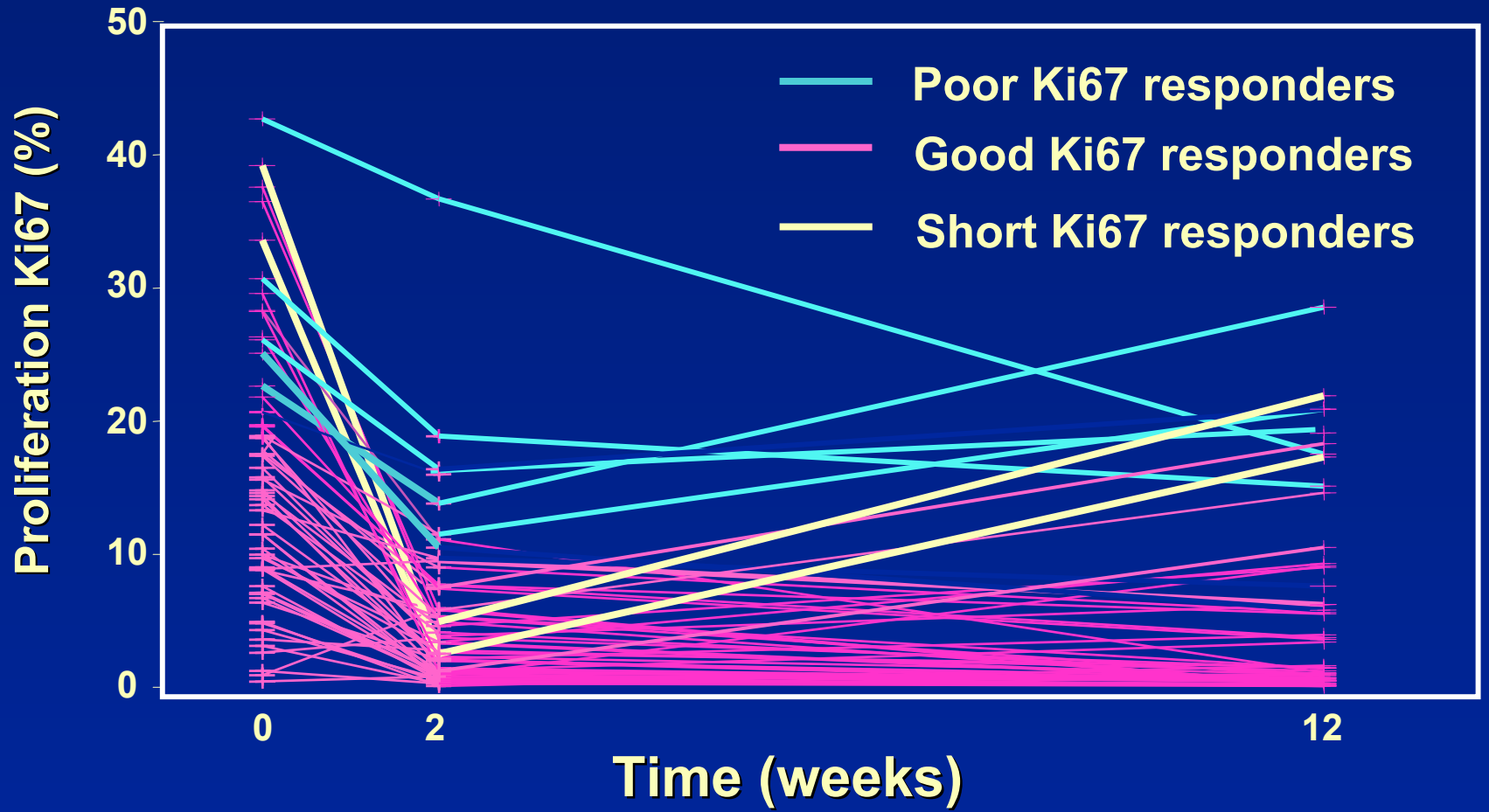
IMPACT: Ki67 % Change (95% CI) from Baseline* During Treatment



