Detection of disease change using a biological marker and clinical application: CA125 in ovarian cancer patients

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Background

- New anti-cancer drugs have to show tumour shrinkage in phase I/II trials before preceding a phase III trial
- Fail to identify new drugs that produce disease stabilisation (cytostatic) rather than tumour shrinkage (cytotoxic)
- New approaches required to effectively and efficiently identify new cytostatic drugs
- A potential method would be to measure the tumour growth rate in individual patients, tumour growth would be slower after staring on an active drug
  - Frequent cross-sectional imaging
  - Monitoring a patient's tumour without giving therapy, purely to measure its growth rate

Asymptomatic ovarian cancer patients

- It is preferable to delay chemotherapy until symptoms developed
- Patients are regularly monitored using the blood serum biomarker CA125
  - Rising CA125 is highly correlated with disease progression
  - CA125 could be measured frequently
- The proposed approach could be applied to asymptomatic ovarian cancer patients with their disease monitored using CA125 assessment

CA125 doubling trial

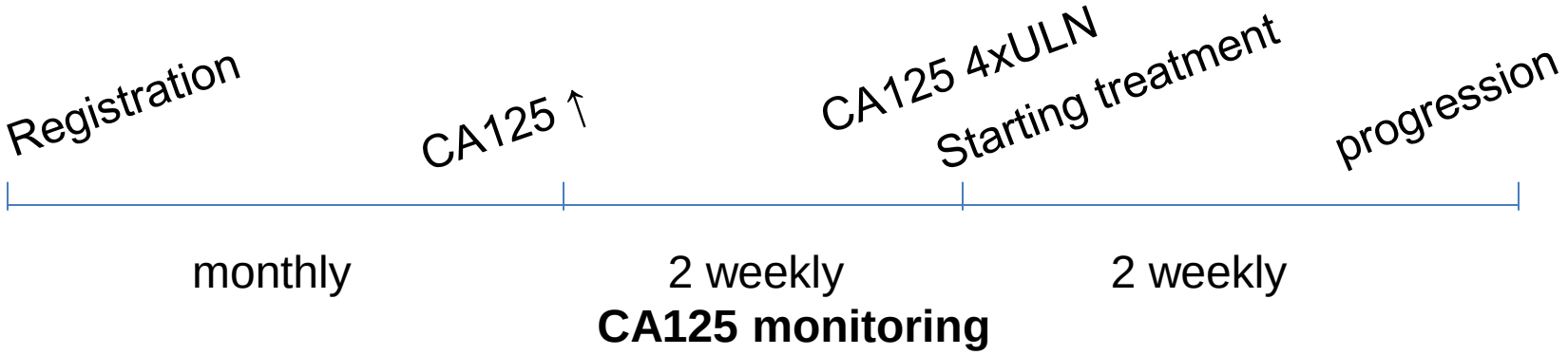
Hypothesis

In asymptomatic ovarian cancer patients there would be sufficient time to compare the rate of rise of CA125 before and after starting treatment with a novel agent

- rate of rise of CA125: log linear trend (slope)
  - Sufficient time: at least 3 measures of CA125 level before and after starting treatment
- difference or reduction

Design of CA125 doubling trial

- Eligible asymptomatic ovarian cancer patients registered centrally
- CA125 measured monthly, then 2 weekly after rising until end of treatment
- treatment started when CA125 > 4xULN



Design of CA125 doubling trial

- tamoxifen as the first test agent
  - minimal toxicity compared to chemotherapy
  - proven activity and often offered to such patients
- Sample size
  - % of patients with log linear CA125 level over time

  200 patients provide an estimate with a se <3.5%
  - Change of rate of rise CA125 level

  No a priori power model, similar latent growth models with moderate effect size (0.3) have power over 85% with 150 and 90% with 200 patients

  Targeted sample size of 200-250 patients was planned

Slope analyses

- Rate of rise of CA125 is measured by the slope, S, of the linear regression of ln(CA125) over days
- Each patient's rate of rise of CA125 pre-tamoxifen, S_{pre}, compared with her own rate in CA125 after starting tamoxifen, S_{on}
- S_{pre} and S_{on} estimated using the 3 CA125 measurements just before and after starting tamoxifen
- Mean (S_{pre}- S_{on}) = the magnitude of change in rate of rise of CA125

