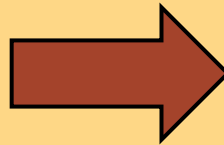
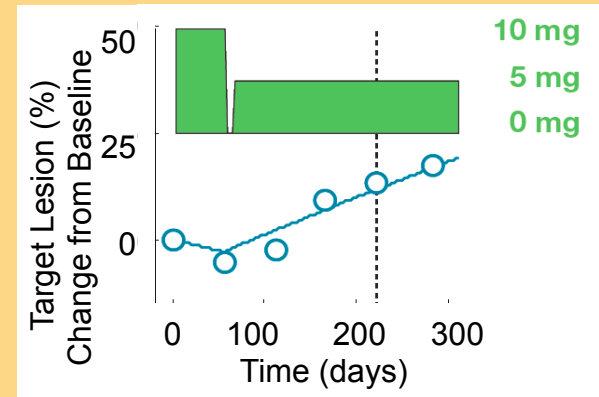


Response Criteria for Solid Tumors (RECIST)



Dose Response



**Dose selection in solid tumor trials:
Making use of all available tumor data.**

PhUSE Boston – June 20, 2013

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Overview

- Oncology Phase III trials have a >40% failure rate¹
- When choosing the dose for Phase III, drug development teams do not take full advantage of the moderately rich tumor data that is available.
- We are developing methodologies for dose selection that take into account all available data, which could potentially lead to reduced failure rates, more efficient trials, and better characterization of the benefit-risk ratio.

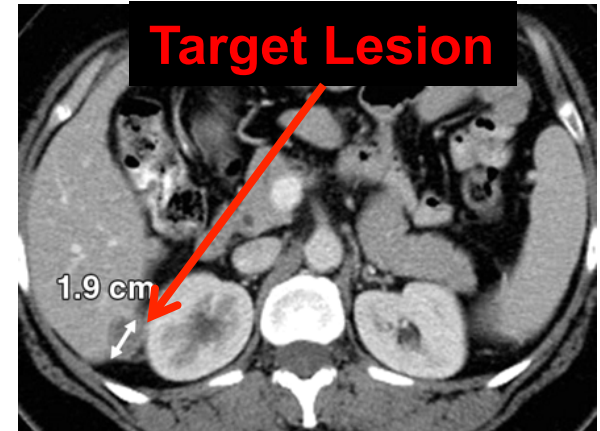
1. DiMasi JA and Grabowski, *J Clin. Oncol.*, 25, 209 (2007)

Background: Solid tumors are imaged using 3d Xray images, i.e. computed tomography (CT)

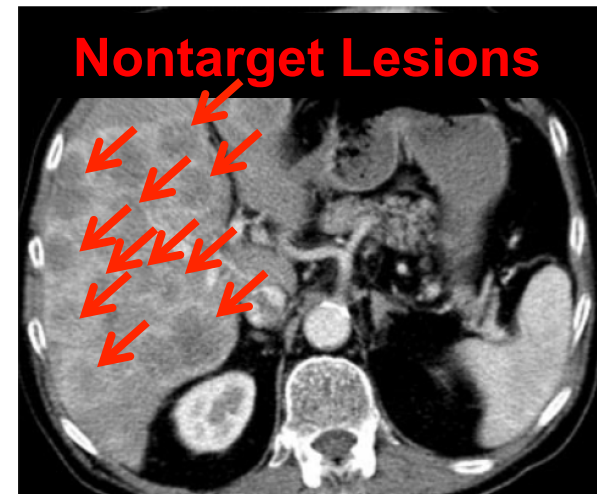


Background: RECIST¹ lesion types

- Target Lesions
 - 1-2 “representative” lesions per organ
 - Lesions must be measurable
 - Longest diameter recorded and summed (SLD²)
- 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



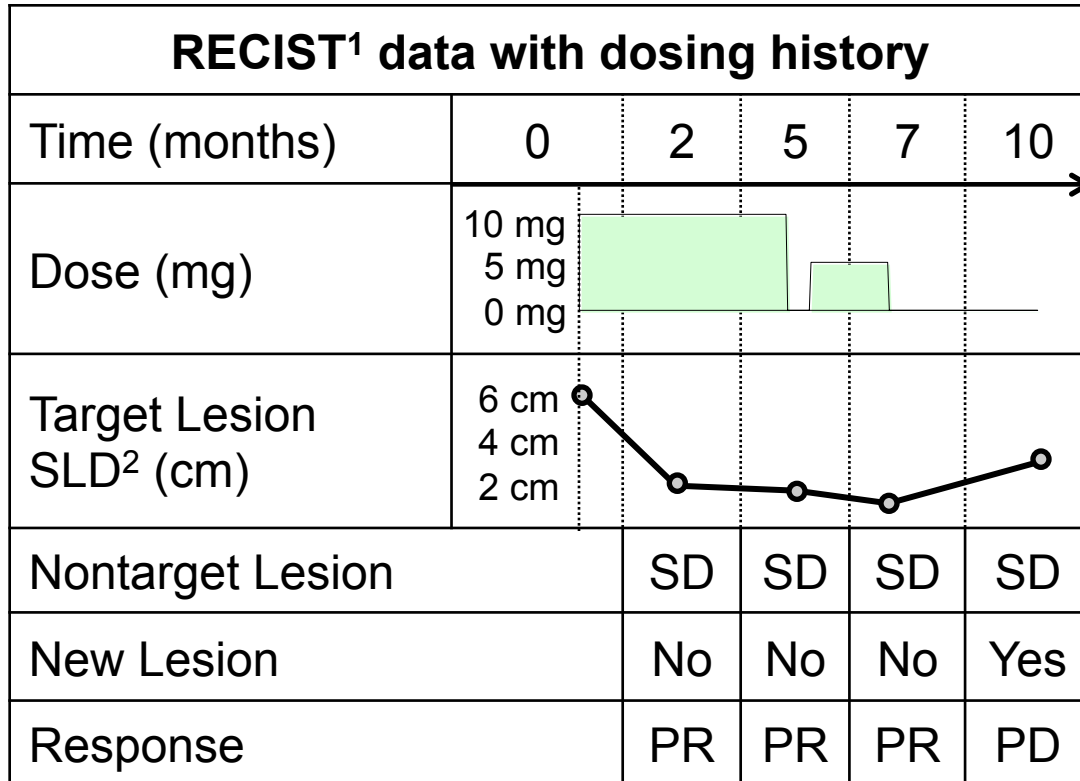
Ovarian cancer metastasis in liver



Rectal cancer metastases in liver.

-
1. RECIST = Response Evaluation Criteria In Solid Tumors
 2. Sum of the Longest Diameters

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: How can we use all available tumor data to better select the dose of new drugs?

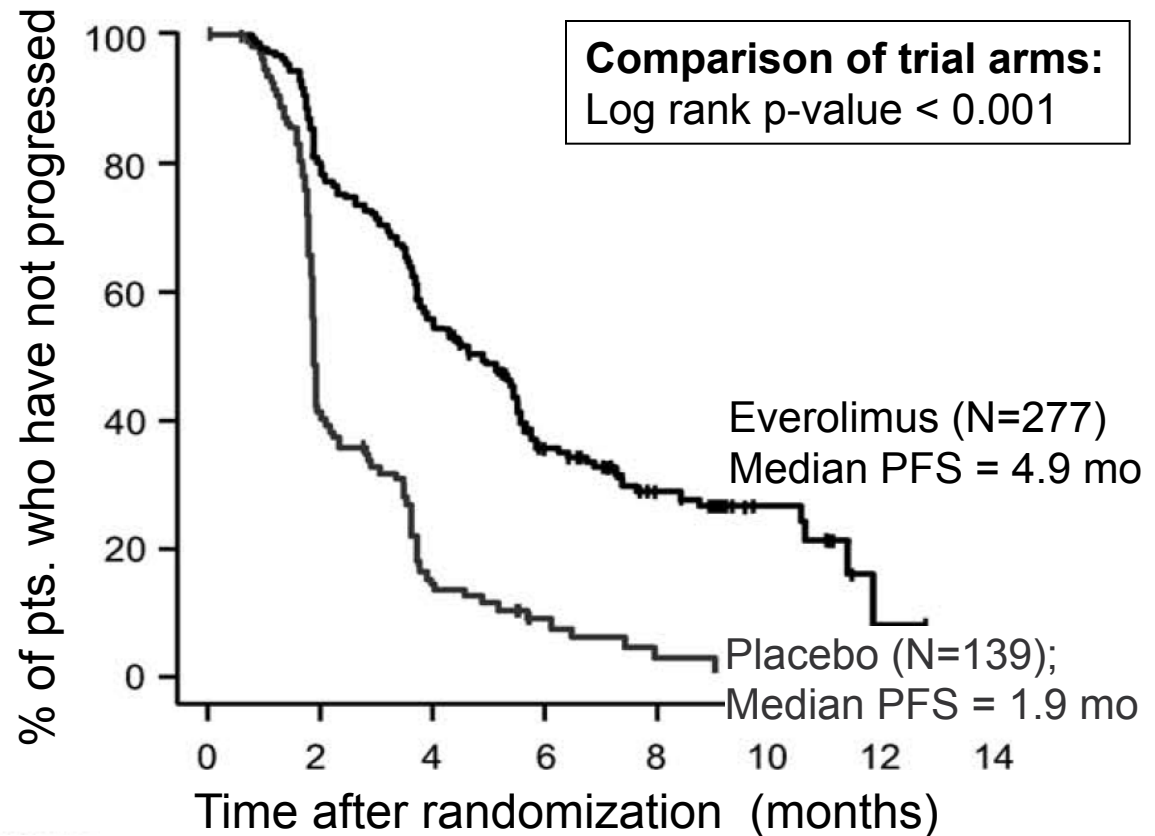
- Standard efficacy endpoints do not incorporate all available data.
 - Median Overall Survival (OS)
 - Median Time to Progression (TTP)
 - Best Overall Response
- Missing data includes
 - Phase I trials can have many dose interruptions and dose escalations, but individual dosing history is ignored.
 - Heterogeneous lesion response is ultimately summarized by only 1-2 binary variables (Progression: yes/no, Response yes/no).

