METRUM
RESEARCH GROUP

Exposure-response in the presence of confounding

Jonathan L. French, ScD

Metrum Research Group LLC

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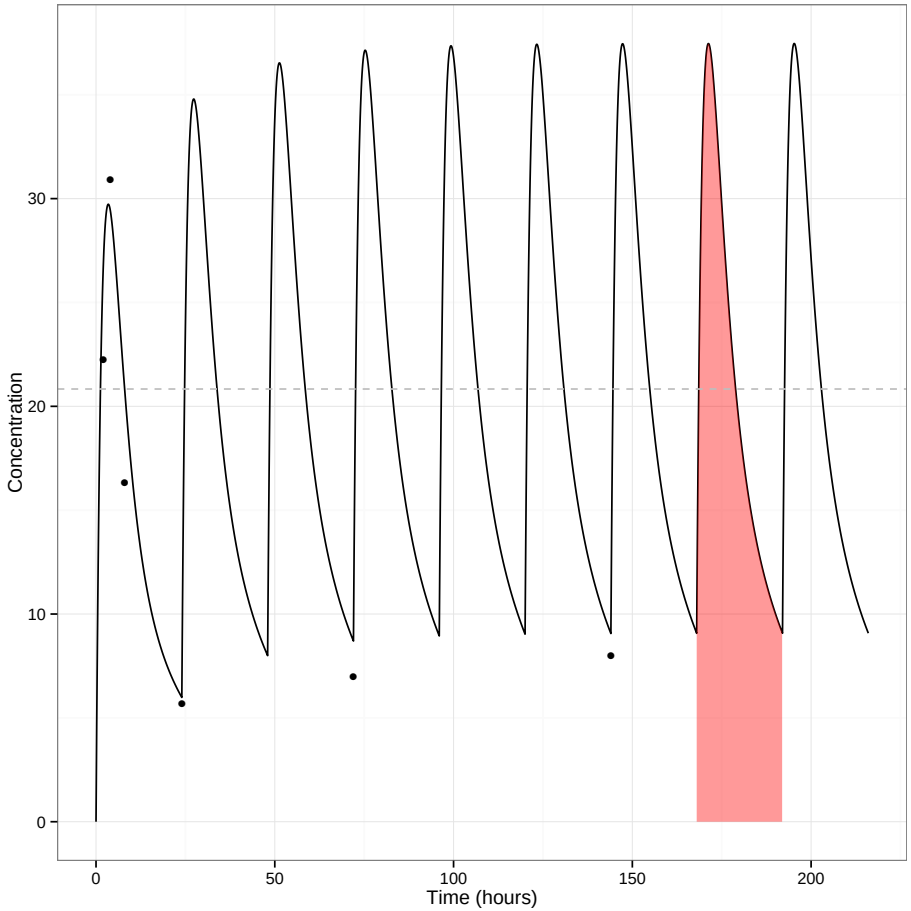
Outline

Exposure-response is in the mind of the beholder

Ranging across . . .

- PK-PD model
- K-PD model
- PD model driven by a summary measure derived from PK model
- PD model based on observed concentrations
- Dose-response

What summary measures?



Some commonly used include:

- AUC_{ss} (Dose/(CL/F))
- $Caverage_{ss}$ (AUC_{ss}/τ)
- Cmax
- Ctrough

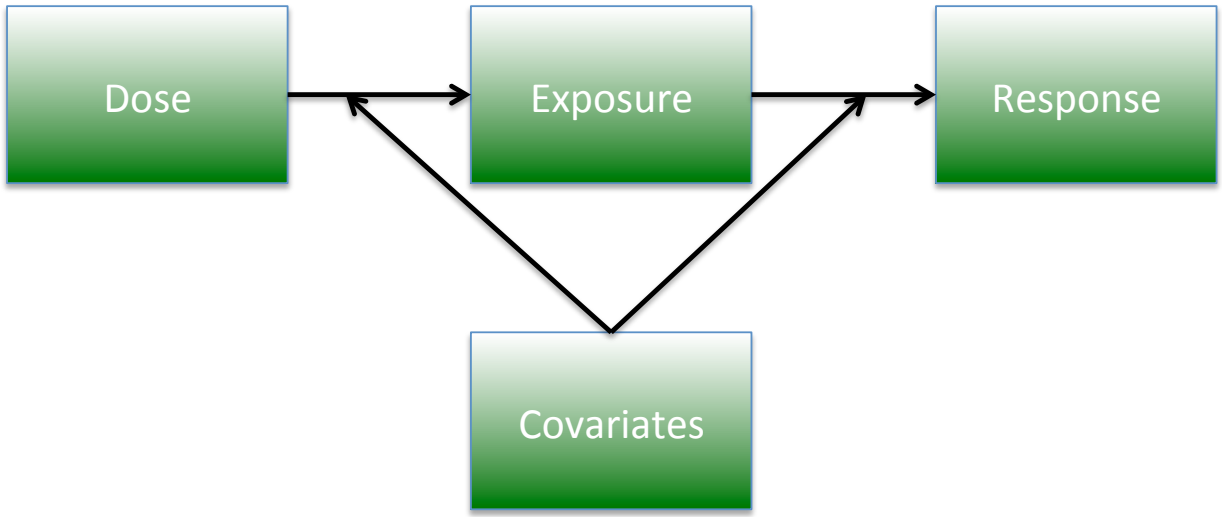
Why do we need exposure-response analyses?

What do they give us that we can't learn from dose-response?

