

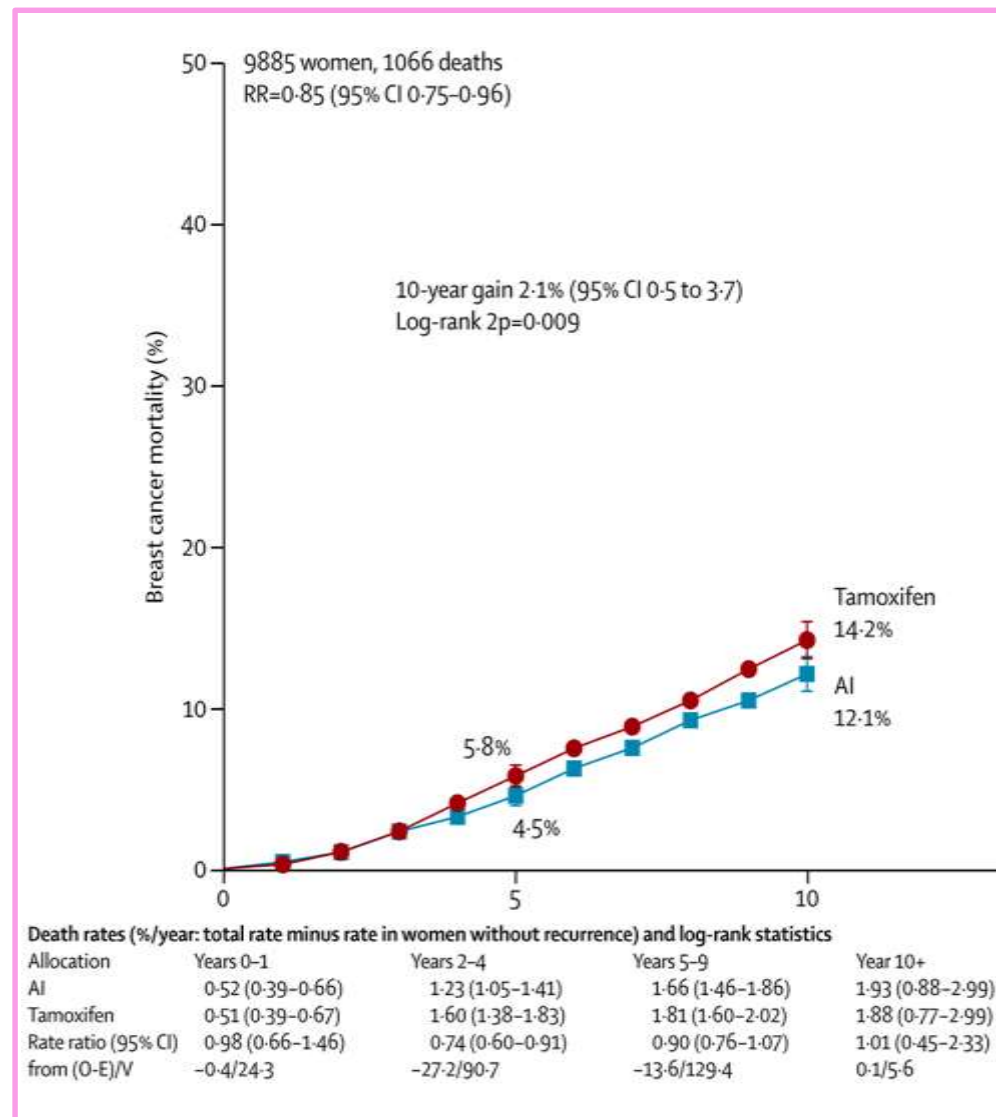
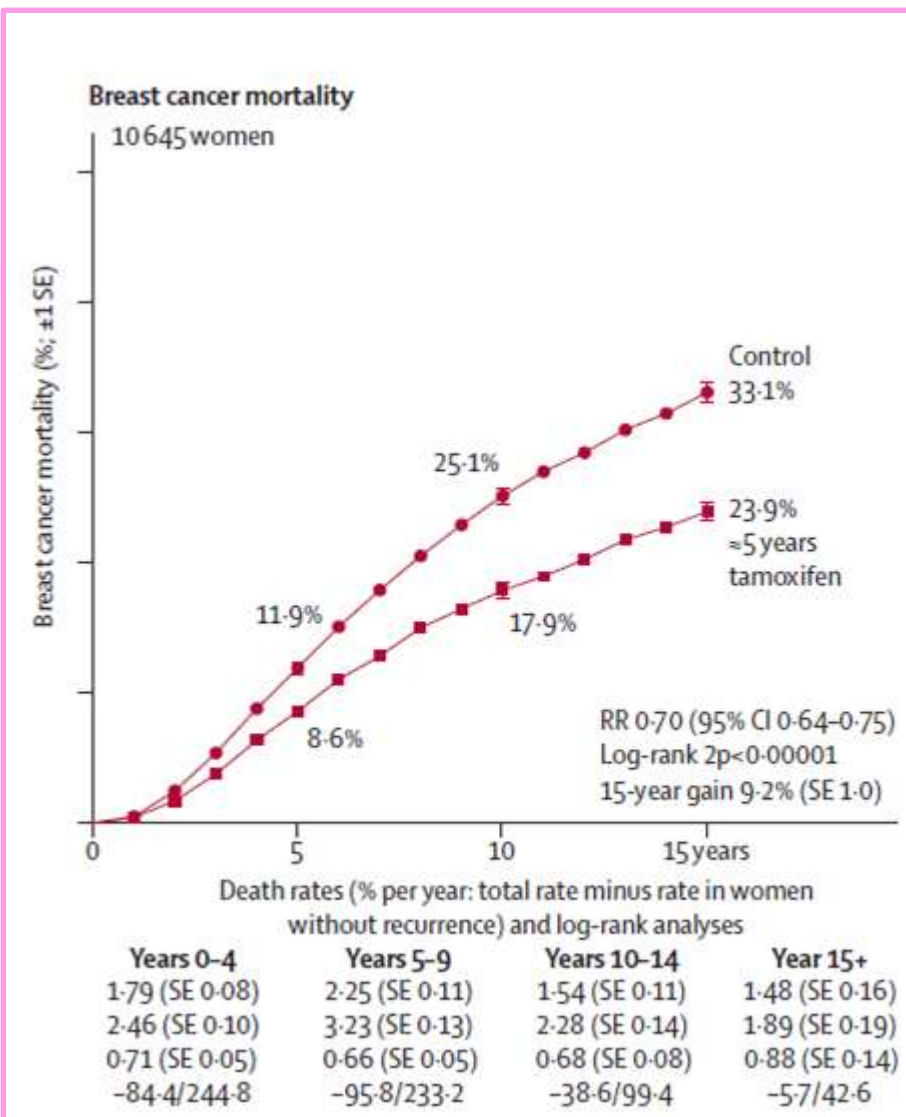


