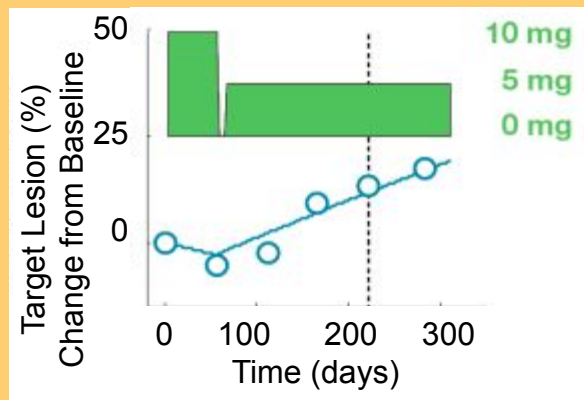


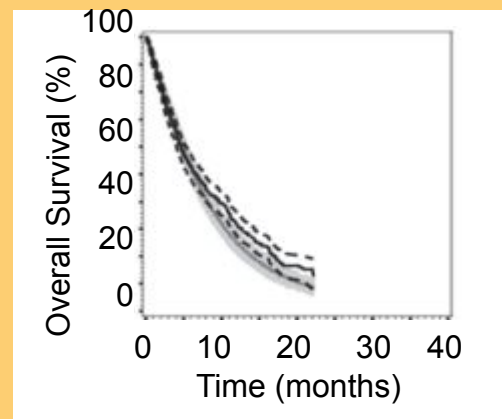
Response Criteria for Solid Tumors (RECIST)



Dose Response



Phase III Survival Prediction Go/No-Go Decision Making



Using longitudinal solid tumor data to improve drug development decisions

ACoP, May 13, 2013

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Background

- Oncology Phase III trials have a >40% failure rate¹
- Suboptimal Phase III decisions (e.g. dose selection, powering of study, go-no/go) may result from not fully using the available tumor data that is collected.
- The pharmacometrics community is developing methodologies that take into account more of the available data, which could potentially lead to more efficient trials and reduced failure rates.

1. DiMasi JA and Grabowski, *J Clin. Oncol.*, 25, 209 (2007)

2 | ACoP | A. Stein | May 13, 2013 | Modeling solid tumor data

Overview: Summarize state of the art for modeling tumor data to improve drug development decisions

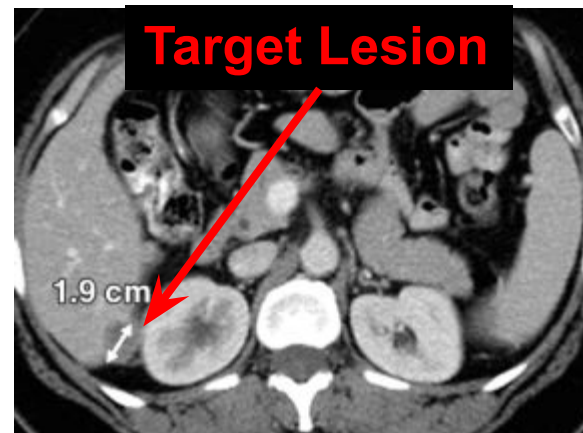
1. Describe underutilized longitudinal tumor data.
2. Example of modeling longitudinal tumor data to support dose selection.
3. Example of modeling longitudinal tumor data to guide go/no-go decisions. Discuss challenges in validating this approach.
4. How to address the above challenges in model based go/no-go decision making.

1. Review of tumor data: Which features in data are underutilized?

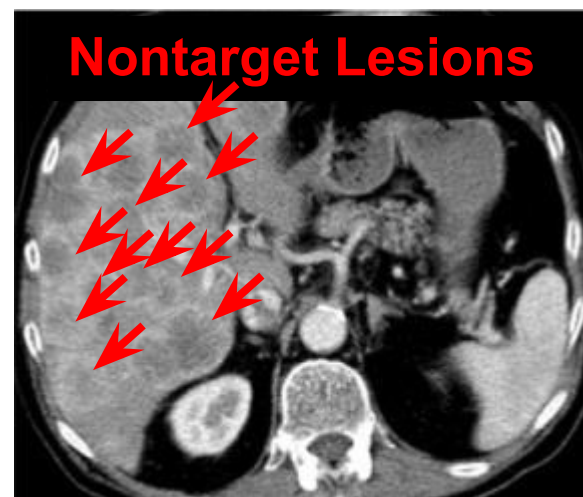


Background: RECIST¹ lesion types²

- Target Lesions
 - 1-2 “representative” lesions per organ
 - Lesions must be measurable
 - Sum of the longest diameters (SLD) is computed
- Nontarget Lesions
 - When >1-2 lesions exist per organ
 - “Unmeasurable” lesions
 - Categorical response recorded
- New Lesions
 - Detectable only after the start of therapy
 - Binary response (yes/no) recorded



Ovarian cancer metastasis in liver

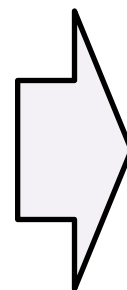
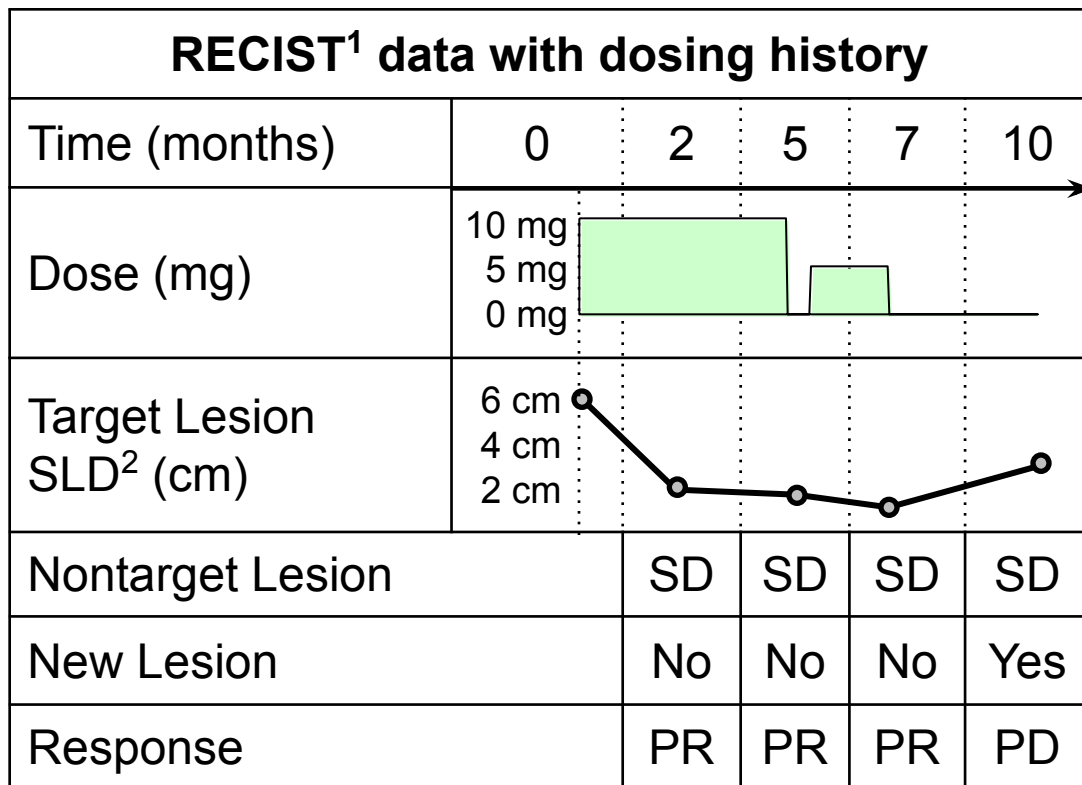


Rectal cancer metastases in liver.

