Drug/Disease Modeling & Simulation in Oncology

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Modeling & Simulation

RESEARCH

DEVELOPMENT

PK and PK/PD

Empirical to mechanistic

Drug

- Efficacy
- Safety
- PK/PD

Trial

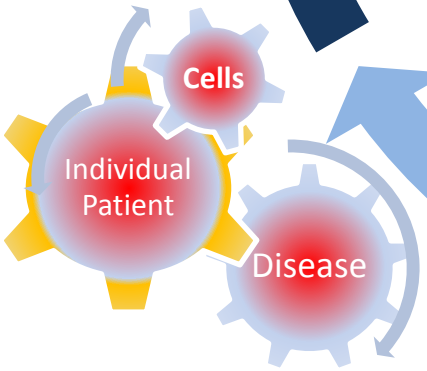
- Population
- Endpoints
- Enrollment
- Drop-out

Disease

- Targets
- Biomarkers
- Progression

Systems Approach

The right treatment for the right patient

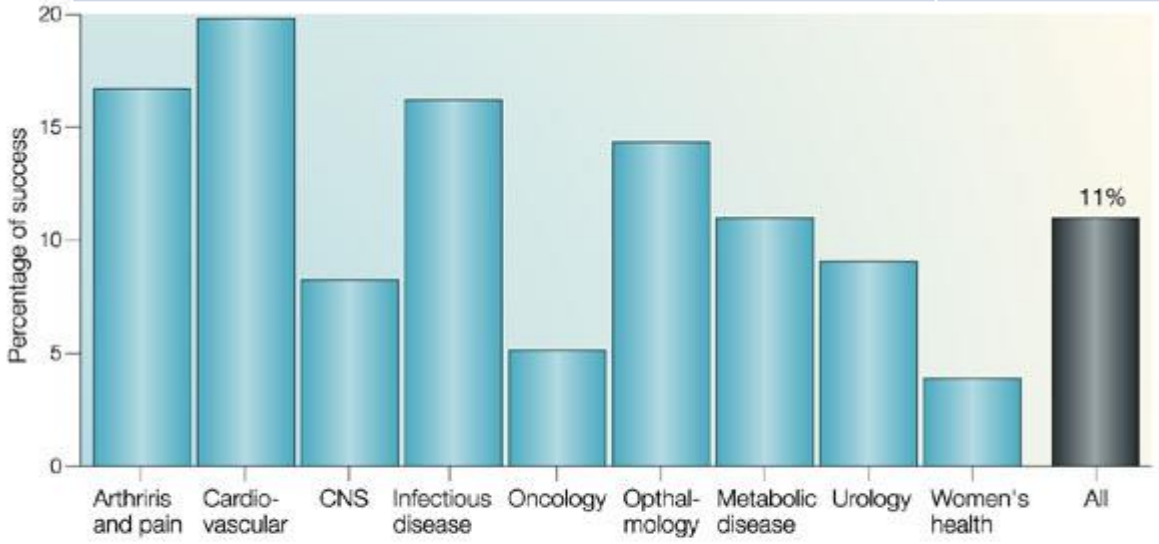


Drug Approvals

New Treatment Options & Companion Diagnostics

Drug/Disease Modeling in Oncology

Problems	Tools to Bring Innovative Solutions
• High Phase 3 attrition rates in oncology drug development • Heterogeneity in clinical outcomes • Challenging adaptive nature of the disease	• Biomarkers • Genomics & …omics • Imaging • **Drug/disease M&S**



Kola & Landis (2004) Nature Reviews | Drug Discovery

Drug/disease M&S Aims
Predict Probability of Success in Phase 3 using Phase 2 data
Using improved **efficacy surrogates** from **longitudinal disease progression models**
Assess exposure/effect relationships for efficacy & safety to determine optimal dose
Incl predictive and prognostic (bio)markers

Milestones: Tumor size can predict Overall Survival

Response rate (dichotomous) has been a poor predictor of Phase 3 success/failure.	Longitudinal tumor size measurements from conventional RECIST measurements are key: Baseline tumor size and change in tumor size (CTS) at first assessment can predict OS.

