

On the Use and Value of Drug-Independent Survival Models to Support Clinical Drug Development in Oncology

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Opportunities

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Outline

Drug development in oncology

A drug-disease modeling framework to support drug development in Oncology

- Tumor growth model
- Survival model

Support to end-of-Phase II development decisions: A retrospective project with capecitabine (Roche)

On the use the FDA NSCLC survival model

- A case study based on erlotinib data

Value of the survival simulations

Conclusions

Drug development in oncology

Lots of new drug candidates with new mechanisms of action

- Major advances in understanding the molecular biology and genetics of the disease have led to the so-called “targeted therapies”
- Highly competitive market

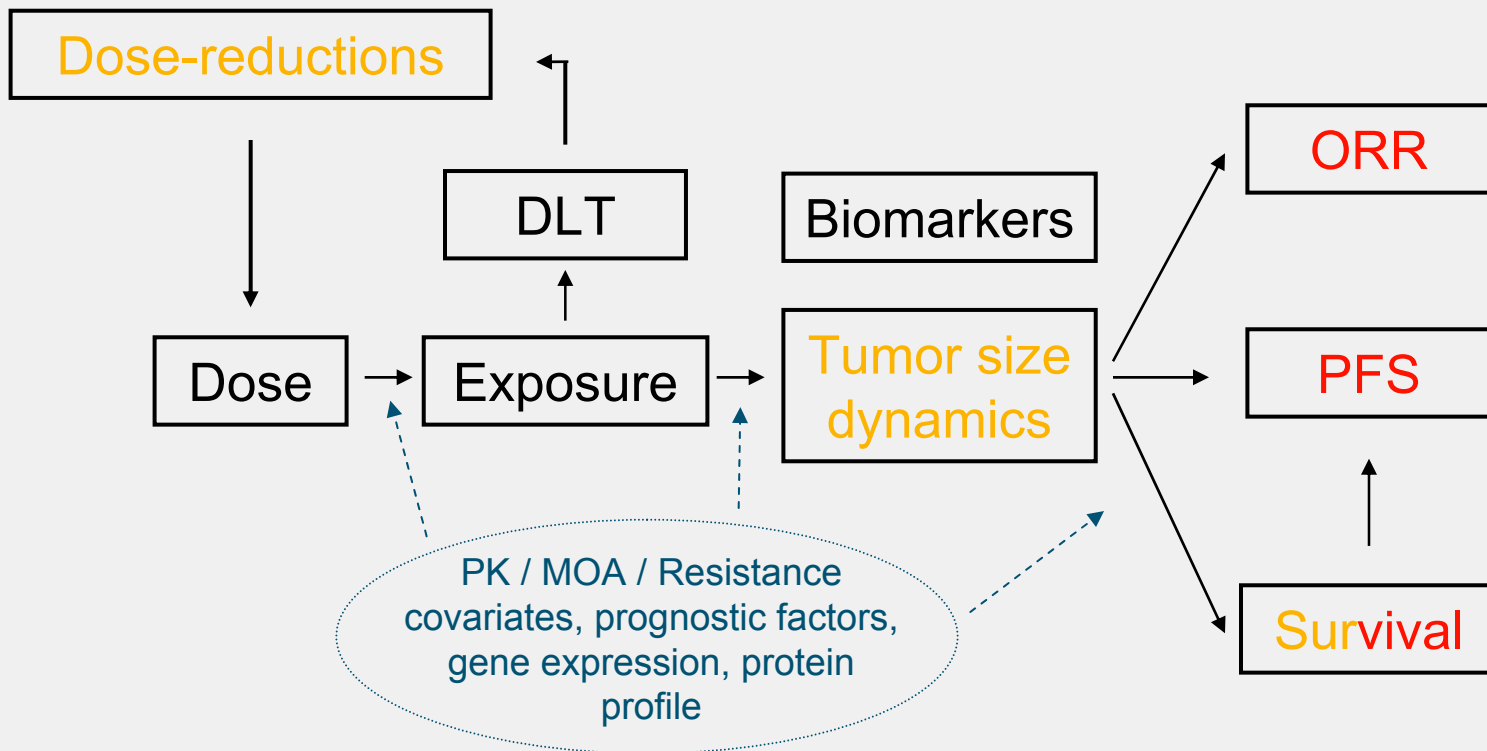
Empirical selection of dose and dosing schedules

- MTD vs. biologically active dose paradigm in Phase I
- Phase II studies not designed to assess dose-response
 - Typical randomized Phase IIb dose-ranging studies are not conducted in oncology
- Analysis of clinical trial data poorly informative (e.g. response rate, neutropenia grade...)