1. RECIST = Response Evaluation Criteria In Solid Tumors (v1.1)

2. EA Eisenhauer, Eur J. Cancer, 24, 228 (2009)

Background: Patient response is summarized by single value measurements; some information is lost



Single value measurements:	
Time to Progression	10 mo.
Best Overall Response	PR
Best Percent Change in SLD	55%

- Summary statistics based on single value measurements are then used to compare trial arms

1. RECIST = Response Evaluation Criteria In Solid Tumors

2. SLD = Sum of Longest Diameters of target lesions

SD = Stable Disease

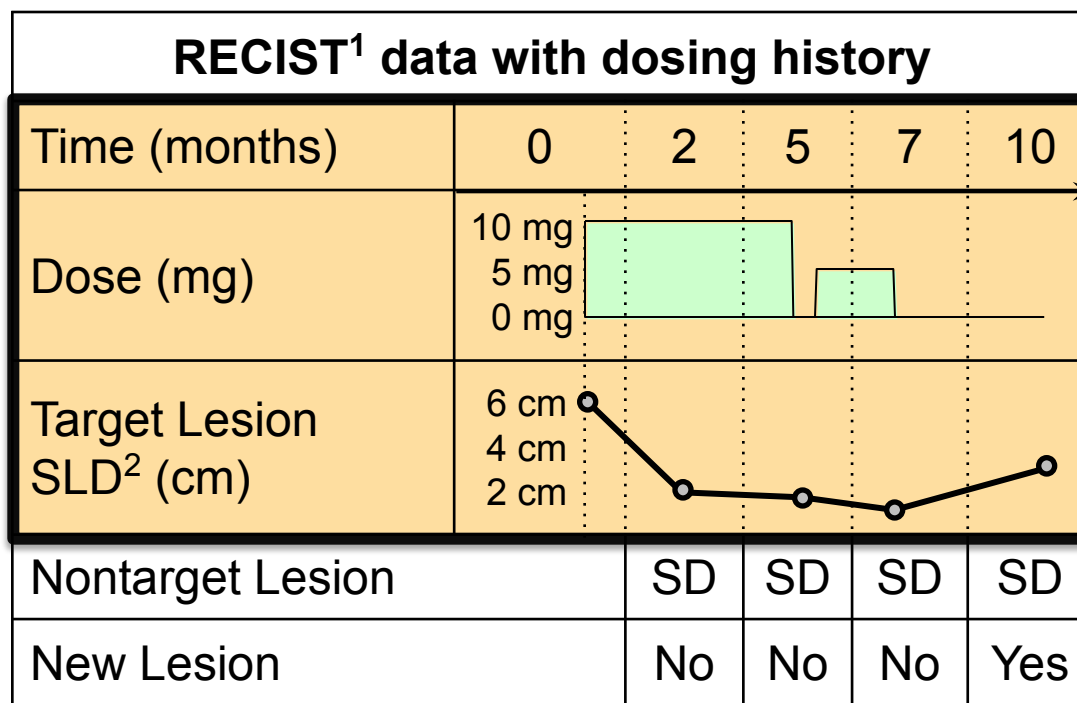
PR = Partial Response

PD = Progressive Disease

Background: Patient response is summarized by single value measurements; some information is lost

- Standard efficacy endpoints (e.g. overall survival, time to progression, best overall response) do not incorporate all available data.
- Effect of dose escalations, reductions, and interruptions on efficacy is ignored.
- Continuous lesion response is reduced to binary variables (Progression: yes/no, Response: yes/no).

2. Assessing Dose-Response using longitudinal tumor data



1. RECIST = Response Evaluation Criteria In Solid Tumors

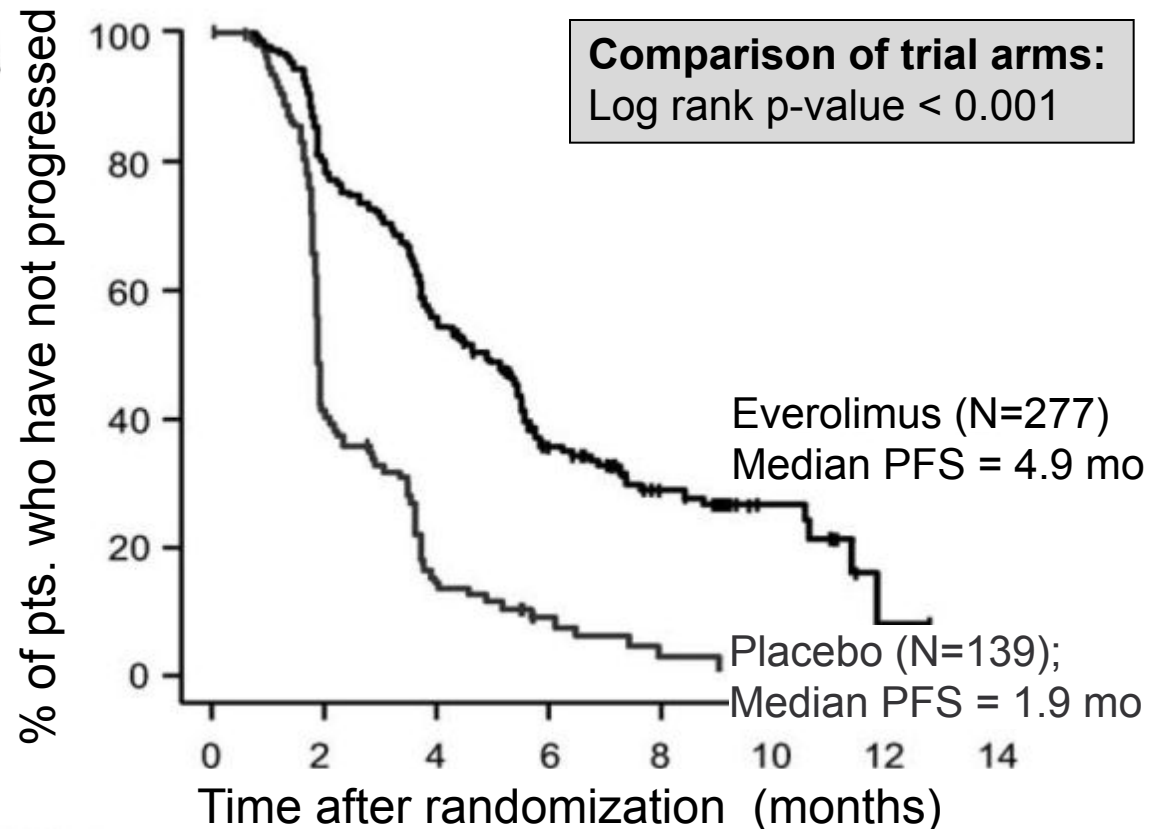
2. SLD = Sum of Longest Diameters of target lesions

