Presentation of Gordon Rustin

1. CA 125 as an endpoint in phase 2 trials

2. CA 125 as an endpoint for time to progression in phase 3 trials

3. How to use rising CA 125 levels in absence of measurable disease to asses drug activity

Use of CA 125 to define response

Selection of active drugs for ovarian cancer based on CA 125 and standard response rates

25 treatment groups in 19 clinical trials of 14 different drugs

	Evaluable
Standard	1457
CA 125	1092

Hypothetical Gehan two stage Phase II trial

Target drug efficacy rate 20%

Rejection error 5%

Selection of active drugs in Phase II trials for ovarian cancer according to CA 125 response rate

Altretamine

Docetaxel

Etoposide

Fosquidone

Gemcitabine

Isotretinoin/Calcitriol

Paclitaxel

Platinum based

Rhizoxin

Tallimustine

Tomudex

Topotecan

Oxaliplatin

Precise definitions based on 50% or 75% fall in CA 125 accurately predicted drug activity

Rustin et al J Clin Oncol 18:1733-39. 2000

CA 125 and standard response criteria concordant in 20 / 25 groups

"Discordant" in 5 groups:

in 4 paclitaxel rejected by standard but not CA 125

in 1 etoposide rejected by CA 125 but not by standard

Simplification of 50% or 75% CA 125 response by just 50% remains very accurate

Guastalla et al ASCO Abstract 815; 2002

CA 125	RECIST (N° of pts)			
	Response	Stable disease	Progressive disease	p
	n= 111	n= 92	n= 33	
Response	78	19	3	< .0001
No Response	33	73	30	

Gynecologic Cancer Intergroup (GCIG) definition of CA 125 response to therapy of relapsed ovarian cancer

A CA 125 response has occurred if after two elevated levels prior to therapy there is at least a 50% fall which is confirmed by a fourth sample

- Requires 2 pre-treatment samples both $\geq$ twice upper limit normal, one within 1 week of starting therapy other within 3 months
- Third sample $\leq$ 50% second sample
- Confirmatory fourth sample $\geq$ 21 days after sample 3 and $\leq$ 50% sample 2
- Not evaluable if interference with pleura/peritoneum in prior 28 days or received mouse antibodies

Rustin et al J Nat Cancer Inst 2004 96; 487-8.

CA 125 response in phase II trials: Recommendations

- Use to support “go/no go” decisions
- Define response rate below which further development should be halted
- Define minimal acceptable response rate
- Define the number of patients required to achieve a 90% power to define response by CA 125.
- If CA 125 response rate is greater than minimal acceptable rate, trial continues so that response can be measured with same power by RECIST

Use of CA 125 to Define Progression

Defining progression of ovarian cancer during follow-up according to doubling of CA125 from upper limit of normal: *Low false positive rate*

Analysis after 87 relapses from 131 evaluable patients whose CA 125 had fallen to $\leq$ 30 U/ml in North Thames of 5 vs 8 courses carboplatin

If CA125 rise confirmed

- Sensitivity 84%
- False positive rate 1.4%
- Median lead time to clinical progression 63 days

Rustin et al Annals of Oncology 7: 361-4, 1996

Confirmed doubling of CA 125 from nadir accurately defines progression (94% sensitivity)

- 302 patients receiving first line chemotherapy
- 88 CA 125 levels always >23 U/ml and at least 4 serial CA 125 levels prior to clinical progression
- True positive 80 (64 had CA 125 PD prior to or on the same day as clinical PD and 16 later).
- False positive 1 (died M.I. 3 weeks after CA125 rise)
- True negative 2
- False negative 5

