

BACKGROUND

- The therapeutic effectiveness of Drug X as a single agent has been clinically established
- The efficacy of Drug X in a drug combination was evaluated in a clinical trial in the target patient population

STUDY DESIGN

- Parallel, fixed doses
 - Group 1 (n=200 pts): Drug combination + Drug X
 - Group 2 (n=200 pts): Drug combination
- PK sampling
 - Up to 4 samples in weeks 1, 4, 12, 24
- Efficacy sampling
 - Up to 7 samples in weeks 0, 2, 4, 8, 12, 16, and 24

OBJECTIVE

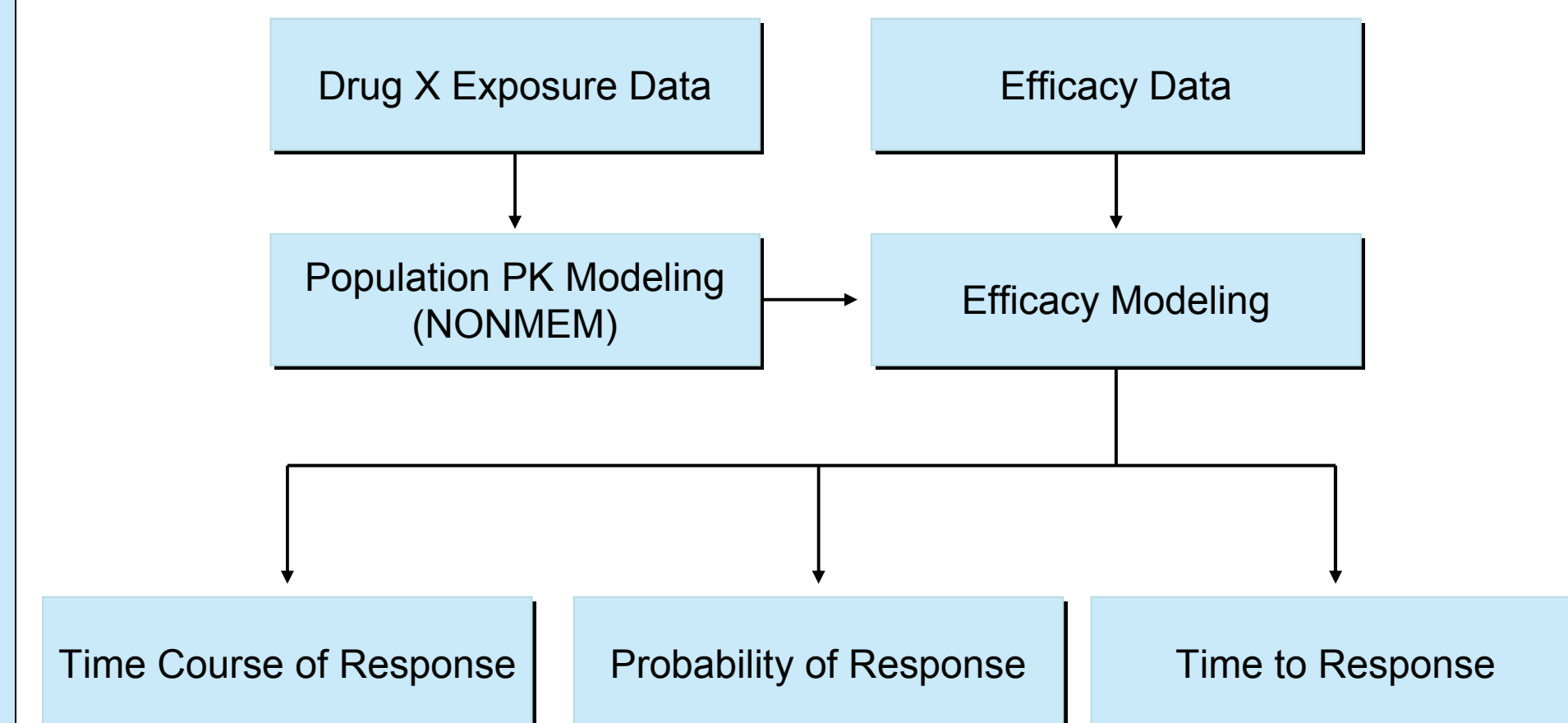
- To quantify the therapeutic value of Drug X in a drug combination

APPROACH

- To evaluate the effect of Drug X by using modeling

METHODS

Analysis Scheme



METHODS (cont'd)

