Simulation with copula formula

SSL syysseminaari 30.10.2014

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Initial remarks

- CRPC regulatory endpoint OS or PFS
- Typically Phase I/II study include relevant data only for PSA and PSA is considered as surrogate biomarker. Correlation between the two is unknown.
- Competitors have PSA data from Phase II and OS data from Phase III trials .
- We have only PSA data from Phase II and need to plan Phase III.

Guidelines for (Prostate) Cancer

- Guideline on the evaluation of anticancer medicinal products in man (adopted 01 Jul 2013)
  - Phase II trials are intended to Assess the probability of response in the target tumour type.
  - In Phase II data on duration of response, TTP/PFS, confirmed ORR (e.g. RECIST) and available data on OS should normally be reported.
  - Acceptable primary endpoints in Phase III include cure rate, OS and PFS/DFS
- Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man (adopted 01 Jul 2013)
  - Changes in prostate specific antigen (PSA) levels during different therapies are used as a biomarker. Individuals' PSA values are not comparable to each other but changes and nadir are prognostic.
  - Progression in bone metastases is often accompanied by PSA increase. PSA increase alone cannot serve as primary end point in confirmatory studies.
  - Time to symptomatic progression, PFS and OS are considered appropriate outcome measures.

Phase II Study

Population	Dose		
	Low	Intermediate	High
Pre-Chemo			
Post-Chemo			
Post-Abiraterone			

PSA Response Rate

MDV300 Phase II Scher et al. Lancet 2010

METHODS: This phase 1-2 study was undertaken in five US centres in 140 patients. Patients with progressive, metastatic, castration-resistant prostate cancer were enrolled in dose-escalation cohorts of three to six patients and given an oral daily starting dose of MDV3100 30 mg. The final daily doses studied were 30 mg (n=3), 60 mg (27), 150 mg (28), 240 mg (29), 360 mg (28), 480 mg (22), and 600 mg (3). The primary objective was to identify the safety and tolerability profile of MDV3100 and to establish the maximum tolerated dose. The trial is registered with ClinicalTrials.gov, number NCT00510718.

FINDINGS: We noted antitumour effects at all doses, including decreases in serum prostate-specific antigen of 50% or more in 78 (56%) patients, responses in soft tissue in 13 (22%) of 59 patients, stabilised bone disease in 61 (56%) of 109 patients, and conversion from unfavourable to favourable circulating tumour cell counts in 25 (49%) of the 51 patients. PET imaging of 22 patients to assess androgen-receptor blockade showed decreased (18)F-fluoro-5alpha-dihydrotestosterone binding at doses from 60 mg to 480 mg per day (range 20-100%). The median time to progression was 47 weeks (95% CI 34-not reached) for radiological progression. The maximum tolerated dose for sustained treatment (>28 days) was 240 mg. The most common grade 3-4 adverse event was dose-dependent fatigue (16 [11%] patients), which generally resolved after dose reduction.

Results from highest tolerated doses PSA decline ≥50% from baseline 71% (48-95)

MDV300 Phase III Beer et al. NEJM 2014

selected daily dose 160 mg

Median time until PSA progression — mo¶	11.2	2.8	0.17 (0.15–0.20)	<0.001
Confirmed change in PSA‖				
Patients with ≥1 post-baseline PSA assessment — no. (%)	854 (98)	777 (92)		
PSA decline of ≥50% from baseline — no./total no. (%)	666/854 (78)	27/777 (3)		<0.001
PSA decline of ≥90% from baseline — no./total no. (%)†	400/854 (47)	9/777 (1)		<0.001

MDV300 Phase III Beer et al. NEJM 2014

- Fewer deaths occurred in the enzalutamide group than in the placebo group (241 of 872 patients [28%] vs. 299 of 845 patients [35%]).
- Treatment with enzalutamide, as compared with placebo, resulted in a 29% decrease in the risk of death (hazard ratio, 0.71; 95% CI, 0.60 to 0.84; P<0.001).
- The median overall survival was estimated at 32.4 months in the enzalutamide group and 30.2 months in the placebo group.

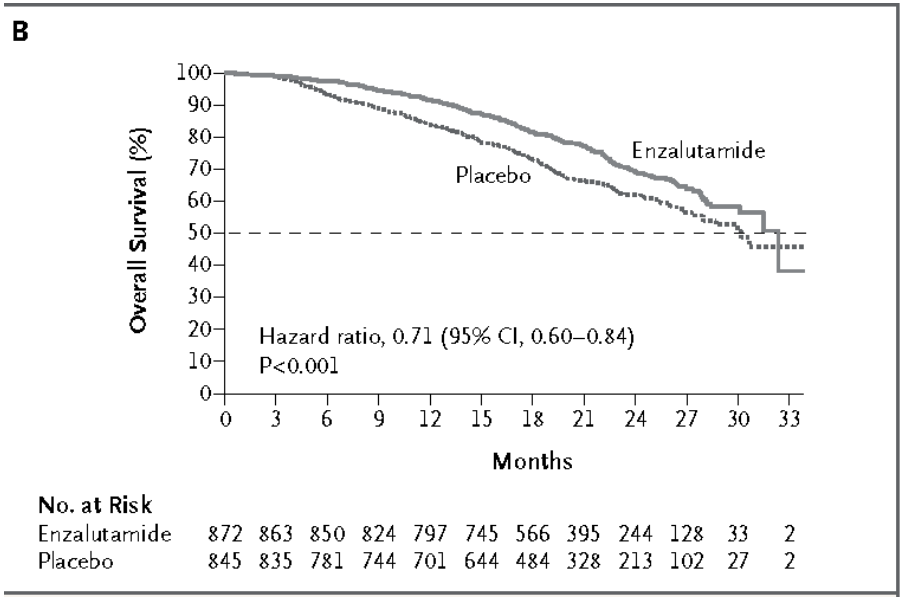

Figure 1. Kaplan–Meier Estimates of Radiographic Progression-free Survival and Overall Survival.