Rustin et al . J Clin Oncol 2001, 19;20:4054-4057

CA 125 definition of progression agreed by GCIG

- **Patients with CA 125 in normal range**

CA 125 ≥ 2x ULN documented on TWO occasions

Date PD: first date of the CA 125 elevation to ≥ 2x ULN

- **Patients whose CA 125 never normalised**

CA 125 ≥ 2x nadir value on TWO occasions

Date PD: first date of the CA 125 elevation to ≥2x nadir value

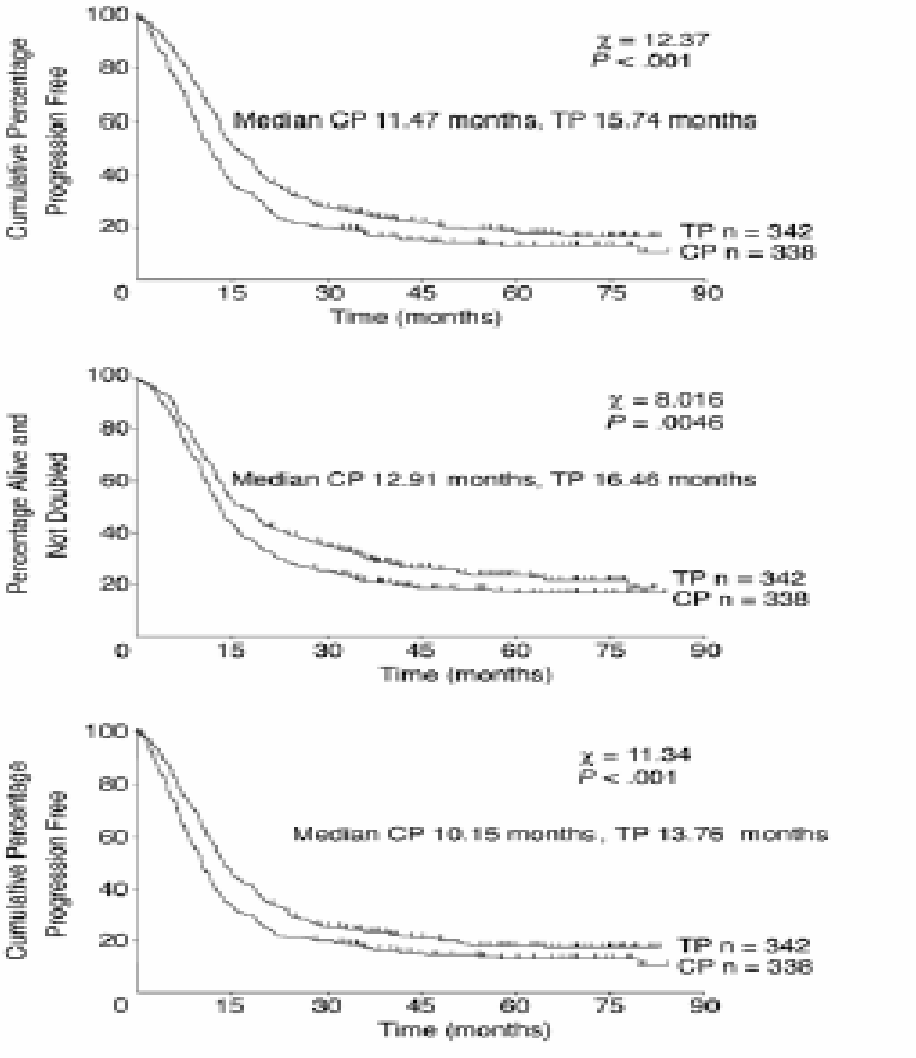
Vergote et al. J Natl Cancer Inst 2000, 92:1534-1535

Comparison of CA-125 and Standard Definitions of Progression in the Intergroup Trial of Cisplatin and Paclitaxel Versus Cisplatin and Cyclophosphamide *Rustin et al J Clin Oncol 24:45-51. 2006*

Standard Definitions

CA 125 Definitions

Combined



CA 125 accurately predicts Progression : Providing

- CA 125 measurements same time-point on all arms of randomised trials
- If mouse antibodies are used they do not interfere with assay
- If *biological/ targeted therapy* used data from phase 2 trials show acceptable number of discordant results.
- If IP therapy given CA 125 levels have returned to within normal range and >28 days from removal of IP catheter.

