DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Division of Biostatistics and Epidemiology (HFM-215)

Memorandum

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FROM: *Teresa Neeman, Ph.D.*

THROUGH: *Peter A. Lachenbruch, Ph.D., Chief, Biostatistics Branch*

SUBJECT: *Statistical review: Herceptin for the treatment of metastatic breast cancer*

TO: *Dr. Susan Jerian, Clinical Reviewer*
Division of Clinical Trial Design and Analysis (DCTDA) HFM-570

CC: *original/Sharon Sickafuse/HFM-588*
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I. BACKGROUND

Study H0648g

This review is based upon two studies, H0648g and H0649g. The first study, H0648g was a randomized controlled study of Herceptin in conjunction with chemotherapy in women with Stage 3/4 metastatic breast cancer, whose tumor cells over-express Her2-neu. A total of 469 patients were enrolled in 199 sites in North America, Europe and Australia/NewZealand between June 1995 and March 1997, and randomized in a 1:1 ratio to receive either Herceptin in conjunction with anthracycline-based chemotherapy (AC) or AC alone. Accrual was slower than anticipated in the first year of the study, with a total enrollment of 100 patients. The study was

changed about that time; more sites were added, inclusion criteria were relaxed and the study went from being placebo-controlled and double-blind, to open-label with concurrent control. The study population was expanded to include patients receiving Taxol™ for metastatic disease. During the discussions with the agency over the proposed changes, the sponsor agreed that overall efficacy would be based upon all of the patients studied, but the treatment effect in the subpopulations defined by concurrent chemotherapy would be carefully scrutinized. The treatment groups were coded as one of 4 categories: anthracycline-based chemotherapy (AC) plus Herceptin, AC alone, Taxol™ plus Herceptin™, or Herceptin™ alone. The major protocol changes fell under Amendment 2, and in the course of the review, we considered the patients who enrolled prior to Amendment 2 as a separate study population.

The primary endpoint was time to disease progression. When the study became open-label, an independent review committee (REC) blinded to treatment assignment was appointed to review the medical records and x-rays of patients who had progressed, in the opinion of the investigator. At the time of the May 1998 submission, a total of 389 records had been reviewed, and the primary endpoint, time to disease progression, was defined as the REC time to progression evaluation. Thirty cases of patients who had not progressed, in the opinion of the investigator, were also reviewed by the REC. For the analysis of the primary endpoint, the REC assessment was used, and only in the absence of a REC evaluation was the investigator assessment used. Because fewer cases of disease progression were found in the Herceptin™ arm, there was a substantial imbalance in the number of cases reviewed by the REC. At the beginning of August 1998, the FDA asked the company to reconvene the REC to review additional 69 cases. Seventeen other cases that had already been reviewed were randomly selected to be re-evaluated, to assess the consistency of the review process.

Secondary endpoints included the objective response rate, the duration of response, and overall survival. Another secondary endpoint, time to treatment failure, was defined as time to death, progression or treatment off-protocol. Treatment failure was defined once the study became open-label. There was concern that the REC may not agree with the investigator assessment of progression, but that the patient would be treated with anti-tumor therapy off-protocol as though they had progressed. Investigator bias may lead to more aggressive treatment in one treatment arm than in the other.

Study H0649g

Study H0649g was a Phase 2, single-arm open-label multi-center study in 222 women with Her-2 neu over-expressing metastatic breast cancer. Eligible patients must have relapsed following one or two chemotherapy regimens for metastatic breast cancer. Accrual to the study began in April 1995 and closed in June 1997. The primary objectives were to determine the overall response rate, and characterize the safety profile of Herceptin™ as a single agent. The secondary objectives were to assess the duration of responses, the times to disease progression, the time to treatment failure, and quality of life.

II. EFFICACY RESULTS

Study H0648

1. Demographics

There were no obvious imbalances seen in the baseline demographic characteristics between the patients who received Herceptin™ and the patients randomized to the control arm. There were differences, however, between the patients who received Taxol™ and those who received AC. These differences were apparent in the disease characteristics and the prior therapies and suggest that the patients receiving Taxol™ had more advanced or aggressive disease.

Baseline Demographic and Disease Characteristics: Study H-0648

		Herceptin™ + AC (N=143)	AC only (N=138)	Herceptin™ + Taxol™ (N=92)	Taxol™ only (N=96)	total (N=469)
Age	Median (yrs) Q1,Q3 range	53 46, 60 (27-76)	54 47, 60 (25-75)	50 44, 58 (25-77)	50 42, 59 (26-73)	53 45, 60 (25-77)
race	Caucasian Black Asian other	127 (89%) 10 (7%) 1 (< 1%) 5 (4%)	124 (90%) 6 (4%) 2 (1%) 6 (4%)	83 (90%) 2 (2%) 3 (3%) 4 (4%)	86 (90%) 3 (3%) 1 (1%) 6 (6%)	420 (90%) 21 (4%) 7 (2%) 21 (4%)
menopausal status	pre- peri- post- missing	44 (31%) 15 (10%) 84 (59%) 0	55 (40%) 8 (6%) 73 (53%) 2 (1%)	47 (52%) 5 (5%) 39 (42%) 1 (1%)	43 (46%) 4 (4%) 47 (49%) 2 (2%)	189 (40%) 32 (7%) 243 (52%) 5 (1%)
region	North America Europe Australia/NZ	90 (63%) 40 (28%) 13 (9%)	84 (61%) 41 (30%) 13 (9%)	74 (80%) 12 (13%) 6 (7%)	83 (86%) 7 (7%) 6 (6%)	331 (71%) 100 (21%) 38 (8%)
hormone receptor status	ER/PR - ER+ or PR+ missing	44 (31%) 71 (50%) 28 (19%)	39 (28%) 67 (49%) 32 (23%)	37 (40%) 45 (49%) 10 (11%)	40 (42%) 43 (45%) 13 (13%)	160 (34%) 226 (48%) 83 (18%)
years from primary diagnosis to metastatic disease	Median Q1,Q3 range # missing	2.3 years (1 , 4.4) (0-18.5) 1	2.2 years (0.1, 4.2) (0-18.7) 2	2.0 years (1.4, 3.1) (0, 16.4) 1	1.7 years (1.3, 2.6) (0.4-8.5) 1	2.0 years (1.1, 3.9) (0, 18.7) 5

Karnofsky score	≤ 70	22 (15%)	28 (20%)	11 (12%)	13 (14%)	74 (16%)
	> 70	116 (81%)	107 (78%)	79 (86%)	81 (84%)	383 (82%)
	# missing	5 (3%)	3 (2%)	2 (2%)	2 (2%)	12 (2%)
Her2-neu overexpression	2+	35 (24%)	42 (30%)	24 (26%)	19 (20%)	120 (26%)
	3+	108 (76%)	96 (70%)	68 (74%)	77 (80%)	349 (74%)
no. of nodes	none	50 (35%)	55 (40%)	12 (13%)	10 (10%)	127 (27%)
	1-3	31 (22%)	25 (18%)	23 (25%)	23 (24%)	102 (22%)
	>3	35 (24%)	30 (22%)	50 (54%)	58 (60%)	173 (37%)
	missing	27 (19%)	28 (20%)	7 (8%)	5 (5%)	67 (14%)

Previous Therapies: Study H0648

		AC + Herceptin™ (N=143)	AC only (N=138)	Taxol™ + Herceptin™ (N=92)	Taxol™ only (N=96)	total (N=469)
prior surgery	none	16 (11%)	18 (13%)	2 (2%)	1 (1%)	37 (8%)
	lumpectomy	31 (22%)	40 (29%)	11 (12%)	11 (11%)	93 (20%)
	mastectomy	96 (67%)	78 (57%)	78 (85%)	83 (87%)	335 (71%)
	missing	0	2 (1%)	1 (1%)	1 (1%)	4 (1%)
adjuvant hormone therapy		55 (39%)	45 (33%)	40 (43%)	43 (45%)	183 (39%)
	missing	1 (<1%)	4 (3%)	3 (3%)	1 (1%)	9 (2%)
adjuvant radiation therapy		46 (32%)	50 (36%)	49 (53%)	61 (64%)	206 (44%)
	missing	0	2 (1%)	3 (3%)	1 (1%)	6 (1%)
adjuvant chemotherapy		81 (57%)	50 (36%)	88 (96%)	95 (99%)	314 (67%)
	missing	1 (<1%)	2 (1%)	1 (1%)	1 (1%)	5 (1%)
bone marrow or PBSC tx		0	0	12 (13%)	21 (22%)	33 (7%)
	missing	1 (<1%)	4 (3%)	1 (1%)	1 (1%)	7 (2%)
Hormone therapy for metastatic disease		49 (34%)	47 (34%)	24 (26%)	26 (27%)	146 (31%)
	missing	1 (<1%)	4 (3%)	3 (3%)	1 (1%)	9 (2%)
radiation therapy for metastatic disease		33 (23%)	33 (24%)	23 (25%)	25 (26%)	114 (24%)
	missing	0	2 (1%)	3 (3%)	1 (1%)	6 (1%)

2. Primary Endpoint/ Sponsor's Analysis

This reviewer confirmed the primary endpoint of time to progression. The p-value for the log rank test comparing the groups randomized to receive Herceptin™ with the groups randomized to control was <0.001. There was a treatment effect observed in both the patients who received AC and the patients who received Taxol™. The graph below shows the Kaplan-Meier estimates for each of the randomized groups. The patients receiving Taxol™ had more previous therapies and tended to be sicker than the patients receiving adriamycin, so a difference in the Kaplan-Meier estimates was expected. Patients randomized to Herceptin™ are represented in the two upper curves, and the patients receiving Taxol™ only appeared to have the worst outcomes. The median times to progression were 20 weeks (95% CI: [19 weeks, 24 weeks]) and 33 weeks (95% CI: [30 weeks, 41 weeks]) for the control arm and the Herceptin arm, respectively.

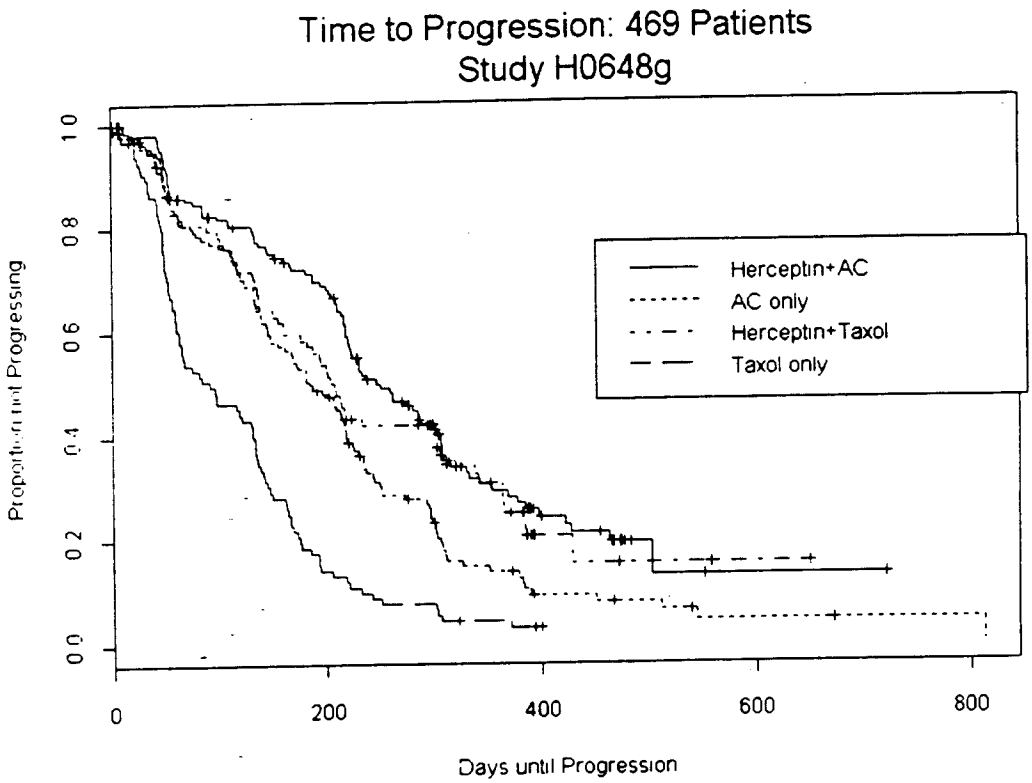


Figure 1: Kaplan-Meier Estimates of Time to Progression, Study H0648g

All Patients: N=469	Herceptin	Control
median time to progression (months)	7.6 months	4.6 months
95% confidence interval	[6.9, 9.4] months	[4.4, 5.5] months
Log rank test	$p < 0.001$	
Relative risk (hazard ratio)	0.51	95% CI (.41, .63)

The relative risk (or hazard ratio of experimental:control) was estimated to be 0.51. This can be interpreted to mean that, on average, at any given time during follow-up, the conditional probability of a patient progressing in the Herceptin arm was approximately half (0.51) the conditional probability of a patient progressing in the control arm.

