

A Modeling and Simulation Framework to Support Oncology Drug Development Decisions

Outline

Questions in early oncology drug development

A drug-disease modeling framework

- Tumor growth inhibition model
- Survival model

Case studies

- Support to end-of-Phase II decisions
- Simulation of ORR and PFS
- Simulation of survival (NSCLC, multiple myeloma)

A new paradigm

- Change in tumor size as an endpoint in early clinical studies

Translational modeling

Problems in early 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 (>50% in the 2002-2007 period, Gobburu, FDA)

Key questions around early clinical oncology studies

POC: Is the drug doing anything?

Dose: Is the dose right?

Schedule: Shorter vs. longer infusion, drug holidays...?

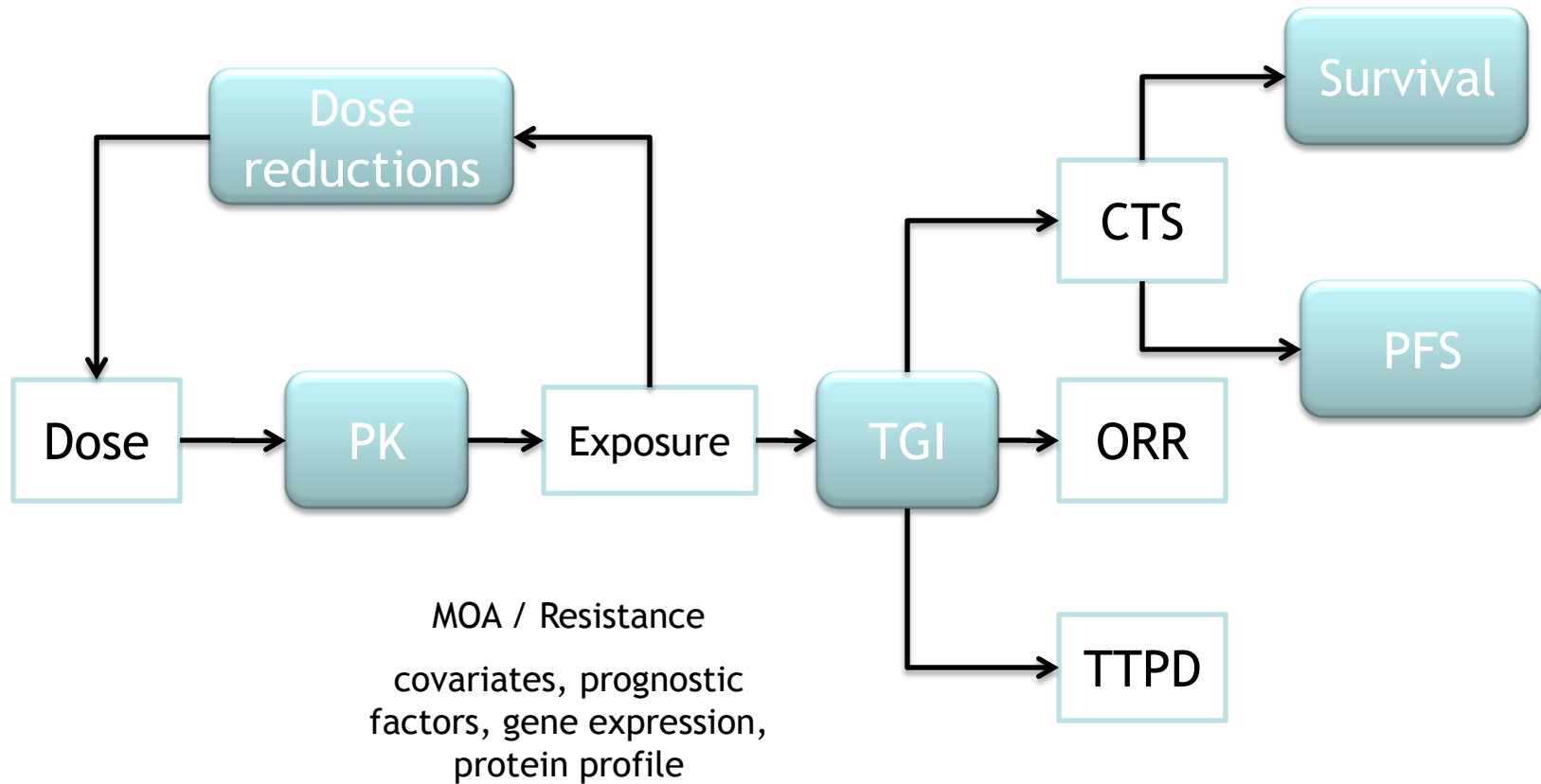
POC, Phase II study design

- Incl. endpoint selection

End-of-Phase II decision: Is the effect seen in Phase II worth it?

Phase III study design and conduct

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 tumor growth inhibition (TGI) model describes the sum of tumor longest diameters as a function of time and dose

$$\frac{dy_t}{dt} = K_L \cdot y_t - K_D(t) \cdot \text{Exposure}_t \cdot y_t$$

Tumor growth rate
Cell-kill rate

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

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)

Claret et al. PAGE 15, (Abstract 1004), 2006

Claret et al. J Clin Oncol 27, 4103-4108, 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
- Has been developed for MBC, CRC, NSCLC, pancreatic cancer, ovarian cancer, H&N carcinoma, multiple myeloma
 - Claret L et al., Proc ASCO, 24 (18S), 307s (Abs 6025), 2006
 - 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
 - Jonson et al. PAGE 2010
- The model can be leveraged to simulate survival for new investigational treatments based on early clinical data

Support to 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 investigational treatment (IT) to standard of care (SOC)
- Based on Phase II IT data and historical SOC data

