

Modeling and Simulation of Clinical Tumor Progression Dynamics: Predicting Phase 3 Survival Outcomes from Tumor Size Measurements in Phase 2

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Outline

Current issues in oncology drug development

A drug-disease modeling framework

- Tumor growth inhibition model
- Dose reduction model
- Survival model

Qualification of the modeling framework

- Simulation of clinical endpoints: ORR and PFS

Simulations of Phase III survival

- Colorectal cancer
- Non-small-cell lung cancer

A new paradigm

- Change in tumor size as a primary endpoint in Phase II studies



Current issues in oncology drug development

A new generation of drugs with new mechanisms of actions: the “targeted therapies”

- Highly competitive market

Empirical selection of dose and dosing schedules

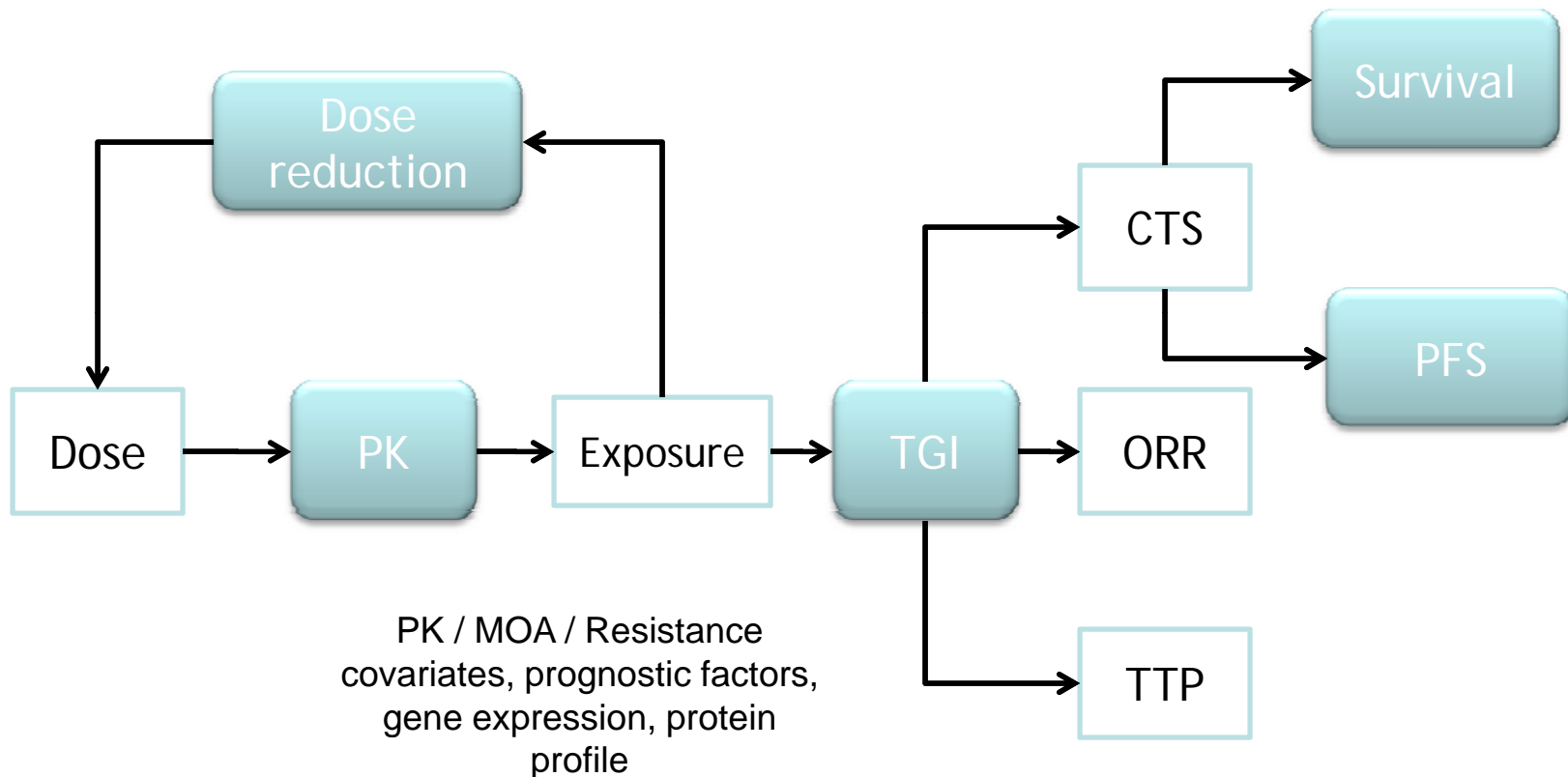
- Maximum tolerated dose (MTD) paradigm in Phase I
 - MTD no longer appropriate for dose selection with new targeted therapies
 - Biologically active dose concept based on biomarkers is not mature yet, hence the importance of Phase II