Shown are data for the coprimary end points of radiographic progression-free survival (Panel A) and overall survival (Panel B). The dashed horizontal lines indicate medians. Hazard ratios are based on unstratified Cox regression models with treatment as the only covariate, with values of less than 1.00 favoring enzalutamide.

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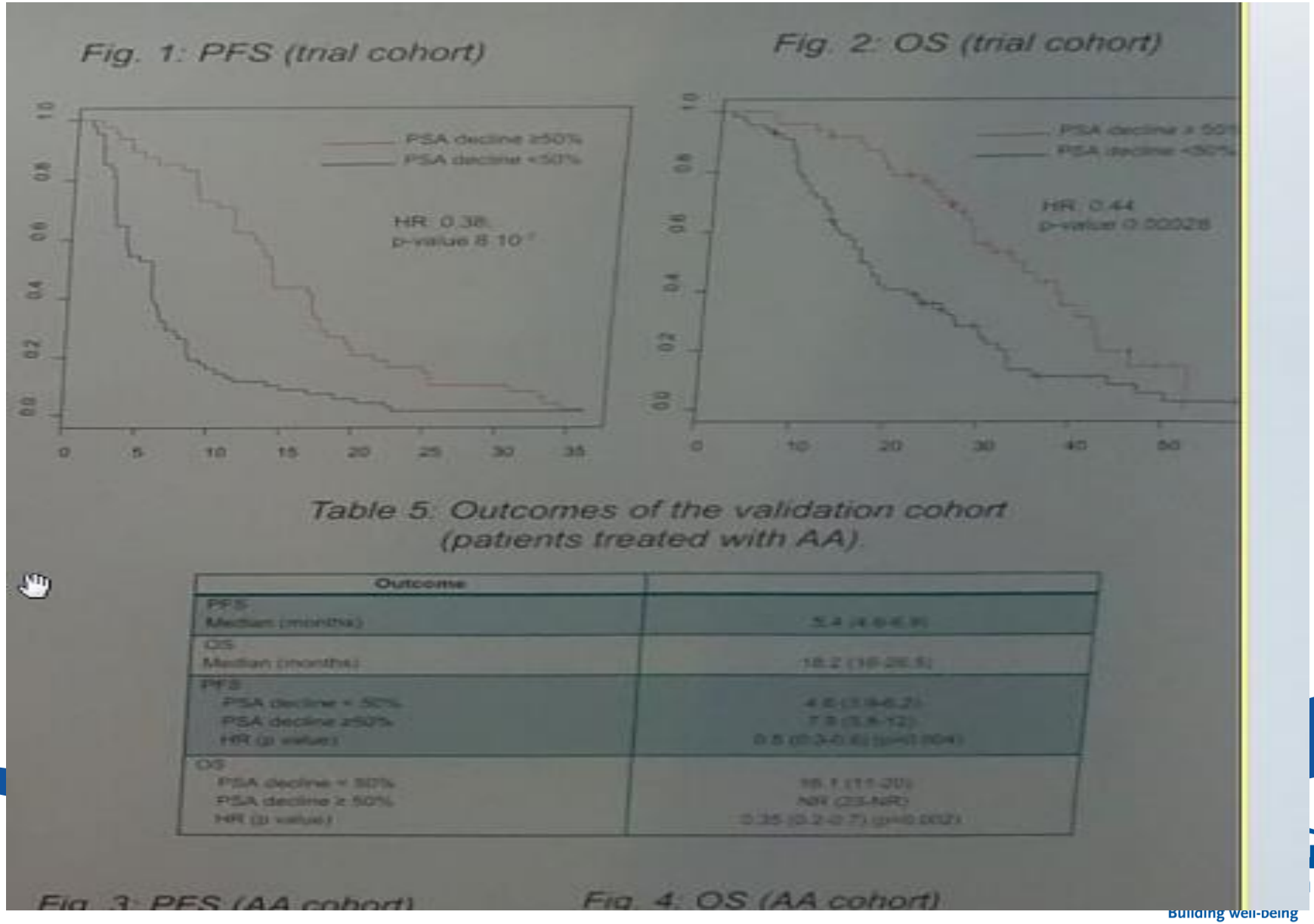
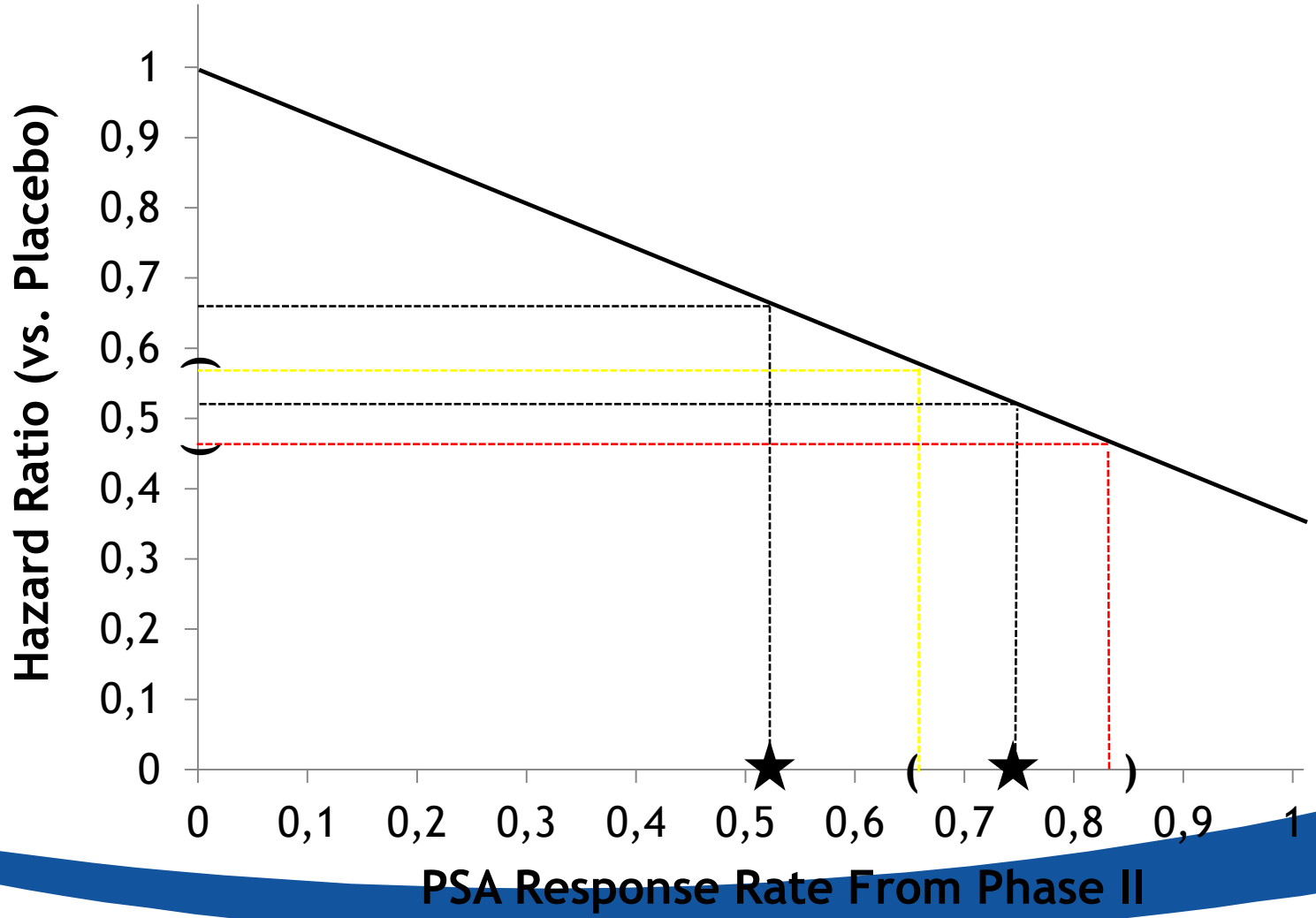
Abstract in ESMO 2014 (N = 118)