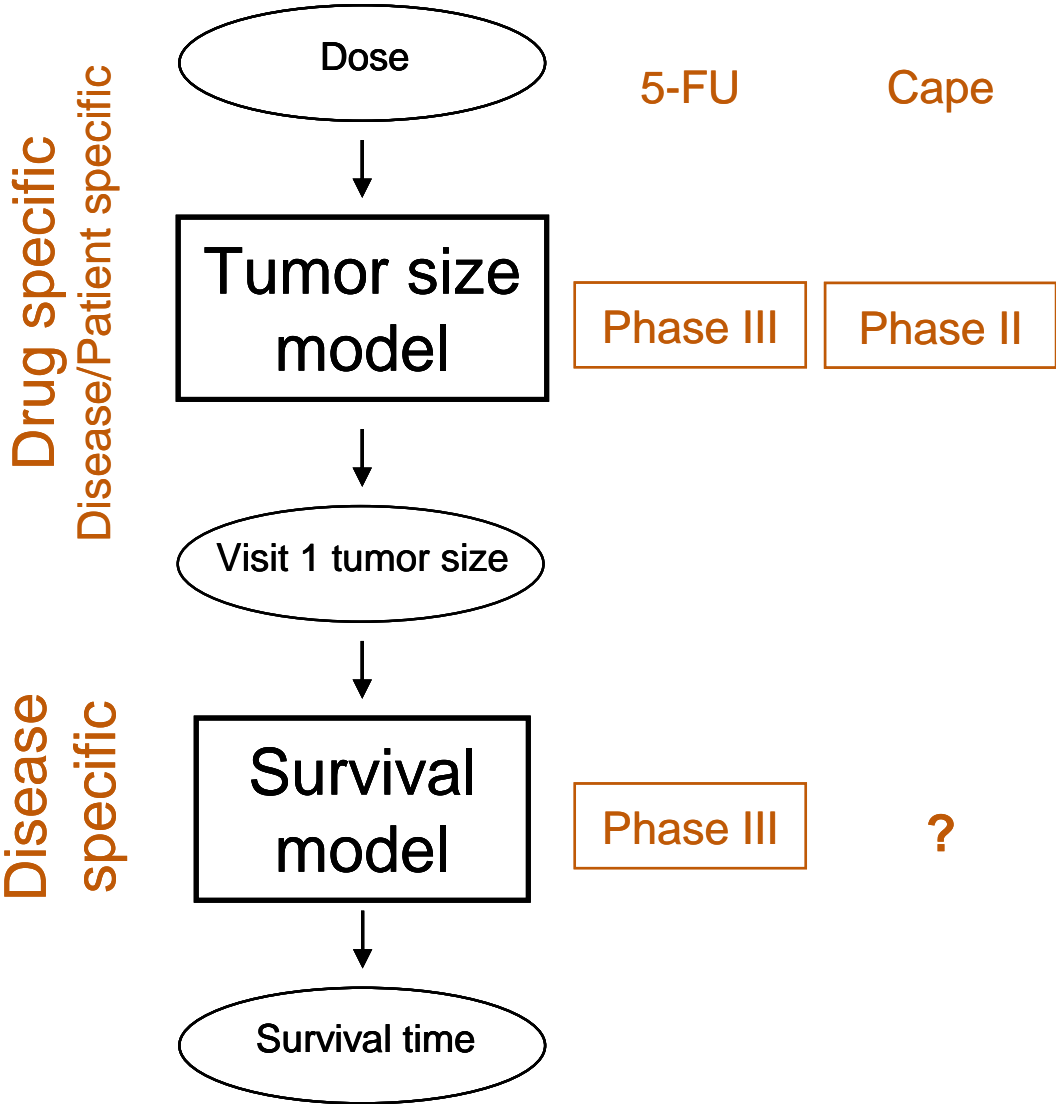
Retrospective project:

- Simulate:
 - Phase III of capecitabine + docetaxel (IT) vs. docetaxel in MBC
 - Phase III of capecitabine (IT) vs. 5-Fu in CRC
- Multiple replicates (n=1000) of the studies were simulated

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

Claret L et al. J Clin Oncol, 27, 4103-4108, 2009

Functional scheme



Simulation of a Phase III study comparing 5-Fu to capecitabine in CRC

Model parameter estimation

- Capecitabine data
 - Phase II (1 study, 34 patients) used for model building
- 5-Fu data
 - Phase III (1 study, 301 patients)

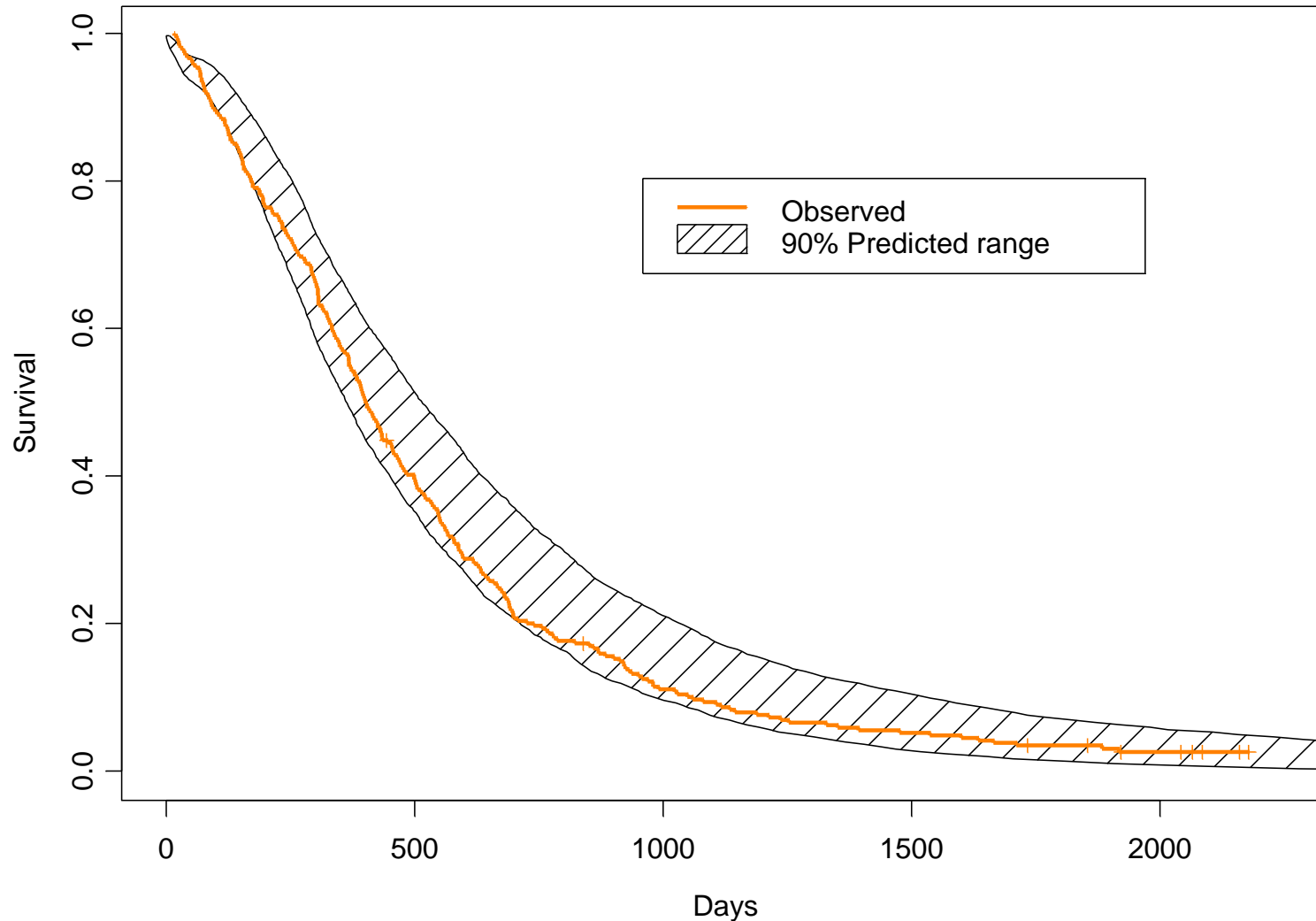
Simulation

- Phase III study of Capecitabine vs. 5-FU (301 patients, 500 replicates)
 - Capecitabine scaled from Phase II to Phase III using disease specific parameters (tumor growth rate)

