

Impact of Modeling and Simulation in Drug Development

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Agenda

→ Modeling and simulation (M&S) in drug development

Case study

- **Oncology: Capecitabine+Docetaxel from Ph II to Ph III**

Drug Model Explorer (DMX)

Conclusion

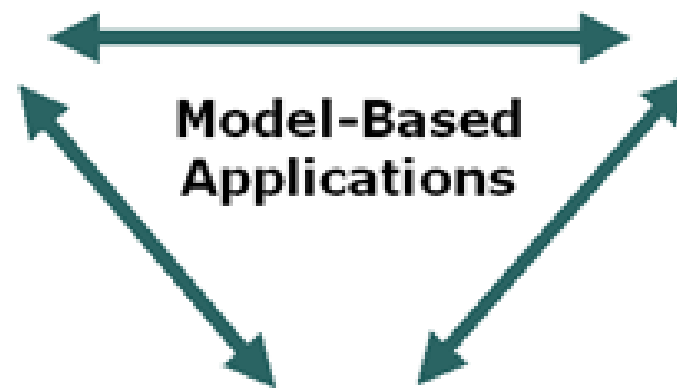
High value M&S Involves the integration of several different models...

Drug & Disease Models

- Optimize treatment, patient, endpoints
- Compare probable safety and efficacy of your drug to competitors

Predictive Market Models

- Choose the decision path with the greatest economic return
- Treatment, patient, endpoints
- Trial design
- Development program



Trial Models

- Optimize clinical trial design via clinical trial simulations

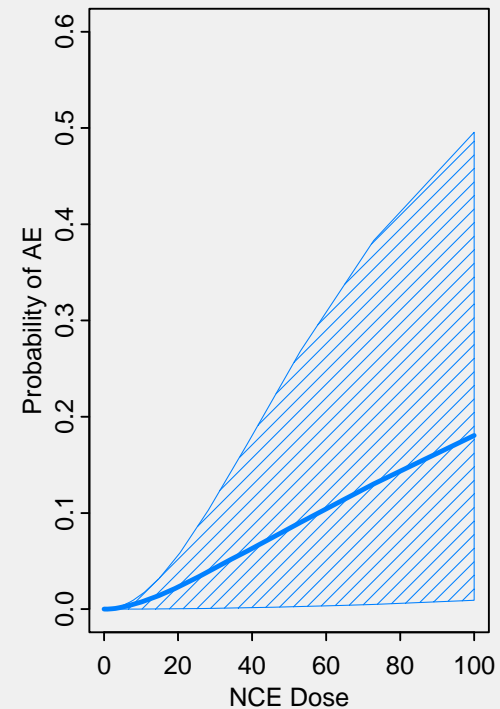
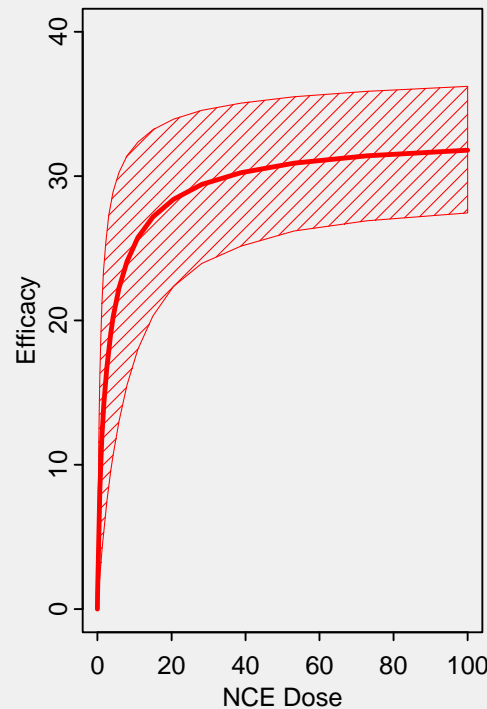
Models integrate available information on compound, analogues and markets to predict outcomes, quantify uncertainty, and manage trade-offs

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High value M&S involves the integration of several different models...

1. Drug & Disease Models

Quantify probability distribution of safety and efficacy measures as a function of drug, patient and disease features given current knowledge and assumptions



Greatest contribution of PK-PD modeling has been to improve dose selection and competitive position by better understanding the treatment strategy for the patient population

High value M&S involves the integration of several different models...

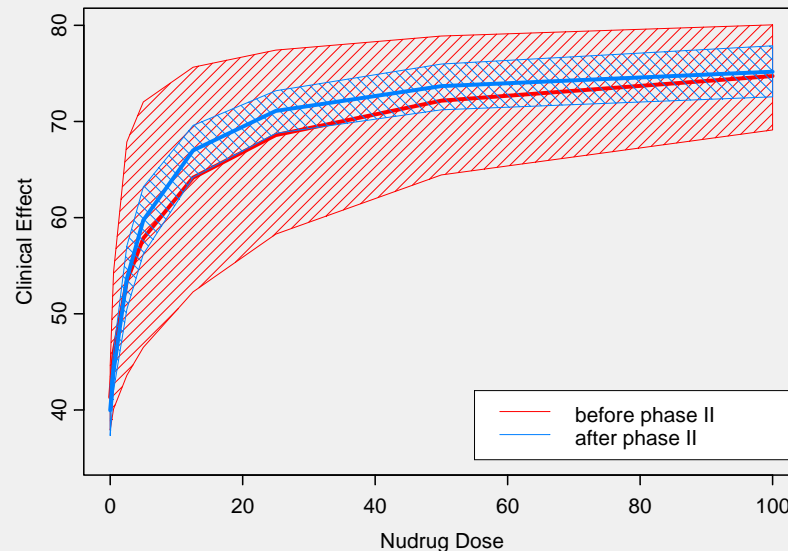
1. Drug & Disease Models

Quantify probability distribution of safety and efficacy measures as a function of drug, patient and disease features given current knowledge and assumptions