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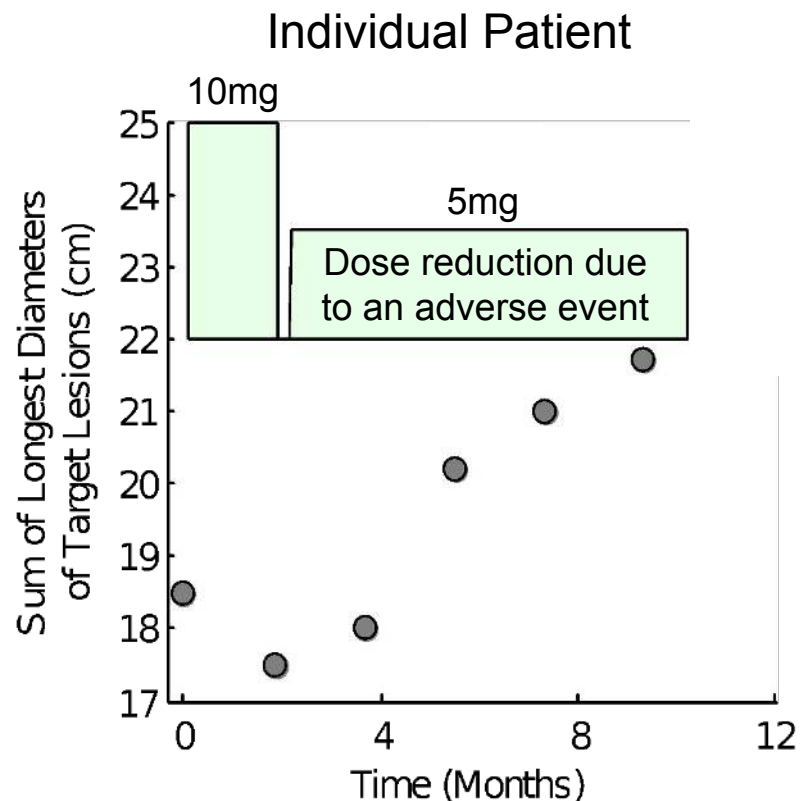
Example: clinical trial comparing 10mg everolimus to placebo in renal cell cancer

- RAD001C2240:
Phase III pivotal trial comparing everolimus 10mg to placebo in 2nd/3rd line renal cell cancer patients.
- Progression free survival was the primary end point.
- Results demonstrated superiority of everolimus 10mg over placebo.



Background: The RAD001C2240 trial with no 5mg arm contains information about the 5mg response.

- Many patients (N=98) were dose-reduced from 10mg to 5mg due to adverse events
- **Is 10mg superior to 5mg? Should patients who are dose-reduced to 5mg be re-challenged with 10mg?**
- Standard statistical tools cannot answer these questions because there was no prospective 5mg arm in the trial.
- Model-based tools can address these questions by relating the daily dosing history to tumor response over time.



Observed solid tumor data from an individual patient: In this patient, target lesions appear to shrink under 10mg, but grow under 5mg.

Methods: model based approach for describing individual patient data.

- Modeling approaches describe the daily change in tumor size for each individual patient¹⁻⁴.

$$\begin{array}{ccccc} \boxed{\begin{array}{l} \text{Tumor Size} \quad (y \text{ [cm]}) \\ \text{Change over Time (t [days])} \end{array}} & = & \boxed{\begin{array}{l} \text{Placebo} \\ \text{Growth Rate} \\ \text{[cm/day]} \end{array}} & - & \boxed{\begin{array}{l} \text{Drug} \\ \text{Effect} \\ \text{[cm/day]} \end{array}} \\ dy/dt & = & r & - & [\text{Eff}_{\text{dose}(t)}]^*y \end{array}$$

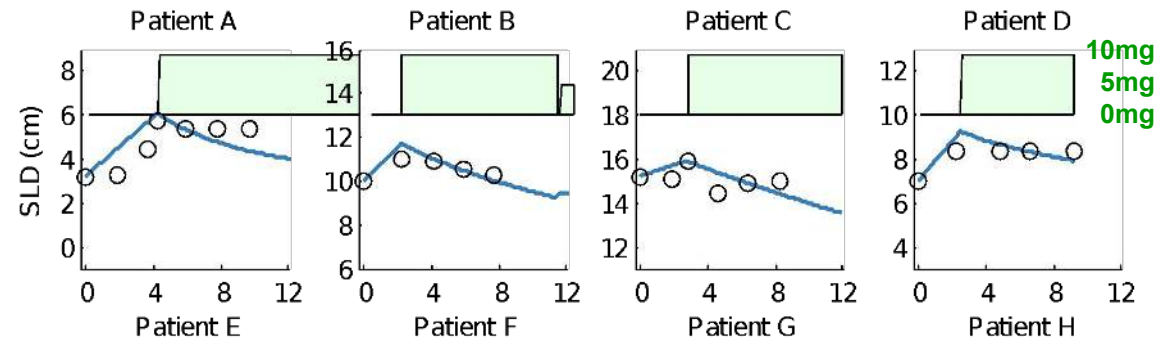
- Using each individual's dosing history and longitudinal tumor size data, we fit all patients from the trial using a nonlinear mixed effect (NLME) model.

1. A. Stein et al., BMC Cancer, 12, 311 (2012)
2. L. Claret et al., J. Clin. Onc. 27, 4103 (2009)
3. L. S. Tham et al., Clin. Canc. Res. 14, 4213 (2008)
4. S. Mu et al. ACoP Meetings Abstract (2009)

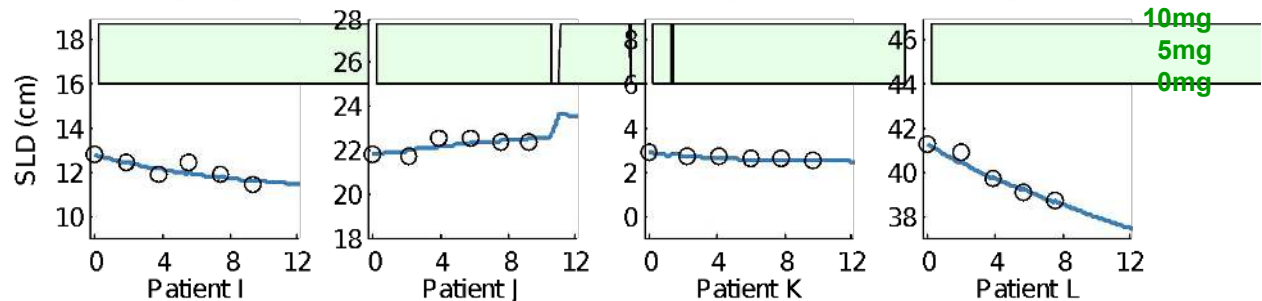
Results: The model well describes representative patient data. 10mg was more effective than 5mg.

KEY ○ Sum of Longest Diameters (SLD)  Dose  Model fit

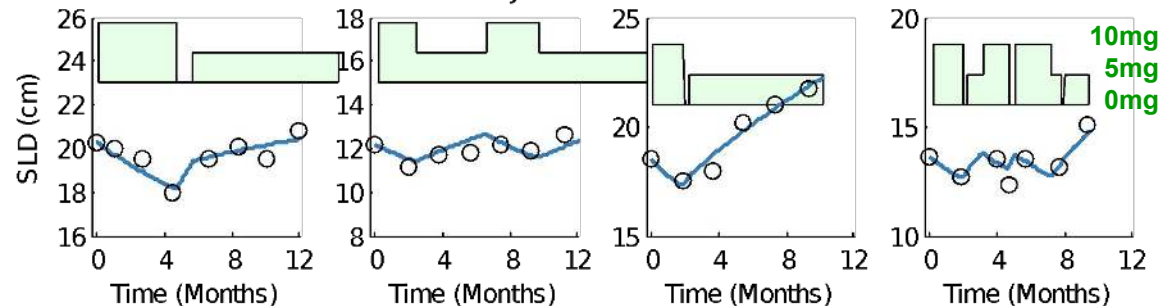
Placebo patients that cross over to Everolimus



