

Population Analysis of Tumor Growth Inhibition and Progression-Free Survival Following Lapatinib Treatment in Patients with Advanced/Metastatic Breast Cancer



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Background

Lapatinib (Tykerb™) is a potent and selective inhibitor of the EGFR and HER2 tyrosine kinases. It is approved for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2.

Objectives

To develop a pharmacodynamic (PD) model to characterize the effect of lapatinib on tumor growth dynamics and to predict the progression-free survival (PFS).

Methods

Patients: A total of 314 cancer patients from 3 Phase II studies contributed 975 tumor size measurements for up to 92 weeks. PFS analysis was based on 1 of the Phase II studies from a total of 124 patients, ranged from 7 weeks to 93 weeks (Table 1).

Table 1. Clinical Study Overview

Study/Phase	Dose(s)	Population	N	Tumor Size Measurement	Progress Free Survival
EGF20002/Phase II	RD: 1250mg/1500mg QD	Advanced or metastatic breast cancer	53	Screening, and every 8 weeks post dose	None
EGF20008/Phase II	RD: 1500mg QD	Advanced or metastatic breast cancer	137	Screening, and every 8 weeks post dose	None
EGF20009/Phase II	RD: 500mg BID/1500mg QD for 12 weeks	Advanced or metastatic breast cancer	124	Screening, Week 8, Week 12, and every 8 weeks thereafter	Yes

Model Development: The population analyses were conducted using a nonlinear mixed-effects modelling approach with NONMEM VI software.

1. Tumor Growth and Inhibition Model: The model was originally developed by Claret *et al* (2006) to characterize tumor growth dynamics, anti-cancer drug effect and drug resistance in metastatic breast cancer. The model used in the current analysis was a variation, as expressed below:

$$\frac{dy(t)}{dt} = K_L \cdot (1 - K_D \cdot e^{-\lambda t}) \cdot y(t)$$

where $y(t)$ denotes the sum of longest diameters (mm) of selected target lesions at time t , with $y(0)$ to be the baseline tumor size (mm). K_L represents the tumor growth rate. K_D represents the drug effect against tumor growth, and λ is the rate constant for development of resistance.

2. Patient Survival Model: A linear model was constructed to determine the predictability of following factors on PFS: Baseline tumor size, age, race, Eastern Corporative Oncology Group (ECOG) performance status (baseline, Weeks 4 & 8), Percentage tumor reduction (PTR) at Weeks 4, 6 & 8 since the start of therapy (predicted by tumor model), tumor HER2 expression (baseline), serum HER2 ECD concentration (baseline, Weeks 4 & 8), and tumor estrogen receptor (ER) expression (baseline). The final model is expressed as:

$$\log(T) = a_0 + a_1 \cdot PTR_{wk8} + \varepsilon$$

where T is the time to disease progression. PTR_{wk8} was found to be the best predictor of PFS.

Table 2. Summary of Patients Characteristics

	EGF20002	EGF20008	EGF20009	All
Total Number	53	137	124	314
Age (yrs)	56 (26, 79)	53 (33, 76)	53 (23, 84)	53 (23, 85)
Race				
White	39 (74)	116 (85)	3 (2)	158 (50)
Black	5 (9)	8 (6)	1 (<1)	14 (4)
Asian	4 (8)	7 (5)	64 (52)	75 (24)
Hispanic	2 (4)	6 (4)	56 (45)	64 (20)
Other	3 (6)	0 (0)	0 (0)	3 (1)
FISH				
<2	7 (13)	37 (27)	0 (0)	44 (14)
≥2	20 (38)	77 (56)	115 (93)	212 (68)
Missing	26 (49)	23 (17)	9 (7)	58 (18)
Baseline Tumor Size (mm)	9 (2, 29)	87 (12, 387)	79 (11, 275)	71 (2, 387)

Note: Continuous variables are summarized as Median (Min, Max); Categorical variables are summarized as N (%)

Results

- Treatment with lapatinib resulted in an average 39% (KD) suppression of tumor growth rate (KL).
- Lapatinib was more effective in patients with FISH ratio ≥ 2 resulting in an average 96% suppression of KL.
- Asian and Hispanic patients were more responsive to lapatinib with an average 81% suppression of KL.
- The estimated resistance rate constant ($\lambda=0.036 \text{ week}^{-1}$) indicated a half-life of 19.4 weeks. It was 46% longer in patients on the twice daily dosing regimen.
- Percentage tumor reduction from baseline at Week 8 (PTR_{wk8}) was found to be the best predictor of PFS.