# Coagulation as a pharmacodynamic biomarker in breast cancer:

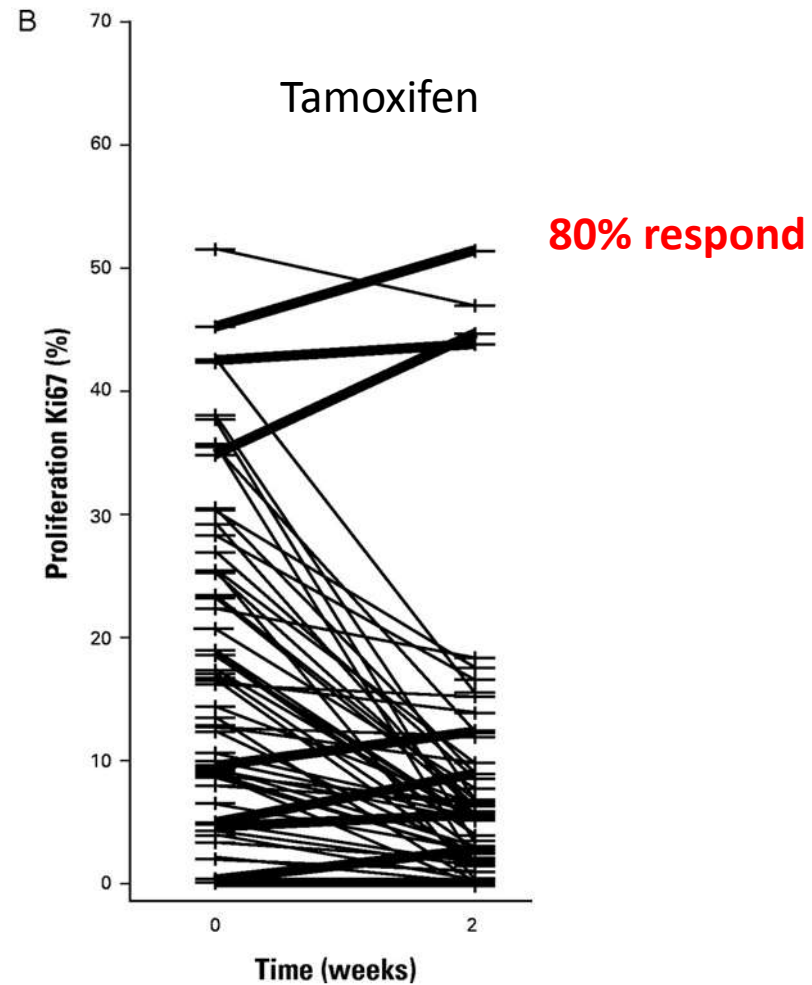
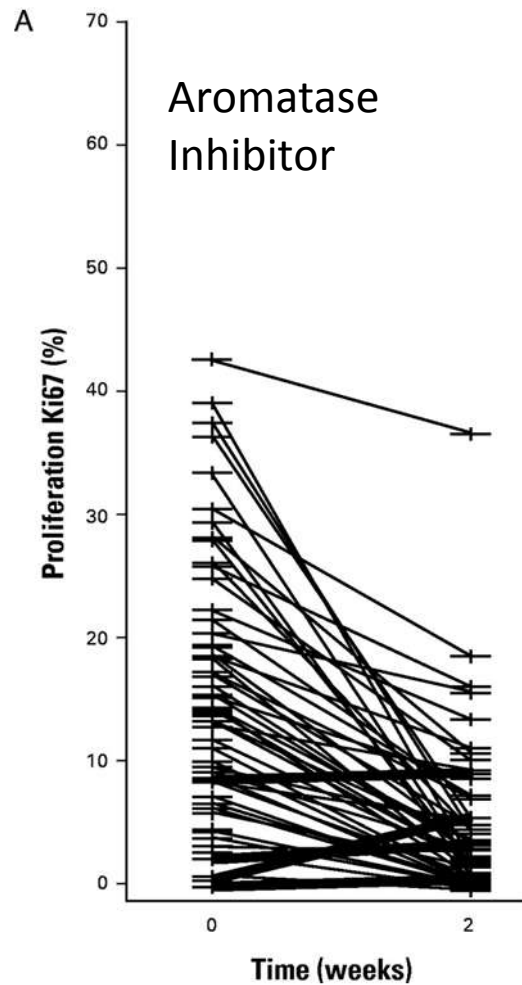
Changes in tumour expression of extrinsic clotting factors in response to breast cancer treatment.

J. Castle, S. Pritchard, M. Dowsett, N.J. Bundred, C.C. Kirwan

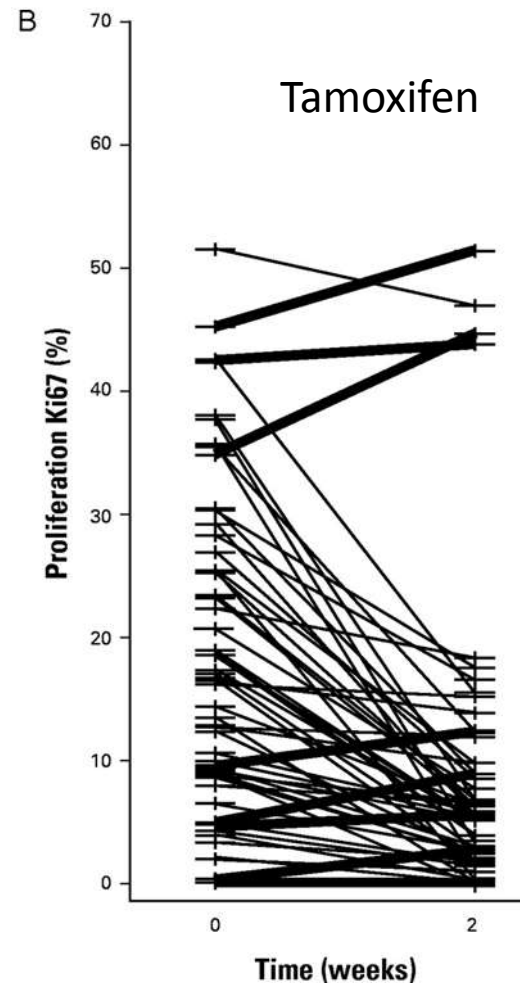
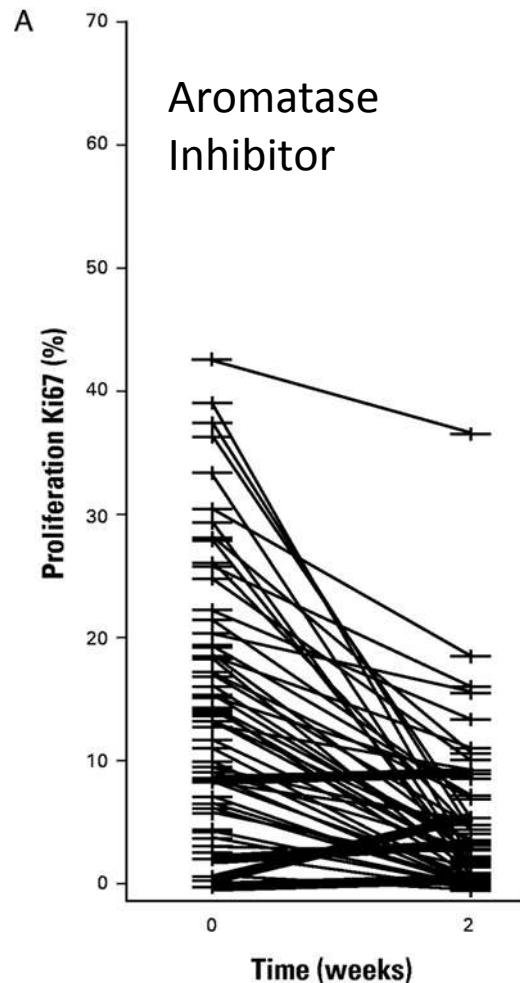
# Endocrine Therapy and Breast Cancer Mortality



