Is prostate-specific antigen a surrogate for survival in advanced prostate cancer?

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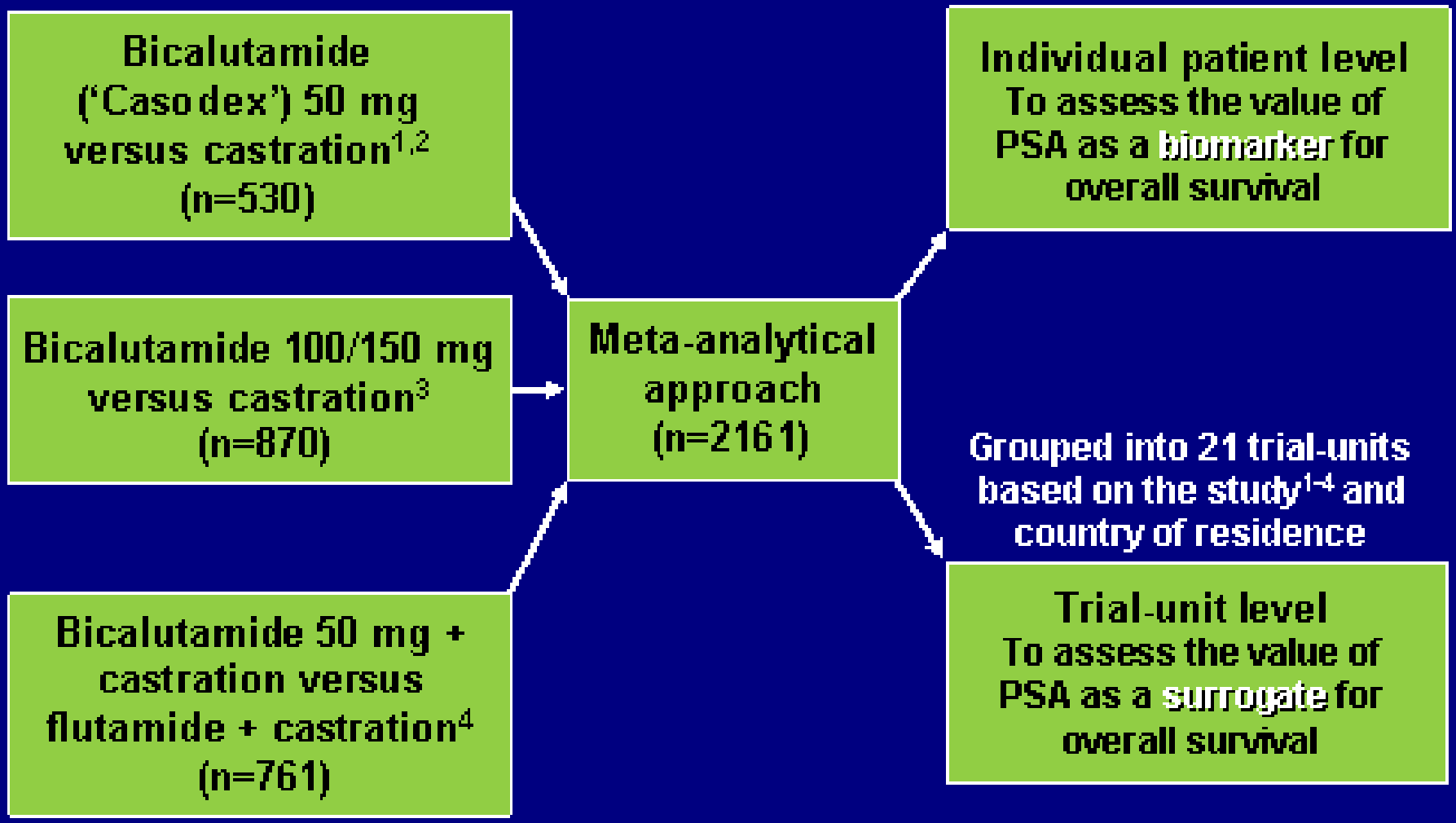
Aims