Use of CA 125 defined progression in clinical Trials: recommendations

- **Should be incorporated into trial protocols of first line and relapse therapy of ovarian cancer.**
- *Progression according to RECIST always takes precedence*
- *Use of CA 125 will shorten progression free survival*
- *Reduces number of CT scans required during follow up.*

See GCIG website

http://ctep.info.nih.gov/resources/gcig/index.html

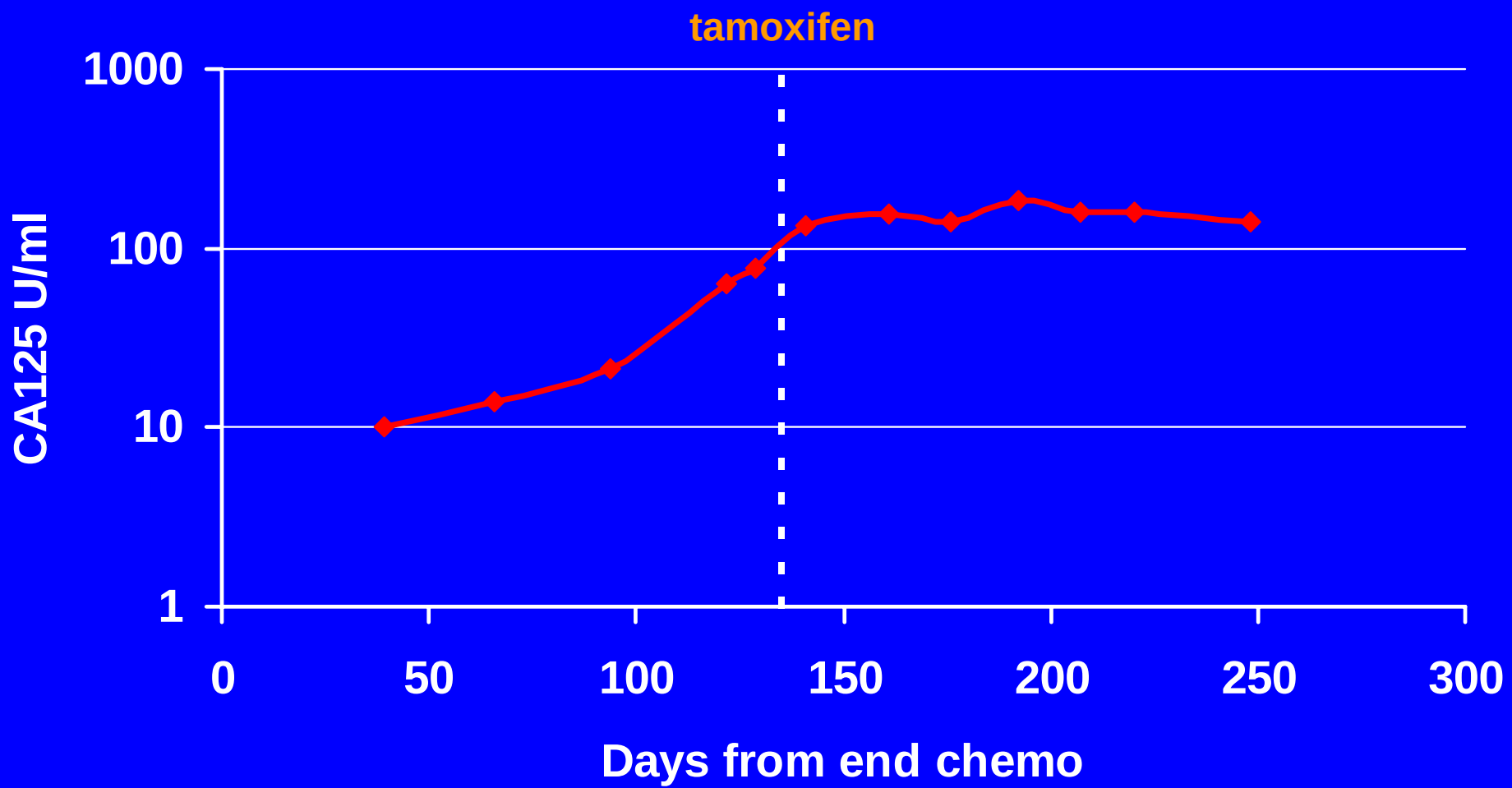
How to use rising CA 125 levels in absence of measurable disease to asses drug activity

How to asses drug activity by using CA 125 levels in patients with only biochemical relapse

- Use CA 125 to determine response by GCIG criteria
- Determine CA 125 doubling time before test therapy
- Determine CA 125 doubling time after test therapy
- Determine proportion of patients in whom rate of rise slows after test therapy

- Easier and quicker endpoint if register patients after responding to relapse therapy rather than after first line therapy

Example of serial CA125 results



Use of changes in CA 125 doubling time to detect activity of cytostatic agents: study 1- Tamoxifen: update to April 06