- Phase II studies not designed to assess dose-response
 - Typical randomized Phase IIb dose-ranging studies are not conducted in oncology
 - Primary clinical endpoints: objective response rate, progression free survival
 - Poorly informative
 - Poorly predictive of clinical benefit

All the above limits the ability to learn from early clinical trials and inform late studies

- High failure rate in Phase III

A drug-disease modeling framework to predict clinical endpoints and support oncology drug development



Modified from Bruno and Claret, Clin Pharmacol Ther, 86, 136-138, 2009



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

Tumor growth rate Cell-kill rate

↓ ↙

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

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

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

$$y(0) = y_0$$

Baseline tumor size

Exposure: Could be dose, AUC, full PK profile

Drug combinations: e.g. assuming additive effects

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)



Dose modification model

Adverse events often require dose adjustments

- Complex dosing algorithms are used in the clinic

One approach would consist of modeling the probability of all dose-limiting side effects and simulate dose intensity using the dosing algorithm

To avoid these complexities, we considered a model of the occurrence of dose reductions and delays as a function of time and (previous) doses

We developed ordered categorical models for the probability of dosing events (daily doses) over time:

- 100% of starting dose
- 75% of starting dose
- 50% of starting dose
- 0% of starting dose

For details on this approach see:

- Claret L et al. PAGE 17, 2008 (Abstr 1312)
- Claret L et al. ACoP 2009



The survival model

Survival time distribution is estimated (parametric model) as a function of prognostic factors and predictors

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

Drug independent, disease specific model

- Fractional change in tumor size taken as a biomarker of drug effect
- Historical Phase III studies can be used to develop the model
- The model can be leveraged to simulate survival for a new investigational treatments
- Has been developed for MBC, CRC, NSCLC, pancreatic cancer, ovarian cancer and multiple myeloma
 - Claret et al. *J. Clin. Oncol.* 27, 4103-4108, 2009
 - Wang et al. *Clin. Pharmacol. Ther.* 86, 167-174, 2009
 - Lindbom et al. *ACoP* 2009
 - Claret et al. *Leiden* 2010



Modeling framework qualification

Simulation of clinical endpoints (ORR, PFS)

An end-of-Phase II prospective project with mosetanib

Motesanib is an orally administered small molecule antagonist of VEGFR1, 2 and 3; PDGFR and Kit

Goal: To support dose selection at end-of-Phase II

- Based on Phase II data I thyroid cancer patients

We simulated expected dose response for clinical endpoints:

- ORR: Proportion of patient with confirmed tumor shrinkage exceeding 30% from baseline
- PFS: Time to progressive disease (> 20% increase in tumor size from minimum) or death

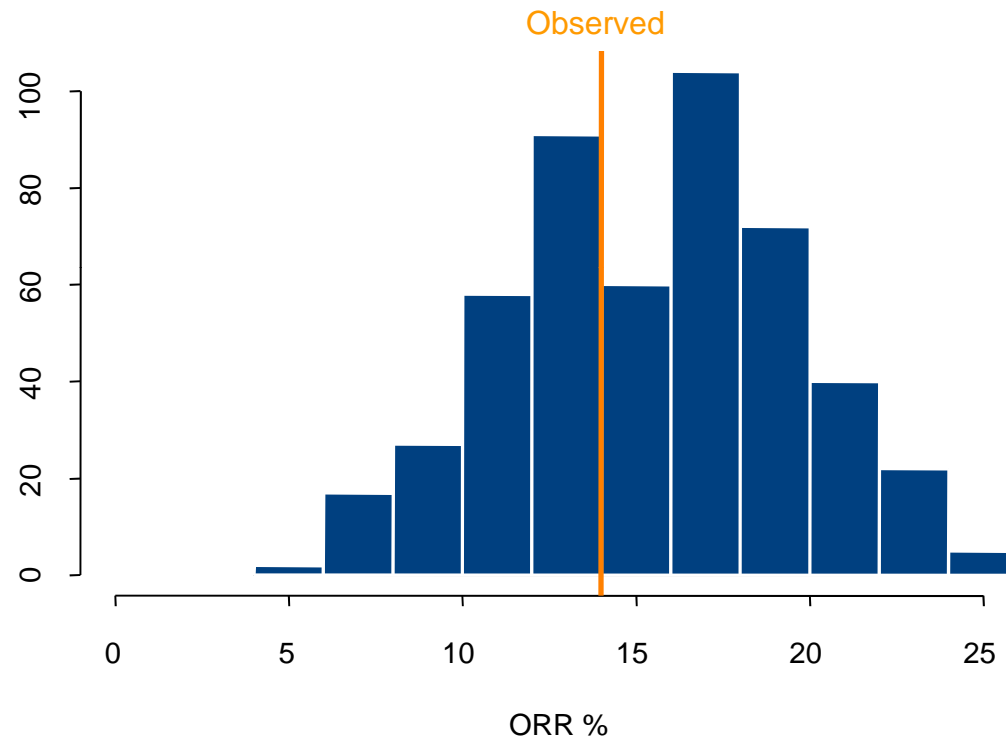
The modeling framework was qualified in simulating these endpoints

