DEC 14 2006

Attachment 11 – Revised 510(k) Summary

510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is K062013.

807.92 (a)(1): Name: Veridex, LLC
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807.92 (a)(2): Device Name – trade name and common name, and classification

Trade name: CellSearch™ Circulating Tumor Cell Kit

Common name: CellSearch™ Circulating Tumor Cell Kit

Classification: Immunomagnetic Circulating Cancer Cell Selection and Enumeration System, Class II, 21 CFR 866.6020, Product Code NQI, Immunology Devices- 82

807.92 (a)(3): Identification of the legally marketed predicate device
CellSearch™ Circulating Tumor Cell Kit, K050245

807.92 (a)(4): Device Description
The CellSearch™ Circulating Tumor Cell Kit contains a ferrofluid-based capture reagent and immunofluorescent reagents. The ferrofluid reagent consists of nanoparticles with a magnetic core surrounded by a polymeric layer coated with antibodies targeting the EpCAM antigen for capturing CTC. After immunomagnetic capture and enrichment, fluorescent reagents are added for identification and enumeration of CTC. The fluorescent reagents include the following: anti-CK-Phycoerythrin (PE) specific for the intracellular protein cytokeratin (characteristic of epithelial cells),

DAPI which stains the cell nucleus, and anti-CD45-Allophycocyanin (APC) specific for leukocytes.

The reagent/sample mixture is dispensed by the CellTracks® AutoPrep® System into a cartridge that is inserted into a MagNest® cell presentation device. The strong magnetic field of the MagNest® device attracts the magnetically labeled epithelial cells to the surface of the cartridge. The CellTracks® Analyzer II or CellSpotter® Analyzer automatically scans the entire surface of the cartridge, acquires images and displays any event to the user where CK-PE and DAPI fluorescence are co-located. Images are presented to the user in a gallery format for final classification. An event is classified as a tumor cell when its morphological features are consistent with that of a tumor cell and it exhibits the phenotype EpCAM+, CK+, DAPI+ and CD45-.

807.92 (a)(5): Intended use

The CellSearch™ Circulating Tumor Cell Kit is intended for the enumeration of circulating tumor cells (CTC) of epithelial origin (CD45-, EpCAM+, and cytokeratins 8, 18+, and/or 19+) in whole blood.

The presence of CTC in the peripheral blood, as detected by the CellSearch™ Circulating Tumor Cell Kit, is associated with decreased progression free survival and decreased overall survival in patients treated for metastatic breast cancer. The test is to be used as an aid in the monitoring of patients with metastatic breast cancer. Serial testing for CTC should be used in conjunction with other clinical methods for monitoring breast cancer. A CTC count of 5 or more per 7.5 mL of blood at any time during the course of the disease is predictive of shorter progression free survival and overall survival.

807.92 (a)(6): Technological Similarities and Differences to Predicate

There have been no material changes to the CellSearch™ Circulating Tumor Cell Kit; this 510(k) is being submitted for an expanded indications for use.

807.92 (b)(1): Brief Description of Non-clinical data

Recovery

Blood samples from a single healthy donor were pooled and five of six 7.5 mL aliquots were spiked with approximately 1300, 325, 81, 20, and 5 cultured breast cancer cells (SK-BR-3). The sixth tube was unspiked pooled blood and served as a zero point. These samples were processed on the CellTracks® AutoPrep System with the CellSearch™ Circulating Tumor Cell Kit and CTC counts were determined on the CellTracks®

Analyzer II. The experiment was repeated for four additional donors. The observed cell counts were plotted against the results of the expected cell count. The results are summarized in **Table 1**.

Table 1. Percent Detection Estimates.

Expected Tumor Cell Count	Mean Observed Tumor Cell Count	Range of Percent Recovery
1300	1215	91 to 95%
325	308	82 to 101%
81	85	80 to 136%
20	22	95 to 140%
5	7	120 to 200%

To determine the overall, or least squares fit, for the comparison of the observed and expected cell counts across all the data, linear regression analysis was performed. The regression equation for these 30 samples was $Y=0.93x + 3.87$ with an $R^2=0.999$ ($R=0.999$). The results of this study indicate that on average, over the tested CTC range, the recovery, as derived from regression analysis, is 93%.

Given the linear response of the tumor cell counts, one would expect the slope of the observed versus expected plot to be 1.0. However, the slope was 0.93. This is because the CellTracks® AutoPrep System with CellSearch™ CTC Kit involves the capture and fluorescent labeling of cells followed by their detection and enumeration by the CellTracks® Analyzer II. The loss of cells could therefore be attributed to one of the following possibilities; 1) the recovery of only 93% of the tumor cells spiked into 7.5mL of blood by the CellTracks® AutoPrep System, 2) the detection of only 93% of the tumor cells present in the sample chamber by the CellTracks® Analyzer II or 3) a combination of both of these sources of error.

Linearity / Reportable Range

Another way to examine the previous data is to analyze it as a dilution series to evaluate test linearity. We removed the confounding variable of percent recovery by using the observed value of the initial sample in the dilution series (i.e. the first tube) divided by the dilution factors to determine the expected values for the dilution series for each patient sample. Regression of all of these numbers of observed tumor cells versus the numbers of expected tumor cells yielded a slope of 1.007, an intercept of 3.0, and an $R^2 = 0.990$ ($R = 0.995$). Therefore, once the percent recovery (cell loss) was factored out of the CTC values of each of the initial samples, the analysis of the data demonstrated that the detection of

CTC was linear over the reportable range of 0 to 1238 tumor cells.

Limits of Detection

One CTC per 7.5 mL can be detected by the CellTracks® Analyzer II resulting in a limit of detection of 1 CTC in a cartridge. Linear regression shows that on average, 93% of CTC present in a 7.5 mL blood sample are recovered using the CellTracks® AutoPrep System (see **Recovery** section). The loss of approximately 7% of the CTC in the sample is not sufficient to reduce the limit of detection of 1 CTC.

Reproducibility:

a. System Reproducibility with CellSearch™ Circulating Tumor Cell Control

Three separate CellSearch™ Circulating Tumor Cell Control samples were prepared and processed each day for over 30 days, per the long run method of NCCLS guideline EP5-A[2]. Each single-use sample bottle contains a low and a high concentration of cells from a fixed cell line that have been pre-stained with two different fluorochromes. Summary statistics for the high and low control cells is presented below.

Table 2. Summary of Precision Analyses

	Low	**High**
N	99	99
Mean cell count	48	969
Total Precision Standard Deviation (S_T) % CV	18%	5%

b. System Reproducibility with Patient Samples

A total of 163 duplicate samples were collected from 47 patients over the course of the clinical study. These samples were processed at multiple sites to determine the reproducibility of CTC measurements. The regression equation for the comparison of these 163 duplicate samples was $Y=0.98x + 0.67$, $R^2=0.99$. **Table 3** shows the summary of the data for replicates where the average of the two CTC results was <5 compared to those where the average (avg.) was ≥5.

Table 3. Reproducibility of CTC Counts in Duplicate Samples (n=163) w/Average of <5 or ≥5 CTC per 7.5 mL of blood.

	CTC <5	CTC ≥5
Number of Duplicates	123	40
Mean CTC Count of Duplicates	0.7	210
Avg. Duplicate Standard Deviation	0.5	12
Avg. %CV of Duplicates	60%	20%

807.92 (b)(2): Brief Description of Clinical Data

EXPECTED VALUES

Healthy volunteers, non-malignant breast disease, non-malignant other disease

Single point CTC analyses were performed on control groups of 145 healthy volunteers, 101 women with non-malignant breast disease, and 99 women with other non-malignant diseases.

Epithelial cells are not expected to be present in the peripheral blood of healthy individuals. Of the 345 total samples from healthy volunteers and women with non-malignant disease, only one subject had more than 5 CTC/7.5 mL. The results are presented in **Table 4**.