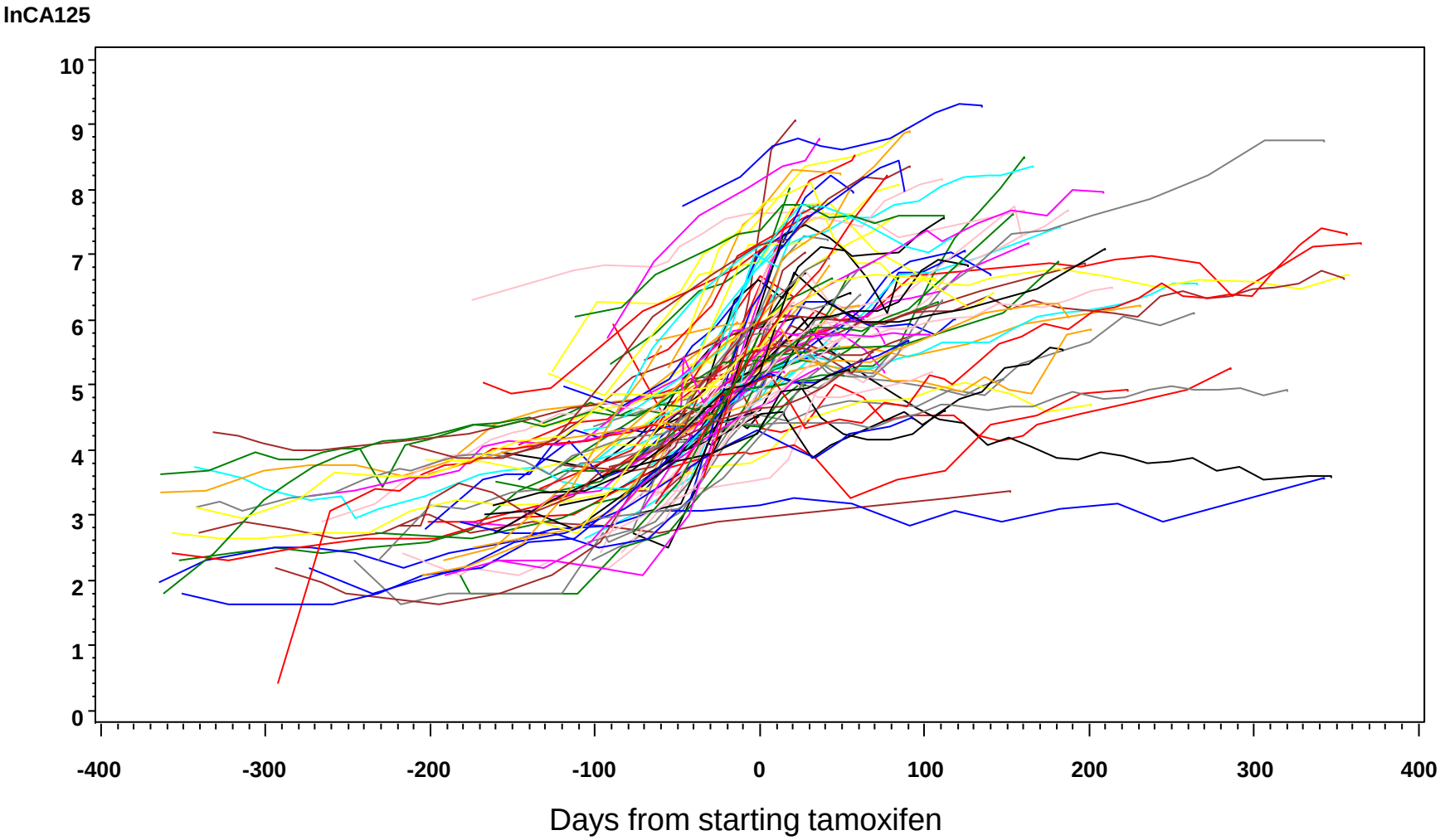
Analysis population

- Evaluable group
  - started tamoxifen within 9 months from date of registration
  - at least 3 CA125 assessments before and after starting treatment
- 9 months group
  - started tamoxifen within 9 months from date of registration
- Full dataset group
  - patients with at least 3 CA125 assessments before and after starting treatment