Claret L et al. ACoP 2009



Modeling framework qualification - ORR

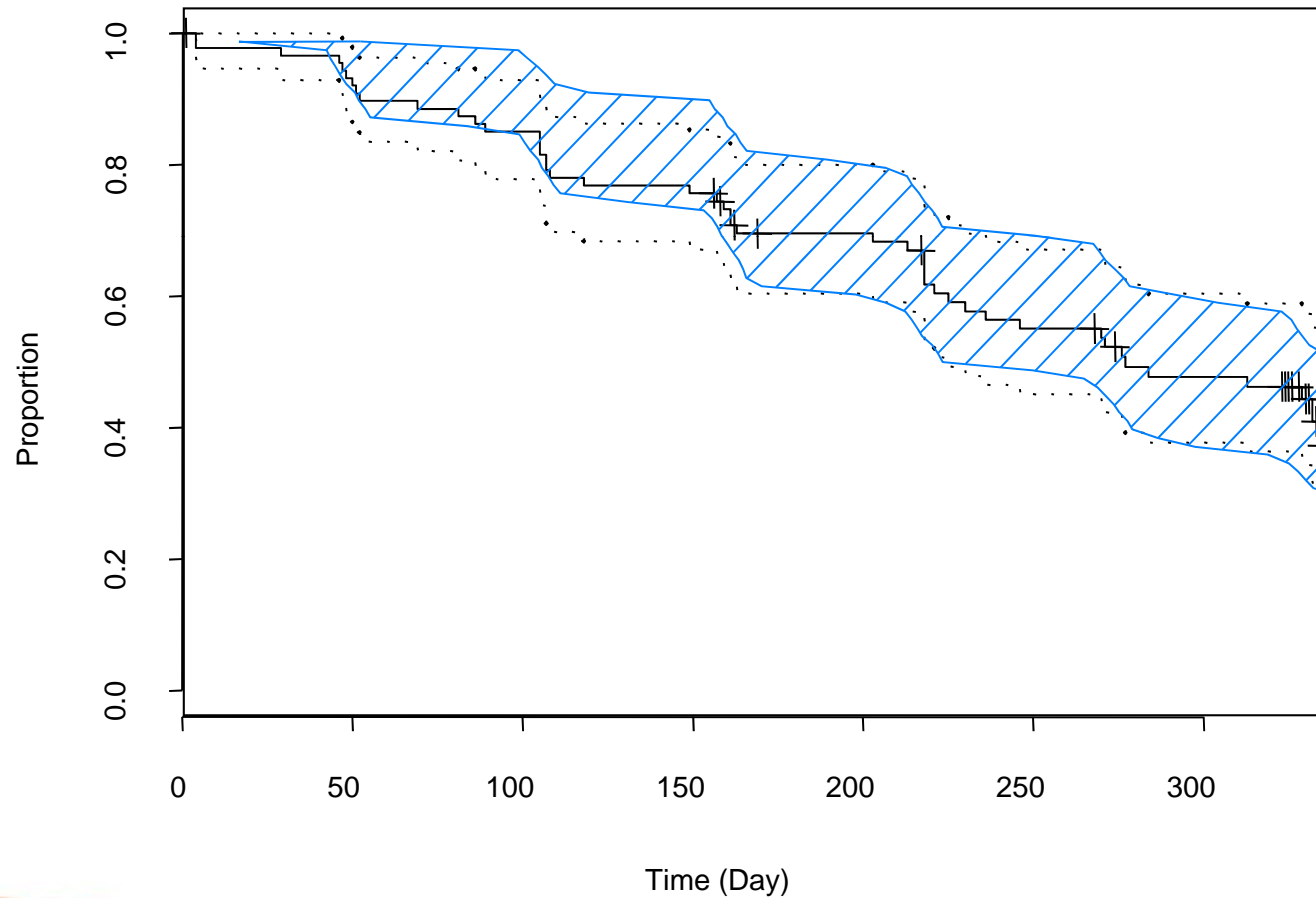
Predictive distribution (500 replicates of 93 patients) vs. observed