2. Trial Models

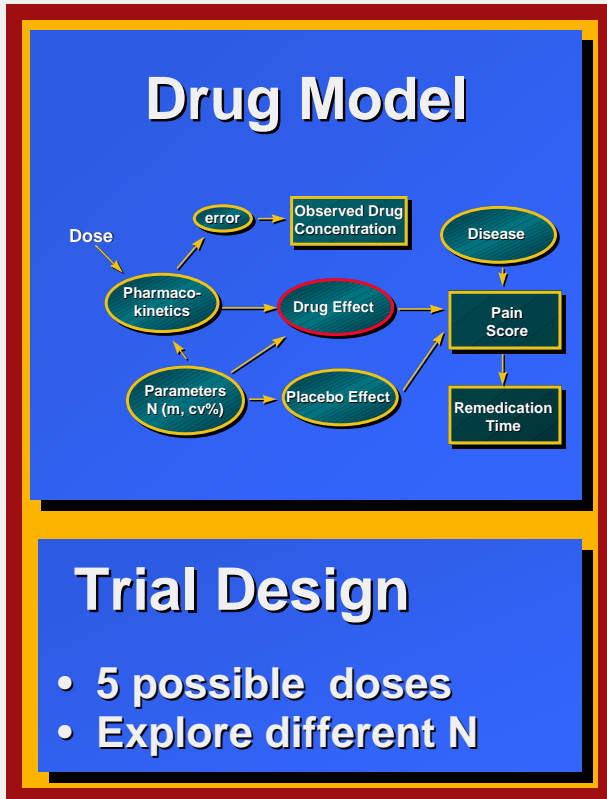
Quantify how a certain trial or trial sequence can reduce uncertainty around safety, efficacy

Trial simulation (CATD) has contributed mostly by improving trial design by better understanding the relationship between information yield of the trial and trial design features, trial cost/duration, and assumptions and uncertainties



Computer Assisted Trial Design (CATD) Process

Run Multiple Replications of Trial



Modify Design and/or Drug Model

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Support end-of-Phase II development decisions: A retrospective project with capecitabine (Roche)

Goal: To support early drug development decisions

- Go/No go
- Design of Phase III studies

Simulate expected survival difference in Phase III

- Comparing a new drug (X) to a reference drug (R)
- Based on Phase II data of X and historical data of R

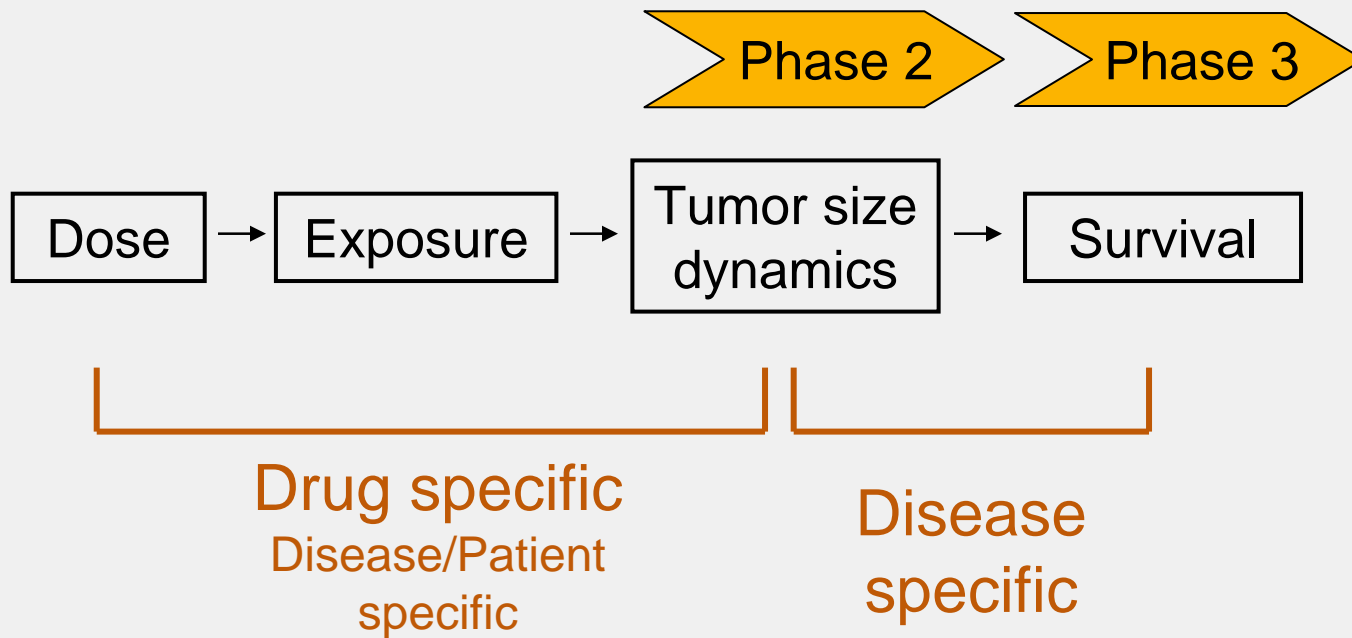
Retrospective project:

- To simulate:
 - Phase III of capecitabine (X) + docetaxel (R) vs. docetaxel in MBC
 - Phase III of capecitabine (X) vs. 5-Fu (R) in CRC

Claret L et al. Model-based predictions of expected anti-tumor response and survival in Phase III studies based on phase II data of an investigational agent. Proc ASCO, 24 (18S), 307s (Abs 6025), 2006.