How to evaluate association between Phase II results and Phase III target



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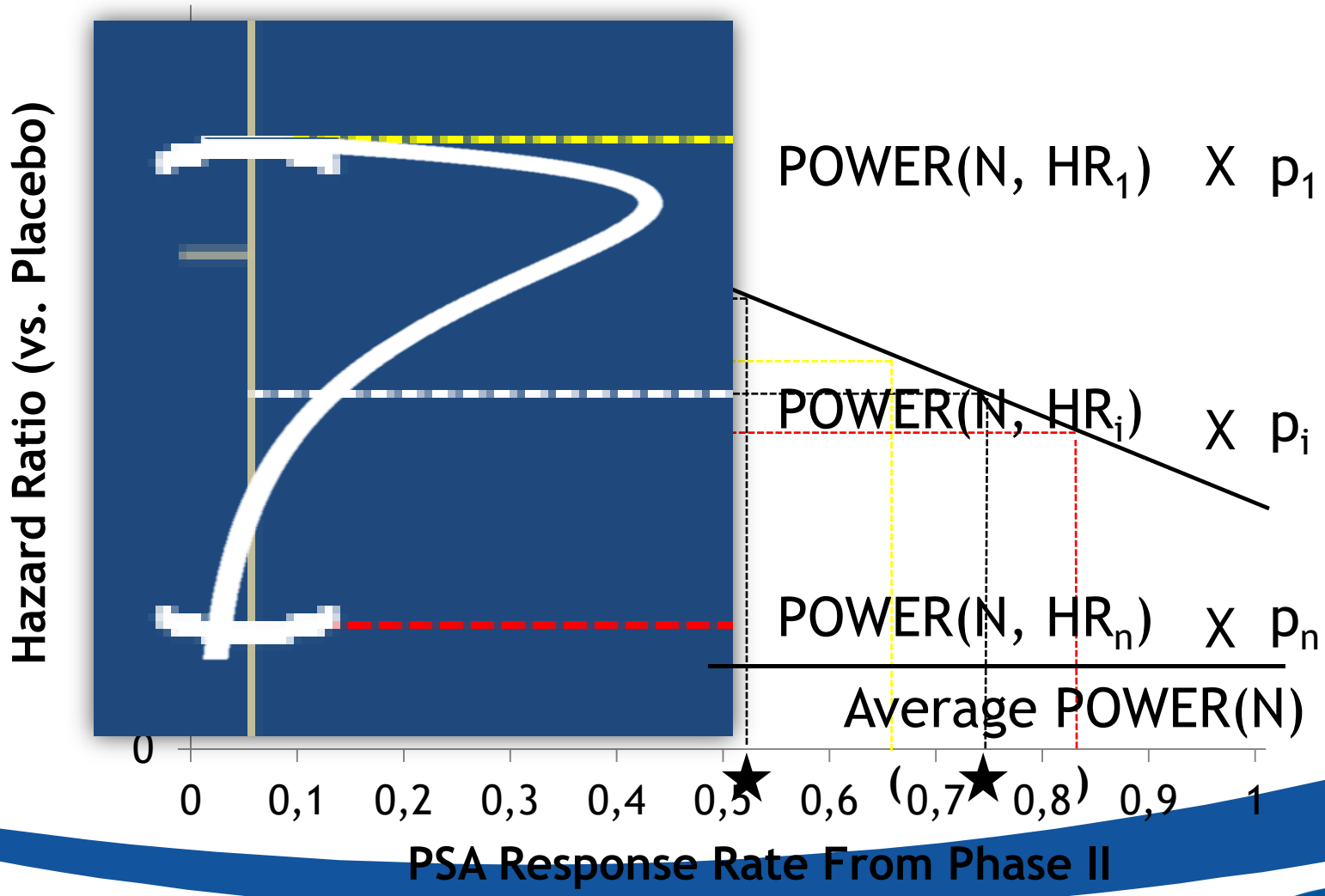
How to evaluate power for Phase III