Modeling framework qualification - PFS

Predictive distribution vs. observed KM plot (500 replicates of 93 pts)





Simulation of Phase III survival

A retrospective project with capecitabine (Roche)

Goal: To support end-of-Phase II 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:

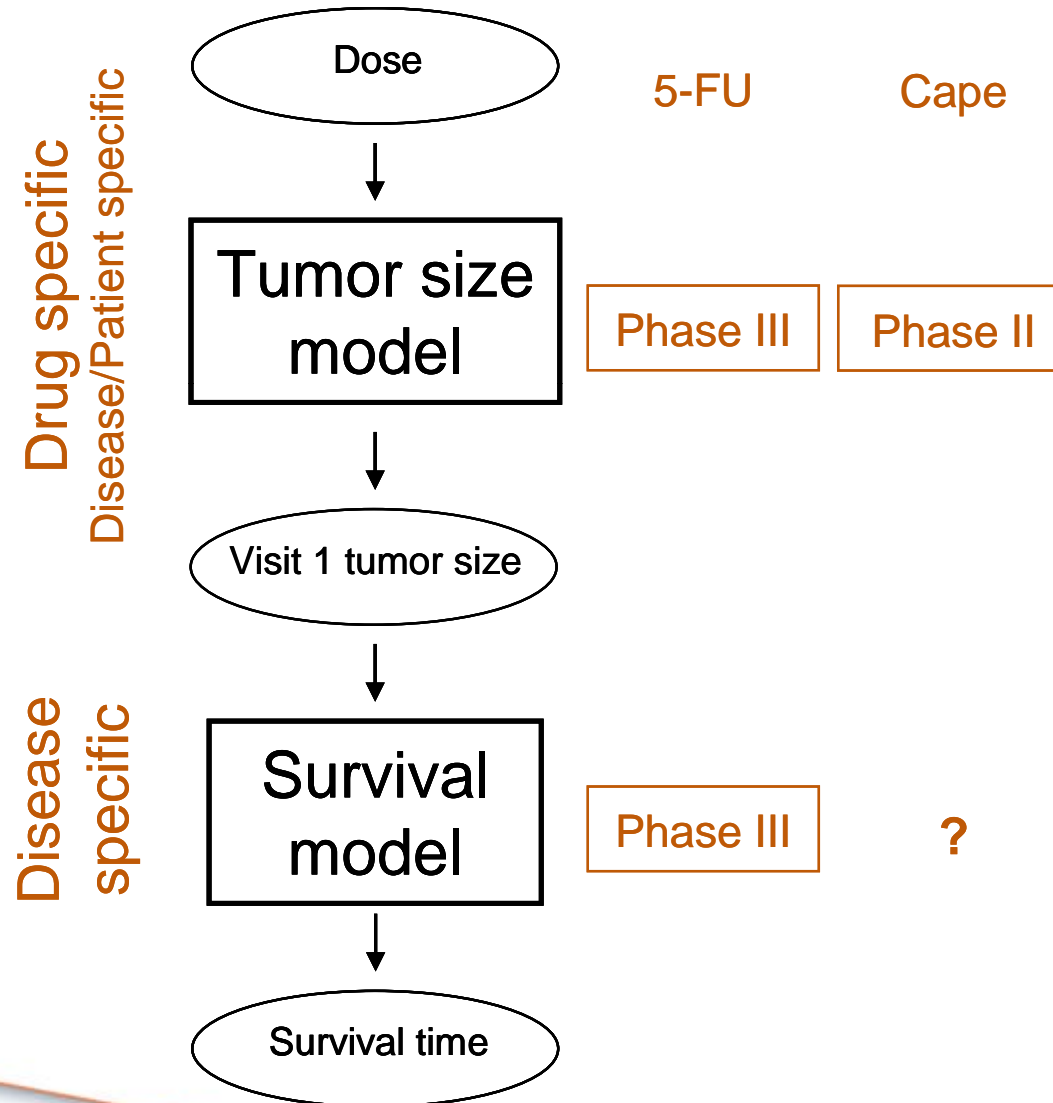
- Simulate:
 - Phase III of capecitabine (X) + docetaxel (R) vs. docetaxel in MBC
 - Phase III of capecitabine (X) vs. 5-Fu (R) in CRC
- Multiple replicates (n=1000) of the studies were simulated
- Drug effect driven by dose
 - Simulations conditioned on observed dose intensity (dosing history)


Claret L et al. Proc ASCO, 24 (18S), 307s (Abs 6025), 2006.