2006:
- An early prediction of Phase 3 OS in CRC and Breast Cancer is obtained from Phase 2 tumor size data

2008:
- Extension to PFS in NSCLC
- Simulations showed improved power using TS over a conventional PFS study
- Effect of exposure

2009:
- Addtl examples in ovarian and thyroid cancer
- Framework extensions for prediction of PFS and ORR

2007: A drug independent disease model for OS in NSCLC developed from 3,398 pts is presented by the FDA

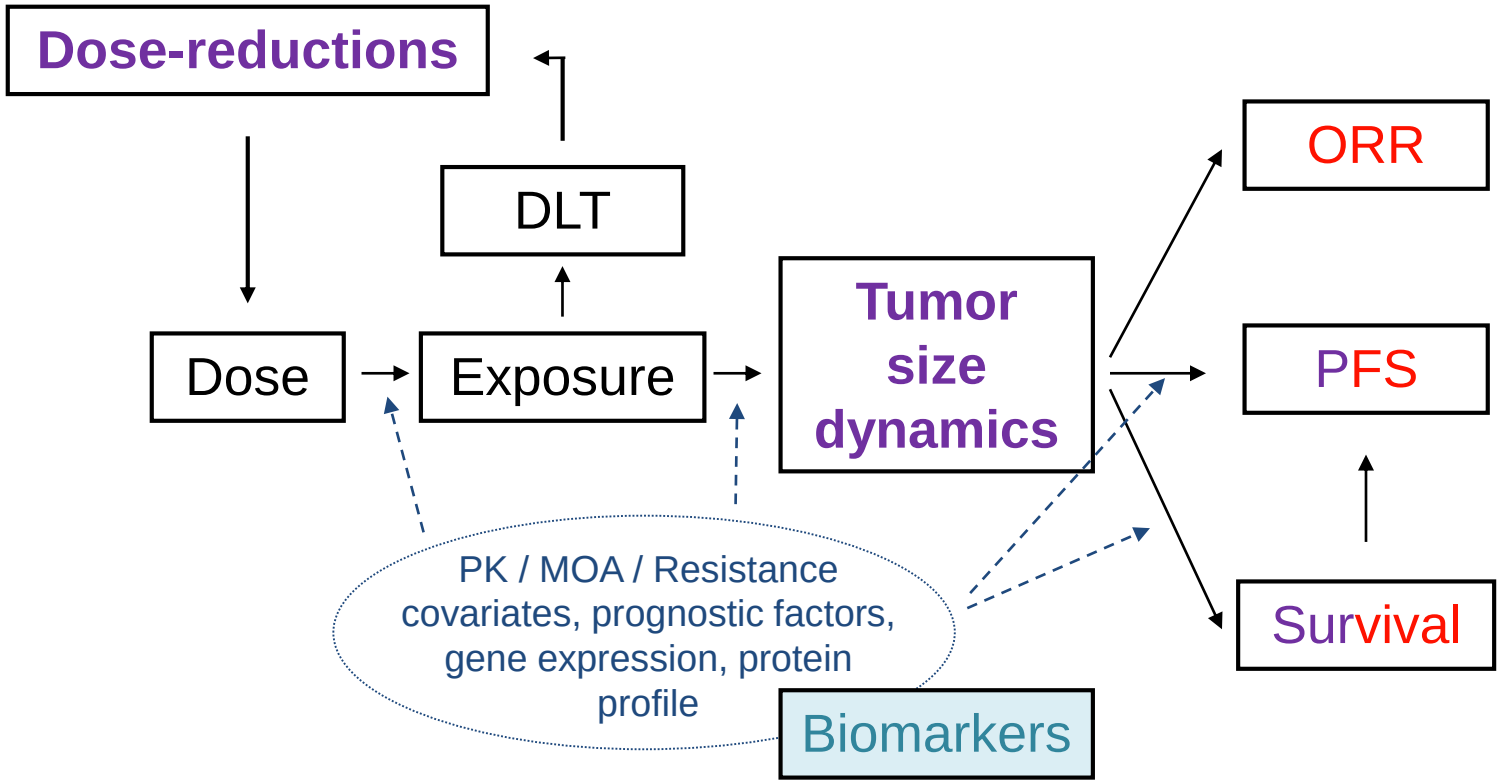
2008: FDA Clinical Pharmacology Advisory Committee

2009-2010: Manuscripts

2007: Randomized Ph2 using CTS as primary endpoint proposed.

