

Neoadjuvant Endocrine Therapy: The Edinburgh Experience

Mike Dixon OBE
Edinburgh Breast Unit



Endocrine Therapy started in Scotland

- **Sir George Beatson**
- Graduated from University of Edinburgh in 1874
- 1896 - 128 Years ago published a
- Series of illustrative cases of premenopausal patients with
Metastatic Breast Cancer who he successfully treated by removal of ovaries
- Thus, Endocrine Therapy was born



Patients suitable for Neoadjuvant Endocrine Therapy

Postmenopausal Women

- **Large or Locally Advanced Cancers with M0 disease**
- **ER Rich Allred score 7-8, >50% cells staining or Histoscore >200**
- **Mostly Luminal A but some Luminal B cancers**
- **Mostly HER2 negative but some HER2 positives**

Now I will explain why

10 Reasons Why you should use Neoadjuvant Endocrine Therapy

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Edinburgh Breast Unit



And here is Number 1...



Reason 1

Neoadjuvant Chemotherapy is less effective in older – postmenopausal – so it is the ideal setting for Neoadjuvant Endocrine Therapy

NSABP:B-18

OPERABLE BREAST CANCER
FNA or Core

Age, T, cN

OPERATION

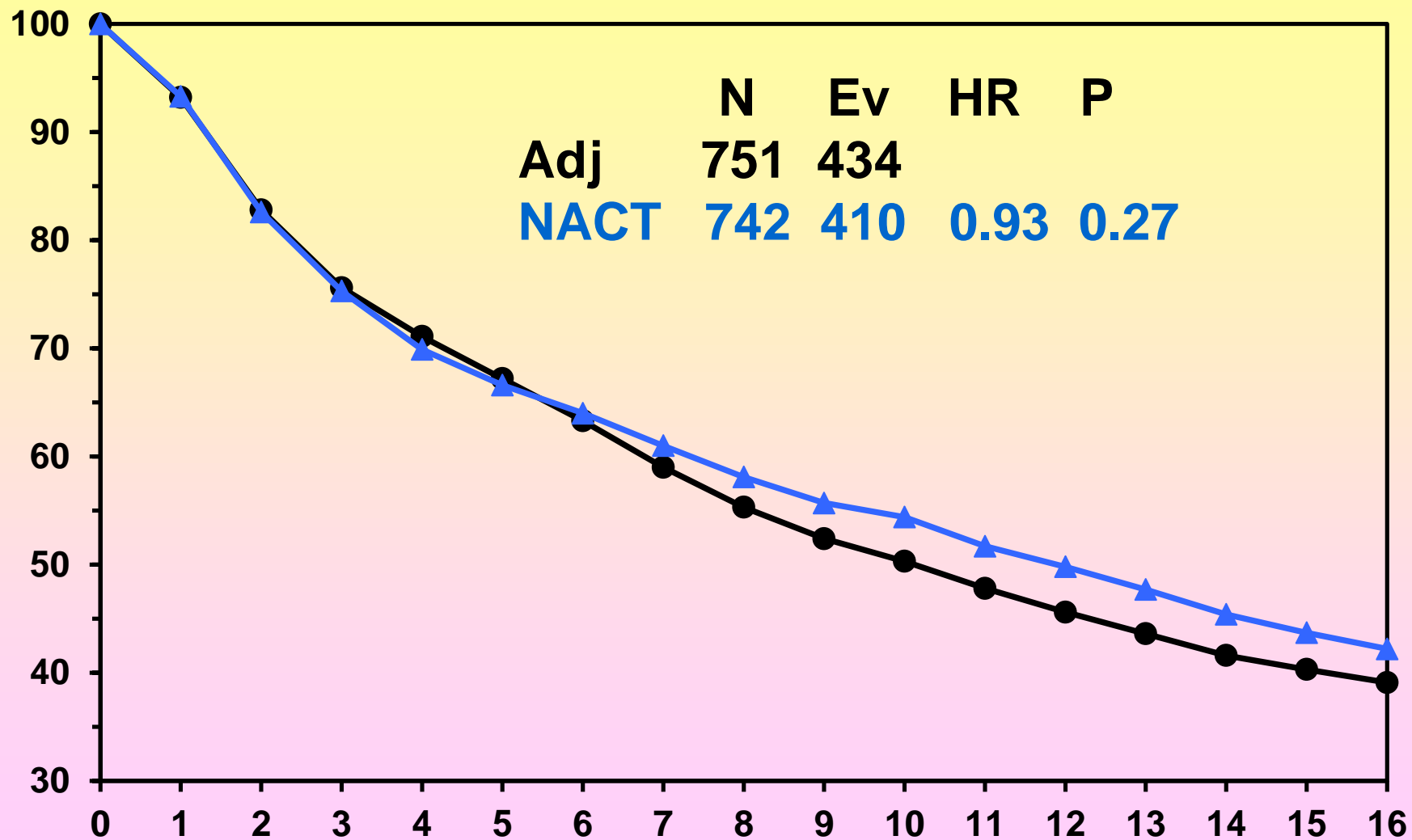
Pre (NACT)
AC x 4

Post (Adj)
AC x 4

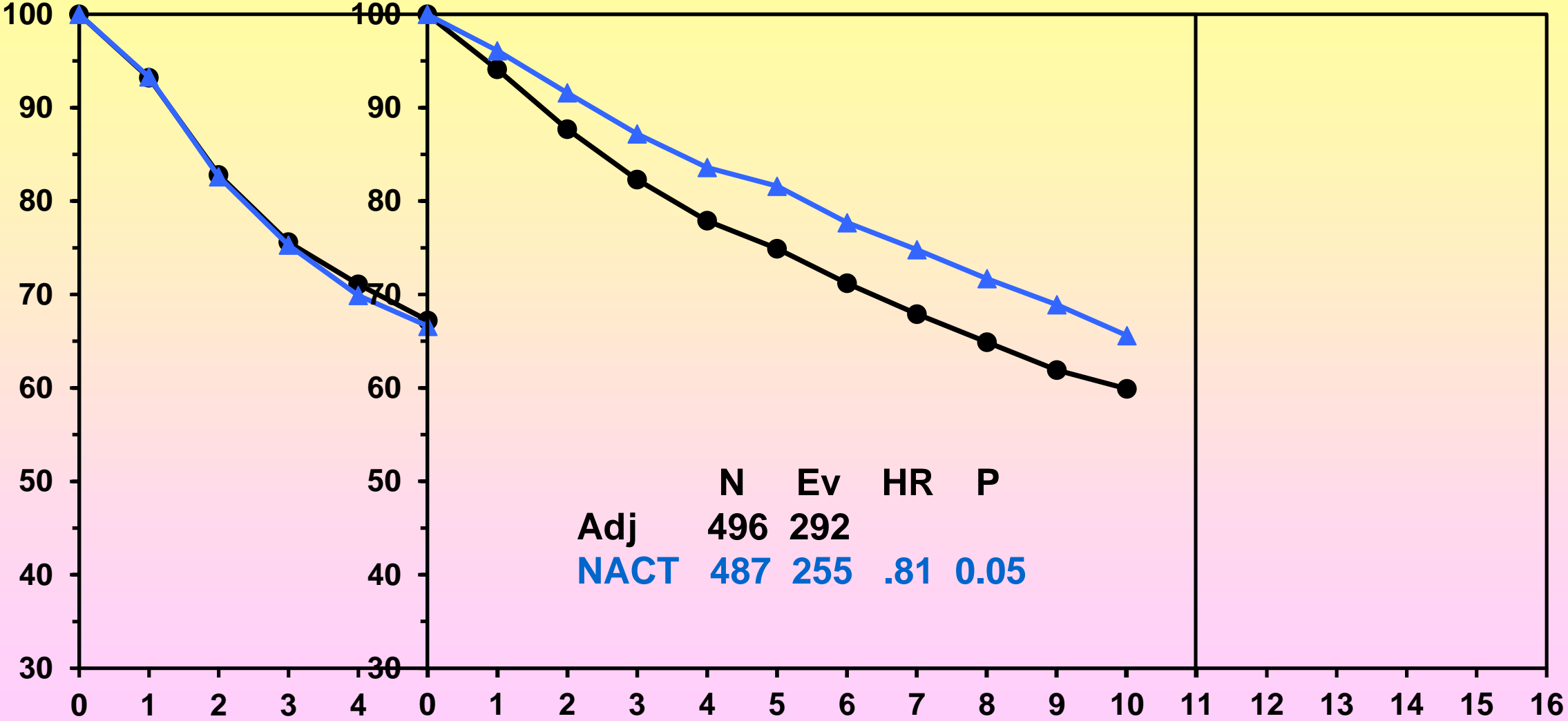
OPERATION

Seq tam for women ≥ 50 yrs. only

B18 Updated DFS

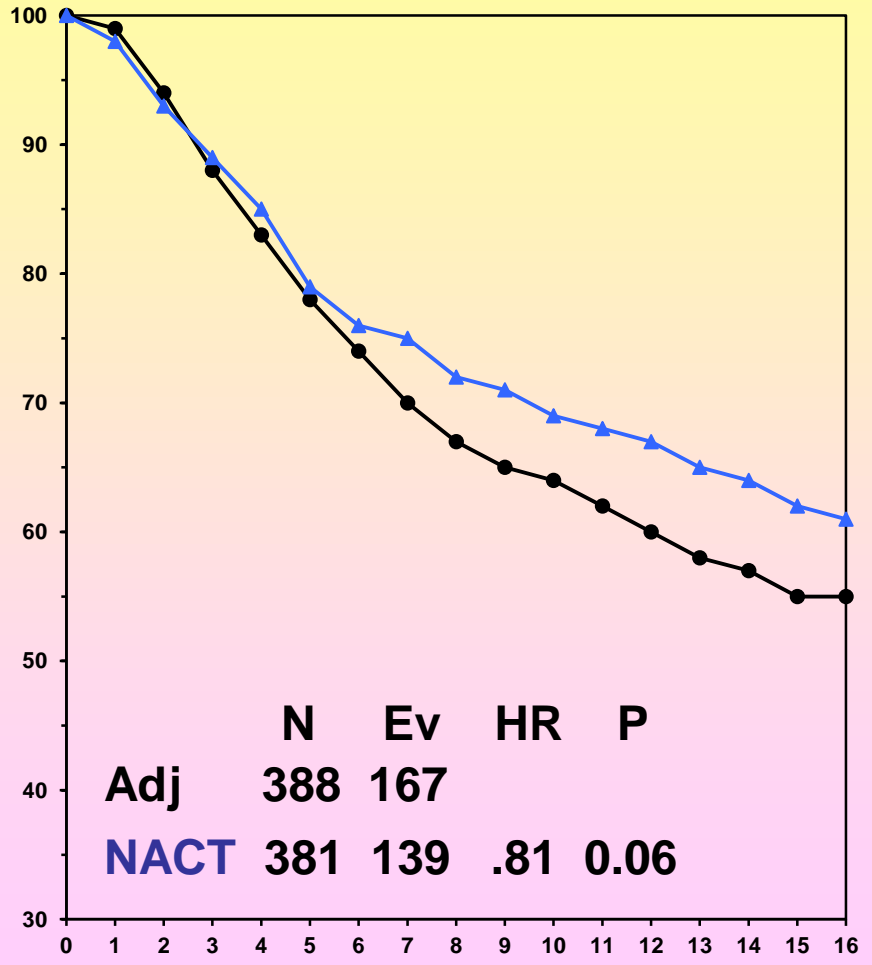


B18 Updated DFS

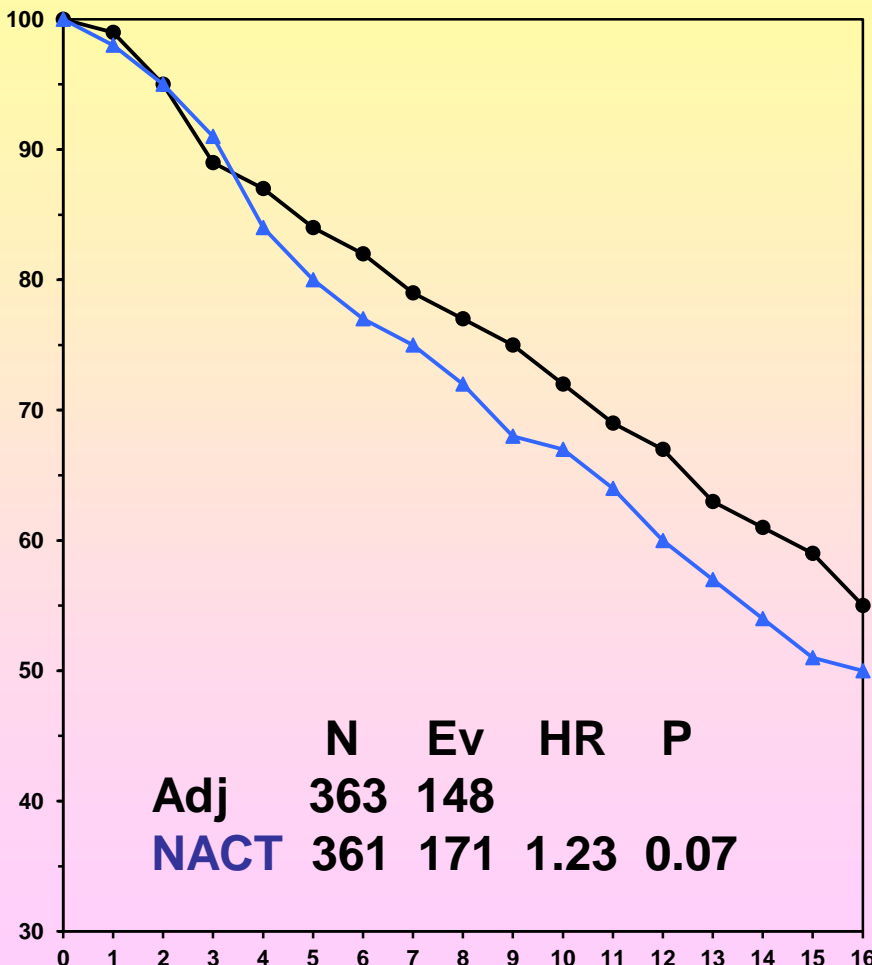


Overall Survival

<50yrs



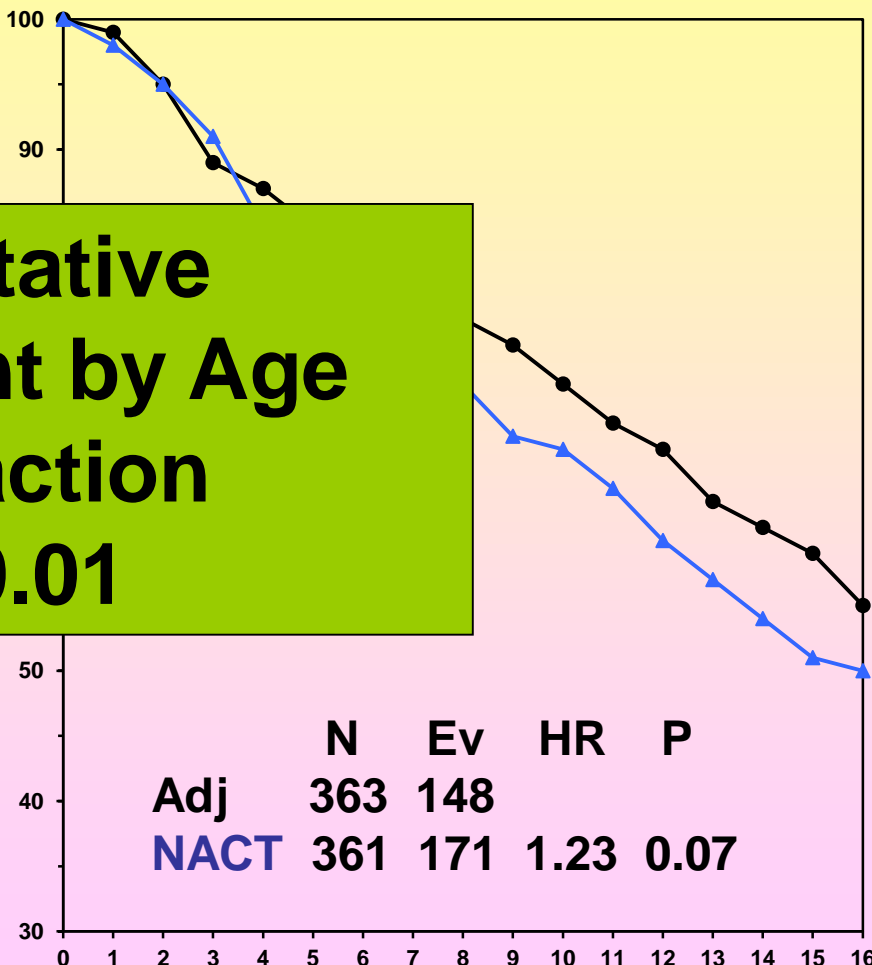
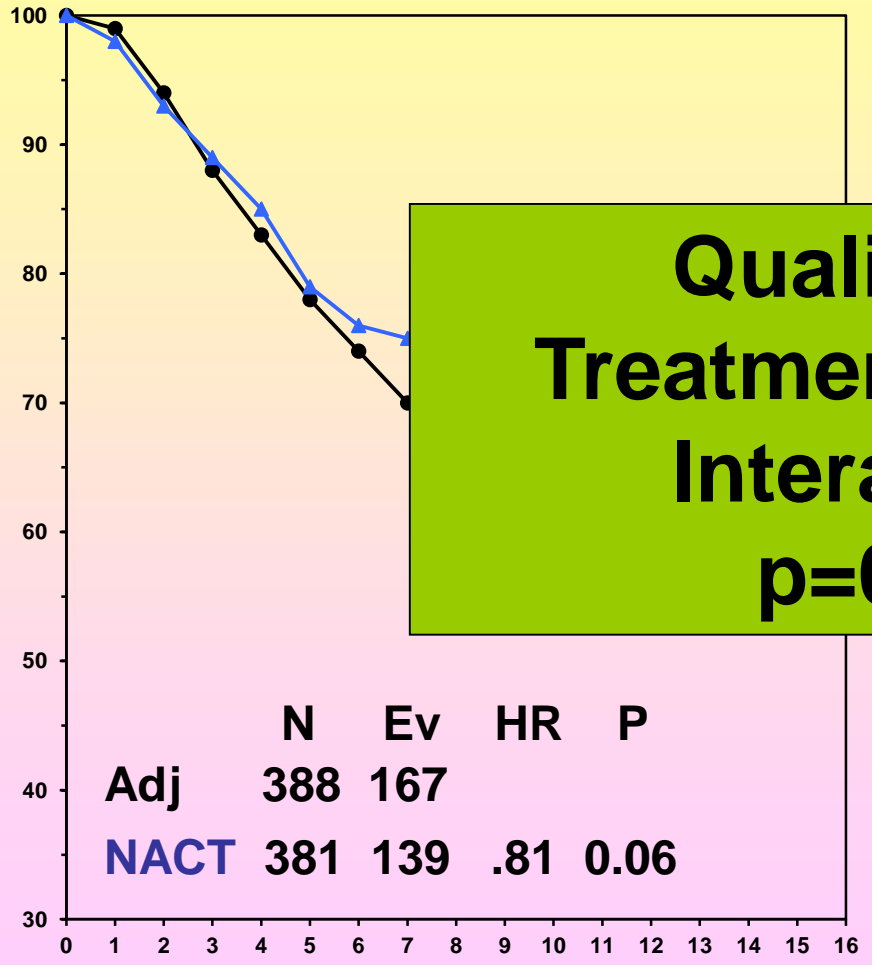
≥50yrs



Overall Survival

<50yrs

≥50yrs



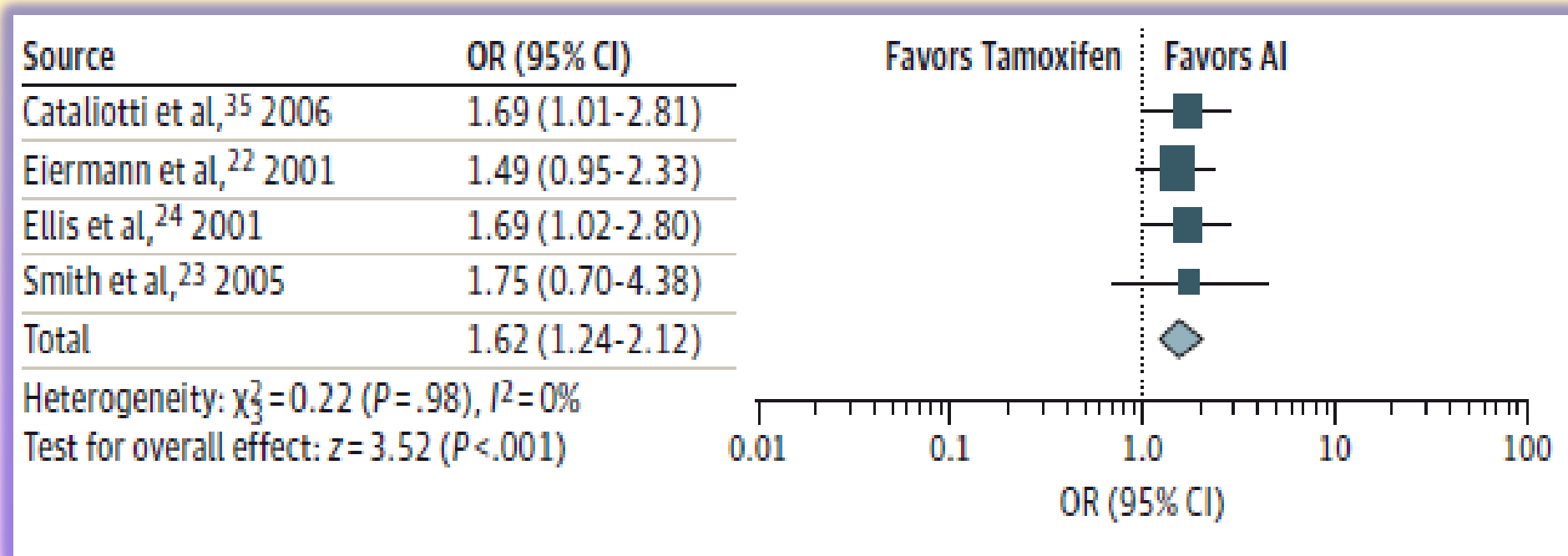
Qualitative Treatment by Age Interaction p=0.01