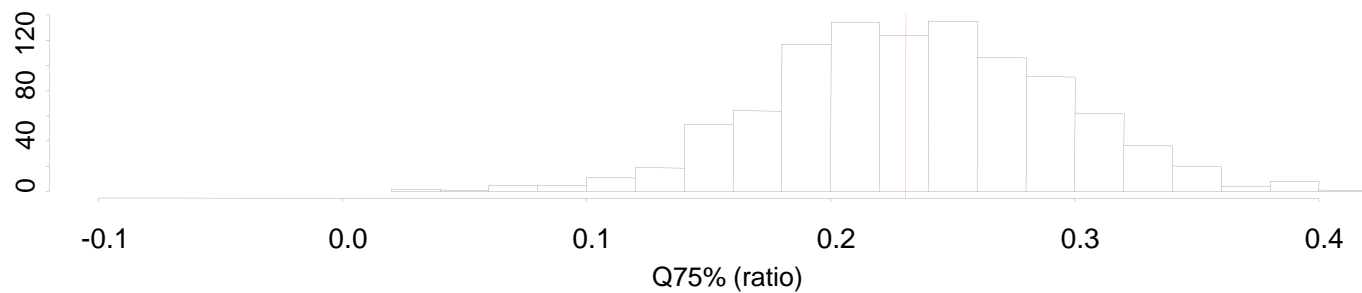
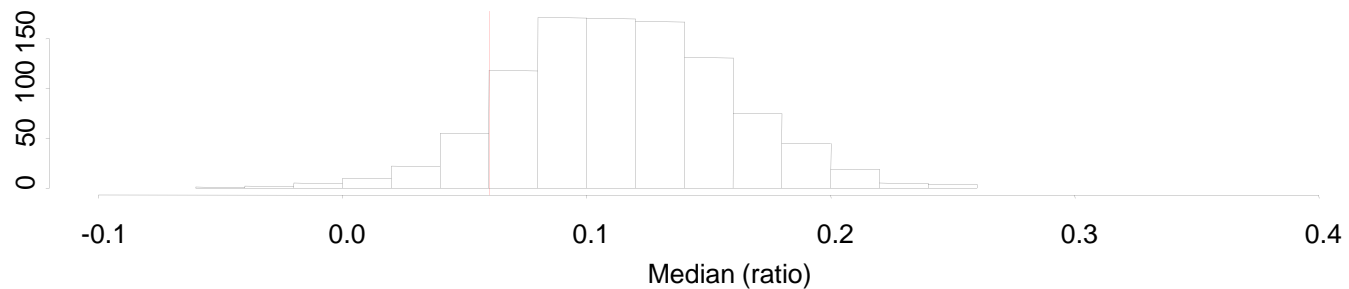
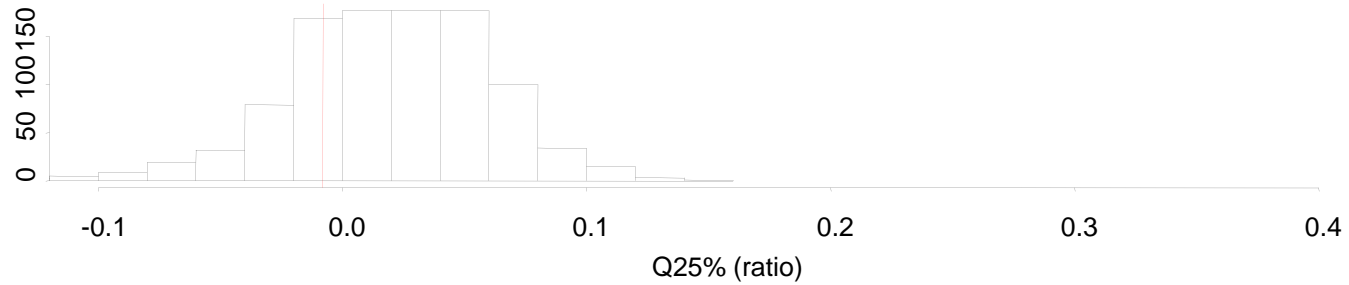
Claret L et al. Journal of Clinical Oncology, 27, 4103-4108, 2009.