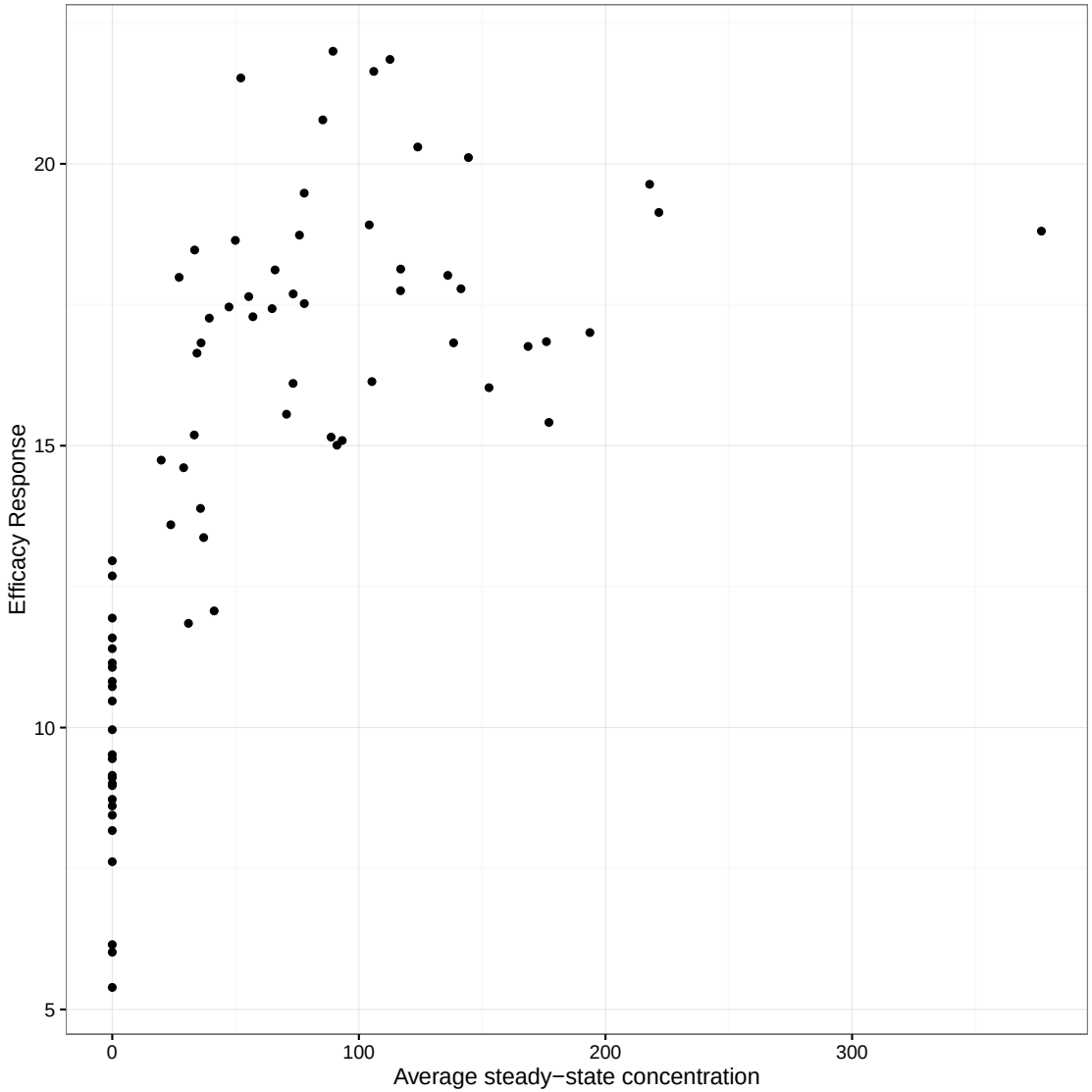
- May be closer to mechanism-based models
  - Concentration of drug $\rightarrow$ biomarker (possibly with a delayed effect)
- May allow more precise estimation when dose-response modeling isn't informed by the design (e.g., only 2-3 dose levels studied).
- May allow more seamless interpolation (or extrapolation) to doses or populations that weren't studied
- May allow us to understand if a higher dose is necessary for a subset of patients

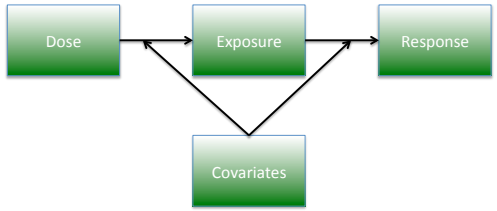
(Simulated) Example of E-R with multiple doses

- Phase 2 dose-ranging study
  - 3 treatment groups: placebo, 3, or 5 mg QD
  - n=25 per group
- Key decision-making endpoints is a continuous landmark endpoint
- Objectives:
  - Estimate E-R relationship in Phase 2 population
  - Predict E-R in Phase 3 population and impact on dose selection



Observed data show an apparant E-R relationship . . .