The exposure - tumor size - survival model: A bridge from Phase II to Phase III endpoints

Three models, a tumor-size, a survival and a dose reduction probability model were used (in Backup)



To predict phase 3 endpoint based on phase 2 endpoint and prognostic factors

Simulation of a Phase III study comparing docetaxel to docetaxel + capecitabine in metastatic breast cancer (MBC)

Model parameter estimation

- **Capecitabine data**
 - Phase II (2 studies, 170 patients)
- **Docetaxel data**
 - Phase III (docetaxel arm, 223 patients)

Simulation

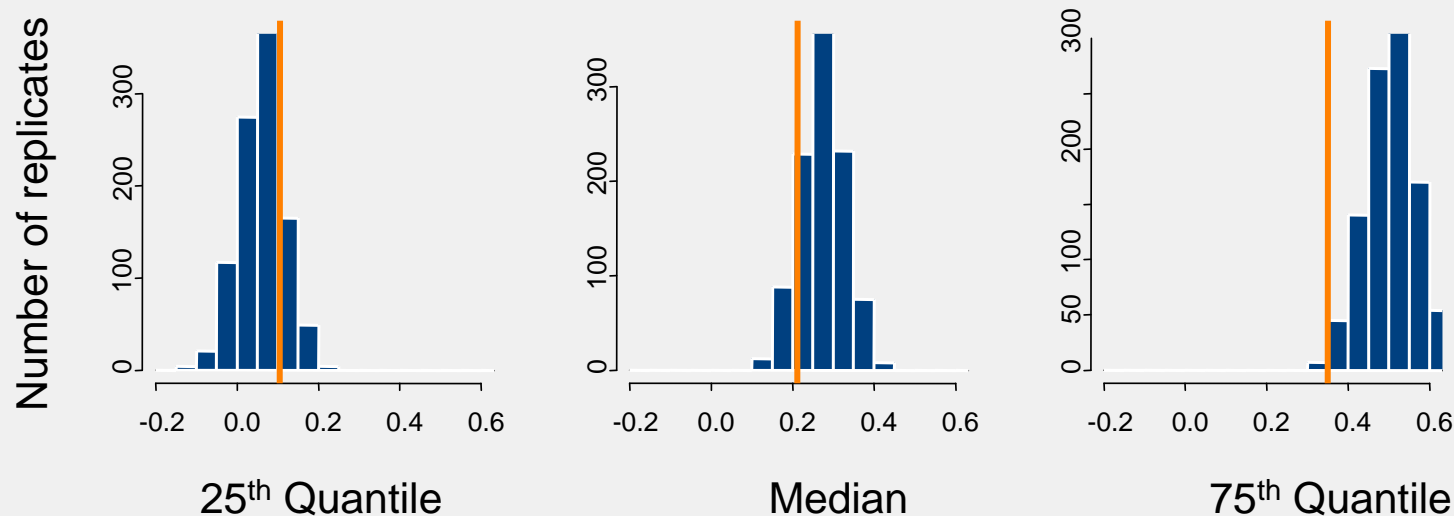
- **Phase III study of capecitabine + docetaxel vs. docetaxel (443 patients, 1000 replicates)**
 - Assumes additive effect for the combination
 - Capecitabine scaled from Phase II to Phase III using disease specific parameters (tumor growth rate)

Focus on efficacy, no model for dose-limiting side-effects

- **Simulations conditioned on observed dose intensity (dosing history)**
- **Drug effect driven by dose**

Simulation of tumor size reduction at week 6 vs. observed in the Phase III study (1000 replicates)

