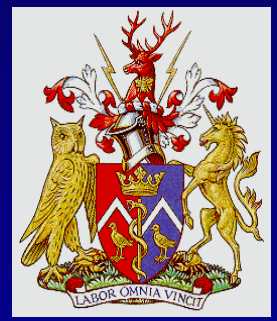
Proliferation and apoptosis as measures of response

Mitch Dowsett
NCI
March, 2007

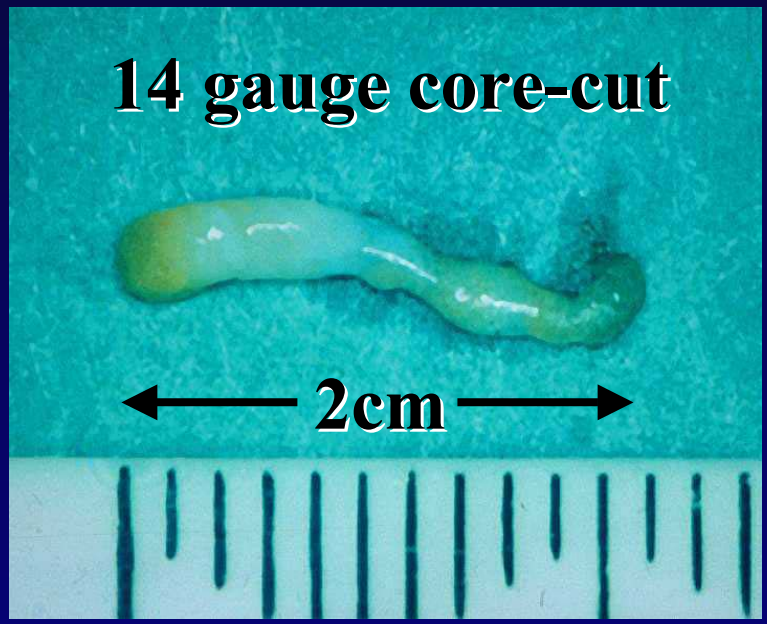


Proliferation and apoptosis as measures of response

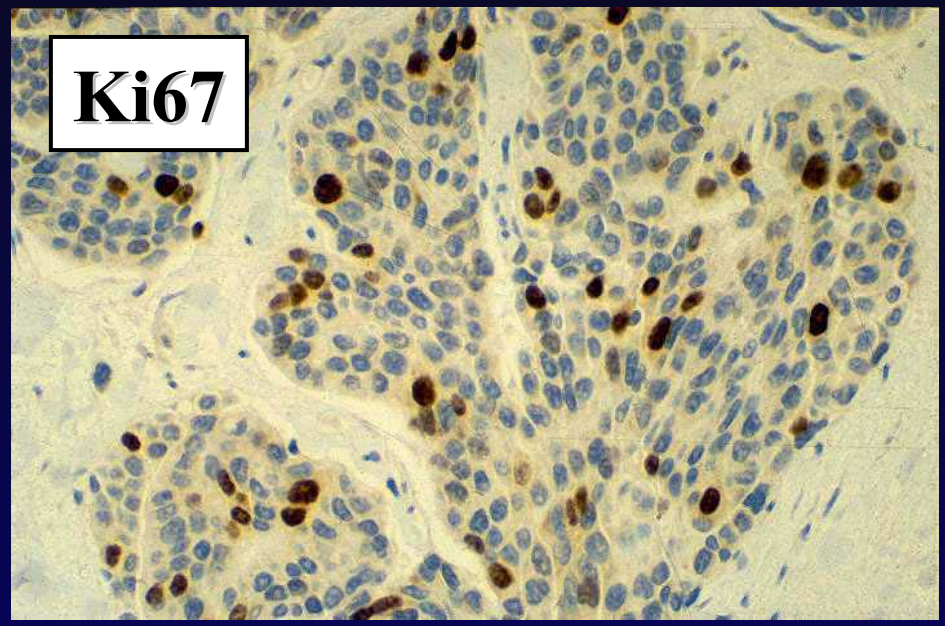
1. Chemotherapy
2. Endocrine therapy

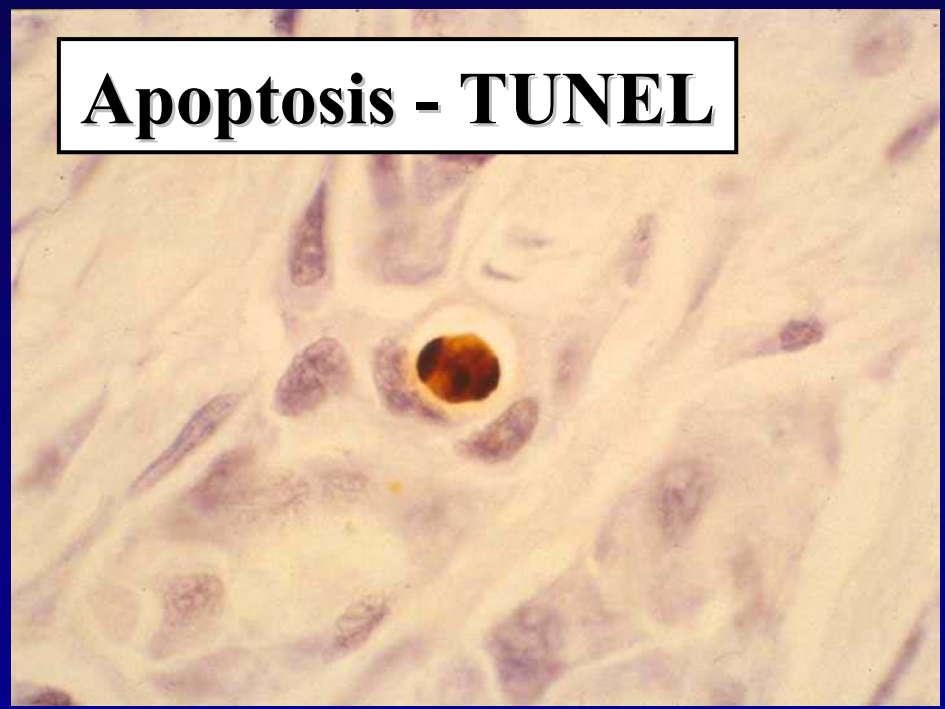
ΔProliferation (Ki67)
ΔApoptosis

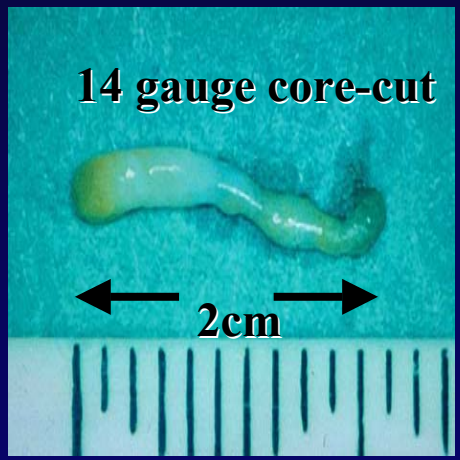
1,000 cells
scored
% positive



3,000 cells
scored
% positive

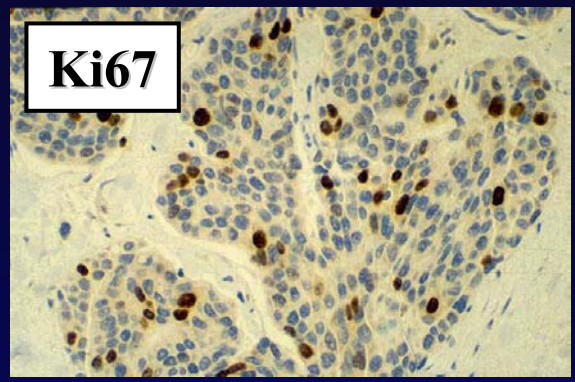






or
FNA

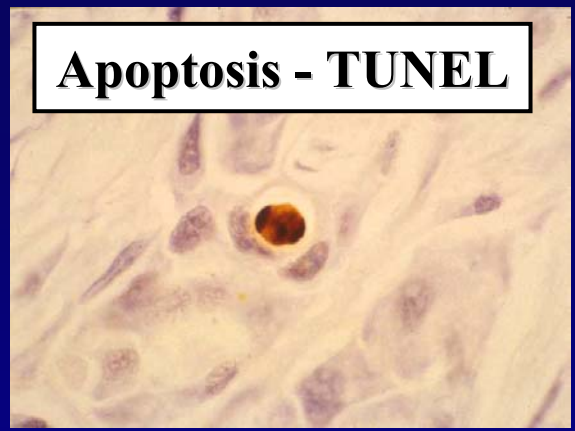
Proliferation



Or:
- s-phase
- mitotic index
- thymidylate synthase
- BrDU

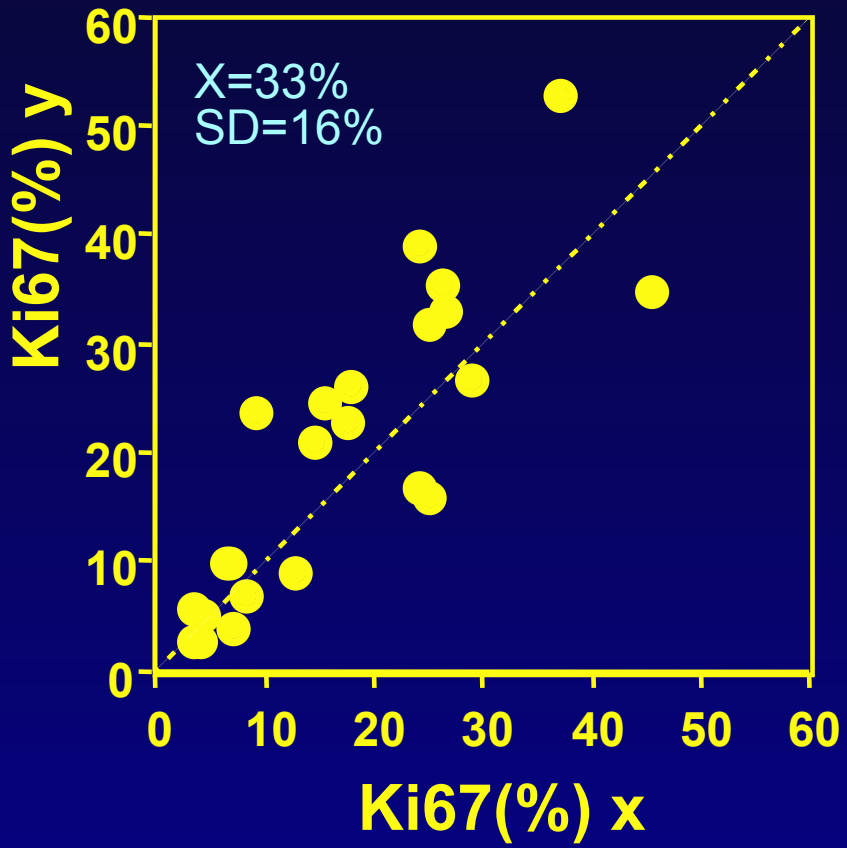
(Urruticoechea et al JCO, 2005, 23, 7212)