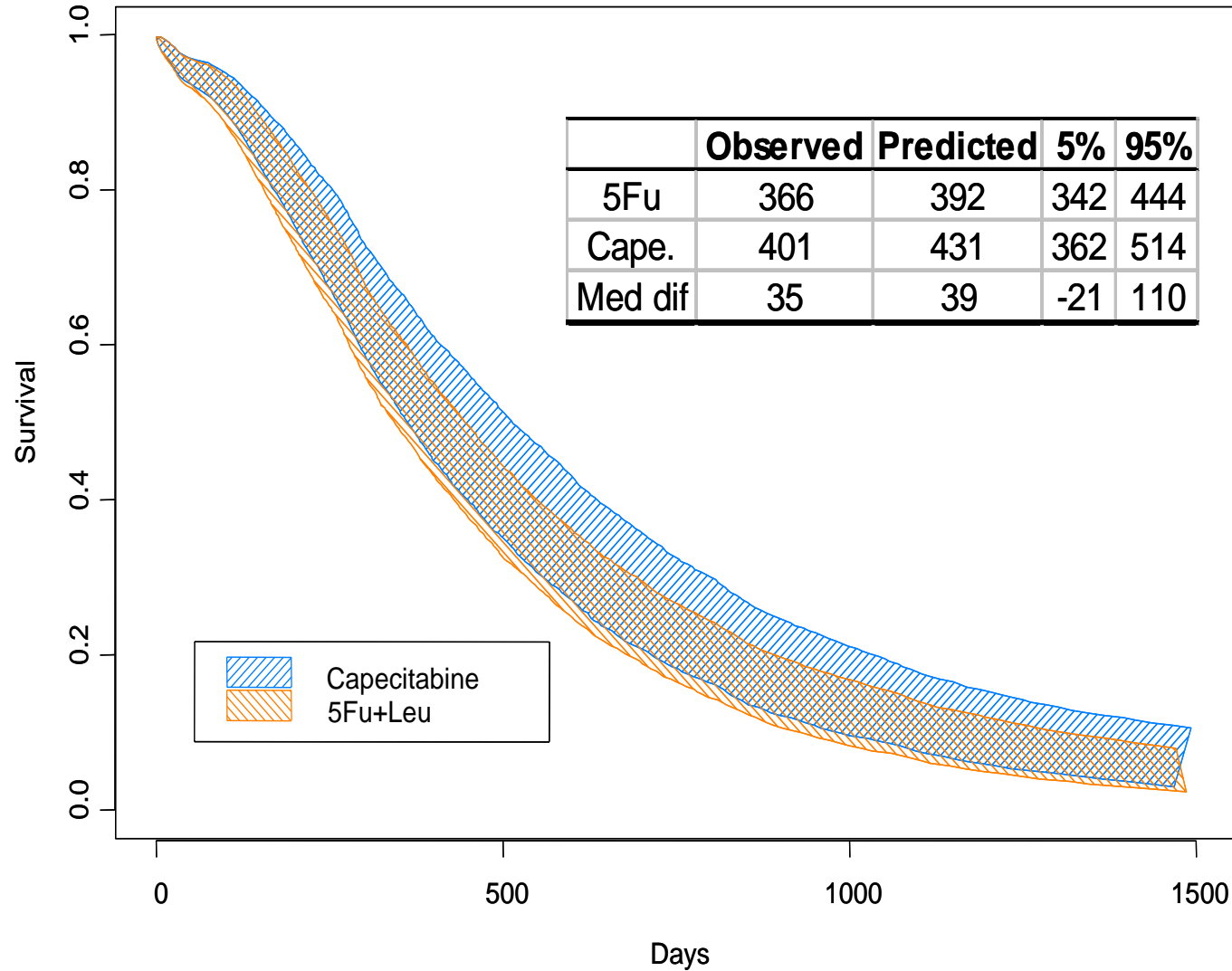
Focus on efficacy, no model for dose-limiting side-effects

- Drug effect driven by dose
- Simulations conditioned on observed dose intensity (dosing history)
 - We subsequently developed a model to predict dose intensity in CRC to assess the impact of using lower starting dose on tumor shrinkage and survival

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



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 in thyroid cancer patients

We simulated expected dose response for clinical endpoints:

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

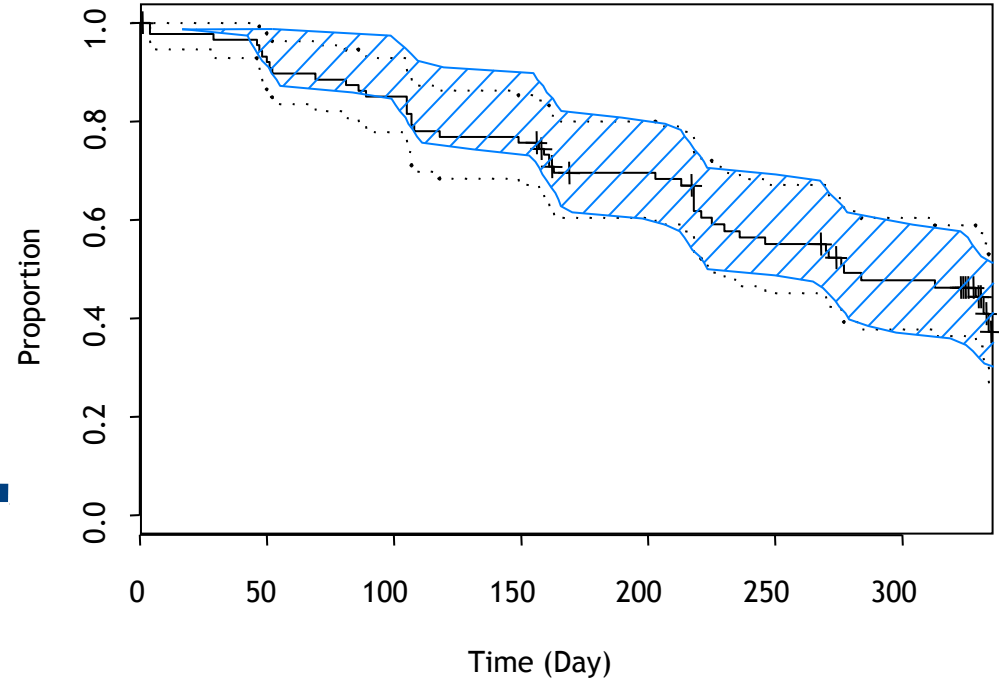
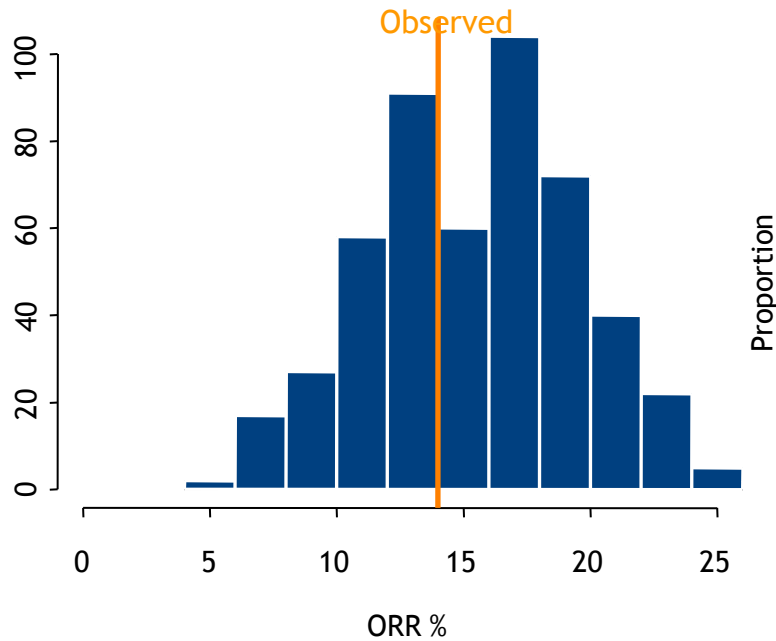
Modeling framework