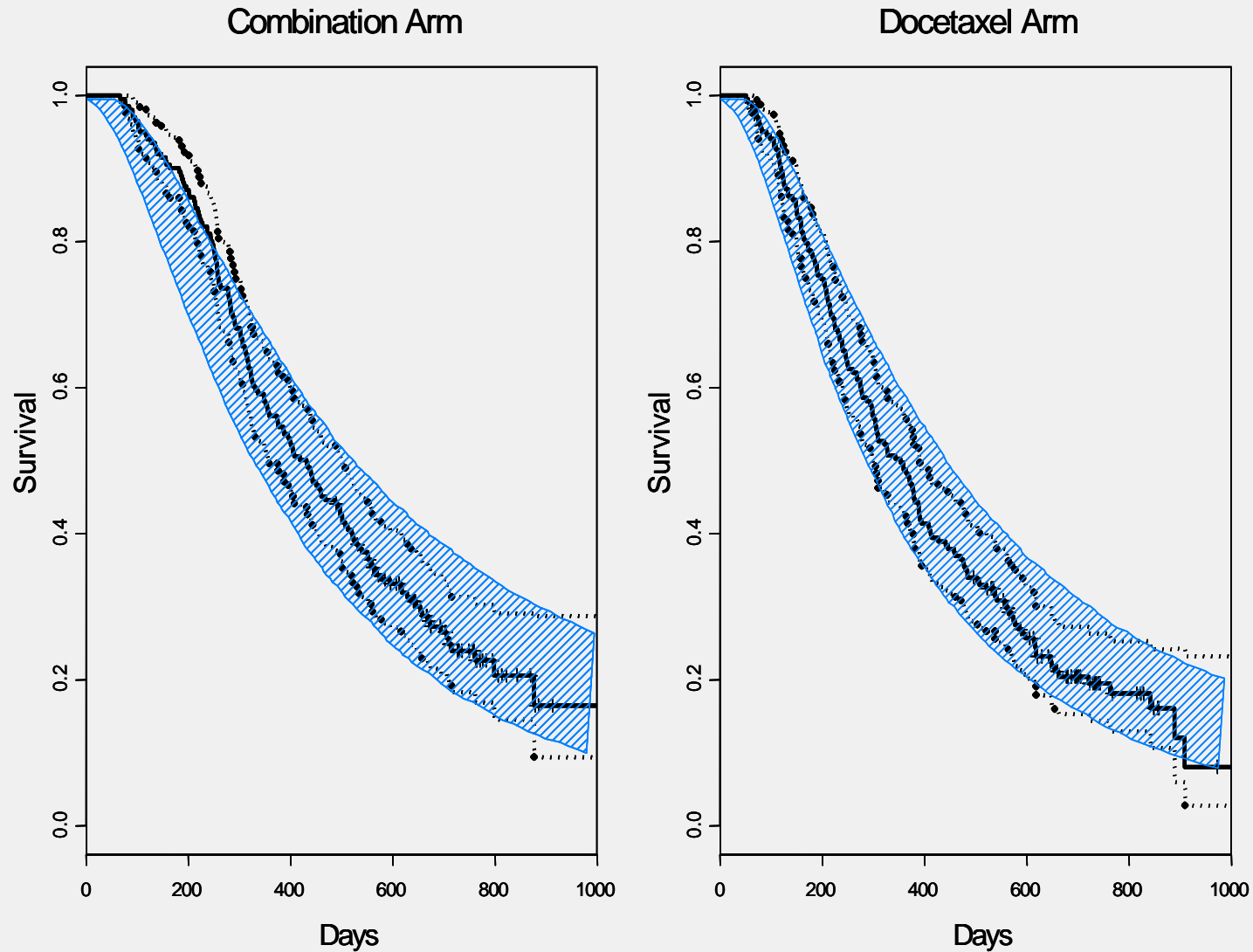
Docetaxel + Capecitabine Arm



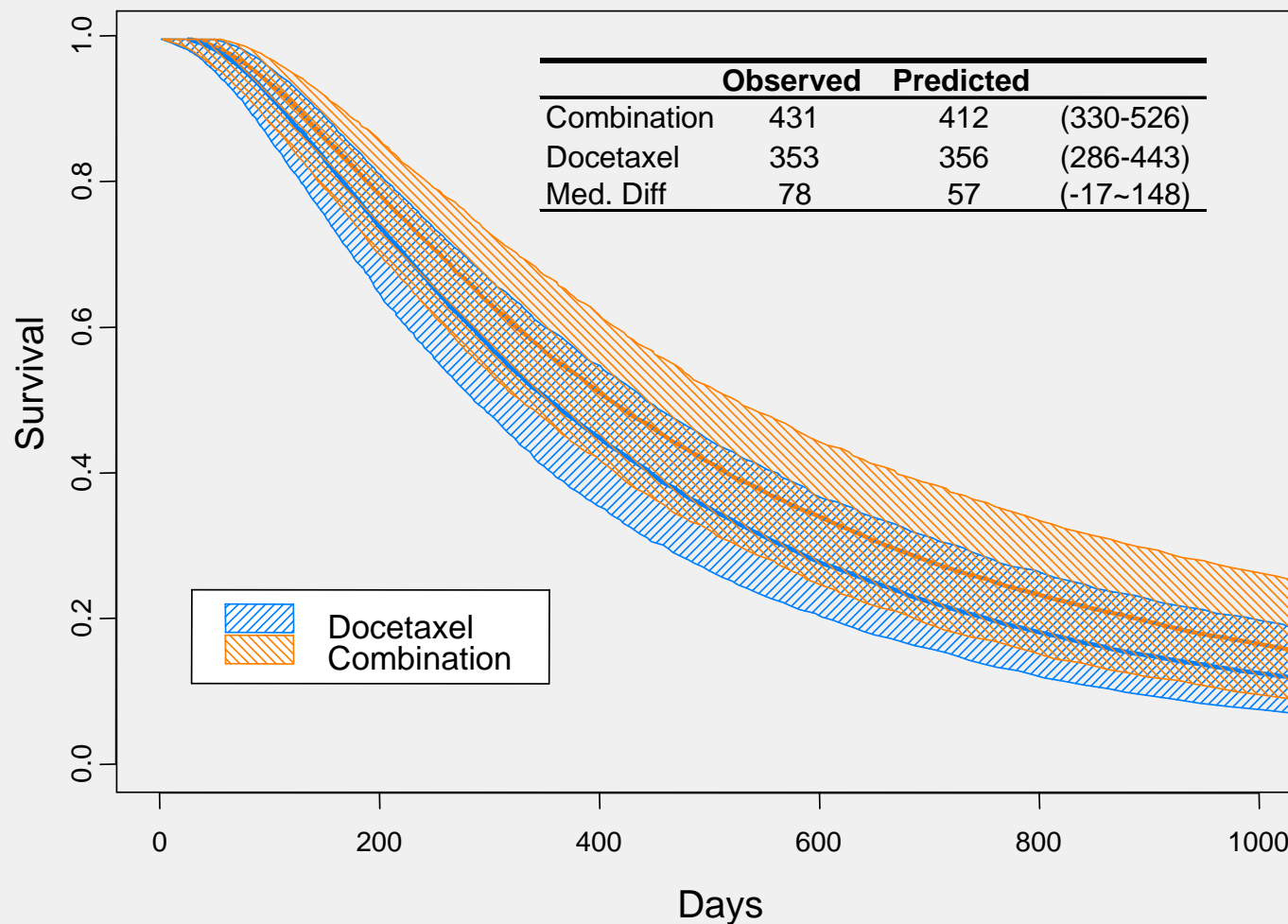
Tumor size reduction relative to baseline

	Observed	Predicted	90%	PI
Median	0.210	0.270	(0.180 - 0.360)	

Simulation of survival vs. observed in the Phase III study of docetaxel + capecitabine vs. docetaxel



Comparison of expected survival in a Phase III study of docetaxel + capecitabine vs. docetaxel



Capecitabine project conclusions

The structure of the tumor size model was robust to predict tumor growth and anti-tumor effect of:

- Three cytotoxic drugs in two tumor types

Change in tumor size was a good predictor of survival

The combined tumor size and survival models:

- Successfully predicted expected treatment differences in a Phase III setting
 - Based on Phase II data of an investigational treatment...
 - ... and historical Phase III data of a reference treatment
- Is a useful approach to support early development decisions:
 - Does the expected survival benefit of the new drug warrant further development?
 - If yes, which Phase III study need be designed to show non-inferiority, superiority?