Limit the ability to learn from early clinical trials

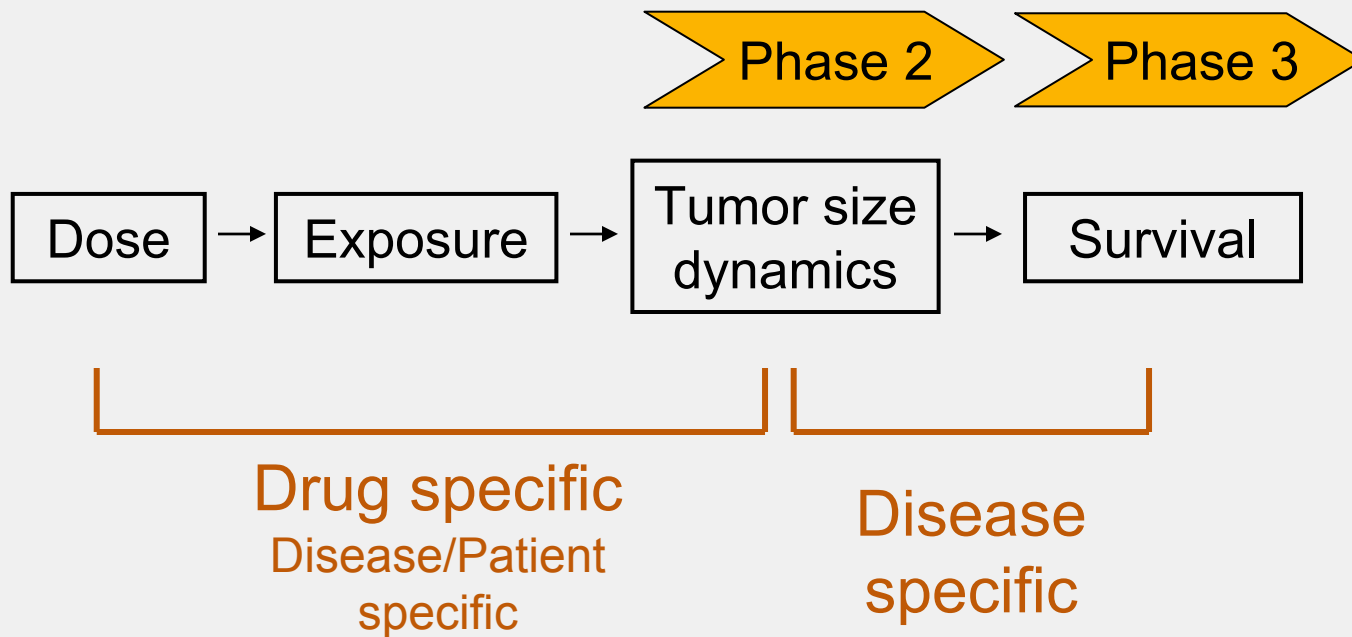
High failure rate in Phase III

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



Models / Endpoints

The exposure - tumor size - survival model: A bridge from Phase II to Phase III endpoints



To predict phase 3 endpoint based on phase 2 endpoint and prognostic factors

Claret L et al. Model-based predictions of expected anti-tumor response and survival in Phase III studies based on phase II data of an investigational agent. Proc ASCO, 24 (18S), 307s (Abs 6025), 2006.

The tumor-size model incorporates tumor growth and drug effect

$$\frac{dy(t)}{dt} = K_L \cdot y(t) - K_D \cdot Exposure(t) \cdot R(t) \cdot y(t) \quad y(0) = y_0$$
$$R(t) = e^{-\lambda t}$$

$y(t)$: Larger diameter at time t (mm), $y(0)$: baseline tumor size

$Exposure(t)$: Exposure at time t (dose, AUC...)