Characterize Time Course of Response

- Inhibitory E_{max} model:
 - Drug effect is a function of time (t) and Drug X exposure (AUC)
 - Linear

$$\text{Log}(\text{Effect})_{ij} = V_{0,i} - \frac{E_{max}(1 + \beta \cdot \text{AUC})t_{ij}}{T_{50,i} + t_{ij}} + \epsilon_{ij}$$

- Non-linear

$$\text{Log}(\text{Effect})_{ij} = V_{0,i} - \frac{E_{max}(1 + \frac{E'_{max} \text{AUC}}{\text{AUC}_{50} + \text{AUC}})t_{ij}}{T_{50,i} + t_{ij}} + \epsilon_{ij}$$

Estimate Probability of Response

- Binary logistic regression model
 - Probability of response: achieve a target effect in a defined treatment period
 - Probability is a function of Drug X exposure: $f(\text{AUC})$

$$p(Y=1) = \frac{e^{\alpha + f(\text{AUC})}}{1 + e^{\alpha + f(\text{AUC})}}$$

Assess Time to Achieve Response

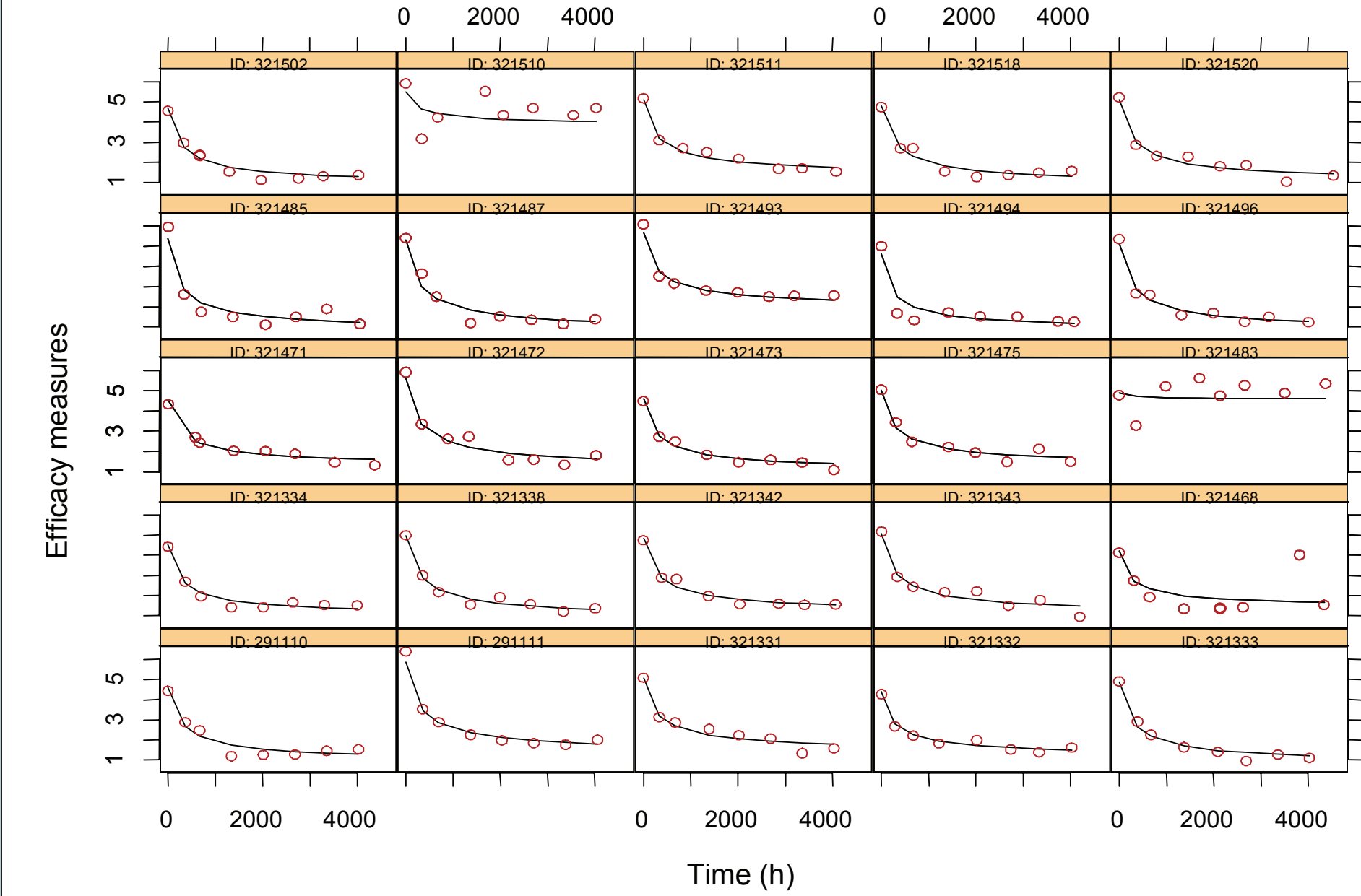
- Cox proportional hazards model to assess the time to achieve the target effect