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Modeling and simulation (M&S) in drug development

Case study

- Oncology: Capecitabine+Docetaxel from Ph II to Ph III

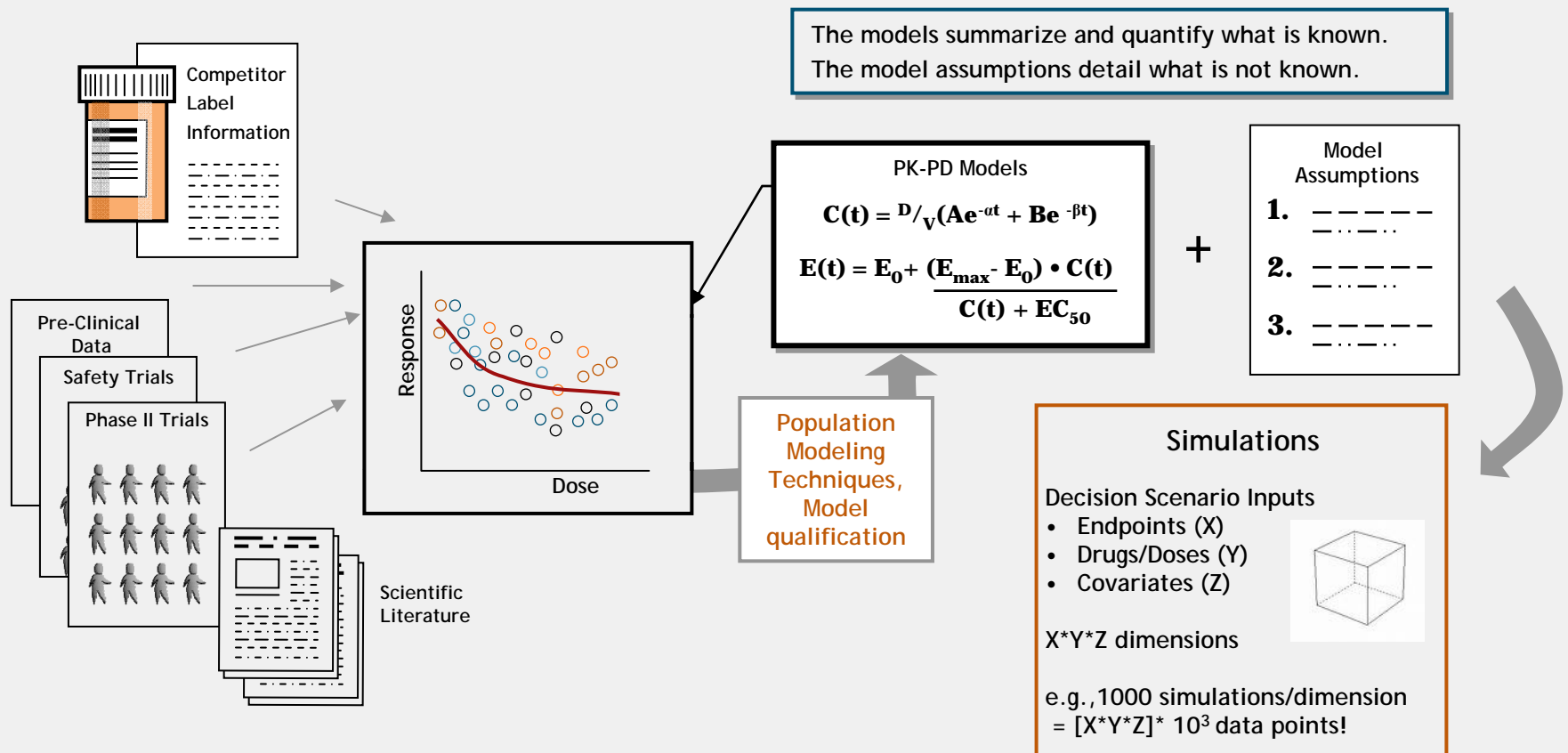
→ Drug Model Explorer (DMX)

Conclusion

Communication is a Key Component of M&S

M&S helps capture the inherent complexity and uncertainty about a drug's properties in a rigorously quantitative fashion.

Now, how best to communicate findings and insights?



The Communication Challenge

Communication is often a significant factor limiting the impact of M&S work to wider audiences. Challenges include...

The Models

- Lack of familiarity with models or modeling techniques leads to distrust of a perceived ‘black box’ methodology

The Questions

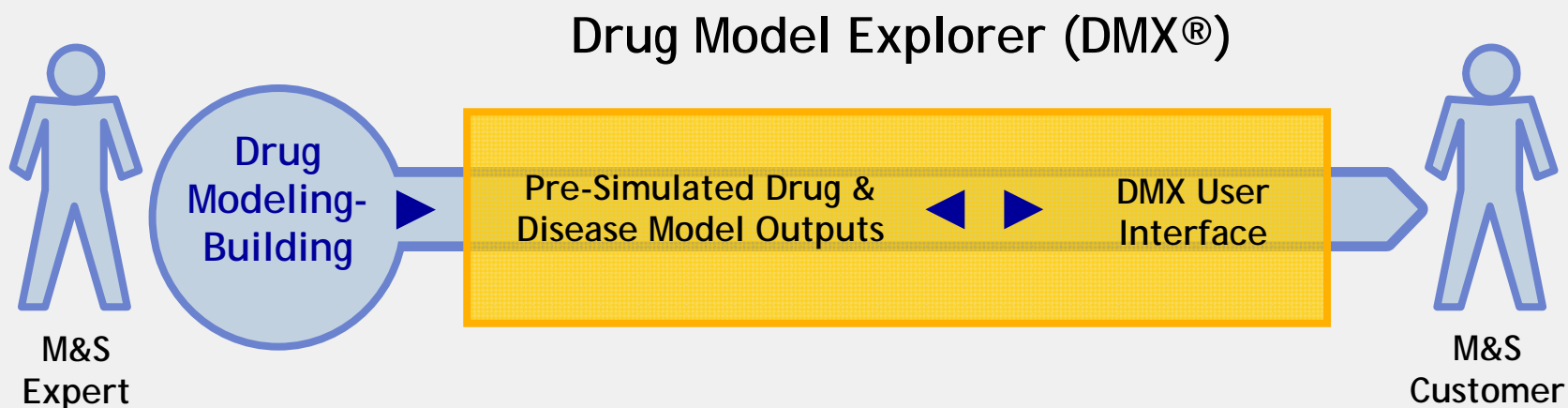
- M&S frequently stimulates dynamic team discussions, where the ability to quickly address “what if” questions is key

The Decisions

- Achievement of consensus on key decision points for the compound attributes can be difficult

DMX[®]: A Tool for Exploring Modeling Results

DMX is a desktop and web-based visualization and communication tool for exploring model-based product profiles.



