



Transforming surrogate outcomes: an Australian review

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(with input from Ian Marschner and Robyn Ward)



Australian STFOWG report

- ◆ **Nov 2007: Established by PBAC under ESC**
- ◆ **Jan 2009: report released as URL:**
 - [http://www.health.gov.au/internet/main/publishing.nsf/Content/B11E8EF19B358E39CA25754B000A9C07/\\$File/STFOWG%20paper%20FINAL.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/B11E8EF19B358E39CA25754B000A9C07/$File/STFOWG%20paper%20FINAL.pdf)
- ◆ **Now: preparing response to feedback and final report**



3 Objective of framework

- ◆ Identify sources of uncertainty
- ◆ Arrange these sources logically
- ◆ Distinguish between types of information for each source that strengthen or weaken confidence in the transformation for the drug
- ◆ Qualitative rather than quantitative overall
- ◆ Place in broader context of appraising the proposed drug



STFOWG assessment framework

- | Step | Summary |
|--------------|---|
| One | Definition, selection and measurement of PSM and TCO |
| Two | Relationship between PSM and TCO <ul style="list-style-type: none">◆ biological reasoning◆ evidence from epidemiological studies |
| Three | Relationship between Δ PSM and Δ TCO <ul style="list-style-type: none">◆ biological and pharmacological reasoning◆ evidence from randomised trials using other treatments |
| Four | Apply to treatment being assessed <ul style="list-style-type: none">◆ biological and pharmacological reasoning◆ Δ PSM |
| Five | Incorporate Δ TCO estimate and uncertainty into economic evaluation |



Two parallel streams

◆ Biological rationale

- pathophysiology and biochemistry (step 2)
- pharmacology (or other mechanism of action)
 - » *other therapies (step 3)*
 - » *proposed therapy (step 4)*
- prespecified > retrospective

◆ Empirical evidence

- epidemiology and observational associations (step 2)
- randomised trials and meta-regressions (step 3)



Step 1 of proposed framework

- ◆ **There are many possible surrogate outcomes and clinical outcomes in each therapeutic area**
 - many ways of measuring each outcome
 - careful definition and selection is needed
- ◆ **Usually requires secondary analyses based on existing research**
 - systematic literature search skills are needed