* Via transformation of geometric mean proportion of baseline

Dowsett and Smith Clin Cancer Res 2005; 11: 951s-958s

IMPACT Ki67 (%): individual patient plots — anastrozole



223 Anastrozole ± Gefitinib
Neoadjuvant Trial Design

206 pts
Randomise

Anastrozole

Anastrozole
Gefitinib

Molecular Response- 2wks
-Ki67
-mRNA

4 mo

4 mo

Clinical Response- 4months

Surgery

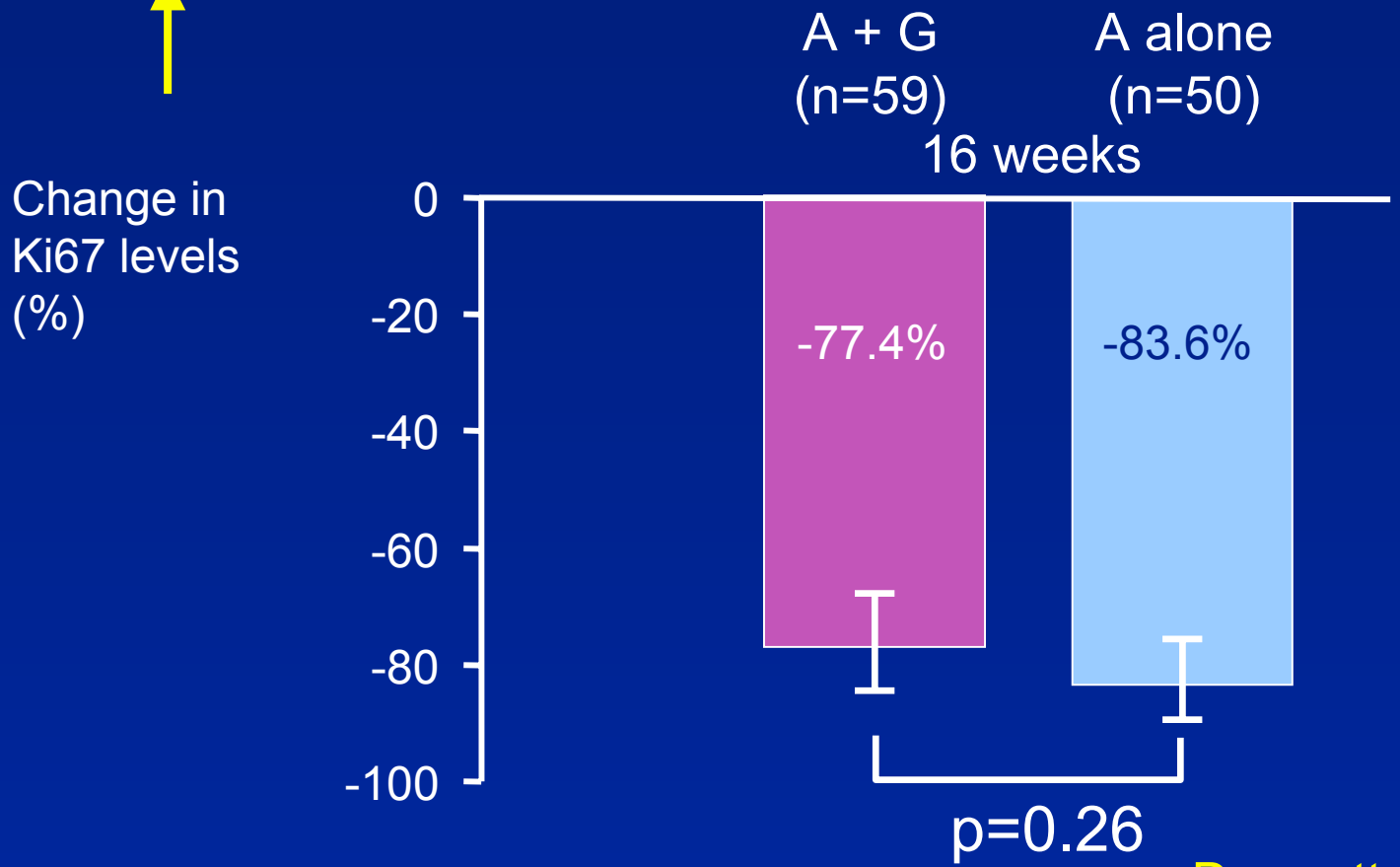
Surgery

Mean change in Ki67: baseline to 16 wks

Anastrozole
Placebo

v.