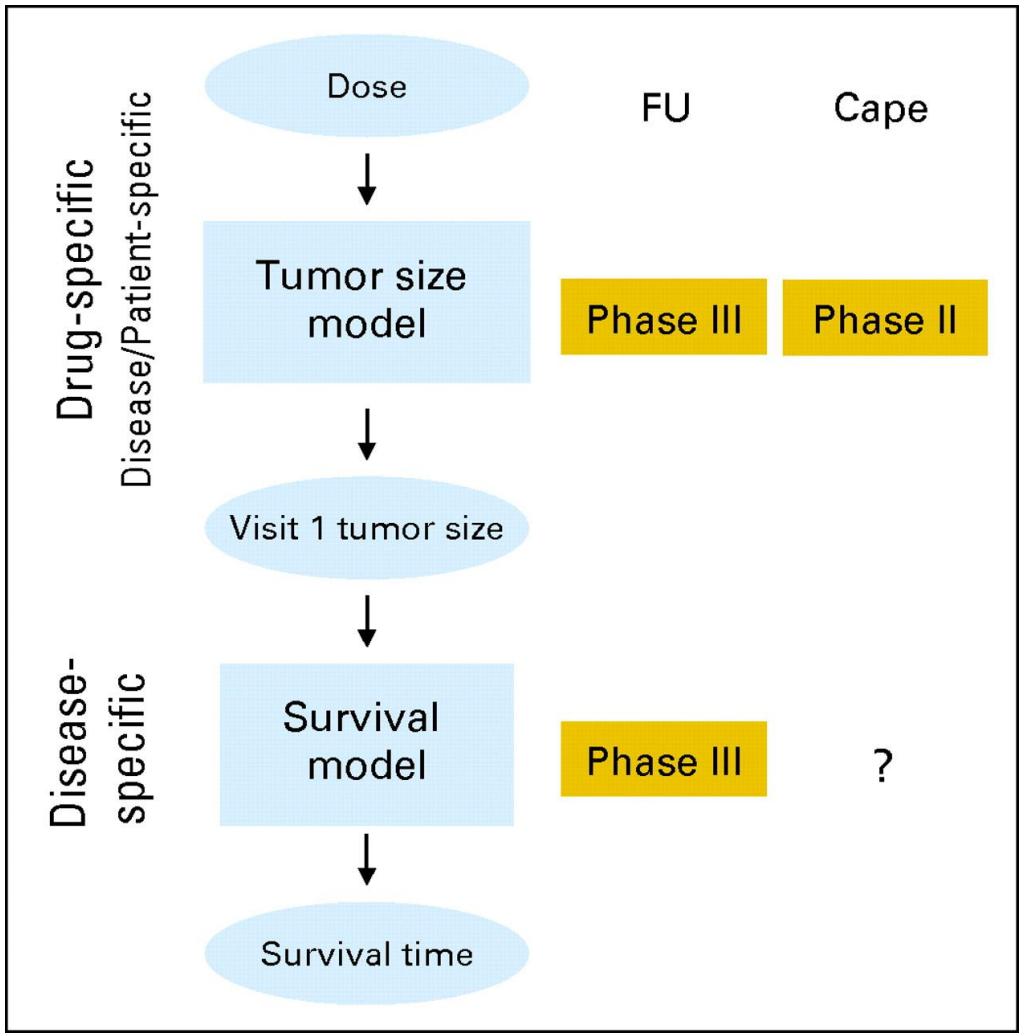
2011

A drug-disease modeling framework to predict clinical endpoints



Adapted from: Claret, Bruno, Lu et al, ASCO2009

Scheme for simulating a phase III study on the basis of phase II data of an investigational agent (here, capecitabine [Cape]) and historical phase III data of a reference drug (fluorouracil [FU]).



