PharmacoMetrica

Pharmacometrics: a new tool for optimizing early drug development

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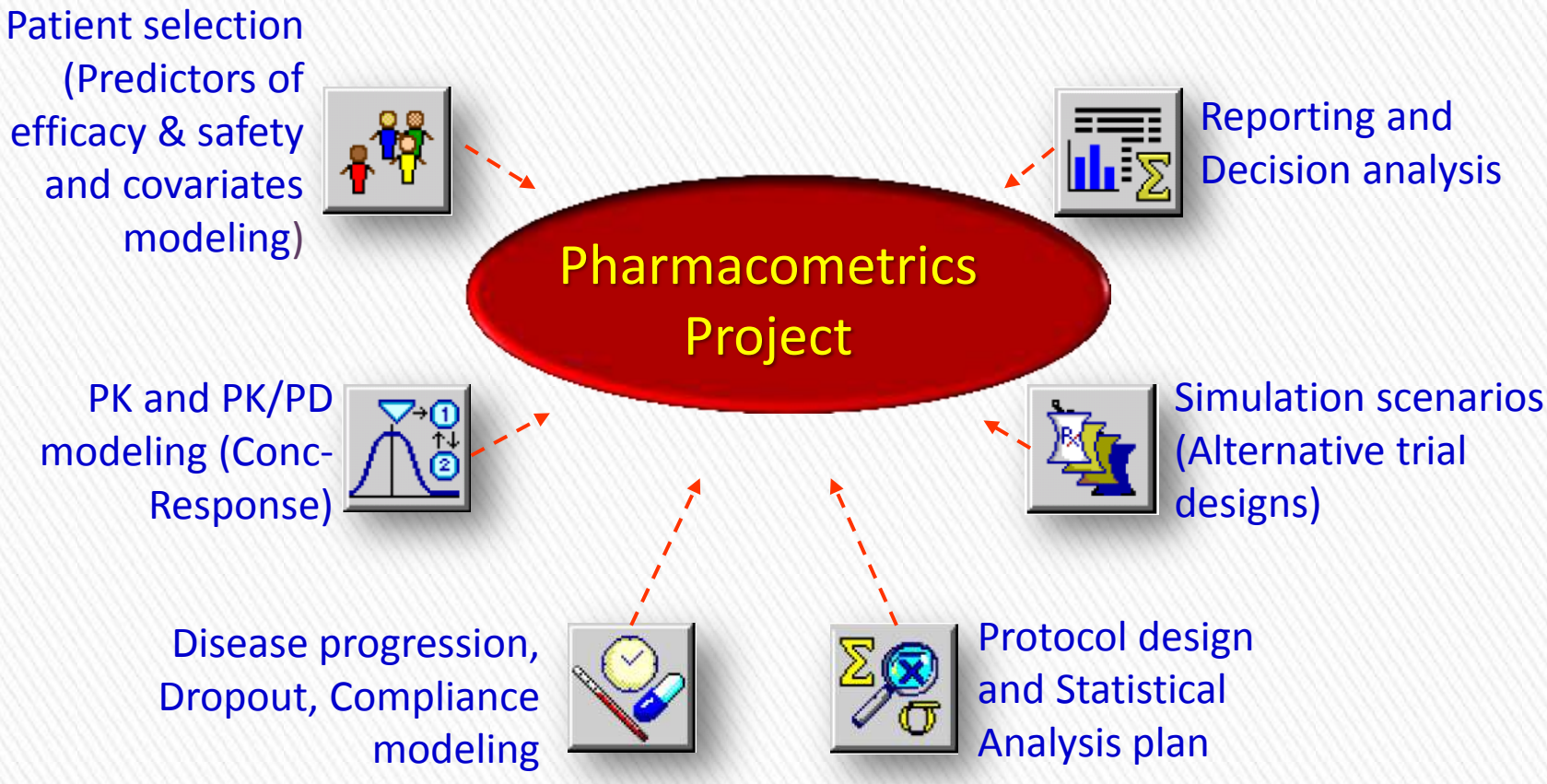
Pharmacometrics

Pharmacometrics is the science of interpreting and describing pharmacology, physiology, disease, and patients' characteristics in a quantitative fashion

by integrating and applying mathematical and statistical models jointly with decision analysis

to characterize, understand, gain insights into the determinants of efficacy and safety outcomes, predict a drug's outcomes, optimize drug development and enable critical decision making

The Pharmacometrics Approach



New Drug Development Paradigm
Question-Based vs. Traditional Approach

"What is the optimal patient population for this drug?"

"Is there a clinical trial design that will show PoC and find the best dose?"

"Should we continue this development program?"

"Is this treatment likely to be as good as the competitors?"

"What's the best dose and schedule for a Phase 3 trial?"

"Which indication should we go into first to maximize the value of the program?"

"What are the most important attributes of a 2nd generation compound?"

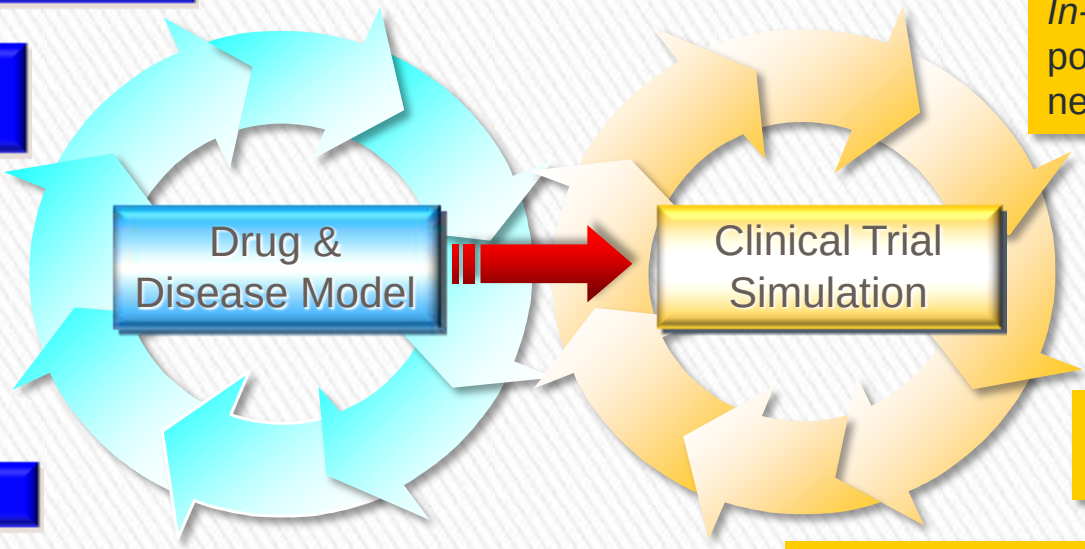
"Is it worth developing a new dosage form?"

"What's the probability of success in Phase 3?"

"Should we in-license or out-license this compound?"

Answer the critical questions at any stage of drug development and facilitate the decisions making process

Implementing a Model-Based Approach



In vitro & In vivo Pre-clinical data

Toxicology data

Competitors & literature data

Placebo & Dropout model

PGx data

Pop PK & PK/PD

Clinical & Epidemiological data

Special population data (ethnic group, paediatric,..)

Rational definition of a preclinical & clinical development plan

In-Silico evaluation of potential interest of new chemical entities

Design FTIM studies from preclinical data

Phase II/III Study Design

Define optimal drug delivery & administration properties (PLE)