We are developing new methods for modeling tumor data for identifying the most efficacious dose.

1. Using longitudinal tumor data, we characterize a difference between two doses, which was not possible using standard statistical approaches.
2. Taking into account multivariate lesion assessment is essential for predicting overall survival.
3. We have developed multivariate, longitudinal models to capture the full dose-efficacy dataset of all lesion types.

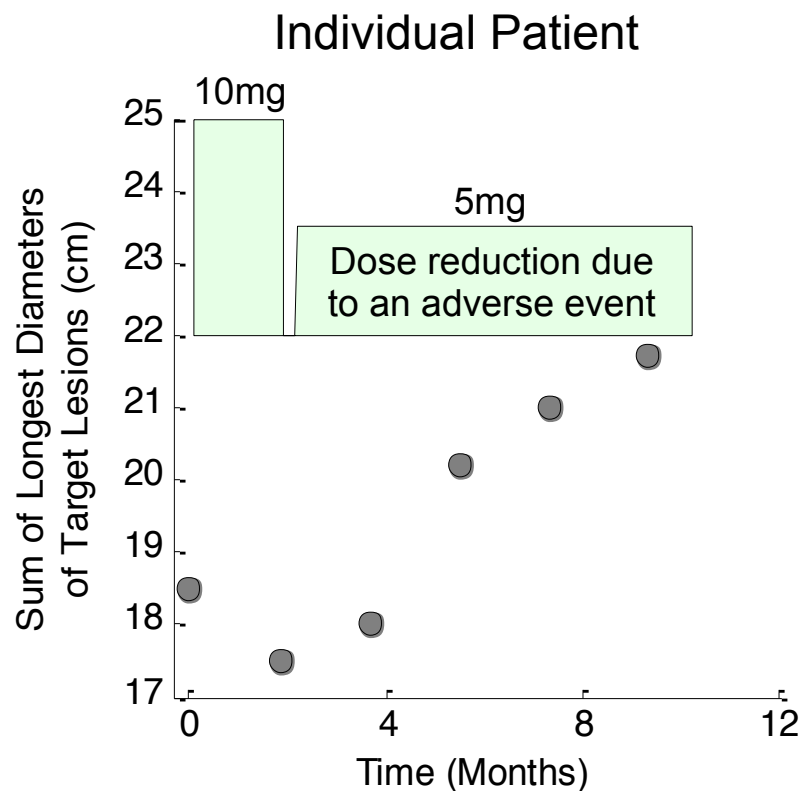
Background Example: clinical trial comparing everolimus to placebo in renal cell cancer

- 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.



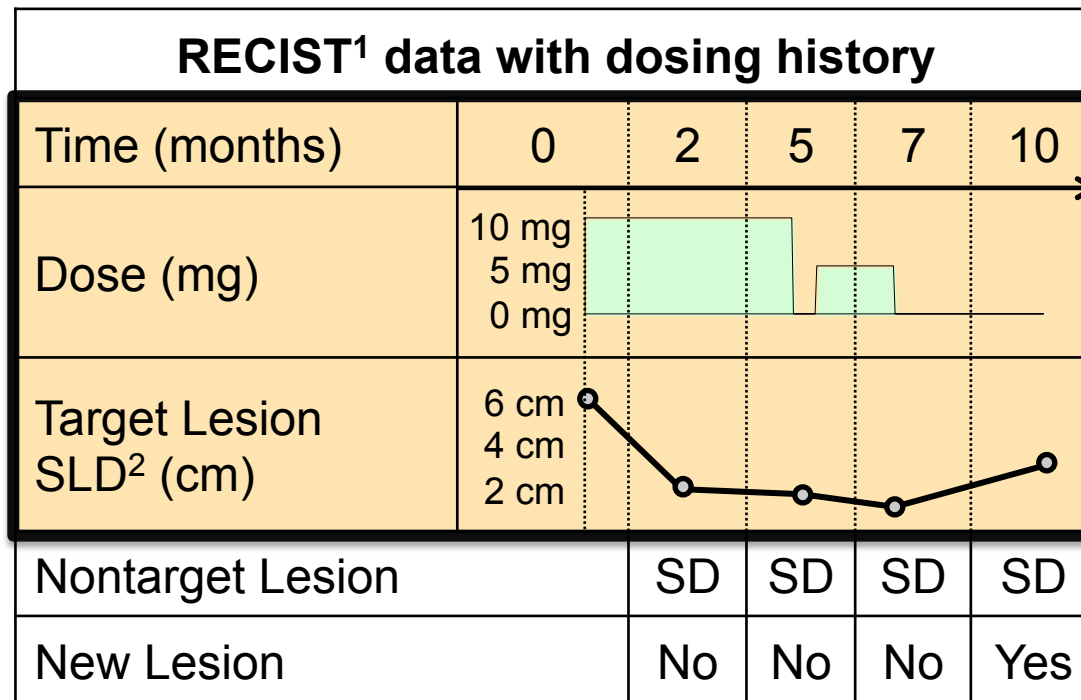
Background: The RAD001C2240 trial with no 5mg arm contains information about the 5mg response.

- 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.

#1 We first focus on using the longitudinal, continuous, target lesion data to compare doses.



1. RECIST = Response Evaluation Criteria In Solid Tumors

2. SLD = Sum of Longest Diameters of target lesions

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Methods: model based approach for describing individual patient data.

- Modeling approaches describe the daily change in tumor size for each individual patient.