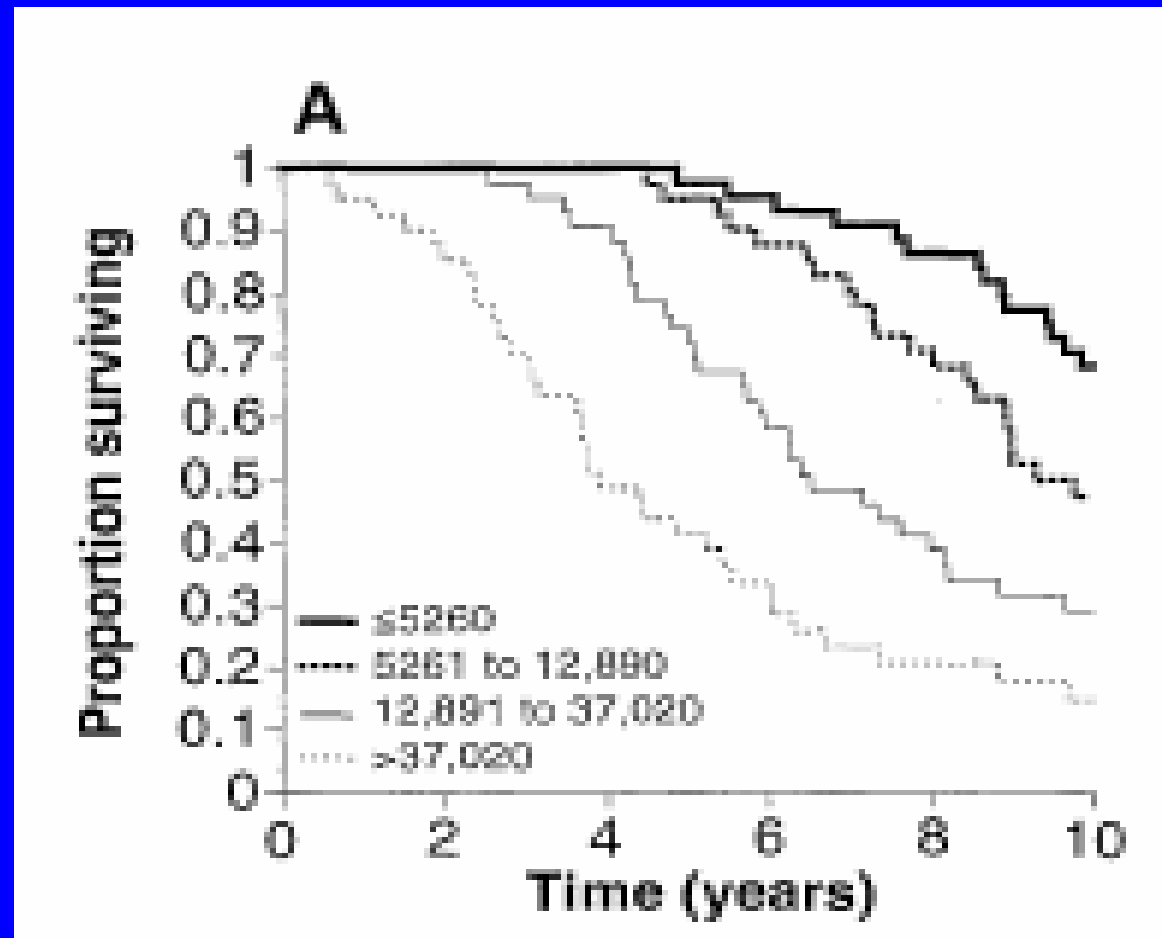
7 Step 2 of proposed framework

- ◆ Review of studies providing information about the association between the proposed surrogate outcome and the target clinical outcome
 - population cohort studies
 - clinical cohorts from placebo arms of randomised trials
- ◆ Review of strength of the association between the surrogate outcome and the clinical outcome
- ◆ Assessment of whether the association is consistent across different epidemiological studies in both qualitative and quantitative terms



Step 2 example: HIV viral load

- ◆ Untreated HIV-infected cohort
- ◆ Higher viral load is very strongly predictive of higher mortality and/or AIDS
- ◆ *Mellors et al, Science 1996;272:1167*





Step 3 of proposed framework

- ◆ **Meta-analysis is the most convincing method to explore the relationship between the treatment effects on the proposed surrogate outcome and on the target clinical outcome**
- ◆ **Ideally use multiple randomised trials which have assessed the effects of other relevant treatments on both the surrogate outcome and the clinical outcome**
 - **meta-regression of the surrogate treatment effect versus the clinical treatment effect**
 - **predictive relationship and associated measures**