Flexible & Adaptive designs for PoC studies

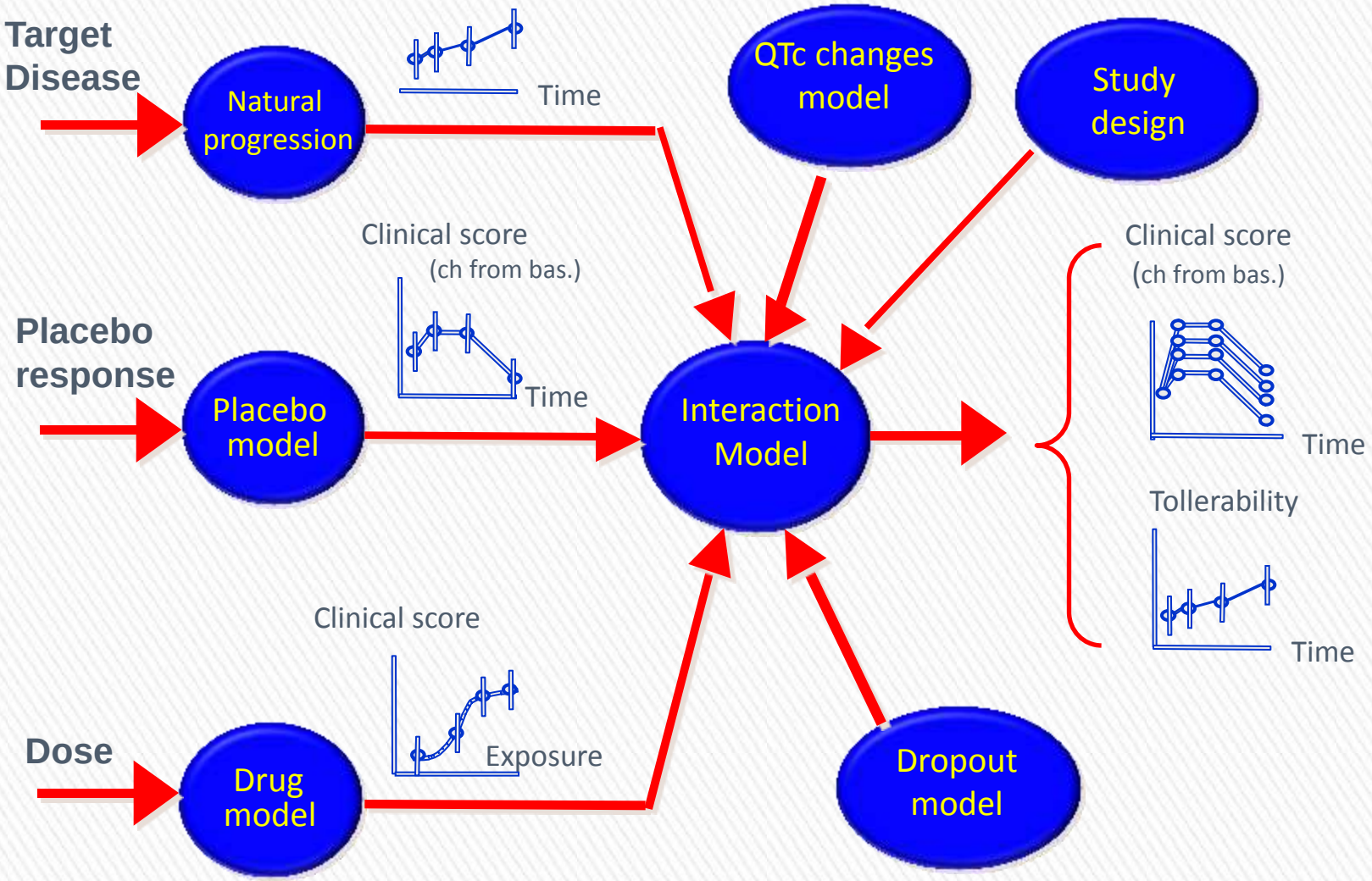
Challenges facing the drug-development industry

- *Pipeline pressures on the back of patent expirations*
- *Profitability in the face of declining research & development budgets*
- *An ageing patient population becoming increasingly reliant on chronic medicines*
- *Global epidemic threats*
- *Fewer new targets, no more low hanging fruit*
- *Limited use of internal and external historical data*

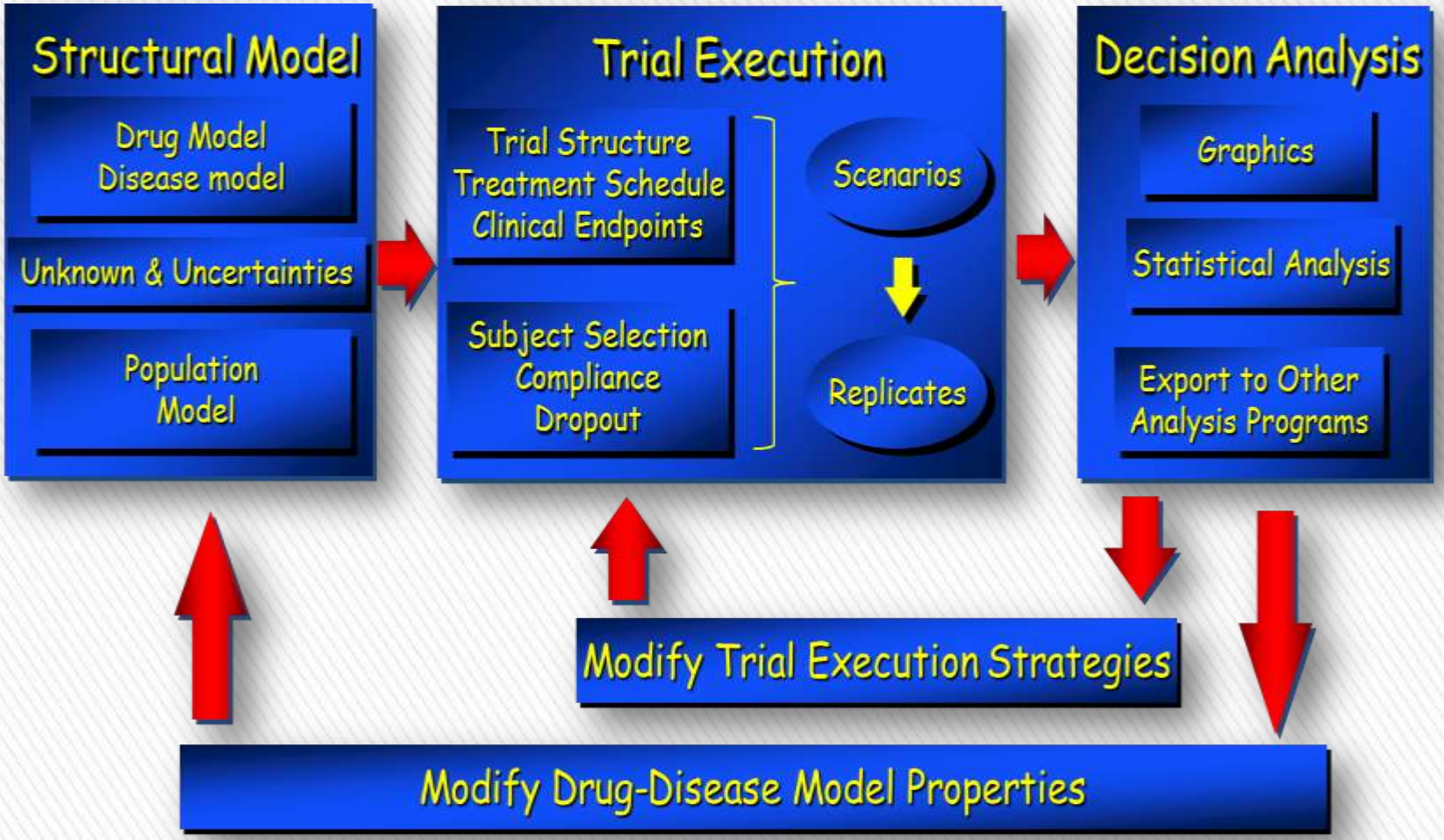
Solutions

Leverage learning and historical knowledge integration by managing and analyzing available data efficiently to generate knowledge and novel insight and support decision-making

Drug-Disease-Trial Model



Clinical Trial Simulation Paradigm



Traditional vs. Pharmacometrics strategy

Traditional Paradigm: re-active

- Dose selection
- Identify covariates that influence exposure and exposure-response relationship
- Provide support for drug label recommendations

Pharmacometrics Paradigm: pro-active

- Drug-Disease-Trial Model Paradigm rather that simply Population PK/PD models to provide rationale for predicting △ (Treatment Effect)
  - *Use model(s) to quantify variability and uncertainty in predicted △*
- Use as data generation model in clinical trial simulations (CTS) to assist in evaluation of designs
- Use meta-analytic model to predict/estimate △ for comparison with competitor

Trial Performance Metrics: Pharmacometrics Paradigm

- Focus on predicting clinical trial outcomes
  - Evaluating the compound's performance in the proposed trial
- Model-based predictions of $\triangle$
- Quantification of variability and uncertainty in $\triangle$
  - $P(\triangle)$ denotes uncertainty distribution specified through the multivariate uncertainty distribution of model parameters
- Evaluate designs based on a quantitative assessment of the compound's capabilities using CTS methods
  - Probability of success – $P(\text{success}) = P(T \geq CRE^*)$
  - Probability of correct decision – P(correct)
    - Correct Go Decision: when $T \geq CRE$ and $\triangle \geq CRE$
    - Correct No Go Decision: when $T < CRE$ and $\triangle < CRE$