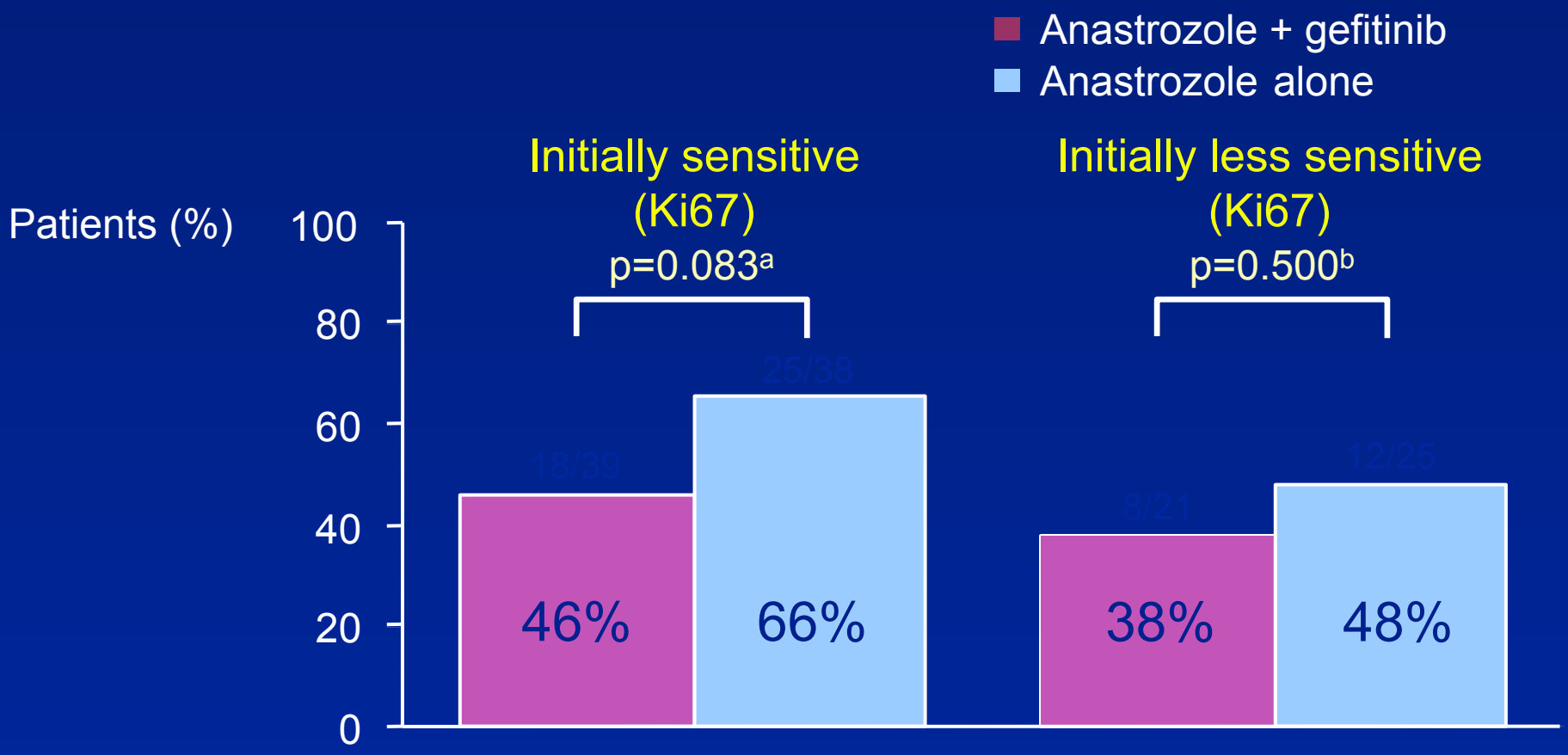
Anastrozole
Gefitinib



Dowsett, Smith et al ASCO 2006