Summary of trial data

- Between Nov 2003 to July 2010 a total of 207 patients registered from 24 sites in the UK
- 175 patients with at least one CA125 measurement
- 113 patients received tamoxifen
  - Longest duration between registration and starting tomxifen was over 3 years and latest assessment was over 4 years after tamoxifen
- 62 patients in evaluable group
- 92 patients started treatment within 9 months
- 80 patients with at least 3 CA125 assessments before and after treatment

Ln(CA125) over time
all patients received treatment



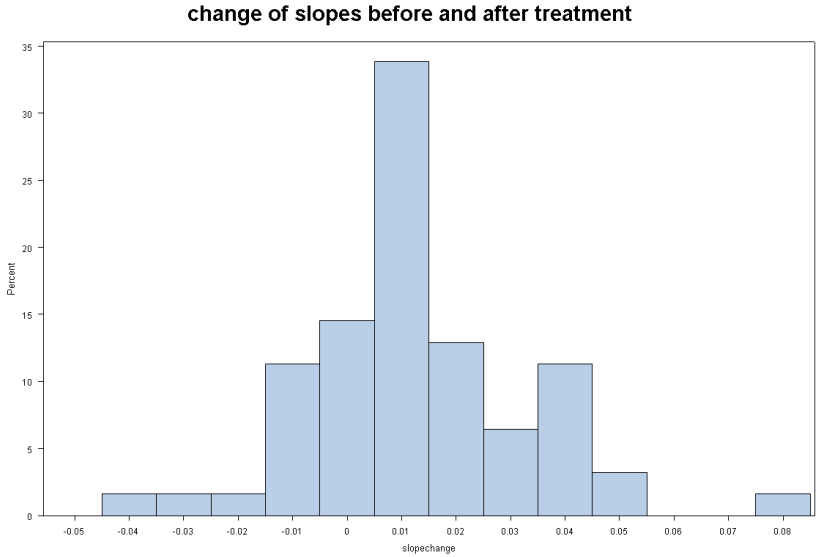
Patients in evaluable group (n=62)

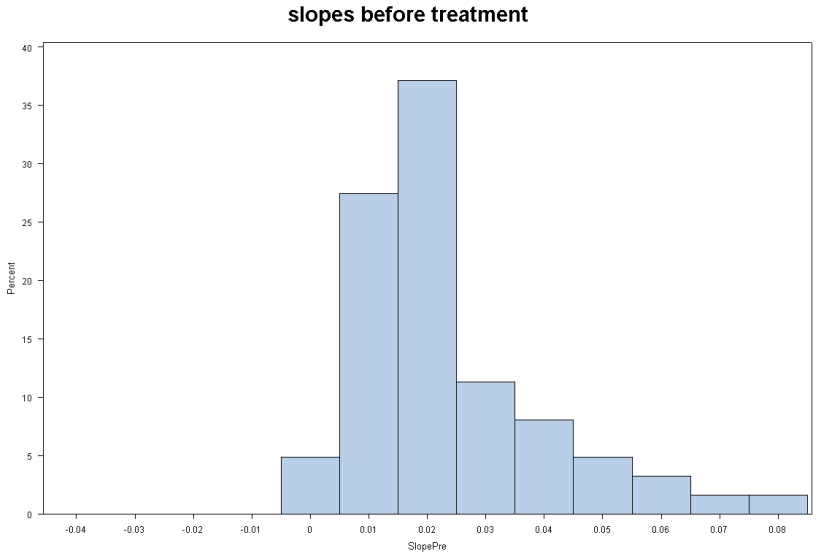
- 50 (81%) patients with decreasing slope after starting tamoxifen