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

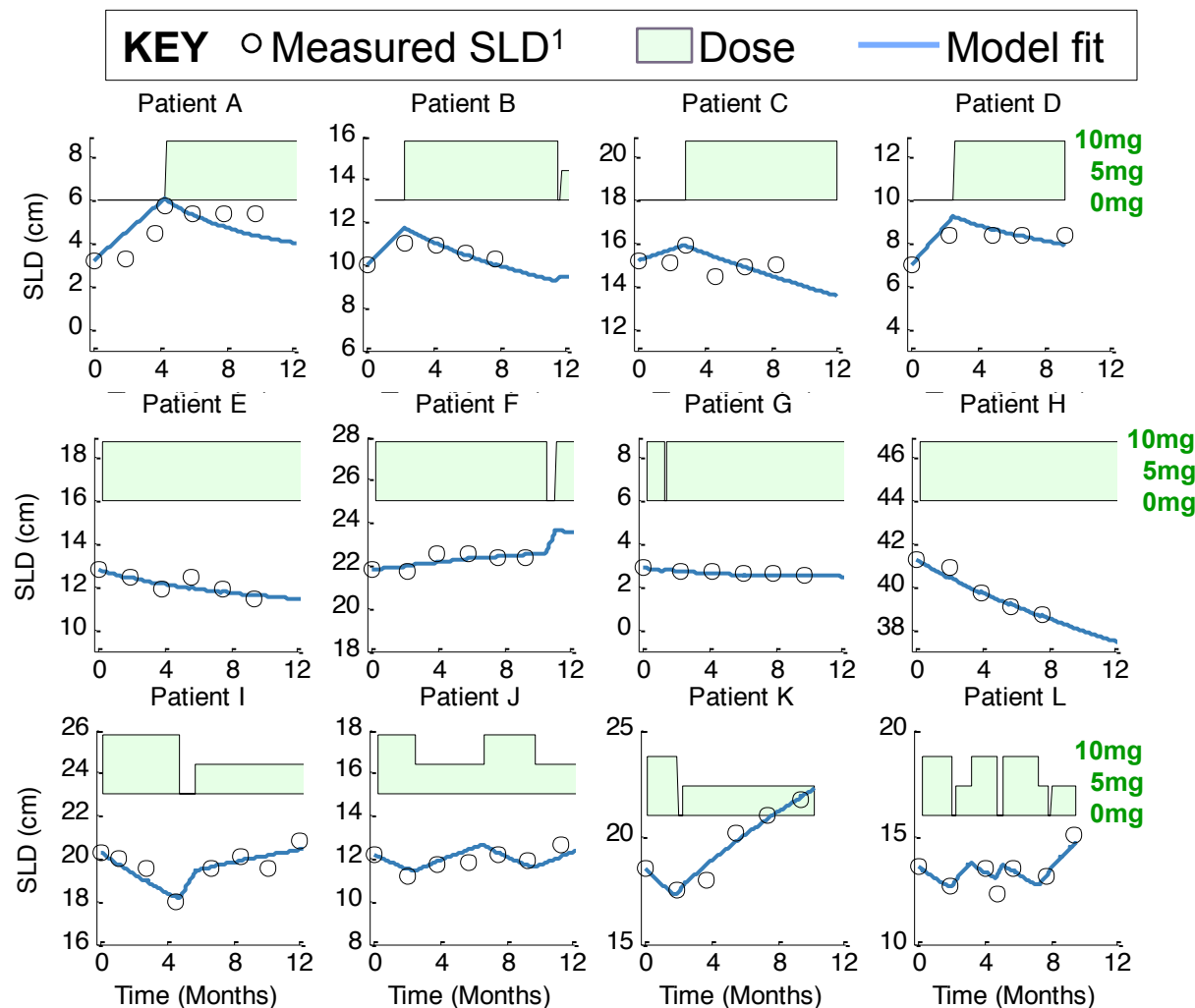
- Using each individual's dosing history and longitudinal tumor size data, we fit all patients from the trial using a nonlinear mixed effect model.

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

Placebo patients that cross over to Everolimus

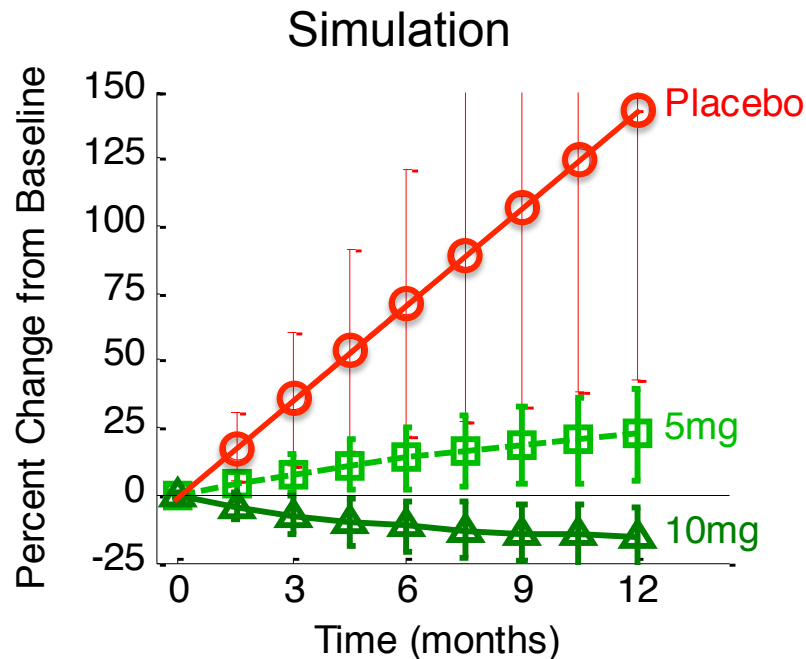
Patients on 10mg

Patients reduced from 10mg to 5mg



1. SLD = Sum of Longest Diameters of target lesions

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

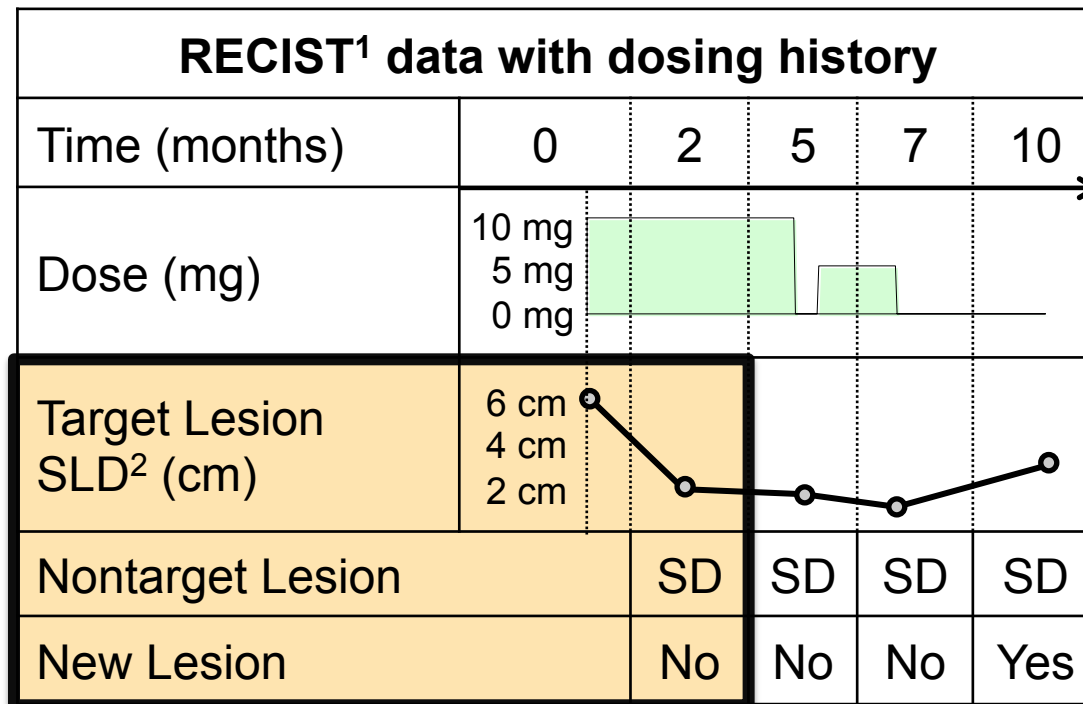


Error bars denote intersubject-variability ($\pm 35\%$)

- 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.

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

#2: We next focus on predicting survival using the first post-baseline multivariate assessment



