A Longitudinal Model for Tumor Growth Size Measurement in Clinical Oncology Studies

Claret, L. (1), P. Girard (2), K.P. Zuideveld(3), K. Jorga (3), J. Fagerberg (3), R. Bruno (1)
(1) Pharsight Corp., Mountain View, CA; (2) INSERM, EA3738 University Lyon Sud, Oulins, France; (3) F. Hoffmann-La Roche, Basel, Switzerland

Introduction

- Phase III efficacy of new anti-cancer treatment is currently assessed using survival data. This endpoint is impractical for go/no go decision during earlier phases. The analysis of tumor response in clinical studies of anti-cancer drugs remains very empirical (assessment based on response rate).
- We developed a longitudinal tumor size model of phase II data in order to predict Phase 3 outcome. This model was applied to retrospective capecitabine Phase II data in metastatic breast cancer and compared to actual Phase 3 data.
- This model can be used to predict Phase 3 survival outcomes (not shown) in order support decision-making.

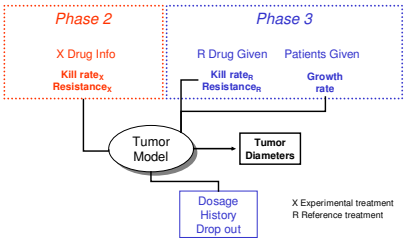

Figure 1. Functional Schema

Data

- Parameter estimation
  - Capecitabine data: phase II (2 studies, 170 patients)
  - Docetaxel data: phase III (docetaxel arm, 223 patients)
- Simulation
  - Tumor size reduction at week 6 in phase III capecitabine + docetaxel vs. docetaxel (443 patients, 1000 replicates) study

The model describes sum of tumor larger diameters in function of time and dose

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

- **Naturally growth**
- **Constant-cell-kill rate**
- **Dose effect = exact amount each time**
- **Resistance apparition = exponentially decreases killing rate**

y(t): Larger diameter at time t (mm)
D(t): Effective Dose at time t (g)
R(t): resistance function decreasing with time, ranging from 1 (no resistance) to 0 (no more drug action)
λ: rate constant of resistance apparition (t^{-1})
K_L: tumor growth rate (t^{-1})
K_D: drug constant-cell-kill rate ($g^{-1}.t^{-1}$)

- Capecitabine: Phase 2 (n=170 with tumor diameter >=10mm and at least one tumor measurement after baseline)

Table I Model parameters for capecitabine Phase 2

	K_L	K_{Dc}	λ_g	Ω_L	Ω_{Dc}	Ω_{DKL}	$\Omega\lambda$
Value	0.022	0.019	0.030	0.699	0.521	0.466	1.080
Ste	0.006	0.004	0.013	0.187	0.304	0.449	0.409

- Docetaxel: Phase 3 (n=223 with tumor diameter >=10mm and at least one tumor measurement after baseline)

Table II Model parameters for docetaxel arm Phase 3

	K_L	K_{Dd}	λ_d	Ω_L	Ω_{Dd}	Ω_{LKD}	Ω_λ
Value	0.009	0.340	0.046	0.425	1.630	1.190	0.961
Ste	0.004	0.107	0.019	0.236	0.856	0.755	0.651

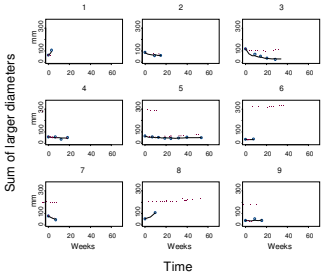

Figure 1.Typical model fits of tumor size data for capecitabine in phase II (MBC patients)

Model simulations

The model was qualified by simulating phase 2 and phase 3 studies. Simulated studies were replicates a large number of times in order to include parameter and study designs uncertainties.

Phase 2 studies

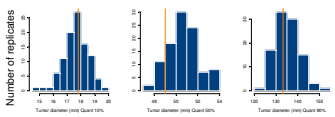

Figure 3. Model checking: 10%, 50% and 90% quantiles of predicted tumor diameter (distributions across 100 replicates) compared with observed quantiles (vertical lines)

Phase 3 Study

Docetaxel + Capecitabine (treatment arm)

Docetaxel (reference arm)

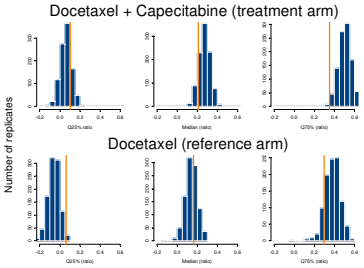

Figure 4. Model prediction: 25%, 50% and 75% quantiles of tumor size reduction (relative to baseline) at week 6 (distribution across 1000 replicates) vs. observed (vertical lines)

Conclusion

- The tumor size model is qualified:
  - To predict tumor diameter at week 6
  - To predict phase 3 tumor diameters changes at week 6 in combination arm
- This model is a part of a modeling framework* to simulate expected clinical response of new compounds and to support end of phase II decisions and design of phase III studies.

*: Claret L. Girard P., O'Shaughnessy J., Hoff P., Van Cutsem E., Blum J., Zuideveld K.P., Jorga K., Fagerberg J., Bruno R. Proc. Am. Soc. Clin. Oncol., 2006 # 6025