- Used by modeling experts to make modeling and simulation results available to teams and decision-makers
- Used by the project team to compare performance vs. competing treatments, evaluate product profiles, and understand trade-offs
- Used by companies to capture knowledge and update as new information becomes available

Example of DMX output: Allows team to view and query model-based drug attributes

DMX The Drug Model Explorer

CA-1209 Version 1
View Model Documentation

Project Index | Help | Log Out

Independent Variable: Dose of Class AB

Inputs | Ranges | Views

Endpoint

- % Change E1
- % Change E2
- % Patients to E1 Target
- % Patients to E2 Target
- % Patients w/AE
- Wellness Score
- Event Relative Risk

Covariates and Parameters

Base E1: 1-2.5, 2.5-5, 5-7.5, 7.5-10, 10-15, Pop.

Base E2: < 5, 5-10, 10-20, 20+, Pop.

E1 Target: < 0.75, < 1, < 2.5

Target E2: < 5, < 7.5, < 10

Update

Overlay: None, Rows, Columns

Plot Size: Small, Medium, Large

Uncertainty Interval 5 % to 95 %

1 Plot, medium size
Download Plots in MSOffice Format

% Change E1 vs Drug B Dose (mg)
Drug 1 Dose (mg): 20

% Change E1

Drug B Dose (mg)

% Change E1 vs Drug B Dose (mg)
Drug 1 Dose (mg): 20

Drug B Dose (mg)	5.0%	mean	95.0%
150	-45	-44	-43
300	-48	-47	-45

Shaded area shows prediction interval for expected dose-response

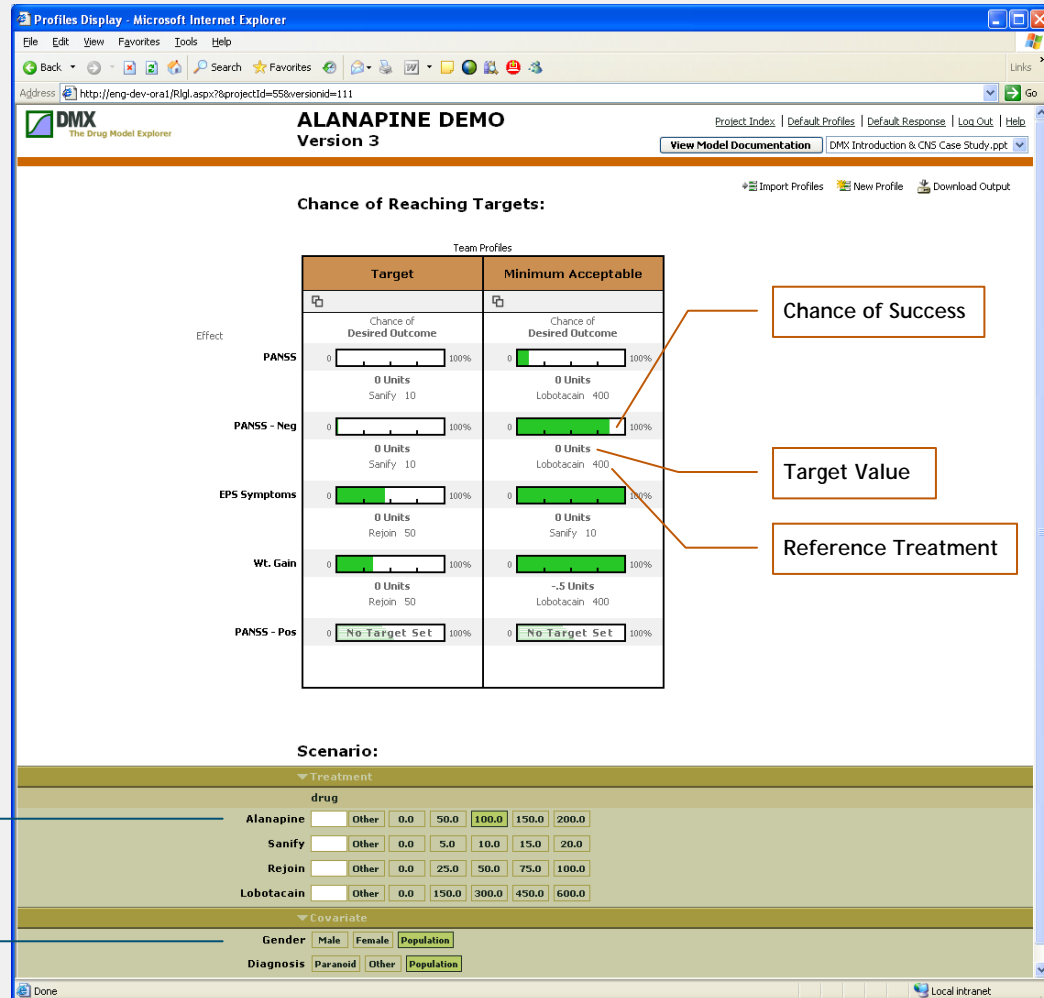
Vertical lines show doses of interest

Tables display quantitative estimates of prediction intervals or other information

Displaying Simulated Product Profiles in DMX

This display makes immediately clear that at 100mg, Alanapine has a some chance for modest market success, but has little chance of meeting the target profile.

Let's examine the components of this display.