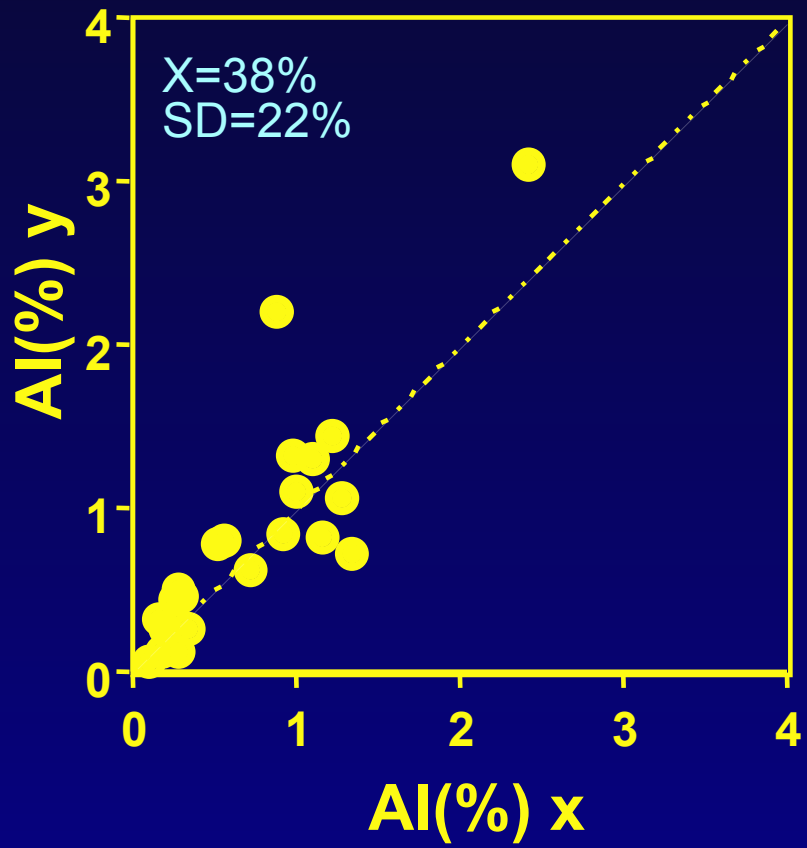
Cell death



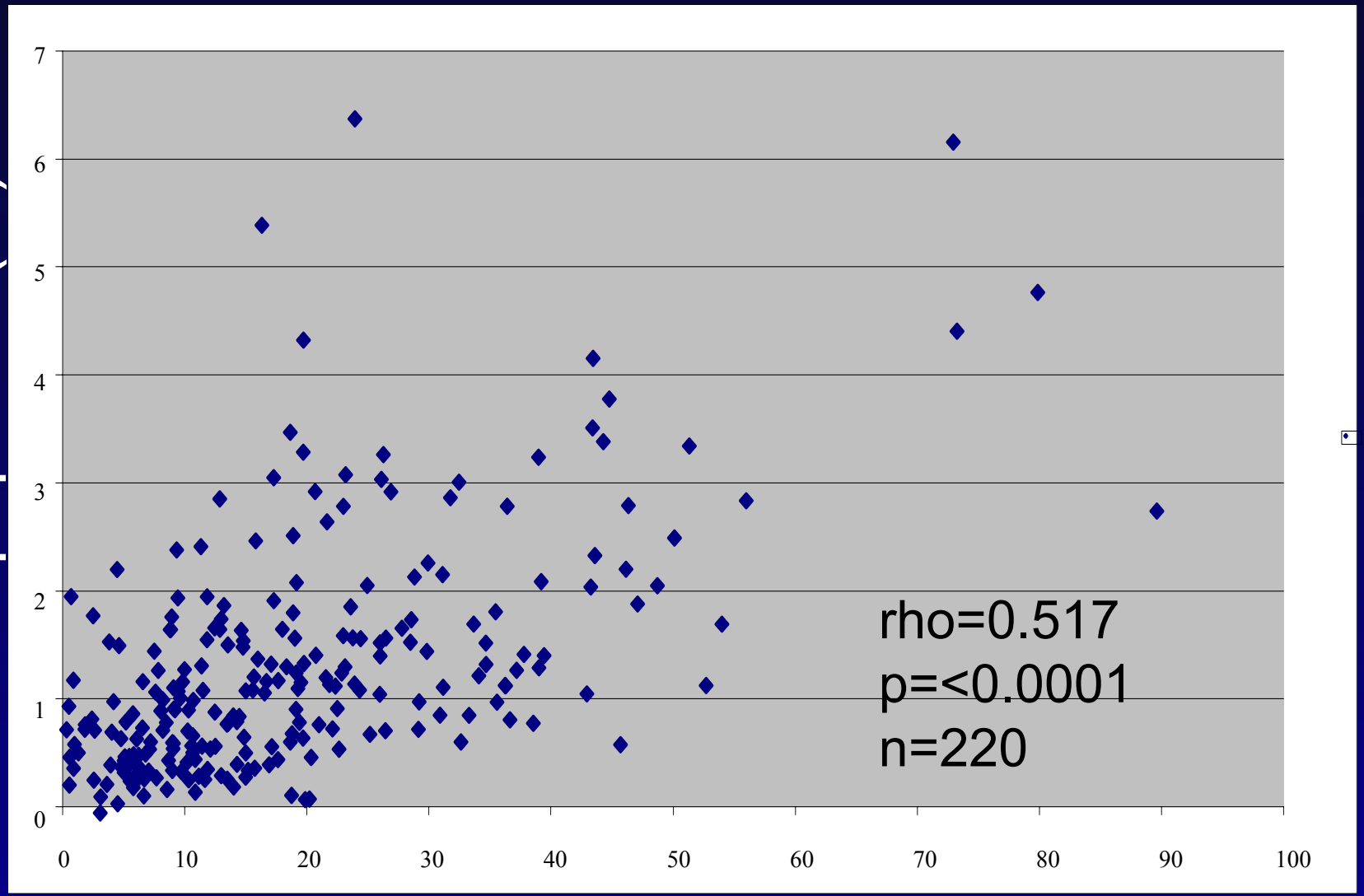
Or:
- morphology
- activated caspase 3
- ? M30 (keratin 8/18) serum assay
- (also autophagy and necrosis)

Precision of measurements of Ki67 and AI in pairs of 14g core-cuts





Relationship between Ki67 and apoptosis (IMPACT baseline)



Chemotherapy

High proliferation pretreatment:

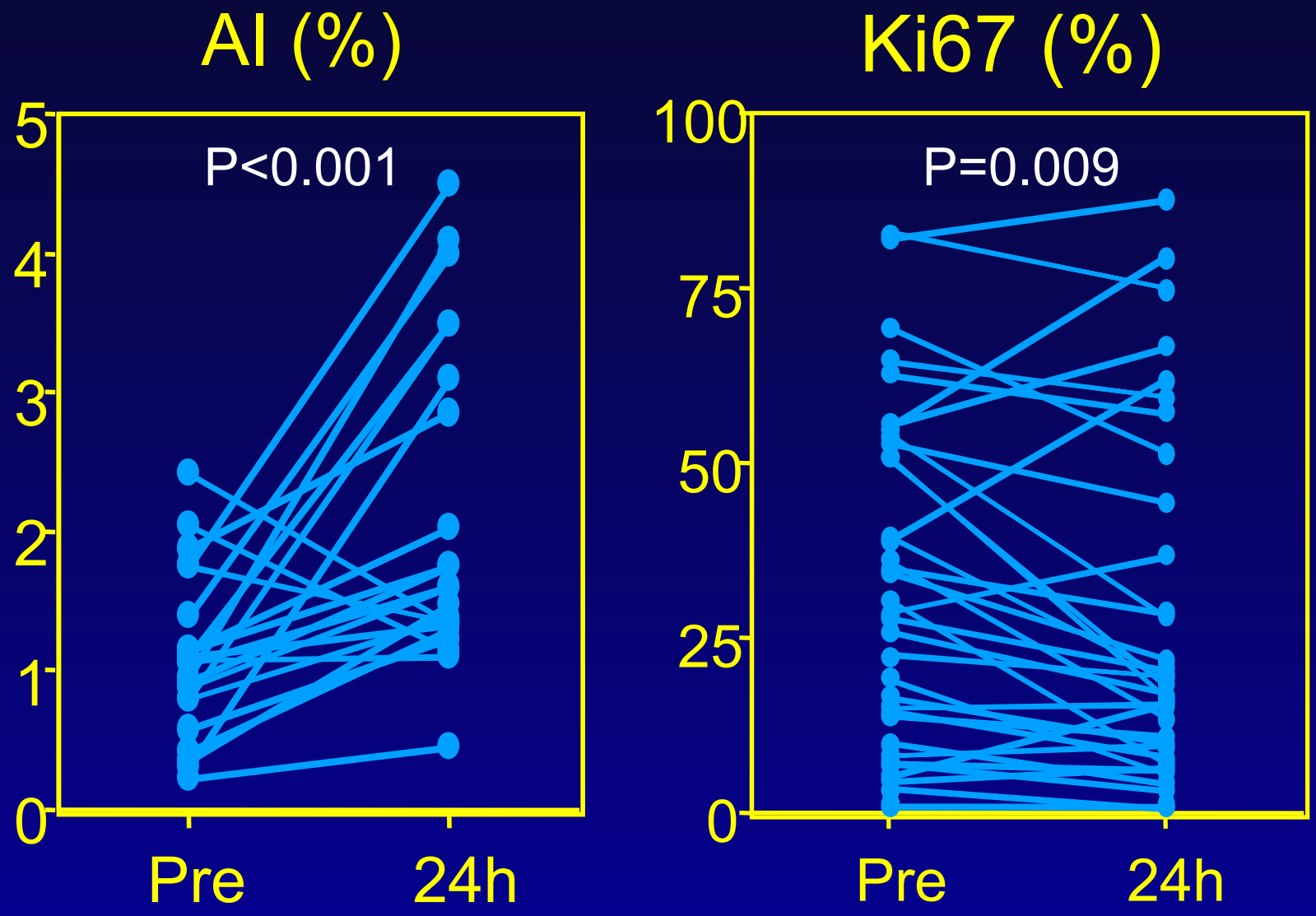
good response to chemotherapy

but

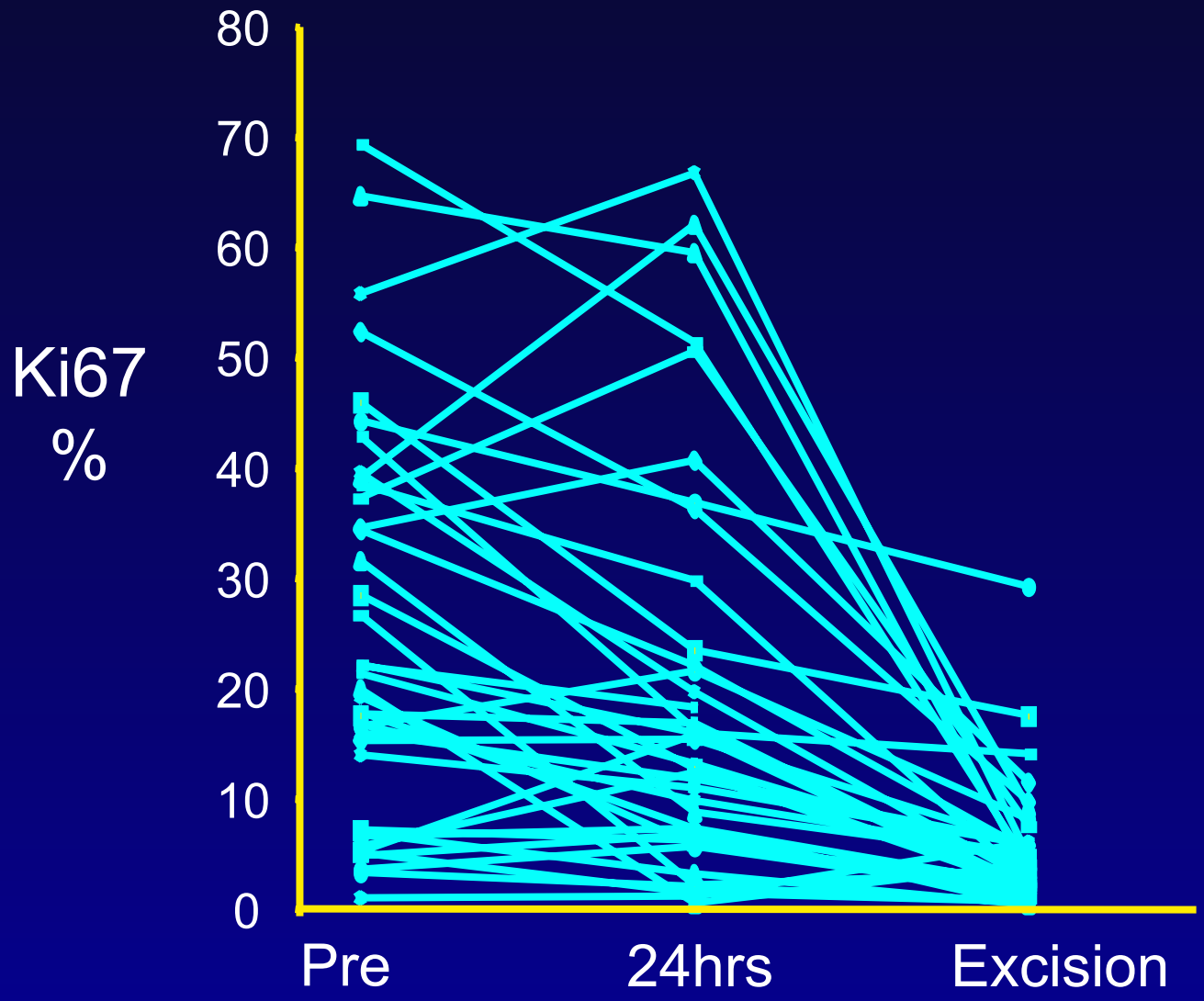
poor long term outcome

NB pCR

Effect of 24 hours chemotherapy on apoptotic index and Ki67



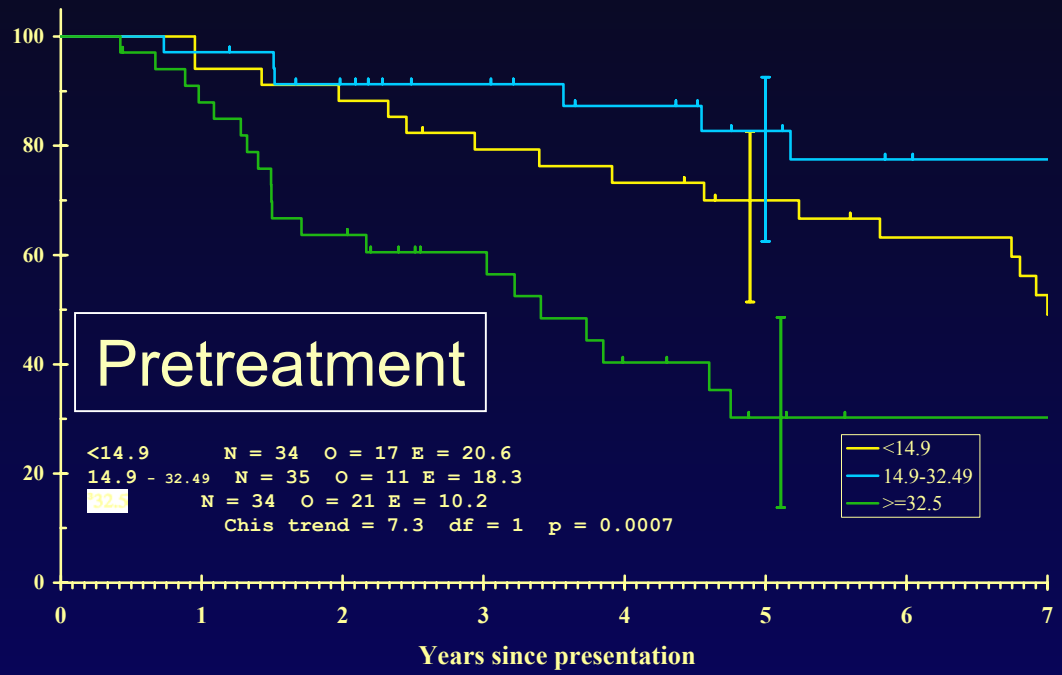
Change in Ki67 with neoadjuvant chemotherapy