Reason 2

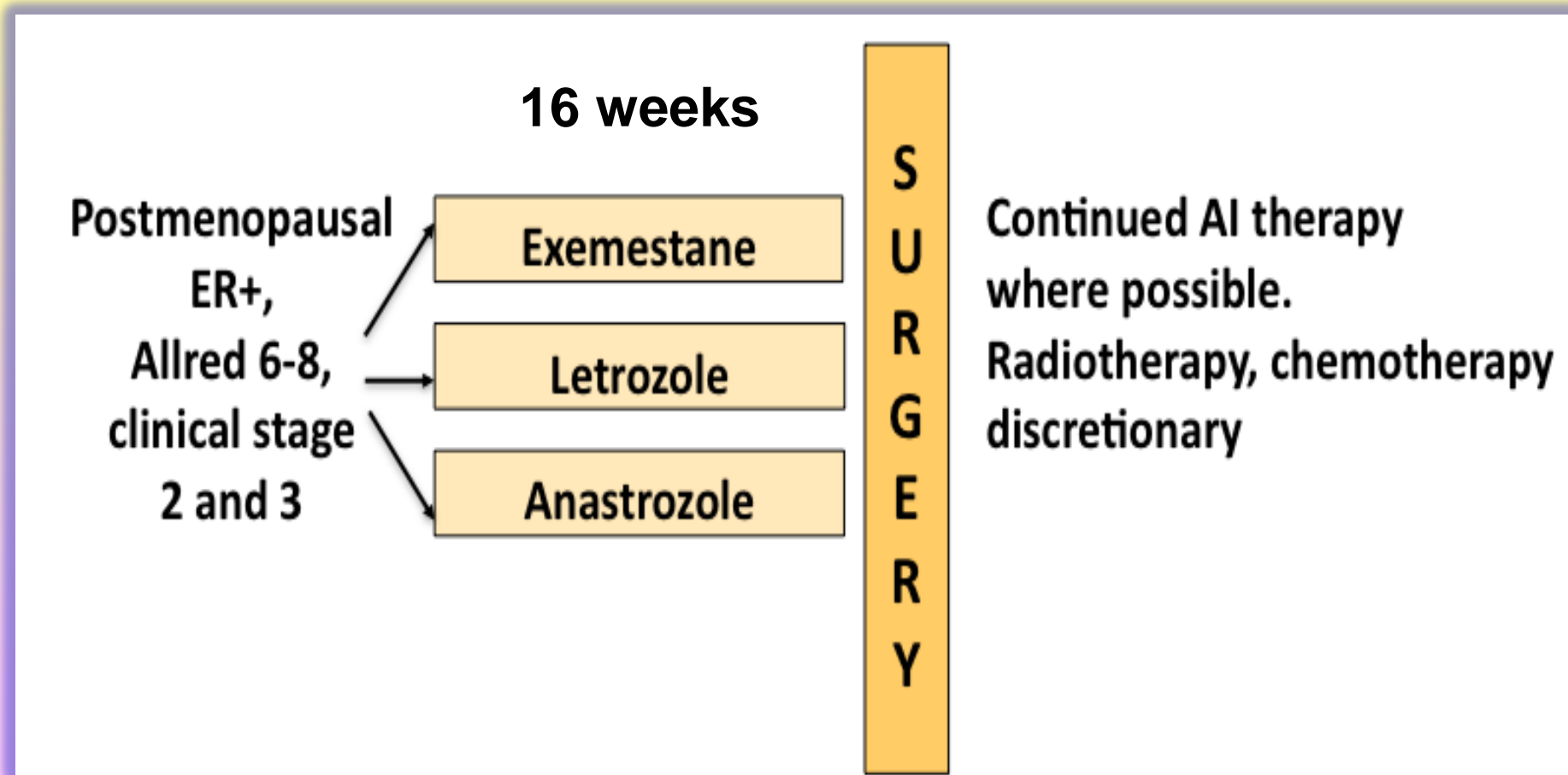
Neoadjuvant Endocrine Therapy has high response rate in patients with Large ER rich Breast Cancers treated with Neoadjuvant Aromatase Inhibitors

Aromatase Inhibitors more effective than Tamoxifen: Breast Conserving Surgery Rates

Spring et al JAMA Oncol doi101001/ jamaoncol 2016.1897



ACOSOG Z1031 Study Design



ACOSOG Z1031 Clinical Responses

Clinical Response	Treatment Arm		
	EXE (n = 124)	LET (n = 127)	ANA (n = 123)
Response Rate	74 (60%)	92 (72%)	83 (68%)
Stable Disease	42 (33%)	29 (23%)	31 (25%)

ACOSOG Z1031 Clinical Responses

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Response Rate	74 (60%)	92 (72%)	83 (68%)
Stable Disease	42 (33%)	29 (23%)	31 (25%)
Progression	8 (7%)	6 (5%)	9 (7%)

Reason 3

Neoadjuvant Endocrine Therapy is associated with similar outcomes to Neoadjuvant Chemotherapy (NACT) in Randomised trials

BUT with many less adverse events

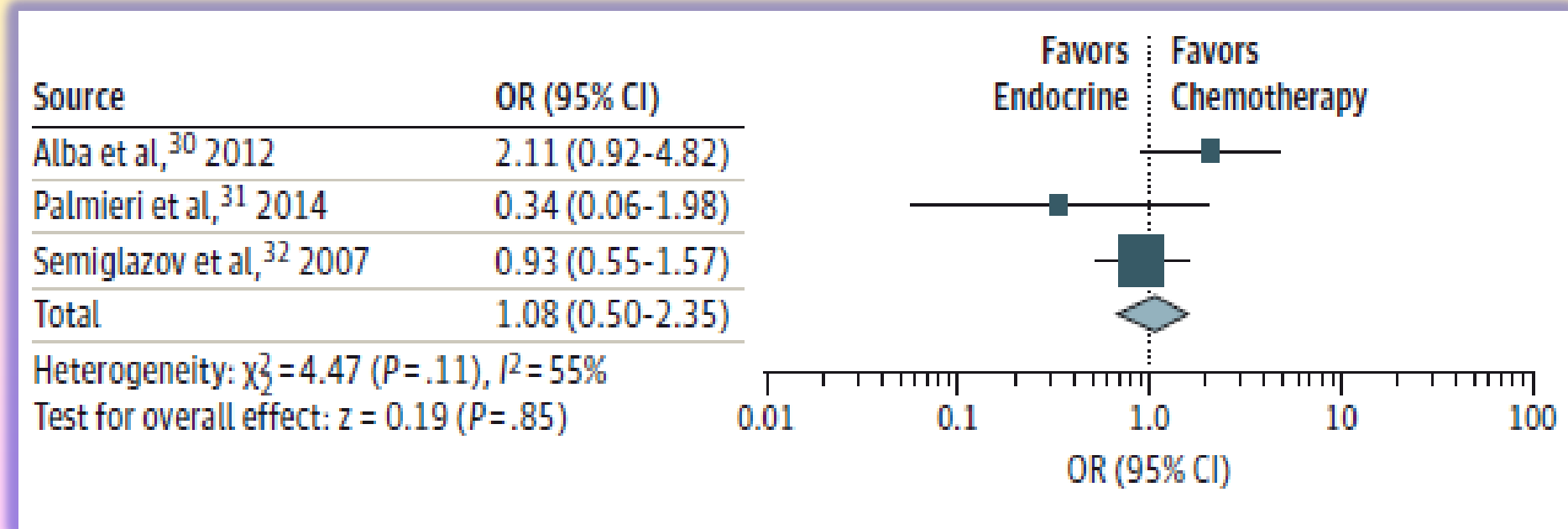
Review and Meta-analysis of studies Comparing Neoadjuvant Chemo and Neoadjuvant Endocrine Therapy

Spring et al JAMA Oncol doi101001/ jamaoncol 2016.1897

20 studies with 3490 Patients

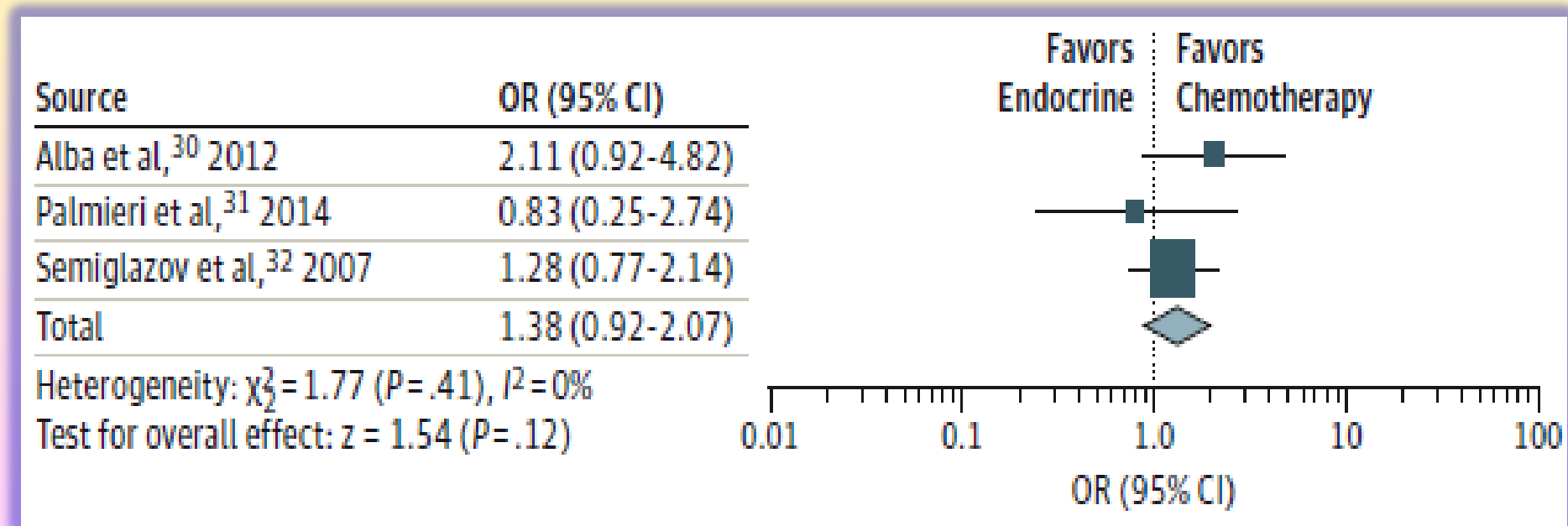
Neoadjuvant Endocrine vs Neoadjuvant Chemotherapy

Clinical Response



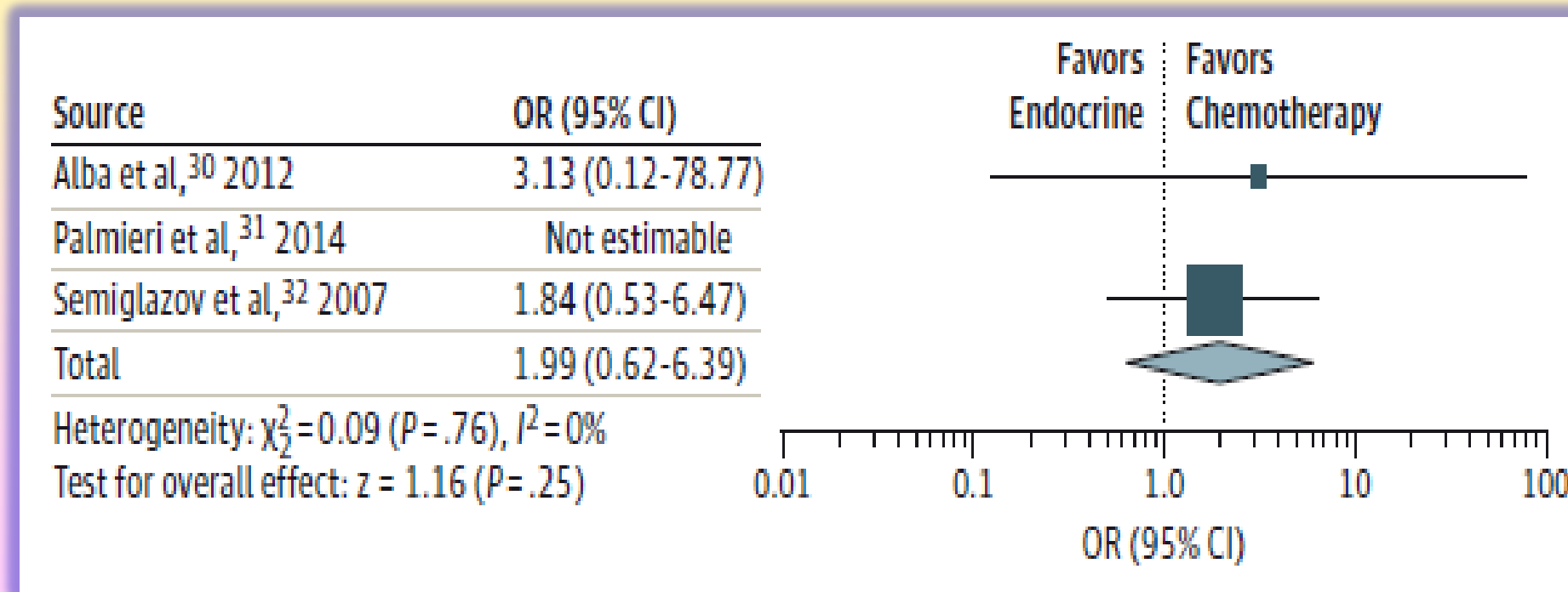
Neoadjuvant Endocrine vs Neoadjuvant Chemotherapy

Radiology Response



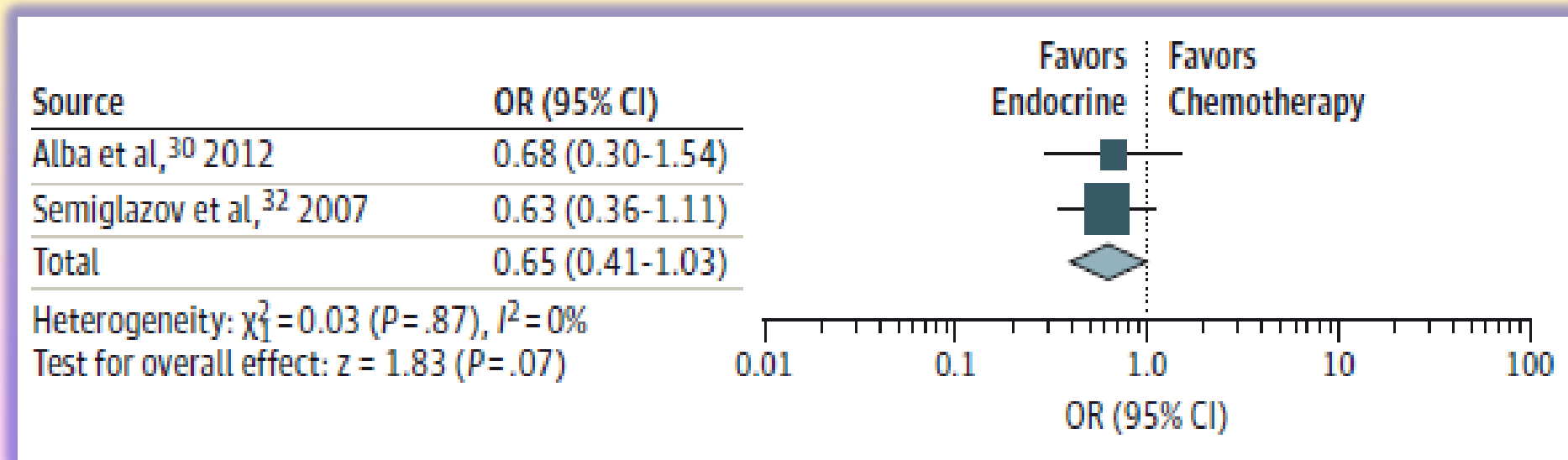
Neoadjuvant Endocrine vs Neoadjuvant Chemotherapy

Path CR Rate

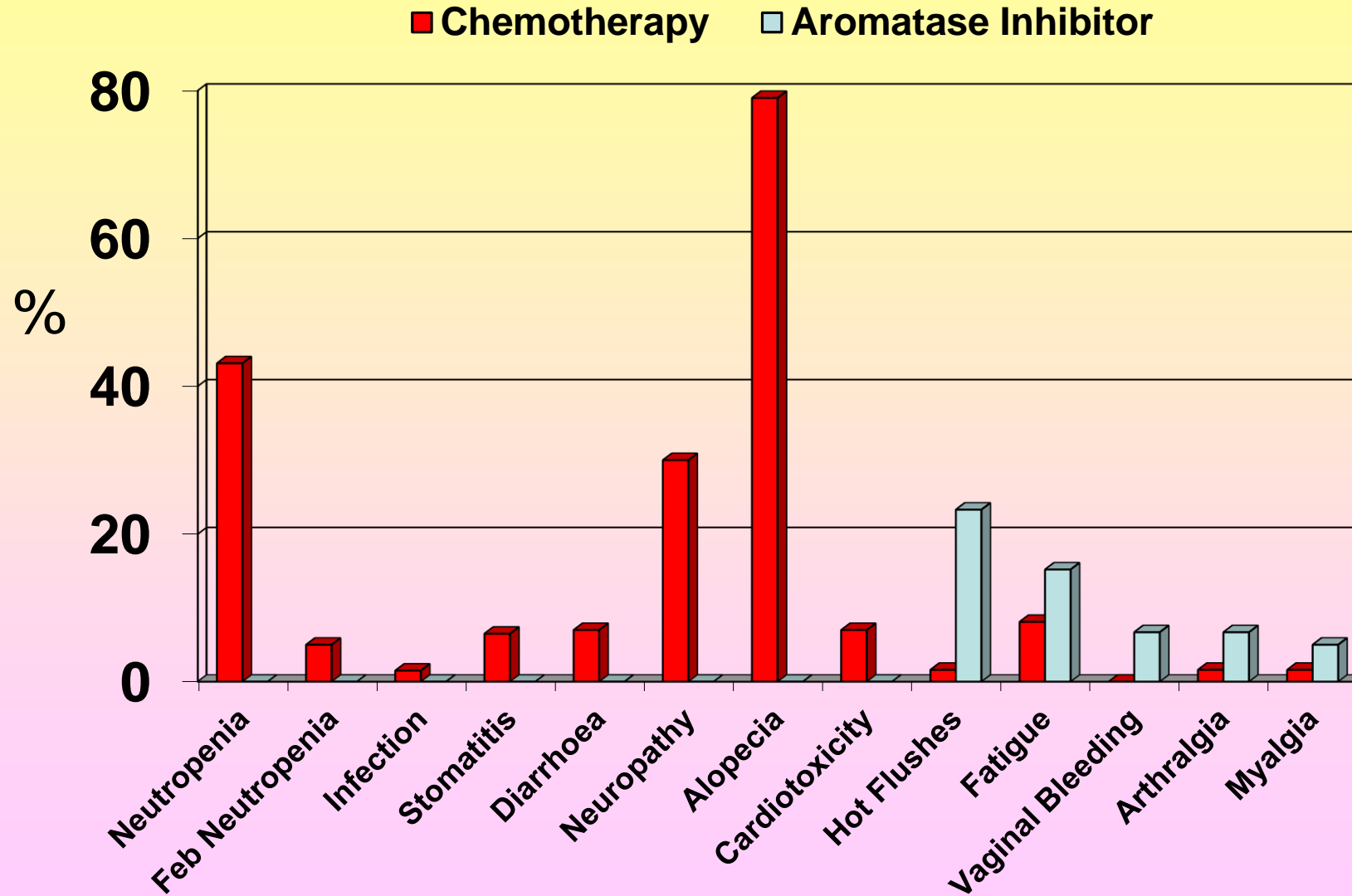


Neoadjuvant Endocrine vs Neoadjuvant Chemotherapy

Breast Conservation Surgery



Adverse Events



Reason 4

Neoadjuvant Endocrine Therapy shrinks the cancers concentrically which allows more patients to preserve their breasts

Response to Letrozole



Pathology after Neoadjuvant Letrozole

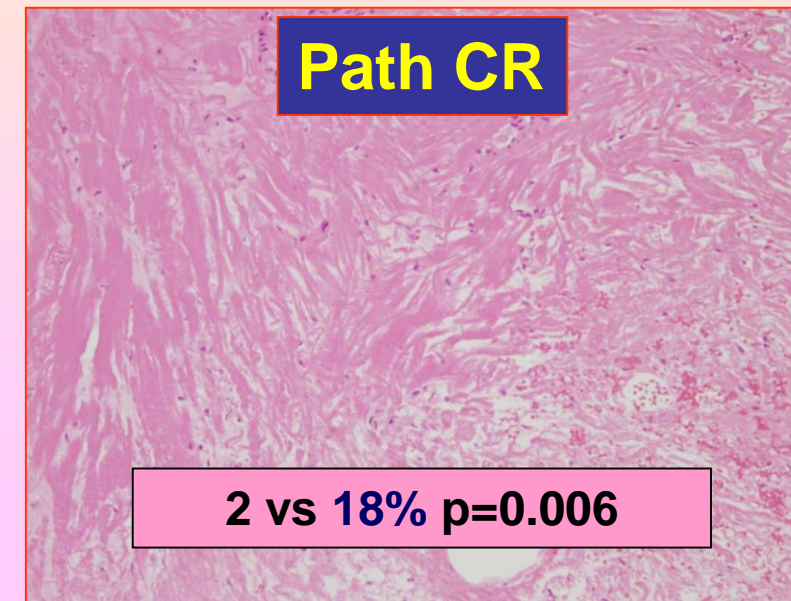
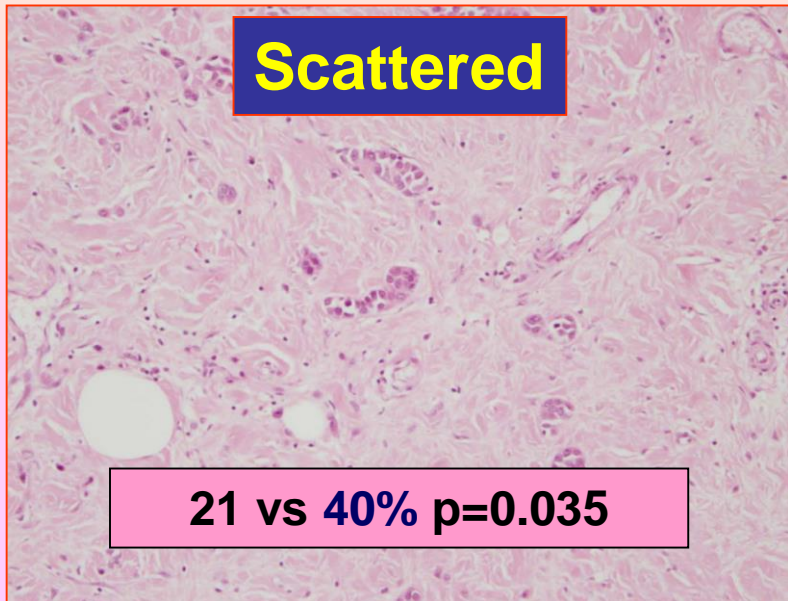
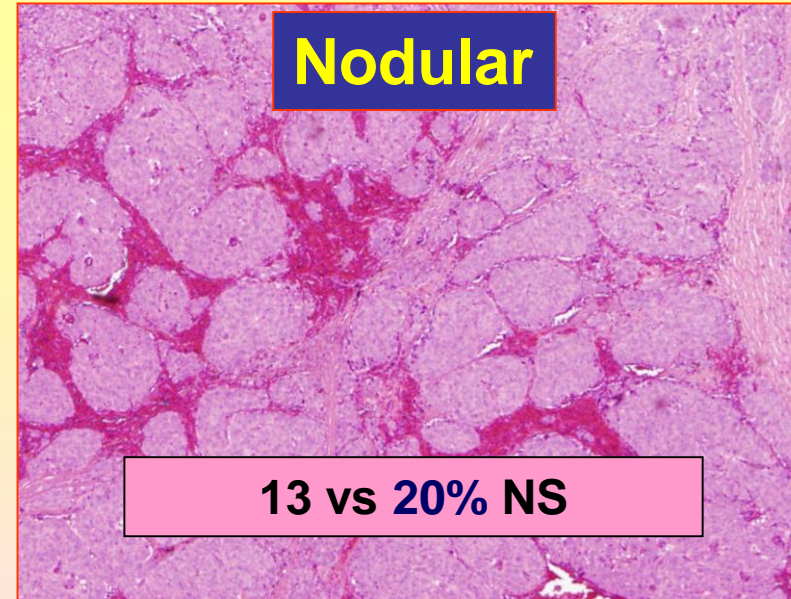
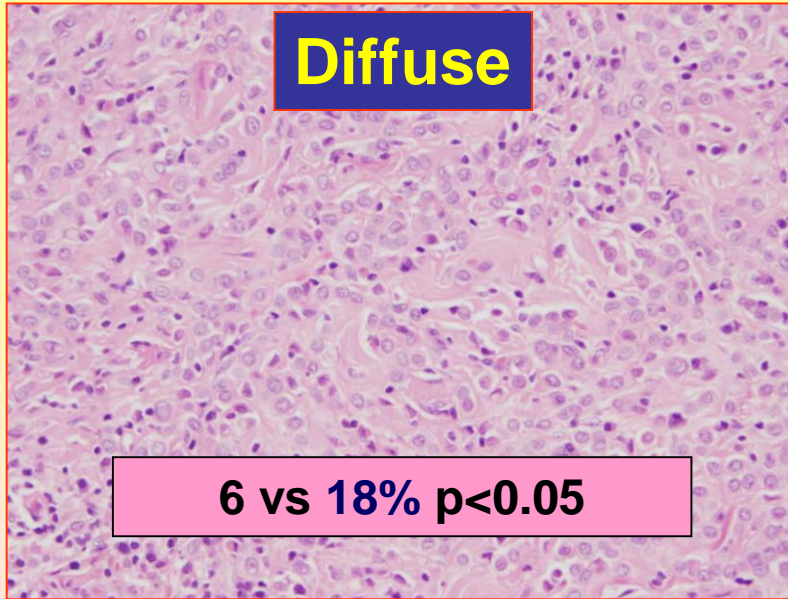