Proposed Treatment

Population Variables

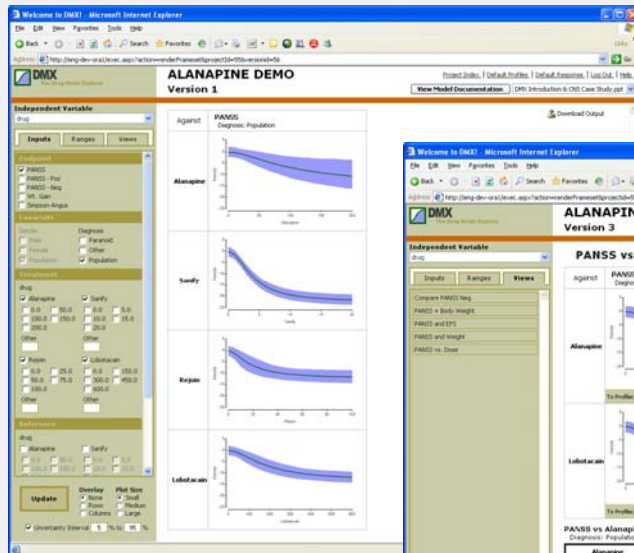
Chance of Success

Target Value

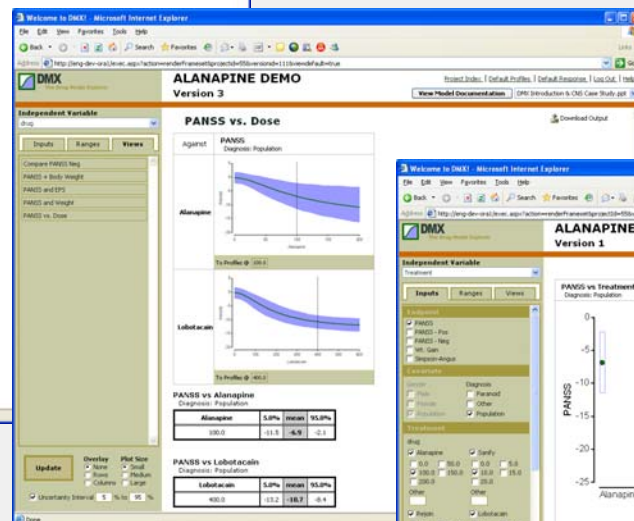
Reference Treatment

DMX: Beyond Profiles

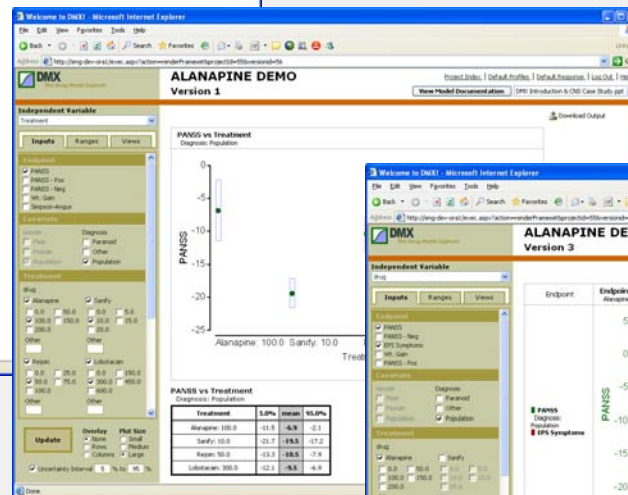
In addition to displaying product profiles, DMX provides several additional visualizations that help teams develop and communicate a variety of insights into the nature and competitive value of their compound.



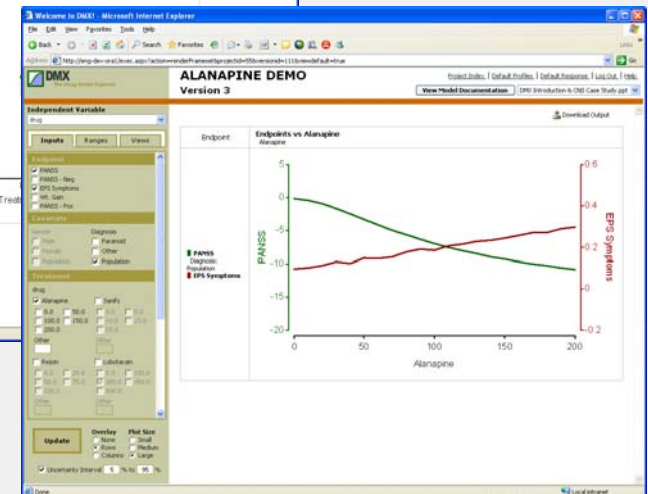
Stratified Dose-Response



Saved Views



Treatment Comparison



Effect Overlay

Benefits of DMX

Modeling results are more effectively communicated to the project team.

- Answer 'what if' questions on-the-spot.
- Rapid generation of statistics on relevant reference and critical success factor "cut-points"
- Facilitates greater acceptance of the model by the entire project team

DMX as a software platform facilitates the incorporation of M&S into the decision making process of an organization

- Supports the methodology and makes it accessible to a broader audience
- Optimizes the workflow and decision making process
- Provides a standardized visual presentation structure for representing complex information

DMX captures current and future knowledge about a compound and its competitors

- Applicable within and across development programs, can be easily updated when new information becomes available

DMX Case Study and References

Published Case Study

- In 2005, *Bio-IT World* announced Pfizer Global R&D as a winner of its Annual Best Practices Award for the application of DMX and decision-focused modeling strategies on a compound in its cardiovascular franchise
 - PK/PD Simulation Speeds Decision Making. *Bio-IT World Best Practices* [serial online]. January 23, 2006. Available at www.bio-itworld.com.

Recent Article Referencing DMX

- Corrigan BW et al. Model-Based Meta-Analyses vs. Clinical Impressionism: Challenges and Rewards. *AAPS Newsmagazine*; September 2007. Available at: www.aapspharmaceutica.com/.

