Is prostate-specific antigen a surrogate for objective clinical progression in early prostate cancer?

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Introduction

- Surrogate endpoints may aid the development of prostate cancer therapies
- The biomarker prostate-specific antigen (PSA) is a promising potential surrogate for prostate cancer progression
- Surrogacy requires that the treatment effect on PSA can predict the treatment effect on objective clinical progression

Objective

To determine whether PSA progression may be a surrogate endpoint for clinical disease progression in patients with early non-metastatic prostate cancer, using data from 8113 patients in the bicalutamide ('Casodex') 150 mg Early Prostate Cancer (EPC) program

The bicalutamide 150 mg EPC program

- Three geographically distinct trials conducted across 21 countries (Trials 23, 24 and 25)
- Examining bicalutamide 150 mg/day (n=4052) or placebo (n=4061) in addition to standard care
- Endpoints
  - overall survival
  - time to objectively confirmed disease progression (progression-free survival)[1]
  - time to PSA progression[2]

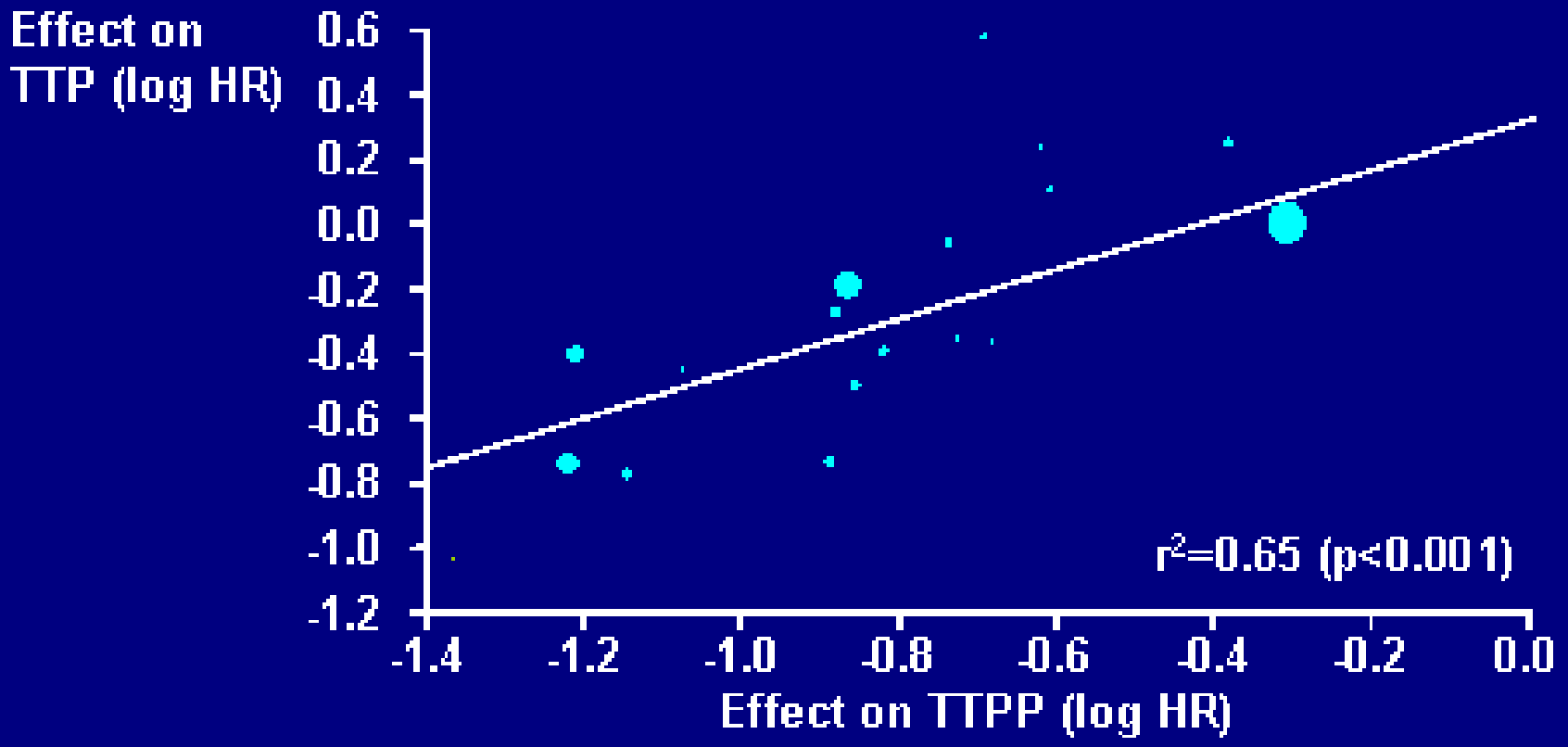
fined as [1]time from randomization to earliest occurrence of objective progression or death from any use without progression; [2]time between randomization and earliest occurrence of PSA doubling from seline, objective progression, or death from any cause in the absence of progression