Patients on 10mg

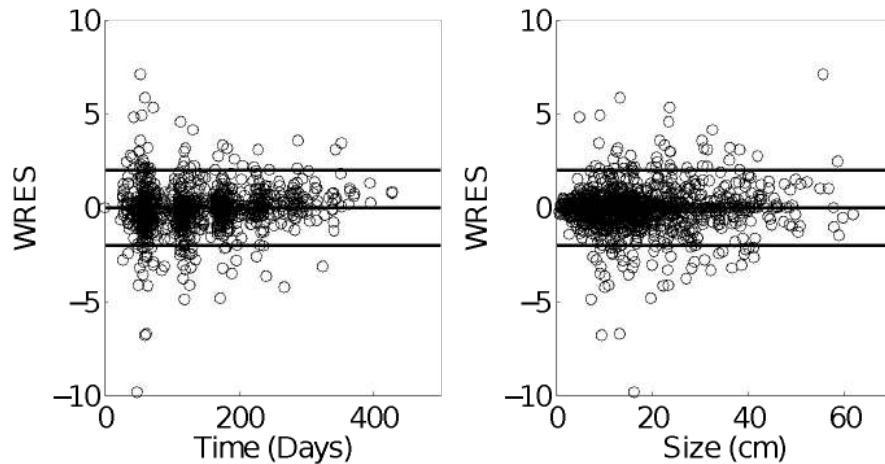


Patients reduced from 10mg to 5mg

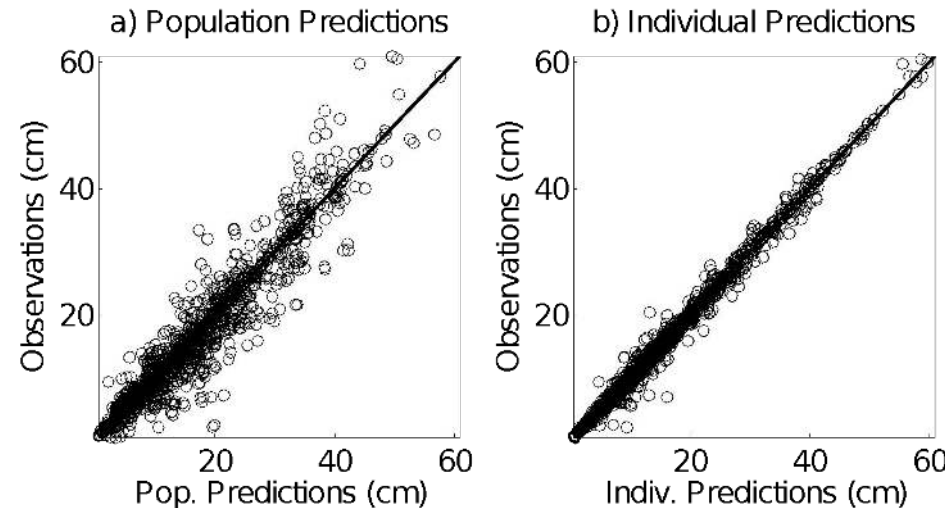


Validation: Standard PKPD diagnostics can be used for model validation.

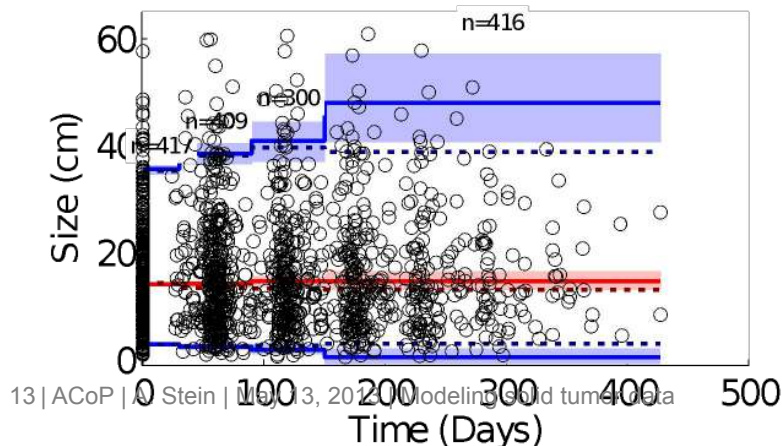
Weighted Residuals (WRES)



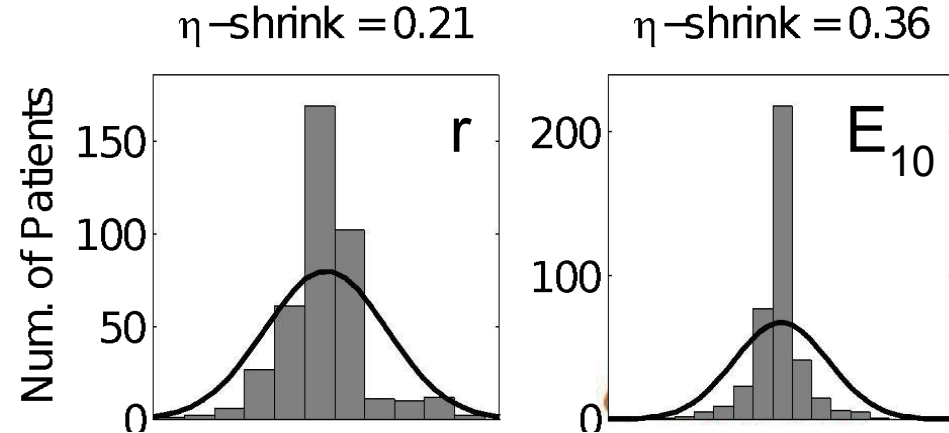
Goodness of Fit



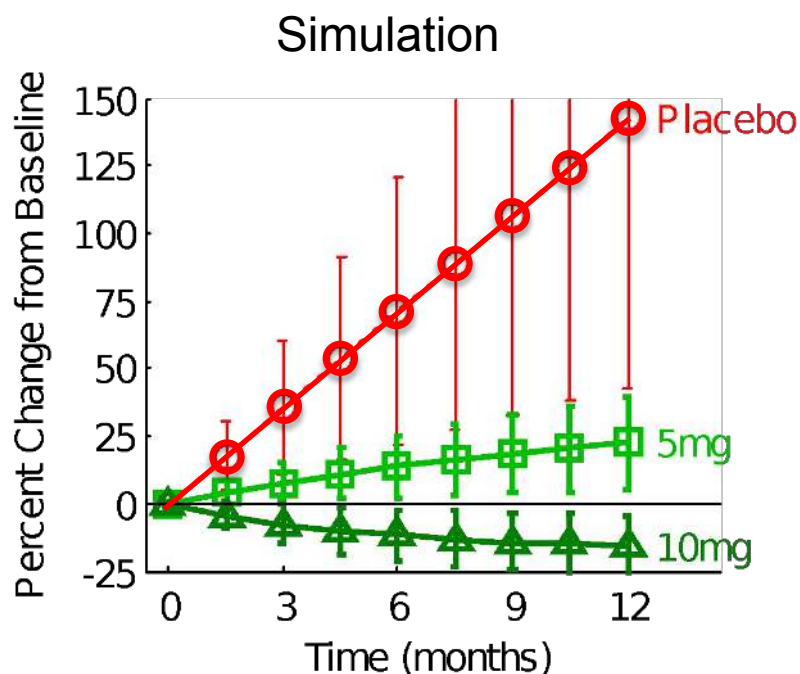
Visual Predictive Check (VPC)



Eta-Shrinkage



Conclusions: Modeling approaches can describe response to 5mg, even without a 5mg arm



- Analysis supports 10 mg as starting dose.
- Analysis demonstrates that 5 mg is superior to placebo when dose reductions are necessary.
- Analysis suggests that patients who are dose-reduced to 5 mg may benefit from a re-challenge at 10 mg.
- Results were published in BMC Cancer¹.