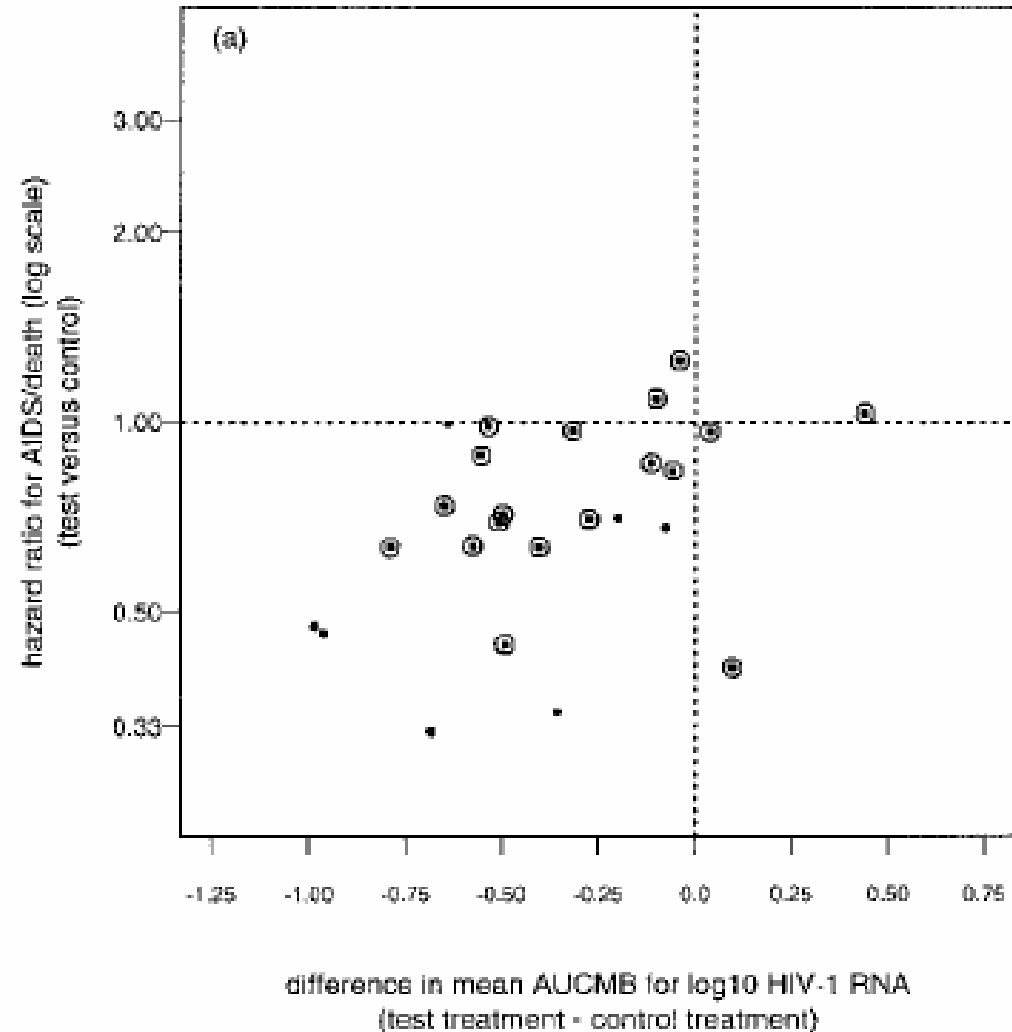
Step 3: single trial only

- ◆ **Assessment of surrogacy based on a single randomised trial is less convincing**
 - proportion of treatment effect explained (PTE) is not recommended
 - “quasi meta-regression” across centres in a multi-centre randomised trial is sometimes informative
- ◆ **If meta-regression is not possible then the epidemiological information in Step 2 becomes very important**
- ◆ **Usually only Step 2 information is available**



HIV viral load: imperfect surrogate

- ◆ In meta-analyses, reduction in viral load predicts a reduction in AIDS/death
- ◆ However, the association is not strong
- ◆ Part (but not all) of the treatment effect is mediated through viral load
- ◆ Viral load reduction is an imperfect surrogate for AIDS/death
- ◆ Other mechanisms (eg CD4 count improvement) explain some of the treatment effect
- ◆ *AIDS Res Hum Ret*, 2000, p.1123



Summary of Steps 2 and 3

- ◆ **A modifiable risk factor may be highly predictive of clinical outcomes, but may not necessarily be a good surrogate outcome for predicting treatment effects on clinical outcomes**