Central Scar

**Central scarring seen in 60% with letrozole vs
4% with Chemotherapy
 $p < 0.0001$**

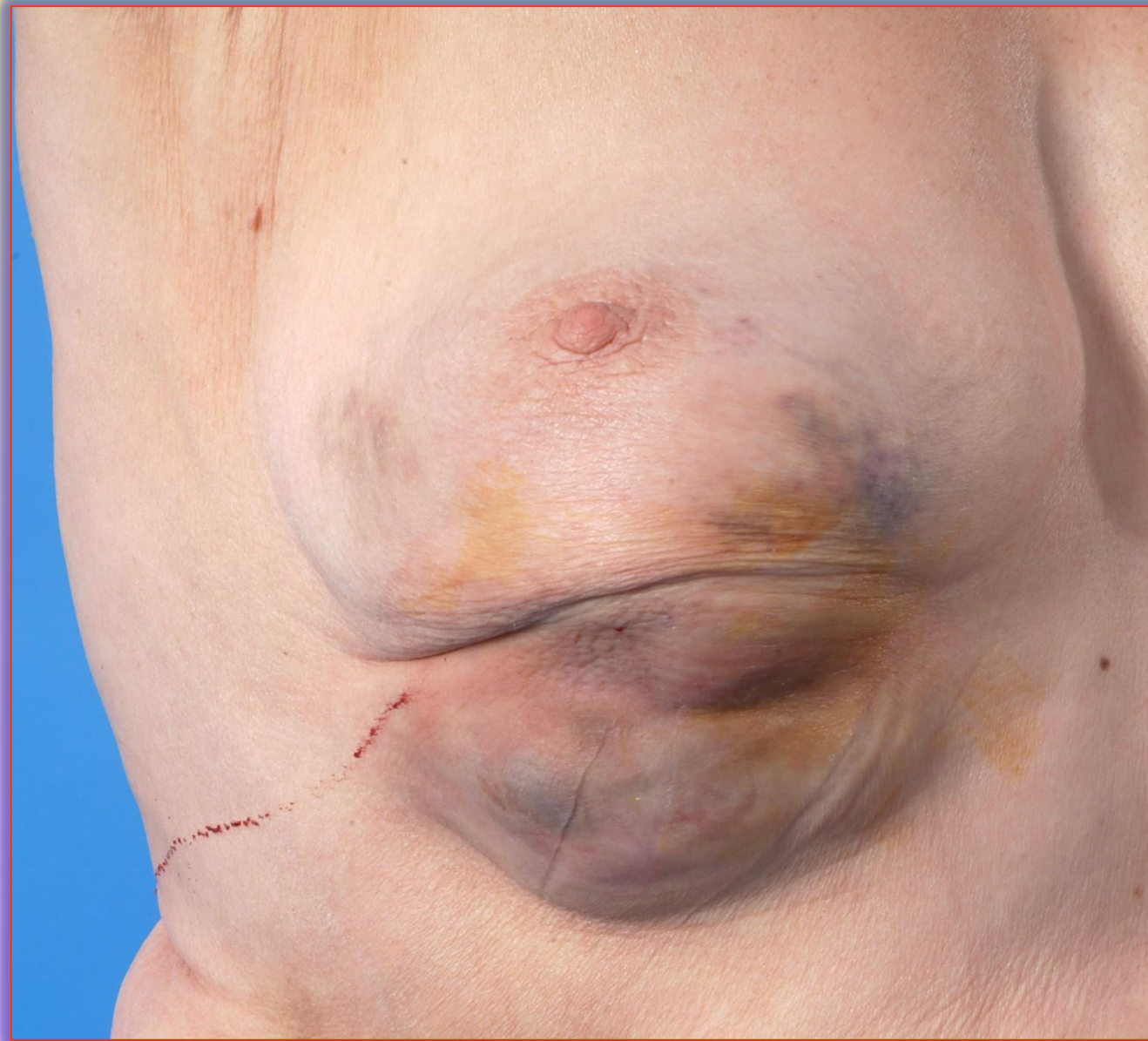
Correlates with clinical response ($p = 0.03$)

Histological Patterns following Neoadjuvant Therapy



**Longer durations of NET increase the rate of Breast
Conserving Surgery**

Patient at Presentation



Following 3 Months Letrozole



After 9 months of Letrozole



Following Wide Local Excision



3 Years Later



Patient at Presentation



Patient at Presentation



Patient after 9 months of Anastrozole



Same Patient after Radiotherapy



Cancer at Diagnosis



After 1 year of Letrozole



After 2 years of Letrozole



After Excision



After Radiotherapy



Patient at Presentation



After Debridement + Maggots



After 6 weeks Letrozole



After 3 months Letrozole



After 6 months Letrozole



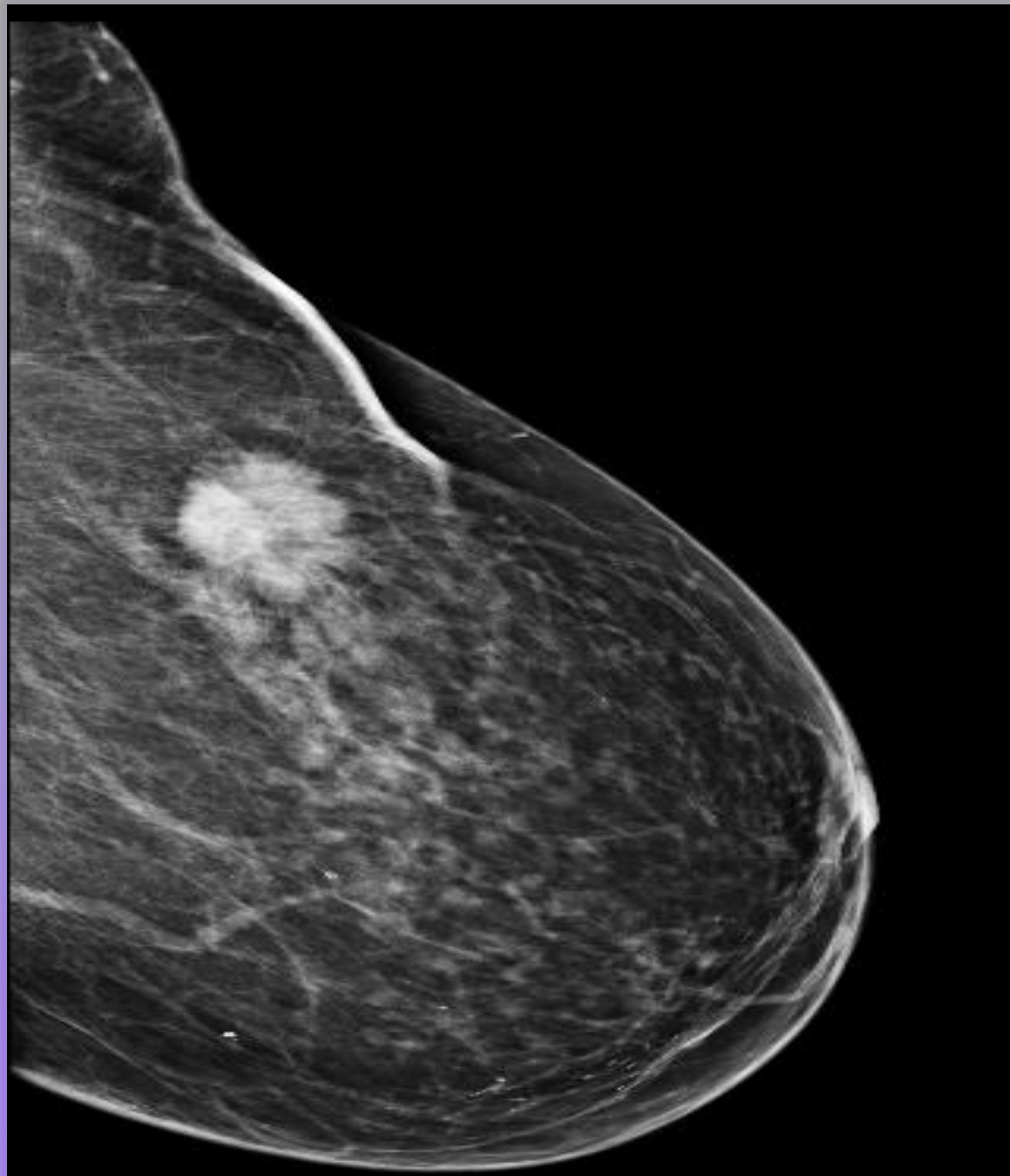
After 2 years Letrozole



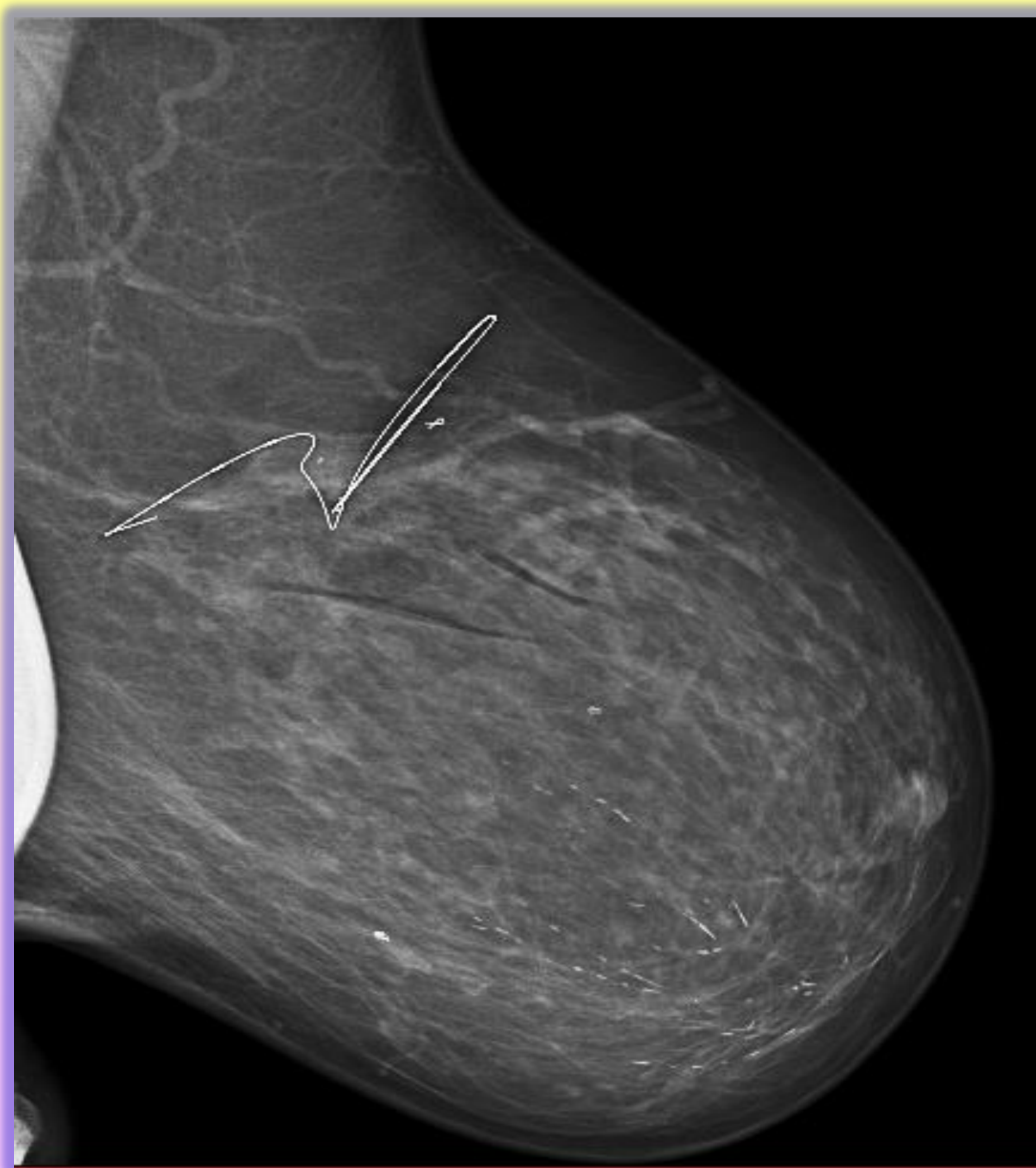
**Cancer at
Diagnosis**



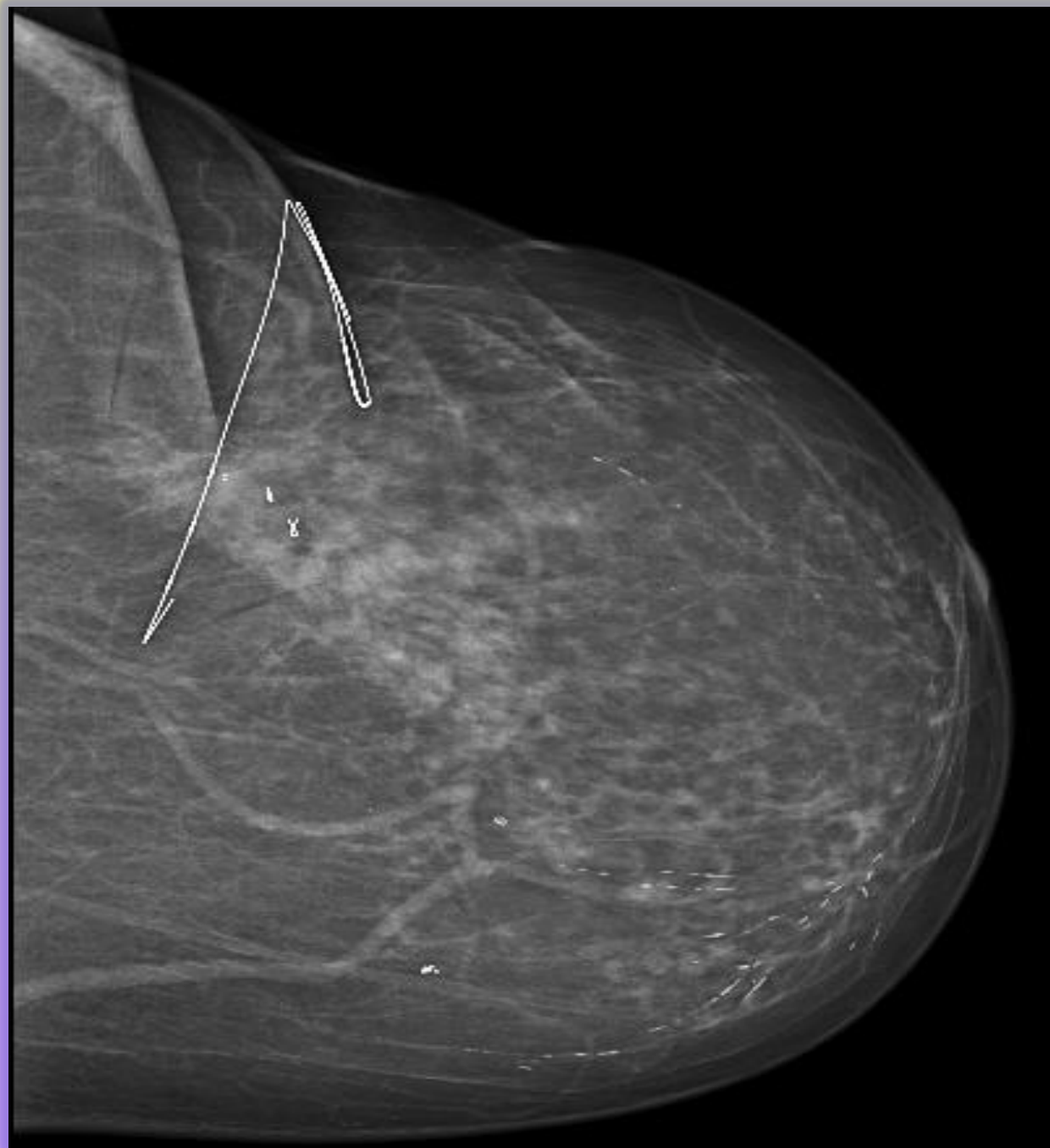
**Cancer at
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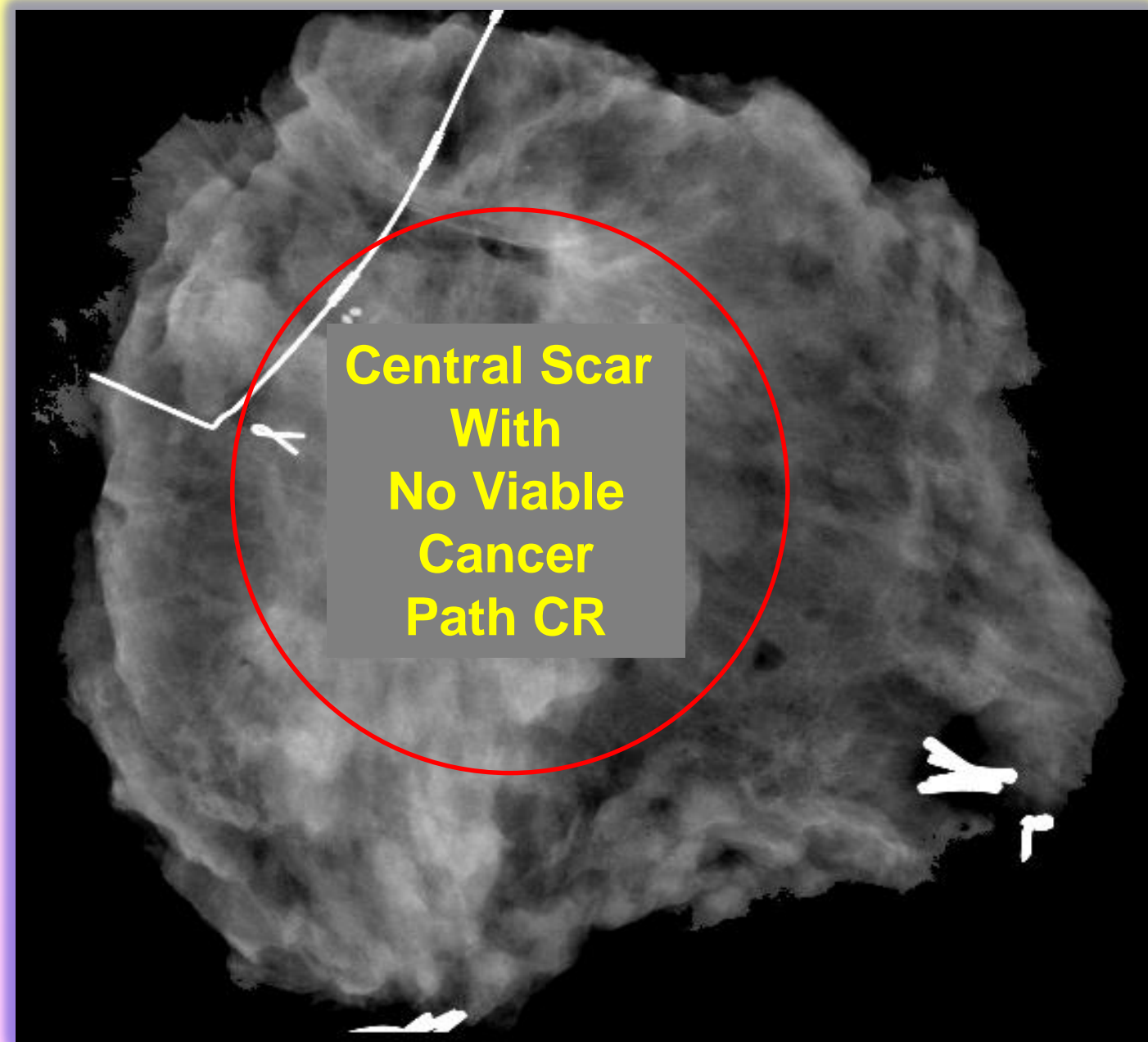
**After 14
Months
Letrozole**