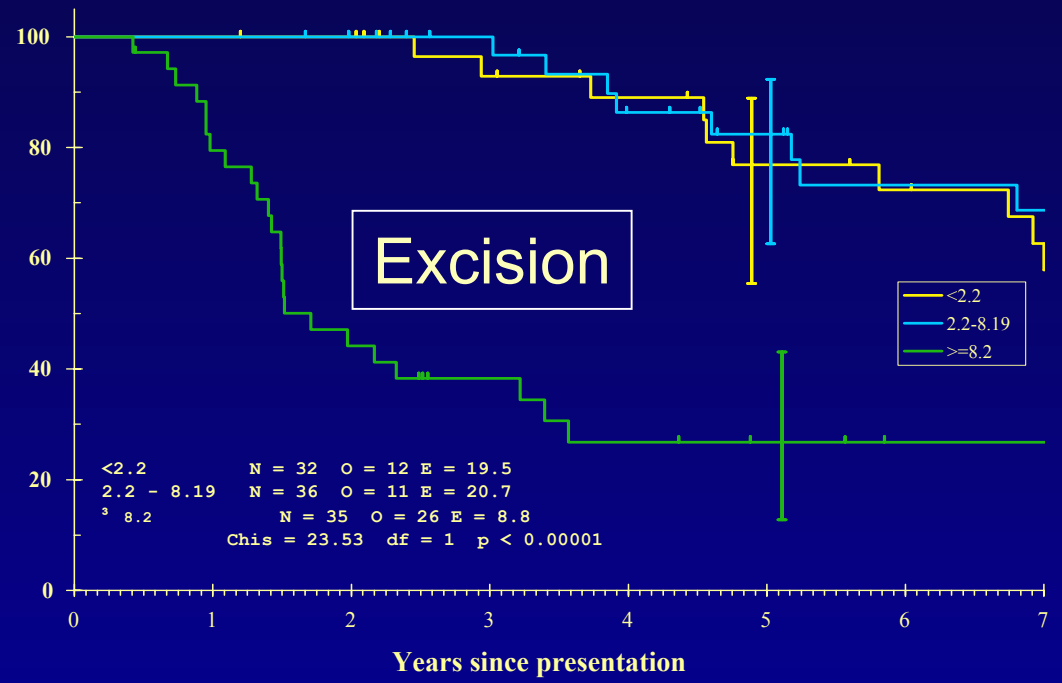


Relationship of clinical response with change in Ki67 or apoptosis

	∆pre/24hr	∆ pre/21d
Ki67↓	Non-significant	Significant: Makris et al 1998 Chang et al 1999 Assersohn 2003
apoptosis↑	Significant: Chang et al 1999 Non-significant: Parton et al 2001	

Pretreatment and excision (matched) Ki67 and RFS with neoadjuvant chemotherapy

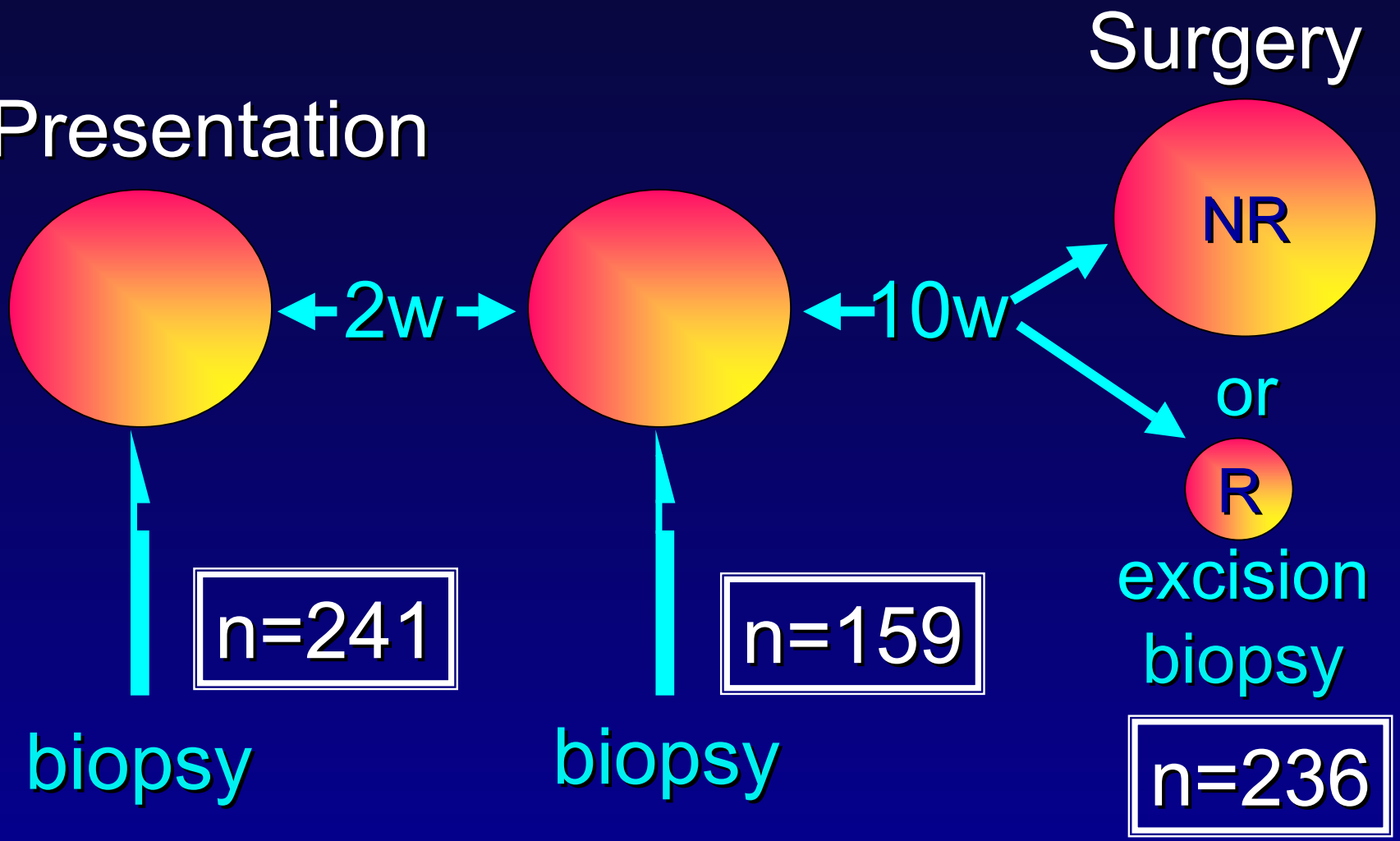




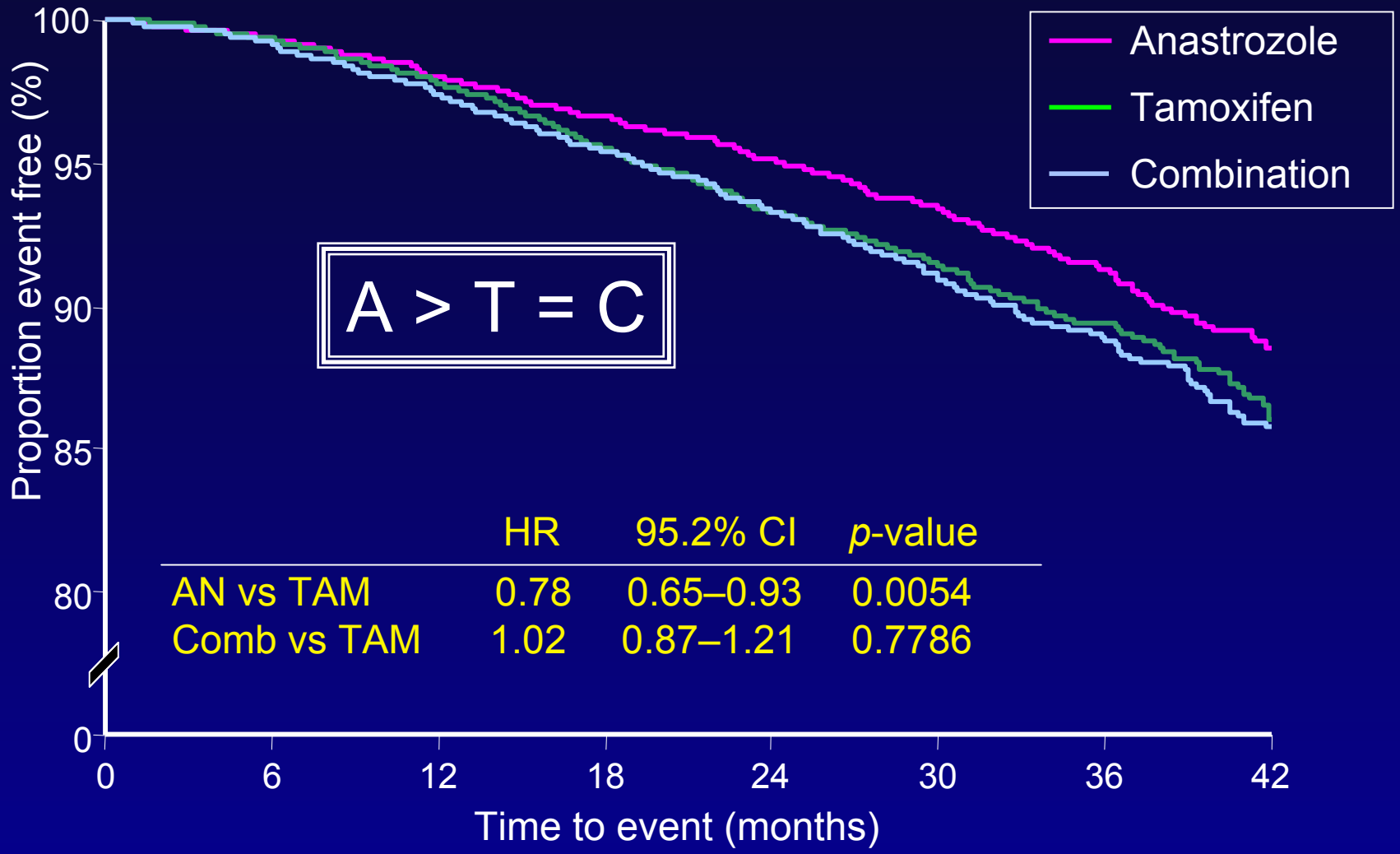
Endocrine therapy

IMPACT: Per Protocol Ki67 Analyses

Anastrozole vs tamoxifen vs combination in ER+ patients



ATAC: Kaplan–Meier Curves of Disease-free Survival in Receptor-positive Population



	HR	95.2% CI	*p*-value
AN vs TAM	0.78	0.65–0.93	0.0054
Comb vs TAM	1.02	0.87–1.21	0.7786

Curves truncated at 42 months

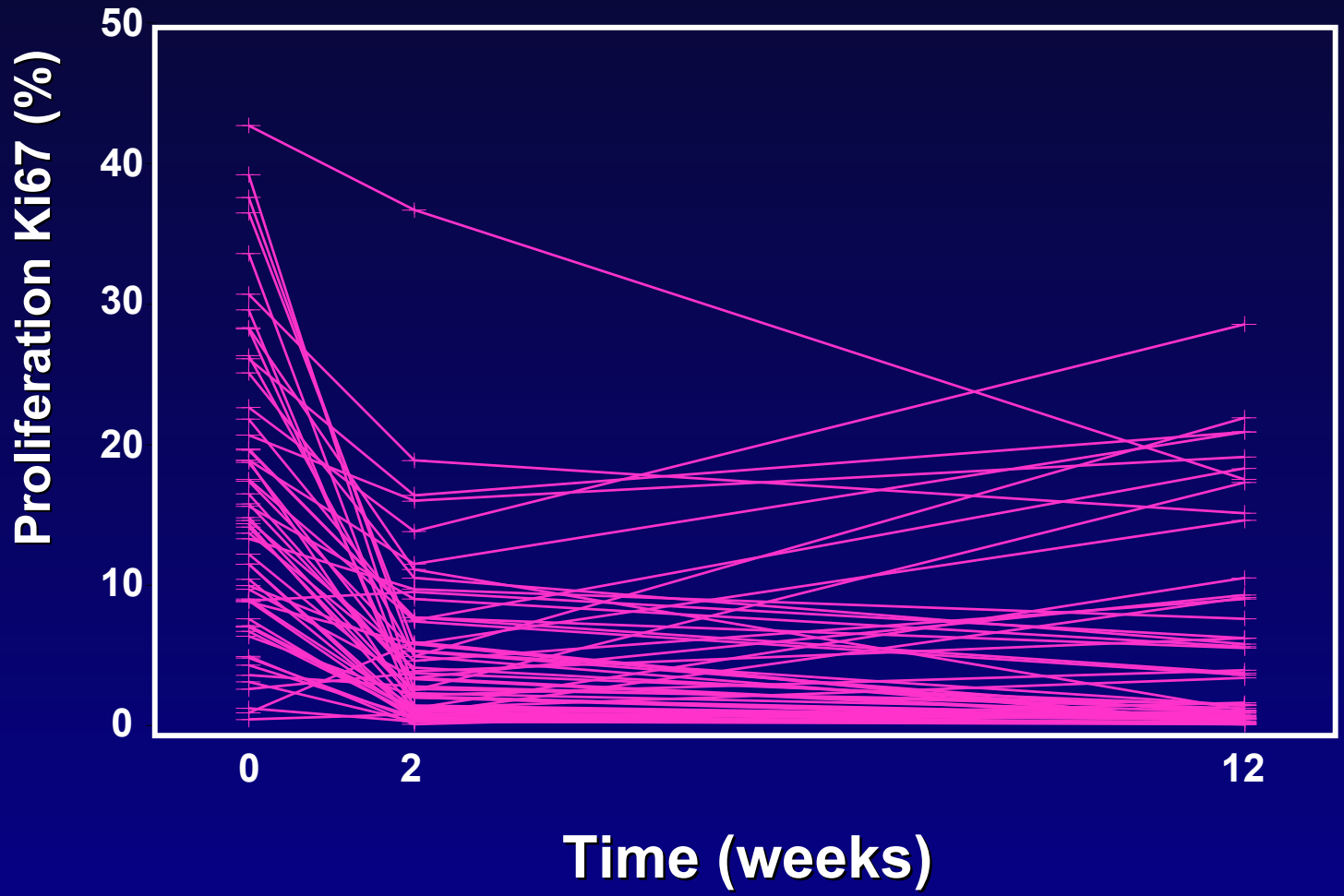
Apoptosis

Decreased with all 3 arms at 2 weeks (15-25%)