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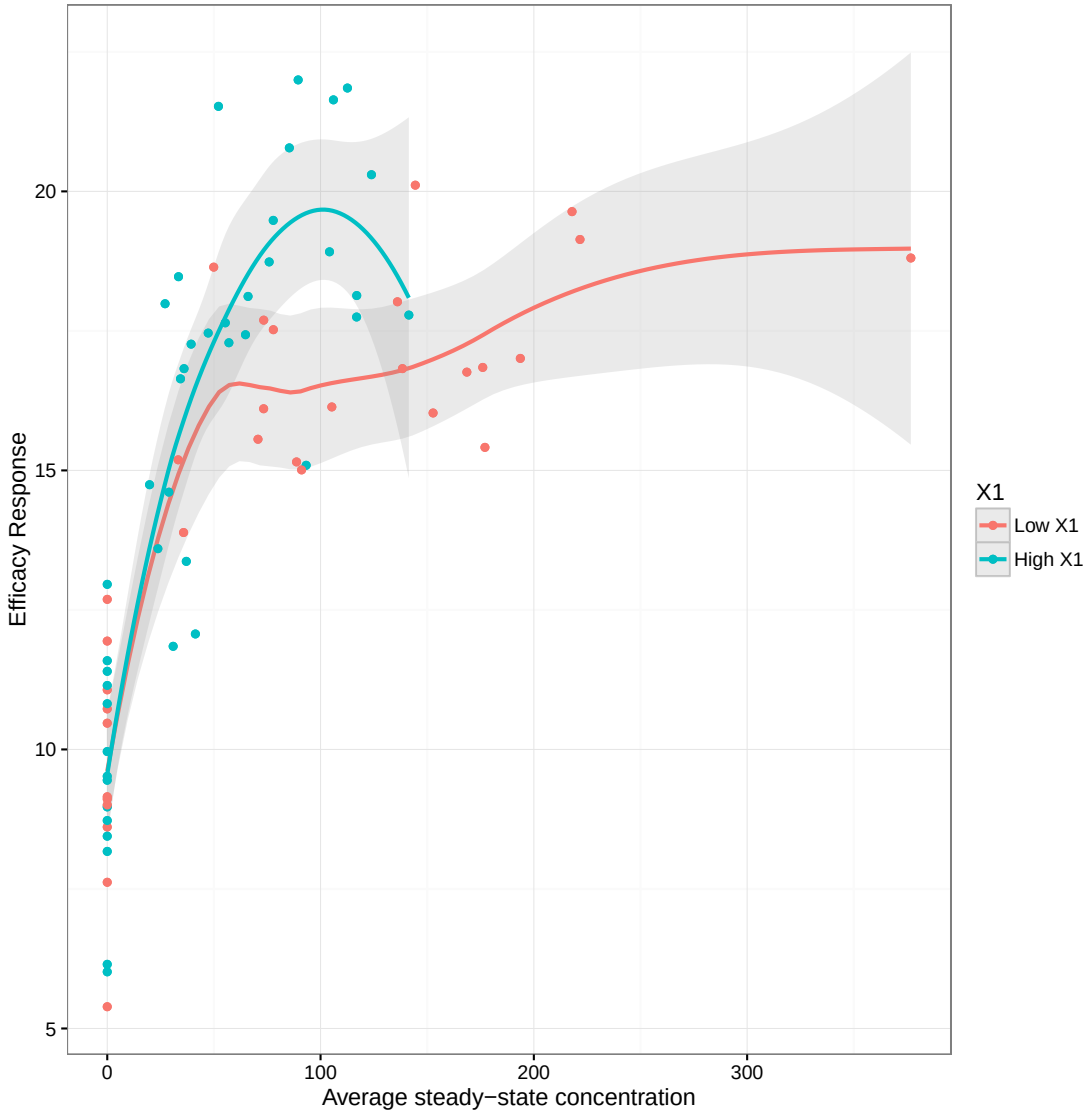
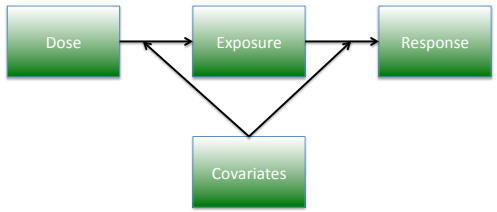
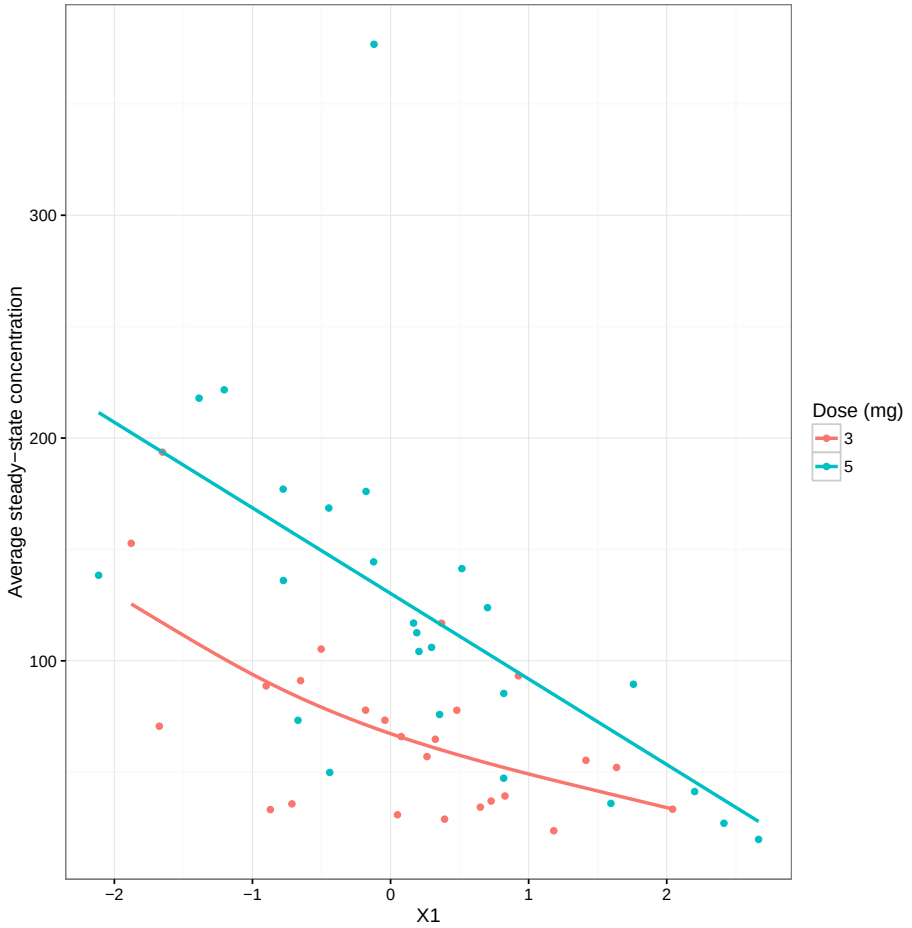
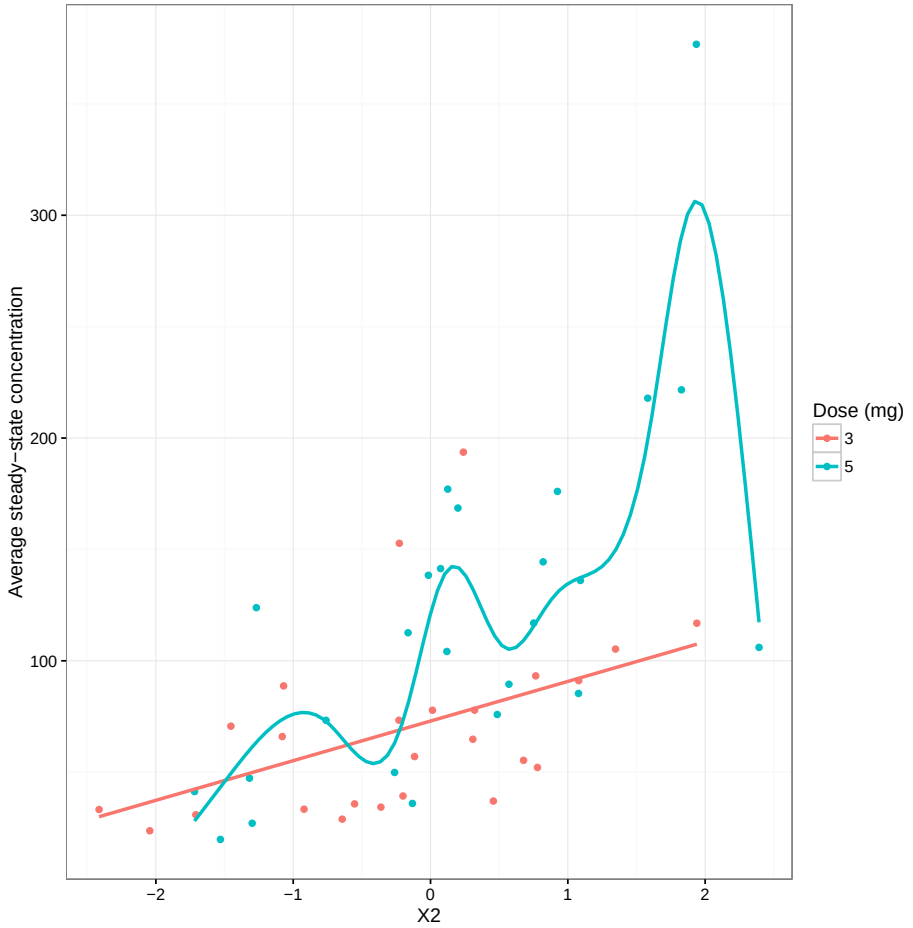