34 patients entered

23 patients have rising CA 125 levels

19/20 (95%) of those $\geq$ 4 levels, have sufficiently linear rise to calculate doubling time: varies from 12- 86 days

Eighteen sites open by summer 06

200 patients will provide estimate of % patients with log linear rise with standard error of about 3%

Trial looks feasible and encouraging

Points for Discussion related to CA 125

What else is required to validate:

1. CA 125 as an endpoint in phase 2 trials

2. CA 125 as an endpoint for time to progression in phase 3 trials

3. How to use rising CA 125 levels in absence of measurable disease to asses drug activity

Points for Discussion related to CA 125

- What proportion of discordant results invalidates CA 125 for specific agents?
- If patients start 2nd line therapy just because of rising CA 125 what is the date of progression?
- Date of progression will depend upon type and frequency of monitoring
- Using CA 125 progression will shorten progression-free survival

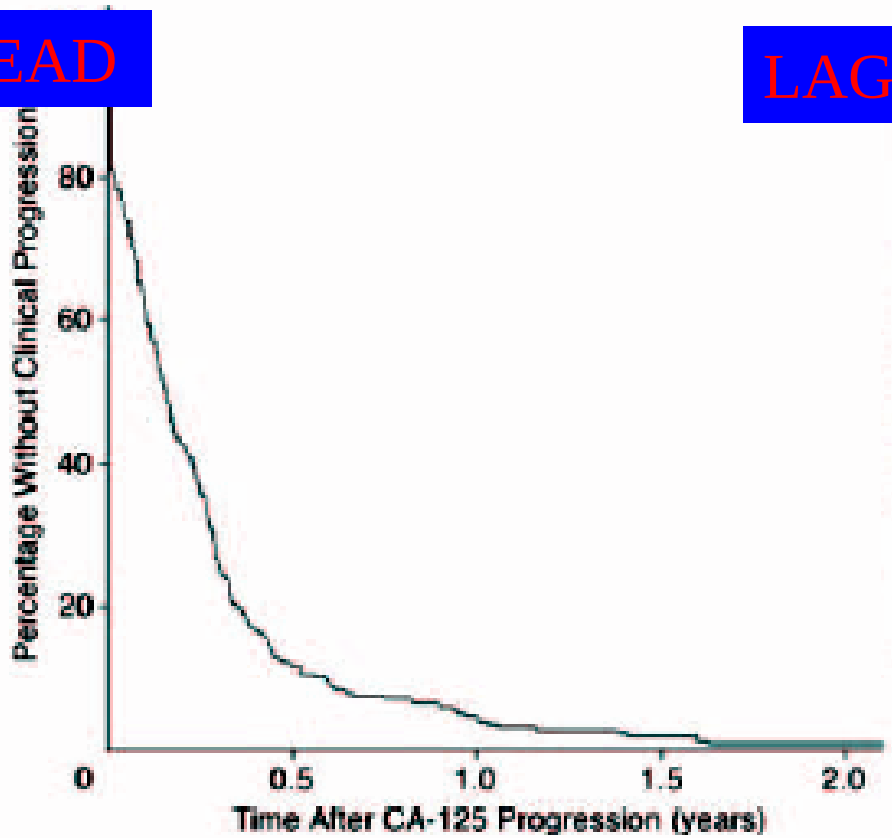
Research Required

1. Register required of trials prospectively recording CA 125 levels
2. Analysis of actual CA 125 levels using GCIG criteria.
3. Validation of CA 125 criteria based on whether it use alters trial result
4. Design trials that study patients with no measurable disease but an asymptomatic rise in CA 125
5. Develop statistical methods for change point analysis