$R(t)$: Resistance function decreasing with time, ranging from 1 (no resistance) to 0 (no more drug action)

λ : Rate constant of resistance appearance

K_L : Tumor growth rate

K_D : Drug constant-cell-kill rate

K_D, λ : drug specific

Y_0, K_L : disease/patient specific

Claret et al. PAGE 15, (Abstract 1004), 2006 [www.page-meeting.org/?abstract=1004]

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 drug (X) to a reference drug (R)
- Based on Phase II data of X and historical data of R

Retrospective project:

- To simulate:
 - Phase III of capecitabine (X) + docetaxel (R) vs. docetaxel in MBC
 - Phase III of capecitabine (X) vs. 5-Fu (R) in CRC

Claret L et al. Model-based predictions of expected anti-tumor response and survival in Phase III studies based on phase II data of an investigational agent. Proc ASCO, 24 (18S), 307s (Abs 6025), 2006.

Simulation of a Phase III study comparing docetaxel to docetaxel + capecitabine in MBC

Model parameter estimation

- **Capecitabine data**
 - Phase II (2 studies, 170 patients)
- **Docetaxel data**
 - Phase III (docetaxel arm, 223 patients)

Simulation

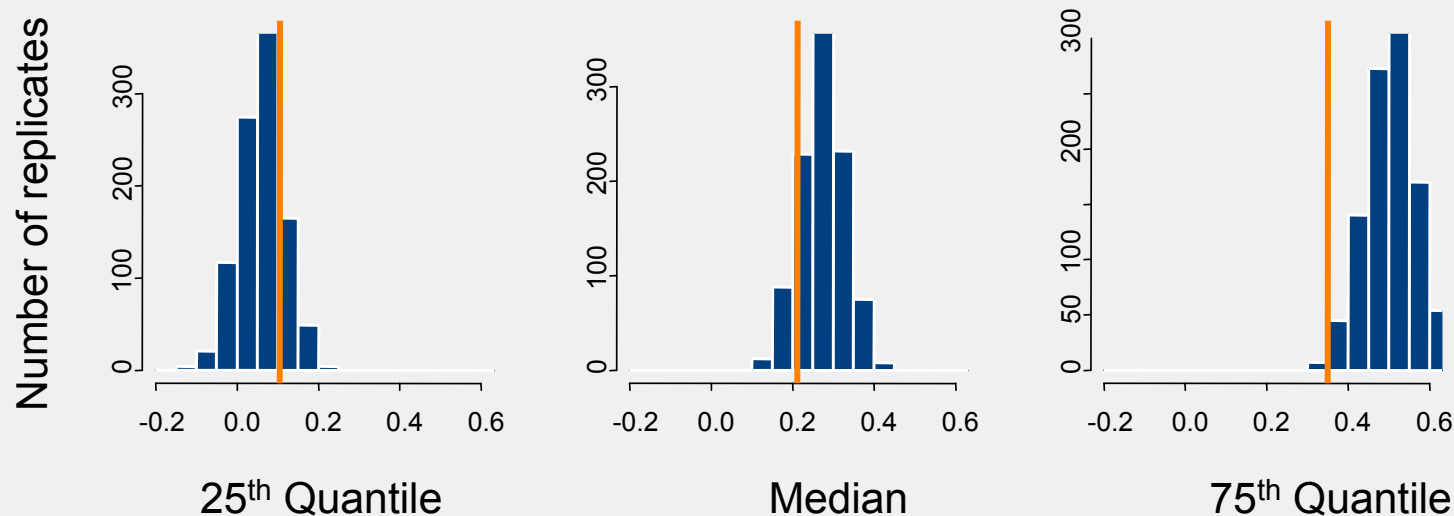
- **Phase III study of capecitabine + docetaxel vs. docetaxel (443 patients, 1000 replicates)**
 - Assumes additive effect for the combination
 - Capecitabine scaled from Phase II to Phase III using disease specific parameters

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

- **Simulations conditioned on observed dose intensity (dosing history)**
- **Drug effect driven by dose**

Simulation of tumor size reduction at week 6 vs. observed in the Phase III study (1000 replicates)