Claret L et al. JCO 2009;27:4103-4108

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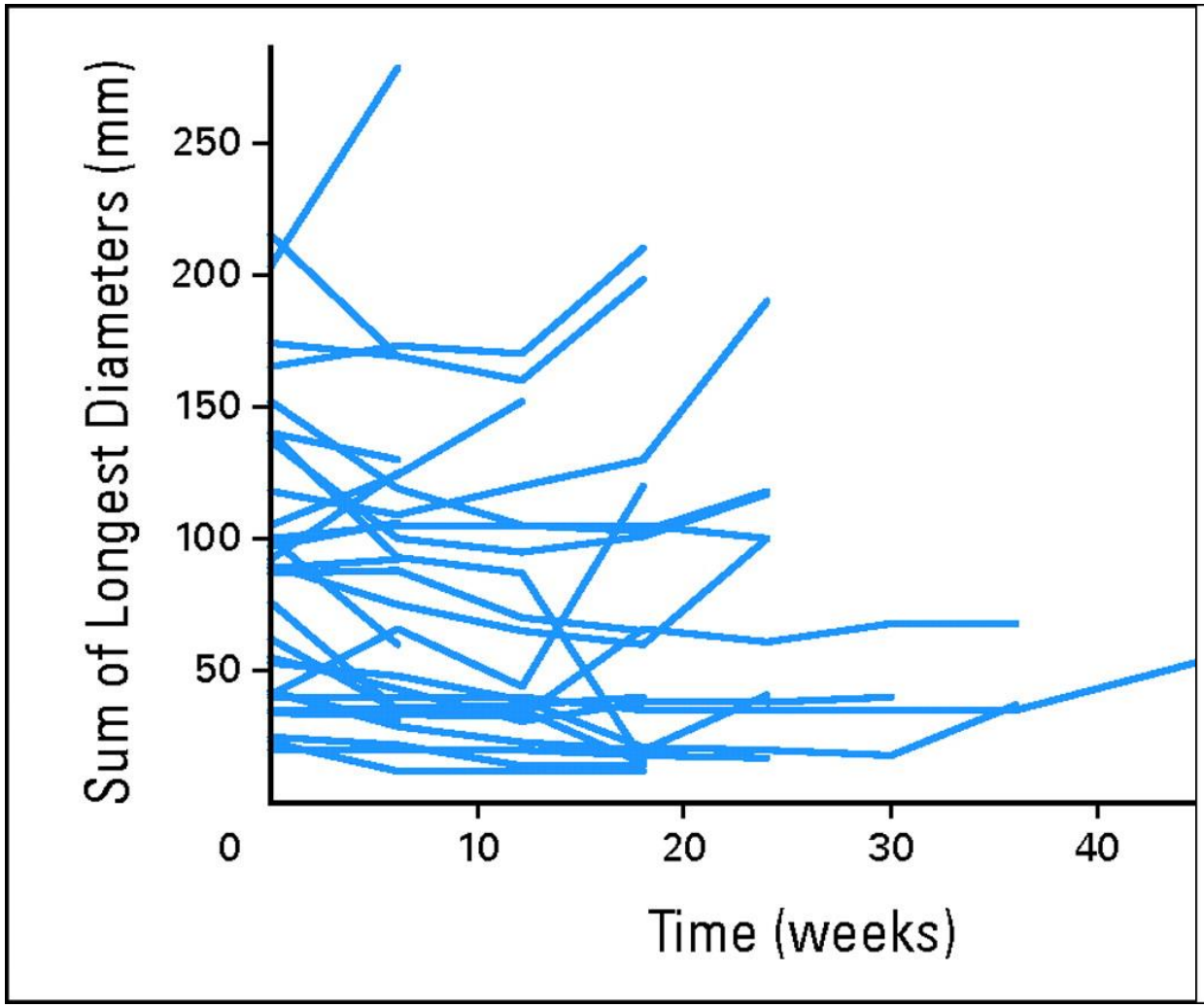
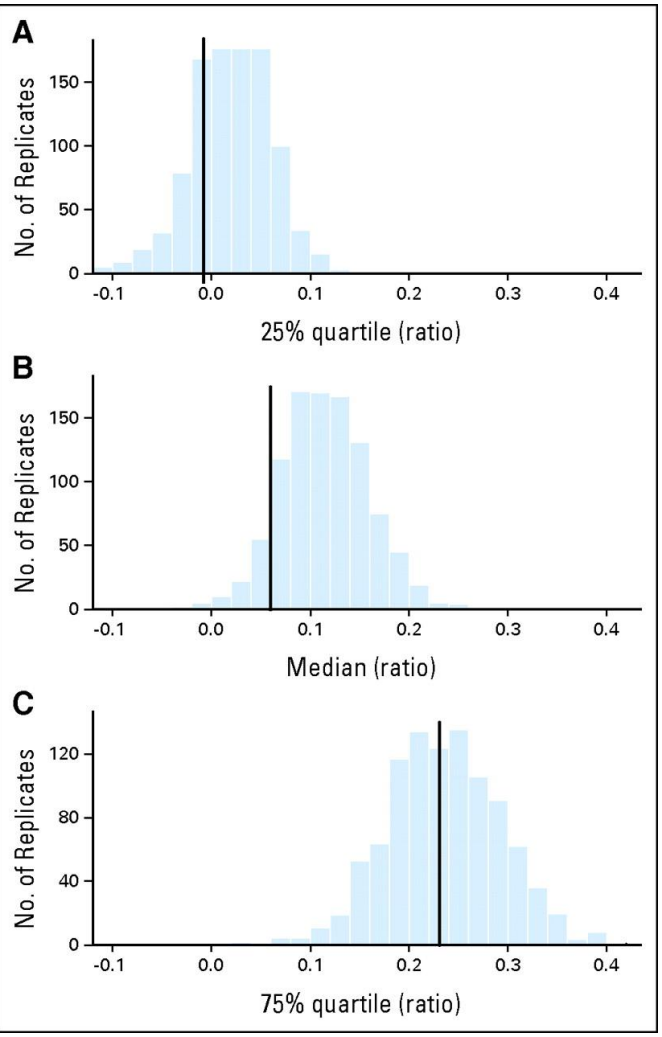
M&S of Tumor Size





Claret L et al. JCO 2009;27:4103-4108 JOURNAL OF CLINICAL ONCOLOGY

Mathematics of Population TS Models

Yaning Wang (FDA)

Linear growth (progression) and exponential tumor shrinkage:

$$TS_i(t) = BASE_i \times e^{-SRi \times t} + PR_i \times t + e^{(\varepsilon i)}$$

- Where, baseline TS $BASE_i$ = M_BASE x $e^{(\eta i)}$, and tumor shrinkage rate SR_i and growth rate PR_i are described similarly.
- Flexible model, developed for interpolation.