Table 4. Control Subjects

Category	N	Mean # CTC	SD	# Patients with ≥ 5 CTC	Min.*	Max.*
Healthy	145	0.1	0.2	0	0	1
Non-malignant breast disease	101	0.2	1.2	1	0	12
Non-malignant other disease	99	0.1	0.4	0	0	3

* NCCLS Guideline C28-A2[3]

A multi-center prospective, clinical trial was conducted to determine whether the number of CTC predicted disease progression and survival. Metastatic breast cancer patients with measurable (N=177) disease starting a new line of therapy were enrolled. Clinical data were analyzed on an intent-to-treat basis.

Table 5. Patient Demographics

Category	Description Numbers	N=177 Patients
Age at Baseline	Mean ± Std. Deviation	58 ± 13
	Median	58
		Number of Subjects (% of total)
Stage	I	26 (15%)
	2	92 (52%)
	3	26 (15%)
	4	20 (11%)
	Unknown	13 (7%)
Race	White	153 (86%)
	Black	14 (8%)
	Hispanic	7 (4%)
	Unknown	3 (2%)
ECOG Score	0	82 (46%)
	1	72 (41%)
	2	18 (10%)
	Unknown	5 (3%)
Disease Site	Visceral	152 (86%)
	Bone	153 (86%)
ER/PR	+	121 (68%)
	-	54 (31%)
	Unknown	2 (1%)
HER2	0	91 (51%)
	1+	12 (7%)
	2+	18 (10%)
	3+	27 (15%)
	Unknown	29 (17%)
Line of Therapy	1st line	82 (46%)
	2nd line	26 (15%)
	≥ 3rd line	67 (38%)
	Unknown	2 (1%)
Type of Therapy	Chemo (Ch)	74 (42%)
	Endocrine (En)	45 (25%)
	Targeted (Ta)	9 (5%)
	Ch/En	10 (6%)
	Ch/Ta	23 (13%)
	En/Ta	7 (4%)
	Ch/En/Ta	2 (1%)
	Miscellaneous	2 (1%)
	Unknown	5 (3%)

Baseline CTC count was determined prior to initiation of a new line of therapy. Follow-up CTC counts were determined after the initiation of therapy at approximately 3 to 4 week intervals. For the baseline analyses, Progression Free Survival (PFS) was measured from the time of the baseline blood draw to the diagnosis of progression by CT scans and/or clinical signs and symptoms, and Overall Survival (OS) was measured from the time of baseline blood draw to the time of death. For the follow-

up analyses, PFS was measured from the time of the follow-up blood draw to diagnosis of progression or death, and OS was measured from the time of the follow-up blood draw to the time of death.

CTC Frequencies

Table 7 summarizes the total number and percentage of patients in the clinical trial that differs from the numbers and percentages of patients for Progression Free Survival shown on **Table 6.** Of the total patient number of 177, 23 were not evaluable at first follow-up. Of these 23 patients, ten patients died before a follow-up blood draw could be obtained, nine patients progressed prior to a follow-up blood draw, and four were lost to follow-up. Notably, each of the ten patients who died had ≥5 to extremely high CTC counts at baseline (CTC counts 9, 11, 15, 24, 111, 126, 301, 1143, 4648 and 23618). Of the 154 patients available for follow-up, 132, 99, 129, and 85 patients had a blood draw at 3-5, 6-8, 9-14, and 15-20 weeks after initiation of therapy, respectively.

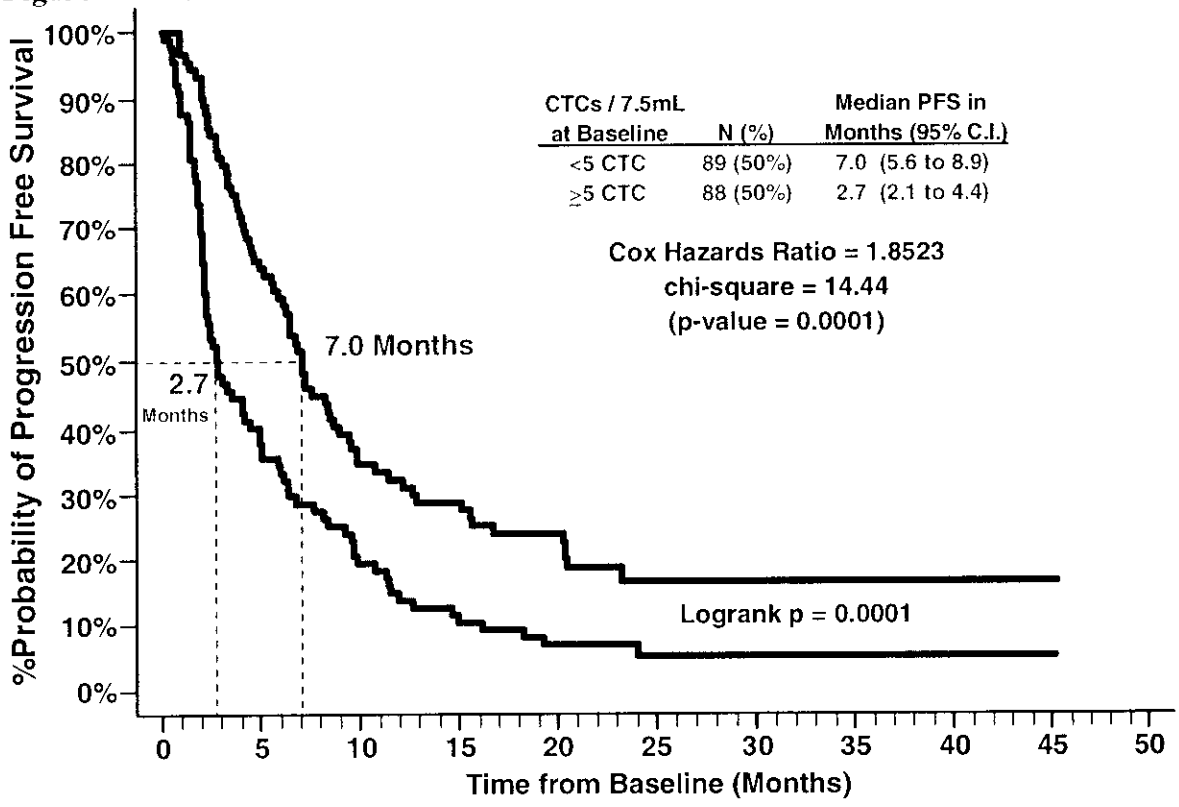
Progression Free Survival (PFS) Analysis

PFS Using Baseline CTC Results

All 177 patients had a baseline CTC test performed. For Kaplan-Meier analysis, patients were segmented into two groups based upon their CTC count at baseline:

- The Favorable group (N=89), represented in **green**, consisted of patients with <5 CTC.
- The Unfavorable group (N=88), represented in **red**, consisted of patients with ≥5 CTC.

Figure 1. PFS of Patients with < 5 or ≥ 5 CTC at Baseline (N=177).



PFS Using Follow-up CTC Results

For Kaplan-Meier analysis, patients were segmented into two groups based upon their CTC count at each of the various follow-up blood draws. Both patient groups at each of the different follow-up blood draw times after initiation of therapy for PFS are illustrated in **Figure 2**. PFS times were calculated from the time of each blood draw, and any patient showing evidence of progression prior to a particular blood draw was excluded from the analysis of that and all subsequent follow-up blood draws. **Figure 2** illustrates the ability of CTCs in patients with <5 and ≥5 CTCs 3-5 weeks, 6-8 weeks, 9-14 weeks, and 15-20 weeks after the initiation of therapy to predict time to clinical progression in 177 patients with metastatic breast cancer.

- The Favorable group represented in **olive green**, **blue**, **purple**, and [illegible] consisted of patients with <5 CTC,
- The Unfavorable group, represented in **brown**, **black**, grey, and [illegible] consisted of patients with ≥5 CTC.