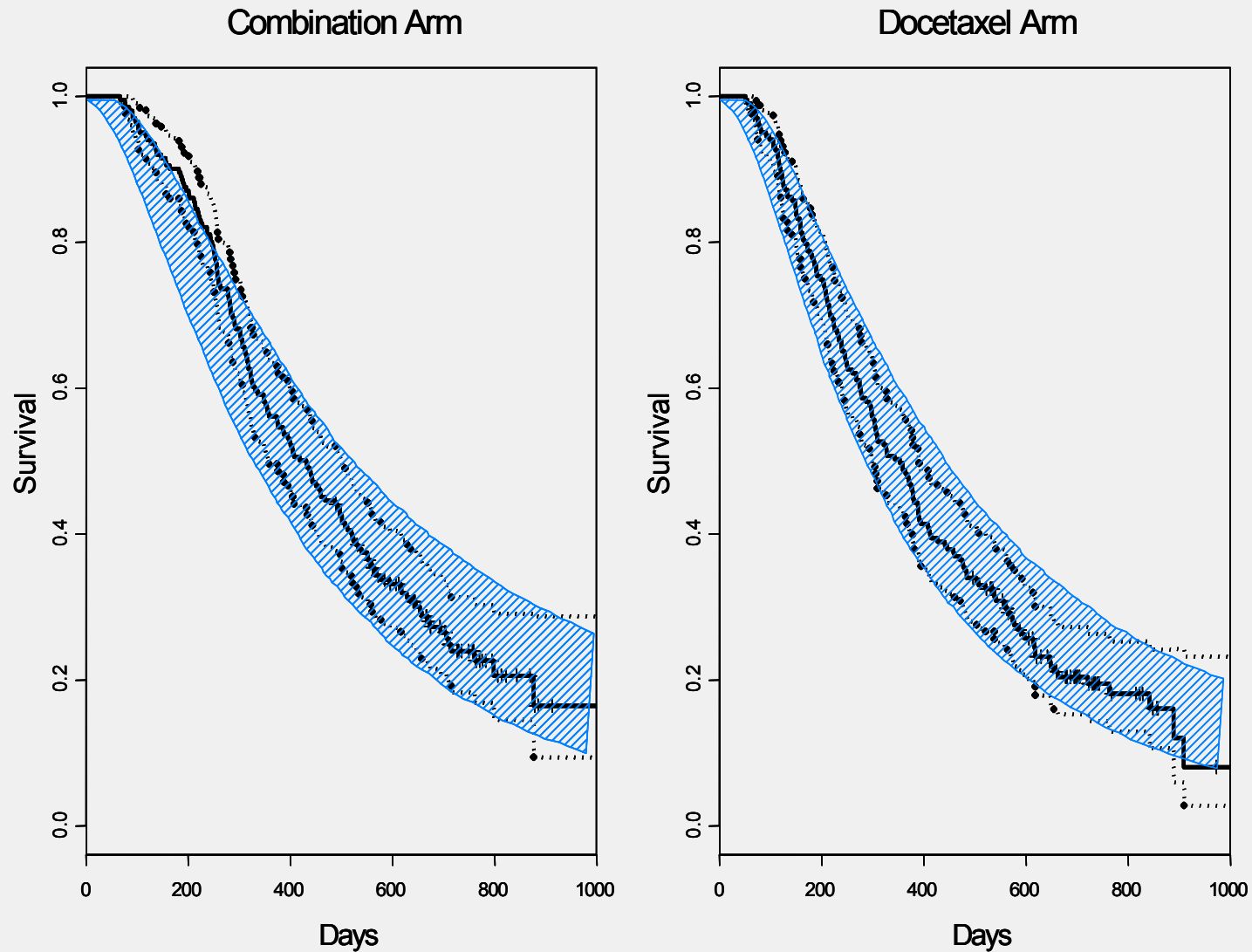
Docetaxel + Capecitabine Arm



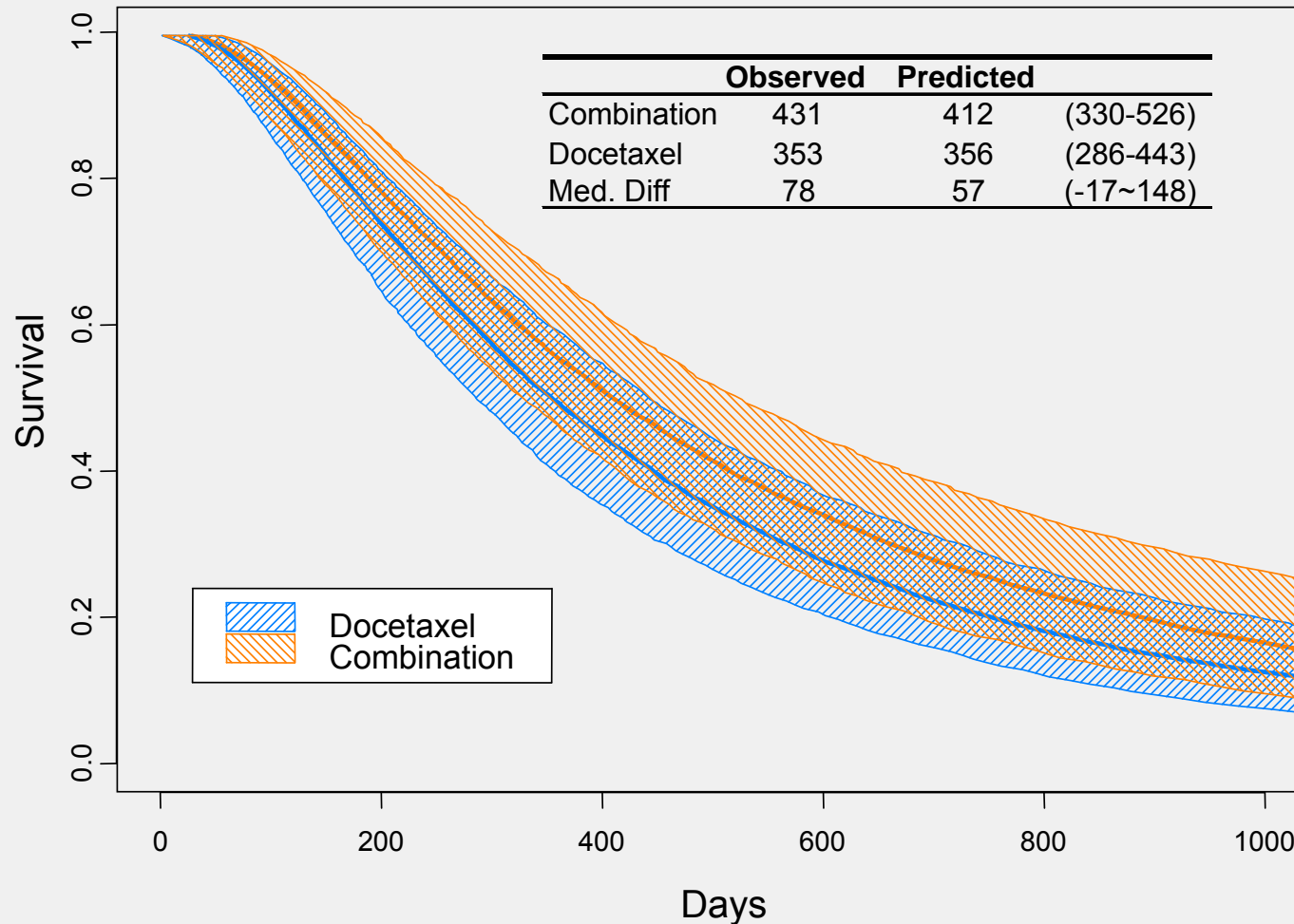
Tumor size reduction relative to baseline

	Observed	Predicted	90%	PI
Median	0.210	0.270	(0.180 - 0.360)	

Simulation of survival vs. observed in the Phase III study of docetaxel + capecitabine vs. docetaxel



Expected survival comparison in a Phase III study of docetaxel + capecitabine vs. docetaxel



Capecitabine project conclusions

The structure of the tumor size model was robust to predict tumor growth and anti-tumor effect of:

- Three cytotoxic drugs in two tumor types

Change in tumor size was a good predictor of survival

- Modeling of longitudinal tumor size data is much more informative than response rate determination
- Poor predictor of survival (primary endpoint in Phase III)
 - Study-level correlations (Buyse Lancet 2000, Shanafelt JCO 2004)
 - Even more problematic with new targeted therapies (cytostatic rather than cytotoxic)

The combined tumor size and survival models:

- Successfully predicted expected treatment differences
- Is a useful approach to support early development decisions:
 - Does the expected survival benefit of the new drug warrant further development?
 - If yes, which Phase III study need be designed to show non-inferiority, superiority?