Methods

- Clinical endpoint: time to objectively confirmed disease progression (TTP)
- Surrogate endpoint: time to PSA progression (TTPP)
- Previously accepted meta-analytic methodology[1] for the assessment of intermediate endpoints and potential surrogates used
- Relative treatment effects on TTP and TTPP estimated by region
- Control analysis performed which excluded data from largest region (Trial 23, conducted in USA and Canada)

[1] Buyse & Molenberghs. *Biometrics* 1998; 54: 1014-29 / Buyse et al. *Biostatistics* 2000; 1: 49-67

Significant correlation between the effects of bicalutamide on TTP and TTPP



Points represent observations in each region; area is proportionate to sample size

HR, hazard ratio

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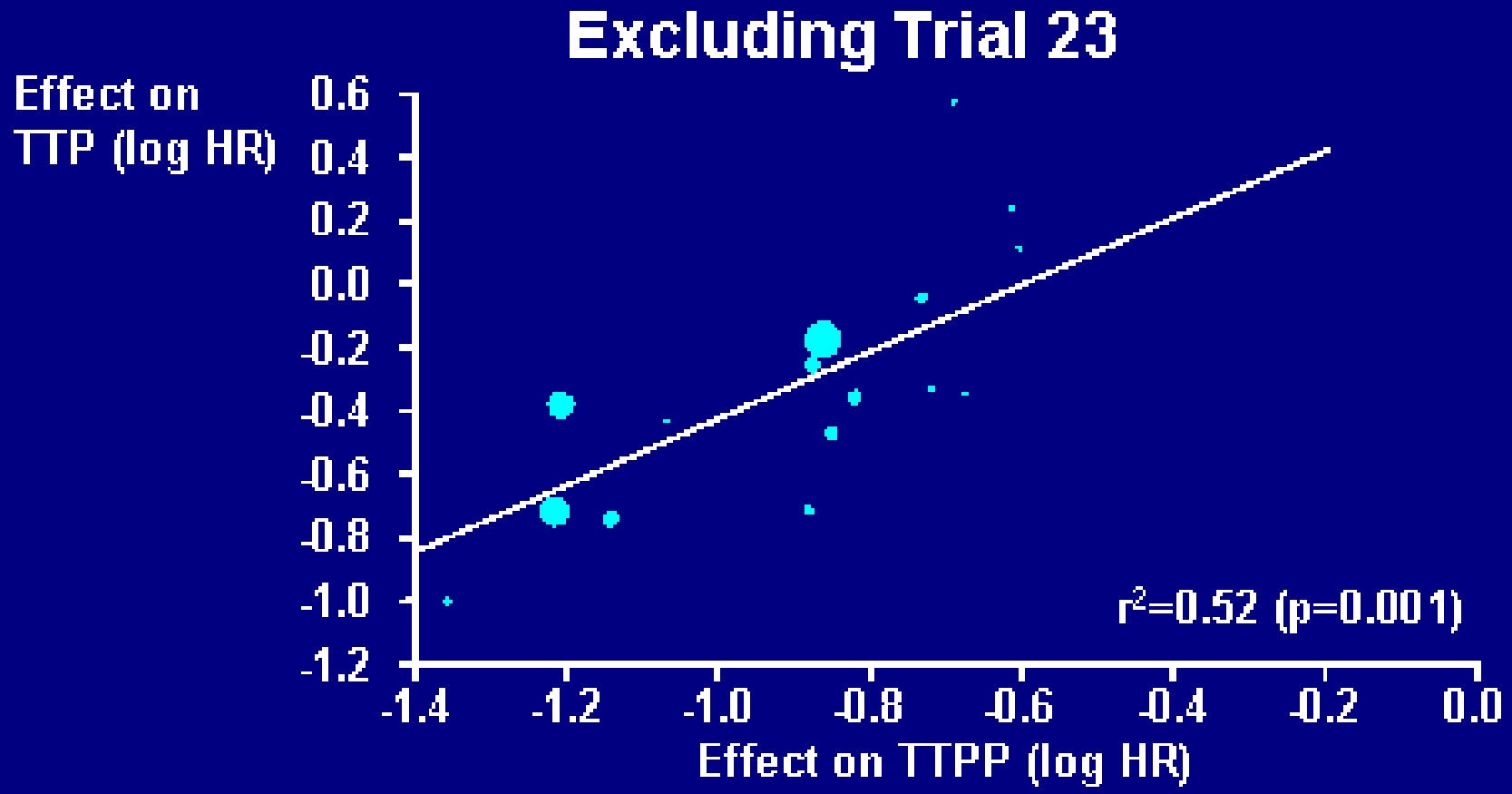