- ◆ **For a modifiable risk factor to be a good surrogate outcome, treatment-induced changes in the proposed surrogate outcome must be highly predictive of treatment-induced changes in clinical outcomes**

Summary cont'd

- ◆ **Step 2 of the proposed framework involves investigating the extent to which the proposed surrogate outcome is predictive of clinical outcomes**
- ◆ **Step 3 of the proposed framework involves investigating the extent to which treatment-induced changes in the proposed surrogate are predictive of treatment-induced changes in clinical outcomes**

Moving to Step 4

- ◆ Steps 2 and 3 necessarily involve the use of data on other treatments (otherwise there would be no need to rely on surrogate outcome data for the new treatment being assessed)
- ◆ Step 4 of the framework requires consideration of whether the experience with other treatments will be relevant to the new treatment ...



Using surrogates in CRC

1. Metastatic setting

- TTP = time to progression

2. Adjuvant chemotherapy

- DFS = disease-free survival

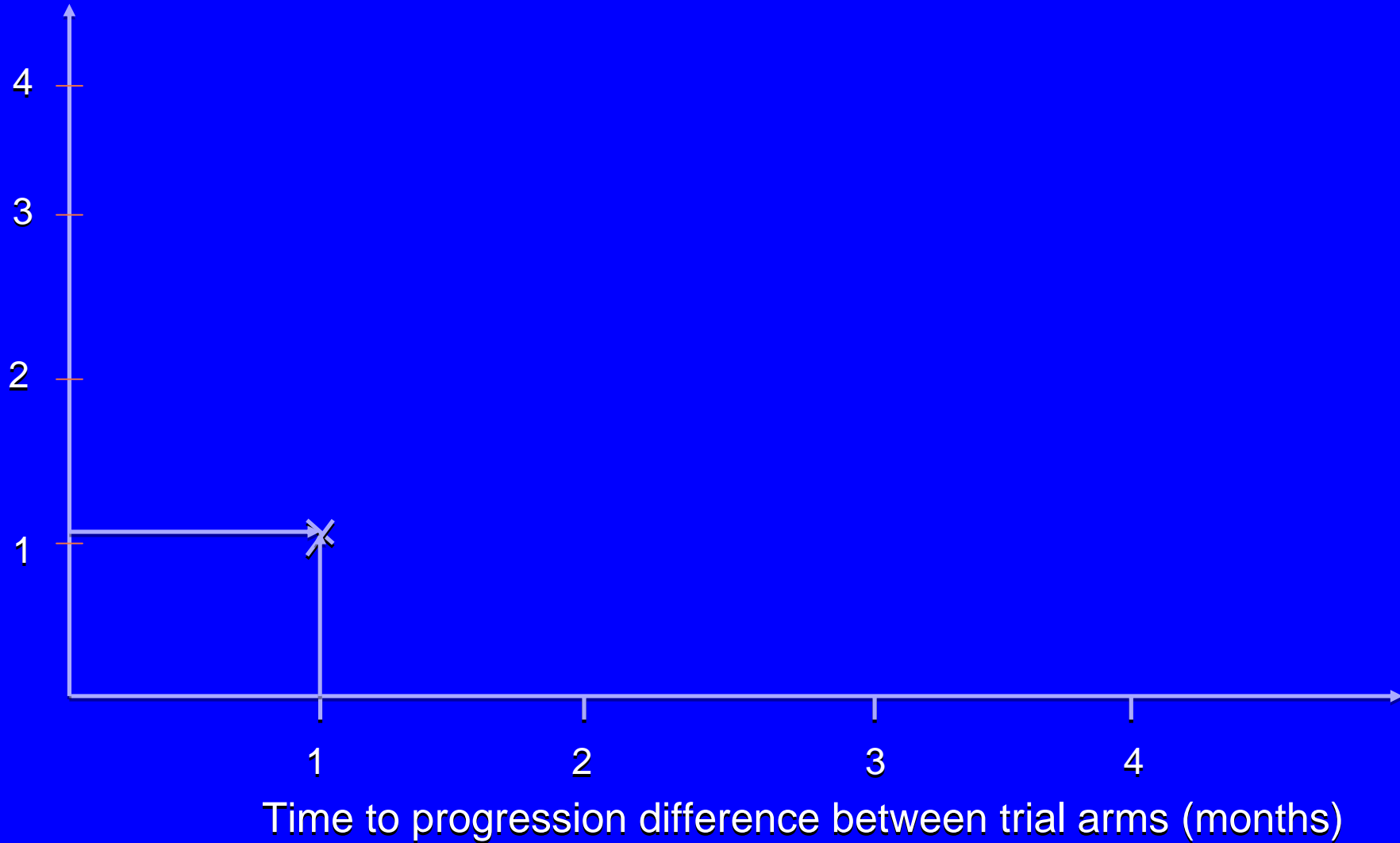
1: Predicting Δ overall survival using Δ time to progression in metastatic CRC