Pharsight uses the FDA NSCLC model

Availability of data to develop the survival model is problematic in many companies

The availability of generic public-domain models is critical

We used the FDA NSCLC model (Wang et al, DIA, 2007) in one of our projects

- Pharsight Uses FDA Disease Model to Support Oncology Drug Development: http://media.corporate-ir.net/media_files/irol/12/121504/Release112007.pdf

The company was interested in getting expectations of survival for a NCE in combination

- To support decision to start a large Phase III study
- They had a Phase Ib combination study in NSCLC (less than 30 patients)
 - We used the FDA model and simulated expected survival based on:
 - Observed tumor shrinkage
 - Patient's prognostic factors
- The Pharmacometry team (Drs. Wang and Gobburu) provided us the information we needed

The model will be used in several other projects soon

A case study to illustrate the use of the FDA NSCLC model with erlotinib data

Tumor shrinkage data are generally not reported in papers

Karrison, Maitland, Stadler and Ratain recently proposed to use change in tumor size as the primary endpoint in randomized Phase II trials

(J Natl Cancer Inst, 99, 1455-1461, 2007)

- In table 1 they report data for change in tumor size from 4 trials
- We used data from the pivotal erlotinib trial in 2nd line patients
(Shepherd et al. New Engl J Med, 353, 123-132)
 - 488 patients in the erlotinib arm
 - ORR: 8.9%
 - Survival: 6.7 months

A case study to illustrate the use of the FDA NSCLC model with erlotinib data (cont.)

Data used for the simulation

- **Week 8 fractional change data based on Karrison reported log ratio**
 - The ratio of tumor size at week 8 to baseline size is normally distributed
 - Log ratio was sampled from normal distribution (Table 1): Mean 0.048, SD: 0.340
 - Shrinkage = $\exp(\text{logratio}) - 1$ (distribution given in backup)
- **Baseline tumor size distribution**
 - Sampled from lognormal distribution
 - Mean: 100 mm, SD: 57 mm (distribution in backup)
- **EGOG 0, 1 proportion (80/20%) based on observed in Shepherd**
 - Shepherd trial included 66 % ECOG 0, 1 and 34 % ECOG 2, 3 patients (Table 1)
 - Among ECOG 0, 1 patients, 20% had ECOG 1 and 80% ECOG 2

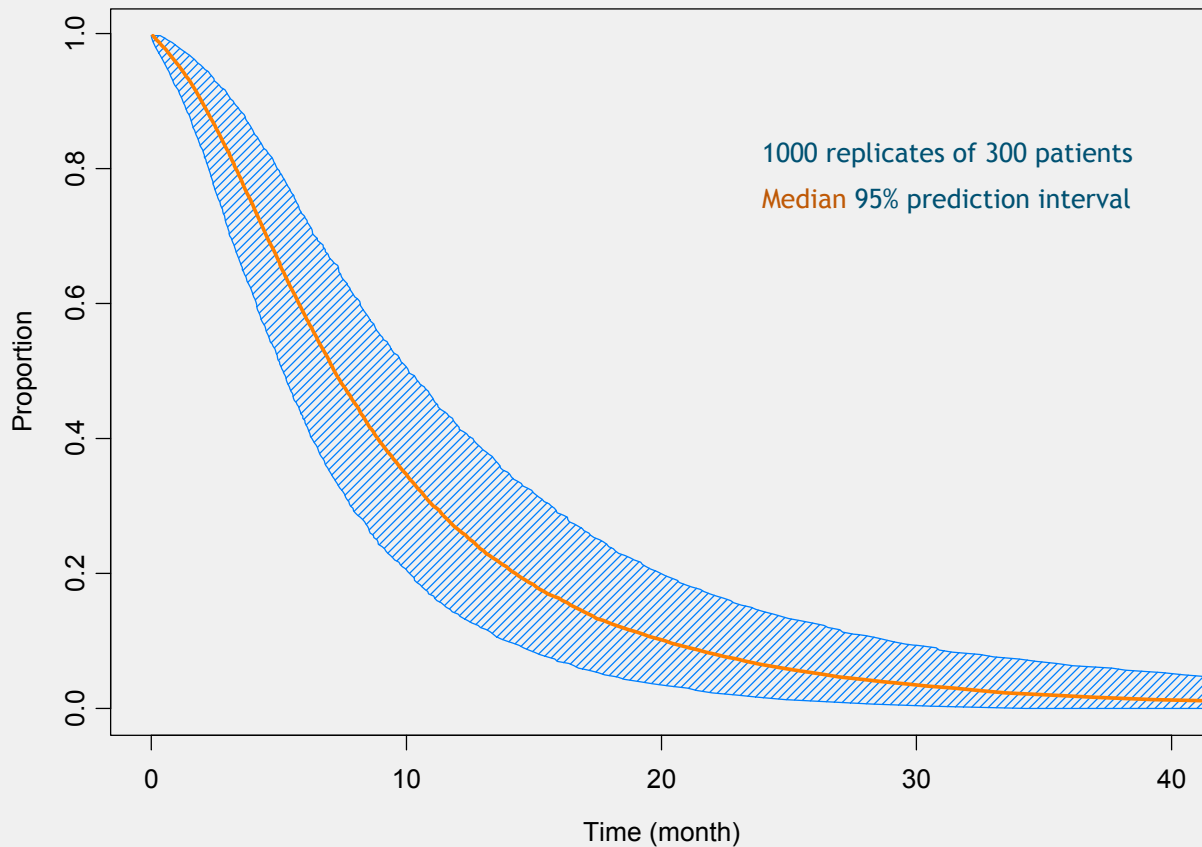
We simulated 1000 replicates of a virtual treatment arm of 300 patients (second-line, ECOG 0 or 1)