Figure 2. PFS of Patients with <5 or ≥5 CTC at different times of Follow-Up

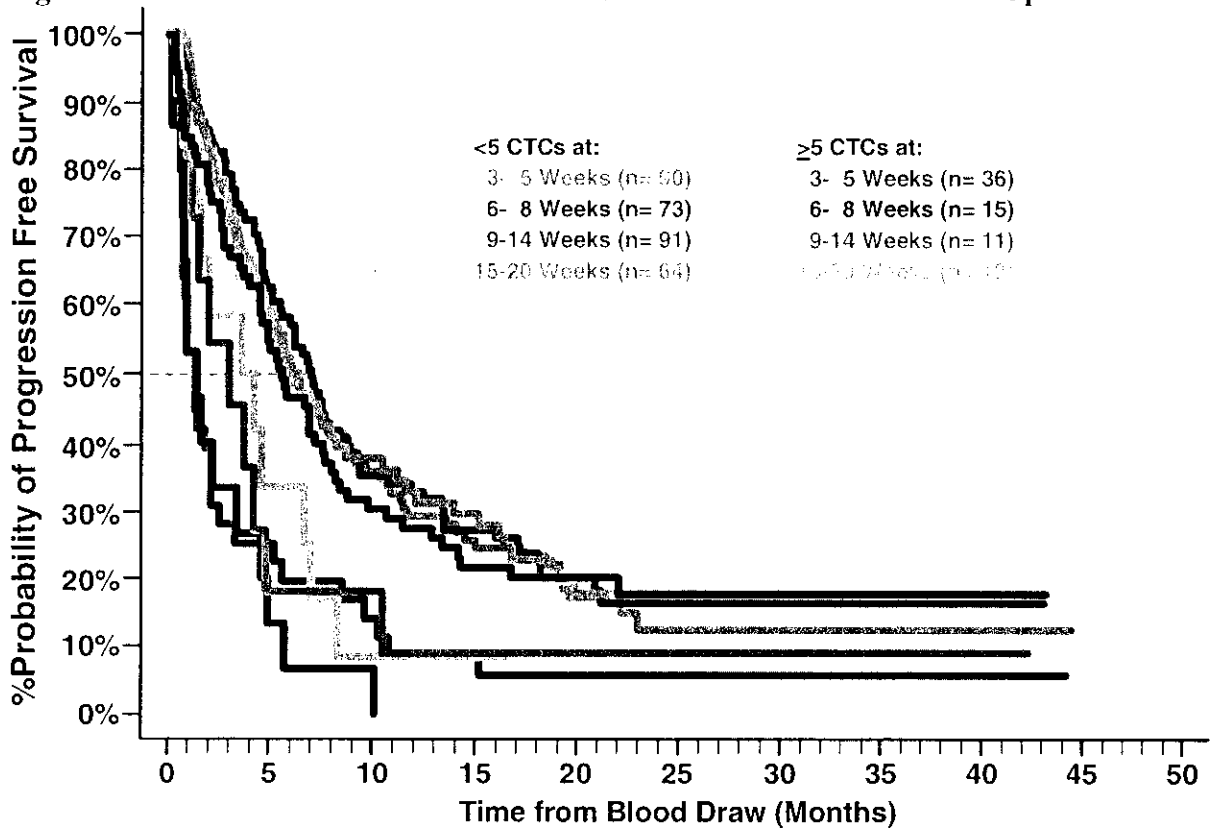


Table 6 summarizes the results of the PFS analysis using the CTC levels and a threshold of ≥5 CTCs/7.5mL at each of the different blood draw time points.

Table 6. Progression Free Survival (PFS) for patients with <5 or ≥5 CTC at different time points

1	2	3	4	5	6
Sampling Time After Tx Initiation	N	≥5 CTC	Median PFS in Months (95% C.I.) <5 CTC	Median PFS in Months (95% C.I.) ≥5 CTC	Log-rank p-value
Baseline	177	88 (50%)	7.0 (5.6 to 8.9)	2.7 (2.1 to 4.4)	0.0001
3-5 Weeks	126	36 (29%)	6.1 (4.7 to 8.6)	1.3 (0.7 to 2.1)	<0.0001
6-8 Weeks	88	15 (17%)	5.6 (4.5 to 7.6)	1.4 (0.6 to 3.4)	0.0001
9-14 Weeks	102	11 (11%)	7.0 (5.1 to 8.8)	3.0 (0.9 to 4.8)	0.0251
15-20 Weeks	76	12 (16%)	5.9 (3.8 to 8.7)	3.6 (0.7 to 7.0)	0.0610

CTC = Circulating Tumor Cells, CI = Confidence Interval, PD = Progressive disease

As illustrated in **Figure 2** and **Table 6**, patients with elevated CTCs (≥5 CTC/7.5mL whole blood) at any of the time points had a much higher likelihood of rapid progression than did those with <5 CTCs. **Table 6**

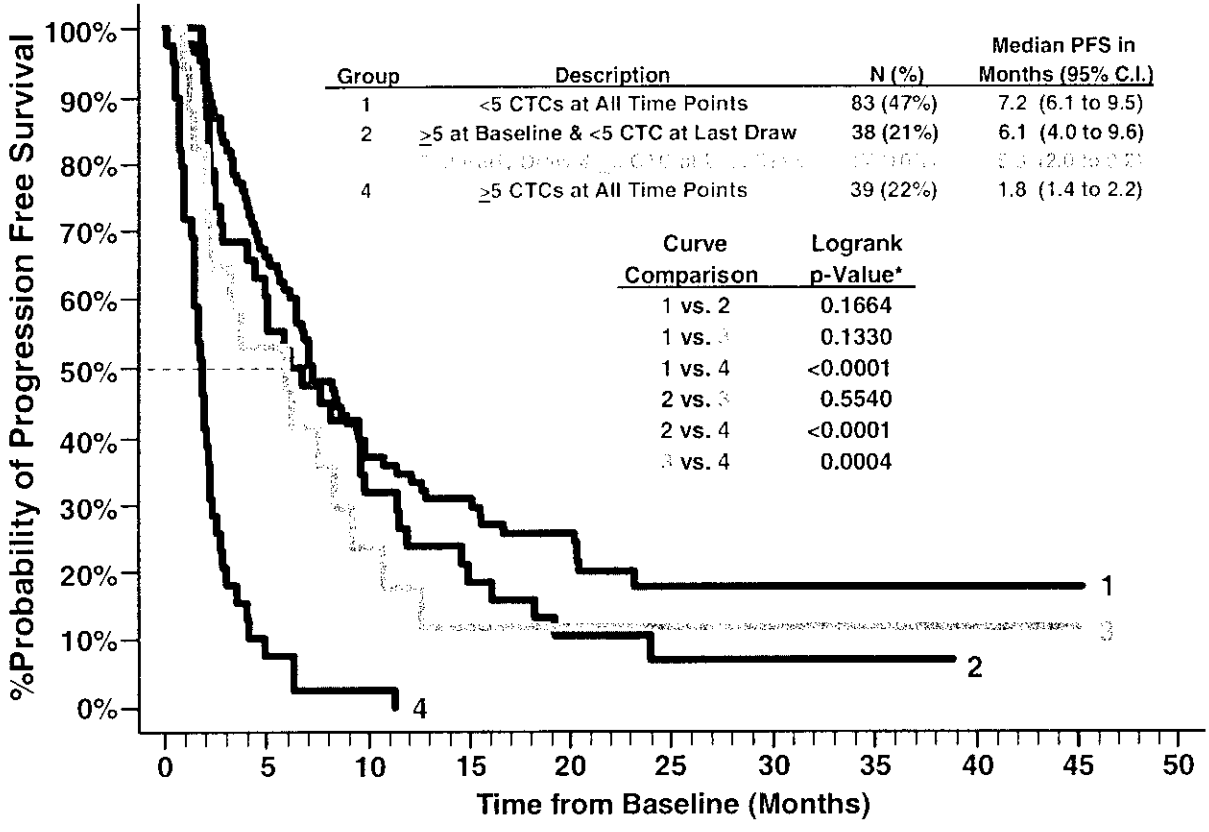
column 4 shows the median PFS times for those patients with <5 CTCs ranged from 5.6 to 7.0 months and were substantially longer than the median PFS times for those patients with ≥5 CTCs, which ranged from 1.3 to 3.6 months (column 5). The difference in the number of patients at each time point is due to the progression of some patients prior to the blood draw and based on the number of patients sampled.