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Intermediate remarks

- Existing Phase II PSA data comes from various populations, different molecules, different doses, studies with low sample size
- Correlation between PSA and OS probably exists, however, magnitude is unknown
- Straightforward attempts to link Phase II and Phase III are probably too simple for the basis of power calculation

Copula in very short

- From Wikipedia: ”In probability theory and statistics, a copula is a multivariate probability distribution for which the marginal probability distribution of each variable is uniform. Copulas are used to describe the dependence between random variables. They are named for their resemblance to grammatical copulas in linguistics.”
- Sklar's Theorem states that any multivariate joint distribution can be written in terms of univariate marginal distribution functions and a copula which describes the dependence structure between the variables.
- Nice reading by Erdman and Sinko SAS Global Forum 2008: ”Using Copulas to Model Dependency Structures in Econometrics”
- And a whole book about it by Trivedi and Zimmer 2005. ”Copula Modeling: An Introduction for Practitioners”
- Multiple different Copulas: Gaussian copula, Student’s t-copula, Clayton copula etc.
- Gaussian copula is flexible allowing equal degrees of positive and negative dependence.

Generate correlated data (1)

```
data S(type=CORR);
input _TYPE_ $ _NAME_ $ x y;
cards;
CORR x  1    -0.1
CORR y -0.1 1
MEAN .  0    0
STD    .  1    1

proc reg;
 A: model y = x;
 run;
```

r	Intercept	Dependent	Root MSE
-0.1	0	-0.100	0.99504
-0.3	0	-0.300	0.95399
-0.8	0	-0.800	0.60003

Generate correlated data (2)

```
data comb;
 do round = 1 to 1;
  do patient = 1 to 1700;
   x = rannor(0);
   y = 0-0.8*x+0.60003*rannor(0);
   output;
  end;
 end;
 run;

proc corr data=comb;
 var x y;
 run;

proc sgplot data=comb;
 scatter x=x y=y;
 run;
```