Objective tumour response rates

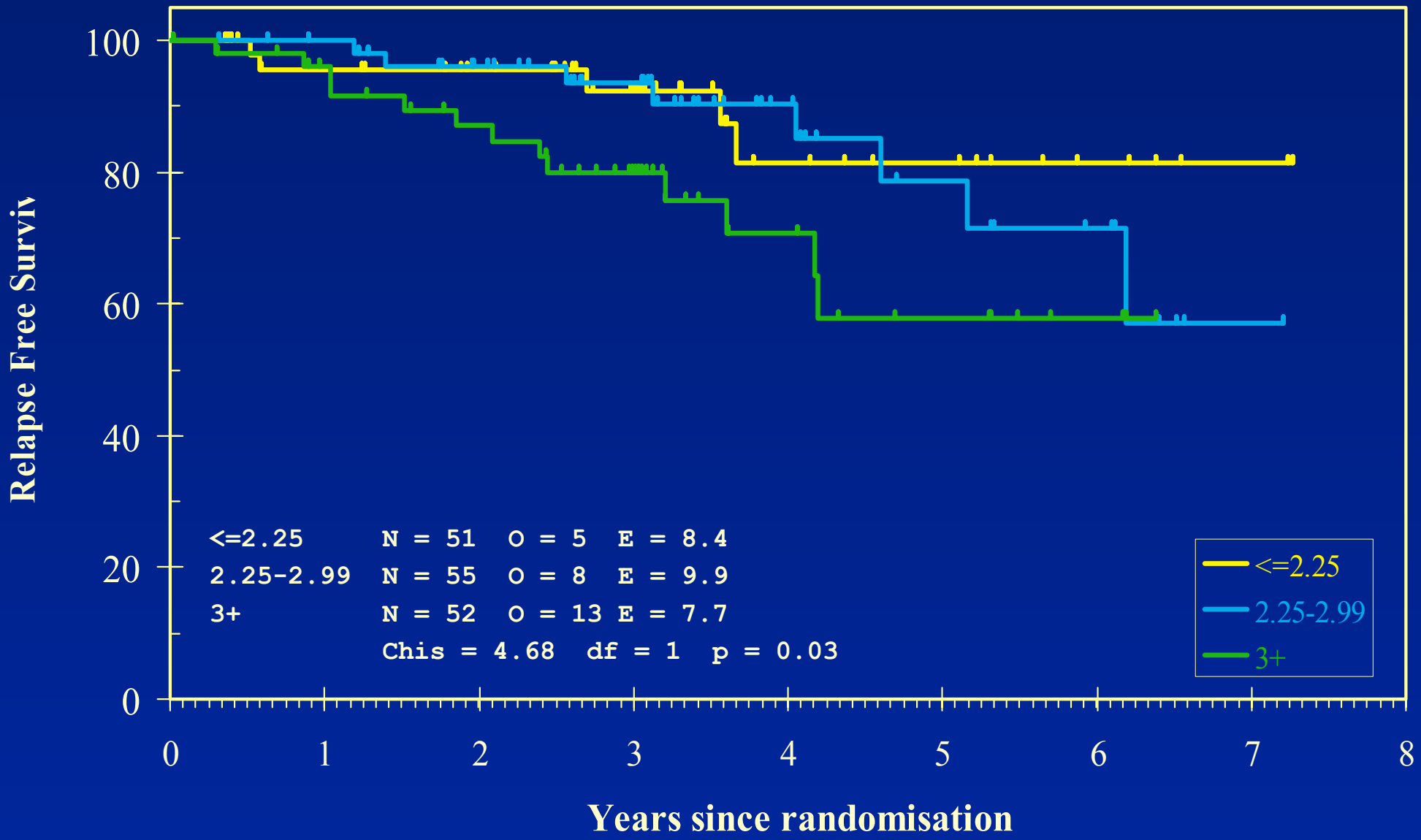
Initially sensitive and less sensitive (Ki67)