**After 14
Months
Letrozole**



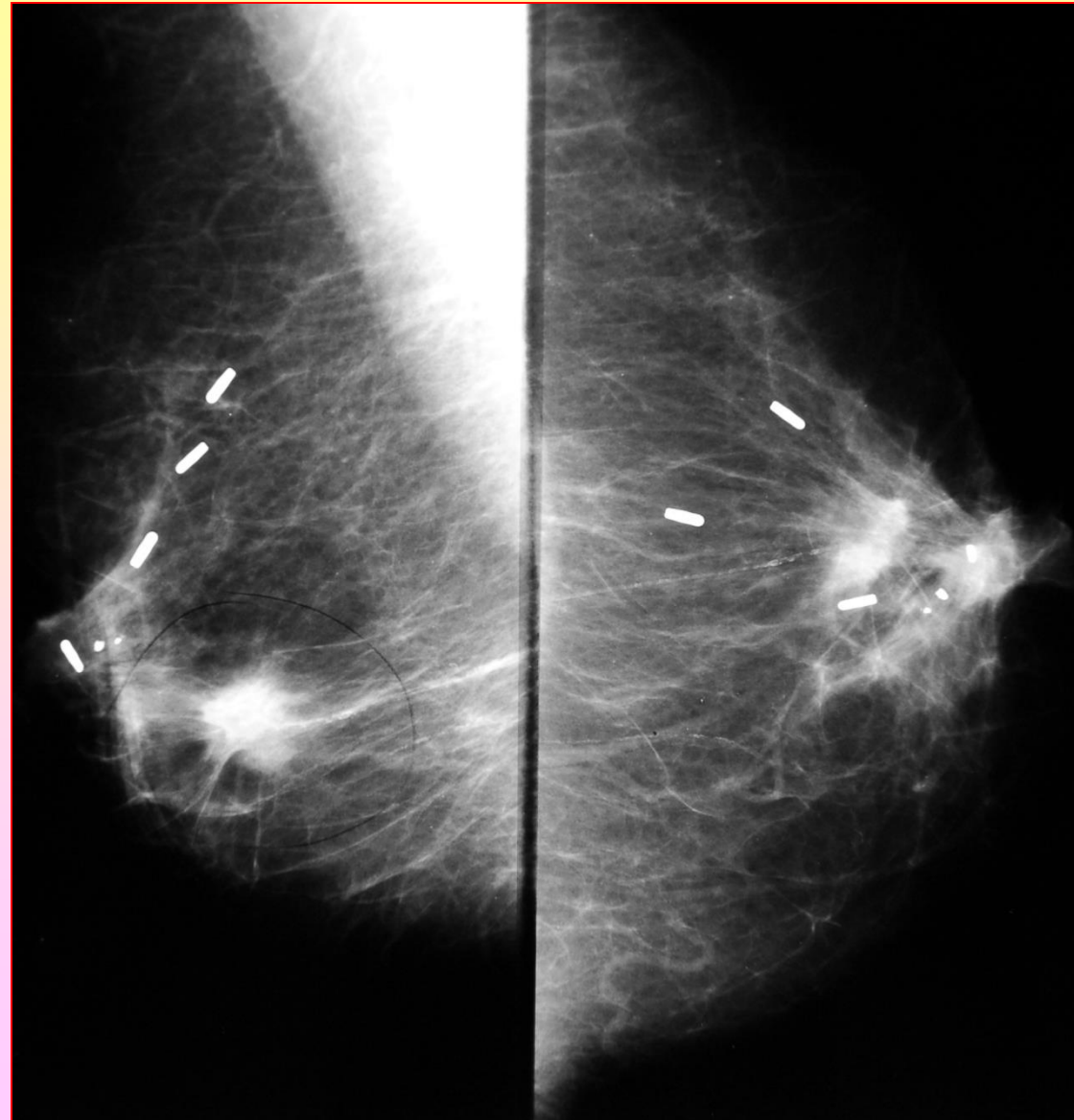
**Specimen
Radiograph**



Cancer with Nipple Invesrion



Cancer Behind Right Nipple at Diagnosis



Cancer Post 8 months Letrozole



Post operative Result



Edinburgh Duration Study

340 patients: Neoadjuvant Letrozole

- **39% eligible for BCS @ 3months**
- **53% eligible for BCS @ 6 months**
- **67% eligible for BCS @ 9-12 months**
- **78% became eligible by 2 years**

- **Longer durations of therapy increase BCS rate**
- **Optimal duration of neoadjuvant AIs 6-9 months**

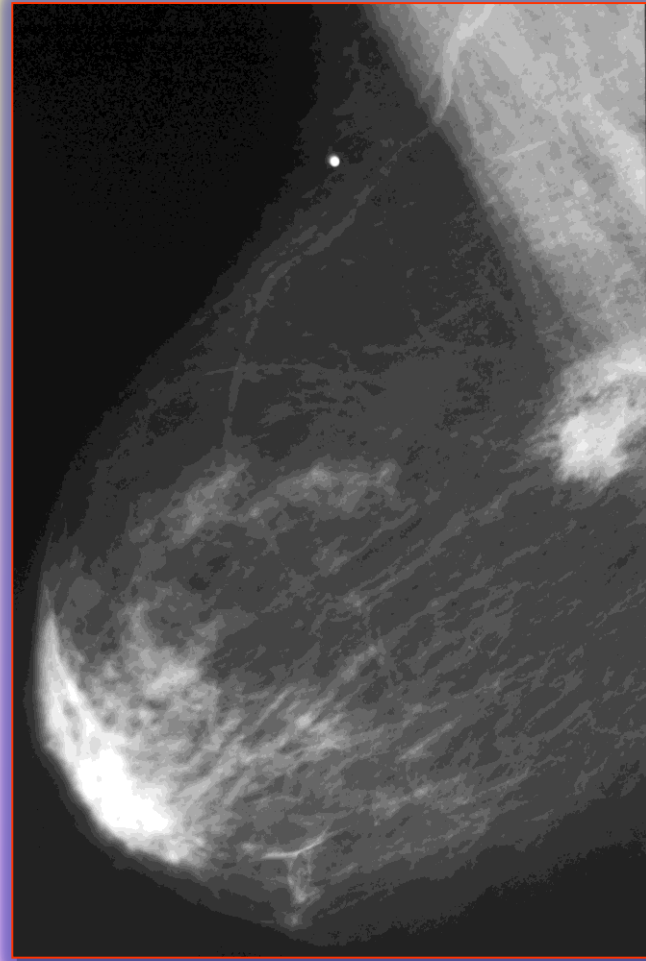
Reason 5

**Neoadjuvant Endocrine Therapy is effective in ER Rich
Invasive Lobular, HER2 positive and Inflammatory Breast Cancers**

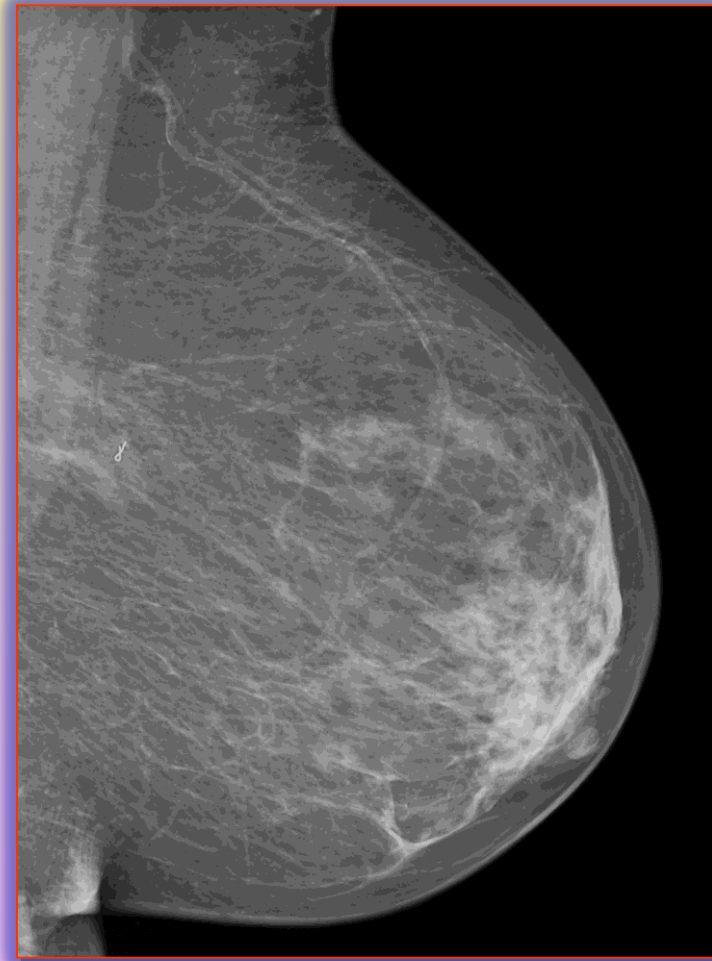
Invasive Lobular Carcinomas Treated by Neoadjuvant Letrozole in EBU

- **63 invasive lobular cancers treated with Letrozole**
- **Mean Age 74.68 yr Range 51 – 91yr**
- **Allred score 8=49, 7=10, 6=2, 5=2**
- **Operable 2-4cm n= 10, >4cm n=33**
- **Locally advanced n=20**
- **Response assessed at 3 months – Single observer**

Mammographic Response in Invasive Lobular Cancer

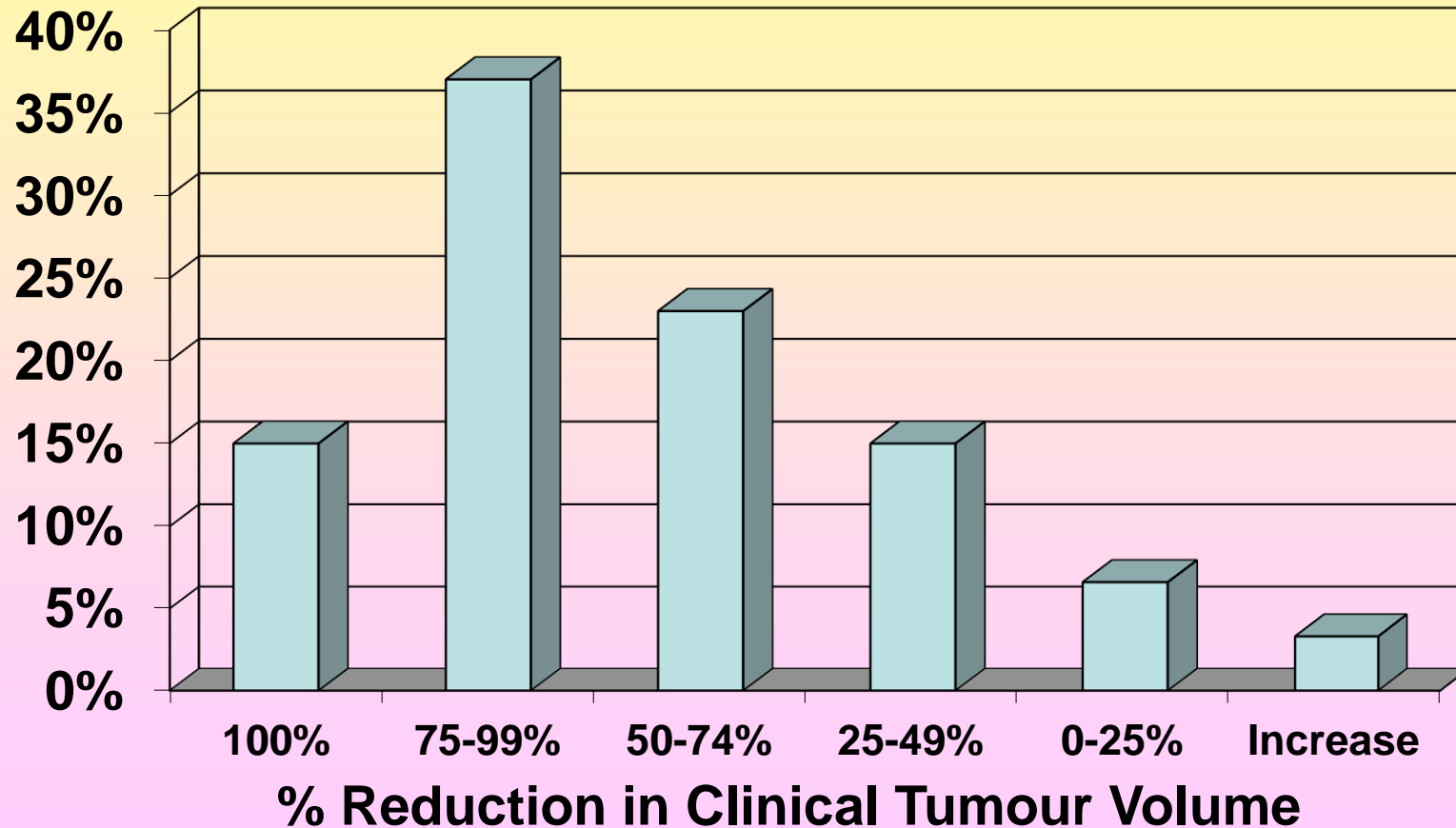


At Diagnosis

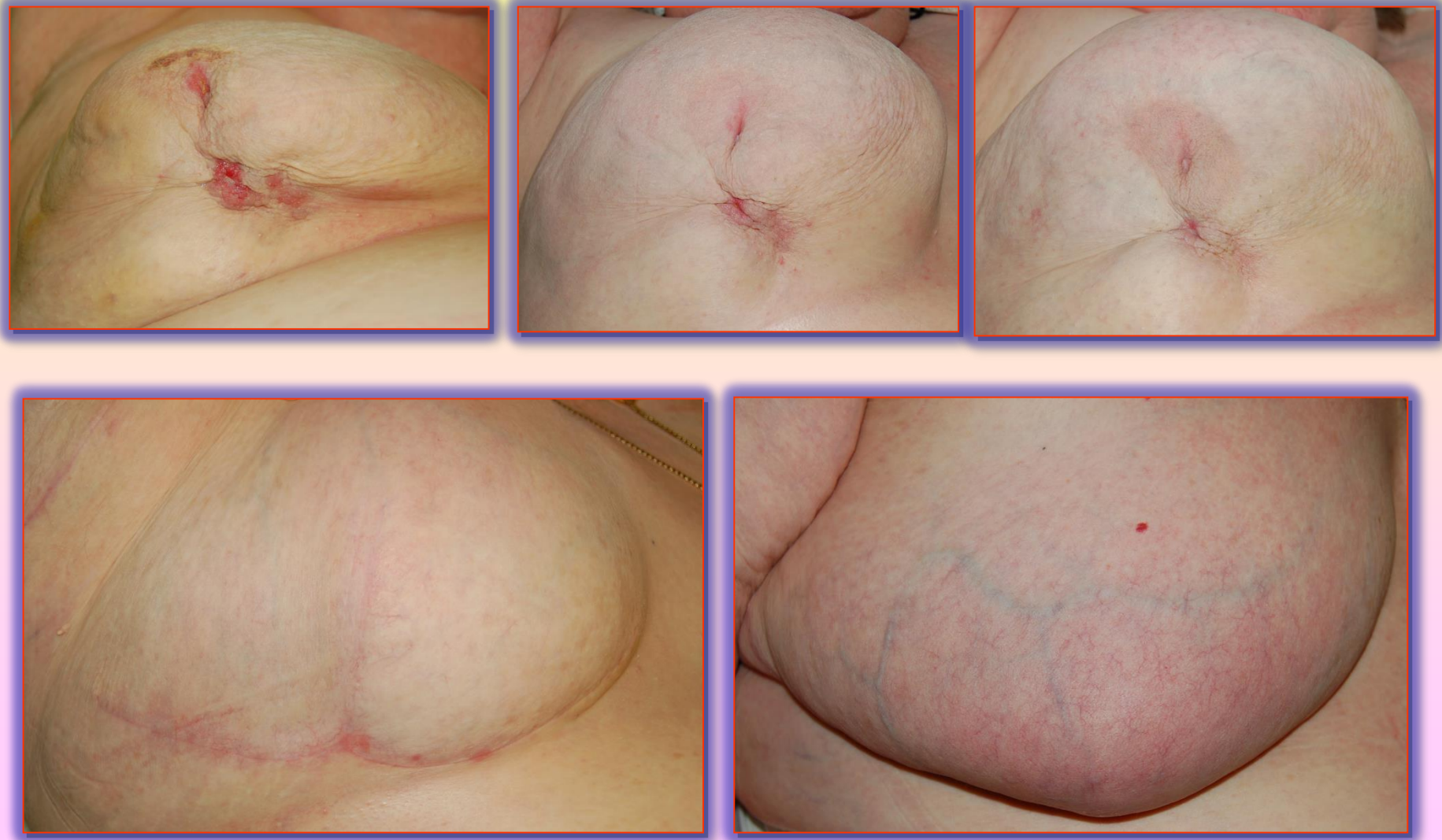


After 3 months Letrozole

Clinical Responses in Invasive Lobular Cancers at 3 months



Response in HER2 Positive Invasive Lobular Cancer



NET in Locally Advanced Breast Cancers including Inflammatory Cancers

At Diagnosis



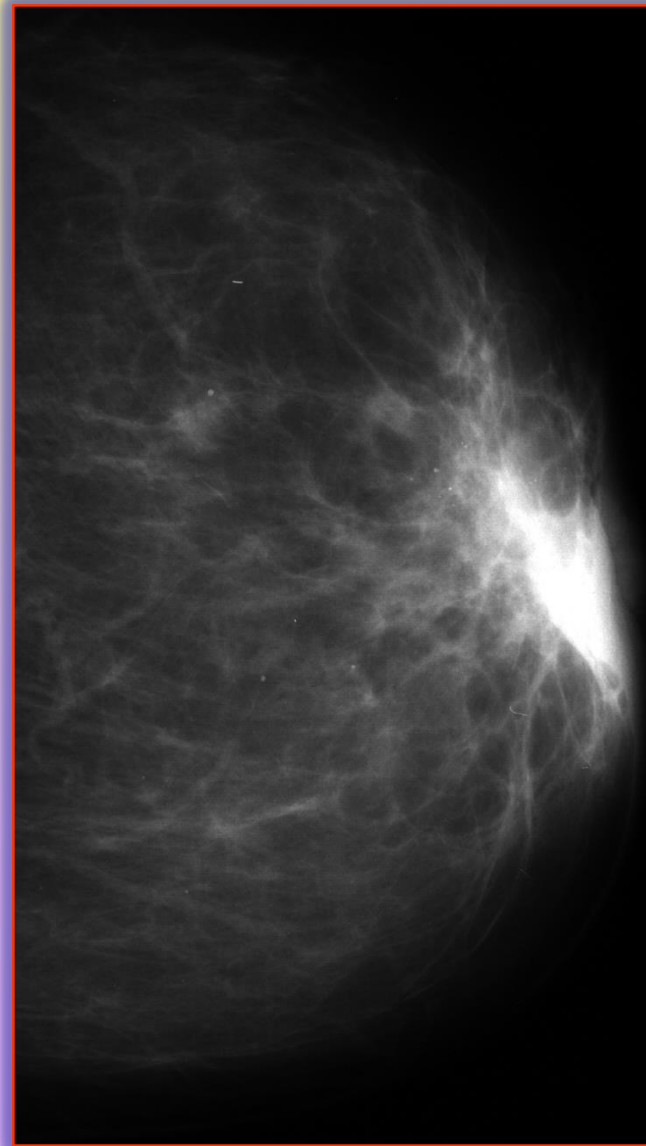
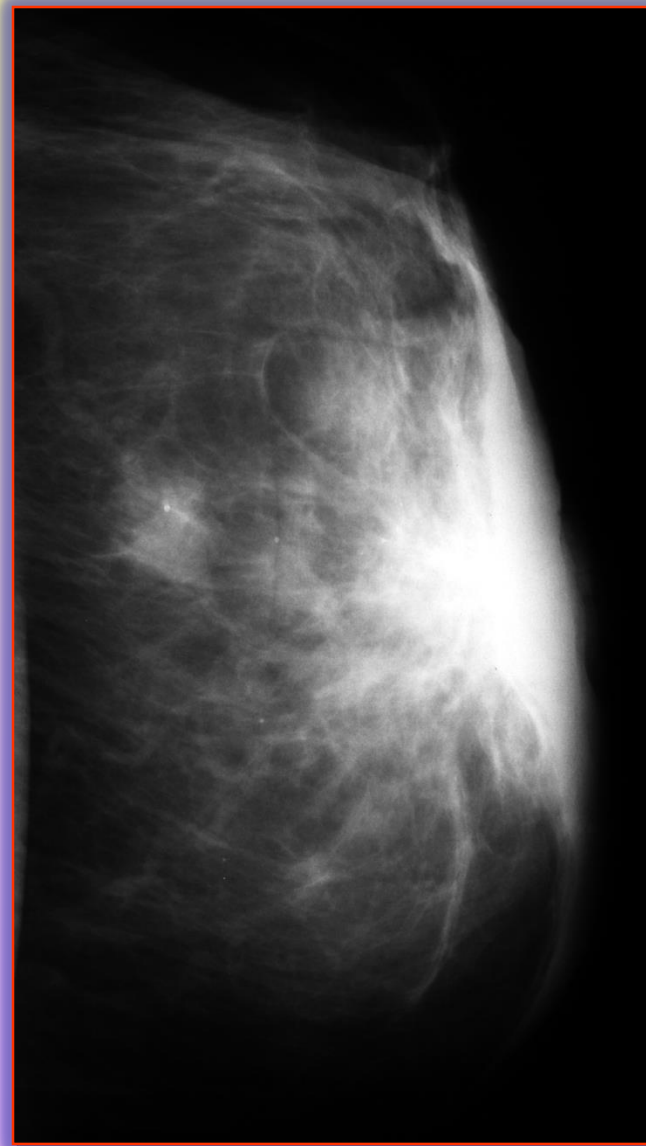
After 3 months Letrozole



After 6 months of Letrozole



Inflammatory Cancer: Response to Letrozole



Inflammatory Breast Cancer Edinburgh

- **35 patients BCT after neoadjuvant therapy**
- **15 deaths: 5 year survival rate of 70.3%.**
- **20 Neoadjuvant Chemotherapy patients**
 - Median survival 12.9 years (95% CI 7.6, 18.1),
- **14 Neoadjuvant Endocrine therapy patients**
 - Median survival 11.8 years (95% CI 1.1, 22.6)
- **5 IBTR between 11 and 72 months after BCT**
 - 4 of these had Mets within 3 months of IBTR
 - 1 second primary in gene carrier
 - NO patients with isolated IBTR