- Dose-reduction model
- Longitudinal tumor size model
 - Drug effect driven by systemic exposure (AUC)
- Survival model
 - Preliminary as we did not have mature survival data in the Phase II study

Claret L et al. Cancer Chemother. Pharmacol. 66, 1141-1149, 2010

Modeling framework qualification - ORR, PFS

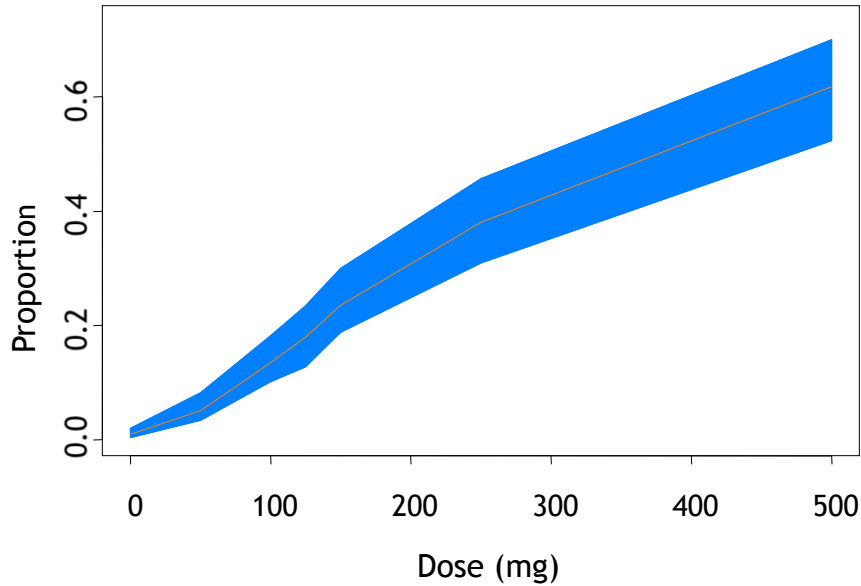
Predictive distribution (500 replicates of 93 patients) vs. observed



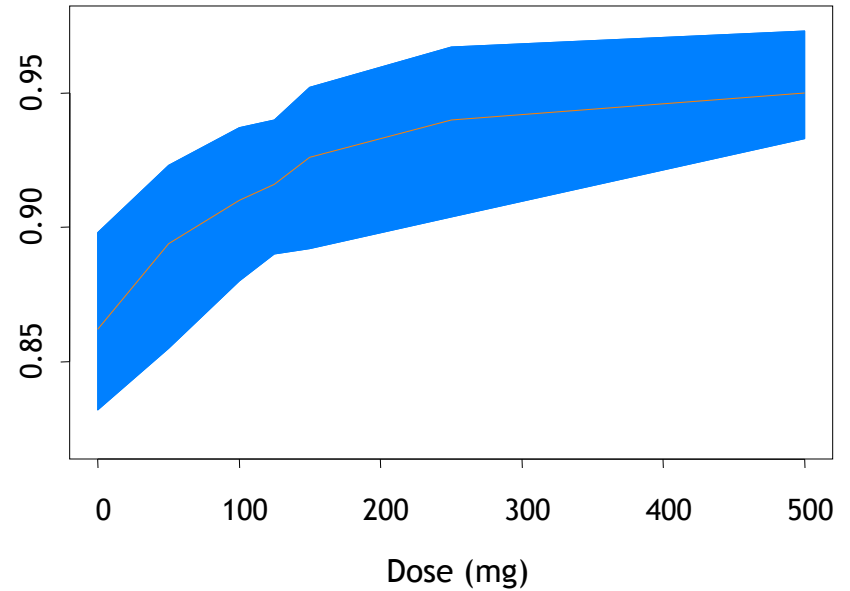
Claret L et al. Cancer Chemother. Pharmacol. 2010

Simulated dose-response for ORR and 3 month PFS (100 replicates of 500 patients)

ORR in DTC versus dose



Proportion of PFS at 3 months



High dose simulations imply extrapolation of the models

FDA NSCLC survival model



NSCLC Database

- Four registration trials (A, B, C, D) for non-small cell lung cancer (NSCLC)
- Eight active treatments and one best supportive care (placebo)
- First-line or second line treatment for locally advanced or metastatic NSCLC (stage IIIA/B, IV)
- N=243-488/arm (total~3500)

Gobburu, Pharmacometrics

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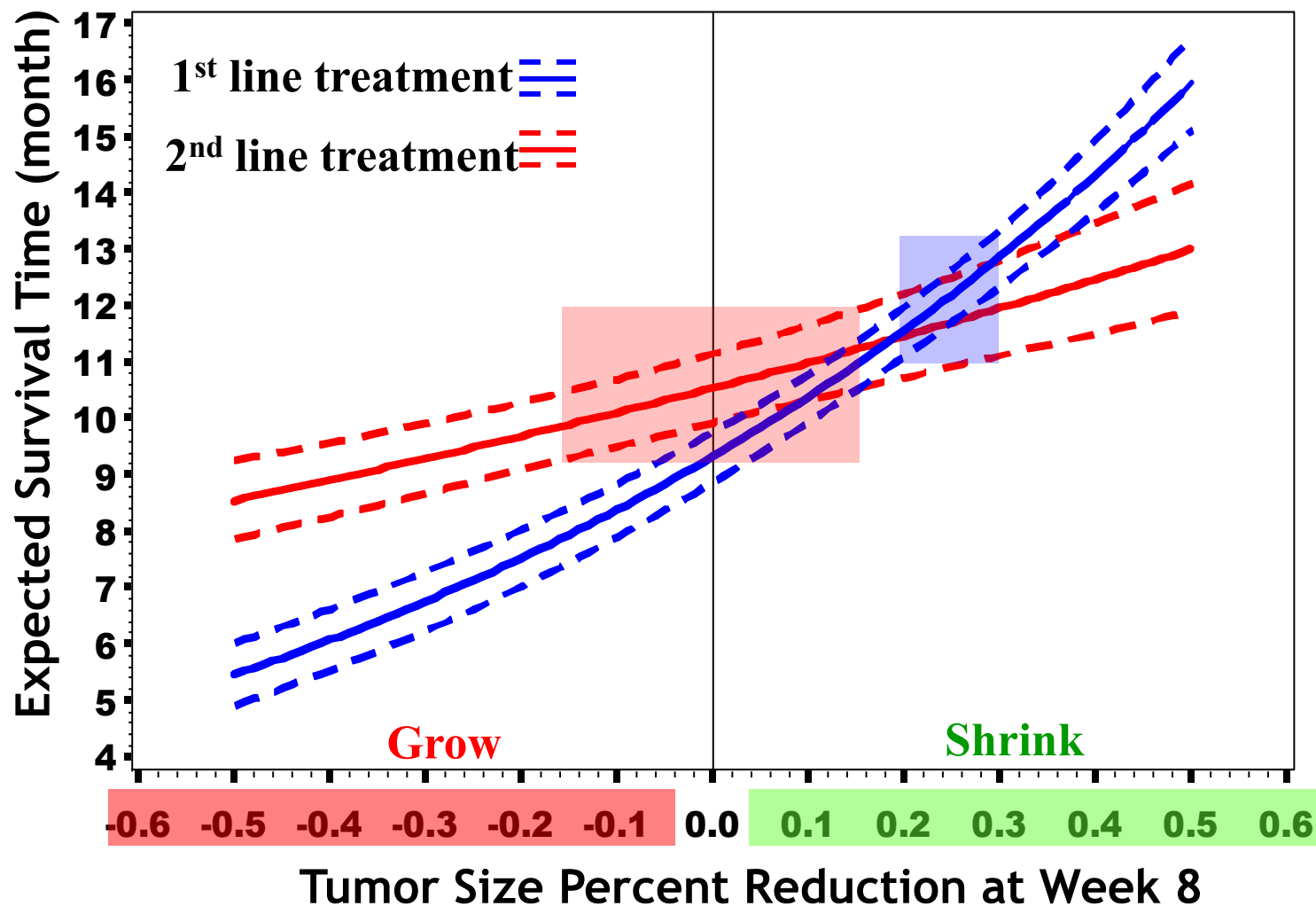
Wang Y et al, FDA Clin. Pharmacol. Advisory Committee meeting, Rockville, March 18, 2008