1. RECIST = Response Evaluation Criteria In Solid Tumors

2. SLD = Sum of Longest Diameters of target lesions

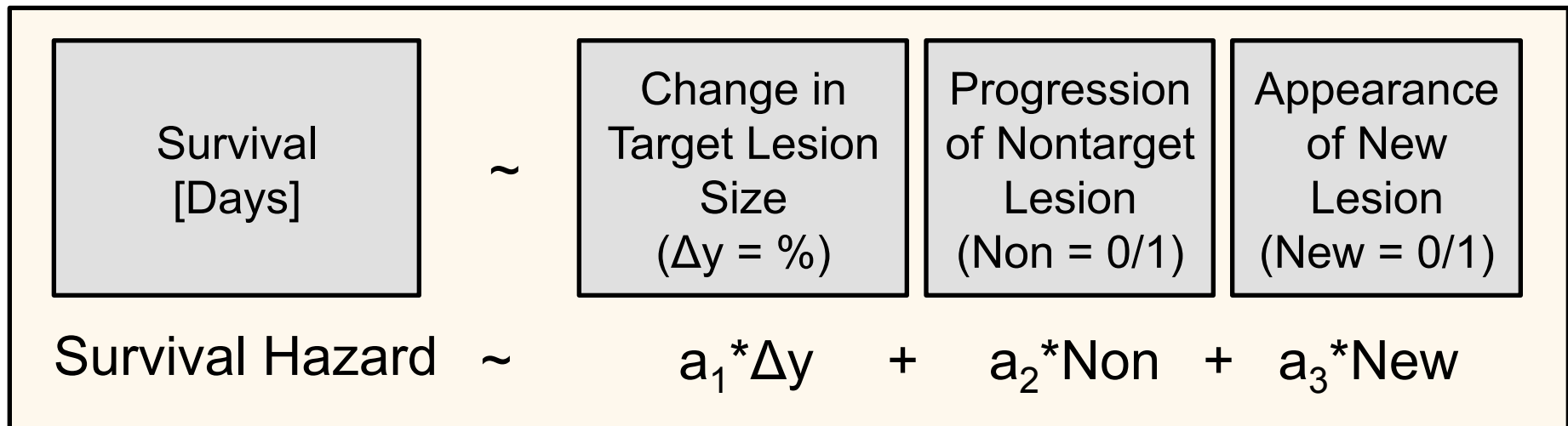
SD = Stable Disease

PR = Partial Response

PD = Progressive Disease

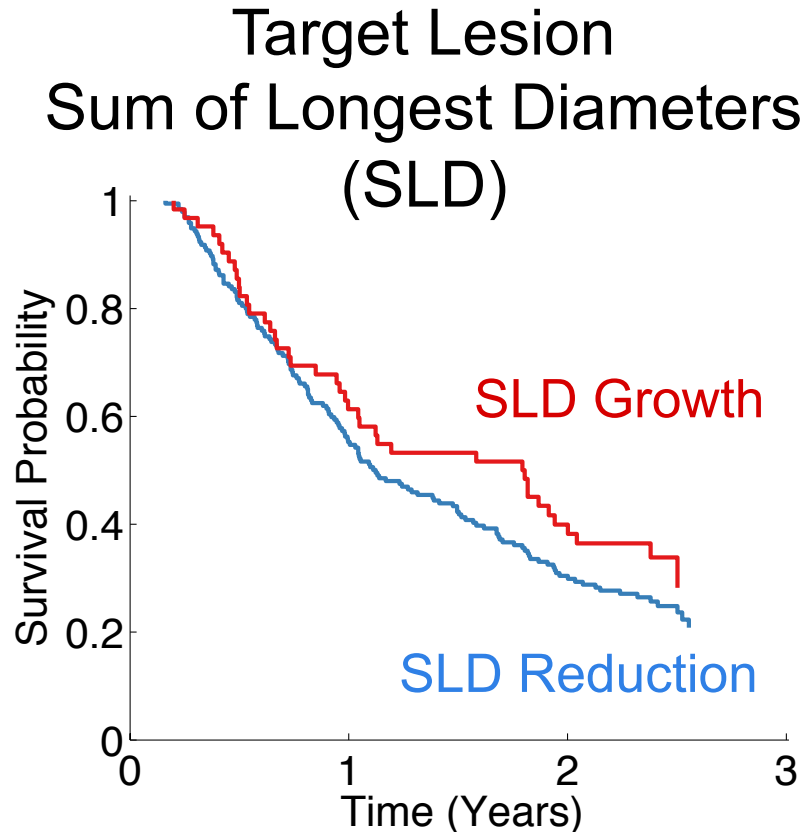
Methods: Cox regression is used to establish the effect of each tumor measure on survival

- Only patients on the everolimus arm are analyzed.
- Response at first assessment (month 2) is correlated with overall survival using Cox regression.



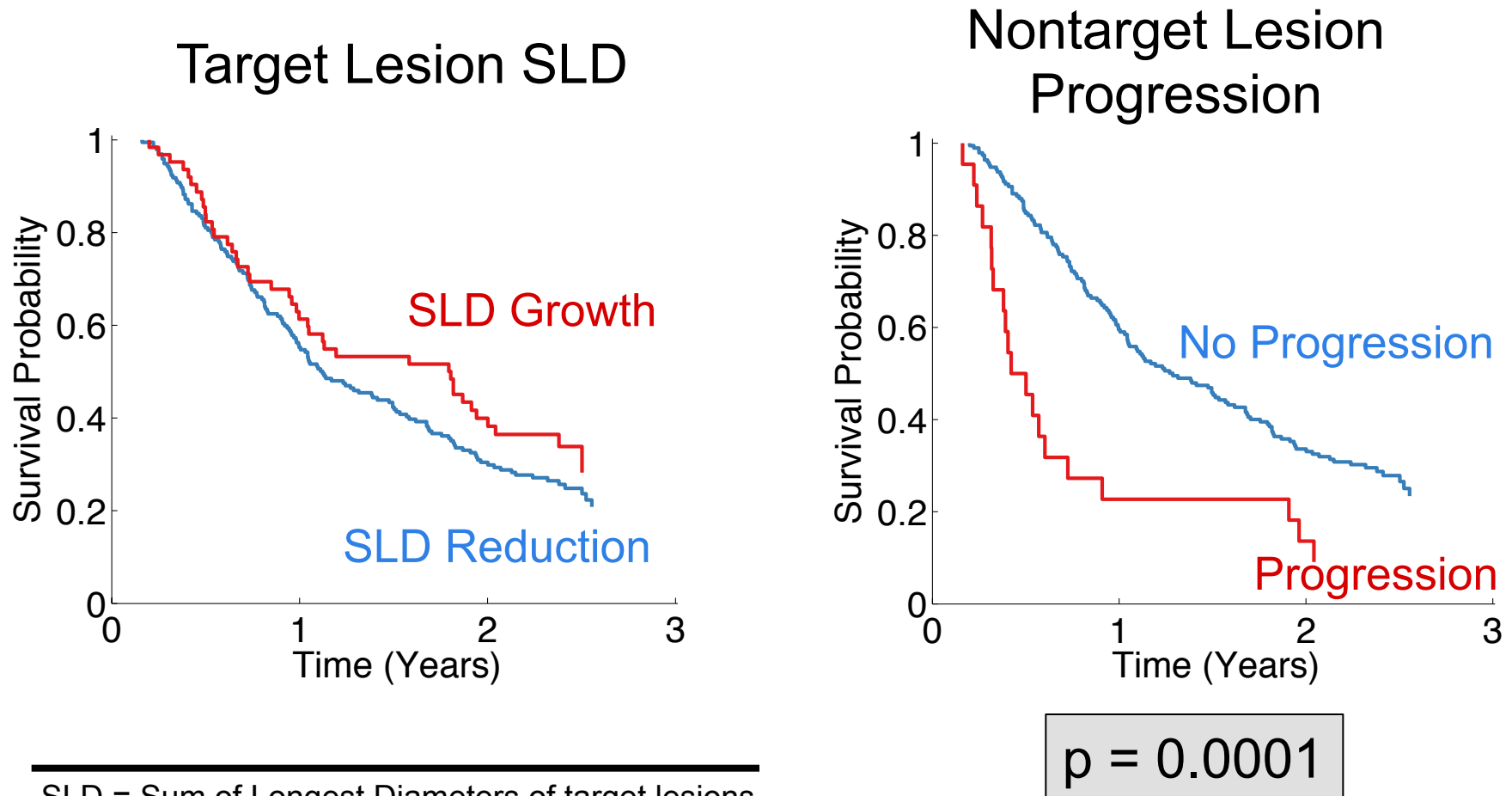
- $\{a_1, a_2, a_3\}$ are Cox coefficients linking each patient measurement to survival.

Results: Change in the sum of the longest diameters (SLD) was not predictive of survival.



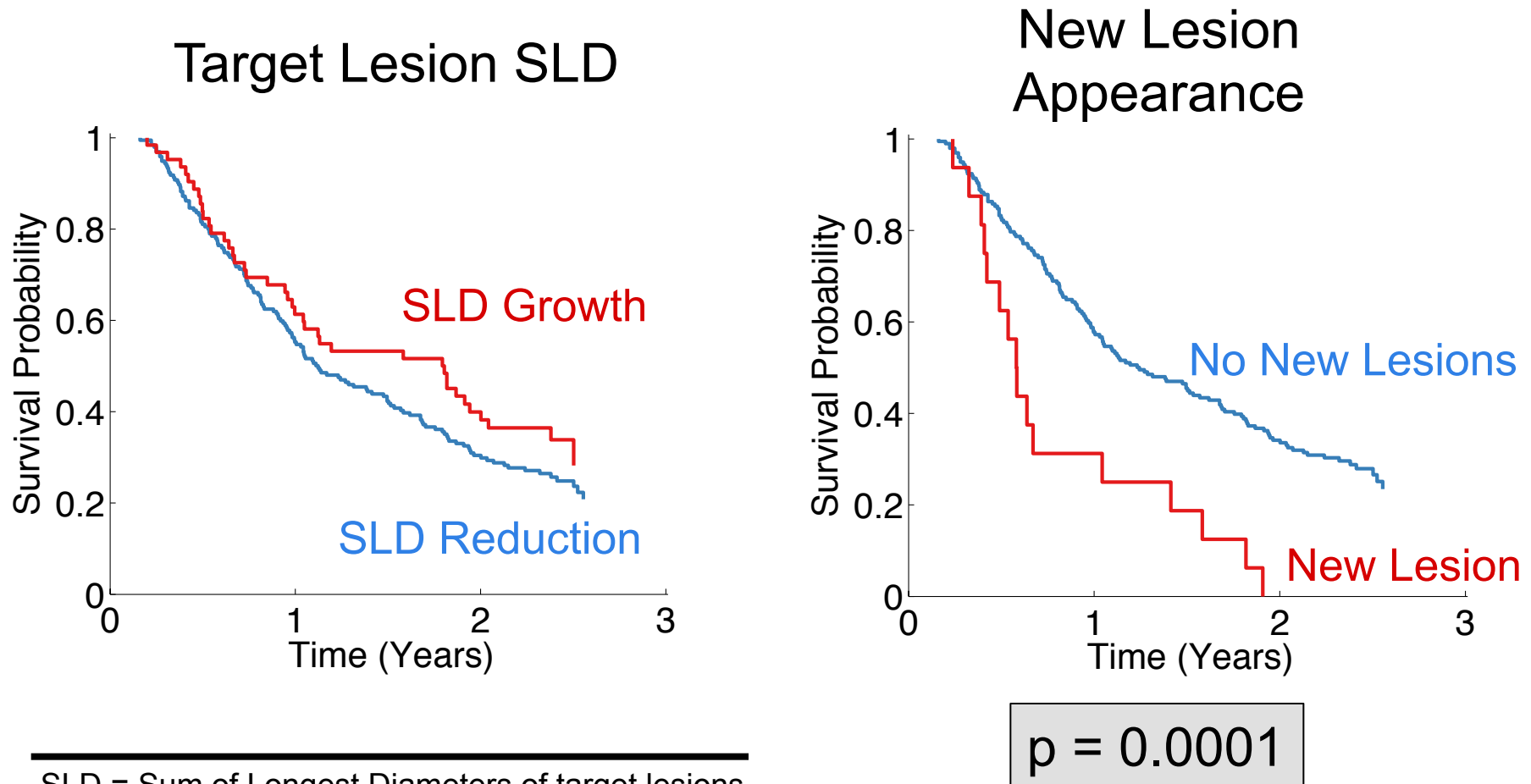
SLD = Sum of Longest Diameters of target lesions