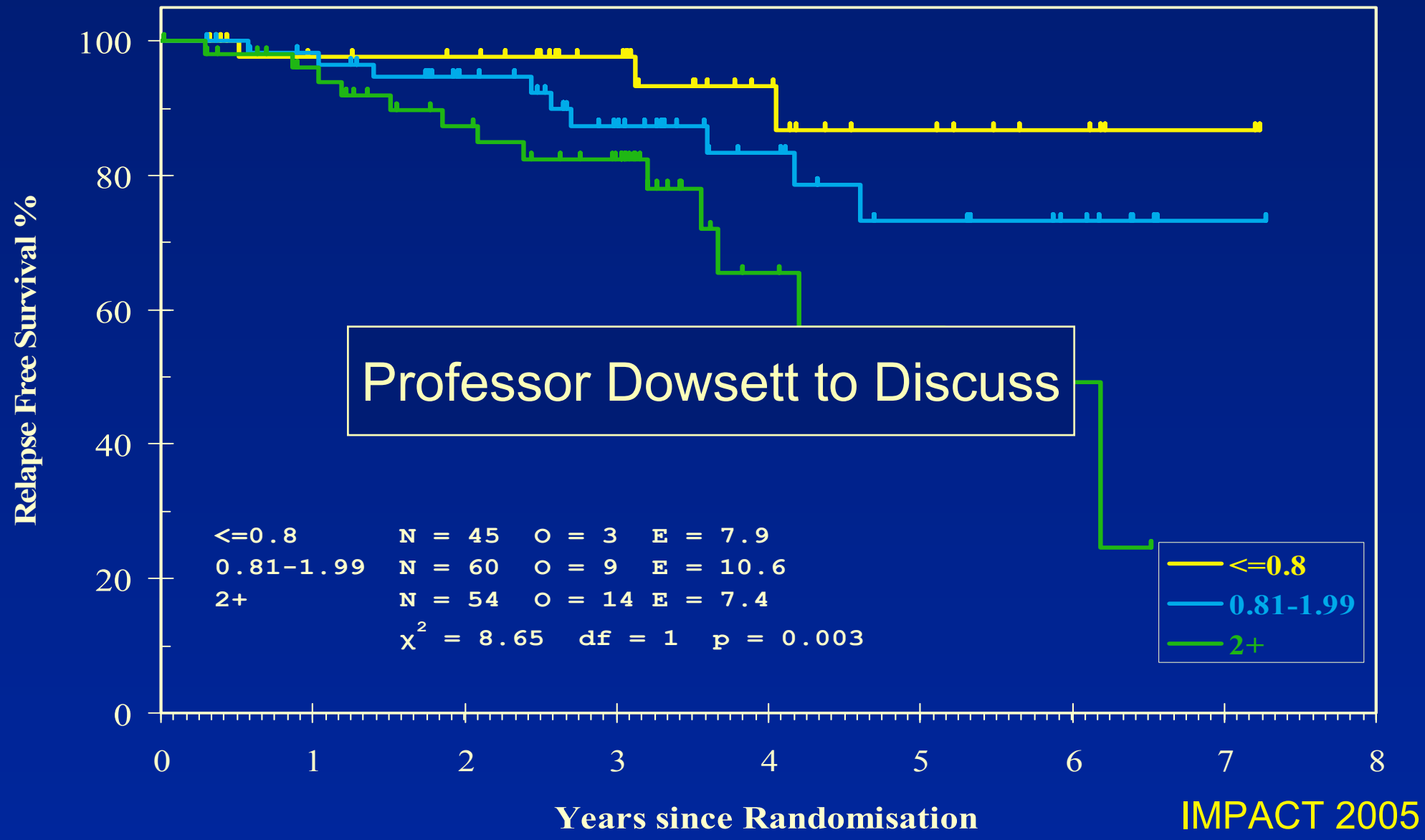
[a]Treatment difference: -19.6 (-41.4, 2.1); [b]Treatment difference: -9.9 (-38.5, 18.6)

Can Short Term Molecular Endpoints With Neoadjuvant Endocrine Therapy Predict for Long Term Outcome *In the Individual Patient*?