Additional References

- Hermann D, Wang W, Falcoz C, Hartman D, Mandema J. Strategies to Improve Model-Based Decision-Making During Clinical Development. [poster]. Presented at: Annual Meeting of the Population Approach Group in Europe (PAGE); June 2005; Pamplona, Spain. Available at www.pharsight.com/library/library_cs.php.
- Mandema JW, Hermann D, Wang W, Sheiner T, Milad M, Bakker-Arkema R, Hartman D. Model-Based Development of Gemcabene, a New Lipid-Altering Agent. *AAPS Journal*. 2005; 7(3). Available at www.aapsj.org.

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How M&S improves the decision-making process?

Integrated, data-driven, model-based decision-making approach:

Integrate all relevant public and proprietary data spanning from discovery to clinical, from in-house data to competitors' information, and from healthy volunteers to patients into a probabilistic model of the compound's product profile in the context of competitive landscape.

Backup

The TGI model describes the sum of tumor longest diameters as a function of time and dose

Tumor growth rate Cell-kill rate

↓ ↙

$$\frac{dy(t)}{dt} = K_L \cdot y(t) - K_D(t) \cdot \text{Exposure}(t) \cdot y(t)$$

$$K_D(t) = K_{D,0} \cdot e^{-\lambda t}$$
$$y(0) = y_0$$

Resistance: exponential decrease of kill rate
 λ : rate constant for resistance appearance, $K_D(0)=K_{D,0}$
Baseline tumor size

The model by incorporating drug specific (K_D , λ) and disease/patient specific (Y_0 , K_L) parameters, allow scaling of drug effect across:

- Patient populations
- Development phases (e.g. Phase II to Phase III)

Claret L et al. PAGE 15, (Abstract 1004), 2006 [www.page-meeting.org/?abstract=1004].

The survival model

Relates survival time to prognostic factors and predictors

- Prognostic factors (e.g. performance status, baseline tumor size, receptor status...)
- Fractional change in tumor size at an early visit (drug effect)

Drug independent, disease specific model

- Historical Phase III studies can be used to develop the model (provided patient-level data are available)
- The model can be leveraged to simulate survival for a new investigational treatment

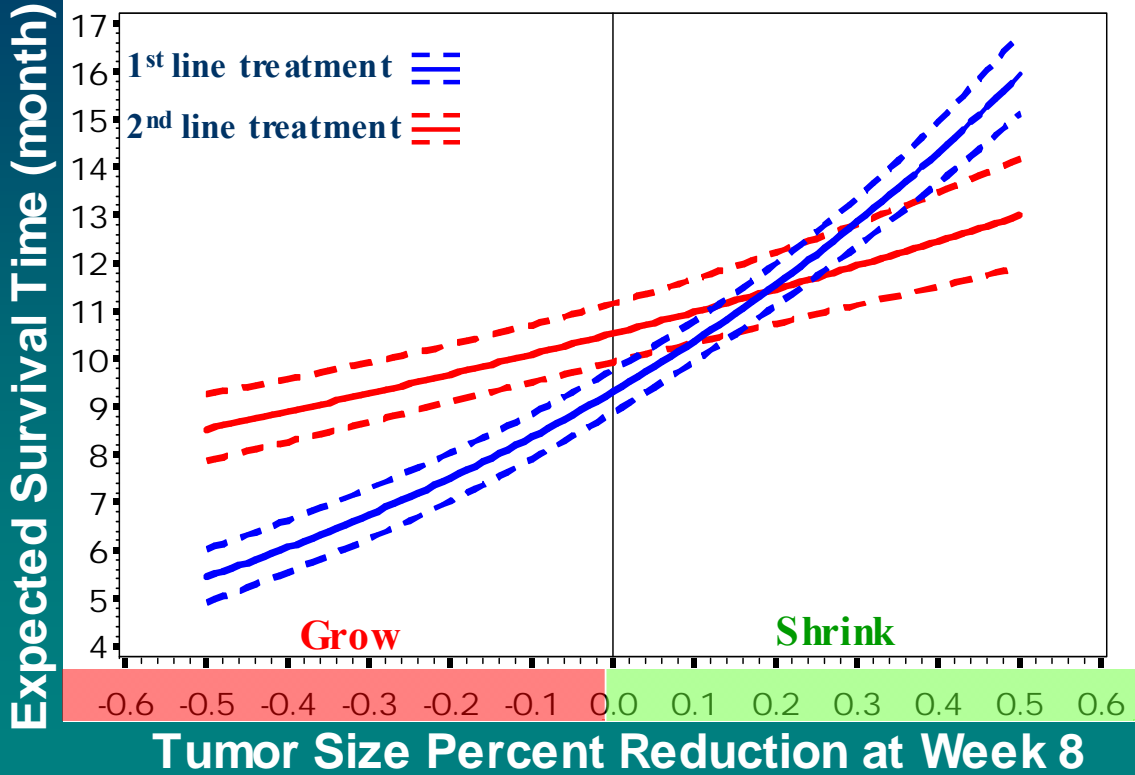
The public-domain FDA NSCLC model can be used to predict expected survival for investigational treatments

- Pharsight Uses FDA Disease Model to Support Oncology Drug Development: http://media.corporate-ir.net/media_files/irol/12/121504/Release112007.pdf
- The company was interested in getting expectations of survival for a NCE in combination
 - To support decision to start a large Phase III study
 - They had a Phase Ib combination study in NSCLC (less than 30 patients)
 - We used the FDA model and simulated expected survival

FDA NSCLC survival model



Tumor Size – Survival Relationship



Gobburu, Pharmacometrics

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The dose-reduction model relates the probability of dosing reductions to time and exposure

Modeling the time course of dose-limiting size effects would be to cumbersome

Dose reductions are modeled as an ordered categorical variable

- e.g. 0%, 25%, 50%, 100% reductions

Dose delays can be modeled the same way

The model simulates the dose intensity over time to drive drug effect

Claret et al. A modeling framework to simulate Xeloda dose intensity and survival in colorectal cancer. PAGE 17 (2008) Abstr 1312 [www.page-meeting.org/?abstract=1312]