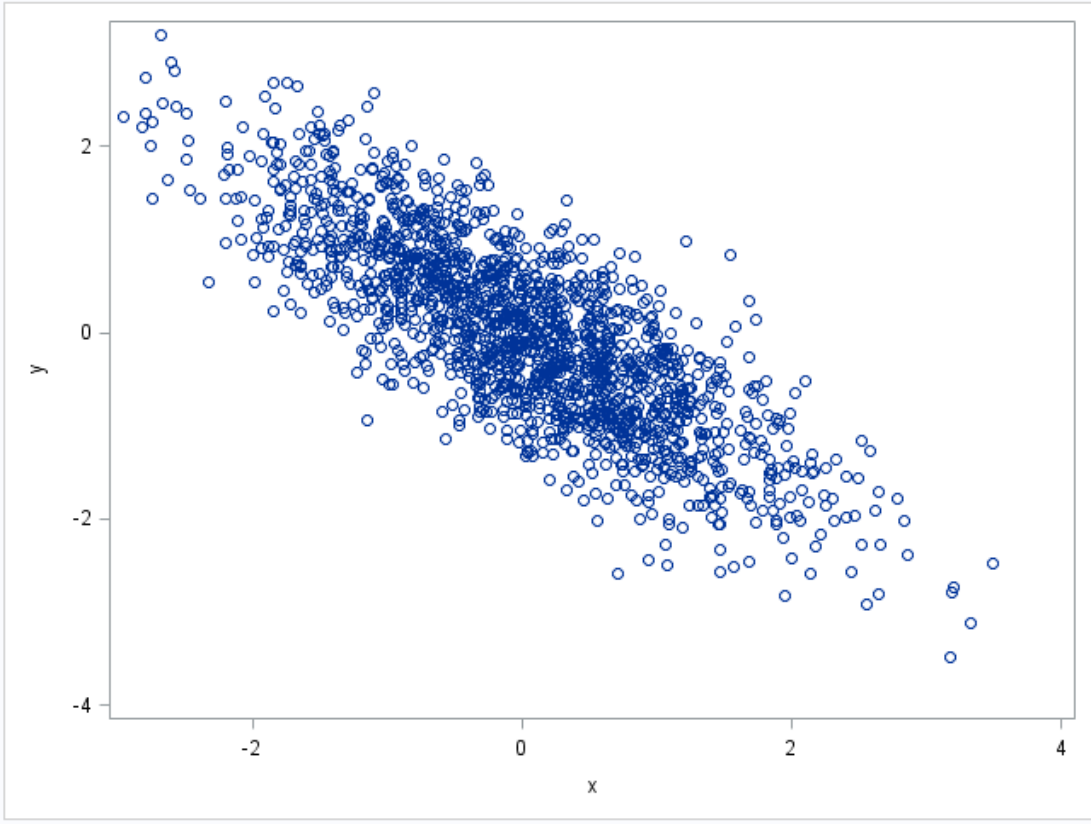
Simple Statistics

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
x	1700	0.01849	1.01297	31.43426	-2.96154	3.49396
y	1700	-0.01008	0.99786	-17.14075	-3.48238	3.19906

Pearson Correlation Coefficients, N = 1700
Prob > |r| under H0: Rho=0

	x	y
x	1.00000	-0.80427
		<.0001
y	-0.80427	1.00000
	<.0001	

Page Break



Generate correlated data (3)

```
data comb;
 do round = 1 to 1;
  do patient = 1 to 1700;
   trt=ranuni(0);
   if trt<.5 then treat='Test      ';
   else treat='Reference';
   x = rannor(0);
   y = 0-0.8*x+0.60003*rannor(0);
   y2=cdf('NORMAL',y);
   x2=cdf('NORMAL',x);
   if treat='Test' then psa=quantile('NORMAL',y2)*45-80;
   else psa=quantile('NORMAL',y2)*45+50;
   if treat='Test' then
os=quantile('EXPONENTIAL',x2)/(log(2)/32.4);
   else os=quantile('EXPONENTIAL',x2)/(log(2)/0.2);
   if psa le -50 then psa_response='YES';
   else psa_response='NO';
   if os le 35 then d
    os_cen=round(
    cen=0;
   end;
   else do;
    os_cen=35;
    cen=1;
   end;
   output;
  end;
 end;
 run;
```

Return to CDF - note some correlation is lost here 80%→78%

Apply distribution of your interest to CDF - note that I have no individual data from MDV for PSA response and μ and SD based on in-house data

treat	Variable	N	Mean	Std Dev	Median	Minimum	Maximum
Reference	psa	894	48.5	47.3	50.2	-116.9	204.0
	os	894	46.5	48.8	30.5	0.0	402.5
Test	psa	806	-79.7	46.1	-81.4	-231.3	56.7
	os	806	47.7	45.6	34.9	0.1	255.1

Pearson Correlation Coefficients, N = 806
Prob > |r| under H0: Rho=0

	psa	os
psa	1.00000	-0.71966
		<.0001
os	-0.71966	1.00000
	<.0001	

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval Transform	[Lower	Upper)
75	.	LOGLOG	.	.
50	30.5000	LOGLOG	28.0000	34.0000
25	12.0000	LOGLOG	11.0000	14.0000

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval Transform	[Lower	Upper)
75	.	LOGLOG	.	.
50	35.0000	LOGLOG	31.0000	.
25	15.0000	LOGLOG	13.0000	16.0000

Table of psa_response by treat

psa_response		treat Reference	Test	Total
NO	Frequency	878	200	1078
	Col Pct	98.21	24.81	
YES	Frequency	16	606	622
	Col Pct	1.79	75.19	
Total	Frequency	894	806	1700

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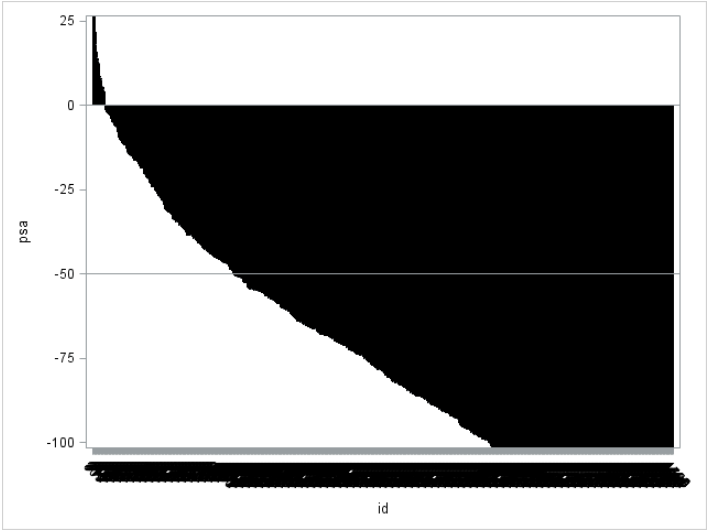
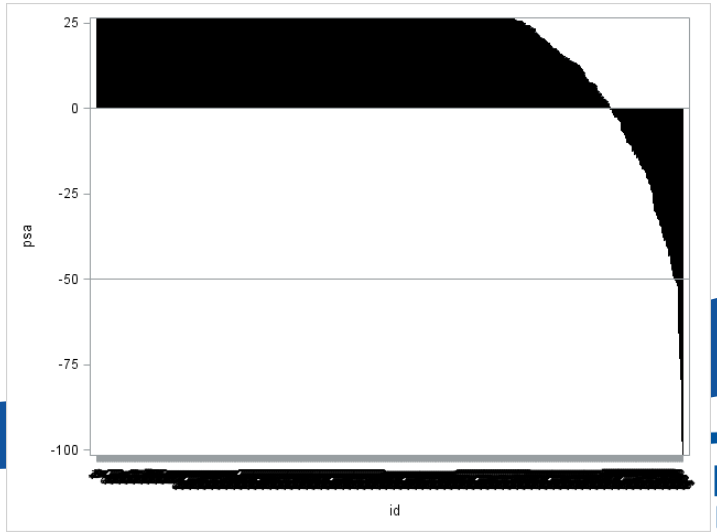
Generate correlated data (4)