- ◆ Drug trials between 1966 – June 2005
- ◆ 1st line pharmacological treatments
- ◆ 146 trials (35,337 participants)



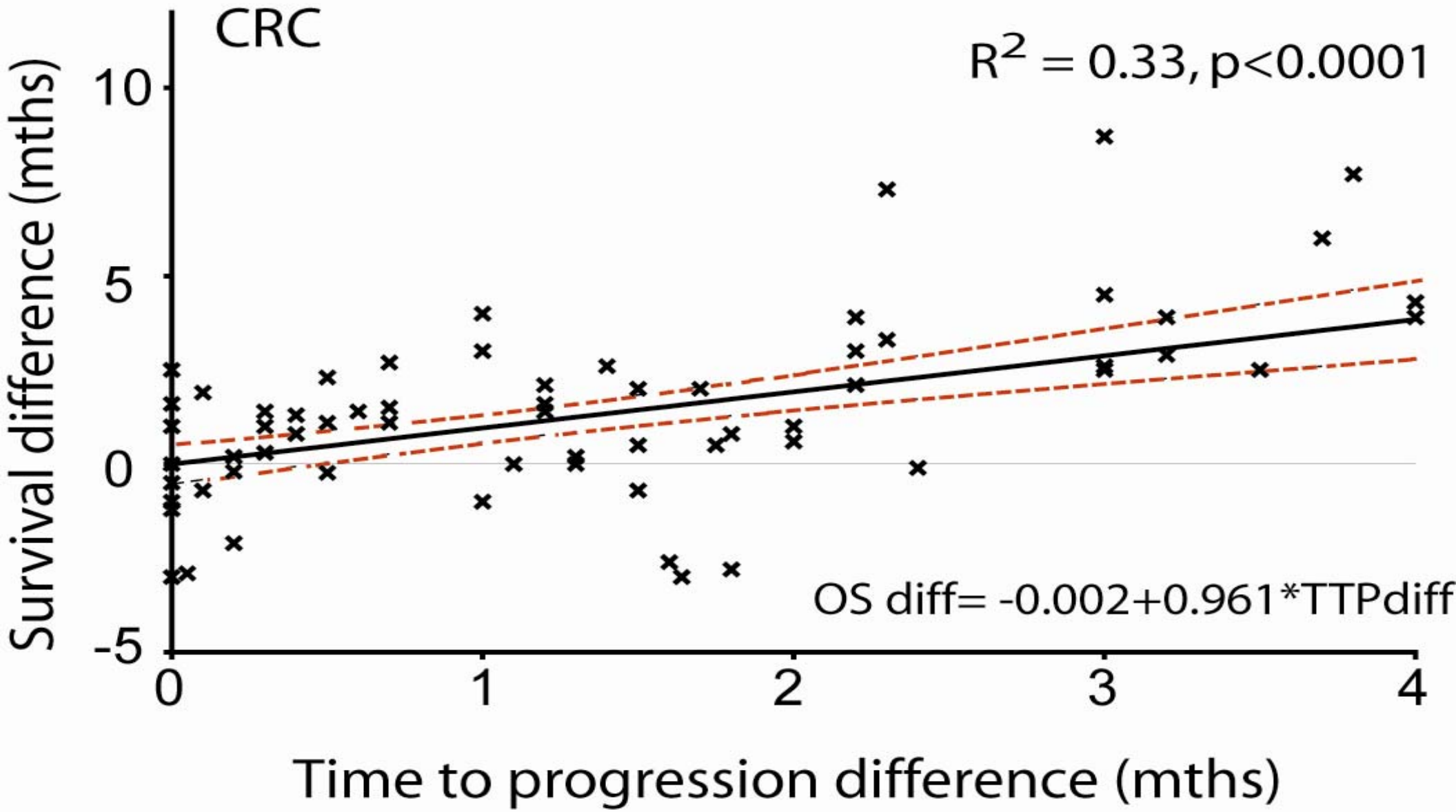
Increments in surrogate vs survival

Overall
survival
difference
between
trial arms
(months)