<http://www.fda.gov/ohrms/dockets/ac/cder08.html#PharmScience>

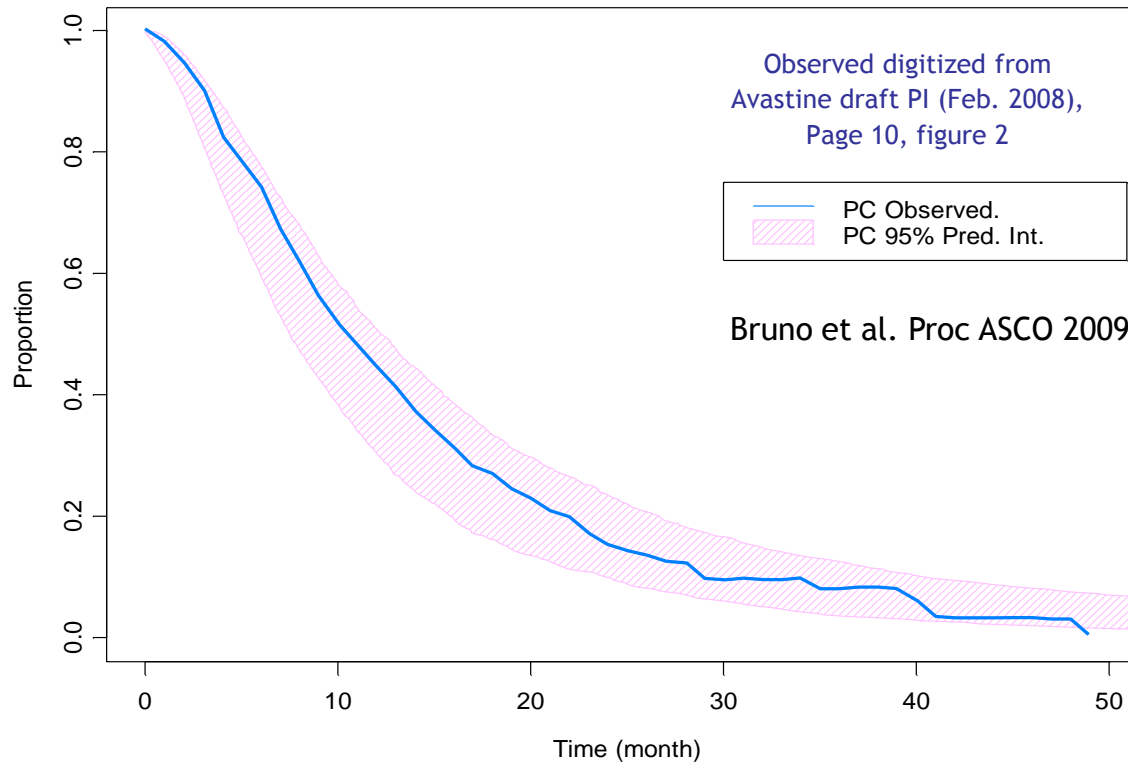
Wang Y et al. Clin. Pharmacol. Ther. 86, 167-174, 2009

1st line and 2nd line models

Wang et al. Clinical Pharmacology Advisory Committee. March 18-19, 2008



Simulation of the Sandler's study (New Engl J Med 355, 2542-2550, 2006) (paclitaxel + carboplatin vs. paclitaxel + carboplatin + bevacizumab)



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

Success in simulating the Amgen MONET1 study of motesanib plus chemotherapy in non-small-cell lung cancer

Last year we simulated an ongoing Phase III study based of Phase II data using the FDA model

- We published the simulations as an abstract at ASCO¹ and a poster at PK/UK²

On March 30, 2011, Amgen released that the study failed³

Our simulations matched the outcome pretty well:

- They got: hazard ratio (95% CI): 0.90 (0.78 - 1.04)
- We predicted: hazard ratio (95% CI): 0.87 (0.71 - 1.10)

1 - Claret et al.

http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=47606

2 - Claret et al. http://www.pkuk.org.uk/ContentImages/PKUK_Programme_and_Abstracts_2010.pdf

3 - http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1544107

Value of survival simulations

The survival probability distribution of an investigational treatment can be quantified based on early tumor shrinkage clinical data (typically available in Phase Ib or II)

- Can be a new NCE
- Can be a new combination treatment

An arm 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

Bruno R. and Claret L. FDA Clinical Pharmacology Advisory
Committee Meeting, Rockville, March 18, 2008

A new paradigm: Change in tumor size as a biomarker to assess drug effect in early clinical oncology studies

Design of Phase II Cancer Trials Using a Continuous Endpoint of Change in Tumor Size:

Theodore G. Karrison, Michael L. Maitland, Walter M. Stadler, Mark J. Ratain
J Natl Cancer Inst 2007;99:1455–61

PERSPECTIVES

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 86 NUMBER 2 | AUGUST 2009

On the Use of Change in Tumor Size to Predict Survival in Clinical Oncology Studies: Toward a New Paradigm to Design and Evaluate Phase II Studies

R Bruno¹ and L Claret¹

Change in tumor size as an endpoint in early clinical 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
- Requires 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
- Can also support interim analyses in Phase II or Phase III studies