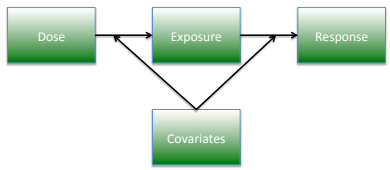
There also appears to be an association with a covariate, x_1.



. . . and two covariates are associated with exposure







Exposure-response models

4-parameter Emax model for efficacy:

$$Y_i = \theta_0 + \frac{\text{Emax}_i \cdot Cavg_{ss}^{\gamma}}{\text{EC50}^{\gamma} + Cavg_{ss}^{\gamma}} + \epsilon_i$$

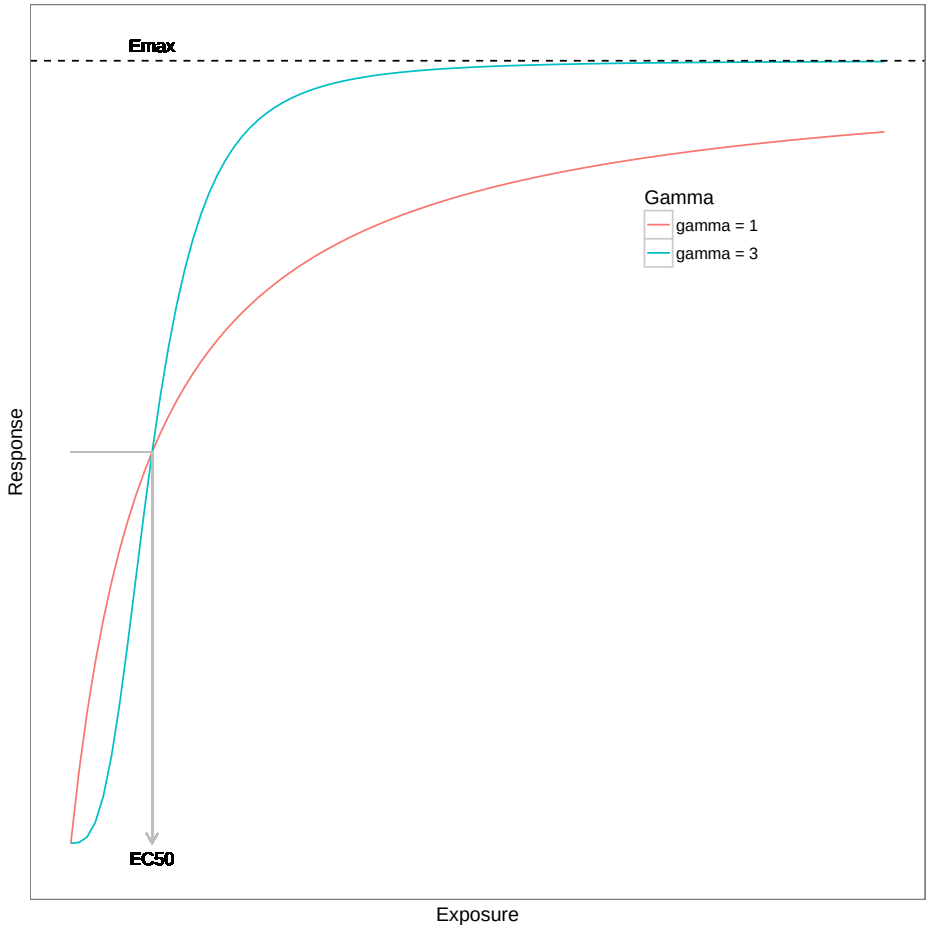
$$\epsilon_i \sim N\left(0, \sigma^2\right)$$

We will model the maximum effect as a function of $X1$:

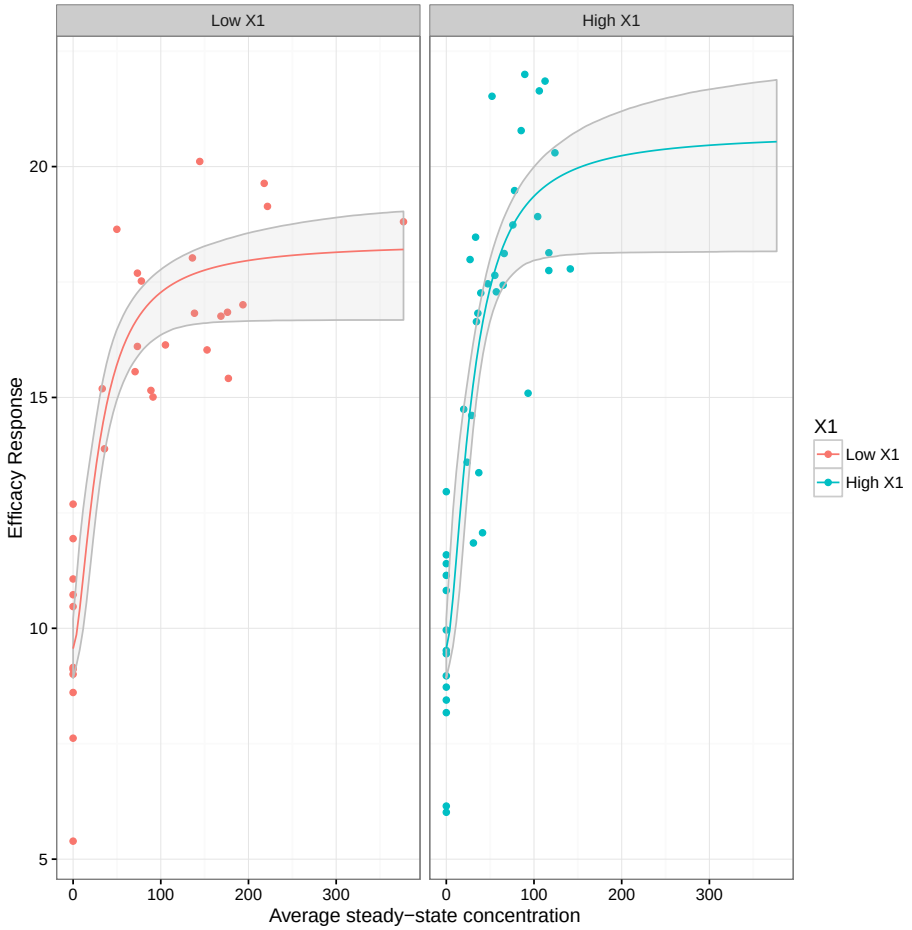
$$\text{Emax}_i = \theta_1 + \theta_2 \, x_{1i}$$