3. Primary Endpoint/ Exploratory Analyses

The clinical review team reviewed every case report form while blinded to treatment assignment, and in some cases, changed the sponsor's evaluation of time to progression. The primary endpoint was re-analyzed using the FDA generated data. The p-values and the median time to progression estimates did not change substantially from the sponsor's summary.

All Patients: N=469	Herceptin	Control
median time to progression (months)*	7.2 months	4.5 months
95% confidence interval*	(6.9, 8.2)	(4.3, 4.9)
Log rank test*	$P < 0.0001$	
Relative risk (hazard ratio)	0.53 95% CI (0.43, 0.65)	

*from September 25, 1998 derived dataset

The exploratory analyses are, at the present time, based upon the sponsor's evaluation of disease progression. For the analyses that may be included in the label, both the FDA and the sponsor's estimates and p-values are included in this review. For other less critical analyses, only the sponsor's numbers are used.

a. *Subsets*

Different Chemotherapies: Since the patients receiving Taxol™ had more aggressive disease than the patients receiving AC, we considered the treatment effect in each of these subgroups, and compared it with the overall treatment effect. In each of the subsets, a statistically significant difference was noted in time to progression. A summary of the FDA-reviewed data appears in the table below:

Patients Receiving Taxol	Herceptin	Control
median time to progression (months)*	6.7 months	2.5 months
95% confidence interval*	[5.2, 9.9] months	[2.0, 4.3] months
log rank test*	p < 0.0001	
Relative risk (hazard ratio)	0.39	95% CI (0.27, 0.53)

Patients Receiving AC	Herceptin	Control
median time to progression (months)*	7.6 months	5.7 months
95% confidence interval*	[7.2, 9.1] months	[4.6, 7.1] months
log rank test*	p = 0.0017	
Relative risk (hazard ratio)	0.65	95% CI (0.47, 0.83)

*from September 25, 1998 derived dataset

We used a Cox Proportional Hazards model to test for a chemotherapy:Herceptin interaction. The interaction term was statistically significant (p=0.003), suggesting that the treatment benefit was more pronounced in the patients receiving Taxol™.

Patients enrolled before Amendment #2: Among other changes in the protocol, amendment #2 loosened the entry criteria and added more study sites. All patients enrolled before amendment #2 were to receive AC. The clinical reviewer was interested in knowing if these patients had a similar outcome to patients enrolled after Amendment #2. In the SAS data set g648anle, we used the variable inprea2 to identify 97 patients enrolled before amendment #2. Although the p-value for the comparison between the Herceptin™ arm and the control arm was not significant (p=0.09), the hazard ratio was similar to that of all of the AC patients. A summary of this comparison is presented in the table below. Also, the Kaplan-Meier estimates appear on the following page. In both this graph and the graph above, although more noticeably on this graph, it appears as though progression is delayed in the Herceptin™ arm, but is not prevented. By 400 days following initiation of treatment, the two arms are indistinguishable.

Patients enrolled pre-Amendment #2 N=97	Herceptin™	Control
median time to progression (months)	7.1 months	5.3 months
95% confidence interval	[6.7, 9.4] months	[3.7, 6.4] months
log rank test	P =0.09	
relative risk (hazard ratio)	0.69	95% CI (.41, 1.05)

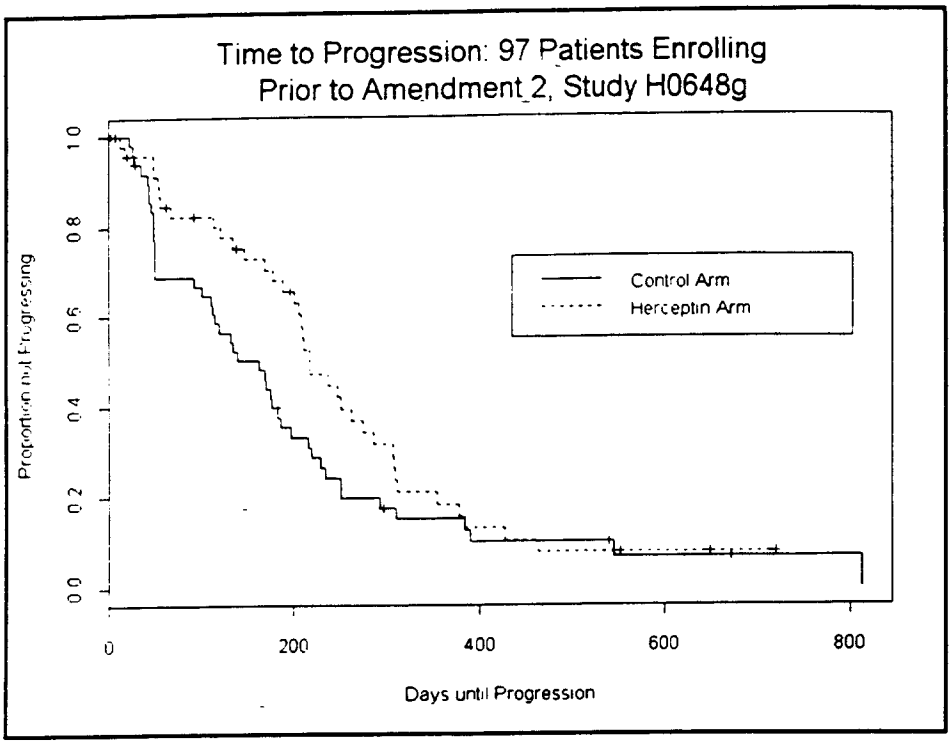


Figure 2: Time to Progression, Subset Analysis, Study H0648g

b. Time to Progression or Death

There were 8 patients who died without having documented progression. Patient numbers and treatment assignments are given below:

Herceptin™ + AC:
Herceptin™ + Taxol™:
Taxol™ only:

None of the deaths occurred on study. All of the patients left the study with no progression, and were censored at the time of discontinuation. Treating these patients as progression/death at the time of death is unlikely to have a significant impact on the estimated median time to progression.

Since seven of the eight patients were in the Herceptin™ arm, we reclassified these patients as treatment failures at the time of death, and repeated the survival analysis. The hazard ratio estimates did not change significantly for the group as a whole or in the chemotherapy subsets. The p-values for the primary endpoint remained highly statistically significant. A summary of these analyses appears in the table below:

All Patients	Herceptin™	Control
Median time to progression (months)	7.6 months	4.6 months
95% confidence interval	[7.1, 9.4] months	[4.4, 5.5] months
log rank test	$p < 0.001$	
relative risk (hazard ratio)	0.52	95% CI (.40, .64)

Patients Receiving AC	Herceptin™	Control
median time to progression (months)	8.5 months	6.2 months
95% confidence interval	[7.1, 9.9] months	[5.1, 7.1] months
log rank test	$p < 0.001$	
relative risk (hazard ratio)	0.61	95% CI (.45, .79)

Patients Receiving Taxol™	Herceptin™	Control
median time to progression (months)	6.7 months	3.0 months
95% confidence interval	[5.3, 9.9] months	[2.1, 4.4] months
Log rank test	$p < 0.001$	
Relative risk (hazard ratio)	0.39	95% CI (0.27, 0.53)

c. ***Covariate Analyses***

In the protocol, the sponsor prospectively defined baseline characteristics to be considered in exploratory analyses of the primary endpoint: age, estrogen receptor status, level of Her2 overexpression (2+ or 3+), [the number of metastatic sites], Karnofsky score, location of metastases, prior hormonal therapy, prior adjuvant therapy, geographic region and time from primary diagnosis to metastatic disease. Prior exposure to anthracycline therapy was also prospectively defined as a possible covariate; however, all patients with prior exposure to anthracycline received Taxol™, and any observed association would have been already been noted when adjusting for concurrent chemotherapy. In addition, we considered other covariates suspected to be prognostic for outcome: menopausal status, number of nodes, prior surgery for breast cancer, chemotherapy received on study (AC vs. Taxol), and bone marrow or PBSC transplant vs. no transplant.

The strategy was to build an explanatory model for time to progression that did not include the Herceptin™ treatment assignment. Conditional upon this new model, one can then test if the treatment arms (Herceptin™ vs. control) differ statistically. Although the p-value associated with a treatment difference does not have the same interpretation as the p-value from the prospectively defined analysis, it can be considered to be supportive, if similar, or raise concerns about important imbalances between the treatment arms, if different. The table below summarizes the results of the Cox model. The likelihood ratio statistic (> 0) is a measure of the departure from

the null model, tha: is, the model with no explanatory variables. When the statistic is close to zero, the addition of a new variable into the model contributes little to the prognostic value of the null model. Large positive values of the likelihood ratio statistic indicate that the variable should be included in the model. Once a variable is included, one can proceed in a stepwise fashion to consider the other variables to improve the predictability of the new model. The measure of the added value of a new variable is the difference between the likelihood ratio statistic of the first model with the likelihood ratio statistic of the proposed model. Large differences indicate that this second variable significantly improves the predict_bility of the model. In this exercise, we did not consider all possible combinations of covariates. For example, we considered only main effects (i.e. no interactions). We tested each of the covariates one by one, and discarded covariates if the associated p-value was greater than 0.15. After the first round of tests, we kept a variable in the model if the associated p-value was less than 0.05. The aim was not to develop a "best" model, but to adjust for possible confounding variables before testing for a treatment (Herceptin) effect. In the summary below, we list only the models that were "significant".

Model considered	Likelihood ratio	Δ likelihood	p-value	group doing better	# missing obs.
Karnofsky score	19.4	-	< 0.001	higher score	12
Taxol™ vs. AC	14.7	-	< 0.001	AC	0
adjuvant chemotherapy	12.1	-	< 0.001	no chemo	5
received transplant	11.3	-	< 0.001	no transplant	7
liver metastases	7.0	-	0.008	no liver mets	4
# of involved nodes	3.4	-	0.06	fewer nodes	67
Hormonal therapy for mets	2.1	-	0.14	therapy	9
Karn score + Taxol™	37.4	18.0	< 0.001		12
Karn score + adj chemo	33.8	14.4	< 0.001		13
Karn score + transplant	32.7	13.3	< 0.001		15
Karn score + liver mets	24.3	4.9	0.03		12
Karn score + hormone ther	24.4	5.0	0.03		15
Karn score + # nodes	21.2	1.8	0.08		73
Karn score+Taxol™ + Adj chemo	40.6	3.2	0.07		13
Karn score +Taxol™ + transplant	44	6.6	0.01		15
Karn score+Taxol ™ + liver mets	45.1	7.7	0.005		12
Karn score+Taxol + hormone ther	40.9	3.5	0.06		15
Karn score+Taxol + liver mets + transplant	52.3	7.2	0.005		15

From the final Cox proportional hazards model which included Karnofsky score, chemotherapy received, presence or absence of liver metastases, and bone marrow or PBSC transplant (Y/N), one can test if being assigned to receive Herceptin™ is an independent predictor of outcome. In the table below, the likelihood ratio statistic for the proposed model, for the proposed model plus Herceptin™ variable, and for the Herceptin™ variable alone are displayed. Of note, the likelihood ratio statistic of Herceptin™ alone is larger than this statistic using any of the other covariates. It is also important to note that the likelihood ratio statistic of 97.7 far exceeds the likelihood ratio statistic of 52.3 for the proposed model with Herceptin™. This analysis, therefore, provides supportive evidence that the effect seen in the Herceptin™ arm was unlikely to be confounded by the other identified covariates.