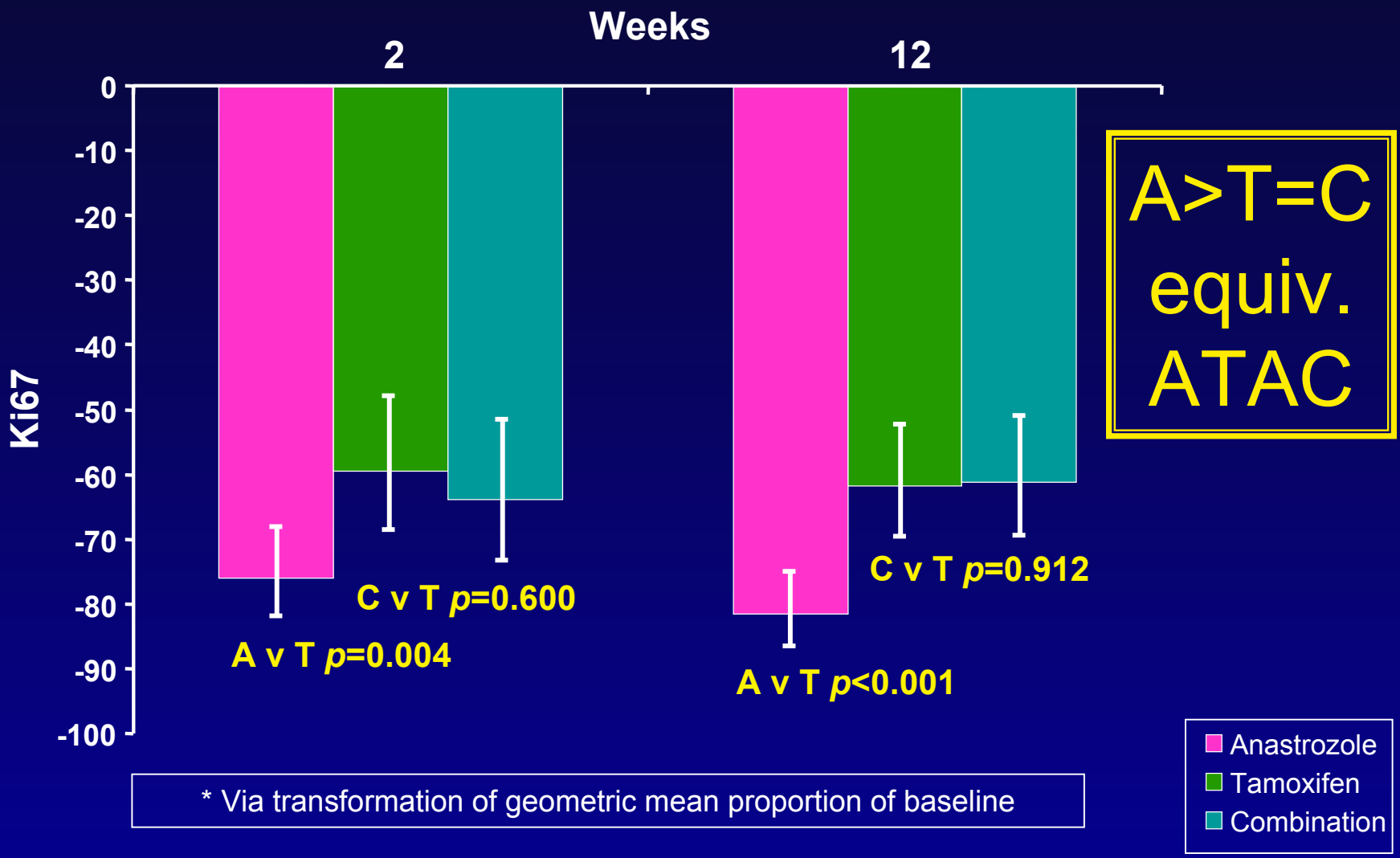
and

at 12 weeks for anastrozole (21%)

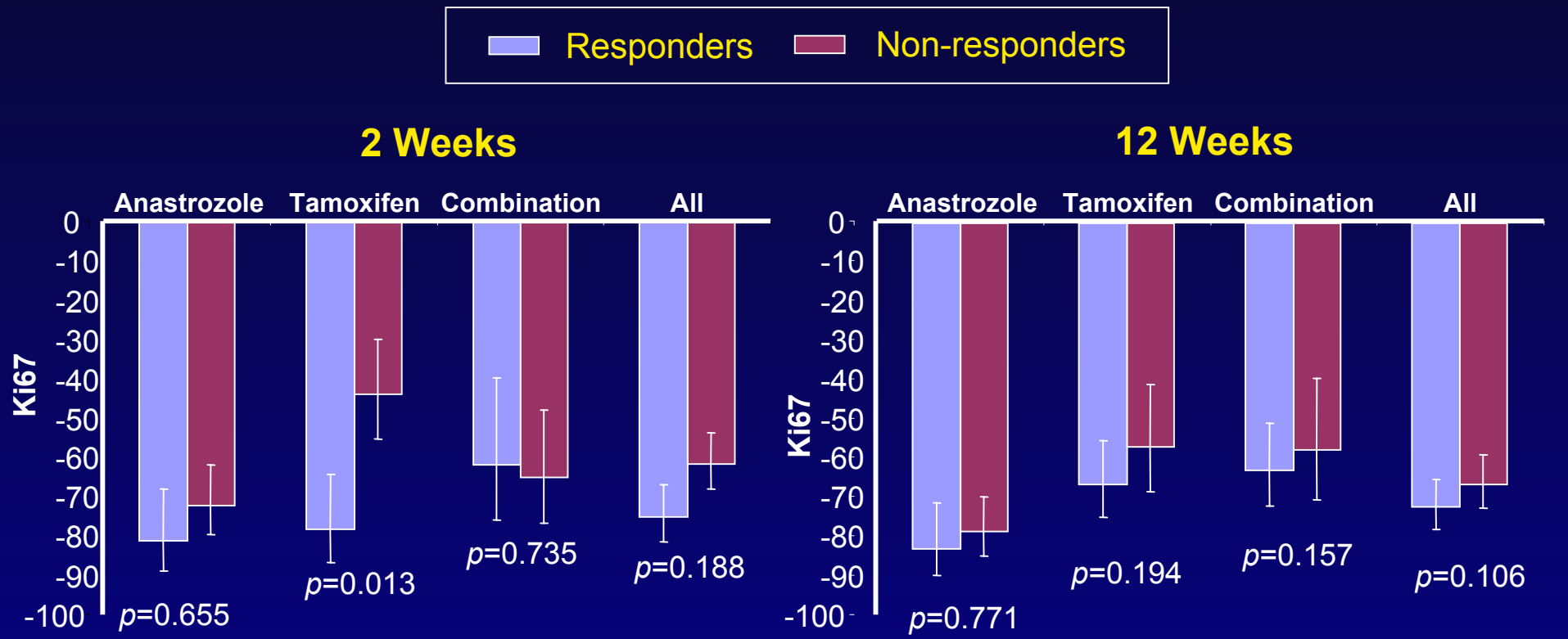
Proliferation Ki67 (%): Individual Patient Plots — Anastrozole (Per-Protocol Population)