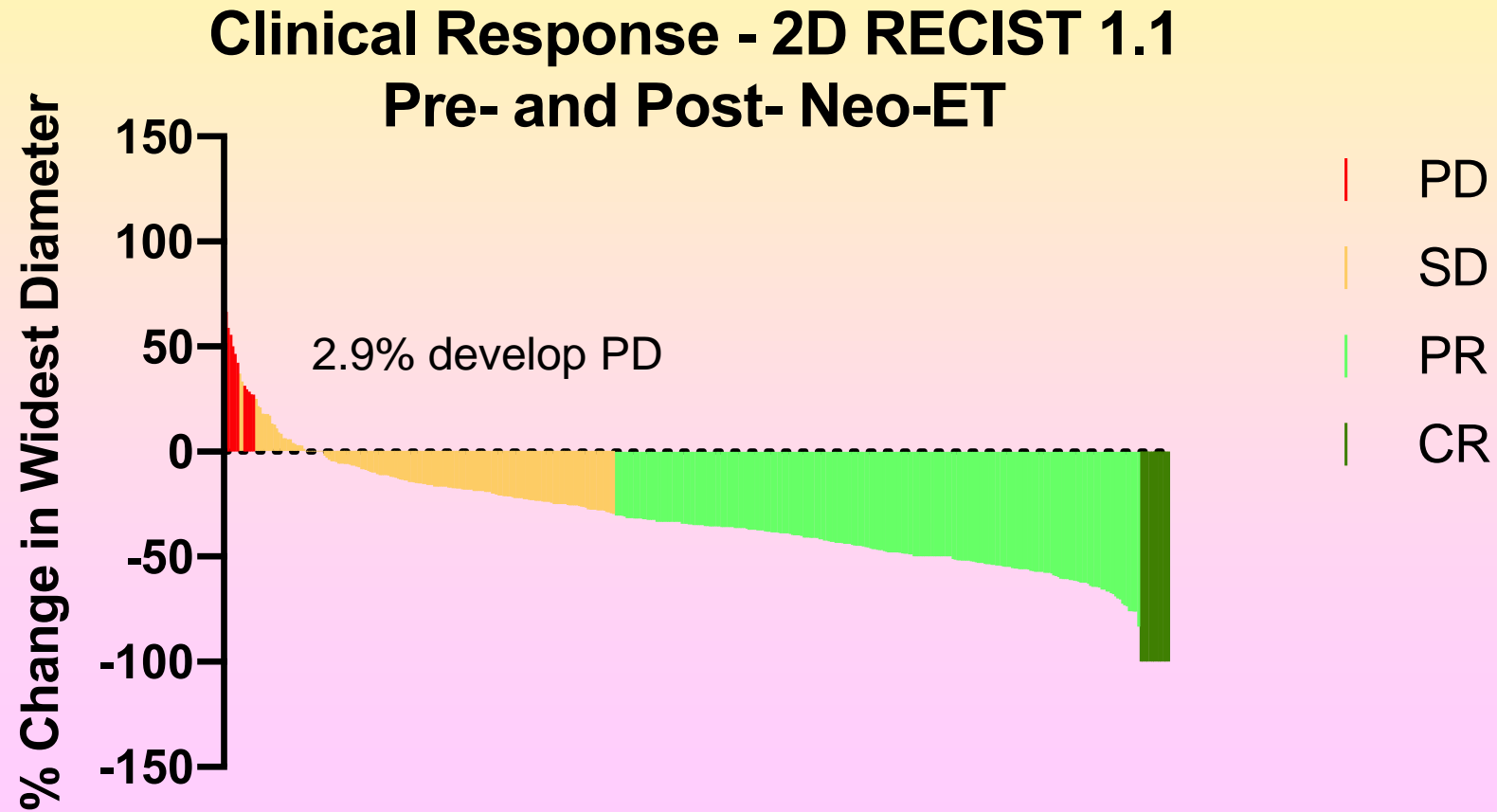
Reason 6

**We understand which clinical factors predict for
Response and long term Survival with
Neoadjuvant Endocrine Therapy**

434 Patients treated with Neoadjuvant Endocrine Therapy: Edinburgh Breast Unit

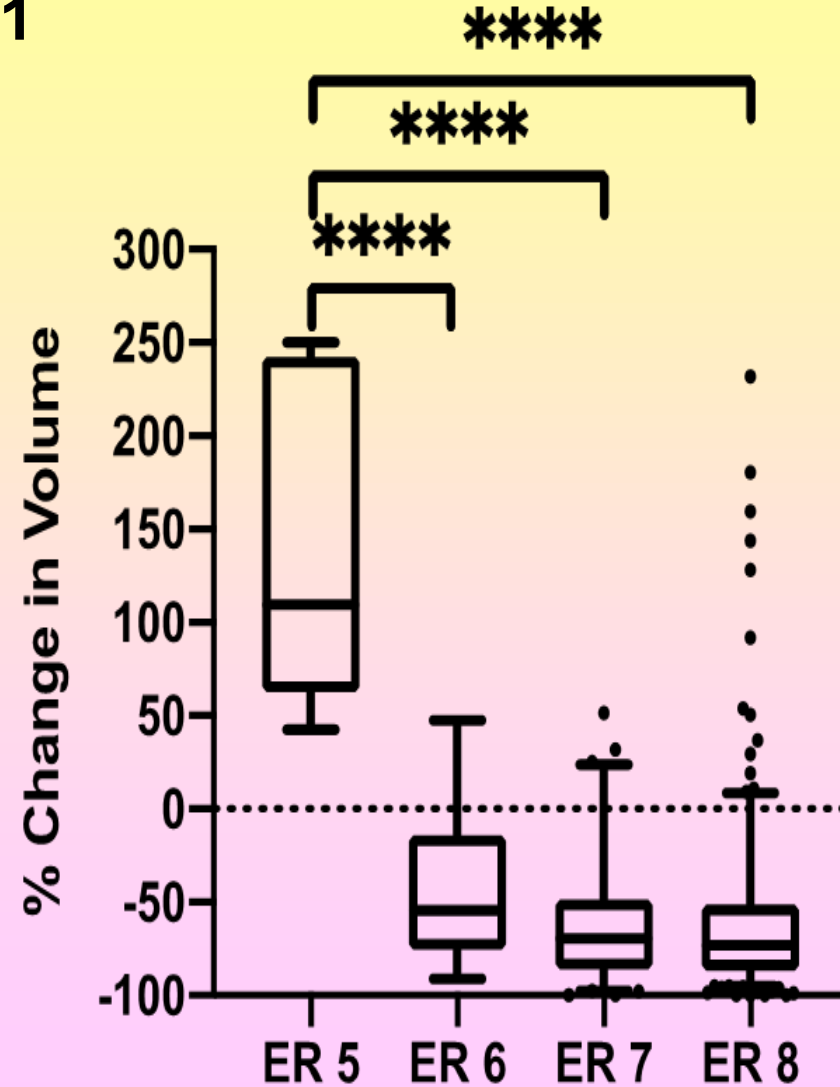
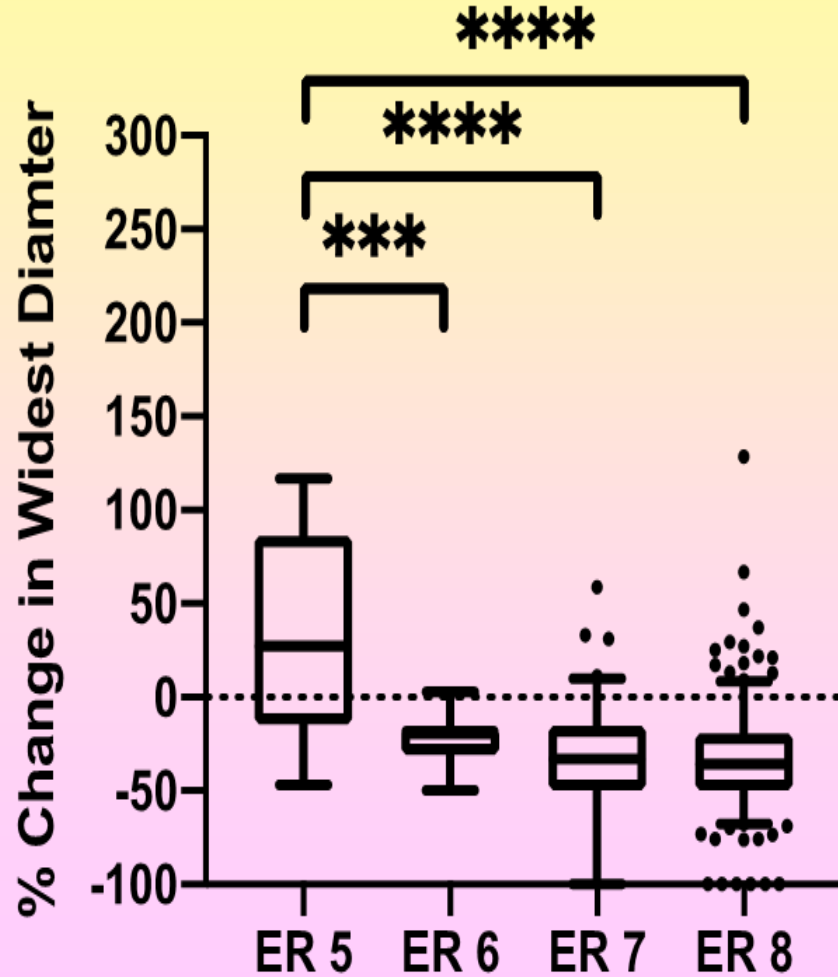
Characteristic	% of Patients	Characteristic	% of Patients
Tumour Size		Nodes	
T1	11%	Positive	30%
T2	54%	Negative	67%
T3	10%	Unknown	3%
T4	25%	ER Allred Score	
Grade		5	1%
1	11%	6	4%
2	44%	7	22%
3	18%	8	73%
Unknown	27%		

Clinical Response – Tumour Size (2D)



ER vs Neoadjuvant Clinical Response

*** $p < 0.001$, **** $p < 0.0001$



Factors Related to Response to Neoadjuvant Endocrine Therapy

Factors Related to Response

- ER level – only ER7 and 8
- IL6ST levels at diagnosis
- 14 day proliferation

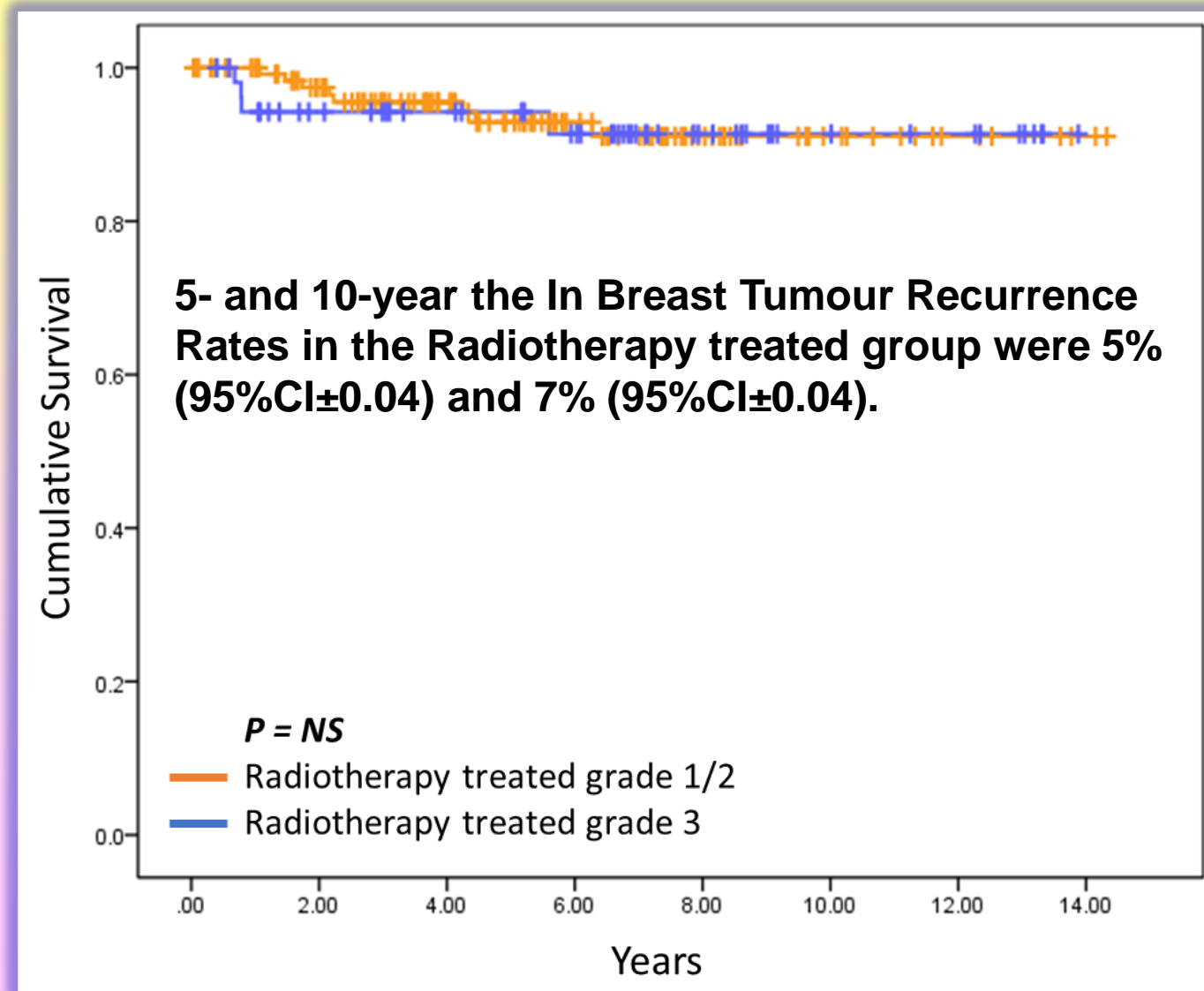
Factors Not Related to Response

- Tumour Grade
- T stage
- Node status
- HER2 status

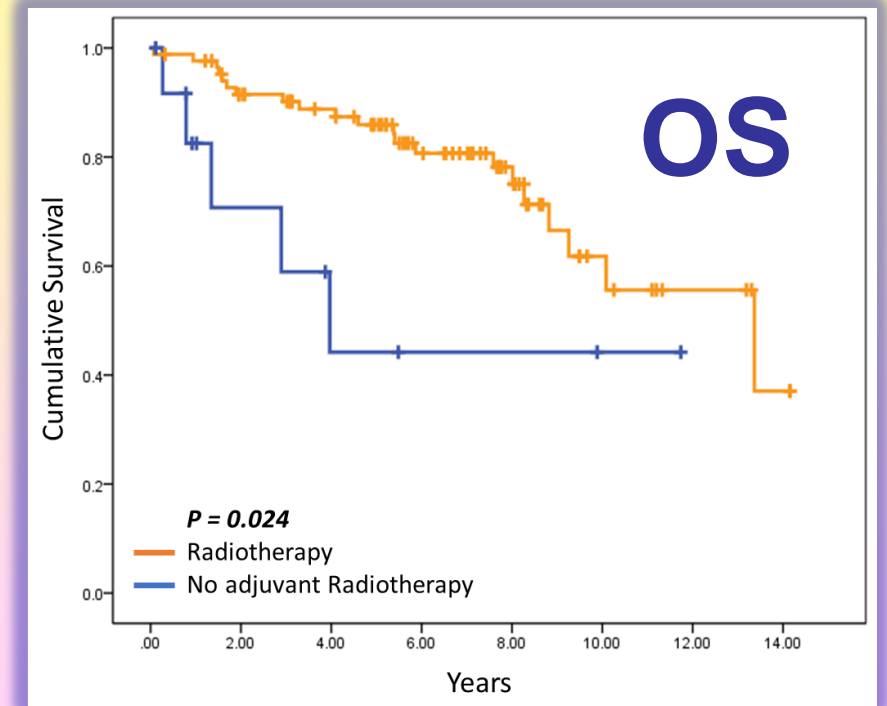
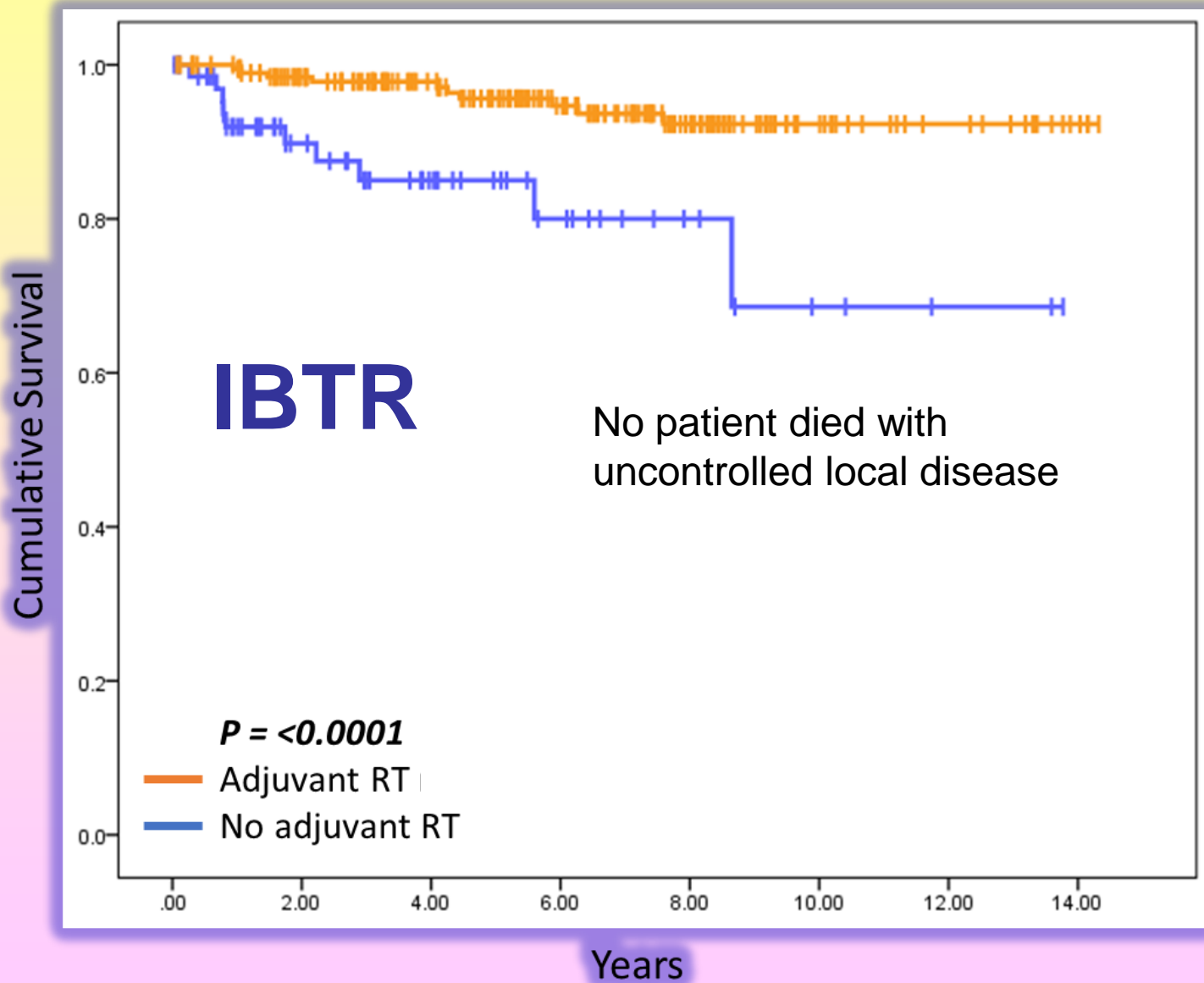
Reason 7

**Local Control and Breast Cancer Specific
Survival after Neoadjuvant Endocrine Therapy is
excellent**

Local Recurrence for Grade 1 or 2 vs Grade 3 cancers BCS + XRT

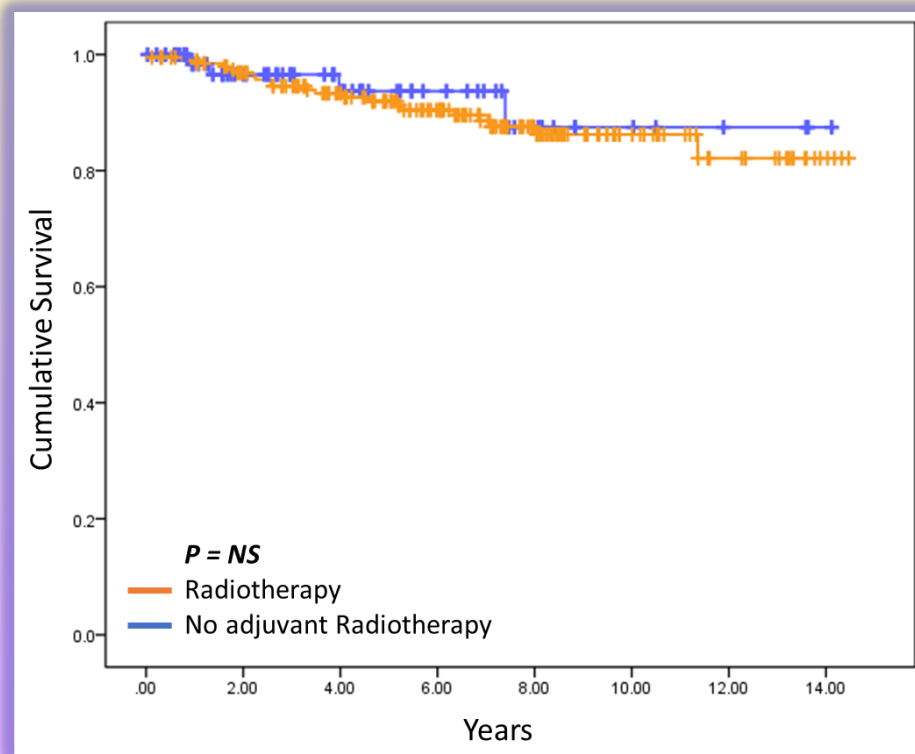


Radiotherapy did Reduce IBTR



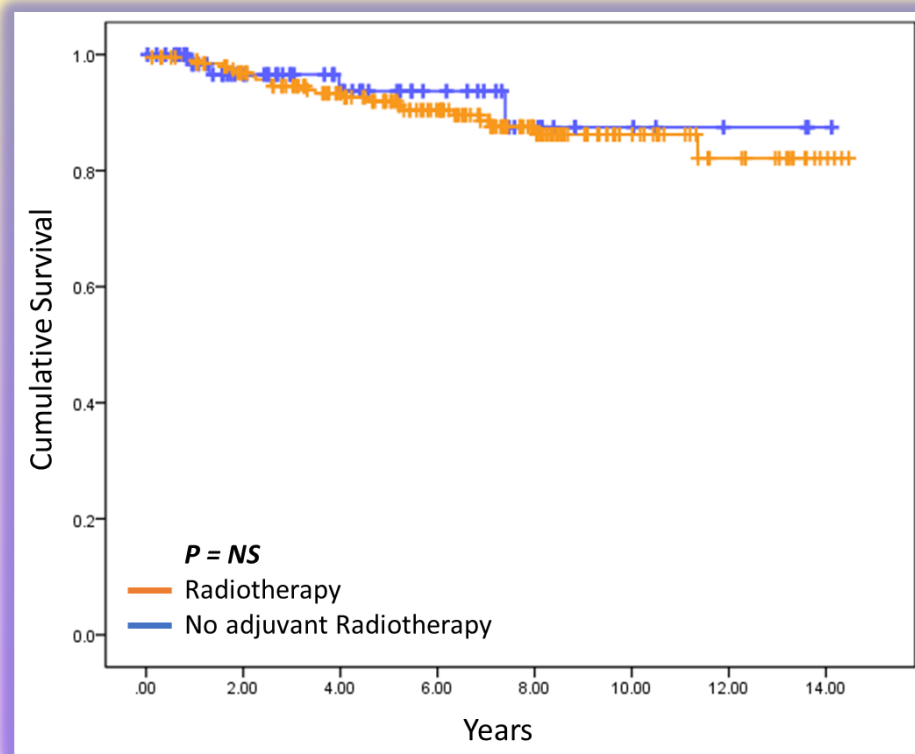
Breast Cancer Specific Survival: Effect of Radiotherapy and Chemotherapy