** Clinically Relevant Effect*

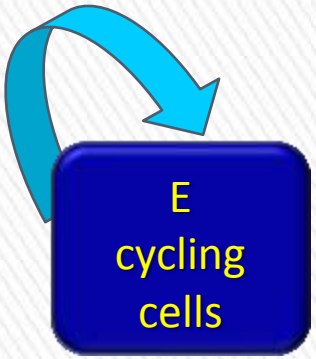
Case study: Optimizing early drug development in oncology

- Tumor Growth Model
- Drug PK Model
- Covariate Model
- PK/Tumor Growth Model
- Survival Model
- AEs Model
- Drug-Disease-Trial Model

Pre-clinical development: Xenograft Models

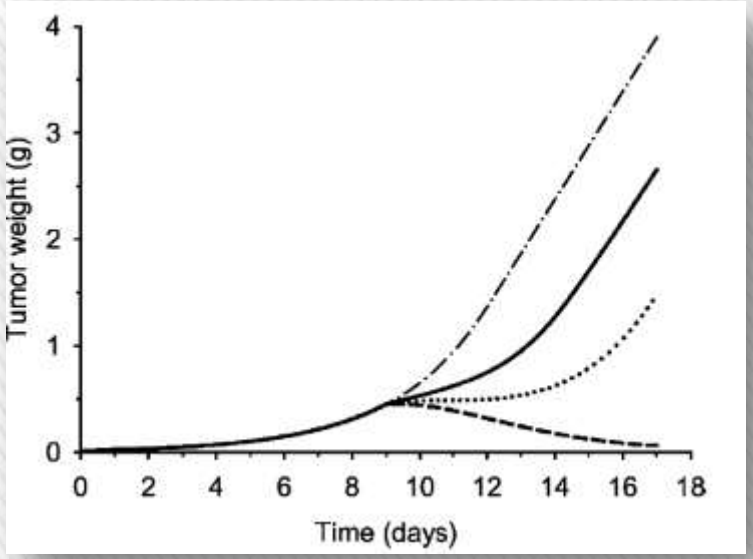
- Most every drug approved in cancer was first tested in a xenograft model to determine its anticancer activity
- Human tumor fragments are subcutaneously implanted into the flank of nude or severe combined immunodeficient mice
- Xenograft mice develop human solid tumors based on implantation of human cancer cells.
- Once the tumors reached a predefined size, the mice are randomized to different treatment groups
- The doses are given and tumor size is measured over a period of time defined by the protocol

Tumor Growth Model



$$\frac{dE}{dt} = \lambda_0 \cdot E \qquad E \leq E_t$$

$$\frac{dE}{dt} = \lambda_1 \qquad E > Et$$



- E natural cells proliferation
- Tumor growth is known to follow an exponential growth followed by a linear growth component
  - *λ_0 and λ_1 represents the rate of exponential and linear growth*
- E_t threshold tumor mass at which the tumor growth switches from exponential to linear

Tumor Growth Structural Model

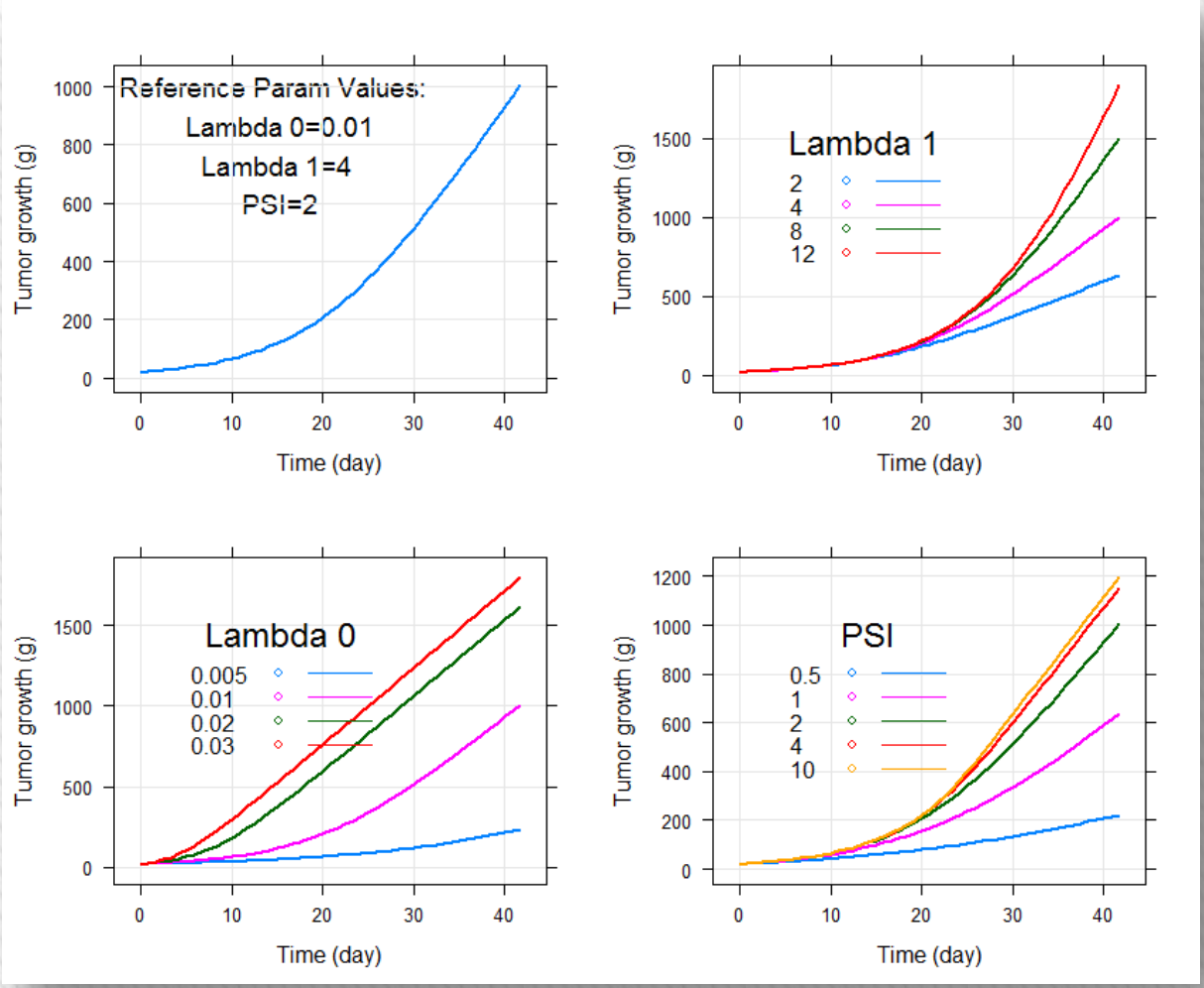
Integrated model accounting for exponential and linear growth

$$\frac{dE}{dt} = \frac{\lambda_0 \cdot E}{\left(1 + \left(\frac{E \cdot \lambda_0}{\lambda_1}\right)^{\psi}\right)^{1/\psi}}$$

- As long as the tumor weight *E* is smaller than E_t, the growth rate is approximated exponential growth
- When the tumor weight *E* becomes larger than E_t, the growth rate becomes linear
- The ψ parameter allows the system to pass from the exponential to linear growth sharply