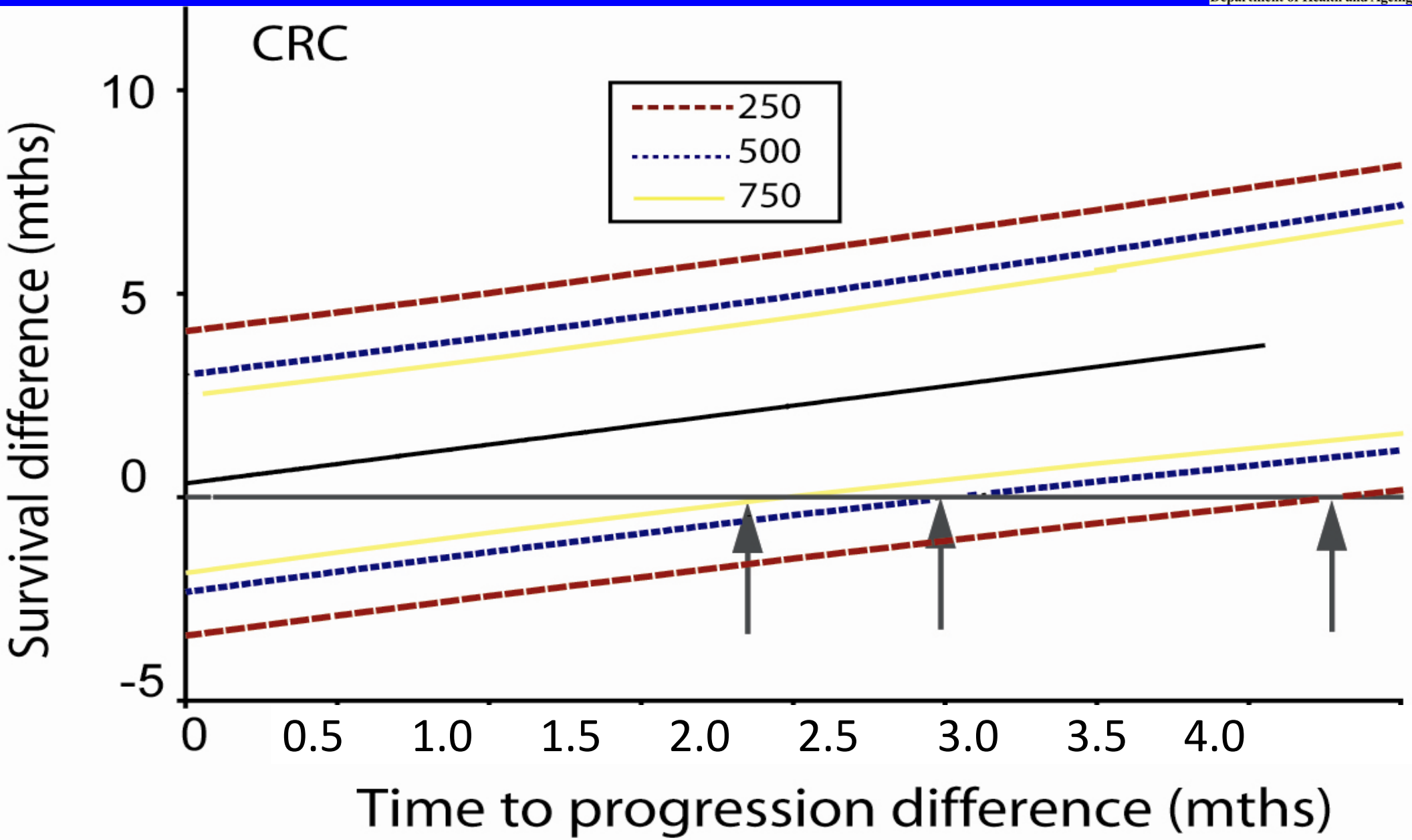
Relationship between Δ TTP and Δ survival





Predict a difference in overall survival using a future observed time to progression by calculating prediction bands for future trials of various sample sizes