Predictive Value of CTC Reduction or Increase on PFS

Elapsed PFS times were calculated from the baseline blood draw. For Kaplan-Meier analysis, patients were segmented into four groups based upon their CTC counts:

- Group 1 (**green** curve), 83 (47%) patients with <5 CTCs at all blood draw time points;
- Group 2 (**blue** curve), 38 (21%) patients with ≥5 CTCs prior to the initiation of therapy but who had decreased to <5 CTCs at the time of their last blood draw;
- Group 3 (**orange** curve), 17 (10%) patients with <5 CTCs prior to the initiation of therapy who increased to ≥5 CTCs at the time of their last blood draw;
- Group 4 (**red** curve), 39 (22%) patients with ≥5 CTCs at all blood draw time points.

Figure 3. A Reduction in CTC Below 5 After the Initiation of Therapy Predicts Longer PFS



Group	Description	N (%)	Median PFS in Months (95% C.I.)
1	<5 CTCs at All Time Points	83 (47%)	7.2 (6.1 to 9.5)
2	≥5 at Baseline & <5 CTC at Last Draw	38 (21%)	6.1 (4.0 to 9.6)
3	[illegible]	[illegible]	[illegible]
4	≥5 CTCs at All Time Points	39 (22%)	1.8 (1.4 to 2.2)

Curve Comparison	Logrank p-Value*
1 vs. 2	0.1664
1 vs. 3	0.1330
1 vs. 4	<0.0001
2 vs. 3	0.5540
2 vs. 4	<0.0001
3 vs. 4	0.0004

*p-values not adjusted for multiple hypothesis tests

Figure 3 shows that patients with ≥5 CTCs at all time points (**Group 4**) had the shortest median PFS, which was significantly different compared to the median PFS of Group 3, **Group 2**, and **Group 1**. Differences between the curves for the other groups in this figure were not significant.

Overall Survival (OS) Analysis

OS Analysis Using Baseline CTC Results

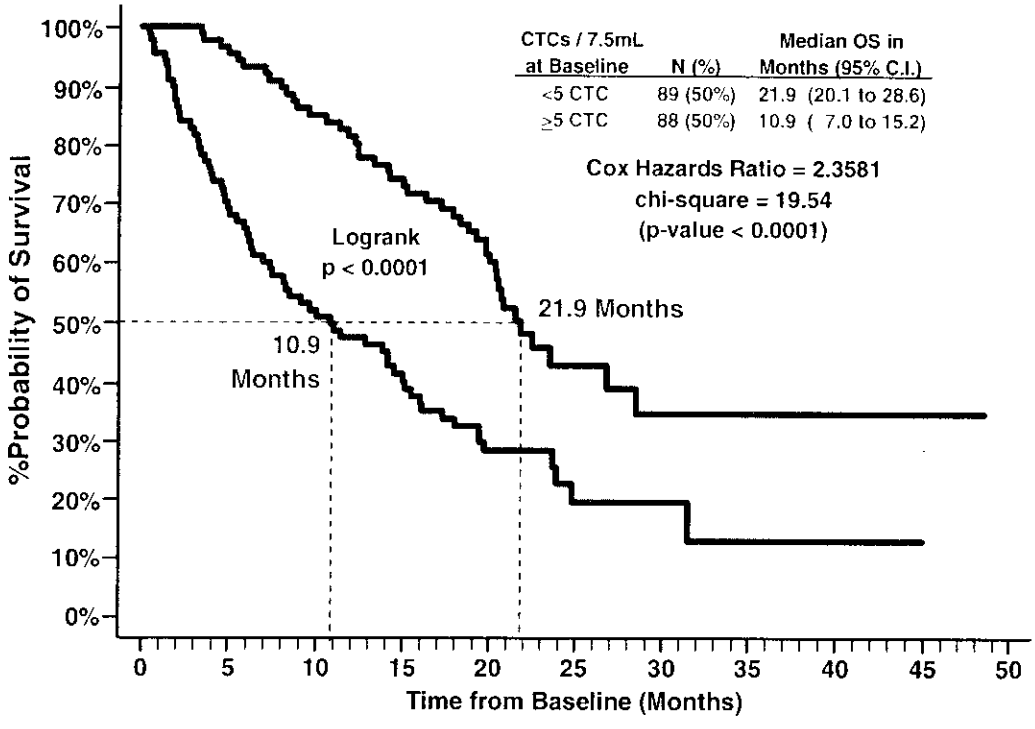
Death occurred in 109 (62%) of the 177 patients, with a mean follow-up time for the 68 (38%) patients still alive of 22.7 ± 9.4 months (median = 21.1, range = 4.4 – 48.6). At the time of these analyses, 44 (49%) of 89 patients from Favorable group (<5 CTC at baseline) compared to 65 (74%) of 88 from Unfavorable group (≥5 CTC at baseline) had died.

For Kaplan-Meier analysis, patients were segmented into two groups based upon their CTC count at baseline:

- ❖ The Favorable group (N=89), represented in **green**, consisted of patients with <5 CTC.
- ❖ The Unfavorable group (N=88), represented in **red**, consisted of patients with ≥5 CTC.

Median OS was 21.9 months for the Favorable group and 10.9 months for the Unfavorable group. The OS difference between the two groups is highly significant. These results are illustrated in **Figure 4**.

Figure 4. OS of Patients with < 5 or ≥ 5 CTC at Baseline (N=177).



OS Using Follow-up CTC Results

The Kaplan-Meier analyses of both patient groups at each of the different follow-up blood draw times after initiation of therapy are illustrated in **Figure 5**. This figure illustrates the ability of CTCs in patients with <5 and ≥5 CTCs 3-5 weeks, 6-8 weeks, 9-14 weeks, and 15-20 weeks after the initiation of therapy to predict time to death in 177 patients with metastatic breast cancer. OS times were calculated from the time of each blood draw.

- ❖ The Favorable group represented in **olive green**, **blue**, **purple**, and [illegible] consisted of patients with <5 CTC,
- ❖ The Unfavorable group, represented in **brown**, **black**, grey, and orange consisted of patients with ≥5 CTC.

Figure 5. OS of Patients with <5 or ≥5 CTC at different times of Follow-Up.

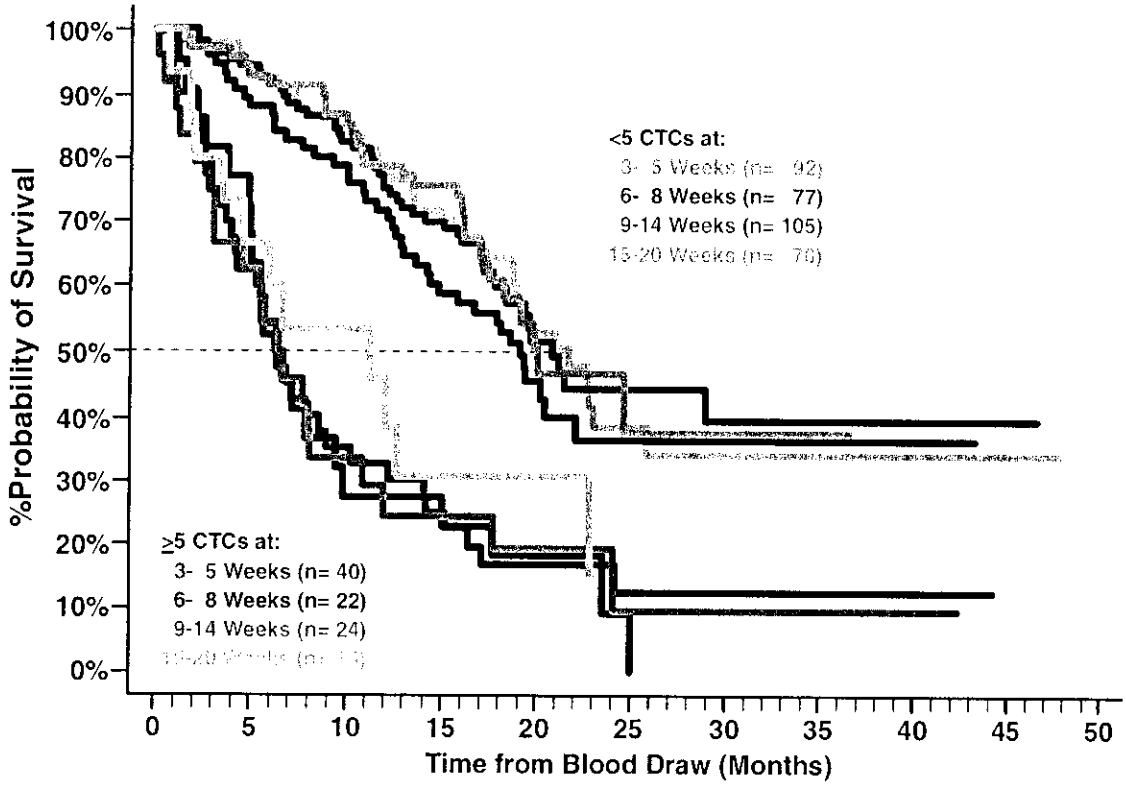


Table 7 summarizes the results of the OS analysis using the CTC levels and a threshold of ≥5 CTCs/7.5mL at each of the different blood draw time points.