# $\Delta$ Ki67 at 2 weeks mirrors survival data



# $\Delta$ Ki67 at 2 weeks mirrors survival data

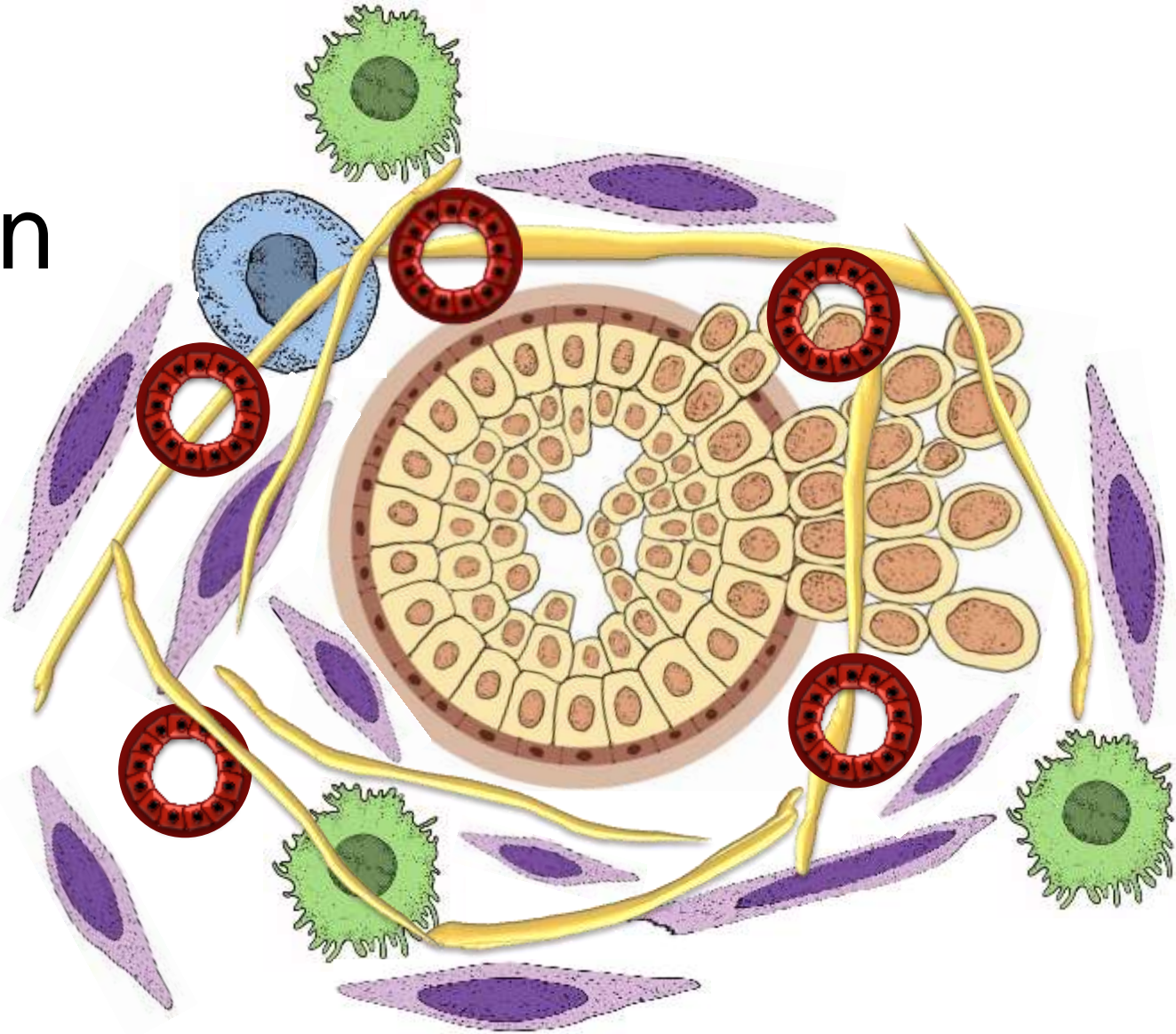


**80% respond**

**Ki67:  
pharmacodynamic  
biomarker of  
treatment response**

# Breast Cancer Development

## Invasion

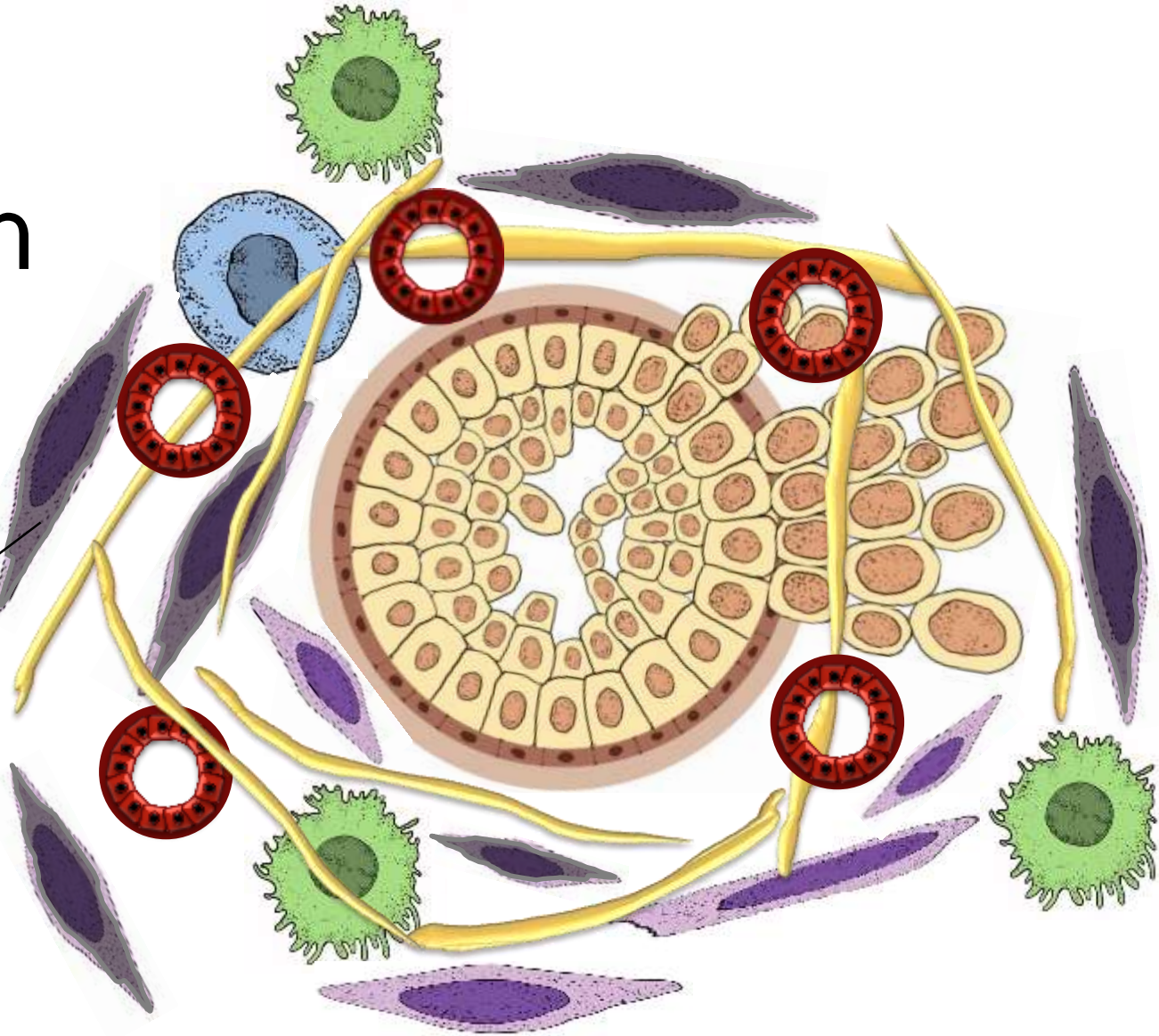




# Breast Cancer Development

## Invasion

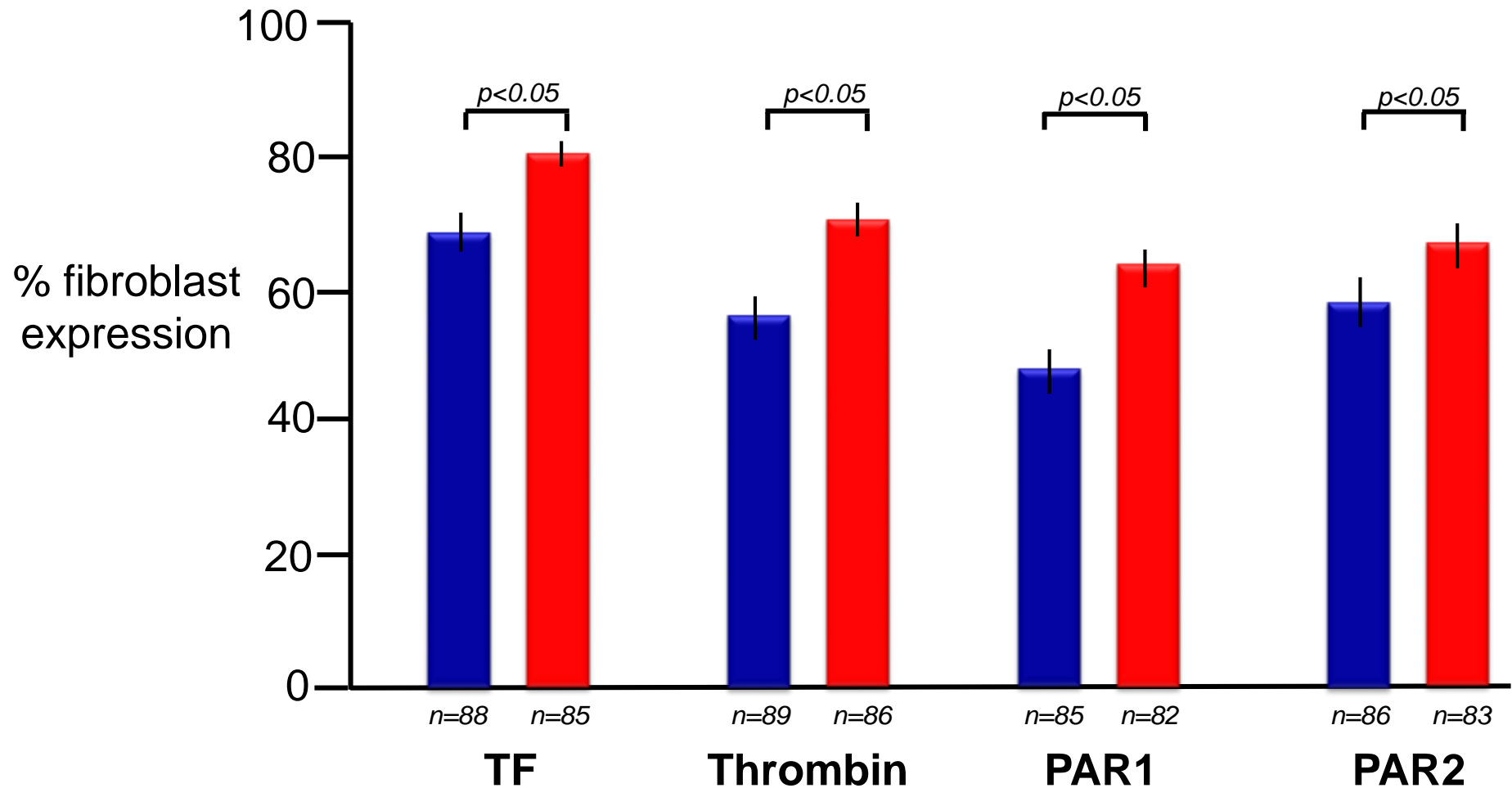
cancer associated  
fibroblasts



# Fibroblast expression of coagulation markers correlate with Ki67 in EBC

Low Ki67

High Ki67



# Aims

To identify novel biomarkers of early breast cancer response to treatment