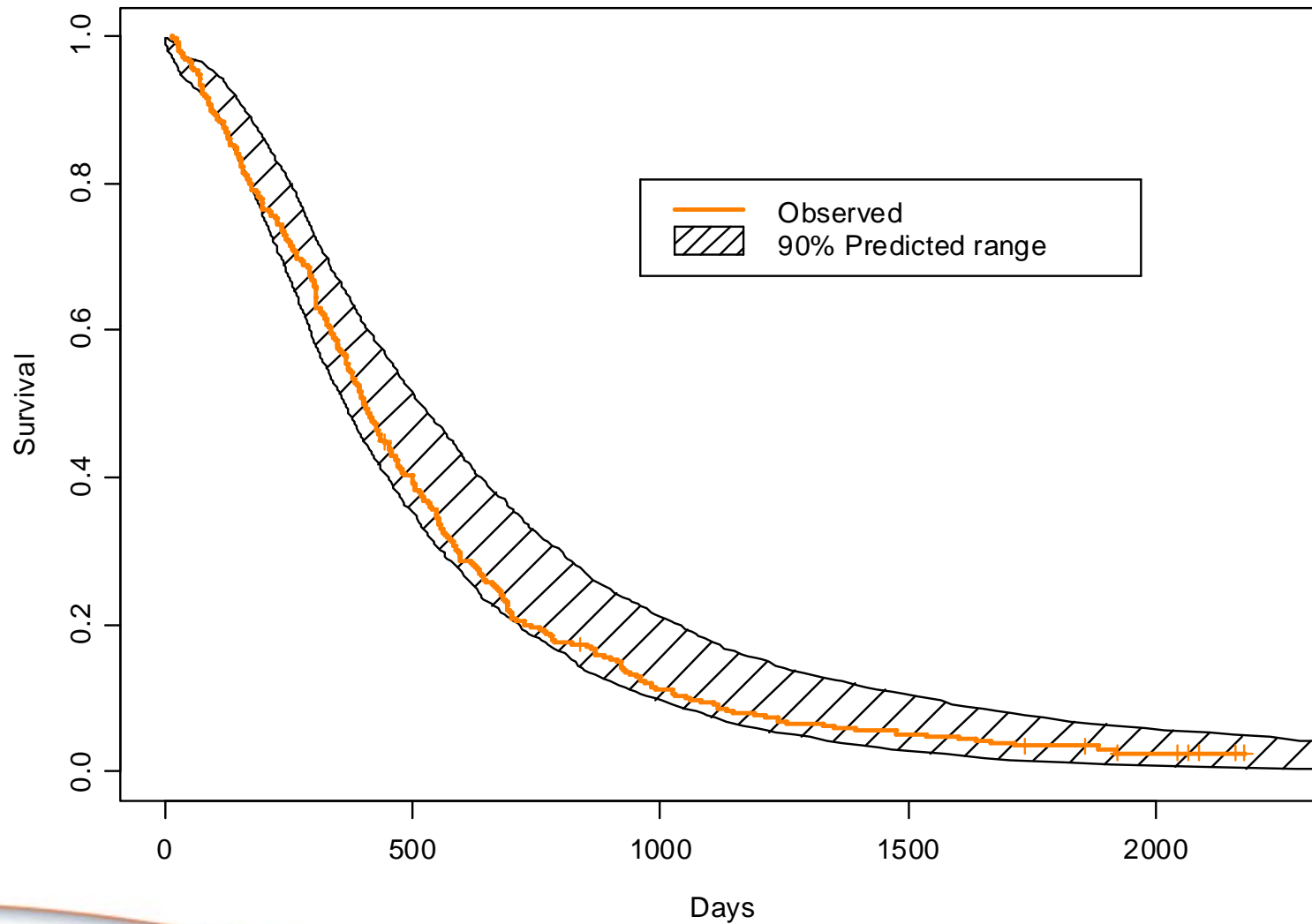
Functional scheme



 Tumor size reduction predicted vs. observed in a Phase III study of capecitabine vs. 5-Fu in CRC patients (capecitabine arm)