Adjuvant Radiotherapy

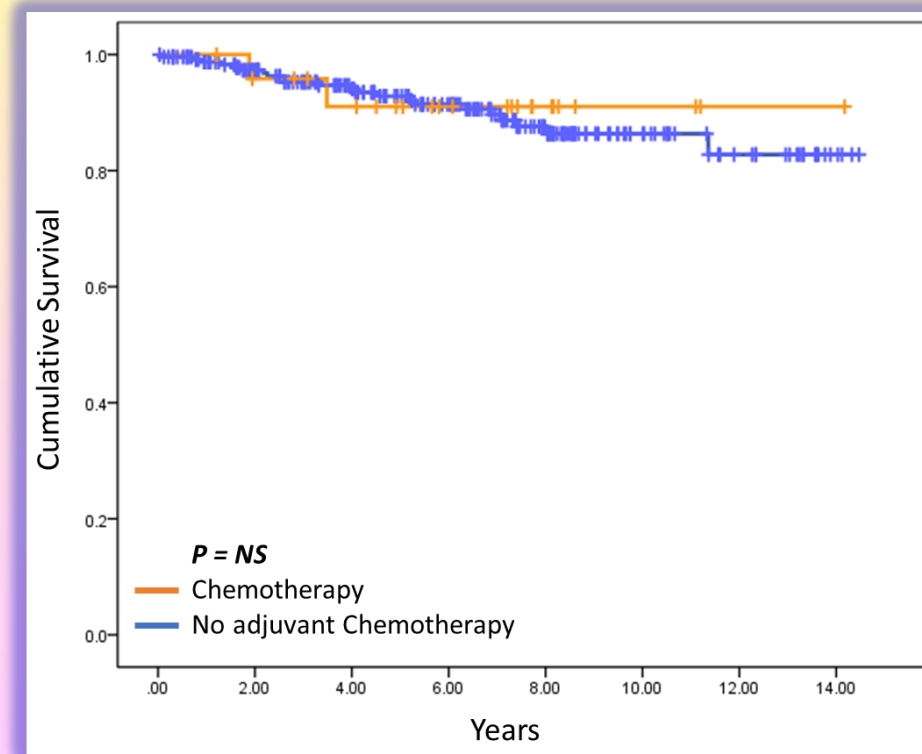


Breast Cancer Specific Survival: Effect of Radiotherapy and Chemotherapy

Adjuvant Radiotherapy



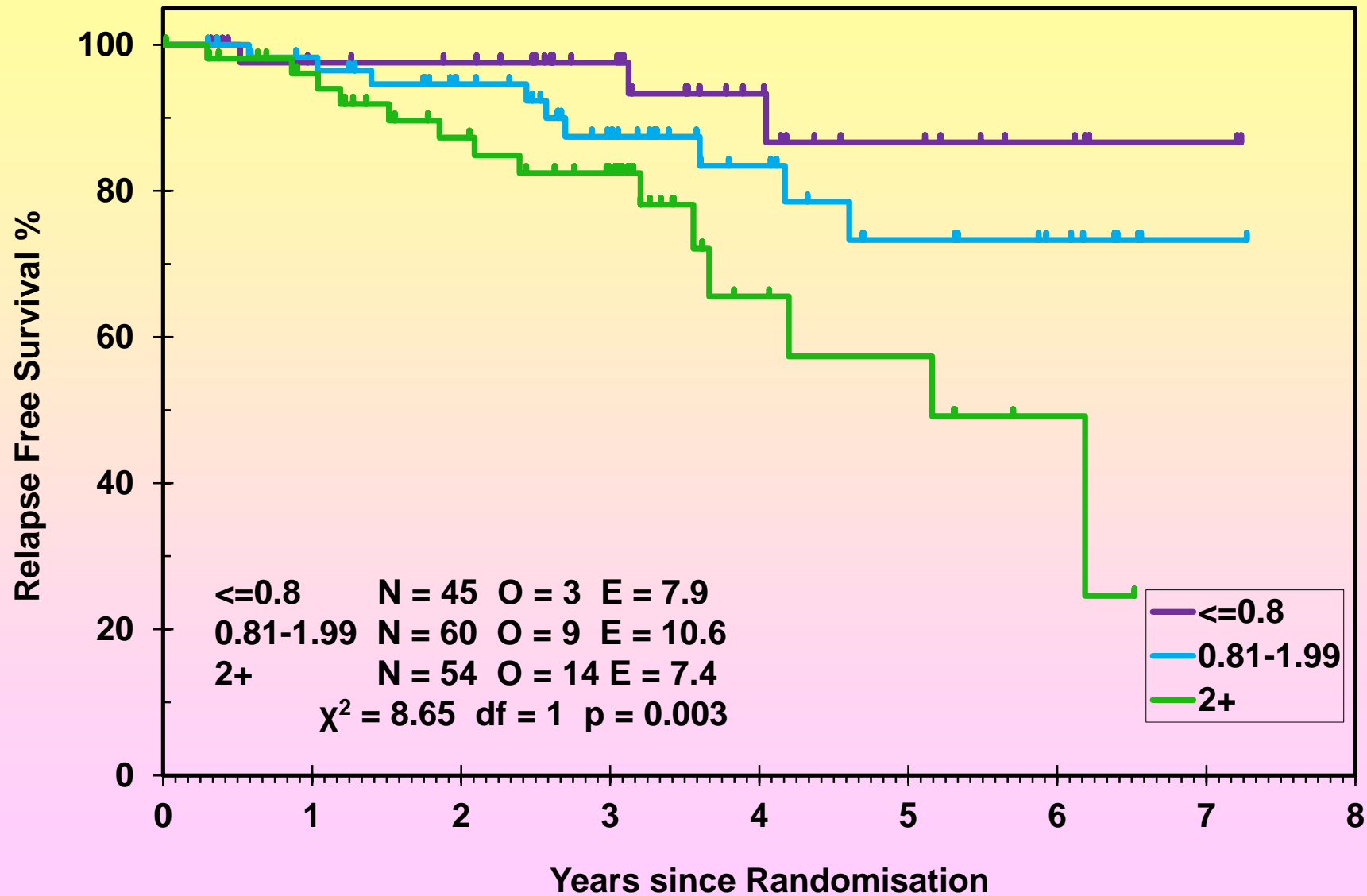
Adjuvant Chemotherapy



Reason 8

Neoadjuvant Endocrine Therapy is an important tool in understanding Resistance and Response

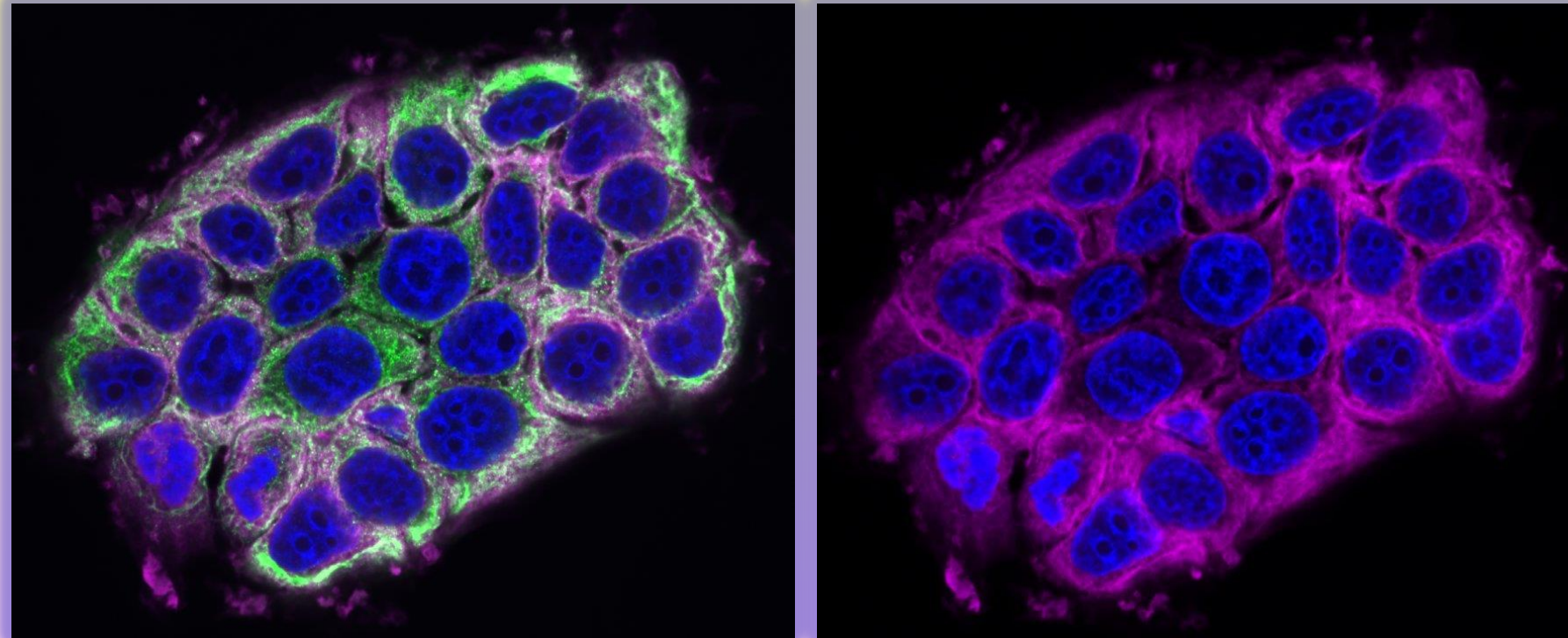
Relapse Free Survival by 2 week Ki67 in IMPACT Trial



Recent Edinburgh Studies using Neoadjuvant Model

- **Developed IHC based predictor**
 - IL6ST at diagnosis
 - MCM4 a proliferation marker at 14 days

Visualising IL6ST

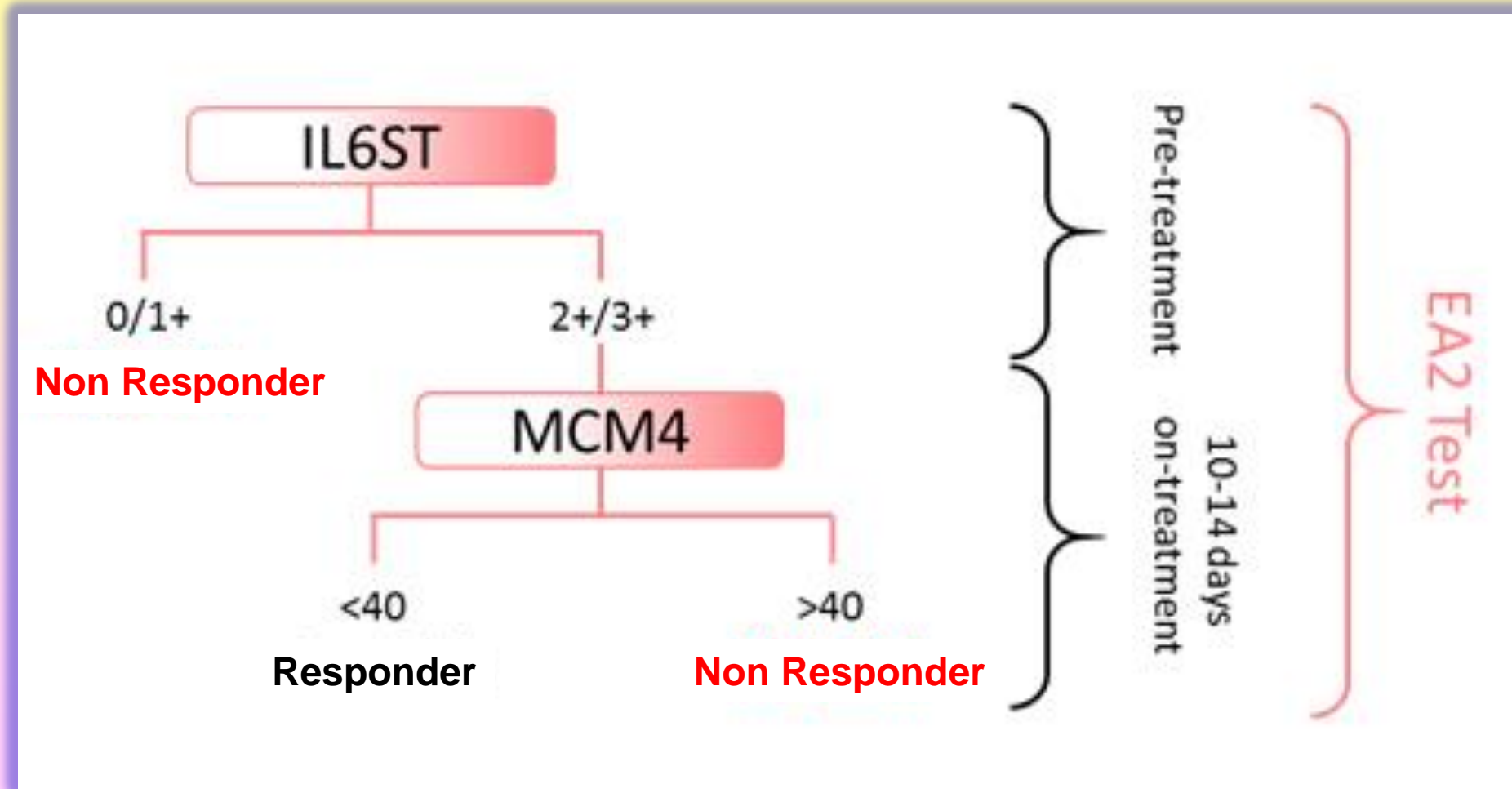


Nucleus - DAPI

Cytokeratin (Dako) Mouse – (FITC) (Alexa Fluor 488 goat anti-mouse)

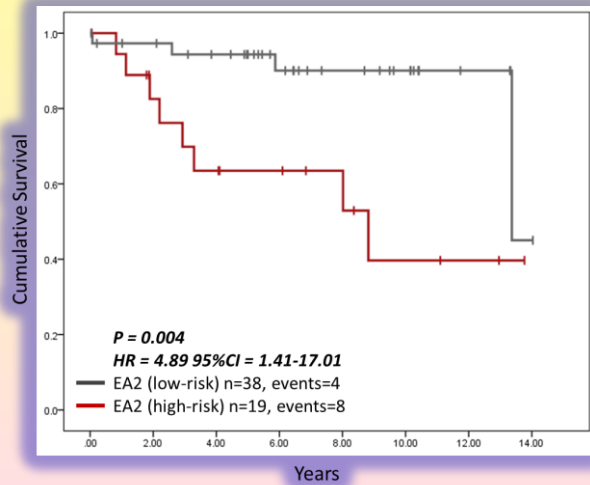
IL6ST (Thermo) Rabbit – (CY5) CY5-tyramide goat anti-rabbit HRP

2 Gene IHC Test

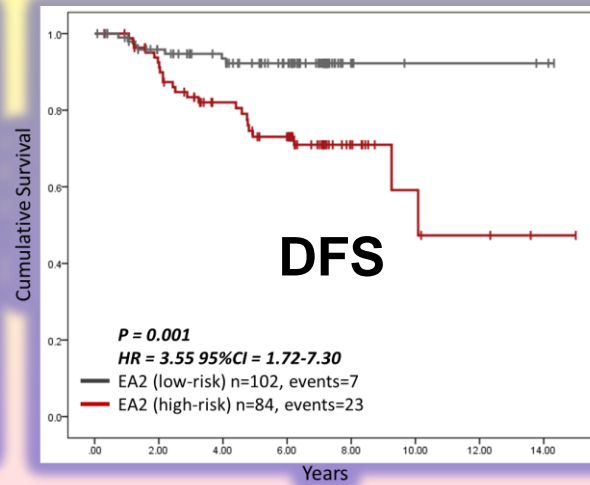


EA2: DFS and BCSS 3 Cohorts

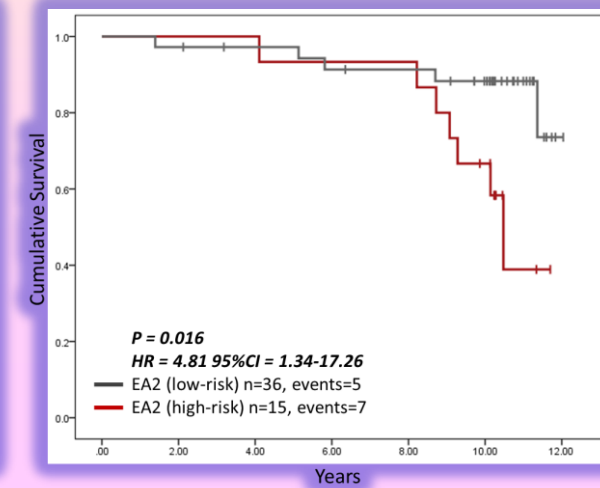
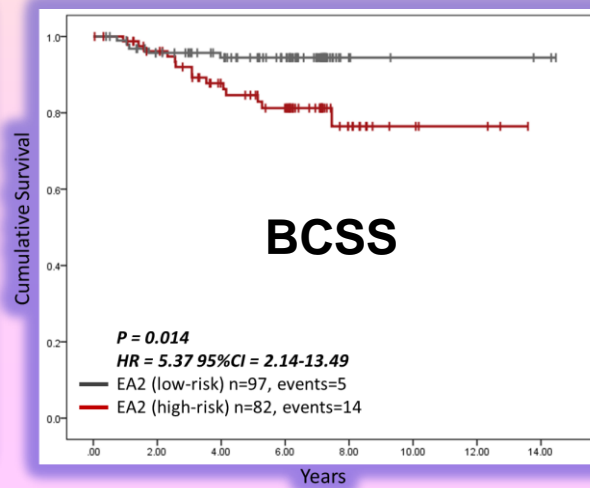
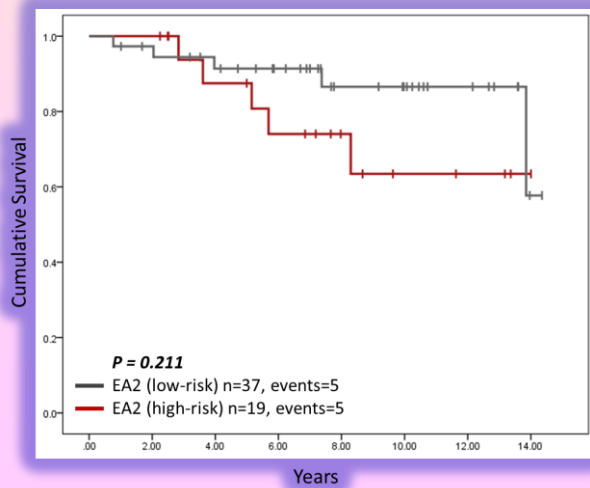
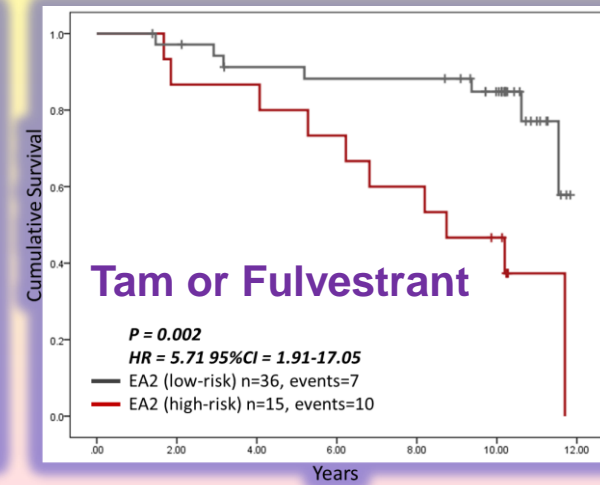
Original AI Training Cohort



Postmenopausal AI Validation



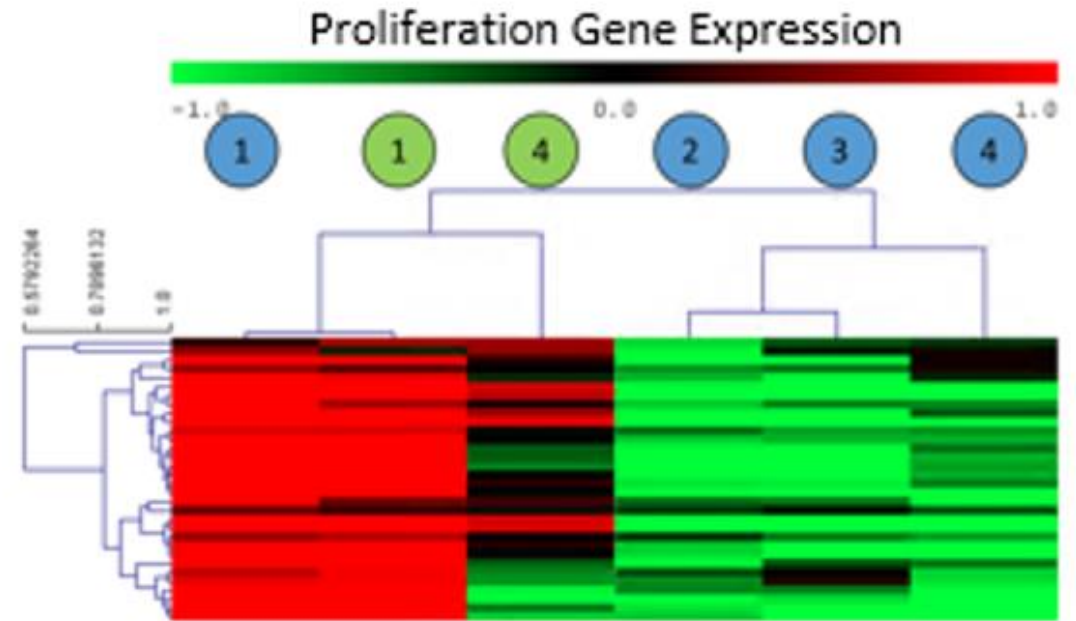
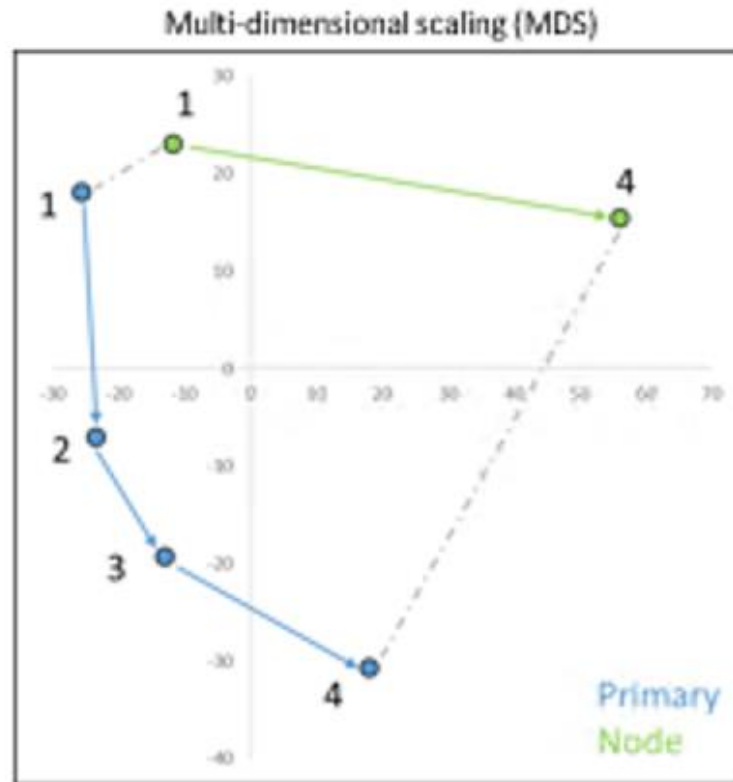
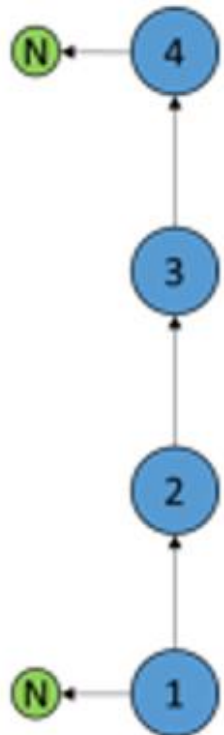
Premenopausal T+F Validation