$$\text{EC50} = \exp(\theta_3)$$

$$\gamma = \exp(\theta_4)$$



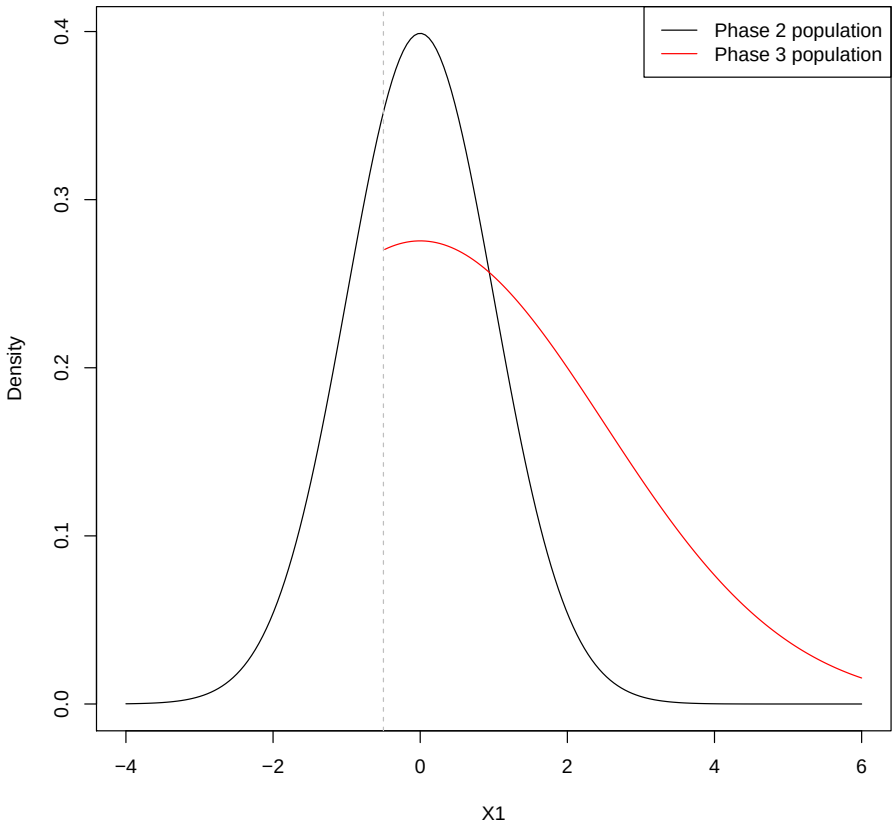
Fitted model

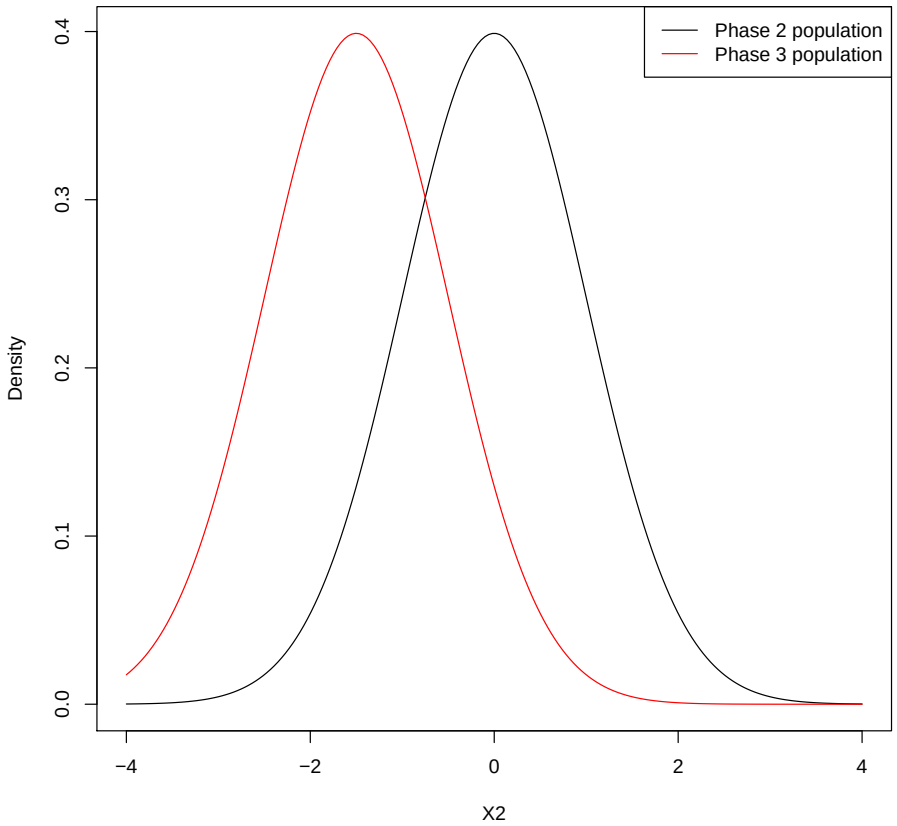


Parameter	Estimate	95% CI
θ_0	9.56	(8.79 , 10.3)
θ_1	9.91	(8.18 , 18.1)
θ_2	1.43	(0.60 , 2.99)
EC50	29.7	(20.0 , 44.0)
γ	1.63	(0.74 , 3.60)
σ	1.92	