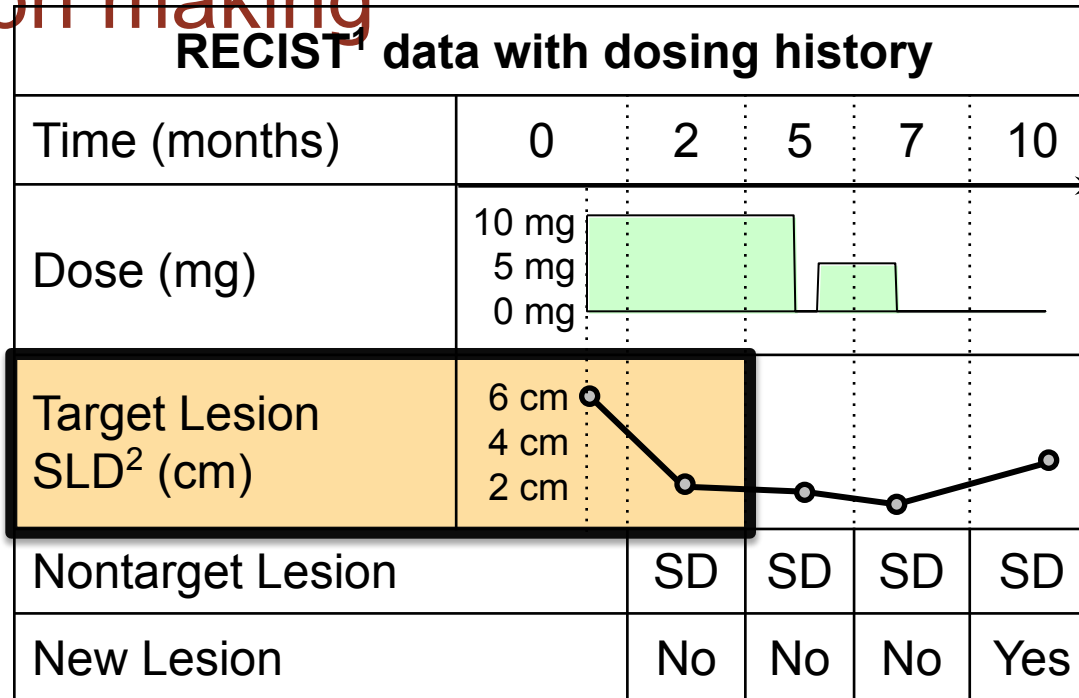
Error bars denote intersubject-variability in tumor size (±35%)

1. Stein et al., *BMC Cancer*, 12:311, 2012

Summary: Application of dose-PD and PKPD models for dose selection

- Models have been developed and applied to optimize dose selection both before and after Phase III
- Models can be readily validated in each application using standard PKPD diagnostic methods.
- Next steps in dose-PD modeling of tumor growth
 - Describing the nontarget and new lesions
 - Describing the heterogeneous response of individual lesions
 - Exploring other metrics of tumor size (e.g. volume)
 - Incorporating additional biomarkers into models (e.g. circulating tumor cells)

3. Predicting overall survival for guiding trial design and go/no-go decision making



1. RECIST = Response Evaluation Criteria In Solid Tumors

2. SLD = Sum of Longest Diameters of target lesions

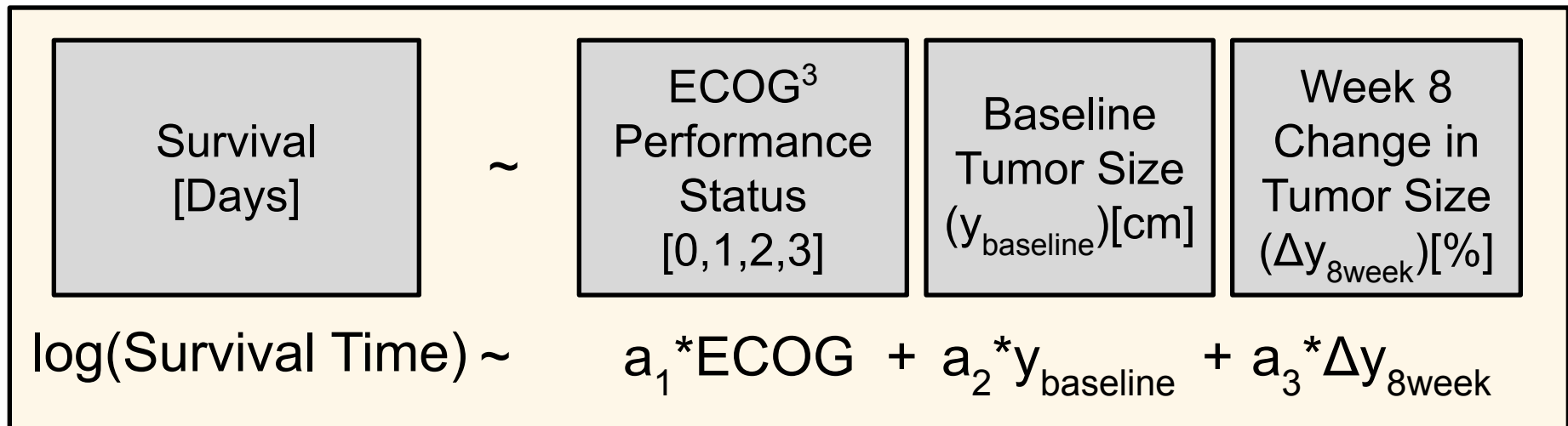
PD = Progressive Disease

SD = Stable Disease

PR = Partial Response

Methods: The FDA developed a model based approach¹ for predicting overall survival in NSCLC²

- Modeling approach can be used to predict overall survival in Phase III based on tumor size measurements in Phase II.