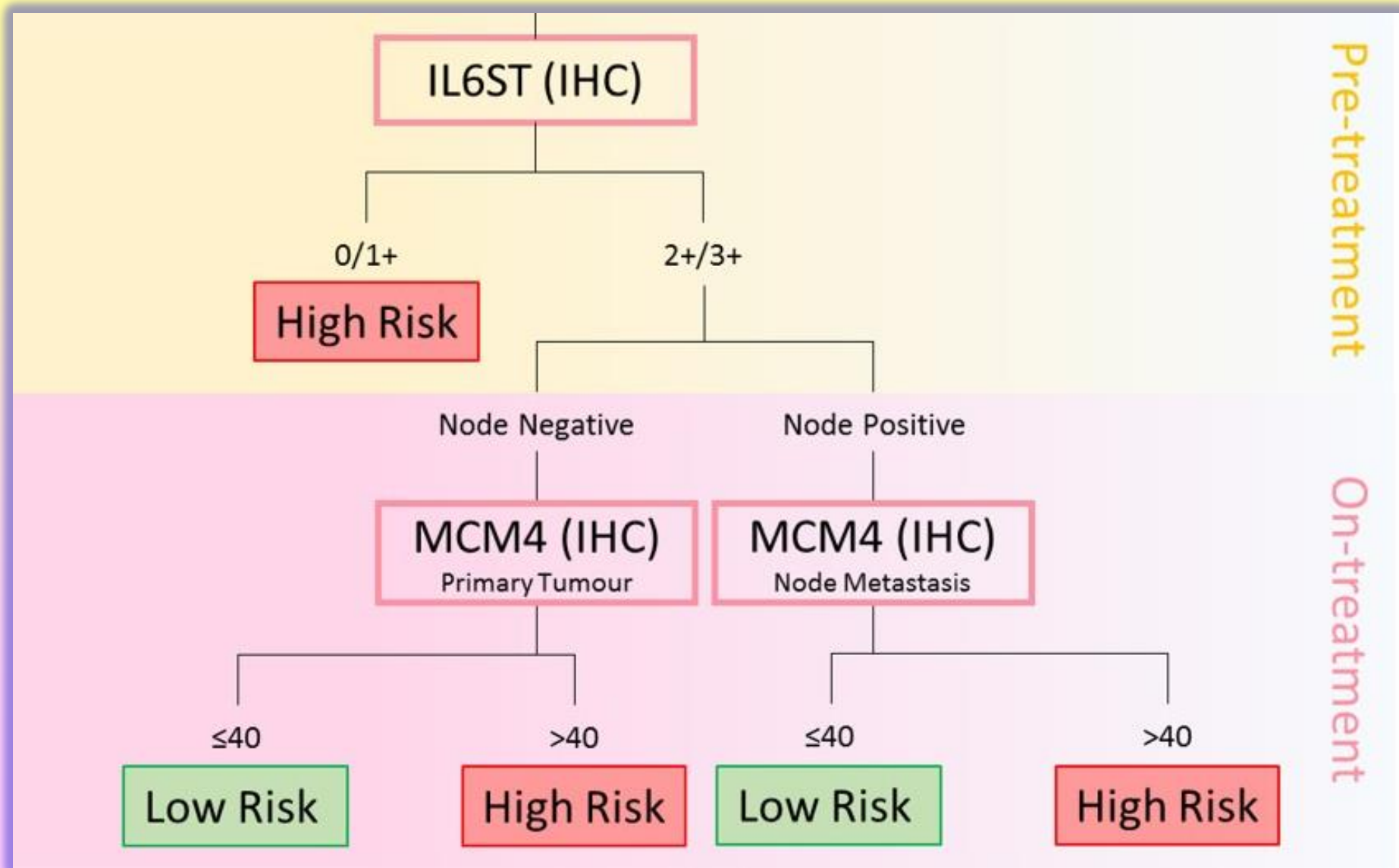
What happens in the axillary nodes during treatment with hormone therapy also determines outcome

Axillary Nodal Metastases do not always behave like the primary tumour

Patient treated with Neoadjuvant Endocrine Therapy

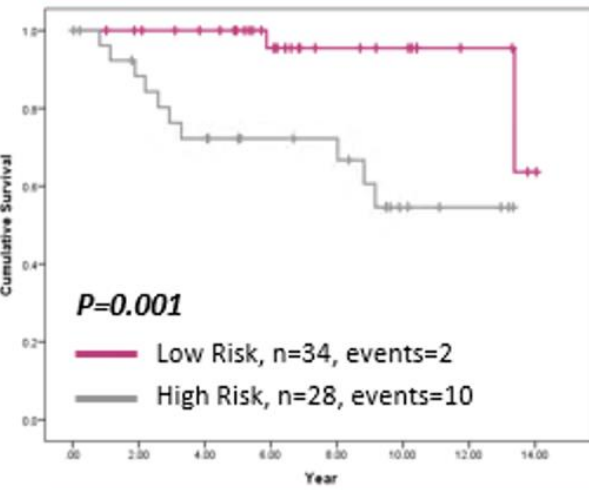


Now Combine Changes in Primary Cancer and the Nodes with Clinical Factors



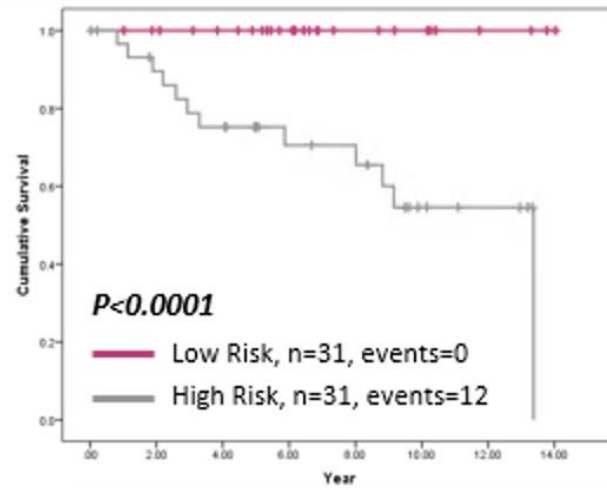
EA2 Clin and EA2 Clin Outcomes: Primary Cohort in Node Positive Patients

Recurrence Free Survival



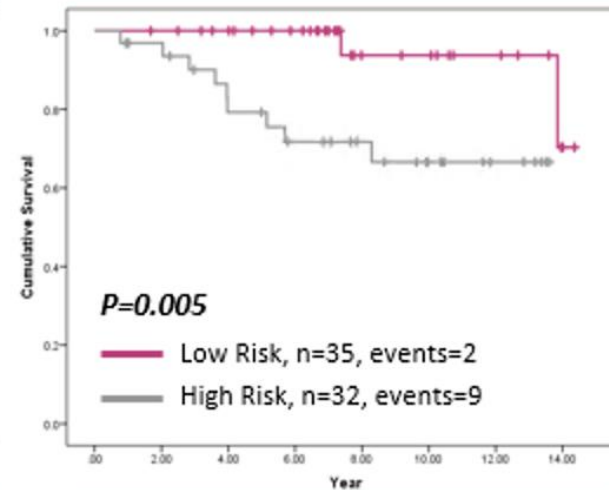
EA2Clin

Recurrence Free Survival

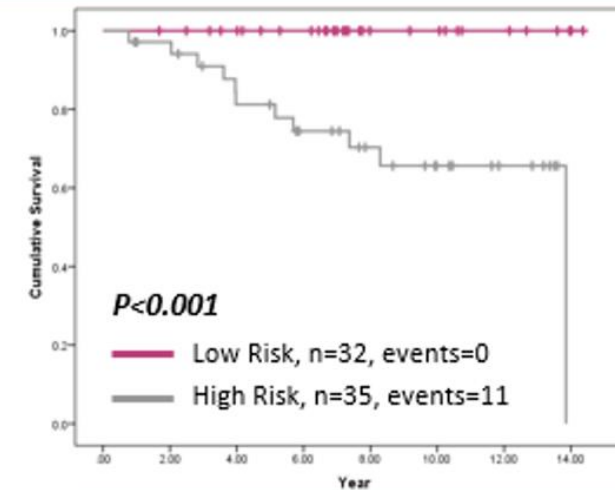


EA2Clin
(Including Assessment of Nodal Metastasis)

Breast Cancer Specific Survival



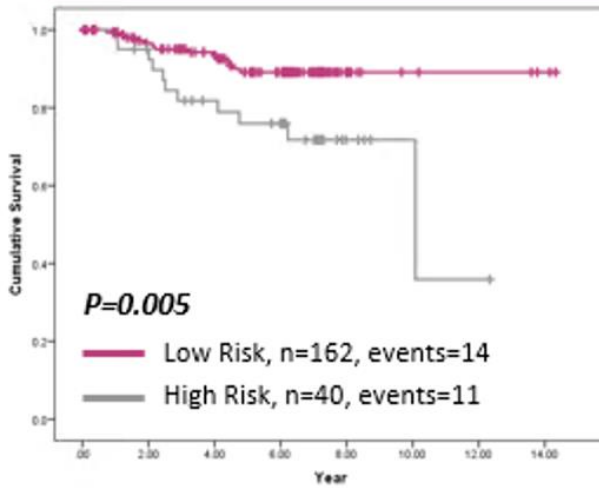
EA2Clin



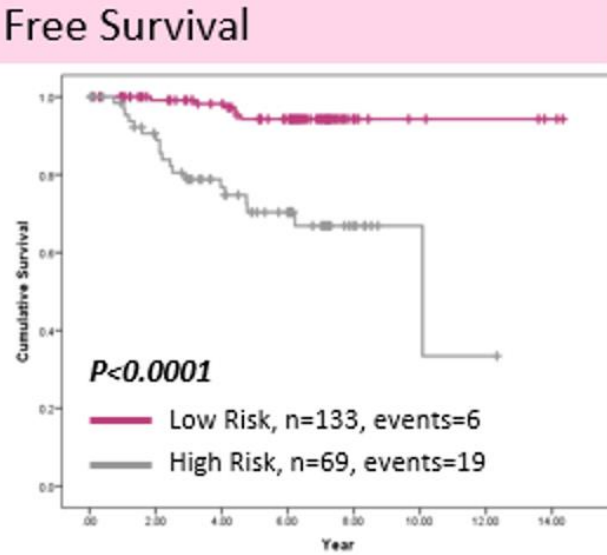
EA2Clin
(Including Assessment of Nodal Metastasis)

EA2 Clin and EA2 Clin Outcomes: Validation Cohort in Node Positive Patients

Recurrence Free Survival

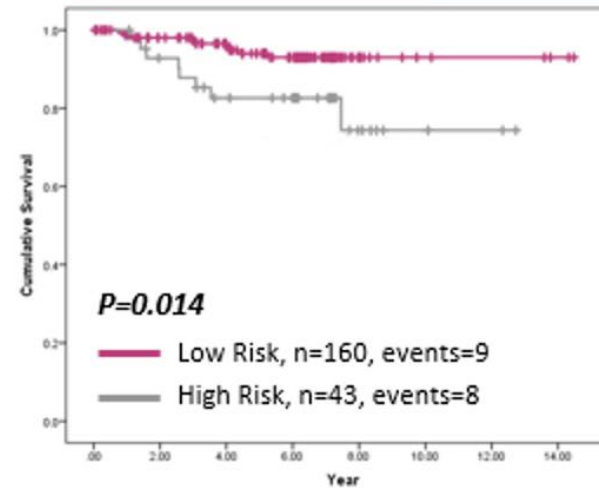


EA2Clin

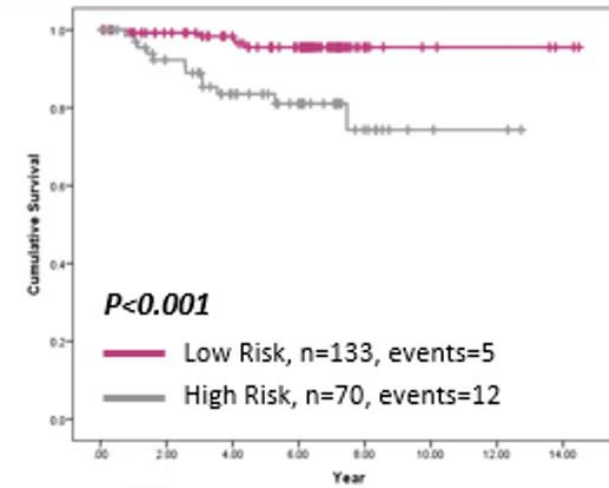


EA2Clin
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Breast Cancer Specific Survival



EA2Clin



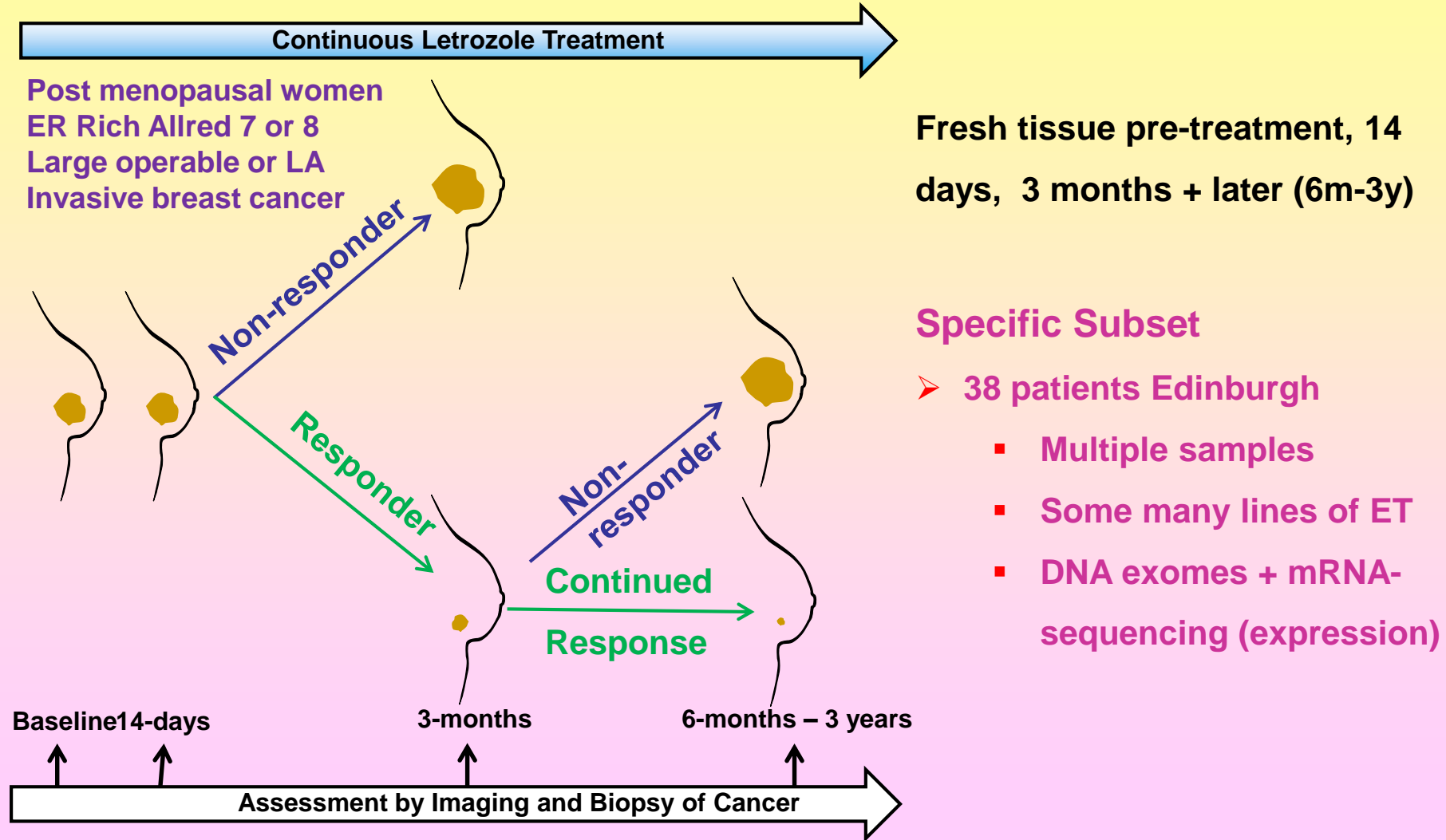
EA2Clin
(Including Assessment of Nodal Metastasis)

NET is a tool to understand Mechanisms of Primary and Acquired Resistance to Endocrine Therapy

More Recent Studies

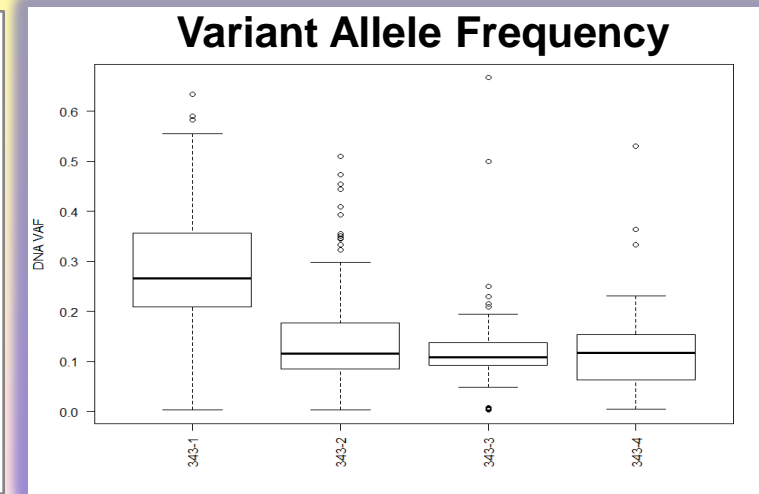
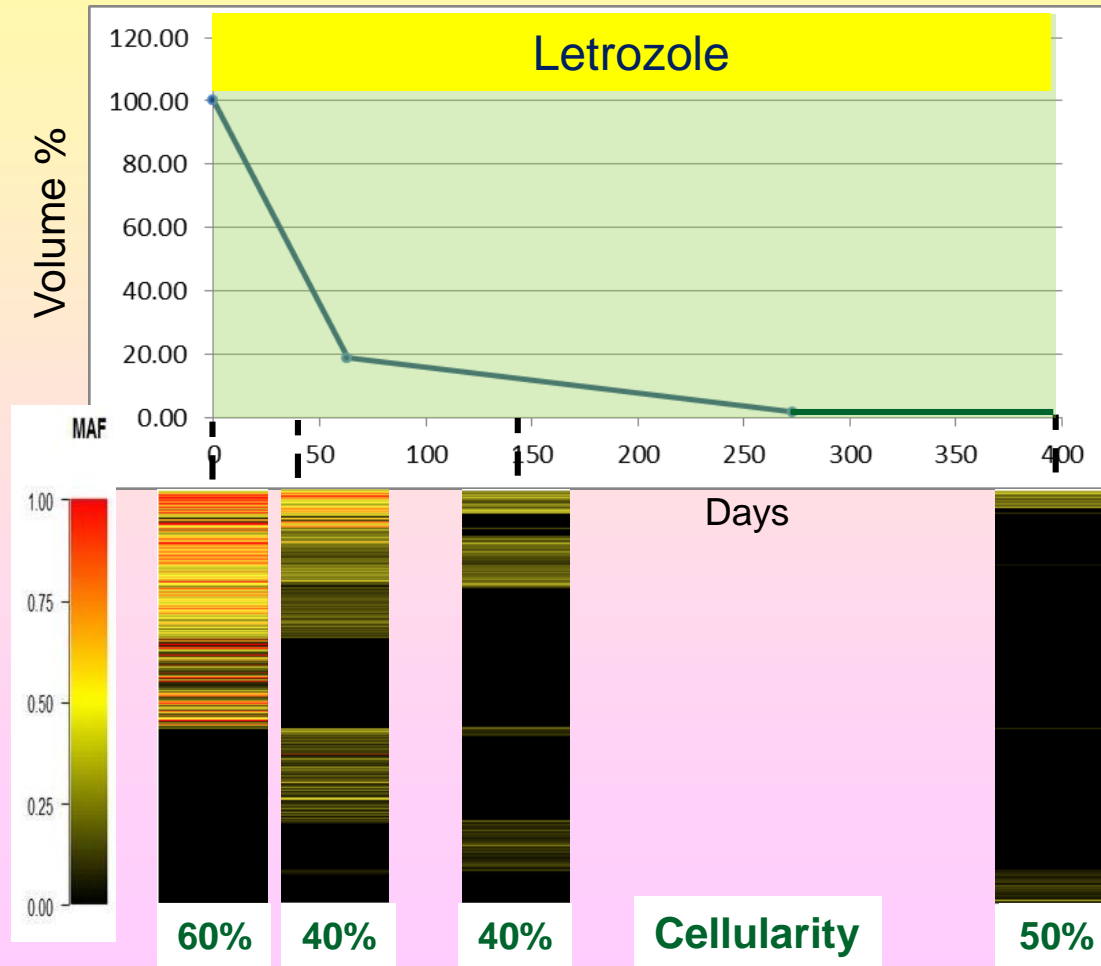
- **IL6ST antibody found no longer reliable**
- **RNA for IL6ST more accurate**
- **RNA for proliferation cassette of genes better than Ki67**
- **New results just being finalized**
- **Changes after Short period of ET predict long term outcome**