20 Predicting survival from TTP





²¹ **Threshold effect size in TTP required to predict a significant gain in overall survival**

Trial sample size	250	500	750
TTP difference (months)	3·2	2·3	1·9



Limitations of this approach

- ◆ **Drug class – 5FU**
- ◆ **Summary data not IPD**
- ◆ **Methodology – use of a linear model**
- ◆ **Participant enrolment: median age 62 years**
- ◆ **Reporting of surrogates (all 144 measured OS):**
 - **TTP in 47% (68 trials)**
 - » *response rate in 99%*
 - » *stable disease in 62% (90 trials)*
 - » *Progression-free survival in 23% (33 trials)*



Possible interpretation



- ◆ Surrogate effect size $>$ threshold
=> safely conclude trial



- ◆ Surrogate effect size $<$ threshold
=> keep going



- ◆ Hierarchy of surrogates - time to progression preferred to response rate



24 2: Predicting oxaliplatin effect on overall survival in adjuvant CRC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer

Thierry André, M.D., Corrado Boni, M.D., Lamia Mounedji-Boudiaf, M.D.,
Matilde Navarro, M.D., Josep Tabernero, M.D., Tamas Hickish, M.D.,
Clare Topham, M.D., Marta Zaninelli, M.D., Philip Clingan, M.D.,
John Bridgewater, M.D., Isabelle Tabah-Fisch, M.D.,
and Aimery de Gramont, M.D., for the Multicenter International Study
of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment
of Colon Cancer (MOSAIC) Investigators

Primary results of MOSAIC

Oxaliplatin has significant advantages over 5FU in terms of reducing the risk of recurrence, but it is more toxic and overall survival is not significantly improved after 3 years

Hazard ratio for recurrence	0.77 (0.62, 0.90)	p=0.002
Hazard ratio for overall survival	0.86 (0.66, 1.11)	



Example of Steps 3 and 4

VOLUME 23 · NUMBER 34 · DECEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Disease-Free Survival Versus Overall Survival As a Primary End Point for Adjuvant Colon Cancer Studies: Individual Patient Data From 20,898 Patients on 18 Randomized Trials

Daniel J. Sargent, Harry S. Wieand, Daniel G. Haller, Richard Gray, Jacqueline K. Benedetti, Marc Buyse, Roberto Labianca, Jean Francois Seitz, Christopher J. O'Callaghan, Guido Francini, Axel Grothey, Michael O'Connell, Paul J. Catalano, Charles D. Blanke, David Kerr, Erin Green, Norman Wolmark, Thierry Andre, Richard M. Goldberg, and Aimery De Gramont

From the North Central Cancer Treatment Group, Mayo Clinic, Rochester.

Sargent's approach

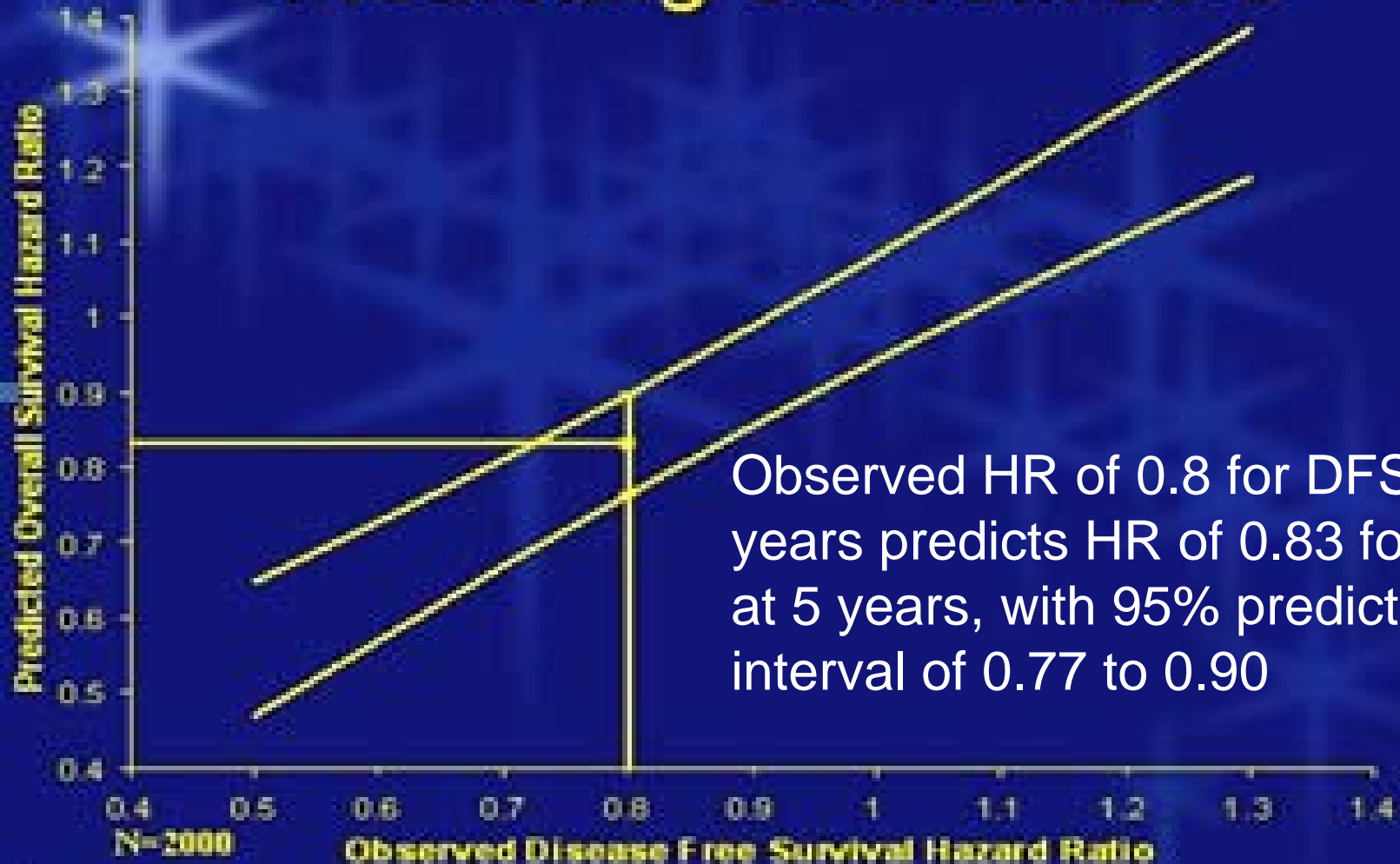
- ◆ **Individual patient data (IPD) from 20,898 participants in 18 phase III randomised trials in adjuvant setting**
- ◆ **Time points: 3 years for DFS and 5 years for OS**
- ◆ **Primary basis for comparison: hazard ratios**