Results: Nontarget lesion progression at month 2 was predictive of survival

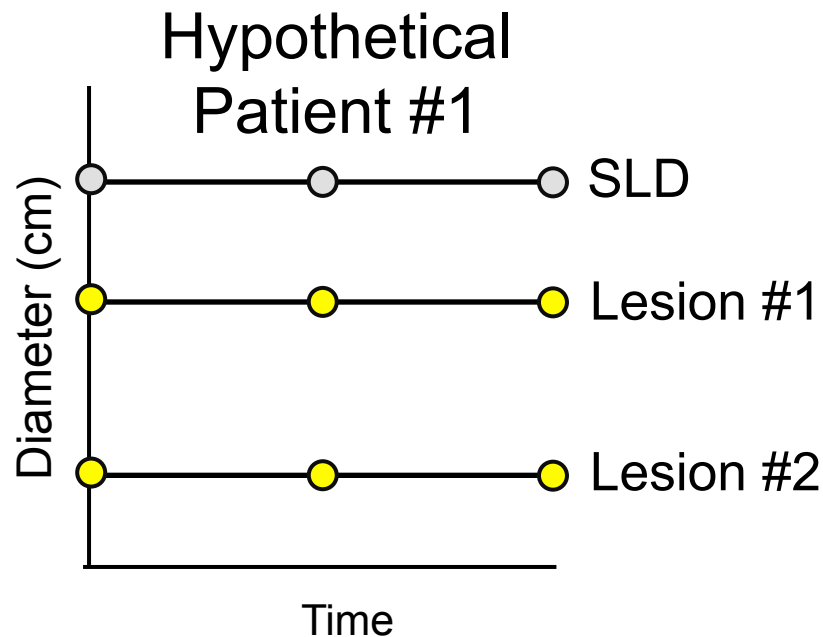


SLD = Sum of Longest Diameters of target lesions

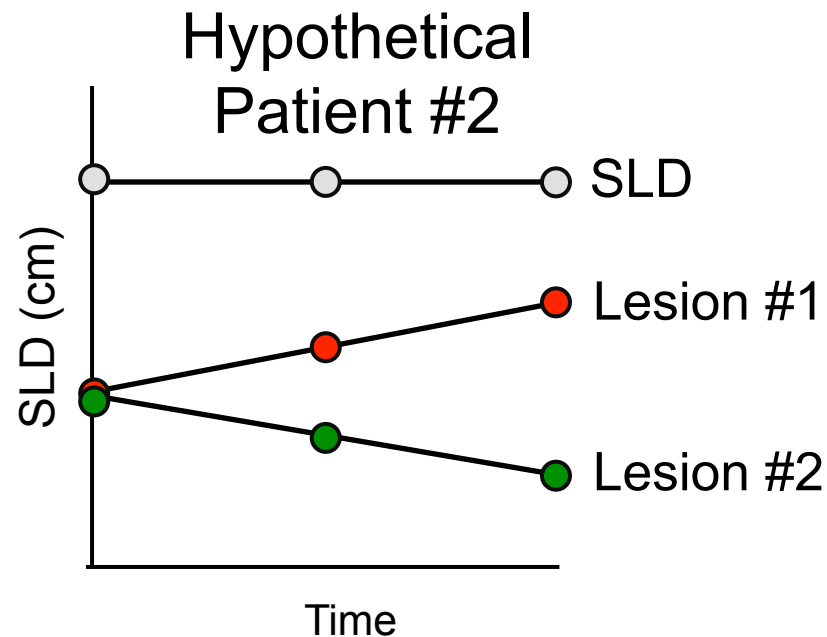
Results: New lesion appearance at month 2 was predictive of survival



Is there another way we can look at target lesion data that would make it predictive?



Stable



Resistant

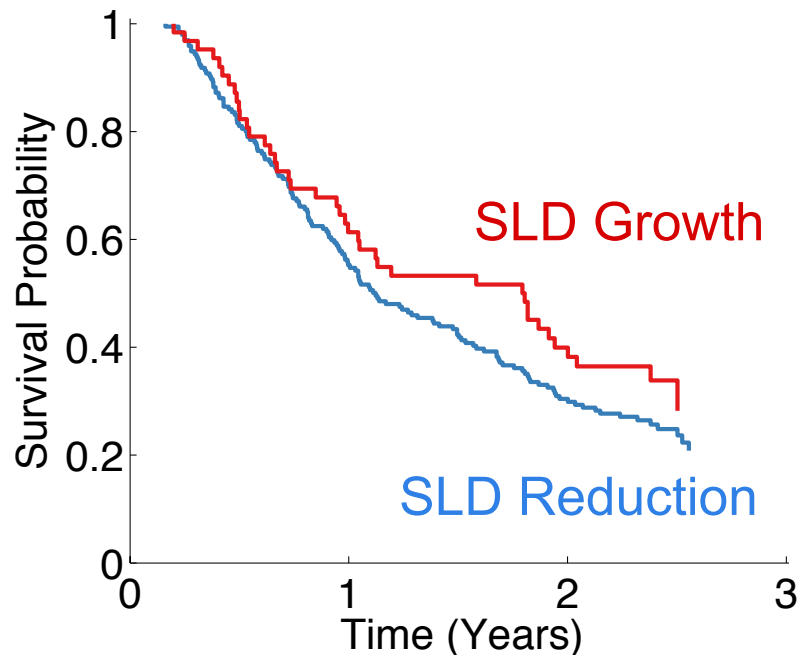
- **Proposal:** look at the “worst lesion” instead of the sum to account for known heterogeneity in tumor response¹

SLD = Sum of longest diameters of target lesions

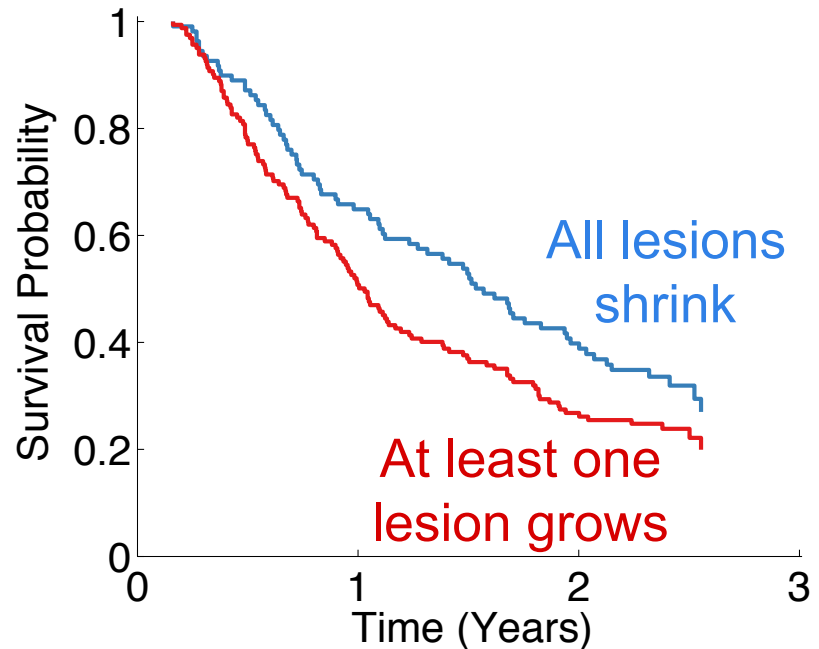
1. Gerlinger et al., *NEJM*, 366, 883 (2012).