- Use of a surrogate endpoint in clinical trials would speed the development of new prostate cancer therapies
- In this study, various prostate-specific antigen (PSA) endpoints were assessed as surrogates for overall survival in advanced (metastatic) prostate cancer

Biomarker:
an intermediate outcome that is correlated with the true clinical outcome at the individual patient level

Surrogate:
a biomarker that is intended to serve as a substitute for the true endpoint in comparative treatment trials. It should allow prediction of the effect of a therapeutic intervention on the true endpoint with sufficient precision

Meta-analytical approach



[1]Iversen et al. *Scand J Urol Nephrol* 1996; 30: 93-98
[2]Kaisary et al. *Eur Urol* 1995; 28: 215-222; [3]Tyrrell et al. *Eur Urol* 1998; 33: 447-456
[4]Schellhammer et al. *Urology* 1995; 45: 745-752

Potential surrogate endpoints for overall survival

Potential surrogate endpoint	Definition
PSA response	A PSA decline from baseline level (≥20 ng/mL) ≥50% at 2 subsequent observations ≥4 weeks apart
Time to PSA progression-1	Time to a ≥20% increase above the nadir and which exceeded the upper normal limit (ie >4 ng/mL)
Time to PSA progression-2	Time to an increase ≥50% above the moving average (based on 3 consecutive measurements) nadir and which exceeded 2.5 times the upper normal limit (ie a level >10 ng/mL). This increase had to be either the last observed value or be sustained for ≥4 weeks
Longitudinal PSA profile	The complete series of PSA measurements in each patient

Statistical methods

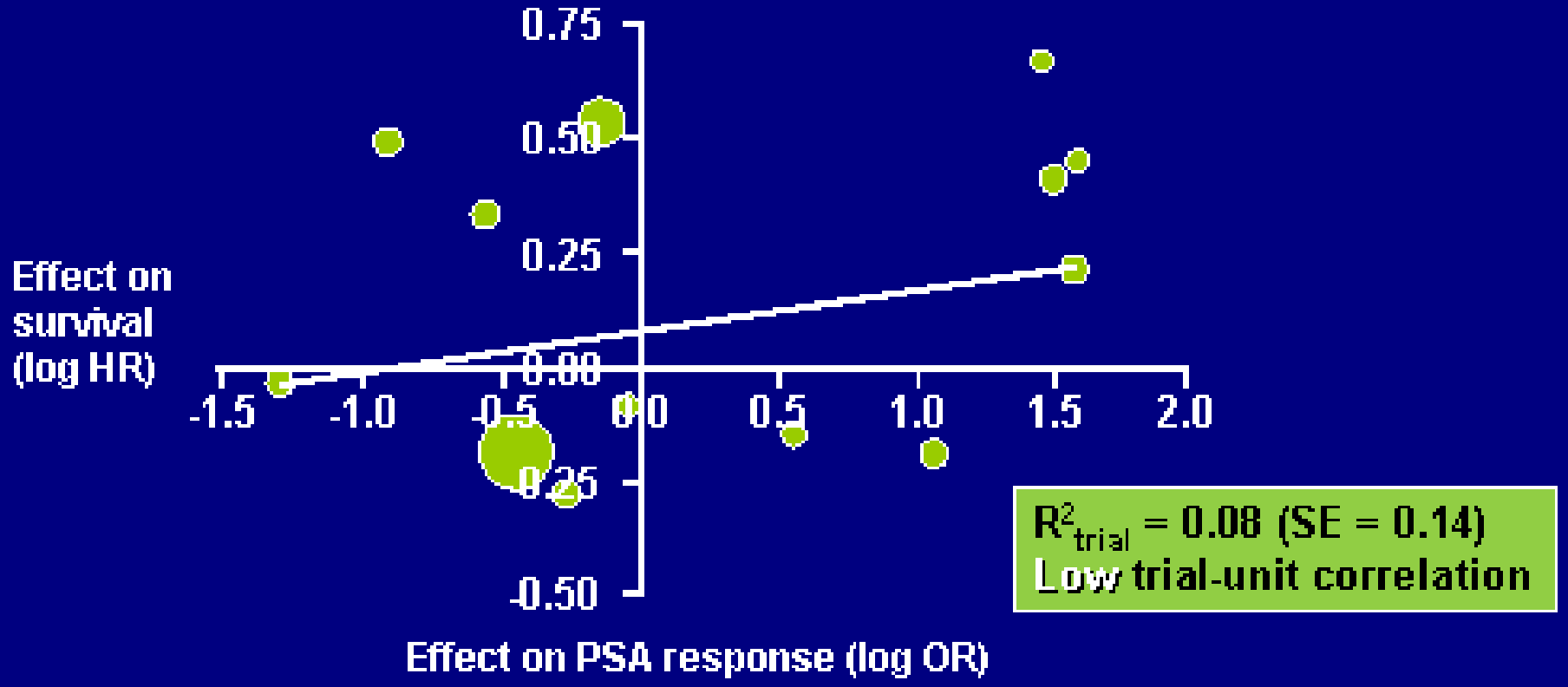
- The relative treatment effects on the survival endpoint (log survival ratio) and on the various PSA endpoints were estimated using the meta-analytical validation approach[1]
- The squared correlation between these treatment effects (R^2_{trial}) was estimated from the slope of the regression line