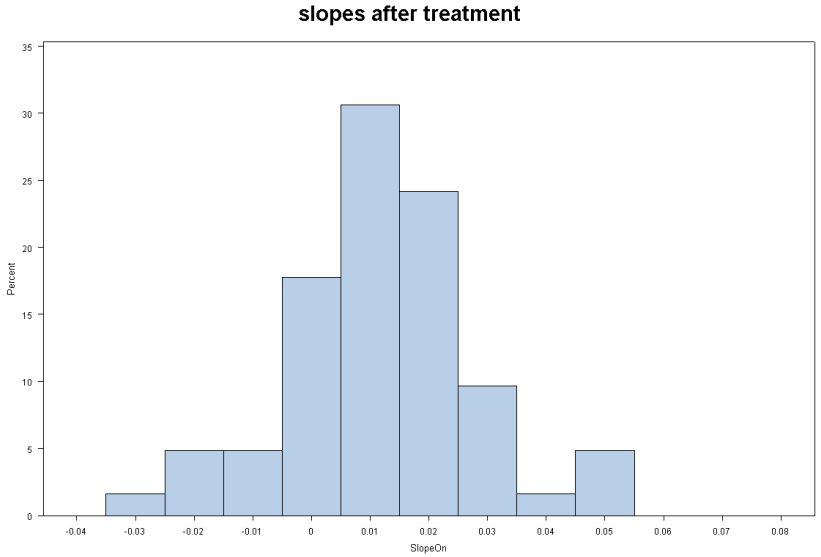
	Mean ln(CA125)/day	LCL	UCL
Pre-tamoxifen	0.0245	0.0197	0.0293
After tamoxifen	0.0123	0.0076	0.0170
change	0.0122	0.0072	0.0173

- Cohen's D for change in slope (95% CI) = 0.61 (0.34 to 0.96)
  - a medium to large effect
  - days of CA125 doubled: 28.3 before to 56.5 after treatment

Histogram of slopes







Patients in 9 months group

No. of CA125 measurements		No. of patients (n= 92)	
Pre-tamoxifen	After tamoxifen	With decreasing slope	total
≥ 3	≥ 3	50	62
≥ 3	2	5	6
2	≥ 3	1	6
≥ 3	0 or 1		18
No. of pts with decreasing slope after treatment = 56 (77%)			

All patients with 3 CA125s before and after treatment

	Mean (slope)	Days (CA125 doubled)	Cohen's D
Evaluable group patients (n=62)			
Pre-tamoxifen	0.0245	28.3	
After tamoxifen	0.0123	56.5	
change	0.0122	28.2	0.61
All patients with 3 CA125 assessments before and after (n=80)			
Pre-tamoxifen	0.0220	31.5	
After tamoxifen	0.0106	65.4	
change	0.0114	33.9	0.60

Summary

- The rate of rise of CA125 could be measured by the slope of log CA125 overtime
- There is a significant reduction in the rate of rise of CA125 level after staring tamoxifen
- The proposed approach could be applied in screening new anti-cancer drugs
  - A new agent is worth further investigation if its Cohen's D is larger than 0.60
  - Sample size: 19 patients who had 3 CA125 readings before and after treatment required for a power of 80% for the Cohen's D=0.60

Summary of trial data

113 patients received tamoxifen with 1563 CA125s

- 62 patients in evaluable group
  - Cohen's D for change in slope = 0.61 (based on 372 CA125s)
- 80 patients with at least 3 CA125 assessments before and after treatment
  - Cohen's D for change in slope = 0.60
- the rest 33 (30%) patients?

Two-piecewise regression model

log CA125 level for the ith patient at the jth time (days from registration), **lnCA125$_{ij}$,**

$$\ln CA125_{ij} = (\beta_0 + \beta_{0i}) + \underbrace{(\beta_1 + \beta_{1i}) \times time_{ij} \times \delta_1}_{before} + \underbrace{(\beta_2 + \beta_{2i}) \times time_{ij} \times \delta_2}_{after} + \varepsilon_{ij,}$$

changing point: time of treatment with δ_1 =1 before starting treatment and δ_2 =1 after starting treatment,

β_0, β_1, β_2: population intercept and slopes of before and after trt

β_{0i}, β_{1i}, β_{2i}: intercept and slopes for the ith patient

ε_{ij}: random error for the ith patient at the jth time

Patient group

- Evaluable group (62 pts, 917 CA125s)
- 9 months group (92 pts, 1105 CA125s)
- All patients received tamoxifen (113 pts, 1563 CA125s)