Study Of Endocrine Sensitivity, and Resistance



Responding Patient with ER Mutation

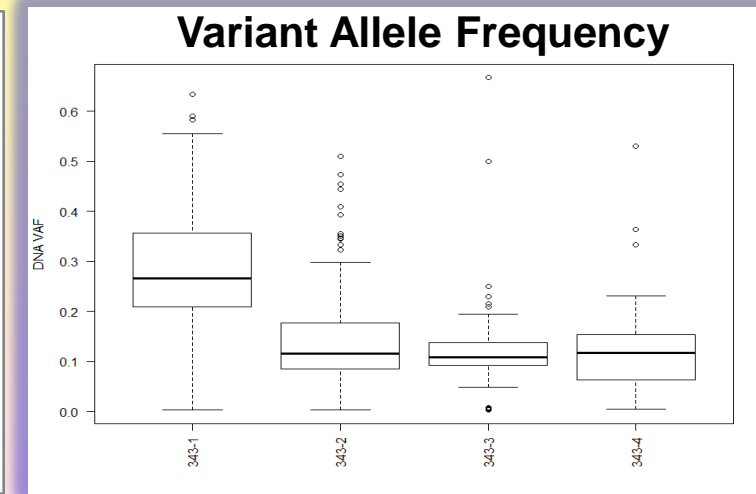
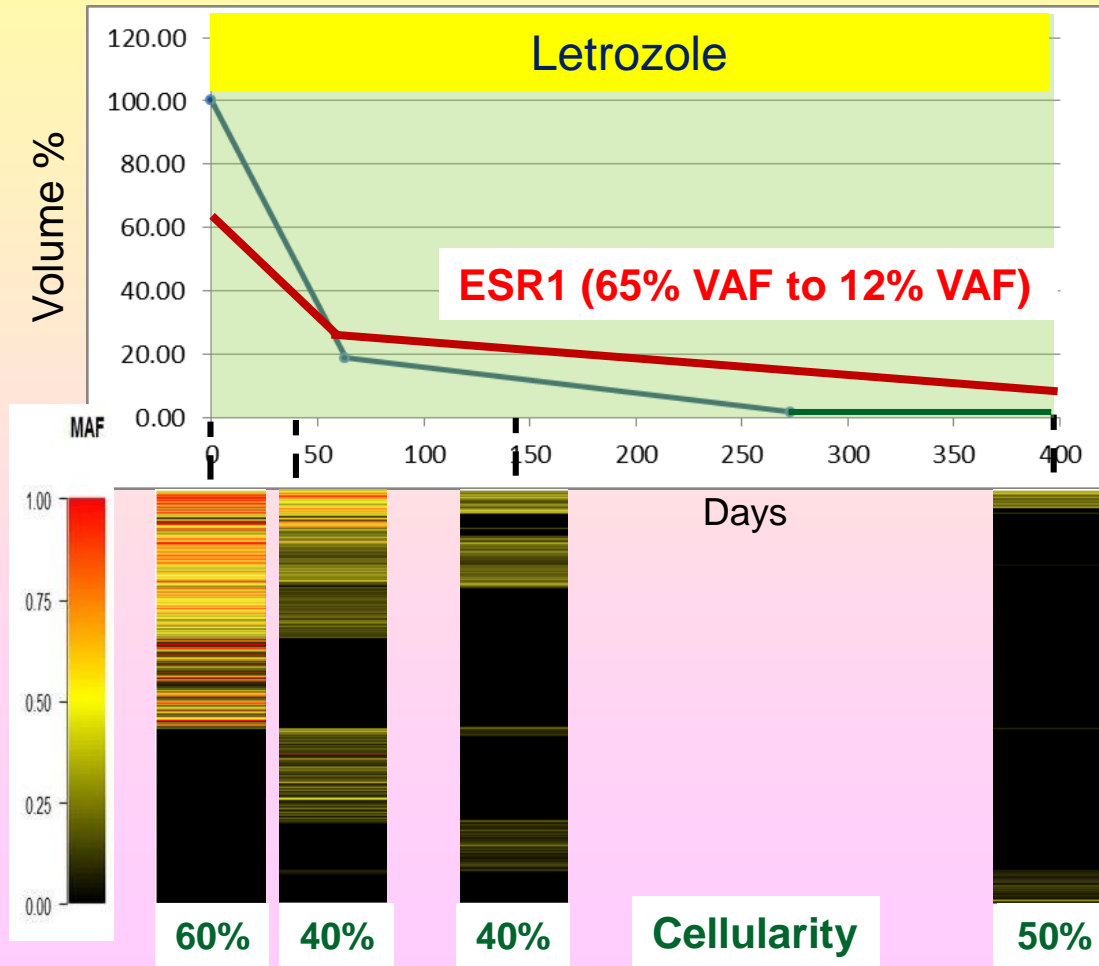
E380Q, in genomic coordinates chr 6: 152,332,832 G->C



← heatmap of somatic mutations: each row is a gene and the color indicates VAF with orange being highest VAF, yellow being moderate VAF, and black representing no variant

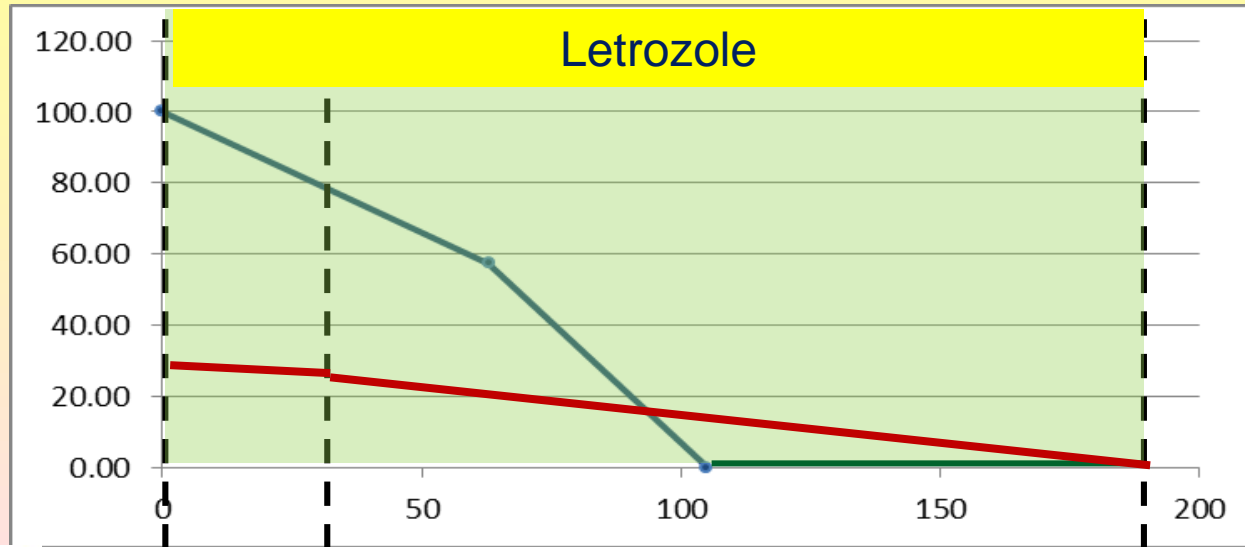
Responding Patient with ER Mutation

E380Q, in genomic coordinates chr 6: 152,332,832 G->C

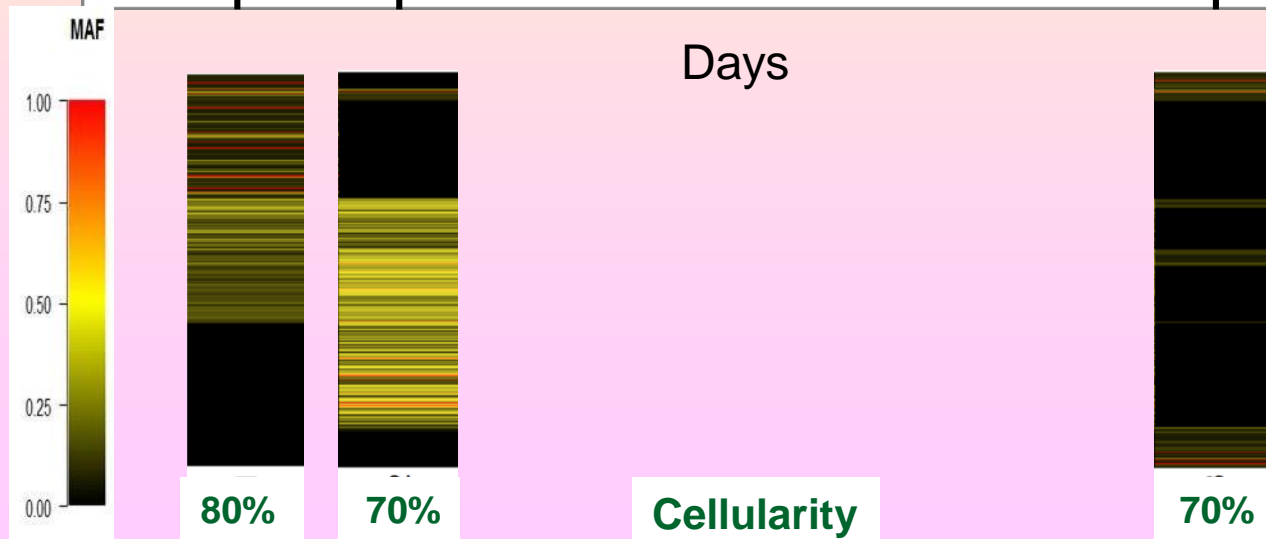


← heatmap of somatic mutations: each row is a gene and the color indicates VAF with orange being highest VAF, yellow being moderate VAF, and black representing no variant

Loss of Clone with Specific Mutation with Response

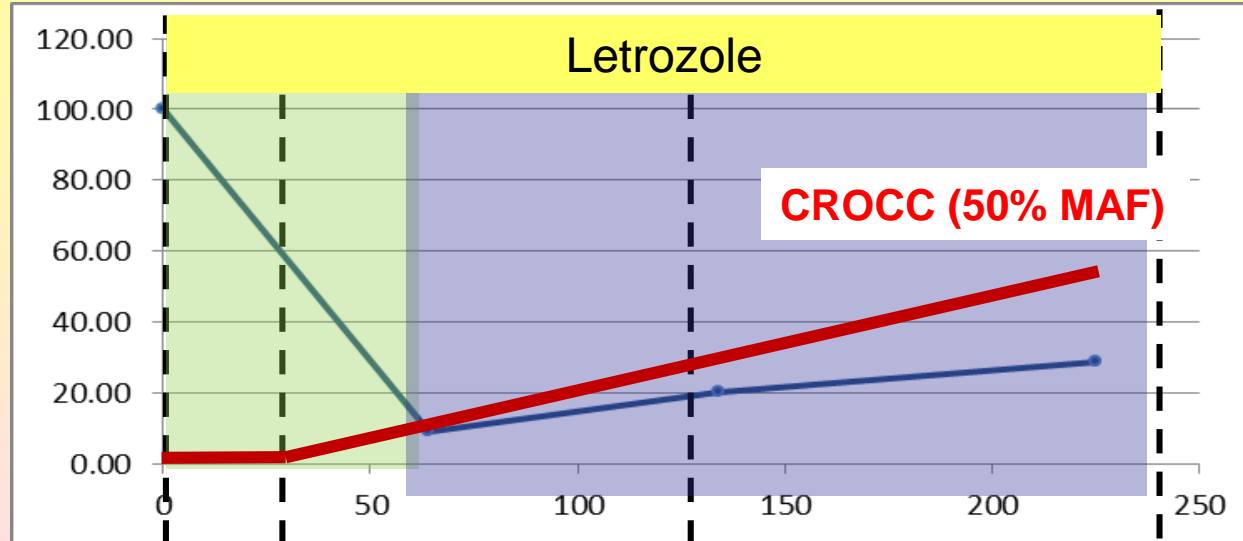


PIK3CA (24%-23%-0%)

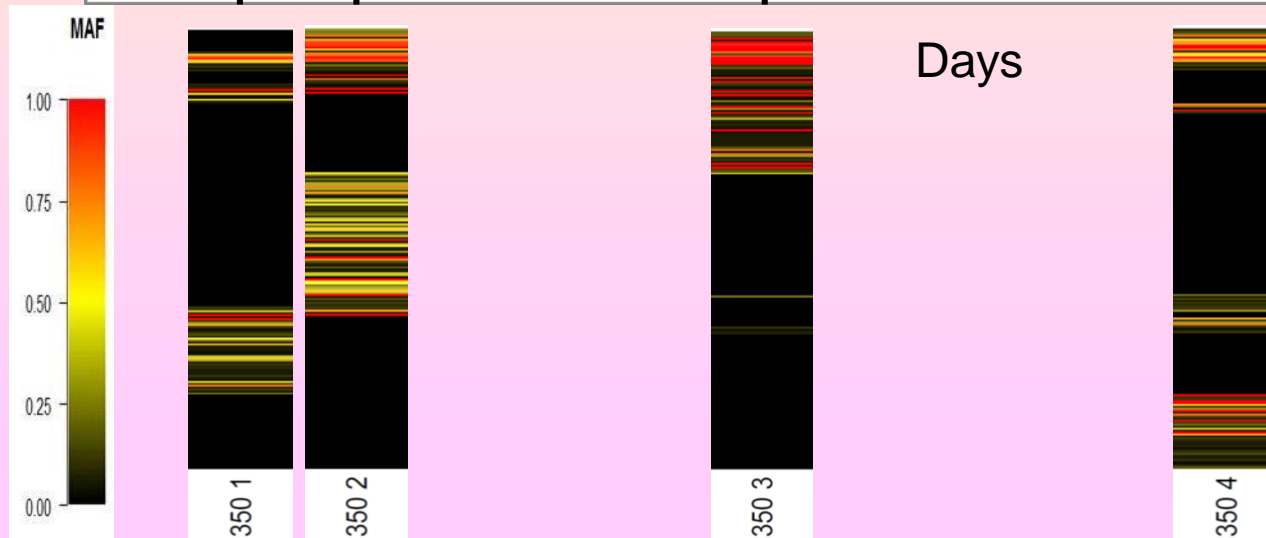


Mutations associated with Resistance

A responsive patient that eventually progresses



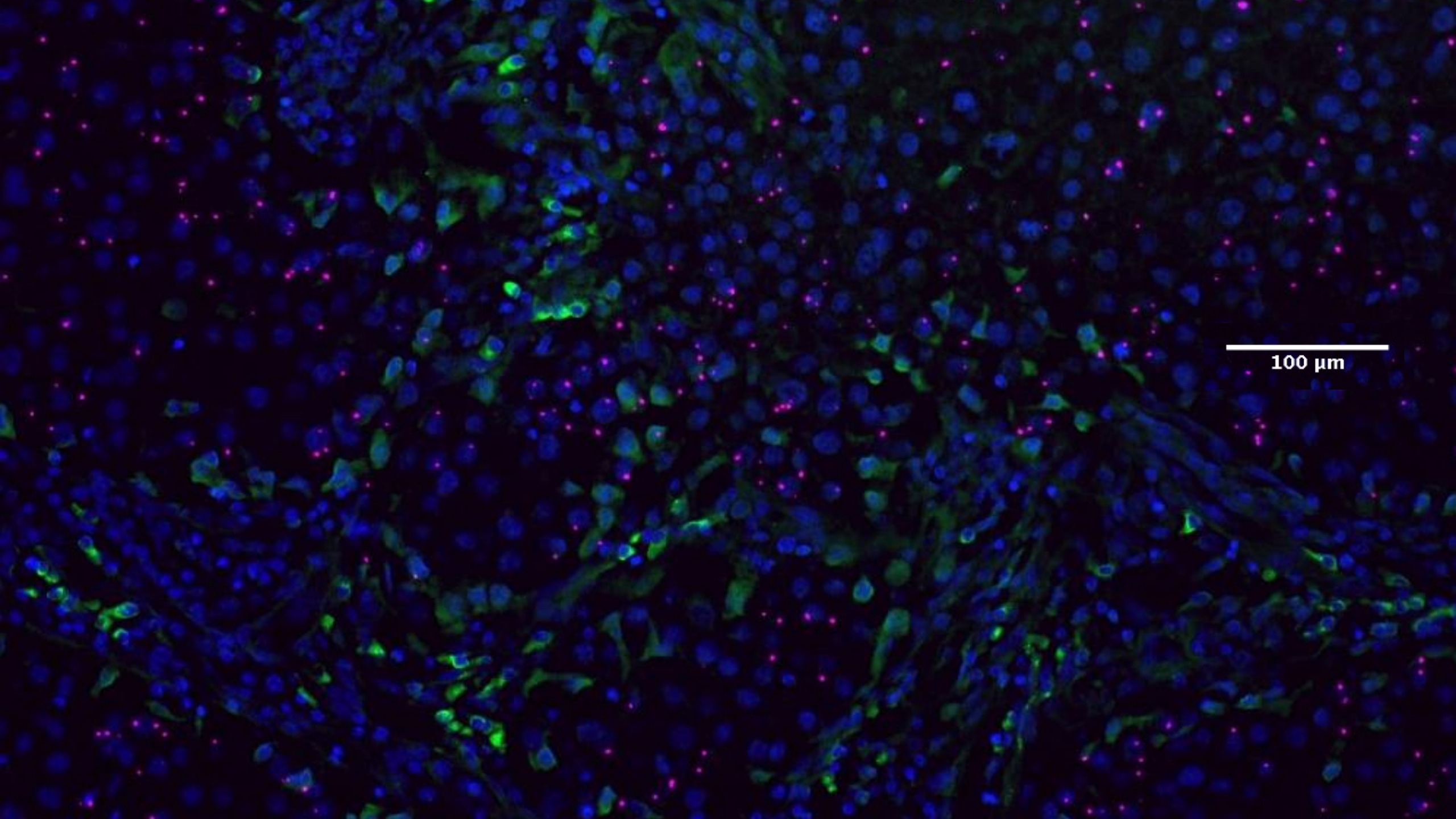
Response, then Progression



CROCC contributes to centrosome cohesion before mitosis. It was prev found to be a tumor antigen in childhood medulloblastoma

Role of ESR Mutations In Endocrine Resistance

- **6/20 with acquired resistance (25%) patients developed ESR1 mutation during Neoadjuvant treatment: 3:L, 1:A, 1:T**
 - 5 had chr6:152419926_A:G (D538G) mutation.
 - 1 novel 297-304 and 305-310 deletion – resulted in loss of ER protein
 - 4 with ESR1 mutations had increase in mutant allele frequency with 2nd line ET (2:Tamoxifen, 2:Exemestane) and further increase in 1 who had 3rd line Exemestane
- **No patients with primary endocrine resistance had ESR1 mutations**
- **Can visualise ESR mutations**



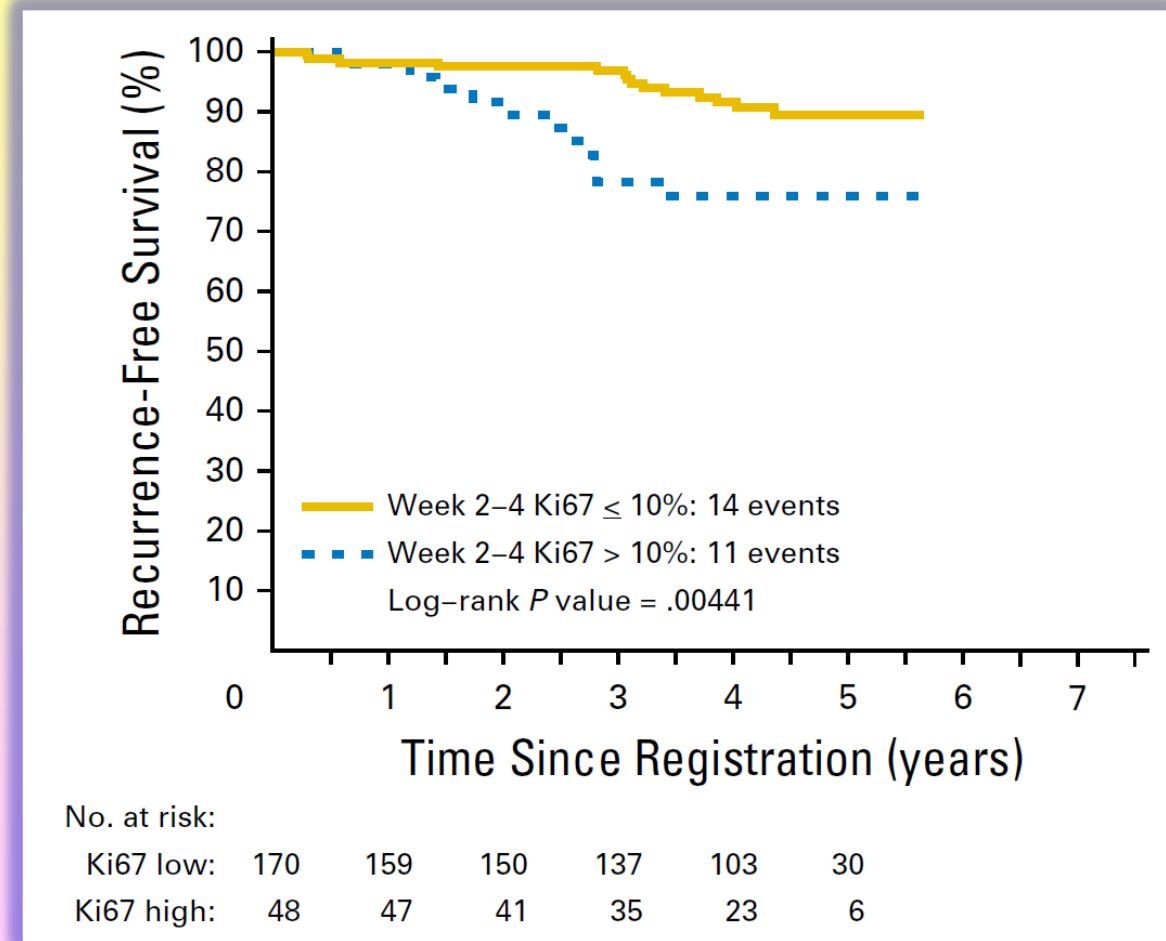
100 μm

Reason 9

If Neoadjuvant AI fails to suppress proliferation, then if you switch Neoadjuvant Chemotherapy is not effective

Z1031B Trial using Ki 67: Ellis M ... Hunt K

- 245 patients Stage II or III
- ER Allred 6-8
- Neoadjuvant AI
- If Ki 67 at 2-4 weeks >10% - NACT
- 35 pts >10% switched to NACT
- 5.7% - 2 of 35 had Path CR
- Cancers that do not respond to AI relatively chemo resistant too



Reason 10

**Can combine Neoadjuvant Endocrine therapy
with other agents such as CDK4/6 inhibitors and
PIK3CA inhibitors**

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with other agents such as CDK4/6 inhibitors and
PIK3CA inhibitors**

BUT only a few need another agent

Patient at Diagnosis



After 9 months of Letrozole + palbociclib



Conclusion

There are many reasons why to use Neoadjuvant Endocrine Therapy

I hope that I have convinced you that Neoadjuvant Endocrine Therapy benefits patients in many ways



The End