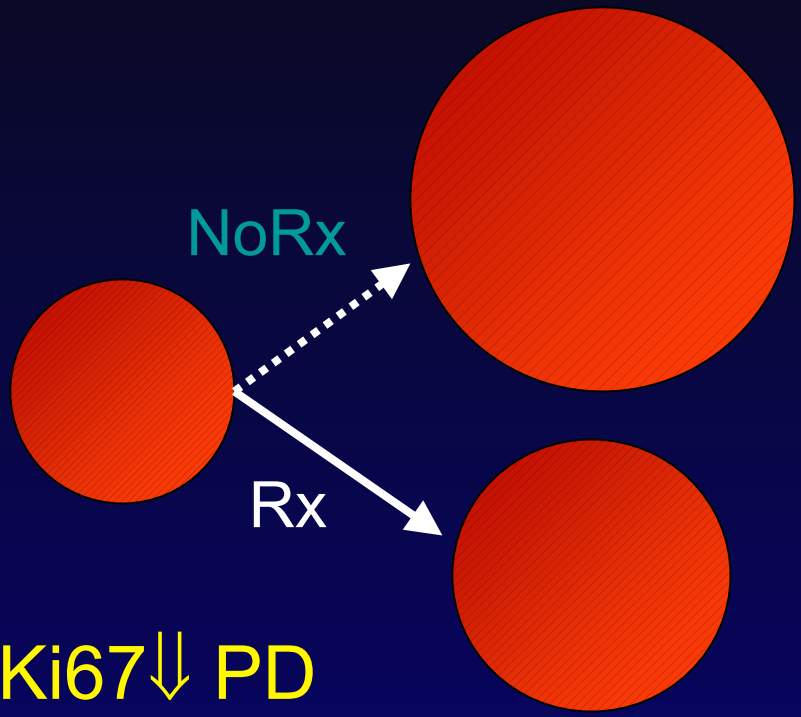


Percentage Ki67 Change (95% CI) from Baseline* During Treatment

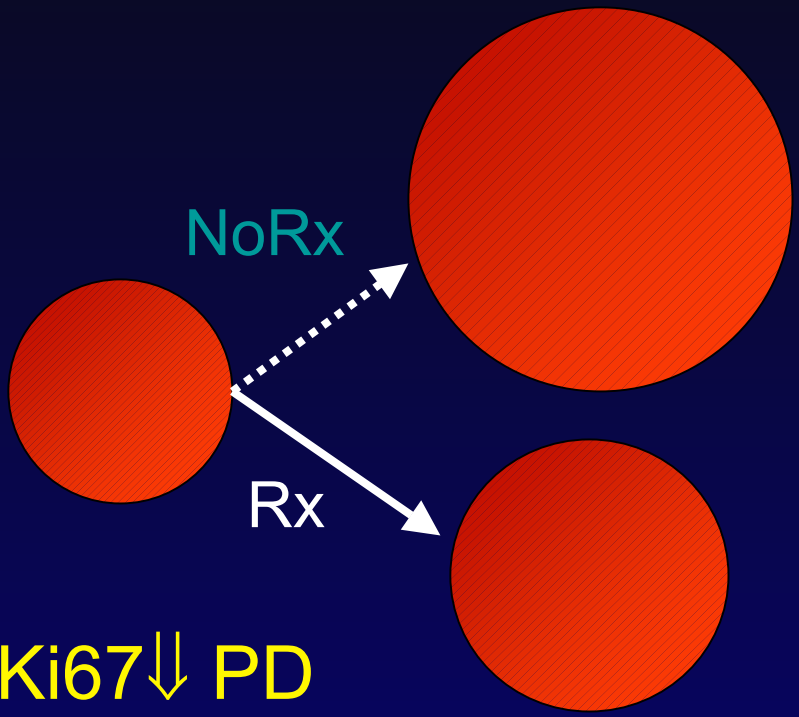


Relationship Between Ki67 Change and Objective Clinical Response

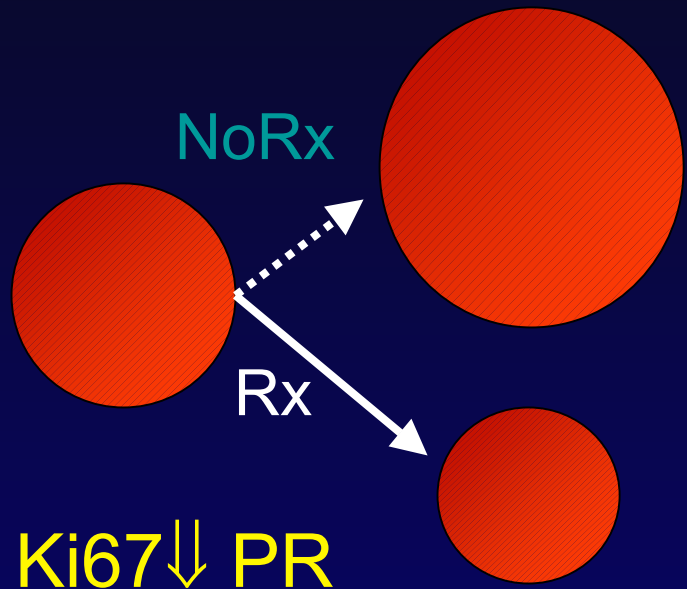




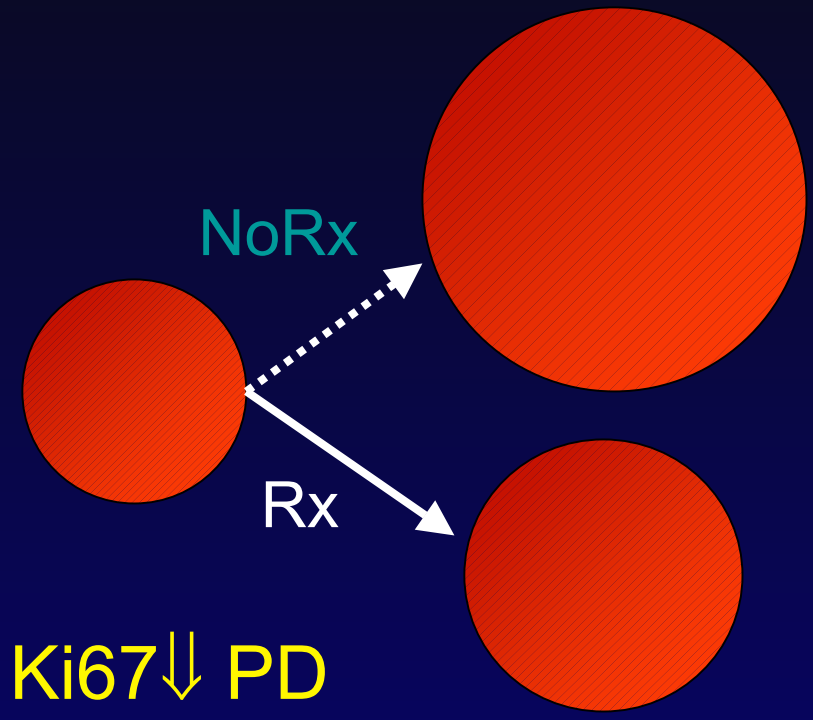
Ki67⇓ PD



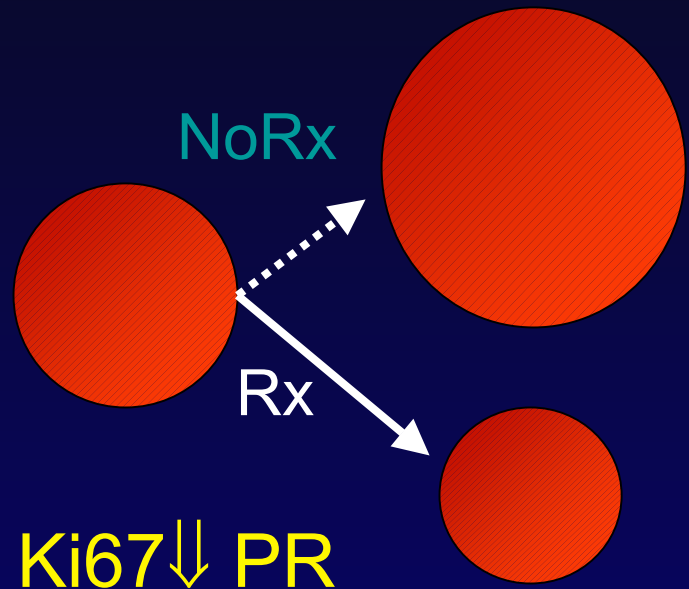
Ki67⇓ PD



Ki67⇓ PR



Ki67⇓ PD



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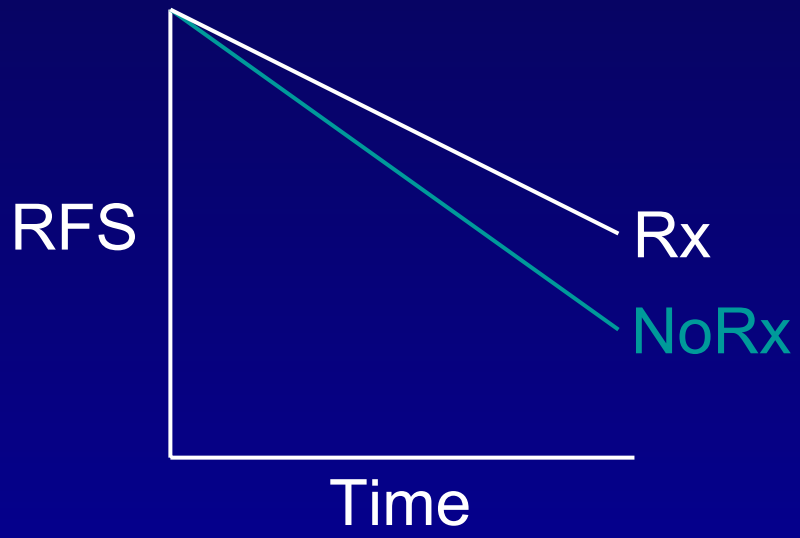
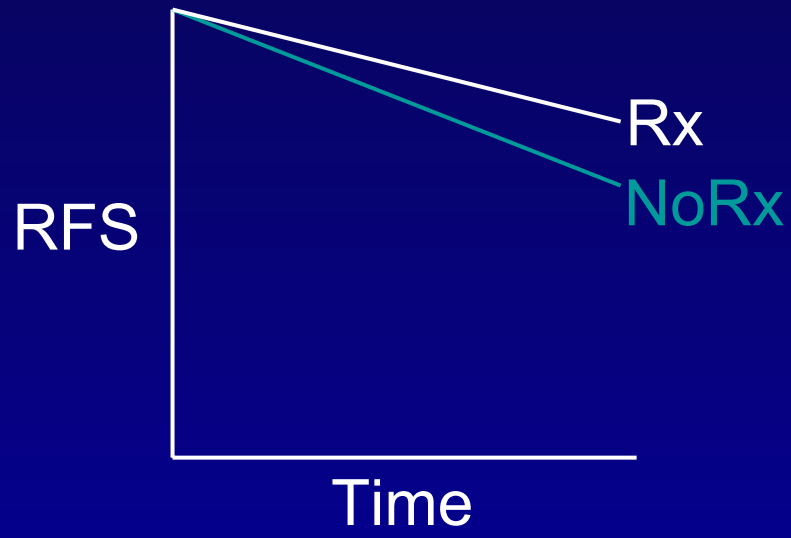
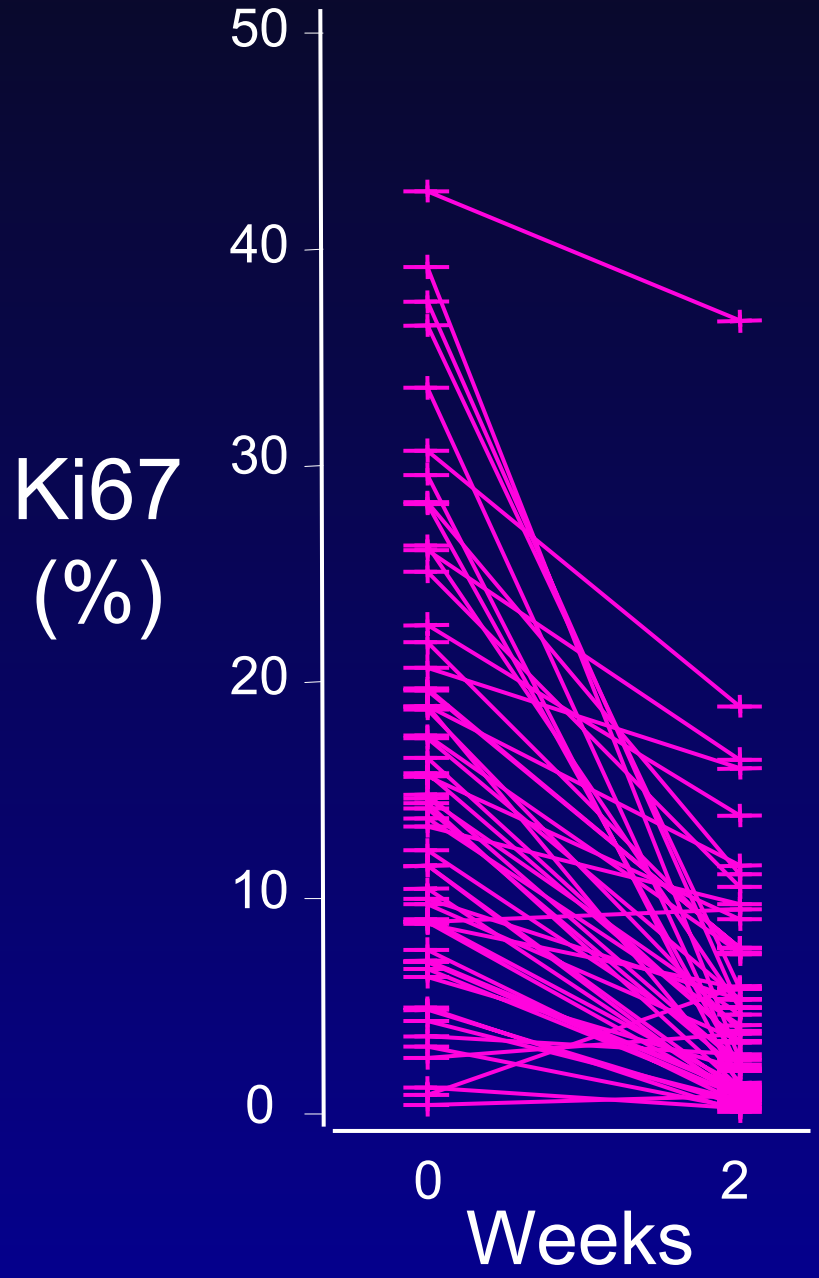
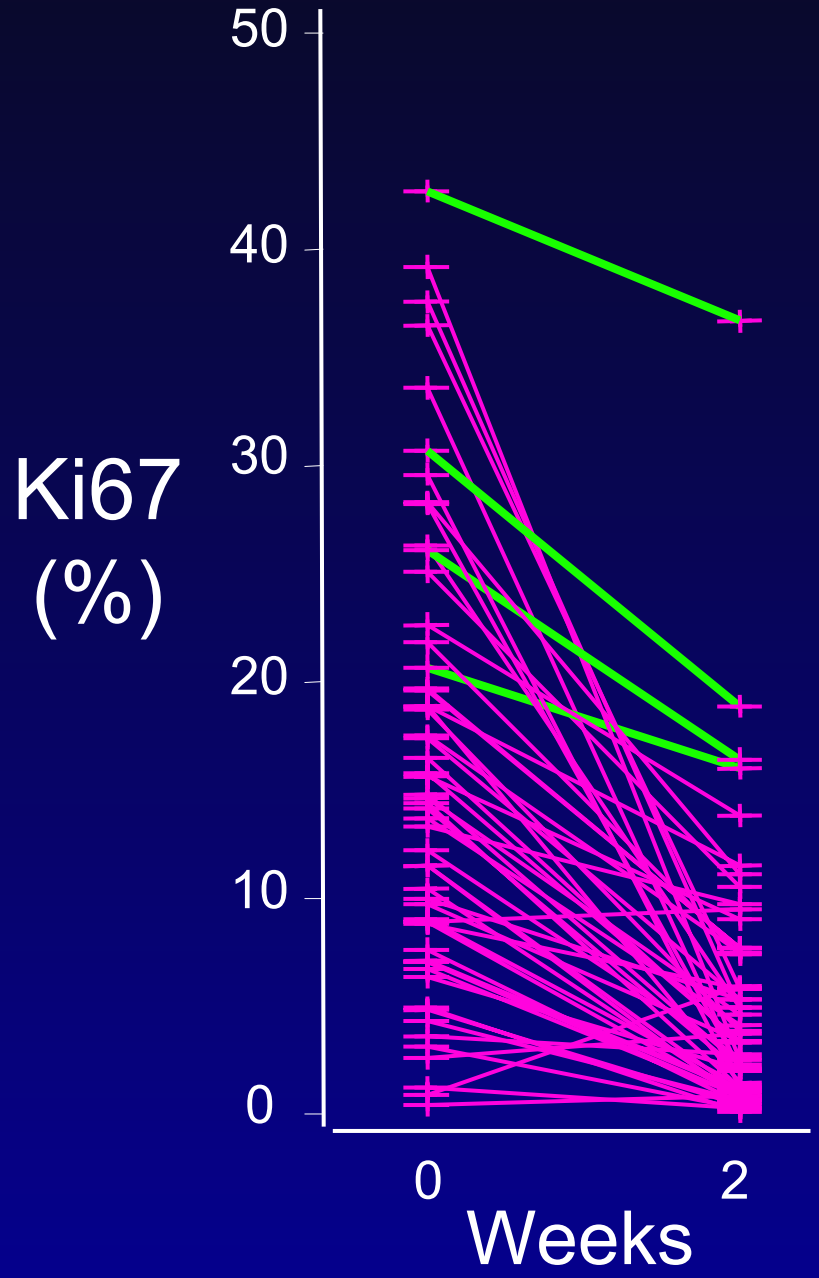