Model considered	likelihood ratio	Δ likelihood	p-value	# missing
Herceptin (Y/N)	39.7	-	< 0.001	0
Karn score+Taxol + liver mets + transplant	52.3	-	-	15
Karn score+Taxol + liver mets + transplant + Herceptin (Y/N)	97.7	45.4	< 0.001	15

Interactions with treatment: We looked for interactions only among factors suggested by the clinical reviewer. It had been noted in other trials that sicker patients do less well on some therapies. An interaction between Karnofsky score and Herceptin was tested, but no significant interaction was noted.

2+ Patients vs. 3+ Patients: Approximately one quarter of the patients enrolled on this study had Her-2 *neu* over-expression of 2+. Although the degree of Her-2 *neu* over-expression (2+ vs. 3+) was not a significant factor in predicting outcome, the sponsor noted that the treatment effect observed among 3+ patients was not observed among 2+ patients. Using the FDA-generated data, we further investigated this interaction for time to progression, overall survival and response rate. With respect to each of these endpoints, no treatment effect was observed in the 2+ patients, whereas a statistically significant treatment effect was apparent in the 3+ patients.

2+ Patients	Herceptin™ N=59	Control N=61
Median time to progression (months)*	6.5 months	5.6 months
95% confidence interval*	(4.4, 7.8)	(4.4, 7.4)
Log rank test*	P= 0.78	
Relative risk (hazard ratio)	0.94	95% CI (0.63, 1.42)

*from September 25 dataset

3+ Patients	Herceptin™ N=176	Control N=173
median time to progression (months)*	7.3 months	4.4 months
95% confidence interval*	(7.1, 9.4)	(3.7, 4.7)
log rank test*	P < 0.0001	
relative risk (hazard ratio)	0.44	(0.34, 0.56)

*from September 25, 1998 dataset

The package insert included this information divided by chemotherapy subset. The tables below reflect the summary data from the package insert.

2+ Patients	Herceptin™ + AC (N=35)	AC alone (N=42)	Herceptin™ + Taxol™ (N = 24)	Taxol™ alone (N=19)
median time to progression (months)*	7.8 months	7.1 months	4.4 months	3.2 months
95% confidence interval*	[6.5, 10.1]	[4.8, 9.8]	[2.2, 6.6]	[2.0, 5.6]

*September 25, 1998 derived dataset

3+ Patients	Herceptin™ + AC (N=108)	AC alone (N=96)	Herceptin™ + Taxol™ (N = 68)	Taxol™ alone (N=77)
median time to progression (months)*	7.3 months	4.9 months	7.1 months	2.2 months
95% confidence interval*	[7.1, 9.2]	[4.5, 6.9]	[6.2, 12.0]	[1.8, 4.3]

*September 25, 1998 derived dataset

d. Consistency of Treatment Effect

Across Regions: Study H0648g was conducted across three continents: North America, Europe and Australia/New Zealand. The sites in North America enrolled 71% (331/469) of the patients, whereas the sites in Europe and Australia/New Zealand enrolled 21% (100/469) and 8% (38/469), respectively. As was noted in the covariate analysis above, region (continent) was not a significant predictor of outcome. The median times to progression for each of the treatment arms in each of the continents is shown in the table below. Although no formal statistical analyses were performed, one can see that both the median times to progression and the proportion of patients progressing were similar in each of the continents. The exception are the patients receiving AC in North America, who appeared to have longer median time to progression than their counterparts in Europe or Australia/New Zealand.

	AC + Herceptin (N=143)	AC only (N=138)	Taxol + Herceptin (N=92)	Taxol only (N=96)	total (N=469)
Percent of Patients progressing:					
North America	63% (57/90)	85% (71/84)	70% (52/74)	93% (77/83)	78% (257/331)
Europe	72% (29/40)	80% (33/41)	50% (6/12)	100% (7/7)	75% (75/100)
Australia/NZ	69% (9/13)	92% (12/13)	83% (5/6)	100% (6/6)	84% (32/38)
Median time to progression:					
North America	41 weeks	31 weeks	29 weeks	14 weeks	
Europe	32 weeks	21 weeks	31 weeks	12 weeks	
Australia/NZ	30 weeks	16 weeks	32 weeks	19 weeks	

Across Centers: There were seven (7) centers which enrolled at least 10 patients: UCLA (#646, 24 patients), Kaiser Permanente (#2217, 11 patients), Hamilton Regional Cancer Centre (#2221, 12 patients), Rush Presbyterian Chicago (#2270, 14 patients), Washington University (#2299, 12 patients), Frauenklinik Munich (#2359, 12 patients), and Auckland Hospital (#2466, 10 patients). These centers accounted for 95 (20%) out of a total enrollment of 469 patients. Although Kaiser Permanente has a single site number, there were, in fact, multiple sites in the Kaiser system participating under this single site number. The percent of patients who progressed in each of the large centers is displayed in the table below, together with the median times to progression.

	Herceptin	Control
Percent of patients progressing:		
UCLA (646)	67% (8/12)	92% (11/12)
Rush Presbyterian (2270)	60% (3/5)	100% (9/9)
Hamilton (2221)	83% (5/6)	83% (5/6)
Washington U (2299)	100% (7/7)	60% (3/5)
Frauenklinik, Munich (2359)	100% (6/6)	83% (5/6)
Kaiser (2217)	57% (4/7)	75% (3/4)
Auckland (2466)	67% (4/6)	100% (4/4)
Median time to progression:		
UCLA (646)	32 weeks	25 weeks
Rush Presbyterian (2270)	30 weeks	20 weeks
Hamilton (2221)	39 weeks	36 weeks
Washington U (2299)	17 weeks	35 weeks
Frauenklinik, Munich (2359)	26 weeks	7 weeks

Kaiser (2217) Auckland (2466)	55 weeks 25 weeks	25 weeks 7 weeks
Percent of patients receiving Taxol:		
UCLA (646)	33% (4/12)	75% (9/12)
Rush Presbyterian (2270)	40% (2/5)	44% (4/9)
Hamilton (2221)	67% (4/6)	17% (1/6)
Washington U (2299)	57% (4/7)	20% (1/5)
Frauenklinik, Munich (2359)	17% (1/6)	17% (1/6)
Kaiser (2217)	71% (5/7)	75% (3/4)
Auckland (2466)	0% (0/6)	0% (0/4)

4. Secondary Endpoints

a. Response Rates

A patient was classified as a responder (PR or CR), if they were observed to have a sustained response over at least a 4 week period. At the time of this writing, most of the films were reviewed by the REC to confirm the investigator evaluation. (Patients not classified as responders by the investigator were not reviewed by the REC. Patients who had not yet progressed also had no REC review.) If the films were assessed by both the investigator and the REC, then the REC assessment was used in the classification. Otherwise, the investigator assessment was used. The results of this classification scheme resulted in the following summary:

REC/investigator assessment of response, Study H0648g

	AC + Herceptin (N=143)	AC only (N=138)	Taxol + Herceptin (N=92)	Taxol only (N=96)	total (N=469)
number of CR (%)	12 (8%)	9 (7%)	6 (7%)	2 (2%)	29 (6%)
number of PR (%)	63 (44%)	50 (36%)	33 (36%)	13 (46%)	159 (34%)
total number of responses (PR + CR) (%)	75 (52%)	59(43%)	39 (42%)	15(16%)	188 (40%)

As a confirmation of the sponsor's analysis, this reviewer compared the proportion of responders (PR+CR) in the Herceptin arms to the proportion of responders (PR+CR) in the control arms using a two-sided Fisher's Exact Test. The resulting p-value is less than 0.001. However, if the chemotherapy subsets are analyzed separately, one notes that the treatment effect appears stronger in the Taxol subset. The odds ratios for the treatment effect are 1.5 and 4.0, for the AC and Taxol subsets, respectively. The Breslow-Day Test for the homogeneity of odds ratios (i.e. treatment effect) had a p-value of 0.02, suggesting that the true benefit of Herceptin may be

smaller in the population treated with AC. Fisher's Exact Test was performed for each of the subsets; the resulting p-values were 0.12 for the AC subset and 0.02 for the Taxol subset. These analyses are summarized in the table below:

Responses by Chemotherapy Subset. Study H0648g

	AC subset N=281	Taxol subset N=188
odds ratio	1.5	4.0
Breslow-Day test	p=0.02	
Fisher Exact Test for treatment effect	0.12	0.02

The FDA clinical team reviewed each of the patient records and re-evaluated each patient for response. The numbers in the summaries below reflect the final dataset generated by the FDA on September 25, 1998.

Tumor Response: FDA data set (September 25, 1998)

	AC + Herceptin (N=143)	AC only (N=138)	Taxol + Herceptin (N=92)	Taxol only (N=96)	total (N=469)
number of CR (%)	7 (5%)	4 (3%)	4 (4%)	2 (2%)	17 (4%)
number of PR (%)	64 (45%)	49 (35%)	31 (34%)	12 (13%)	156 (33%)
total number of responses (PR + CR) (%)	71 (50%)	53 (38%)	35 (38%)	14 (15%)	173 (37%)

Tumor Response: 2+ and 3+ Patients (September 25, 1998)

		AC + Herceptin	AC only	Taxol + Herceptin	Taxol only
2+ patients:	*number of responses (PR + CR) (%)*	14/35 (40%)	18/42 (43%)	5/24 (21%)	3/19 (16%)
3+ patients:	*number of responses (PR + CR) (%)*	57/108 (53%)	35/96 (36%)	30/68 (44%)	11/77 (14%)

b. Duration of Response

From the final FDA generated data set (September 25, 1998), the duration of response was computed for each responder. The median times in response as well as the 25% and 75%

quantiles were generated for each of the randomization groups. Since responders cannot be validly compared across treatment groups, p-values were not computed.

	Herceptin™ + AC (N=71)	AC alone (N=53)	Herceptin™ + Taxol™ (N = 35)	Taxol™ alone (N=14)
median duration of response (months)*	8.4 months	6.4 months	8.3 months	4.3 months
25%, 75% quantiles*	[5.8, 14.8]	[4.5, 8.5]	[5.3, 11.0]	[3.7, 7.4]

* from September 25, 1998 dataset

c. Time to Treatment Failure

Time to treatment failure was defined as the time from randomization to the earliest date of documented disease progression, death, treatment discontinuation due to adverse events or patient request, of commencement of concurrent immunotherapy, non-protocol specified chemotherapy or hormonal therapy. The review of these data used the derived failure time variable in the SAS dataset (FAILTIME), rather than "primary" data. In the study report, the sponsor compared the Herceptin arm with the control arm based upon the evaluable patients. The analysis presented here is based upon the intent-to-treat population. The median times to treatment failure and the conclusions based upon p-values for the log-rank tests do not differ substantially from the sponsor's analyses.