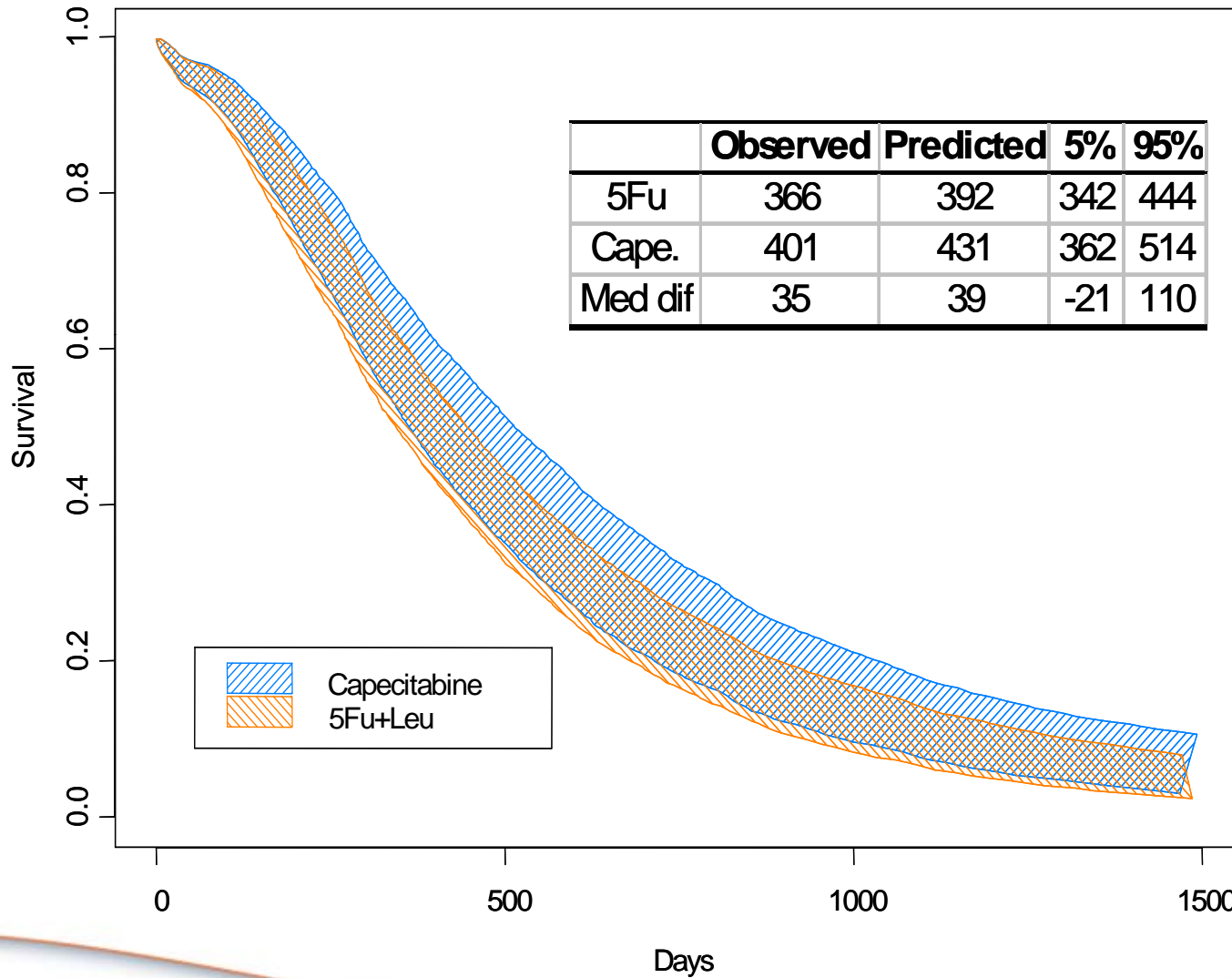


Survival prediction vs. observed in a Phase III study of capecitabine vs. 5-Fu in CRC patients (capecitabine arm)





Expected survival difference in a Phase III study of capecitabine vs. 5-FU in CRC





FDA NSCLC modeling framework

Drug-independent models linking survival to change in tumor size at week 8 (W8 CTS) were developed in 1st line and 2nd line patients based on 4 NSCLC registration trials

- **First line:**
 - Bevacizumab: B+CP vs. CP (Sandler et al, New Engl J Med 355, 2542-2550, 2006)
 - Docetaxel: D+Cis vs. D+C vs. Vino+Cis (Fossella et al, J Clin Oncol 21, 3016-3024, 2003)
- **Second-line:**
 - Erlotinib: E vs. BSC (Shepherd et al, New Engl J Med 353, 123-132, 2005)
 - Pemetrexed: P vs. D (Hanna et al, J Clin Oncol 22, 1589-1597, 2004)

The model can be used to simulate clinical trials based on week 8 change in tumor size (Bruno et al, Proc ASCO 2009)