- **C and D models (assumed to be second line treatments) were used to simulate 1000 replicates**
 - 25% of the replicates with C1, C2, D1 and D2
 - Parameters for each of the replicates were sampled in uncertainty of estimates
- **Adjusted with early dropouts**

The FDA SSCLC model can be used to simulate expected survival based on tumor shrinkage data

Expected median survival: 7.2 months (95% PI: 5.2 to 10.1 months)

- Slightly longer than in Shepherd (was 6.7 months)
- But only concerns ECOG 0, 1 patients



Value of the 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

Conclusions

Change in tumor size is a good predictor of survival

- Response rate (the primary endpoint in Phase II) is a poor predictor of survival
 - Study-level correlations (Buyse Lancet 2000, Shanafelt JCO 2004)
- Modeling of longitudinal tumor size data is much more informative than response rate determination to predict clinical benefit
- Supports use of change in tumor size as a primary endpoint in Phase II studies

Drug-independent survival models allow to predict survival expectations or simulate Phase III trials based on early Phase Ib or Phase II data

- Availability of these models is limited
- FDA is in a unique position to develop such models without disclosing proprietary information
- Models for other endpoints (e.g. PFS) might be needed

A modeling framework combining longitudinal tumor size models and drug independent survival models can be used

- To predict expected treatment efficacy (ORR, Survival, PFS)
- To simulate clinical trials
- To support
 - Drug development decisions
 - Clinical trial design
 - Drug registration

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- P. Girard, Pharsight corporation, now with INSERM, University of Lyon, France
- K. Zuideveld, K. Jorga, J. Fagerberg, F. Sirzen, M. Abt, F. Hoffmann-La Roche J. O'Shaughnessy, Baylor-Sammons Cancer Center
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- J. Blum, US Oncology Dallas