Laurent Claret (Pharsight)

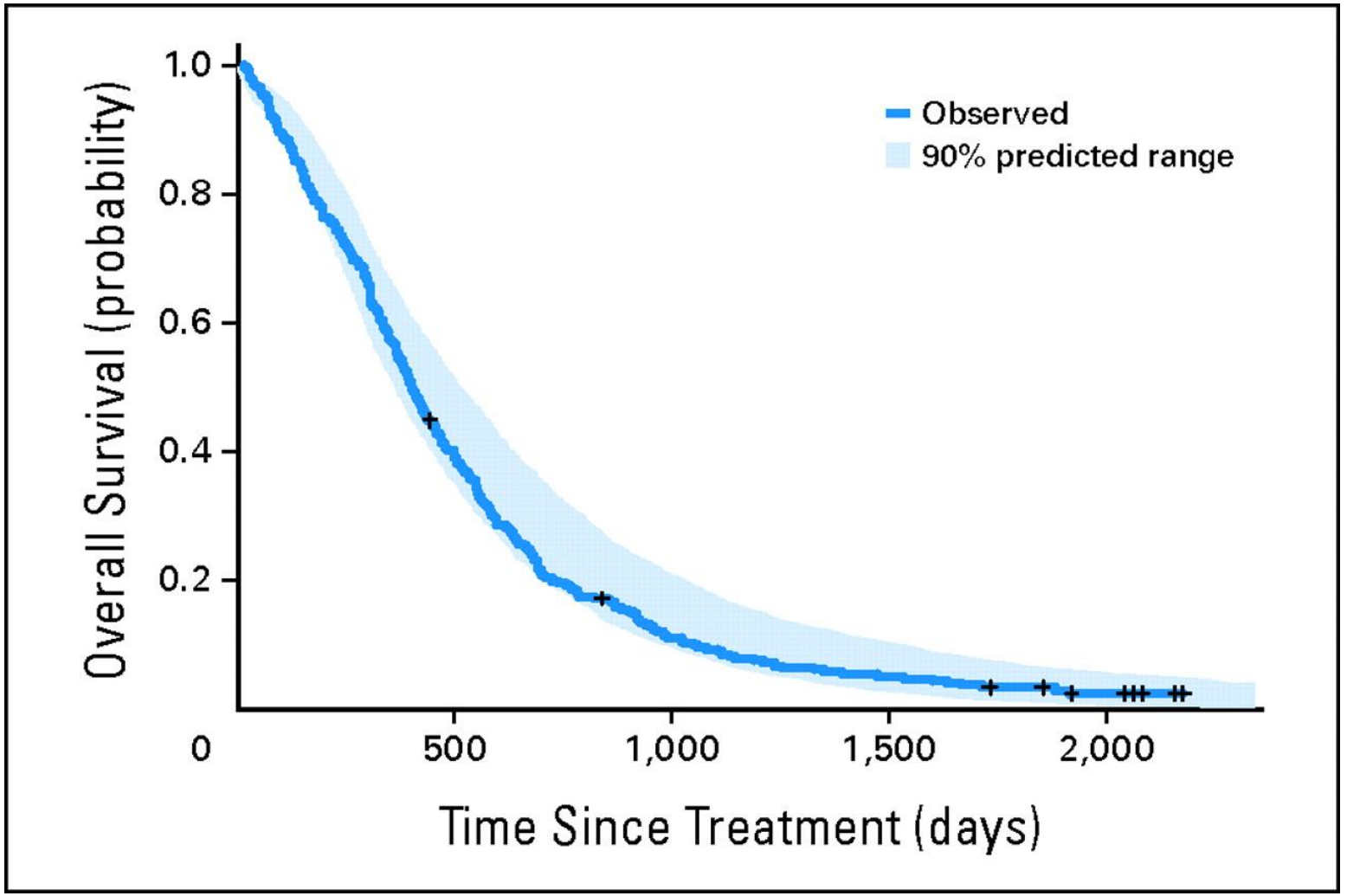
Exponential growth, proportional shrinkage and a separate resistance term

$$dTS_i/dt = K_L + K_D \times PK_{(t)} \times R_{(t)} \times TS_{i(t)}$$

- Where, $TS_{i(0)}$ = M_BASE, and tumor shrinkage rate K_D and growth rate K_L are described as for Wang and

- $\mathbf{PK_{(t)}}$ denotes exposure at time t
- Resistance function $\mathbf{R_{(t)}} = e^{-\lambda \times t}$

The 90% prediction interval (light blue area) and observed (line) survival curve for capecitabine in the phase III study.