Analysis of Treatment Failure, Study H0648g

	AC + Herceptin N=143	AC only N=138	Taxol+ Herceptin N=92	Taxol only N=96
number of patients w/ treatment failure	117 (82%)	127 (92%)	70 (76%)	93 (97%)
median time to treatment failure (months)	7.1 months	5.6 months	5.3 months	2.7 months
95% CI	(6.2, 7.8) months	(4.6, 5.6) months	(4.1, 7.1) months	(2.0, 4.3) months
p-value (log-rank test)	p=0.001		p < 0.001	

d. One Year Survival

The study was closed to enrollment in March 1997, and the database sent to the FDA in June 1998 had survival information up to December 31, 1997. A substantial number of patients did not have one year follow-up. The agency has requested updated survival data from the sponsor. The table below summarizes the one year survival data available from the June 1998 submission:

	Herceptin N=235	Control N=234
died within 1 year	49 (21%)	73 (32%)
alive after 1 year follow-up	127 (54%)	107 (46%)
alive, but not followed for 1 year	59 (25%)	54 (22%)
total	235 (100%)	234 (100%)

A valid comparison of one year survival between the two arms can be made, if the assumption of independence between censoring and survival time holds. In this case, where patients are censored because there is no follow-up beyond December 1997, this assumption is likely to hold. One appropriate analysis would be to look at the Kaplan-Meier estimates of one year survival in each arm, compute the Greenwood estimates of standard error of these estimates and compute the Z-statistic for the test of the differences of the estimates. The computations were done using the "survfit" command in ——. These estimates were 0.78 (s.e. 0.029) for the Herceptin arm and 0.68 (s.e. 0.031) for the control arm. The Z-statistic of 2.3 corresponds to a two-sided p-value of 0.02, which is suggestive of a survival benefit in the Herceptin arm. A summary of this analysis appears in the table below:

	Herceptin N=235	Control N=234
Kaplan-Meier 1 year survival estimate	0.78	0.68
standard error	0.029	0.031
formula for Z-statistic	$(0.78 - 0.68)/ (0.029^2+0.031^2)^{1/2}$	
Z-statistic/p-value	2.3	0.02

The same estimates were made separately for patients classified by 2+ and 3+ over-expressions. Although p-values were not calculated, the difference between the treatment effect in these subsets is apparent from the estimates and 95% confidence intervals.

One Year Survival for Patients Classified as 2+

	Herceptin N=58	Control N=60
Kaplan-Meier 1 year survival estimate	0.71	0.74
95% CI	(0.60, 0.84)	(0.63, 0.86)

One Year Survival for Patients Classified as 3+

	Herceptin N=176	Control N=172
Kaplan-Meier 1 year survival estimate	0.79	0.66
standard error	(0.73, 0.86)	(0.59, 0.73)

e. Overall Survival

Although overall survival was not a prospectively defined endpoint, it was felt to be an important endpoint to assess the value of delaying disease progression. It should be noted, however, that patients who progressed were offered Herceptin as part of the continuation protocol H0659g, so that any treatment effect may be diluted as a result of cross-overs. A total of 157 patients, about 33% of the total number of enrolled patients, elected to go on the continuation protocol. From the Kaplan-Meier estimates displayed below for each of the four arms, it is evident there was little information beyond the first year of the study, and therefore estimates of the median survival may not be very reliable. The log rank test comparing the Herceptin arm with the control arm yielded a p-value of 0.03. The treatment arm in each of the chemotherapy subsets (AC and Taxol) showed better survival than the corresponding control arms, although the differences were not statistically significant (0.09 in the AC arms and 0.22 in the Taxol arms).

Survival Data. Study H0648g

Patients Receiving AC	Herceptin N=143	Control N=138
number of deaths	38 (27%)	50 (36%)
median survival time(months)	24.8 months	24.2 months
95% confidence interval	[18.1, NR*] months	[15.7, NR*] months
log rank test	p = 0.09	

*NR means "not reached".

Patients Receiving Taxol	Herceptin N=92	Control N=96
number of deaths	32 (35%)	42 (44%)
median survival time (months)	19.3 months	18.3 months
95% confidence interval	[14.2, NR]	[12.6, NR]
log rank test	p = 0.22	

All Patients: N=469	Herceptin N=235	Control N=234
number of deaths	70 (30%)	92 (39%)
median survival time (months)	24.8 months	21.4 months
95% confidence interval	[17.7, NR]	[15.4, NR]
log rank test	p = 0.03	

In addition, we reviewed the overall survival data for patients enrolled before Amendment #2. In general, this data was more complete and follow-up continued beyond one year. These data show no difference in the survival times between patients randomized to receive Herceptin and those randomized to placebo. The p-value for the log-rank test was 0.92.

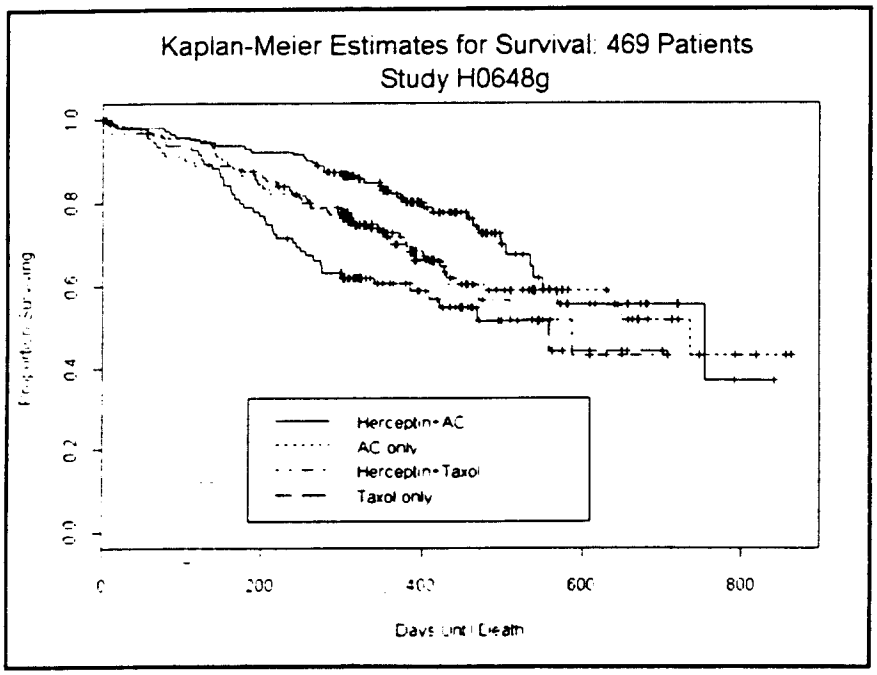
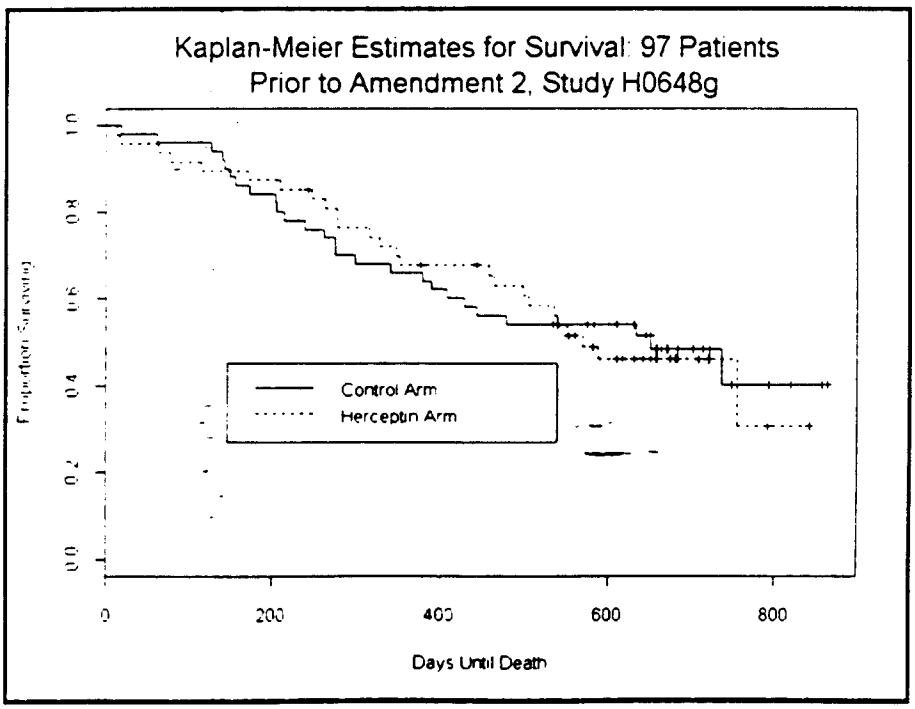


Figure 3: Survival Estimates, All Patients



III. SAFETY RESULTS

1. Cardiotoxicity

a. Association between Herceptin and Cardiotoxicity

The clinical reviewer prepared a data set from the patient narratives of patients who had experienced cardiac toxicity. This review is current as of July 1998. Most of the cases were reviewed by an independent committee and classified by severity on a four-point scale, although some cases were listed as not evaluable. In addition, the clinical reviewer reviewed all cases of suspected cardiac toxicity and sometimes reclassified these patients on the same four-point scale. There were some differences in the committee classification and the clinical reviewer's classification, but these differences did not change the overall conclusions. We present the two summaries in this report so that the magnitude of this difference can be noted. However, all subsequent analyses will be done based upon the FDA evaluation.

One patient, [redacted] was classified as a patient receiving Taxol. In fact, this patient received only one dose of Taxol, and 5 cycles of adriamycin. Since the focus in this section is on the cardiac toxicity associated with adriamycin and its combined use with Herceptin, we reclassified this patient as one receiving adriamycin.

Toxicities were summarized by any cardiac toxicity (classes 1-4), and more severe cardiac toxicities (classes 3-4). See the tables below:

Cardiac Toxicities: FDA analysis (from final data set, received October 1, 1998)

	AC + Herceptin	AC alone	Taxol + Herceptin	Taxol alone	total
any cardiac event	40/143 (28%)	10/138 (7%)	11/92 (12%)	1/96 (1%)	62/469 (13%)
cardiac event class 3 or 4	28/144 (20%)	4/138 (3%)	4/92 (4%)	1/96 (1%)	37/469 (8%)

Cardiac Toxicities: independent committee analysis

	AC + Herceptin	AC alone	Taxol + Herceptin	Taxol alone	total
any cardiac event	37/144 (26%)	8/138 (6%)	8/91 (9%)	0/96 (0%)	53/469 (11%)
cardiac event class 3 or 4	24/144 (17%)	3/138 (2%)	2/91 (2%)	0/96 (0%)	29/469 (6%)

Based upon the FDA assessment, we modeled the cardiac event data using logistic regression, where cardiac event (Y/N) was the response, and the randomization groups were the covariates. Using this model based approach, we estimated the additive effects of AC and Herceptin as well as the possible synergistic effect of the two agents used simultaneously. The contribution of each of the main effects as well as the interaction were assessed using likelihood ratio tests: A likelihood ratio test statistic of 3.8 or higher, corresponded to a p-value (chi-squared test with 1 degree of freedom) of 0.05. As can be seen from the table below, both Herceptin and adriamycin were significant independent factors for predicting cardiotoxicity at all functional classes and also when restricted to class 3/4. The cardiotoxicity associated with Herceptin appeared to be stronger than that associated with adriamycin, as evidenced by the log-odds ratio, reported below. In neither of the analyses did the interaction term make a statistically significant contribution to the underlying model.

Modeling Cardiotoxicity Based on Treatment Assignment: Any Cardiac Event (October 1, 1998)

Model Considered	Coefficient (log-odds ratio)	Likelihood Ratio Test Statistic	p-value
Herceptin (Y/N)	1.7	32.0	$p < 0.001$
Taxol (Y/N)	-0.58	13.9	$p < 0.001$
Herceptin+Taxol (additive model)	*	13.7	$p < 0.001$
Herceptin*Taxol (model w/interaction)	*	0.9	0.34

Modeling Cardiotoxicity Based Upon Treatment Assignment: Cardiac Events Class 3/4 (Oct. 7)

Model Considered	Coefficient (log-odds ratio)	Likelihood Ratio Test Statistic	p-value
Herceptin (Y/N)	2.0	23.5	$p < 0.001$
Taxol (Y/N)	-0.8	13.5	$P < 0.001$
Herceptin+Taxol (additive model)	*	13.5	$p < 0.001$
Herceptin*Taxol (model w/interaction)	*	0.2	0.65

b. Cardiotoxicity in Patients enrolled prior to Amendment 2

There was one patient, _____ for whom the timing of enrollment was not clear with respect to Amendment 2. According to the clinical reviewer, this patient was randomized by mistake to receive Herceptin (along with Taxol) on this protocol, when she should have been enrolled on the open-label study. Although this patient is included in the efficacy analysis, she was officially not treated on this protocol. The summary below is based upon the remaining 468 patients.