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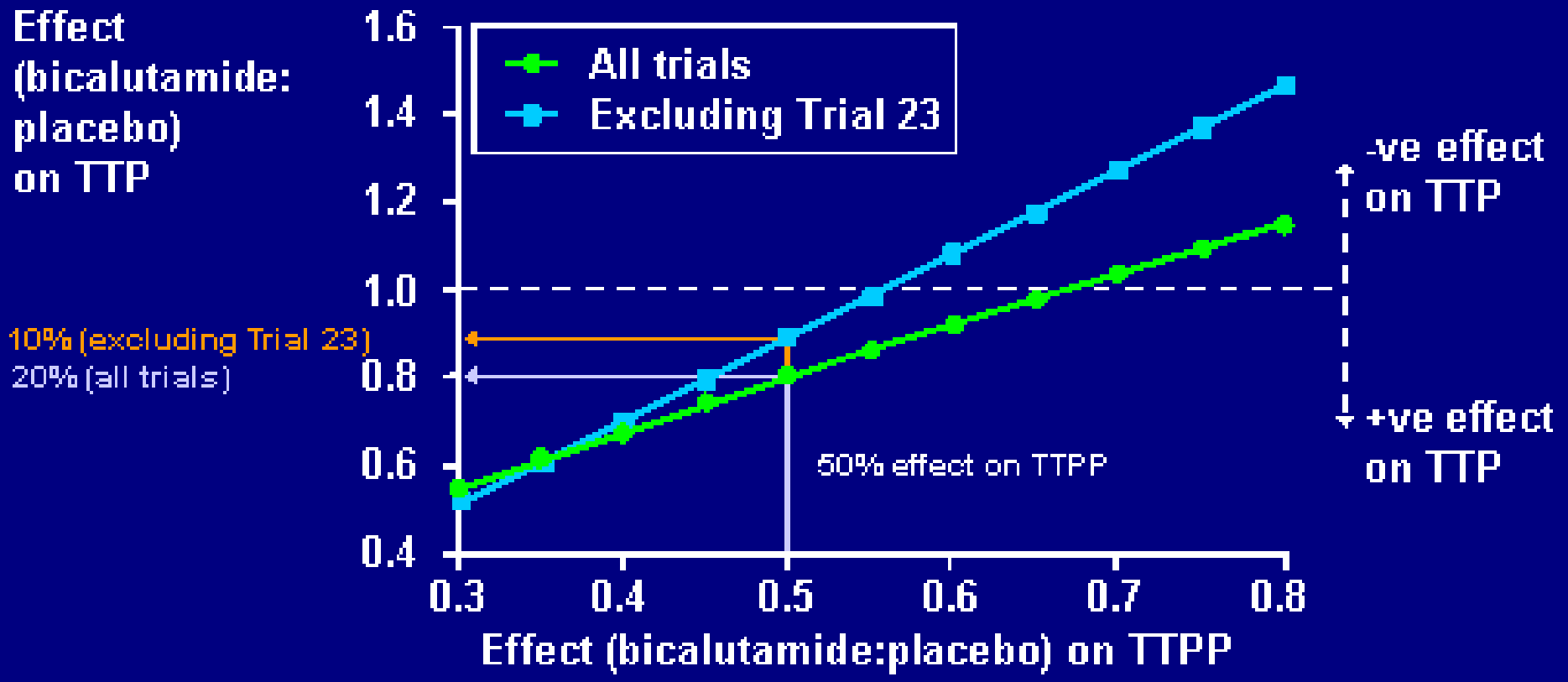
Prediction of treatment effect on TTP from effect observed on TTP



50% reduction in risk of PSA progression results in a 10-20% reduction in risk of objective clinical progression

Conclusions

In early prostate cancer

- The effect of hormonal treatment on the surrogate endpoint of PSA progression is moderately predictive for the effect on objective clinical progression
- A large positive effect on time to PSA progression is reasonably likely to reflect a clinically important delay in objective clinical progression