Figure 1. Observed Tumor Response to Lapatinib

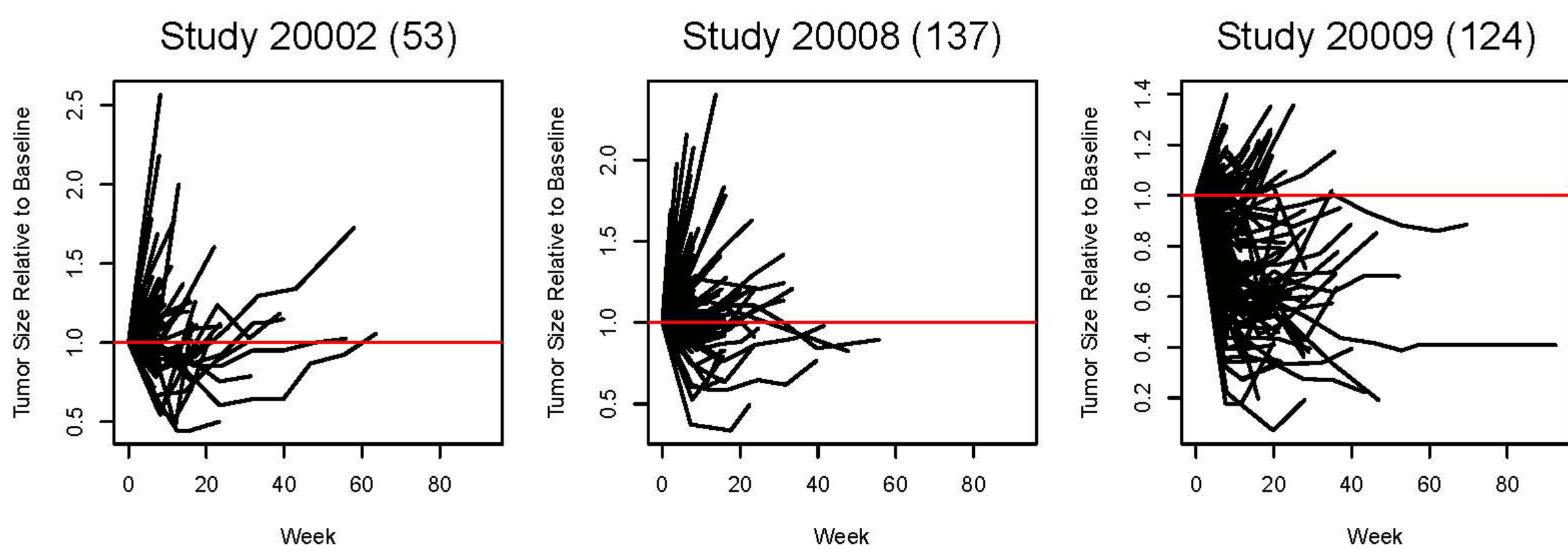


Table 3. Parameter Estimates of the Tumor Growth and Inhibition Model

Parameters (Units)	Estimate (%RSE)	BSV/WSV	Estimate (%RSE)
KL (1/week)	0.0325 (12.6)	ω^2_{KL}	0.66 (17.9)
KD	0.39 (12.5)	ω^2_{KD}	1.16 (27.1)
λ (1/week)	0.0357 (21.1)	ω^2_{λ}	2.02 (25.0)
EGF20009~KL	0.594 (15.8)	$\text{Cov}(\lambda, \text{KD}, \lambda)$	1.33 (25.3)
FISH2~KD	2.45 (10.9)		
Asian/Hispanic~KD	2.07 (11.2)	σ^2_{prop}	0.00423 (22.5)
BID~ λ	0.683 (23.6)	σ^2_{add}	0.0794 (63.4)