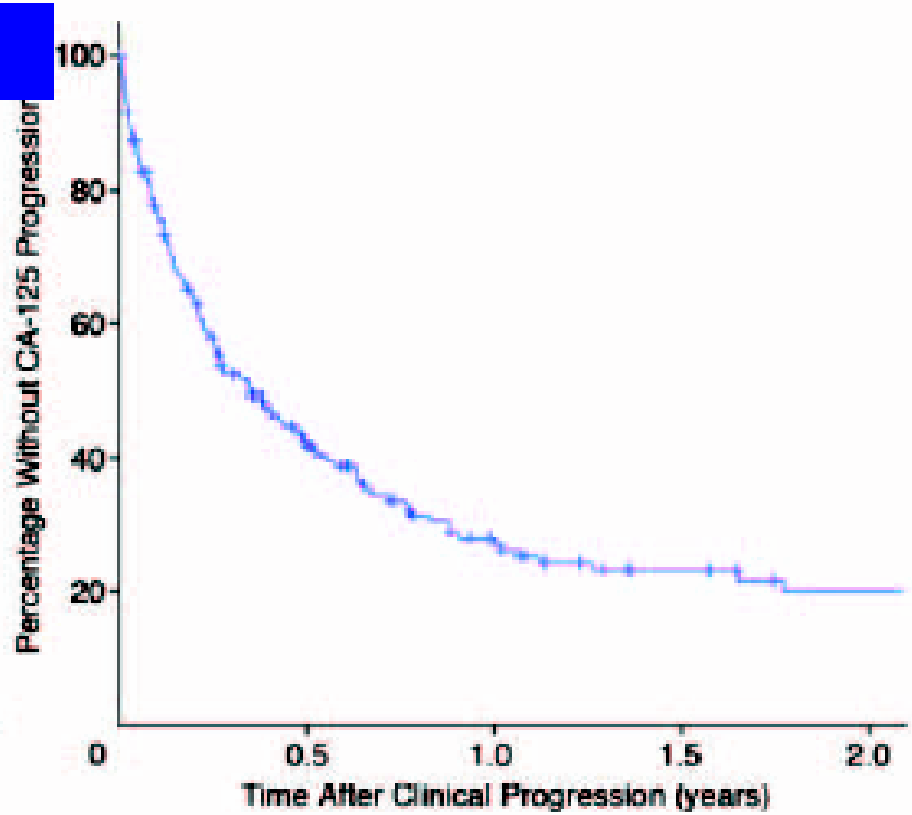
Spare Slides to answer specific questions

Lead and Lag time comparing CA 125 and standard date of progression in Intergroup Trial (Mean lead 54 days)