Results: Looking at growth/shrinkage of the “least responsive” lesion was predictive of survival

Target Lesion SLD



Behavior of “worst” lesion



$p = 0.03$

SLD = Sum of Longest Diameters of target lesions

Conclusions

- This work¹, adds to a growing body of literature²⁻⁴, demonstrating the importance of accounting for all lesion types (target, nontarget, new).
- The heterogeneity of the target lesion response may also be useful in predicting survival.
- Dose-response modeling methods should take into account the additional available data.
- There is a need to further investigate use of image processing algorithms for capturing the dynamics of all lesions types

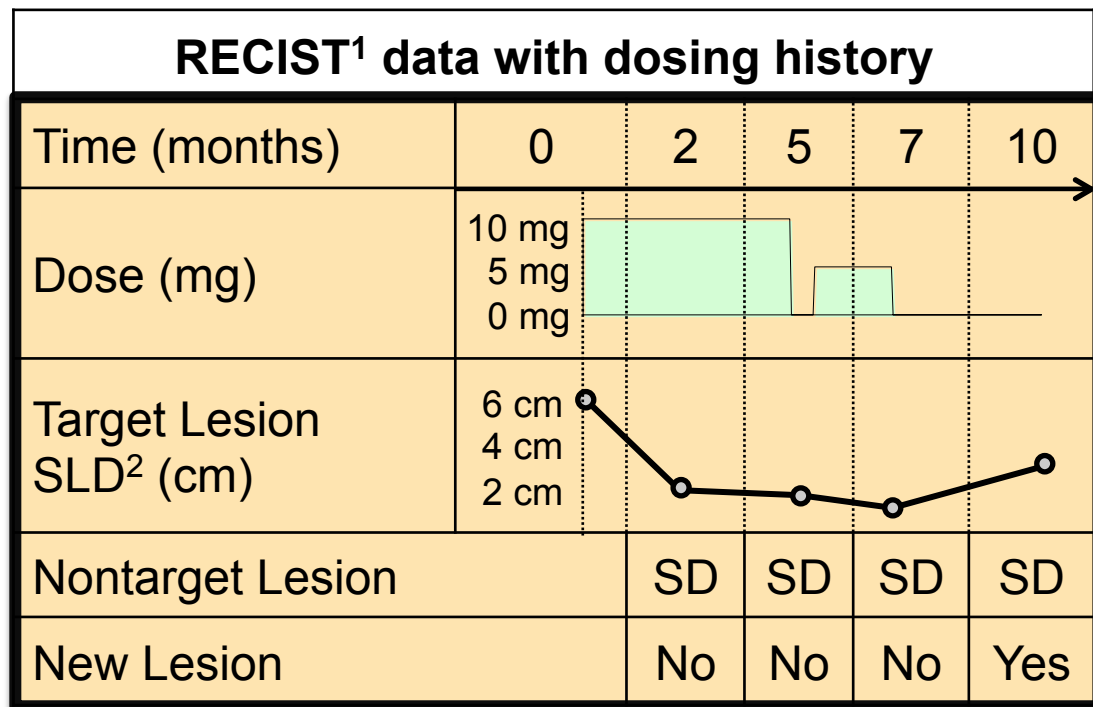
1. Stein et al., *European Urology*, in press, 2013.

3. Mietlowski et al., *J Clin. Oncol.*, abstr 2543, 2012

2. Suzuki et al., *Annals of Oncology*, 23.948, 2012.

4. Litiere et al., *J. Clin. Oncol.*, 30, abstr 10602, 2012

#3: Finally, we focus on modeling the full, multivariate tumor time-course.



1. RECIST = Response Evaluation Criteria In Solid Tumors

2. SLD = Sum of Longest Diameters of target lesions

SD = Stable Disease

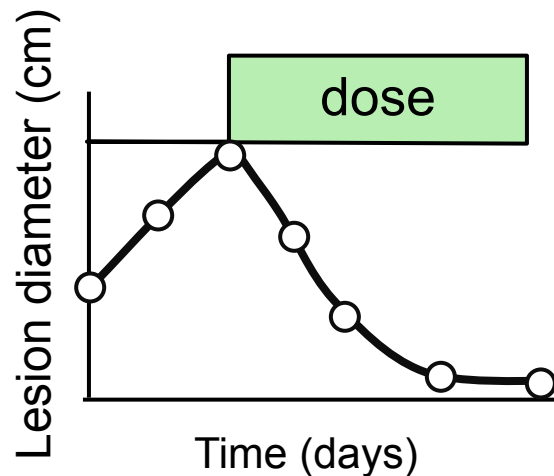
PR = Partial Response

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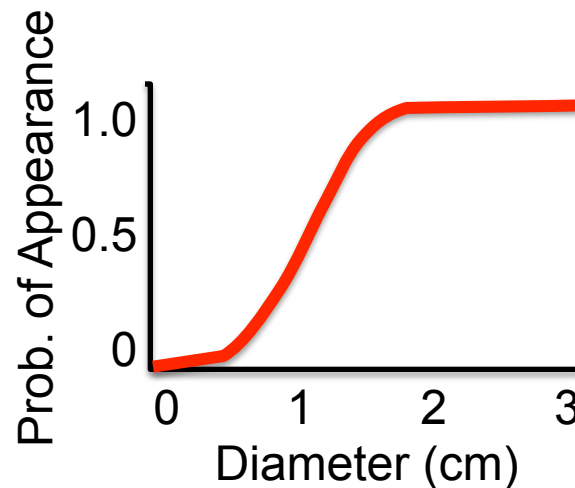
Methods: Can we use the same model we had for the target lesions to also describe the new lesions?