M. Simeoni et al., Cancer research 64, 1094–1101, 2004

Simulated Tumor Growth Trajectories



PK Model

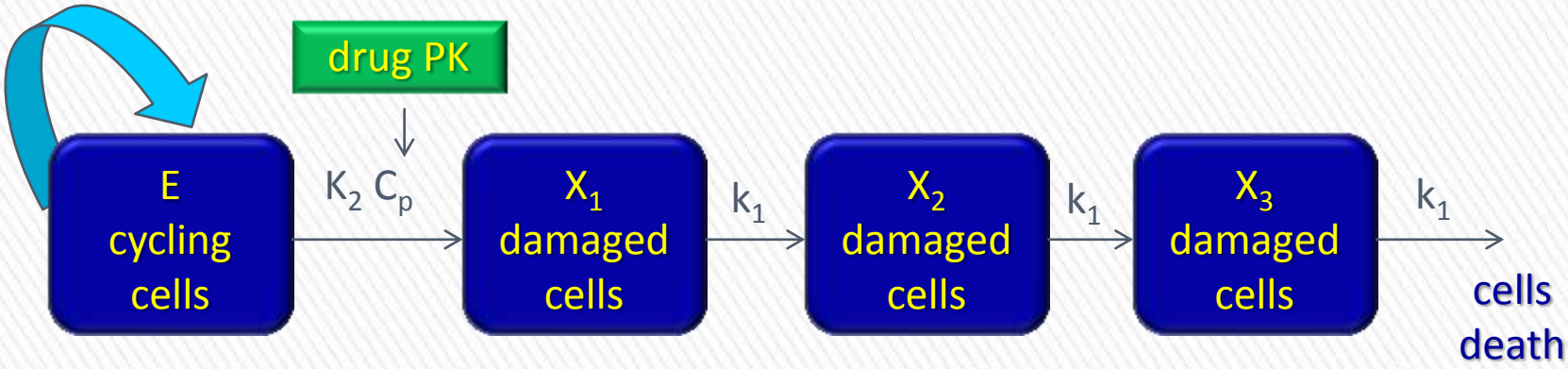
$$\frac{dA}{dt} = -k_a \cdot A$$

$$\frac{dC}{dt} = k_a \cdot A - k_{el} \cdot C$$

$$k_{el} = \frac{Cl}{V}$$

$$Conc = \frac{C}{V}$$

Linking Tumor Growth to Drug Exposure



- The delay between drug administration and tumor cells death is modeled using a transit compartment model (named x_1, x_2 and x_3), this is characterized by a damage rate constant k_1. The average time-to-death of a damaged cell is equal to n/k_1 (where n is the number of transit compartments), In the present case the average time-to-death is: $3/k_1$

- The model assumes that the drug elicits its effect decreasing the tumor growth rate by a factor proportional to C_p (drug concentration) time E through a constant parameter k_2, which is, thus, an index of drug efficacy (potency)

M. Simeoni et al., Cancer research 64, 1094–1101, 2004

PK/Tumor Growth Structural Model

$$k_{el} = \frac{Cl}{V}$$

$$\frac{dA}{dt} = -k_a \cdot A$$

$$\frac{dC}{dt} = k_a \cdot A - k_{el} \cdot C$$

$$Conc = \frac{C}{V}$$

PK

$$\frac{dE}{dt} = \frac{\lambda_0 \cdot E}{\left(1 + \left(\frac{w(t) \cdot \lambda_0}{\lambda_1}\right)^{\psi}\right)^{1/\psi}} - k_2 \cdot E \cdot Conc$$

$$\frac{dx_1}{dt} = k_2 \cdot E \cdot Conc - k_1 \cdot x_1$$

$$\frac{dx_2}{dt} = k_1 \cdot (x_1 - x_2)$$

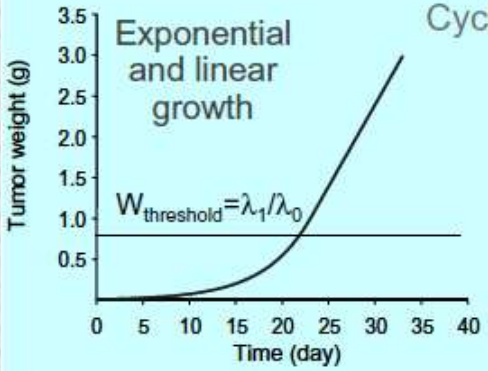
$$\frac{dx_3}{dt} = k_1 \cdot (x_2 - x_3)$$

$$w(t) = E + x_1 + x_2 + x_3$$

Tumor Growth

Integrated model

Tumour growth in control animals



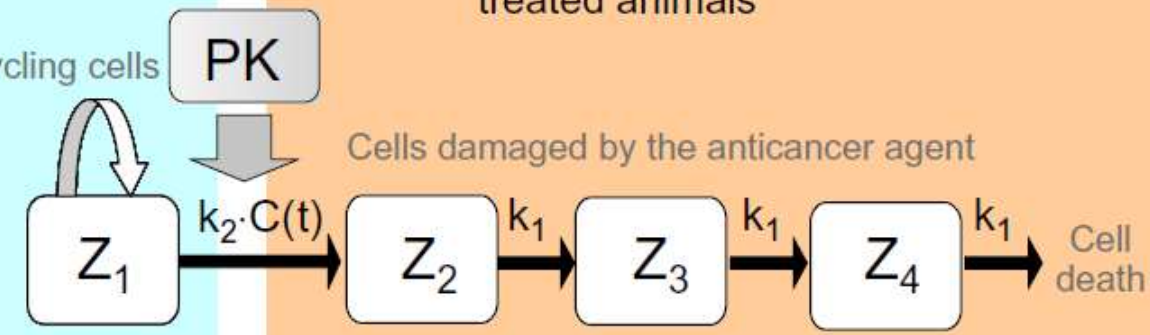
Differential equations for controls:

$$\frac{dW}{dt} = \lambda_0 \cdot W(t) \qquad W(t) < W_{threshold}$$

$$\frac{dW}{dt} = \lambda_1 \qquad W(t) \geq W_{threshold}$$

$$\frac{dW}{dt} = \frac{\lambda_0 \cdot W(t)}{\left[\left(1+\frac{\lambda_0}{\lambda_1}\cdot W_1(t)\right)^{\psi}\right]^{\frac{1}{\psi}}} \qquad W(0) = W_0$$

Tumour growth in treated animals



Overall system of differential equations:

$$\frac{dZ_1(t)}{dt} = \frac{\lambda_0 \cdot Z_1(t)}{\left[\left(1+\frac{\lambda_0}{\lambda_1}\cdot W(t)\right)^{\psi}\right]^{\frac{1}{\psi}}} - k_2 \cdot C(t) \cdot Z_1(t)$$

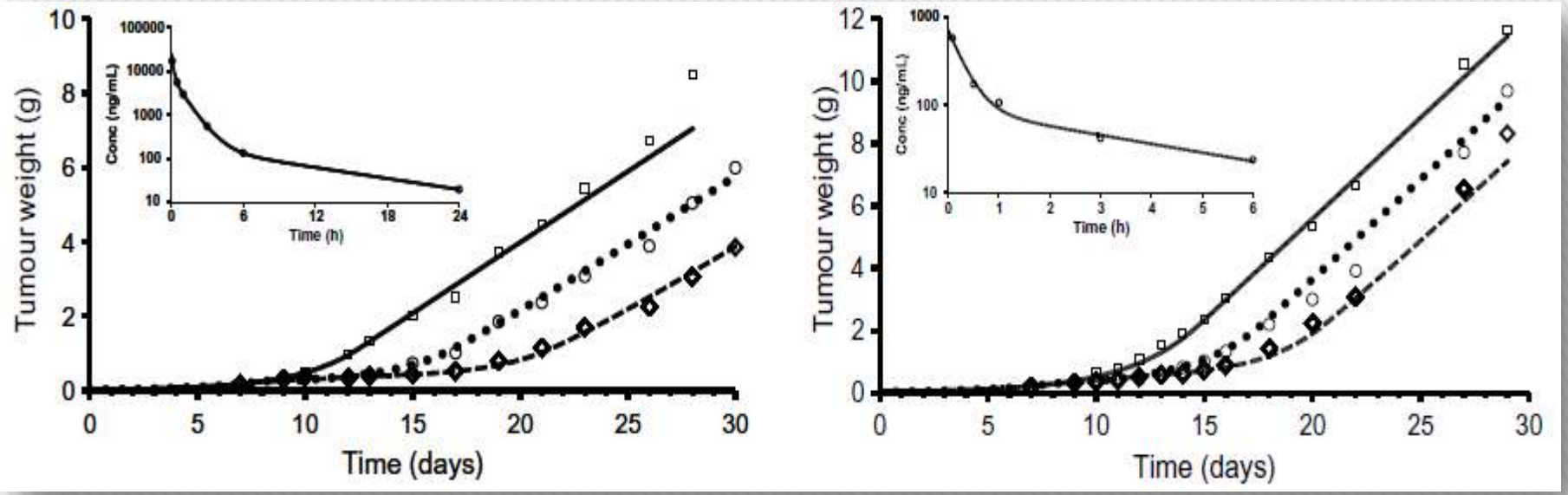
$$\frac{dZ_2(t)}{dt} = k_2 \cdot C(t) \cdot Z_1(t) - k_1 \cdot Z_2(t)$$

$$\frac{dZ_3(t)}{dt} = k_1 \cdot Z_2(t) - k_1 \cdot Z_3(t) \qquad Z_1(0) = w_0$$

$$\frac{dZ_4(t)}{dt} = k_1 \cdot Z_3(t) - k_1 \cdot Z_4(t) \qquad Z_{2,3,4}(0) = 0$$

$$W(t) = Z_1(t) + Z_2(t) + Z_3(t) + Z_4(t)$$

Model outcomes



Docetaxel

- vehicle (□)
- 10 mg/kg as single dose (o) , or
- once every 4 days for 2 treatments (◊)