Predicted OS hazard ratios based on observed DFS hazard ratios

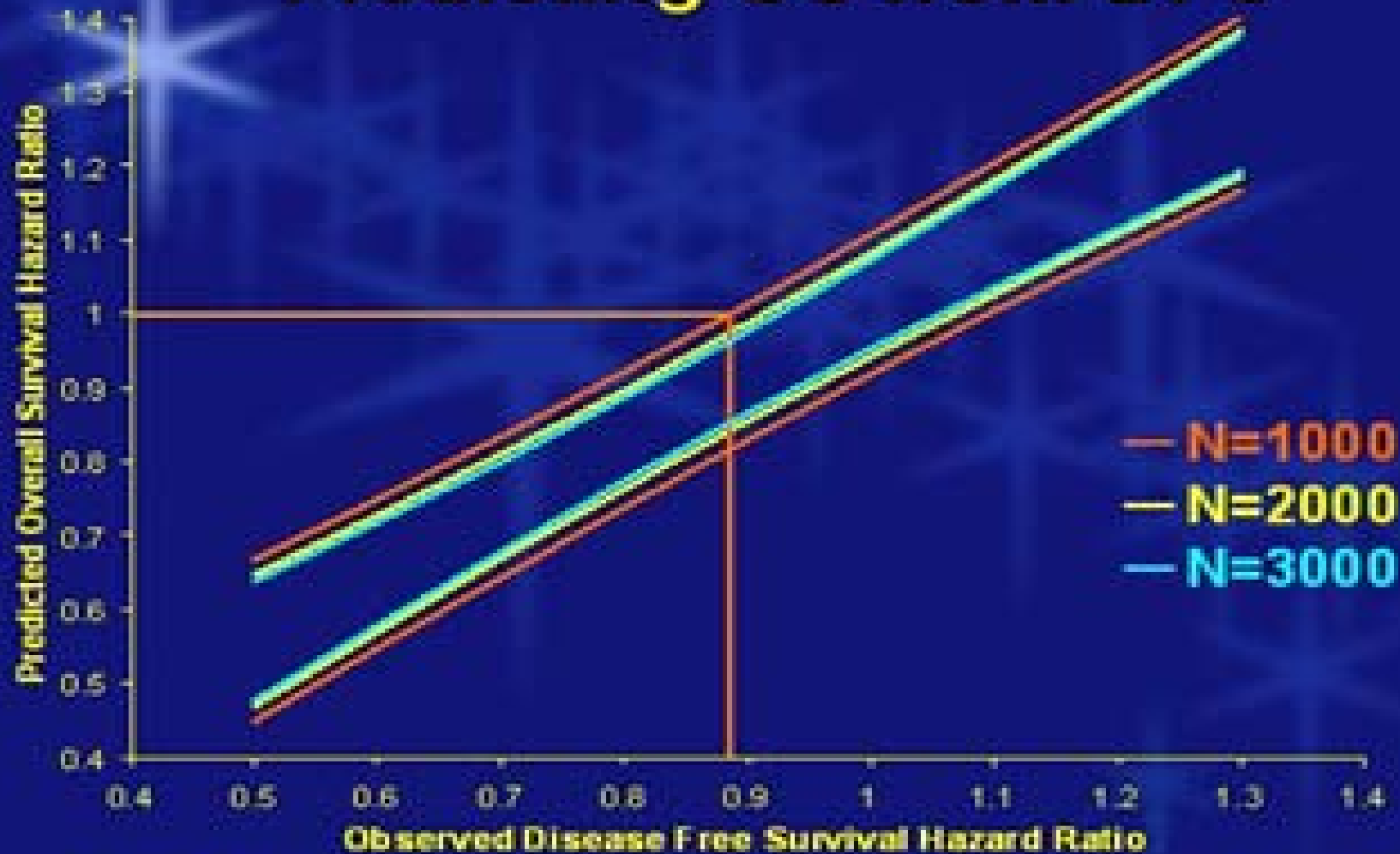


Observed DFS HR (N=2,000)	Predicted overall survival	
	Hazard ratio	95% prediction intervals
0.50	0.57	0.49 to 0.65
0.60	0.65	0.58 to 0.73
0.70	0.74	0.68 to 0.81
0.80	0.83	0.77 to 0.90
0.90	0.92	0.86 to 0.99
1.0	1.01	0.95 to 1.08

Predicting OS from DFS



Predicting OS from DFS





Conclusions from Sargent et al

- ◆ DFS appears to predict overall survival in this clinical setting
- ◆ Treatment effects appear to attenuate between DFS and OS
- ◆ All trials used only 5FU regimens
- ◆ Concordance may decrease if oxaliplatin delays rather than prevents recurrence

Summary of Step 4

**Trial-based comparative treatment effect on proposed surrogate outcome for new therapy being assessed
CTE on PSO ($\pm 95\%$ CI)**

Information from Step 2 or 3 on transforming PSO to TCO

**Predicted comparative treatment effect on target clinical outcome for new therapy being assessed
CTE on TCO (\pm uncertainty)**

Step 5: impact on c/ea

- ◆ **Multiple sources of transformation uncertainty not readily captured by a distribution around treatment effect variable**
- ◆ **How represent uncertainty around predicted incremental treatment effect on clinical outcome?**
 - 95% confidence interval around surrogate outcome too narrow
 - unbounded confidence interval too broad
- ◆ **More attention needed in sensitivity analyses**
 - probability sensitivity analysis probably inadequate

Conclusions

- ◆ **Framework identifies intrinsic uncertainty**
- ◆ **Stronger information increases confidence**
- ◆ **Weaker information decreases confidence**
 - consequences for diminishing marginal returns
 - consequences for funding decisions?
 - implications for ethics of trial design?
- ◆ **Issue needs to be seen in broader policy contexts of appraising new health technologies**

STFOWG acknowledgements

◆ Members:

- Michael Adena, Jim Buttery, Jonathan Craig, Jenny Doust, Marissa Lassere, Ruth Lopert, Kerri Mackay, Grant Macarthur, Ian Marschner, Lloyd Sansom, Mark Schulz, Rosalie Viney (Chair), Robyn Ward, Alison Wright

◆ Secretariat:

- Jacqueline French, Kent Johnson, Clare King, Andrew Mitchell, Sze-Ling Ng, Adriana Platona

Slides for possible questions





Increasing HDL: not a surrogate

- ◆ HDL (good) cholesterol is one of the strongest predictors of coronary events in epidemiological studies
- ◆ Change in HDL may be a useful surrogate outcome for treatments that improve HDL
- ◆ CETP-inhibitors, including torcetrapib, substantially improve HDL levels



Clear effect on HDL

- ◆ **60% increase in HDL level for torcetrapib+statin versus statin alone**
- ◆ **13% reduction in LDL level for torcetrapib+statin versus statin alone**
- ◆ **12% reduction in triglycerides for torcetrapib+statin versus statin alone**
- ◆ **Highly positive effect on HDL**
- ◆ *RADIANCE 2 & ILLUSTRATE trials*



HDL effect to clinical effect?

- ◆ Closer surrogate: arterial thickening
 - measures of arterial thickening continued to increase
 - no significant difference between torcetrapib+statin and statin alone
- ◆ Clinical outcome:
 - 60% increase in mortality
- ◆ Possible adverse mechanism:
 - 4mmHg increase in systolic blood pressure
 - other adverse mechanisms are also possible
- ◆ *ILLUMINATE, RADIANCE 2 & ILLUSTRATE trials*



40 Do comparisons using Δ DFS reach same conclusion as using Δ OS?

Total 22 adjuvant trials	No effect on DFS or OS	Significant improvement in both DFS and OS	DFS significantly improved but OS unchanged
Number of trials	N = 14 trials	N = 5 trials	N = 3 trials