Cardiac Toxicities in patients enrolled prior to Amendment 2: FDA analysis

	AC + Herceptin	AC alone	Taxol + Herceptin	Taxol alone	total
any cardiac event	6/35 (17%)	2/38 (5%)	2/12 (17%)	0/12 (0%)	10/97 (10%)
cardiac event class 3 or 4	5/35 (14%)	1/38 (3%)	1/12 (8%)	0/12 (0%)	7/97 (7%)

Cardiac Toxicities in patients enrolled after Amendment 2: FDA analysis

	AC + Herceptin	AC alone	Taxol + Herceptin	Taxol alone	total
any cardiac event	34/109 (31%)	7/100 (7%)	8/78 (10%)	0/84 (0%)	10/97 (10%)
cardiac event class 3 or 4	21/109 (19%)	2/100 (2%)	3/78 (4%)	0/84 (0%)	26/371 (7%)

Although the incidence of toxicity is fairly consistent in the two groups of patients, there appears to be a higher incidence of cardiac toxicity in the AC + Herceptin patients who enrolled after Amendment 2 (31% vs. 17%).

c. Cardiac toxicity and response rate

In this trial, both the response rate and the cardiac event rate was higher in the Herceptin arm than in the control arm. Since response and toxicity tend to go hand in hand, one can consider if the additional cardiac toxicity seen could be attributable to this presumed association. To address this question, we compared the toxocity:response association, measured by the odds ratio between the Herceptin arm and the control arm. A summary of these data appear in the table below:

Association of Cardiac Toxicities and Response Rates: FDA analysis (October 1, 1998)

	Herceptin Arm		Control Arm	
	response (PR or CR)	no response	response (PR or CR)	no response
any cardiac event	28	23	6	5
no cardiac event	78	106	61	162
odds ratio 95% CI	1.65 (0.9. 3.1)		3.2 (0.9, 10.8)	

Both odds ratios. 1.6 and 3.2, point to a positive association between response and cardiac toxicity, although the odds ratio of 3.2 in the control arm indicates a stronger assocation than the

odds ratio of 1.6 in the Herceptin arm. The Breslow-Day test was used in StatXact to test the hypothesis of the equality of the odds ratios. The p-value was 0.35, which was insufficient evidence to suggest that the true-odds ratios are different.

d. Cumulative Dose of Adriamycin and Cardiac Toxicity

The association between higher cumulative doses of adriamycin and cardiac toxicity is well-established. The possibility exists that the higher rates of cardiac toxicity in the Herceptin arm can be attributed to higher doses of adriamycin given in the Herceptin arm. Both the FDA and the sponsor looked at the cardiac event rate conditional upon the cumulative dose of adriamycin received. This was done using a Kaplan-Meier estimates at each dose level (mg/m2), shown below both for any cardiac event and any cardiac event of functional class 3 or 4 (FDA assessment). There were 244 patients in this analysis: 125 randomized to receive Herceptin and 119 randomized to the control arm.

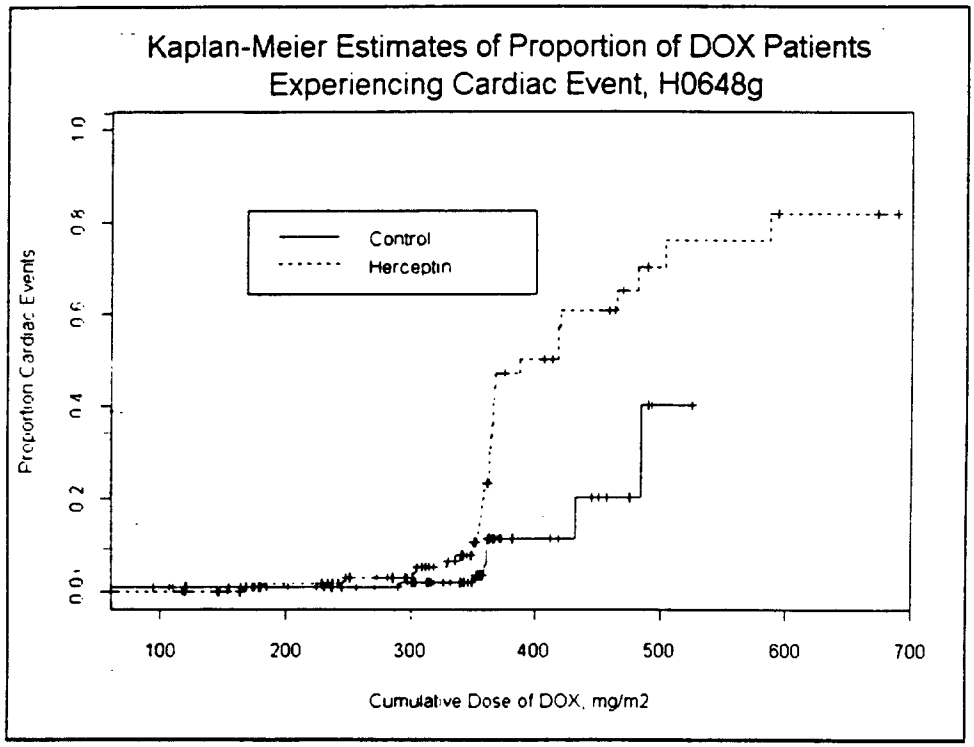


Figure 5

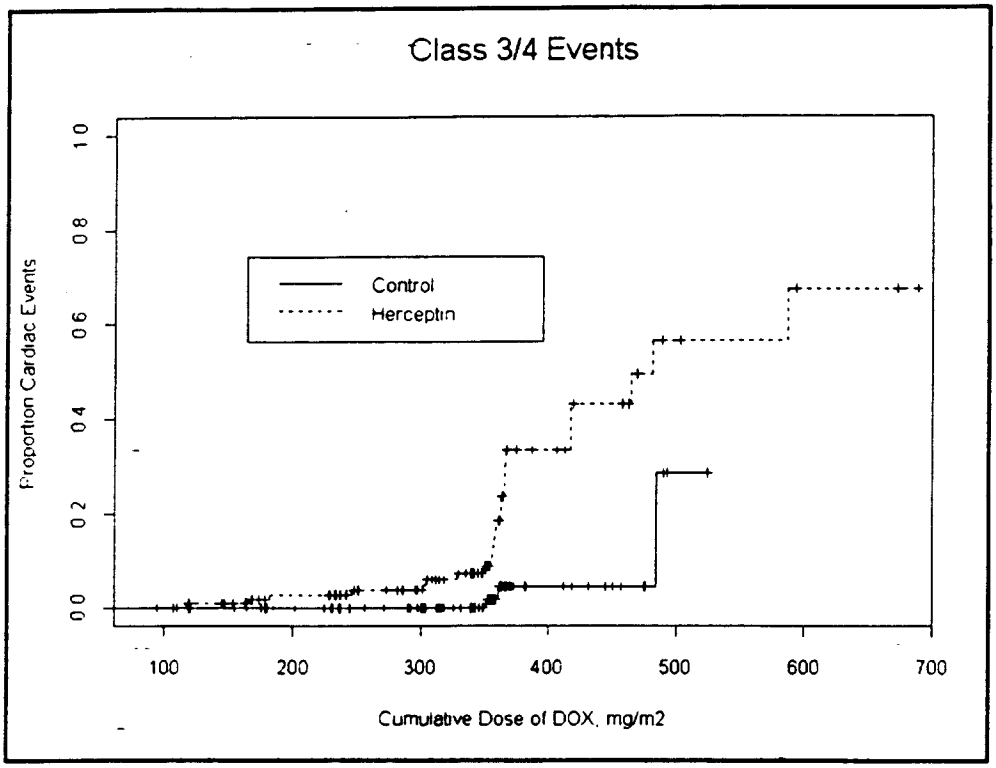


Figure 6: Cumulative Probability of Cardiac Event, Class 3/4

While the risk of cardiotoxicity is low among low dose levels of adriamycin, the risk becomes quite substantial with cumulative doses between 300 and 400 mg/m2. Comparisons between Kaplan-Meier curves are often made using hazard ratios. Although hazard ratios at any particular time may vary, the Cox proportional hazards model estimates a sort of overall average hazard ratio, under the assumption that the true hazard ratio is constant. Using a likelihood ratio test, one can test the null hypothesis that the true hazard ratio is equal to 1. The computations using the FDA assessments and the REC assessments were very similar. We report the summary of this analysis using the FDA assessments in the table below:

Comparison of Cardiac Toxicity Rates between DOX and DOX+Herceptin

	Hazard ratio	likelihood ratio test
any cardiac event	3.5	$p < 0.001$
cardiac event, class 3/4	6.7	$p = 0.002$

Because the assumptions of a constant hazard ratio are likely to be untenable, it is also helpful to look at rates in subgroups defined by dose received. On the advice of the clinical reviewer (S. Jerian), cumulative doses were grouped by the classifications: less than 300 mg/m2, 300-450

mg/m2, and greater than 450 mg/m2. The incidence of cardiotoxicity in each of these groups is given in the table below:

	cumulative DOX dose	Herceptin	Control
proportion of patients experiencing any cardiac event	< 300 mg/m2	4/42 (10%)	2/35 (6%)
	300-449 mg/m2	28/72 (39%)	4/76 (5%)
	≥ 450 mg/m2	4/11 (36%)	3/8 (37%)
proportion of patients experiencing a cardiac event, class 3/4	< 300 mg/m2	4/42 (10%)	0/35 (0%)
	300-449 mg/m2	16/72 (22%)	2/76 (3%)
	≥ 450 mg/m2	3/11 (27%)	1/8 (12%)

V. EFFICACY ENDPOINTS/ STUDY H0649G

In this open-label study of Herceptin™ as a single agent, the primary endpoint was the overall (CR + PR) response rate. The clinical reviewer reviewed all of the case report forms and generated a JMP data set that included the dates of best response and the dates of disease progression. This reviewer imported these data into SAS and summarized the findings. These summaries appear in the table below.

	Herceptin (N=222)
Overall Response Rate (CR + PR)	31/222 (14%)
CR	5 (2%)
PR	26 (12%)
Median Duration of Overall Response	9 months
Duration of Response (1^{st}-3^{rd} quartiles)	4.4 months- 15.7 months
Duration of Responses (CR)	2.7*, 4.6*, 7.6, 10.6*, 11.7*

* response ongoing

For the secondary endpoints, this reviewer relied upon the SAS data sets provided by the sponsor. The sponsor's numbers were verified and the summaries appear below:

	Herceptin (N=222)
Median Time to Progression	3.1 months
95% CI	(2.3-3.4) months
Median Time to Treatment Failure	2.3 months
95% CI	(1.9-3.0) months
Median Overall Survival	12.8 months
95% CI	(9.9-NA) months

VI. CONCLUSIONS

The statistical analyses support the claim that the addition of Herception™ to chemotherapy for metastatic breast cancer is associated with a delay in the time to disease progression, an increased response rate, and an increased proportion of survivors at one year. Differences in these endpoints were observed in each of the chemotherapy subsets, although the treatment effect was stronger in the Taxol™ subset. Exploratory analyses suggest that benefit of Herceptin™ may be limited to patients whose tumors strongly over-express Her-2 neu. The overall benefit was consistent across regions and was evident in most of the large centers.

The increase in cardiotoxicity among patients receiving AC concurrently was of particular concern to the members of the Oncological Drugs Advisory Committee (ODAC) at the Spetember 2, 1998 meeting. They voted that, while the risk:benefit ratio was favorable for patients receiving concurrent Taxol™, it was not acceptable for patients receiving concurrent AC.