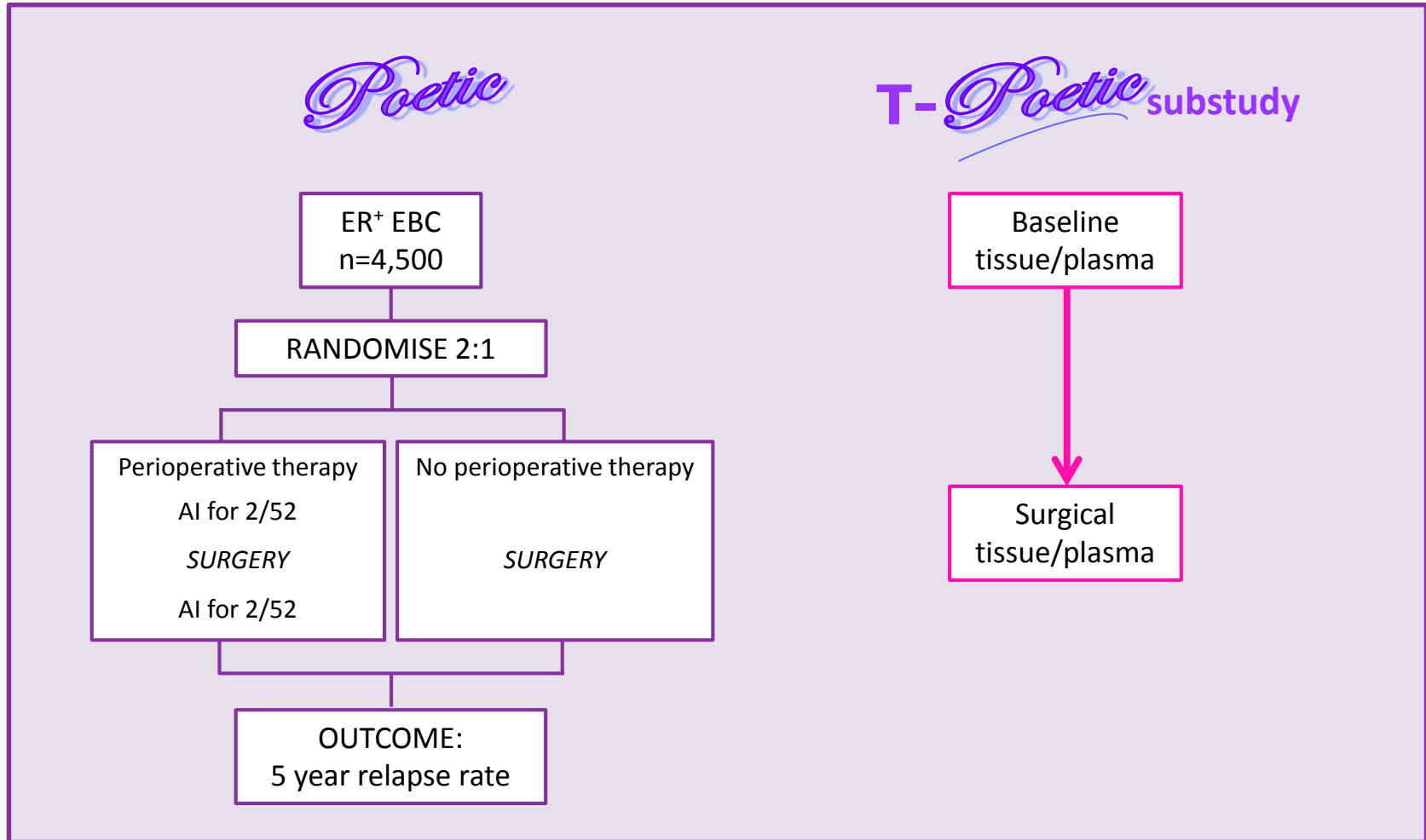
- plasma coagulation
- tumour expression of coagulation
- circulating tumour cells

## Hypothesis

Short term AI induced changes in proliferation will be mirrored by changes in cancer hypercoagulability



# Methods



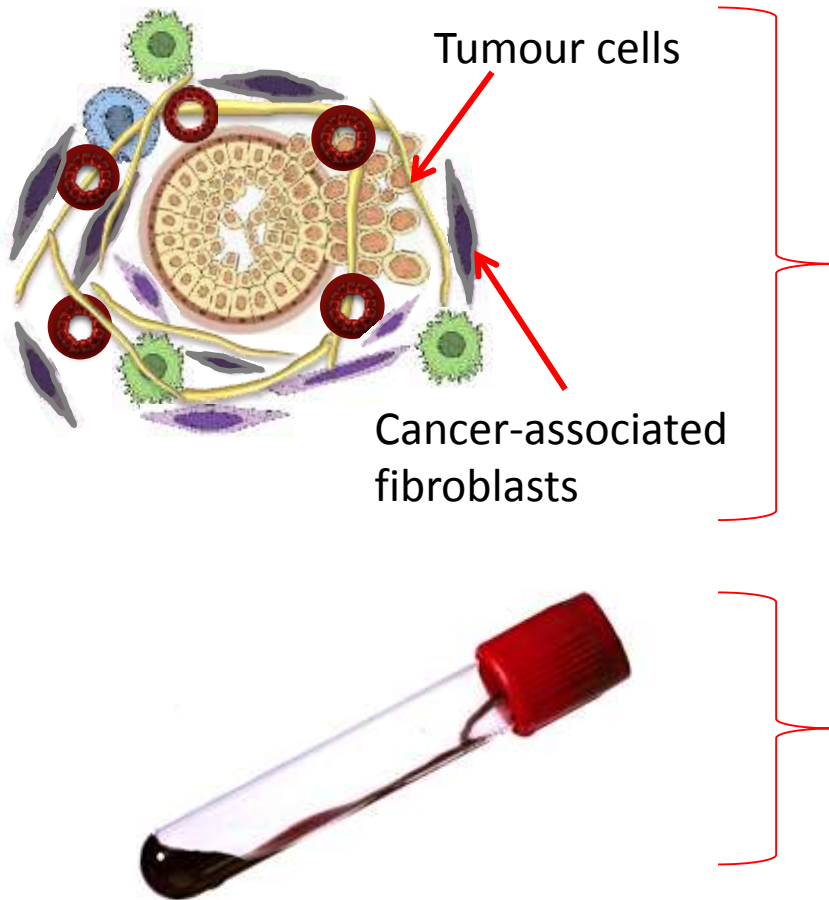
Sample size: AI, n=75; no AI (control) n=40

Presuming 80% response rate (reduction in Ki67) and 33% drop-out rate (i.e. insufficient tissue/non-compliance).

Allows comparison of 10 non-responders versus 40 responders versus 25 controls.