Tumor Dynamics

Continuous Data

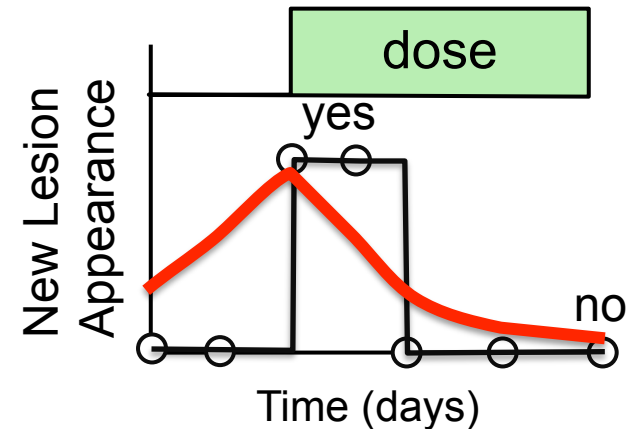


Probability of Detection



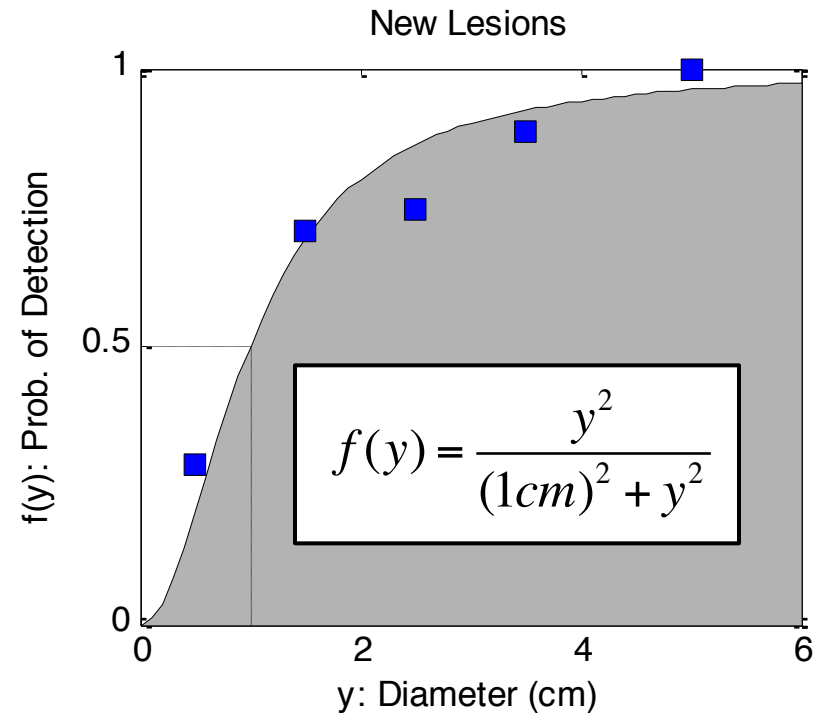
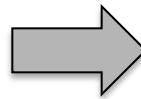
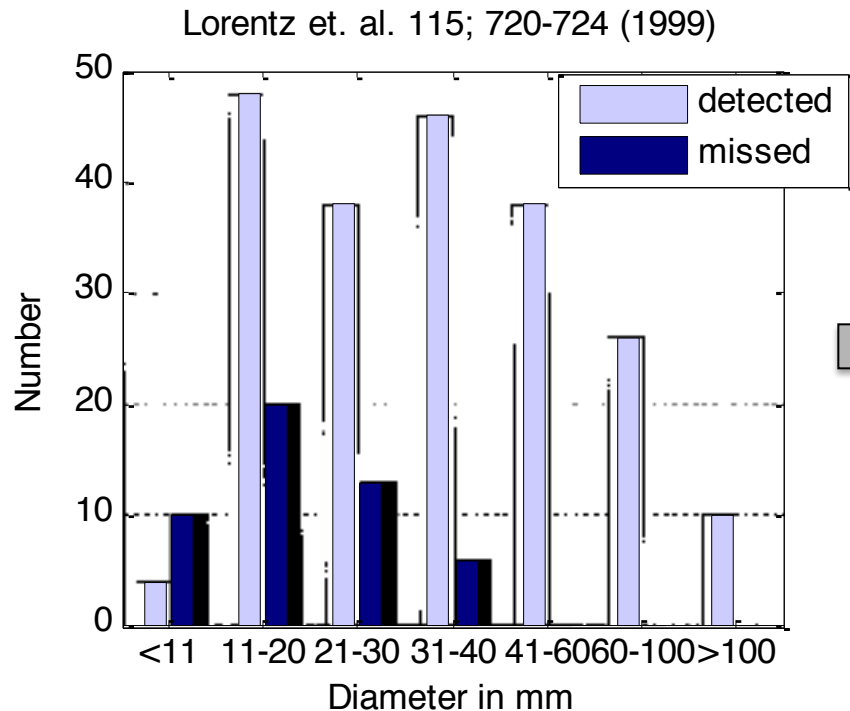
New Lesions

Binary Data



$$\frac{dy}{dt} = r - E_{dose} \cdot y \quad \Rightarrow \quad f(y) = \frac{y^2}{(1cm)^2 + y^2} \quad \Rightarrow \quad \text{Probability of Detection} = f(y)$$

Methods: The new lesion detection function can be estimated from literature data.



- Imaging resolution has improved since 1999, so it is assumed that lesions that were 0.5 cm in diameter were detected with 50% probability.
- Model also requires of an assumption of the initial lesion size (we choose 0.1cm)

1. Lorentz et al, *Chest*, 115; 720-724 (1999)

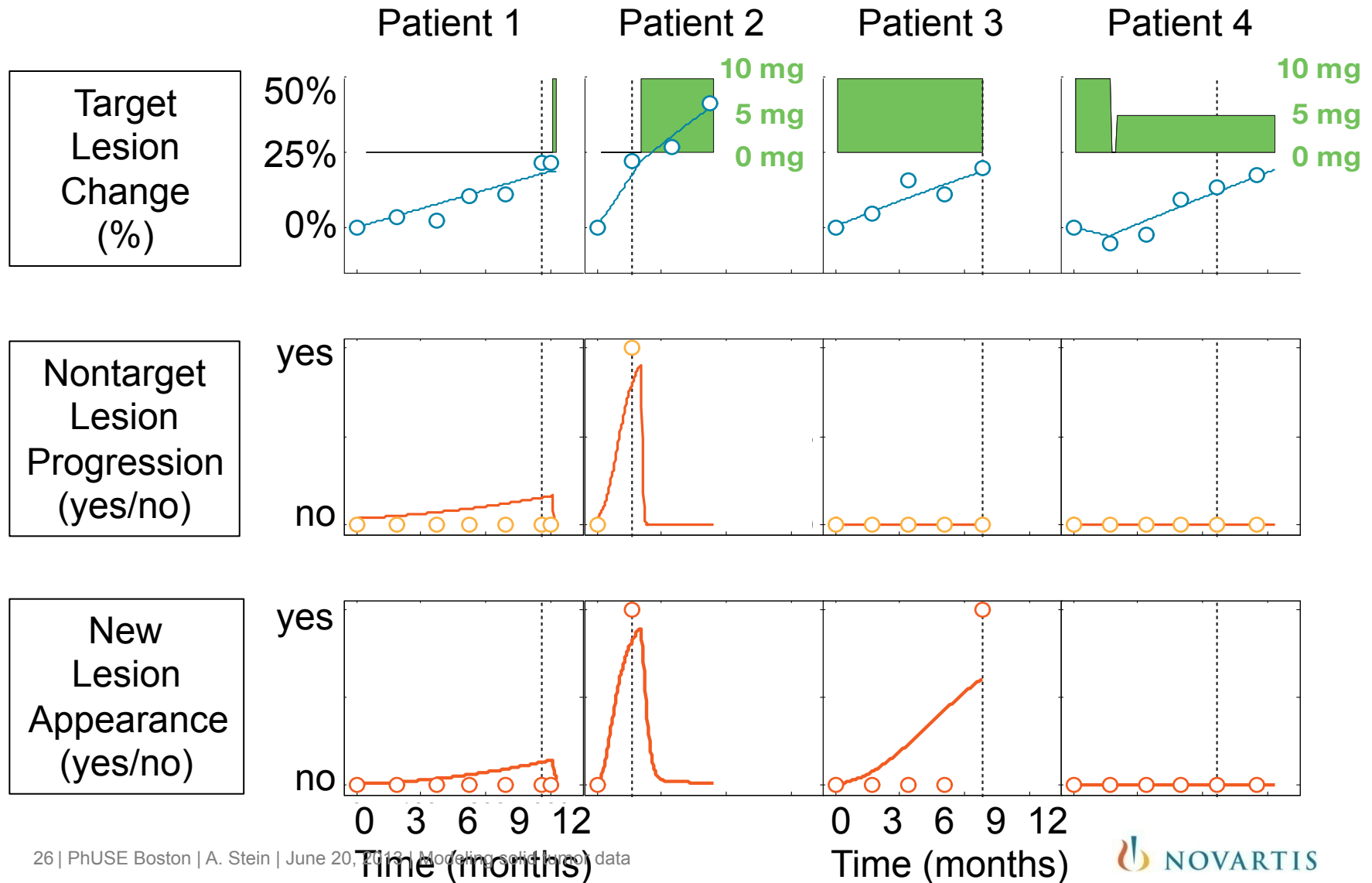
Methods: model based approach for describing individual patient data.

- We model all three lesions types for each individual patient using the target lesion model.