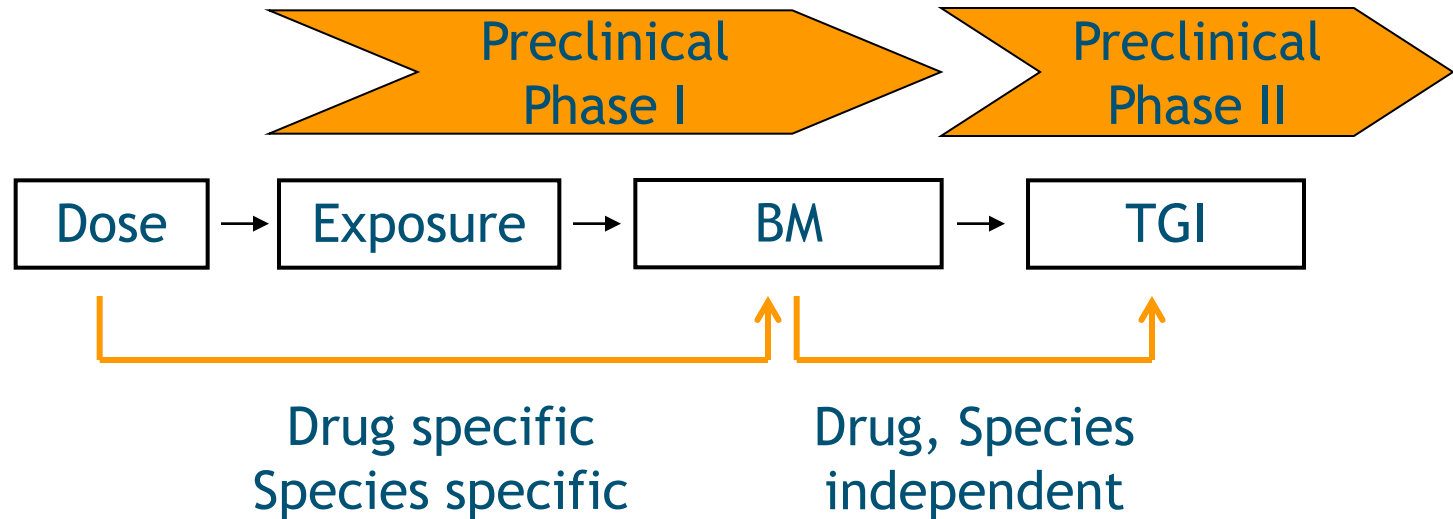
In a simulation study (Claret et al. PAGE 2008)

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

Translational pharmacology:

The exposure - biomarker response - TGI model:

A bridge from preclinical to clinical response



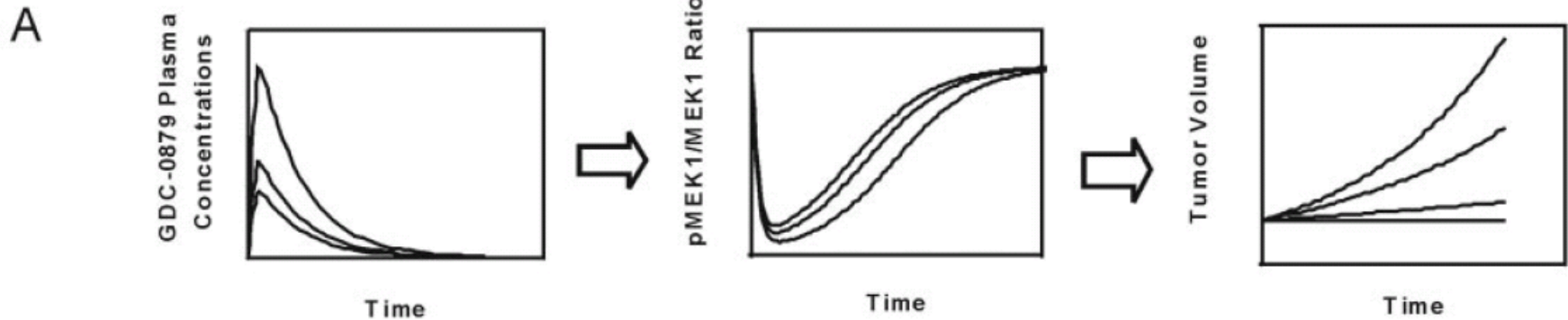
Biomarker responses as a potential link between preclinical and clinical responses

Biomarker responses to assess targets for Phase I studies and to predict phase II response (e.g. probability to achieve 30% shrinkage)

Scale up efficacy from lead to backups (relative potency estimates)

GDC-08769, a B-RAF inhibitor

Wong et al. JPET 329:360–367, 2009



A threshold of $>40\%$ pMEK1 inhibition is required for tumor growth inhibition, and a minimum of $\sim 60\%$ pMEK1 inhibition is required for stasis in A375 xenografts treated with GDC-0879.

Question: Biomarker response in tumor biopsies vs. surrogate tissues

- Back-translation exercises are ongoing

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Pharsight

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Backups

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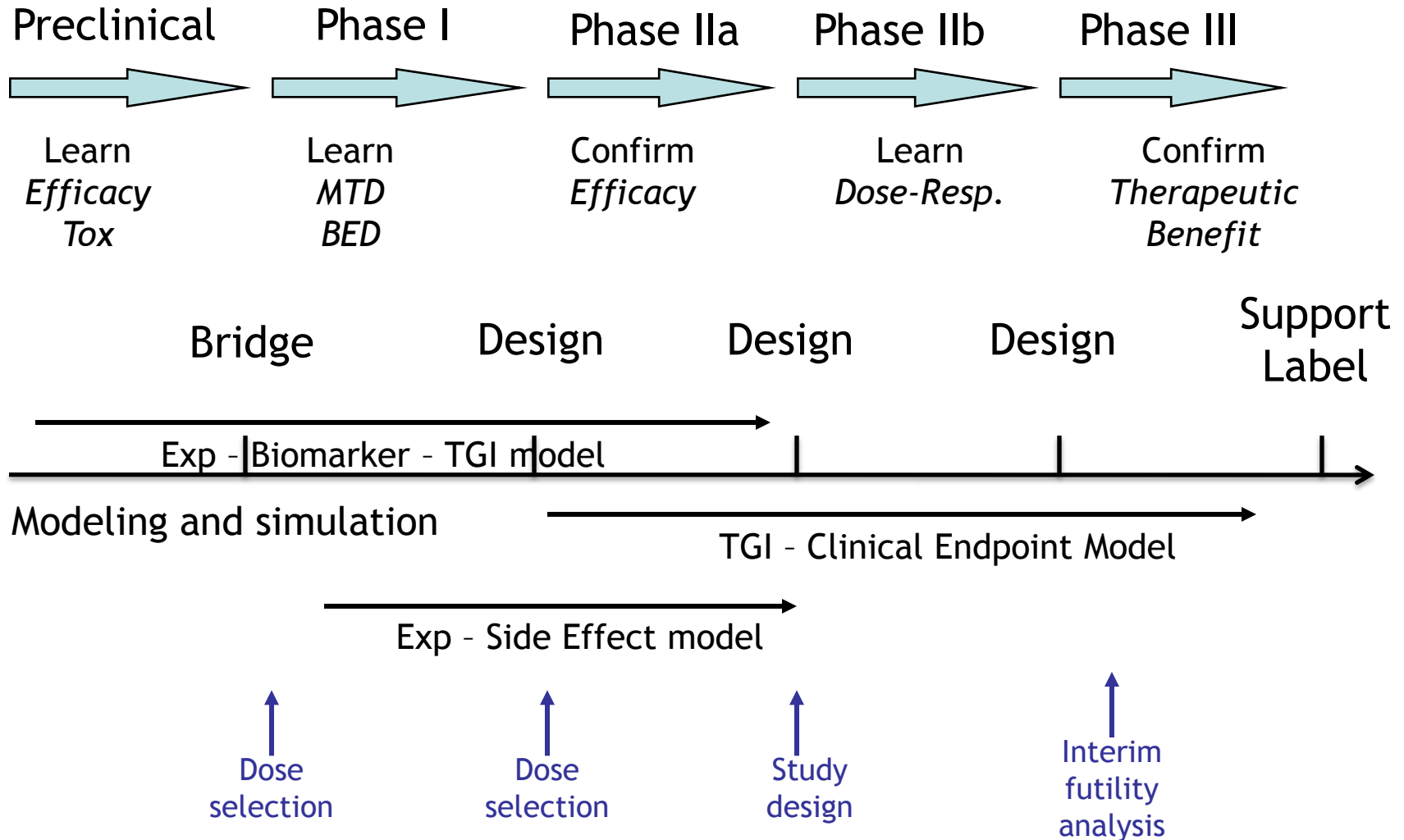
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Integration of modeling activities and drug development steps (by Lew Sheiner, CPT, 1997)