Extrapolation to phase 3 population

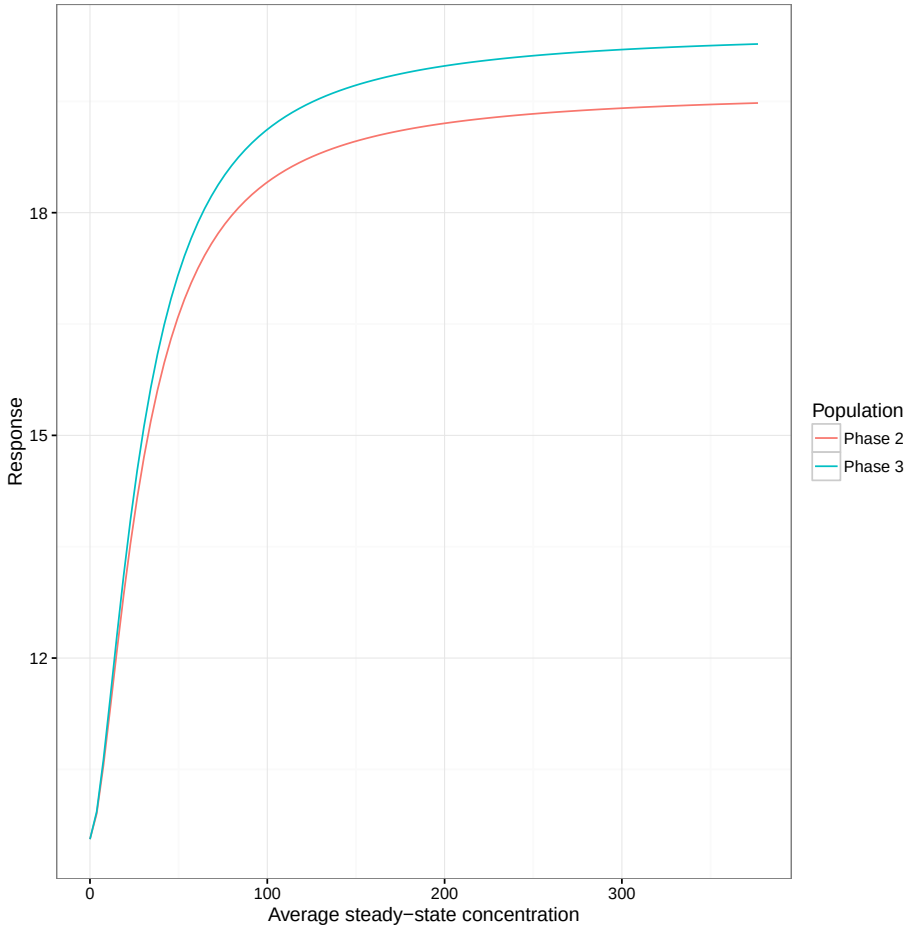
Based on the planned inclusion criteria the Phase 3 population is expected to have different distributions for X_1 and X_2.



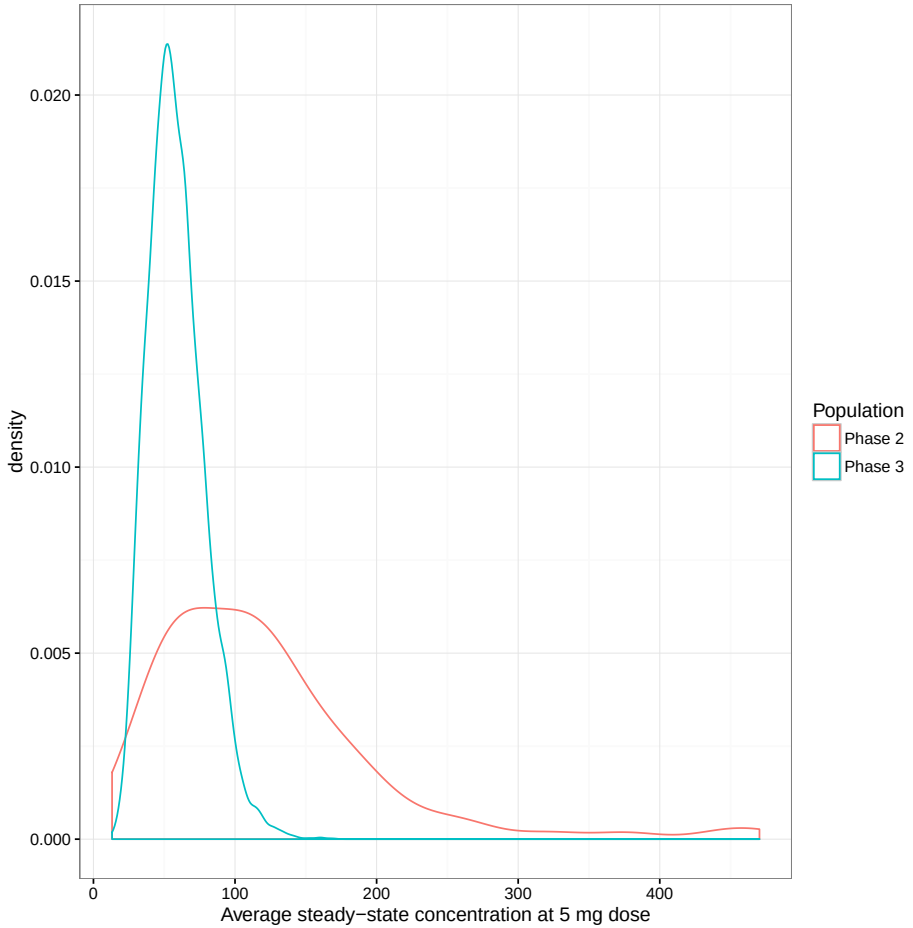


Expected exposure and response

Higher response given exposure



Lower exposure given covariates



How do we translate this to dose-response?