$$\lambda(t) = \lambda_0(t) \times e^{\beta}$$

- Treatment group was used as a categorical covariate

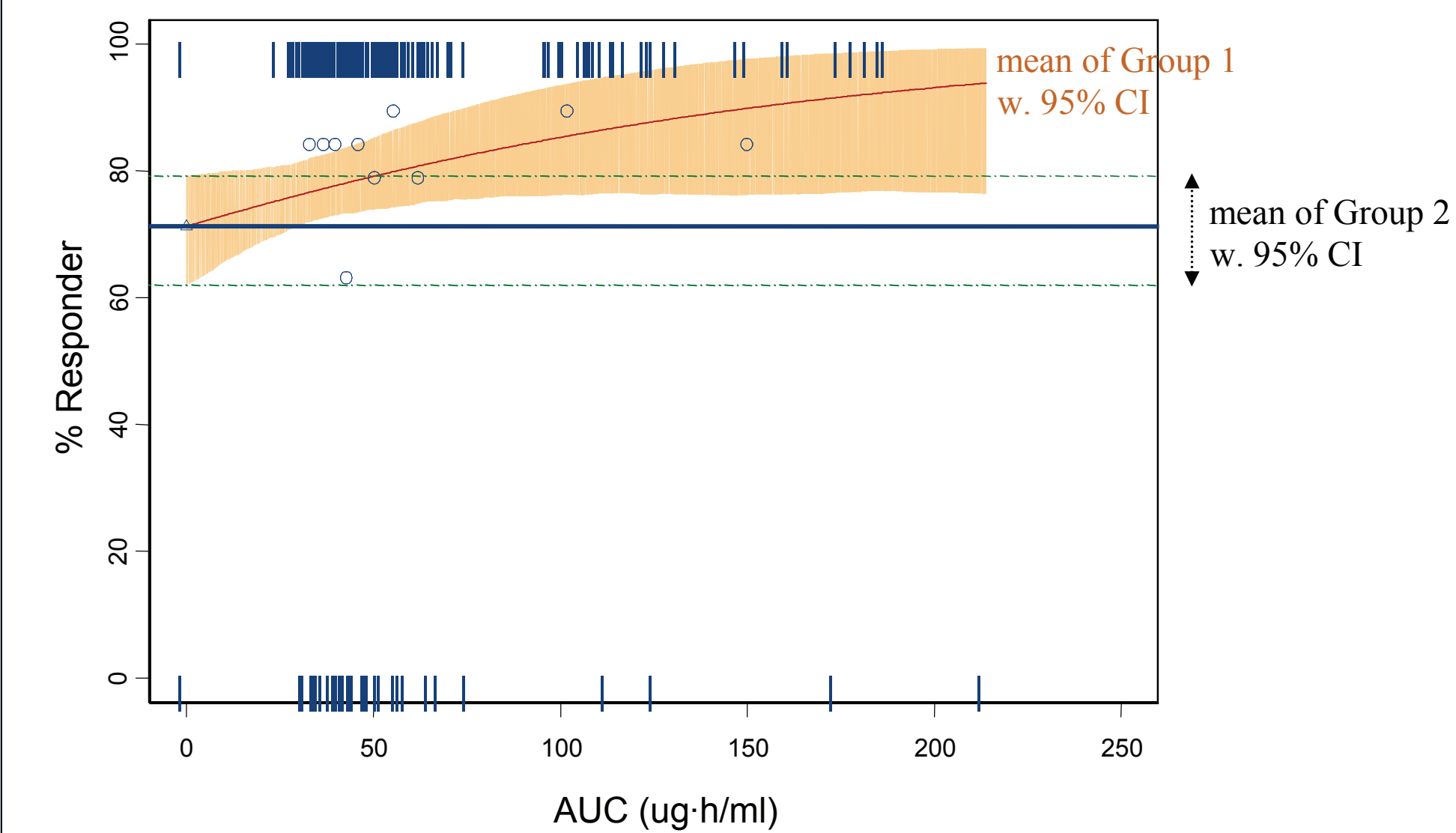
RESULTS

Time Course of Response



The maximal effect is achieved over 24 weeks at the observed exposure range

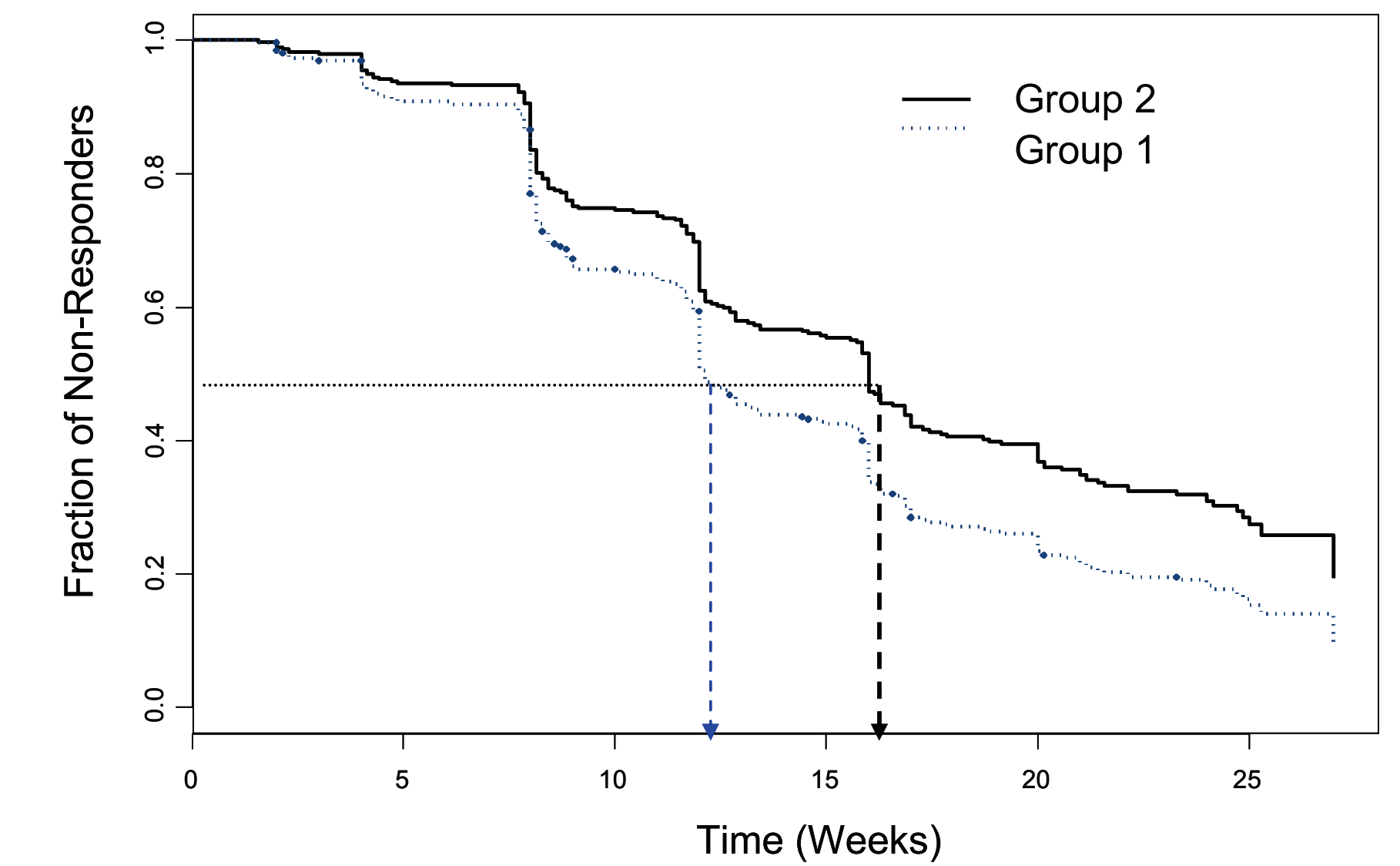
Probability of Response



% Responder in Group 1 (>85%) is higher than that in Group 2 (67%)

RESULTS (cont'd)

Time to Achieve Target Response



Patients in Group 1 reached to the target response earlier

Drug Combination + Drug X (Group 1) vs. Drug Combination (Group 2)

- Compare to the efficacy observed in Group 2
 - The maximal drug effect is positively associated with Drug X levels and is 23% larger in Group 1 at steady state
 - Fraction of responders in Group 1 is at least 18% higher
 - The median time to achieve the target response in Group 1 is 4 weeks earlier

CONCLUSION

- A model-based approach allows the evaluation of effect of a single drug in a combination therapy and is useful to
 - Assess the therapeutic value of Drug X in a drug combination
 - Establish a scientific rationale for inclusion of Drug X in the combination therapy