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 four NSCLC registration trials (Wang et al. Clin Pharmacol Ther, 86, 167-174, 2009)

- **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)

Multiple Myeloma model goals (Celgene)

To use serum M protein level as a marker of tumor burden and develop a modeling framework similar to the one used in solid tumors

Leverage lenalidomide multiple myeloma Phase III data

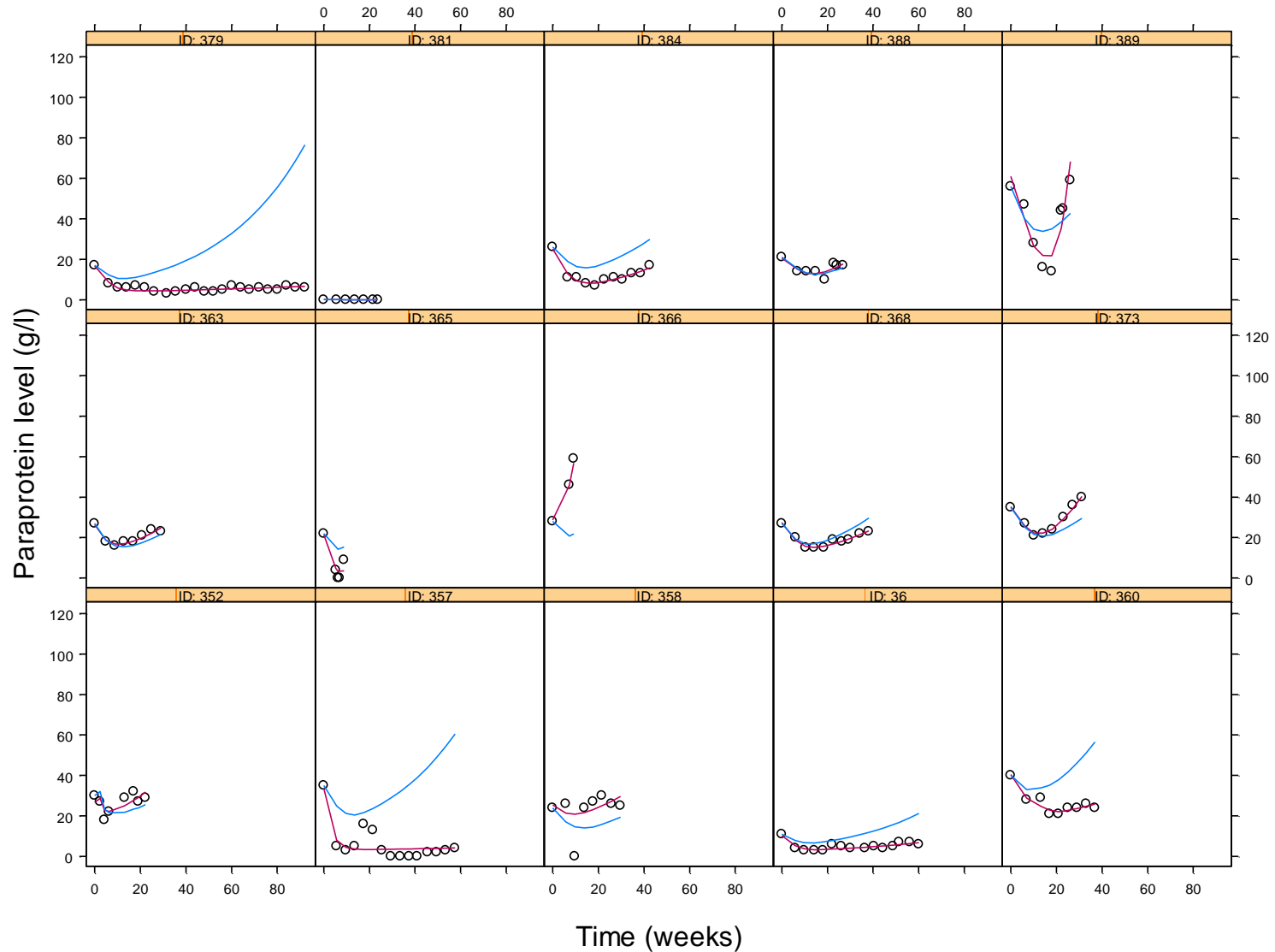
- To develop a drug-specific tumor growth inhibition model for dexamethasone based on serum M-Protein
- To develop drug-independent models linking early change in M-protein level (end of cycle 2, week 8) to clinical response (survival and PFS)
 - Two phase III studies (over 700 patients)

To support drug development of new drug candidates in multiple myeloma

Jonsson et al. PAGE 2010

Claret et al. Leiden 2010

Example of TGI model fit to individual serum M-protein data (dots=observed, blue= population pred, red= individual predictions)