LEAD

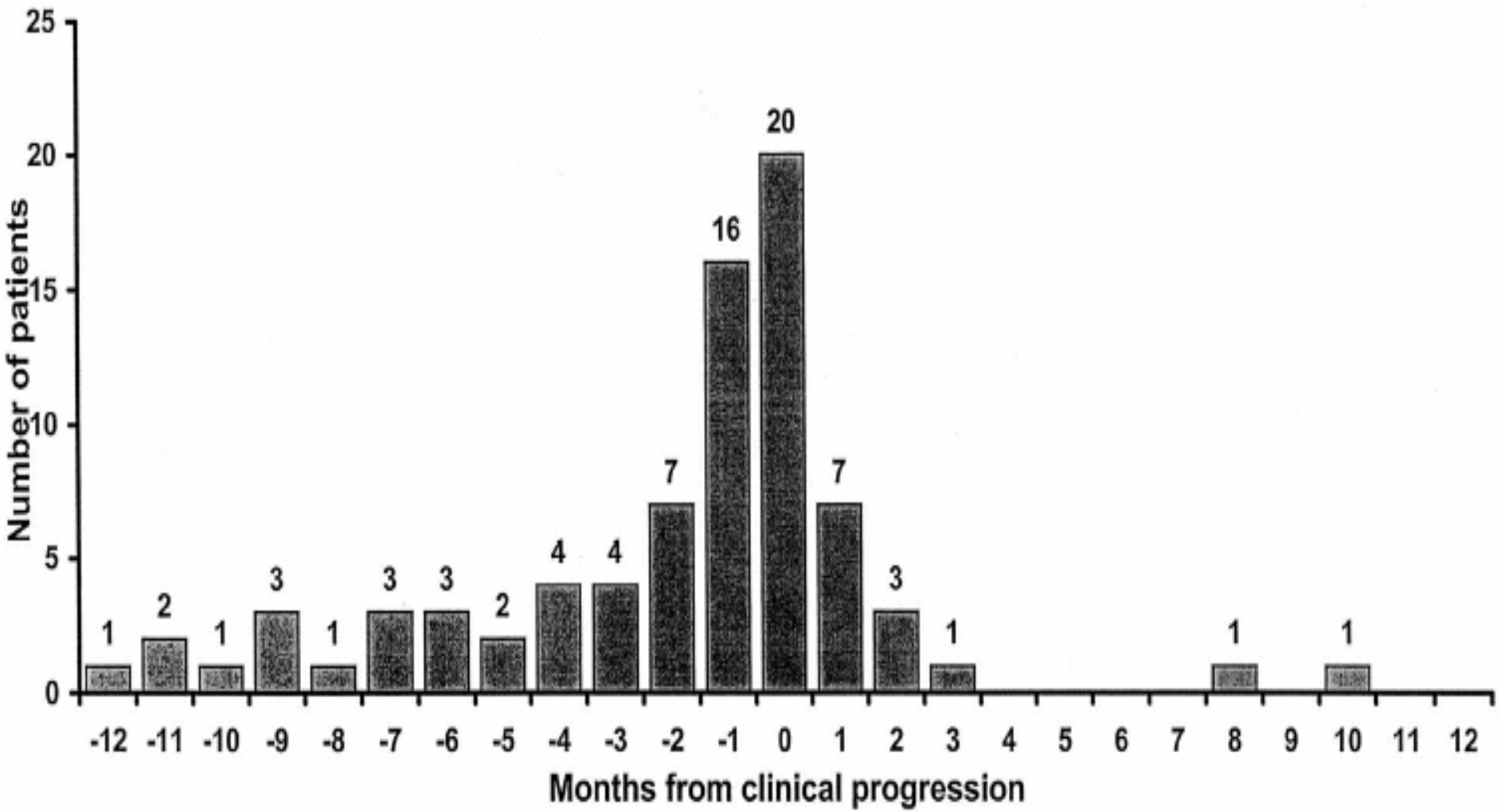


LAG



Rustin et al J Clin Oncol 24:45-51. 2006

Timing of CA-125 doubling relative to date of clinical progression.



CA 125 as an endpoint in Relapse trials:
1 Progression Free Survival

- Accepted that not validated for relapse but providing CA 125 measurements same time-points on both arms, difficult to conceive that change in CA 125 is affected by number of relapses.
- Accept that the number of patients with doubling from nadir will decrease with later relapses if CA 125 level already very elevated
- Same caveats as for first line trials

Pitfalls associated with response measurements

Should there be different criteria for first line and 1st, or subsequent relapse?

Should always be intention to treat analysis of all eligible patients who are evaluable at start of trial therapy

Response measurements must be carried out at time points stated in protocol. (CA 125 will always be more frequent than CT scans)