Vinblastine

- vehicle (□)
- 3 mg/kg as single dose (o) , or
- once every 4 days for 2 treatments(◊)

Target plasma concentration

The target plasma concentration (C_T) associated with the tumor eradication can be estimated from the tumor growth model

$$C_T = \lambda_0/k_2$$

When the animals are exposed to a steady state drug concentration:

$$\mathbf{C_{ss} > CT}$$

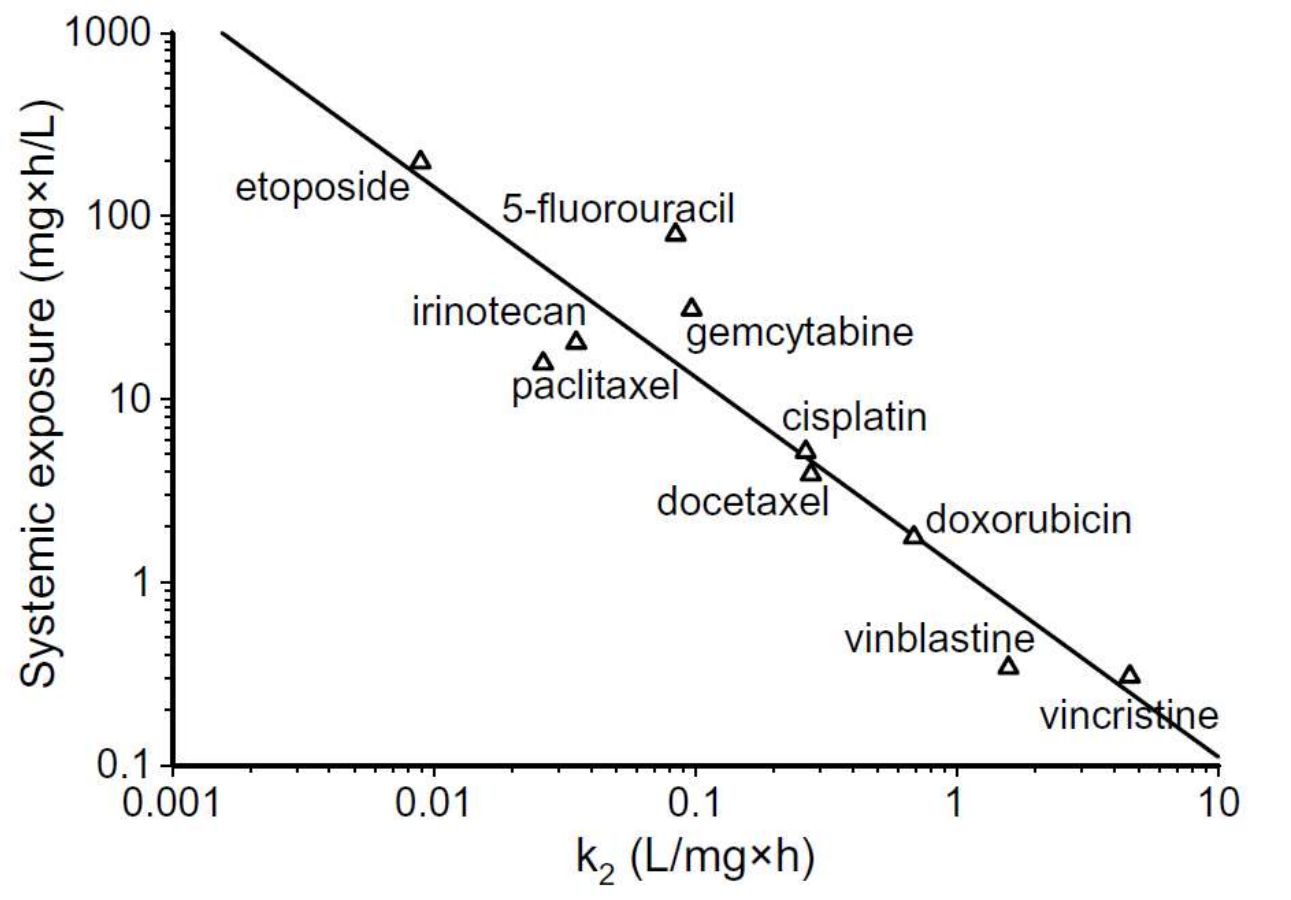
the model predicts the tumor eradication

Can the activity of new compounds in humans be predicted from preclinical data?

- Pre-clinical xenograft studies were conducted on:
  5-fluorouracil, cisplatin, docetaxel, doxorubicin,etoposide, gemcytabine, irinotecan, paclitaxel, vinblastine, vincristine
- The pre-clinical data were used to evaluate the potency parameters(k_2) of each drug
- Strategy: Establish a correlation of the active clinical doses of the selected anticancer agents the with the pre-clinical model-based parameters
- Active clinical dose: the lowest and highest commonly used dose levels defined as the cumulative amount given over a 3-week period

M. Rocchetti et al. European journal of cancer 43 (2007) 1862 –1868

Predicting the activity of new compounds in humans from preclinical data



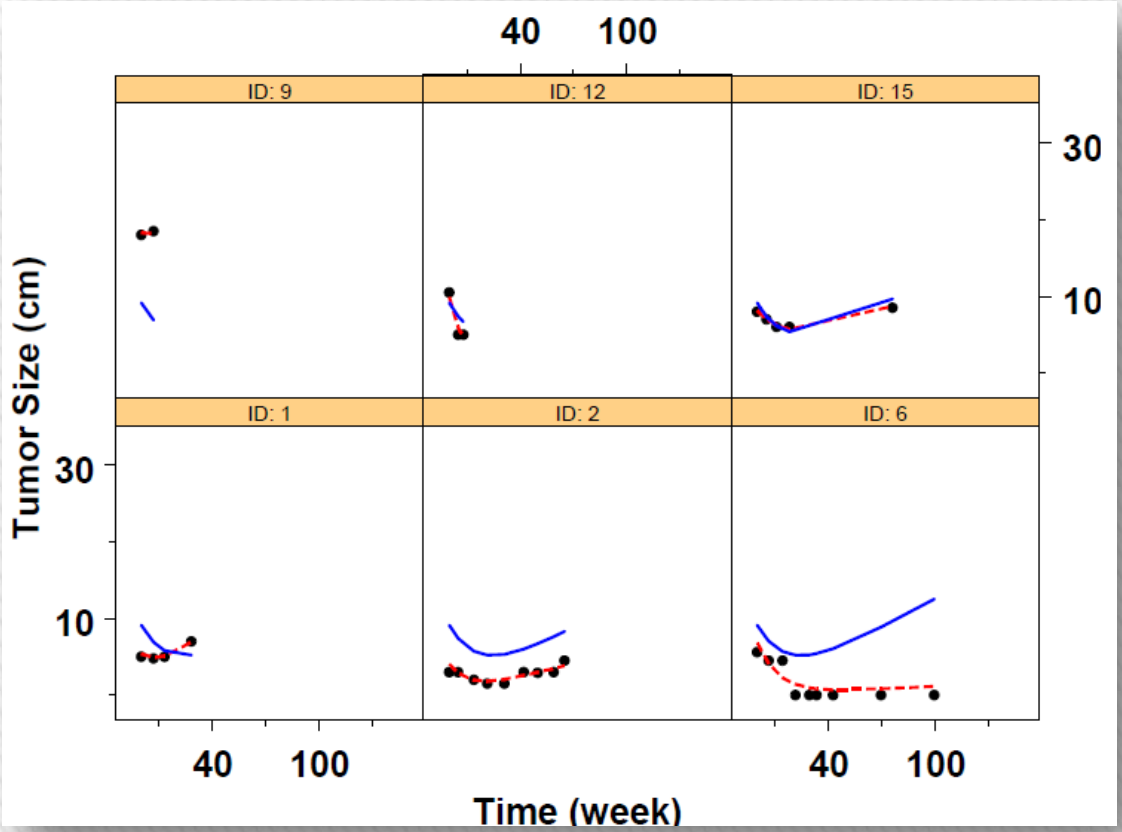
Scatter plot of the systemic exposures, simply derived from the clinical doses as AUC = Dose/CLh (where AUC = area under the plasma concentration-time curve and Dose = midpoint of the range of active clinical doses), versus the k_2 values estimated in animals

Clinical development: Non-small cell lung cancer (NSCLC) disease model

- Four registration trials for NSCLC provided 9 different regimens that were either first-line or second-line treatments for locally advanced or metastatic NSCLC
- Various risk factors for survival were screened based on Cox proportional hazard model. Tumor size dynamic data were described with a disease model that incorporates both the tumor growth property and the regimen's anti-tumor activity
- Patient survival times were described with a parametric survival model that includes various risk factors and tumor size change as predictors

Wang Y., Sung C., Dartois C., Ramchandani R., Booth B.P., Rock E., and Gobburu J. (2009) Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development. Clin. Pharmacol. Ther. 86, 167-174.