- After one round simulation PSA data follows approximately the anticipated normal distributions by treatment
- Frequency of PSA responders is slightly less than anticipated
- Waterfall plots truncated at -100% and +25%



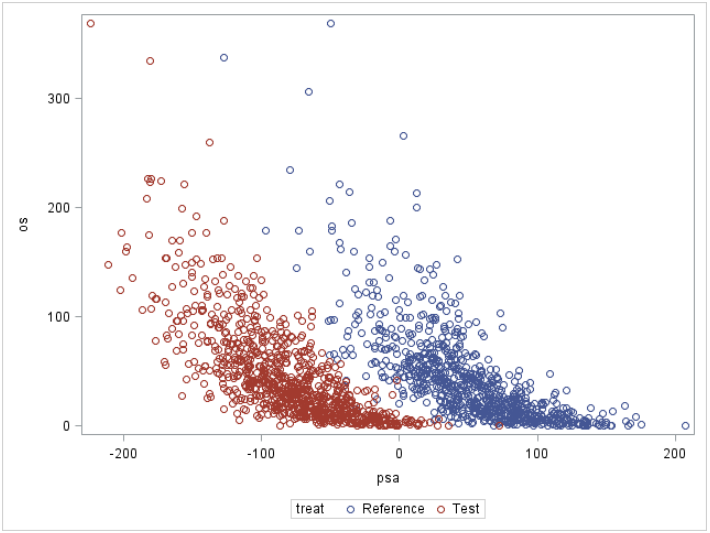
Analysis Variable : psa						
treat	N	Mean	Std Dev	Median	Minimum	Maximum
Reference	808	50.9	45.9	49.5	-127.8	207.2
Test	892	-80.2	43.6	-78.9	-224.1	72.2

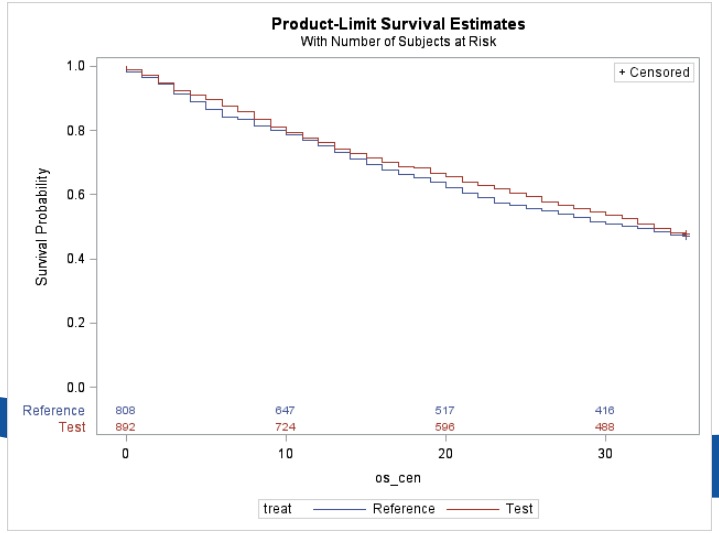
		Reference	Test	Total
psa_response				
NO	Frequency	797	217	1014
	Col Pct	98.64	24.33	
YES	Frequency	11	675	686
	Col Pct	1.36	75.67	
Total	Frequency	808	892	1700

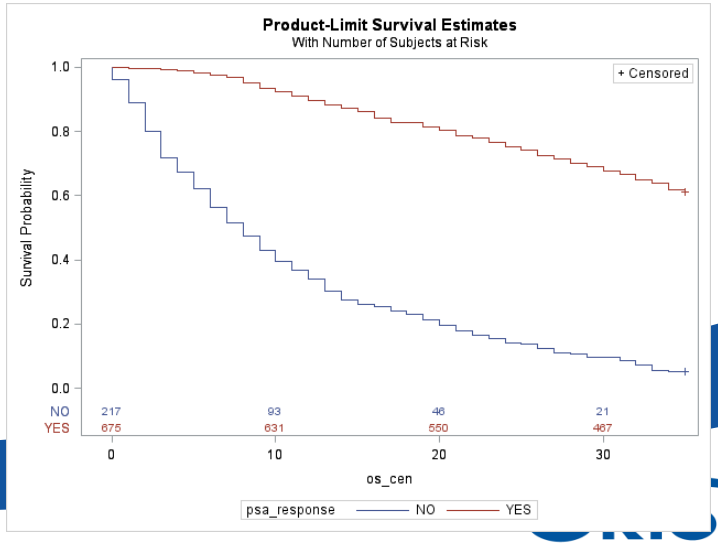


Generate correlated data (5)

- One round simulated OS data shows less impressive treatment effect than published median estimates 33 vs. 32 months giving HR = 0.97
- PSA vs. OS correlation r = 0.8 seems too high and K-M curves (in test arm) separate too strongly compared to published data