# T-Poetic Methods

## Aromatase Inhibitor vs control



### Baseline

TF  
Thrombin  
PAR1  
PAR2

### Surgery

TF  
Thrombin  
PAR1  
PAR2

### 2/52 post op

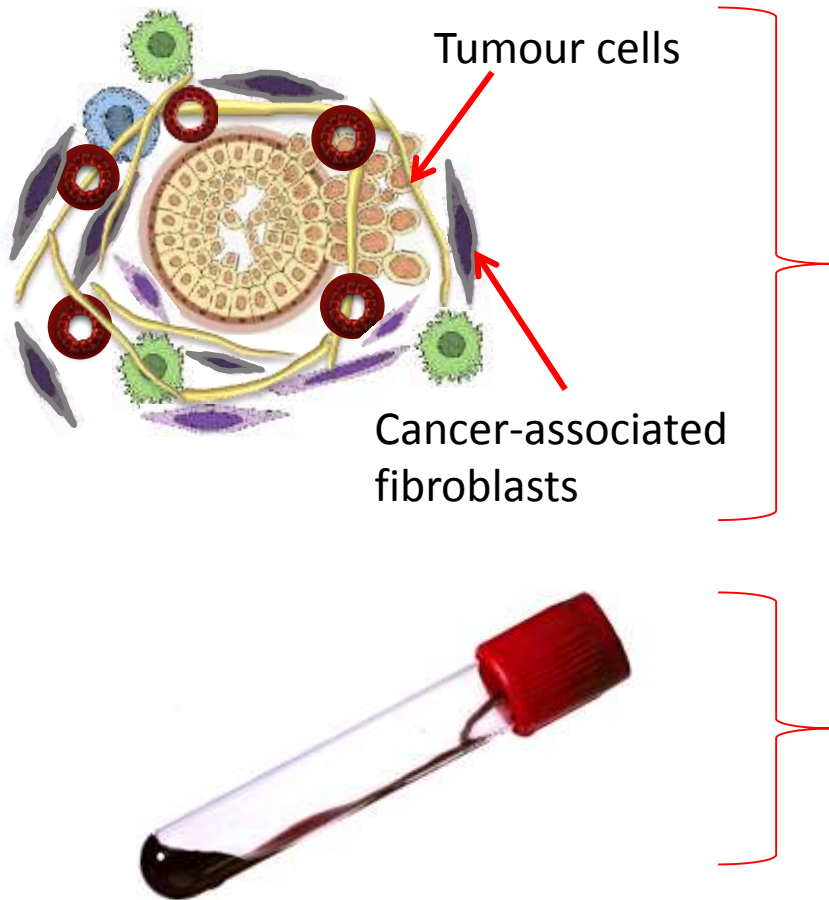
TF  
Thrombin-  
antithrombin  
D-dimer  
CTCs

TF  
Thrombin-  
antithrombin  
D-dimer  
CTCs

TF  
Thrombin-  
antithrombin  
D-dimer  
CTCs

# T-Poetic Methods

## AI responders vs AI resistant



### Baseline

TF  
Thrombin  
PAR1  
PAR2

TF  
Thrombin-  
antithrombin  
D-dimer  
CTCs

### Surgery

TF  
Thrombin  
PAR1  
PAR2

TF  
Thrombin-  
antithrombin  
D-dimer  
CTCs

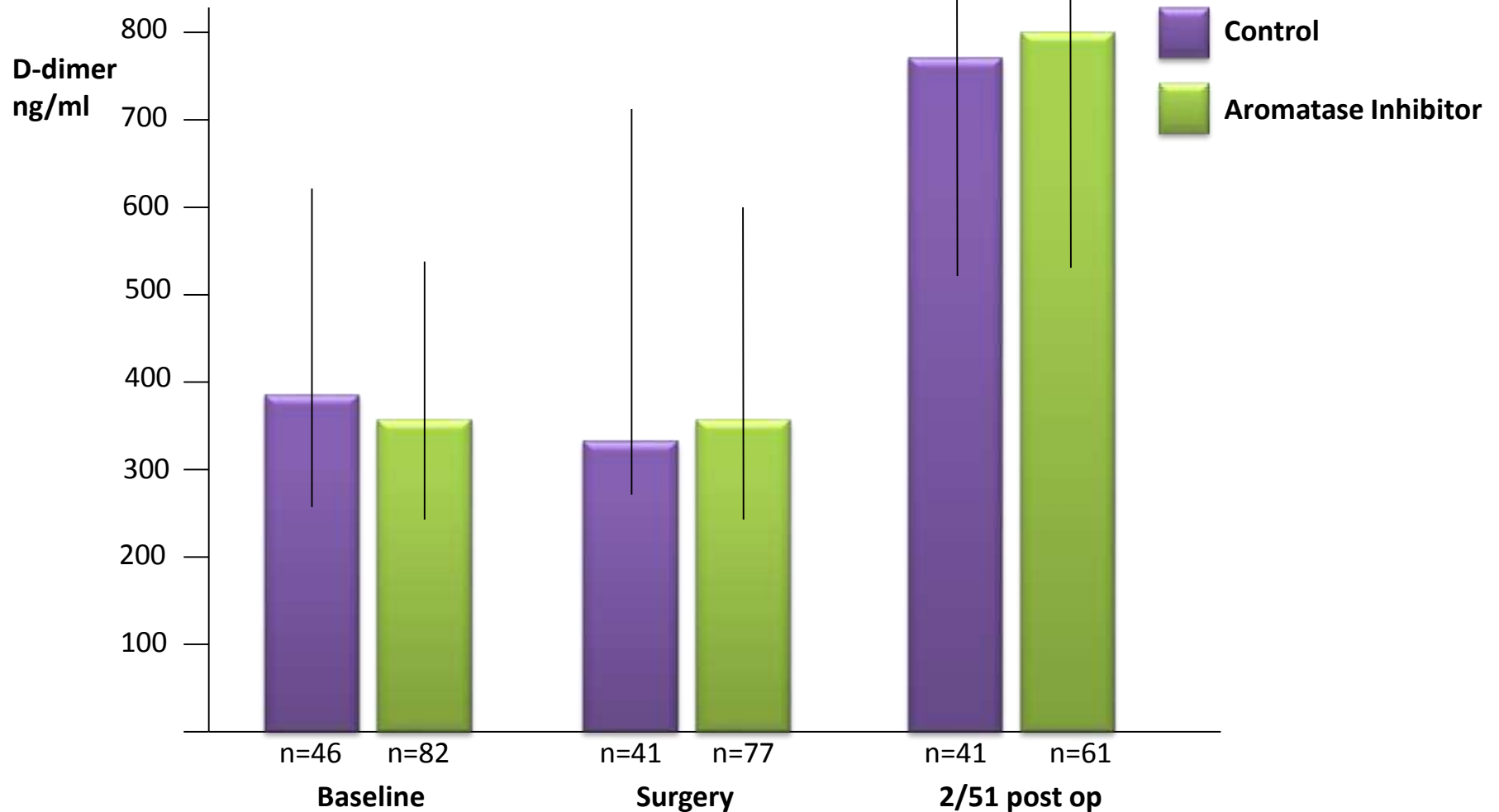
### 2/52 post op

TF  
Thrombin-  
antithrombin  
D-dimer  
CTCs

# Demographics

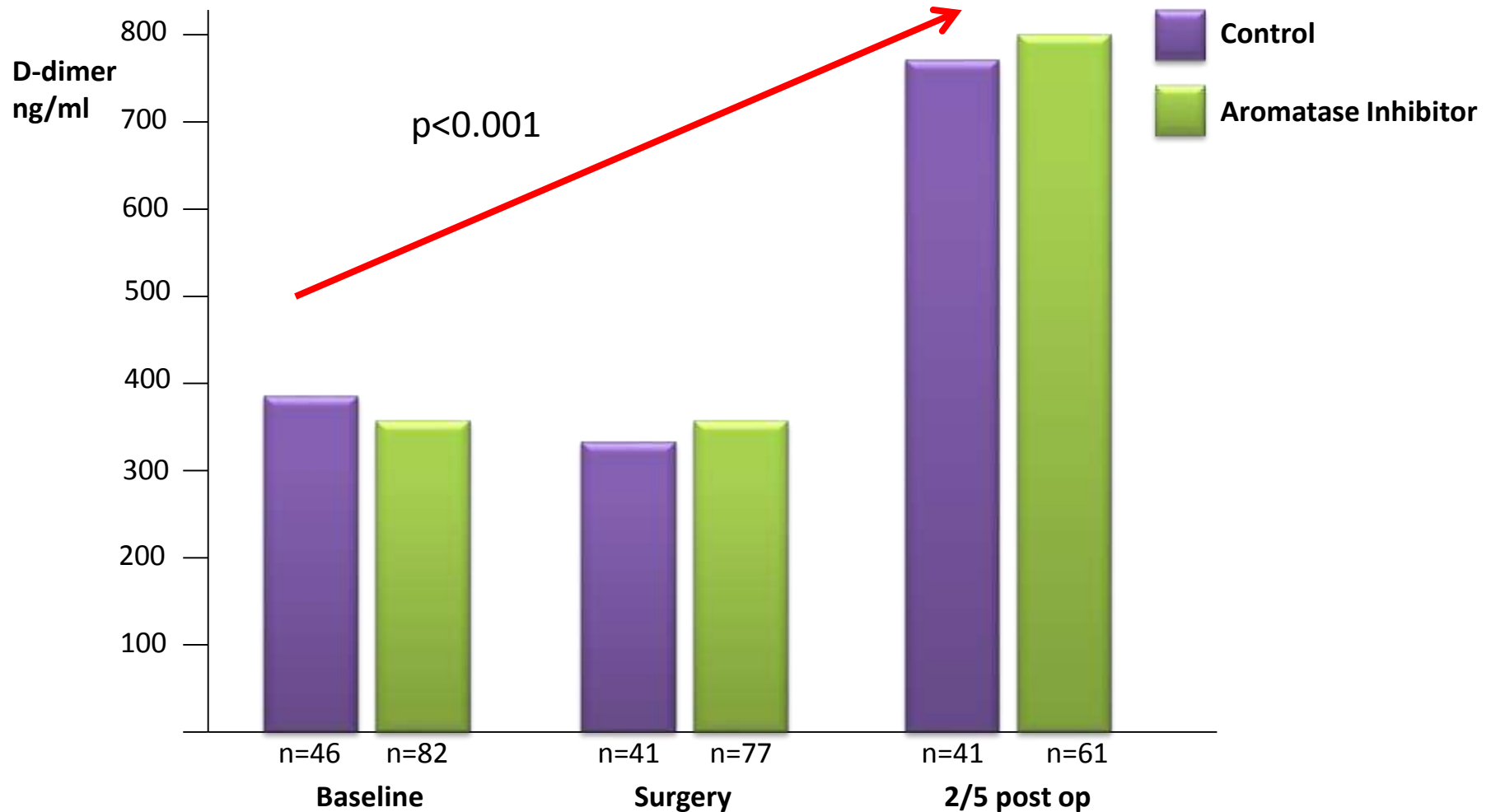
	AI n=86	Control n=46
Age (mean)	66	64
BMI (mean)	28.3	27.4
Tumour size (mean)	25.4mm	26.3mm
Grade 1:2:3 (%)	20:70:10	11:63:26
node positive	36%	26%
Her2 positive	6%	7%