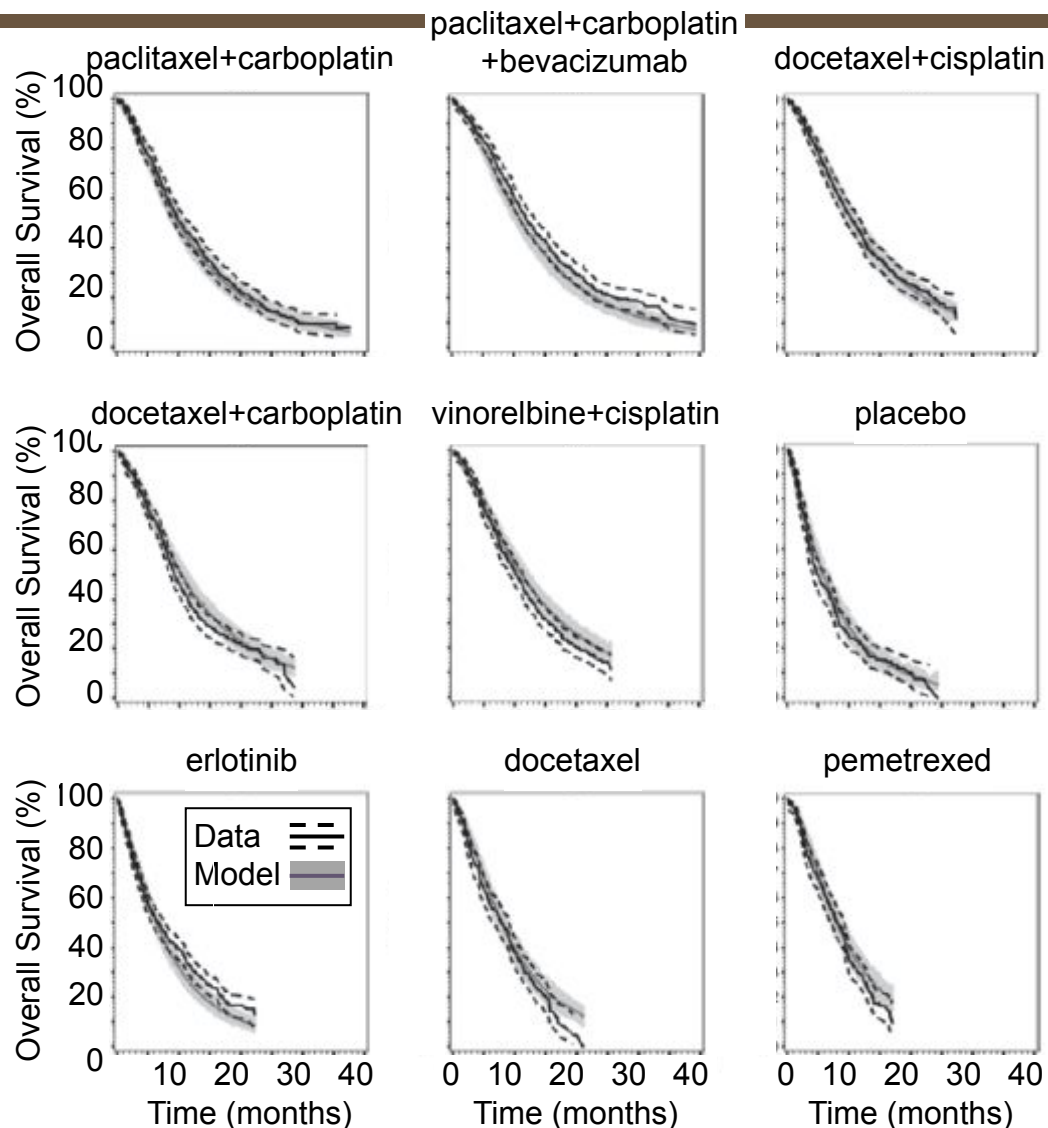


- Change in tumor size can be based on actual data or model interpolation
- $\{a_1, a_2, a_3\}$ are coefficients linking each assessment to survival.
- FDA used a parametric log-normal survival model to fit >3000 NSCLC pts.

1. Wang et al. *Clin. Pharm. Ther.*, 86, 167-174 (2009) 3. ECOG = European Cooperative Oncology Group

2. NSCLC = Non-Small Cell Lung Cancer

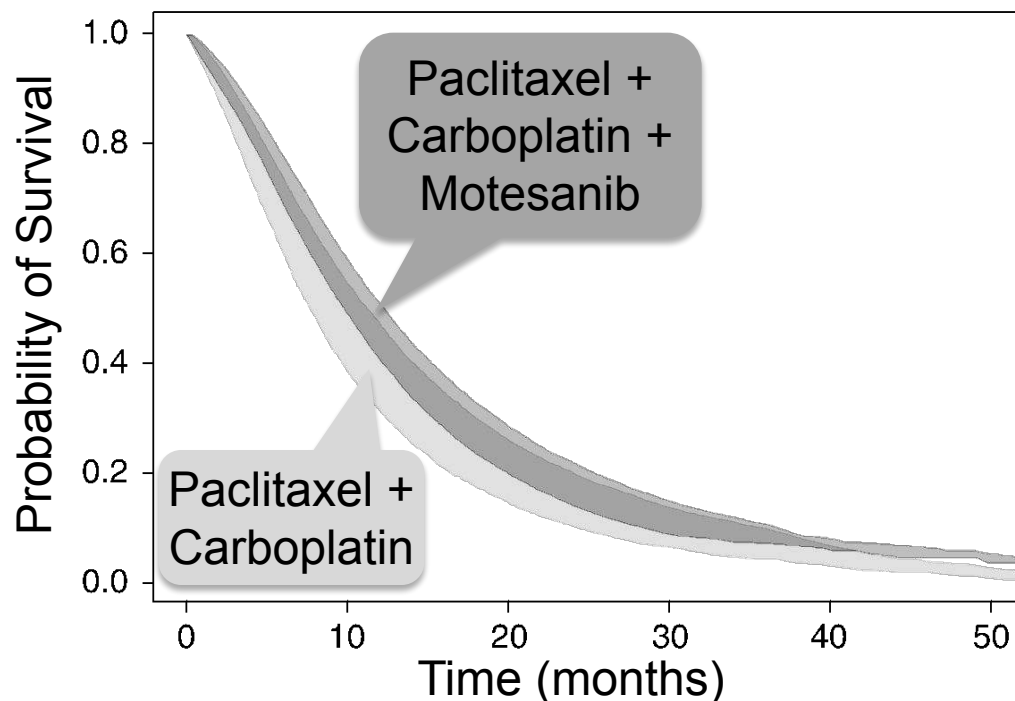
Results: FDA fit models to nine different trial arms. Models described the data well.



- The same model with was used to describe >3000 patients from four different trials.
- Regression coefficients $\{a_1, a_2, a_3\}$ differed only between 1st and 2nd line therapy.
- The same model was then used to *prospectively* predict the results of the MONET1 study comparing P/C¹ to P/C¹ + motesanib (VEGF inhibitor)

1. Paclitaxel + Carboplatin

Result: FDA model used to prospectively predict Phase III outcome. *Prediction was correct.*



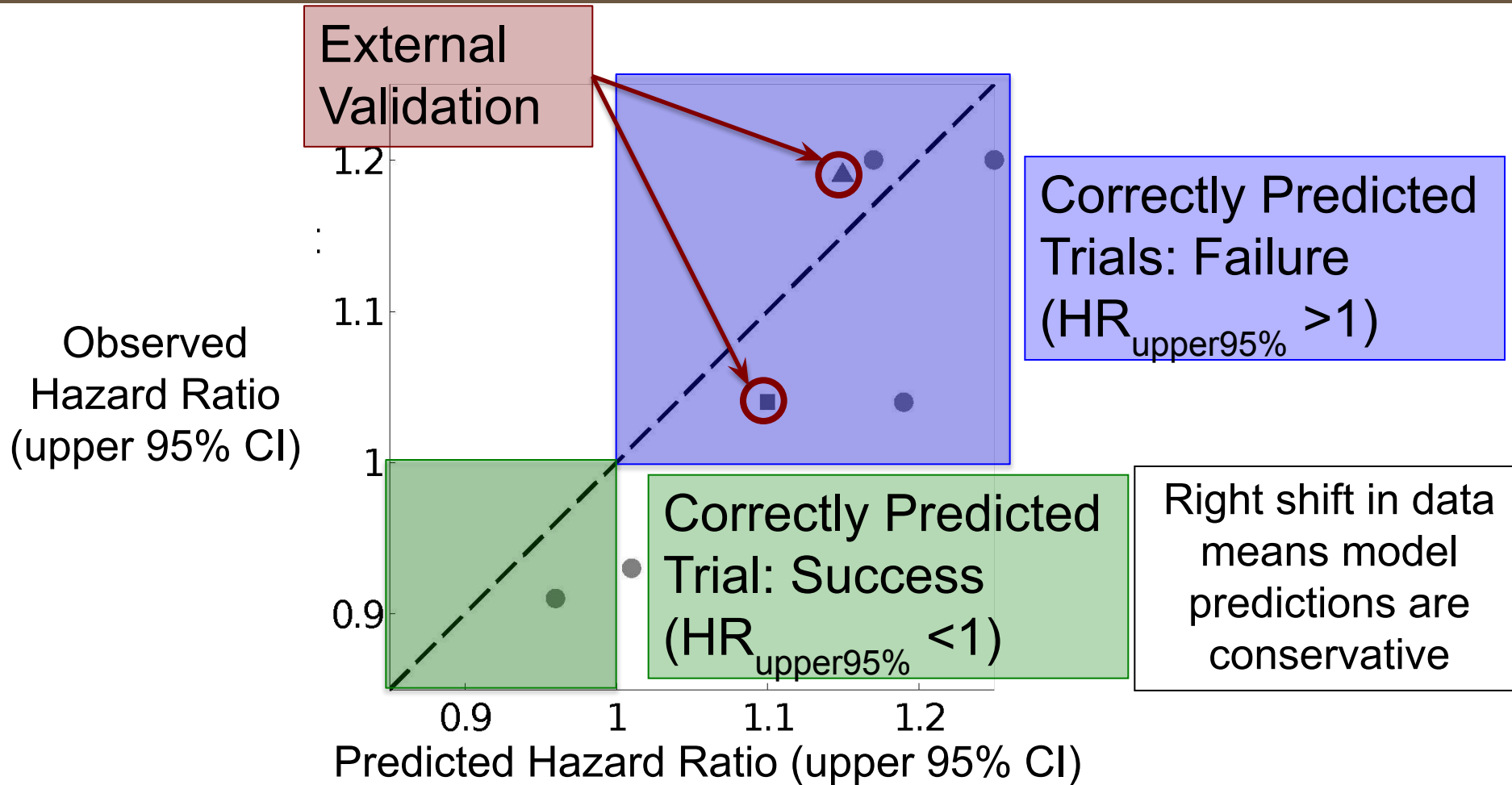
	Hazard Ratio	Confidence Interval
Model Prediction¹ (2010)	0.87	0.71-1.1
Clinical Result² (2012)	0.90	0.78-1.0