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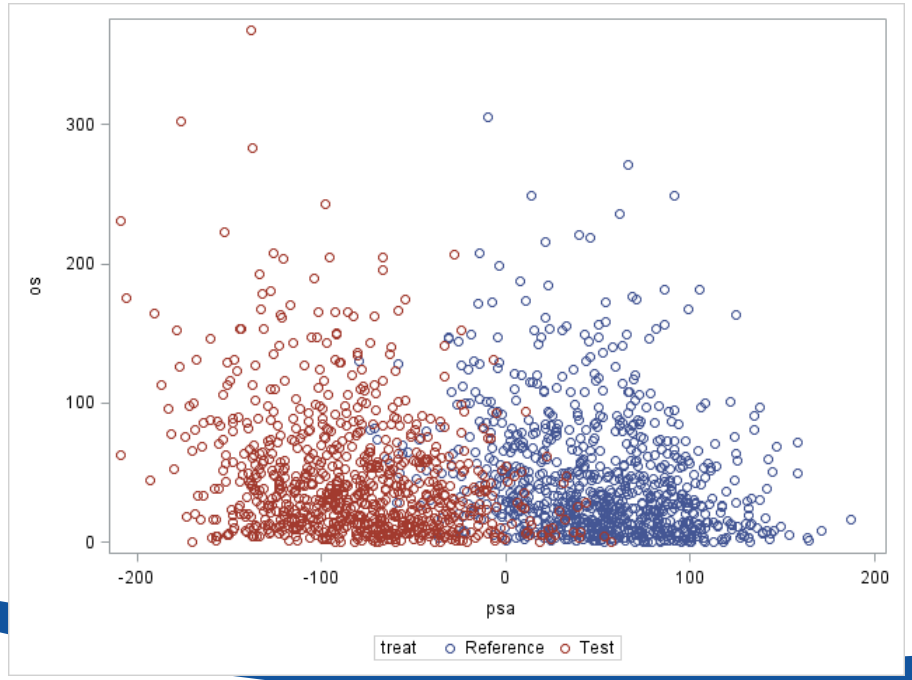
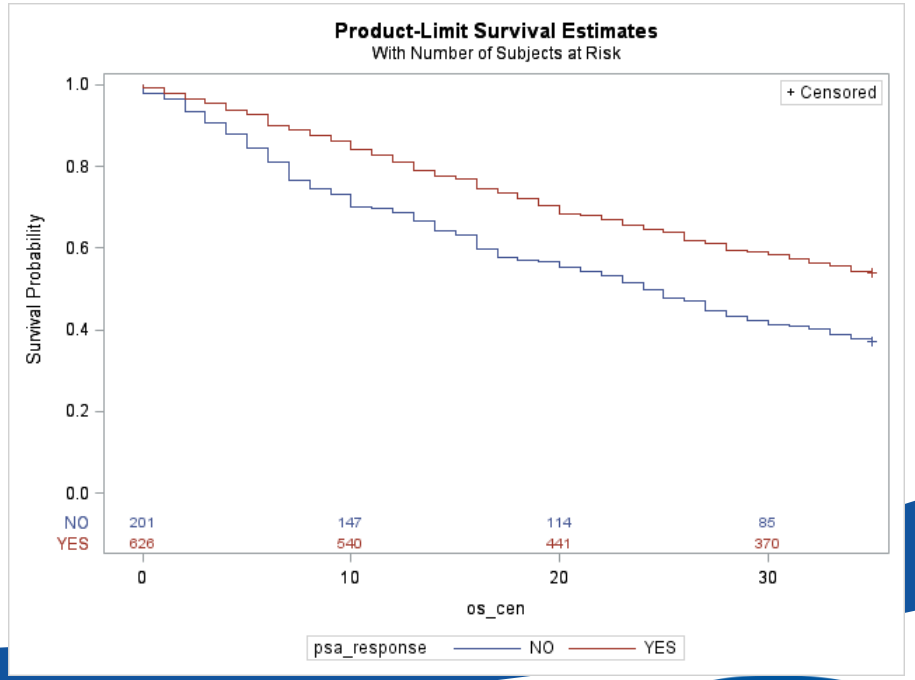
Generate correlated data (6)

- PSA vs. OS correlation r = 0.3 looks more appropriate compared to published data





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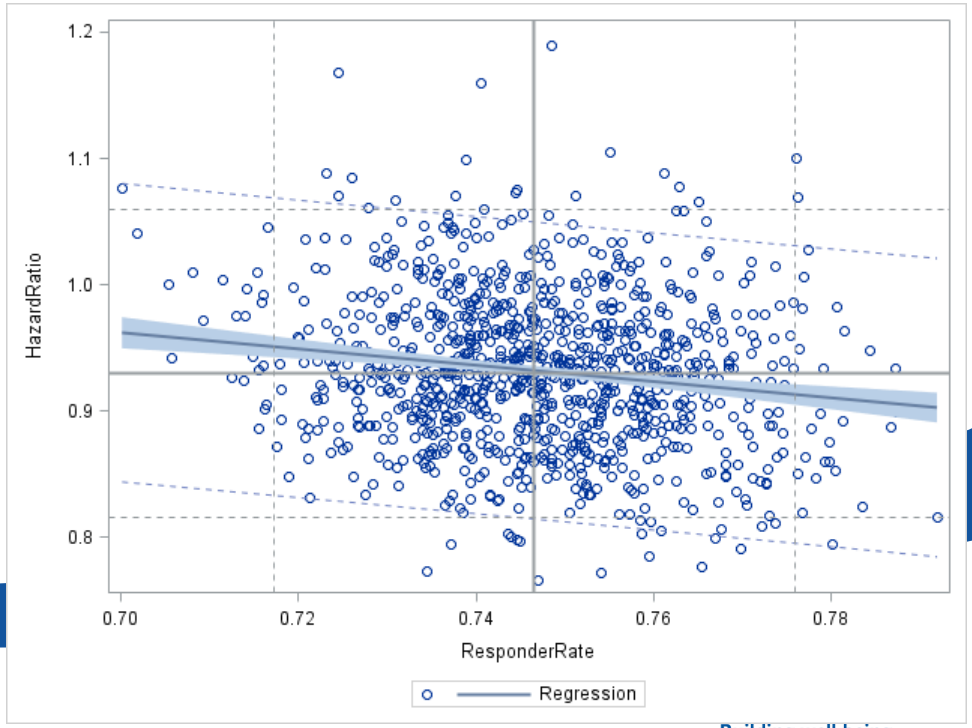
Association between hazard ratio and responder rate