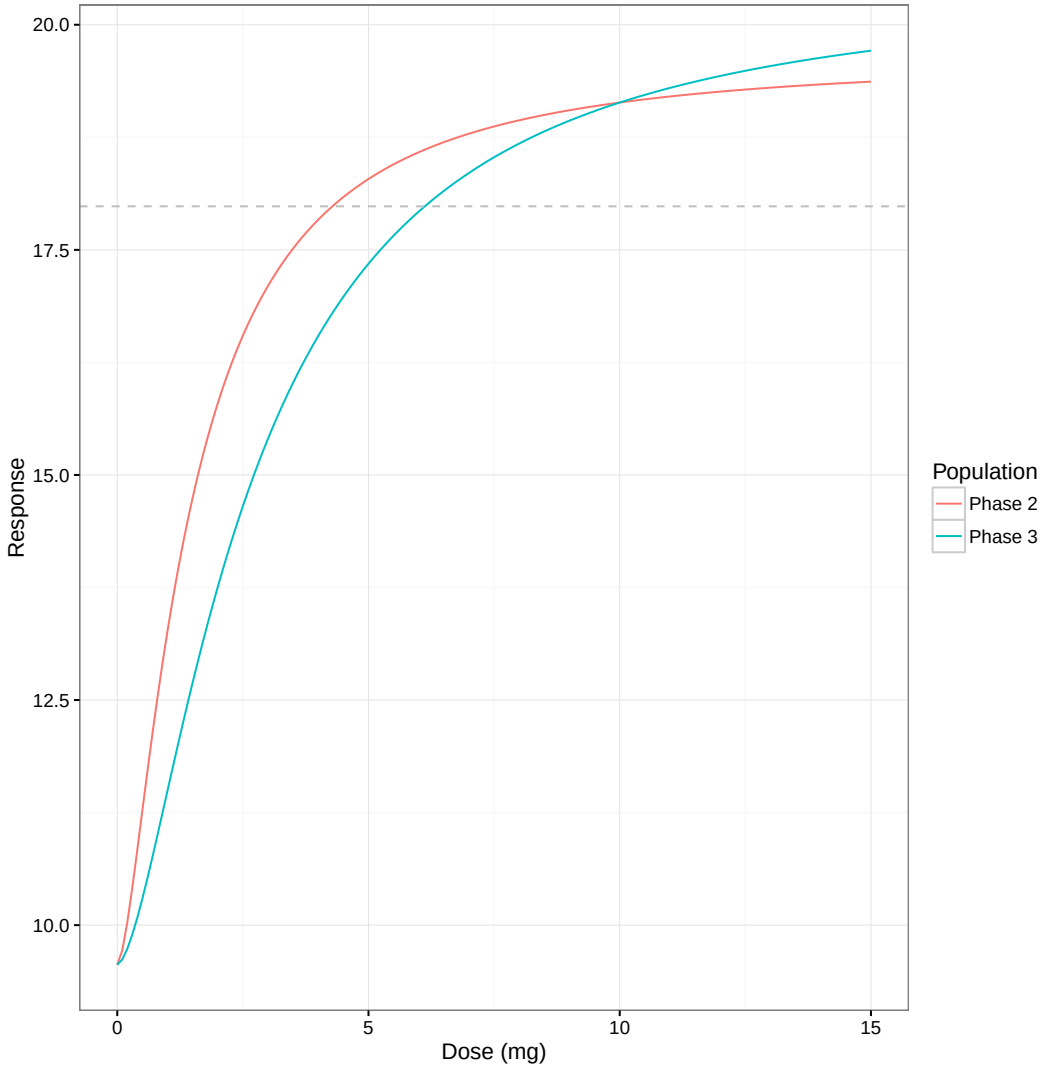
If we focus on the expected response, then

$$\mathrm{E}(Y \mid \text{dose}, X) = \int \mathrm{E}(Y \mid Cavg_{ss}, X)\, f(Cavg_{ss} \mid \text{dose}, X) dCavg_{ss}$$

and

$$\mathrm{E}(Y \mid \text{dose,Popn}) = \int \mathrm{E}(Y \mid Cavg_{ss}, X)\, f(Cavg_{ss} \mid \text{dose}, X)\, f(X|\text{Popn})\, dCavg_{ss}\, dX$$

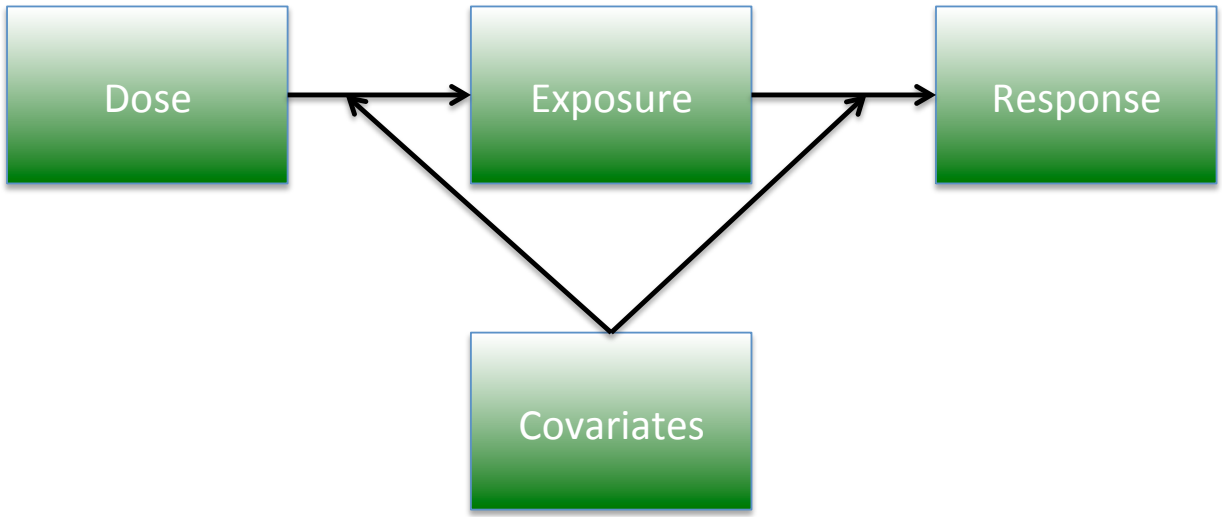
Comparison of expected dose-response



A 4 mg dose gives ∼ 85% of maximal response in Phase 2 population.

Equivalent expected response at 6 mg dose in Phase 3 population.