1. R Bruno et al. J Clin Oncol 28, 2010 (abs)

2. L Claret et al. Clin Pharmacol Ther 92, 631-634, (2012)

Model Validation in Non Small Cell Lung Cancer

More data is needed (especially in successful trials)



■ L Claret et al., Clin. Pharm. Ther. 92, 631 (2012)

● Y Wong et al., Clin. Pharm. Ther. 86, 167 (2009)

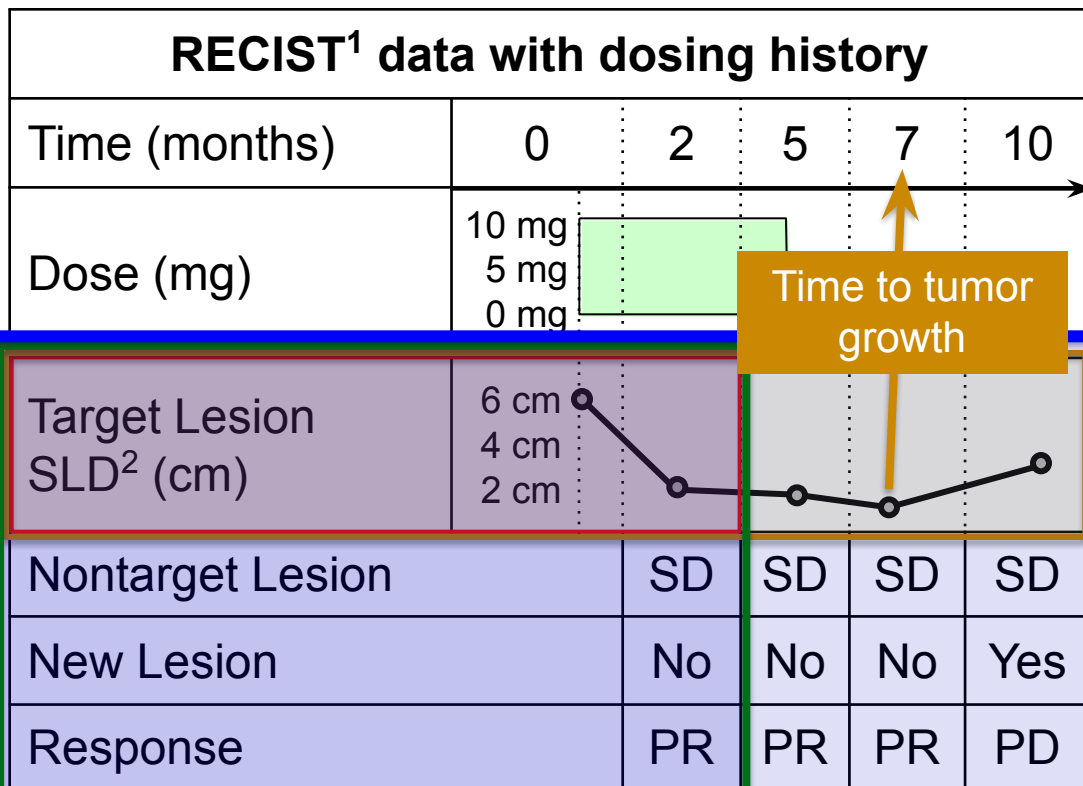
▲ W Sallas et al. ACoP (2011)

Validation: Survival prediction literature is growing, but more examples of model validation are needed.

Cancer	Num. Trials	Num. model tests using external data	References
Non-small cell lung cancer	11	2	Y Wang et al., Clin. Pharm. Ther. 86, 167 (2009) W Sallas et al., ACoP Poster (2011) L Claret et al., Clin. Pharm. Ther. 92, 631 (2012)
Colorectal cancer	5	1	L Claret et al., J. Clin. Onc. 27, 4103 (2009) L Claret et al., J. Clin. Onc. In press (2013)
Breast cancer	3	1	L Claret et al., J. Clin. Onc., 24, 6025 (2006) R Bruno et al., Clin. Pharm. Ther.: Pharmacometry System Pharm. 1, e19 (2012)
Multiple Myeloma	3	1	R Bruno et al., Blood 118, 1881 (Abstract) (2011)
Ovarian cancer	2	0	L Lindborn et al., ACoP Poster (2009)
Gastrointestinal stromal tumors	1	0	EK Hansson et al., PAGE Abstract A-28 (2011)
Thyroid cancer	1	0	L Claret et al., Canc. Chemother. Pharm. 66, 1141 (2010) J Lu et al., Canc. Chemother. Pharm. 66, 1151 (2010)

Lit Review: Other metrics are also available for predicting survival. Best metric is not yet known.

RECIST¹ data with dosing history



Change in tumor size at first assessment

Tumor dynamic metrics that account for longitudinal time course of the target lesions¹⁻³

Full tumor response at first assessment metrics account for all lesion types⁴⁻⁶

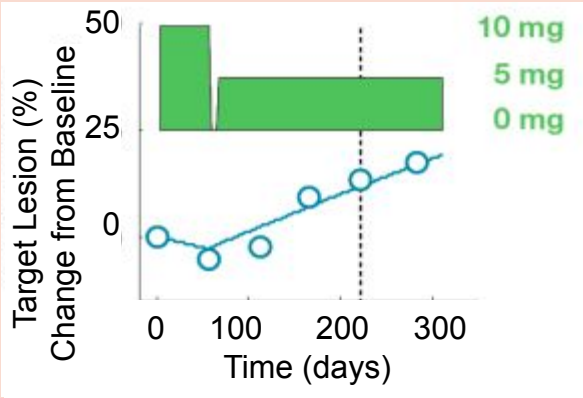
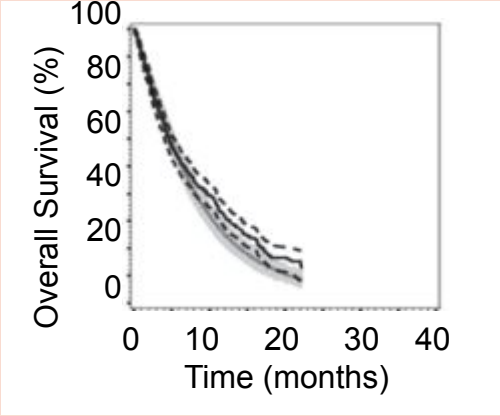
Multivariate longitudinal data metrics can take into account all available data⁷

1. L Claret et al., JCO in press (2013)
2. M Maitland et al., CPT 93, 345 (2013)
3. E Stein et al., Oncologist, 13, 1046 (2008)
4. W Mietlowski et al., JCO, 30, 10602 (2012)
5. A Stein et al., Eur. Uro, in press (2013)
6. Suzuki et al., Ann. Onc., 23, 948 (2012)
7. A Stein et al., JCO, 4602 (2011)