Table 7. Overall Survival (OS) for patients with <5 or ≥5 CTC at different time points

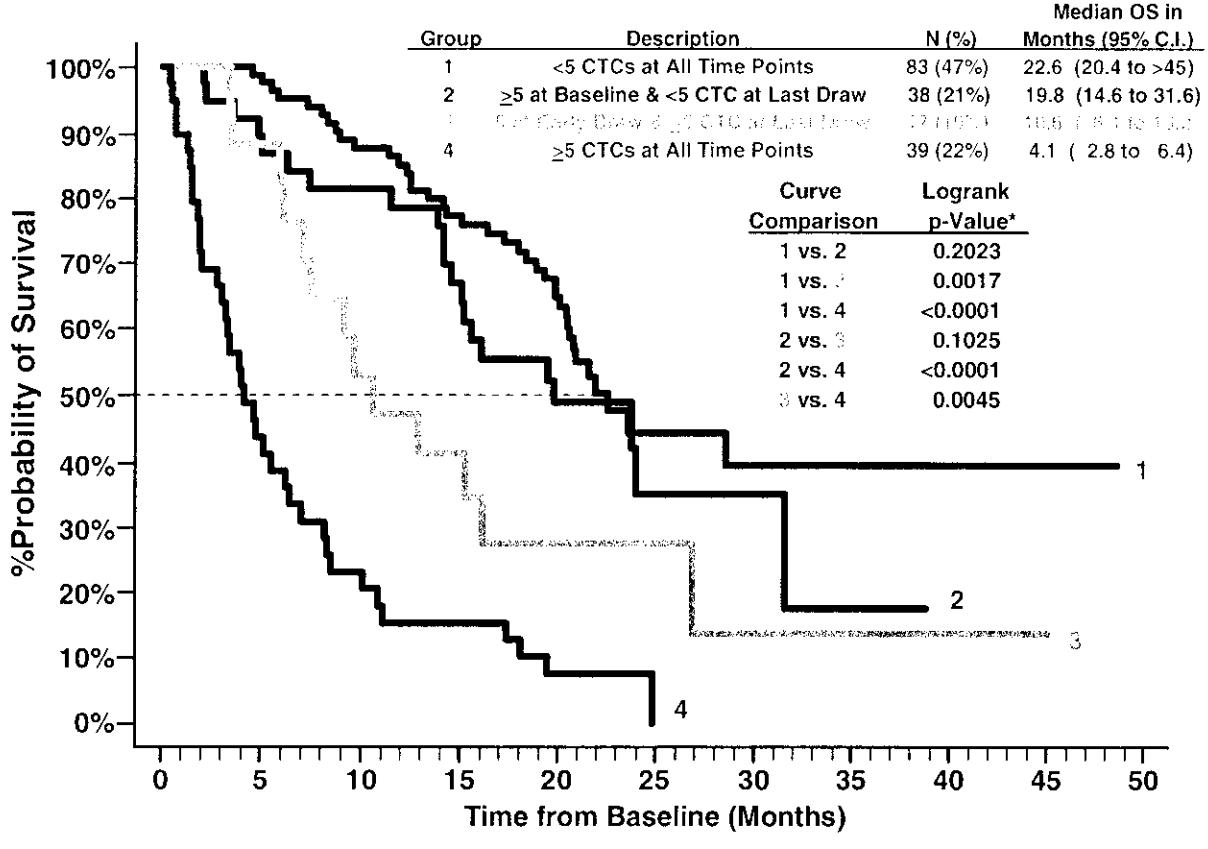
1	2	3	4	5	6
Sampling Time After Tx Initiation	N	≥ 5 CTC	Median OS in Months (95% C.I.) <5 CTC	≥ 5 CTC	Log-rank p-value
Baseline	177	88 (50%)	21.9 (20.1 to 28.6)	10.9 (7.0 to 15.2)	<0.0001
3-5 Weeks	132	40 (30%)	21.7 (18.8 to 25.9)	6.2 (4.1 to 8.9)	<0.0001
6-8 Weeks	99	22 (22%)	19.1 (14.2 to 22.1)	6.3 (4.8 to 9.8)	0.0001
9-14 Weeks	129	24 (19%)	20.8 (17.8 to >45)	6.4 (3.0 to 10.9)	<0.0001
15-20 Weeks	85	15 (18%)	20.1 (17.1 to >35)	11.3 (2.0 to 22.9)	0.0021

Predictive Value of CTC Reduction or Increase on OS

Elapsed *OS* times were calculated from the baseline blood draw. For Kaplan-Meier analysis (**Figure 6**), patients were segmented into four groups based on their CTC counts:

- ❖ Group 1 (**green** curve), 83 (47%) patients with <5 CTCs at all blood draw time points;
- ❖ Group 2 (**blue** curve), 38 (21%) patients with ≥5 CTCs prior to the initiation of therapy but who had decreased to <5 CTCs at the time of their last blood draw;
- ❖ Group 3 (curve), 17 (10%) patients with <5 CTCs prior to the initiation of therapy who increased to ≥5 CTCs at the time of their last blood draw;
- ❖ Group 4 (**red** curve), 39 (22%) patients with ≥5 CTCs at all blood draw time points.

Figure 6. A Reduction in CTC Below 5 After the Initiation of Therapy Predicts Longer OS whereas an Increase in CTC Count to 5 or above Predicts Shorter OS



*p-values not adjusted for multiple hypothesis tests

Figure 6 shows that patients who exceed the threshold of 5 CTCs at any point after the initiation of *therapy* are at a significantly higher risk of dying sooner. Patients with ≥5 CTCs at all time points (**Group 4**) had the shortest median OS, which was significantly different compared to the

median OS of [redacted], **Group 2**, and **Group 1**. The difference in the median survival between [redacted] and **Group 1** was also significant, and although the median OS for [redacted] was shorter compared to **Group 2**, the difference was not statistically significant. **Figure 6** also shows that patients who have ≥5 CTCs at baseline but eventually decrease to <5 CTCs after the initiation of therapy have approximately the same risk of death as those patients who never exceed the 5 CTC threshold.

As illustrated in **Figure 6** and **Table 7** in columns 4 & 5, patients with ≥5 CTCs at any of the time points had a much higher probability of dying sooner than did those with <5 CTCs. The median OS times for those patients with <5 CTCs ranged from 19.1 to 21.9 months and were substantially longer than the median OS times for those patients with ≥5 CTCs, which ranged from 6.2 to 11.3 months.

Univariate Cox Regression Analysis

The following parameters were analyzed using Univariate Cox regression analysis to evaluate association with PFS and OS: patient age (continuous), stage of disease at diagnosis (1-4), time to metastasis (continuous), ECOG status before initiation of a new line of therapy (0-2), ER/PR status (+/-), HER2/neu status (0-3+), line of therapy (≥2nd or 1st), type of therapy (chemo only or hormonal / combination), baseline CTC count (≥5 or <5 CTC/7.5mL), and follow-up CTC counts 3-5 weeks, 6-8 weeks, 9-14 weeks, and 15-20 weeks after the initiation of therapy (≥5 or <5 CTC/7.5mL). **Table 8** shows the results of this analysis and presents the Cox hazard ratio (HR), chi-squared result (chi^2) and associated p-value, and the number of patients in each evaluation.