- 1000 simulation iterations performed with model assuming
  - N = 1700 with 1:1 allocation
  - OS 32.4 vs. 30.2 mo
  - Active arm PSA response -80% +/- 45%
  - Intra subject correlation between OS and PSA r = -0.30
- Hazard ratio and responder rate calculated from each of iteration round
- 95% CLI around linear fit very wide and there seems not to be responder rate window that would implicate hazard ratio below 1

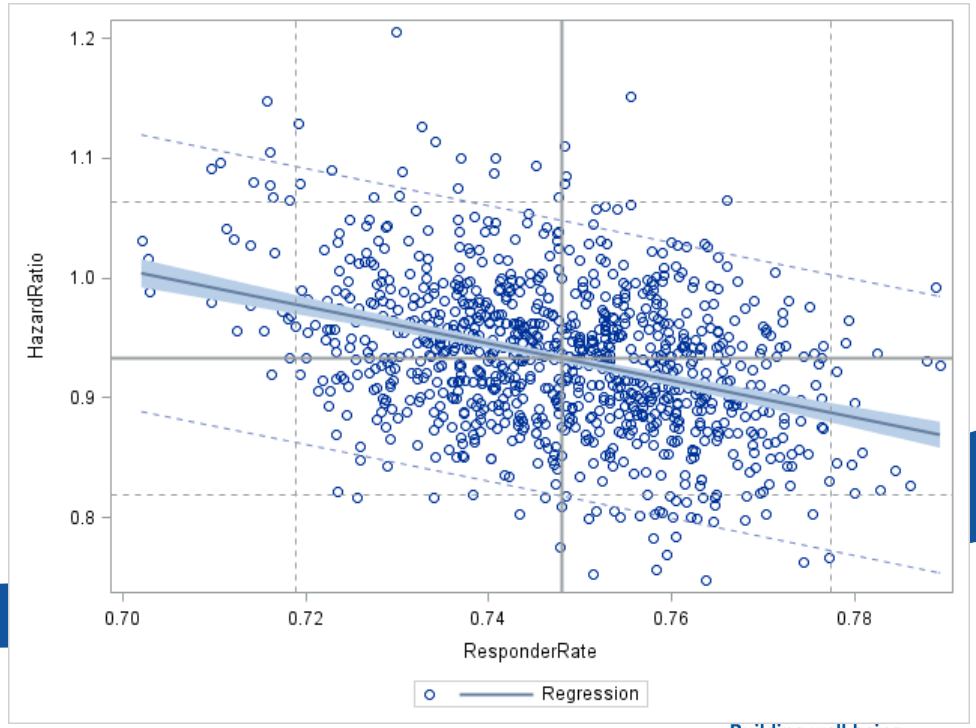
Variable	N	Mean	Std Dev	Median	Minimum	Maximum
HazardRatio	1000	0.93	0.06	0.93	0.77	1.19
HRLowerCL	1000	0.82	0.05	0.82	0.67	1.04
HRUpperCL	1000	1.06	0.07	1.06	0.87	1.36
ResponderRate	1000	0.75	0.01	0.75	0.70	0.79
rrlowercl	1000	0.72	0.02	0.72	0.67	0.76
rruppercl	1000	0.78	0.01	0.78	0.73	0.82



Association between hazard ratio and responder rate

- Assuming higher intrasubject correlation between OS and PSA r = -0.80 allow tighter 95% CLI
- Intrasubject correlation may be unrealisticly high and even with this the predictive power of responder rate is very low $R^2 = 0.13$
- Note that published HR 0.71 seems not plausible with reported median times

Variable	N	Mean	Std Dev	Median	Minimum	Maximum
HazardRatio	1000	0.93	0.06	0.93	0.75	1.17
HRLowerCL	1000	0.82	0.05	0.82	0.66	1.03
HRUpperCL	1000	1.06	0.07	1.06	0.86	1.33
ResponderRate	1000	0.75	0.01	0.75	0.69	0.79
rrlowercl	1000	0.72	0.02	0.72	0.66	0.76
rruppercl	1000	0.78	0.01	0.78	0.72	0.82



Concluding remarks

- In simulation models assumed within subject correlation makes a difference
- Copula method allows to simulate correlated data from various different distributions
- Within subject correlation between PSA response and overall survival is likely to be small, but clinically meaningful in mCRPC patients
- Predictive power of phase II PSA responder rate is low for phase III OS

What happened

- We changed population, picked up dose not studied in Phase II, changed endpoints, picked up the sample size similar to competitors
- Study is ongoing EudraCT Number: 2013-003820-36
- We got partner to run the study with us http://www.orion.fi/en/Orion-group/media/stock-exchange-releases/2014/orion-and-bayer-enter-global-agreement-for-development-and-commercialization-of-novel-prostate-cancer-treatment---orion-upgrades-full-year-outlook-for-2014--/

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