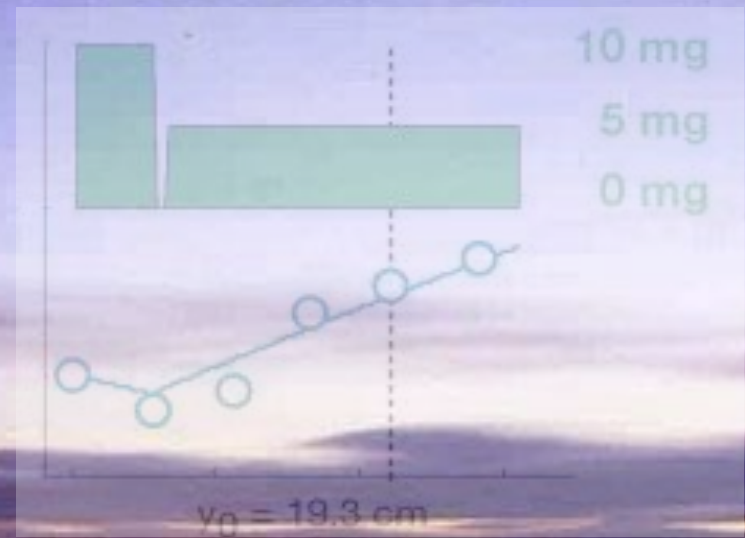
Conclusions: Outcome of Phase III trial was prospectively predicted using model-based approach

- Models linking tumor size to overall survival have been developed and are publicly available
 - The model has been used to prospectively predict the difference in survival (hazard ratio) between two arms in a Phase III clinical study based on Phase II data.
- Prediction of the hazard ratio based on early tumor growth inhibition data (Phase Ib, II) can be used to support:
 - Go/no go decision making
 - Phase III clinical trial design
- More examples of model validation are needed.
- Further work is needed to identify the most predictive factors of overall survival.

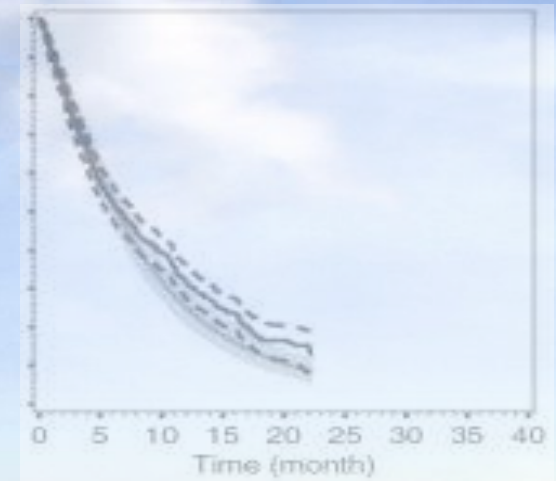
Comparison of the two modeling methods for guiding decision making.

	Dose selection	Phase III go/no-go
Modeling approach	Dose/Exposure Response 	Survival Prediction 
Goal	Understand response to new drug	Predicting response of new drug
Validation	Standard diagnostics	Pool many studies
Number of Trials Needed	One	Many

Validation of PKPD models for guiding dose selection can be done using a single trial.



Validation of survival models
for go/no-go decision making
requires a global effort.



Collaboration across academia, industry, and health authorities is needed to validate predictive models.

■ ISoP Subteam Formation

- An ISoP subteam could help in moving the discussion forward and planning the next steps.

■ Knowledge Integration

- Develop website (e.g. ISoP wiki) to provide a repository of literature, code, and recommendations for further validating models

■ Data Liberation

- As individualized data becomes more publicly available, validation may become easier.

Acknowledgements

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- Daniel Lusk (Intern)
- Bill Mietlowski
- Norbert Hollaender
- Dennis Kim
- Sandra Chica
- Dean Bottino
- Anna Georgieva
- Don Stanski

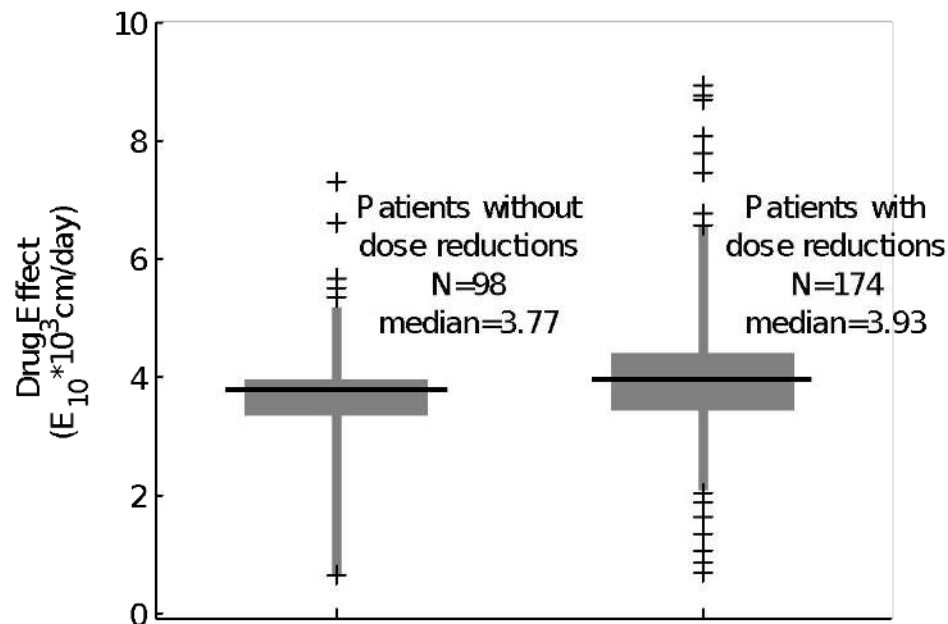
Pharsight

- Pascal Girard (now with Mark-Serono)
- Laurent Claret
- Francois Mercier

BACKUPS

Everolimus showed similar effect on target lesions among patients with and without dose reductions.

- Because there was not a randomized 5mg arm, the patients who are dose-reduced to 5mg represent a biased sample of patients who experience an adverse event.
- We compare the 10mg drug effect for patients with and without dose-reductions to see if tumor shrinkage is different across the different subgroups.
- The right hand plot demonstrates that the effect of 10mg on tumor size is similar for both subgroups of patients, irrespective of whether the patient had an adverse effect.



Drug Effect in patients without (left) and with (right) dose interruptions is similar for both groups.

Lit. Review: A diverse range of PD tumor growth models have been applied to clinical oncology data

Ref.	Permit Dose Change	Placebo Model	Model eqn: y = tumor size, g = growth rate, E = drug effect
1	No	Linear	$y(t) = gt - Ee^{-\lambda t}$
2	No	Linear	$y(t) = y_0 + gt - Ey$
	No	Linear	$y(t) = gt + y_0 * t^E$
3	No	Expon.	$y(t) = C_0 + G_0 e^{gt} - E_0 e^{-Et}$
4	Yes	Linear	$dy/dt = g - Ey$
5	Yes	Expon.	$dy/dt = gy - Eye^{-\lambda t}$
6	Yes	Logistic	$dy/dt = gy - Ey^2$
7	Yes	Gompertz	$dy/dt = gy - Ey \log y$

Because models are validated based on their ability to describe and simulate clinical data, evaluating which model is “best” is not critical.

1. Y. Wang et al., Clin. Pharm. Ther. 86, 167 (2009)
2. M. Maitland et al., Clin. Pharm. Ther. 93, 345 (2013)
3. E. Stein et al., Oncologist 13, 1046 (2008)
4. A. Stein et al., BMC Cancer, 12, 311 (2012)
5. L. Claret et al., J. Clin. Onc. 27, 4103 (2009)
6. L. S. Tham et al., Clin. Canc. Res. 14, 4213 (2008)
7. S. Mu et al. ACoP Meetings Abstract . 2009,