The data to support the activity of Herceptin™ as a single agent in patients who have already undergone chemotherapy for metastatic breast cancer was reviewed and found to be consistent with the sponsor's analyses.

```
Call: survfit(formula = Surv(tprogfda/30.4, FDAPROG) ~ TRTCHEMR, data =
 Finaleff)

              n events mean se(mean) median 0.95LCL 0.95UCL
TRTCHEMR=1  143     99 9.66    0.776   7.60    7.17    9.11
TRTCHEMR=2  138    116 6.90    0.510   5.72    4.61    7.07
TRTCHEMR=3   92     66 8.33    0.769   6.68    5.16    9.87
TRTCHEMR=4   96     91 3.67    0.298   2.50    1.97    4.34
```

```
Call: survfit(formula = Surv(tprogfda/30.4, FDAPROG) ~ HERCTXT, data =
Finaleff)

             n events mean se(mean) median 0.95LCL 0.95UCL
HERCTXT=1 235    165 9.51    0.614   7.17    6.91    8.22
HERCTXT=2 234    207 5.62    0.350   4.54    4.28    4.87
```

```
Call: survfit(formula = Surv(tprogfda/30.4, FDAPROG) ~ HERCTXT, data =
Finaleff[
        Finaleff$HER2 == 2,  ])

            n events mean se(mean) median 0.95LCL 0.95UCL
HERCTXT=1 59     45 6.59    0.609   6.45    4.38    7.83
HERCTXT=2 61     49 6.79    0.837   5.56    4.38    7.37
```

```
Call: survfit(formula = Surv(tprogfda/30.4, FDAPROG) ~ HERCTXT, data =
Finaleff[
        Finaleff$HER2 == 3,  ])

            n events mean se(mean) median 0.95LCL 0.95UCL
HERCTXT=1 176    120 10.2    0.731   7.30    7.14    9.44
HERCTXT=2 173    158  5.2    0.358   4.41    3.68    4.70
```

```
Call: survfit(formula = Surv(tprogfda/30.4, FDAPROG) ~ TRTCHEMR, data =
  Finaleff[
        Finaleff$HER2 == 2,  ])

              n events mean se(mean) median 0.95LCL 0.95UCL
TRTCHEMR=1 35     24 7.82    0.860   7.83    6.45   10.10
TRTCHEMR=2 42     31 8.21    1.154   7.14    4.84    9.77
TRTCHEMR=3 24     21 4.93    0.709   4.41    2.20    6.61
TRTCHEMR=4 19     18 3.93    0.693   3.19    2.01    5.59
```

```
Call: survfit(formula = Surv(tprogfda/30.4, FDAPROG) ~ TRTCHEMR, data =
 Finaleff[
        Finaleff$HER2 == 3,  ])

             n events mean se(mean) median 0.95LCL 0.95UCL
TRTCHEMR=1 108     75 9.91    0.883   7.34    7.14    9.21
TRTCHEMR=2  96     85 6.35    0.528   4.90    4.54    6.91
TRTCHEMR=3  68     45 9.49    0.959   7.14    6.18   11.97
TRTCHEMR=4  77     73 3.61    0.329   2.24    1.84    4.34
```

```
Call: survfit(formula = Surv(respdur/30.4, FDAPROG) ~ TRTCHEMR, data =
Finaleff[
        Finaleff$RESP == T,  ])
```

TRTCHEMR=1

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
2.83	66	1	0.985	0.0150	0.9558	1.000
3.32	65	1	0.970	0.0211	0.9292	1.000
3.42	64	1	0.955	0.0256	0.9056	1.000
3.65	63	1	0.939	0.0294	0.8836	0.999
3.72	62	1	0.924	0.0326	0.8626	0.990
4.41	61	1	0.909	0.0354	0.8423	0.981
4.54	59	1	0.894	0.0380	0.8222	0.971
4.84	55	1	0.877	0.0406	0.8013	0.961
5.07	54	1	0.861	0.0430	0.7809	0.950
5.26	53	2	0.829	0.0471	0.7413	0.926
5.30	51	1	0.812	0.0489	0.7220	0.914
5.53	50	3	0.764	0.0535	0.6658	0.876
5.79	46	1	0.747	0.0548	0.6470	0.863
6.12	45	1	0.730	0.0561	0.6285	0.849
6.18	44	1	0.714	0.0572	0.6101	0.835
6.25	43	1	0.697	0.0582	0.5920	0.821
6.41	42	1	0.681	0.0592	0.5741	0.807
6.45	41	1	0.664	0.0600	0.5563	0.793
6.48	40	1	0.647	0.0608	0.5387	0.778
6.68	39	1	0.631	0.0614	0.5213	0.764
6.88	38	1	0.614	0.0620	0.5040	0.749
7.07	37	1	0.598	0.0625	0.4869	0.734
7.17	35	1	0.581	0.0630	0.4693	0.718
7.43	33	1	0.563	0.0635	0.4513	0.702
7.73	31	1	0.545	0.0640	0.4328	0.686
7.83	30	1	0.527	0.0644	0.4144	0.669
7.96	28	1	0.508	0.0648	0.3955	0.652
8.39	25	1	0.488	0.0653	0.3750	0.634
8.52	24	1	0.467	0.0657	0.3547	0.615
9.08	21	1	0.445	0.0662	0.3324	0.596
9.31	20	1	0.423	0.0665	0.3105	0.575
10.53	19	1	0.400	0.0666	0.2890	0.555
10.59	18	1	0.378	0.0666	0.2679	0.534
10.99	17	1	0.356	0.0663	0.2472	0.513
12.24	14	1	0.331	0.0662	0.2232	0.490
14.84	3	1	0.220	0.1002	0.0904	0.537
14.87	2	1	0.110	0.0926	0.0212	0.572

TRTCHEMR=2

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
2.50	52	1	0.9808	0.0190	0.9441	1.000
2.53	51	1	0.9615	0.0267	0.9107	1.000
2.76	50	2	0.9231	0.0370	0.8534	0.998
3.09	47	1	0.9034	0.0411	0.8264	0.988
3.52	46	1	0.8838	0.0446	0.8005	0.976
3.59	45	1	0.8642	0.0477	0.7755	0.963

3.75	44	1	0.8445	0.0505	0.7510	0.950
3.78	43	1	0.8249	0.0530	0.7272	0.936
3.91	42	2	0.7856	0.0573	0.6809	0.906
4.44	38	1	0.7649	0.0594	0.6569	0.891
4.51	37	1	0.7443	0.0613	0.6333	0.875
4.70	36	1	0.7236	0.0630	0.6101	0.858
5.20	35	1	0.7029	0.0645	0.5872	0.841
5.30	34	1	0.6822	0.0658	0.5647	0.824
5.39	33	1	0.6616	0.0670	0.5424	0.807
5.53	31	2	0.6189	0.0692	0.4972	0.770
5.56	29	2	0.5762	0.0707	0.4531	0.733
5.79	27	1	0.5549	0.0712	0.4315	0.714
5.82	26	1	0.5335	0.0716	0.4101	0.694
5.89	25	1	0.5122	0.0718	0.3891	0.674
6.38	22	1	0.4889	0.0722	0.3660	0.653
7.04	20	1	0.4644	0.0726	0.3418	0.631
7.27	19	1	0.4400	0.0728	0.3181	0.609
7.99	18	1	0.4156	0.0728	0.2948	0.586
8.16	17	1	0.3911	0.0725	0.2720	0.562
8.26	15	2	0.3390	0.0716	0.2241	0.513
8.29	13	1	0.3129	0.0707	0.2010	0.487
8.36	12	1	0.2868	0.0694	0.1785	0.461
8.49	11	1	0.2607	0.0678	0.1566	0.434
8.52	10	1	0.2347	0.0659	0.1354	0.407
8.62	9	1	0.2086	0.0635	0.1149	0.379
10.76	8	1	0.1825	0.0607	0.0951	0.350
11.74	6	1	0.1521	0.0577	0.0723	0.320
11.88	5	1	0.1217	0.0536	0.0513	0.288
14.34	3	1	0.0811	0.0487	0.0250	0.263

TRTCHEMR=3

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
2.70	35	1	0.971	0.0282	0.918	1.000
3.22	33	1	0.942	0.0398	0.867	1.000
3.39	32	1	0.913	0.0482	0.823	1.000
3.65	31	1	0.883	0.0549	0.782	0.998
3.95	30	1	0.854	0.0605	0.743	0.981
4.51	29	1	0.824	0.0652	0.706	0.962
4.80	28	1	0.795	0.0692	0.670	0.943
4.87	27	1	0.765	0.0726	0.636	0.922
5.30	26	1	0.736	0.0755	0.602	0.900
5.36	24	1	0.705	0.0784	0.567	0.877
5.59	23	1	0.675	0.0807	0.534	0.853
6.32	22	1	0.644	0.0827	0.501	0.828
7.30	20	1	0.612	0.0846	0.467	0.802
8.12	16	1	0.574	0.0875	0.425	0.773
8.22	14	1	0.533	0.0903	0.382	0.743
8.29	12	2	0.444	0.0946	0.292	0.674
10.46	6	1	0.370	0.1038	0.213	0.641
10.95	5	1	0.296	0.1062	0.146	0.598
11.05	4	1	0.222	0.1022	0.090	0.547

TRTCHEMR=4

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
2.76	14	1	0.929	0.0688	0.8030	1.000
2.86	13	1	0.857	0.0935	0.6921	1.000
3.55	12	1	0.786	0.1097	0.5977	1.000
3.68	11	1	0.714	0.1207	0.5129	0.995
3.72	10	1	0.643	0.1281	0.4351	0.950
3.88	9	1	0.571	0.1323	0.3630	0.899
4.14	8	1	0.500	0.1336	0.2961	0.844
4.38	7	1	0.429	0.1323	0.2341	0.785
4.44	6	1	0.357	0.1281	0.1769	0.721
4.77	5	1	0.286	0.1207	0.1248	0.654
7.37	4	1	0.214	0.1097	0.0786	0.584
11.32	2	1	0.107	0.0935	0.0194	0.593

```
Call: survfit(formula = Surv(respdur/30.4, FDAPROG) ~ HERCTXT, data = F
inaleff[
        Finaleff$RESP == T,  ])
```

HERCTXT=1

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
2.70	101	1	0.990	0.00985	0.9710	1.000
2.83	99	1	0.980	0.01393	0.9532	1.000
3.22	98	1	0.970	0.01701	0.9373	1.000
3.32	97	1	0.960	0.01955	0.9225	0.999
3.39	96	1	0.950	0.02176	0.9084	0.994
3.42	95	1	0.940	0.02371	0.8947	0.988
3.65	94	2	0.920	0.02710	0.8685	0.975
3.72	92	1	0.910	0.02859	0.8557	0.968
3.95	91	1	0.900	0.02998	0.8432	0.961
4.41	90	1	0.890	0.03127	0.8309	0.954
4.51	89	1	0.880	0.03248	0.8187	0.946
4.54	87	1	0.870	0.03364	0.8065	0.938
4.80	84	1	0.860	0.03480	0.7940	0.931
4.84	82	1	0.849	0.03592	0.7816	0.923
4.87	81	1	0.839	0.03697	0.7692	0.914
5.07	80	1	0.828	0.03797	0.7570	0.906
5.26	79	2	0.807	0.03980	0.7329	0.889
5.30	77	2	0.786	0.04143	0.7091	0.872
5.36	74	1	0.776	0.04221	0.6971	0.863
5.53	73	3	0.744	0.04431	0.6618	0.836
5.59	70	1	0.733	0.04493	0.6501	0.827
5.79	68	1	0.722	0.04554	0.6384	0.817
6.12	67	1	0.712	0.04612	0.6267	0.808
6.18	66	1	0.701	0.04667	0.6150	0.798
6.25	65	1	0.690	0.04718	0.6034	0.789
6.32	64	1	0.679	0.04766	0.5919	0.779
6.41	63	1	0.668	0.04810	0.5805	0.770
6.45	62	1	0.658	0.04852	0.5691	0.760
6.48	61	1	0.647	0.04891	0.5578	0.750
6.68	60	1	0.636	0.04927	0.5465	0.740
6.88	59	1	0.625	0.04960	0.5353	0.730
7.07	58	1	0.615	0.04990	0.5241	0.721
7.17	56	1	0.604	0.05020	0.5128	0.710
7.30	53	1	0.592	0.05053	0.5010	0.700
7.43	51	1	0.581	0.05086	0.4890	0.689
7.73	49	1	0.569	0.05118	0.4767	0.678
7.83	48	1	0.557	0.05147	0.4646	0.667
7.96	45	1	0.544	0.05179	0.4519	0.656
8.12	43	1	0.532	0.05211	0.4389	0.644
8.22	41	1	0.519	0.05243	0.4256	0.632
8.29	39	2	0.492	0.05301	0.3986	0.608
8.39	34	1	0.478	0.05339	0.3838	0.595
8.52	32	1	0.463	0.05377	0.3686	0.581
9.08	27	1	0.446	0.05444	0.3508	0.566
9.31	26	1	0.429	0.05498	0.3333	0.551
10.46	25	1	0.411	0.05539	0.3160	0.536