Multiple myeloma survival model

A lognormal distribution provided the best fit of the data for both survival

$$T \sim \text{pdf}(t)$$

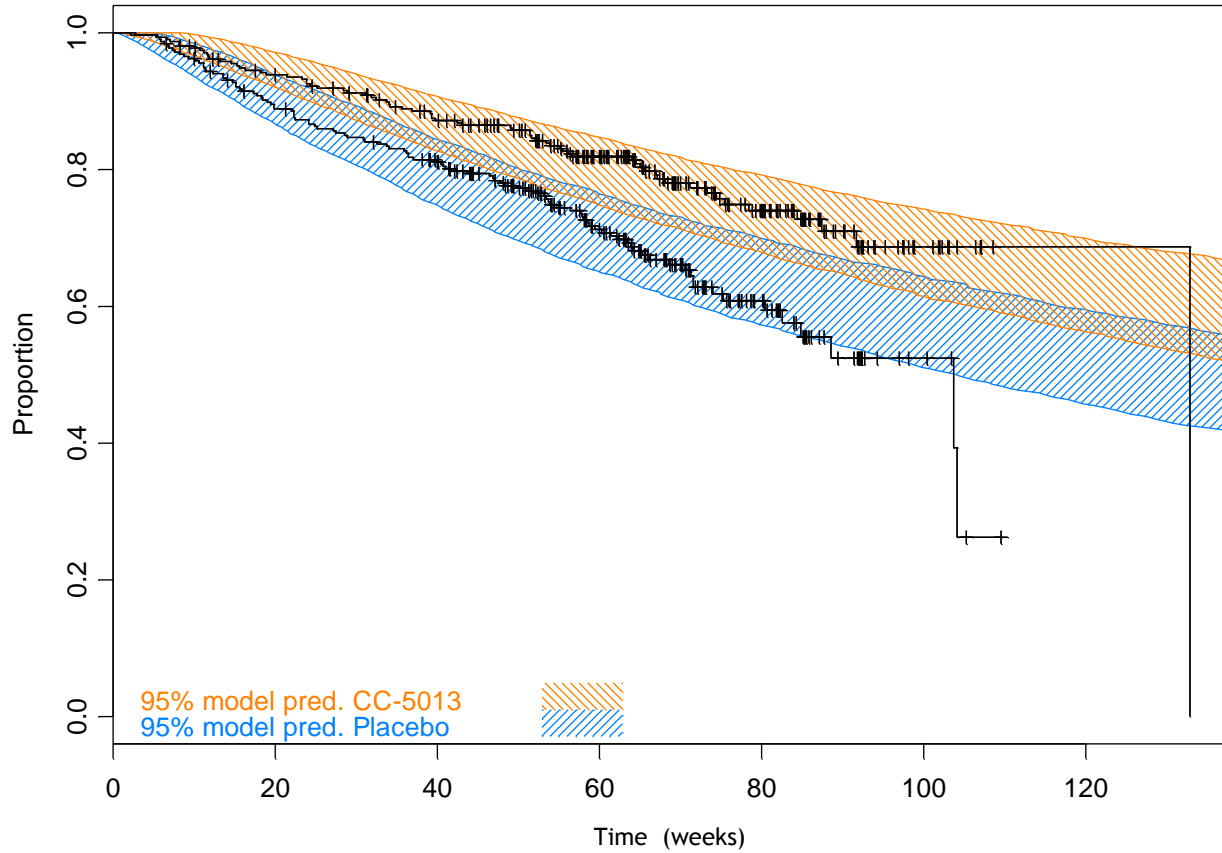
$$\log T \sim N(\alpha, \sigma^2)$$

α is a function of covariates

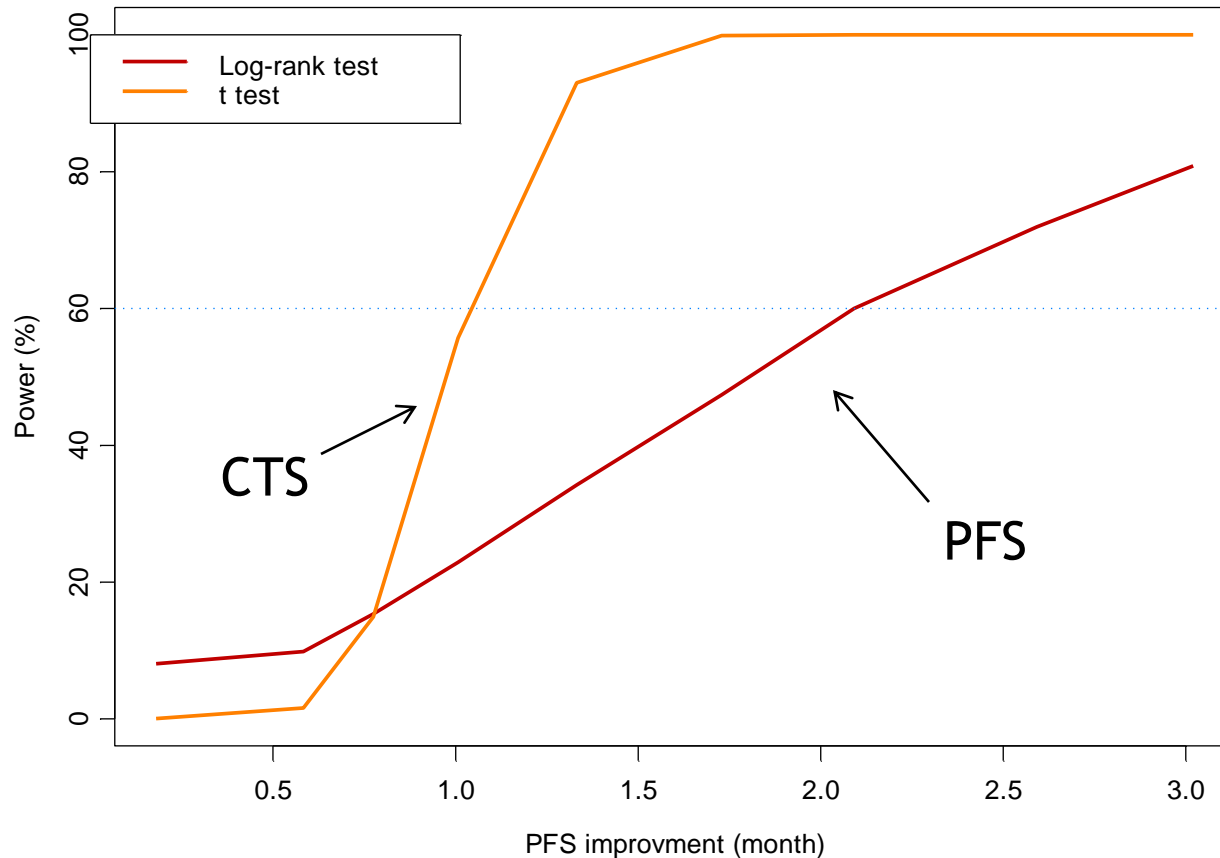
Backward deletion log-likelihood ratio test $p < 0.01$

| | Estimate | SE |
|------------|----------|-------|
| Intercept | 3.317 | 0.552 |
| Pred SMP2 | -0.996 | 0.158 |
| ECOG | -0.648 | 0.194 |
| Albumin | 0.464 | 0.135 |
| Hemoglobin | 0.108 | 0.041 |
| Creatinine | -0.582 | 0.179 |
| Log(scale) | 0.202 | 0.059 |

Survival model qualification



Power of a 120-patient randomized Phase II with an investigational treatment vs. docetaxel (2:1 randomization) in 2nd line NSCLC to demonstrate a pre-specified PFS benefit



Claret L, Andre V, de Alwis D, Bruno R. Modeling and simulation to assess the use of change in tumor size as primary endpoint in Phase II studies in oncology. PAGE 17. 2008.