Figure 2. Visual Predictive Check of Final Tumor Model

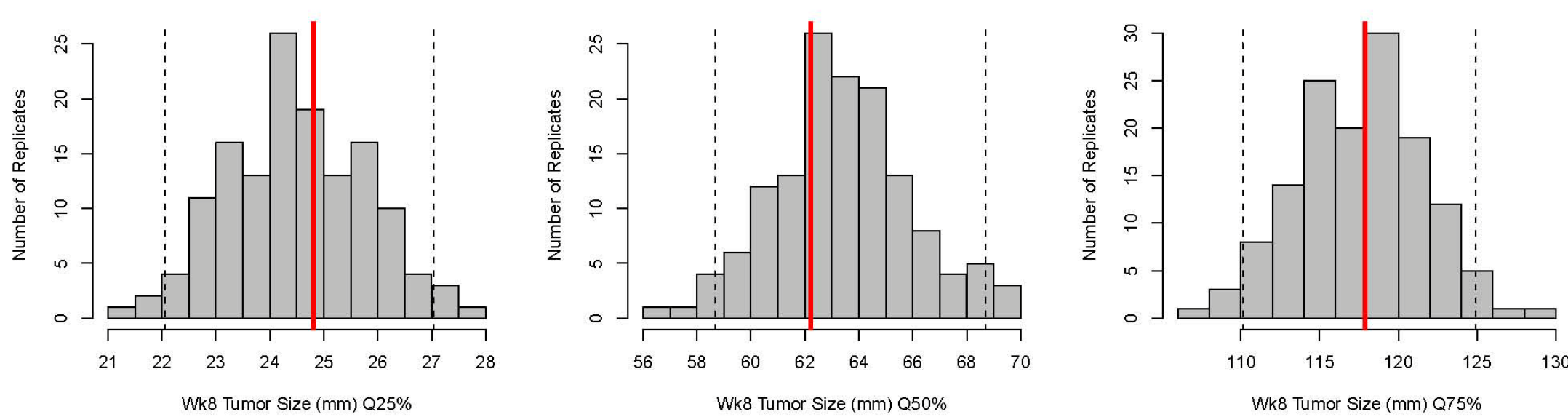
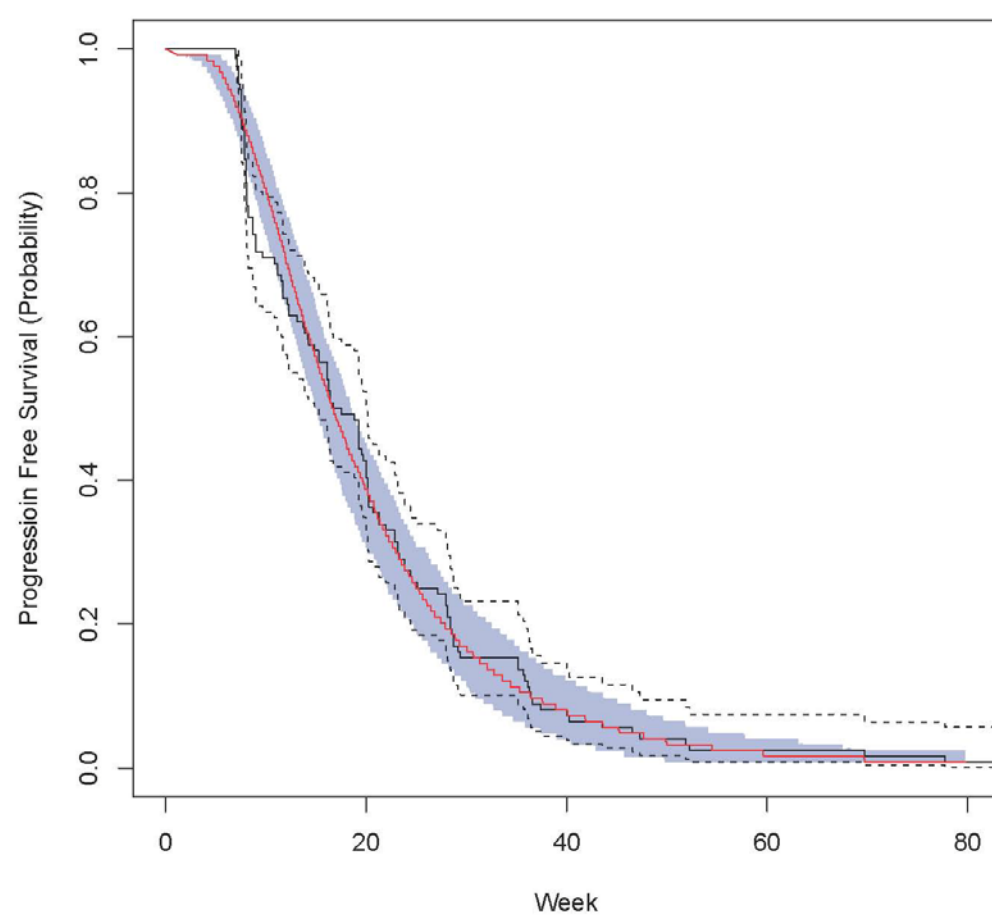


Table 4. Parameter Estimates of the Survival Model

Parameter	Estimate	RSE(%)
α_0	2.59	2.35
α_1	0.012	14.4
σ^2	0.305	13.4

Figure 5. Predictive Check of the Survival Model



Conclusions

The population models developed in this analysis adequately characterized tumor growth inhibition by lapatinib and its impact on progression-free survival in patients with advanced/metastatic breast cancer. Our findings confirm some aspects of clinical practice and may guide future investigation to improve therapy.

References

- [1] Claret L. et al. J.Clin.Oncol. (2009). 27:4103-4108.
- [2] Wang Y. et al. Clin.Pharmacol.Ther. (2009). 86:167-174.