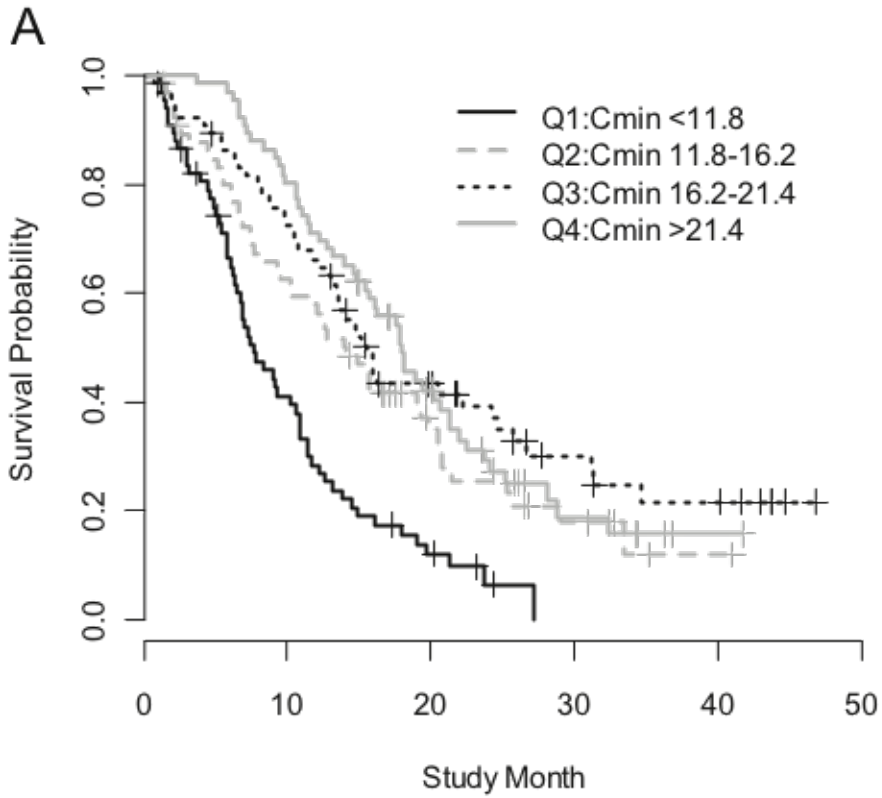
Potential for higher response rates in Phase 3 population at higher doses?


Dose
Exposure
Response
Covariates

Can we use E-R modeling when we've only studied one dose?

- Sometimes (e.g. in oncology), a single dose is studied in Phase 2 (and Phase 3).
- We may have some variation in exposure . . .
- . . . but what if exposure is related to measured (or unmeasured) confounding variables?

An apparent exposure-response relationship. . .



Yang et al. (2012) The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making

Suppose we want to . . .

- Estimate exposure-response relationship on the hazard ratio for trastuzumab relative to control
- Estimate the hazard ratio for Q1 relative to control
- Predict the effects of a higher dose in patients with lower exposure

. . . in an unbiased (causal) manner.

What if there are covariates associated with exposure and outcome . . .

Table 2. Summary of categorical covariates in low-exposure vs high-exposure patients in the T+FC arm.

Covariate	First Quartile (n = 67), %	Combined Second to Fourth Quartiles (n = 199), %
ECOG PS		
0	14.9	40.2
1	61.2	454.8
2	23.9	5.0
Prior gastrectomy		
Yes	13.6	29.7
No	86.4	70.3
Number of metastatic sites		
>2	64.2	40.4
1-2	35.8	59.6
Asian ethnicity		
Yes	46.3	57.3
No	53.7	42.7
IHC3+ status		
Yes	47.8	48.7
No	52.2	51.3

A stepwise Cox regression model identified 5 negative prognostic factors for OS: ECOG PS; no prior gastrectomy; non-Asian; immunohistochemistry (IHC) 0, 1, or 2+ HER2 tumor overexpression; and more than 2 sites of metastatic disease. The exposure of trastuzumab remained a significant ($P < .05$) contribution to the OS after adjusting for these risk factors. In addition to the 5 listed variables, we also tested other variables such as age (continuous), age (≥60 vs <60 years), body weight, body surface area, extent of disease (local vs metastatic), gender, primary site (stomach vs gastroesophageal junction), and type of cancer (mixed vs intestinal, diffuse vs intestinal). These are not significant contributors for overall survival in the phase 3 trial.

Yang et al. (2012) The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making

. . . and the distribution is different across the exposure range?

	Before Matching		
Treatment	FC	Q1 T+FC	*P* Value
No.	296	67	
ECOG PS (0-1 vs 2)	0.909	0.761	.0026
Prior surgery (yes vs no)	0.213	0.134	.1755
Asia (yes vs no)	0.561	0.463	.1745
Number of metastatic sites (1-2 vs >2)	0.505	0.358	.0310
IHC3+ status (yes vs no)	0.483	0.478	1.0000

Yang et al. (2012) The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making

Potential solutions to confounded E-R

- Include potential confounders as covariates in the E-R model
- Treat the analysis as if it were from an observational study (e.g., using matching)
  - Categorize exposure (e.g., quantiles)
  - Calculate propensity scores (for each exposure category relative to placebo)
  - Use for matched or weighted regression analyses

Exposure-response modeling is a key ingredient in drug development

- ”Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs.” – FDA Guidance for Industry: Exposure-Response Relationships ? Study Design, Data Analysis, and Regulatory Applications
- Uses an understanding of pharmacology of the drug (dose $\rightarrow$ exposure)
- May allow the use of models closely tied to the action of the drug (exposure $\rightarrow$ response)
- Need to consider potential for confounding/effect modification (particularly if E-R based on one dose level)

Many opportunities for interdisciplinary collaboration

- Identifying development questions to address through exposure-response modeling (at portfolio level as well as compound level)
- Design of studies to inform exposure-response modeling
- Execution of M&S work

What can statisticians do to get more involved?

- Be open to learning a new topic
- Share what you do know in a collaborative manner (e.g., knowledge of study population vs. knowledge of pharmacology)

Back-up Slides

E-R for what endpoints? (editorial aside)

- E-R is most believable when you're modeling endpoints that are most closely related to the mechanism of action of the drug.
  - Concentration of drug $\rightarrow$ biomarker (possibly with a delayed effect)
- As we move farther away from MOA, K-PD or summary measures of exposure may be reasonable
  - e.g., average concentration $\rightarrow$ tumor growth inhibition
- Even farther away, we may need to rely on some scientifically-based hand waving
  - e.g., Average concentration in Cycle 1 $\rightarrow$ survival