Table 8: Univariate Analysis

Parameter	Categories		PFS Risk from Baseline			OS Risk from Baseline	
	Pos	Neg	# of Patients	HR	p-value	HR	p-value
Age at Baseline Blood Draw	Age in Years		175	0.9922	0.1734	0.9938	0.3745
Stage at Primary Diagnosis	4 vs. 3 vs. 2 vs. 1		164	0.9670	0.7226	0.9957	0.9694
ER/PR	Pos	Neg	175	0.8441	0.3265	0.5294	0.0020
Her-2/neu	3+ vs. 2+ vs. 1+ vs. 0		148	0.9110	0.2070	0.9322	0.4221
ECOG Status	2 vs. 1 vs. 0		172	1.1353	0.3067	1.6421	0.0005
Time to Metastasis	Time in Years		175	0.9706	0.0483	0.9535	0.0180
Line of Therapy	≥ 2nd	1st	175	1.5490	0.0074	1.9090	0.0012
Type of Therapy	Chemo Only	H / C and/or I	172	1.9699	<0.0001	2.2222	<0.0001
Baseline CTC Number	≥5	<5	177	1.8523	0.0001	2.3581	0.0000
3 - 5 Week CTC Number	≥5	<5	132	2.5243	0.0000	3.3013	0.0000
6 - 8 Week CTC Number	≥5	<5	99	3.5709	0.0000	2.8668	0.0001
9 - 14 Week CTC Number	≥5	<5	129	2.8898	<0.0001	3.6360	0.0000
15 - 20 Week CTC Number	≥5	<5	85	1.8563	0.0412	2.8457	0.0035

Pos – Positive; **Neg** – Negative
H / C / and/or I – Hormonal or Immunotherapy alone or Combination of Hormonal and/or Chemo and/or Immunotherapy

Multivariate Cox Regression Analysis

Multivariate Cox regression analyses were conducted to evaluate the independent predictive power of CTC count by adjusting for the effects of the known important clinical factors that are statistically significant in the univariate analyses. CTCs were found to be strong predictors of PFS and OS.

USE OF CTC TO MONITOR CLINICAL STATUS

Relationship between survival, CTCs and disease assessment by imaging

Radiological imaging is one of the primary means of determining disease status and response to therapy in metastatic breast cancer patients. To establish the relationship of CTCs, measured at two different timepoints, to clinical status as determined by imaging, CTCs and imaging results

were compared 1) to the true clinical endpoint overall survival and 2) to each other.

CTC

Previous data has shown that patients with ≥5 CTCs / 7.5mL of blood at any succeeding follow-up visit after the initiation of therapy had a higher likelihood of progressive disease and decreased overall survival compared to patients with <5 CTCs / 7.5mL of blood.

Imaging

All imaging sites were in compliance with Digital Imaging and Communications in Medicine (DICOM) standards. Using standardized digital images, two expert radiologists (readers), working individually and blinded to clinical information, classified each follow-up disease assessment (total of 231 imaging studies) from 138 patients with measurable disease as indeterminate (I), stable disease (S), partial response (PR), or progressive disease (PD) according to World Health Organization (WHO) bi-dimensional criteria. Measurable disease was defined as the presence of at least one lesion ≥2cm in its longest dimension. Readers identified up to eight lesions per patient per time point by describing the longest dimension of the lesion and the longest perpendicular dimension. These two dimensions were multiplied and the "cross product" was reported. Summed measurements for the cross-products were calculated, and percent change from the previous time point was determined. Although all patients had measurable disease, non-measurable lesions (still detectable by radiology) were included in the determination of patient status as described in the WHO guidelines. Progressive disease was defined as a >25% increase in the sum of all lesions or appearance of a new measurable or non-measurable lesion. Partial response was defined as a decrease in the sum of all lesions of ≥50% and no new lesions.

- Radiology interpretations from the two expert radiologists were classified as followed:
  - S and PR were considered to both reflect non-progressive disease (NPD)
  - PD was considered to reflect progressive disease
  - In situations where one of the radiologists rendered a classification of Indeterminate (I) but the other radiologist rendered a classification of S, PR or PD, the classification of the latter radiologist was used for comparison to CTCs (n=11)
  - When both radiologists rendered a classification of Indeterminate (I), then the data was not used in the comparison to CTCs (n=3)

- A third independent radiologist adjudicated disagreements between the two primary readers regarding PD and NPD (n=27)
- In situations where the third independent radiologist rendered a classification of Indeterminate (I), the data was not used in the comparison to CTCs (n=2)
- In serial imaging studies, radiology results that were less than one month from a previous tabulated observation were not used (n=1).

- The CTC results obtained within ± one month of the imaging study were classified as <5 CTC and ≥5 CTC. If more than one CTC value was obtained within ± one month of the imaging study, the CTC result obtained closest to the date of the imaging study was used.

Relationship between survival to imaging and CTC

Separate Kaplan-Meier analyses were performed to compare the overall survival of patients in the Favorable (<5 CTCs) and Unfavorable (≥5 CTCs) groups using CTC results at two different time points and the first follow-up imaging study. Using results from the first follow-up imaging studies, performed 10.1 ± 5.1 weeks (median = 9.0 weeks) after initiation of therapy (i.e. the baseline blood draw), the median survival of the 96 (70%) patients determined by imaging to have NPD was 23.8 months (95% CI 20.4 to 28.6) (**Figure 7.A, Table 9**). For the 42 (30%) patients determined by imaging to have PD, the median survival was 12.9 months (95% CI 7.1 to 19.3).

For CTCs at the first follow-up blood draw, performed 4.3 ± 2.5 weeks (median = 4.0 weeks) after initiation of therapy, the median survival of 104 (75%) patients with Favorable CTC results (<5 CTCs) was 21.9 months (95% CI 20.4 to 26.9) (**Figure 7.B, Table 9**). Thirty-four (34) patients (25%) with Unfavorable CTC results (≥5 CTCs) had a median survival of 8.3 months (95% CI 5.9 to 15.1).

To determine if CTC assessments performed closer to the time of the imaging resulted in similar survival prospects compared to CTC assessments done approximately 4 weeks after the initiation of therapy, only those patients with CTC assessments performed within ± one month of the first follow-up imaging study (9.9 ± 5.1 weeks, median = 8.8 weeks, after the initiation of therapy) were analyzed (**Figure 7.C, Table 9**). One hundred and thirty four (134) of the 138 patients (97%) had CTC assessments within one month of the first follow-up imaging study. The median survival of 105 (78%) patients with Favorable CTC results was 21.9 months (95% CI 19.9 to 31.6). For 29 (22%) patients with Unfavorable CTC results, the median survival was 8.5 months (95% CI 5.5 to 15.1). These data show that CTC assessments at both time points

provide similar results to imaging conducted approximately 12 weeks after the initiation of therapy.