FDA pharmacometrics team

- Y. Wang and J. Gobburu

Backups

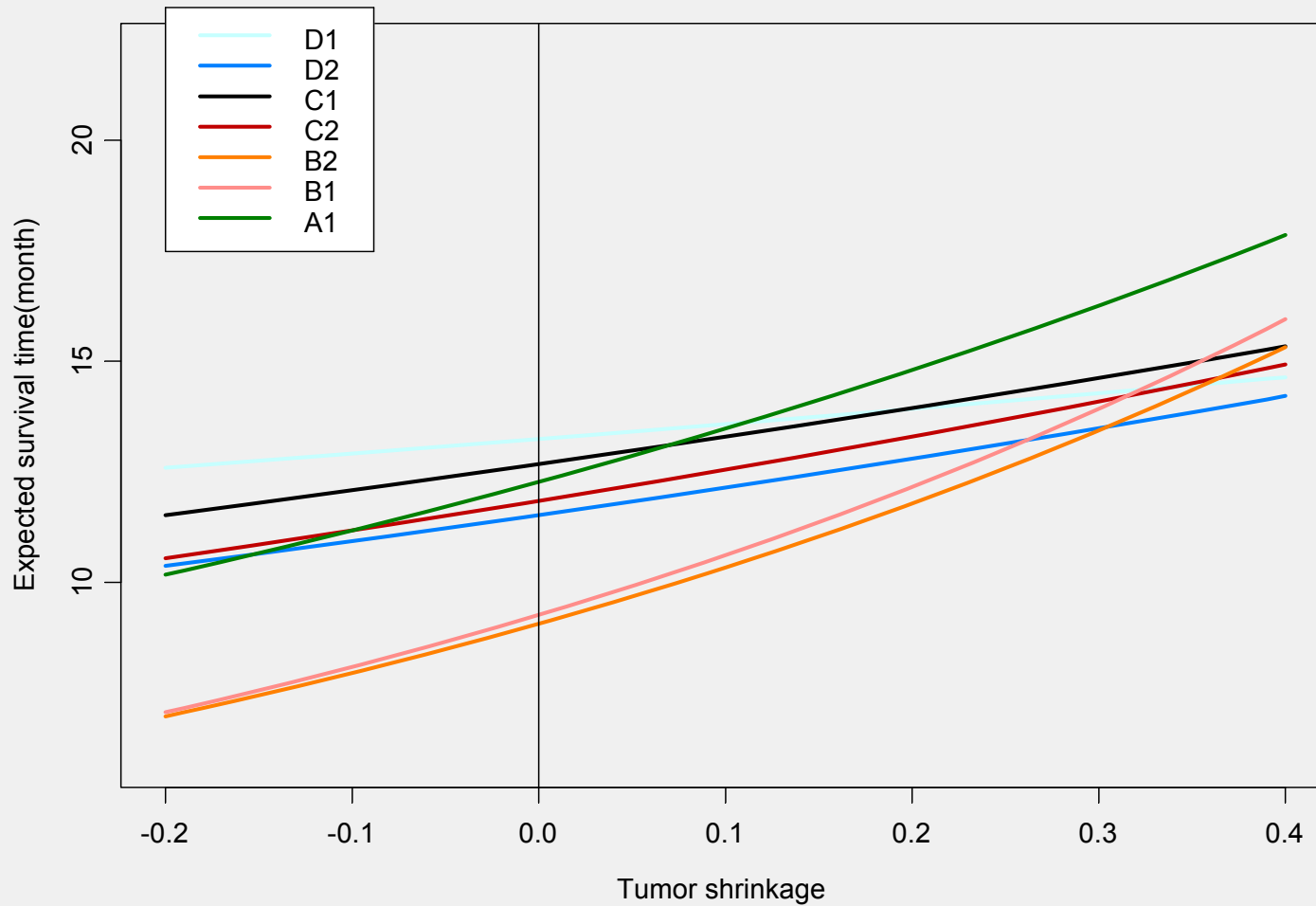
On the use of the FDA NSCLC survival model

The FDA developed 9 models based on 9 arms from 4 large pivotal studies

- 243 to 488 patients per arm
- The FDA model assumes a lognormal distribution of survival time
- The predictors are tumor size at baseline, tumor shrinkage at week 8 and ECOG performance status
 - 20 to 30 % of patients were excluded due to lack of tumor size data (early dropouts)
 - ECOG 2 and 3 patients excluded in arms C and D
- FDA provided parameter estimates with more digits than in Wang's DIA presentation (slide 19) (see table below)

Parameter	A1	A2	B1	B2	B3	C1	C2	D1	D2
Intercept	5.9222	5.8341	5.6411	5.6191	5.7617	5.9545	5.8865	5.9982	5.859
SE	0.093	0.071	0.072	0.067	0.067	0.15	0.13	0.13	0.11
Baseline	-0.029	-0.028	-0.03	-0.022	-0.037	-0.047	-0.035	-0.02	-0.035
SE	0.0073	0.0079	0.0092	0.007	0.009	0.012	0.01	0.0084	0.0097
ECOG	-0.309	-0.2	-0.178	-0.092	-0.37	-0.515	-0.258	-0.431	-0.344
SE	0.084	0.084	0.092	0.085	0.082	0.16	0.14	0.14	0.12
Tumor	0.9376	0.7965	1.3587	1.3124	0.959	0.4766	0.5793	0.2513	0.5252
SE	0.21	0.17	0.2	0.19	0.15	0.2	0.23	0.1	0.14
Scale	0.7174	0.7352	0.7399	0.6683	0.6477	0.6939	0.7987	0.6824	0.6017
SE	0.033	0.033	0.038	0.034	0.032	0.053	0.048	0.046	0.038

The figure on slide 20 of the DIA presentation was reproduced to validate the implementation of the simulation code



Models predictions are adjusted with early dropouts based on the information the FDA provided us

Patients without tumor size at week 8 were removed from the FDA analysis

- The FDA provided us for each of the arms
 - Proportion of early dropouts
 - Median survival for these patients

A number of early dropouts were sampled from the binomial law defined by the proportion provided by the FDA

Survival time of these patients was sampled from an exponential distribution defined by the observed median survival

Fractional change and baseline tumor size distributions in the erlotinib case (1000 samples)