Effect of anastrozole on Ki67 in individual patients



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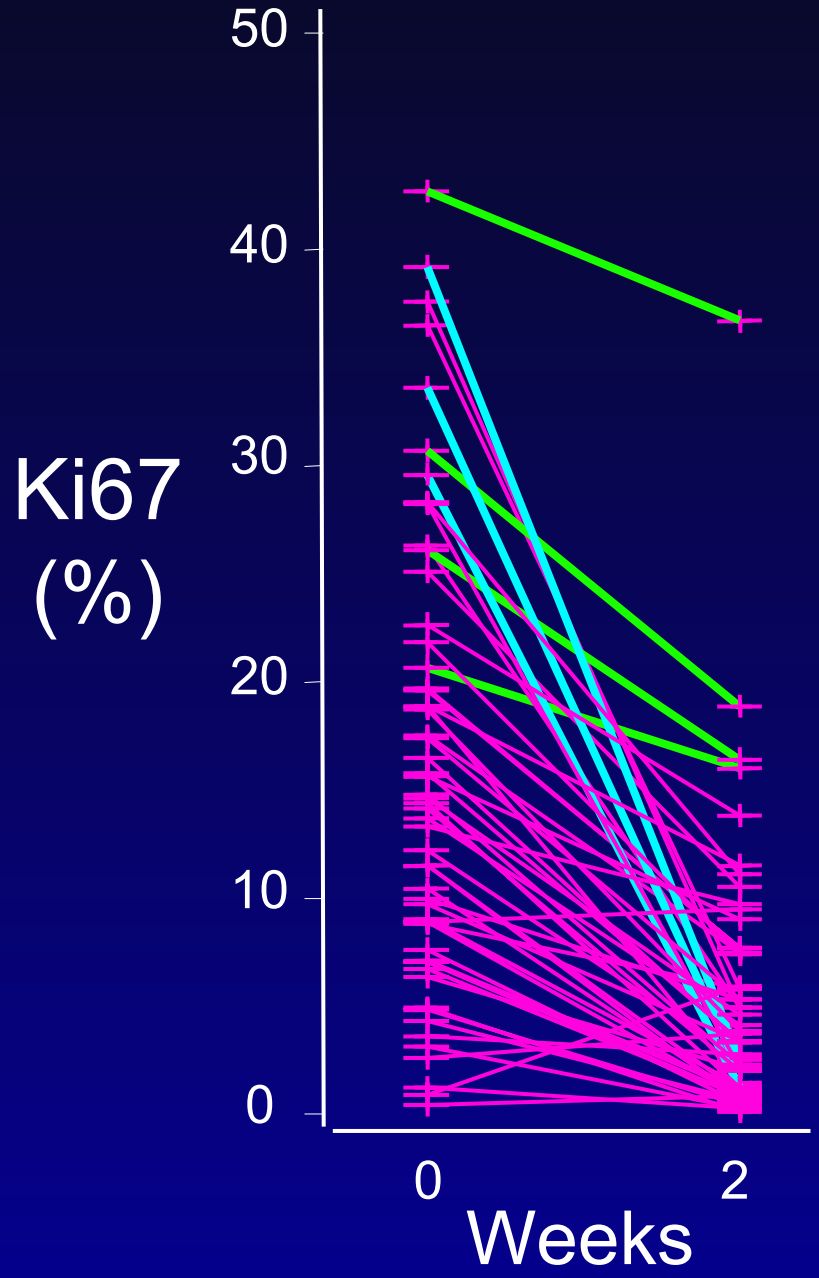

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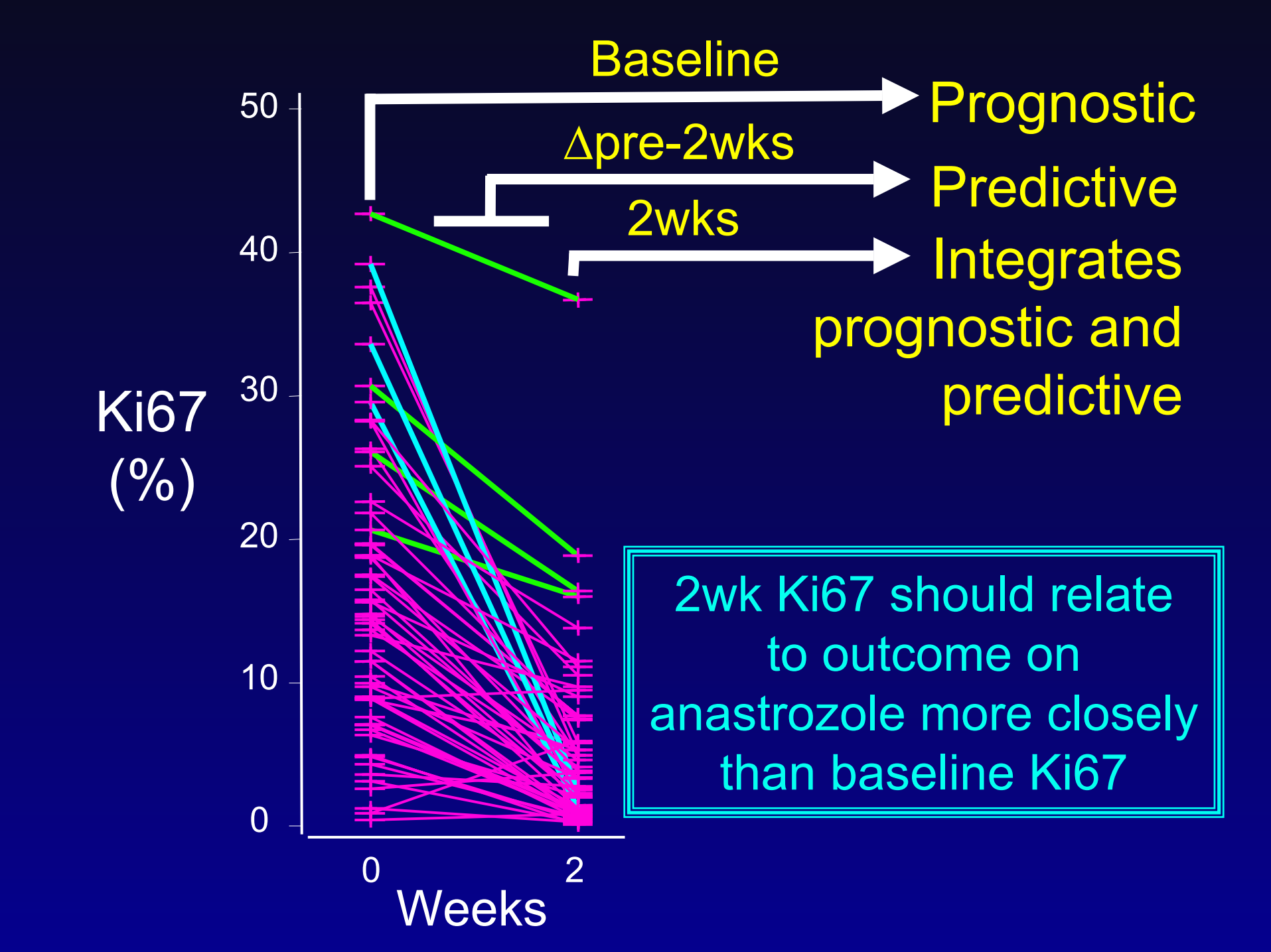
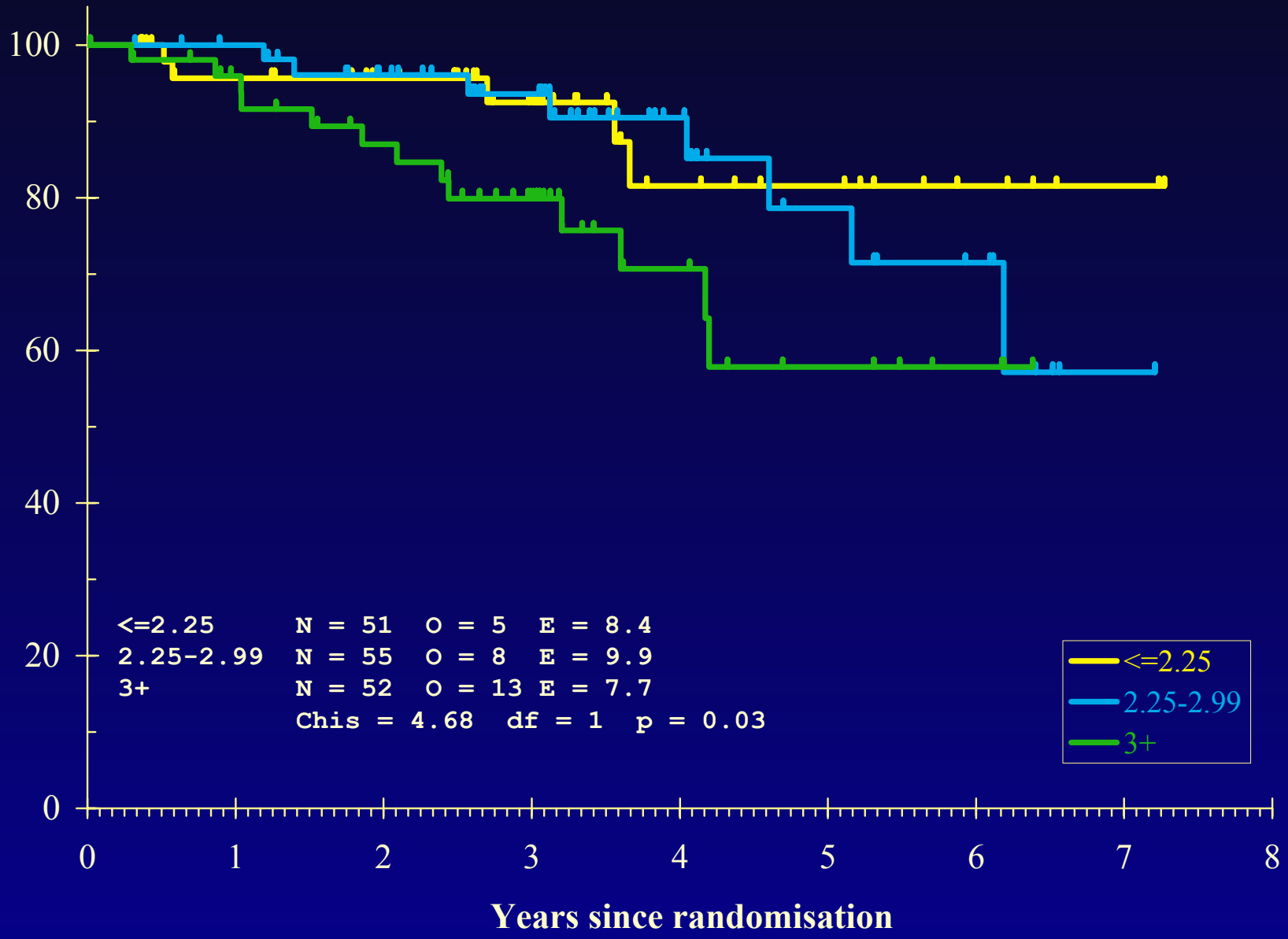
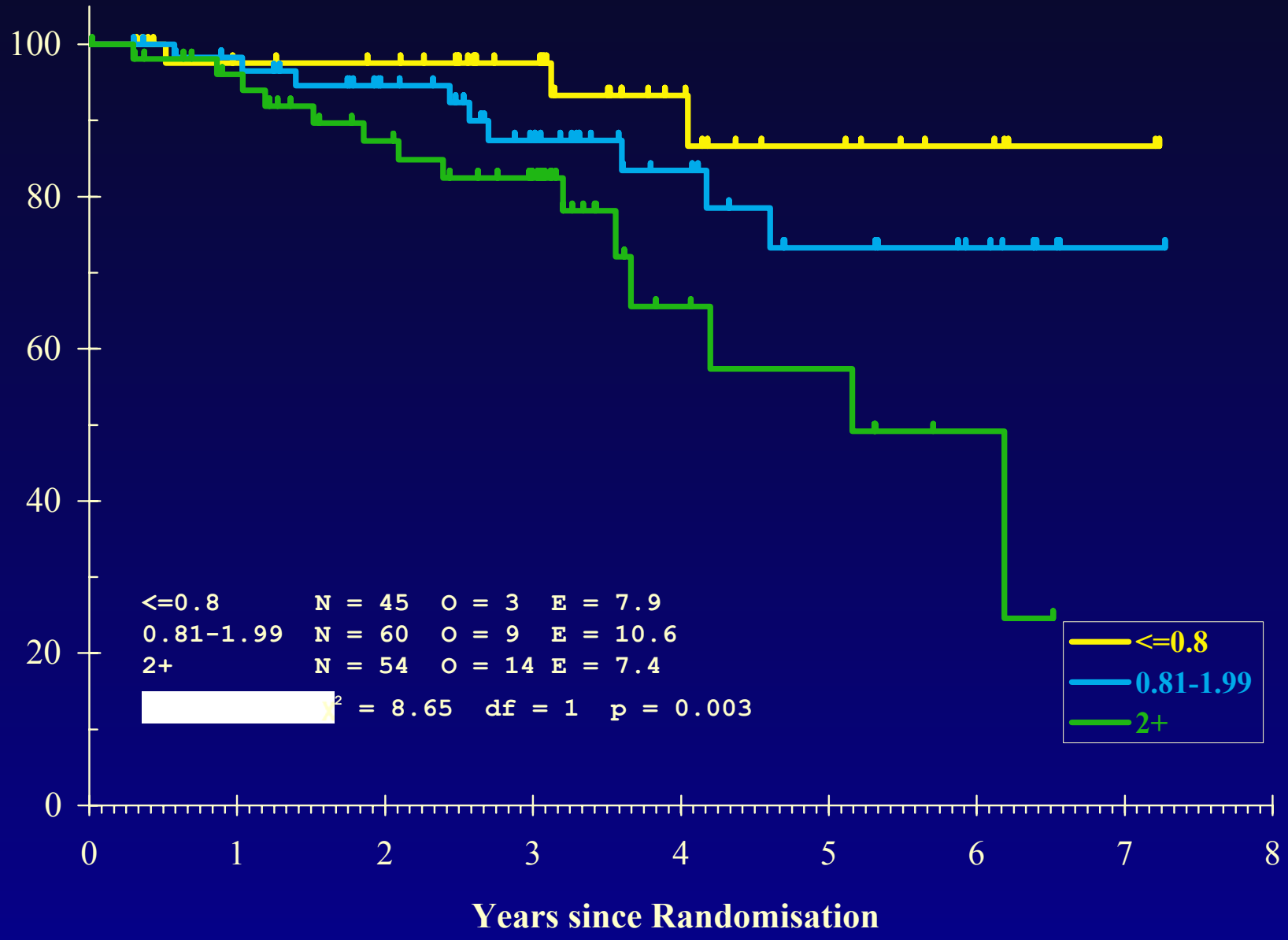