R^2_{trial} close to 1 = proof of surrogacy
(ie a precise prediction of the treatment effect on survival from the treatment effect on the PSA endpoint)

[1]Buyse et al. *Biostatistics* 2000; 1: 49-68

Estimated treatment effects on the PSA response

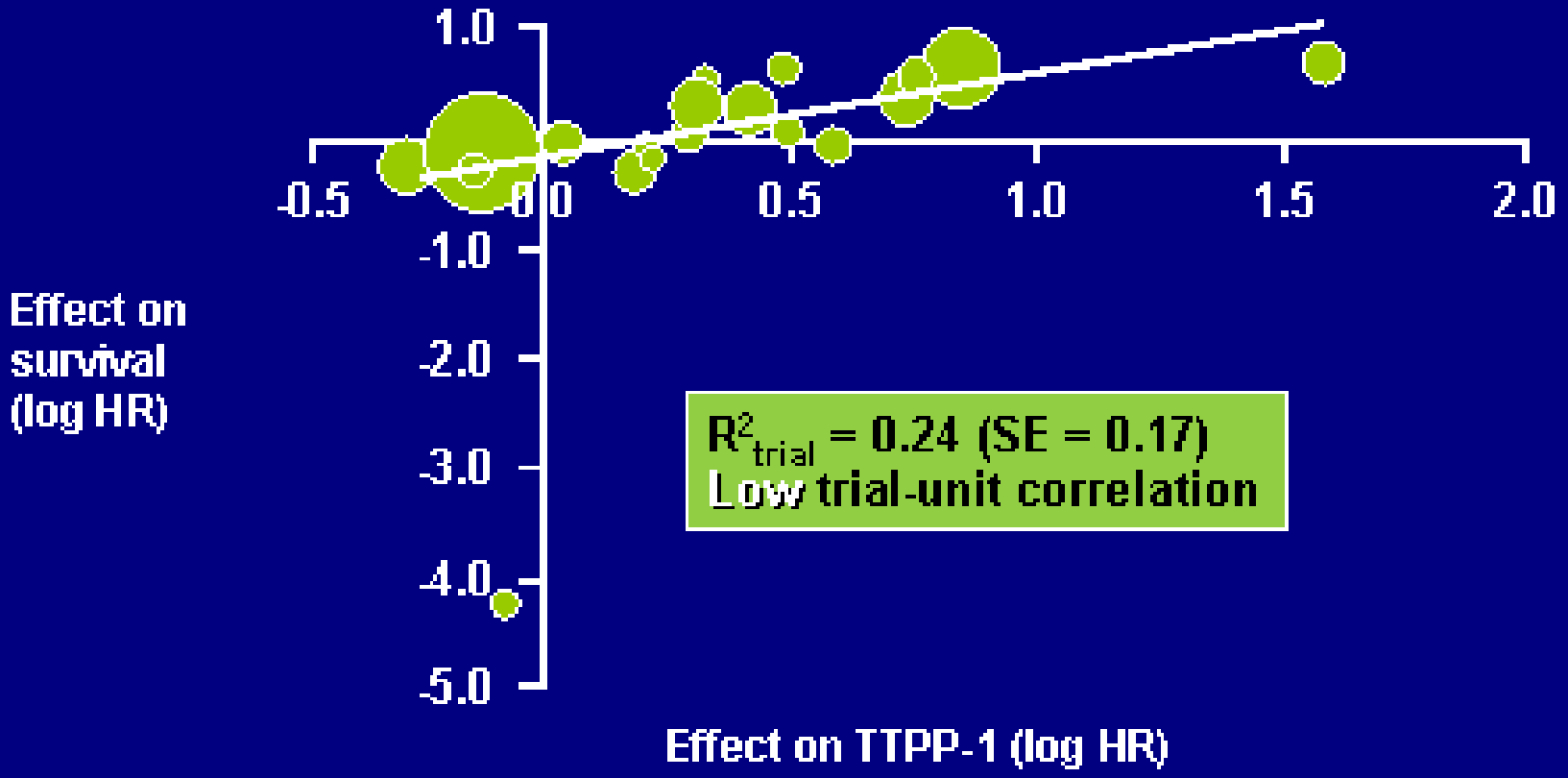
Trial-unit level



Survival HR was analyzed for 13 trial-units (n=1606)
Each circle represents an individual trial-unit and their size is proportionate to the sample size
The line represents the prediction from an estimated (weighted) regression line
HR, hazard ratio; OR, odds ratio; PSA, prostate-specific antigen; SE, standard error