Date of progression will depend upon type and frequency of investigations

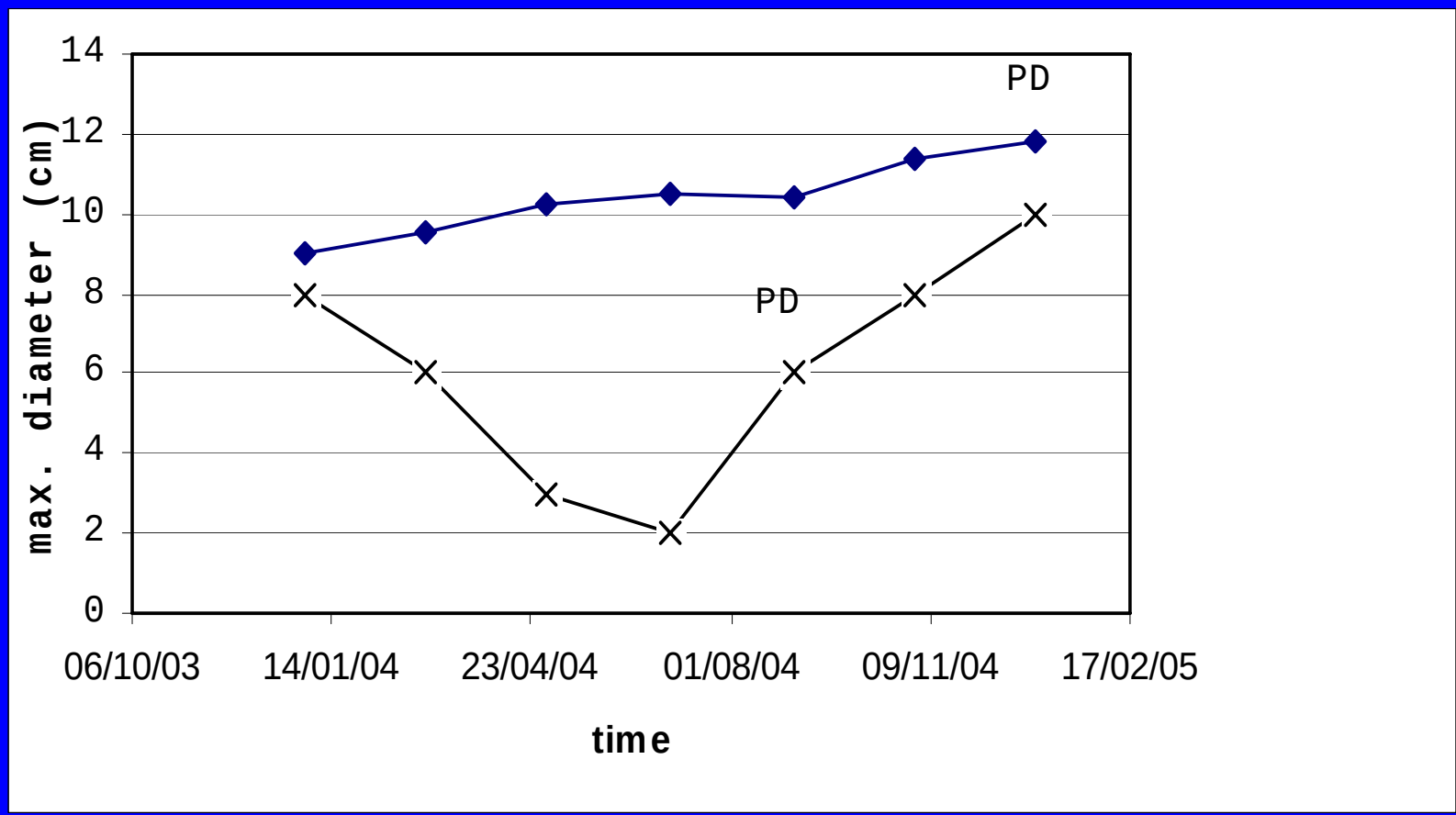
would % progression free at 3,6,9,12 months etc be better?

Correlation between clinical and CA 125 response to paclitaxel for relapsed ovarian cancer

	Evaluable	*Response Rate*	*Spearman Correlation*
15% change	259	62%	0.275
Markman 90% fall	228	10%	-0.047
Markman 50% fall	228	42%	0.112
Rustin 50% or 75% fall	209	21%	0.354
Clinical response	382	21%	

(van der Burg et al 1998)

Problems with progression free survival Changing the baseline in responding patients influences date of PD.



Should endpoints differ based on nature of agent?

Survival- no change

Progression free survival- could agent interfere with rise in CA 125?

- Murine antibodies could cause false rise, blocking agents available
- Difficult to conceive of an agent that could prevent a rise, but should always use RECIST as well.

Response- RECIST no change, CA125 worst case scenario abandon drug that is active but induces CA 125, if drug is inactive but makes CA 125 fall will be realised when RECIST expansion.

Drugs/trials classified according to rejection errors in the first stage of a Gehan two stage phase II study

		Probability of rejection by CA 125 response	
		Less than 5%	More than 5%
Probability of rejection by standard response	Less than 5%	9	1
	More than 5%	4	11

(p-value of difference in classification by McNemar's test: p=0.38)

Rustin et al J Clin Oncol 18:1733-39. 2000

Simplification of 50% or 75% CA 125 response by just 50% remains very accurate

Guastalla et al ASCO Abstract 815; 2002

	criteria of response	No. of pts	PFS (days)	p
CA 125				
	Response	165	297	.00001
	Lack of response	226	174	
RECIST				
	Response	136	310	.00001
	Stable disease	120	191	
	Progressive disease	79	56	

Requirements before using CA 125 in patients who have received mouse antibodies

Determine whether CA 125 assay influenced by HAMA

Use method of Taylor and Haverstick JNCI 97, 151-2, 2005

(serially dilute HAMA containing serum plus constant amount purified CA125 and see if same result at each dilution by each assay method)

State which patients received antibody when reporting results