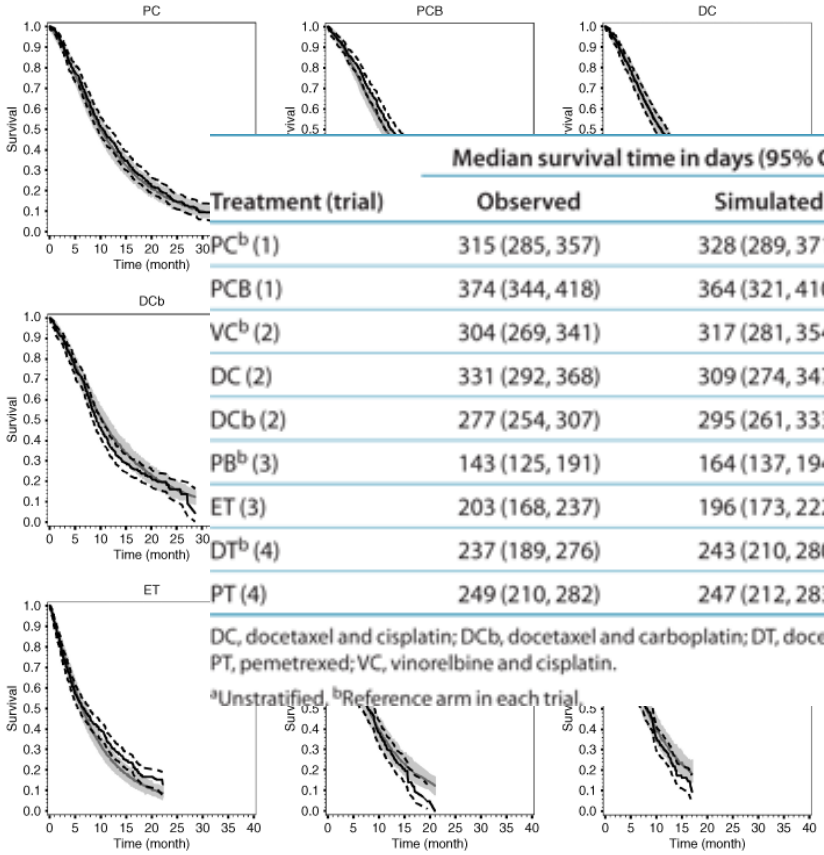
Claret L et al. JCO 2009;27:4103-4108

Yaning Wang's (FDA) NSCLC Model

- OS in NSCLC predicted from
  A. Baseline tumor size, ECOG performance status and early assessment of week 8 change in tumor size.
  B. ECOG where post-treatment TS is missing.
- 3,398 pts from 4 trials and 9 different treatment arms incl. placebo.
- A disease model as good OS predictions are obtained without additional drug-specific terms.
- Tumor-size interpolated using drug-specific parameters.
- Published on-line with covariance matrix to enable M&S to fully utilise the model, also simulating from parameter uncertainty.

Elucidation of Relationship Between Tumor Size and Survival in Non-Small-Cell Lung Cancer Patients Can Aid Early Decision Making in Clinical Drug Development

Y Wang[1], C Sung[1,2], C Dartois[1], R Ramchandani[2], BP Booth[2], E Rock[3] and J Gobburu[1]



Treatment (trial)	Median survival time in days (95% CI)		Survival benefit in days (95% CI)		Hazard ratio[a] (95% CI)	
	Observed	Simulated	Observed	Simulated	Observed	Simulated
PC[b] (1)	315 (285, 357)	328 (289, 371)				
PCB (1)	374 (344, 418)	364 (321, 410)	59	41 (−5, 84)	0.8 (0.69, 0.93)	0.88 (0.78, 1.01)
VC[b] (2)	304 (269, 341)	317 (281, 354)				
DC (2)	331 (292, 368)	309 (274, 347)	27	−7 (−55, 41)	0.89 (0.76, 1.04)	1.04 (0.9, 1.19)
DCb (2)	277 (254, 307)	295 (261, 333)	−27	−22 (−71, 24)	1.03 (0.88, 1.2)	1.07 (0.93, 1.25)
PB[b] (3)	143 (125, 191)	164 (137, 194)				
ET (3)	203 (168, 237)	196 (173, 222)	60	32 (2, 64)	0.76 (0.65, 0.91)	0.83 (0.7, 0.96)
DT[b] (4)	237 (189, 276)	243 (210, 280)				
PT (4)	249 (210, 282)	247 (212, 283)	12	4 (−40, 48)	0.99 (0.82, 1.2)	0.99 (0.85, 1.17)

DC, docetaxel and cisplatin; DCb, docetaxel and carboplatin; DT, docetaxel; ET, erlotinib; PB, placebo; PC, paclitaxel and carboplatin; PCB, paclitaxel, carboplatin, and bevacizumab; PT, pemetrexed; VC, vinorelbine and cisplatin.