IMPACT RFS by Baseline Ln Ki67



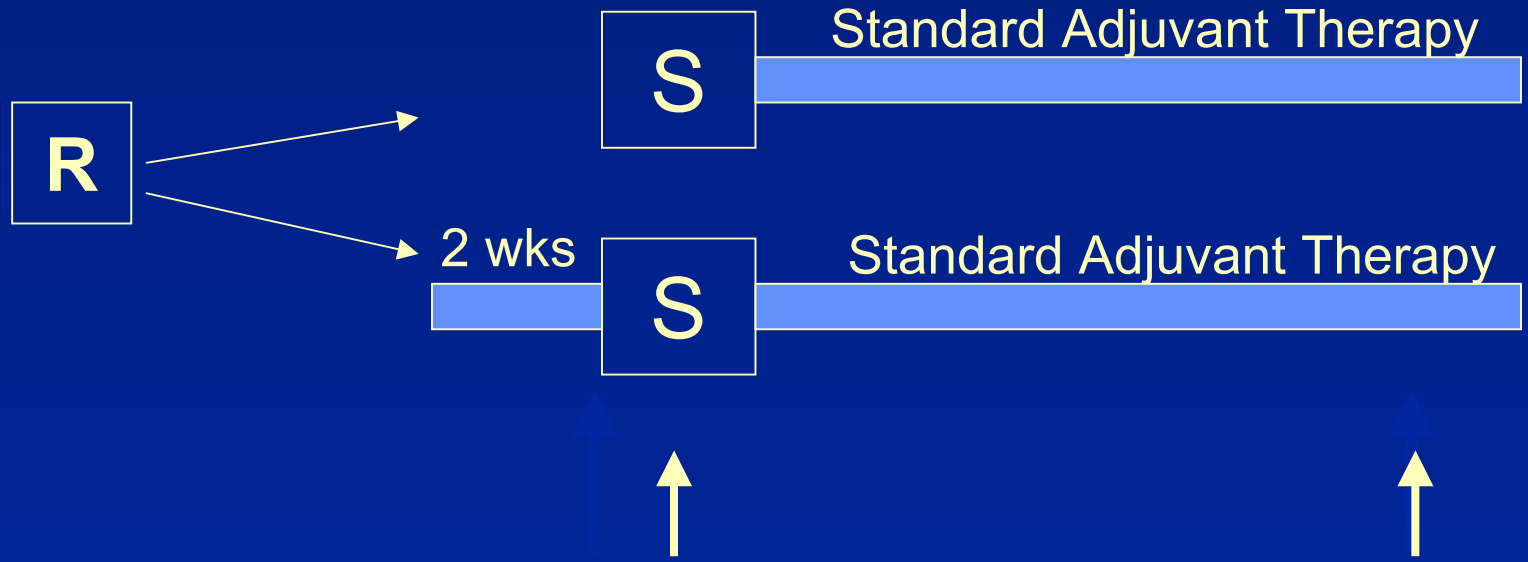
IMPACT RFS by 2 week Ln Ki67



IMPACT 2005

UK POETIC Trial
Preoperative Endocrine Therapy
Individualising Care

- Postmenopausal.
- HR+ve



Preoperative EndocrineTherapy: Conclusions (1)

- Aromatase inhibitors are more effective than tamoxifen
- Around 50% objective responses
- Breast conservation in >40% initially requiring mastectomy

Preoperative EndocrineTherapy: Conclusions (2)

- Optimum duration uncertain but at least 4 months
- Well worth thinking about instead of chemotherapy in older patients with strongly ER/PgR+ cancers
- How to select?

Preoperative Hormonal Therapy Conclusions (3)

- Clinical response is not a reliable surrogate for long term outcome
- PathCRs are too rare to be a useful surrogate
- Molecular markers (including after short term therapy) are more likely to be useful as short term predictors of outcome