Baseline
Prognostic
Δpre-2wks
Predictive
2wks
Integrates prognostic and predictive
Ki67 (%)
50
40
30
20
10
0
0
2
Weeks
2wk Ki67 should relate to outcome on anastrozole more closely than baseline Ki67

Relapse Free Survival by baseline LnKi67



Relapse Free Survival by 2 week LnKi67



Multivariate analysis: RFS

		HR (95%CI)	p-value
Tumour size	per cm	1.67 (1.35 - 2.06)	<0.001
Ki67 (2 wks)	2.7x increase	2.01 (1.28 - 3.15)	0.002
ER (2wks)	2.7x increase	0.79 (0.62 - 0.99)	0.04

Multivariate analysis: RFS

		HR (95%CI)	p-value
Tumour size	per cm	1.67 (1.35 - 2.06)	<0.001
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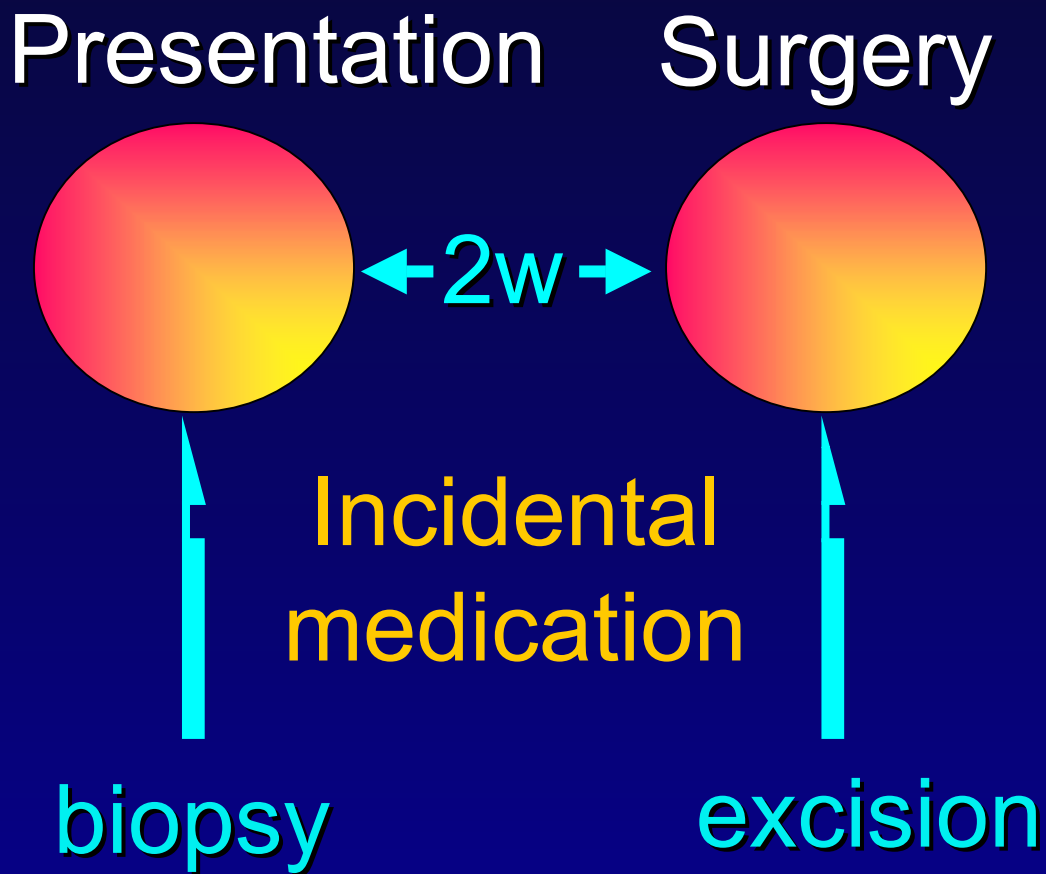
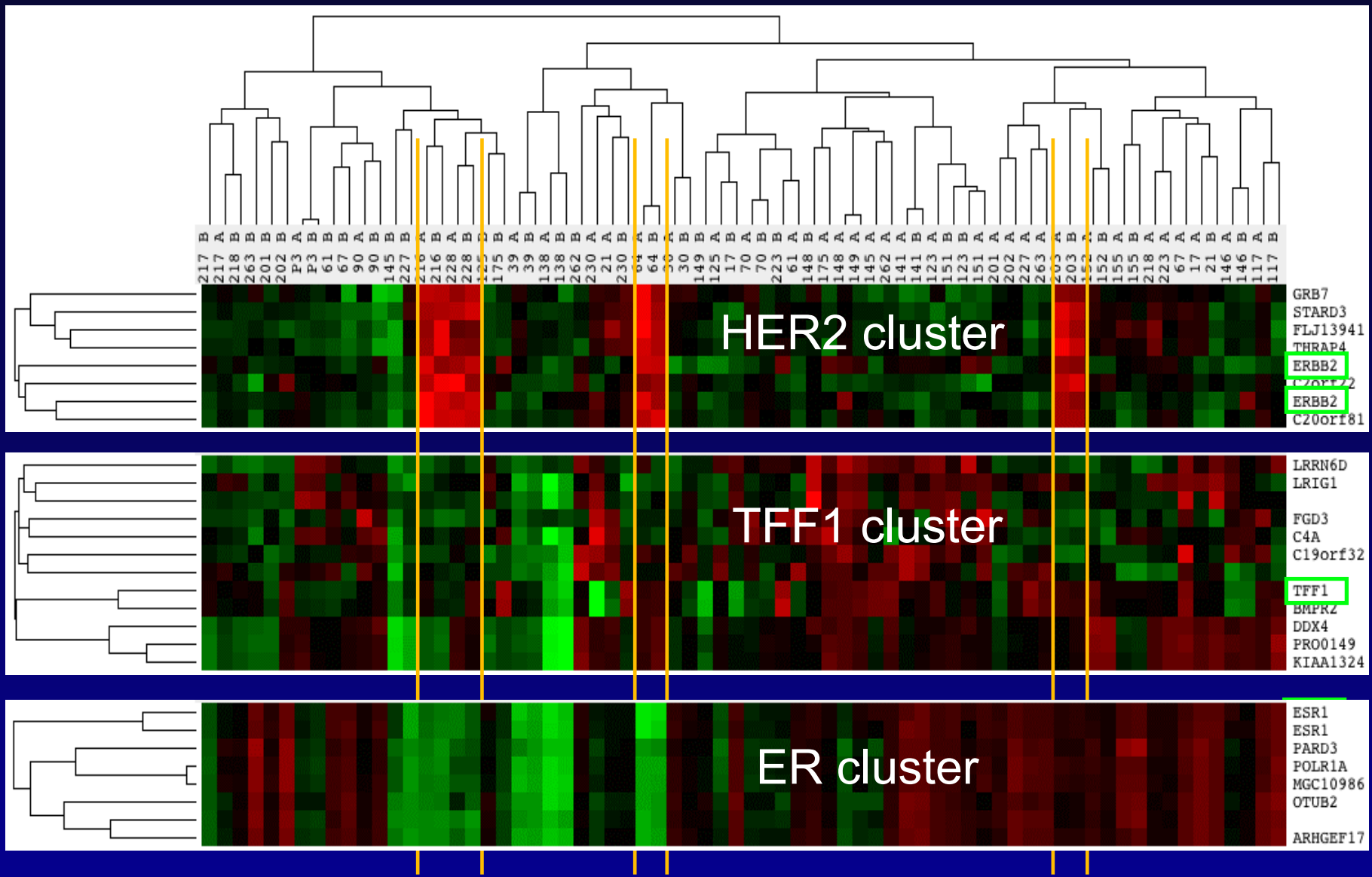
→POETIC

Short-term presurgical treatment:
Biological characteristics of AI response



- 35 ER+ patients
- anastrozole or letrozole
- RNA T7 amplified
- cDNA microarray (17,468 features)

Selected clusters from heirarchical clustering based on 2680 most variable genes



Global index of dependence on estrogen (GIDE)

- Number of genes which change [up or down] beyond a given threshold (x2)
- How does this index vary according to:
  - [ER]
  - HER2

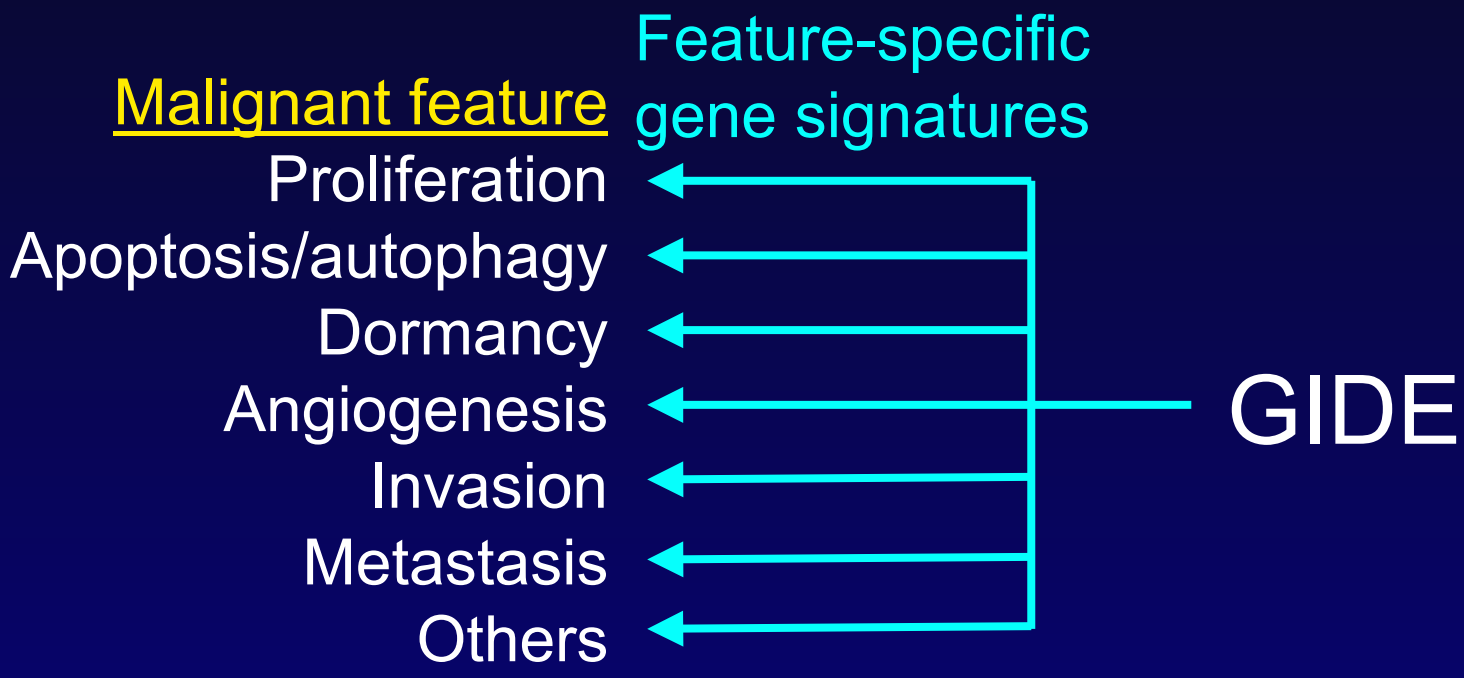
Comparison of GIDE with other markers

Patient	GIDE	ER	HER2
145	4126	3	31
21	2502		30
263	2343		
125	2069		34
227	2052		
262	2036		
17	1811	1	
67	1728		
218	1443		
175	1336		
148	1299	9	
223	1171		
202	1027	6	
117	1017	4	
61	862	2	
230	856		
151	818		
217	811	32	
138	802	35	32
149	760	7	
90	688		
201	675		
30	653	8	35
123	616		
228	597	34	3
152	512		
146	480		33
216	472	33	1
70	398		
64	376		2
155	349	5	
39	321	30	
141	141		
P3	139	31	
203	79		4