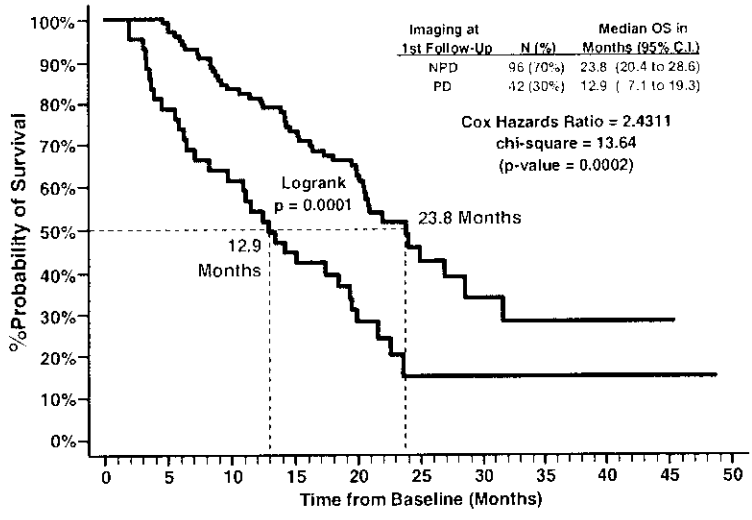
Table 9. OS of Patients with CTC assessment approximately one month after the initiation of therapy and within one month of the radiological assessment

	N	Median Survival & (95% CI) Months
Imaging	138	
favorable (NPD)	96 (70%)	23.8 (20.4 - 28.6)
unfavorable (PD)	42 (30%)	12.9 (7.1 - 19.3)
1st follow-up CTCs	138	
favorable (<5)	104 (75%)	21.9 (20.4 - 26.9)
unfavorable (≥5)	34 (25%)	8.3 (5.9 - 15.1)
CTC (±1 Month of Imaging)	134*	
favorable (<5)	105 (78%)	21.9 (19.9 - 31.6)
unfavorable (≥5)	29 (22%)	8.5 (5.5 - 15.1)

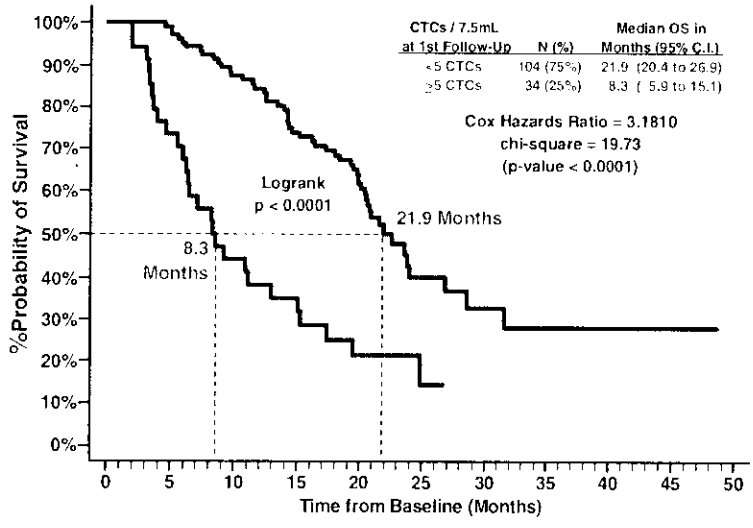
*134 /138 patients had CTC assessments performed within (±) 1 month of Imaging.

Figure 7. Correlation of Radiological and CTC Assessment with OS

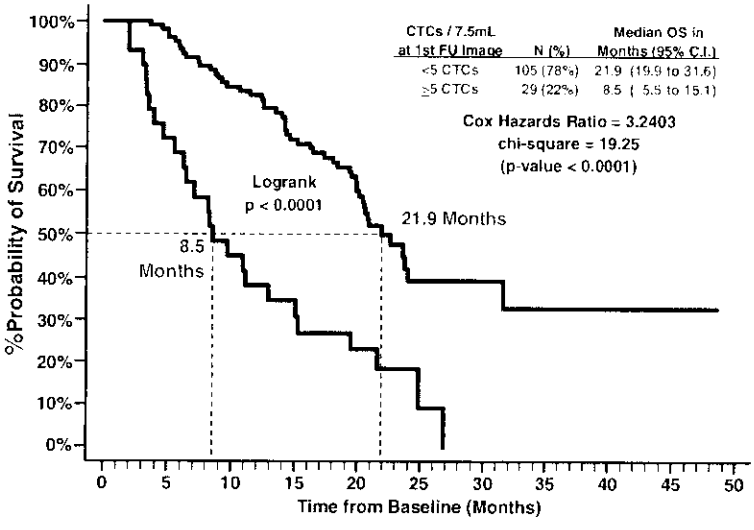
7A. OS of Patients with NPD or PD at 1st Follow-Up Imaging Study (N=138)



7B. OS of Patients with <5 or ≥5 CTCs at 1st Follow-Up after Initiation of Therapy (N=138)



7C. OS of Patients with <5 or ≥5 CTCs within ±1 Month of 1st Follow-Up Imaging Study (N=134)



Concordances between CTC and Radiological Monitoring

As noted above, imaging studies are a major component of the current standard of care for determining disease progression and response to treatment in the metastatic breast cancer setting. To further support the effectiveness of CTCs in making these clinical assessments, two-by-two tabulations of concordant and discordant observations between CTCs and radiological imaging were constructed using the previously described criteria.

Using only the 1st follow-up imaging study, the radiological response at this visit was compared with the CTC results obtained within ± one month of this imaging study. A total of 134 of the 138 patients (97%) had CTC results that met this criteria. The result of this "patient-wise" comparison between CTCs and imaging is shown in **Table 10**.

Table 10. Patient-Wise Comparison of CTC and Imaging

Response at 1st Follow-Up Imaging Study	CTCs within ± 1 Month of Imaging		Total
	<5 CTCs / 7.5mL	≥5 CTCs / 7.5mL	
Non-Progressive Disease	85	9	**94**
Progressive Disease	20	20	**40**
Total	**105**	**29**	**134**

Measurement	Estimate	Lower 95% CI	Upper 95% CI
Positive % Agreement	50%	34%	66%
Negative % Agreement	90%	83%	96%
Positive Predictive Value	69%	49%	85%
Negative Predictive Value	81%	72%	88%
Overall Agreement	78%	70%	85%
Odds Ratio	9.4	3.4	26.8

Using all of the follow-up imaging studies performed after the initiation of therapy on the 138 patients that rendered useable radiological response results (n=225), these results were then compared to CTC results obtained within ± one month of the imaging study. A total of 219 of the 225 (97%) imaging studies had CTC results meeting this criterion. The result of this "observation-wise" comparison between CTCs and imaging is shown in **Table 11**.

Table 11. Observation-Wise Comparison of CTC and Imaging

Response at All Follow-Up Imaging Studies	CTCs within ± 1 Month of Imaging		Total
	<5 CTCs / 7.5mL	≥5 CTCs / 7.5mL	
Non-Progressive Disease	151	16	**167**
Progressive Disease	30	22	**52**
Total	**181**	**38**	**219**

Measurement	Estimate	Lower 95% CI	Upper 95% CI
Positive % Agreement	42%	29%	57%
Negative % Agreement	90%	85%	94%
Positive Predictive Value	58%	41%	74%
Negative Predictive Value	83%	77%	89%
Overall Agreement	79%	73%	84%
Odds Ratio	6.9	3.0	15.8

In serial observations, only a minority of the transitions for imaging results between non progressive disease and progressive disease coincided with a matching transition of CTC counts between <5 and ≥5 CTCs / 7.5 mL (see Limitations).

Because the prognostic value of the CTC results at an earlier time-point were equivalent to that of the CTC results at the time of imaging (**Figures 7B** & **7C**), a patient-wise comparison using results from only the 1st follow-up imaging study, performed approximately 9 weeks after the initiation of therapy, and the CTC results obtained at the 1st follow-up, performed approximately 4 weeks after initiation of therapy, was constructed. All 138 patients had CTC results meeting this criterion. The result of this "patient-wise" comparison between CTCs at an earlier time point and imaging is shown in **Table 12**.