Clinical Models for Tumor Growth



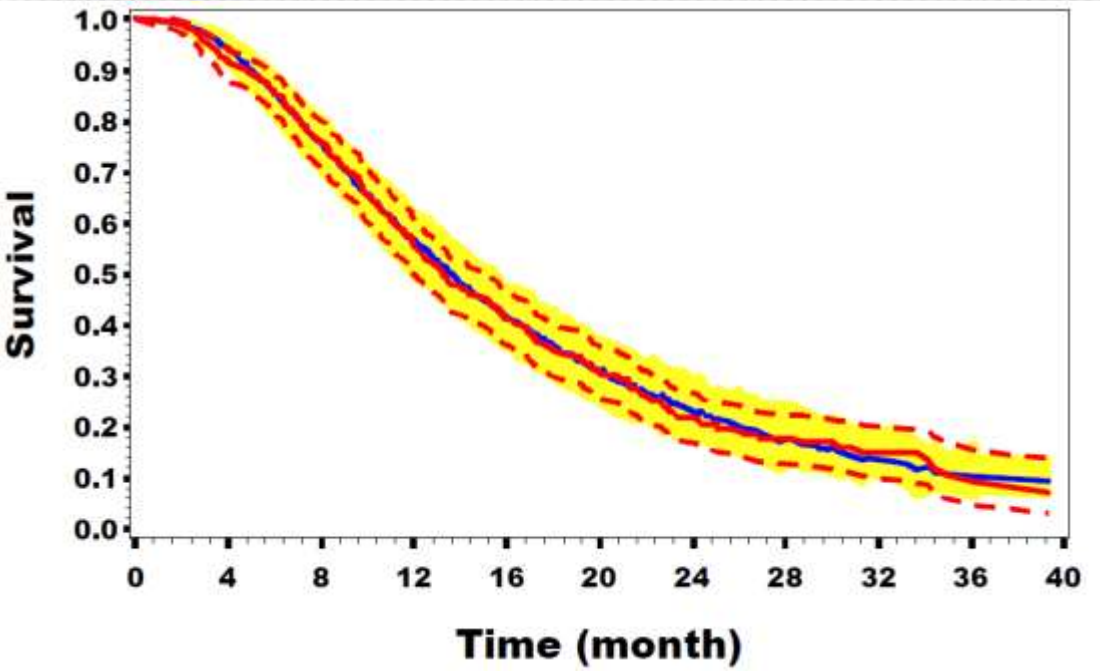
$$TS_i(t) = BASE_i \cdot e^{-SR_i \cdot t} + PR_i \cdot t$$

- TS(t) tumor size at time t for the ith individual
- BASEi is the baseline tumor size
- SRi is the exponential tumor shrinkage rate constant,
- PRi is the linear tumor progression rate

Wang Y., Sung C., Dartois C., Ramchandani R., Booth B.P., Rock E., and Gobburu J. (2009) Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development. Clin. Pharmacol. Ther. 86, 167-174.

Survival model

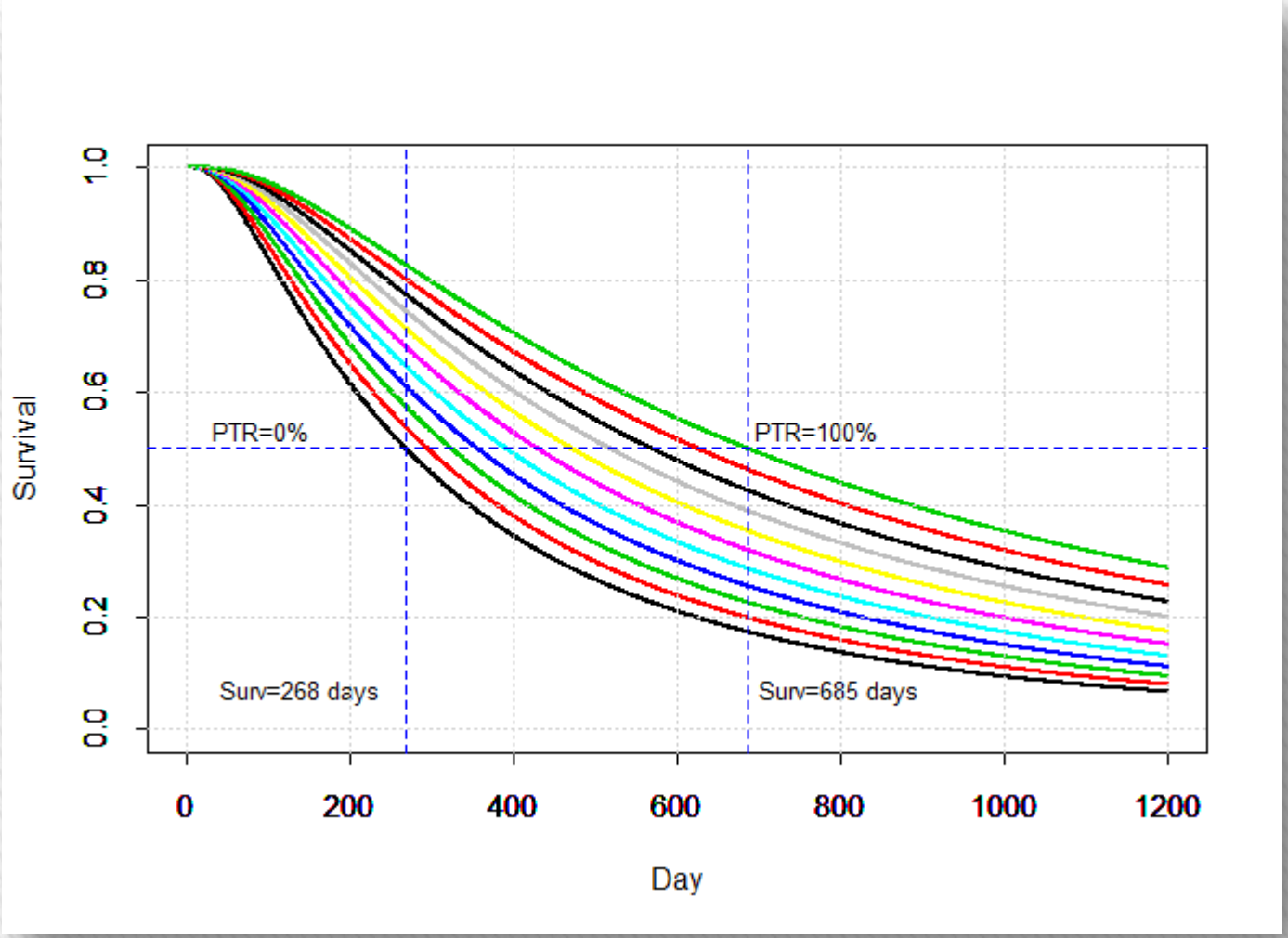
$$\log(T) = \alpha_0 + \alpha_1 \times ECOG + \alpha_2 \times (Baseline - 8.5) + \alpha_3 \times PTR_{wk8} + \varepsilon_{TD}$$



- T is the time to death (day),
- α_0 is the intercept,
- α_1, α_2, and α_3 are the slopes for ECOG (Performance Status grade), , centered baseline, and PTR_{wk8} (percentage tumor reduction from
- baseline at week 8),
- ε_{TD} is the residual variability

Wang Y., Sung C., Dartois C., Ramchandani R., Booth B.P., Rock E., and Gobburu J. (2009) Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development. Clin. Pharmacol. Ther. 86, 167-174.