10.53	24	1	0.394	0.05567	0.2989	0.520
10.59	23	1	0.377	0.05583	0.2821	0.504
10.95	22	1	0.360	0.05586	0.2656	0.488
10.99	21	1	0.343	0.05577	0.2492	0.472
11.05	20	1	0.326	0.05555	0.2331	0.455
12.24	16	1	0.305	0.05568	0.2136	0.437
14.84	5	1	0.244	0.07048	0.1388	0.430
14.87	4	1	0.183	0.07478	0.0823	0.408

HERCTXT=2

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
2.50	66	1	0.9848	0.0150	0.9558	1.000
2.53	65	1	0.9697	0.0211	0.9292	1.000
2.76	64	3	0.9242	0.0326	0.8626	0.990
2.86	61	1	0.9091	0.0354	0.8423	0.981
3.09	59	1	0.8937	0.0380	0.8222	0.971
3.52	58	1	0.8783	0.0403	0.8027	0.961
3.55	57	1	0.8629	0.0425	0.7835	0.950
3.59	56	1	0.8475	0.0444	0.7647	0.939
3.68	55	1	0.8320	0.0462	0.7462	0.928
3.72	54	1	0.8166	0.0479	0.7280	0.916
3.75	53	1	0.8012	0.0494	0.7101	0.904
3.78	52	1	0.7858	0.0508	0.6924	0.892
3.88	51	1	0.7704	0.0521	0.6749	0.880
3.91	50	2	0.7396	0.0543	0.6404	0.854
4.14	47	1	0.7239	0.0554	0.6230	0.841
4.36	45	1	0.7078	0.0565	0.6053	0.828
4.44	44	2	0.6756	0.0583	0.5705	0.800
4.51	42	1	0.6595	0.0591	0.5533	0.786
4.70	41	1	0.6434	0.0598	0.5363	0.772
4.77	40	1	0.6273	0.0604	0.5194	0.758
5.20	39	1	0.6113	0.0610	0.5027	0.743
5.30	38	1	0.5952	0.0615	0.4861	0.729
5.39	37	1	0.5791	0.0619	0.4697	0.714
5.53	35	2	0.5460	0.0626	0.4361	0.684
5.56	33	2	0.5129	0.0630	0.4031	0.653
5.79	32	1	0.4964	0.0631	0.3868	0.637
5.82	30	1	0.4798	0.0632	0.3707	0.621
5.89	29	1	0.4633	0.0631	0.3547	0.605
6.38	26	1	0.4455	0.0632	0.3374	0.588
7.04	24	1	0.4269	0.0632	0.3194	0.571
7.27	23	1	0.4083	0.0631	0.3016	0.553
7.37	22	1	0.3898	0.0629	0.2841	0.535
7.99	21	1	0.3712	0.0626	0.2667	0.517
8.16	20	1	0.3527	0.0622	0.2496	0.498
8.26	18	2	0.3135	0.0611	0.2139	0.459
8.29	16	1	0.2939	0.0604	0.1965	0.440
8.36	15	1	0.2743	0.0594	0.1794	0.419
8.49	14	1	0.2547	0.0583	0.1626	0.399
8.52	13	1	0.2351	0.0570	0.1461	0.378
8.62	12	1	0.2155	0.0555	0.1300	0.357
10.76	10	1	0.1940	0.0540	0.1124	0.335

11.32	9	1	0.1724	0.0521	0.0953	0.312
11.74	6	1	0.1437	0.0507	0.0719	0.287
11.88	5	1	0.1149	0.0480	0.0507	0.261
14.34	3	1	0.0766	0.0448	0.0244	0.241

```
Call: survfit(formula = Surv(TLASTC/30.4, DIED) ~ trtr, data = h648all4
[h648all4$her2 ==
        2,  ])
```

trtr=1

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
2.57	35	1	0.971	0.0282	0.918	1.000
2.99	34	1	0.943	0.0392	0.869	1.000
3.59	33	1	0.914	0.0473	0.826	1.000
6.15	32	1	0.886	0.0538	0.786	0.998
7.86	31	1	0.857	0.0591	0.749	0.981
8.26	30	1	0.829	0.0637	0.713	0.963
9.11	28	1	0.799	0.0680	0.676	0.944
9.84	25	1	0.767	0.0724	0.638	0.923
12.43	19	1	0.727	0.0790	0.587	0.899
15.03	10	1	0.654	0.0990	0.486	0.880
15.46	8	1	0.572	0.1156	0.385	0.850
24.84	1	1	0.000	NA	NA	NA

13%

59%, 90%

trtr=2

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
0.395	41	1	0.976	0.0241	0.930	1.000
4.441	40	1	0.951	0.0336	0.888	1.000
4.507	39	1	0.927	0.0407	0.850	1.000
5.822	38	1	0.902	0.0463	0.816	0.998
6.743	35	1	0.877	0.0517	0.781	0.984
7.730	33	1	0.850	0.0565	0.746	0.968
8.388	32	1	0.824	0.0607	0.713	0.952
10.362	30	1	0.796	0.0646	0.679	0.933
12.204	21	1	0.758	0.0718	0.630	0.913
13.388	15	1	0.708	0.0829	0.562	0.890
13.882	13	1	0.653	0.0927	0.495	0.863
14.079	12	1	0.599	0.0997	0.432	0.830
14.145	11	1	0.544	0.1044	0.374	0.793

63%, 91%

trtr=3

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
1.88	23	1	0.957	0.0425	0.877	1.000
3.39	22	1	0.913	0.0588	0.805	1.000
3.78	21	1	0.870	0.0702	0.742	1.000
5.72	20	1	0.826	0.0790	0.685	0.996
8.19	19	1	0.783	0.0860	0.631	0.971
10.33	17	1	0.737	0.0925	0.576	0.942
11.64	15	1	0.687	0.0985	0.519	0.910
11.84	14	1	0.638	0.1030	0.465	0.876
12.80	11	1	0.580	0.1087	0.402	0.838
13.95	7	1	0.497	0.1207	0.309	0.800
14.18	6	1	0.415	0.1259	0.229	0.752
16.78	4	1	0.311	0.1303	0.137	0.707
19.31	2	1	0.155	0.1278	0.031	0.778

trtr=4

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
0.263	19	1	0.947	0.0512	0.852	1.000
2.401	18	1	0.895	0.0704	0.767	1.000
3.947	17	1	0.842	0.0837	0.693	1.000
4.079	16	1	0.789	0.0935	0.626	0.996
4.836	15	1	0.737	0.1010	0.563	0.964
8.125	13	1	0.680	0.1080	0.498	0.928
8.980	12	1	0.623	0.1129	0.437	0.889

```
Call: survfit(formula = Surv(TLASTC/30.4, DIED) ~ trtr, data = h648all4
[h648all4$her2 ==
        3,  ])
```

trtr=1

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
0.362	108	1	0.991	0.00922	0.973	1.000
0.428	107	1	0.981	0.01297	0.956	1.000
0.559	106	1	0.972	0.01581	0.942	1.000
2.796	105	1	0.963	0.01817	0.928	0.999
4.046	104	1	0.954	0.02022	0.915	0.994
4.638	103	1	0.944	0.02204	0.902	0.989
5.888	102	1	0.935	0.02369	0.890	0.983
8.355	101	1	0.926	0.02520	0.878	0.977
8.618	100	1	0.917	0.02660	0.866	0.970
8.816	99	1	0.907	0.02789	0.854	0.964
9.079	97	1	0.898	0.02913	0.843	0.957
10.362	80	1	0.887	0.03085	0.828	0.949
10.757	78	1	0.875	0.03249	0.814	0.942
11.414	76	1	0.864	0.03404	0.800	0.933
11.513	74	1	0.852	0.03553	0.785	0.925
11.842	67	1	0.840	0.03720	0.770	0.916
12.105	65	1	0.827	0.03881	0.754	0.906
13.158	54	1	0.811	0.04100	0.735	0.896
13.553	51	1	0.795	0.04317	0.715	0.885
15.263	37	1	0.774	0.04705	0.687	0.872
16.382	25	1	0.743	0.05441	0.644	0.858
16.579	23	1	0.711	0.06088	0.601	0.841
17.599	20	1	0.675	0.06741	0.555	0.821
17.730	19	1	0.640	0.07263	0.512	0.799
18.125	17	1	0.602	0.07749	0.468	0.775
18.717	13	1	0.556	0.08424	0.413	0.748

trtr=2

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
0.428	96	1	0.990	0.0104	0.969	1.000
0.987	95	1	0.979	0.0146	0.951	1.000
1.875	94	1	0.969	0.0178	0.935	1.000
2.039	93	1	0.958	0.0204	0.919	0.999
2.664	92	1	0.948	0.0227	0.904	0.993
3.816	91	1	0.938	0.0247	0.890	0.987
4.572	90	2	0.917	0.0282	0.863	0.974
4.671	88	1	0.906	0.0297	0.850	0.966
4.901	87	1	0.896	0.0312	0.837	0.959
5.132	86	1	0.885	0.0325	0.824	0.951
5.164	85	1	0.875	0.0338	0.811	0.944
5.362	84	1	0.865	0.0349	0.799	0.936
6.250	83	1	0.854	0.0360	0.786	0.928
6.612	82	1	0.844	0.0371	0.774	0.920
7.204	81	1	0.833	0.0380	0.762	0.911
7.237	80	1	0.823	0.0390	0.750	0.903
7.796	78	1	0.812	0.0399	0.738	0.894

7.829	77	1	0.802	0.0407	0.726	0.886
8.454	76	1	0.791	0.0415	0.714	0.877
8.586	74	2	0.770	0.0431	0.690	0.859
9.211	72	1	0.759	0.0438	0.678	0.850
9.342	71	1	0.748	0.0444	0.666	0.841
9.803	70	1	0.738	0.0451	0.655	0.832
9.967	66	1	0.727	0.0458	0.642	0.822
10.888	57	1	0.714	0.0467	0.628	0.812
11.414	53	1	0.700	0.0477	0.613	0.800
12.434	47	1	0.686	.0490	0.596	0.789
12.632	46	1	0.671	0.0501	0.579	0.776
12.763	45	1	0.656	0.0512	0.563	0.764
13.191	42	1	0.640	0.0523	0.545	0.751
14.572	32	1	0.620	0.0543	0.522	0.736
15.774	30	1	0.599	0.0563	0.499	0.721
20.855	14	1	0.557	0.0666	0.440	0.704
21.414	12	1	0.510	0.0755	0.382	0.682
24.211	4	1	0.383	0.1241	0.203	0.723

trtr=3

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
0.230	68	1	0.985	0.0146	0.957	1.000
0.296	67	2	0.956	0.0249	0.908	1.000
2.072	64	1	0.941	0.0286	0.886	0.999
2.204	63	1	0.926	0.0318	0.866	0.991
2.401	62	1	0.911	0.0347	0.846	0.982
2.766	61	1	0.896	0.0372	0.826	0.972
5.425	60	1	0.881	0.0394	0.807	0.962
6.316	59	1	0.866	0.0415	0.789	0.952
6.414	58	1	0.851	0.0434	0.770	0.941
6.612	57	1	0.836	0.0451	0.752	0.930
6.908	56	1	0.821	0.0467	0.735	0.918
8.092	54	1	0.806	0.0483	0.717	0.907
8.553	52	1	0.791	0.0498	0.699	0.895
9.803	50	1	0.775	0.0512	0.681	0.882
10.132	40	1	0.756	0.0535	0.658	0.868
11.349	32	1	0.732	0.0568	0.629	0.852
12.533	28	1	0.706	0.0605	0.597	0.835
15.461	11	1	0.642	0.0823	0.499	0.825

trtr=4

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
0.592	76	1	0.987	0.0131	0.962	1.000
1.579	75	1	0.974	0.0184	0.938	1.000
2.566	74	1	0.961	0.0223	0.918	1.000
2.599	73	1	0.947	0.0256	0.898	0.999
3.651	72	1	0.934	0.0284	0.880	0.992
4.178	71	1	0.921	0.0309	0.862	0.984
4.507	70	1	0.908	0.0332	0.845	0.975
4.868	69	1	0.895	0.0352	0.828	0.966
4.967	68	1	0.882	0.0371	0.812	0.957
5.000	67	1	0.868	0.0388	0.796	0.948