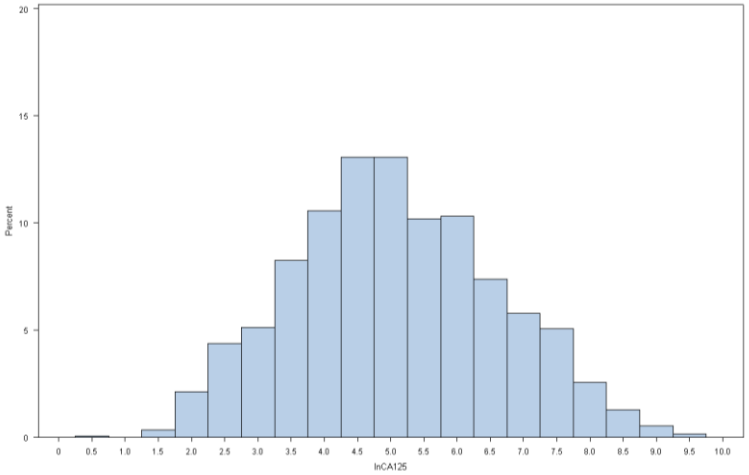
Results of fitted models

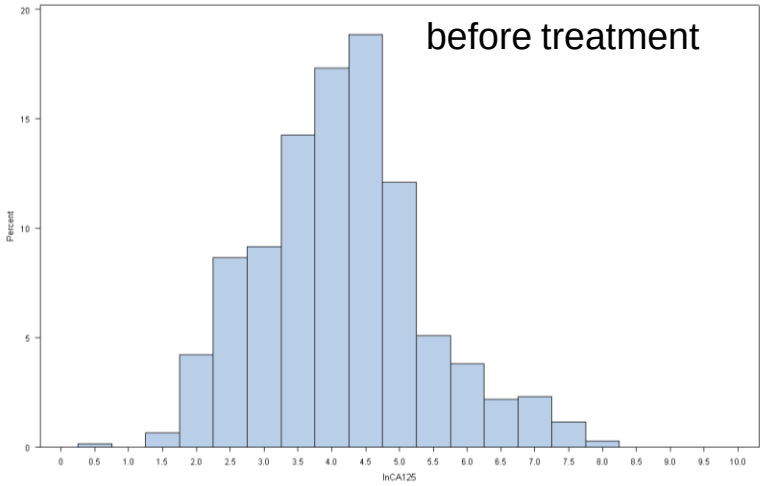
#pts	#CA125s	effect	estimate	SE	Pr>|t|
62	917	pre-trt	0.0200	0.0015	<.0001
		after trt	0.0118	0.0016	<.0001
Cohen'D =0.52, n=27		diff	0.0083	0.0022	0.0004
92	1105	pre-trt	0.0216	0.0013	<.0001
		after trt	0.0155	0.0018	<.0001
Cohen'D =0.38, n=45		diff	0.0061	0.0021	0.0044
113	1563	pre-trt	0.0194	0.0012	<.0001
		after trt	0.0140	0.0014	<.0001
Cohen'D =0.36, n=50		diff	0.00536	0.00170	0.0023

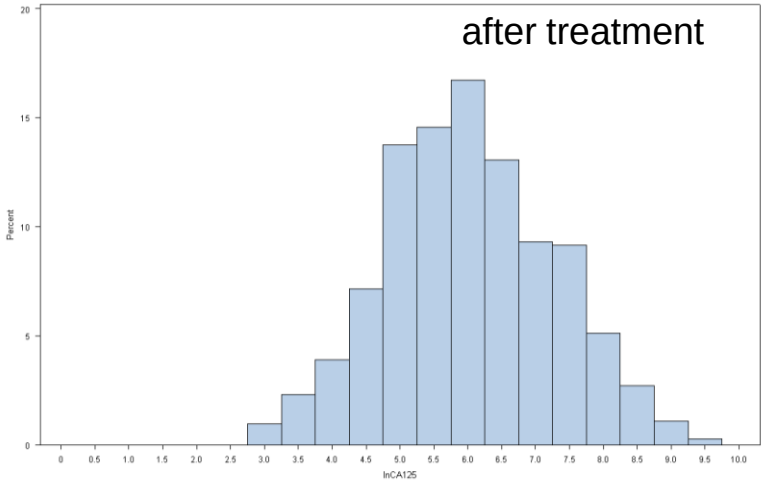
Slope analysis (372 CA125s): Cohen's D for change in slope = 0.61 (0.34 to 0.96)