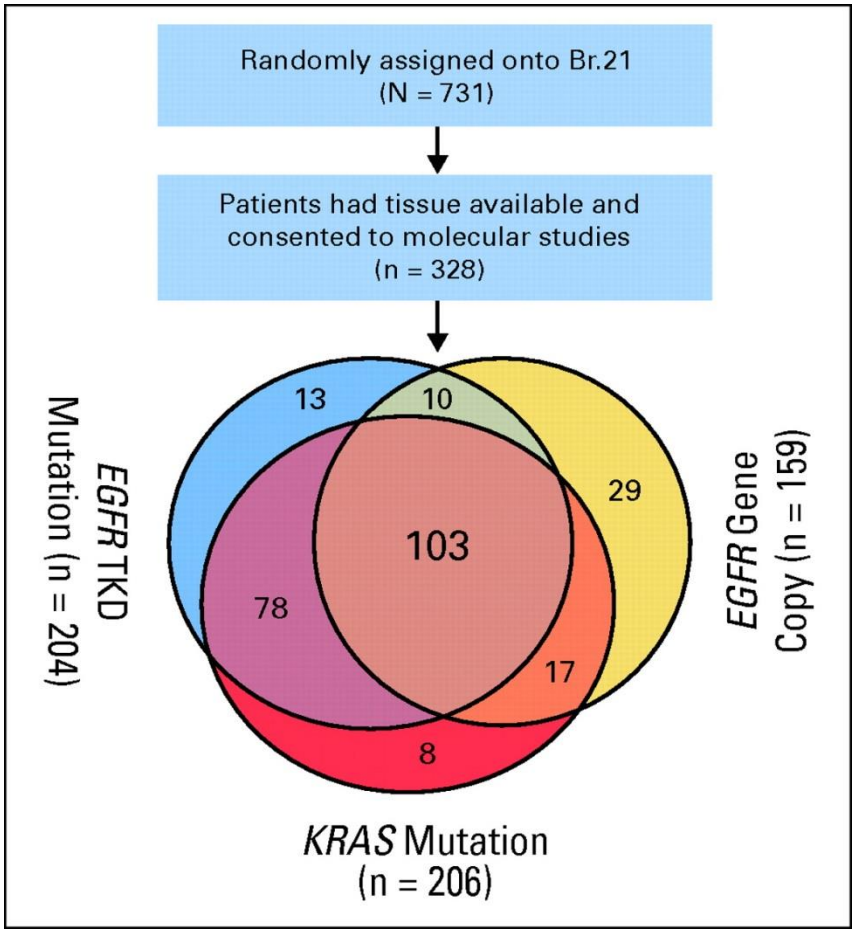
[a]Unstratified, [b]Reference arm in each trial.

Yaning Wang, CP&T, 2009, 86(2): 167-174

Incorporating Biomarkers in the Longitudinal Tumor Size Model

- Erlotinib is particularly active in patients with activating EGFR mutations and/or overexpression and tumor shrinkage is observed (almost) exclusively for this subgroup.

- Yaning Wang estimated separate SR_i parameters for two subpopulations, with greater shrinkage in 11% of the population.
- Potentially EGFR status could have been incorporated as a predictive covariate for SR_i to provide quantitative assessment of associations between EGFR status and either parameters of drug sensitivity and/or disease progression.



Yaning Wang, CP&T, 2009, 86(2): 167-174

Zhu C et al. JCO 2008;26:4268-4275 JOURNAL OF CLINICAL ONCOLOGY

Incorporating Biomarkers in the Longitudinal Tumor Size Model (ACoP 2011)

PKPD Modeling of VEGF, sVEGFR-2, sVEGFR-3 and sKIT as Biomarkers of Tumor Response Following Sunitinib Treatment in GIST

UPPSALA UNIVERSITET

Emma K. Hansson[1], Paul Westwood[1], Michael Amantea[2], Peter A. Milligan[2], Mats O. Karlsson[1], Lena E. Friberg[1]

[1]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, [2]Pfizer Global Research and Development

Background and Objectives

Identified objective measurements of early response to treatment could ultimately lead to a biomarker-guided treatment optimization strategy in order to increase treatment outcome.