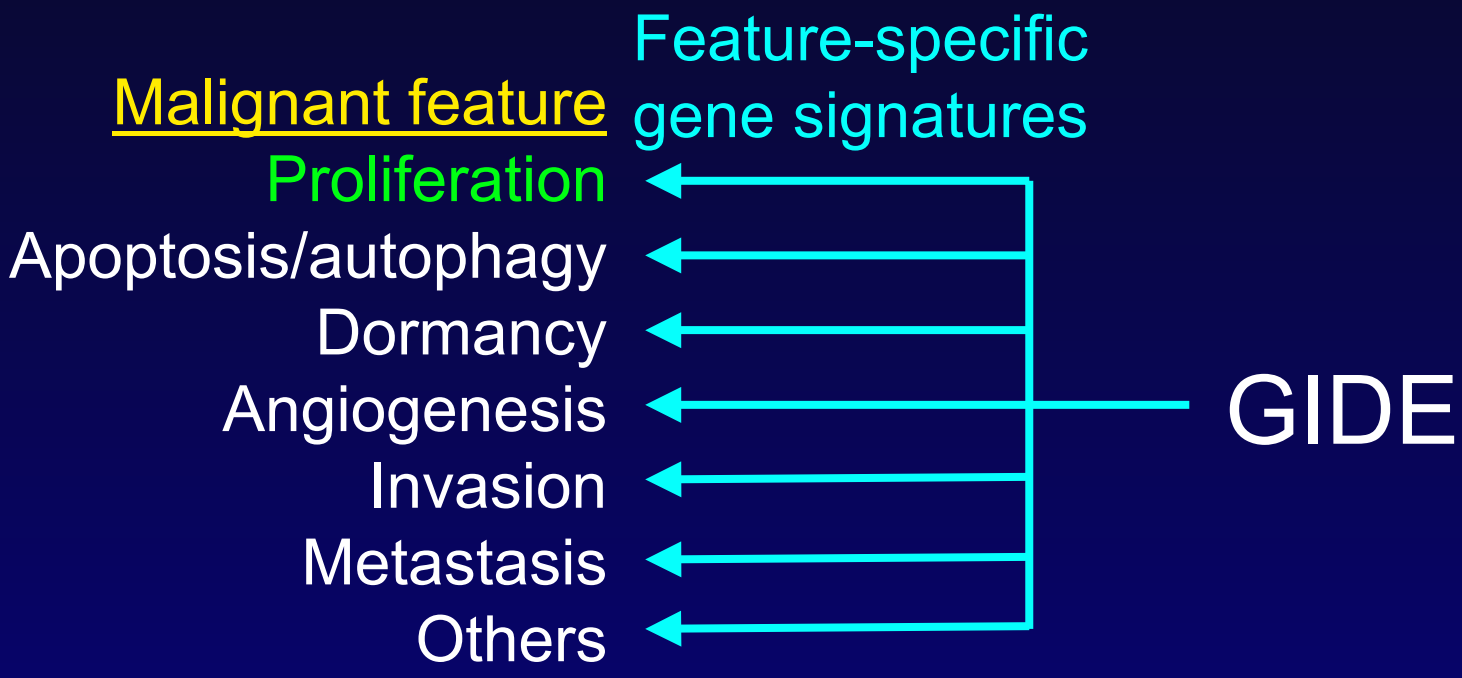
High

Low

Biological disaggregation

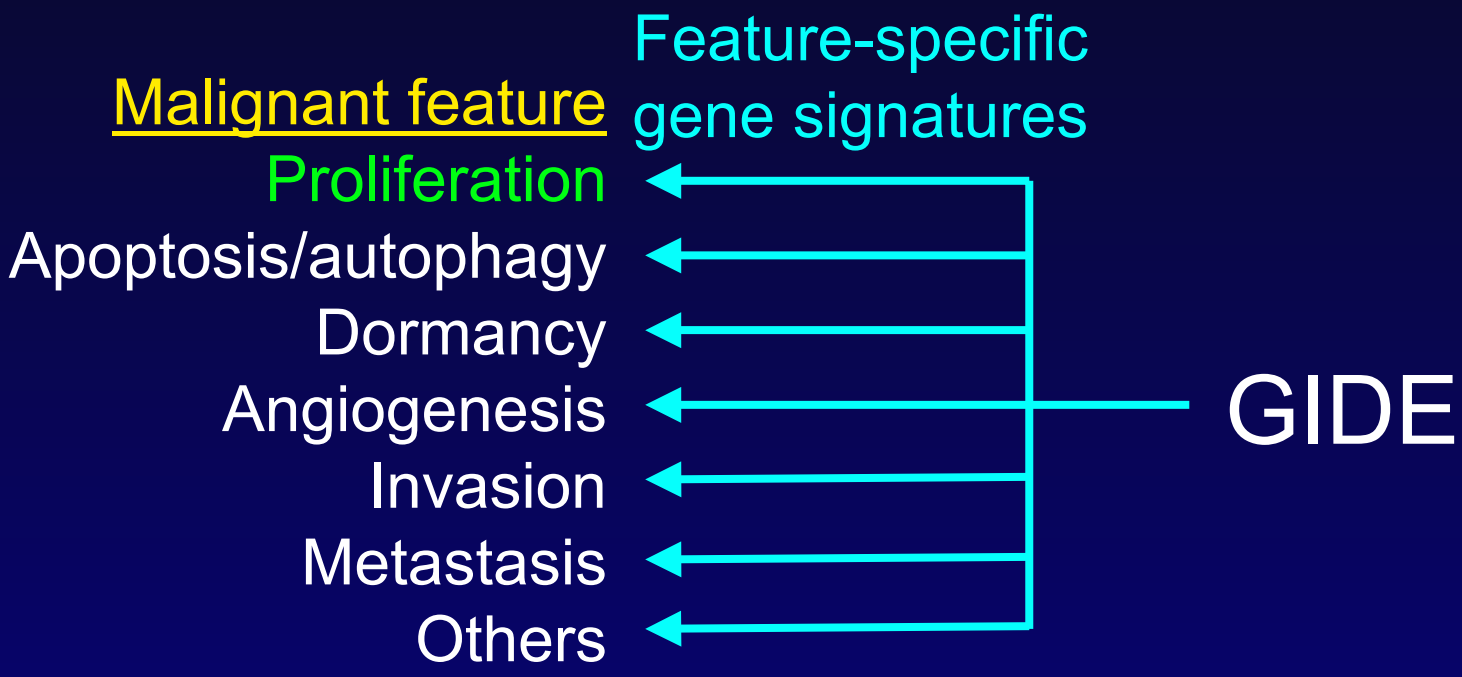


Biological disaggregation



- Oestrogen dependency of feature
- Importance in clinical benefit from E-deprivation
- Determinants of response of feature to E-deprivation

Biological disaggregation



- Oestrogen dependency of feature
- Importance in clinical benefit from E-deprivation
- Determinants of response of feature to E-deprivation

→POETIC

Summary
Chemotherapy

- decreased proliferation is associated with response to treatment
- high residual Ki67 is associated with poor RFS
- increased apoptosis occurs in response to therapy but no close relationship with response

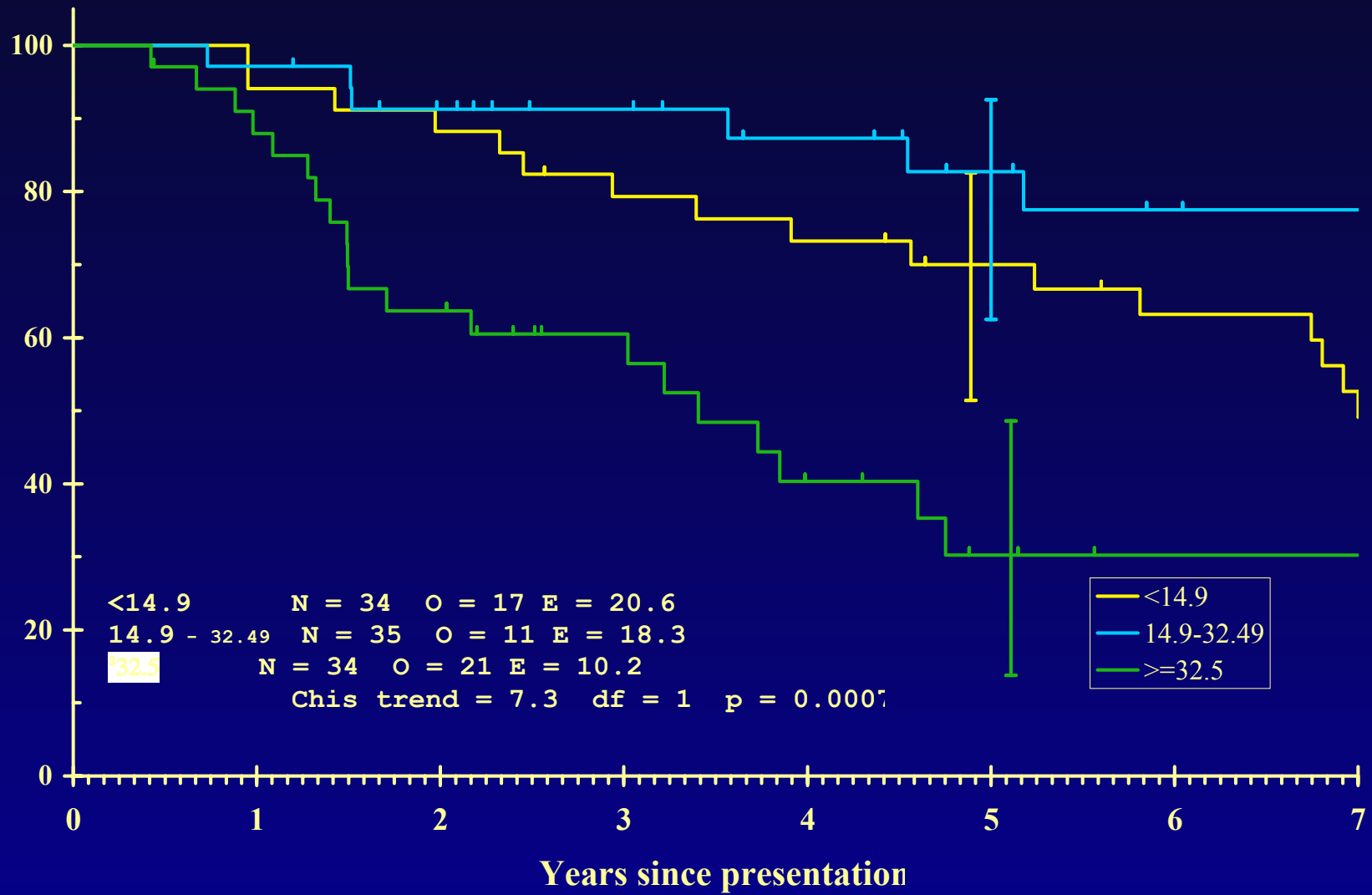
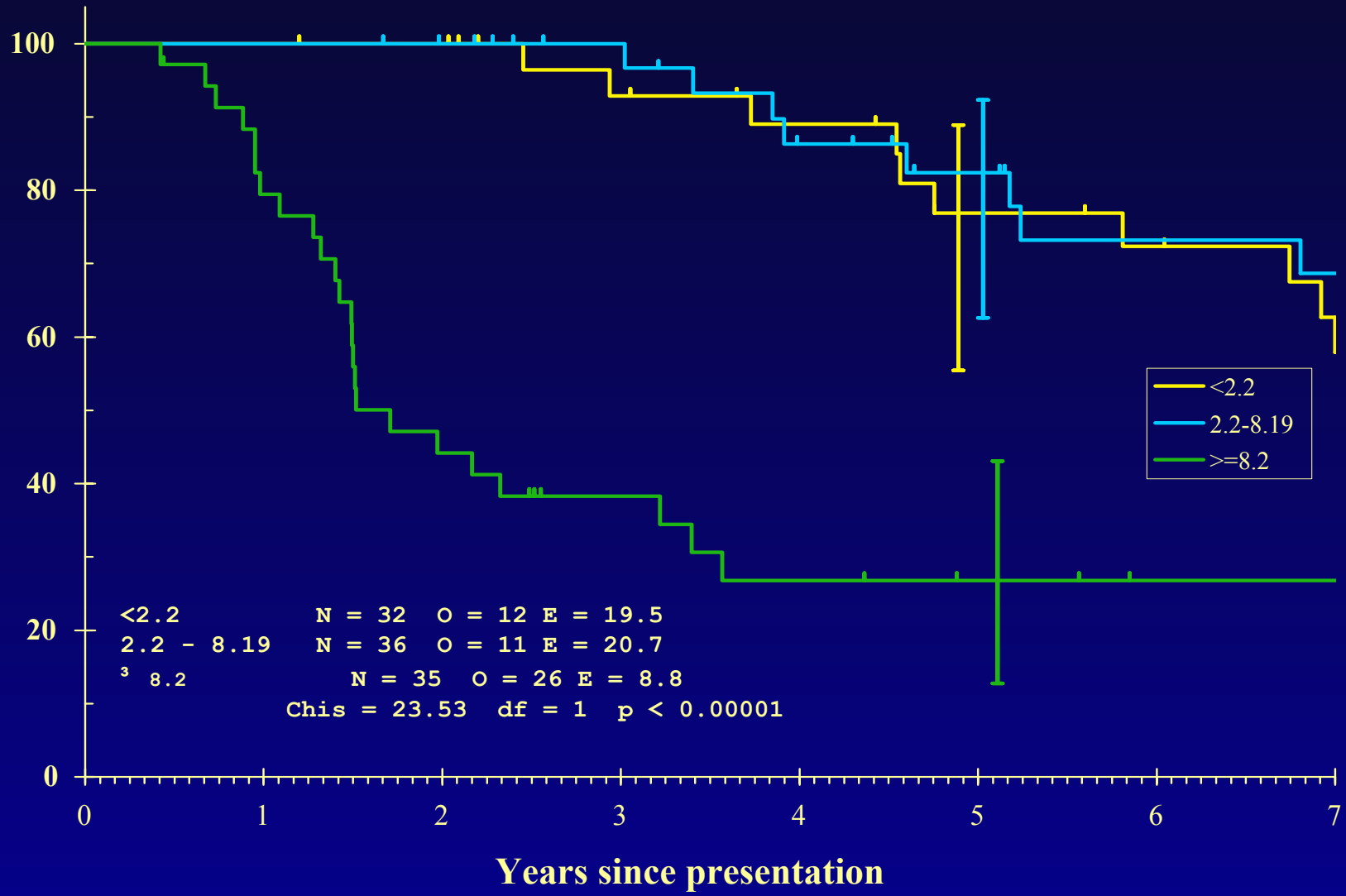
Summary
Endocrine therapy

- decreased proliferation may predict for treatment benefit but no close relationship with clinical response
- high 2 week Ki67 is associated with poor RFS
- increased apoptosis does not occur at 2 weeks or 12 weeks with tamoxifen or AI

Novel agents

Open-minded about effects on apoptosis and proliferation during early studies

Pre-chemotherapy Ki67 and Relapse Free Survival (matched)



Post-chemotherapy Ki67 and Relapse Free Survival (matched)