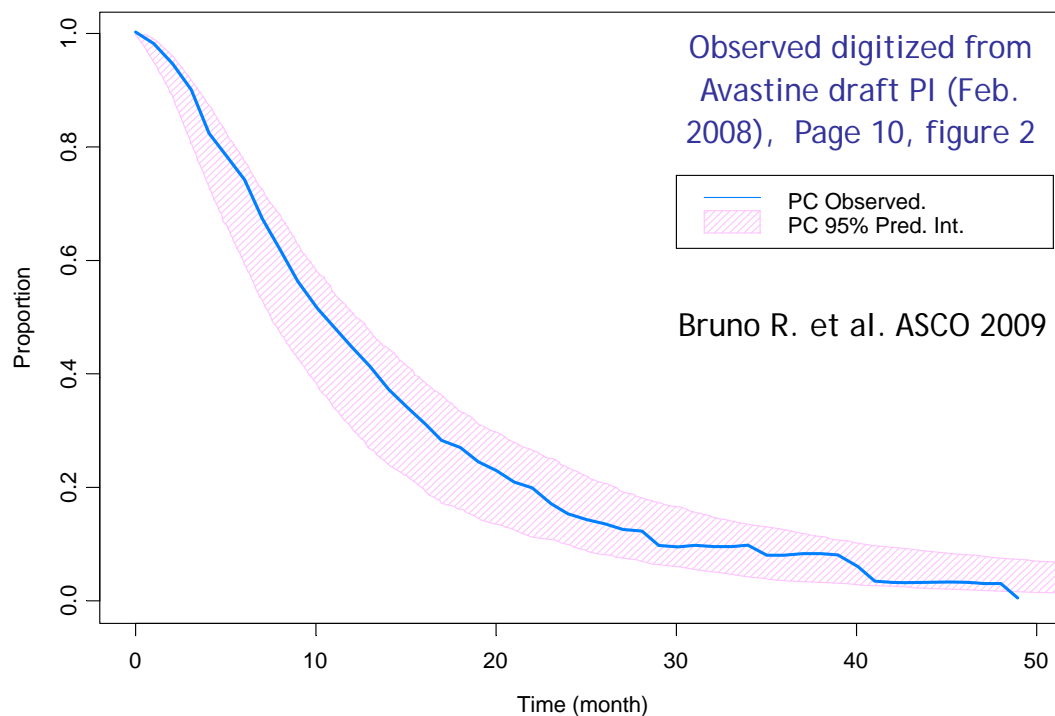
- The FDA modeling framework tend to generate conservative estimates of the treatment effect differences (risk ratio)

Wang et al. Clin Pharmacol Ther, 86, 167–174, 2009



Simulation of the Sandler's study

(paclitaxel + carboplatin vs. paclitaxel + carboplatin + bevacizumab)



	Pred.	2.5%	97.5%	Obs.
PCB	11.0	8.5	14	12.3
PC	9.7	7.5	12.3	10.3
HR	0.93	0.78	1.09	0.80



Value of survival simulations

The survival probability distribution of an investigational treatment can be predicted based on early tumor shrinkage clinical data (e.g. Phase Ib or II)

- Can be a NCE, a new combination, a new schedule

Survival of the investigational treatment can be simulated conditional on a sample size

- To mimic a clinical trial arm

These simulations can be compared to a survival distribution from a reference treatment

- Expected treatment arm difference can support
 - Go/no go decision
 - Phase III clinical trial design

Phase III clinical trials can be simulated to assess probability of success

Comparison with historical data (e.g. using the FDA tumor size model) still questionable

- Best to have actual tumor size data in a randomized Phase II study with reference treatment



Change in tumor size as a primary endpoint in Phase II studies

The use of ORR (or PFS) as primary endpoint based on RECIST criteria for tumor response evaluation in Phase II studies has been questioned

- Precludes the conduct of informative randomized dose-response Phase II studies
- Would require too many patients to establish dose-response relationships or to compare alternative schedules

Change in tumor size (CTS) from baseline has been proposed to be used as the primary endpoint in Phase II studies

- The use of CTS, a continuous patient-level endpoint rather than categorizing the changes is more sensitive in assessing treatment effect
- Randomized studies to assess dose-response, optimal scheduling... can therefore be envisaged

In a simulation study

- The power of a 120-patient randomized Phase II with an investigational treatment vs. standard of care (docetaxel) (2:1 randomization) to show a 2 months increase in PFS (2nd line NSCLC) would be 60% based on PFS and 100% based on CTS

Karrison et al. J Natl Cancer Inst, 99, 1455-1461, 2007

Bruno and Claret, Clin Pharmacol Ther, 86, 136-138, 2009

Claret L et al. PAGE 2008, Abstract 1386



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Backups



FDA NSCLC modeling framework

Longitudinal (empirical) tumor size model

- Assumes a combination of linear tumor growth and exponential tumor shrinkage with time
- There is one model for each of the 9 treatment arms in the 4 trials

Survival model

- Describes the log-normal distribution of survival time as a function of:
 - Change in tumor size from baseline at week 8 (i.e. end of cycle 2): Assessment of treatment effect
 - Prognostic factors (baseline tumor size and ECOG performance status, 0 and 1 only)
- There is one model for first line patients (2 trials) and one model for second line patients (2 trials)

Adjustment models

- Describe the log-normal distribution of survival time for early dropout patients with ECOG 0 and 1, i.e. those patients who did not have end of cycle 2 tumor size measurements ...
- ... and for ECOG 2 and 3 patients (2nd line only, not considered in survival models)