This study aimed to investigate **dose-exposure-biomarker-tumor response relationships** following treatment with the anti-angiogenic drug Sutent® (sunitinib) with focus on the **potential biomarkers VEGF, sVEGFR-2, sVEGFR-3 and sKIT** (Figure 1).

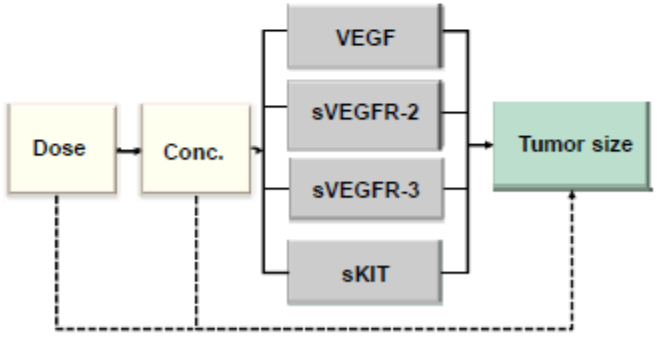


Fig 1. Investigated relationships for the evaluation of VEGF, sVEGFR-2, sVEGFR3 and sKIT as biomarkers of tumor response following sunitinib treatment.

Methods

Results

Table 1. Tumor model parameter estimates

Parameter	Estimate	RSE (%)	IIV (CV %)	RSE (%)
K_L (week^{-1})	0.012	10	54	19
K_{Drug} (week^{-1} x AUC^{-1})	0.0050	40	119	12
K_{sKIT} (week^{-1} x pg^{-1} mL)	0.0028	14	243	16
K_{sVEGR3} (week^{-1} x pg^{-1} mL)	0.037	21	-	-
λ (week^{-1})	0.022	27	-	-
Res error (%)	12.5	9.7	-	-

$$\frac{dy}{dt} = K_L \cdot y(t) - (K_{sKIT} \cdot sKIT(t) + K_{sVEGFR3} \cdot sVEGFR3(t) + K_{Drug} \cdot AUC_{0\text{-}24}) \cdot R(t) \cdot y(t)$$

$$R(t) = e^{-\lambda t}$$

$$y(0) = y_0 + residual$$

y(t): Sum of tumor diameters (mm)
R(t): Tumor resistance function
K_L: Tumor growth rate constant
K_{drug}: Tumor size reduction rate constant
K_{sKIT}: Tumor size reduction rate constant
$K_{sVEGFR3}$: Tumor size reduction rate constant
λ: Resistance apparence rate constant

The longitudinal tumor size data following placebo and sunitinib treatment were well characterized. Using the predicted time course (relative to baseline) for **sKIT** as a predictor of drug effect described the longitudinal tumor size data statistically significantly better than dose or daily AUC. However, the model improved significantly when also **AUC** and **sVEGFR-3** were added as predictors (Table 1, Eq.1)

Survey of ClinicalTrials.Gov (03MAY11)

- Search for “change in tumor size” shows applications as
  - Primary endpoints in randomised Ph 2 trials
    - “Change in tumor size from baseline to end of cycle 2 as” in a randomised Ph 2 NSCLC trial of LY2181308 in combination with docetaxel *vs* docetaxel
    - “Change in tumour size at 12 weeks” in a study of AZD4547 plus exemestane in ER+ / FGFR1 breast cancer
  - Secondary endpoints in other Ph2 and 3 trials
  - Primary endpoint in small single arm studies

Future Prospects

- Increased publication of disease models for NSCLC and other cancer types.
- Developing model libraries for control / reference treatments.
- Increased utilisation of tumor size / survival relationships to predict PFS and OS.
- Incorporation of predictive and prognostic biomarkers.
- Synergies with improved imaging modalities to measure disease progression (e.g. volumetric CT and PET).

Summary

- Oncology M&S aims to describe the dynamics of PK, PD effects on the drug target and also on efficacy and safety outcomes.
- Tumour size at baseline and change in tumour size shortly after treatment are a good starting point for modelling OS and PFS.
- Longitudinal / repeated continuous measures preferred over single dichotomous responder classification (in general!).
- M&S framework is a useful drug/development tool to describe
  - Impact of drug on disease as a function of exposure and predictive markers
  - Disease progression as a function of prognostic markers and drug activity
  - Relationship between drug exposure and AEs / dose modifications / drop-outs

Acknowledgements

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- Raymond Miller and Daiichi-Sankyo TMCP / M&S