Histogram of ln(CA125) level (n=113)

before and after treatment

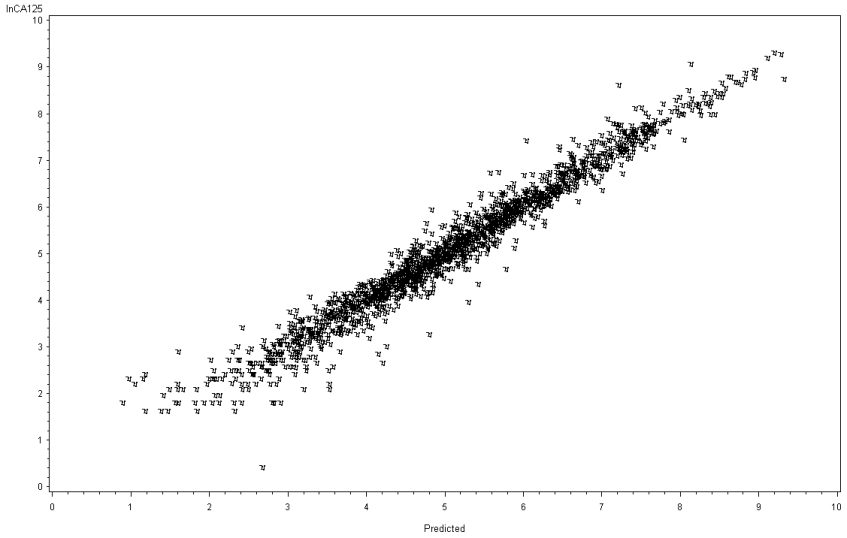




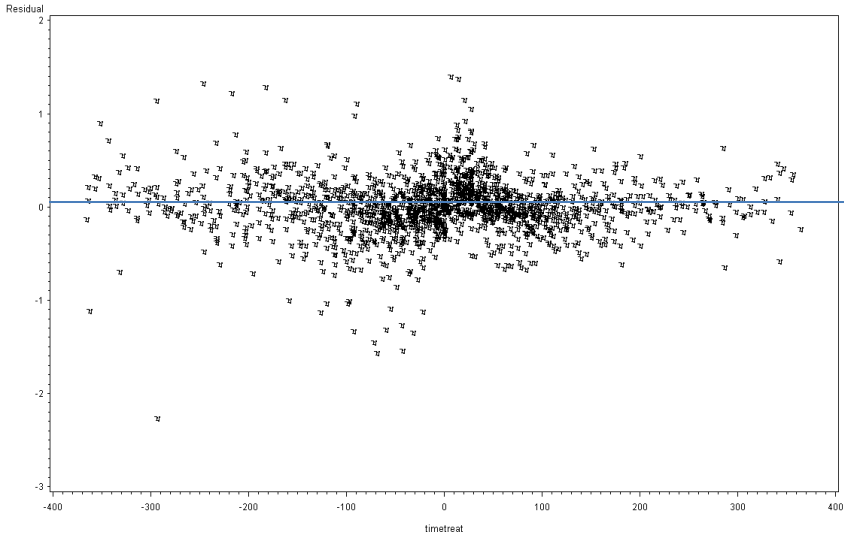


Goodness fit of regression model (n=113)

predicted value against observed



residuals over time



Thank you!

Discussion

- Magnitude of slope change: piece wise regression

- Analysis population : change points
  - Patients received treated with 9 month (n=92)
    - 24 patients were with less than 3 CA125 assessments after starting treatment
  - Patients received treatment (n=113)
    - 21 patients started treatment after 9 months from registration
  - 175 patients with at least 1 CA125 assessments, ranged (1, 52) with median of 10 assessments
    - 62 patients not received treatment (mainly disease progression)
      - 34 patients with more than 6 CA125 assessments