Table 12. Patient-Wise Comparison of CTC and Imaging

Response at 1st Follow-Up Imaging Study	CTCs at 1st Follow-Up		Total
	<5 CTCs / 7.5mL	≥5 CTCs / 7.5mL	
Non-Progressive Disease	84	12	**96**
Progressive Disease	20	22	**42**
Total	**104**	**34**	**138**

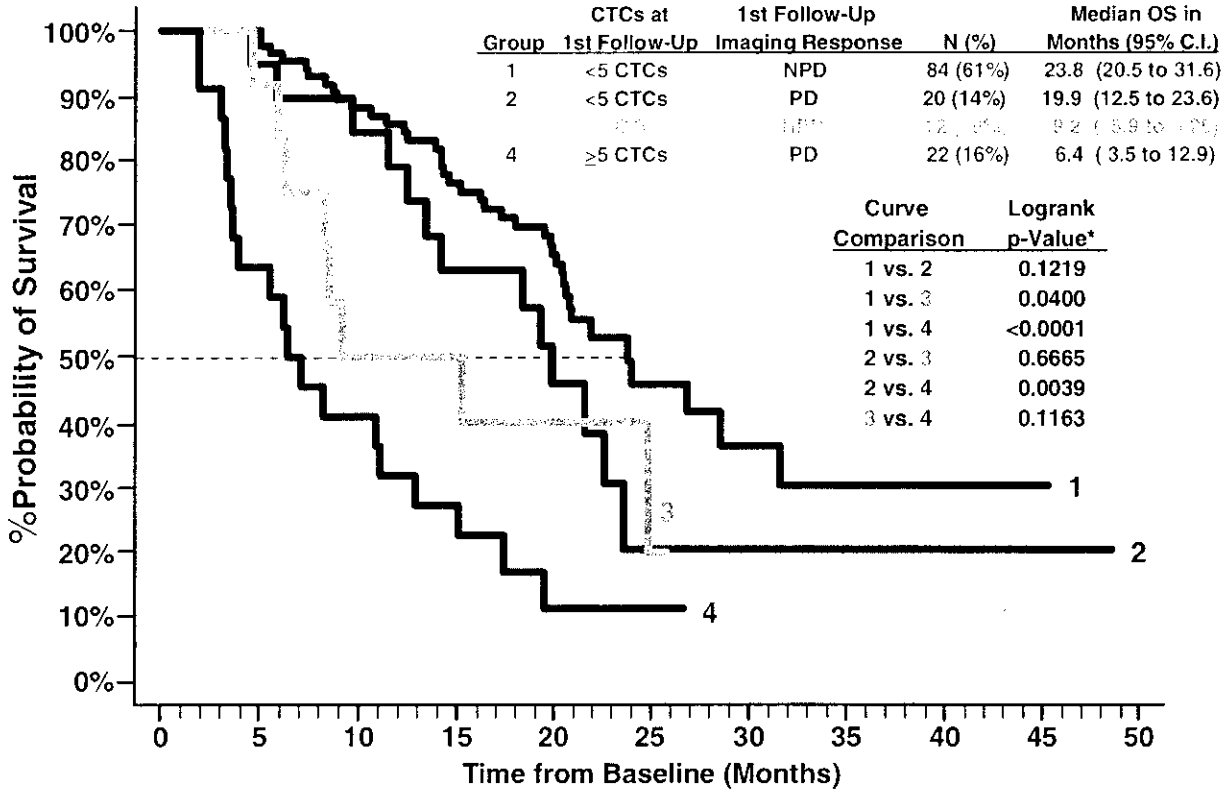
Measurement	Estimate	Lower 95% CI	Upper 95% CI
Positive % Agreement	52%	36%	68%
Negative % Agreement	88%	79%	93%
Positive Predictive Value	65%	46%	80%
Negative Predictive Value	81%	72%	88%
Overall Agreement	77%	69%	84%
Odds Ratio	7.7	3.0	19.9

CTC AS AN ADJUNCT TO IMAGING

While the overall agreement between CTCs and imaging was good (approximately 78%), there was disagreement in approximately 22% of the patients. As the information from CTC assessments is intended to be used in conjunction with other diagnostic modalities to make treatment decisions, CTC assessment at 1st follow-up (approximately 4 weeks after the initiation of therapy) and imaging in the following groups were compared to OS to determine which of the discordant results better reflected the prognosis of the patient.

These results suggest that CTC determination is a strong independent predictor of overall survival. This figure also suggests that the combination of CTC and radiological assessments provides the most accurate assessment of prognosis.

Figure 8. OS of Patients in Groups 1, 2, and 4 using the 1st Follow-up CTC assessment after Initiation of Therapy (n=138) and the Disease Status Determined at the 1st Follow-Up Imaging Study



*p-values not adjusted for multiple hypothesis tests

VARIABILITY OF CTC AND RADIOLOGICAL ASSESSMENTS

CTCs

Inter-reader variabilities for the CTC counts at the first follow-up blood draw was determined by counting the number of instances where the operator at the testing site was not in concordance with the central laboratory in classifying a sample as ≥5 CTCs versus <5 CTCs. In a subset of 71 patients, two tubes of blood were drawn and processed, and the classification of ≥5 CTCs versus <5 CTCs in each of the two tubes as determined by the site as well as by the central laboratory was compared.

Imaging

Inter-reader variability was determined by comparing the radiological interpretations of the two radiologists, classified as NPD vs. PD. Intra-reader variability was calculated by comparing the radiological interpretations of the two radiologists in a subset of patients where each radiologist determined the response at three separate sittings, each sitting separated by a minimum of one week.

Imaging segments of later assessments in these 138 patients and CTC assessments before initiation of therapy and at later follow-ups were studied also.

Table 13. Variability of Radiological and CTC Assessments

	Radiology NPD vs. PD		CTC / 7.5mL <5 vs. ≥5	
	n	**disagreement**	**n**	**disagreement**
Inter-reader				
1st Follow-Up	132	11.4%	138	0.7%
Any Follow-Up	217	13.4%	695	1.0%
Intra-reader				
1st Follow-Up				
Reader 1 (Radiology)	24	25.0%	---	---
Reader 2 (Radiology)	22	9.1%	---	---
Any Follow-Up				
Reader 1 (Radiology)	30	20.0%	---	---
Reader 2 (Radiology)	28	10.7%	---	---
CTCs Tube to Tube				
1st Follow-Up	---	---	71	5.6%
Any Follow-Up	---	---	403	5.5%

The inter-reader variabilities of the radiological determinations were significantly higher in both the first follow-up disease assessment and in all subsequent disease follow-up assessments when compared to the inter-

reader variability of the CTC counts in the same groups (Fisher's $P<0.001$).

807.92 (b)(3): Conclusions from Clinical Testing

The data demonstrate that CTC counts, obtained at various points in the clinical course of metastatic breast cancer, have prognostic value. The prognostic information from CTC measurements is similar in degree and adds to the prognostic information available from radiologic assessments of disease. In addition, CTC measurements are less variable than radiological assessments. Changes in CTC and radiologic status do not occur simultaneously, suggesting that CTC and radiologic assessments focus on different aspects of tumor biology. Nevertheless, the overall concordance of CTC and radiologic assessments supports the use of CTC to monitor the progression of metastatic breast cancer.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Veridex, LLC
A Johnson and Johnson Company
c/o Ms Debra J. Rasmussen
Worldwide executive director Regulatory and Quality Affairs
33 Technology Drive
Warren, NJ 07059

DEC 14 2006

Re: k062013
Trade/Device Name: CellSearch™ Circulating Tumor Cell Kit (Epithelial)
Regulation Number: 21 CFR 866.6020
Regulation Name: Immunomagnetic Circulating Cancer Cell Selection and Enumeration System
Regulatory Class: Class II
Product Code: NQI
Dated: July 14, 2006
Received: July 17, 2006

Dear Ms. Rasmussen:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (240) 276-0484. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Robert L. Becker, Jr., M.D., Ph.D.
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

INDICATIONS FOR USE

510(K) Number (if known): K062013

Device Name: CellSearch™ Circulating Tumor Cell Kit

Indications for Use:
The CellSearch™ Circulating Tumor Cell Kit is intended for the enumeration of circulating tumor cells (CTC) of epithelial origin (CD45-, EpCAM+, and cytokeratins 8, 18+, and/or 19+) in whole blood.

The presence of CTC in the peripheral blood, as detected by the CellSearch™ Circulating Tumor Cell Kit, is associated with decreased progression free survival and decreased overall survival in patients treated for metastatic breast cancer. The test is to be used as an aid in the monitoring of patients with metastatic breast cancer. Serial testing for CTC should be used in conjunction with other clinical methods for monitoring breast cancer. A CTC count of 5 or more per 7.5 mL of blood at any time during the course of the disease is predictive of shorter progression free survival and overall survival.

(PLEASE DO NOT WRITE BELOW THIS LINE- CONTINUE ON ANOTHER PAGE AS NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use _X_ AND/OR Over –the-Counter Use ___
(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

Maria M Chan
Division Sign-Off

Office of In Vitro Diagnostic
Device Evaluation and Safety

510(k) K062013