Models predicted survival as a function of Tumor Size reduction



Modeling the Probability of AE (Rash)

A logistic model was used to describe the probability (p) of observing a Rash event as function of the maximal individual plasma concentration (C_{max})

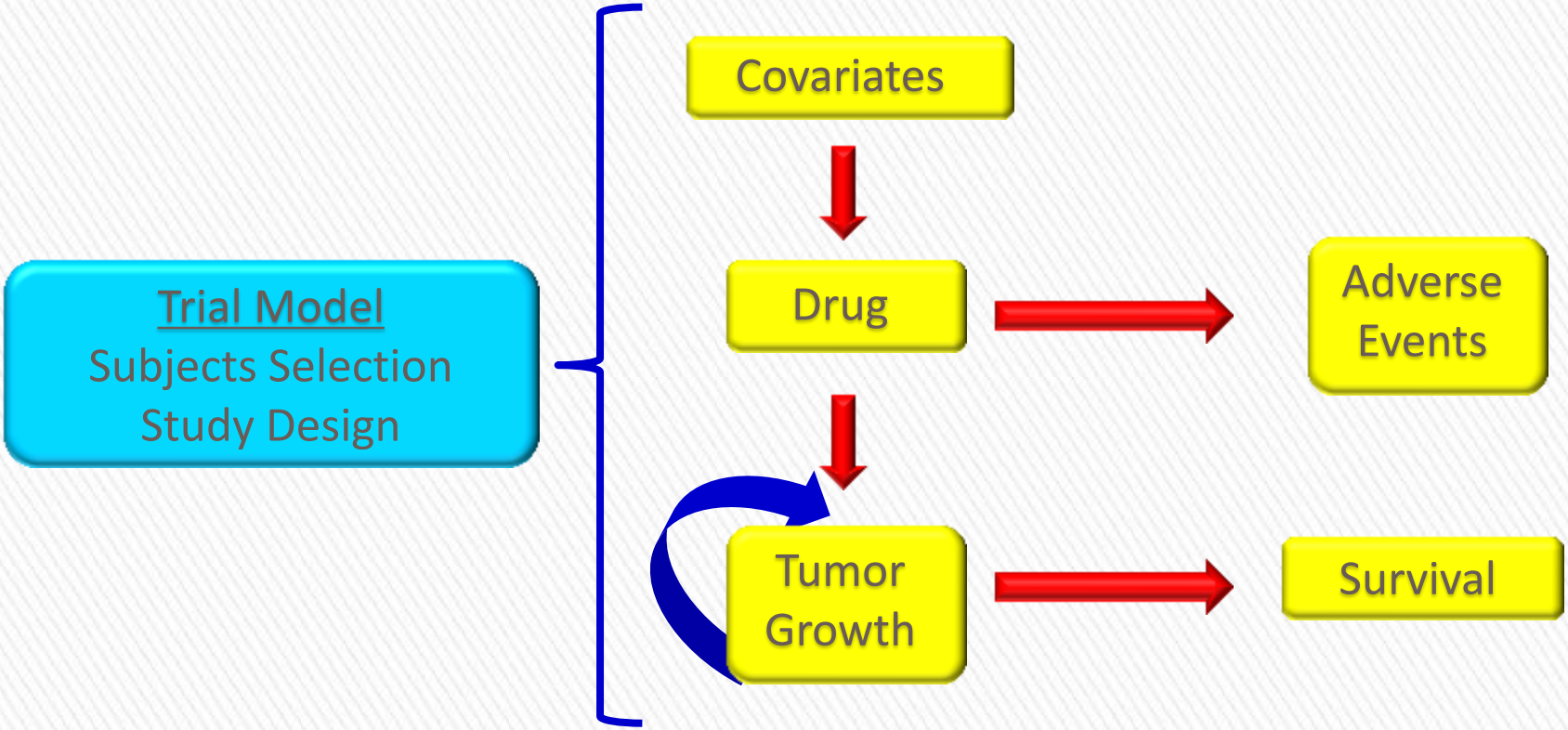
The probability p was estimated by :

$$\lambda = \text{intercept} + \text{slope} \cdot C_{max}$$

$$p = \frac{e^{\lambda}}{1+e^{\lambda}}$$

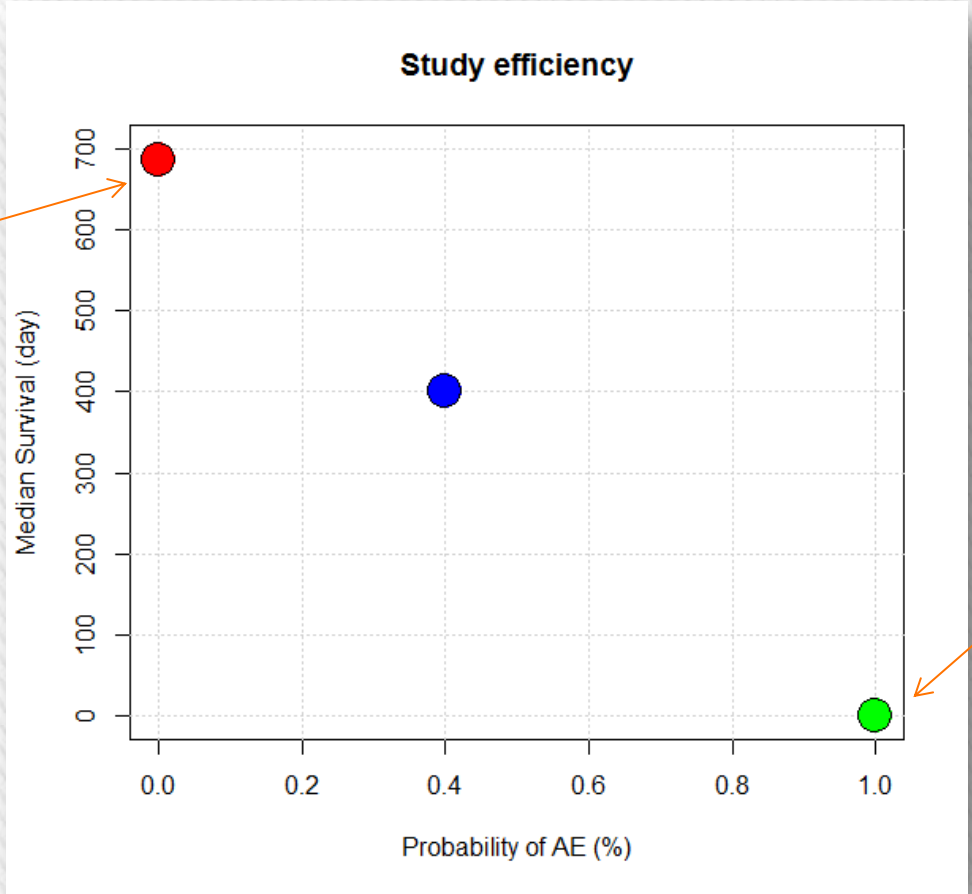
Where: λ is the logit function, '*intercept*' is the intercept of the logistic function and '*slope*' is the coefficient of the predictor variable

Drug-Disease-Trial Model



Definition of Study Efficiency

An ideal treatment would provide complete response (max median survival time) for all subjects in the trial without AE