# Perioperative D-Dimer and AI

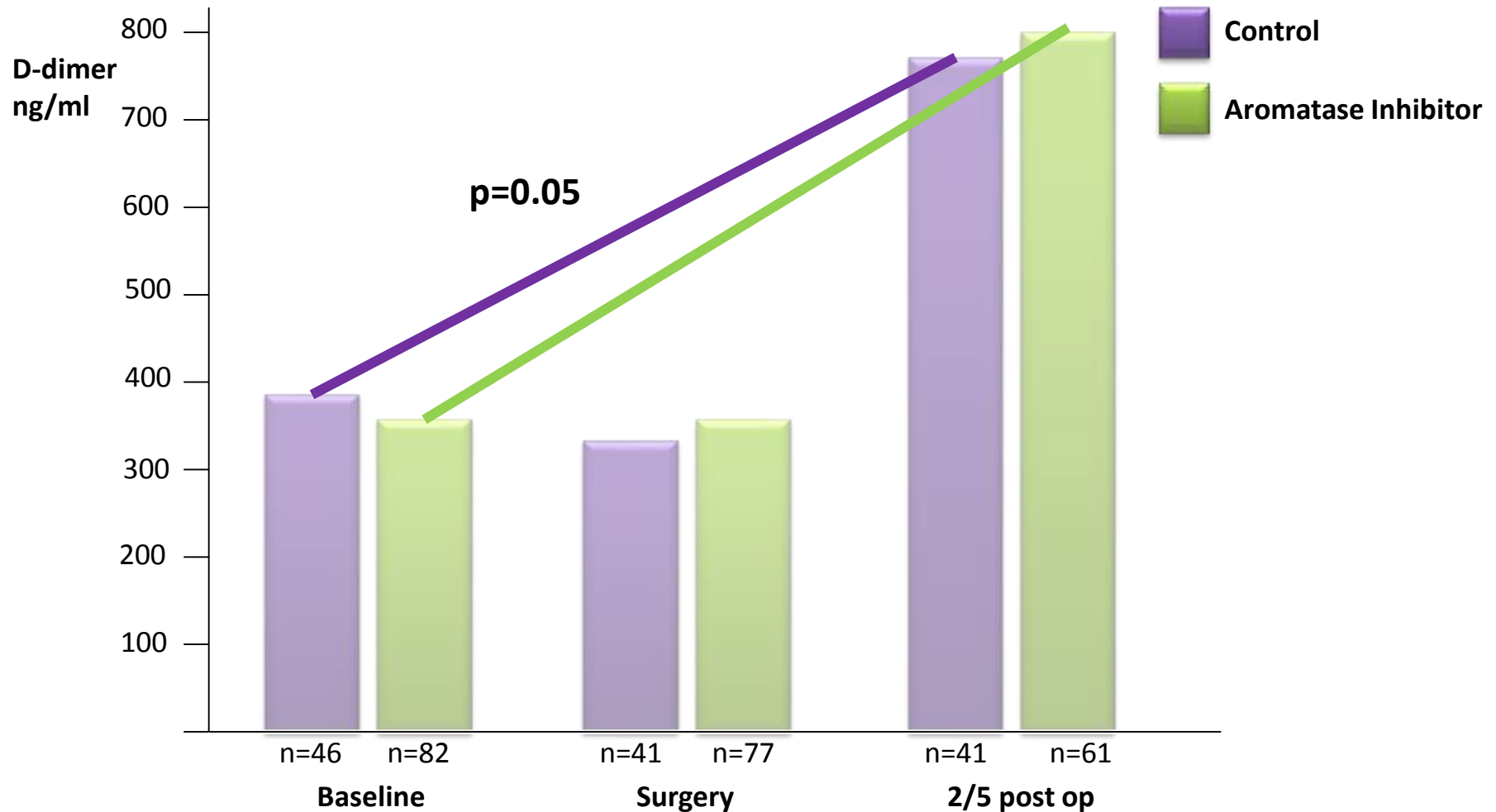




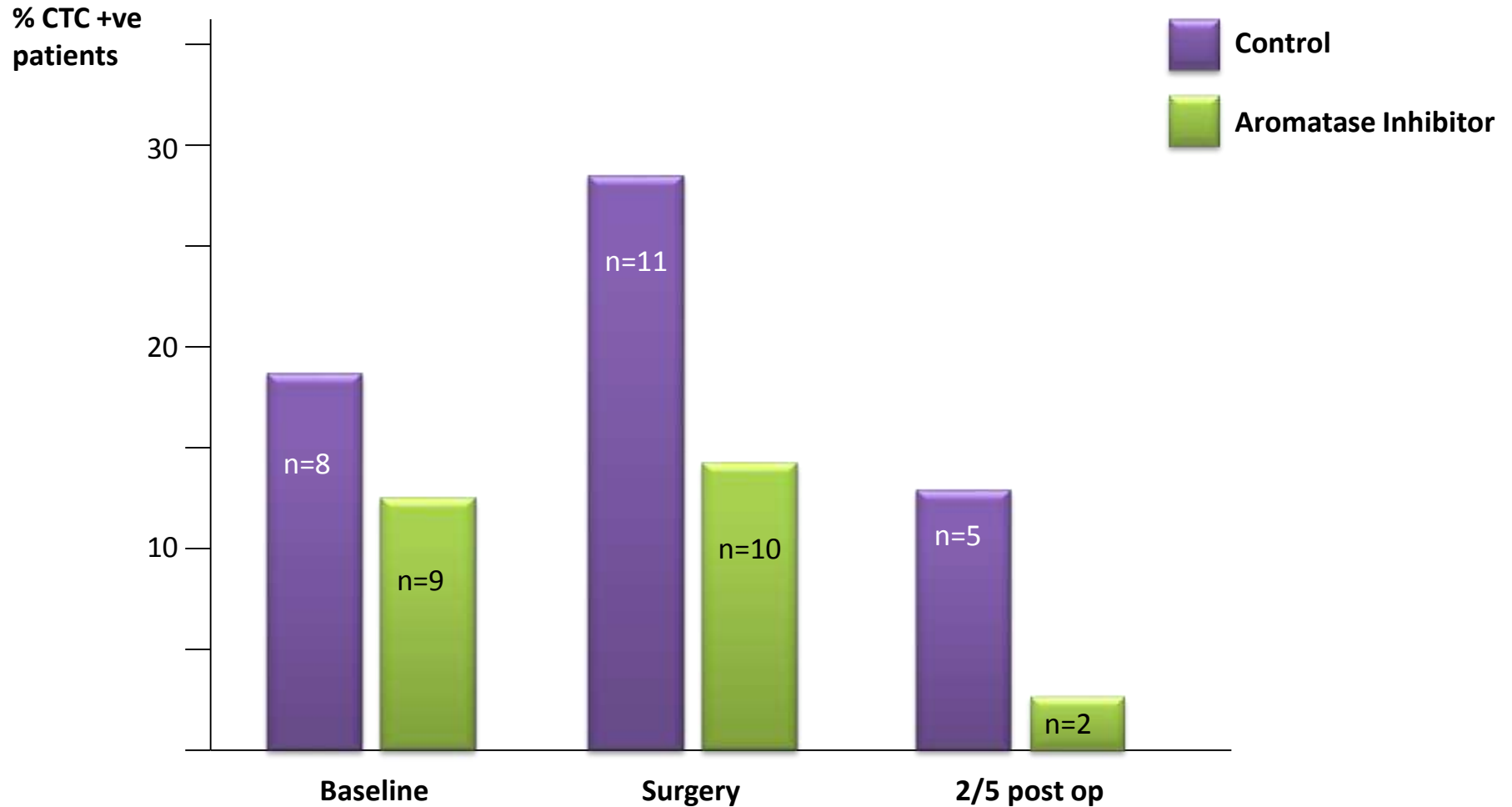
# Perioperative D-Dimer and AI



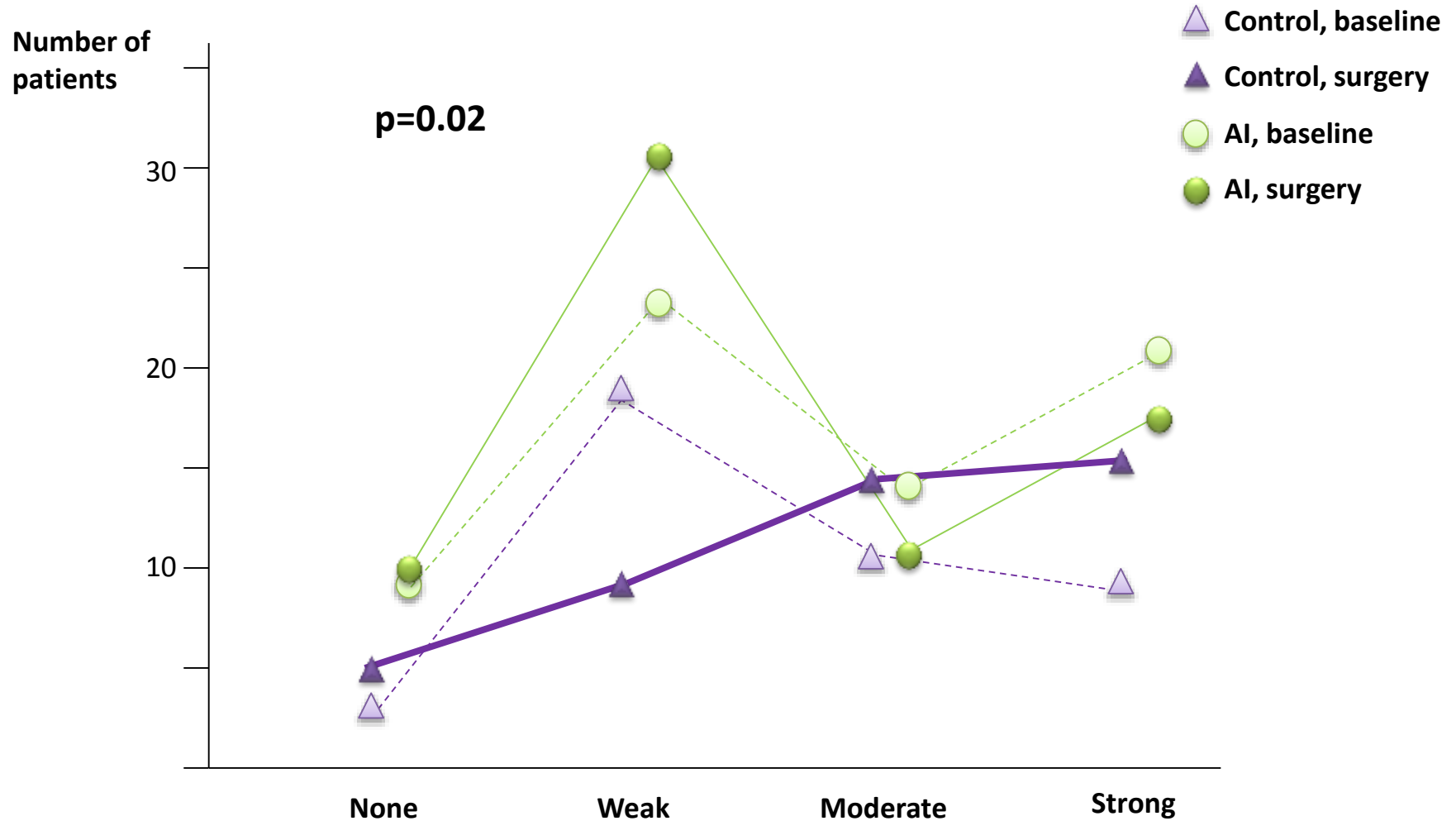
# Perioperative D-Dimer and AI



# Perioperative Circulating Tumour Cell Enumeration



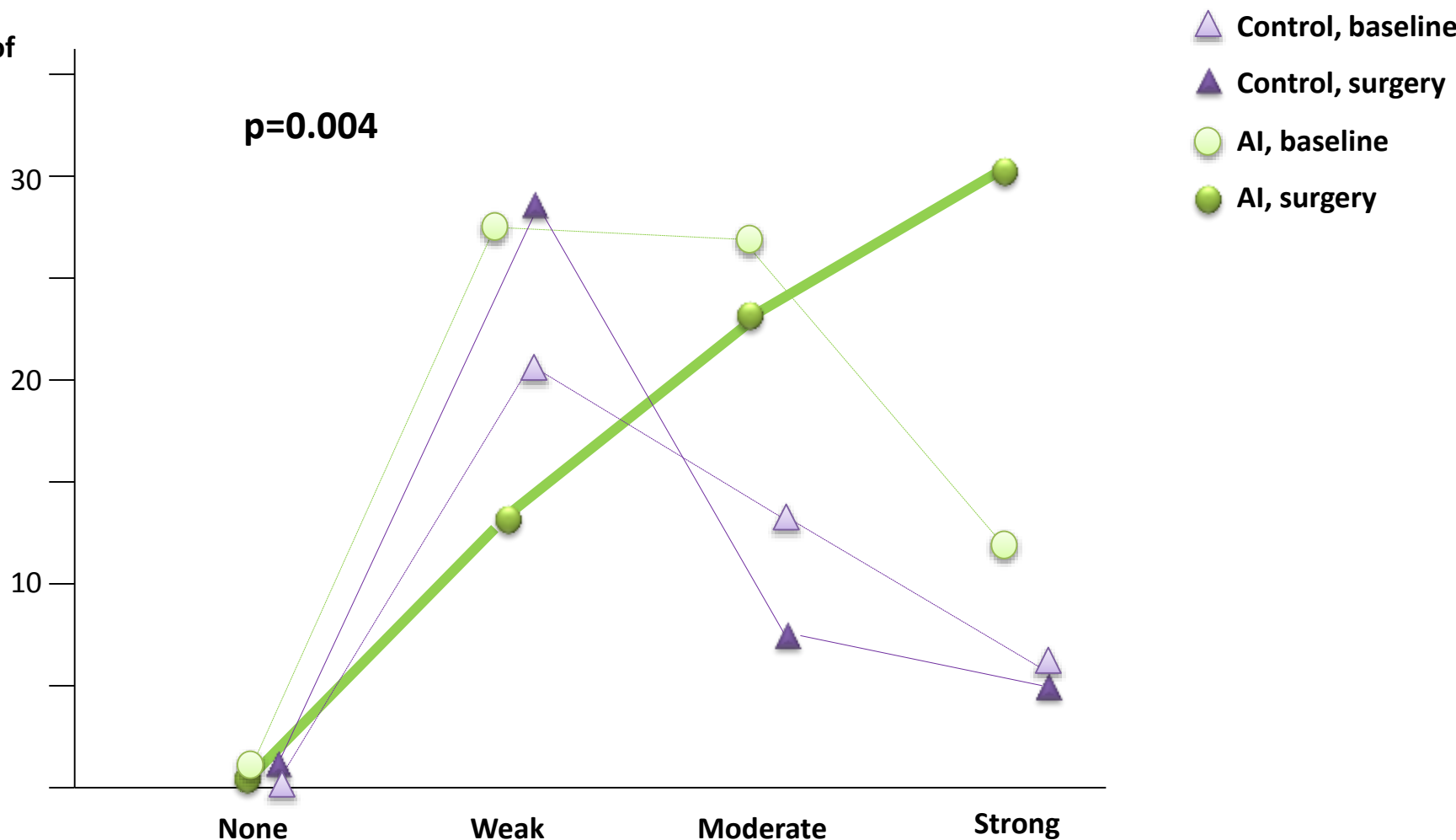