5.296	66	1	0.855	0.0404	0.780	0.938
5.329	65	1	0.842	0.0418	0.764	0.928
5.461	64	1	0.829	0.0432	0.748	0.918
5.691	63	1	0.816	0.0445	0.733	0.908
5.855	62	1	0.803	0.0457	0.718	0.897
6.217	61	1	0.789	0.0468	0.703	0.887
6.513	60	1	0.776	0.0478	0.688	0.876
6.711	59	1	0.763	0.0488	0.673	0.865
6.743	58	1	0.750	0.0497	0.659	0.854
7.007	57	1	0.737	0.0505	0.644	0.843
7.072	56	1	0.724	0.0513	0.630	0.832
7.204	55	1	0.711	0.0520	0.616	0.820
7.829	54	1	0.697	0.0527	0.601	0.809
7.961	53	1	0.684	0.0533	0.587	0.797
8.355	52	1	0.671	0.0539	0.573	0.785
8.651	51	1	0.658	0.0544	0.559	0.774
9.013	50	2	0.632	0.0553	0.532	0.750
9.868	46	1	0.618	0.0558	0.518	0.738
11.184	37	1	0.601	0.0567	0.500	0.723
12.664	30	1	0.581	0.0583	0.477	0.707
13.454	26	1	0.559	0.0602	0.452	0.690
13.882	24	1	0.535	0.0620	0.427	0.672
15.428	14	1	0.497	0.0684	0.380	0.651
18.355	7	1	0.426	0.0881	0.284	0.639

```
Call:
crosstabs( ~ RESPSUS + TRTCHEMR, data = Finaleff)
469 cases in table
+-----------+
|N          |
|N/RowTotal|
|N/ColTotal|
|N/Total    |
+-----------+
RESPSUS|TRTCHEMR
       |1       |2       |3       |4       |RowTotl|
-------+--------+--------+--------+--------+-------+
1      | 7      | 4      | 4      | 2      |17     |
       |0.4118  |0.2353  |0.2353  |0.1176  |0.036  |
       |0.0490  |0.0290  |0.0435  |0.0208  |       |
       |0.0149  |0.0085  |0.0085  |0.0043  |       |
-------+--------+--------+--------+--------+-------+
2      |64      |49      |31      |12      |156    |
       |0.4103  |0.3141  |0.1987  |0.0769  |0.333  |
       |0.4476  |0.3551  |0.3370  |0.1250  |       |
       |0.1365  |0.1045  |0.0661  |0.0256  |       |
-------+--------+--------+--------+--------+-------+
3      |13      | 7      |10      | 3      |33     |
       |0.3939  |0.2121  |0.3030  |0.0909  |0.070  |
       |0.0909  |0.0507  |0.1087  |0.0312  |       |
       |0.0277  |0.0149  |0.0213  |0.0064  |       |
-------+--------+--------+--------+--------+-------+
4      |59      |78      |47      |79      |263    |
       |0.2243  |0.2966  |0.1787  |0.3004  |0.561  |
       |0.4126  |0.5652  |0.5109  |0.8229  |       |
       |0.1258  |0.1663  |0.1002  |0.1684  |       |
-------+--------+--------+--------+--------+-------+
ColTotl|143     |138     |92      |96      |469    |
       |0.30    |0.29    |0.20    |0.20    |       |
---------------+--------+--------+--------+-------+
Test for independence of all factors
        Chi^2 = 43.33409 d.f.= 9 (p=1.871581e-006)
        Yates' correction not used
        Some expected values are less than 5, don't trust stated p-valu
e
```

Call:
crosstabs(~ RESP + TRTCHEMR + HER2, data = Finaleff)
469 cases in table

N					
N/RowTotal					
N/ColTotal					
N/Total					

HER2=2

RESP	TRTCHEMR 1	2	3	4	RowTotl
FALSE	21	24	19	16	80
	0.2625	0.3000	0.2375	0.2000	0.67
	0.6000	0.5714	0.7917	0.8421	
	0.0448	0.0512	0.0405	0.0341	
TRUE	14	18	5	3	40
	0.3500	0.4500	0.1250	0.0750	0.33
	0.4000	0.4286	0.2083	0.1579	
	0.0299	0.0384	0.0107	0.0064	
ColTotl	35	42	24	19	120
	0.29	0.35	0.20	0.16	

HER2=3

RESP	TRTCHEMR 1	2	3	4	RowTotl
FALSE	51	61	38	66	216
	0.2361	0.2824	0.1759	0.3056	0.62
	0.4722	0.6354	0.5588	0.8571	
	0.1087	0.1301	0.0810	0.1407	
TRUE	57	35	30	11	133
	0.4286	0.2632	0.2256	0.0827	0.38
	0.5278	0.3646	0.4412	0.1429	
	0.1215	0.0746	0.0640	0.0235	
ColTotl	108	96	68	77	349
	0.31	0.28	0.19	0.22	

Test for independence of all factors
Chi^2 = 41.54883 d.f.= 10 (p=9.01929e-006)
Yates' correction not used

Call:
crosstabs(~ RESP + TRTCHEMR, data = Finaleff)
469 cases in table

N					
N/RowTotal					
N/ColTotal					
N/Total					
RESP	TRTCHEMR				
	1	2	3	4	RowTotl
FALSE	72	85	57	82	296
	0.243	0.287	0.193	0.277	0.63
	0.503	0.616	0.620	0.854	
	0.154	0.181	0.122	0.175	
TRUE	71	53	35	14	173
	0.410	0.306	0.202	0.081	0.37
	0.497	0.384	0.380	0.146	
	0.151	0.113	0.075	0.030	
ColTotl	143	138	92	96	469
	0.30	0.29	0.20	0.20	

Test for independence of all factors
Chi^2 = 30.709 d.f.= 3 (p=9.788288e-007)
Yates' correction not used

Call:
crosstabs(~ RESP + HERCTXT, data = Finaleff)
469 cases in table

N			
N/RowTotal			
N/ColTotal			
N/Total			
RESP	HERCTXT		
	1	2	RowTotl
FALSE	129	167	296
	0.44	0.56	0.63
	0.55	0.71	
	0.28	0.36	
TRUE	106	67	173
	0.61	0.39	0.37
	0.45	0.29	
	0.23	0.14	
ColTotl	235	234	469
	0.5	0.5	

Test for independence of all factors
Chi^2 = 13.66822 d.f.= 1 (p=0.0002181151)
Yates' correction not used

```
Call:
crosstabs( ~ FDACARD + TRTCHEMR, data = Finalcard)
469 cases in table
+----------+
|N         |
|N/RowTotal|
|N/ColTotal|
|N/Total   |
+----------+
FDACARD|TRTCHEMR
       |1       |2       |3       |4       |RowTotl|
-------+--------+--------+--------+--------+-------+
0      |103     |128     | 81     | 95     |407    |
       |0.2531  |0.3145  |0.1990  |0.2334  |0.87   |
       |0.7203  |0.9275  |0.8804  |0.9896  |       |
       |0.2196  |0.2729  |0.1727  |0.2026  |       |
-------+--------+--------+--------+--------+-------+
1      | 40     | 10     | 11     |  1     |62     |
       |0.6452  |0.1613  |0.1774  |0.0161  |0.13   |
       |0.2797  |0.0725  |0.1196  |0.0104  |       |
       |0.0853  |0.0213  |0.0235  |0.0021  |       |
-------+--------+--------+--------+--------+-------+
ColTotl|143     |138     |92      |96      |469    |
       |0.30    |0.29    |0.20    |0.20    |       |
-------+--------+--------+--------+--------+-------+
Test for independence of all factors
        Chi^2 = 43.95839 d.f.= 3 (p=1.540215e-009)
        Yates' correction not used
```

```
Call:
crosstabs( ~ FDACARD34 + TRTCHEMR, data = Finalcard)
469 cases in table
+----------+
|N         |
|N/RowTotal|
|N/ColTotal|
|N/Total   |
+----------+
FDACARD34|TRTCHEMR
         |1       |2       |3       |4       |RowTotl|
---------+--------+--------+--------+--------+-------+
0        |115     |134     | 88     | 95     |432    |
         |0.2662  |0.3102  |0.2037  |0.2199  |0.921  |
         |0.8042  |0.9710  |0.9565  |0.9896  |       |
         |0.2452  |0.2857  |0.1876  |0.2026  |       |
---------+--------+--------+--------+--------+-------+
1        | 28     |  4     |  4     |  1     |37     |
         |0.7568  |0.1081  |0.1081  |0.0270  |0.079  |
         |0.1958  |0.0290  |0.0435  |0.0104  |       |
         |0.0597  |0.0085  |0.0085  |0.0021  |       |
---------+--------+--------+--------+--------+-------+
ColTotl  |143     |138     |92      |96      |469    |
         |0.30    |0.29    |0.20    |0.20    |       |
---------+--------+--------+--------+--------+-------+
Test for independence of all factors
        Chi^2 = 39.40985 d.f.= 3 (p=1.421117e-008)
        Yates' correction not used
```

```
Call:
crosstabs( ~ FDACARD + RESP + HERCTXT, data = Finalcard)
469 cases in table
+----------+
|N         |
|N/RowTotal|
|N/ColTotal|
|N/Total   |
+----------+
HERCTXT=1
FDACARD|RESP
       |FALSE  |TRUE   |RowTotl|
-------+-------+-------+-------+
0      |106    | 78    |184    |
       |0.576  |0.424  |0.783  |
       |0.822  |0.736  |       |
       |0.226  |0.166  |       |
-------+-------+-------+-------+
1      | 23    | 28    |51     |
       |0.451  |0.549  |0.217  |
       |0.178  |0.264  |       |
       |0.049  |0.060  |       |
-------+-------+-------+-------+
ColTotl|129    |106    |235    |
       |0.55   |0.45   |       |
-------+-------+-------+-------+
HERCTXT=2
FDACARD|RESP
       |FALSE  |TRUE   |RowTotl|
-------+-------+-------+-------+
0      |162    | 61    |223    |
       |0.726  |0.274  |0.953  |
       |0.970  |0.910  |       |
       |0.345  |0.130  |       |
-------+-------+-------+-------+
1      |  5    |  6    |11     |
       |0.455  |0.545  |0.047  |
       |0.030  |0.090  |       |
       |0.011  |0.013  |       |
-------+-------+-------+-------+
ColTotl|167    |67     |234    |
       |0.71   |0.29   |       |
-------+-------+-------+-------+
Test for independence of all factors
        Chi^2 = 53.45661 d.f.= 4 (p=6.838619e-011)
        Yates' correction not used
```