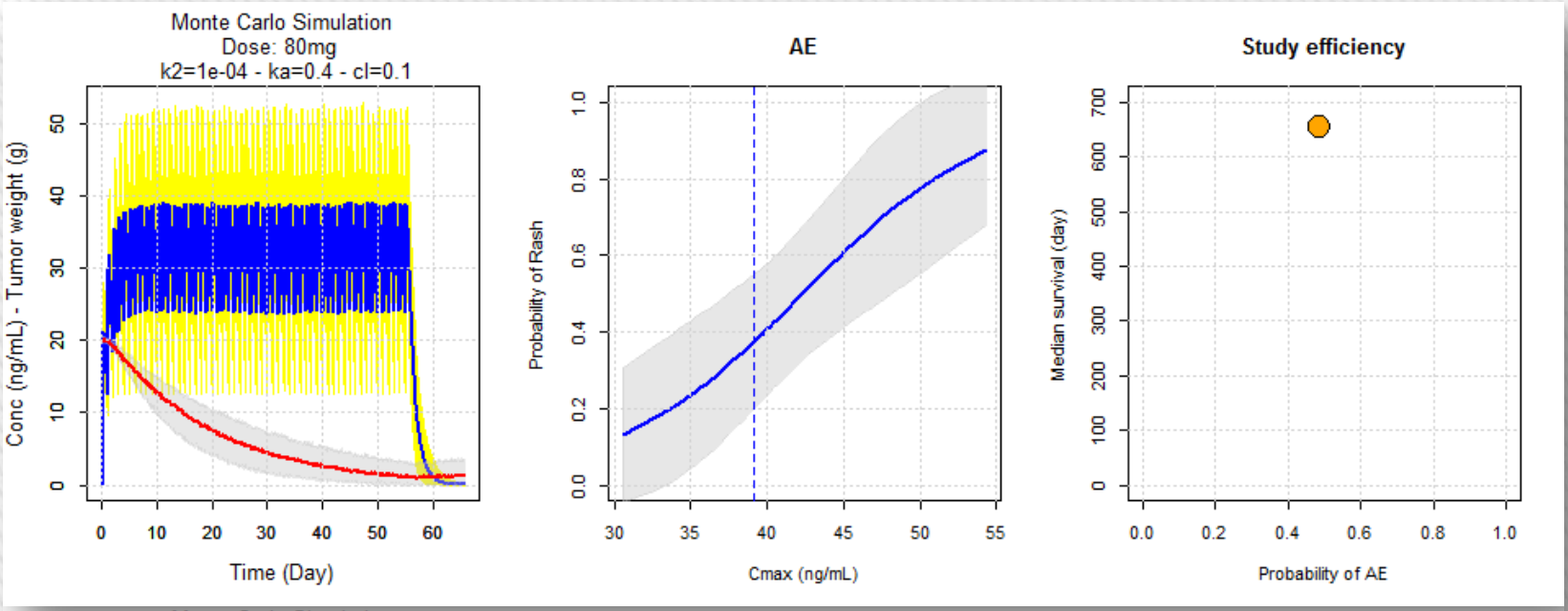
An ineffective treatment is characterized by a poor medial survival and a high incidence of AEs

Problems

Use Clinical Trial Simulation to address the clinical development questions:

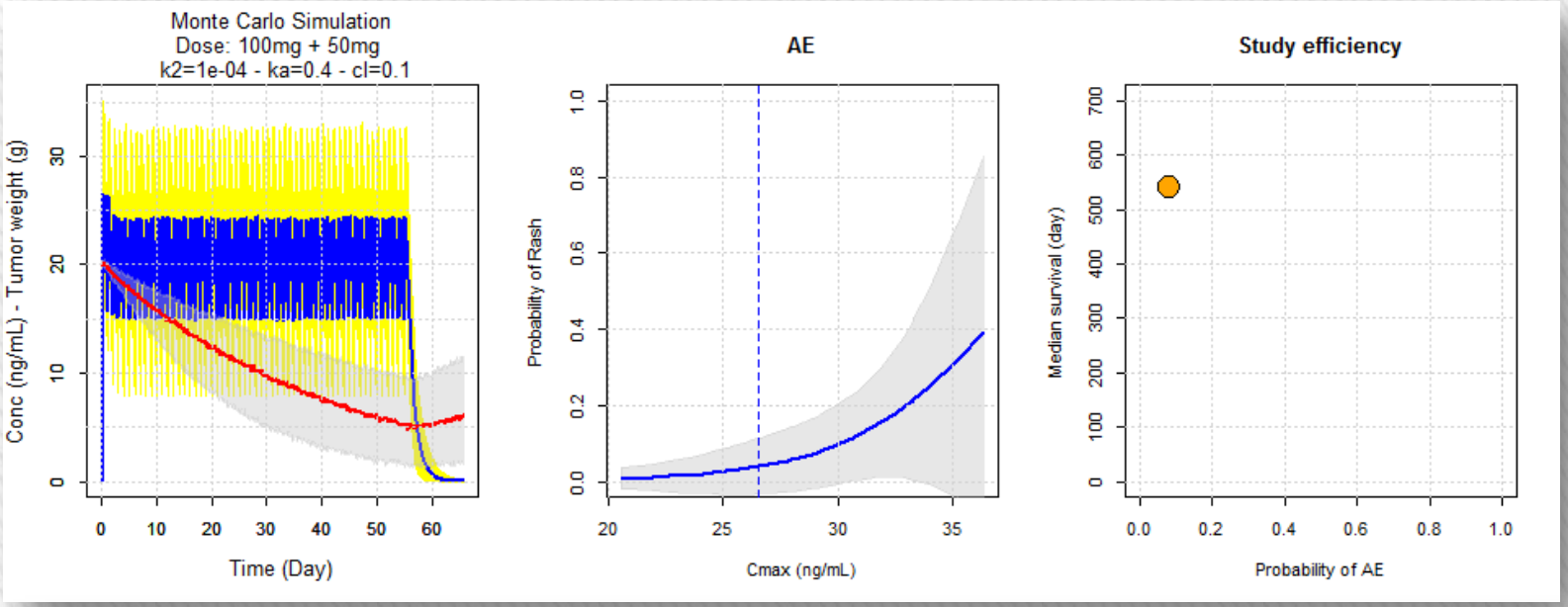
1. *What about the efficiency of a study based on a dosage regimen of 80mg/day or 100mg/day?*
2. *What about the efficiency of a study based on a dosage regimen of 50mg/day with a loading dose of 100mg (the first day)?*
3. *What about a back-up compound with a clearance reduced by 25%?*

Clinical Trial Simulation: I

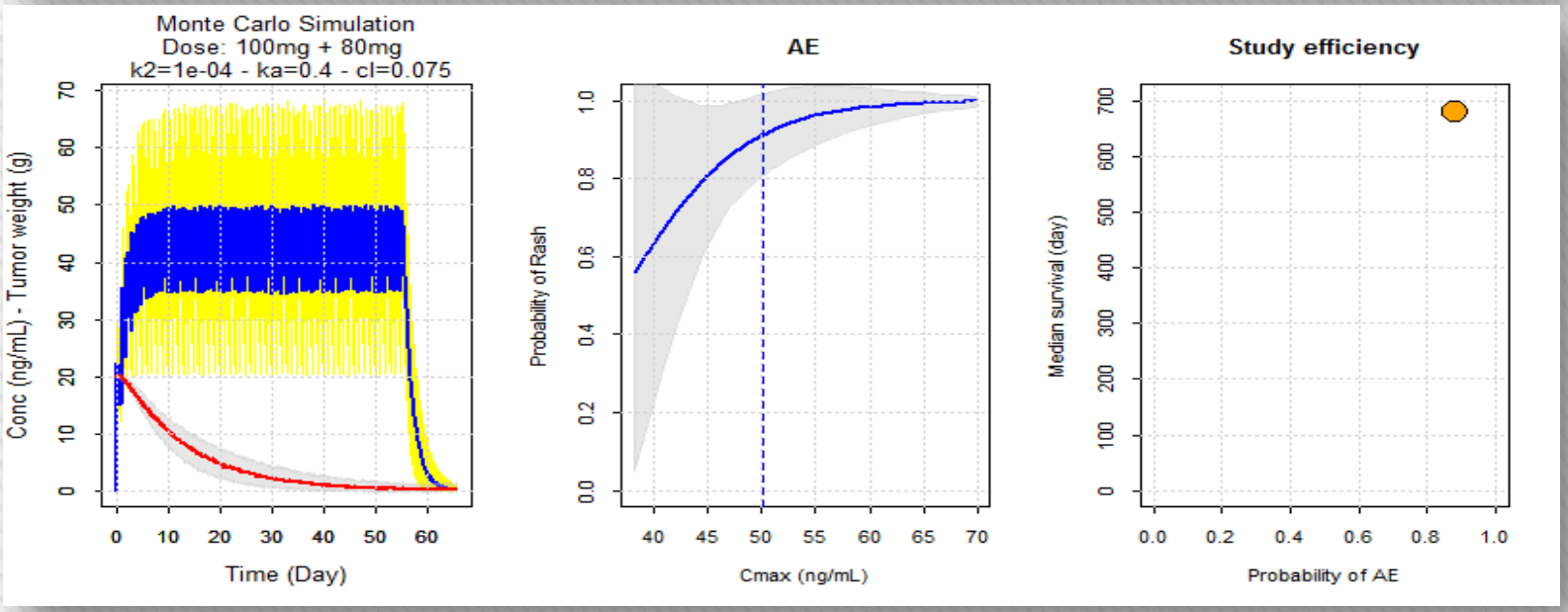


Clinical Trial Simulation: II & III

II



III



Conclusion

The Simulation 4 (loading dose strategy) provide the best efficient study design scenario ….