Estimated treatment effects on survival against TTPP-1

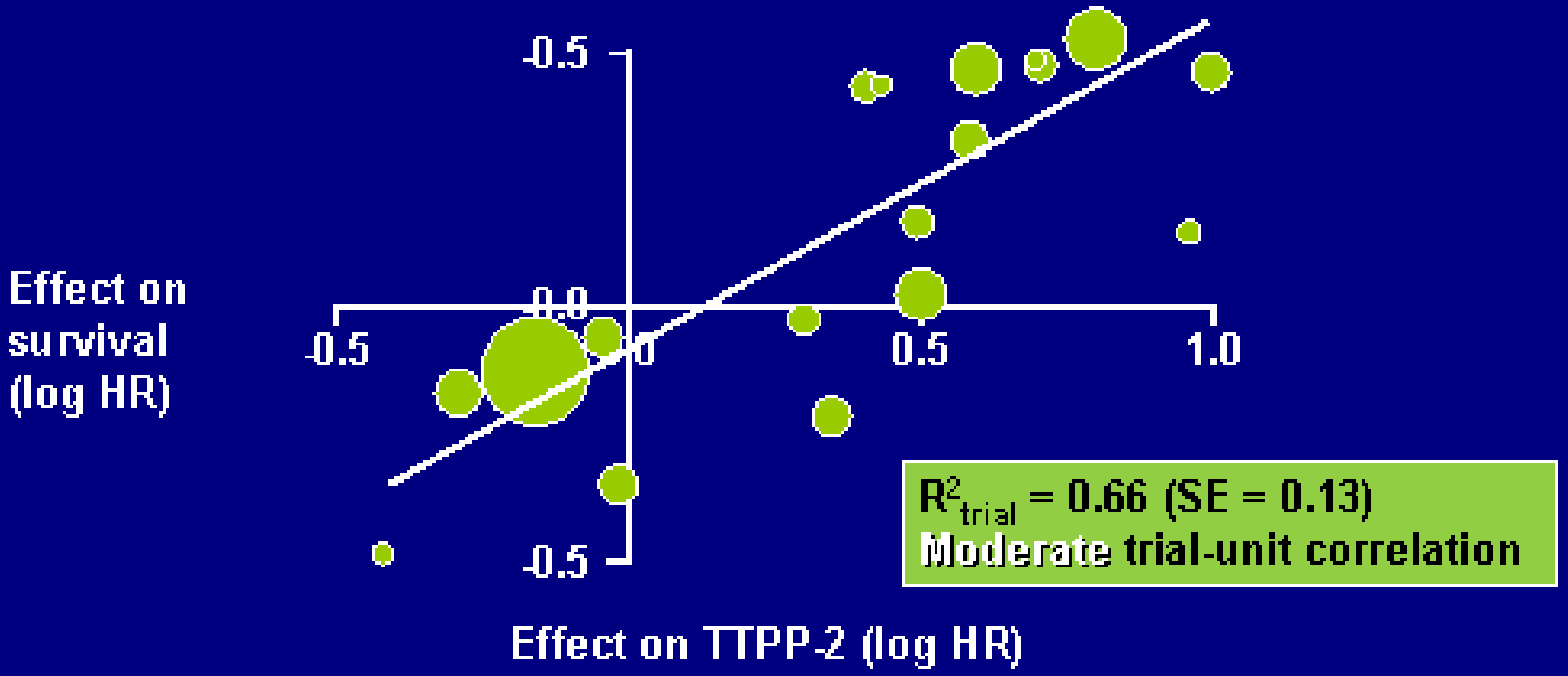
Trial-unit level



TTPP-1 was analyzed for 19 trial-units (n=2070)
Each circle represents an individual trial-unit and their size is proportionate to the sample size
The line represents the prediction from an estimated (weighted) regression line
HR, hazard ratio; SE, standard error; TTPP-1, time to prostate-specific antigen progression-1

Estimated treatment effects on survival against TTPP-2

Trial-unit level



TTPP-2 was analyzed for 18 trial-units (n=2043)
Each circle represents an individual trial-unit and their size is proportionate to the sample size
The line represents the prediction from an estimated (weighted) regression line
HR, hazard ratio; SE, standard error; TTPP-2, time to prostate-specific antigen progression-2

Correlation between longitudinal PSA and overall survival

Trial-unit level

- The mean profiles of log-transformed PSA measurements for groups of patients with similar observation times showed a quadratic curvature
- PSA profiles were therefore modeled as a function of time and the square root of time
- At the trial-unit level:

R^2_{trial} = 0.68 (SE = 0.12)
Moderate trial-unit correlation

Association between PSA endpoints and survival*

	Individual patient correlation	Trial-unit correlation
PSA response	High	Low
Time to PSA progression-1	Moderate	Low
Time to PSA progression-2	Moderate	Moderate
Longitudinal PSA	High	Moderate

True surrogacy = a high correlation between the treatment effect on the surrogate and the treatment effect on the true endpoint (overall survival), which needs to be established across groups of patients treated with the new and standard interventions

*Median 3.25 years' follow-up

Conclusions

- At the individual patient level, the analyses confirm the known association between PSA endpoints and overall survival, and thus the value of PSA as a biomarker
- At the trial-unit level, the association between PSA-based endpoints and overall survival was generally low to moderate
- Overall survival cannot therefore be reliably predicted across groups of patients on the basis of PSA
- Analysis using prostate cancer survival as the true endpoint led to similar findings

PSA is unlikely to be a valid surrogate for overall survival for use in Phase III clinical trials of hormonal treatments in advanced prostate cancer