# Change in Tumour TF expression



# Change in Tumour Thrombin expression

Number of patients

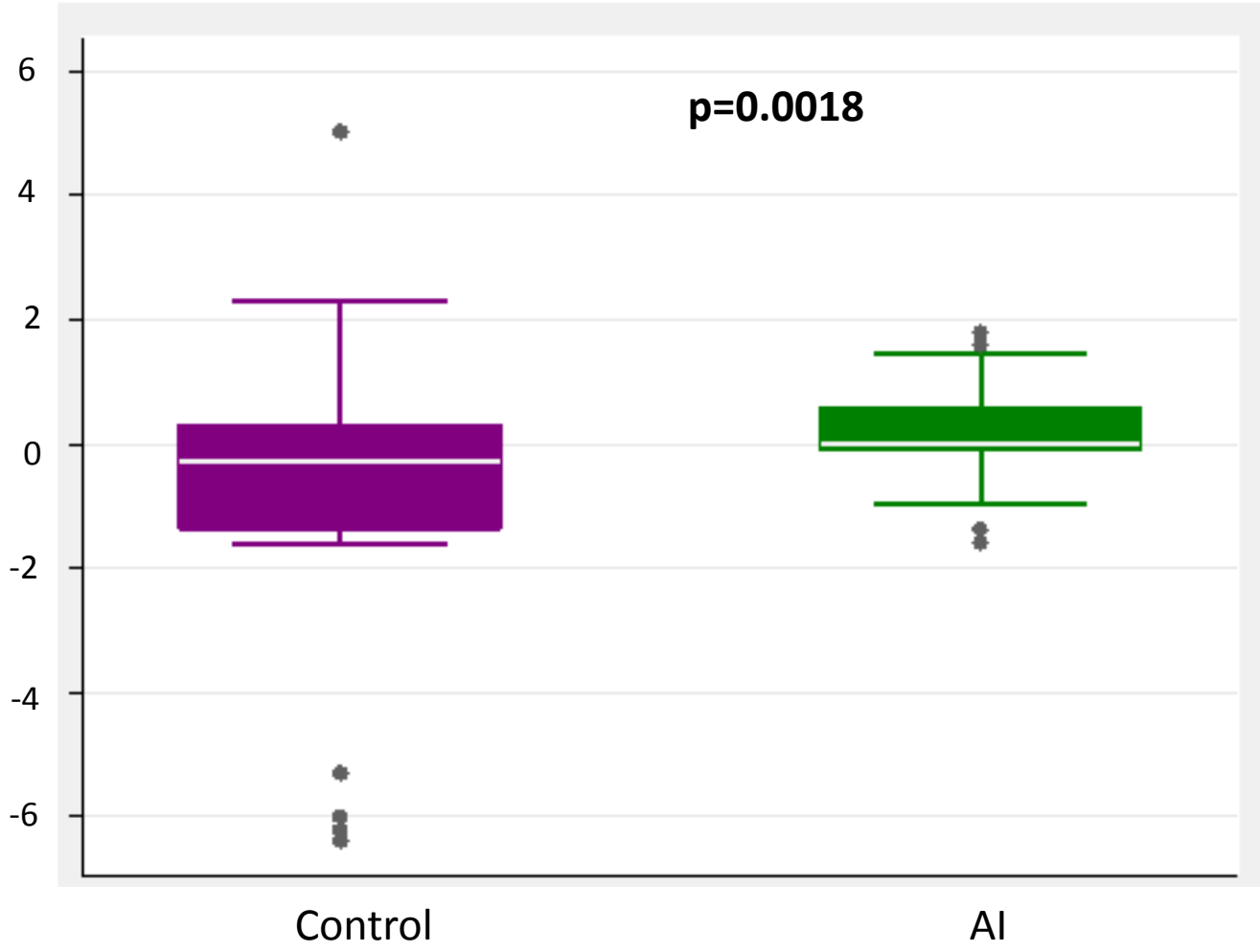
$p=0.004$





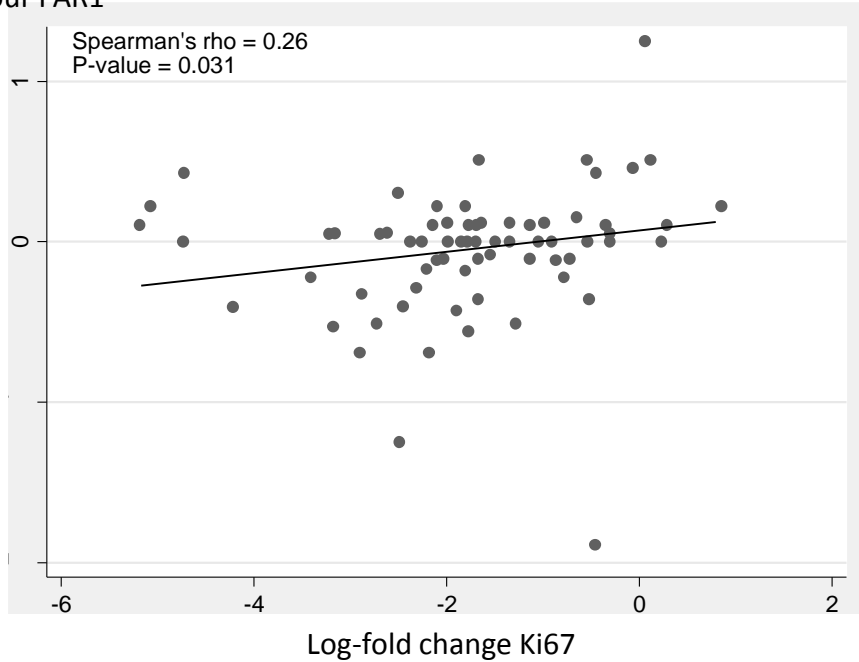
# Change in peri-tumour fibroblast thrombin expression

Log-fold change  
in % tumour  
fibroblast  
thrombin  
expression

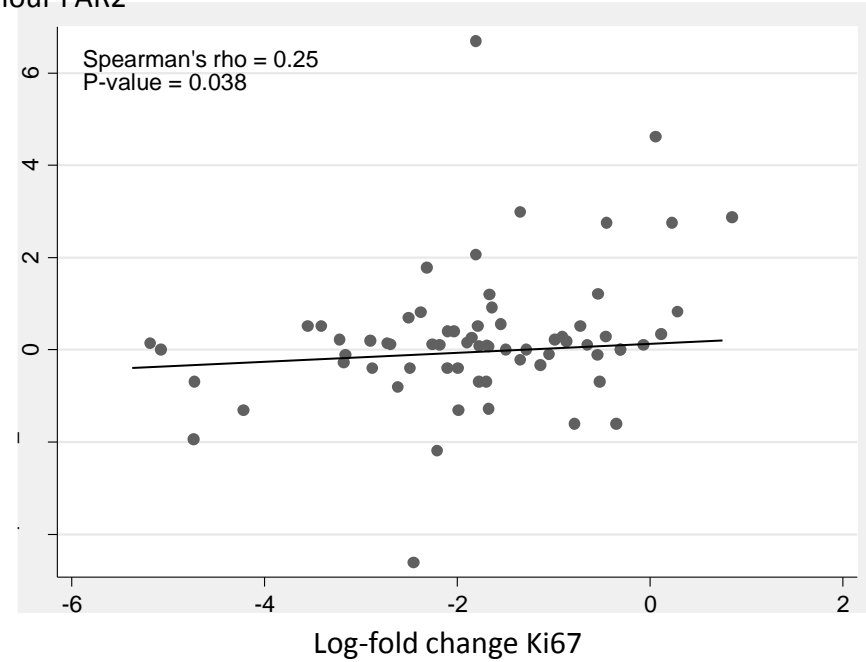


# Tumour procoagulant expression and response to AI

Log-fold change  
tumour PAR1



Log-fold change  
tumour PAR2



# Conclusion

In patients receiving Als:

- increased hypercoagulable response to surgery
- possible reduction in residual CTC load
- increased tumour thrombin expression
- increased fibroblast thrombin expression

Tumour PAR 1 and 2 are possible biomarkers of response to AI