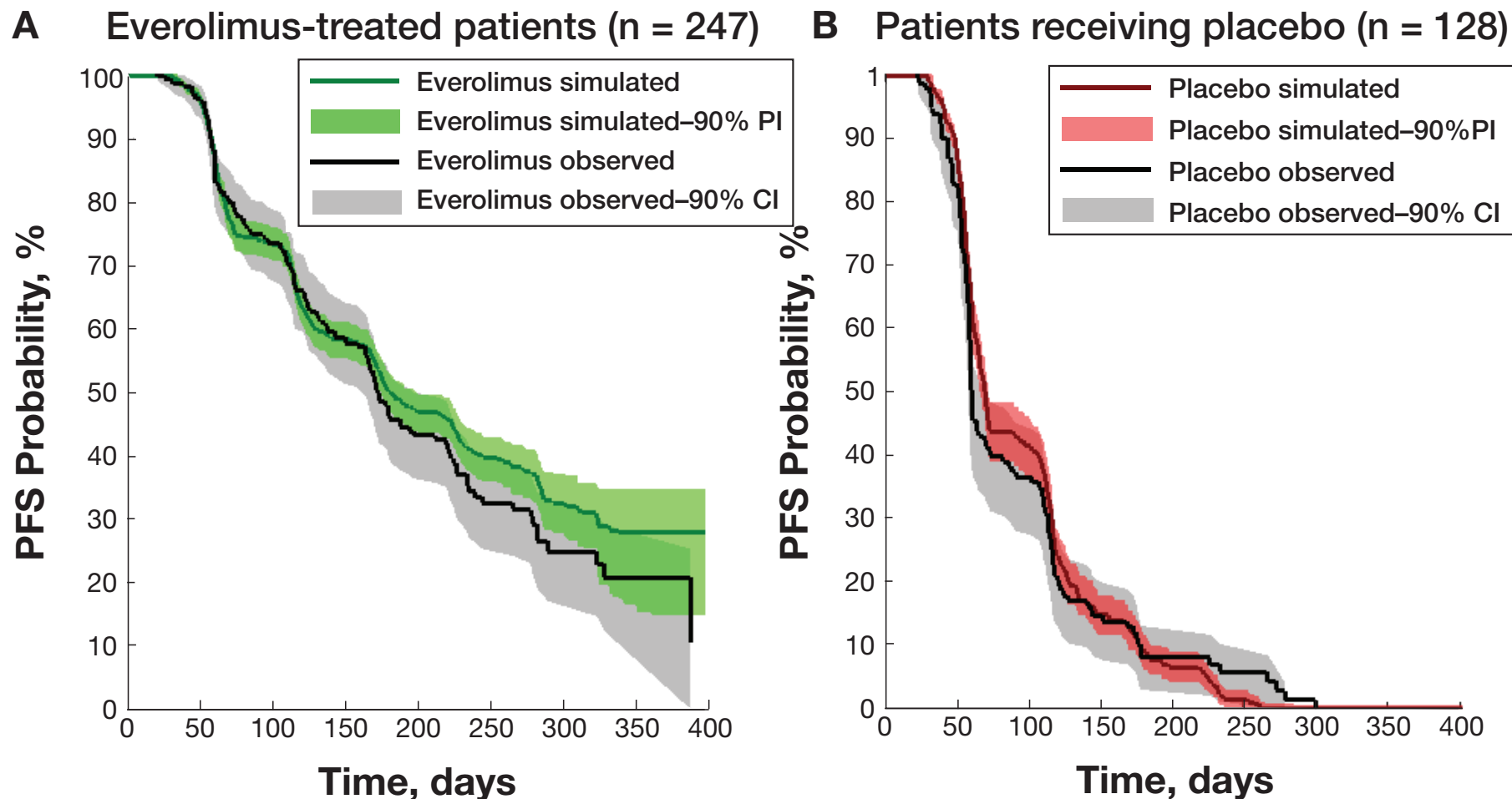
$$\begin{array}{ccccc} \boxed{\begin{array}{l} \text{Tumor Size} \quad (y \text{ [cm]}) \\ \text{Change over Time (t [days])} \end{array}} & = & \boxed{\begin{array}{l} \text{Placebo} \\ \text{Growth Rate} \\ \text{[cm/day]} \end{array}} & - & \boxed{\begin{array}{l} \text{Drug} \\ \text{Effect} \\ \text{[cm/day]}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

- **Target lesions:** fit model to sum of longest diameters (as before)
- **New lesions:** use the “detection function” to transform the diameter (y) to a probability of detection between 0 and 1.
- **Nontarget lesions:** construct a similar “progression function” to transform the diameter (y) to a probability of progression.

Results: The model well describes representative patient data.

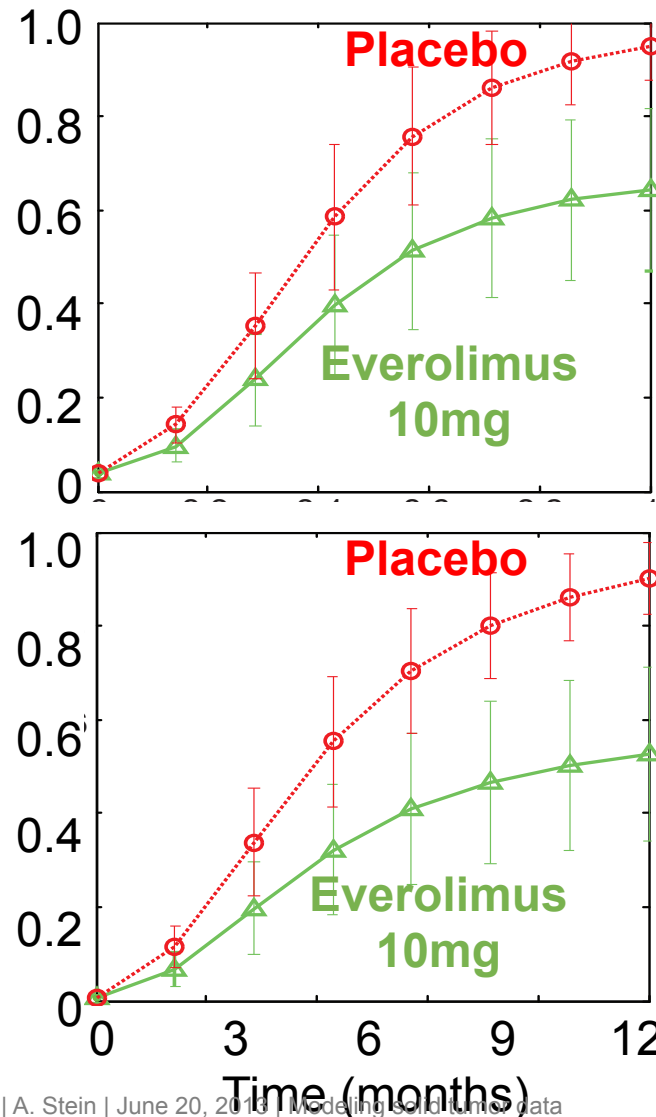


Results: Model can be qualified using the primary endpoint (Progression Free Survival)



Stein et al., *J Clin Oncol*, Abs#4602, 2011 (ASCO Poster)

Conclusions: 10 mg everolimus was superior to placebo, but 5- and 10-mg could not be differentiated



- For nontarget and new lesions, 5mg and 10mg could not be differentiated.
 - There may be a true lack of difference between the two doses in the nontarget and new lesions.
 - Poor resolution of categorical lesion data may make the dose-response relationship more difficult to detect.
- Improved methodologies for characterizing nontarget and new lesions are warranted.

Next Steps

- Add PK to model (has been done in other indications)
- Improve resolution of the tumor data
 - Model each individual lesion instead of the sum
 - Integrate information from multiple readers
 - Apply automated algorithms for assessing the size of all available lesions (not just target lesions).
- Characterize therapeutic window using safety data.

Recap: We have developed new methods for modeling tumor data for identifying the most efficacious dose.

1. Using longitudinal target lesion data, we characterize the difference in efficacy between two doses, which was not possible using standard statistical tools.
2. Taking into account multivariate lesion assessment is essential for predicting overall survival.
3. We have developed multivariate, longitudinal models to capture the full dose-efficacy dataset of all lesion types.
4. **Next Steps:** incorporate PK and explore the use of richer tumor data to capture additional efficacy information for dose selection.

Acknowledgements

■ M&S Oncology Cluster

- Gabriel Helmlinger
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- Daniel Lusk (Intern)

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- Norbert Hollaender

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- Sandra Chica

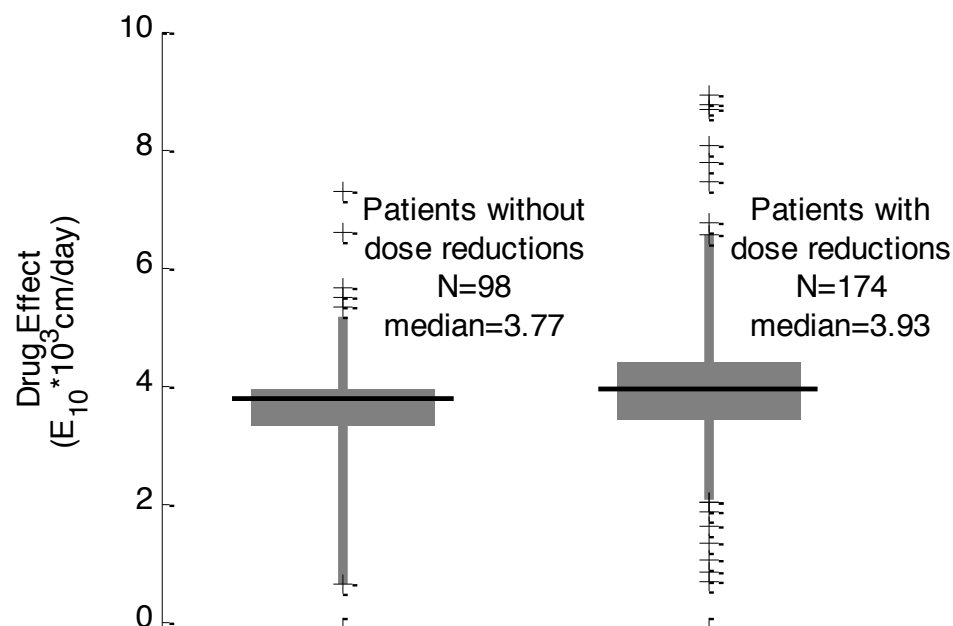
■ MPI Workshop (NJIT)

- Linda Cummings
- Richard Moore
- Tom Witelski + team

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.